A Randomized, Multicentre, Open-Label Controlled Phase II Trial of Foxy-5 as Neo-Adjuvant Therapy in Subjects with Wnt-5a Low Colon Cancer.

Published: 29-10-2018
Last updated: 11-04-2024

Primary Objectives* To assess the safety and tolerability of Foxy-5 in subjects with colon cancer.* To assess circulating tumour DNA (ctDNA) in plasma as a surrogate parameter for disease recurrences in subjects with Wnt-5a low colon cancer treated…

Ethical review	Approved WMO
Status	Will not start
Health condition type	Miscellaneous and site unspecified neoplasms benign
Study type	Interventional

Summary

ID

NL-OMON45868

Source
ToetsingOnline

Brief title
NeoFox

Condition

- Miscellaneous and site unspecified neoplasms benign

Synonym
Colon cancer

Research involving
Human

Sponsors and support

Primary sponsor: WntResearch AB

Source(s) of monetary or material Support: WntResearch AB

Intervention

Keyword: Colon Cancer, Foxy-5, Neo-adjuvant, Wnt-5a protein

Outcome measures

Primary outcome

* The incidence of adverse events (AEs) related to Foxy-5 administration of Grade 3 and higher according to the National Cancer Institute * Common Terminology Criteria for Adverse Events (CTCAE, version 5.0) and the Clavien-Dindo classification of surgical complications.

* The level of ctDNA in plasma of subjects with Wnt-5a low colon cancer as a surrogate parameter for disease recurrence in subjects with Wnt-5a low colon cancer treated with Foxy-5 compared to subjects with Wnt-5a low colon cancer who are in the Control Arm.

Secondary outcome

* OS at 2 years after resection of the colon cancer;

* DFS at 2 years after resection of the colon cancer;

* RFI

* The level of ctDNA in plasma of subjects with Wnt-5a high colon cancer.

exploratory endpoint:

* The level of thymidine kinase activity in serum in relationship to Wnt-5a expression in the tumour

Study description

Background summary

Wnt-5a protein belongs to the Wnt family of secreted glycoproteins and it has been demonstrated to play an important role in cell adhesion and cell migration. There is a correlation between low/no expression of Wnt-5a protein in epithelial cancer cells and high risk of recurrence in metastatic disease, and shortened survival in cancer patients (Anastas & Moon, 2013). Low-level expression of Wnt-5a protein has been correlated to higher histological grade (poor differentiation) and shortened recurrence free survival in patients with primary invasive breast carcinomas. A similar association between low Wnt-5a protein expression in cancer cells and disease outcome has been described for both colon and prostate cancer (Dejmek, 2005; Khaja, 2011; Khaja, 2012). In addition to these, investigations on Wnt-5 expression in cancer cells from patients with epithelial ovarian cancer have also shown that high expression of Wnt-5a in ovarian cancer is correlated to a significantly prolonged overall survival for epithelial ovarian cancer patients (Bitler, 2011).
Professor Tommy Andersson (Chief Scientific Officer of WntResearch AB) has developed a peptide that mimicked the effect of the intact Wnt-5a molecule on breast cancer cell migration. Based on sequence analysis of Wnt-5a, structural bioinformatics and computational chemistry design (performed through a collaboration with Dr. Villoutreix, INSERM, Paris), a short list of molecules were rationally proposed for in vitro assays. Two bioactive molecules were identified and the smallest of these (12 amino acids long) was step-wise shortened from the N-terminal side. It was found that when this peptide only contained 6 amino acids it had lost its bioactivity properties. However, a chemical modification (formylation) of the N-terminal side restored and increased its bioactive properties and made it more resistant to degradation in vivo. Thus, through a combined in silico-in vitro-in vivo work, Dr. Andersson's research group found that this chemically modified 6-amino-acid peptide molecule could mimic the effects of Wnt-5a on intracellular signalling and breast cancer cell migration (Säfholm et al., 2006). This small compound was named Foxy-5. Foxy-5 is a synthetic hexapeptide with a formylated N-terminus, derived from the protein sequence of the Wnt-5a protein.
The metastatic process, resulting in the formation of distant metastases in other organs, is strongly associated with cancer related mortality, and a medical treatment that specifically targets this process would be an important therapeutic step in the treatment of cancer.

Study objective

Primary Objectives
* To assess the safety and tolerability of Foxy-5 in subjects with colon cancer.
* To assess circulating tumour DNA (ctDNA) in plasma as a surrogate parameter for disease recurrences in subjects with Wnt-5a low colon cancer treated with

Foxy-5 compared to subjects with Wnt-5a low colon cancer who are in the Control Arm.

Secondary Objectives
To determine the preliminary efficacy of Foxy-5 in subjects with colon cancer by assessing:
* Overall survival (OS) defined as the time from surgery until death due to any cause, assessed at two years after surgery.
* Disease-free survival (DFS) defined as the time from surgery to tumour recurrence or death due to any cause, assessed at two years after surgery.
* Recurrence-free interval (RFI) defined as the time from randomization to tumour recurrence.
* Circulating tumour DNA (ctDNA) in plasma as a surrogate for disease recurrence in subjects with Wnt-5a high colon cancer treated with Foxy-5 compared to subject with Wnt-5a high colon cancer who are in the Control Arm.

Exploratory Objective
* To assess the correlation between thymidine kinase activity in serum and Wnt-5a expression in the tumour.

Study design

A Randomized, Multicentre, Open-Label Controlled Phase II Trial

Intervention

Up to 180 subjects will be randomized as 1:1 in the trial. From which up to 90 subjects will be treated with Foxy-5 throughout the entire treatment period and up to 90 subjects will serve as control (no placebo treatment).

Study burden and risks

Burden: Each patient will undergo assessments as specified in the Schedule of Assessments. This includes for all patients: Informed consent, physical examination, height and weight, vital signs and ECGs. The frequency of assessments is limited for the patients in the control group.
Patients will receive a maximum of 39 administrations of Foxy-5 (the control group will not receive Foxy-5 administrations).

Risks: Foxy-5 appeared to be safe and well tolerated in patients in previous studies, with no dose limiting toxicities observed at any dose.
There are risks of trial related procedures such as blood sampling, IV injections and diagnostic procedures. Blood draws and IV injections may cause pain, bleeding, bruising, nerve injury and/or infections at the site of cannula insertion.
Together, the positive outcome of the preclinical studies and the Phase I

clinical trial of Foxy-5, warrant further clinical trials to evaluate Foxy-5*s clinical efficacy in relevant clinical settings, such as for the treatment of colon cancer (especially in subject with Wnt-5a negative).

Benefit: Foxy-5 is expected to decrease migration of cancer cells and hence result in lower recurrence and have a better overall survival.

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. Ability to understand and willingness to provide written informed consent before any trial-related activities.
2. Age *18 years.
3. Male or female subjects with adenocarcinoma of the colon, judged by CT or MRI as either

one of the following stages per TNM classification of colon cancer (8th edition, 2017):
T1-4, N1-2, M0 or
T4, N0, M0
and who are considered to fulfil the local criteria for adjuvant post-operative chemotherapy after scheduled surgery.
4. Scheduling of surgery according to local practice allows at least 9 pre-surgery administrations of Foxy-5 for the subject. (Please note: surgery should not be postponed for trial purposes).
5. Sexually active women of childbearing potential (WOCBP) and males with WOCBP partners who are randomized to the Foxy-5 Arm must use a highly effective method of contraception for the treatment duration and for 28 days after last Foxy-5.
6. Eastern Cooperative Oncology Group (ECOG) performance status of 0-1.
7. Clinical laboratory values at screening:
a. Absolute neutrophil count *1.5 x 109/L
b. Haemoglobin * 9 g/dL
c. Platelets * 100 x 109/L
d. Aspartate Transaminase (AST) and Alanine Transaminase (ALT) *1.5x Upper Limit of Normal (ULN)
e. Serum bilirubin *1.5 x the ULN
f. Creatinine clearance >60 mL/min (determined by Cockcroft-Gault Equation).

Exclusion criteria

Candidates will be excluded from trial entry if any of the following exclusion criteria is met:
1. Assessed as not suitable or unable to tolerate adjuvant chemotherapy.
2. Evidence of distant metastatic (M1) disease at Screening (N1-2 is allowed).
3. Any surgery (except tumour biopsy) or therapy with immune suppressive agents or bone marrow stimulating factors within the last two weeks prior to randomization.
4. Any active infection requiring IV antibiotic treatment at the time of screening.
5. History of hematologic or primary solid tumour malignancy. Subjects in complete remission for at least 5 years or judged as cured by the Investigator may be included. Subjects with any prior non-invasive basal and squamous skin cell carcinoma, cervical carcinoma of Stage 1B or less, and non-invasive superficial bladder cancer may be included.
6. Pregnant or breastfeeding women.
7. Currently participating in another trial and receiving trial therapy or received investigational therapy within 4 weeks of the first dose of Foxy-5.
8. Any other condition or treatment that, in the opinion of the Investigator, might interfere with the trial or current drug or substance abuse.
9. Inability to understand the protocol requirements, instructions and trial-related restrictions, the nature, scope, and possible consequences of the trial.
10. Unlikely to comply with the protocol requirements, instructions and trial-related restrictions; e.g., uncooperative attitude, inability to return for follow-up visits, and improbability of completing the trial.
11. Legal incapacity or limited legal capacity.
12. Any condition, which results in an undue risk for the subject during the trial participation

according to the Investigator.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Other

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	24
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Foxy-5
Generic name:	Foxy-5

Ethics review

Approved WMO Date:	29-10-2018
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	28-01-2019
Application type:	Amendment

Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	11-04-2019
Application type:	First submission
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
EudraCT	EUCTR2018-003074-27-NL
ClinicalTrials.gov	NCT02020291,NCT02655952
CCMO	NL67224.100.18