Evaluating the efficacy and safety of neoadjuvant pembrolizumab in patients with stage I–III MMR-deficient colon cancer: a national, multicentre, prospective, single-arm, phase II study protocol

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ABSTRACT

Introduction Within the last two decades, major advances have been made in the surgical approach for patients with colorectal cancer. However, to this day we face considerable challenges in reducing surgery-related complications and improving long-term oncological outcomes. Unprecedented response rates have been achieved in studies investigating immunotherapy in patients with mismatch repair deficient (dMMR) colorectal cancer. This has raised the question of whether neoadjuvant immunotherapy may change the standard of care for localised dMMR colon cancer and pave the way for organ-sparing treatment.

Methods and analysis This is an investigator-initiated, multicentre, prospective, single-arm, phase II study in patients with stage I–II dMMR colon cancer scheduled for intended curative surgery. Eighty-five patients will be treated with one dose of pembrolizumab (4 mg/kg) and within 5 weeks will undergo a re-evaluation with an endoscopy and a CT scan— to assess tumour response— before resection of the tumour. The primary endpoint is the number of patients with pathological complete response, and secondary endpoints include safety (number and severity of adverse events) and postoperative surgical complications. In addition, we aspire to identify predictive biomarkers that can point out patients that achieve pathological complete response.

Ethics and dissemination The Regional Committee for Health Research and Ethics and the Danish Medicines Agency have approved this study. The study will be performed according to the Helsinki II declaration. Written informed consent will be obtained from all participants. The results of the study will be submitted to peer-reviewed journals for publication and presented at international congresses.

Trial registration number NCT05662527.

INTRODUCTION

Within the last two decades, the implementation of enhanced recovery protocols after surgery and minimally invasive surgical techniques have resulted in a dramatic reduction in short-term morbidity and mortality for patients with colorectal cancer (CRC). However, despite these developments, postoperative complications, reduced long-term survival as well as the risk of recurrence are still an immense concern.

The optimal length of treatment interval, the interval from the date of diagnosis of cancer until the date of the curative intended surgery, is suggested to be up to 7 weeks based on clinical guidelines and recent literature. Oncological treatments can be undertaken in this period to improve the long-term...
Immunotherapy, in particular immune checkpoint inhibitors (ICIs), has been an immense breakthrough leading to oncological outcomes in several cancers. ICIs either target receptors on immune cells, in particular cytotoxic CD8 T cells, including programmed cell death protein 1 (PD-1) and cytotoxic T lymphocyte antigen 4 (CTLA-4) or their ligands located on tumour or immune cells. The ICIs, such as the anti-PD-1 pembrolizumab, revitalise dysfunctional immune cells to enhance the anticancer immune response. For the majority of patients with CRC, ICIs show limited efficacy, however, for the subgroup of patients with dMMR tumours promising results have been found. Patients with dMMR CRC account for approximately 15% of cases, with a higher prevalence in localised compared with metastatic CRC (4–13%). Finally, dMMR status is more common in CC (15–20%) compared with rectal cancer (<5%). In the Neoadjuvant Immune Checkpoint Inhibition and Novel Combinations in Early-Stage Colon Cancer (NICHE) and NICHE-2 studies, patients with localised (stage I–III) dMMR CC received a single dose of ipilimumab (anti-CTLA-4) and two doses of nivolumab (anti-PD-1) before surgery. Pathological complete responses (pCR) were observed in 69% (22/32) and 67% (72/107) of the patients, in the two studies, respectively. Further, at a median 25 months of follow-up, none of the patients had disease recurrence in the NICHE study.

In patients with dMMR stage II–III rectal cancer, a study recently investigated the efficacy of dostarlimab (anti-PD-1). Twelve patients had completed 6 months anti-PD-1 treatment with at least 6 months of follow-up and all 12 patients had a clinical complete response. These unprecedented response rates have raised the question of whether neoadjuvant immunotherapy may pave the path for organ-sparing treatment in localised dMMR CC. Supported by higher response rates of immunotherapy seen in localised compared with metastatic dMMR CRC. However, as the correlation between preoperative CT scans and response to immunotherapy has been shown generally to underestimate treatment response. Developing methods for predicting response to immunotherapy is one of the challenges in developing a potential organ-sparing approach. In addition, minimising the risk of adverse events is of importance in the neoadjuvant setting, as adverse events may delay surgery. One potential solution is a monotherapy approach, considering monotherapy is related to a lower rate of adverse events and to still maintain efficacy compared with combination therapy.

The aim of this study is to evaluate the efficacy and safety of neoadjuvant treatment with pembrolizumab before colonic resection in patients with stage I–III dMMR CC. This study will further investigate possible predictive biomarkers for identification of patients who achieve pCR.

### METHODS AND ANALYSIS

#### Study design and population

The study is designed as an investigator-initiated, multicentre, prospective, single-arm, phase II study in patients with stage I–III dMMR CC scheduled for intended curative surgery to determine the efficacy and safety of pembrolizumab in the neoadjuvant setting. The protocol adheres to the SPIRIT (Standard Protocol Items: Recommendations for Interventionsal Trials) statement recommendations. Patients will receive one dose of pembrolizumab (dosage of 4 mg/kg, maximum of 400 mg) following diagnosis. Tumour restaging will be performed 3–5 weeks later to assess tumour response followed by standard surgery for resection of the tumour. Thus, surgery will be performed within 3–5 weeks of the pembrolizumab treatment. The patients will undergo follow-up as per the standard Danish guidelines with CT scans of the chest.
and abdomen at 1 and 3 years after surgery (see figure 1). The study was started in February 2023 with an estimated enrolment period of 2–3 years.

Feasibility
Assessing MMR status at the time of diagnosis of CC is a routine procedure in Denmark. Patients with stage I–III dMMR tumours account for approximately 545 patients (18.2%) annually.29 To ensure the inclusion of the necessary number of patients, agreements have been made with 10 Danish hospital centres to participate: Aalborg University Hospital, Aarhus University Hospital, Bispebjerg Hospital, Herlev and Gentofte University Hospital, Horsens Regional Hospital, Odense University Hospital, Randers Regional Hospital, Rigshospitalet, Vejle Hospital and Zealand University Hospital. All centres cover surgical and/or oncological services. The participating centres routinely treat patients with CC.

Sample size
The primary endpoint of the study is the number of patients with pCR (see box 1 for list of endpoints), which is the basis for the sample size calculations. The sample size is based on Simon’s two-stage minimax design.30 This design will ensure an early study termination if there is insufficient efficacy. A standard pathological response evaluation of the resected specimen will be done after surgery. A pCR rate of less than 20% after pembrolizumab treatment is not clinically relevant. Assuming a significance level at 0.05 (α=0.05) and a power at 90% (β=0.10) 42 patients should be included in the first part plus another 35 patients in the second part of the study. If 6 out of the first 42 patients achieve pCR, a pCR rate of at least 20% cannot be excluded and the study will continue until a total of 77 patients have been included. If 21 out of 77 patients achieve pCR, a pCR rate of 35% cannot be excluded, and it will be concluded that the treatment is effective enough to continue with future studies. Anticipating a dropout rate of 10% we will include a total of 85 patients.

Patient enrolment procedure
Each potential patient must be given a patient information sheet and full written informed consent must be obtained from the patient before registration on to the trial (see online supplemental material 1 for participant consent form). Potential patients will be screened based on information from patient records. If eligible and willing to participate, then enrolled in the clinical trial on the basis of the eligibility criteria (see box 2) by a medical doctor at one of the participating hospital departments. Only patients fulfilling all inclusion criteria and not fulfilling any exclusion criteria can be registered.

Interventions
Patients will receive pembrolizumab (4 mg/kg, maximum of 400 mg) as an intravenous infusion administered over 30 min for one cycle before surgery. The colonic resection is a standard surgical procedure performed under general anaesthesia. The procedure consists of a resection of the tumour-bearing part of the bowel and a healthy part of the colon on either side of the tumour, together with the mesenteric vessels and local lymph nodes. The colonic resection will be scheduled 3 weeks (+14 days) after the pembrolizumab treatment (see table 1). In case of severe toxicity related to pembrolizumab, surgery may be postponed until recovery or resolving to grade 1.

Data collection, management and analysis
Radiological and endoscopic assessments
CT scans of the thorax and abdomen will be done before and after immunotherapy and evaluated by a multidisciplinary team and a centralised comity of radiologists according to the Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 criteria as well as clinical TNM staging,31 to assess if treatment response can be predicted. Pictures and videos of the tumour will be obtained from colonoscopies before and after immunotherapy. These will be assessed by a systematic approach including the Paris Classification of Superficial Neoplastic Lesions and the narrow-band imaging international colorectal endoscopic (NICE) classification.32 33

Pathological assessments
The resected tumour specimen will be collected during surgery and evaluated by using the Mandard tumour regression grading system.34 Further, a novel quantitative estimate of the percentage of residual viable tumour in the macroscopically identified tumour bed will be determined by an objective, unbiased, digital pathology algorithm developed in collaboration with Visiopharm.

Box 1 Study endpoints

Primary endpoint:
⇒ Number of patients with pathological complete response (pCR) evaluated according to the Mandard tumour regression grading system.

Secondary endpoints:
⇒ Safety and tolerability of pembrolizumab administered before surgery. Safety will be assessed by quantifying the toxicities and grades experienced by subjects who have received pembrolizumab using Common Terminology Criteria for Adverse Events, V.5.0. Further, delay in surgery defined as surgery performed more than 5 weeks after dose of pembrolizumab will be assessed.
⇒ Number of postoperative surgical complications determined by the Clavien-Dindo classification system.
⇒ Assessment of potential predictive biomarker by investigating immunological markers across pretreatment and post-treatment biopsies and sequential blood samples.
⇒ Treatment response evaluated by methylated circulating cell-free DNA (cfDNA) specific for colon cancer analysed across sequential blood samples using the TriMeth test.

Exploratory endpoints:
⇒ Tumour histology, gene expression, cfDNA, T-cell receptor repertoire, CT scans, endoscopic photo documentation and patient journals will be analysed with the purpose of identifying biomarkers for predicting patients with pCR.
Box 2 Inclusion and exclusion criteria

**Inclusion criteria:**
1. Histologically confirmed localised stage cT1N0M0 to cT4N2M0 (stage I-IIII) deficient mismatch repair colon carcinoma.
2. Indication for elective curative intended surgery without neoadjuvant chemotherapy.
3. Age of ≥18 years.
4. Written informed consent.
5. Eastern Cooperative Oncology Group performance status of 0 or 1.
6. Adequate bone marrow function defined as:
   - Haemoglobin ≥8.2 mmol/L or ≥100 g/L.
   - Absolute neutrophil count ≥1.5×10⁹/L.
   - Platelet count ≥100×10⁹/L.
7. Adequate kidney function defined as:
   - Glomerular filtration rate ≥60 mL/min or creatinine ≤1.5× upper limit of normal (ULN).
8. Adequate liver function defined as:
   - Total bilirubin: ≤1.5 × ULN.
   - Alanine aminotransferase: ≤2.5 × ULN.
   - Alkaline phosphatase: ≤2.5 × ULN.
9. Follow the conditions regarding fertility, pregnancy and lactation:
   - Female and male participants of reproductive potential (PORP) must agree to avoid becoming pregnant or impregnating a partner, respectively, while receiving pembrolizumab and for 120 days after the dose.
   - PORPs must use, or have their partner use, an acceptable method of contraception, for example, intrauterine device, contraceptive rod implanted into the skin or hormonal contraceptive and male condom during heterosexual activity, while receiving pembrolizumab and for 120 days after the dose.
   - Women of reproductive potential must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L human chorionic gonadotropin) within 72 hours prior to receiving pembrolizumab.
   - Women must not be breast feeding.

**Exclusion criteria:**
1. Any serious or uncontrolled medical disorder that, in the opinion of the investigator or treating physician, may increase the risk associated with study participation, impair the ability of the subject to receive protocol therapy or interfere with the interpretation of study results.
2. Autoimmune disorders (except thyroiditis with replacement therapy, type 1 diabetes mellitus and vitiligo and psoriasis not requiring systemic treatment).
3. Prior treatment with immune checkpoint inhibitors or any other antibody/drug specifically targeting the T-cell co-stimulation or checkpoint pathways.
4. A known history of HIV, active chronic, or acute hepatitis B or hepatitis C.
5. A condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids and adrenal replacement doses >10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.
6. Prior participation in another study with an investigational medicinal product.
7. Live vaccines within 30 days prior to pembrolizumab study treatment. Seasonal influenza vaccines for injection are allowed.

**Assessment of the systemic response**
Sequential blood samples will be obtained at three time points: before and after pembrolizumab and after surgery. The blood samples will be analysed by gene expression analyses on an mRNA level and by flow cytometry. Hypermethylation of cell-free DNA is highly tumour-specific, thus, the validated circulating tumour DNA (ctDNA) test—the TriMeth test—will be used to identify three CC specific DNA methylation markers. The samples will be scored as ctDNA positive if two out of three TriMeth markers show any signal. The test is validated and has achieved high sensitivity for all stages of CRC (80% for stage I, 85% for stage II and 89% for stage III) and efficiently discriminate healthy individuals from patients with localised CRC with a specificity of 99% in independent cohorts.35

**T-cell receptor assessments**
T-cell receptor sequencing (TCR-Seq) will be performed to investigate the role of the adaptive immune system in mediating the effect of pembrolizumab. We will do TCR-Seq on DNA and RNA extracted from tumour tissue and blood samples to (1) determine the TCR profiles in the tissues, (2) establish the TCR profiles in the blood, (3) monitor changes in the TCR repertoire over time and in response to treatment and (4) compare the profiles of blood and tissue. For TCR-Seq the AmpliSeq for Illumina Immune Repertoire Plus, TCR beta Panel or similar will be used. Further, RNA-Seq will be used to investigate TCR clonality. Data will be generated on the Illumina NovaSeq platform or similar.

**Biobank**
All samples (biopsies, resected tumour tissue and blood samples) will be collected and stored in a biobank created for this study, located at the Research Lab, Surgical Department at Zealand University Hospital, and in accordance with Danish legislation and the Danish Data Protection Agency. Samples will be collected locally at each site, and sent to the (Hørsholm, Denmark). A minimum of six tumour biopsies will be collected during a colonoscopy procedure before and after immunotherapy. The biopsies will be examined by immunohistochemistry analysis of markers including CD3, CD8 and PD-L1, to characterise and quantify the intratumoural and peritumoural inflammatory infiltrates. Gene expression analyses by messenger RNA (mRNA) will be performed to quantify the expression of genes central to the tumour microenvironment and immune evasion of cancer among others. On a subgroup of patients, gene expression analyses on a spatial level using mRNA and protein will also be done. Finally, single-cell sequencing will be applied to identify cell-type specific biomarkers.

**Box 2 Continued**
8. A history of allergy to study drug components or a history of severe hypersensitivity reaction to any monoclonal antibody.
biobank from the respective study sites in bulk once or twice during the course of the study. All biobanked blood samples and biopsies will be retained (pseudo anonymised) and stored until analysis. The project is approved by the Danish Data Protection Agency and all formal requirements and maintenance of the biobank will be performed accordingly.

**Registration of adverse events**

Adverse events/reactions are recorded from the day of treatment with pembrolizumab until 4 weeks after surgery. All adverse events/reactions will be described in medical terminology in the patient’s file and recorded in the electronic case report form (eCRF) by the investigator. Investigators must immediately and within 24 hours report a new serious adverse event to sponsor, except planned hospitalisations in relation to the cancer treatment and hospitalisations for reasons unrelated to the cancer or its treatment.

**Data management**

All information about participants is subjected to ‘General Data Protection Regulation’ and ‘Data Protection Act’ as well as the approval from the Danish Data Protection Agency. Authorised representatives from the Local Ethical Committee are granted inspection of documents related to the study if needed. All information will be treated with strict confidentiality and stored as confidential material according to the Danish legislation. The data will be handled and stored in specifically developed eCRFs to promote data quality and later transferred into a predesigned study database approved for the purpose. Data includes patient records and adverse events registration. Patients that have been withdrawn from the study will continue to be tracked and assessed (unless the patient explicitly declines). The investigators will retain investigational records, eCRF and source documentation for the time period required by the regulatory authorities.

**Statistics**

**Interim analysis**

An interim analysis will be performed when the first 42 patients have undergone treatment. The analysis will include safety (eg, postponed surgery, adverse events, anastomosis leakage) and efficacy endpoints (ie, pCR).
The statistical considerations will be identical as to the final analyses.

Final analyses
After all participants have undergone surgery, the final analyses will be performed. The analyses will begin with an exploration of the data to check for anomalies that might require data queries to be raised. Data will be presented as mean (SD and 95% confidence limits), median (IQR) or frequencies and percentages, as appropriate. The level of significance will be set at p<0.05. Data will be analysed via parametric or non-parametric statistics depending on their distribution. Missing values, dropouts, selection or exclusion of observations and variables in the statistical analysis will be described carefully. A principal analysis will be performed according to the intention-to-treat principle. A per-protocol analysis will also be performed.

Statistical analysis for transcriptomic data
Multiplex protein and RNA expression data will be quality controlled using integrated positive and negative control probes. Data will be analysed using supervised and unsupervised strategies. The supervised strategy comprises differential gene expression between complete, major and non-responders using linear mixed models, parametric or non-parametric tests where appropriate. P values and false discovery rates will be controlled for multiple comparisons when necessary, by the Benjamini-Hochberg method.36 Gene expression will also be analysed at a signature level using gene set enrichment analysis based on key pathways identified through the Kyoto Encyclopaedia of Genes and Genomes37 or similar. All other data will be analysed using R or Stata.

Patient and public involvement
Patients were involved in the preparation of the subject information document. The public has been informed of the study through public media. Further, the protocol has been presented to the Scientific Forum to be classified as a national Danish Colorectal Cancer Group study. All included patients will at enrolment be offered to receive information about the study results when published.

Ethics and dissemination
This protocol has been approved by the Regional Committee for Health Research and Ethics (SJ-966), by the Danish Medicines Agency (EudraCT 2021-006046-12) and by the Danish Data Protection Agency (REG-155–2021). The ethics approval covers all participating sites. The study will be conducted according to the principles of the Helsinki II Declaration. Protocol amendments will be submitted to the competent authority for written approval. All participants in this study have to give their consent concerning participation in the study without any explanation. The participants of the current study may not directly benefit from the participation. However, the knowledge gained from the study will have multifarious clinical implications moving forward. The study will provide essential information about the efficacy and safety of immunotherapy in patients with stage I–III dMMR CC and possibly identify predictive biomarkers for predicting patients with pCR.

Dissemination policy
The results of this study will be published in peer-review journals regardless of the results coming out negative, positive or inconclusive following the Vancouver declaration. Efficacy and safety results from the first part of the study (42 patients) will be published during the study period followed by the publication of efficacy, safety and translational outcomes when data is available for both the first and second part of the study. In addition, the study has been registered at www.clinicaltrials.gov which will be updated according to the study progress, including publishing of results after the study is completed. In the event that part of the analysis is changed from the statistical analysis plan, these changes will be described and justified. Publications based on the long-term survival analyses will be undertaken when sufficient follow-up data is available.

Data sharing
In accordance with good academic practice, the study data (health data and genomic data) is planned to be transferred in anonymised form to the secure database European Genome-Phenome Archive (EGA).38 This will happen after the study has been completed. The purpose is to enable sharing of the data with other research groups for future research, inside and outside of Denmark. In all cases, data access decisions will be made by the study protocol committee. Data sharing will be conducted in accordance with the European data protection regulations, including The Danish Data Protection Act and the General Data Protection Regulation. The EGA is part of the European life-sciences Infrastructure for biological Information (ELIXIR) research infrastructure, which is partly funded by the European Commission.39

DISCUSSION
Remarkable efficacy of immunotherapy has been shown in dMMR CRC in recent studies21 22 24 25, raising the question of whether immunotherapy may pave the path for organ-sparing treatment in localised dMMR CC. The first knowledge gap to be resolved on the way towards organ-sparing treatment is the evidence on the pCR rate and safety of ICIs in the patient population. The second knowledge gap concerns duration of treatment and if a single treatment suffice. The third gap revolves around predicting and assessing patients who achieve a pCR. Gaps this study aims to determine. Looking forward, if more than 27% of the patients do achieve a pCR, a
subsequent large scale study will be conducted to investigate pembrolizumab treatment followed by a watchful waiting approach. The biomarkers investigated in the current study will be employed in the subsequent study to allocate patients with a predicted pCR to a watchful waiting arm. Promising results in the subsequent study may pave the way for implementing watchful waiting to patients with dMMR CC in the years to come.

The study design presents some limitations. First, the single-arm design does not allow for comparison of no treatment, however, it is very unlikely to see tumour regression without neoadjuvant treatment, which is why a randomised controlled trial was not conducted. Second, the single-arm design limits the generalisability to the general patient population. Third, the study may be subject to survival bias, as only patients that survive until study evaluation can be included in the study. However, the risk of this is deemed minimal due to patients receiving urgent cancer patient pathways. Fourth, identifying improved biomarkers for a subsequent investigation of a watchful waiting regimen is ambitious and challenging. Employing several novel analyses in combination with clinical assessments may overcome this challenge.

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Contributors IG, CQ, PP, TFJ and LST conceived and designed the study, IG, CQ and TFJ drafted the manuscript. IG, CQ, PP and TFJ drafted the statistical plan. PP and CQ calculated the sample size. CQ is the sponsor and IG is the primary investigator of the study. IG, CQ, PP, TFJ and LST discussed the plan of the study, revised the manuscript for important intellectual content, read and approved the final manuscript.

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Competing interests None declared.

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