A double-blind, randomised, placebo controlled Phase III study of nintedanib plus best supportive care (BSC) versus placebo plus BSC in patients with colorectal cancer refractory to standard therapies.

Published: 28-08-2014
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The objective of this Phase III study is to evaluate the efficacy and safety of nintedanib in patients with mCRC after failure of previous treatment with standard chemotherapy and biological agents.

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

Summary

ID

NL-OMON42006

Source
ToetsingOnline

Brief title
LUME- Colon 1

Condition

- Malignant and unspecified neoplasms gastrointestinal NEC
- Gastrointestinal neoplasms malignant and unspecified

Synonym
bowel cancer, colorectal adenocarcinoma

Research involving
Human

Sponsors and support

Primary sponsor: Boehringer Ingelheim
Source(s) of monetary or material Support: Industrie: Boehringer Ingelheim bv.

Intervention

Keyword: angiogenesis, Best Supportive Care, BIBF1120 (nintedanib), colorectal cancer

Outcome measures

Primary outcome

Co-primary endpoints: progression-free survival (PFS) by central review

assessment and overall survival (OS)

Secondary outcome

Secondary endpoints:

* - Objective tumour response (CR + PR) by central review assessment

* - Disease control (CR + PR + SD) by central review assessment

Further endpoints

* - Time to objective tumour response by central review assessment

* - Duration of objective tumour response by central review assessment

* - Duration of disease control by central review assessment

* - Tumour shrinkage by central review assessment

* - Time to treatment failure

* - Objective tumour response (CR + PR) by investigator assessment

* - Disease control (CR + PR + SD) by investigator assessment

* - PFS by investigator assessment

* - Time to objective tumour response by investigator assessment

* - Duration of objective tumour response by investigator assessment

* - Duration of disease control by investigator assessment

* - Tumour shrinkage by investigator assessment

* - The change scores from baseline to 16 weeks for the physical functioning

scale and

global health status/QoL scale measured on the EORTC QLQ-C-30 questionnaire

Study description

Background summary

Colorectal cancer (CRC) has high incidence (about 2.6 million new cases/year) and it is the second leading cause of cancer-related deaths in Western countries. Even though most of the newly diagnosed patients initially underwent surgery with curative intent and received adjuvant systemic treatment, about half of patients eventually develop metastatic disease. 5-fluorouracil (5-FU) has been the mainstay of treatment for metastatic CRC for several decades. Modulation of 5-FU with folinic acid, modification of 5-FU scheduling, addition of new chemotherapeutic agents as oxaliplatin irinotecan have all contributed to a significant improvement in the overall survival of patients with metastatic CRC.The addition of biologically targeted treatments (bevacizumab, cetuximab, panitumumab, aflibercept) to chemotherapy regimens and recent introduction of regorafenib has increased patients* survival further.

As indicated by bevacizumab and aflibercept clinical experience, angiogenesis is highlyrelevant for CRC cancer growth and development of metastases. Vascular Endothelial Growth Factor (VEGF) and its high affinity receptor VEGFR-2 are crucial for the formation of new tumour vessels. In addition, there is preclinical evidence that fibroblast growth factor (FGF) and platelet-derived growth factor (PDGF) and their associated receptor tyrosine kinases substantially contribute to tumour angiogenesis. The VEGF - VEGFR-2 axis, besides promoting angiogenesis, may also be involved in stimulating growth of tumour cells themselves via an autocrine growth factor loop. Therefore, suppression of neoangiogenesis
via inhibition of VEGFR-2 and other pathways is a promising strategy for the treatment of CRC. A substantial number of clinical trials with various inhibitors of VEGF or VEGFRs performed recently in CRC demonstrated this

approach can convey clinical benefit, in particular in combination therapy with standard chemotherapeutic drugs. Moreover recent data with a regorafenib Phase III trial indicate that angiogenesis inhibition with small tyrosine-kinase inhibitors may be also effective for CRC refractory to conventional chemotherapies as well as biological agents including bevacizumab. Nintedanib is a potent, orally available triple kinase inhibitor targeting VEGFRs, PDGFRs, and FGFRs. The specific and simultaneous abrogation of these pathways results in effective growth inhibition of both endothelial and, via PDGF- and FGF-receptors of perivascular cells, which may be more effective than inhibition of endothelial cell growth via the VEGF pathway alone. Furthermore, signalling by FGF-receptors has been identified as a possible escape mechanism for tumour angiogenesis when the VEGF pathway is disrupted Present trial will investigate the efficacy and safety of nintedanib in patients with refractory CRC after failure of standard chemotherapy drugs and biological agents currently used for CRC.

Study objective

The objective of this Phase III study is to evaluate the efficacy and safety of nintedanib in patients with mCRC after failure of previous treatment with standard chemotherapy and biological agents.

Study design

This is a Phase III multi-centre double-blind, randomised trial to evaluate the efficacy and safety of nintedanib in combination with best supportive care (BSC) in patients with mCRC after failure of standard drugs in comparison to placebo plus BSC. The trial will be performed by investigators specialised in the treatment of patients with colorectal cancer. Patients eligible for this study will have best supportive care as the only remaining standard available therapy for refractory CRC as specified in the inclusion criteria. After completion of screening assessments, patients will be randomly assigned based on a randomisation ratio 1:1 to receive either nintedanib + best supportive care (BSC) (Arm A) or matching placebo + BSC (Arm B). The randomised patients will be treated until unequivocal progression or undue toxicity; no other anti-cancer treatment will be allowed until study medication is discontinued (see Section 3.3.3). End of treatment, regardless of the reason of EOT, will be followed by a Residual Effect Period (REP) which starts from last treatment intake and ends 28 days later.

Patients who discontinue trial medication but did not progress on treatment will have follow-up period for PD until PD, start of new anti-cancer treatment, death, lost to follow-up or when the required OS events for the OS analysis have been reached.

Safety parameters will be continuously followed-up during the duration of the

trial. Evaluation of tumour response will be assessed by imaging according to RECIST (version 1.1) every 6 weeks. Decision on continuation of treatment will be based on assessment of tumour response and progression by the investigator. Independent blinded assessment of tumour images will also be performed by a central imaging unit but will not be used for clinical decision by investigator.

Intervention

Addition of BIBF 1120 (nintedanib) or placebo to the standard therapy given (best supportive care).

Study burden and risks

This study investigates the addition of BIBF 1120 or placebo to best supportive care. The subjects have metastic colorectal cancer refractory to standard therapies. A disease that is difficult to treat and has no other options for therapy. BIBF 1120 has a favourable toxicity profile and can potentially enhance survival of these patients.
The patient already would undergo a number of procedures (blood draw, vital signs, CT scans), regardless of study participation. If he/ she thus would like to participate and receive additional therapy, some additional assesments will be performed (e.g.blood draws, vital signs and CT- scans) will be required for this study.
In this study blood is drawn for pharmacokinetics and pharmacogenetic analysis. The subject can refuse participation in the pharmacogenetic testing, but may continue to participate in the main study.

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

- Age >< = 18 years
- Signed informed consent
- Histologically or cytologically confirmed colorectal adenocarcinoma
- Metastatic or locally advanced disease not amenable to curative surgery and/or radiotherapy
- mECOG performance status * 1
At least one measurable lesion according to RECIST 1.1
- Progression on standard therapies or withdrawn from standard treatment due to unacceptable toxicity. Previous standard treatment must include all of the following:
* * flouropyrimidine
* * oxaliplatin: Patients treated with oxalipatin in adjuvant setting should have progressed within 6 months of completion of adjuvant therapy or they must have been treated with oxaliplatin for metastatic disease
** irinotecan
* * bevacizumab or aflibercept
* * cetuximab or panitumumab for patients with K-Ras wt or Ras wt tumours
- The remaining standard available therapy as recommended by investigator is best supportive care (note: previous treatment with regorafenib is allowed if available to patient according to local standards as determined by investigator)

Exclusion criteria

- Previous treatment with nintedanib.
- Known hypersensitivity to the trial drugs or their excipients.
- toxicity attributed to previous anticancer therapy that did not resolve to CTCAE grade *1 with exception of Hb, alopecia, pigmentation and oxaliplatin related neurotoxicity.
- History of severe haemorrhagic or thromboembolic event in the past 12 months (excluding

central venous catheter thrombosis and peripheral deep vein thrombosis). Known inherited predisposition to bleeding or to thrombosis.
- Bleeding or thrombotic disorders requiring anticoagulant therapy such as warfarin, or similar agents requiring therapeutic INR monitoring (treatment with low molecular weight heparin and/or heparin flush as needed for maintenance of an indwelling intravenous device is allowed)
- Inflammatory bowel disease and other serious medical conditions increasing the risk of perforation or bleeding according to investigator*s judgment.
- Gastrointestinal disorders or abnormalities that would interfere with absorption of study drug.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	24-11-2014
Enrollment:	25
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	not yet known
Generic name:	nintedanib

Ethics review

Approved WMO Date:	28-08-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-11-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-11-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-12-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-04-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-06-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2012-000095-42-NL
CCMO	NL49492.018.14