A Phase II/III Study of MK-0646 Treatment in Combination with Cetuximab and Irinotecan for Patients with Metastatic Colorectal Cancer

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Ethical review	Approved WMO
Status	Pending
Health condition type	Miscellaneous and site unspecified neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON34904

Source
ToetsingOnline

Brief title
MK0646-004

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
Colorectal Cancer

Research involving
Human

Sponsors and support

Primary sponsor: Merck Sharp & Dohme (MSD)
Source(s) of monetary or material Support: Merck;Sharp & Dohme (MSD)

Intervention

Keyword: cetuximab, Colorectal cancer, irinotecan, MK0646-004

Outcome measures

Primary outcome

1. To determine overall survival of patients with metastatic colorectal cancer expressing the wtKRAS genotype treated with the combination of MK-0646, cetuximab, and irinotecan compared to patients treated with cetuximab and irinotecan alone.

2. To evaluate progression-free survival of patients with metastatic colorectal cancer expressing the wtKRAS genotype treated with the combination of MK-0646, cetuximab, and irinotecan compared to patients treated with cetuximab and irinotecan alone.

3. To assess the safety profile of MK-0646 of patients with metastatic colorectal cancer expressing the wtKRAS genotype treated with the combination of MK-0646, cetuximab, and irinotecan compared to patients treated with cetuximab and irinotecan alone.

Secondary outcome

1. To evaluate the objective response rate of patients with metastatic colorectal cancer expressing the wtKRAS genotype treated with the combination

of MK-0646, cetuximab and irinotecan compared to patients treated with

cetuximab and irinotecan alone.

Study description

Background summary

Colorectal cancer is the third most common cause of cancer-related death in men and women in the world. For patients with metastatic colorectal cancer, standard of care treatments with a fluoropyrimidine, irinotecan, oxaliplatin, or bevacizumab (in combination or sequentially) result in a median survival from 18 to 21 months [1, 2, 3, 4]. However, once these standard drugs have failed, there are limited available options for patients. Those patients with progressive metastatic disease, despite having received current first and second line chemotherapies, who have tumor-specific expression of the epidermal growth factor receptor (EGFR) can, receive third line treatment with irinotecan and cetuximab. Cetuximab, is a monoclonal antibody that specifically blocks EGFR, a member of the ErbB family of receptors [5]. EGFR is overexpressed in up to 80 percent of colorectal cancers and is associated with poor survival [6, 7, 8]. Despite treatment with cetuximab, the prognosis for patients in this population is still poor with a response rate of 22.9 percent, a median time to progression of 4.1 months [9] and a median overall
survival of 8.6 months.
MK-0646 is a humanized IgG1 kappa antibody targeting the Insulin-like Growth Factor Receptor Type 1 (IGF-1R). Signaling through IGF-1R mediates cell growth and proliferation as well as resistance to apoptosis in all of the major solid tumors including colorectal cancer [10]. There are two possible mechanisms of action of MK-0646: (1) inhibition of IGF-1-mediated cell signaling, and (2) antibody dependent cell-mediated
cytotoxicity (ADCC). In preclinical studies, MK-0646 significantly improved the activity of other chemotherapeutic compounds. MK-0646 was additive to the activities of anti-EGFR antibodies, cetuximab and 225, in the subcutaneous HT29 colon cancer and orthotopic A549 lung cancer xenograft mouse models respectively. Additionally, there is emerging evidence of cross-talk between EGFR and IGF-1R signaling pathways [10]. Hence, concurrent inhibition of IGF-IR and EGFR functions provides a logical rationale for combining anti-IGF-IR and anti-EGFR strategies in the treatment of cancer.
There are two ongoing Phase I studies of MK-0646 to determine safety profile, tolerability, and pharmacokinetics of MK-0646 in patients with a broad range of advanced cancers. These studies have not yet defined an MTD, but preliminary evidence of receptor saturation and inhibition of proliferative signaling was observed at the 5 mg/kg dose and above. Thus, this study will examine efficacy of these doses using two different regimens, a weekly and an alternate week

regimen that is of potential convenience to the patient (see Section 3.2.3.5.7 for details on treatment arms and regimens).
Additional background information on preclinical pharmacology, toxicology, and pharmacokinetics may be found in the Investigator Brochure.

Study objective

There will be three formal interim analyses during the study.

Interim Analysis 1 will occur at the end of Phase II when approximately 162 PFS events (defined as disease progression or death due to any cause, whichever occurs first) have been observed in wtKRAS patients in the blinded portion of the study. Enrollment will continue until Interim Analysis 1 is completed at which time enrollment is expected to be 296 wtKRAS patients.

The test at Interim Analysis 1 is designed to continue the trial to a Phase III stage if substantial benefit is observed at this point. The trial has 85% probability of detecting an increase in PFS at Interim Analysis 1 when either of the two MK-0646 arms
provides a 37% decrease in the hazard rate versus control. At most one of the two treatment arms will be carried forward beyond Interim Analysis 1. If both arms achieve proof of concept, only one MK-0646 treatment arm will be continued with guidance for selection provided to the DSMB in the DSMB charter that will be based on comparison of progression-free survival and other factors such as response rate, overall survival and safety assessment between the two MK-0646 treatment arms. If neither experimental arm achieves proof of concept criteria, both MK-0646 treatment arms will be terminated at Interim Analysis 1. If terminated at this point, the study will be unblinded and evaluated as a Phase II trial before considering further development.

Interim Analysis 2 will be based solely on the assessment of progression-free survival and will take place after approximately 152 total PFS events (including events which occur prior to Interim Analysis 1) in wtKRAS patients have been observed in the continuing arms in the blinded portion of the study. Total enrollment at this stage is expected to be 478 patients and is projected to take place approximately 20-25 months
after the first patient is randomized. Collectively, the PFS tests for the first two interim analyses have a 78% chance of detecting an increase in PFS when either of the two MK-0646 arms provides a 37% decrease in the hazard rate versus control. As with Interim Analysis 1, the trial will be terminated and evaluated as a Phase II trial if the target increase in PFS is not achieved.

Interim Analysis 3 will take place when approximately 310 total deaths in wtKRAS patients occur in both the placebo and the continuing treatment arm in the blinded portion of the study. This interim analysis should take place approximately 30-35 months after the first patient is enrolled with an anticipated total enrollment of 939 patients at this time. Interim Analysis 3

will be based on overall survival (OS) and has adequate power (over 80%) to detect a relatively large improvement in OS (40% decrease in the hazard rate versus control). Patient enrollment will not be halted during Interim Analysis 2 or 3.

Study design

This is a multicenter, double-blind, randomized, Phase II/III study of MK-0646 administered to patients with metastatic colorectal cancer who previously failed both oxaliplatin and irinotecan-based chemotherapies. These patients should have progressed upon completion of therapy with objective radiological evidence of progression.

Intervention

Cetuximab
Cetuximab will be given at an initial dose of 400 mg/m2 over 120 minutes followed by weekly infusions of 250 mg/m2 over 60 minutes. Patients will be premedicated with a histamine-receptor antagonist prior to the first cetuximab dose. Premedication for subsequent cetuximab doses will be at the discretion of the investigator.

Irinotecan
Irinotecan will be infused over 30-90 minutes at the same dose and schedule as that given during their most recent pre study therapy. Current examples of irinotecan regimens are 125 mg/m2 once every week for 4 weeks followed by 2 weeks rest, 180 mg/m2 once every two weeks or 350 mg/m2 once every three weeks.

MK-0646
Patients assigned to a MK-0646 containing regimen will additionally receive MK-0646
as per one of the two specified regimens. In Arm A, MK-0646 will be infused once weekly at 10 mg/kg over 60 or 120 minutes. In Arm B, patients will be infused with an
initial (loading) dose of 15 mg/kg MK-0646 over 60 or 120 minutes followed by infusions at 7.5 mg/kg (maintenance) dose over 60 or 120 minutes beginning every alternate week. MK-0646 infusions will be started one week after the first dose of
cetuximab infusion to distinguish between toxicities due to either drug. Normal saline
will be substituted in the weeks MK-0646 is not given.

Study burden and risks

MK-0646
The following side effects have been reported in treatments with MK-0646: an

infusion reaction or hypersensitivity to MK-0646, a skin disorder with rash on arms, legs, back and buttocks, a reduced number of blood platelets in the blood, hyperglycemia, rash on the whole body as a result of vasculitis, dyspnoea as a result of a pneumonia.

Cetuximab
A side effect of cetuximab is a reaction to the infusion when the medicine is injected into the vein for the first time. A reaction to the infusion is defined by short of breath, skin rash, hypotension etc. Other frequent common side effects are hyperglycemia and acneform rash. With several patients who received this medicine, hypomagnesia and other electrolyte disturbances in the blood were reported.

Irinotecan
Most common side effects of irinotecan are nausea, vomiting and diarrhea, drowsiness, hair-loss, fever and stomache pain. Some patients may get a stuffy nose, hot flashes, increased salivation and lacrimation. With some patients the treatment with irinotecan causes a decrease of white blood cells, anaemia andthrombocytopenia.

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. Patient has histologically or cytologically confirmed colorectal cancer.
2. Patient has at least one measurable lesion greater than or equal to 15 mm.
3. Patient has previously failed both irinotecan and oxaliplatin containing regimens and should have progressed on or within 3 months of completing their last line of therapy with objective radiological evidence of progression as verified by previous radiologic scans. Note: Failing oxaliplatin would include failure due to toxicities.
4. Patient is male or female, and *18 years of age on the day of signing informed consent.
5. Patient has performance status 0-1 on the ECOG Performance Scale.
6. Patient has adequate organ function as indicated in the summary of laboratory values, Protocol pag. 23, number 6.
7. Female patient of childbearing potential has a negative serum or urine *-hCG pregnancy test at baseline.
8. Patient, or patient*s legal representative, has voluntarily agreed to participate by giving written informed consent.
9. Patient has archival (recent or remote) tumor available for analysis for biomarker studies.
10. Patient has a wtKRAS metastatic colorectal cancer determined by (1) testing at the program central laboratory during the screening period as outlined in the MK0646-004 Assay Charter; or (2) a documented history that the colorectal cancer was determined to be *wtKRAS* by a test conducted at a local laboratory in the period between first diagnosis and consideration for enrollment in the study (see Protocol, page section 3.1.4.1.1)

Exclusion criteria

1. Patient who has had chemotherapy, radiotherapy, or biological therapy within 2 weeks prior to initial dosing on this study, or whose toxicities from agents administered 2 weeks earlier have not resolved to at least grade 1 or baseline, or who is within 3 weeks from a prior surgery.
2. The patient has colorectal cancer whose tumors contain an activating KRAS mutation.
3. Patient has experienced intolerable toxicity to irinotecan therapy.
4. Patient is < 18 years.
5. Patient is known to be Human Immunodeficiency Virus (HIV)-positive.
6. Patient has known active Hepatitis B or C.
7. Patient is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the study.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	30-06-2010
Enrollment:	29
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Cetuximab, Erbitux
Generic name:	IMC-C225
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Irinotecan, Campto
Generic name:	CPT-11
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Nog niet beschikbaar
Generic name:	Dalotuzumab

Ethics review

Approved WMO Date:	01-04-2010
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-09-2010
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	EUCTR2007-001116-22-NL
CCMO	NL31802.018.10