CLINICAL TRIAL CENTER
NORTH

Single-arm, open-label, single-center Phase II study evaluating the efficacy and safety of BIBW 2992 (Afatinib) for the treatment of patients with HER2-positive, hormone-refractory prostate cancer after failure of treatment with docetaxel or ineligible for treatment with docetaxel

Clinical Study Report

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Sponsor	University Medical Center Hamburg-Eppendorf Martinistraße 52 20246 Hamburg , Germany
Principal Investigator	Prof. Dr. med. Walter Fiedler Klinik und Poliklinik für Onkologie, Hämatologie und Knochenmarktransplantation Martinistraße 52 20246 Hamburg Germany

Sponsor Signature Page

This Final Report has been approved by the University Medical Center Hamburg-Eppendorf.

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Investigator Signature Page

I hereby confirm that I have read this Final Report and confirm that it describes the conduct and the results of the study.

Principal Investigator Signature | Date

Principal Investigator Name

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2 ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AMG	Arzneimittelgesetz
ASE	American Society of Echocardiography
ASCO	American Society of Clinical Oncology
AST	Aspartate Aminotransferase
AUC	Area Under the Concentration-time curve of the analyte in plasma
$AUC_{T,SS}$	Area Under the Concentration curve for the last dosing interval from administration to the last measured concentration
BC	Bronchial Carcinoma
BI	Boehringer-Ingelheim
CA	Competent Authority
CBC	Complete Blood Count
CEP	Centromer Enumeration Probe
C_{max}	Maximum measured concentration of the analyte in plasma
$C_{max, SS}$	Highest concentration determined in the measuring interval after multiple dosage
CBC	Complete Blood Count
CNS	Central Nervous System
CK-ELPR	Creatinine Kinase Electrophorese
CPK	Creatine Phosphokinase
CR	Complete Response
CRA	Clinical Research Associate
CRF	Case Report Form
CT	Computed Tomography
CTC	Circulating Tumour Cells
CTCAE	Common Terminology Criteria for Adverse Events
CSP	Clinical Study Protocol
TMF	Trial Master File
EC	Ethics Committee
eC_{CR}	Estimated Creatinine Clearance Rate
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal Growth Factor Receptor
EOT	End of Treatment
ER-positive	Estrogen Receptor Positive
EU	Europe
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FFPE	Formalin Fixed Paraffin Embedded
FISH	Fluorescence In-Situ Hybridization
FU	Follow-Up
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GnRH	Gonadotropin Releasing Hormone
GFR	Glomerular Filtration Rate
GP	General Practitioner
HDPE	High Density Polyethylene

HER1	Human Epidermal Growth Factor Receptor
HER2	Human Epidermal Growth Factor Receptor
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IHC	Immunohistochemistry
ILD	Interstitial Lung Disease
IMP	Investigational Medicinal Product
INR	International Normalised Ratio
ISF	Investigator Site File
i.v.	intravenous
IVRS	Interactive Voice Response System
LVEF	Left Ventricular Ejection Fraction
mBC	Metastatic Breast Cancer
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute
NIMP	Non-Investigational Medicinal Product
nM	Nanomolar
NSCLC	Non Small Cell Lung Carcinoma
NYHA	New York Heart Association
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease
PFS	Progression Free Survival
P-gp	P-glycoprotein substrate
PI	Prescribing Information
PK	Pharmacokinetic
PR	Partial Response
PSA	Prostate Specific Antigen
RBC	Red Blood cells Count
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	Serious Adverse Event
s.c.	subcutaneous
SD	Stable Disease
SmPC	Summary of Product Characteristics
SPF	Sun Protection Factor
t_{max}	Time from (last) dosing to the maximum measured concentration of the analyte in plasma
TNM	Tumour, (lymph) Nodes, Metastasis
US	United States
WBC	White Blood cells Count

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4 SYNOPSIS

Study Title	Single-arm, open-label, single-center Phase II study evaluating the efficacy and safety of BIBW 2992 (Afatinib) for the treatment of patients with HER2-positive, hormone-refractory prostate cancer after failure of treatment with docetaxel or ineligible for treatment with docetaxel
Protocol No.	1200.138
EudraCT-No.	2010-024164-18
Phase	Phase II
Study Dates	First/last patient screened: 03.08.2011 First/ last patient dosed: 12.08.2011 Last patient last treatment: 24.08.2011 Last patient last visit: 25.08.2011
Study Type	Open-label, single-arm, single-center phase II study
Investigational medicinal product	BIBW 2992 (Afatinib), 50 mg per day per os
Indication	HER2-positive (HER2-overexpressing, i.e. either HER2 2+ or 3+ by immunohistochemistry (IHC) and/or HER2-amplified by fluorescence in-situ hybridization (FISH) according to the manufacturers' instructions, hormone-refractory prostate cancer.
Study Duration	Initially the recruitment phase was scheduled for 2 years. The maximal treatment phase was scheduled for 3 years. The database of the Institute of Pathology with more than 1000 patients who had surgical resection of their prostate was screened. More than 100 patients with HER 2+ or 3+ prostate cancer were identified. All these patients or their treating urologists were contacted. But unfortunately none of these more than 100 patients fulliled the eligibility criteria and could be entered into the study..Therefore, the whole study was prematurely discontinued. The study duration was 14 months. Only 1 patient was screened and enrolled in the study. He prematurely discontinued the trial after visit 3 in course 1 as he experienced tumour progression and finally died.
Study Duration per patients	Initially the maximal treatment phase was scheduled for 3 years. In fact, the single patient was only treated for 13 days before he prematurely discontinued the intake of study medication due to adverse events. Overall study duration was 22 days for this patient.
Duration of Treatment	Continuous treatment in the absence of disease progression or adverse events
Number of patients	1 patient was enrolled
Rationale	Currently, no effective treatment is available for patients with

	advanced prostate cancer who have undergone endocrine therapy and/or chemotherapy with docetaxel. Prostate cancer cells express both EGFR (HER1) and HER2. A recent study on more than 2,000 patients (2) showed that approximately 20% of patients with prostate cancer overexpress HER2 and that such overexpression is clearly associated with an adverse prognosis. This suggests that HER2 may drive the progression and treatment resistance of prostate cancer and that an even higher percentage than 20% of patients with advanced stages of prostate cancer overexpress this growth factor receptor. BIBW 2992 is a dual irreversible EGFR/HER2-inhibitor and showed clinical efficacy in HER2-overexpressing patients with metastatic breast cancer who failed prior trastuzumab treatment. Therefore, HER2-targeted treatment such as with the irreversible, dual EGFR- and HER2-tyrosine kinase inhibitor BIBW 2992 in patients proven to overexpress this protein may be an effective treatment.
Criteria for efficacy:	Primary end point: Objective PSA responses according to Bubley criteria Secondary end points: Objective response rate (ORR) based on Response Evaluation Criteria in Solid Tumours (RECIST 1.1), Duration of PSA-response (Bubley criteria) or objective responses, and Safety
Criteria for safety:	Adverse events according to Common Terminology Criteria for Adverse Events (CTCAE Version 3.0)
Statistical methods:	The primary objective was to determine the objective PSA response rate according to Bubley criteria of BIBW 2992 in patients with hormone-refractory prostate cancer after failure of docetaxel chemotherapy. It was planned that, according to the two-step Gehan design and assuming a meaningful PSA response rate of 10%, a total of 29 patients was required in the first stage of the study. If ≥ 1 response was observed in these 29 patients, the second stage should have been opened; otherwise the drug would have been judged as ineffective. The number of patients in the second stage depended on the number of responses observed in the first stage and ranges between 4 and 28 patients. As only one patient was enroled into the study and this patient prematurely discontinued the trial due to tumour progression with a fatal outcome, no statistical evaluation was performed.

Objective	To investigate the efficacy and safety of BIBW 2992 (Afatinib) in patients with HER2-positive, hormone-refractory prostate cancer after failure of docetaxel or ineligible for treatment with docetaxel
Main Criteria for Inclusion	• Patients must provide written informed consent • Age ≥ 18 years • Patients must have histological proven, hormone-refractory prostate cancer • Patients must have failed prior therapy with docetaxel or must be ineligible for treatment with docetaxel • Patients must have ECOG performance status ≤ 2 • Patients must not have received any prior therapy targeting EGFR or HER2 • Patients must have adequate bone marrow, renal and hepatic function • Patients must not have a history of severe heart disease • Patients must not have had a myocardial infarction within the previous six months • Patients must have normal left ventricular ejection fraction (LVEF ≥ normal limit of institution) • Patients must not have symptomatic brain or leptomeningeal metastatic disease • Patients must have recovered from previous treatment-related adverse effects to National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 (CTCAE) grade ≤ 1
Main Criteria for Exclusion	• Prior treatment with EGFR/HER2-targeted small molecules or antibodies, i.e. trastuzumab and/or lapatinib • Known pre-existing interstitial lung disease • Radiotherapy, chemotherapy, hormone therapy (with the exception of GnRH agonists), immunotherapy or surgery (other than biopsy) within 4 weeks prior to start of treatment with BIBW 2992. GnRH-agonists are allowed at the discretion of the investigator. • Active brain metastases (defined as stable for < 4 weeks and/or symptomatic and/or requiring changes of treatment with anticonvulsants or steroids within the past 4 weeks and/or leptomeningeal disease). Patients with known history of brain metastases should undergo a baseline brain image to ensure that the disease is stable. • Any other current malignancy or malignancy diagnosed within the past five (5) years (other than non-melanomatous skin cancer). • Significant or recent acute gastrointestinal disorders with diarrhoea as a major symptom, e.g. Crohn's disease, malabsorption or CTC grade ≥ 2 diarrhoea of any aetiology. • History or presence of clinically relevant cardiovascular

	abnormalities such as uncontrolled hypertension, congestive heart failure NYHA classification of 3, unstable angina or poorly controlled arrhythmia. Myocardial infarction within 6 months prior to randomisation. • Cardiac left ventricular function with resting ejection fraction of less than 50%. • Any other concomitant serious illness or organ system dysfunction which in the opinion of the investigator would either compromise patient's safety or interfere with the evaluation of the safety of the test drug. • Absolute neutrophil count (ANC) < 1500 / mm^3. • Platelet count < 75,000 / mm^3 • Calculated creatinine clearance < 60 ml / min (using Cockcroft-Gault formula for GFR estimate, see **Fehler! Verweisquelle konnte nicht gefunden werden.**) or serum creatinine > 1.5 times upper limit of normal. • Uncontrolled hypercalcemia • Patients unable to comply with the protocol. • Known hepatitis B infection, known hepatitis C infection or known HIV carrier. • Known or suspected active drug or alcohol abuse. • Requirement for treatment with any of the prohibited concomitant medications listed in section 10.2.2.1. • Any contraindications for therapy with BIBW 2992. • Known hypersensitivity to BIBW 2992. • Use of any investigational drug within 4 weeks of start of treatment.

Study Treatment	BIBW 2992 dose 50 mg per day (oral)
Safety Results	Only 1 patient was enrolled in the study. The patient prematurely discontinued the trial due to tumour progression with a fatal outcome. Three adverse events were reported with a possible relationship to the study medication: vomiting, which worsened from mild to moderate during the course of the study, and nausea. Due to these AEs, the administration of the study medication was interrupted. The permanent discontinuation of study drug administration was caused by tumour progression with a consecutive decreased general condition of the patient and finally, a fatal outcome. Two serious adverse events occurred in the patient, urosepsis and tumour progression, documented by a total of 12 adverse events (not considering the 3 AEs with a possible relationship to the IMP as described above). As only 1 patient was enrolled and he was only treated with the study medication for 13 days, only limited conclusions concerning the safety of BIBW 2992 could be made. Overall the reported serious adverse events are common for a trial population with prostate cancer and both SAEs were judged to be unrelated to the study medication. Concerning other safety parameters (vital signs, laboratory values) there were no relevant changes between screening and the 3 visits which were attended by the patient.
Conclusion	Only 1 patient was enrolled in the study. In general, the study medication was well tolerated. 2 serious adverse events appeared, which are common for a trial population with prostate cancer. There were no relevant changes in clinical laboratory variables or vital signs. As only one patient was enroled in the study and not up to 57 as planned, no statistical evaluation and no evaluation of the study objectives was possible.

5 FLOW CHART

Table 1: Flow Chart

Study Period	Screening*	Treatment Courses**						EOT ***	FU 1 ****	Add. FU ****	OP *****
		C 1			C 2 onwards						
Visit		1	2	3	1	2******					
Days	-14 to -1	1	8 (± 2)	15 (±2)	1 (± 2)	15 (± 2)			+28		Every 90 days
Informed Consent (1)	x										
Demographics/medical history	x										
Review of In-/Exclusion criteria	x										
Complete physical examination	x							x			
Limited physical examination		x			x				x		
Vital Signs	x	x	x	x	x	x		x	x		
ECOG performance status	x	x			x			x	x		
Healthcare resource use		x			x			x	x	x	
12-Lead ECG (3)	x (3)		x (3)		x (3)			x (3)			
LVEF (4)	x				x (4)			x (4)			
Safety lab (5)	x	x	CBC	x +CBC (5)	x	CBC		x	x		
Tumour sample for HER2-	x (6)										
Tumour assessment (7)	x	See schedule below (7)									
Tumour markers (8)	x	x			x			x	x		
Concomitant medications	x	x	x	x	x	x		x	x		
Compliance Check BIBW 2992			x	x	x	x		x			
Adverse events	x	x	x	x	x	x		x	x	x (10)	
Dispense BIBW 2992		x			x						
BIBW 2992 treatment		Continuous									
Termination of study								x			
Study Completion									x (11)	x (11)	
Collection vital status and											x (12)

* The screening visit had to be performed within 14 days prior first drug administration of BIBW 2992. HER2 -testing was performed prior to the first drug administration.
** All courses were 4 weeks (28 days) in duration. Patients could continue on treatment until the criteria for stopping medication were met (see section 9.3.4) (max. 3 years).
*** If the decision to permanently discontinue study treatment was taken during a scheduled visit, the End of Treatment visit should have been performed instead of the scheduled visit (within 0-14 days after last drug administration).
**** All patients should have had a follow-up visit 28 days (± 7days) after the EOT visit. Patients who had not progressed and not started further treatment at EOT should have had further limited follow-up visits at scheduled tumour assessment until progression or start of further treatment.
***** Observation period for vital status information every 90 days after last follow-up visit
****** Visit 2 on day 15 ± 2 only during courses 2 and 3

1 Written informed consent must have been obtained before any protocol specific screening assessments were performed. Informed Consent must have included consent to collection of demographic data and consent to obtaining a tumour tissue (for archived tumour sample collection purpose, informed consent could have been obtained earlier than 14 days prior to therapy).
2 Includes height (at screening only) and weight.
3 A 12-lead resting ECG was performed at Screening, on V2 of C1, then at V1 of every third course (C4, 7, 10, etc.), and at EOT (if not performed in the previous 8 days).
4 LVEF was evaluated at Screening, on Day 1 of Course 4 and then at every third course (Course 7, 10, 13 etc.), and at EOT (if not performed in the previous 8 days).
5 Includes: Haematology, serum biochemistry and INR. Urinalysis only at baseline and EOT. CBC at V2 and V3 of course 1 and at V2 of course 2 and 3.
6 (Archival) Tumour tissue must have been available for HER2-testing. An optional Biopsy for additional fresh tumour tissue for HER2-testing would have been recommended (if patient gave additional consent and if the location of the metastatic lesion was accessible)
7 Tumour assessments should have included CT scans of the chest and abdomen and, if clinically indicated, imaging of any other known or suspected sites of disease (e.g. pelvis, brain) using an appropriate method (CT scan or MRI). The same radiographic procedure must have been used throughout the study. Bone scans and correlative imaging should have been performed when clinically indicated (see section 11.1.2 for more detail). Assessment was performed at the following timepoints until progression/start of further treatment:
   - At screening (within 28 days prior start of treatment was accepted)
   - Every 8 weeks: during week 8 (49-56 days after start of treatment), during week 16 (105-112 days after start of treatment), during week 24 (161-168 days after start of treatment), during week 32 (217-224 days after start of treatment), during week 40 (273-280 days after start of treatment, during week 48 (329-336 days after start of treatment) and during week 56 (385-392 days after start of treatment)
   - Every 12 weeks after week 56.

   In the event of early discontinuation or an interruption/delay to treatment the tumour assessment schedule must not have been changed.
8 Tumour marker PSA at screening, visit 1 of every other cycle, EOT, and follow-up 1. Circulating tumour cells were determined at baseline, on the first day of cycle 2 and at EOT
9 Check on day 8 & 15 C1, on days 1 & 15 C2 and C3, then at the end of every course and at EOT
10 AEs that were drug related only
11 Study completion has to be filled out at FU (at 1st or additional FU where applicable) when PD occurs or when new treatment was started or when consent was withdrawn.
12 Collection of information on progression, further treatment and death. Information should have been collected from patient's notes or by telephone contact with the patient. A formal study visit was not required.

6 INVESTIGATOR AND STUDY ADMINISTRATIVE STRUCTURE

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7 INTRODUCTION

7.1 MEDICAL BACKGROUND

7.1.1 Prostate Cancer and HER2-Inhibition

Currently, no effective treatment has been available for patients with advanced prostate cancer who have undergone and eventually failed endocrine therapy and/or chemotherapy with docetaxel. But recently, cabazitaxel has been shown to prolong survival in docetaxel pretreated HRPC patients in comparison to mitoxantrone [1]. No further effective chemotherapeutic option is available for this patient group thereafter. Cabazitaxel is not yet approved in Germany at this time, but may become available during the course of this study.

Prostate cancer cells express both EGFR (HER1) and HER2. A recent study on more than 2,000 patients [2] showed that approximately 20% of patients with prostate cancer overexpress HER2 and that such an overexpression of HER2 is clearly associated with an adverse prognosis. This suggests that HER2 may drive the progression and treatment resistance of prostate cancer and that an even higher percentage than 20% of patients with advanced stages of prostate cancer overexpress this growth factor receptor. Therefore, HER2-targeted treatment such as with the irreversible, dual EGFR- and HER2-tyrosine kinase inhibitor BIBW 2992 in patients proven to overexpress this protein may be an effective treatment. A technical protocol to reliably detect HER2 overexpression in prostate cancer tissue by immunohistochemistry has been established and validated at the Institute of Pathology at the University Hospital Hamburg-Eppendorf.

7.1.2 HER2-testing by immunohistochemistry and fluorescence in-situ hybridization

Targeted therapy with monoclonal antibodies directed against the human epidermal growth factor receptor 2 (HER2), e.g. trastuzumab, or with kinase inhibitors targeting the intracellular tyrosine kinase of HER2, e.g. the reversible, dual EGFR/HER2-tyrosine kinase inhibitor lapatinib, is restricted to breast cancer patients whose tumours overexpress the HER2-protein on the surface of the tumour cells as detected via immunohistochemistry (IHC) or have HER2-gene amplification as detected via fluorescence in-situ hybridization (FISH).

The scoring system of membrane staining for HER2-protein (over)expression according to the DAKO HercepTest™ differentiates 4 different scores of HER2-immunostaining:

HER2 score 0:	no staining or membrane staining observed in < 10% of tumour cells;
HER2 score 1+:	faint/barely visible membrane staining in > 10% of tumour cells;
HER2 score 2+:	weak to moderate, complete (circumferential) membrane staining observed in > 10% of tumour cells;
HER2 score 3+:	strong (intense), complete (circumferential) membrane staining observed in > 10% of tumour cells.

HER2 scores 0 and 1+ are classified as being negative, whereas HER2 score 3+ is classified as being HER2-positive warranting HER2-targeted therapy; HER2 score 2+ is being considered intermediate necessitating confirmation of HER2-status via FISH-testing. HER2-positivity according to FISH-testing is defined as a ratio of HER2/CEP17 (centromer 17 enumeration probe) ≥ 2.0 in invasive tumour cells.

7.2 DRUG PROFILE

BIBW 2992 is a novel oral EGFR/HER2-inhibitor that offers the chance to control both recurrent as well as distant metastatic disease on an outpatient basis with continuous treatment. BIBW 2992 final formulation is available in 30, 40 and 50 mg film-coated tablets to be used for clinical studies up to Phase III.

BIBW 2992 is a potent, irreversible, combined EGFR/HER2-inhibitor both *in vitro* and *in vivo*. Receptor tyrosine kinases other than the EGFR (Class I) family and non-receptor type tyrosine kinases were not inhibited. BIBW 2992 is bioavailable after oral administration in several species.

7.2.1 Preclinical pharmacology and toxicology

In mice, BIBW 2992 reaches efficacious plasma exposure with once-daily dosing throughout the treatment period. BIBW 2992 displays antitumour activity, including tumour regression, against established subcutaneous xenografts in nude mice either as a single agent or in combination with a cytotoxic agent like docetaxel. The necessary maximum plasma concentrations were between 80 to 285 nM for single agent activity. The absolute bioavailability was medium-high in rats (45%). The median t_{max} after oral administration was 4 hours and the terminal half-life was 4.5 hours. The terminal half-life of the radiolabelled compound was considerably longer indicating persistence of metabolites in the system. The exposure was dose proportional without gender-related effects. Some accumulation in the 13-week and 26-week toxicology study appeared more pronounced in males. In minipigs there was a slight tendency towards supra-proportional increases in $AUC_{0\text{-}24h}$ with increasing doses, which was considered to be of minor relevance. A consistent effect on accumulation was not seen.

In the whole body autoradiography in rats, BIBW 2992 was distributed in all organs with the exception of the CNS after oral administration. The highest concentrations were found in the kidney, liver, lung, and spleen. In general, a slow elimination of radioactivity was seen. The major excretion pathway is via faeces (91%). BIBW 2992 covalently binds to plasma proteins. Whether such protein haptens are immunogenic and capable of inducing allergic reactions is unknown.

BIBW 2992 did not show relevant inhibition or induction of cytochrome P450 isoenzymes, and it appears unlikely that drug-drug interactions as based on this mechanism will occur [3]. *In vivo*, BIBW 2992 was metabolised only to a minor extent and the metabolism was governed by adduct formation to proteins or nucleophilic small molecules. It was found that metabolism is of subordinate role for BIBW 2992 and that enzyme-catalyzed metabolic reactions play a negligible role for the metabolism of BIBW 2992 *in vivo*. Only approximately 2 % of the dose were metabolised by FMO3 *in vivo*. The CYP3A4-dependent N-demethylation was even too low to be quantitatively detected in human volunteers [4][5][6]. Therefore, intrinsic (e.g. genetic predisposition) or extrinsic (e.g. by comedications) effects on the activity of FMO3 or CYP3A4 *in vivo* are expected to be of little, if any, relevance for the pharmacokinetics of BIBW 2992.

In vitro, BIBW 2992 was found to be a P-gp substrate (estimated K_m 10-30 µM) and a moderate to weak inhibitor of P-gp (estimated K_i of 3.4 µM). It cannot be excluded that concomitant treatment with other P-gp substrates or P-gp inhibitors may alter the plasma concentrations of BIBW 2992. Since I/K_i of BIBW 2992 is resulting in values considerably below 0.1 which would be the defined “cut off” value for considerable drug-drug interactions based on P-gp (BIBW 2992 acting as a P-gp inhibitor) it is unlikely that BIBW 2992 may alter the plasma concentrations of other P-gp substrates.

Safety pharmacology studies (GLP) in rats indicate no adverse effects on behaviour or respiratory function. BIBW 2992 in the doses tested was essentially devoid of effects on the CNS and pulmonary system. Lack of organ specific toxicity was also true for the cardiovascular system with the exception of reduced contractility at higher intravenous doses.

An effect on renal and liver function was seen with a very high oral dose of 300 mg/kg in rats. Furthermore, a dose dependent effect on gastrointestinal function was seen, leading to a substantial inhibition at the highest dose. *In vitro* data, together with the lack of effect on the ECG in pigs and minipigs, do not indicate a risk for QT prolongation related arrhythmias.

A variety of single and repeated dose studies were conducted with BIBW 2992 [3]. The main target organs were the skin (rat), the gastrointestinal tract (both species) and the kidneys (rat). The severity of the findings resulted in premature sacrifices and mortality of rats at high dose groups in repeat dose studies.

In the gastrointestinal tract, increasing systemic exposure was associated with dose dependent atrophy of the epithelium and concomitant focal erosions/ulcerations in the stomachs of rats and minipigs. Clinically, this was characterized by diarrhoea in both species and faecal occult blood in a single minipig. Other organs affected by the epithelial atrophy in the rat were the skin, prostate, uterus, and vagina. In minipigs, the upper respiratory tract, seminal vesicles, and the corneal epithelium were affected by epithelial atrophy. In the gastrointestinal and respiratory tract, atrophy of the mucinous glands, e.g. salivary glands, was also found. These atrophic changes were minimal to slight and fully reversible during the recovery periods and are most likely related to the pharmacodynamic mechanism of BIBW 2992.

Findings in rat kidneys include papillary necrosis and dilated tubules. The kidney as a target organ in animals is also described for the EGFR-inhibitors gefitinib (Iressa™) and erlotinib (Tarceva™).

BIBW 2992 is not irritating to intact skin. BIBW 2992 is slightly mutagenic in a single bacteria strain, but it did not show genotoxic potential *in vivo* when tested up to overt toxic/lethal doses. Because of the pharmacodynamic mechanism, BIBW 2992 is probably embryo-/fetotoxic [3].

Based on these toxicological findings and the experience with other EGFR- and HER2-inhibitors, the risks of anti-EGFR and anti-HER2 therapy with BIBW 2992 might primarily consist of gastrointestinal effects (including diarrhoea) and skin rash.

7.2.2 Clinical pharmacokinetic and safety

PK data available from clinical trials until now indicate that BIBW 2992 was moderately fast absorbed after oral administration, with median t_{max} values mainly between 1 and 6 hours. For BIBW 2992 there was no deviation from dose-proportionality detectable. However, moderate to high inter- and intra-individual differences in plasma concentrations were seen. BIBW 2992 was highly distributed out of the blood and had a moderate to high clearance. The gMean terminal half-life was mainly in the range of 13-57 h. Steady state was reached no later than 8 days after the first administration. The major route of elimination of BIBW 2992 was via the faeces. After food intake, a decreased systemic exposure was observed compared to administration of BIBW 2992 under fasted conditions. Typically, an accumulation ratio based on AUC values between 1.8 and 4.0 has been observed. At doses of 40 mg and above individual $C_{max,ss}$ and $AUC_{\tau,ss}$ values were mainly in the same range as those found to demonstrate anti-tumour activity in nude mouse tumour xenograft models.

Adverse events observed with BIBW 2992 are consistent with those reported for other EGFR- and dual EGFR/HER2-inhibitors (gastrointestinal and oral symptoms as well as skin toxicity including rash and acne). Gastrointestinal toxicities include diarrhoea, oral symptoms (e.g., mucositis/stomatitis), nausea and vomiting. A smaller number of patients experienced dehydration likely secondary to gastrointestinal AEs. In some cases, dehydration led to renal insufficiency and electrolyte abnormalities. Reported skin symptoms include pruritus, dry skin, eczema, and folliculitis. Fatigue, anorexia and epistaxis have been reported relatively frequently. A higher incidence of CTCAE Grade 3 adverse events (especially diarrhoea) have been observed in phase II trials at 50 mg. Continuing exposure of greater numbers of patients with cancer to BIBW 2992 will allow a better understanding and further refinement of the side effect profile.

The safety profile of BIBW 2992 is characterized by a significant incidence of dose-dependent gastrointestinal and skin adverse events. Early, proactive, and effective management of these adverse events is mandated in ongoing and forthcoming clinical trials with early intervention to manage diarrhoea and skin toxicities.

One related case of fatal interstitial lung disease (ILD) was reported in a NSCLC patient. A contributing role of BIBW 2992 could not be excluded. As this is a known class effect of other EGFR/HER2-inhibitors, patients with known ILD will be excluded from clinical trials with BIBW 2992 and careful monitoring of pulmonary symptoms with sudden onset is warranted in all clinical trial protocols. The risk benefit ratio remains unchanged in light of this event. For further details and regular updates on listed adverse events please refer to the current IB [3].

7.2.3 Clinical efficacy

Objective responses and durable stable disease in patients with advanced solid tumours have been observed in phase I monotherapy studies as well as in phase I combination studies.

Ongoing phase II studies show clinical activity of BIBW 2992 in patients with EGFR-mutation positive NSCLC and patients with HER2-positive breast cancer.

BIBW 2992 is currently in phase III clinical testing.

Overall 14 patients with metastatic breast cancer were included in the Phase I BIBW 2992 monotherapy trials. Of these 4 patients showed stable disease (SD) as best response to treatment with duration of at least 12 weeks in 3 patients, and duration of 24 weeks in 1 patient. Another five patients with metastatic breast cancer were entered into Study 1200.20, a Phase I BIBW 2992 trial in combination with docetaxel. BIBW 2992 was administered on days 2-4 following a docetaxel administration on day 1, in a 21 day cycle. One patient showed a complete response (CR), two patients a partial response (PR) while on BIBW 2992 treatment and another patient had stable disease.

Three phase II trials have so far been conducted in patients with metastatic breast cancer. Four of 34 patients who were evaluable for response in a phase II trial in HER2-positive mBC patients who failed prior trastuzumab treatment showed a partial response (PR). 15 patients had stable disease (SD). The median PFS was 106 days and the median overall survival was 427 days. Time to response was between 52 and 110 days. The mean duration of objective response was 153 days. One of the responders was on treatment for 63 weeks until disease progression. All patients responding to BIBW 2992 monotherapy had been heavily pre-treated with trastuzumab for up to 29 months prior to progression. Five patients included into a combination trial with letrozole in ER-positive, hormone-refractory patients had stabilisation of disease for more than 4 courses. Remarkably, most of these patients were HER2-negative. Three triple negative patients included into another monotherapy trial again showed stabilization of disease for ≥ 4 treatment courses.

8 RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

8.1 Rationale for performing the study

Currently, no effective treatment is available for patients with advanced prostate cancer who have undergone endocrine therapy and/or chemotherapy with docetaxel. Prostate cancer cells express both EGFR (HER1) and HER2. A recent study on more than 2,000 patients [2] showed that approximately 20% of patients with prostate cancer overexpress HER2 and that such overexpression is clearly associated with an adverse prognosis. This suggests that HER2 may drive the progression and treatment resistance of prostate cancer and that an even higher percentage than 20% of patients with advanced stages of prostate cancer overexpress this growth factor receptor.

BIBW 2992 is a dual irreversible EGFR/HER2-inhibitor and showed clinical efficacy in HER2-overexpressing patients with metastatic breast cancer who failed prior trastuzumab treatment.

Therefore, HER2-targeted treatment such as with the irreversible, dual EGFR- and HER2-tyrosine kinase inhibitor BIBW 2992 in patients proven to overexpress this protein may be an effective treatment.

8.2 Study objectives

This open-label, single-arm, single-center phase II study was performed in patients with HER2-positive, hormone-refractory prostate cancer who failed docetaxel therapy or who were not eligible to docetaxel treatment. (Pretreatment with cabazitaxel or mitoxantrone was also allowed). The main objective of the trial was to evaluate the efficacy and safety of BIBW 2992 in this patient population.

As only one patient was enrolled and this patient prematurely discontinued the trial due to tumour progression with a fatal outcome, the study did not show any results concerning efficacy of BIBW 2992 and only very limited results for safety of BIBW 2992.

8.3 Benefit-risk assessment

There is currently no effective treatment option available for patients with hormone-refractory prostate cancer who have failed docetaxel, (and cabatitaxel) therapy after having developed resistance to hormonal therapy. An irreversible dual EGFR/HER2 - tyrosine kinase inhibitor like BIBW 2992 (Afatinib) might provide a reasonable therapeutic approach in the subset of patients with HER2-positive prostate cancer by inhibiting both EGFR- and HER2-receptor tyrosine kinases.

BIBW 2992 had been tested in phase I and II trials in monotherapy and combination treatment and was currently in phase III clinical development. It had shown clinical efficacy in NSCLC and BC. Adverse events observed were largely class effects of EGFR inhibitors (mainly gastrointestinal and cutaneous adverse events). BIBW 2992 proved to be tolerable, and side effects in general were reversible. For details please refer to the IB [3]. At present no increase in cardiac AEs was observed unlike what was observed with trastuzumab.

9 DESCRIPTION OF DESIGN AND STUDY POPULATION

9.1 Overall study design and plan

This phase II open-label, single-arm study was designed to evaluate the efficacy and safety of BIBW 2992 for the treatment of patients with hormone-refractory advanced prostate cancer whose tumours were HER2-positive. The primary endpoint of the study was the rate of objective PSA responses according to Bubley criteria [7].

The study was performed by investigators specialised in the treatment of prostate cancer. It was planned that up to a maximum of 57 patients were enrolled in the study. All patients were required to provide archived tumour sample at screening for HER2-testing to confirm HER2-status; the HER2 -test results must have been available prior to confirmation of patients' eligibility. The tumour usually growths slowly and therefore archived tumour samples would have been sufficient for a diagnosis in the course of the study. However, a fresh sample would have been recommended for further scientific research (e.g. further HER2 testing). Therefore, an optional biopsy would have been conducted, if the patient gave additional consent and if the location of the metastatic lesion was accessible.

Patients received continuous daily treatment with BIBW 2992 50 mg until disease progression, unacceptable adverse events or other reasons necessitating withdrawal (refer to section 9.3.4). The treatment was administered as courses of 28 days. The starting dose of BIBW 2992 was 50 mg orally once daily. As detailed in section 10.1.3.1.1, dose reduction occured in the event of certain drug-related adverse events.

All patients visited the investigator at regular intervals for assessment of safety parameters and adverse events as outlined in the Flow Chart. Assessments of response were made regularly (see Flow Chart) until progression or withdrawal for another reason (e.g. withdrawal of consent). Patients who hade to stop the active treatment for another reason than progression should have been retained in the study and should have undergone further visits according to the tumour assessment schedule.

The end of treatment (EOT) information had to be obtained when the study treatment was permanently discontinued. EOT was defined as permanent discontinuation of BIBW 2992. All patients who ended the study treatment for any other reason than progression of disease were followed up for tumour assessment and drug-related adverse events as described in sections 12.2.3. At disease progression or at start of new treatment, patients were then discontinued from the study.

The study was to be terminated as soon as the last patient had completed the last additional follow-up visit documenting disease progression or the start of new treatment. In case patients would still have been on treatment when the report of the study was performed, these patients would either have been included in a follow-up trial or alternatively kept on treatment in this trial. Those patients and their additional data on secondary endpoints would have been reported in an addendum to the report.

Tumour response and progression were assessed using the Bubley criteria [7] and RECIST 1.1 [8] and assessment at the investigator site was sufficient for decisions on continuation of treatment (refer to appendix 4). On-site monitoring was performed by a CRO appointed by the Principal Investigator.

All study relevant documentation was stored in the Trial Master File (TMF) at CTC North. In addition the site had an Investigator Site File (ISF) containing all study documents relevant for the site.

The Principal Investigator and his sub-investigators in the study had experience of this type of study and investigations. The Principal Investigator signed the clinical study report.

9.2 Discussion of study design

The primary objective of this study was to evaluate the efficacy and safety of BIBW 2992 in patients with hormone-refractory, HER2-positive prostate cancer who had failed prior docetaxel treatment (pretreatment also with cabazitaxel and mitoxantrone allowed) or who were ineligible for docetaxel treatment. Patients should have been followed until progression. After progression, for the purpose of analysing overall survival, information on vital status and subsequent treatment should have been collected.

9.3 Selection of study population

A log of all patients screened in the study (i.e. having given informed consent) was to be maintained in the ISF at the investigational site irrespective of whether they had been treated with investigational drug or not. It was planned that a total number of up to 57 patients were enrolled. In fact, only one patient could be enrolled. Although more than 1000 patients with prostate cancer were screened fom the database of the Institute of Pathology and more than 100 patients with HER 2+ or 3+ prostate cancer were identified, none fulfilled the inclusion/eclusion criteria and could be entered into the study. Therefore the study was terminated prematurely.

9.3.1 Main diagnosis for study entry

All patients that were included into the study must have been diagnosed with histological confirmed, HER2-positive prostate adenocarcinoma.

9.3.2 Inclusion criteria

1. Histological proven prostatic adenocarcinoma overexpressing HER-2 either by FISH analysis or Immunohistochemistry (2+ or 3+).
2. Hormone-refractory prostate cancer (pretreatment with abiraterone or analogues was allowed).
3. Patients must had failed prior therapy with docetaxel or had to be ineligible for treatment with docetaxel.
4. Patients must had progressed under prior hormonal treatment with LH-RH analogues or orchiectomy and anti-androgens, given either concomitantly or sequentially (previous treatment with estracyt is allowed). Progressive disease is defined as PSA progression documented by PSA increase recorded at 2 consecutive measurements over a previous reference .
5. Patients must had a demonstrated continued elevation of PSA for at least 6 weeks after discontinuation of antiandrogens prior to registration on study.
6. Last PSA value ≥ 5 ng/ml within 2 weeks prior to registration before entry on study and continue on LHRH agonist therapy.
7. Progressive disease according to PSA or RECIST criteria under Taxotere (pretreatment with cabazitaxel and/or mitoxantrone was also allowed).
8. Age ≥ 18 years.
9. ECOG performance status ≤ 2.
10. Adequate hematological functions as assessed by neutrophils ≥ 1.5 x 10^9/l, platelets ≥ 100 x 10^9/l.
11. Adequate liver function as assessed by bilirubin < 1.5 times the upper limit of the normal range and transaminases ≤ 5 times the upper limit of normal range in case of liver metastases and ≤ 2.5 times the upper limit of the normal range in absence of liver metastases.
12. Adequate renal function as assessed by serum creatinine ≤ 150 µmol/l (≤ 1.7 mg/dl).
13. Psychological, familial and geographical conditions must permit adequate medical follow-up and compliance with the study protocol.
14. Written informed consent according to ICH-GCP.

9.3.3 Exclusion criteria

1. Prior treatment with EGFR/HER2-targeted small molecules or antibodies, i.e. trastuzumab and/or lapatinib.
2. Known pre-existing interstitial lung disease.

3. Radiotherapy, chemotherapy, hormone therapy (with the exception of GnRH agonists), immunotherapy or surgery (other than biopsy) within 4 weeks prior to start of treatment with BIBW 2992. GnRH-agonists were allowed at the discretion of the investigator.
4. Active brain metastases (defined as stable for < 4 weeks and/or symptomatic and/or requiring changes of treatment with anticonvulsants or steroids within the past 4 weeks and/or leptomeningeal disease). Patients with known history of brain metastases should have undergone a baseline brain image to ensure that the disease was stable.
5. Any other current malignancy or malignancy diagnosed within the past five (5) years (other than non-melanomatous skin cancer).
6. Significant or recent acute gastrointestinal disorders with diarrhoea as a major symptom, e.g. Crohn's disease, malabsorption or CTC grade ≥ 2 diarrhoea of any aetiology.
7. History or presence of clinically relevant cardiovascular abnormalities such as uncontrolled hypertension, congestive heart failure NYHA classification of 3, unstable angina or poorly controlled arrhythmia. Myocardial infarction within 6 months prior to randomisation.
8. Cardiac left ventricular function with resting ejection fraction of less than 50%.
9. Any other concomitant serious illness or organ system dysfunction which in the opinion of the investigator would either compromise patient's safety or interfere with the evaluation of the safety of the test drug.
10. Absolute neutrophil count (ANC) < 1500 / mm^3.
11. Platelet count < 75,000 / mm^3
12. Calculated creatinine clearance < 60 ml / min (using Cockcroft-Gault formula for GFR estimate, see appendix 1) or serum creatinine > 1.5 times upper limit of normal.
13. Uncontrolled hypercalcemia.
14. Patients unable to comply with the protocol.
15. Known hepatitis B infection, known hepatitis C infection or known HIV carrier.
16. Known or suspected active drug or alcohol abuse.
17. Requirement for treatment with any of the prohibited concomitant medications listed in section 10.2.2.1.
18. Any contraindications for therapy with BIBW 2992.
19. Known hypersensitivity to BIBW 2992.
20. Use of any investigational product within 4 weeks prior to start of treatment.

9.3.4 Removal of patients from therapy or assessments

A patient had to be withdrawn from study therapy in case any of the following applied:

1. The patient withdrew consent to further study treatment.
2. Documented progressive disease (refer to section 11.1.2)
3. The patient was no longer able to receive the study drug (e.g. adverse events, concomitant diagnoses, concomitant therapies or administrative reasons). In these cases, the investigator should have recorded the reason for treatment discontinuation in the case report form (CRF).
4. Significant deviation from the protocol or eligibility criteria.
5. Diagnosis of interstitial lung disease.
6. Further dose reductions considered necessary but not allowed according to the protocol (for exceptions, refer to section 10.1.3.)

For safety reasons it was recommended that the patient was encouraged to return for at least the follow-up visit.

Except for reason 2 "progression of disease", it should have been attempted to retain the patient in the study and to perform additional follow-up visits at tumour assessment schedule until progression of disease or start of new treatment.

A patient had to be withdrawn from study and any further study assessment (except collection of survival data) in case any of the following applied:

1. documented progressive disease (refer to section 11.1.2)
2. start of new anti-cancer treatment
3. withdrawal of consent

If the stopping criteria were not met within the maximum study duration of 3 years per patient, the therapy could have been continued but would not have been part of the study anymore.

9.3.5 Premature discontinuation of the study as a whole

The Principal Investigator (according to § 40 AMG, German Drug Law) of the clinical study bore legal responsibility for the discontinuation of the study as a whole.
The study might be discontinued by the Principal Investigator at any time for the following reasons:

1. Failure to meet expected enrolment goals.
2. Emergence of any safety information that could have significantly affected the continuation of the study, i.e. more than 25% of the included patients experiencing at least one serious adverse event that was judged by the Principal Investigator as certainly, probably or possibly related to the investigational product.
3. Violation of GCP and/or the clinical trial protocol, disturbing the appropriate conduct of the study.

10 TREATMENTS

10.1 Treatments to be administered

Patients received BIBW 2992.

10.1.1 Identity of investigational product

Substance (INN):	**BIBW 2992**
Pharmaceutical form:	Film-coated tablets
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	50 mg, 40 mg, and 30 mg film-coated tablets (the dose of BIBW 2992 in the film-coated tablets is related to the free base equivalent of BIBW 2992)
Duration of use:	Continuous daily dosing until progression, unacceptable adverse events or other reason necessitating withdrawal. For administrative purposes treatment was divided into courses which were 4 weeks (28 days) each in duration.
Route of administration:	Oral (swallowed)
Posology:	50 mg once daily

10.1.2 Selection of doses in the study

The maximal tolerated dose for BIBW 2992 given orally as monotherapy was determined at 50 mg BIBW 2992 given continuously in a 28-day treatment course. This was the recommended phase II and phase III dose.

In this study, BIBW 2992 was used as follows:

- BIBW 2992 was taken every day in the morning at a dose of 50 mg preferably at the same time every day and at least one hour before any food intake and at least three hours after food intake

10.1.3 Drug assignment and administration of doses for each patient

10.1.3.1 BIBW 2992

For administrative purposes treatment was divided into treatment courses, which were 4 weeks (28 days) each in duration. Patients took a single oral dose of 50 mg BIBW 2992 every day in the morning.

The medication should have been taken at the same time every day (± 2 hours) at least one hour before food intake and at least three hours after food intake. However, beverages were allowed ad libitum also during this time. The tablet should have been swallowed with a glass of water. BIBW 2992 tablets were film-coated and therefore should not have been chewed or crushed, but might be administered via G-tube (gastric-tube) after dispersing the BIBW 2992 tablets according to the following procedure: Place the tablet into a glass containing 50 mL isotonic sodium chloride solution. Stir until the tablet is broken up into very fine particles (about 15 minutes). Drink the suspension immediately or administer via a G-tube. Rinse the glass with another 50 ml of isotonic sodium chloride solution and drink or administer the supplementary solution via the G-tube again (to pick up any drug remaining in the glass/gastric-tube). However, administration of BIBW 2992 via G-tube had to be recorded in the CRF.

Missed doses of BIBW 2992 could have been made up if taken within 6 hours of the regularly scheduled time. Otherwise, the dose should have been skipped and patients should have taken the next scheduled dose at the usual time. Patients with emesis should not have taken a replacement dose.

10.1.3.1.1 Dose reduction scheme for BIBW 2992

In the event of treatment-related toxicities, the treatment with BIBW 2992 should have been handled according to the schedule in Table 2.

Table 2: Dose reduction scheme

AE type and grade	Action	Dose reduction scheme
Events related to study drug: • Any **drug related** AE CTCAE Grade ≥ 3. • CTCAE Grade ≥ 2 diarrhoea persisting for 2 or more consecutive days (48 hours) despite adequate anti-diarrhoeal medication/hydration. • CTCAE Grade ≥ 2 nausea and/or vomiting persisting for 7 or more consecutive days despite anti-emetic treatment/ hydration. • CTCAE Grade ≥ 2 worsening of renal function as measured by serum creatinine, newly developed proteinuria, or newly developed decrease in glomerular filtration rate of more than 50% from baseline.	Pause treatment with BIBW 2992 until patient has recovered to CTCAE Grade ≤ 1 or baseline[1]. Resume treatment at reduced dose according to schedule opposite. If patient has not recovered to CTCAE Grade ≤ 1 or baseline[1] within 14 days study treatment should be permanently discontinued[2].	If patient was receiving 50 mg, resume treatment at a dose of 40 mg. If patient was receiving 40 mg, resume treatment at a dose of 30 mg. If patient was receiving 30 mg, discontinue BIBW 2992.

1 Baseline was defined as the CTCAE Grade until start of treatment

2 In the event that the patient was deriving obvious clinical benefit in the opinion of the investigator, but had not recovered within 14 days, the further treatment of the patient was decided by the Principal Investigator in agreement with the investigator.

Dose reduction should always have followed a treatment pause. In the event of a treatment pause, subsequent visits/courses should not have been delayed.

Patients discontinued treatment if they experienced deterioration in left ventricular cardiac function (LVEF) to CTCAE Grade ≥ 3.

In the event of a prolonged (≥ 7 consecutive days) Grade 2 drug-related event not listed in Table 2, which is poorly tolerated by the patient, the investigator might choose to pause the medication for up to 14 days to allow the patient to recover followed by a dose reduction according to the schedule in Table 2.

In the event of any unrelated adverse events or unrelated serious adverse events, the investigator might choose to pause the medication for up to 7 days to allow the patient to recover, but no dose reduction should have occured. If the investigator chose to pause the medication for more than 7 days and believed that the patient would have derived clinical benefit from continuing medication, the decision to continue medication was to be made by the Principal Investigator.

10.1.4 Packaging, labelling, and storage

Medication numbers were unique to each bottle and were used for tracking purposes only.

10.1.4.1 BIBW 2992

BIBW 2992 was supplied as film-coated tablets. Available dosage strengths were 30 mg, 40 mg and 50 mg. Tablets were supplied in HDPE, child-resistant, tamper-evident bottles.

Bottles/boxes were labelled according to local regulations and included the following as a minimum:

- Study number (1200.138)
- Product name (BIBW 2992)
- Contents of the bottle (30 tablets)
- Tablet strength (30 mg, 40 mg or 50 mg)
- Batch number
- Medication number
- Use-by date
- Storage information
- Instructions for use
- Sponsor name and address
- A statement that the medication is for clinical study use only
- A caution statement

A new bottle of medication was dispensed on day 1 of each course, regardless of the number of tablets remaining in the bottle from the previous course. The patient initially received one bottle of 50 mg tablets and in the event that dose reduction was necessary the patient returned to the clinic and new medication was dispensed.

10.1.4.2 Storage conditions

BIBW 2992 was stored in the original packaging. Film-coated tablets are humidity sensitive and therefore bottles were kept tightly closed. Tablets were stored at the study site in a limited access area and were stored in accordance with the instructions on the label.

10.1.5 Drug accountability

Drug supplies, which were provided by Boehringer Ingelheim, were kept in a secure, limited access storage area under the storage conditions. Where necessary, a temperature log was maintained to make certain that the drug supplies were stored at the correct temperature.

The responsible person maintained records of the product's delivery to the study site, the inventory at the site, the use by each patient, and the return to the Boehringer Ingelheim or alternative disposition of unused product(s).

These records included dates, quantities, batch/serial numbers, expiry ('use by') dates, and the unique code numbers assigned to the investigational product(s) and study patients. The responsible person maintained records that documented adequately that the patients were provided the doses specified by the CSP and reconciled all investigational product(s) received from Boehringer Ingelheim. The responsible person verified that all unused or partially used drug supplies had been returned by the clinical study patient.

10.2 Concomitant therapy, restrictions and rescue treatment

10.2.1 Rescue medication, emergency procedures, and additional treatment(s)

Rescue medications to reverse the actions of BIBW 2992 were not available. Side effects of these treatments should have been treated symptomatically. Growth factor support was used following ASCO Guidelines [9].

The current version of the Investigator Brochure lists the AEs expected with BIBW 2992 [3]. Suggested treatments for diarrhoea, nausea, vomiting and rash/acne are described in section 10.2.3.

During study participation symptomatic treatment of tumour associated symptoms was allowed. Treatment with corticosteroids was allowed. Concomitant medications or therapy to provide adequate care might be given as clinically necessary. All concomitant (non-oncological) medications which were taken between study informed consent and the first follow-up visit should have been recorded in the case report form (CRF) with the start and end of treatment dates, the total daily dose, the respective unit and the reason for use.

Careful assessment of all patients with an acute onset and/or unexplained worsening of pulmonary symptoms (dyspnoea, cough, fever) should have been performed to exclude ILD. Study drug should have been interrupted pending investigation of these symptoms. If interstitial lung disease was diagnosed, study drug should have been permanently discontinued and appropriate treatment instituted as necessary. However. during this study, no lung disease was diagnosed.

10.2.2 Restrictions

10.2.2.1 Restrictions regarding concomitant treatment

Patients should not have received any additional experimental anti-cancer treatment, chemotherapy, immunotherapy, hormone treatment with the exemption of continuing therapy with GnRH analogues, or radiotherapy within 4 weeks prior start of treatment with BIBW 2992 until the end of treatment visit. Bisphosphonates treatment was allowed for patients with bone metastasis.

For BIBW 2992:

BIBW 2992 is a substrate of P-gp and its plasma concentrations can be affected by the use of P-gp inhibitors (data on file) and it is likely that P-gp inducers could also influence BIBW 2992 plasma concentrations. The use of potent P-gp inhibitors (including cyclosporin, erythromycin, ketoconazole, itraconazole, quinidine, phenobarbital salt with quinidine, ritonavir, valspodar, verapamil) and potent P-gp inducers (including St John's wort, rifampicin) had to be avoided during treatment with BIBW 2992.

10.2.2.2 Restrictions on diet and life style

In the event of diarrhoea patients should have been advised to avoid lactose-containing products or any foods known to aggravate diarrhoea.

To prevent skin related adverse events it was currently proactively recommended to avoid intense irradiation with UV light, e.g. sunbathing or visiting a solarium, and to use strict sun protection during the treatment period of the study. In case of sun exposure a sunscreen of Sun Protection Factor 15 (SPF 15) or higher, preferably containing zinc oxide, should have been used, preferably a thick, alcohol-free emollient cream. Harsh detergents should have been avoided.

10.2.3 Concomitant therapy

10.2.3.1 Management of diarrhoea following treatment with BIBW 2992

Close monitoring and proactive management of diarrhoea was essential for successful treatment of patients with BIBW 2992. Early and appropriate intervention could prevent the development of more severe diarrhoea. In most cases, loperamide controls diarrhoea caused by BIBW 2992. Loperamide should have been available at the start of therapy and kept with the patient at all times; it was therefore advisable that patients be given a prescription at the time of initiating treatment with BIBW 2992. Loperamide was considered as a NIMP. For loperamide use, please refer to the applicable SmPC/PI.

The recommendations for management were as follows:

- see also 10.2.2.2
- If any diarrhoea was experienced (CTCAE Grade 1), two 2 mg loperamide tablets should have been taken immediately, followed by one 2 mg tablet with every loose bowel movement, up to a maximum daily dose of 10 tablets (20 mg).
- Oral hydration was essential regardless of severity; appropriate rehydration (1.5 L/m²/day plus equivalent of actual fluid loss) and electrolyte replacement had to be ensured in the event of CTCAE Grade 2 and Grade 3 adverse events.
- For CTCAE Grade 2 or 3 diarrhoea lasting ≥ 2 days (48 hours) despite adequate antidiarrhoeal treatment, BIBW 2992 had to be paused until recovery to CTCAE ≤ Grade 1. Upon recovery, BIBW 2992 should have been resumed at a reduced dose according to the dose reduction scheme outlined in section 10.1.3.1.1.

The occurrence of diarrhoea and the outcome of treatment was recorded in the AE section of the CRF.

If despite optimal supportive care and a treatment pause diarrhoea did not resolve to CTC Grade ≤ 1 within 14 days, the patient had not to receive any further BIBW 2992 treatment.

The patient enrolled did not suffer from diarrhoea, hence, this section was not relevant for him.

10.2.3.2 Management of nausea and vomiting following treatment with BIBW 2992

Nausea and vomiting might significantly affect patients' adherence to the treatment and their quality of life. In order to reduce the occurrence and the intensity of emesis, the patients should have been treated according to the recommendation given in Table 3.

Table 3: Management of nausea and vomiting

CTCAE Grade	Antiemetic treatment
Nausea = grade 0 **and** Vomiting = grade 0	No antiemetic prophylactic treatment
Nausea = grade 1 **and** Vomiting = grade 0	Antiemetic treatment if deemed necessary by the investigator
Nausea = grade 2 **and** Vomiting = grade 0 Nausea = grade 0, 1 or 2 **and** Vomiting = grade 1 or 2	Antiemetic treatment[1] Pause BIBW 2992 treatment if grade 2 vomiting or grade 2 nausea persists for 7 or more consecutive days despite optimal supportive care. Resume treatment when CTCAE Grade ≤ 1.
Vomiting ≥ grade 3 **or** Nausea ≥ grade 3	Antiemetic treatment[1] Pause BIBW 2992 treatment until return to CTCAE Grade ≤ 1 or baseline[2].

1 Antiemetic treatment should have followed the recommendations given in the Consensus Statement of the Antiemetic Subcommittee of the Multinational Association of Supportive Care in Cancer (MASCC): Prevention of chemotherapy- and radiotherapy-induced emesis: Results of the Perugia Consensus Conference .

2 Baseline was defined as the CTCAE Grade at the start of treatment.

After a treatment pause the dose of BIBW 2992 should have been reduced according to the dose reduction scheme in Table 2.

The occurrence of nausea and/or vomiting and the outcome of treatment was recorded in the AE section of the CRF.

In case of nausea and/or vomiting ≥ CTCAE Grade 2, appropriate hydration (1.5 L/m²/day plus hydration deficit) had to be ensured.

10.2.3.3 Management of rash following treatment with BIBW 2992

A proactive and early approach to management of rash was crucial. Rash could be managed by a variety of treatment options to relieve symptoms and to reduce the rash.

The recommendations for management were as follows:

- General/Prevention: see 10.2.2.2
- CTCAE Grade 1 rash: mild rash might not need treatment. However, if treatment was considered necessary, topical hydrocortisone (1% or 2.5%) cream and/or clindamycin 1% gel could be used.
- CTCAE Grade 2 rash: relief from major symptoms caused by CTCAE Grade 2 skin-related adverse events should have been achieved by a combination of local and systemic therapies including:

  1) Systemic antibiotics (e.g. doxycycline or minocycline, etc.).

  2) Topical treatment (e.g. hydrocortisone 2.5% cream, clindamycin 1% gel, pimecrolimus 1% cream).

  And / or

  1) Antihistamines (e.g. diphenhydramine, etc.)

  2) Oral corticosteroid (low dose and short term, i.e. < 10 days treatment) might be added at the investigator's discretion.

- Systemic and topical treatment should have been initiated at the start of CTCAE Grade 2 rash and continued until improvement or resolution to CTCAE Grade ≤ 1. If grade 2 rash persisted for ≥ 7 days despite treatment and was poorly tolerated by the patient, the investigator might choose to pause treatment for up to 14 days followed by a reduction in the dose of BIBW 2992 according to the dose reduction scheme in Table 2.
- CTCAE Grade 3 (or greater) rash: might be treated in a manner similar to CTCAE Grade 2 rash. In the event of CTCAE Grade ≥ 3 rash, treatment with BIBW 2992 should have been paused until recovery to CTCAE Grade ≤ 1. Treatment should have been resumed at a reduced dose (see section 10.1.3.1.1). If CTCAE Grade ≥ 3 rash did not resolve to CTCAE Grade ≤ 1 within 14 days of stopping BIBW 2992 treatment and despite optimal supportive care, the patient should not have received any further treatment with BIBW 2992.

10.3 Treatment compliance

Study medications were given in accordance with the protocol and under the instruction of the investigator.

Patients receiving BIBW 2992 should have taken the first dose of BIBW 2992 treatment at the study site; subsequent doses were taken at home. A compliance check should have been performed on day 8 of course 1 to ensure that the medication was being taken correctly. Subsequently, at the end of each course of treatment the patient should have brought all remaining medication to the site and a compliance check should have been performed. Discrepancies between the number of tablets

remaining and the calculated number of tablets the patient should have taken should have been documented and explained. At the end of each course any remaining medication should have been collected. If the patient was eligible for a further course of treatment a new bottle should have been dispensed.

Patients experiencing emesis should not have taken a replacement dose. BIBW 2992 should not have been taken more than once a day under any circumstances.

11 VARIABLES AND THEIR ASSESSMENT

11.1 Efficacy

11.1.1 End point(s) of efficacy

11.1.1.1 Primary endpoint

The primary end point of this study was the rate of objective PSA responses evaluated according to the Bubley criteria [7].

Objective PSA-based response was used as the primary end point in this trial. PSA responsiveness was defined as a confirmation by a second PSA value, not less than 4 weeks apart, of a PSA decline of at least 50%. PSA response started on the date of the first 50% decline in PSA. Complete response based on PSA does not exist; however, the number of patients achieving a PSA < 0.2 ng/ml was to be reported separately.

Definition of PSA-based response

For a given patient, response to the treatment could have been one of the three following possibilities: a PSA response was defined as a diminution of the PSA level of 50% or more. No distinction between complete and partial response was done, but the number of patients achieving a PSA < 0.2 ng/ml was to be reported. Similarly, the notion of stable PSA is not reliable. It was replaced by the time to consistent progression as defined in the following paragraph. In case of detection of a PSA response, a confirmation assessment had to be performed 4 or more weeks after the first documentation of the response.

Progressive disease was defined as follows:

1. For patients without PSA decrease since entry on study, progression was a PSA increase of 25% over baseline value, by at least 5 ng/ml.

2. For patients whose PSA had decreased but had not reached response criteria, progressive disease was defined as an increase of 25% in PSA value taking as reference the nadir provided that this increase in the absolute value exceeded 5 ng/ml (HYBRITECH equivalent).

3. For patients who had a PSA response, progressive disease was defined as a 50% increase over the nadir if it was more than 5 ng/ml (HYBRITECH equivalent). This progression had to be confirmed by an additional measurement at least 4 weeks afterwards. Patients for whom PSA measurements could not be made available were to be declared "not assessable for PSA response".

Confirmatory measurement

In the present study, PSA should have been re-evaluated every 8 weeks (2 courses) during treatment, and 4 or more weeks after the first observation of a complete or partial response. After discontinuation of the protocol treatment, patients who had not progressed should still have been re-evaluated every 6 weeks, unless they had started a new anti-cancer therapy. To be assigned a status of PSA response or progression, changes in the PSA level should have been confirmed by repeated measurements that should have been performed not less than 4 weeks after the first 50% decrease or 25% increase. The start date of the time to PSA progression would have been the date the patient was registered in the study. The end date would have been the date of first PSA increase following the definition of PSA progression as defined above.

Definition of best overall response

The best overall response was the best PSA response recorded from the start of the treatment until progression/recurrence (taking as reference for progressive disease the nadir of PSA value recorded since the treatment started). The patient's best PSA response assignment depended on the achievement of both the smallest PSA measurement and confirmation criteria. If a response could not be confirmed due to lack of PSA measures, the best overall response was "not assessable for PSA response".

Duration of PSA response

The duration of overall response was measured from the time measurement criteria are first met for the PSA response until the first date that progressive PSA was objectively documented (taking as the lowest measurement recorded since the treatment started).

Reporting of results

All patients included in the study had to be assessed for response to treatment, even if there was major protocol treatment deviation or if they were ineligible. Each patient was assigned one of the following categories: 1) PSA response, 2) progressive disease, 3) early death from malignant disease, 4) early death from toxicity, 5) early death from other cause, or 6) unknown (not assessable, insufficient data).

11.1.1.2 Secondary endpoints

Secondary endpoints included objective response rate (ORR) based on Response Evaluation Criteria in Solid Tumours (RECIST 1.1), safety, and duration of response according to RECIST criteria.

11.1.2 Assessment of efficacy

The efficacy was measured by PSA response which was to be performed every 2 courses (8 weeks).

For patients with measurable disease efficacy was evaluated according to RECIST 1.1 [9]. Complete Response (CR), Partial Response (PR), Stable Disease (SD) or Progressive Disease (PD) were assessed by the investigator.

Every effort should have been made to objectively evaluate tumour response and confirm tumour progression with radiological tumour imaging for all patients who entered into the study, including those who discontinued prematurely.

One to five target lesions (not exceeding two lesions per organ) should have been identified at screening by Computed Tomography (CT) or MRI.

Individual lesions detected at screening were numbered and recorded in the CRF. These lesions should have been followed up with the same method(s) used at screening and the same numbering should have been applied. The size of the target lesions was recorded in millimetres. Measurements should have been performed at screening and every 8 weeks during the treatment with BIBW 2992. After week 56, assessments should have been performed every twelve weeks. If contrast media was medically contra-indicated at any time during the study, MRI scans might substitute CT scans.

Tumour assessment did not need to be repeated at the screening visit if there were valid results available from assessments which have been performed as part of routine clinical practice within the allowed time window (within 28 days prior to start of treatment).

Target lesions should have been selected based on their size (those with the longest diameter) and suitability for accurate repeated measurements. All other lesions should have been identified as non-target lesions and were recorded at baseline. The non-target lesions were followed during the patient's participation and were taken into consideration when determining the patient's response.

Details regarding imaging-assessment according to revised RECIST-criteria (version 1.1) were provided in the imaging charter and the ISF.

Correlative imaging (e.g. brain scan, bone scan) should have been performed when clinically indicated.

In case of skin lesions, these should have been measured with calliper and photographic documentation should have been performed. However, skin lesion should not have been considered as target lesion in this study. Patients exclusively showing skin metastasis were not eligible for this study.

Bone metastases were considered as non-target lesions. A bone scan should have been performed at baseline in cases of clinical suspicion of previously unknown bone metastasis (e.g. bone or joint pain associated with relevant increases of calcium and alkaline phosphates). If the patient had known bone metastases or if bone metastases were detected at screening, correlative imaging (X-ray or CT scan) should have been done of the respective lesion(s) at baseline and subsequently correlative imaging of known bone lesions should have been performed at every imaging timepoint. During study treatment, bone scans should have been performed when medically indicated, e.g. in case of suspected new bone metastases.

In the event of a delay, interruption or discontinuation of treatment, tumour assessment should have continued to follow the original schedule. The schedule should have been followed until progression was observed or until the patient commenced further treatment for disease, whichever occured first.

Eligibility and treatment decisions were based on the assessment of disease by the investigator (refer to appendix 4).

11.2 Safety

11.2.1 Endpoint(s) of safety

Safety of BIBW 2992 was evaluated as indicated by intensity and incidence of adverse events, graded according to US NCI CTCAE Version 3.0. Safety endpoints included:

- events leading to dose reduction
- events leading to permanent treatment discontinuation
- the overall incidence and CTC criteria grade of adverse events, as well as relatedness of adverse events to treatment
- causes of death

11.2.2 Assessment of adverse events

11.2.2.1 Definitions of adverse events

Adverse event

An adverse event (AE) was defined as any untoward medical occurrence, including an exacerbation of a pre-existing condition, in a patient in a clinical investigation who received a pharmaceutical product. The event did not necessarily have to have a causal relationship with this treatment.

Serious adverse event

A serious adverse event (SAE) was defined as any AE which resulted in death, was immediately life-threatening, resulted in persistent or significant disability / incapacity, required or prolonged patient hospitalisation, was a congenital anomaly / birth defect, or was to be deemed serious for any other reason if it was an important medical event when based upon appropriate medical judgement which might jeopardise the patient and might require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.
Patients might be hospitalised for administrative or social reasons during the study (e.g. days on which infusion takes place, long distance from home to site, etc.). These and other hospitalisations planned at the beginning of the study did not need to be reported as a SAE in case they had been reported at screening visit in the source data and had been performed as planned.

Intensity of adverse event

The intensity of adverse events should have been classified and recorded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 in the CRF.

Causal relationship of adverse event

Medical judgment should have been used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history. Assessment of causal relationship should have been recorded in the case report forms.

Yes: There was a reasonable causal relationship between the investigational product administered and the AE.
No: There was no reasonable causal relationship between the investigational product administered and the AE.

Worsening of underlying disease or other pre-existing conditions

Expected fluctuations or expected deterioration of the underlying disease were not recorded as an AE. If progressive disease occured and was associated with symptoms or meets one of the seriousness criteria as mentioned above, the signs and symptoms of progressive disease were reported as an adverse event or a serious AE (if applicable).

A pre-existing condition should not have been recorded as an AE unless at least one of the following criteria was met:

- worsening of the condition or symptom meets the criteria for a SAE,
- action was taken with the investigational drug, i.e the investigational drug was discontinued or the dose was reduced,
- additional treatment was required, i.e. concomitant medication was added or changed,
- an unexpected deterioration from baseline had occurred in the opinion of the investigator.

Changes in vital signs, ECG, physical examination, and laboratory test results

Changes in vital signs including blood pressure, pulse rate, ECG, physical examination, and laboratory tests were only recorded as AEs if they were not associated with an already reported AE, symptom or diagnosis, and the investigational drug was either discontinued or reduced, or additional treatment was required, i.e. concomitant medication was added or changed.

11.2.2.2 Adverse event and serious adverse event reporting

Upon inclusion into the study, the patient's condition was assessed (e.g. documentation of history / concomitant diagnoses and diseases), and relevant changes from baseline were noted subsequently.

All adverse events, serious and non-serious, occurring during the course of the clinical trial (i.e., from signing the informed consent onwards through the 28 days follow-up period) were collected, documented and reported to the sponsor by the investigator on the appropriate CRFs / SAE reporting forms. Reporting was done according to the specific definitions and instructions detailed in the 'Adverse Event Reporting' section of the Investigator Site File.

For each adverse event, the investigator provided the onset date, end date, CTC AE grade, treatment required, outcome, seriousness, and action taken with the investigational drug. The investigator determined the relationship of the investigational drug to all AEs as defined in section 11.2.2.1.

Adverse events with onset within first administration of BIBW 2992 therapy and 28 days after last administration of BIBW 2992 were considered as on treatment. All AEs, including those persisting after end of study treatment had to be followed up until they had resolved or had been sufficiently characterised or the Principal Investigator decided to not further pursue them.

Serious and non-serious adverse events occurring later than 28 days after last administration of trial drugs were only reported in case they were considered drug-related or trial (procedure) related.

Deaths (unless they were considered drug-related or trial related) were not reported as SAE when they occured later than 28 days after last administration of the trial.

The sponsor was responsible for the evaluation of all pharmacovigilance information of BIBW 2992. The risk-benefit assessment for this study might be changed or suitable remediable actions should have been arranged by the sponsor if required. To guarantee that the sponsor received all information of safety issues, the investigator had to report safety issues immediately (SAE within 24 hours) after awareness of the event. Furthermore, if Boehringer-Ingelheim (BI) identified and confirmed a safety

issue within other currently running studies with BIBW 2992, BI had to inform the sponsor accordingly without undue delay.

11.2.2.3 Assessment of healthcare resource use

In case patients would have been hospitalized due to AEs, the duration of hospital stay as well as the need to stay and the duration in the intensive care unit were documented in the CRF.

Information on caregiver support (home care), GP, outpatient and hospital visits (other than scheduled visits) were collected in the CRF to inform on healthcare resource use required to treat the trial indication and adverse events observed during the trial.

11.2.3 Assessment of safety laboratory parameters

Blood samples were collected at the time points specified in the Flow Chart and analysed in a laboratory facility at (or close to) the investigational site. Safety laboratory examinations included haematology and biochemistry. In case of neutropenia, blood was examined as clinically indicated at the discretion of the investigator until recovery.

Safety laboratory assessment might be performed according to local practice but had to include at least the following parameters:

Haematology	Red blood cell count (RBC), neutrophils, haemoglobin, white blood cell count (WBC) and differential, platelets.
Biochemistry	Sodium, potassium, calcium, magnesium, creatinine, aspartate amino-transferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, lactate dehydrogenase, total bilirubin, urea, uric acid, creatine phosphokinase (CPK). In case of pathological CPK further evaluation (e.g., by Troponin assays, CK-ELPR and ECG exam) should have been performed and the findings documented in the CRF. Glomerular Filtration Rate (GFR) was estimated by the Cockcroft-Gault Formula utilising serum creatinine values (see appendix 1)
Coagulation	INR
Urinalysis	pH, glucose, erythrocytes, leukocytes, protein, nitrite will be analysed by dipstick at baseline and EOT only. In case of abnormal findings, further evaluation (g/24 hrs urine sampling) should have been performed and the findings documented in the CRF.

11.2.4 Electrocardiogram

A 12-lead resting ECG was performed at the time points specified in the Flow Chart. The investigator should have review the ECG data at the time of the visit and this was used to make decisions on eligibility for the study and treatment.

11.2.5 Assessment of other safety parameters

11.2.5.1 Physical examination, performance score

A physical examination was performed at screening and at the time points specified in the Flow Chart.

A full physical exam served as a clinical tumour assessment and should have included a cardiopulmonary examination and an assessment of the mental and neurological status. Additional symptoms which had not been reported during a previous examination should have been clarified. Wherever possible the same investigator should have performed this examination.

Measurement of height (in cm), body weight (in kg) and body temperature and the evaluation of the ECOG performance score was performed at the time points specified in the Flow Chart.

11.2.5.2 Left ventricular function

Left Ventricular Ejection Fraction (LVEF) as measured by echocardiography was assessed at time points specified in the Flow Chart. The same method of measurement had to be used throughout the study.

Echocardiography (ECHO) was performed to assess the LVEF according to the standard guidelines of the American Society of Echocardiography (ASE).

11.2.5.3 Vital signs

Vital signs (blood pressure and pulse after 2 minutes supine rest) and temperature were recorded at the screening visit and at the time points specified in the Flow Chart.

11.3 Other

11.3.1 Demographics and history

Demographics (sex, birth date), information on smoking and alcohol history, and baseline conditions were collected during the screening visit.

The date of first histological diagnosis (month and year may be sufficient), type of tumour histology, HER2-status, and initial levels of tumour marker PSA were reported in the CRF. The number and locations of metastatic sites (liver, lung, peritoneum, brain, other) as well as the stage according to the tumour, (lymph) node, metastasis (TNM) classification were provided as obtained at diagnosis and at the inclusion into the trial. Previous surgery and radiotherapy were reported.

Previously administered chemo- or radiotherapy were reported including start and end dates (month and year may be sufficient), the therapy protocol with the number of courses (chemotherapy), total radiation dose and radiation field (radiotherapy) and the best response obtained (complete response, partial response, stable disease, progressive disease, unknown).

11.4 Appropriateness of measurements

The RECIST criteria 1.1 to be used for evaluation of tumour response are well established and scientifically accepted. The US NCI CTCAE criteria Version 3.0 are used in the assessment of adverse events in cancer patients.

11.5 Biomarker(s)

11.5.1 Pharmacogenetic analysis

11.5.1.1 Genetic markers in tumour tissue

Archived tissue (mandatory biomarkers):

Formalin Fixed Paraffin Embedded (FFPE) tumour blocks or slides (15 to 18 slides) from the primary tumour or from metastases should have been examined using approved kits for HER2- testing by IHC and/or FISH in order to confirm the eligibility of the patients.

11.5.2 Protein biomarkers

The tumour marker PSA was assessed as part of routine tumour assessment at baseline, at C1V1, on day 1 every other treatment course, and at the end of treatment.

11.5.3 Biomarkers in archived tumour tissue

FFPE tumour blocks or slides (15 to 18 slides) from primary tumour or metastasis should have been tested for the following biomarkers:

- HER2 by IHC and FISH testing using a test kit
- EGFR by IHC
- EGFR-mutations

11.5.4 Circulating tumour cells

The number of circulating tumour cells (CTC) was determined by the cellsearch system at baseline, after one cycle and at the end of treatment. Optionally HER2 expression on CTCs could be assayed by FISH or IHC.

12 INVESTIGATIONAL PLAN

This was an open-label, single-arm, single-center phase II study in patients with HER2-positive, hormone-refractory, advanced or metastatic prostate cancer. Patients meeting the inclusion and exclusion criteria and who had given their written informed consent were eligible for participation in the study.

12.1 Visit schedule

Written informed consent was obtained before any protocol specific screening assessments were performed. Informed consent included consent to collection of demographic data and consent to testing of biopsy material.

The screening visit was performed within 14 days before the first administration of treatment. For archived tumour sample collection purpose, the informed consent could be obtained earlier than 14 days prior to therapy.

A treatment course had a duration of 28 days. Visit 1 was the first day of each treatment course. Each subsequent visit during the treatment period occured on day 29 (+/- 2 days) of the preceding first day course. Intermediary visits were to be performed on day 15 (+/- 2 days) during courses 1 to 3.

Patients might continue on treatment, until the criteria for stopping medication were met (see section 9.3.4). The maximum duration of the study per patient could have been 3 years. If the stopping criteria were not met within this time frame, the therapy could have been continued but would not have been part of the study anymore.

If the decision to permanently discontinue the study treatment was taken during a scheduled visit, the end of treatment (EOT) visit should have been performed as soon as possible instead of the scheduled visit (within 0 to 14 days after last treatment administration).

All randomized and treated patients should have had a follow-up visit 28 days (+/-7 days) after the EOT visit.

During this study only 1 patient was enrolled. He interrupted the intake of study medication due to vomiting and nausea and did not restart the study treatment due to tumour progression. He prematurely discontinued the trial after only 22 days of study duration and finally died. No EOT visit could have been performed.

Due to recruitment difficulties the whole study was prematurely discontinued and no further patients were enrolled.

12.2 Details of study procedures at selected visits

The investigations as outlined in the Flow Chart were performed at the respective visits as described in detail in the following sections.

12.2.1 Screening period

Table 4: Screening period

Informed consent	Written informed consent had to be obtained before any protocol specific screening assessments were performed. Informed consent had to include consent to collection of demographic data and consent to obtaining and testing (archived) tumour tissue for HER2-status. Additional consent had to be obtained for obtaining and testing fresh tumour tissue.
Demographics	Sex and birth date
Medical history	Oncological history (including details on previous anti-cancer therapies) and relevant non oncological history
Eligibility	Review of in- and exclusion criteria
Physical examination	Complete physical examination including body weight and height
Vital signs	Blood pressure, pulse rate, body temperature
ECOG performance status	According to ECOG scale (see appendix 3)
ECG	12-lead resting ECG
Echocardiogram	Cardiac left ventricular ejection fraction (LVEF) assessment
Safety lab	Hematology (including differential), serum biochemistry, INR, urinalysis
Tumour markers	PSA, CTCs
Tumour sample(s)	Optional biopsy for fresh tumour tissue (if patient gives additional consent and if the location of the metastatic lesion is accessible).
Tumour assessment	PSA measurements were performed prior to therapy and then every 8 weeks. In case of a partial remission a confirmatory PSA was performed after 4 weeks. Tumour assessments should have included CT scans of the chest and abdomen and, if clinically indicated, imaging of any other known or suspected sites of disease (e.g. bone metastases, pelvis, brain) using an appropriate method (bone scan, CT scan or MRI). The same radiographic procedure had to be used throughout the study (see exception if contrast media is medically contra-indicated). Bone scans and correlative imaging should have been performed when clinically indicated (see section 11.1.2 for more detail). Baseline assessment within 28 days prior to start of treatment was acceptable.
Concomitant medications	All concomitant therapies had to be reported
Adverse events	Relevant AEs

12.2.2 Treatment period(s)

Table 5: Course 1, visit 1 (day 1 = day of very first treatment administration)

To be obtained/performed before treatment administration	
Physical examination	Limited physical examination including body weight
Vital signs	Blood pressure, pulse rate, body temperature
ECOG performance status	According to ECOG scale (see appendix 3)
Healthcare resources use	Hospital stay, homecare giver, GP
Safety lab	Hematology (including differential), serum biochemistry, and INR
Blood sample for tumour marker analyses	PSA
Concomitant medications	All concomitant therapies were documented
Adverse events	Occurrence of AEs since last visit
Treatment administration:	
Dispensing study drug	Sufficient trial study drug for 28 days was dispensed

Table 6: Course 1, visit 2 (day 8)

Vital signs	Blood pressure, pulse rate, body temperature
ECG	12-lead resting ECG
Safety lab	CBC, safety lab
Concomitant medications	All concomitant therapies were documented
Adverse events	Occurrence of AEs since last visit
BIBW 2992 compliance check	Remaining study medication was counted

Table 7: Course 1, visit 3 (day 15 ± 2)

Vital signs	Blood pressure, pulse rate, body temperature
Safety lab	CBC only
Concomitant medications	All concomitant therapies were documented
Adverse events	Occurrence of AEs since last visit
BIBW 2992 compliance check	Remaining study medication was counted

Table 8: Course 2 and 3, visit 1 (day 1 of new course)

Physical examination	Limited physical examination including body weight
Vital signs	Blood pressure, pulse rate, body temperature
ECOG performance status	According to ECOG scale (see appendix 3)
Healthcare resources use	Hospital stay, homecare giver, GP
Safety lab	Hematology (including differential), serum biochemistry, and INR

Tumour markers	PSA, CTCs (after course 1 only)
Concomitant medications	All concomitant therapies were documented
Adverse events	Occurrence of AEs since last visit
BIBW 2992 compliance check	Remaining study medication was counted
Dispensing study drug	Sufficient study drug for 28 days was dispensed

Table 9: Course 2 and 3, visit 2 (day 15 ± 2)

Vital signs	Blood pressure, pulse rate, body temperature
Safety lab	CBC only
Concomitant medications	All concomitant therapies were documented
Adverse events	Occurrence of AEs since last visit
BIBW 2992 compliance check	Remaining study medication was counted

Table 10: Course 4 (and onwards), visit 1

Physical examination	Limited physical examination including body weight
Vital signs	Blood pressure, pulse rate, body temperature
ECOG performance status	According to ECOG scale (see appendix 3)
Healthcare resources use	Hospital stay, homecare giver, GP
ECG (every 3 courses)	12-lead resting ECG
Echocardiogram (every 3 courses i.e. C4, C7, C10, …)	Cardiac left ventricular ejection fraction assessment
Safety lab	Hematology (including differential), serum biochemistry, and INR
Tumour markers	PSA
Concomitant medications	All concomitant therapies were documented
Adverse events	Occurrence of AEs since last visit
Compliance check	Remaining study medication was counted
Dispensing study drug	Sufficient study drug for 28 days was dispensed

Tumour assessment	Every 8 weeks; from week 56 onwards every 12 weeks until disease progression or start of further treatment (see section 11.1.2).

12.2.3 End of study treatment and follow-up period

End of study treatment:

The end of treatment information had to be obtained when the patient discontinued the study treatment permanently.

Table 11: End of study treatment

Physical examination	Complete physical examination including body weight
Vital signs	Blood pressure, pulse rate, body temperature
ECOG performance status	According to ECOG scale (see appendix 3)
Healthcare resources use	Hospital stay, homecare giver, GP
ECG	12 lead resting ECG (if not performed in the previous 8 days)
Echocardiogram	Cardiac left ventricular ejection fraction assessment (if not performed in the previous 8 days)
Safety lab	Hematology (including differential), serum biochemistry, INR and urinalysis
Tumour markers	PSA, CTCs
Tumour assessment	In case progressive disease was suspected, an image needed to be done at any time when active treatment ended.
Concomitant medications	All concomitant therapies had to be reported
Adverse events	Occurrence of AEs since last visit
BIBW 2992 compliance check	Remaining study medication was counted
Termination of study medication	Date of last administration of study drugs and reason for discontinuation

First follow-up visit:

The following was obtained/performed 28 days after EOT and before start of any new treatment:

Table 12: First follow-up visit

Physical examination	Limited physical examination including body weight
Vital signs	Blood pressure, pulse rate, body temperature
ECOG performance status	According to ECOG scale (see appendix 3)
Healthcare resources use	Hospital stay, homecare giver, GP
Safety lab	Hematology (including differential), serum biochemistry, and INR.
Tumour markers	PSA
Tumour assessment	
Concomitant medications	All concomitant therapies had to be reported
Adverse events	Relevant AEs since last visit. Follow-up on ongoing AEs at EOT
Study completion	If applicable (patients who were progressing or who were starting new treatment)

Additional follow-up visit (where applicable, refer to section 12.1):

If patient had not progressed at EOT nor did receive further treatment since EOT, every effort should have been made to retain the patient in the study and FU visits should have been performed according to tumour assessment schedule. The following information should have been collected at each visit:

- Tumour assessment (according to the tumour assessment schedule)
- Any drug related adverse events
- Healthcare resources use
- Study completion at progression or at start of new treatment

Once a patient was reported as progressive or receiving further treatment, the patient entered the observation period.

Observation period:

A contact should have been done every 90 days after the follow-up visit.

Information to be collected from patient's notes or by telephone contact (a formal visit is not required):

- Date of contact and method of contact
- Further treatment (including details of regimen with drug names, start and stop dates and reason for stopping)
- Death

12.3 Volume of blood to be drawn from each subject

Table 13: Volume of Blood to be Drawn From Each Subject

Assessment	Screening	Course 1			Course 2		Course 3		Course 4 - x	EOT	FU1
		V1	V2	V3	V1	V2	V1	V2	V1		
Safety Lab	15 ml	15 ml		15 ml	15 ml		15 ml		15 ml	15 ml	15 ml
PSA	5 ml	5 ml			5 ml		5 ml		5 ml	5 ml	5 ml
CTC		10 ml			10 ml					10 ml	
CBC			5 ml			5 ml		5 ml			
Sum	**15 ml**	**50 ml**			**35 ml**		**25 ml**		**20 ml**	**30 ml**	**20 ml**

Note: The above amount of blood to be taken for each assessment was an estimate. The amount of blood to be taken might vary according to the instructions provided by the manufacturer or laboratory for an individual assessment. However, the total volume drawn per course of the study should have been approximately 50 mL in the first, 35 mL in the second, 25 mL in the third and approximately 20 mL in the fourth and following courses. When more than 1 blood assessment was to be done at the time point/period, if they require the same type of tube, the assessments might be combined.

13 STATISTICAL METHODS

13.1 Statistical design-model

This was an open-label, single-arm, single-center study. The primary objective was to evaluate the rate of objective PSA responses according to the Bubley criteria.

13.2 Planned analyses

13.2.1 Primary analyses

The primary objective was to determine the objective PSA response rate according to Bubley criteria of BIBW 2992 in patients with hormone refractory prostate cancer after failure of docetaxel chemotherapy.

According to the two-step Gehan design and assuming a meaningful PSA response rate of 10%, a total of 29 patients was required in the first stage of the study. If ≥ 1 response was observed in these 29 patients, the second stage was opened; otherwise the drug was judged as ineffective. The number of patients in the second stage depended on the number of responses observed in the first stage and ranged between 4 and 28 patients.

13.2.2 Secondary analyses

13.2.2.1 Best RECIST assessment

Each patient was assigned to one of the following RECIST categories, irrespective of protocol violations or missing data:

- CR (complete response)
- PR (partial response)
- SD (stable disease)
- PD (progressive disease)
- unknown (not assessable, insufficient data)

Objective response was defined as CR or PR. Time to objective response was the time from randomization to the date of first documented CR or PR. The duration of objective response was the time from first documented CR or PR to the time of progression or death. Disease control was defined as CR, PR, or SD.

Descriptive statistics were to be calculated for the duration of objective response and duration of disease control.

13.2.2.2 Overall survival (OS)

The OS-analysis should describe the overall pattern of time to death, together with the extent and influence of post-progression treatment.

The analysis should describe the extent and influence of post-progression intervention:

- describe the cumulative proportion of deaths at each scheduled tumour assessment time point
- tabulate the specific anti-cancer treatments after progression
- describe the effect of additional anti-cancer treatment, by separating patients into the following sub-groups
    - those not eligible for additional treatment
        - patients who did not progress
        - patients who died within one month of progression
- those eligible for additional treatment
        - did not take additional treatment

- did take additional treatment

13.2.3 Other endpoints

13.2.3.1 Tumour shrinkage

Tumour response was evaluated at the pre-specified timepoints and categorized according to the Response Evaluation Criteria in Solid Tumours (RECIST) 1.1.

13.2.4 Safety analyses

All treated patients were included in the analysis of safety.

The primary analysis of adverse events was based upon events that begin after the start of treatment up to 28 days after the last administration of the study medication.

Adverse events as well as laboratory parameters were graded according to CTCAE Version 3.0. Key safety measures included:

- events leading to dose reduction
- events leading to permanent treatment discontinuation
- the overall incidence and CTCAE Grade of adverse events, as well as relatedness of adverse events to treatment
- causes of death
- gastrointestinal events (diarrhoea, vomiting, nausea)
- skin disorders
- mucosal inflammation
- renal insufficiency
- elevated liver function tests,
- haematological abnormalities (anaemia, thrombocytopenia, neutropenia)
- CTCAE Grade 2 with increase by at least one CTCAE Grade from baseline, for selected laboratory tests:
    - (high values) INR, creatinine, AST, ALT, total bilirubin, alkaline phosphatase,
    - (low values) haemoglobin, neutrophils, platelets, WBC, magnesium, potassium,
    - descriptive statistics for change from baseline for all laboratory tests.

Additional, more in-depth analyses were performed as needed. These analyses examined the influence of extent of exposure and time to event onset.

Key adverse event tables were reproduced to examine the effect of BIBW 2992 among special populations, e.g. elderly.

13.3 Handling of missing data

Patients continued to be followed for both progression and death after discontinuation of study treatment.

Table 14 describes how patients were classified for the analysis of death. Patients were censored at the date of last contact if the investigator was no longer able to contact a patient or caregiver, and vital status could not otherwise be determined, provided that no other information indicated that the patient has been near death at that point.

Table 14: Endpoint determination for overall survival

Situation	Outcome (event or censored)	Date of death or censoring
Patients died and the date of death is known	event	Date of death
Patients died and date of death is unknown	censored	Date of last contact when the patient was known to be alive
Patient alive	censored	Date of last contact
Unknown	censored	Date of last contact when the patient was known to be alive

14 INFORMED CONSENT, DATA PROTECTION, STUDY RECORDS

The study was carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, version as of October 2008 (as long as local laws do not require to follow other versions), in accordance with the ICH Harmonised Tripartite Guideline for Good Clinical Practice (GCP). Standard medical care (prophylactic, diagnostic and therapeutic procedures) remained in the responsibility of the treating physician of the patient.

The rights of the investigator and of the sponsor with regard to publication of the results of this study were described in the investigator contract. As a general rule, no study results should have been published prior to finalisation of the clinical study report.

Insurance cover: The terms and conditions of the insurance cover were made available to the investigator and the patients via documentation in the ISF (Investigator Site File).

14.1 Study approval, patient information, and informed consent

This study was initiated after all required legal documentation had been reviewed and approved by the responsible Ethics Committee (EC) and competent authority (CA) according to national and international regulations. The same applied for the implementation of changes introduced by amendments.

Prior to patient participation in the study, written informed consent was obtained from each patient (or the patient's legally accepted representative) according to ICH GCP and to the regulatory and legal requirements of the participating country. Each signature was personally dated by each signatory and the informed consent and any additional patient information form retained by the investigator as part of the study records. A signed copy of the informed consent and any additional patient information were given to each patient or the patient's legally accepted representative.

An additional informed consent was obtained for patients who consented to undergo biopsies of the metastases.

The patient was informed that his/her personal study-related data were used by the Principal Investigator in accordance with the local data protection law. The level of disclosure was also explained to the patient.

The patient was informed that his / her medical records might be examined by authorised monitors (CRA) or Clinical Quality Assurance auditors appointed by the Principal Investigator, by appropriate EC members, and by inspectors from regulatory authorities.

14.2 Data quality assurance

For data quality assurance, on-site monitoring was performed by a CRO appointed by the Principal Investigator.

14.3 Records

Case Report Forms (CRFs) for individual patients were provided by the Principal Investigator. For drug accountability, refer to section 10.1.5.

14.3.1 Source documents

Source documents provided evidence for the existence of the patient and substantiated the integrity of the data collected. Source documents were filed at the investigator's site.

Data entered in the CRFs that were transcribed from source documents had to be consistent with the source documents or the discrepancies had to be explained. The investigator might need to request previous medical records or transfer records, depending on the study; also current medical records had to be available.

For CRFs all data had to be derived from source documents.

14.3.2 Direct access to source data and documents

The investigator / institution had to permit study-related monitoring, audits, EC review and regulatory inspection, providing direct access to all related source data / documents. CRFs and all source documents, including progress notes and copies of laboratory and medical test results had to be available at all times for review by the clinical study monitor, auditor and inspection by health authorities (e.g. EMA). The Clinical Research Associate (CRA) / on site monitor and auditor might review all CRFs, and written informed consents. The accuracy of the data was verified by reviewing the documents described in section 14.3.1.

14.4 Listedness and expedited reporting of adverse events

14.4.1 Listedness

To fulfil the regulatory requirements for expedited safety reporting, the sponsor evaluated whether a particular adverse event was "listed", i.e. was a known side effect of the drug or not. Therefore a unique reference document for the evaluation of listedness needed to be provided. For BIBW 2992, this was the current version of the Investigator's Brochure. The current version of the Investigator's Brochure was to be provided in the ISF.

14.4.2 Expedited reporting to health authorities and EC

Expedited reporting of suspected unexpected serious adverse reactions (SUSARs), to health authorities and EC was done according to local regulatory requirements.

14.5 Statement of confidentiality

Individual patient medical information obtained as a result of this study was considered confidential and disclosure to third parties was prohibited with the exceptions noted below. Patient confidentiality was ensured by using patient identification code numbers.

Treatment data might be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated as a result of the study needed to be available for inspection on request by the participating physicians, the sponsor's representatives, by the EC and the regulatory authorities.

14.6 Completion of study

The Ethics Committee/Competent Authority were notified about the end of the trial (last patient/patient out, unless specified differently in section 12.2.3 of the CSP) or early termination of the trial.

15 STUDY PATIENTS

The clinical part of the study was performed between 03.08.2011 (first screening examination) and 25.08.2011 (last visit in the patient). The study had been open to further recruitment until 08.11.2012.

15.1 Disposition of patient

One patient was screened and enrolled for the study.

The patient prematurely discontinued the trial. He experienced two serious adverse events (uropsepsis and tumour progression) and finally died on 01.09.2011.

He attended the screening examination and visits 1 to 3 during course 1 of the study and was treated with the study medication for 13 days. Overall study duration was 22 days for him.

Due to intolerance during course 1 (nausea and vomiting) the patient interrupted the intake of study medication. Due to the tumour progression, the administration of study medication was not restarted and finally permanently stopped.

Recruitment difficulties led to premature discontinuation of the whole study and no further patients were screened and enrolled.

15.2 Demographic and other baseline characteristics

The patient was a 59 year old white man who suffered from prostate cancer since September 2007. He was an ex-smoker and did not consume any alcohol.

He was 175 cm tall and the body weight at screening was 70 kg (body mass index 22.9 kg/m^2).

Anamnestically he reported a Morbus Duhring, ongoing since 1983, a prostatectomy in October 2007 and a nephrostomy in August 2008.

Initially the patient showed an ECOG status of 2 (symptoms, but ambulatory; restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature).

For medication used prior to study see section 16.2.

15.2.1 Initial status of study disease

The tumour was hormone and docetaxel refractory and showed a HER2-status of 2+. The TNM classification was T4a N1 M1oss.

The tumour marker PSA showed an initial level of 128.7 µg/l.

The target lesion was examined at baseline visit on 11.08.2011 by MRI (Magnetic Resonance Imaging) and was found dorsal of the bladder with a size of 63 mm in diameter.

Non-target lesions were also examined on 11.08.2011 by MRI and were located diffuse intraosseous and subcutaneous dorsal of the left iliac wing.

15.2.2 Biopsy of fresh tumour tissue

A biopsy of the tumour was performed on 27.06.2011. The tumour tissue was graded as HER2 positive (2+), EGFR negative and EGFR-mutations negative.

15.3 Measurement of study compliance

15.3.1 Application of study medication

BIBW 2992 was taken every day in the morning at a dose of 50 mg preferably at the same time every day and at least one hour before any food intake and at least three hours after food intake.

Sufficient study medication was dispensed during each visit at the study site and re-collected and counted during the next visit to check patient's compliance.

15.4 Protocol deviations

There were no protocol deviations.

15.5 Statistical issues

As only 1 patient was enrolled and this patient prematurely discontinued the trial, no statistical evaluation was performed.

15.5.1 Multicenter studies

The study was a single center study.

16 SAFETY EVALUATION

The patient treated was included in the safety evaluation.

16.1 Study medication

For administrative purposes treatment was divided into treatment courses, which were 4 weeks (28 days) each in duration. The patient took a single oral dose of 50 mg BIBW 2992 every day in the morning. In case of intolerances the dose could be reduced according to a reducing scheme (see Table 2).

The patient enrolled received oral doses of the study medication (50 mg once daily) for 13 consecutive days. Medication was interrupted then since subject experienced vomiting and asthenia and was not restarted due to tumour progression.

Total drug exposure with BIBW 2992 for patient 001 was 650 mg.

16.2 Prior and concomitant medication

Prior to and during the study the patient was treated with several substances due to the prostate cancer and consequential diseases.

For details of previous anti-cancer therapy see the following table:

Table 15: Previous anti-cancer therapy of Patient 001

Substance	Frequency	Route	Start and End Date	Indication
Docetaxel 35 mg/ m^2	once per week	i.v.	04/2009 – 04/2009	PSA increase
Docetaxel 75 mg/ m^2	once per 3 weeks	i.v.	05/2009 – 08/2009	PSA increase
Docetaxel 75 mg/ m^2	once per 3 weeks	i.v.	2010 – 10/2010	PSA increase
Carboplatin/ Docetaxel	unknown	i.v.	10/2010 – 10/2010	PSA increase progress

For details of concomitant medication see the following table:

Table 16: Concomitant Medication of Patient 001

Trade Name or Substance	Frequency	Route	Start and End Date	Indication
Pamidronat 90 mg	Once per 4 weeks	i.v.	03/2011 – 01.09.2011	Bone metastases
Oxycodon 80 mg	Twice daily	oral	07/2011 – 21.08.2011	Pain abdomen
Novaminsulfon 500 mg	2-3 times daily	oral	03/2011 – 21.08.2011	
Lyrica 50mg	Twice daily	oral	07/2011 – 21.08.2011	
Sevredol 20 mg	As needed	oral	07/2011 – 21.08.2011	
Abstral 200 µg	twice daily	sl*	25.08.2011 – 26.08.2011	
Abstral 200 µg	As needed	sl*	26.08.2011 - 30.08.2011	
Lyrica 50 mg	once daily	oral	21.08.2011 – 24.08.2011	
Lyrica 75 mg	Twice daily	oral	22.08.2011 – 26.08.2011	
Lyrica 150 mg	twice daily	oral	25.08.2011 – 30.08.2011	
Novaminsulfon 1 g	once daily	oral	21.08.2011 – 23.08.2011	
Novaminsulfon 1 g	4x daily	oral	22.08.2011 – 25.08.2011	
Novaminsulfon Tropfen	1g 4x daily	oral	24.08.2011 – 30.08.2011	
Oxygesic 80 mg	Once daily	oral	21.08.2011 – 23.08.2011	
Palladon 1.3 mg	As needed	oral	24.08.2011 – 27.08.2011	
Palladon 4 mg	Once daily	oral	23.08.2011 – 24.08.2011	
Palladon 4 mg	Twice daily	oral	25.08.2011 – 30.08.2011	
Palladon 8 mg	Twice daily	oral	22.08.2011 – 30.08.2011	
Palladon Bolus	As needed	i.v.	30.08.2011 – 01.09.2011	
Palladon Perfusor 12 mg/40 ml	1.5 ml/h	i.v.	29.08.2011 – 30.08.2011	
Palladon Perfusor 12 mg/ 40 ml	2.5 ml/h	i.v.	30.08.2011 – 31.08.2011	
Palladon 12 mg/ 40 ml	3.5 ml/h	i.v.	31.08.2011 – 01.09.2011	
Trenatone	Once per 3 months	s.c.	2007 – 01.09.2011	Hormones
Dapson 50 mg	Twice daily	oral	1983 – 30.08.2011	M.Duhring
MCP Tropfen 5mg/ml	As needed	Oral	21.08.2011	Nausea/ vomitting
Haldol 5 mg/ml	2.5 mg 3x per day	i.v.	22.08.2011 - 25.08.2011	
Haldol 0.2% Tropfen	5 drops once daily	oral	21.08.2011 - 23.08.2011	
Haldol 0.2% Tropfen	15 drops once daily	oral	24.08.2011 - 26.08.2011	
MCP 10 mg/ 2ml	Once daily	i.v.	27.08.2011 – 28.08.2011	
Paspertin Tropfen 6.7 mg	Once daily	oral	21.08.2011 – 23.08.2011	
Paspertin Tropfen 6.7 mg	4x daily	oral	25.08.2011 – 30.08.2011	
Vomex A 62 mg/10 ml	As needed	i.v.	24.08.2011 – 30.08.2011	
Vomex A 62 mg/ 10 ml	Once daily	i.v.	21.08.2011 – 24.08.2011	
Buscopan 20 mg/ml	As needed	i.v.	26.08.2011 – 30.08.2011	Lung sounds
Erythrocyte concentrate	2x 250 ml	i.v.	22.08.2011	Haemoglobin decrease
NaCl 0.9% 1000 ml	Twice daily	i.v.	21.08.2011 – 27.08.2011	Asthenia
Ringer Lösung 1000 ml	Once daily	i.v.	22.08.2011	
Saroten 75 mg	Once daily	oral	25.08.2011 – 31.08.2011	Depression
Tavor 1 mg Expidet	Once daily	Oral	29.08.2011 – 30.08.2011	Anxiety
Tavor 2 mg	As needed	oral	29.08.2011 – 01.09.2011	
Zienam 500 Infusionslösung	3x daily	i.v.	21.08.2011 – 30.08.2011	Fever

* sl: sublingual

16.3 Death, other serious adverse events, and other significant adverse events

The patient experienced two serious adverse events, urosepis (AEs: fever and renal-urinary infection) which led to hospitalisation and tumour progression (with several symptoms, see adverse events), the latter with a fatal outcome on 01.09.2011.

Overall the reported serious adverse events are common for a trial population with prostate cancer and both events were judged to be unrelated to the study medication.

For details see Table 17.

Table 17: Serious Adverse Events of Patient 001

Serious Adverse Event	Related Adverse Events	Start and End Date of SAE	Reason for Seriousness
Urosepsis	fever, renal-urinary infection	21.08.2011 – 01.09.2011	hospitalisation
Tumour progression	pain abdomen, asthenia, anxiety, depression, anorexia, haemoglobin decrease, sweating, edema genital and limb	21.08.2011 – 01.09.2011	fatal outcome

16.4 Adverse events

Adverse events during the study were to be evaluated as endpoint of safety. Adverse events were recorded, if applicable, after a non-leading question on the subject's well-being or whenever they occurred and were reported spontaneously.

The patient enrolled reported a total of 15 adverse events.

Nausea and vomiting were the only events which were evaluated as related to the study medication. As consequence the administration of study medication was interrupted.

All other events were not related to the study medication but were probably caused by the tumour progression and urosepsis. Due to the massive decrease of patient's general condition the administration of the study drug was permanently discontinued.

Five of 15 adverse events were of mild intensity (CTCAE Grade 1), 6 of 15 AEs were evaluated as moderate (CTCAE Grade 2; the intensity of vomiting changed from CTCAE Grade 1 to grade 2) and one AE as severe (CTCAE Grade 3). 3 events were considered to be life-threatening (CTCAE Grade 4).

5 adverse events resolved completely, 1 AE resolved with sequelae. Since the tumour progression finally led to the death of the patient all other events were considered to be not resolved, for one AE the outcome is unknown.

10 of 15 adverse events needed to be treated with concomitant medication. For details see Table 16

For details of adverse events see the following table:

Table 18: Adverse Events of Patient 001

Description	SAE	CTCAE Grade	Start Date	Stop Date	Outcome	IMP action because of this AE	IMP Relationship	Other action taken because of this AE	Comments
Nausea	no	2	15.08.2011	23.08.2011	resolved	none	yes	Concomitant medication	
Vomiting	no	1	15.08.2011	23.08.2011	Not resolved	none	yes	Concomitant medication	
Fever	yes	1	21.08.2011	22.08.2011	resolved	none	no	Concomitant medication	Caused by urosepsis
Pain abdomen	no	4	21.08.2011	01.09.2011	Not resolved	none	no	Concomitant medication	
Vomiting	no	2	24.08.2011	01.09.2011	Not resolved	Interruption of treatment with IMP	yes	None	
Asthenia	yes	4	21.08.2011	01.09.2011	fatal	Treatment with IMP discontinued	no	Concomitant medication	Caused by tumour progression
Lung sounds	no	2	29.08.2011	01.09.2011	Not resolved	none	no	Concomitant medication	
Anxiety (mood alteration)	no	2	29.08.2011	01.09.2011	Not resolved	none	no	Concomitant medication	
Depression (mood alteration)	no	2	25.08.2011	01.09.2011	Not resolved	none	no	Concomitant medication	
Xerostomia	no	1	23.08.2011	23.08.2011	resolved	none	no	None	
Anorexia	no	1	22.08.2011	01.09.2011	Resolved with sequelae	none	no	none	
Hemoglobin decrease	no	3	22.08.2011	22.08.2011	resolved	none	no	Concomitant medication	
Sweating	no	2	21.08.2011	21.08.2011	resolved	none	no	None	
Edema genital, limb	no	1	22.08.2011	01.09.2011	Not resolved	none	no	None	
Infection renal-urinary-tract	yes	4	21.08.2011	01.09.2011	unknown	none	no	Concomitant medication	

16.5 Clinical laboratory evaluation

16.5.1 Haematology, biochemistry

Blood samples for safety evaluation were drawn during screening examination and during each visit at the study site (the patient attended visit 1 to 3 of course 1).

Hematology results were available from each of these visits, biochemistry results only for screening, visit 1 and visit 2.

For haematology, decreased values for red blood cell count, haemoglobin and haematocrit were observed (minimal haemoglobin of 9 g/l on 11.08.2011). The patient received two erythrocyte concentrates on 22.08.2011, and the values were still decreased but improved on 25.08.2011 (haemoglobin of 10.3 mg/l).

All other haematological values were within normal limits or only mildly abnormal but clinically not relevant.

Biochemistry showed normal or abnormal, but clinically not relevant results which were relative stable for all visits. As permanently abnormal values, calcium was mildly decreased, creatinine, alkaline phophatase and LDH mildly increased.

The tumour marker PSA was evaluated during screening examination and visit 1 and showed relatively stable increased values of 128.7 µg/l and 129.6 µg/l, respectively.

Additionally, circulating tumour cells (CTC) were counted during screening examination with a result of 220 cells (70 relative intact and 150 apoptotic cells).

16.5.2 Urinalysis

A urine dipstick test was performed on visit 1 (Day 1) of course 1. The result showed highly positive values for blood (erythrocytes and leucocytes) and protein.

16.6 Vital Signs, ECG, echocardiography and ECOG

16.6.1 Vital signs

16.6.1.1 Blood pressure and pulse rate

Blood pressure and pulse rate was measured during screening examination and during each visit.

All measured values were within normal limits. Systolic blood pressure values ranged between 104 and 115 mmHg, diastolic blood pressure values between 65 and 70 mmHg. Pulse rate was between 68 and 71/min.

16.6.1.2 Body temperature

Body temperature was measured during screening examination and during each visit and was always within normal limits (ranged between 36.4°C and 36.9°C).

16.6.1.3 Body weight

Body weight was measured during screening and during visit 1 and stable with 70 kg in both cases. According to adverse events the patient experienced anorexia during the course of the study, but no body weight is available for this period.

16.6.2 ECG, echocardiography

ECG and echocardiogram were scheduled for screening examination and visit 2 (only ECG). But both measurements were not performed.

16.6.3 Eastern Cooperative Oncology Performance Status (ECOG)

The ECOG status was determined during screening examination and visit 1. In both cases, the status was determined as 2 (2= symptoms but ambulatory; restricted in physical strenous activity, but

ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work).

16.6.4 Safety conclusion

Only 1 patient was enrolled into the study.

Three adverse events were reported with a possible relationship to the study medication: vomiting, which worsened from mild to moderate during the course of the study, and nausea. Due to these AEs, the administration of the study medication was interrupted.

The permanent discontinuation of study drug administration was caused by tumour progression with a consecutive decreased general condition of the patient and finally, a fatal outcome.

Two serious adverse events occurred in the patient, urosepsis and tumour progression, documented by a total of 12 adverse events (not considering the 3 AEs with a possible relationship to the IMP as described above).

As only 1 patient was enrolled and he was only treated with the study medication for 13 days, only limited conclusions concerning the safety of BIBW 2992 could be made.

Overall the reported serious adverse events are common for a trial population with prostate cancer and both SAEs were judged to be unrelated to the study medication.

Concerning other safety parameters (vital signs, laboratory values) there were no relevant changes between screening and the 3 visits which were attended by the patient.

17 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSIS

All modifications of the protocol were authorized by the sponsor and the investigator in writing.

Changes to the study protocol were classified by the sponsor and the study center as:

Note-to-File: This referred to clarifications which were not considered changes to § 10 (1) GCP-V of the study protocol which have no effect on the safety or welfare of the trial subjects, and do not impose an additional burden on the subjects; such changes do not necessitate approval by the Ethics Committee/Competent Authorities.

Study protocol amendment: This referred to changes according to §10 (1) GCP-V. Changes to the study protocol may also induce revision of the subject information sheet/informed consent form. Accordingly, subjects undergoing trial assessment procedures at the time of implementation of the change have to be given the amended version and have to be asked for consent to continue on this amended trial.

18 DISCUSSION AND CONCLUSION

Only 1 patient was enrolled into the study. The patient prematurely discontinued the trial due to tumour progression with a fatal outcome.

In general, the study medication was well tolerated.

2 serious adverse events appeared, which are common for a trial population with prostate cancer.

There were no relevant changes in clinical laboratory variables or vital signs.

As only one patient was enrolled and he was only treated with the study medication for 13 days, only limited conclusions concerning the safety of BIBW 2992 could be made. In this study the overall safety could be judged as safe. There was no change in the risk-benefit evaluation detected.

Due to the premature discontinuation of the study due to recruitment difficulties and the enrolment of a single patient there are no conclusions concerning the efficacy of BIBW 2992 in patients with HER2-positive, hormone-refractory prostate cancer possible.

19 REFERENCES

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20 APPENDICES