Neoadjuvant treatment in rectal cancer with radiotherapy followed by atezolizumab and bevacizumab (TARZAN-trial)

Published: 29-08-2018
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This study has been transitioned to CTIS with ID 2024-517119-59-00 check the CTIS register for the current data. *- To explore efficacy of neoadjuvant atezolizumab and bevacizumab following radiotherapy in low- to intermediate-risk rectal cancer• To...

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

Summary

ID

NL-OMON52486

Source
ToetsingOnline

Brief title
Neoadj treatment in rectalcancer with RT,atezo & beva (TARZAN)

Condition

- Gastrointestinal neoplasms malignant and unspecified

Synonym
rectal cancer, rectum

Research involving
Human

Sponsors and support

Primary sponsor: Nederlands Kanker Instituut

Source(s) of monetary or material Support: Hoffmann-La Roche,medicatie via Roche

Intervention

Keyword: atezolizumab, bevacizumab, neoadjuvant, rectal cancer

Outcome measures

Primary outcome

Clinical complete and near-complete response rate (cCCR) assessed at week 12 post-RT:

• Complete response is defined as lack of any visible lesion at rectoscopy* (except a flat scar, telangiectasia or whitening of the mucosa; and lack of absence of any residual tumor in the primary site and draining lymph nodes on imaging with MRI including DWI

• Near complete response is defined as only a small flat ulceration on endoscopy and/or a small residual focus on DWI, with otherwise no signs of residual tumor.

Secondary outcome

• Safety: incidence and severity of AEs (with severity determined according to NCI CTCAE v4.03), vital signs and clinical laboratory test results.

• Pre-operative treatment-related complications leading to delays in systemic treatment and/or surgery (excluding non-treatment-related and logistical reasons).

• Relapse-free survival (RFS), defined as the time from study enrolment to disease recurrence or disease-related death during follow-up

• Local recurrence rate (LRR) at 1 year follow-up

• Proportion of patients who undergo organ preserving treatment

• Pathological complete and near-complete response (pCR), defined as Mandard

TRG 1-2, if available

• Radiological tumor regression using MRI (ESGAR consensus guidelines)

Study description

Background summary

In a substantial proportion of patients with rectal cancer, neoadjuvant (chemo-)radiotherapy can result in a complete response, obviating the need for major surgery and often avoiding a definitive stoma. Although still controversial, this so-called organ preservation approach can markedly improve the patients* quality of life. In this context, exploring the therapeutic potential of combined inhibition of PD-L1 and VEGF to increase the rate and depth of responses following standard-of-care radiotherapy in low and intermediate risk rectal cancers is a compelling path forward in organ preservation.

Overall, combining radiotherapy with immune stimulation may support the immune modulating potential of RT by interfering with the local immunosuppressive milieu.

The immunomodulatory effect of bevacizumab is expected to increase CD8+ T cell recruitment and relieve intratumoral immunosuppression, thereby boosting the effects of atezolizumab.

Study objective

This study has been transitioned to CTIS with ID 2024-517119-59-00 check the CTIS register for the current data.

*- To explore efficacy of neoadjuvant atezolizumab and bevacizumab following radiotherapy in low- to intermediate-risk rectal cancer

• To evaluate safety/tolerability and pre-operative treatment-related complications with atezolizumab and bevacizumab following radiotherapy
• To explore efficacy with regard to preventing/delaying disease relapse and to organ preservation

Study design

In this single-center, open-label exploratory study evaluating the safety and

efficacy of atezolizumab and bevacizumab following standard-of-care RT in stage 1-3 rectal cancer, a minimum of 38 patients with rectal cancers will be enrolled.

• 5 x 5Gy radiotherapy (RT) followed 3 weeks later by
• 3 x bevacizumab 5mg/kg IV at 2-weekly (q2w) intervals
- 3 x atezolizumab 840mg IV q2w, starting 2 weeks after the first bevacizumab dose

Intervention

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• 3 x bevacizumab 5mg/kg IV at 2-weekly (q2w) intervals
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Study burden and risks

Patients will undergo a proctoscopy for determination of the required resection margins and for acquisition of study-related biopsies. Repeat scopy for this patient category is common practice at our institute prior to start of treatment. At baseline and before each treatment, blood samples will be drawn, for both follow-up of treatment effects and for research purposes.

Participation will mean 2 additional scopies, one after radiotherapy and before start monotherapy and 1 prior to the first cycle of combination treatment. Site visits for the treatment with chemotherapy and immunotherapy is comparable to that of patients not being treated within the study.

Additional risks of the investigational treatment includes immune related side effects associated with atezolizumab

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

- Signed informed consent form
- Age >=18 years
- Histologically confirmed adenocarcinoma of the rectum, and known microsatellite stability status
- Patients with intermediate risk rectal cancer (cT1-3N1 or cT3c/dN0 MRF-) or low risk rectal cancer (cT1-3bN0 MRF-) in patients who wish to pursue organ preservation
- No signs of distant metastases on CT of thorax and abdomen, MRI pelvis < 4 weeks to inclusion
- Patients must be willing to undergo proctoscopy and biopsies prior to start of treatment and during treatment at defined timepoints
- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1
- Evaluable disease
- Adequate hematologic and end-organ function

Exclusion criteria

- Clinical symptoms or radiological suspicion of perforation
- Other malignancies within 3 years prior to registration in the study with the exception of those with a negligible risk of metastasis or death , or treated with expected curative outcome
- Prior radiation therapy within 30 days prior to C1D1 and/or persistence of radiation-related adverse effects or previous radiation therapy preventing 5x5Gy as specified in this study

- Prior allogeneic bone marrow transplantation or solid organ transplant for another malignancy in the past
- Spinal cord compression not definitively treated with surgery and/or radiation
- Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures
- Uncontrolled tumor pain
- Treatment with any investigational agent or approved therapy within 28 days or two investigational agent half-lives (whichever is longer) prior to C1D1
- Prior treatment with CD137 agonists or immune checkpoint blockade therapies
- Current or recent (within 10 days of study enrollment) use of acetylsalicylic acid (> 325 mg/day), clopidogrel (> 75 mg/day) or current or recent (within 10 days of C1D1) use of therapeutic oral or parenteral anticoagulants or thrombolytic agents for therapeutic purposes

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):	22-10-2019
Enrollment:	38
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Avastin
Generic name:	Bevacizumab
Registration:	Yes - NL intended use

Product type:	Medicine
Brand name:	MPDL3280A
Generic name:	Atezolizumab

Ethics review

Approved WMO Date:	29-08-2018
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	29-08-2019
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	27-02-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	28-05-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-06-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	29-06-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	29-07-2022
Application type:	Amendment
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	CTIS2024-517119-59-00
EudraCT	EUCTR2018-002463-25-NL
CCMO	NL66124.031.18