METIMMOX: COLORECTAL CANCER METASTASIS – SHAPING ANTI-TUMOR IMMUNITY BY OXALIPLATIN

Protocol Acronym: METIMMOX

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SIGNATURE PAGE

Title **METIMMOX: Colorectal Cancer METastasis – Shaping Anti-Tumor IMMunity by OXaliplatin**

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Ethics Committee no. 2017/1850

I hereby declare that I will conduct the study in compliance with the Protocol, International Conference on Harmonization – Good Clinical Practice, and the applicable regulatory requirements:

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PROTOCOL SYNOPSIS

METIMMOX: Colorectal Cancer METastasis – Shaping Anti-Tumor IMMunity by OXaliplatin

Sponsor	Akershus University Hospital
Phase and study type	Multicenter open-label randomized phase 2 study
Investigational medical products	Control arm: the Nordic FLOX regimen Experimental arm: repeat sequential FLOX and nivolumab
Centers	Akershus University Hospital St. Olavs Hospital – Trondheim University Hospital Haukeland University Hospital Hospital of Southern Norway Oslo University Hospital
Study period	Estimated date of first patient enrolled: 1 March 2018 Anticipated recruitment period: 12 months Estimated date of last patient completed: 1 September 2020
Treatment duration	Expected treatment duration per patient: Experimental arm: 18 months (until failure of treatment strategy) Control arm: 9 months (until failure of treatment strategy)
Follow-up	Expected follow-up period per patient: Experimental arm: 30 months (12 months following failure of treatment strategy) Control arm: 21 months (12 months following failure of treatment strategy)
Objectives	Hypothesis: Most patients with metastatic colorectal cancer (CRC) harbor tumor that can be transformed into an immunogenic disease by oxaliplatin, and may thereby benefit from the addition of immune-modulating therapy to improve outcome of the current oxaliplatin-based standard-of-care. Primary objective: To determine progression-free survival (PFS), in terms of failure of treatment strategy, of sequential treatment with the Nordic FLOX regimen and nivolumab compared with the standard-of-care Nordic FLOX regimen in previously untreated microsatellite-stable (MSS) metastatic CRC. Secondary objectives: To determine safety and tolerability of sequential treatment with the Nordic FLOX regimen and nivolumab compared with the standard-of-care Nordic FLOX regimen. To monitor and compare quality-of-life (QoL) alterations during therapy courses.

End points	Primary end point: PFS Secondary end points: safety (incidence of adverse events), tolerability (grading of adverse events), objective response rate, duration of response, secondary surgical curative resection rate, overall survival
Study design	Multicenter open-label randomized phase 2 study in previously untreated MSS metastatic CRC
Main inclusion criteria	– Patient has histologically verified CRC adenocarcinoma – Patient has radiologically measurable metastatic disease – Patient has a metastatic lesion that can be biopsied – Patient has not had previous systemic therapy for the metastatic disease – Patient is eligible for the Nordic FLOX regimen
Main exclusion criteria	– Patient has initially resectable metastatic disease for which neoadjuvant therapy is deemed superfluous – Patient does not consent to biopsy sampling – Patient has metastatic disease to lungs as the sole site – Patient has untreated or symptomatic brain metastasis (patient must be symptom-free without the use of corticosteroids) – Patient experiences a period of less than 6 months since discontinuation of adjuvant oxaliplatin-containing chemotherapy – Patient is ineligible for full chemotherapy doses (100% doses) at start of study treatment – Patient has had radiation therapy within 4 weeks of start of study treatment – Patient has a nervous system disorder worse than grade 1 of the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 – Patient has any medical condition or has undergone any treatment within 4 weeks of start of study treatment that will preclude him/her from cancer immune-modulating therapy (treatment with Investigational Medical Product) – Patient has any medical condition that will preclude him/her from receiving a component of the FLOX regimen (treatment with Investigational Medical Product) – Patient has Eastern Cooperative Oncology Group performance status 2 or worse – Patient has serum/plasma C-reactive protein of 60 mg/L or higher – Patient does not meet the following requirements at baseline: adequate bone marrow function without current use of colony-stimulating factors (minimum values of neutrophils 1.5 $x10^9$/L, platelets 100 $x10^9$/L, hemoglobin 10 g/dL), adequate liver function (maximum values of AST/ALT 5 xULN and bilirubin 2 xULN; albumin value of 30 g/L or higher; INR within normal level), adequate renal function (maximum creatinine value of 1.5 xULN) – Patient has any other reason, in the opinion of Clinical Investigator, not to participate in the study

Sample size	100 patients (50 in each study arm)
Efficacy assessments	Radiologic assessment every 8 weeks (following 4 cycles of FLOX or the alternative 2 cycles each of FLOX and nivolumab), according to the Response Evaluation Criteria in Solid Tumors (RECIST) and the RECIST consensus guideline for assessment of response to immune-modulating therapies (iRECIST).
Safety assessments	Recording of adverse events, according to CTCAE v4.0, will be done continuously and formally recorded at each new treatment cycle on active study therapy and every 8 weeks in planned breaks from active study therapy; safety (incidence of adverse events) and tolerability (grading of adverse events) will be reported. Formal QoL assessments will be undertaken at study enrolment, completion of the active therapy of the first treatment sequence (after 16 weeks), and disease progression, using the consensus modules EORTC QLQ-C30, EORTC QLQ-CIPN20, and EQ-5D-5L.
Other assessments	Tertiary objective: To compare costs for the resource use (in diagnostic work-up, treatment, and any adverse events) for the sequential therapy with that of the standard-of-care, applying a model specifically developed for CRC. Exploratory objectives: 1) Development of circulating marker tools: (a) To quantify phosphatase activity in serial peripheral blood mononuclear cells samples, collected corresponding to each change of therapy (from FLOX to nivolumab and reverse) in the sequential regimen, as surrogate measure of cytotoxic T lymphocyte activity. (b) To monitor alterations of circulating tumor DNA and exosomal miRNA in plasma samples collected at the same sampling points, as surrogate response marker. (c) To monitor factors reflecting systemic anti-tumor immunity in peripheral blood samples collected at the same sampling points, as marker of immunogenic cell death. 2) Functional magnetic resonance (MR) imaging: To investigate responses of the tumor microenvironment in abdominal metastases caused by oxaliplatin and nivolumab by repeat functional MR imaging, undertaken corresponding to each change of therapy during the first two months of the sequential regimen, and correlate changes with RECIST/iRECIST measures and PFS. 3) Histologic and molecular analyses: To investigate immune responses in liver/peritoneal metastases by histologic and molecular profiling of repeat liver/peritoneal biopsy samples, collected corresponding to each change of therapy during the first two months of the sequential regimen, and correlate changes with RECIST/iRECIST measures and PFS.

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ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Explanation
ADL	activity of daily life
AE	adverse event(s)
BMS	Bristol-Myers Squibb
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CR	complete response
CRC	colorectal cancer
CRF	case report form(s)
CRT	chemoradiotherapy
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
DILI	drug-induced liver injury
DOR	duration of response
ECOG	Eastern Cooperative Oncology Group
EDSMC	External Data and Safety Monitoring Committee
Flt3L	fms-like tyrosine kinase 3 ligand
GCP	Good Clinical Practice
HR	hazard ratio
IB	Investigator's Brochure
ICB	immune checkpoint blockade
ICD	immunogenic cell death
ICF	informed consent form
ICH	International Conference on Harmonization
iCPD	immune-confirmed progressive disease
iCR	immune-complete response
IEC	Independent Ethics Committee
IMP	investigational medicinal product(s)
iPR	immune-partial response

irAE	immune-related adverse event(s)
IRB	Institutional Review Board
iSD	immune-stable disease
IV	intravenous(ly)
iRECIST	RECIST for immune-modulating therapies
iUPD	immune-uncomfirmed progressive disease
LARC	locally advanced rectal cancer
MR	magnetic resonance
MSI	microsatellite-instable
MSS	microsatellite-stable
NACT	neoadjuvant chemotherapy
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cells
PD	progressive disease
PD-1	programmed death receptor 1
PD-L1	ligand of PD-1
PFS	progression-free survival
PR	partial response
QoL	quality-of-life
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event(s)
SC	subcutaneous(ly)
SD	stable disease
SmPC	summary of product characteristics
SOP	standard operating procedure
SSCRR	secondary surgical curative resection rate
SUSAR	suspected unexpected serious adverse reaction
TME	tumor microenvironment
ULN	upper limit of normal
WOCBP	woman of childbearing potential

1 INTRODUCTION

1.1 Background and rationale

Advanced colorectal cancer – the public health and clinical challenges

Colorectal cancer (CRC), owing to an aging population, is a disease common in both sexes and among all adult age groups but with a significant rise in incidence from the age of 60 [Ferlay *et al.,* 2013]. Due to the overall increase in age of populations, it is a disease that is becoming more common over time. In 2014, the CRC incidence rate in the Norwegian population of 5.2 million persons added up to almost 4,200 individuals (www.kreftregisteret.no/en/). About half of CRC patients proceed to metastatic disease. Generally, no curative treatment for multi-organ metastasis exists. In the past two decades, several new systemic therapies such as cytotoxic and biologically targeted agents have come into routine use for advanced CRC, extending patients' life and, importantly, alleviating their symptoms. Still, unresectable metastases particularly in abdominal cavity organs remain the cause of high morbidity and dismal survival [Hadden *et al.,* 2016]. New insights into the biology of early systemic tumor propagation may show a path to the next milestone in CRC management, which will be the control of metastatic progression.

In recent years, the potential for using the immune system to combat tumor progression has gained much attention. Tumor immunogenicity includes both tumor antigen recognition and the action of cytotoxic immune cells, and therefore the abnormality of a malignant tumor may make it a target it for immune-mediated elimination. However, a tumor is also 'self'. Protective mechanisms against auto-immunity will therefore impede tumor immune surveillance. This counterbalance between tumor and the immune system creates a state of equilibrium, or immune tolerance, which can be edited therapeutically. Immune-modulating therapy focuses on how to circumvent tumor-induced immune-suppressive mechanisms and invoke a tumor-directed immune response. So far, this concept has proven successful in the treatment of highly immunogenic tumors. Less immunogenic tumors, such as CRC and many other entities, will need additional stimulation to breach the immune tolerance in order for patients to achieve durable and beneficial treatment responses.

The tumor microenvironment and its immune attributes

The tumor microenvironment (TME) consists of stromal elements, of which the immune cells have preferentially adopted activities that support immune tolerance [Whiteside *et al.,* 2016]. Tumor cell expression of the ligand of programmed death receptor 1 (PD-1), PD-L1, renders the tumor cells more effective in binding to PD-1 on cytotoxic T lymphocytes [Smyth *et al.,* 2016]. This causes silencing of this tumor cell-killing T cell population via elevation of intracellular PTEN phosphatase activity [Riley, 2009; Patsoukis *et al.,* 2013]. Antibodies against PD-1 or PD-L1, which are approved for treatment of metastatic renal, urothelial, or non-small cell lung carcinoma, melanoma, and classic Hodgkin lymphoma, unleash the binding of PD-L1 from PD-1, which causes abrogation of PTEN activity and cytotoxic T cell activation. This phenomenon is commonly referred to as immune checkpoint blockade (ICB). However, the efficient activation of tumor-targeting T lymphocytes also requires their priming for tumor antigens by antigen-presenting dendritic cells, which ultimately leads to full anti-tumor immunity.

In CRC, the influence of the TME with its immune effectors for disease outcome is increasingly acknowledged [Galon *et al.,* 2014; Anitei *et al.,* 2014]. The recent studies demonstrating favorable survival following ICB in metastatic disease from mismatch repair-deficient, or microsatellite-instable (MSI), tumors with a high density of immunogenic neo-antigens [Le *et al.,* 2015; Le *et al.,* 2017] are already regarded as landmark contributions to the concept of possible immune modulation in advanced CRC. Nevertheless, the great majority of CRC patients suffer from mismatch repair-proficient, or microsatellite-stable (MSS), disease with a low mutational load and consequently, low antigenicity [Cancer Genome Atlas Network, 2012; Goldstein *et al.,* 2014].

Immunogenic cell death by oxaliplatin

The concept referred to as immunogenic cell death (ICD) essentially implies cytotoxic damage of tumor cells by either radiation or systemic therapies and the resulting priming of tumor-targeting T lymphocytes via capture and presentation of shed tumor antigens by dendritic cells [Galluzzi *et al.,* 2015]. Preclinical studies have highlighted oxaliplatin as an ICD-inducing agent [Tesniere *et al.,* 2010; Zitvogel *et al.,* 2010]. In mouse models, oxaliplatin has been shown to sensitize CRC and other adenocarcinomas to ICB therapy via enhanced tumor infiltration of cytotoxic T lymphocytes [Gou *et al.,*

2014; Pfirschke *et al.,* 2016]. Increasing clinical evidence also supports the notion that oxaliplatin is able to induce ICD [Pol *et al.,* 2015] and thereby invoke efficacious anti-tumor immunity.

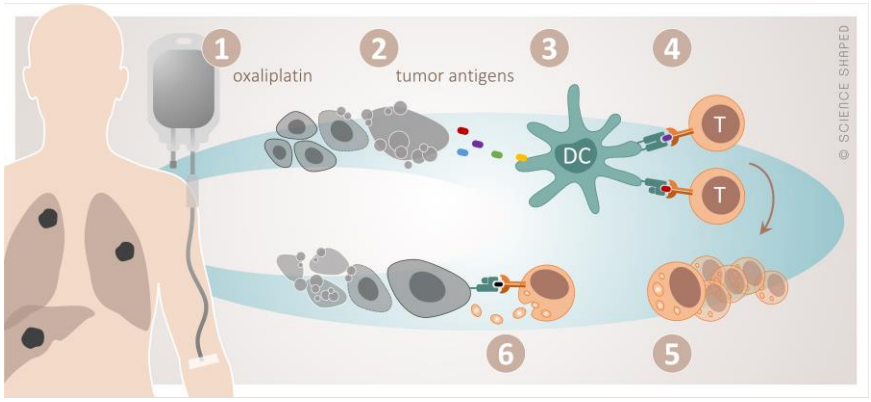

Figure 1 – the ICD concept. Cytotoxic damage by oxaliplatin (1) causes release of tumor antigens from the dying tumor (2). These are taken up (3) by dendritic cells (DC) and presented to cytotoxic T cells (4), resulting in their activation and clonal proliferation (5). This will in principle enable specific T cell targeting of any tumor manifestation systemically (6).

Our prospective study *Locally Advanced Rectal Cancer – Radiation Response Prediction* (NCT00278694) enrolled almost 100 patients with locally advanced rectal cancer (LARC) from October 2005 through March 2010, who were followed for five years (until August 2015). The patients were given curative intention neoadjuvant treatment before surgery [Ree *et al.,* 2015]. Estimated five-year progression-free survival (PFS) was 61% and almost all of the recorded PFS events were metastatic disease progression [Dueland *et al.,* 2016].

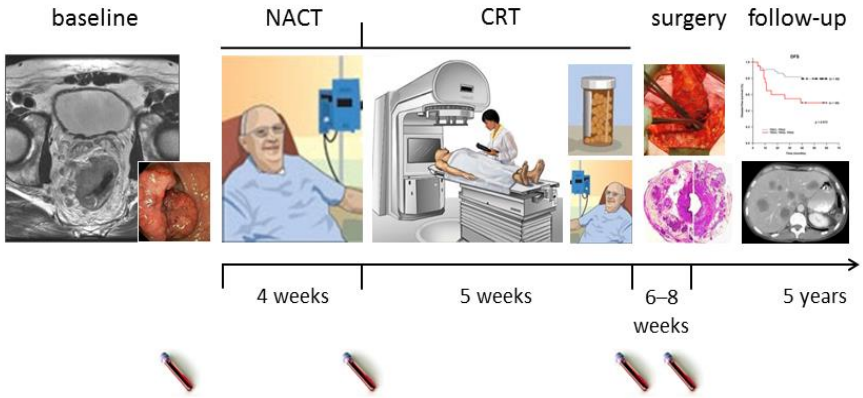

Figure 2 – the LARC-RRP study. Study patients received intensified neoadjuvant treatment consisting of oxaliplatin-containing induction NACT followed by CRT and pelvic surgery. Any progress to metastatic disease was recorded for five years after surgery. Serial serum and plasma samples were collected at sampling points indicated by tubes.

The treatment protocol consisted of oxaliplatin-based induction neoadjuvant chemotherapy (NACT; two cycles of the Nordic FLOX regimen[1]) followed by long-course chemoradiotherapy (CRT) and final surgery. NACT was found to be highly tolerable, with dose adjustments required for only 9% of patients [Dueland *et al.,* 2016]. Importantly, Nordic FLOX is a cost-effective regimen in terms of inexpensive chemotherapeutics and short administration time with a relatively low requirement for oncology nurse staffing. It remains a mainstay in first-line therapy of metastatic CRC.

In the LARC-RRP study, we made a set of remarkable observations. First, in a study population with considerable locally advanced disease (41% organ-invasive T4 cases and a majority of patients with lymph node involvement), five-year overall survival (OS) was as high as 83% [Dueland *et al.,* 2016]. Next, the short-course NACT alone led to substantial tumor volume reduction, as measured by magnetic resonance (MR) volumetry [Flatmark *et al.,* 2016]. And most noteworthy, patients who during the two induction FLOX cycles experienced a pronounced increase in circulating immune factors had significantly better PFS than patients without such immune responses [Meltzer *et al.,* 2016; Kalanxhi *et al.,* 2017]. For example, we assessed circulating levels of the fms-like tyrosine kinase 3 ligand (Flt3L) at baseline and following induction NACT and sequential CRT, with both modalities containing oxaliplatin. Flt3L is a factor that both reflects the direct cytotoxic effect of chemotherapy and causes expansion of the pool of antigen-presenting dendritic cells. The data indicated that induction of high circulating Flt3L by the two FLOX cycles and maintenance by oxaliplatin at mildly myelosuppressive doses during the CRT may favor survival without metastatic progression in high-risk T4 cases [Kalanxhi *et al.,* 2017]. In summary, low-cost and easy-to-administer oxaliplatin-based treatment was associated with favorable long-term outcome in a LARC population given curative intention pelvic radiation and surgery for locally advanced tumors commonly prone to metastatic progression. These findings suggest that systemic tumor-targeting effects may have been invoked by oxaliplatin.

Moreover, in the recently concluded prospective study *Oslo Randomized Laparoscopic Versus Open Liver Resection for Colorectal Metastasis Study* (NCT01516710), 254 patients with resectable CRC liver metastases were enrolled and will be followed for five years [Fretland *et al.,* 2017]. Approximately half of study patients received neoadjuvant FLOX. The ongoing exploration of oxaliplatin-induced effects in the surgical specimens indicates strong influx of T cells (CD3-positive) and particularly cytotoxic T cells (CD8-positive), but not FoxP3-positive regulatory T cells, following neoadjuvant FLOX (3–8 cycles).

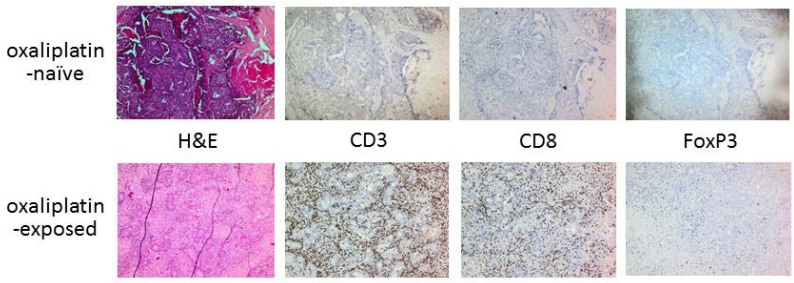

Figure 3 – anti-tumor immune activation in liver metastases. Histologic sections of surgical specimens from two representative patients with liver-metastatic CRC, stained with hematoxylin & eosin (H&E) or antibodies detecting various T lymphocyte populations within the TME (Dagenborg *et al.,* manuscript in preparation).

[1] **The Nordic FLOX regimen**: oxaliplatin 85 mg/m^2 (over 30–60 minutes) on day 1; bolus (over <5 minutes) 5-fluorouracil 500 mg/m^2 and 30 minutes later bolus (over <10 minutes) folinic acid on days 1 and 2; IV administration every 2 weeks.

1.2 Rationale for the chosen FLOX administration

Administration of the FLOX regimen will be according to the schedule that was used in the NORDIC-VII Study [Tveit *et al.,* 2012], which in recent years has also been implemented in clinical practice.

Please refer to the summary of product characteristics (SmPC) of each drug component of FLOX for reference safety information. If drug-related toxicities are observed in the this study, the guidelines outlined in *Paragraph 5.7* will apply.

1.3 Nivolumab

Nivolumab is a fully human monoclonal antibody that binds to PD-1 with nanomolar affinity and a high degree of specificity. Nivolumab is currently (as per May 2017) approved in Norway for treatment of metastatic renal, urothelial, non-small cell lung, or head-and-neck carcinoma, melanoma, and classic Hodgkin lymphoma based on clinical studies showing improved survival. Please refer to the Investigator's Brochure (IB) version 16 (as of 23 June 2017), Chapter 5.6 (Reference Safety Information), for detailed information on safety of nivolumab in humans.

1.4 Rationale for dose selection of nivolumab

As detailed in the IB, nivolumab is safe and well tolerated up to 10 mg/kg Q2W dose level. Furthermore, in non-small cell lung cancer, nivolumab at a dose of 10 mg/kg Q3W has been shown to be safe when given concomitantly with chemotherapeutic agents such as cisplatin, pemetrexed, paclitaxel, docetaxel, or even some of these in combination. Finally, a flat dose of 240 mg Q2W has been shown to be similar to 3 mg/kg Q2W, and infusion time can be shortened to 30 minutes.

According to the IB for nivolumab version 16, the safety and efficacy of 240 mg Q2W flat dose of nivolumab is expected to be similar to the 3 mg/kg Q2W dosing regimen. The 240 mg Q2W dose was selected since it is identical to a dose of 3 mg/kg for subjects weighing 80 kg, the observed median body weight in nivolumab-treated cancer patients. Using a population pharmacokinetics model, the overall distributions of nivolumab exposures are comparable after treatment with either 3 mg/kg or 240 mg nivolumab. The predicted range of nivolumab exposures (median and 90% prediction intervals) resulting from a 240 mg flat dose across the 35–160 kg weight range is maintained well below the corresponding exposures observed with the 10 mg/kg Q2W dosage. Across various tumor types, nivolumab has been shown to be safe and well tolerated up to a dose of 10 mg/kg Q2W. Given the similarity of nivolumab pharmacokinetics across tumor types and the similar exposures predicted from administration of 240 mg Q2W flat dose and the 3 mg/kg Q2W regimen, it is expected that the safety and efficacy profile of the two regimens will be similar. Hence, the 240 mg Q2W flat dose regimen has been incorporated into currently ongoing clinical studies.

If drug-related toxicities are observed in the this study, the guidelines outlined in *Paragraph 5.7* will apply.

2 STUDY OBJECTIVES AND END POINTS

***Hypothesis**:* Most patients with metastatic CRC harbor tumor that can be transformed into an immunogenic disease by oxaliplatin, and may thereby benefit from the addition of immune-modulating therapy to improve outcome of the current oxaliplatin-based standard-of-care.

	Objectives	***End points***
Primary	To determine PFS, in terms of failure of treatment strategy, on sequential treatment with the Nordic FLOX regimen and nivolumab[2] compared with the standard-of-care Nordic FLOX regimen in previously untreated MSS metastatic CRC. [2] **Nivolumab** is an ICB agent.	– PFS: radiologic assessment every 8 weeks (following 4 cycles of FLOX or the alternative 2 cycles each of FLOX and nivolumab), according to the Response Evaluation Criteria in Solid Tumors (RECIST) and the RECIST consensus guideline for assessment of response to immune-modulating therapies, iRECIST (*c.f.,* **Appendices 1 and 2**).
Secondary	To determine safety and tolerability of sequential treatment with the Nordic FLOX regimen and nivolumab compared with the standard-of-care Nordic FLOX regimen.	– Safety: incidence of adverse events (AE), as reported according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (*c.f.,* **Appendix 3**) recorded on onboing basis, and summarized every 4 weeks on active study therapy and every 8 weeks in planned breaks from active study therapy. – Tolerability: AE grading, as assessed by CTCAE v4.0 recorded on onboing basis, and summarized every 4 weeks on active study therapy and every 8 weeks in planned breaks from active study therapy.
	To determine objective response rate (ORR), duration of response (DOR), secondary surgical curative resection rate (SSCRR), and OS.	– ORR: the percentage of patients with a confirmed complete or partial response. – DOR: the time from the first documentation of a complete or partial response to disease progression. – SSCRR: the percentage of patients with a confirmed resection of metastatic disease with microscopically free margin (R0). – OS: the time from randomization to death of any cause.

	To monitor and compare quality-of-life (QoL) alterations during therapy courses.	– QoL: assessment undertaken at study enrolment, completion of the active therapy of the first treatment sequence (after 16 weeks), and disease progression, using the consensus modules EORTC QLQ-C30, EORTC QLQ-CIPN20, and EQ-5D-5L (http://groups.eortc.be/qol/ , http://www.euroqol.org/).
Tertiary	To compare costs for the resource use (in diagnostic work-up, treatment, and any AE) for the sequential therapy with that of the standard-of-care, applying a model specifically developed for CRC.	– Cost estimate: model described in Joranger P *et al., Med Decis Making* **2015**; 35, 256–65.
Exploratory	To develop circulating biomarkers of cytotoxic T lymphocyte activity.	– Surrogate measure of cytotoxic T lymphocyte activity: phosphatase activity in serial peripheral blood mononuclear cells (PBMC) samples, collected corresponding to each change of therapy (from FLOX to nivolumab and reverse) of the sequential regimen.
	To develop circulating biomarkers of tumor response.	– Surrogate response marker: alterations of circulating tumor DNA (ctDNA) and exosomal miRNA in plasma samples, collected corresponding to each change of therapy in the sequential regimen.
	To develop circulating biomarkers of ICD.	– Measures of circulating immune factors and T cell phenotypes in serial serum/plasma/whole blood samples collected corresponding to each change of therapy in the sequential regimen.
	To develop functional MR imaging biomarkers.	– TME responses in abdominal metastases: repeat functional MR imaging, undertaken corresponding to each change of therapy (from FLOX to nivolumab and reverse) during the first two months of the sequential regimen (three recordings in total), and correlate such changes with RECIST/iRECIST measures and PFS.

To develop histologic and molecular tumor biomarkers.	– Immune responses in liver/peritoneal metastases: histologic and molecular profiling in repeat liver/peritoneal biopsy samples collected corresponding to each change of therapy (from FLOX to nivolumab and reverse) during the first two months of the sequential regimen (three biopsy procedures in total), and correlate such changes with RECIST/iRECIST measures and PFS.

3 OVERALL STUDY DESIGN

The METIMMOX study is a multicenter open-label randomized phase 2 trial in first-line treatment of MSS metastatic CRC using the standard-of-care Nordic FLOX regimen (control arm) or sequential therapy with the Nordic FLOX regimen and nivolumab (experimental arm), to investigate whether the experimental arm shows superiority in PFS, safety, tolerability, and QoL.

Study period	Estimated date of first patient enrolled: 1 March 2018 Anticipated recruitment period: 12 months Estimated date of last patient completed: 1 September 2020
Treatment duration	Expected treatment duration per patient: Experimental arm: 18 months (until failure of treatment strategy) Control arm: 9 months (until failure of treatment strategy)
Follow-up	Expected follow-up period per patient: Experimental arm: 30 months (12 months following failure of treatment strategy) Control arm: 21 months (12 months following failure of treatment strategy)

4 STUDY POPULATION

4.1 Selection of study population

Centers across Norway will participate. The **Institutions** are:

- Akershus University Hospital, Lørenskog, Norway (catchment population of 500,000).
- St. Olavs Hospital – Trondheim University Hospital, Trondheim, Norway (catchment population of 450,000).
- Haukeland University Hospital, Bergen, Norway (catchment population of 450,000).
- Hospital of Southern Norway, Kristiansand, Norway (catchment population of 290,000).
- Oslo University Hospital, Oslo, Norway (catchment population of 500,000).

All citizens of Norway have equal access to public health services. As a consequence, there will be no selection of patients onto the METIMMOX study other than that based on specific inclusion and exclusion criteria. This population-based study accrual will provide a unique opportunity to investigate the generalizability of the study concept across a majority of patients with metastatic CRC. Importantly, algorithms for personalized allocation of first-line treatments in patients with metastatic CRC are uniform across Scandinavian countries and also incorporated in the respective national guidelines for management of CRC. Finally, there is no other study currently planned for this CRC population that might compete for patients.

As seen from the above list of Institutions, the total catchment population from the participating Norwegian centers is close to 2.2 million, or more than 40% of the nation's population. It is therefore reasonable to assume an annual figure of almost 850 metastatic CRC cases among these centers. Therefore, if the study manages to enroll well over one tenth of these patients, the study accrual phase should last approximately one year.

This project will actively use the Norwegian Clinical Research Infrastructures Network (www.norcrin.no) and their resources in the planning for and conducting the study. For example, this enables the access to the Viedoc system, which includes web-based case report forms (CRF) with an ancillary eDatabase, randomization procedures, and validation of data, along with study monitoring, all of which meet regulatory requirements for clinical therapy trials.

4.2 Number of patients

100 patients will be included in this trial (50 in each study arm).

4.3 Inclusion criteria

All the following conditions must apply to the prospective patient at screening prior to receiving study treatment:

- Patient has histologically verified CRC adenocarcinoma (also comprising the mucinous adenocarcinoma and signet-ring cell carcinoma entities).
- Patient is ambulatory with Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 (*c.f.,* **Appendix 4**).
- Patient is at least 18 years of age.
- Patient has radiologically measurable metastatic disease.
- Patient has an intra-abdominal metastatic lesion that can be biopsied.
- Patient has not had previous systemic therapy for the metastatic disease.
- Patient is eligible for the Nordic FLOX regimen.
- Patient has the following laboratory values, as measured in serum/plasma within 14 days prior to study entry, indicative of adequate organ function:
    - Hemoglobin at least 10.0 g/dL.
    - Neutrophils at least 1.5 $x10^9$/L (without current use of colony-stimulating factors).
    - Platelets at least 100 $x10^9$/L.
    - C-reactive protein less than 60 mg/L.
    - AST/ALT no higher than 2xULN when patient does not have metastatic disease in the liver or no higher than 5xULN when patient has metastatic disease in the liver.
    - Bilirubin no higher than 1.5xULN when patient does not have metastatic disease in the liver or no higher than 2xULN when patient has metastatic disease in the liver.
    - Albumin no lower than 30 g/L.
    - INR within normal level.
    - Creatinine no higher than 1.5xULN.
- Woman of childbearing potential (WOCBP)[3] must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study drug.
- WOCBP will use an adequate method[4] to avoid pregnancy for a period of 26 weeks (which includes the required 30 days plus the time required for nivolumab to undergo five half-lives) after the last therapy dose, irrespective of study arm.
- Woman is not breastfeeding.

- Male who is sexually active with WOCBP must agree to follow instructions for method(s) of contraception[4] for a period of 26 weeks (which includes the required time to ensure duration of sperm turnover plus the time required for the investigational drugs to undergo five half-lives) after the last therapy dose, irrespective of study arm.
- Signed informed consent form (ICF) and expected cooperation of the patients for the treatment and follow-up must be obtained and documented according to International Conference on Harmonization (ICH) – Good Clinical Practice (GCP) and national/local regulations.

[3] **WOCBP** is defined by the Clinical Trial Facilitation Group's document "Recommendations related to contraception and pregnancy testing in clinical trials" version 2014-09-15 (http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf). A woman is considered WOCBP, *i.e.,* fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single measurement of the follicle-stimulating hormone level is insufficient.

[4] **Highly effective birth control methods** are defined by the same recommendations. They include:

- Combined (estrogen- and progesterone-containing) hormonal contraception associated with inhibition of ovulation:
  - oral
  - intravaginal
  - transdermal
- Progesterone-only hormonal contraception associated with inhibition of ovulation:
  - oral
  - injectable
  - implantable
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner
- Sexual abstinence

4.4 Exclusion criteria

Patient will be excluded from the study if she/he meets any of the following criteria:

- Patient has initially resectable metastatic disease for which neoadjuvant therapy is deemed superfluous.
- Patient does not consent to biopsy sampling.
- Patient has metastatic disease to lungs as the sole site.
- Patient has untreated or symptomatic brain metastasis (patient must be symptom-free without the use of corticosteroids).
- Patient has experienced a period of less than 6 months since discontinuation of adjuvant oxaliplatin-containing chemotherapy.
- Patient is ineligible for full chemotherapy doses (100% doses) at start of study treatment.
- Patient has had radiation therapy against the only measurable lesion within 4 weeks of start of study treatment.
- Patient has a medical condition treated with anticoagulant medication that cannot be replaced by low molecular weight heparin during active study treatment.

- Patient has a nervous system disorder worse than CTCAE grade 1.
- Patient has any medical condition that will preclude him/her from cancer immune-modulating therapy, such as:
  - Active or chronic hepatitis B or hepatitis C.
  - Known history of human immunodeficiency virus or acquired immunodeficiency-related illnesses.
  - Diagnosis of immunodeficiency or medical condition requiring systemic steroids or other forms of immunosuppressive therapy.
  - Autoimmune disease that has required systemic therapy within the past 2 years.
  - Receipt of live attenuated vaccination within 30 days prior to study entry or within 30 days of receiving study therapy.
  - Active infection or chronic infection requiring chronic suppressive antibiotics.
  - Known history of previous diagnosis of tuberculosis.
- Patient with current or prior use of immunosuppressive medication within 28 days before the first dose of study therapy, with the exceptions of intranasal corticosteroids or systemic corticosteroids at physiological doses that do not exceed 10mg/day of prednisone or an equivalent corticosteroid.
- Patient has any medical condition or needs to use medication, as listed in the SmPC of each Investigational Medical Product (IMP), that will preclude him/her from receiving treatment with IMP, such as:
  - Pernicious anemia or anemias due to vitamin B_{12} deficiency (SmPC-listed contraindications for folinic acid).
  - Other SmPC-listed contraindications for folinic acid and SmPC-listed contraindications for the other IMPs are covered by other exclusion criteria.
- Patient has undergone treatment with any IMP that may interfere with the study treatment within 4 weeks prior to first administration of study drug.
- Patient has known hypersensitivity to any of the study IMP components.
- Patient has ECOG performance status 2 or worse.
- Patient has serum/plasma CRP of 60 mg/L or higher.
- Patient does not meet the following requirements at baseline: adequate bone marrow function without current use of colony-stimulating factors (minimum values of neutrophils 1.5 $x10^9$/L, platelets 100 $x10^9$/L, hemoglobin 10 g/dL), adequate liver function (maximum values of AST/ALT 5xULN and bilirubin 2xULN; albumin value of 30 g/L or higher; INR within normal level), adequate renal function (maximum creatinine value of 1.5xULN).
- Patient has history of other prior malignancy, with the exception of curatively treated basal cell or squamous cell carcinoma of the skin, cervical cancer stage IB, stage I prostate cancer considered not necessary to treat, and another malignancy that was treated with curative intent more than 5 years ago and has not relapsed later.
- Patient has significant cardiac, pulmonary, or other medical illness that would limit activity of daily life (ADL) or survival.
- Patient is pregnant or breastfeeding.
- Patient has any other reason, in the opinion of Clinical Investigator, not to participate in the study.

4.5 Patient stratification

Subjects will be stratified according to sidedness[5] and *(K)RAS/BRAF* mutation status of the primary tumor (right-sided *versus* left-sided and *(K)RAS/BRAF* wild-type *versus* mutation) of two reasons. Firstly, patients in good performance status (ECOG 0–1) with *(K)RAS/BRAF* wild-type tumor (which frequently is left-sided) will commonly and according to national guidelines be offered an irinotecan-containing regimen with the addition of an EGFR inhibitor. A block-randomization within each study stratum will ensure that this therapeutic option does not compromise enrolment onto any of the other groups (*c.f., Paragraph 10.1*). Secondly, stratification will enable outcome analysis (PFS) within each of the defined groups, among which the study treatment may show differential effects. Ideally, tumor MSS status should be determined to avoid inclusion of MSI cases; however, the current logistics of this analysis at hospitals commonly

precludes it from being undertaken swiftly enough before the commencement of active therapy. In order to meet this challenge, tumor MSS status will be determined as per current practice. It is expected that approximately 5% of enrolled patients will harbor non-MSS tumor [Cancer Genome Atlas Network, 2012; Goldstein *et al.,* 2014], and the statistical power analysis (*c.f., Paragraph 10.2.1*) has been adjusted to enable removal of these few cases before data analysis.

[5] **Sidedness** is defined as follows: *right-sided,* primary tumor in cecum, ascending colon, or transverse colon; *left-sided,* primary tumor in splenic flexure, descending or sigmoid colon, or rectum.

4.6 Risk/benefit assessment

Study patients will in general benefit from follow-up of their disease and treatment within the frame of a prospective trial. Safety and efficacy for control arm patients (*c.f., Paragraph 5.5*) are well known from a number of previous studies and routine clinical practice over two decades.

For experimental arm patients (*c.f., Paragraph 5.5*), particular hazards and benefits may prevail. Patients suffering from MSS metastatic CRC do not possess an inherently immunogenic disease and may experience untoward effects from sequential nivolumab following the short-course treatment with FLOX. In addition, these patients will receive half the number of FLOX cycles over a defined treatment period compared to the standard-of-care. Each of these aspects may occasion detrimental treatment responses. Also, keeping in mind that the repeat sequential treatment is a novel design with no safety data known as of yet, new and unexpected toxicities may appear.

On the other hand, experimental arm patients will have an unprecedented opportunity to receive treatment, in terms if ICB, that is currently not available for the vast majority of patients with metastatic CRC. If the study hypothesis prevails and oxaliplatin treatment transforms MSS metastatic CRC into an immunogenic disease, there is an opportunity for durable treatment effects from the sequential ICB, similar to those observed with single-agent ICB in MSI metastatic CRC [Le *et al.,* 2015; Le *et al.,* 2017]. It is also conceivable that sequential ICB may dampen common side effects of the FLOX regimen, which might ultimately result in tolerability to a higher number of FLOX cycles than usual for the standard-of-care.

5 TREATMENT

For this study, nivolumab (Opdivo®), oxaliplatin, 5-fluorouracil, and folinic acid (Leucovorin) are defined as IMP.

5.1 Drug handling

With regard to nivolumab, the drug will be provided by Bristol-Myers Squibb (BMS) as flat dosing kits, each containing 240 mg of the drug (two vials of 100 mg each and one vial of 40 mg). In the event of availability constraints of 40-mg vials, 100-mg vials will be provided for dispense. The Hospital Pharmacy of Mid Norway Trust (Sykehusapoteket, Trondheim) will be used as vendor to provide import, labeling, storage, and dispatch of the drug from BMS to each participating center in Norway in accordance with the environmental conditions (temperature, light, humidity) as determined by BMS. At each center, the product storage manager at the study pharmacy will ensure that nivolumab is stored and dispensed in accordance with these conditions. If concerns regarding the quality or appearance of nivolumab arise, the study drug will not be dispensed and BMS will be contacted immediately. Please refer to the BMS IB for nivolumab regarding drug-related information such as handling, storage, infusion, *etc.*

At each center, oxaliplatin, 5-fluorouracil, and folinic acid will be provided by the study pharmacy as per routine practice.

IMP documentation will be maintained. This includes all processes required to ensure that the drugs are accurately administered. Also, it includes documentation of drug storage, administration, and, as applicable, storage temperatures, reconstitution, and use of required processes (*e.g.,* diluents, administration sets).

Infusion-related supplies (*e.g.,* bags, in-line filters, 0.9% sodium chloride injection, 5% dextrose injection) will be supplied by each study site and purchased locally if permitted by local regulations.

The IMPs will be stored in a secure area according to local regulations. It is the responsibility of the investigators to ensure that IMPs are only dispensed to study subjects. The IMPs will be dispensed only from official study sites by

authorized personnel according to local regulations. Please refer to the current IB version and/or pharmacy reference sheets for complete storage, handling, dispensing, and infusion information for nivolumab. The infusion will be administrated by nurses with experience in treatment with immunotherapy.

The Nordic FLOX regimen is standard-of-care; thus, drug administration will be according to each participating department's standard operating procedure (SOP). Likewise, expenses for the actual drugs and their administration will be covered by the participating departments' standard budget.

5.2 Drug accountability

The responsible site personnel will confirm receipt of study drug and will use the study drug only within the framework of this study and in accordance with this protocol. Receipt, distribution, and destruction (if any) of the study drug will be properly documented according to Sponsor's agreed and specified procedures. Any destruction of nivolumab will be reported back to BMS.

Pertaining to each of the study drugs, Clinical Investigator will prescribe the actual dose and treatment cycle in sufficient detail within a predefined study-specific form in the Hospital's electronic prescription system. Each prescription will be documented in an electronic logbook at the study pharmacy, which will identify which study patient has received which study drug (name, dose, batch number, shelf life, and amount). The study pharmacy will apply procedures that guarantee the traceability of this information.

5.3 Drug labeling

The IMP (nivolumab), as dispatched from the Hospital Pharmacy of Mid Norway Trust, will have a label permanently affixed to the outside of the vials/kits and will be labeled according with ICH GCP and national regulations, stating that the material is for clinical trial / investigational use only and should be kept out of reach of children.

Labeling of IMP should be done according to Eudralex volume 4, Annex 13 (http://ec.europa.eu/health/files/eudralex/vol-4/2009_06_annex13.pdf).

For Norway, labeling is required according to Chapter 4.4 in "Forskrift om klinisk utprøving av legemidler til mennesker" (http://www.lovdata.no/for/sf/ho/xo-20091030-1321.html). However, because the infusion bags for all four IMPs will be dispensed and administered by authorized personnel at the study sites, immediately following the prescription by Clinical Investigator, the Norwegian Medicines Agency is entitled to make an exception from the labeling requirements. Nevertheless, all IMP bags will have an affixed label with blank lines for:

- patient's initials
- patient's enrolment code
- protocol code
- date dispensed
- name of prescribing doctor
- name of Principal Investigator

5.4 Dosage, drug administration, and common toxicities

FLOX: oxaliplatin 85 mg/m^2 (over 30–60 minutes) on day 1; bolus (over <5 minutes) 5-fluorouracil 500 mg/m^2 and 30 minutes later bolus (over <10 minutes) folinic acid on days 1 and 2; IV administration every 2 weeks.

Common toxicities are acute allergic reactions (laryngopharyngeal dystonia, anaphylaxia), moderate nausea and vomiting, diarrhea, hand-foot-syndrome, hyperpigmentation, mucositis, fatigue, neuropathy, febrile neutropenia, and thrombocytopenia.

Nivolumab: 240 mg flat dose over 30 minutes, IV administration every 2 weeks.

In general, the use of ICB leads to a unique spectrum of side effects termed immune-related AE (irAE) or, occasionally, AE of special interest. The irAE include dermatologic, gastrointestinal, hepatic, endocrine, and other less common inflammatory events. These are believed to arise from general immunologic enhancement. Temporary immune suppression with corticosteroids, tumor necrosis factor-alpha antagonists, mycophenolate mofetil, or other agents can be an effective treatment in most cases.

5.5 Duration of therapy

The **control arm** will consist of intermittent treatment with the Nordic FLOX regimen in terms of 8 cycles (16 weeks) before a break until disease progression, when therapy is reintroduced and administered for another 8 cycles before a new break. This go-and-stop schedule, which is chosen because continuous FLOX treatment commonly causes unacceptable toxicity in the palliative setting, will be continued until progressive disease on ongoing therapy (defining PFS in terms of failure of treatment strategy), unacceptable toxicity, withdrawal of consent, or death, whichever occurs first.

The estimated median PFS in the control arm is 9 months (*i.e.,* 39 weeks), as detailed in *Chapter 10*. During this period, it is assumed that the 'average' patient will receive 1 full go-and-stop treatment sequence, consisting of 16 weeks of active therapy followed by 8 weeks of break until disease progression, before the second treatment period results in progressive disease after 16 weeks on ongoing therapy; hence, a PFS of 40 weeks. During the entire treatment, this patient will receive 2 sequences of active therapy, each containing 8 FLOX cycles.

The **experimental arm** will consist of repeat 2 cycles of the Nordic FLOX regimen followed by 2 cycles of nivolumab for a total of 8 individual cycles (16 weeks) before a break until disease progression, when therapy is reintroduced and administered for another total of 8 individual cycles before a new break. This go-and-stop schedule will be continued until progressive disease on ongoing therapy (defining PFS in terms of failure of treatment strategy), unacceptable toxicity, withdrawal of consent, or death, whichever occurs first.

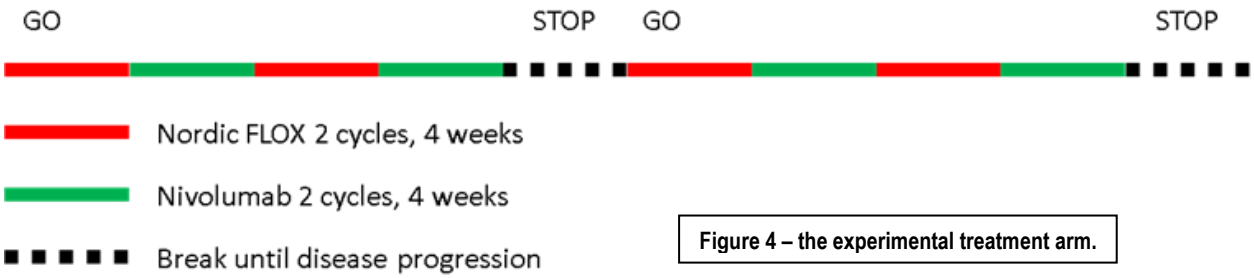

Figure 4 – the experimental treatment arm.

The estimated median PFS in the experimental arm is 18 months (*i.e.,* 78 weeks), as detailed in *Chapter 10*. During this period, it is assumed that the 'average' patient will receive 3 full go-and-stop treatment sequences, each consisting of 16 weeks of active therapy followed by 8 weeks of break until disease progression, before the fourth treatment period results in progressive disease after 8 weeks on ongoing therapy; hence, a PFS of 80 weeks. During the entire treatment, this patient will receive 4 sequences of active therapy, each containing 4 cycles each of FLOX and nivolumab.

The optimum duration of immune-modulating therapy is currently unknown. However, because such therapy engages the immune system to control the tumor, continuous treatment, as is required with other types of biologically targeting agents or systemic cytotoxic therapies, may not be necessary.

Accumulating evidence from different clinical trials in different tumor types with nivolumab or nivolumab combined with the ICB drug ipilimumab indicates that most of the responses are generally occurring early, with a median time to response of 2–4 months [Brahmer *et al.,* 2015; Borghaei *et al.,* 2015; Hellmann *et al.,* 2016; Larkin *et al.,* 2015; Motzer *et al.,* 2015]. A recent analysis in a melanoma study suggests the majority of patients who discontinue nivolumab and/or ipilimumab for toxicity maintain disease control in the absence of further treatment (Schadendorf D *et al.,* reported at the 2016 Annual Meeting of the European Association of Dermato-Oncology in Vienna, Austria). Furthermore, a limited duration of ipilimumab including only 4 induction doses resulted in long-term survival in patients with metastatic melanoma, with a sustained plateau in survival starting at around year 3 [Schadendorf *et al.,* 2015].

For these reasons, in the present study, a total of 24 months of active sequential FLOX and nivolumab therapy will be administered, given the absence of disease progression (while the subject is on active therapy) or unacceptable toxicity at an earlier treatment time. After 24 months, FLOX alone may be administered as per the study dosing schedule in the control arm. Experimental arm subjects who complete a total of 24 months of active sequential FLOX and nivolumab therapy and have subsequent disease progression (on or off FLOX alone) may, at the discretion of Clinical Investigator, reinitiate sequential FLOX and nivolumab at the same dose and schedule given previously on study, and continue such treatment for up to 1 additional year. Continuation of treatment with FLOX beyond a total of 24 months of active sequential FLOX and nivolumab therapy (*i.e.,* 12 months of active FLOX) is contingent on continued tolerance for FLOX.

5.6 Monitoring

Common vital signs (*e.g.,* blood pressure, heart rate) are to be assessed before commencement of infusion of FLOX or nivolumab. For the former, the patient will receive premedication (typically ondansetron and dexamethasone) according to each participating department's SOP.

The risks related to nivolumab therapy must be thoroughly discussed with patients randomized to the experimental arm. These subjects will also be provided with a Patient Information Card upon starting treatment. They will further receive a prescription of prednisone in case of irAE, and be informed to contact Clinical Investigator swiftly in case of suspected irAE.

5.7 Schedule modifications

5.7.1 IMP (investigational medicinal products) schedule

Continuation of IMP treatment with suspected progression is permitted; *c.f., Paragraph 5.7.2.4*. Discontinuation from study treatment may result from any of the criteria listed in *Paragraph 5.7.2.3*.

If required, subjects may receive IMP up to 3 days before or after the scheduled date. A cycle started more than 3 days after the intended dose date will be considered a delay. Subsequent dosing should be based on the actual date of administration of the previous drug cycle.

Subjects will be monitored for infusion reactions during IMP administration. If an acute reaction is noted, subjects will be managed according to *Paragraph 5.7.2.7*. IMP doses may be interrupted, delayed, or discontinued as per requirement.

5.7.2 Dose modifications for IMP

Dose modification is only allowed in case of dose-limiting toxicity; *c.f.,* **Appendices 5 and 6** for general guidelines for practical management.

5.7.2.1 Dose delay criteria for IMP

Dose delay criteria apply for all drug-related AE. A treatment delay up to 4 weeks*, i.e.,* ≤6 weeks calculated from start of the previous therapy cycle, is allowed. A treatment delay beyond 6 weeks is not allowed (*Paragraph 5.7.2.3*).

Tumor assessments should continue as per protocol schedule, even if dosing is delayed.

Nivolumab administration will be delayed for the following reasons (in CTCAE grading):

- Any grade ≥2 non-skin drug-related AE, except for fatigue and laboratory abnormalities.
- Any grade 3 skin drug-related AE.
- Any grade 3 drug-related laboratory abnormality.
- Any AE, laboratory abnormality, intercurrent illness, or other reason which, in the judgment of Clinical Investigator, warrants delaying the dose of study medication.

Subjects who require delay of nivolumab will be re-evaluated weekly, or more frequently if clinically indicated. Nivolumab dosing can be resumed on the established dosing schedule when retreatment criteria are met (*Paragraph 5.7.2.2*).

FLOX administration will be delayed for the following reasons (in CTCAE grading):

- Grade 2 diarrhea (increase of 4–6 stools per day over baseline; moderate increase in stoma output compared to baseline; not interfering with ADL).
- Grade 3 diarrhea (increase of 7 or more stools per day over baseline; incontinence; severe increase in stoma output compared to baseline; interfering with ADL).
- Grade 2 myelosuppression (neutrophils of 1.0 $x10^9$/L to less than 1.5 $x10^9$/L, or platelets of 50 $x10^9$/L to less than 75 $x10^9$/L).
- Grade 3 myelosuppression (neutrophils of 0.5 $x10^9$/L to less than 1.0 $x10^9$/L, or platelets of 25 $x10^9$/L to less than 50 $x10^9$/L).
- Grade 4 myelosuppression (neutrophils less than 0.5 $x10^9$/L, or platelets less than 25 $x10^9$/L).
- Grade 2 sensory neuropathy (sensory alteration or paresthesia persisting between two oxaliplatin doses with no or only minor improvement, moderate symptoms, limiting instrumental ADL).

Subjects who require delay of FLOX will be re-evaluated weekly, or more frequently if clinically indicated. FLOX administration will be resumed when retreatment criteria are met (*Paragraph 5.7.2.2*).

5.7.2.2 Criteria to resume dosing for IMP

Subjects may resume treatment with study drug when the drug-related AE resolves to CTCAE grade ≤1 or baseline value, with the following exceptions:

For nivolumab:

- Subjects may resume nivolumab treatment in accordance with the below criteria irrespective of whether FLOX or nivolumab was administered in the preceding cycle.
- Subjects may resume treatment in the presence of CTCAE grade 2 fatigue.
- Drug-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed.
- Subjects with drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment.
- Subjects who received systemic corticosteroids for management of any drug-related toxicity must be off corticosteroids or have tapered down to an equivalent dose of prednisolone ≤10 mg/day.

For FLOX:

- Subjects may resume FLOX treatment in accordance with the below criteria (in CTCAE grading) irrespective of whether FLOX or nivolumab was administered in the preceding cycle.
- Grade 2 diarrhea; the following pertaining to both oxaliplatin and fluorouracil: interrupt until grade 1 or less, then 100% dose first time, 75% dose second time, 50% dose third time.
- Grade 3 diarrhea; the following pertaining to both oxaliplatin and fluorouracil: interrupt until grade 1 or less, then 75% dose first time, 50% dose second time, discontinue third time.
- Grade 2 myelosuppression; the following pertaining to both oxaliplatin and fluorouracil: interrupt until grade 1, then 100% dose first time, 75% dose and consider support with granulocyte-colony stimulating factor (*e.g.,* pegfilgrastim) second or subsequent times.
- Grade 3 myelosuppression; the following pertaining to both oxaliplatin and fluorouracil: interrupt until grade 1 or less, then 75% dose and consider support with granulocyte-colony stimulating factor (*e.g.,* pegfilgrastim) first or subsequent times.
- Grade 4 myelosuppression; the following pertaining to both oxaliplatin and fluorouracil: interrupt until grade 1 or less, then 50% dose and consider support with granulocyte-colony stimulating factor (*e.g.,* pegfilgrastim) first or subsequent times.
- Grade 2 sensory neuropathy; the following pertaining only to oxaliplatin: interrupt until grade 1 or less, then 75% dose first time, 50% dose second time, discontinue third time.

5.7.2.3 Treatment discontinuation criteria for IMP

For nivolumab, treatment will be permanently discontinued for the following reasons (in CTCAE grading):

- Any grade 4 drug-related AE.
- Any grade 2 drug-related uveitis, eye pain, or blurred vision that does not respond to topical therapy and does not improve to grade 1 severity within the re-treatment period or requires systemic treatment.
- Any grade 3 non-skin, drug-related AE lasting >7 days, with the following exceptions for laboratory abnormalities, drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reactions, infusion reactions, and endocrinopathies:
  - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reaction, or infusion reaction of any duration (requires discontinuation).
  - Grade 3 drug-related endocrinopathies that are adequately controlled with only physiologic hormone replacement (do not require discontinuation).
  - Grade 3 drug-related laboratory abnormalities (do not require treatment discontinuation) except grade 3 drug-related thrombocytopenia >7 days or associated with bleeding (requires discontinuation).
- Any drug-related liver function test abnormality that meets the following criteria (requires discontinuation):
  - AST or ALT >5xULN.
  - Total bilirubin >3xULN.
- Any grade 4 drug-related AE or laboratory abnormality, except for one of the following events (does not require discontinuation):
  - Grade 4 neutropenia ≤7 days.
  - Grade 4 lymphopenia or leukopenia.
  - Isolated grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis. Study Conduct Group (*c.f., Paragraph 11.3*) should be consulted for grade 4 amylase or lipase abnormalities.
  - Isolated grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset.
  - Grade 4 drug-related endocrinopathy adverse events, such as adrenal insufficiency, ACTH deficiency, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from Study Conduct Group.
- Any event that leads to delay in dosing lasting >6 weeks from start of the previous therapy cycle requires discontinuation, with the following exceptions:
  - Dosing delays to allow for prolonged steroid tapers to manage drug-related adverse events (allowed).
  - Dosing delays lasting >6 weeks from the previous dose that occur for non-drug-related reasons (may be allowed if approved by Study Conduct Group).
  - Prior to re-initiating treatment in a subject with a dosing delay lasting >6 weeks, Study Conduct Group must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.
- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of Clinical Investigator, presents a substantial clinical risk to the subject with continued nivolumab dosing.

For detailed information, please refer to the IB for nivolumab.

For FLOX, treatment will be permanently discontinued for the following reasons (in CTCAE grading):

- Grade 4 diarrhea (life-threatening consequences, urgent intervention indicated).
- Grade 3 sensory neuropathy (sensory alteration or paresthesia, severe symptoms, limiting self-care ADL).

5.7.2.4 Continuing nivolumab with suspected progression

Accumulating evidence indicates that a minority of subjects treated with immune-modulating therapy may derive clinical benefit despite initial evidence of disease progression, such as inflammatory reaction simulating progression, so-called pseudo-progression. Subjects may, at the discretion of Clinical Investigator, continue study treatment in the setting of suspected progression until progression is confirmed, in accordance with the evaluation algorithm detailed for RECIST/iRECIST (*c.f., Paragraph 7.6*). If Clinical Investigator believes that the subject continues to derive clinical benefit by continuing treatment, the subject should continue monitoring/assessments according the same schedule as patients without tumor progression, with more frequent radiologic assessment if clinically indicated (see below).

Subjects may continue study treatment beyond initial (suspected) progression only if they meet the following criteria:

- Subject is in stable performance status (ECOG 0–1) and tolerates study treatment.
- Treatment will not delay intervention to prevent imminent complications.
- There is overall clinical benefit as judged by Clinical Investigator.

Radiographic assessment should be repeated after suspected progression as clinically required in order to determine whether there has been a decrease in the tumor size or continued progression. Potential for clinical benefit should be balanced by clinical judgment as to whether the subject is clinically deteriorating and unlikely to receive benefit from continued study treatment. Study treatment will be permanently discontinued upon confirmation of progression.

5.5.2.5 Management algorithms for immuno-oncology agents

These agents are associated with irAE that can differ in severity and duration from AE caused by other therapeutic classes. Nivolumab is considered an immuno-oncology agent in this protocol. Early recognition and management of irAE associated with immuno-oncology agents may mitigate severe toxicity. Management algorithms have been developed to assist investigators in assessing and managing the following groups of irAE:

- gastrointestinal
- renal
- pulmonary
- hepatic
- endocrinopathy
- skin
- neurological

Refer to **Appendix 5** for management details.

5.7.2.6 Management algorithms for the Nordic FLOX regimen

Refer to **Appendix 6** for further details.

5.7.2.7 Treatment of IMP-related infusion reactions

For **nivolumab infusion reactions**, the following information will be taken into consideration:

Since nivolumab contains only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypotension, hypertension, bronchospasm, or other allergic-like reactions. Any CTCAE grade 3 or 4 infusion reaction will be reported within 24 hours as a serious adverse event (SAE) if it meets the criteria (*c.f., Paragraph 8.1.2*). Infusion reactions will be graded according to the CTCAE v4.0 guidelines.

Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines, as appropriate:

For grade 1 symptoms (mild reaction; infusion interruption not indicated; intervention not indicated):

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

For grade 2 symptoms (moderate reaction requiring therapy or infusion interruption but responding promptly to symptomatic treatment, such as antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids; prophylactic medications indicated for ≤24 hours):

- Stop the nivolumab infusion, begin IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or paracetamol (acetaminophen) 325 to 1000 mg; remain with patient and monitor until resolution of symptoms. Corticosteroid and/or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur, no further nivolumab shall be administered at that visit.
- For future infusions, the following prophylactic premedications are recommended: diphenhydramine 50 mg (or equivalent) and/or paracetamol (acetaminophen) 325 to 1000 mg should be administered at least 30 minutes before nivolumab infusion. If necessary, corticosteroids (up to 25 mg of SoluCortef or equivalent) may be used.

For grade 3 or 4 symptoms (severe reaction; *grade 3*: prolonged, *i.e.,* not rapidly responsive to symptomatic medication and/or brief interruption of infusion; recurrence of symptoms following initial improvement; hospital admission indicated for other clinical sequelae, *e.g.,* renal impairment, pulmonary infiltrates); *grade 4*: life threatening; pressor or ventilatory support indicated):

- Immediately discontinue infusion of nivolumab. Begin IV infusion of normal saline and treat the subject as follows: recommend bronchodilators, epinephrine 0.2–1 mg of a 1:1000 solution for SC administration or 0.1– 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until Clinical Investigator is comfortable that the symptoms will not recur. Nivolumab will be permanently discontinued. Clinical Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery of the symptoms.

In case of late-occurring hypersensitivity symptoms (*e.g.,* appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (*e.g.,* oral antihistamine or corticosteroids).

For **FLOX infusion reactions**, management will be according to each participating department's SOP.

5.8 Concomitant treatments

It is expected that enrolled subjects will have systemic corticosteroids tapered as quickly as clinically appropriate during screening phase, and discontinued if possible prior to inclusion.

All concomitant medication (including over-the-counter drugs) used by the patient will be recorded.

Supportive care for all disease-related or treatment-related AE will be maximized for all subjects on this study.

5.8.1 Prohibited and/or restricted treatments

Immunosuppressive agents, including systemic corticosteroids, are prohibited during study treatment unless utilized to treat a drug-related AE. Subjects with a condition requiring systemic treatment with either corticosteroids (>20 mg daily prednisolone, >3 mg dexamethasone daily, or equivalent) or other immunosuppressive medications (including within 14 days of inclusion) are excluded. Subjects continuing to require supraphysiologic steroids (prednisolone >20 mg daily, >3 mg dexamethasone daily, or equivalent) may not be enrolled. Inhaled or topical steroids and adrenal replacement steroid doses (≤20 mg daily prednisolone daily, ≤3 mg dexamethasone daily, or equivalent) are permitted in the absence of active autoimmune disease.

Anticoagulant medication other than low molecular weight heparin is not permitted during active study treatment.

Brivudine, sorivudine, or analogs (antiviral drugs) are contraindicated during the use of fluoropyrimidine analogs and therefore not permitted during study treatment and the initial 4 weeks of planned treatment breaks.

5.8.2 Permitted therapy

Subjects are permitted to use topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Adrenal replacement steroid doses of >10 mg daily prednisone are permitted. A brief (less than 3

weeks) course of corticosteroids for prophylaxis (*e.g.,* contrast dye allergy) or for treatment of non-autoimmune conditions (*e.g.,* delayed-type hypersensitivity reaction caused by a contact allergen) is permitted.

Steroid use should be minimized prior to inclusion. Systemic corticosteroid use or physiologic replacement doses of steroids are permitted, even >20 mg/day prednisolone equivalents, for: a) treatment-related AE or b) treatment of non-autoimmune conditions (*e.g.,* prophylaxis for contrast dye allergy, contact hypersensitivity). Details regarding corticosteroid use prior to and during the study will be collected (name of medication, doses utilized, start and stop dates, frequency of use, route of administration). Information regarding concomitant corticosteroid use may be analyzed with regard to study outcome measures. Subjects requiring chronic treatment with corticosteroids should be treated with histamine-2 receptor antagonists or proton pump inhibitors as prophylaxis for potential gastrointestinal adverse reactions (ulceration, perforation, hemorrhage) unless otherwise contraindicated.

Support with granulocyte-colony stimulating factor (*e.g.,* pegfilgrastim) in case of myelosuppression is permitted.

Oral anticoagulant therapy is permitted during study treatment breaks.

Concomitant medications are recorded at baseline and throughout the study treatment sequences. All medications (prescriptions or over-the-counter medications) continued at the start of the study or started during the study and different from the study drug will be documented.

All treatments that Clinical Investigator considers necessary for a subject's welfare may be administered at the discretion of Clinical Investigator in keeping with the community standards of medical care. All concomitant medication will be recorded, including all prescription, over-the-counter, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be recorded.

All concomitant medications received within 28 days before the first dose of study treatment and 30 days after the last dose of study treatment will be recorded. Concomitant medications administered later than 30 days after the last dose of study treatment should be recorded for SAE.

5.9 Subject numbering

Each subject is identified in the study by a unique subject number that is assigned when subject signs the ICF and is randomized. Once assigned the subject number cannot be reused for any other subject. The study treatment will be dispensed/administered to the subject by authorized site personnel only.

6 STUDY FLOW CHART

Trial period	Screening phase		Treatment sequence [1]							
Scheduling window; visit (V), cycle (C), day(D)	V-1 (D -15 to D-1)	V0 (D -14 to D0)	V1 C1 D1 (±3 days)	V2 C2 D1 (±3 days)	V3 C3 D1 (±3 days)	V4 C4 D1 (±3 days)	V5 C5 D1 (±3 days)	V6 C6 D1 (±3 days)	V7 C7 D1 (±3 days)	V8 C8 D1 (±3 days)
Administrative procedures										
Informed consent	X									
Inclusion/exclusion criteria		X								
Tumor *(K)RAS/BRAF* mutation status [3]		X								
Medical history		X								
Prior [4] and concomitant medication review		X	X	X	X	X	X	X	X	X
Post-study anticancer therapy status										
Questionnaires (QoL)		X								
Clinical procedures										
Review adverse events		X	X	X	X	X	X	X	X	X
Full physical examination [7]		X [8]								
Directed physical examination			X	X	X	X	X	X	X	X
Vital signs and weight		X	X	X	X	X	X	X	X	X
ECOG performance status		X	X	X	X	X	X	X	X	X
Survival follow-up										
Laboratory procedures										
Pregnancy test [9]		X [10]			X [10]		X		X [10]	
HIV, HBV, and HCV tests		X								
Laboratory analyses [13]		X	X	X	X	X	X	X	X	X
Urine analysis [15]		X	X	X	X	X	X	X	X	X
Treatment administration										
FLOX			X	X	X [16]	X [16]	X	X	X [16]	X [16]
Nivolumab					X [16]	X [16]			X [16]	X [16]
Evaluation procedure(s)										
CT [17]		X [18]					X			
Correlative study procedures										
Whole blood sampling			X							
Plasma and serum sampling			X		X		X		X	
PBMC sampling [19]			X		X		X		X	
Functional MR liver acquisition [19,20]		X			X		X			
Liver/peritoneal biopsy sampling [21]		X			X		X			

Trial period	Break period [2]	End of study visit	Withdrawal visit (if applicable)	Post-treatment phase		
Scheduling window; visit (V), cycle (C), day(D)	Every 8 weeks	At the time of treatment discont.	At the time of withdrawal	Safety follow-up (approx. D30 after discont.)	Follow-up year 1 after discont. (every 3 months ±7 days)	Survival follow-up
Administrative procedures						
Informed consent						
Inclusion/exclusion criteria						
Tumor *(K)RAS/BRAF* mutation status [3]						
Medical history						
Prior [4] and concomitant medication review	X	X	X	X		
Post-study anticancer therapy status				X	X	
Questionnaires (QoL)	X [5]	X				
Clinical procedures						
Review adverse events	X	X	X [6]	X [6]	X [6]	
Full physical examination [7]				X		
Directed physical examination	X	X	X			
Vital signs and weight	X	X	X	X		
ECOG performance status	X	X	X	X		
Survival follow-up						X
Laboratory procedures						
Pregnancy test [9]	X [11]	X	X	X	X [12]	
HIV, HBV, and HCV tests						
Laboratory analyses [13]	X	X [14]	X [14]	X [14]	X [14]	
Urine analysis [15]	X	X [14]	X [14]	X [14]	X [14]	
Treatment administration						
FLOX						
Nivolumab						
Evaluation procedure(s)						
CT [17]	X	X				
Correlative study procedures						
Whole blood sampling						
Plasma and serum sampling	X	X				
PBMC sampling [19]	X	X				
Functional MR liver acquisition [19,20]						
Liver/peritoneal biopsy sampling [21]						

[1] Repeat after break period with disease progression, continue until progressive disease on ongoing therapy.

[2] Until disease progression.

[3] Analysis on primary or metastatic tumor.

[4] Only at visit 2.

[5] By completion of the active therapy of the first treatment sequence (after 16 weeks), *i.e.,* at first visit in first treatment break.

[6] Until all study drug-related AE are resolved, have returned to baseline, or are deemed irreversible; reported for at least 100 days after last dose administration of IMP.

[7] To be undertaken if clinically indicated from V1 onward, but mandatory at the 30 days safety follow-up visit.

[8] May be omitted if full physical examination has been undertaken 14 days or less prior to the first dose of trial treatment.

[9] For WOCBP.

[10] Within 24 hours prior to the start of study drug.

[11] Every 4 weeks.

[12] Every 4 weeks; in the control arm, for 30 days after the last dose of study drug; in the experimental arm, for 160 days after the last dose of study drug.

[13] Laboratory tests: Hb, HCT, WBC (including differential counting), platelets, liver factors (ALT, AST, ALP, LDH, GGT, total bilirubin, total albumin, INR), creatinine or urea, Na, K, Ca, Mg, phosphate, glucose, TSH, free T4, CEA, Ca19.9, Ca125.

[14] Until all study drug-related abnormalities are resolved, have returned to baseline, or are deemed irreversible.

[15] Dipstick.

[16] FLOX in control treatment arm, nivolumab in experimental treatment arm.

[17] In addition to computed tomography (CT) scan, MR scans or other radiologic evaluations will be performed if indicated.

[18] Baseline CT scan must be taken within 28 days prior to the start of study drug.

[19] Participation is optional for study centers.

[20] Patient must not present contraindication to the procedure. Procedure must be done before a metastatic lesion in the liver/peritoneum is sampled.

[21] Baseline sampling is mandatory; follow-up sampling is optional.

7 STUDY PROCEDURES

The Study Flow Chart (*Chapter 6*) summarizes study procedures to be performed at each visit. Individual procedures are described in detail below. It may be necessary to perform these procedures at unscheduled times if deemed clinically necessary by Clinical Investigator.

Furthermore, additional evaluation/testing may be deemed necessary by Sponsor and/or BMS for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (*e.g.,* human immunodeficiency virus, hepatitis C), and thus local regulations may require that additional informed consent be obtained from the subject. In these cases, such evaluation/testing will be performed in accordance with those regulations.

7.1 Informed consent

Clinical Investigator will obtain documented consent from each subject prior to participation in the trial. Consent must be documented by the subject's dated signature on the ICF along with the dated signature of the person conducting the consent discussion. A copy of the signed and dated ICF will be given to the subject before participation in the trial.

The initial ICF, any subsequent revised written ICF, and any written information provided to the subject must receive approval of Institutional Review Board (IRB) and Independent Ethics Committee (IEC) in advance of use. The subject will be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised ICF or addendum to the original consent form that captures the subject's dated signature.

The informed consent will adhere to IRB/ERC requirements, applicable laws and regulations, and Sponsor requirements.

7.2 Inclusion and exclusion criteria

All inclusion and exclusion criteria will be reviewed by Clinical Investigator or a qualified designee to ensure that the subject qualifies for the trial.

7.3 Medical history

A medical history will be obtained by Clinical Investigator or a qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by Clinical Investigator. Details regarding the disease for which the subject has enrolled in this study will be recorded separately and not listed as medical history.

7.3.1 Prior medications

Clinical Investigator or a qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the subject within 28 days before starting the trial. Treatment for the disease for which the subject has enrolled in this study will be recorded separately and not listed as prior medication.

7.3.2 Concomitant medications

Clinical Investigator or a qualified designee will record medication, if any, taken by the subject during the trial.

7.3.3 Other diseases

Clinical Investigator or a qualified designee will obtain prior and current details regarding disease status.

7.3.4 Prior treatment details

Clinical Investigator or a qualified designee will review all prior cancer treatments including systemic treatments, radiation, and surgery.

7.3.5 Subsequent anti-cancer therapy status

Clinical Investigator or a qualified designee will review all new anti-neoplastic therapy initiated after the last dose of trial treatment. If a subject initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the 30 day safety follow-up visit must occur before the first dose of the new therapy. Once new anti-cancer therapy has been initiated the subject will move into survival follow-up.

7.4 Safety assessments

At baseline, a medical history will be obtained to capture relevant underlying conditions. The baseline examinations will include weight, height, ECOG status, blood pressure, heart rate, and temperature, and will be performed within 14 days prior to first dose. Baseline signs and symptoms are those that are assessed within 14 days prior to first dose of study drug. Concomitant medications including steroid dose will be collected within 14 days prior to first dose of study drug and through the study treatment period.

Baseline local laboratory assessments will be done within 14 days prior to first dose and will include the following serum/plasma assessments: Hb, HCT, WBC (including differential counting), platelets, liver factors (ALT, AST, ALP, LDH, GGT, total bilirubin, total albumin, INR), creatinine or urea, Na, K, Ca, Mg, phosphate, glucose, TSH, free T4, CEA, Ca19.9, and Ca125. Additionally, urine analysis will be done.

The following baseline local laboratory assessments should be done within 28 days prior to first treatment: hepatitis B and C testing, according to each Institution's SOP.

Pregnancy testing of WOCBP must be performed within 24 hours prior to Day 1 and then every 4 weeks.

While on study treatment, the same local laboratory assessments as those of baseline will be done within 3 days prior to each dose.

Subjects will be evaluated for safety and tolerability if they have received any study drug. Toxicity assessments will be continuous during the treatment phase and formally recorded at each new therapy cycle, and every 8 weeks during planned breaks from active study therapy, and should be done in person. Once subjects reach the survival follow-up phase, either in-person or documented telephone calls to assess the subject's status are acceptable.

AE and laboratory values will be graded according to CTCAE v4.0.

The start and stop time of the study therapy infusions will be documented.

Additional measures, including non-study required laboratory tests, will be performed as clinically indicated or to comply with local regulations. Laboratory toxicities (*e.g.,* suspected drug-induced liver enzyme evaluations) will be monitored during the follow-up phase via local laboratories until all study drug-related toxicities resolve, return to baseline, or are deemed irreversible.

Some of the assessments referred to in this section may not be captured as data in the CRF. They are intended to be used as safety monitoring by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations.

7.5 Physical examination

7.5.1 Full physical examination

Clinical Investigator or a qualified designee will perform a complete physical examination during the screening period. Clinically significant abnormal findings should be recorded as medical history. A full physical examination will also be performed at the 30 days safety follow-up visit and if clinically indicated otherwise during the study.

7.5.2 Directed physical examination

For study visits that do not require a full physical examination as per Study Flow Chart, Clinical Investigator or a qualified designee will perform a directed physical examination as clinically indicated prior to trial treatment administration.

7.5.3 Vital signs

Clinical Investigator or a qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment, and at treatment discontinuation as specified in Study Flow Chart. Vital signs should include temperature, pulse, weight, and blood pressure. Height will be measured at screening only.

7.5.4 ECOG performance status

Clinical Investigator or a qualified designee will assess ECOG status at screening, prior to the administration of each dose of trial treatment, every 8 weeks during planned breaks from active study therapy, at discontinuation of trial treatment, and during follow-up, as specified in Study Flow Chart.

7.6 Tumor imaging and assessment of disease procedures

7.6.1 Evaluation of efficacy

The imaging assessments will be performed by CT, typicall a thoracic/abdominal/pelvic CT scan. Tumor treatment response will be assessed according to RECIST v1.1 as the primary method and iRECIST as the secondary method. After baseline tumor assessments, evaluation of tumor response will be performed every 8 weeks (±7 days). Additional MR scans or other radiologic evaluations will be performed if indicated.

All radiologic examinations will be transmitted to Study Radiologist at Akershus University Hospital within 1 working day after the scan is performed. A radiologist at the actual study center will evaluate the images for incidental findings that may have a therapeutic consequence (*e.g.,* pulmonary embolism, immune therapy-related findings that require emergency actions).

Study Radiologist will be blinded to patient treatment, but will be informed about treatment breaks in the go-and-stop schedule. Study Radiologist will primarily assess tumor measures according to RECIST v1.1. If disease progression is concluded by means of RECIST v1.1, Study Radiologist will also assess tumor measures according to iRECIST. The radiology report will detail the criteria used for Clinical Investigator to make a decision about further study treatment (*c.f., Paragraph 5.7.2.4*).

PFS will be calculated from the day of randomization to first recorded disease progression according to RECIST v1.1 or iRECIST when applicable, or death. Patients who have not had disease progression at the time of final analysis will be censored at the date last known to be alive and progression-free.

7.6.2 Measurability of tumor lesions at baseline

7.6.2.1 Definitions

- *Measurable disease:* The presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature will be confirmed by cytology/histology prior to treatment.
- *Measurable lesions:* Tumor lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥10 mm with CT.
    - Bone lesions are considered measurable only if assessed by CT and have an identifiable soft tissue component that meets these requirements (soft tissue component ≥10 mm with CT).
    - Malignant lymph nodes must be ≥15 mm in the short axis to be considered measurable; only the short axis will be measured and followed.

All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters). Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

- *Non-measurable lesions:* All other lesions (or sites of disease), including small lesions, are considered non-measurable disease. Bone lesions without a measurable soft tissue component, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, lymphangitic involvement of lung or skin and abdominal masses followed by clinical examination, are all non-measurable. Nodes that have a short axis <10 mm at baseline are considered non-pathological and should not be recorded or followed.

- *Target lesions:* When more than one measurable tumor lesion or malignant lymph node is present at baseline, all lesions up to a maximum of 5 (or 3, if only three are present) lesions in total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions, and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeat measurements. Note that pathological lymph nodes must meet the criterion of a short axis of ≥15 mm by CT and only the short axis of these nodes will contribute to the baseline sum. At baseline, the sum of the target lesions (longest diameter of tumor lesions plus short axis of lymph nodes; overall maximum of 5) is to be calculated and recorded.
- *Non-target lesions:* All non-measurable lesions (or sites of disease), including pathological nodes (those with short axis ≥10 mm but <15 mm), plus any measurable lesions over and above those listed as target lesions are considered non-target lesions. Measurements are not required, but these lesions should be noted at baseline and should be followed as present or absent.

All baseline evaluations should be performed as closely as possible to the beginning of treatment and every 8 weeks during treatment and planned treatment breaks.

7.6.2.2 Methods of measurements

CT of the thoracic/abdominal/pelvic cavities (preferably with IV contrast) is the best currently available and reproducible method to measure lesions selected for response assessment in metastatic CRC. This protocol has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

- Evaluation will be done every 8 weeks.
- The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.
- While on study, all target lesions recorded at baseline should have their actual measurements recorded on the CRF at each subsequent evaluation.
- If it is the opinion of Study Radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned.

For lesions which fragment/split add together, the longest diameter of the fragmented portions will be measured. For lesions which coalesce, the maximal longest diameter for the 'merged lesion' will be measured.

7.6.3 RECIST version 1.1

All patients will have their best response from the start of study treatment until the end of treatment, classified as such:

- *Complete response* (CR): Disappearance of all target and non-target lesions. Pathological lymph nodes must have short axis measures <10 mm (note: continue to record the measurement even if <10 mm and considered CR). Tumor markers must have normalized. Residual lesions (other than nodes <10 mm) thought to be non-malignant should be further investigated (by cytology or positron emission tomography) before CR can be accepted.
- *Partial response* (PR): At least a 30% decrease in the sum of measures (longest diameter for tumor lesions and short axis measure for nodes) of target lesions, taking as reference the baseline sum of diameters. Non-target lesions must be non-PD.
- *Stable disease* (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameters on study.
- *Progressive disease* (PD): At least 20% increase in the sum of diameters of measured lesions taking as references the smallest sum of diameters recorded on study (including baseline) *and* an absolute increase of ≥5 mm. Appearance of new lesions will also constitute PD (including lesions in previously unassessed areas). In exceptional circumstances, unequivocal progression of non-target disease may be accepted as evidence of disease progression, where the overall tumor burden has increased sufficiently to merit discontinuation of treatment, for example where the tumor burden appears to have increased by at least 73% in volume (which is the increase in volume when all dimensions of a single lesion increase by 20%). Modest increases in the size of one or more non-

target lesions are *not* considered unequivocal progression. If the evidence of PD is equivocal (target or non-target lesions), treatment may continue until the next assessment, but on further documentation, the earlier date must be used.

CR or PR may be claimed only if the criteria for each are met at a subsequent time point at least 8 weeks later.

Assignments of timepoint response using RECIST v1.1:

Response: First time point	Subsequent time point	BEST overall response	Also requires
CR	CR	CR	Normalization of tumour markers, tumour nodes < 10 mm
CR	PR	SD, PD or PR (see comment*)	
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD	
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD	
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE	
PR	CR	PR	
PR	PR	PR	
PR	SD	SD	
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD	
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE	
NE	NE	NE	

* may consider PR providing initial "CR" likely PR on subsequent review – then original CR should be corrected. Recurrence of lesion after true CR is PD.

7.6.4 iRECIST

In the experimental arm, iRECIST will be used in the case of new lesion(s) or increase in size of known lesion(s), and if the patient is clinically deteriorating. This is categorized as *immune-unconfirmed progressive disease* (iUPD). An *immune-confirmed progressive disease* (iCPD) is only assigned if at next assessment after iUPD (4–8 weeks later) additional new lesions appear or an increase in size of new lesions is seen (≥5 mm for sum of new target lesion or any increase in new non-target lesion). The appearance of new lesions when none have previously been recorded can also confirm iCPD.

However, if progression is not confirmed but instead tumor shrinkage occurs (compared with baseline), which meets the criteria of *immune-complete response* (iCR), *immune-partial response* (iPR), or *immune-stable disease* (iSD), then the bar is reset so that iUPD needs to occur again (compared with nadir values) and then be confirmed (by further growth) at the next assessment, for iCPD to be assigned. If no change in tumor size or extent from iUPD occurs, then the time point response would again be iUPD. This approach allows atypical responses, such as delayed responses that occur after pseudoprogression, to be identified, further understood, and better characterized.

Response criteria are essentially based on a set of measurable lesions identified at baseline as target lesions, and, together with other lesions that are denoted as non-target lesions, followed until disease progression.

For direct comparison of iRECIST with RECIST v1.1 [Seymour *et al.,* 2017], please refer to **Appendix 2**.

iCR or iPR may be claimed only if the criteria for each are met at a subsequent time point at least 8 weeks later.

Assignments of timepoint response using iRECIST:

	Timepoint response with no previous iUPD in any category	Timepoint response with previous iUPD in any category
Target lesions: iCR; non-target lesions: iCR; new lesions: no	iCR	iCR
Target lesions: iCR; non-target lesions: non-iCR/non-iUPD; new lesions: no	iPR	iPR
Target lesions: iPR; non-target lesions: non-iCR/non-iUPD; new lesions: no	iPR	iPR
Target lesions: iSD; non-target lesions: non-iCR/non-iUPD; new lesions: no	iSD	iSD
Target lesions: iUPD with no change, or with a decrease from last timepoint; non-target lesions: iUPD with no change, or decrease from last timepoint; new lesions: yes	Not applicable	New lesions confirm iCPD if new lesions were previously identified and they have increased in size (≥5 mm in sum of measures for new lesion target or any increase for new lesion non-target) or number; if no change is seen in new lesions (size or number) from last timepoint, assignment remains iUPD
Target lesions: iSD, iPR, iCR; non-target lesions: iUPD; new lesions: no	iUPD	Remains iUPD unless iCPD is confirmed on the basis of a further increase in the size of non-target disease (does not need to meet RECIST 1.1 criteria for unequivocal progression)
Target lesions: iUPD; non-target lesions: non-iCR/non-iUPD, or iCR; new lesions: no	iUPD	Remains iUPD unless iCPD is confirmed on the basis of a further increase in sum of measures ≥5 mm; otherwise, assignment remains iUPD
Target lesions: iUPD; non-target lesions: iUPD; new lesions: no	iUPD	Remains iUPD unless iCPD is confirmed based on a further increase in previously identified target lesion iUPD in sum of measures ≥5 mm or non-target lesion iUPD (previous assessment need not have shown unequivocal progression)
Target lesions: iUPD; non-target lesions: iUPD; new lesions: yes	iUPD	Remains iUPD unless iCPD is confirmed on the basis of a further increase in previously identified target lesion iUPD sum of measures ≥5 mm, previously identified non-target lesion iUPD (does not need to be unequivocal), or an increase in the size or number of new lesions previously identified

7.6.5 Frequency of tumor re-evaluation

Frequency of tumor re-evaluation will be every 8 weeks in both arms and during planned study treatment breaks. In the case of suspected clinical progression or iUPD according to iRECIST, the next evaluation may be preponed to after 4 weeks.

Evaluation will be with routine CT of the thoracic/abdominal/pelvic cavities, preferably with contrast in the case of adequate renal function.

If brain or bone metastasis is suspected, supplemental MR evaluations may be undertaken. However, bone scans only need to be repeated when CR is identified in target disease or when progression in bone is suspected.

All target and non-target sites are assessed at each evaluation.

After discontinuation of protocol treatment, patients who have not progressed will still be re-evaluated every 8 weeks until end-of-study, as per protocol.

7.6.6. Date of progression

This is defined as the first day when RECIST (v1.1) PD is observed in the control arm and after iRECIST iCPD is observed in the experimental arm.

7.6.7 Reporting of tumor response

All patients included in the study must be assessed for response to treatment, even if there is a major protocol treatment deviation or if they are ineligible, or not followed/re-evaluated. Each patient will be assigned one of the following categories: CR/iCR, PR/iPR, SD/iSD, PD/iCPD, early death from malignant disease, early death from toxicity, or early death from other cause or unknown (not assessable, insufficient data).

Early death is defined as any death occurring <30 days after randomization. Clinical Investigator will decide if the cause of death is malignant disease, toxicity, or other.

Patients for whom response is not confirmed will be classified as *Unknown*, unless they meet the criteria for SD/iSD (or the criteria for PR/iPR in case of an unconfirmed CR/iCR). Patients' response will also be classified as *Unknown* if insufficient data were collected to allow evaluation per these criteria.

7.6.8 Response duration

This will be measured from the time of randomization, or until the first date that recurrent or progressive disease is objectively documented. Patients who have not had PD/iCPD at the time of final analysis will be censored at the date last known to be alive and progression-free.

7.6.9 Stable disease duration

This will be measured from the time of randomization until the criteria for progression are met. Patients who have not had PD/iCPD at the time of final analysis will be censored at the date last known to be alive and progression-free.

7.7 Other study procedures

7.7.1 Screening period

Approximately 7–14 days prior to subject allocation, potential subjects will be evaluated to determine that they fulfill the entry requirements. Results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame. Screening procedures can not be completed earlier than 14 days prior to the first dose of trial treatment except for WOCBP, for whom a serum pregnancy test will be performed within 24 hours prior to the first dose of trial treatment. A urine test may be considered if serum test is not appropriate.

Subjects may be rescreened after initially failing to meet the inclusion/exclusion criteria. Results from assessments performed during the initial screening period are acceptable in lieu of a repeat screening test if performed within the specified time frame and the inclusion/exclusion criteria are met.

7.7.2 Treatment period

Visit requirements are outlined in *Chapter 6* – Study Flow Chart. Specific procedure-related details are provided in *Chapter 7* – Study Procedures.

7.7.3 Post-treatment visits

7.7.3.1 Safety follow-up visit

The mandatory safety follow-up visit will be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All AE that occur prior to the safety follow-up visit should be recorded. Subjects with an AE of CTCAE grade >1 will be followed until the resolution of the AE to grade 0–1 or stabilization, or until the beginning of a new anti-neoplastic therapy, whichever occurs first. SAE that occurs within

the full duration of the study (*c.f., Paragraph 7.8*) or before initiation of a new anti-cancer treatment will also be followed and recorded.

7.7.3.2 Follow-up visits

When a subject discontinues study treatment, for whatever reason (PD/iCPD, unacceptable toxicity, or withdrawal of consent), the subject will move into the follow-up phase. The patient will be assessed every 3 months (±7 days) the first year after discontinuation to monitor disease status. Every effort will be made to collect information regarding disease status until the start of a new anti-neoplastic therapy, disease progression, death, or end of the study. Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated.

7.7.3.3 Survival follow-up

Once a subject discontinues study treatment or starts a new anti-cancer therapy, the subject moves into the survival follow-up phase. We will monitor survival status every 6–12 months (by phone call, subject visit, contact with patient's general practitioner) until the end of the study. The survival status and, if applicable, the cause of death will be recorded.

7.7.4 Withdrawal or discontinuation

When a subject discontinues or withdraws prior to trial completion, all applicable activities scheduled for the final trial visit will be performed at the time of discontinuation. Any AE which are present at the time of discontinuation will be followed in accordance with the safety requirements outlined in *Chapter 8*.

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of Clinical Investigator should any untoward effect occur. In addition, a subject may be withdrawn by Clinical Investigator or Sponsor if enrolment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. A subject must be discontinued from the trial for any of the following reasons:

- AE/SAE as specifically described.
- The subject withdraws consent.
- Confirmed disease progression; *c.f., Paragraph 7.6*.
- Any clinical AE, laboratory abnormality, or intercurrent illness which, in the opinion of Clinical Investigator, indicates that continued participation in the study is not in the best interest of the subject.
- Intercurrent illness that prevents further administration of treatment.
- Clinical Investigator's decision to withdraw the subject.
- The subject has a confirmed positive pregnancy test.
- Non-compliance with trial treatment or procedure requirements.
- The subject is lost to follow-up.
- Administrative reasons.

After the end of treatment, each subject will be followed for 30 days for AE monitoring. Subjects who discontinue for reasons other than PD/iCPD will have post-treatment follow-up for disease status until disease progression, starting a non-study cancer treatment, withdrawing consent, or becoming lost to follow-up. After documented disease progression, information on survival will be obtained until death, withdrawal of consent, or the end of the study, whichever occurs first.

7.8 End of study

The end of study is defined as "last patient last visit", in accordance with European Commission guidelines. However, as mentioned in *Paragraph 5.5*, accumulating evidence from a number of clinical trials in different tumor types with nivolumab indicates that patients may obtain durable responses, even if they discontinue nivolumab for toxicity. Such observations are acknowledged as general features of ICB [Emens *et al.,* 2017] and may call for a redefinition of the end-of-study term during the study conduct.

7.9 Study termination

Early trial termination may be the result of one of the following criteria:

- Quality or quantity of data recording is inaccurate or incomplete.
- Poor adherence to protocol and regulatory requirements.
- Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects.
- Plans to modify or discontinue the development of the study drug.

In the event of BMS decision to no longer supply study drug, ample notification will be provided so that appropriate adjustments to subject treatment can be made.

The whole trial may be discontinued at the discretion of Principal Investigator or Sponsor in the event of any of the following:

- Occurrence of AE/SAE unknown to date in respect of their nature, severity, and duration.
- Medical or ethical reasons affecting the continued performance of the trial.
- Difficulties in the recruitment of patients.
- Cancellation of drug development.

Sponsor and Principal Investigator will inform all investigators and the relevant Competent Authorities and Ethics Committees of the termination of the trial along with the reasons for such action. If the study is terminated early on grounds of safety, the Competent Authorities and Ethics Committees will be informed within 15 days.

7.10 Ancillary study procedures

The below listed procedures do not represent a mandatory list of what are to be performed, but instead provide an overview of the current plans. The priority of analyses and assays will be subject to review during and after finalization of the trial. Additional investigations may be performed, reflecting ongoing developments in the field. Some assays will be performed only for selected patients because of costs and work load.

For the precise timing of the various procedures described below, please refer to the Study Flow Chart – *Chapter 6*.

7.10.1 Repeat quality-of-life recording

Formal QoL recording will undertaken at study enrolment, completion of the active therapy of the first treatment sequence (after 16 weeks), and disease progression, using the consensus modules EORTC QLQ-C30, EORTC QLQ-CIPN20, and EQ-5D-5L (http://groups.eortc.be/qol/, http://www.euroqol.org/). Please refer to the information in **Appendices 7–9**.

Participation in the QoL sub-study is *mandatory* for study centers.

7.10.2 Repeat collection of serum and plasma

Up to ten tubes of 5–10 mL peripheral blood will be drawn immediately before start of treatment, after every completed 2 therapy cycles (immediately before start of the next cycle or at treatment interruption) until disease progression, unacceptable toxicity, withdrawal of consent, death by any reason, or end-of-follow-up, whichever occurs first, and every 8 weeks during planned treatment breaks. The tubes will be used to prepare EDTA plasma, citrate plasma, and serum, according to specified SOP documents (in Investigator Site File). A small volume of the whole blood collected immediately before start of treatment will be used for isolation of germ-line DNA. The samples will be stored at –80ºC at the local study center and dispatched to the study biobank at Akershus University Hospital upon request.

The circulating biomarker study program will comprise ctDNA [Spindler *et al.,* 2017], exosomal miRNA (published in the PhD thesis of S. Meltzer 2017, manuscript in preparation), and ICD factors [Kalanxhi *et al.,* 2016; Meltzer *et al.,* 2016; Kalanxhi *et al.,* 2017].

Participation in the above-mentioned circulating biomarker sub-studies is *mandatory* for study centers.

7.10.3 Repeat collection of PBMC

Currently, no robust biomarker of cytotoxic T cell activity exists for clinical use, but PTEN phosphatase activity is high in T lymphocytes silenced by PD-1 binding to PD-L1 [Riley, 2009; Patsoukis *et al.,* 2013]. Building on our long-standing collaboration with the Dutch biotechnology company PamGene International B.V. (www.pamgene.com), we will apply their recently developed phosphatase array [Hovestad-Bijl *et al.,* 2016] on PBMC samples [Noé *et al.,* 2016], as readily accessible surrogate tissue for the monitoring of cytotoxic T cell activity, at the proteomic facility at Department of Clinical Molecular Biology, Akershus University Hospital [Ree *et al.,* 2015].

Moreover, together with Department of Cellular Therapy / Immunomonitoring Laboratory, Oslo University Hospital, *ex vivo* cytokine analysis, applying the ELISPOT assay, will be done on PBMC or specific subsets of CD4-positive and CD8-positive T cells.

One tube of 10 mL peripheral blood will be drawn for this purpose immediately before start of treatment and after every completed 2 therapy cycles (immediately before start of the next cycle or at treatment interruption) until disease progression, unacceptable toxicity, withdrawal of consent, death by any reason, or end-of-follow-up, whichever occurs first, and every 8 weeks during planned treatment breaks. PBMC will be isolated by density-gradient centrifugation in Ficoll, stored at –80ºC at the local study center, and dispatched to the study biobank at Akershus University Hospital upon request. Please refer to the specified SOP document (in Investigator Site File).

Participation in the above-mentioned circulating biomarker sub-studies is *optional* for study centers.

7.10.4 Repeat functional MR imaging

Experiental arm patients will undergo repeat MR recordings of abdominal metastases at time points corresponding to each change of therapy (from FLOX to nivolumab and reverse) during the first two months of the sequential regimen (*i.e.,* three recordings in total), using a discrete number of functional MR sequences with readouts reflecting TME biology. Specifically, we will apply our recently developed multi-echo contrast-enhanced sequence, which can predict metastatic progression with high diagnostic accuracy [Grøvik *et al.,* 2016]. Importantly, the MR procedure must be done before a metastatic lesion is sampled by biopsy. Control arm patients may be exempt from MR imaging at the discretion of Clinical Investigator. Please refer to the specified SOP document (in Investigator Site File).

Participation in the functional MR imaging biomarker sub-study is *optional* for study centers.

7.10.5 Repeat collection of metastatic tissue

Experimental arm patients will undergo repeat sampling of core biopsies from liver/peritoneal metastases at time points corresponding to each change of therapy (from FLOX to nivolumab and reverse) during the first two months of the sequential regimen (*i.e.,* three sampling procedures in total; one or both of the resampling procedures, *i.e.,* others than that at baseline, are excused if the total number of three procudures is not feasible). Control arm patients will undergo biopsy sampling at baseline and may also be exempt from repeat sampling at the discretion of Clinical Investigator. For an individual patient, repeat sampling will preferentially be from the same lesion every time. The sampling procedure will be ultrasound-guided. Ideally, to ensure that the material from the sampling locus is representative, a regular smear from a fine-needle aspirate will be assessed by a pathologist at site. Next, 1–3 core biopsies will be taken and tumor cell content estimated by tissue imprint prior to freezing in liquid nitrogen [Ree *et al.,* 2017]. The samples will be dispatched to the study biobank at Akershus University Hospital upon request. Please refer to the specified SOP document (in Investigator Site File).

The 1–3 biopsy samples will be utilized in the following priority: 1) histology/immune histochemistry, 2) RNA applications, and 3) DNA applications. Specifically, the total number of T cells (CD3-positive) will be determined, with identification of T cell subpopulations by their expression of specific proteins (CD8-positive cytotoxic and FoxP3-positive regulatory T cells), as recently shown in a pilot study (Dagenborg *et al.,* manuscript in preparation). Also, CRC liver metastasis samples were recently analyzed by gene expression microarrays and indicated immune activity profiles in patients who had received neoadjuvant FLOX [Østrup *et al.,* 2017]. Comprehensive gene mutation analysis will be done [Ree *et al.,* 2017]. Of note, a number of RNA-based methods will be applied to specifically investigate novel mechanisms of anti-tumor immunity. Also, tumor PD-L1 expression, consensus molecular subtype, and mutation burden may be determined.

Participation in the histologic and molecular investigational sub-studies is *mandatory* (baseline biopsy sampling; follow-up biopsy sampling is *optional*) for study centers.

8 SAFETY MONITORING AND REPORTING

The investigators are responsible for the detection and documentation of events meeting the criteria and definition of AE or SAE. Each patient will be instructed to contact Clinical Investigator immediately should they manifest any signs or symptoms they perceive as serious.

8.1 Definitions

An AE is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a subject administered a study drug and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not cautionally related to the medicinal (investigational) product.

The causal relationship to a study drug is determined by a physician and can be one of the following:

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

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship. AE can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject.

8.1.1 Non-serious adverse event(s)

The term AE is used to include both SAE and non-serious AE.

Non-serious AE are CTCAE grade ≤2 events or reactions listed in the the IB/SmPC of nivolumab. For FLOX, non-serious AE are CTCAE grade ≤2 events. Non-serious AE do *not* need to be *reported*. Also, AE or SAE that are definitely due to disease progression do *not* need to be *reported*; *c.f., Paragraph 8.3*.

If an abnormal laboratory value or vital sign is associated with clinical signs and symptoms, the sign/symptom should be *reported as an AE* and the associated laboratory result/vital sign will be considered additional information to be collected on the relevant CRF.

The collection of non-serious AE information will begin at initiation of study drug and last until 100 days from the last dose of study drug (the 100-day injunction pertains to experimental arm patients only). Non-serious AE will be followed to resolution or stabilization, or *reported as SAE* if they become serious. Follow-up is also required for non-serious AE that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate. Identified non-serious AE will be *recorded* on a designated page of the CRF.

8.1.2 SAE (serious adverse events)

An SAE is any untoward medical occurrence that at any dose:

- Results in death.
- Is immediately life-threatening.
- Requires in-patient hospitalization or prolongation of existing admission.
- Results in persistent or significant disability or incapacity.
- Is a congenital abnormality or birth defect.
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above. Examples of such events include but are not limited to intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization. Potential drug-induced liver injury (DILI) is also considered an important medical event (see *Paragraph 8.7* for the definition of potential DILI).

Suspected transmission of an infectious agent (*e.g.,* pathogenic or nonpathogenic) via the study drug is an SAE.

Although pregnancy, overdose, cancer, and potential DILI are not always serious by regulatory definition, these events must be handled as SAE (see *Paragraph 8.5* for reporting pregnancies).

Any component of a study end point that is considered related to study therapy (*e.g.,* death is an end point; if death occurred due to anaphylaxis, anaphylaxis must be reported) should be reported as SAE.

Note:

The following hospitalizations are not considered SAE in this study:

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

8.2 SAE (serious adverse events) collection and reporting

For nivolumab, the IB represents the reference safety information to determine expectedness of SAE for expedited reporting. For the FLOX regimen, the SmPC of each of the drug components represents the reference safety information. Following the subject's written consent to participate in the study, all SAE (in both study arms), whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAE must be collected that occur during the screening period and within 100 days of the last dose of nivolumab. If applicable, SAE must be collected that relate to any later protocol-specified procedure.

Clinical Investigator must report any SAE that occurs after these time periods and that is believed to be related to any IMP or protocol-specified procedure, pertaining to the full duration of the study (*c.f., Paragraph 7.8*), which is in accordance with European Commission guidelines.

An SAE report must be completed for any event where doubt exists regarding its seriousness.

If Clinical Investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship must be specified in the narrative section of the SAE report form.

SAE, whether related or not related to study drug, and pregnancies, must be reported to Sponsor (or designee) within 24 hours of awareness of the event. SAE will be recorded on the Suspect Adverse Reaction Report form by the Council for International Organizations of Medical Sciences (CIOMS), *c.f.* **Appendix 10**. Pregnancies will be recorded on a Pregnancy Surveillance Form.

If only limited information is initially available, follow-up reports are required. All SAE must be followed to resolution or stabilization.

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, the SAE report must be updated and submitted within 24 hours to Sponsor (or designee) using the same procedure used for transmitting the initial SAE report.

Sponsor's representative for SAE notifications has the following address:

a.h.ree@medisin.uio.no

and

Cell Phone: (+47) 482-57968

Sponsor will immediately forward SAE notifications (in experimental arm patients) to the following address:

Worldwide.Safety@BMS.com

or

Facsimile Number: (+1) 609-818-3804

8.3 Disease progression or recurrence

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the IMP is being studied. It may be an increase in the severity of the disease under study and/or increase in the symptoms of the disease. Expected progression of the disease under the study and/or expected progression of signs and symptoms of the disease under study, unless more severe in intensity or more frequent than expected for the patient's condition, will not be reported as AE. Events which are definitely due to disease progression will not be reported as AE. However, if Clinical Investigator considers that there was a causal relationship between treatment with IMP or protocol design/procedures and the disease progression/recurrence, this will be reported as SAE.

Death due to progressive disease will be recorded on a specific form in the CRF and not as SAE. Any new primary cancer (non-related to the cancer under study) will be considered for reporting as SAE.

8.4 Laboratory test abnormalities

The following laboratory test abnormalities will be captured on the non-serious AE CRF page or SAE report form as appropriate:

- Any laboratory test result that is clinically significant or meets the definition of SAE.
- Any laboratory test result abnormality that requires the subject to have study drug discontinued or unintendedly interrupted.
- Any laboratory test result abnormality that requires the subject to receive specific corrective therapy.

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

8.5 Pregnancy

If, following initiation of the study drug, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of study exposure, including during at least 5 half-lives after administration of nivolumab, Clinical Investigator must immediately notify Sponsor of this event and complete and forward a Pregnancy Surveillance Form (provided upon request from BMS) to Sponsor and BMS (in the case of an experimental arm patient) within 24 hours of awareness of the event and in accordance with SAE reporting procedures.

In this case, the IMP will be permanently discontinued in an appropriate manner.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form.

Any pregnancy that occurs in a female partner of a male study participant should be reported to Sponsor and BMS (in the case of an experimental arm patient). Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

8.6 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as SAE.

8.7 Potential drug-induced liver injury (DILI)

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILI, meeting the defined criteria, must be reported as SAE.

Potential DILI is defined as:

1. ALT or AST elevation >3xULN

and

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

and

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

8.8 Other safety considerations

Any significant worsening noted during interim or final physical examinations, radiology examination, or any other potential safety assessment required or not required by protocol should also be recorded as a non-serious AE or SAE, as appropriate, and reported accordingly.

8.9 AE (adverse events) recording

If the patient has experienced an AE, Clinical Investigator will record the following information in the CRF:

- The nature of the AE will be described in precise standard medical terminology (*i.e.,* not necessarily the exact words used by the patient).
- The duration of the event will be described in terms of event onset date and event ended date.
- The intensity of the AE will be defined according to CTCAE v4.0.
- The causal relationship of the event to the IMP will be assessed as one of the following:

  Unrelated: There is no temporal relationship to IMP administration (too early or late, or IMP not administered), or there is a reasonable causal relationship between non-investigational product, concurrent disease, or circumstance and the AE.

  Unlikely: There is a temporal relationship to IMP administration, but there is not a reasonable causal relationship between the IMP and AE.

  Possible: There is reasonable causal relationship between the IMP and AE. Dechallenge information is lacking or unclear.

  Probable: There is a reasonable causal relationship between the IMP and AE. The event responds to dechallenge. Rechallenge is not required.

  Definite: There is a reasonable causal relationship between the IMP and AE.
- Action taken.
- The outcome of the AE – whether the event is resolved or still ongoing.

It is important to distinguish between serious and severe AE. Severity is a measure of intensity whereas seriousness is defined by the criteria in *Paragraph 8.1.2*. An AE of severe intensity needs not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but is not an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke, but would be an SAE.

8.10 Reporting procedure

8.10.1 AE (adverse events) and SAE (serious adverse events)

All AE and SAE will be recorded in the patient's CRF.

SAE must be reported by Clinical Investigator to Sponsor by email and telephone to Principal Investigator, within 24 hours after the site has gained knowledge of the SAE (*c.f., Paragraph 8.2*). Every SAE must be documented by Clinical Investigator on the SAE pages (to be found in Investigator Site File). The SAE report form must be completed, signed, and sent to Sponsor. The initial report shall promptly be followed by detailed, written reports if necessary. The initial and follow-up reports shall identify the trial subjects by unique code numbers assigned to the latter.

Sponsor will keep detailed records of all SAE reported by the investigators and performs an evaluation with respect to seriousness, causality, and expectedness.

8.10.2 SUSAR (suspected unexpected serious adverse reactions)

SUSAR will be reported to the Competent Authority and Ethics Committee according to national regulation. The following timelines should be followed (pertaining to both study arms):

Sponsor will ensure that all relevant information about SUSAR that are fatal or life-threatening is recorded and reported as soon as possible to the Competent Authority and Ethics Committee, in any case no later than seven (7) days after knowledge by Sponsor of such a case, and that relevant follow-up information is subsequently communicated within an additional eight (8) days.

All other SUSAR will be reported to the Competent Authority concerned and Ethics Committee as soon as possible but within a maximum of fifteen (15) days of first knowledge by the sponsor.

SUSAR will be reported using the CIOMS form.

8.10.3 Annual safety report

Once a year throughout the clinical study, Sponsor will provide the Competent Authority with an annual safety report. A final safety report will also be provided at study conclusion. The format will comply with national requirements.

8.10.4 Clinical study report

The AE and SAE occurring during the study will be discussed in the safety evaluation part of the clinical study report.

8.11 Procedures in case of emergency

Clinical Investigator is responsible for assuring that there are procedures and expertise available to cope with emergencies during the study.

9 DATA MANAGEMENT AND MONITORING

9.1 Database management

All data will be collected and collated in the the web-based data management system, termed Viedoc, which includes web-based CRF with an ancillary eDatabase, randomization procedures, and validation of data, and which meets regulatory requirements for clinical therapy trials. This service will be purchased from the South-Eastern Norway Regional Health Authority's Clinical Trial Unit, Oslo University Hospital.

9.2 CRF (case report forms)

The designated investigator staff will enter the data required by the protocol into the electronic CRF. Clinical Investigator is responsible for assuring that data entered into the CRF is accurate and complete. The signature of Clinical Investigator will attest the accuracy of the data on each CRF. If any assessments are omitted, the reason for such omissions will be noted on the CRF. Corrections, with the reason, will also be recorded.

After database lock, Principal Investigator will receive copies of the subject data for archiving at the investigational site.

9.3 Source data

The medical records for each patient will contain information which is important for the patient's safety and continued care, and to fulfill the requirement that critical study data will be verifiable.

To achieve this, the medical records of each patient should clearly describe at least:

- That the patient is participating in the study, *e.g.,* by including the enrolment number and the study code or other study identification.
- Date when ICF was obtained from the patient and statement that patient received a copy of the signed and dated ICF.
- Results of all assessments confirming a patient's eligibility for the study.
- Diseases (past and current, both the disease studied and others, as relevant).
- Treatments withdrawn/withheld due to participation in the study.
- Results of assessments performed during the study.
- ECOG performance status assessments conducted as part of the study.
- Treatments given, changes in treatments during the study, and the time points for the changes.
- Visits to the clinic and telephone contacts during the study, including those for study purposes only.
- Non-serious AE and SAE (if any), including causality assessments.
- Date of and reason for discontinuation from study treatment.
- Date of and reason for withdrawal from study.
- Date of death and cause of death, if available.
- Additional information according to local regulations and practice.

9.4 External Data and Safety Monitoring Committee

The External Data and Safety Monitoring Committee (EDSMC) will oversee the trial during its entire course. EDSMC will consist of two board-certified specialists in oncology and one medical statistician, all of whom are independent from Sponsor and with no competing interests. EDSMC will review treatment response and safety data after each twentieth consecutive study patient has been accrued, or more frequently should there be a medical indication for a review identified by an EDSMC member or an investigator.

EDSMC will have particular focus on data indicating unexpectedly good treatment responses (*e.g.,* a 'miraculous' response leading to potential curation of patient), possible responses detrimental for experimental arm patients, and unexpected toxicities from the sequential therapy (*i.e.,* SUSAR or SAE and SUSAR-like toxicities not foreseen and therefore not described in the study protocol). In case of such data, EDSMC will immediately confer with Study Conduct Group (*c.f., Paragraph 11.3*) about the immediate further conduct and management of the study.

EDSMC actions related to interim analyses are detailed in *Paragraph 10.4.2*. If the number of PFS events in the experimental arm at any review is twice the number of PFS events in the control arm, EDSMC may consider early study termination.

The EDSMC members will be:

- Dr. Marta Nyakas, MD PhD, Oslo University Hospital (expertise in clinical immune therapy studies)
- Dr. Svein Dueland, MD PhD, Oslo University Hospital (expertise in clinical CRC studies)
- Dr. Morten W. Fagerland, PhD, Oslo University Hospital (expertise in statistical methods in medical research)

9.5 Study monitoring

Monitoring will be provided by the the South-Eastern Norway Regional Health Authority's Clinical Trial Unit, Oslo University Hospital. Each local site will be visited on a regular basis by Monitor, who will check the following:

- Informed consent process.
- Reporting of AE/SAE and all other safety data.
- Adherence to protocol.
- Maintenance of required regulatory documents.
- Study supply accountability.
- Facilities and equipment.
- Data completion on the relevant CRF documents, including source data verification.

Monitor will review the relevant CRF documents for accuracy and completeness, and will ask the site staff to adjust any discrepancies as required.

Sponsor's representatives (*e.g.,* monitors, auditors) and/or Competent Authorities will be allowed access to source data for source data verification in which case a review of those parts of the hospital records relevant to the study may be required.

9.6 Confidentiality

Principal Investigator shall arrange for the secure retention of the patient identification and the code list. Patient files shall be kept for the maximum period of time permitted by each hospital. The study documentation (CRF, Investigator Site File, *etc.*) shall be retained and stored during the study and for 25 years after study closure. All information concerning the study will be stored in a safe place inaccessible to unauthorized personnel.

10 STATISTICAL METHODS AND DATA ANALYSIS

10.1 Determination of sample size

Calculation of sample size was performed for PFS – the primary end point – and based on PFS data from recent publications. A median PFS of 9 months was assumed for the standard-of-care (control arm) [Cartwright, 2012; Tveit *et al.,* 2012; Cremolini *et al.,* 2015]. Regarding the therapy concept of ICB, there is no PFS data published as yet for the setting of interest. In the study of patients with treatment-refractory metastatic CRC, median PFS was not reached in the cohort with mismatch repair-deficient disease at the time of reporting [Le *et al.,* 2015]. In the study of previously untreated patients with advanced non-small cell lung cancer, which is a tumor entity with considerably poorer prognosis than advanced CRC, patients with PD-L1-positive tumors that were randomized to ICB showed median PFS of 10.3 months compared to 6.0 months for standard chemotherapy [Reck *et al.,* 2016].

Extrapolating to the setting of interest, with a median PFS of 9 months for standard-of-care, a median PFS twice as long (18 months) was entered for the sequential therapy. Assuming the exponential distribution of survival functions, the median PFS estimates were converted to hazard ratio (HR) of 0.5. Allowing for 10% censoring rate of subjects, the required sample size was estimated to be 40 patients in each arm to be able to show that HR of 0.5, implying the risk of a PFS event in the experimental group is 50% lower than in the control group, is significantly different from 1 with the power of 80% at significance level of 5%, given that log-rank test will be used.

However, it was necessary with several adjustments of the above calculations to maintain sufficient power. First, the sample size was adjusted to enable removal of a maximum of 5% enrolled cases with non-MSS tumor before data analysis. Next, keeping in mind the condition of patients, it is not unlikely that some will be lost from the study before a valid PFS event has been reached. Also, a number of analyses stratified by primary tumor sidedness and *(K)RAS/BRAF* mutation status will be performed. Hence, to enable high enough power in the statistical analysis, the sample size was increased by an additional 20%. After incorporating the adjustments, the final sample size was estimated to be 100 patients, 50 in each arm, with 1:1 randomization.

With the total catchment populations of the participating centers (*c.f., Paragraph 4.1*) we envisage an accrual duration period of approximately 12 months to procure the sufficient number of study cases. As there is no PFS data published as of yet for the novel therapy concept of repeat sequential immunogenic chemotherapy and ICB, and further, the optimum duration of immune-modulating therapy is currently unknown (*c.f., Paragraph 5.5*), the study duration of the expected

longer-lasting arm (experimental arm) was estimated to 30 months (12 months following failure of treatment strategy). Because these estimates were pure conjecture, they were not entered into the sample size calculation.

10.2 Randomization

10.2.1 Randomization procedure

The patients will be block-randomized into treatment arms with ratio 1:1 following a computer-randomized allocation sequence. The blocks will be defined according to sidedness and *(K)RAS/BRAF* mutation status of the primary tumor (right-sided *versus* left-sided and *(K)RAS/BRAF* wild-type *versus* mutation) (*c.f., Paragraph 4.5*). The allocation sequence will be generated by the web-based Viedoc system.

10.2.2 Blinding

Study Statistician (along with Study Radiologist) will not have access to the information on treatment arms before the study conduct is concluded and all analyses have been performed. An emergency unblinding for Study Statistician should not be required at any time of the study conduct since EDSMC will oversee the trial during its entire course (*c.f., Paragraph 9.4*).

10.3 Populations for analysis

The following study populations will be defined:

- Intention-to-treat population: Includes all randomized participants, regardless of protocol adherence. We expect about 5% of randomized patients to have non-MSS tumor. These patients will be excluded from the analysis post-randomization. According to Fergusson and co-workers [Fergusson *et al.,* 2002], such exclusion does not introduce bias and may be legitimate if an independent, blinded adjudication committee makes the decision on exclusion after evaluating all randomized patients. Sample size calculations include necessary adjustments to preserve the same power after exclusion of misdiagnosed patients. The sample size calculation has included necessary adjustments to maintain the same power after exclusion of patients with non-MSS tumor.
- Safety population: Includes all randomized participants who have received at least one dose of study medication and had at least one sequential safety-related observation. Subjects who withdraw from the study will be included in the safety analysis given the safety population criteria are otherwise met. A list of withdrawn subjects, preferably with the reasons for withdrawal, will be made.
- Per-protocol population: Includes all subjects who have adhered to all protocol-defined treatments and outcome assessments.

We will account for all of the patients registered in the study. The number of patients who are not evaluable, or who die or withdraw before treatment has begun, will be specified. The distribution of follow-up time will be described and the number of patients lost to follow-up will be given. Start of follow-up will be defined as the date of randomization.

10.4 Statistical analysis of clinical end points

10.4.1 Main statistical analyses

The main statistical analysis is planned after the last patient has fulfilled the pre-defined follow-up period. PFS will be calculated from the day of randomization to first recorded disease progression according to RECIST v1.1 or when applicable iRECIST, or death. Patients who have not had disease progression at the time of final analysis will be censored at the date last known to be alive and progression-free. The analyses will compare the treatment groups in total as well as groups stratified by primary tumor sidedness and *(K)RAS/BRAF* mutation status.

Deviation from the original statistical plan will be described and justified in the clinical study report. Amendments to plan can be done until the day of database lock.

10.4.2 Interim analyses

Interim analyses will particularly apply to data on safety, tolerability, possible detrimental effects, and curative outcomes, and will be based on purely clinical judgment by the EDSMC (*c.f., Paragraph 9.4*). In particular, CTCAE grade 3–5, PFS

measures considerably shorter than 9 months, CR/iCR, and secondary surgical curative resection events will be counted. These types of data will be reported as the number of events.

10.4.3 Descriptive statistics

Demographic and clinical characteristics will be presented as means and standard deviations, medians with minimum and maximum values, or frequencies and percentages, as appropriate. Further statistical analyses will be separated to primary analyses, including only comparison of primary end point between two treatment arms, and secondary analyses, including stratified analyses on primary and secondary end points as well as number of analyses on secondary end points.

10.4.4 Primary analysis

Median *PFS time* will be compared between study arms by drawing Kaplan-Meier survival curves and performing log-rank test. HR with the corresponding 95% confidence interval (CI) and *p*-values will be estimated by Cox proportional hazards model.

10.4.5 Secondary analyses

Distribution of *PFS times* stratified by the primary tumor sidedness and *(K)RAS/BRAF* mutation status will be illustrated graphically by Kaplan-Meier curves and compared by log-rank test. To assess the hazard rates for disease progression within each strata, Cox proportional hazards model will be estimated and, if appropriate, adjusted for relevant covariates. The results will be presented as HR with the corresponding 95% CI and *p*-values.

Safety: The number of SAE will be summarized and presented by trial arm and according to the MedDRA System Organ Class (www.meddra.org). In addition, information will be given on the number of SAE per participant, together with details on the causality, expectedness, and outcome of each SAE experienced. Summaries of SUSAR events will also be presented by trial arm.

Tolerability: Summaries by trial arm will be produced to show the proportion of participants experiencing each grade of CTCAE toxicities overall and during each treatment cycle. For more detailed summaries, this information will also be broken down into the different types of toxicities.

QoL: This will be summarized for each treatment arm at study enrolment, completion of the active therapy of the first treatment sequence (after 16 weeks), and disease progression, using the consensus modules EORTC QLQ-C30, EORTC QLQ-CIPN20, and EQ-5D-5L. The data will be illustrated graphically and presented as mean scores with 95% CI at separate time points. The differences in QoL between two treatment arms throughout the study period will be assessed by estimating a linear mixed model with fixed effects for time and treatment arm and the interaction between these two. Random effects for patients will be included. A significant interaction will quantify differences between the groups and serve as an omnibus test.

Safety and tolerability in the treatment arms will be compared by χ^2 or Fisher's exact test, as appropriate.

ORR is defined as the percentage of patients with a confirmed CR or PR. The proportion of participants achieving at least PR will be summarized with corresponding 95% CI for each treatment arm. The difference between the trial arms in the proportion of participants achieving at least PR will also be presented with corresponding 95% CI. The difference between participants achieving at least PR and remaining participants will be assessed using logistic regression adjusting for treatment group and stratification factors. Odds ratios with corresponding 95% CI and *p*-values will be presented for all variables incorporated in the model.

SSCRR is defined as the percentage of patients with a confirmed resection of metastatic disease with microscopically free margin (R0). Corresponding analyses as those to be performed for ORR will be applied for SSCRR.

DOR is defined as the time from the first documentation of CR/iCR or PR/iPR to disease progression. DOR Kaplan-Meier curves will be drawn and compared by log-rank test. The median DOR with corresponding 95% CI will be presented by treatment group. Stratified analyses will be performed as well. The Cox proportional hazards model, adjusting for the stratification factors, will also be used to compare DOR between the treatment groups. HR, 95%CI and *p*-values will be presented for all variables incorporated in the model.

OS is defined as the time from randomization to death of any cause. The same analyses as for DOR will be performed for OS.

The assumptions for the statistical method considered will be assessed by using standard techniques. In the case the assumptions are not met, the necessary adjustments for methods specified above will be introduced and reported.

10.5 Analysis of other end points

Cost modeling and validation will apply a model specifically developed for CRC by Investigator at Health Services Research Center, Akershus University Hospital [Joranger *et al.,* 2015].

For *exploratory analyses*, appropriate statistical methods will be applied to analyze the various outcome measures.

10.6 Statistical software

SPSS Statistics, SAS, STATA, and GraphPad Prism (the most recent versions for all) are relevant software for statistical analyses of the study data.

11 STUDY MANAGEMENT

11.1 Study documentation

All investigators must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol amendments, ICF, and documentation of IRB approval.

11.2 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. All significant protocol deviations will be recorded and reported in the clinical study report.

11.3 Study Conduct Group

This will consist of the following investigators:

- Professor Anne Hansen Ree, Akershus University Hospital
- Professor Kjersti Flatmark, Oslo University Hospital
- Professor Halfdan Sørbye, Haukeland University Hospital
- Dr. Christian Kersten, Hospital of Southern Norway

These investigators will communicate about study issues on regular basis and promptly whenever requested by other investigators or BMS.

11.4 Study amendments

If it is necessary for the study protocol to be amended, the amendment and/or a new version of the study protocol must be reported to and approved by the Competent Authority and Ethics Committee according to EU and national regulations.

11.5 Investigator Site File

This will contain the following:

- letters
- all forms
- research protocol
- information for the subjects

- questionnaires
- SOP documents for exploratory sub-studies
- information about the participating site and respective contact persons
- safety information
- progress reports and study results

11.6 Audit and inspections

Authorized representatives of a Competent Authority, Ethics Committee, and BMS may visit the centers to perform inspections, including source data verification. Likewise, the representatives from Sponsor may visit the centers to perform an audit. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported according to the protocol, ICH-GCP, and any applicable regulatory requirements. Principal Investigator, in cooperation with the actual Clinical Investigator, will ensure that the inspectors and auditors will be provided with access to source data and documents.

12 ETHICAL AND REGULATORY REQUIREMENTS

12.1 Compliance with laws and regulations

This study will be conducted in full conformance with the ICH E6 guideline for GCP and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting), in addition with the EU Clinical Trial Directive (2001/20/EC). The protocol will also have been registered in the ClinicalTrials database (www.ClinicalTrials.gov) before inclusion of the first patient.

12.2 ICF (informed consent form)

The definition of informed consent is given in *Paragraph 7.1*.

The ICF will contain separate sections that address any hazards related to the biopsy sampling and how a possible complication may delay the commencement of the treatment, and also the use of samples in the study biobank and of the study-specific MR sequences for exploratory research. Clinical Investigator or a designee will explain to each patient the objectives of the exploratory research. The patient's ICF signature documents his/her agreement to allow specimens to be used for exploratory research.

The consent forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of patient to participate. The final revised IRB/IEC-approved consent forms must be provided to Sponsor for health authority submission purposes.

Patients must be reconsented to the most current version of the consent form (or to a significant new information/findings addendum in accordance with applicable laws and IRB/IEC policy) during their participation in the study. For any updated or revised consent form, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised consent form for continued participation in the study.

A copy of each signed ICF must be provided to the patient. All signed and dated ICF documents must remain in each patient's study file or Investigator Site File and must be available for verification by study monitors at any time.

12.3 Ethics Committee

This protocol, the ICF, any information to be given to the patient, and relevant supporting information have been submitted to the Ethics Committee and have been reviewed and approved according national regulations. This will also be valid for any amendments and/or new versions of the study protocol (amended protocol).

12.4 Confidentiality

Sponsor will maintain confidentiality standards by coding each patient enrolled on the study through assignment of a unique patient identification number. This means that patient names are not included in data sets.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the ICF (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of the Competent Authority, Sponsor, and Monitor.

13 STUDY FUNDING

The study has received funding from the Norwegian Cancer Society (Grant 182496) with associated funding from the University of Oslo. BMS supports the study through the provision of nivolumab at no cost for the investigators.

14 TRIAL INSURANCE

The investigators have insurance coverage for this study through membership of the Drug Liability Association.

15 PUBLICATION POLICY

Upon study completion and finalization of the study report, the results of this study will be submitted for publication and/or posted in a publicly accessible database of clinical study results.

The results of this study will also be submitted to the Competent Authority and the Ethics Committee according to EU and national regulations.

All personnel who have contributed significantly to the planning and performance of the study may be included in the list of authors, according to the Vancouver Protocol: Uniform Requirements for Manuscripts Submitted to Biomedical Journal.

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17 APPENDICES

Appendix 1 – Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1

Please click on links below or copy and paste them into your browser:

http://recist.eortc.org/recist-1-1-2/

http://recist.eortc.org/wp-content/uploads/2015/03/RECISTGuidelines.pdf

http://www.radiologytutor.com/index.php/cases/oncol/139-recist

Appendix 2 – RECIST for immune-modulating therapies (iRECIST)

Comparison of RECIST v1.1 and iRECIST:

	RECIST 1.1	iRECIST
Definitions of measurable and non-measurable disease; numbers and site of target disease	Measurable lesions are ≥10 mm in diameter (≥15 mm for nodal lesions); maximum of five lesions (two per organ); all other disease is considered non-target (must be ≥10 mm in short axis for nodal disease)	No change from RECIST 1.1; however, new lesions are assessed as per RECIST 1.1 but are recorded separately on the case report form (but not included in the sum of lesions for target lesions identified at baseline)
Complete response, partial response, or stable disease	Cannot have met criteria for progression before complete response, partial response, or stable disease	Can have had iUPD (one or more instances), but not iCPD, before iCR, iPR, or iSD
Confirmation of complete response or partial response	Only required for non-randomised trials	As per RECIST 1.1
Confirmation of stable disease	Not required	As per RECIST 1.1
New lesions	Result in progression; recorded but not measured	Results in iUPD but iCPD is only assigned on the basis of this category if at next assessment additional new lesions appear or an increase in size of new lesions is seen (≥5 mm for sum of new lesion target or any increase in new lesion non-target); the appearance of new lesions when none have previously been recorded, can also confirm iCPD
Independent blinded review and central collection of scans	Recommended in some circumstances—eg, in some trials with progression-based endpoints planned for marketing approval	Collection of scans (but not independent review) recommended for all trials
Confirmation of progression	Not required (unless equivocal)	Required
Consideration of clinical status	Not included in assessment	Clinical stability is considered when deciding whether treatment is continued after iUPD

Appendix 3 – Common Terminology Criteria for Adverse Events (CTCAE) version 4.0

Please click on links below or copy and paste them into your browser:

HTTPS://EVS.NCI.NIH.GOV/FTP1/CTCAE/CTCAE_4.03_2010-06-14_QUICKREFERENCE_5X7.PDF

https://www.uptodate.com/contents/common-terminology-criteria-for-adverse-events

Appendix 4 – Eastern Cooperative Oncology Group (ECOG) performance status

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair

Appendix 5 – Management algorithms for adverse events of immuno-oncology agents and regimens

Please refer to the content of the specific document provided by BMS.

Appendix 6 – Management algorithms for adverse events caused by the Nordic FLOX regimen

The below criteria come to use each time a new series of FLOX cycles is commenced (irrespective of study treatment arm).

CTCAE grade	Description	Oxaliplatin	Fluorouracil
Diarrhea, grade 2	Increase of 4-6 stools per day over baseline; moderate increase in stoma output compared to baseline; not interfering with ADL	Interrupt until grade 1, then 100% dose first time, 75% dose second time, 50% dose third time	Interrupt until grade 1, then 100% dose first time, 75% dose second time, 50% dose third time
Diarrhea, grade 3	Increase of 7 or more stools per day over baseline; incontinence; severe increase in stoma output compared to baseline; interfering with ADL	Interrupt until grade 1, then 75% dose first time, 50% dose second time, discontinue third time	Interrupt until grade 1, then 75% dose first time, 50% dose second time, discontinue third time
Diarrhea, grade 4	Life-threatening consequences, urgent intervention indicated	Discontinue	Discontinue
Myelosuppression, grade 2	Neutrophils of 1.0 to less than 1.5, or platelets of 50 to less than 75	Interrupt until grade 1, then 100% dose first time, 75% dose and consider support with granulocyte-colony stimulating factor (*e.g.,* pegfilgrastim) second or subsequent times	Interrupt until grade 1, then 100% dose first time, 75% dose and consider support with granulocyte-colony stimulating factor (*e.g.,* pegfilgrastim) second or subsequent times
Myelosuppression, grade 3	Neutrophils of 0.5 to less than 1.0, or platelets of 25 to less than 50	Interrupt until grade 1, then 75% dose and consider support with granulocyte-colony stimulating factor (*e.g.,* pegfilgrastim) first or subsequent times	Interrupt until grade 1, then 75% dose and consider support with granulocyte-colony stimulating factor (*e.g.,* pegfilgrastim) first or subsequent times
Myelosuppression, grade 4	Neutrophils of less than 0.5, or platelets less than 25	Interrupt until grade 1, then 50% dose and consider support with granulocyte-colony stimulating factor (*e.g.,* pegfilgrastim) first or subsequent times	Interrupt until grade 1, then 50% dose and consider support with granulocyte-colony stimulating factor (*e.g.,* pegfilgrastim) first or subsequent times
Sensory neuropathy, grade 2	Sensory alteration or paresthesia persisting between two oxaliplatin doses with no or only minor improvement, moderate symptoms, limiting instrumental ADL	Interrupt until grade 1, then 75% dose first time, 50% dose second time, discontinue third time	NA
Sensory neuropathy, grade 3	Sensory alteration or paresthesia, severe symptoms, limiting self-care ADL	Discontinue	NA

Units of measurement: neutrophils, $x10^9$/L; platelets, $x10^9$/L.

Abbreviations: ADL, activity of daily life; CTCAE, Common Terminology Criteria for Adverse Events; NA; not applicable.

Appendix 7 – EORTC QLQ-C30 specimen questionnaire

Please click on the link below or copy and paste it into your browser. **A Norwegian version** is available in Investigator Site File.

http://groups.eortc.be/qol/sites/default/files/img/slider/specimen_qlq-c30_english.pdf

Appendix 8 – EORTC QLQ-CIPN20 questionnaire

The form can be requested from justyna.mierzynska@eortc.be. **A Norwegian version** is available in Investigator Site File.

Chemotherapy-induced peripheral neuropathy (CIPN) is a major, potentially dose-limiting side effect of various chemotherapeutic agents. The CIPN20 is a 20-item quality of life questionnaire, which has been developed to elicit patients' experience of symptoms and functional limitations related to CIPN. The CIPN20 has 3 subscales: a sensory, a motor, and an autonomic subscale. In combination with the more classical, physician-based clinical rating scales, the CIPN20 should yield a more complete picture of the nature, frequency, and severity of CIPN in a wide range of oncology patient populations.

Appendix 9 – EQ-5D-5L questionnaire user guide

Please click on the link below or copy and paste it into your browser. **A Norwegian version of the questionnaire** is available in Investigator Site File.

https://euroqol.org/wp-content/uploads/2016/09/EQ-5D-5L_UserGuide_2015.pdf

Appendix 10 – Council for International Organizations of Medical Sciences (CIOMS) Suspect Adverse Reaction Report form

Please click on the link below or copy and paste it into your browser:

http://www.basg.gv.at/fileadmin/_migrated/content_uploads/CIOMS_form.pdf