Synospis Clinical Study Report

Protocol Identification No.:	IOM-510-2 (ERBIMOX)
Trial Identification No.:	EudraCT No.: 2006-002744-28
Title:	Optimization of efficacy and reduction of toxicity in first-line therapy of metastatic colorectal cancer
Short Title:	ERBIMOX
Development Phase:	Phase II
Investigational Product(s):	Cetuximab
Drug/Dosage:	400 mg/m^2 initial, followed by 250 mg/m^2 weekly
Treatment Duration:	First-line therapy until progression
Indication:	Stage IV *KRAS* wild-type Metastatic Colorectal Cancer
Trial Design:	Open, two arm-randomized, controlled, multicenter, parallel group design
Trial Initiation Date:	September 2006
Trial Completion Date:	16 Apr 2014
Coordinating / Principal Investigator(s):	Prof. Dr. Hans Tesch
Sponsor:	iOMEDICO AG
Sponsor Contact:	iOMEDICO AG, Hanferstr. 28, D-79108 Freiburg Germany
Date of Report:	15-Apr-15

This trial was performed in compliance with Good Clinical Practice (GCP).

1 SYNOPSIS

Title of Trial:

Optimization of efficacy and reduction of toxicity in first-line therapy of metastatic colorectal cancer

Coordinating Investigator:

Professor Dr. Hans Tesch, Frankfurt, Germany

Trial Center(s):

In total 23 office-based medical oncology centers participated in the study:

No	Center (Name of trial physician), City	N Patients
1	Müller, Leer	32
2	Sahm, Offenbach	27
3	Lerchenmüller, Münster	20
4	Tesch, Frankfurt	18
5	Depenbusch, Gütersloh	16
6	Schliesser, Giessen	10
7	Freier, Hildesheim	8
8	Tessen, Goslar	8
9	Becker, Porta Westfalica-Barkhausen	7
10	Abenhardt, München	5
11	Aldaoud, Leipzig	5
12	Köchling, Villingen-Schwenningen	5
13	Schlag, Würzburg	5
14	Söling, Kassel	5
15	Hutzschenreuter, Nordhorn	4
16	Köhler, Langen	4
17	Schröder, Mülheim a. d. Ruhr	4
18	Marschner, Freiburg	3
19	Messmann, Augsburg	3
20	Müller, Offenburg	3
21	Rauh, Witten	2
22	Kröning, Magdeburg	1
23	Musch (ex Kindler), Berlin	1

Publication (reference):

N/A; So far, no data from the clinical trial have been published

Trial Period (years):	**Phase of Development:**
2006 - 2014	Phase II

Objectives:

Primary objective was to demonstrate superiority of additional cetuximab administration to modified FOLFOX7 (Arm B, ERBIMOX) compared with modified FOLFOX7 alone (Arm A, OPTIMOX) as first-line treatment of patients with *KRAS* wild-type metastatic colorectal cancer. Primary endpoint was Objective Response Rate (ORR).

Secondary objectives were:

- To explore duration of response rates (CR / PR)
- To explore duration of progression free survival (PFS)
- To assess PFS rates after 4, 6, 9, and 12 months
- To assess overall survival (OS)
- To assess resection rates
- To assess safety and tolerability according to NCI CTCAE v3.0 criteria.

Methodology:

An open-label, randomized, two-arm, parallel group, multicenter, phase II trial was developed to investigate safety and efficacy using an oxaliplatin based chemotherapy backbone (FOLFOX7) during a 16-week induction period followed by a chemotherapy maintenance period without oxaliplatin until PD. In the experimental arm (ERBIMOX), the anti-EGFR antibody cetuximab was added continuously throughout the induction and maintenance period.

Number of Patients:

	Treatment Groups		**Total**
Analysis Sets	**Arm A OPTIMOX**	**Arm B ERBIMOX**	
Patients randomized	96	100	196
m-ITT population	63	75	138
Safety population	95	96	191
PP population	49	46	95

Diagnosis and Main Criteria for Inclusion:

- Histologically confirmed *KRAS* wild-type colorectal cancer (stage IV)
- At least one measurable lesion according to RECIST 1.0 confirmed within the last four weeks prior to study enrollment

- Inoperable or unresectable measurable lesions
- Indication for first-line colorectal cancer therapy.

Test Product(s): Dose and Mode of Administration, Batch Number(s):

Cetuximab 400 mg/m^2 i.v. loading dose on day 1 followed by 250mg/m^2 i.v. weekly

Reference Therapy(ies), Dose and Mode of Administration, Batch Number(s):

Not applicable.

All patients in treatment Arm A and B respectively received following dosage of modified FOLFOX 7 regimen:

Induction period: 5-FU 2,400mg/m^2 i.v. over 48 hours on day 1 **plus** *dl*-leucovorin 400mg/m^2 i.v. **plus** oxaliplatin 85mg/m^2 i.v.

Maintenance period: 5-FU 3,000mg/m^2 i.v. over 48 hours on day 1 **plus** *dl*-leucovorin 400mg/m^2 i.v.

Duration of Treatment:

Induction period: 8 x 2-weekly cycles; Maintenance period: 2-weekly cycles until PD

Criteria for Evaluation:

Efficacy:

To assess objective response rate (ORR, primary objective), response duration, PFS, OS, and resection rates (secondary objectives).

Safety:

To provide summaries of AEs, ADRs, fatal AEs and serious adverse events (SAEs) according to NCI CTCAE v3.0 toxicity criteria and assigned to SOC classifications and preferred terms.

Statistical Methods:

ORR was evaluated using chi-square test. For grouped categorical data (i.e. sex and chemotherapeutic pre-treatment) Cochran-Mantel-Haenszel test was used.

For the estimation of PFS, OS, and response duration the Kaplan-Meier (KM) method and log-rank tests were applied. A Cox proportional hazard model was performed to identify the influence of possible confounders.

Summary and Conclusions:

Efficacy Results:

ORR (CR + PR) was comparable between treatment groups without statistically significant difference (chi-squared = 1.0432, df = 1, p = 0.3071). However, ORR tended to be higher in Arm B as compared to Arm A (64.0% vs. 54.0%). Nevertheless the primary endpoint was not met, since the results did not confirm superiority of Arm B. ORR in men was higher than in women (67.4% vs. 41.9%), ORR was generally higher in Arm B (men 71.7% vs. women 45.5%) than in Arm A (men 61.9% vs. 38.1%).

Response duration and PFS were comparable in both treatment groups and tended to be longer in Arm B than in Arm A without statistically significant difference (Response duration: 10.2 vs. 6.4 months, HR 0.84; 95% CI 0.50 - 1.40; p = 0.50; PFS: 9.6 vs. 8.8 months, HR 0.94; 95% CI 0.65 - 1.37; p = 0.76).

OS was not statistically significant between treatment Arm B vs. Arm A (25.6 vs. 30.9 months, HR 1.12; 95% CI 0.75-1.69, p = 0.58).

Resection rates were generally low (5.1%, n=7 of 138 patients) and comparable between Arm A and Arm B (6.3%, n=4; 4.0%, n=3).

Safety Results:

In Arm B, a higher number of any AEs was reported as compared to Arm A: 58.5% vs. 41.5%. In Arm B, patients experienced grade 3/4 skin toxicities and gastrointestinal disorders more often (21.9% vs. 2.1% and 13.5% vs. 9.5%). Cutaneous manifestations (e.g. rash, acne) were the most common toxicities associated with cetuximab. The majority of the cetuximab related AEs were mild or moderate by nature. Grade 3 rash occurred in seven patients treated with cetuximab while no grade 4 was reported.

The ERBIMOX regimen presented a reduced toxicity profile compared to those reported in OPUS and COIN-B. Grade 3 or 4 rash occurred in 7.3%, 11% and 22%; diarrhea was reported in 7.3% vs. 9% vs. 24%; neuropathy in 1% vs. 1% vs. 4%; and neutropenia in 1% vs. 35% vs. 24% in the ERBIMOX, OPUS and COIN-B trials, respectively.

In Arm B, a higher number of SAEs was reported than in Arm A: 36.5% vs. 26.3%. Five cetuximab related SAEs were documented in 4 (4.2%) patients.

In total, 11 deaths occurred since enrollment and during course of treatment (3 in Arm A; 8 in Arm B). None of the deaths in Arm B were classified by the investigator as related to the IMP cetuximab.

Conclusions:

The ERBIMOX trial did not meet the criteria for superiority of the combination therapy (i.e. modified FOLFOX7 + cetuximab) in terms of ORR. In contrast to OPUS and other trials exploring chemotherapy + cetuximab as first-line treatment in colorectal cancer no statistical improvement in PFS and OS was observed. Nevertheless, the median OS observed in the ERBIMOX trial represents the upper limit of what can be expected with oxaliplatin based chemotherapy alone, and even with anti-EGFR antibody combination.

Limitations on the outcome worth to be discussed are the reduced statistical power due to premature termination of recruitment, the retrospective/prospective analysis of *KRAS* wild-type tumors, the unknown rate of additional *RAS* mutations that remained undetected, and the unidentified second or further line therapies.

In terms of toxicities, the ERBIMOX regimen - as defined in this trial - shows a favorable toxicity profile and warrants further investigation.

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