A Phase 2, Single-Arm, Open-Label Study with Dostarlimab Monotherapy in Participants with Untreated Stage II/III dMMR/MSI-H Locally Advanced Rectal Cancer

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This study has been transitioned to CTIS with ID 2023-509583-22-00 check the CTIS register for the current data. Primary objective:To estimate the efficacy of dostarlimab in participants with Stage II/III (locally advanced) dMMR/MSI-H rectal cancer...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Malignant and unspecified neoplasms gastrointestinal NEC
Study type	Interventional

Summary

ID

NL-OMON56158

Source
ToetsingOnline

Brief title
219369

Condition

- Malignant and unspecified neoplasms gastrointestinal NEC

Synonym
rectal cancer

Research involving
Human

Sponsors and support

Primary sponsor: GlaxoSmithKline
Source(s) of monetary or material Support: GlaxoSmithKline B.V.

Intervention

Keyword: Dostarlimab, Rectal cancer

Outcome measures

Primary outcome

cCR12 (complete clinical response) as assessed by ICR (independent central review), defined as maintenance of cCR for 12 months. The 12-month period starts from the first disease assessment after last dose of study intervention that demonstrates cCR by ICR.

Secondary outcome

• cCR24 as assessed by ICR, defined as maintenance of cCR for 24 months. The 24-month period starts from the first disease assessment after last dose of study intervention that demonstrates cCR by ICR.

• cCR36 as assessed by ICR, defined as maintenance of cCR for 36 months. The 36-month period starts from the first disease assessment after last dose of study intervention that demonstrates cCR by ICR.

• EFS3 as assessed by investigator assessment, defined as remaining alive and free of 1) disease progression precluding surgery, 2) local recurrence, and 3) distant recurrence, as assessed by investigator at 3 years from the first dose of study intervention.

• EFS by investigator assessment defined as time from the date of first dose of study intervention to any of the following events: 1) progression of disease

that precludes surgery, 2) local recurrence, 3) distant recurrence (all as assessed by the investigator), or 4) death due to any cause

• cCR12 by investigator assessment

• cCR24 by investigator assessment

• cCR36 by investigator assessment

• ORR by an ICR, defined as achieving a PR, nCR, or cCR at PIDA or at least 4 weeks but no longer than 8 weeks after PIDA for participants with nCR or iCR (PIDA 2)

• ORR at PIDA by investigator assessment

• Organ preservation rate at 3 years, defined as not undergoing TME, either as primary management or for local recurrence, or who did not have a permanent colostomy created, at any time up to 3 years

• DSS, Disease-Specific Survival, defined as time from the date of first dose of study intervention to death due to disease under study

• DSS5, defined as not dying due to disease under study at 5 years from the first dose of study intervention

• OS, defined as time from first dose of study intervention to death from any cause

• OS5, defined as being alive at 5 years from first dose of study intervention

• Frequency and severity of AEs, SAEs, irAEs, and AEs leading to death or discontinuation of study intervention

• Serum concentrations and PK parameters (C-EOI and Ctrough) for dostarlimab

• Incidence of ADA against dostarlimab

Study description

Background summary

The widely accepted standard of care SOC in the United States and Europe for locally advanced rectal cancer is neoadjuvant therapy followed by surgery and adjuvant chemotherapy. However, there is an evolving body of literature supporting treatment with both concurrent chemoradiotherapy and chemotherapy in the neoadjuvant setting.
Unfortunately, chemo- and radiotherapy for locally advanced rectal cancer results in significant morbidity for patients, including bowel, urinary, and sexual dysfunction; secondary malignancy; infertility; and substantially impaired quality of life.
Results from clinical studies in various tumor types have demonstrated that anti-PD-1 antibodies, including dostarlimab, are effective in metastatic dMMR tumors regardless of tissue of origin.
Studies of immunotherapy in early-stage dMMR/MSI-H colon cancer provide further support to the use of immunotherapy in this population.
The purpose of this study is to investigate dostarlimab monotherapy in participants with locally advanced mismatch-repair deficient (dMMR)/microsatellite instability-high (MSI H) rectal cancer who have received no prior treatment.

Study objective

This study has been transitioned to CTIS with ID 2023-509583-22-00 check the CTIS register for the current data.

Primary objective:
To estimate the efficacy of dostarlimab in participants with Stage II/III (locally advanced) dMMR/MSI-H rectal cancer that has not been previously treated

Secondary Objectives:
- To further estimate the efficacy of dostarlimab in participants with Stage II/III (locally advanced) dMMR/MSI-H rectal cancer that has not been previously treated
- To assess the safety and tolerability of dostarlimab in participants with Stage II/III (locally advanced), dMMR/MSI-H rectal cancer that has not been previously treated
- To describe the PK of dostarlimab in participants with Stage II/III (locally advanced), dMMR/MSI-H rectal cancer that has not been previously treated
- To determine the immunogenicity of dostarlimab in participants with Stage II/III (locally advanced), dMMR/MSI-H rectal cancer that has not been previously treated

Study design

All participants will complete a Screening Period of up to 28 days to assess eligibility. Eligible participants who have pathologically confirmed, previously untreated locally advanced rectal cancer that is dMMR/MSI-H (as assessed by local testing) will enroll in the Intervention Period and be treated with dostarlimab 500 mg intravenously every 3 weeks for 9 cycles, although study intervention can be discontinued early in the event of disease progression or intolerable toxicity. Pharmacokinetic and immunogenicity samples will be obtained from all participants at certain time points. Safety evaluation will include collection of treatment-emergent adverse events, clinical laboratory assessments, electrocardiograms, Eastern Cooperative Oncology Group (ECOG) performance status, physical examinations, concomitant medications, and vital signs.
At any point during study intervention administration, if the participant has evidence of disease progression, they will be transitioned to standard of care therapy, which will be selected at the investigator*s discretion. Details of the selected subsequent anticancer therapy, response, and survival outcomes of these participants will be collected. Any participants achieving complete clinical response prior to the end of the Intervention Period will continue to receive study intervention .
Following completion of the Intervention Period, participants will undergo the post intervention disease assessment, including endoscopy, rectal MRI, and CT CAP. These assessments will be reviewed to determine clinical response. Treatment decisions will be made based upon the investigator*s assessment of clinical response.
If the participant meets criteria for clinical response, they will begin the non-operative management period. If the participant has any response less than a clinical response, they will proceed to standard of care therapy.

Intervention

Dostarlimab 500 mg intravenously every 3 weeks for 9 cycles

Study burden and risks

These side effects are considered very common in patients who took dostarlimab (may affect more than 1 in 10 people):
• Decrease in the number of red blood cells that carry oxygen. Low red blood cells count may make you feel tired or short of breath and symptoms may require a blood transfusion (Anaemia)
• Underactive thyroid gland (Hypothyroidism)
• Feeling sick to the stomach (Nausea)
• Vomiting
• Frequent watery stools (Diarrhoea)
• Itchy skin (Pruritus)

• Rash
• Fever (Pyrexia)
• Increased levels of substances in the blood produced by the liver which may be a sign of liver injury (AST increased; ALT increased) (Transaminases increased)

These side effects are considered common in patients who took dostarlimab (may affect up to 1 in 10 people):
• Decreased production of adrenal hormones resulting in possible weakness and/or low blood pressure (Adrenal insufficiency)
• Overactive thyroid gland (Hyperthyroidism)
• Inflammation of the lungs which can cause shortness of breath and difficulty breathing (Pneumonitis)
• Inflammation of the pancreas causing pain in the upper abdomen. This could become severe and cause nausea and vomiting, fever and rapid heart rate (Pancreatitis)
• Inflammation of the colon that can cause stomach pain or diarrhoea (Colitis)
• Muscle pain (Myalgia)
• Chills

These side effects are considered uncommon in patients who took dostarlimab (may affect up to 1 in 100 people):
• Destruction of red blood cells which can cause tiredness, dizziness, yellow skin or fast heart rate (Autoimmune haemolytic anaemia)
• Inflammation of the thyroid gland (Thyroiditis)
• Pituitary gland inflammation (Hypophysitis)
• Severe high blood sugar due to uncontrolled diabetes (Diabetic Ketoacidosis)
• Diabetes requiring insulin (Type 1 Diabetes Mellitus)
• Inflammation in the brain (encephalitis)
• Inflammation of the eye which can cause redness, blurred vision or vision loss (Uveitis)
• Inflammation of the heart muscle (myocarditis)
• Inflammation of the Liver (Hepatitis)
• Muscle pain involving several muscles (Polymyalgia rheumatica)
• Kidney inflammation (Nephritis)
• Myasthenia gravis
• Immune-mediated arthritis
• Inflammation of the lining of the stomach (Gastritis)
• Inflammation of the food pipe (Esophagitis)
• Inflammation of the small intestine (Enteritis)
• Inflammation of blood vessels in the gastrointestinal tract (Vasculitis gastrointestinal)
• Inflammation of the muscle which can cause weakness, swelling and pain (Myositis)
• Inflammation throughout the whole body leading to high or low temperatures, low blood pressure, increased heart rate, increased rate of breathing and low or high white blood cell count (Systemic Inflammatory Response Syndrome)

• Infusion-related reactions which can occur within 24 hours after receiving an intravenous infusion, or which can be delayed for up to about 2 weeks. Infusion-related reactions may include dizziness or fainting, flushing, rash, fever, chills, shortness of breath, increased or decreased blood pressure, increased heart rate, swelling of the lips, tongue or face, feeling sick to your stomach, back pain or pain at the site of infusion. Although infusion-related reactions are usually reversible, they can be severe or life threatening. (Infusion related reactions)

There are rare but serious immune-related adverse events which have been seen when dostarlimab was used alone or in combination with other medicines:
• Overactive immune-system cells which damage body tissues and organs leading to signs of uncontrolled fever, enlarged spleen, low blood count and liver test abnormalities. This disease can be fatal. (Hemophagocytic Lymphohistiocytosis)
• A neurological disorder where the immune system attacks part of the peripheral nervous system that can cause tingling in the feet and hands, pain, muscle weakness, and problems with coordination (Guillain-Barre syndrome).

Risks of measurements:
- Blood draw: pain, bruising, irritation, or redness from the needle, fainting/ feeling faint may occur. In rare cases, an infection and/or swelling and redness along a vein may occur.
- ECG: skin irritation from the patches.
- CT Scan: exposure to radiation (total of 171 mSv) and possible allergic reaction to the contrast dye (mild to to severe (such as breathing difficulties and shock)). There is a risk that the injection of dyes may cause pain, swelling, bruising, irritation, or redness at the site. In rare cases, an infection may occur.
- Biopsy during endoscopy: discomfort, feeling faint, local mild pain, pressure or pain from the needle, soreness, or tenderness at the biopsy site, swelling or redness, and scarring at the biopsy site. In rare cases, an infection may occur.

Risks related to the expected outcome of treatment:
Dostarlimab is still experimental for people who have rectal cancer. In another, ongoing clinical trial that is testing dostarlimab in patients living with early-stage rectal cancer, it has been shown that dostarlimab has helped the patients with the ability to delay surgery and chemotherapy and radiation for an extended amount of time. However, there is a risk that treatment during this study does not lead to the desired cancer remission. In that case, the patient will receive the standard of care consisting of chemotherapy, radiation and/or surgery.

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

1. Is at least 18 years of age (or the local legal age of consent) at the time of signing the ICF.
2. Has histologically confirmed Stage II to III (T3-T4, N0, or T any, N+), locally advanced rectal adenocarcinoma.
3. Has radiologically and endoscopically evaluable disease.
4. Has a tumor demonstrating the presence of either:
a. dMMR status; MMR status must be assessed by IHC for MMR protein expression (MLH1, MSH2, MSH6, PMS2) where loss of 1 or more proteins indicates dMMR; MMR status may be determined either locally or by the central reference laboratory;
or
b. MSI-H phenotype as determined by polymerase chain reaction or by tissue next generation sequencing; MSI-H may be determined locally.

NOTE: Participants who are known to have Lynch syndrome and have been found to carry a specific germline mutation in an MMR gene (MLH1, MSH2, MSH6, PMS2 or ECPAM) may be eligible to participate.
5. Has an archival FFPE tissue sample that must be available and submitted to the central reference laboratory for testing at Screening. If no archival tissue is available, a fresh baseline biopsy will be required.
6. A female participant is eligible to participate if she is not pregnant or breastfeeding, and if a woman of child bearing potential (WOCBP), is using a contraceptive method that is highly effective
7. Has an ECOG performance status of 0 or 1.
8. Has adequate organ function, as defined in Table 8 of the protocol.

Exclusion criteria

1. Has distant metastatic disease.
2. Has received prior radiation therapy, systemic therapy, or surgery for management of rectal cancer. Note: Endoscopy guided biopsy is not considered surgery.
3. Has a tumor that, in the investigator*s judgment, is causing symptomatic bowel obstruction or otherwise requires urgent/emergent local intervention.
4. Has a known additional malignancy that progressed or required active treatment within the past 2 years. Exceptions include adequately treated superficial skin cancers, superficial bladder cancers, and other in situ cancers.
5. Is immunocompromised in the opinion of the investigator.
6. Has an active autoimmune disease that has required systemic treatment in the past 2 years, see protocol 5.2.1. item 6 for details.
7. Is unable to undergo MRI.
8. Has experienced any of the following with prior immunotherapy: see protocol 5.1.1. item 8 for details
9. Has undergone any major surgical procedure, open biopsy, or experienced significant traumatic injury within 28 days prior to enrollment.
10. Has any history of interstitial lung disease or pneumonitis.
11. Has cirrhosis or current unstable liver or biliary disease per investigator assessment, see protocol 5.2.1. item 11 for details.
12. Has a history or current evidence of any medical condition, therapy, or laboratory abnormality that might confound the study results, interfere with participation for the full duration of the study intervention, or indicate it is not in the best interest of the participant to participate, in the opinion of the investigator.
13. Has a history of or evidence of cardiac abnormalities such as serious, uncontrolled cardiac arrhythmia or clinically significant ECG abnormalities within the 6 months prior to enrollment, see protocol 5.2.1. item 14 for details.
14. Is receiving any other anticancer or experimental therapy, see protocol

5.2.1. item 15 for details.
15. Is receiving immunosuppressive medication.
16. Has received systemic corticosteroids (>10 mg daily prednisone or equivalent) within 7 days of first dose of study intervention, see protocol 5.2.1. item 17 for details.
17. Has received any live vaccine within 30 days prior to enrollment. see protocol 5.2.1. item 18 for details.
18. Has received or plans to receive an organ or stem cell transplant that uses donor stem cells (allogeneic stem cell transplant)
19. Has documented presence of HBsAg at Screening, a positive HCV antibody test result at Screening , a positive HCV RNA test result at Screening ,
20. a known history of HIV infection, see protocol 5.2.1. item 19, 20, 21 & 22 for details.
For a detailed list of Exclusion Criteria please refer to the protocol section 5.2.1.

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):	22-08-2023
Enrollment:	5
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	Jemperli

Generic name:	Dostarlimab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	10-01-2023
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	13-06-2023
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	25-07-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	20-09-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	20-10-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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
Other	219369
EU-CTR	CTIS2023-509583-22-00
EudraCT	EUCTR2022-003289-18-NL
CCMO	NL83464.100.22