Phase Fase II examination of irinotecan, cetuximab and everolimus for patients resistant to chemotherapy with metastatic colorectal cancer and KRAS mutation or with KRAS wildtype after progression on therapy with irinotecan og cetuximab – effect and biological markers.

Name of Study Drug:

Everolimus, Cetuximab, irinotecan

Name of Active Ingredient:

Everolimus, Cetuximab, irinotecan

Coordinating Investigator:
Chief Consultant Benny Vittrup Jensen, Department of Oncology, Herlev Hospital, University of Copenhagen, Denmark

Study Sites:
3 sites in Denmark.
Oncology Department, Herlev Hospital, 2730 Herlev
Oncology Unit, Odense University Hospital, 5000 Odense,
Oncology Department Ålborg Hospital, 9100 Ålborg

Publications: One article on circulating tumor DNA was published for this study.

Studied Period (Years):
First Subject First Visit: 11 January 2010 October 2008
Last Subject Last Visit: 09 december 2011

Phase of Development: 2

Objectives:
The primary objective of the study was to assess if the addition of the mTOR inhibitor everolimus to cetuximab and irinotecan in heavily pre-treated patients metastatic colorectal cancer mCRC with 1) KRAS wildtype mCRC cancer that had progressed on therapy with cetuximab and irinotecan had any effect or 2) whether the addition of everolimus to irinotecan and cetuximab to patients with mCRC with a KRAS mutation had any effect.

Main objective:

- Disease control as the sum of number of patients with CR, PR and SD.
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Secondary objectives:

- Time to progression from start of therapy
- Length of disease control. (CR, PR, SD)
- Survival from date of start of therapy.
- Safety and toxicity of the therapy
- Influence of smoking on disease control, response, survial and time to progression and other effect parameters in the investigation.
- **Blood:** Examine the influence of potentiel predictive and prognostic tumour biomarcers in blood as LDH, CEA, VEGF, EGFR, HER-2, YKL-40, IL-6, TIMP-1, P1NP, P3NP, gen-, microRNA- and protein-array profiles, metabolomics and CRP 2 weeks after start of therapy and thereafter every 8.weeks on disease control, response, survival and time to

progression and other parameters investigated.

- **Tissue:** Examine possible predictive and prognostic biomarkers in tissue from primary tumour or metastases for micro-RNA-array profiles, mutations in K-RAS, BRAF, PIK3CA, EGFR, p53, and protein expression and polymorphisms of PTEN, EREG, AREG, IGF-1, IGF-1R, VEGF, p53, Topo1, YKL-40, and TIMP-1
  Correlation between possible predictive and prognostic biomarkers in blood and tissue.

Methodology:

Trial design: An open, multicentre phase II trial of therapy with a combination of cetuximab, and irinotecan every second week combined with a daily dose of everolimus to patients with metastatic colorectal-cancer with KRAS mutation or to patients with KRAS wildtype mCRC that had progressed on therapy cetuximab and irinotecan.

Method: Multicentre, open, phase II trial
Patients fulfilling the inclusion criteria will be treated with cetuximab, irinotecan and everolimus.

Duration of Treatment:
Therapy was to continue until disease progression and/or or unacceptable side effects prohibited further continuation or the patient want to stop therapy.

Diagnosis and Main Criteria for Inclusion:
Inclusion criteria:

1. Patients with histologically-verified adenocarcinoma of the colon or rectum, with non-resectable or metastatic disease
2. Patients with measurable disease as per RECIST criteria
3. Patients with progressive disease following either oxaliplatin-based or Irinotecan-based treatment
4. Patients with Irinotecan-resistant disease – defined as progressive disease after at least 6-weeks treatment with Irinotecan-based treatment or within 6 months following discontinuation of such treatment. Irinotecan-based treatment should not necessarily be given immediately before inclusion, but oxaliplatin-based treatment may be.
5. Performance status (WHO) less than 3
6. An expected survival time of at least 3 months
7. Neutrophil count (ANC) $\geq$1.5 x 10^9/l and thrombocytes ≥100 x 10^9/l
8. Normal liver function with Bilirubin <1.5 x UNL (upper limit of normal) and ASAT/ALAT < 5 x UNL.
9. All should be exposed to Oxaliplatin-based treatment
10. The signed informed consent as per requirements of the Scientific Ethical Committees.

Exclusion criteria:

1. Previous or other concomitant malignant disease, excluding treated basal cell carcinoma or *in situ* cervical cancer.
2. Patients who are unable to follow the treatment- and evaluation plan
3. Any condition or therapy which in the view of the investigators exposes the patient to risk or affects the aims of the trial
4. Pregnant or nursing women. In women of child-bearing potential this is safeguarded by virtue of a negative pregnancy test or use of an effective method of contraception, as defined in the Danish Medicines Agency's guidelines, throughout the entire trial period and for at least 3 months after conclusion of the treatment.

5. Patients with active infections or other serious concomitant medical condition that may prevent them being able to receive the protocol-based treatment.
6. Known hypersensitivity to one or more of the components in the treatment
7. Minors

Test and Reference Product, Dose/Strength/Concentration, Mode of Administration.

Cetuximab:

Cetuximab 500 mg/m² is given intravenously every second week. The infusion time is registered in the CRF. The first dose of cetuximab 500 mg/m^2 is given during a 120 min. infusion followed by irinotecan 180 mg/m^2 as a 30 min. infusion.

At subsequent treatments cetuximab 500 mg/m^2 is given with an infusion time of 1 hour immediately followed by irinotecan 180 mg/m^2 as a 30 min. infusion.

Irinotecan:

Irinotecan 180 mg iv. infusion during 30 min. every second week. By the 1. series of cetuximab there will be a delay of 1 hour after cetuximab before irinotecan is given. At subsequent treatments irinotecan is given immediately after cetuximab.

Everolimus:

Tablets with 2,5 mg per day for 14 days. If toxicity is acceptable the dose is increased to 5 mg daily for 14 days. If toxicity is acceptable the dose is increased to 7,5 mg daily for 14 days. If toxicity is acceptable the dose is increased to 10 mg daily, which is the final maximal dose.

Criteria for Evaluation

Efficacy:

Resonse rate, Progression free survival (PFS) and overall survival (OS).

Other measurements:

Tissue and blood samples and registration of adverse events will be collected for pharmacodynamic studies.

Safety:

Adverse events, laboratory assessments, vital signs, and physical examinations.

Statistical Methods

Evaluable patients are patients with at least one objective response evaluation 6 weeks after starting treatment unless there is early progression.

The two patient populations are evaluated separately:
Group 1: Patients with KRAS mutation.
Group 2: Patients with KRAS wildtype that have progressed on therapy with cetuximab and irinotecan.

With an expected 20% or 12 patients in each arm that will not be able to fulfille the criteria for being evaluable a calculated 60 patients will be included in each arm.

Median overall and progression free survival was calculated using the Kaplan Meier Method and the log rank test for comparison.

Comparison between groups according to response with the chi-square test.

Safety:

Safety summaries were presented for each drug regimen and included all subjects who received at least 1 dose of study drug.

The number and percentage of subjects having treatment-emergent adverse events were tabulated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 3.0 toxicity grade and relationship to study drug. Serious adverse events, events leading to discontinuation of study drug, events leading to interruption of treatment or reduction of dosage, adverse events of special interest, and events leading to death were summarized by study drug regimen.

Summary/conclusions

A total of 105 patients were included.

The primary endpoint – Response rate

75 patients were evaluable for response.

KRAS wildtype tumors:

35 patients were evaluable, one (2.9%) obtained a complete remission, no one a partial remission, 23 (65.7%) stable disease and 10 (28.6%) progressive disease.

A clinical benefit was thus seen in 24 patients (68.6%).

KRAS mutated tumors:

40 patients were evaluable, no one obtained a complete remission, two (5%) a partial remission, 20 (50%) stable disease and 18 (45%) progressive disease.

A clinical benefit was thus seen in 22 patients (55%).

Data were statistical similar in the two groups.

Secondary endpoint – Progression free (PFS) and overall survival (OS)

KRAS wildtype tumors:

48 patients were evaluable for PFS and OS.
Median PFS was 3.49 months (95%CI 2.6-4.4 months)
Median OS was 7.53 months (95% CI 3.3-9.7 months)

KRAS Mutated tumors:

57 patients were evaluable for PFS and OS.
Median PFS was 2.4 months (95%CI 1.8-3.0 months)
Median OS was 7.24 months (95% CI 5.0 - 9.5 months)

Safety results

Subjects receiving everolimus had more adverse events than expected, especially including more severe skin adverse events generally leading to the administration of a very low dose or even to discontinuation.

Conclusions:

No statistically significant differences in response rates, PFS or mOS were noted for KRAS wildtype or KRAS mutated heavily pretreated patients with metastatic colorectal cancer.

Subjects receiving everolimus had more adverse events especially skin-toxicity, including more grade 3 adverse events than expected, and more adverse events leading to a significant lowering or even discontinuation of everolimus.

The mTOR inhibitor Everolimus cannot be recommended in addition to cetuximab and irinotecan in heavily pretreated patients with KRAS wildtype tumors that has progressed on cetuximab and irinotecan nor can I be recommended in patients with KRAS mutant tumors as an effort to bypass KRAS induced resistance to EGFR inhibitors.

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