1. Clinical Study Report

Study Title	**Capecitabine and bevacizumab with or without vinorelbine in first-line treatment of HER2/neu-negative metastatic or locally advanced breast cancer: final efficacy and safety data of the randomized, open-label superiority phase 3 CARIN trial**
Study Title German	Capecitabine und Bevacizumab +/- Vinorelbin in der Erstlinientherapie des HER2/neu-negativen metastasierten oder lokal fortgeschrittenen Mammakarzinoms
Short Title	CARIN
Protocol No.	IOM-080-2
EudraCT No	2008-003779-37
Investigational product	Capecitabine + Bevacizumab + Vinorelbine
Comparator	Capecitabine + Bevacizumab
Dosage	Capecitabine 1000 mg/m^2 (per os twice daily, d1-14 q3w), Bevacizumab 15 mg/kg (i.v. d1 q3w) Vinorelbine 25 mg/m^2 (i.v. d 1+8 q3w)
Indication	First-line therapy in HER2(-) locally advanced or metastatic breast cancer
Design	Open-label, prospective, multicenter, two-arms, controlled, randomized (1:1)
Development phase	Phase 3
Sponsor	iOMEDICO AG, Freiburg, Germany
Coordinating investigator	[redacted]
Author of report	[redacted] iOMEDICO AG
Study initiation date	18-February-2009
Study completion date	27-October-2015
Report based on data from	15-January-2016
Version and date of report	V 2.0 17-Oct-2016

This study was performed in compliance with International Conference of Harmonization (ICH) Good Clinical Practices (GCP) regulations/guidelines. Essential documents will be retained in accordance with ICH-GCP.

iOMEDICO AG
Hanferstraß2 28
D-79108 Freiburg
Tel.: +49 761 152 42-0
Fax: +49 761 152 42-10

2. Synopsis

Name of Sponsor/Company: iOMEDICO AG	Volume: Pages:	(For National Authority Use Only)
Name of Finished Product: Xeloda® / Avastin® / Navirel®		
Name of Active Ingredient: Capecitabine / Bevacizumab /Vinorelbine		

Title of study:

Capecitabine and bevacizumab with or without vinorelbine in first-line treatment of HER2/neu-negative metastatic or locally advanced breast cancer: final efficacy and safety data of the randomized, open-label superiority phase 3 CARIN trial

Coordinating investigator:

[redacted]

Study centre(s):

68 sites in Germany, 59 sites enrolled patients (refer to section 2.2)

Publication (reference):

Breast Cancer Research and Treatment, 03-03-2016, The article is available as 'Online First': http://link.springer.com/article/10.1007/s10549-016-3727-x

Studied period (years):		**Phase of development**:
(FPI, date of first enrollment)	2009-02-18	3
(LPI , date of last enrollment)	2012-10-26	
(LPLV , date of patients' last visit)	2015-10-27	

Objectives:

Primary objective:

- To determine clinical superiority of capecitabine/bevacizumab/vinorelbine compared to capecitabine/bevacizumab in terms of progression-free survival (PFS).

Secondary objectives:

- To evaluate objective response rate (ORR)
- To determine overall survival (OS)
- To assess safety and tolerability
- To assess potential changes in plasma biomarker during treatment (translational research: immunohistochemistry, protein and gene expression)
- To evaluate health outcome parameters

Methodology:

Open-label, prospective, multicenter, two-arms, controlled, randomized (1:1)

Name of Sponsor/Company: iOMEDICO AG	Volume: Pages:	(For National Authority Use Only)
Name of Finished Product: Xeloda® / Avastin® / Navirel®		
Name of Active Ingredient: Capecitabine / Bevacizumab /Vinorelbine		

Number of patients (planned and analyzed):	**planned and randomized**: 600 (Arm A: 300, Arm B: 300 **screened**: 600 (Arm A: 300, Arm B: 300	**allocated to treatment**: 592 (Arm A: 297; Arm B 295) **completed**: 592 (Arm A: 297; Arm B 295)	**analyzed efficacy**: 592 (Arm A: 297; Arm B 295) **analyzed safety**: 592 (Arm A: 297; Arm B 295)

Diagnosis and main criteria for inclusion:

HER2/neu-negative measurable or non-measurable disease, locally recurrent or metastatic breast cancer (MBC), no previous chemotherapy for advanced disease, ECOG performance status ≤ 2, ≥ 18 years, no sign of brain metastases.

Test product, dose and mode of administration:

Arm A: Capecitabine (CAP) per os at 1000 mg/m^2 twice daily, days 1-14 every 21 days (q3w, i.e., one cycle, including 7 days off-treatment), combined with intravenous bevacizumab (BEV) at 15 mg/kg (day 1 q3w).

Arm B: Intravenous vinorelbine (VIN) was added to CAP/BEV at 25 mg/m^2 (day 1+8 q3w).

Duration of treatment:

Treatments were administered until disease progression was objectively documented or until unacceptable toxicity occurred, which required discontinuation of study treatment. The expected treatment duration was approximately 30 months.

Reference therapy, dose and mode of administration:

Arm A: CAP per os at 1000 mg/m^2 twice daily, days 1-14 every 21 days (q3w, i.e., one cycle, including 7 days off-treatment), combined with intravenous BEV at 15 mg/kg (day 1 q3w)

Criteria for evaluation:

Efficacy:

Primary endpoint

- PFS, defined as time from randomization until progression of disease (PD) or death

Secondary endpoints:

- ORR (i.e., complete response [CR] + partial response [PR])
- OS

Safety:

- Adverse events and NCI-CTCAE (v3.0) toxicities
- Any laboratory abnormalities until end of treatment (EOT)
- Frequencies and duration of hospitalizations until PD

Name of Sponsor/Company: iOMEDICO AG	Volume: Pages:	(For National Authority Use Only)
Name of Finished Product: Xeloda® / Avastin® / Navirel®		
Name of Active Ingredient: Capecitabine / Bevacizumab /Vinorelbine		

Translational Research:

- Changes in methylated plasma DNA (PDNA) (i.e., translational research parameters)

Health Outcome:

- Brief Fatigue Inventory (BFI)
- FACT-bone pain (FACT-BP)
- FACT-diarrhea (FACT-D)
- EORTC QLQ-C30
- EORTC QLQ-BR23

Sample size estimation:

Sample size estimation bases on a Log Rank Test and the following assumptions: 2-sided test, alpha 0.05, power 0.8, follow up 14 months, recruitment period 48 months. Median PFS1 8 months, median PFS2 10.3 months.

Median PFS1 was calculated based on the following data. With study XCALIBr performed by Sledge et. al. a TTP of 5.7 months has been observed based on a sample size of 106 patients. With study RIBBON1 a PFS of 8.6 months based on a sample size of 409 patients was observed. The weighted average resulting was ((106*5,7)+(409*8,6))/515=8 months.

Based on this assumptions 544 patients (272 patients per treatment arm) are required to detect a significant difference. This is equivalent to a number of 494 events (247 events per treatment arm).

Considering a drop out rate of approximately 10 %, the total sample size was 600 patients (300 patients per treatment arm).

Statistical methods:

Treatment effects on PFS were calculated using the time-to-event analysis by Kaplan-Meier. Kaplan-Meier estimators were presented as survival curves by treatment arm; median PFS times were computed with 95% CIs for both treatment arms. Differences between treatment arms with respect to PFS were analyzed by log-rank test at a significance level of $\alpha = 0.05$ (primary analysis). The treatment effect was estimated in a Cox regression model as hazard ratio with associated 95% CIs. Under a basic model, only treatment arm was included as independent variable.

In a second multiple Cox regression analysis, the effect of seven (7) pre-defined covariates on PFS was modelled by entering the variables 'age (< vs ≥ 65 years)', 'disease free interval (≤ 12 vs > 12 months), 'number of metastatic sites (< 3 vs ≥ 3 sites)', '(neo-)adjuvant therapy (chemotherapy vs taxane-/ anthracycline therapy vs no chemotherapy)', 'visceral disease (yes/no)', 'hormone-receptor status (+/-)' in addition to 'treatment (Arm A/Arm B)' to identify potential predictors of PFS and OS. The type I error rate was set at 0.05 with no multiplicity adjustment.

The analysis of the secondary efficacy variables ORR, and OS were merely descriptive in nature. Patients were considered evaluable for response if they had measurable disease at baseline. Objective response was defined as status of complete or partial response according to RECIST v1.0. ORR was analyzed using the chi-squared test at a significance level of $\alpha = 0.05$. The relative risk and the 95% CIs were specified. ORR was additionally stratified by prior (neo-)adjuvant therapy with anthracycline and/or taxane (AT, yes/no) and hormone receptor status (+/-). The stratified ORR was analyzed using the Cochran-Mantel-Haenszel chi-squared test at a significance level of $\alpha = 0.05$.

Name of Sponsor/Company: iOMEDICO AG	Volume: Pages:	(For National Authority Use Only)
Name of Finished Product: Xeloda® / Avastin® / Navirel®		
Name of Active Ingredient: Capecitabine / Bevacizumab /Vinorelbine		

OS was estimated using average hazard ratios by weighted Cox regression method (26), since the OS curve characteristics appeared non-proportional.

For continuous and quasi-continuous variables, the following descriptive statistics were computed, broken down by treatment arm: number of observations, median, quartiles, mean, standard deviation, minimum and maximum.

Categorical variables were summarized by frequencies and percentages in contingency tables by treatment arm.

Summary - Conclusions:

Efficacy results:

Baseline characteristics:

Patient baseline characteristics were generally balanced. The full analysis population was characterized by a considerable portion of patients older than 65 years (Arm A: 105 [35.4%]; Arm B 132 [44.7%]). ECOG performance status ≤ 2 was one of the inclusion criteria and > 50% of patients were assessed as ECOG 0 (159; 53.5% in Arm A and 166; 56.3% in Arm B). The majority of patients was pre-treated with (neo-)adjuvant chemotherapy (Arm A: 193 [65.0%]; Arm B: 195 [66.1%]), including 114 (38.4%) and 95 (32.2%) patients with prior (neo-)adjuvant taxane treatment in Arm A and Arm B, respectively. The proportion of patients with TNBC was identical in both arms (Arm A: 61 [20.5%]; Arm B: 61 [20.7%]).

Primary efficacy:

Median PFS was slightly enhanced in CAP/BEV/VIN treatment Arm B: 9.6 months vs 8.8 in Arm A. The log-rank test for effect of treatment on PFS was significantly different favoring Arm B (HR = 0.83; 95% CI = 0.690 - 1.000; p = 0.0474).

Secondary efficacy:

Confirmed ORRs were significantly lower in Arm A compared to Arm B (36.3% vs 47.5%, p=0.047).

The median OS was 25.1 months in Arm A, and 27.2 months in Arm B. The log-rank test of average hazard ratio method revealed no significant treatment effect on OS (p = 0.1376; HR = 0.85; 95% CI = 0.706-1.049).

Safety results:

Exposure:

Median duration of treatment was longer in Arm A as compared to Arm B. With regard to application of capecitabine, patients in treatment Arm A received in median 8.0 cycles (26.1 weeks) compared to patients in Arm B, receiving capecitabine in 7.0 cycles (23.9 weeks). The same, albeit less pronounced, applies to the administration of bevacizumab, in Arm B, 8.0 cycles (26.3 weeks), in Arm A 9.0 cycles (27.0 weeks). Relative dose intensities were accordingly higher in Arm A as compared to Arm B regarding both capecitabine (82.2% vs 77.9%) and bevacizumab (96.2% vs 92.8% vs 96.2%). In Arm B, patients received vinorelbine in 6.0 cycles (21.0 weeks) with 83.2% relative dose intensity.

Adverse events and NCI-CTCAE toxicities:

- AEs with any grade 3/4 severity, were significantly more frequently reported in Arm B (218 patients; 73.9%) as compared to Arm A (176 patients; 59.3%).
- Grade 3/4 events classified as treatment related by the investigator were also significantly more often in Arm B (189 patients; 64.1%) than in Arm A (125 patients; 42.1%).

Name of Sponsor/Company: iOMEDICO AG	Volume: Pages:	(For National Authority Use Only)
Name of Finished Product: Xeloda® / Avastin® / Navirel®		
Name of Active Ingredient: Capecitabine / Bevacizumab /Vinorelbine		

- The incidence of SAEs was significantly higher in Arm B (150 patients; 50.8%) as compared to Arm A (112 patients; 37.7%); the occurrence of SAEs with outcome death was not significantly different between both treatment arms (Arm A: 18 patients; 6.1%, Arm B: 25 patients; 8.5%).
- In Arm A, most commonly observed AEs were
  - Skin and subcutaneous tissue disorders (227 patients; 76.4%), including palmar-plantar erythrodysesthesia syndrome (196 patients; 66.0%), and alopecia (20 patients; 6.7%).
  - Gastrointestinal disorders (204 patients; 68.7%), including nausea and diarrhea (97 patients; 32.7%, respectively).
  - General disorders and administration site conditions (184 patients; 62.0%), including fatigue (89 patients; 30.0%), and mucosal inflammation (57 patients; 19.2%).
- In Arm B, most commonly observed AEs were
  - Gastrointestinal disorders (238 patients; 80.7%), including nausea (133 patients; 45.1%), diarrhea (85 patients; 28.8%), and constipation (70 patients; 23.7%).
  - General disorders and administration site conditions (221 patients; 74.9%), including fatigue (128 patients; 43.4%), and mucosal inflammation (68 patients; 23.1%).
  - Skin and subcutaneous tissue disorders (181 patients; 61.4%), including palmar-plantar erythrodysesthesia syndrome (120 patients; 40.7%), and alopecia (59 patients; 20%).
- Comparing Arm B vs Arm A (patients; %), frequently reported PTs of grade 3/4 were
  - [Blood and lymphatic system disorders] neutropenia (57; 19.3% vs 3; 1.0%) and leucopenia (52; 17.6% vs 3; 1.0%),
  - [Gastrointestinal disorder] nausea (13; 4.4% vs 6; 2.0%) and diarrhea (9; 3.1% vs 13; 4.4%).
  - [Skin and subcutaneous tissue disorders] palmar-plantar erythrodysesthesia syndrome] (43; 14.6% vs 70; 23.6%) and
  - [Vascular disorders] hypertension (6; 2.0% vs 19; 6.4%).

In summary, AEs of grade 3/4, serious AEs, and AEs leading to permanent treatment discontinuations occurred more frequently in Arm B as compared to Arm A.

Conclusion:

The results of this study indicate that the triple combination CAP/BEV/VIN was an active and feasible regimen with manageable toxicities. Nevertheless, toxicities and permanent treatment discontinuations were enhanced in Arm B, and OS was not superior compared to Arm A.

Date of report: 17-Oct-2016

2.1 Clinical Study Protocol / Amendments

The clinical study report (CSR) is based on the final study protocol version 3.0 dated 30-Jun-2011 and its amendment 4 dated 01-Sep-2014. The initial study protocol, dated 16-Oct-2008 was revised and amended as documented in Table 2-1.

Changes to the protocol could be implemented exclusively in the form of a written amendment and only subsequent to approval/favorable opinion by the competent authority and the independent EC respectively. Please refer to Appendix 15.1.3 for letters of approval and details on the EC.

Table 2-1 Approval of the Clinical Study Protocol and its Amendments by the EC / CA

Protocol / Amendment	Type of Amendment	Changes implemented	Protocol Version / Date	Favorable opinion of the leading ethics committee (Date)	Approval of the relevant competent authority (Date)
Initial Study Protocol	Initial submission	N/A	16-Oct-2008	N/A due to additional claims by CA from 15-Dec-2008	N/A due to additional claims by CA from 15-Dec-2008
Revised Initial Study Protocol	Initial submission (revised)	Revision, Translational Research Implemented	1.0 / 21-Jan-2009	04-Feb-2009	05-Feb-2009
Amendment 1 (Addendum 1.0 to the Protocol)	Substantial	Epigenetic Profiling of Plasma DNA in Response to Chemotherapy Treatment	Addendum 1.0 / 09-Jun-2009	23-Sep-2009	01-Sep-2009
Amendment 2 (Protocol Version 2.0)	Substantial	Capture of lab values extended even to lab values considered non-pathological, capture of tumor evaluations independent of individual treatment cycles	2.0 / 15-Feb-2011	14-Mar-2011	28-Feb-2011
Amendment 3 (Protocol Version 3.0)	Substantial	Increase of patient number from 400 to 600 Usage of bevacizumab and capecitabine as article of trade	3.0 / 30-Jun-2011	09-Aug-2011	09-Aug-2011
Amendment 4 (Protocol Amendment 4)	Substantial	Classification of the trial as Phase III, Analysis of 1° endpoint with less events and lower power	1.0 / 01-Sep-2014 The amendment is a standalone document, the entire protocol was not changed.	21-Oct-2014	16-Sep-2014