Pembrolizumab for locally advanced, irresectable, non-metastatic dMMR colorectal cancers. The PUMA study.

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Gastrointestinal neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON51364

Source
ToetsingOnline

Brief title
PUMA

Condition

- Gastrointestinal neoplasms malignant and unspecified

Synonym
colorectal cancer

Research involving
Human

Sponsors and support

Primary sponsor: Antoni van Leeuwenhoek Ziekenhuis
Source(s) of monetary or material Support: medicatie via MSD,Merck Sharp & Dohme (MSD)

Intervention

Keyword: colorectal cancer, Deficient mismatch repair system, Pembrolizumab

Outcome measures

Primary outcome

Objective Response Rate (ORR) according to RECIST 1.1 and iRECIST criteria.

Secondary outcome

• To assess the major pathological response (MPR, <=10% viable tumor rest) in patients undergoing surgery

• To find biomarkers and evaluation strategies able to accurately assess complete and near-complete responses in order to pursue organ-sparing treatment (omission of surgery) in this patient population,

o Post-treatment CT-scans

o ctDNA analysis

• To possibly perform translational analyses:

o RNA sequencing and inflammatory signatures to validate current findings and identify predictors of response;

o Analysis of immune cell infiltration and differences between responders and non-responders

o Immunogenic mutational load by tumor tissue DNA WES.

• Date of relapse, as determined by disease recurrence or disease-related death during follow-up after surgery.

• Association between microbiota composition and treatment outcomes and the effect of neoadjuvant pembrolizumab on the gut microbiota composition

Study description

Background summary

Currently, patients with irresectable dMMR tumors, who are neither potentially eligible for the NICHE study, nor for 1st line treatment with pembrolizumab, receive standard of care (induction) chemotherapy with low response rates, whereas immune checkpoint inhibition (ICI) is expected to be highly effective in a much larger proportion of patients, leading to more cure, less surgery and limited toxicity. This is a clinical unmet need, for which data should be generated. In turn, these data could lead to the extension of the label for pembrolizumab in dMMR colon cancers.

Study objective

This study has been transitioned to CTIS with ID 2023-509707-32-00 check the CTIS register for the current data.

To investigate whether the response rate of pembrolizumab exceeds the response rate of the historic control in locally advanced, irresectable, non-metastatic dMMR colorectal cancer.

Study design

Single-center, single arm, open-label, phase II study. The efficacy of pembrolizumab in patients with locally advanced, irresectable dMMR colorectal cancer will be assessed in 25 patients. Treatment consists of pembrolizumab 200 mg intravenously for a maximum duration of 2 years, or until the tumor becomes resectable.

Intervention

Treatment will consist of pembrolizumab 200 mg intravenously every three weeks for a maximum duration of 2 years, or until the tumor becomes resectable.

Study burden and risks

Subjects within this trial are at risk of developing immune-related adverse events (irAEs). Algorithms have been developed to treat patients developing pembrolizumab related irAEs. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. Moreover, the Keynote-177 trial, which included patients with dMMR metastatic colorectal cancer, demonstrated that pembrolizumab monotherapy led to fewer treatment-related adverse events and significantly longer progression-free

survival than first-line chemotherapy.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

• Signed written informed consent;
• Patients at least 18 years of age;
• Locally advanced, irresectable adenocarcinoma of the colon or rectum, not amenable to surgery, or for which induction therapy is required to reconsider surgery, or where free margins can only be obtained by major extension of the surgical procedure, as defined by one of the following:
o Invasion of the duodenum, stomach, spleen or pancreatic head, for which major extension of the surgical procedure would be required to obtain free margins, and/or for which the chances of positive resection margins are high

o Invasion or encasement of major blood vessels (superior mesenteric vessels, iliac vessels, portal vein)
o Invasion or encasement of the ureter
• Histologically or cytologically confirmed microsatellite instability-high (MSI-H) or MMR-deficient (dMMR) status
• No signs of distant metastases on CT-scan and physical examination; patients may not be eligible for first-line treatment with pembrolizumab according to SoC
• Patients may not be eligible for standard of care first-line pembrolizumab for metastatic disease
• Patients may not be potentially eligible for the NICHE study: patients with primarily resectable disease, for which relatively minor extension of the procedure is required to acieve free margins, such as but not limited to a small bowel segment, abdominal wall
• ECOG performance status of 0 or 1. Evaluation of ECOG is to be performed within 7 days prior to the first dose of study intervention;
• Screening laboratory tests must meet the criteria as defined in Table 1 and should be obtained within 10 days prior to the start of study intervention: Absolute neutrophil count (ANC) >=1500/µL; Platelets >=100 000/µL; Hemoglobin >=9.0 g/dL or >=5.6 mmol/L, Creatinine OR Measured or calculated creatinine clearance (GFR can also be used in place of creatinine or CrCl) <=1.5 × ULN OR >=30 mL/min for participant with creatinine levels >1.5 × institutional ULN; Total bilirubin <=1.5 ×ULN OR direct bilirubin <=ULN for participants with total bilirubin levels >1.5 × ULN; AST (SGOT) and ALT (SGPT) <=2.5 × ULN; International normalized ratio (INR) OR prothrombin time (PT) <=1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants; Activated partial thromboplastin time (aPTT) <=1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants;
• A male participant must agree to use a contraception as detailed in Appendix 2 of this protocol during the treatment period and for at least 200 days (90 days plus the time required for pembrolizumab to undergo five half-lives) after the last dose of study treatment and refrain from donating sperm during this period.
• Women of childbearing potential must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 72 hours prior to registration (see appendix 2). If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required;
• A female participant is eligible to participate if she is not pregnant (see appendix 2), not breastfeeding, and at least one of the following conditions applies:
o Not a woman of childbearing potential (WOCBP) as defined in appendix 2 OR
o A WOCBP who agrees to follow the contraceptive guidance in appendix 2 during the treatment period and for at least 120 days (30 days plus the time required for pembrolizmab to undergo five half lives) after the last dose of study

treatment.
• CT-scan must be performed within 28 days prior to registration.

Exclusion criteria

• Previous treatment with immune checkpoint inhibitors targeting including but not limited to CTLA-4, PD-1 or PD-L1;
• Previous treatment with chemotherapy for the disease under study;
• Prior radiotherapy for the disease under study;
• Prior radiotherapy for other indications than the disease under study within 2 weeks of start of study intervention. Participants must have recovered from al radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis.
• History of (non-infectious) pneumonitis/interstitial lung disease that required steroids or has current pneumonitis/interstitial lung disease;
• Allergies and Adverse Drug Reaction
o History of allergy to study drug components
o History of severe hypersensitivity reaction to any monoclonal antibody
• Intercurrent illnesses, including but not limited to infections, unstable angina pectoris;
• Known history of Human Immunodeficiency Virus (HIV) infection and known history of Hepatitis B (defined as Hepatitis B surface antigen [HBsAg] reactive) or known active Hepatitis C virus (defined as HCV RNA [qualitative] is detected) infection.
• Underlying medical conditions that, in the investigator*s opinion, will make the administration of the study drug hazardous or obscure the interpretation of toxicity determination of adverse events;
• Active autoimmune disease requiring systemic treatment in the past 2 years;, or other medical conditions requiring systemic steroid or immunosuppressive medications, Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment and is allowed.
• Diagnosis of immunodeficiency or conditions 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;
• Live vaccines in the 4 weeks prior to inclusion;
• History of uncontrolled medical or psychiatric illness;
• Psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule;
• Current pregnancy or breastfeeding;
• Active malignancies other than disease under study within 3 years prior to inclusion, except for malignancies with a negligible recurrence rate (e.g. <10%

in 5 years);
• Allogenic tissue/solid organ transplant.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	22-12-2022
Enrollment:	25
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Keytruda
Generic name:	pembrolizumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	23-08-2022
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	25-10-2022

Application type:	First submission
Review commission:	METC NedMec

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EU-CTR	CTIS2023-509707-32-00
EudraCT	EUCTR2021-005731-23-NL
CCMO	NL79505.031.22