MoTriColor: A phase II study of vinorelbine in advanced BRAF-like colon cancer

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To determine the anti-tumor activity, as defined as doubling of progression free survival (PFS) of vinorelbine treatment in patients with BRAF-like colon cancer.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Gastrointestinal neoplasms malignant and unspecified
Study type	Observational invasive

Summary

ID

NL-OMON47411

Source
ToetsingOnline

Brief title
Vinorelbine in BRAF-like colon carcinoma

Condition

- Gastrointestinal neoplasms malignant and unspecified

Synonym
bowel cancer, colon carcinoma

Research involving
Human

Sponsors and support

Primary sponsor: Antoni van Leeuwenhoek Ziekenhuis
Source(s) of monetary or material Support: EU

Intervention

Keyword: BRAF-like, colon cancer, colon carcinoma, vinorelbine

Outcome measures

Primary outcome

Efficacy, as defined as doubling of progression free survival (PFS) of vinorelbine treatment in patients with BRAF-like colon cancer. This means that by vinorelbine treatment the rate of progression at 6 weeks drops to 25%.

Secondary outcome

* To characterize the safety and tolerability of vinorelbine, as assessed by the incidence and severity of adverse events.

* To assess efficacy of vinorelbine, as measured by overall response rate, duration of response, time to response and overall survival (OS).

* To compare the activity of vinorelbine in patients with KRAS mutant, BRAF wildtype, BRAF-like colon cancer vs. KRAS wildtype, BRAF mutant, BRAF-like colon cancer.

* To explore determinants (gene alteration/expression) of response to vinorelbine, as measured by baseline molecular status (mutation/ expression) in tumor tissue of potential predictive markers of tumor response.

* To explore the potential mechanism of resistance to vinorelbine, as measured by gene alterations/expression profiles (i.e. baseline, relapse) in tumor tissue upon progression.

Study description

Background summary

Approximately 8-10% of colon cancer (CC) patients carry an activating mutation in BRAF. This CC subtype is associated with poor outcome and with resistance, both to current chemotherapeutic treatments and to tailored drugs.
Popovici et al.and Sun et al. showed that BRAF (V600E) colon cancers (CCs) have a characteristic gene expression signature which is found also in subsets of KRAS mutant (30%) and KRAS-BRAF wild type (18%) (WT2) tumors. Tumors having this gene signature are referred to as *BRAF-like* and have a similar poor prognosis irrespective of the presence of BRAF(V600E) mutation.
By using a lentiviral-based short hairpin RNA (shRNA) approach targeting the genes belonging to the BRAF signature Vecchione et al identified RANBP2 to be straight lethal with BRAF V600E gene mutation in a panel of colorectal cancer (CRC) cell lines. RANBP2 is implicated in mitotic spindle formation, chromosome segregation, mitotic progression and kinetochore function. In particular, RANBP2 depletion induces abnormal chromosomal segregation, improper mitotic progression and mitotic catastrophe. Vecchione et al showed that suppression of RANBP2 results in mitotic defects only in BRAF-like CC cells, which leads to cell death. Mechanistically, RANBP2 silencing reduces microtubule outgrowth from the kinetochores, thereby inducing spindle perturbations, providing an explanation for the observed mitotic defects.
Vinorelbine prevents the microtubule polymerization, thus by inducing loss of dynamic stability and lack of normal microtubule function, it leads to cell death following prolonged mitotic arrest.
In particular, the preclinical work shows BRAF V600E and BRAF-like CRC cell lines to be 10-100000-fold more sensitive to vinorelbine than wild type CC cell lines. Moreover, this exquisite sensitivity of BRAF-like CC cell lines to vinorelbine is not related to an increased proliferation rate since the proliferation rate of BRAF-like CC cell lines is not significantly different from that of non-BRAF-like cell lines and importantly, BRAF(V600E) CC cells lines have an IC50 for vinorelbine that is similar to that of breast and lung cancer cell lines, two solid tumors for which vinorelbine is used in clinical practice.
These preclinical data represent a strong rationale to also explore the anti-tumor activity of vinorelbine in patients with advanced BRAF-like (both BRAFm and BRAF wild type) CC. Since vinorelbine is standard of care in advanced breast and NSCLC, there is ample experience with the dose and schedule as well as with the safety profile and supportive measures required to prevent side-effects.
In 2017 new clinical data were published regarding the efficacy of vinorelbine in BRAFV600E mutated metastatic colorectal cancer. In a multicenter, phase II trial in Italy a small group of 20 patients was treated with vinorelbine and the primary endpoint was objective response rate. No responses were observed, only one patient revealed stable disease. (4) Based on this new results two cohorts will be explored in the current clinical trial in which BRAF-like BRAFmt or BRAF-like KRASmt colorectal cancer patients will be enrolled and

treated with vinorelbine. These 2 cohorts will have the same primary endpoint, namely progression free survival at 6 weeks, and will be compared in this study.

Study objective

To determine the anti-tumor activity, as defined as doubling of progression free survival (PFS) of vinorelbine treatment in patients with BRAF-like colon cancer.

Study design

Two-stage double arm multi-center open-label phase II study with 40 patients with BRAF-like CC treated with vinorelbine 30 mg/m2 day 1, 8, Q day 21.

Study burden and risks

- Blood will be drawn for pharmacokinetic, pharmacodynamic and pharmacogenetic research
- Tumor biopsies will be taken pre-, upon and at end of treatment for histological analyses of biomarkers, genetics and immune infiltration
- Patients will be asked to keep a diary and note daily what they ate and when they took the medication.

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. Written informed consent (+ TR (translational research)) must be given according to ICH/GCP and national/local regulations
2. Written documentation of BRAF-like signature CC, including BRAFm and BRAFwt, as determined by the validated assay of Agendia
3. written documentation of KRAS and BRAF mutational status
4. Age * 18 years
5. Histologically proven and measurable (RECIST criteria v.1.1) metastatic adenocarcinoma of the colon not in a previously irradiated area, treated with one or two lines of standard of care therapy, including BRAF inhibitors, for locally advanced disease and metastatic disease
6. WHO performance status of 0-1
7.Life expectancy > 3 months allowing adequate follow up of toxicity evaluation and antitumor activity
8. Negative urine pregnancy test for female patients with childbearing potential

Exclusion criteria

1. Any treatment with investigational drugs, including BRAF inhibitors, within 28 days prior to receiving the first dose of investigational treatment
2. Symptomatic or untreated leptomeningeal disease;3. Symptomatic brain metastasis. Patients previously treated or untreated for these conditions that are asymptomatic in the absence of corticosteroid and anticonvulsant therapy (for at least 4 weeks) are allowed to enroll. Radiotherapy for brain metastasis must have been completed at least 6 weeks prior to start of study treatment. Brain metastasis must be stable with verification by imaging (e.g. brain MRI or CT completed at screening demonstrating no current evidence of progressive brain metastases). Patients are not permitted to receive enzyme inducing anti-epileptic drugs or corticosteroids;4. Impairment of gastrointestinal (GI) function or GI disease (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, any condition inducing malabsorption, small bowel resection);5. Other uncontrolled concomitant illness, including serious uncontrolled intercurrent infection;6. Known allergy or any other adverse reaction to any of the drugs or to any related compound;7. Women who are pregnant or breast feeding;8. Unreliable contraceptive methods. Both men and women enrolled in this trial must agree to

use a reliable contraceptive method throughout the study (adequate contraceptive methods are: condom, sterilization, other barrier contraceptive measures preferably in combination with condoms);9. Patients who have undergone any major surgery within the last 2 weeks prior to starting study drug or who would not have fully recovered from previous surgery;10. Uncontrolled infectious disease or known Human Immunodeficiency Virus HIV-1 or HIV-2 type patients;11. Patients with a known history of hepatitis B or C;12. Known hypersensitivity to study drug or excipients

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	25-10-2018
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	vinorelbine
Generic name:	vinorelbine ditartraat
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	01-12-2016

Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	09-02-2017
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	08-03-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	15-03-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	29-08-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	30-08-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

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	EUCTR2016-002364-13-NL
CCMO	NL59133.031.16

Study results

Date completed: 17-03-2020

Actual enrolment: 0

Summary results
Trial is onging in other countries