1. TITLE PAGE

Medizinische Hochschule Hannover (MHH)

CLINICAL STUDY REPORT

Study Title:	A single arm, open-label multicenter phase II trial of everolimus in patients with relapsed/refractory germ cell cancer (RADIT)
Investigational Product:	Everolimus
Indication Studied:	Relapsed/refractory germ cell cancer
Sponsor:	Hannover Medical School (MHH) Carl-Neuberg-Str. 1 D-30625 Hannover
Secondary Sponsor	German Testicular Cancer Study Group (GTCSG)
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EudraCT No.:	2009-014383-18
Development Phase of Study:	II
Study Start:	16 DEC 2010 (first patient first visit)
Study End:	14 MAR 2014 (last patient last visit)
Coordinating Investigator:	Dr. med. Martin Fenner Department of Hematology, Hemostaseology, Oncology and Stem Cell Transplantation Medizinische Hochschule Hannover Carl-Neuberg-Str. 1 D-30625 Hannover Telephone: +49-511-532-4077 Fax: +49-511-532-8077 E-mail: Fenner.Martin@mhh-hannover.de

Good Clinical Practice:	This study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) regulations/ guidelines. Essential documents will be retained in accordance with ICH GCP.
Report Version/ Date:	Final/30 MAR 2015

Confidential Information

SIGNATURE PAGE

Study Title: A single arm, open-label multicenter phase II trial of everolimus in patients with relapsed/refractory germ cell cancer (RADIT)

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

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Signature

Date

2. SYNOPSIS

Name of Sponsor/Company: **Hannover Medical School**	**Individual Study Table Referring to Part of the Dossier**	***(For National Authority Use only)***
Name of Finished Product: AFINITOR®	**Volume:**	
Name of Active Ingredient: Everolimus	**Page:**	

STUDY TITLE:
A single arm, open-label multicenter phase II trial of everolimus in patients with relapsed/refractory germ cell cancer (RADIT)

INVESTIGATOR(S):
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[redacted], Universitätsklinikum Schleswig-Holstein, Campus Kiel
[redacted], Universitätsklinikum Marburg und Gießen GmbH Standort Marburg
[redacted], Klinikum Harlaching, Städtisches Klinikum München GmbH
[redacted], Universitätsklinikum Tübingen

STUDY CENTRE(S):
A total of 8 study centers in Germany were initiated and 6 study centers enrolled patients.

PUBLICATION(S): Not applicable.

STUDY PERIOD:	**PHASE OF DEVELOPMENT:**
16 DEC 2010 - 14 MAR 2014	Phase II

OBJECTIVES:

Primary:

- To evaluate the efficacy of everolimus as monotherapy for the treatment of germ cell cancer. Efficacy is defined as the percentage of patients progression-free at 12 weeks.

Secondary:

- Objective response rate
- Disease control rate (stable disease, partial remission, complete remission)
- Progression-free survival
- Overall survival
- Safety profile

METHODOLOGY:
This was an open-label, single arm, non-randomized, single stage phase II study.
Screening phase: Baseline evaluations were performed within 2 weeks before the first dose of the study drug.
Treatment phase: All patients received everolimus until disease progression (by response evaluation criteria in solid tumors [RECIST] or tumor markers) or unacceptable toxicity or study discontinuation for other reasons. A treatment cycle consisted of 3 weeks. Dose reductions and dose interruptions (for up to 2 weeks) were allowed for intolerable toxicity.
Follow-up phase: All patients were followed for survival.

NUMBER OF PATIENTS:
Planned Sample Size*:* 25 evaluable patients were planned to be included
Actual Sample Size: Of 26 patients screened, 25 patients were eligible and included in the study.

DIAGNOSIS AND MAIN INCLUSION CRITERIA:
Diagnosis: Relapsed/refractory germ cell cancer
Main Inclusion Criteria:

- Male patients ≥18 years old.
- Patients with histologically proven seminomatous or non-seminomatous germ cell cancer
- Disease progression during cisplatin-based chemotherapy
  or disease progression or relapse after high-dose chemotherapy
  or disease progression or relapse after at least 2 different cisplatin-based regimens and contraindications for high-dose chemotherapy.
- Patients must have received prior combination chemotherapy with gemcitabine, oxaliplatin and paclitaxel (GOP). Prior treatment with a combination of two of these drugs is allowed in case of contraindications for GOP.
- Disease progression at study entry: progressive disease according to RECIST criteria in baseline examinations

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or tumor marker increase >25% within 4 weeks before study entry.

- Eastern Cooperative Oncology Group (ECOG) performance status ≤2.
- Life expectancy ≥3 months.
- Adequate bone marrow function: absolute neutrophil count $\geq 1.5\times10^9$/L, platelets $\geq 75\times10^9$/L, haemoglobin >9 g/dL.
- Adequate liver function: serum bilirubin: ≤1.5×ULN (upper limit of normal), ALT (alanine aminotransferase) and AST (aspartate phosphatase) ≤2.5×ULN. For patients with known liver metastases: AST and ALT ≤5×ULN.
- Adequate renal function: serum creatinine ≤2.0×ULN.
- Patients must agree to effective contraception during the entire study treatment.
- Signed written informed consent.

TEST AND REFERENCE PRODUCTS, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER:

Everolimus 10 mg per os daily. The test drug was supplied by Novartis. Batch numbers supplied: 10024, 10106, 10313, 10360, 10428.

DURATION OF TREATMENT:

Total study duration including the follow-up period was estimated at 42 months; actual study duration was 39 months (from the first visit of the first patient on 16 DEC 2010 to the last visit of the last patient on 14 MAR 2014)

CRITERIA FOR EVALUATION:

Primary Efficacy Endpoint:

- Progression-free rate after 12 weeks of treatment, according to RECIST criteria or tumor marker measurements

Secondary Efficacy Endpoints:

- Objective response rate (by RECIST and tumor markers)
- Disease control rate
- Progression-free survival
- Overall survival

Secondary Safety Endpoint:

- The safety profile of the study drug

STATISTICAL METHODS:

A two-sided 80 % confidence interval was calculated for the progression-free survival rate after 12 weeks. The null-hypothesis would have been rejected if there were at least 4 of the 25 patients progression free after 12 weeks (the lower boundary of the 80%-confidence interval should exceed 5%). If at least 10 patients would have been progression-free after 12 weeks, the 80%-confidence interval would be larger than 25%.

The secondary endpoints were objective response rate (by RECIST and tumor markers), disease control rate, progression-free survival, overall survival and the safety profile. Likewise estimates and confidence intervals were provided for response rates.

Kaplan-Meier curves were used for the secondary endpoint progression-free survival. The assessment of safety was based mainly on the frequency of adverse events. Adverse events are summarized by presenting the number and percentage of patients having any adverse event by body system, type of adverse event, and maximum severity according to Common Terminology Criteria (CTC) grade. Those adverse events that result in death, discontinuation or are serious were to be presented separately.

All laboratory values are converted into SI (International System of Units) units. The absolute and relative number of patients with clinically relevant abnormal laboratory values is presented.

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SUMMARY - CONCLUSIONS

Efficacy Results:

- Primary efficacy: progression-free survival rate after 12 weeks of treatment was 0.000 in the ITT population.
- Objective response rate was 0.000 in the ITT population
- Disease control rate was 0.045 in the ITT population
- Progression-free survival was 6.714 weeks (median value; lower confidence limit: 5.7143, upper confidence limit: 7.429) in the ITT population
- Overall survival was 9.286 weeks (median value; lower confidence limit: 6.000, upper confidence limit: 12.429) in the ITT population
- The efficacy conclusions based on the PP population are similar to those based on the ITT population

Safety Results:

- Of 25 patients treated with everolimus, treatment-emergent AEs were reported for 16 patients (64%); 10 patients (40%) experienced AEs that were considered at least possibly related to the study drug
- The most common AE was dyspnoea (reported by 24% of the patients), followed by anaemia (20%) and pain (20.0%). The most common AEs assessed as at least possibly related were dyspnoea (37.5%) and anaemia (22.5%), nausea (17.5%) and rash (15.0%).
- No SUSARs (suspected unexpected serious adverse reactions) were reported during the study
- There was no indication of unexpected, clinically significant changes in laboratory parameters or vital signs during treatment
- Overall, the safety profile observed in this study is consistent with the safety data already known for everolimus

Conclusion:

Preclinical data from many tumor models, including germ cell tumors, suggest that everolimus could play a role in inhibiting tumor cell proliferation in germ cell cancer. Moreover, everolimus also inhibits angiogenesis and therefore tumor growth indirectly. Given the paucity of therapeutic alternatives for patients with relapsed/refractory metastatic germ cell cancer, a prospective study with 25 patients treated with several cycles of everolimus as monotherapy was performed to evaluate this option.

Efficacy: The primary efficacy endpoint to evaluate everolimus as monotherapy in patients with metastatic germ cell cancer was the progression-free survival rate after 12 weeks of treatment. The rate was found to be 0.000 in the ITT population, thus all patients either showed disease progression or died during this time. As for the secondary efficacy endpoint of objective response rate the same value of 0.000 was found (in the ITT population; 22 patients). The disease control rate (in the ITT population) was 0.054 due to one patient displaying stable disease during the 12-week treatment phase. The median progression-free survival was 6.714 weeks (in the ITT population) and median overall survival was 9.286 weeks (in the ITT population).

Safety: Of 25 patients (the safety population) treated with everolimus, treatment-emergent AEs were reported for 16 patients (64%); 10 patients (40%) experienced AEs that were considered at least possibly related to the study drug. The most common AE was dyspnoea (24% of patients), followed by anaemia (20%) and pain (20.0%). The most common AEs assessed as at least possibly related were dyspnoea (37.5%) and anaemia (22.5%), nausea (17.5%), and rash (15.0%). No SUSARs were reported during the study. There was no indication of unexpected, clinically significant, changes in laboratory parameters or vital signs during treatment. Overall, the safety profile observed in this study is consistent with the safety data already known for everolimus.

Administration of everolimus in metastatic germ cell cancer resulted in a 0% progression-free survival of patients after 12 weeks of treatment. The safety profile did not reveal unexpected events apart from the known safety profile of everolimus.

Date of the report:
25 SEP 2015

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Explanation
AE	Adverse event
AFP	Alpha-fetoprotein
AKT	Protein kinase B
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
AST	Asparate aminotransferase
AUC	Area under the blood concentration-time curve
BEP/PEB	Bleomycin, etoposide and cisplatin chemotherapy
BMI	Body mass index
C_{max}	Maximum blood concentration
CPK	Creatine phosphokinase
CR	Complete response
CRF	Case report form
CRO	Clinical research organization
CSR	Clinical study report
CT	Computed tomography
CTC	Common Terminology Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CYP3A4	Cytochrome P450 3A4
DLCO	Diffusion capacity of the lung for carbon monoxide
EC	Ethics committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EudraCT	European Union Drug Regulating Authorities Clinical Trials
GCP	Good clinical practice
G-CSF	Granulocyte colony-stimulating factor
GGT	Gamma-glutamyl transferase
GOP	Gemcitabine, oxaliplatin and paclitaxel chemotherapy
GTCSG	German Testicular Cancer Study Group
HBs-Ag	Hepatitis B surface antigen
HBc	Hepatitis B core protein
HBV	Hepatitis B virus
HCG	Human chorionic gonadotropin
HCV	Hepatitis C virus

Abbreviation	Explanation
HD-CE	High-dose carboplatin and etoposide chemotherapy
HDL	High-density lipoprotein
HIF-1	Hypoxia-inducible factor 1
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Conference on Harmonisation
IGCCCG	International Germ Cell Cancer Collaboration Group
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
MedDRA	Medical Dictionary for Regulatory Activities
MHH	Medizinische Hochschule Hannover (Hannover Medical School)
MRI	Magnetic resonance imaging
mTOR	Mammalian target of rapamycin
N	Number of patients
NCI	National Cancer Institute
NYHA	New York Heart Association
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
P-gp	P-glycoprotein
pH	Potential hydrogen
PI	Principal investigator
PI3K	Phosphoinositide 3-kinase
PK	Pharmacokinetics
PL	Phospholipids
PR	Partial response
PT	Prothrombin time
PTEN	Phosphatidylinositol-3,4,5-trisphosphate 3-phosphatase
RECIST	Response evaluation criteria in solid tumors
SAE	Serious adverse event
SI	International System of Units
SD	Standard deviation
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment emergent adverse event
t_{max}	Peak blood levels

Abbreviation	Explanation
ULN	Upper limit of normal
VEGF	Vascular endothelial growth factor
VIP/PEI	Etoposide, ifosfamide and cisplatin chemotherapy

5. ETHICS

5.1 Independent Ethics Committee (IEC)

This clinical study report (CSR) is based on the final Study Protocol Version 2.0 dated 12 MAR 2010 and the Amendment to Study Protocol Version 2.4 dated 24 JAN 2013.

The Study Protocol dated 12 MAR 2010 and the Informed Consent Form (ICF) were approved by the Ethics Committee (EC) of the Hannover Medical School (date of approval: 24 JUN 2010). The Amendment to the Study Protocol (Version 2.4) was approved by the EC of the Hannover Medical School on: 25 MAR 2013. Please refer to Appendix 16.1.3 for letters of approval and details of the EC.

5.2 Ethical Conduct of the Study

This study was conducted in compliance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practice (GCP) and the applicable laws and regulations, as described in:

1. Declaration of Helsinki, concerning medical research in humans in the 2008 version. (World Medical Association Declaration of Helsinki, 59th World Medical Association General Assembly, Seoul, October 2008)
2. International Conference on Harmonisation (ICH) Tripartite Guidelines for Good Clinical Practice 1996 (ICH Harmonised Tripartite Guideline of Good Clinical Practice: Practice: Note for Guidance on Good Clinical Practice [ICH Topic E6, Step 5] adopted by CPMP, July 1996, issued as CPMP/ICH/135/95).

The Principal Investigator (PI) agreed, when signing the Study Protocol, to adhere to the instructions and procedures described in it and thereby to adhere to the principles of GCP and to conduct the study in accordance with the 2008 revision of the Declaration of Helsinki. A copy of the Declaration of Helsinki was located in the Investigator's file.

5.3 Patient Information and Consent

Prior to undergoing any study specific procedure, each potential patient, provided signed acknowledgement of his/her freely given informed consent. Either the PI or a designated person qualified to meet any applicable local regulation, who was equally knowledgeable about the study, explained the aims, methods, anticipated benefits and potential hazards of the study and any discomfort it may entail. A corresponding written explanation was also provided and the patient was allowed sufficient time to consider the study information.

Prior to signing the ICF, the patient was given the opportunity to discuss any issues concerning the study with a physician who had suitable knowledge of the study and to have all questions answered openly and honestly. Patients were also notified that they were free to discontinue their participation in the study at any time.

If the patient was willing to participate in the study, two copies of the ICF were signed and personally dated by the patient, the physician taking the consent and, if applicable, the designated person who explained the nature of the study. The patient received one copy including the information sheet. The second copy was retained with the study records at the PI's site.

A model patient information and ICF are attached in Appendix Section 16.1.3.

The patient was informed that any medical information obtained in the course of the study was considered confidential, but that in accordance with local data protection laws his or her medical records might be examined by authorized clinical monitors, clinical quality assurance auditors appointed by the Sponsor, appropriate EC members and by inspectors from regulatory authorities.

Confidentiality of subject data was ensured by the use of depersonalized subject identification codes, where necessary.

6. STUDY PERSONNEL

Addresses, phone- and fax numbers of organisations and study personnel involved in the conduct, analysis and reporting are listed below.

Sponsor:	Hannover Medical School (MHH) Carl-Neuberg-Str. 1 D-30625 Hannover
Secondary Sponsor	German Testicular Cancer Study Group (GTCSG)
Sponsor's Representative:	Prof. Dr. med. Heiko von der Leyen Hannover Clinical Trial Center Carl-Neuberg-Str. 1 D-30625 Hannover Telephone: +49-511-533-333-0 Fax: +49-511-533-333-99 E-mail: vdleyen@clinical-trial-center.de
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A list of investigators including their role in the study and their qualifications is provided in the Appendix Section 16.1.4.

7. INTRODUCTION

7.1 Overview of metastatic germ cell cancer

Most patients with metastatic germ cell cancer can be cured with cisplatin-based chemotherapy, ranging from around 50% for poor prognosis patients (according to the [International Germ Cell Cancer Collaboration Group] IGCCCG criteria) to 90% for good prognosis patients (1). Unfortunately, 20% to 30% of patients treated with cisplatin-based chemotherapy will relapse and only 10-30% of these patients will achieve long-lasting remissions with a second cisplatin-based chemotherapy (usually containing cisplatin, ifosfamide and either etoposide or paclitaxel). Long-lasting remissions are also observed after high-dose chemotherapy with autologous stem cell support (2).

Long-lasting remissions are rare for patients who have progressive disease during the initial cisplatin-based chemotherapy (absolute refractory disease), relapse after high-dose chemotherapy or relapse after a second cisplatin-based chemotherapy and have contraindications for high-dose chemotherapy. Despite a large number of drugs tested,

objective responses with single agent chemotherapy have only been observed with oral etoposide, gemcitabine, paclitaxel or oxaliplatin in this patient population.

Two drug combinations with these drugs have shown higher response rates, and the three drug combination gemcitabine, oxaliplatin and paclitaxel chemotherapy (GOP) is currently the most active treatment regimen (see Table 1) with some patients achieving long-lasting complete remissions (3).

Most patients with relapsed/refractory disease have remissions of only short duration and the median overall survival in these patients is 6 months or less. The investigation of new therapeutic options therefore remains a priority for these patients. Targeted therapies have changed the standard of care for many advanced solid tumors, but so far only case reports and small clinical trials with thalidomide and imatinib have been reported for patients with relapsed/refractory germ cell cancer.

Table 1: Clinical trials in patients with relapsed/refractory germ cell cancer

Regimen	Endpoint	Response	Reference
Capecitabine	objective response rate progression-free at week 12 median overall survival	0/14 (0%) 0/14 (0%) 4 months	Oechsle 2008 (4)
Irinotecan	objective response rate progression-free at week 12 median overall survival	0/15 (0%) 0/15 (0%) 3 months	Kollmannsberger 2002 (5)
Oxaliplatin	objective response rate progression-free at week 12 median overall survival	4/32 (13%) 5/32 (16%) 5 months	Kollmannsberger 2002 (6)
Thalidomide	objective response rate progression-free at week 12	0/15 (0%) 4/15 (27%)	Rick 2006 (7)
Sunitinib	objective response rate	0/10 (0%)	Feldman 2009 (8)
	objective response rate progression-free at week 12 median overall survival	4/32 (13%) 8/32 (26%) 4 months	Oechsle 2011 (9)
Gemcitabine Oxaliplatin	objective response rate progression-free at week 12 median overall survival	16/35 (46%) 11/35 (31%) 6 months	Kollmannsberger 2004 (10)
Gemcitabine Oxaliplatin Paclitaxel	objective response rate median progression-free survival median overall survival	22/41 (51%) 3 months 6 months	Bokemeyer 2008 (3)

7.2 Overview of everolimus

Everolimus (RAD001) is a derivative of rapamycin and acts as a signal transduction inhibitor. Everolimus targets mTOR (mammalian target of rapamycin), a key protein kinase regulating cell growth, proliferation and survival. Everolimus was approved in 2003 in many countries including Germany for the prevention of kidney and heart transplant rejection. The PI3K (phosphoinositide 3-kinase) /AKT (protein kinase B) pathway, deregulated in many human cancers, modulates mTOR pathway activity.

Everolimus is being investigated as an anticancer agent based on its potential to act:

- directly on the tumor cells by inhibiting tumor cell growth and proliferation,
- indirectly by inhibiting angiogenesis leading to reduced tumor vascularity (via potent inhibition of tumor cell HIF-1 (hypoxia-inducible factor 1) activity and VEGF (vascular endothelial growth factor) production and VEGF-induced proliferation of endothelial cells).

7.2.1 Experimental antitumor activity

Everolimus inhibits the proliferation of a range of human tumor cell lines in vitro, including cell lines originating from lung, breast, prostate, and colon cancer. Everolimus also inhibits the proliferation of human umbilical vein endothelial cells (HUVEC) in vitro, with particular potency against VEGF-induced proliferation, suggesting that everolimus may also act as an antiangiogenic agent. Everolimus is a potent inhibitor of tumor growth in vivo, as demonstrated in different mouse models with xenograft and syngenic tumors. Tumors in mice treated with everolimus also had reduced vascularity (vessel density), indicating an in vivo angiogenetic effect.

The relative sensitivity to everolimus in vitro correlates with the degree of phosphorylation (activation) of the AKT protein kinase and the S6 ribosomal protein, in some cases there is also a correlation with PTEN (phosphatidylinositol-3,4,5-trisphosphate 3-phosphatase) (gene) status. Studies with everolimus in experimental animal tumor models showed that everolimus monotherapy typically reduced tumor cell growth rates rather than producing tumor regressions.

KIT, RAS, BRAF, MEK, PI3K, AKT and also mTOR have been identified as potential targets in cisplatin-resistant metastatic germ cell tumors (11). A high incidence of the *BRAF* mutation V600E and microsatellite instability has been described in a series of tumors from patients with cisplatin-resistant germ cell tumors (12). BRAF interacts with the PI3 kinase signalling pathway via AKT. Loss of PTEN marks the transition from intratubular germ cell neoplasias to invasive germ cell tumors (13). Knocking out *PTEN* in germ cells leads to development of testicular teratoma in a mouse model (14). Everolimus sensitizes tumor cells with wild-type p53 (as are almost all germ cell tumors) to DNA-damaged induced apoptosis by cisplatin (15).

7.2.2 Pharmacokinetics

The pharmacokinetics of everolimus have been extensively investigated in the context of the development as an immunosuppressant in solid organ transplantation as a part of a multi-drug regimen including ciclosporin and glucocorticoids. More recent Phase I studies also provided steady-state pharmacokinetics for both the weekly and daily schedules at varying dose levels in patients with advanced cancers. Everolimus is rapidly absorbed after oral administration, with a median time to peak blood levels (t_{max}) of 1-2 hours post dose. The extent of absorption is estimated at above 11%. The area under the blood concentration-time curve (AUC) is dose-proportionate for the dose ranges tested while maximum blood concentration (C_{max}) appears

to plateau at dose levels higher than 20 mg. The terminal half-life in cancer patients averaged 30 hours, which is similar to that in healthy subjects.

Everolimus is mainly metabolized by CYP3A4 (Cytochrome P450 3A4) in the liver and to some extent in the intestinal wall. Everolimus is also a substrate of P-glycoprotein (P-gp). Therefore, absorption and subsequent elimination of systematically absorbed everolimus may be influenced by concomitant medications that interact with CYP3A4 and/or P-glycoprotein. In phase III clinical trials in kidney transplantation patients, strong inhibitors of CYP3A4 (e.g. imidazole antifungals, ciclosporin or erythromycin) have been shown to reduce the clearance of everolimus. Rifampicin, a strong inducer of CYP3A4, increases the clearance of everolimus. In subjects with mild to moderate hepatic impairment, the mean AUC of everolimus is increased twofold, whilst renal impairment does not affect the pharmacokinetics of everolimus. Everolimus can increase serum levels of strong CYP3A4 inhibitors, and patients taking these drugs should be advised and closely monitored for side effects.

Pharmacokinetic/pharmacodynamic modeling based on inhibition in a peripheral biomarker (S6 kinase inhibition in peripheral blood mononuclear cells) suggests that 5-10 mg daily should be an adequate dose to produce a high degree of sustained target inhibition.

7.2.3 Safety data in clinical studies

Safety data are available from three monotherapy phase I clinical studies (RAD001C2101, RAD001C2102 and RAD001C2107) given to 147 patients with advanced solid tumors in various doses and schedules (weekly dosing 5-70 mg and daily dosing 5-10 mg). Approximately 46% of patients reported rash and erythema, sometimes accompanied by pruritus (16%), skin dryness (10%) or nail disorders (6%). Maximum severity was Grade 1-2 in all but one case, and no patient discontinued everolimus because of these adverse events. Stomatitis, mucositis or mouth ulcers were reported in 40% of patients. In most cases these appeared rapidly after the start of therapy (51% within two weeks, 73% within four weeks). Most of these adverse events were Grade 1-2, everolimus was interrupted in 8/59 patients with Grade 3 severity, and discontinued in two patients. Fatigue (33%) and nausea (27%) are other common adverse events.

Drug-related hematologic abnormalities were recorded in a total of 28 patients. Myelosuppression is a recognised effect of rapamycins, but severe, suspected drug-related cytopenia is uncommon, and was reason for discontinuation in 3 patients. Grade 4 thrombocytopenia ($< 20\times10^9$/L) was recorded in one patient. Hyperlipidemia, a recognised side-effect of rapamycins, was observed in 16 patients, mostly as hypercholesterolemia. Grade 3 hypertriglyceridemia was noted in 2 patients. Eleven patients initiated lipid-lowering drug therapy while on study drug. Hyperglycemia was recorded as a suspected adverse drug reaction in 12 patients (Grade 3 in 5 patients).

Non-infectious pneumonitis is a recognised effect of rapamycins. Severe pneumonitis suspected as drug-related has been reported as a serious adverse event in oncologic studies with everolimus. Pneumonitis was observed in 8% of patients in the RECORD-1 trial (3% Grade 3, no Grade 4). In addition, acute respiratory distress syndrome (n=2), alveolitis (n=1) and allergic alveolitis (n=1), interstitial lung disease (n=10), lung infiltration (n=23), cryptogenic organizing pneumonia, lung consolidation, pulmonary alveolar hemorrhage, pulmonary toxicity and pulmonary fibrosis (n=1, each) have been reported. One fatal case of

drug-related pneumonitis has been reported among 2568 oncology patients receiving everolimus. Data from two investigator-initiated trials, which included serial lung scans in patients, suggest a high frequency of pneumonitis with either grade 1 (asymptomatic, evident radiologically only) or Grade 2 (mild symptoms not interfering with activities of daily living), but the majority of patients could be treated without dose reductions.

7.2.4 Efficacy data in clinical studies

Everolimus has shown promising single agent responses in patients with metastatic clear cell renal cell cancer. A phase II study using everolimus 10 mg daily reported promising results in 41 previously treated metastatic renal cell cancer patients (16). Objective responses were seen in 32% (12 partial responses), progression-free survival was 11.2 months (2.0-31.5+), and overall survival (39 patients) was 24.2+ months. A phase III randomized placebo controlled trial (RECORD-1) in patients with metastatic renal cell cancer who had failed tyrosine kinase inhibitor therapy reported a significantly prolonged progression-free survival compared to the placebo arm (4.0 versus. 1.9 months) (17). Based on these results, everolimus was approved in 2009 in many countries including Germany for the treatment of patients with metastatic renal cell cancer who had failed tyrosine kinase inhibitor therapy.

7.3 Rationale for Performing the Trial

Preclinical data from many tumor models, including germ cell tumors, suggest that everolimus could have a role in inhibiting tumor cell proliferation in germ cell cancer by interrupting the IGF-1/PI3K/mTOR signaling cascade. Moreover, everolimus also inhibits angiogenesis and therefore tumor growth indirectly. Given the paucity of therapeutic alternatives for patients with relapsed/refractory metastatic germ cell cancer, a prospective study is needed to investigate the efficacy of the oral mTOR inhibitor everolimus in this indication. The risks of everolimus treatment are well known from treating other cancer patients. The potential benefit of inhibiting disease progression in these patients that have no standard treatment options clearly outweighs these risks.

8. STUDY OBJECTIVES

This is a single-arm, open-label, multicenter Fleming one-stage phase II trial to determine the efficacy and safety of everolimus monotherapy in patients with refractory/relapsed germ cell cancer.

8.1 Primary Endpoints

- To evaluate the efficacy of everolimus as monotherapy in patients with metastatic germ cell cancer. Efficacy is defined as the percentage of patients progression-free at 12 weeks.

8.2 Secondary Endpoints

- Objective response rate (ORR)
- Disease control rate (stable disease + partial remission + complete remission)
- Progression-free survival (PFS)
- Overall survival (OS)
- Safety profile

9. INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan-Description

The study is a single arm, open-label, multicenter phase II trial of everolimus in patients with relapsed/refractory germ cell cancer. All patients had to have received at least one cisplatin-based chemotherapy regimen and had to have no other chemotherapy treatment options, including high-dose chemotherapy or chemotherapy with GOP.

The primary objective of the trial was to show in an uncontrolled design that everolimus is at least equally effective as other active agents used in this therapeutic situation. For the sample-size calculation it was thus assumed that the progression-free rate at week 12 is 25% or larger. Other drugs in this indication demonstrated progression-free rates of up to 25% as single agents. The continuation of the development in this indication would be of no interest if the progression free rate of everolimus at week 12 was 5% or lower.

After baseline evaluation, patients were to receive study treatment in therapeutic cycles of 21 days. Treatment was to be continued until disease progression (by response evaluation criteria in solid tumors [RECIST] or tumor markers), unacceptable toxicity, or study discontinuation for other reasons. The duration of the enrolment period was estimated to be 24 months. The planned total study duration, defined by enrolment, treatment and follow up period was 33 months.

9.2 Discussion of Study Design, including the Choice of Control Groups

A single arm, open-label study design was chosen, given the paucity of therapeutic alternatives for patients with relapsed/refractory metastatic germ cell cancer. A prospective study was needed to investigate the efficacy of the oral mTOR inhibitor everolimus in this indication.

A placebo group was not included in the trial for ethical reasons.

9.3 Selection of Study Population

9.3.1 Inclusion Criteria

Patients had to fulfil all of the following criteria to be eligible for the study:

- Male patients ≥18 years old
- Patients with histologically proven seminomatous or non-seminomatous germ cell cancer
- Disease progression during cisplatin-based chemotherapy
  or disease progression or relapse after high-dose chemotherapy
  or disease progression or relapse after at least 2 different cisplatin-based regimens and contraindications for high-dose chemotherapy
- Patients must have received prior combination chemotherapy with GOP. Prior treatment with a combination of two of these drugs is allowed in case of contraindications for GOP.
- Disease progression at study entry: progressive disease according to RECIST criteria in baseline examinations or tumor marker increase >25% within 4 weeks before study entry.
- Eastern Cooperative Oncology Group (ECOG) performance status ≤2
- Life expectancy ≥3 months
- Adequate bone marrow function: absolute neutrophil count $\geq 1.5\times10^9$/L, platelets $\geq 75\times10^9$/L, hemoglobin >9 g/dL.
- Adequate liver function: serum bilirubin: ≤1.5×ULN (upper limit of normal), ALT (alanine aminotransferase) and AST (Asparate aminotransferase) ≤2.5×ULN. For patients with known liver metastases: AST and ALT ≤5×ULN.
- Adequate renal function: serum creatinine ≤2.0×ULN.
- Patients must either be surgically sterile or must agree to use effective contraception in the form of either hormonal contraception (implantable, patch) or double-barrier method (any double combination of intrauterine device, male or female condom with spermicidal gel, diaphragm, sponge, cervical cap) during study treatment
- Signed written informed consent

9.3.2 Exclusion Criteria

Patients were to be excluded from the study if there was evidence of any of the following criteria:

- Systemic antitumor treatment within 21 days before study entry

- Simultaneous radiotherapy of the only target lesion(s)
- Patients who have previously received mTOR inhibitors (sirolimus, temsirolimus, everolimus)
- Patients receiving chronic systemic treatment with corticosteroids (dose of ≥20 mg/day methylprednisone equivalent) or another immunosuppressive agent
- Patients with unstable angina pectoris, myocardial infarction ≤6 months prior to first study treatment, congestive heart failure with New York Heart Association (NYHA) class III-IV or serious uncontrolled cardiac arrhythmias
- Patients with severely impaired lung function: spirometry or diffusion capacity of the lung for carbon monoxide (DLCO) <50% of the normal predicted value
- Uncontrolled diabetes: fasting serum glucose >2.0×ULN.
- Patients with an active or uncontrolled infection, including chronic hepatitis B or C.
- Patients who have a history of another primary malignancy and are off treatment for ≤3 years, with the exception of non-melanoma skin cancer
- Patients who have undergone major surgery within 4 weeks prior to starting study drug (e.g. intra-thoracic, intra-abdominal, or intra-pelvic) or significant traumatic injury, or who have not recovered from the side effects of any of the above
- Patients who have participated in another clinical trial within 30 days before study entry
- Other serious medical conditions that could impair the ability of the patient to participate in the study
- Patients unwilling or unable to comply with the protocol

9.3.3 Removal of Patients from Therapy and Assessment

Study drug discontinuation refers to the complete withdrawal from study treatment. One of the following reasons was to be documented:

- Adverse event(s)
- Disease progression
- Protocol violation
- Subject withdrew consent
- Lost to follow-up
- Administrative problems

Patients who discontinued the study were to perform an end of treatment visit with the assessments outlined in Table 7 within 2 weeks of study drug discontinuation. An end of study visit was to be performed four weeks after the last dose of everolimus was taken. No further serious adverse event (SAE) information was to be collected beyond the 28 day follow-up safety interval.

9.4 Treatments

9.4.1 Treatments Administered

The study drug everolimus was provided by Novartis. Everolimus was formulated as tablets of 5 mg for oral administration. Tablets were to be removed from their packaging only at the time of administration as the drug is both hygroscopic and light-sensitive. Medication labels were to comply with legal requirements and the storage conditions were to be described on the medication label.

Patients were required to bring their fully used medication, including empty packaging to the clinic at each visit. The investigator or his/her designee was to assess compliance at each visit using pill counts. The investigator or his/her designee was to keep documentation (overall drug accountability for the study as well as individual study drug accountability for each patient) of tablets administered, tablets used, dose changes, and dates dispensed.

9.4.2 Identity of Investigational Product(s)

Study Drug

Name:	Afinitor®
Active Compound:	Everolimus (RAD001)
Form and Description:	Tablets, white to light yellow, elongated, with bevelled edges, without score, engraved with „5“ on the one side and „NVR“ on the other
Strength and Packaging:	5 mg everolimus per tablet
Manufacturer:	(Marketing Authorisation Holder) Novartis Europharm Limited Wimblehurst Road Horsham West Sussex, RH12 5AB United Kingdom

9.4.3 Method of Assigning Patients to Treatment Groups

This study featured only one treatment group; therefore, no particular method of patient allocation was used.

9.4.4 Selection of Doses in the Study

Patients were instructed to take everolimus at a dose of 10 mg daily.

Study drug dosing was to be interrupted or modified for any adverse drug reaction according to the guidelines in Table 2. If a patient had already decreased two dose levels (to level -2), no further dose reduction was permitted and everolimus was to be discontinued. Everolimus was to be discontinued for any haematological or non-haematological toxicity requiring an everolimus interruption for ≥14 days.

Table 2: Everolimus dose level modification guidelines

Dose level	Dose and schedule
Starting dose	10 mg daily
Decrease one dose level (-1)	5 mg daily
Decrease two dose levels (-2)	5 mg every other day

Adverse events were monitored according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) (18). Patients whose treatment was interrupted or permanently discontinued for any adverse event suspected to be related to everolimus were to be followed weekly until the adverse event returned to Grade ≤1. Adverse event monitoring was to be continued until four weeks after the last dose of everolimus (end of study visit).

The criteria for dose modification for suspected everolimus toxicity (except non-infectious pneumonitis) used are described in Table 3.

Table 3: Criteria for dose modification for suspected everolimus toxicity (except non-infectious pneumonitis) according to NCI CTCAE (Version 3.0 dated 09 AUG 2006) (18)

CTCAE Grade	Actions
2	If the toxicity is tolerable, maintain the same dose. If the toxicity is intolerable, proceed as for Grade 3 toxicity.
3[a]	Interrupt everolimus until recovery to Grade ≤1. Then reintroduce everolimus at the same dose level. If event returns to Grade 2, interrupt everolimus until recovery to Grade ≤1. Then reintroduce everolimus at a lower dose level. Discontinue everolimus if patient already at dose level -2.
3[b]	Should be managed using standard medical therapies. No dose interruption of everolimus required.
3[c]	Interrupt everolimus until resolution of fever and recovery of neutropenia to Grade ≤1. Then reintroduce everolimus at a lower dose level. Discontinue everolimus if patient already at dose level -2.
4[d]	Discontinue everolimus.
4[e]	Proceed as for Grade 3 febrile neutropenia.

a except hyperlipidemia and febrile neutropenia
b hyperlipidemia hypercholesterolemia, hypertriglyceridemia or both
c febrile neutropenia
d except neutropenia
e neutropenia

9.4.4.1 Management of mucositis/stomatitis/mouth ulcers

Mucositis, stomatitis and mouth ulcers considered related to everolimus were to be treated according to Table 4. Agents containing hydrogen peroxide, iodine and thyme derivatives tend to worsen mouth ulcers and were to be avoided. Prophylactic antifungal and antiviral agents were to be avoided. Topical antifungal agents were to be preferred for the treatment of fungal infections, because systemic imidazole antifungal agents (e.g. fluconazole or voriconazole) are strong inhibitors of everolimus metabolism.

Table 4: Management of mucositis/stomatitis/mouth ulcers

CTCAE Grade	Management
1	Non-alcoholic mouthwash or salt water (NaCl 0.9%) several times a day until resolution.
2	Topical analgesic mouth treatments (benzocaine, etc.) with or without topical corticosteroids (triamcinolone, etc.). Dose modification according to Table 2 was to be considered
3 and 4	Local supportive care as for Grade 2. Dose modification according to Table 2.

9.4.4.2 Management of hyperlipidemia

Treatment of hyperlipidemia had to take into account the pre-treatment status and dietary habits. For hypercholesterolemia Grade ≥2 (>300 mg/dL or 7.75 mmol/L) or hypertriglyceridemia Grade ≥2 (>2.5×ULN) treatment with a statin, fibrate or another appropriate lipid-lowering medication in addition to diet was to be considered. Statins can have drug interactions with everolimus and pravastatin and atovarstatin was to be preferred in case statin treatment became necessary. Drug interactions with everolimus were to be considered for statins and everolimus was to be dosed according to Table 3.

9.4.4.3 Management of non-infectious pneumonitis

Both asymptomatic radiological changes (CTCAE Grade 1) and symptomatic non-infectious pneumonitis (CTCAE Grade ≥2) have been observed in patients receiving everolimus and other mTOR inhibitors. These patients were to be managed according to the guidelines in Table 5.

Table 5: Management of non-infectious pneumonitis

CTCAE Grade	Required investigations	Management	Everolimus dose adjustment
1	Computed tomography (CT) scan of the lung repeated every 2 cycles until return to baseline	No therapy required	None
2	CT scan of the lung repeated every cycle until return to baseline. Bronchoscopy was to be considered	Symptomatic. Corticosteroids were to be considered if cough was troublesome.	Everolimus was to be interrupted until recovery to Grade ≤1. Everolimus was then to be reintroduced at the same dose level If event returns to Grade 2, everolimus was to be interrupted until recovery to Grade ≤1. Everolimus was then to be reintroduced at a lower dose level Everolimus was to be discontinued if the patient was already at dose level -2
3	CT scan of the lung and pulmonary function tests (spirometry, DLCO and room air O_2 saturation at rest). Bronchoscopy was recommended	Corticosteroids were to be considered if the infective origin had been ruled out. Taper as medically indicated	Everolimus was to be interrupted until recovery to Grade ≤1. Everolimus was then to be reintroduced at a lower dose level Everolimus was to be discontinued if the patient was already at dose level -2
4	CT scan of the lung and pulmonary function tests (spirometry, DLCO and room air O_2 saturation at rest). Bronchoscopy was recommended	Corticosteroids were to be considered if the infective origin had been ruled out. Taper as medically indicated	Everolimus was to be discontinued

9.4.5 Selection and Timing of Dose for Each Patient

Patients were instructed to take everolimus orally at a dose of 10 mg with a glass of water once daily, in a fasting state or with a light fat-free meal, and as close as possible to the same time each day. If vomiting occurred no attempt was to be made to replace the dose. Everolimus was taken daily from Visit 2 until study drug discontinuation (see Section 9.5.1). Study drug was to be administered continuously and for purposes of this study, a treatment cycle was considered to last 21 days.

9.4.6 Blinding

This trial was open label, no blinding took place.

9.4.7 Prior and Concomitant Therapy

All medications (other than study treatment) and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient started treatment with everolimus was to be documented. Drugs or substances known to be inhibitors, inducers or substrates of the isoenzyme CYP3A (see Table 6) were to be avoided unless use of the drug was essential and no substitute was available. Patients required to take strong CYP3A4 inhibitors were to be closely monitored for side effects. Examples of drugs and substances that were to be avoided include imidazole antifungals such as fluconazole, voriconazole and grapefruit juice. The PT (prothrombin time) /INR had to be tested at least weekly in cycle 1, and at least every 14 days starting with cycle 2 in patients treated with oral anticoagulants such as warfarin or phenprocoumon because of potential drug interactions.

Erythropoiesis-stimulating agents were to be used at the discretion of the treating physician. Granulocyte colony-stimulating factor (G-CSF) may only be used in case of Grade 4 neutropenia with or without fever. Radiotherapy was permitted, unless it was radiotherapy of the only target lesion(s). No other approved or investigational anticancer treatment was permitted during the study period. No other investigational drug was to be used during treatment on this protocol.

Table 6: Clinically relevant substrates, inducers and inhibitors of CYP3A

Competitive inhibitors	
Antibiotics	Calcium channel blockers
Clarithromycin	Amlodipine
Erythromycin	Felodipine
Telithromycin	Nifedipine
Antiarrhythmics	Nisoldipine
Quinidine	Nitrendipine
Benzodiazepine	HMG Coa reductase inhibitors
Alprazolam	Cerivastatin
Diazepam	Lovastatin
Midazolam	Simvastatin
Triazolam	Miscellaneous
Immunemodulators	Aprepitant
Ciclosporin	Buspirone
Tacrolimus	Haloperidol
HIV (human immunodeficiency virus) protease inhibitors	Methadone
Indinavir*	Pimozide
Ritonavir*	Quinine
Saquinavir*	Sildenafil
Prokinetics	Tamoxifen
Cisapride	Trazodone
Antihistamines	Vincristin
Astemizole	
Chlorpheniramine	
Inducers	
Carbamazepine	Rifampicin*
Phenobarbital	St. John's wort
Phenytoin*	Troglitazone
Rifabutin*	
Inhibitors	
Amiodarone	Indinavir
Cimetidine	Itraconazole*
Clarithromycin	Ketoconazole*
Delaviridine	Voriconazole*
Diltiazem	Posaconazole*
Erthyromycin	Mibefradil
Fluvoxamine*	Nefazodone*
Grapefruit juice	Nelfinavir*
Sevilla orange	Troleandomycin
	Verapamil

* denotes strong inhibition or induction

9.4.8 Treatment Compliance

Patients were required to bring their fully used medication, including empty packaging to the clinic at each visit. The investigator or his/her designee assessed compliance at each visit using pill counts. The investigator or his/her designee had to keep documentation (overall drug accountability for the study as well as individual study drug accountability for each patient) of tablets administered, tablets used, dose changes, and dates dispensed.

9.5 Efficacy and Safety Variables

9.5.1 Efficacy and Safety Measurements Assessed and Flow Chart

An overview of the assessments performed during the study and the corresponding time points is provided in the Study Flow Chart in Table 7. The local laboratories performed all standard clinical laboratory analyses described below. The kind and frequency of radiology assessments (CT and/or MRI [magnetic resonance imaging] scans) was consistent with the clinical standard in this patient population. Patients did not receive additional radiology assessments because of study participation. All data from these assessments was to be supported to the patient's source documentation. Each treatment cycle was considered to last 21 days. The end of treatment visit was to be performed no later than two weeks after the last everolimus dose. The end of study visit was to take place four weeks after the last everolimus dose. After the end of study, only survival information was to be collected.

Table 7: Study Flow Chart: Visit evaluation schedule

Assessment	Screening	Cycle number			End of treatment	End of study
		1	2	≥3		
Visit	1	2[n]	3	4+		
Day (of the respective cycle)	-14 to 0	1	1	1		
Written informed consent	×					
Medical history[a]	×					
Adverse events[b]		×	×	×	×	×
Concomitant medications[c]	×	×	×	×	×	×
Vital signs, weight and ECOG[d]	×	×	×	×	×	×
Physical examination	×	×	×	×	×	×
Hematology and coagulation studies[e]	×		×	×	×	×
Coagulation studies[f]	×		×			
Serum chemistry including lipid profile[g]	×		×	×	×	×
Tumor markers[h]	×		×	×	×	×
Virology[j]	×					
Urinanalysis[j]	×					
Pulmonary function tests[k]	×					
ECG	×					
CT scan or MRI of chest/abdomen[l]	×			×	×	
CT scan or MRI of brain and bone scan[m]	×					
Registration	×					
Everolimus dispensation		×	×	×		

CT=computed tomography, ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group (performance status), MRI=Magnetic resonance imaging

a Medical history included previous operations, chemotherapy and radiotherapy for germ cell cancer, complications of that treatment (e.g. polyneuropathy), and unrelated medical conditions.

b Start and end date, severity using the NCI CTCAE version 3.0 (18), treatment (concomitant medications or procedures), and causal assessment (whether there existed a reasonable possibility that the investigational product caused or contributed to the adverse event). Patients had to be followed for AEs from Informed Consent signature up to 28 days after last study drug administration. If patient commenced alternative anti-cancer therapy <28 days after the last dose of study drug administration, the AE reporting period ended at the time the new treatment was started. Each AE had to be reported once for cycle, at the worst CTCAE grade.

c Start and end date, route, dose, schedule and indication (medical history or adverse event).

d Vital signs included body blood pressure, heart rate and temperature. Weight and ECOG was also to be documented.

e Hematology included hemoglobin, hematocrit, red blood cell count, white blood cell count, neutrophil count and platelet count.

f Coagulation studies included PT/INR and PTT.

g Serum chemistry included sodium, potassium, calcium, magnesium, phosphate, glucose, creatinine, blood urea nitrogen, uric acid, LDH (lactate dehydrogenase), AST, ALT, alkaline phosphatase, GGT (gamma-glutamyl transferase), bilirubin, protein and albumin. Lipid profiles included total cholesterol, triglycerides, LDL (low-density lipoprotein) and HDL (high-density lipoprotein). The patient had to be in a fasting state (at least 12 hours) at the time of blood sampling.

h Tumor markers included AFP (alpha-fetoprotein) and HCG (human chorionic gonadotropin).

i Virology included Hbs-Ag (hepatitis B surface antigen), anti-Hbs, anti-Hbc (anti-hepatitis B core protein) and anti-HCV (anti-hepatitis C virus). HBV (hepatitis B virus) -DNA was to be measured in patients with positive Hbs-Ag or anti-Hbc, HCV-RNA was to be measured in patients positive for anti-HCV.

j Urinalysis included dipstick assessment with specific gravity, pH (potential hydrogen), protein, glucose, bilirubin, ketones, blood cells and leucocytes.

k Pulmonary function tests (spirometry and DLCO) and room air O_2 saturation at rest was performed at baseline. These tests were to be repeated whenever there was evidence of non-infectious pneumonitis (see Table 5).

l A CT scan or MRI of the chest and abdomen was performed at baseline (within 2 weeks prior to the first dose of study treatment). During the study period, CT scan or MRI of chest/abdomen was performed every 6 weeks (±1 week). The same type of scan (CT or MRI) used at screening had to be used for all subsequent follow-up assessments. A CT scan or MRI of chest/abdomen was to be performed every 6 weeks until disease progression was documented, even in those patients no longer taking study drug.

m A CT scan or MRI of the brain and bone scan was only performed at baseline in patients with known brain or bone metastasis or when clinically indicated. In case of positive findings, a CT scan or MRI of the brain was repeated every 12 weeks (±2 weeks). Bone lesions were followed by CT scan or MRI every 12 weeks (±2 weeks).

n Visit 1 and visit 2 could be performed on the same day.

9.5.2 Appropriateness of Measurements

Efficacy and safety measurements applied to this study are generally regarded as reliable, precise and valid.

9.5.3 Primary Efficacy Variable(s)

Tumor response was assessed using CT scan or MRI of chest/abdomen using the RECIST criteria (version 1.1)(19) and by tumor marker measurements according to the schedule in Table 7. Patients with brain or bone metastasis were examined by CT scan/MRI of the brain and bone scans. Patients who were allergic/sensitive to the radiographic contrast media used in CT scans and MRIs were to have a CT scan of the chest without contrast or an MRI of the abdomen and pelvis without contrast. Ultrasound scans were not to be used to measure tumor lesions. All patients were to have at least one measurable disease lesion by CT scan or MRI or by physical exam. The same type of scan (CT or MRI with contrast) used at screening was to

be used for all subsequent follow-up visits. Results of the CT scan or MRI were to be obtained before starting the next cycle. Progression was to be assessed by central review of radiological studies, and this assessment was to be the basis for the primary analysis of the primary study endpoint, the proportion of patients progression-free at 12 weeks.

9.5.3.1 Measurable lesions

Tumor lesions had to be accurately measured in at least one dimension (longest diameter in the plane of measurement was to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers were to be recorded as non-measurable).
- 20 mm by chest X-ray

To be considered pathologically enlarged and measurable, a lymph node had to be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis was to be measured and followed.

9.5.3.2 Non-measurable lesions

All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis) were considered to be non-measurable lesions. Lesions considered truly non-measurable included: leptomeningeal disease, ascites, pleural or pericardial effusion, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that was not measurable by reproducible imaging techniques.

Bone scans, positron emission tomography (PET) scans or plain films were not considered adequate imaging techniques to measure bone lesions. However, these techniques could have been used to confirm the presence or disappearance of bone lesions. Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI could be considered as measurable lesions if the soft tissue component met the definition of measurability described above. Blastic bone lesions are non-measurable.

Lesions that met the criteria for radiographically defined simple cysts were not to be considered as malignant lesions (neither measurable nor non-measurable). Cystic lesions thought to represent cystic metastases were considered as measurable lesions, if they met the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these were to be preferred for selection as target lesions. Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, were not considered measurable, unless progression in the lesion had been demonstrated.

Unequivocal progression of non-measurable disease means an increase in the overall disease burden comparable in magnitude to the increase that would be required to declare PD (progressive disease) for measurable disease, e.g. increase of a pleural effusion from trace to large or an increase in lymphangitic disease from localized to widespread.

9.5.3.3 Tumor response evaluation

When more than one measurable lesion was present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs were identified as target lesions and were to be recorded and measured at baseline. Target lesions were to be selected on the basis of their size (lesions with the longest diameter), had to be representative of all involved organs, but in addition were to be those that lended themselves to reproducible repeated measurements. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions was to be calculated and reported as the baseline sum diameter. The baseline sum diameters were to be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease. All other lesions (or sites of disease) including pathological lymph nodes were to be identified as non-target lesions and were to be recorded at baseline. Measurements were not required and these lesions were followed as *present*, *absent* or *unequivocal progression*. In addition, it was possible to record multiple non-target lesions involving the same organ as a single item (e.g. multiple liver metastases).

9.5.3.4 Response criteria

The best overall response was defined as the best response recorded from the start of the study treatment until the end of treatment, taking into account a confirmation after ≥4 weeks for complete and partial responses. See Table 8 for details of the response evaluation.

Complete response (CR): Disappearance of all target and non-target lesions and normalisation of tumor markers. Any pathological lymph nodes (whether target or non-target) were to have a reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameter of target lesions, taking as reference the baseline sum diameters. Patients with tumor marker normalisation and radiological partial response were classified as marker negative partial response. Patients without tumor marker normalisation but radiological partial response were classified as marker positive partial response. Patients with tumor marker positive relapse only and no radiologically evaluable disease were considered to have a marker positive partial response if the tumor marker decreased ≥90%. Patients with tumor marker reduction ≥90% and radiologically disease stabilisation or tumor regression of any extent were considered a marker positive partial response.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this included the baseline sum if that was the smallest on study). In addition to the relative increase of 20%, the sum also had to demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions, unequivocal progression of existing non-target lesions or a tumor marker increase of

>25% (compared to the lowest value on study, and this includes the baseline value), if confirmed in a second measurement after 3 weeks) were also considered progressive disease.

Stable Disease: Neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study. Unchanged tumor markers. Patients with stable tumor size, but tumor marker reductions ≥90% were considered a marker positive partial response.

Patients with global deterioration in their health status requiring discontinuation of treatment without objective evidence of disease progression at that time should were to be reported as symptomatic deterioration. Every effort was to be made to document the objective progression even after discontinuation of treatment.

Table 8: Response evaluation

Target lesions	Non-target lesions	New lesions	Tumor marker	Overall response	Also requires
CR	CR	No	Normalization	CR	
CR	Non CR / non PD	No	Normalization	PR marker negative	≥4 week confirmation
CR	Non CR / non PD	No	Elevation	PR marker positive	≥4 week confirmation
PR	Non PD	No	Normalization	PR marker negative	≥4 week confirmation
PR	Non PD	No	Elevation	PR marker positive	≥4 week confirmation
Stable disease	Non PD	No	≥90% reduction	PR marker positive	Documented at least once ≥6 weeks from baseline
Stable disease	Non PD	No	No change	Stable disease	Documented at least once ≥6 weeks from baseline
PD	Any	Yes/No	Increase	PD	No prior Stable disease, PR or CR

CR Complete response
PD Progressive disease
PR Partial response

9.5.4 Drug Concentration Measurements

No drug concentration measurements were performed.

9.6 Data Quality Assurance

All inclusion criteria and primary and secondary endpoints were verified by source documentation.

On-site quality control was performed throughout the study. The CRO (ICRC-Weyer) contacted the investigator and scheduled monitoring visits.

The sponsor was to conduct audits at study sites to ensure quality of data, study integrity, and compliance with the protocol and the various applicable regulations and guidelines. No audits were performed in the course of the study.

9.7 Statistical Methods Planned in the Protocol and Determination of Sample Size

9.7.1 Statistical and Analytical Plans

All variables and analyses reported in this section are based on the final Study Protocol Version 2.0 dated 12 MAR 2010 and the Amendment to Study Protocol Version 2.4 dated 24 JAN 2013 (Appendix 16.1.9).

The null-hypothesis of this trial was that the true probability for progression-free survival after 12 weeks is less than or equal to 5% (the response rate of inactive agents used in this situation is <5%, see Section 7.1). The progression-free rate at week 12 of other single agents used in this therapeutic situation is up to 25% (see Section 7.1), therefore a progression-free rate of 25% is assumed for sample-size calculation purposes. The type-1-error was set to 20% (two sided) and the study was planned to have 95% power to reject the null-hypothesis.

A two-sided Wald 80% confidence interval was planned to be calculated for the progression-free survival rate after 12 weeks. The null-hypothesis would be rejected if there were at least 4 of the 25 patients progression free after 12 weeks (the lower boundary of the 80%-confidence interval should exceed 5%). If at least 10 patients were progression-free after 12 weeks, the 80%-confidence interval would be larger than 25%.

The secondary endpoints were objective response rate (by RECIST and tumor markers), disease control rate, progression-free survival, overall survival and safety profile. Likewise estimates and confidence intervals were to be provided for response rates.

Kaplan-Meier curves were used for the secondary endpoint progression-free survival. The assessment of safety was based mainly on the frequency of adverse events. Adverse events are summarized by presenting the number and percentage of patients having any adverse event by body system, type of adverse event, and maximum severity according to CTC (Common Terminology Criteria) grade. Those adverse events that result in death, discontinuation or are serious are presented separately.

All laboratory values were to be converted into SI (International System of Units) units. The absolute and relative number of patients with clinically relevant abnormal laboratory values was to be presented.

9.7.2 Determination of Sample Size

Sample size calculation was done with nQuery 4.0.

The null-hypothesis of this trial was that the true probability for progression-free survival after 12 weeks is less than or equal to 5% (the response rate of inactive agents used in this situation is <5%, see Section 7.1). The progression-free rate at week 12 of other single agents

used in this therapeutic situation is up to 25% (see Section 7.1), therefore, a progression-free rate of 25% is assumed for sample-size calculation purposes. The type-1-error was set to 20% (two sided) and the study was planned to have 95% power to reject the null-hypothesis. Under these assumptions and with a Fleming one-stage design, 25 evaluable patients were to be included into the trial, (the normal approximation to the binomial distribution was been used here). The sample size was calculated based on the intent-to-treat population.

An interim analysis was intended after 13 patients had been observed for 6 weeks. It was the aim to stop the trial for futility, if amongst these 13 patients not at least one patient had achieved a progression free survival of at least 6 weeks. If required, recruitment would have been halted at this point in time until 6 week results were available.

The type-1-error was not adjusted for this interim analysis as the sole purpose was to stop the trial for futility and definitely no positive conclusions could have been taken from the trial at this point in time.

9.8 Changes in the Conduct of the Study or Planned Analyses

With the amendment to Study Protocol Version 2.4, dated 24 JAN 2013, the conduct of the study was modified in a few aspects:

- Concerning concomitant medications (see Section 9.4.7 of this report), it was added that patients required to take strong CYP3A4 inhibitors were to be closely monitored for side effects (this information was added also to the patient information)
- Concerning haematological screening of the patients (see Section 9.5.1 of this report), it was clarified that neutrophil count was a required measurement
- Concerning serum chemistry assessment, glucose measurement was added to the list of parameters (see Section 9.5.1 of this report)

In respect to the planned analyses it was clarified that:

- "the primary safety and efficacy analyses will be conducted on all patient data at the time all patients who are still receiving study drug will have completed week 12" (clinical study protocol, Section 7.1) - see Section 11.1 of this report.
- The planned calculation of Wald confidence intervals for response rates was not applicable to the observed data. Wilson confidence intervals were used instead.

10. STUDY PATIENTS

10.1 Disposition of Patients

A total of 25 patients were enrolled and signed ICFs. Six patients did not fulfil the entry criteria and were thus excluded from the per-protocol population. A total number of 24 patients completed the study. One patient (Patient 13) discontinued the study drug after

disease progression and commenced to be treated in an external hospital (see Listing 16.2.1.2). An overview on patient disposition is given in Table 9.

Table 9: Patient disposition (all enrolled patients: N=25)

	n (%)
Screened patients	25 (100)
Eligible patients	19 (76)
Completed patients	24 (96)
Discontinued patients	1 (4)

Source: Table 14.1.1

10.2 Protocol Deviations

Protocol deviations were reported for 11 patients (patient numbers 2, 5, 6, 8, 9, 11, 13, 14, 18, 25 and 26):

- Six patients (patient numbers 5, 9, 11, 13, 18 and 26) screening assessments were performed before the date of the informed consent. These were considered to be minor protocol deviations by the principal investigator as these screening assessments were performed in the course of the ongoing treatment of the severely ill patients studied here and it was considered to be unreasonable to perform those assessments twice in short succession.

- Three patients (patient numbers 8, 25 and 26) exclusion criterion number 1 was met: their last systemic antitumor treatment ended less than 21 days before the start of the study reported here. These were considered to be minor protocol deviations by the principal investigator.

- Two patients (patient numbers 2 and 14) failed inclusion criterion number 4: the patients received only a monotherapy with either paclitaxel or gemcitabine as previous therapy and not a combination of gemcitabine, oxaliplatin and paclitaxel.

- Two patients (patient numbers 6 and 11) failed inclusion criterion number 8: adequate bone marrow function as assessed by absolute neutrophil count, number of platelets and haemoglobin. These were considered to be minor protocol deviations by the principal investigator.

- Patient number 25 was not completely assessed for inclusion criterion number 9: adequate liver function was not fully assessed as AST was not measured at screening.

- Patient number 26 was not completely assessed for exclusion criterion number 6: at screening the patient suffered from thoracotomy and therefore no pulmonary function test was performed. Hence, a severely impaired lung function was not to be ruled out even though the patient was assessed as having an ECOG performance status of 2.

- Patient number 26 paused administration of the study medication for more than 14 days (the maximum number of days allowed by the protocol). This was considered to be a major protocol deviation by the principal investigator.

Additional information on individual protocol deviations are given in Section 16.2.2.1.

11. STUDY EVALUATION

11.1 Data Sets Analysed

The primary safety and efficacy analyses were to be conducted on all patient data at the time all patients who were still receiving study drug would have completed week 12. The following populations were to be used for analysis (see Table 14.1.2):

- Safety population: Consisted of all patients who received at least one dose of study drug: 25 patients (100%).

- Intent-to-treat population: The intent-to-treat population contained all patients of the safety population that completed the post-baseline assessments after 12 weeks of treatment. Patients with documented progressive disease (based on RECIST criteria and tumor markers) or patients that died prior to week 12 were also included: 22 patients (88%).

- Per-protocol population: Consisted of all patients of the intent-to-treat population who showed no major protocol violations, i.e. violations that might have had an impact on the study outcome: 19 patients (76%).

The primary safety analysis was to be conducted on the safety population; the primary efficacy analysis was to be conducted on the intent-to-treat population. The analysis sets are summarised in Table 10.

Table 10: Disposition of patients per analysis population (all enrolled patients: N=25)

Analysis set	n (%)
Safety population	25 (100)
Intent-to-treat population	22 (88)
Per-protocol population	19 (76)

Source: Table 14.1.2

11.2 Demographic and Other Baseline Characteristics

11.2.1 Demographic characteristics

Demographic characteristics are summarised in Table 11 (Source: Table 14.1.3 and 14.1.4). All patients were male (as required by the inclusion criterion number 1 of the study protocol)

and white. The median age of the study population at screening was 33.0 years, ranging from 21 to 58 years. Individual information is provided in Listing 16.2.4.1.

Table 11: Summary of demographic characteristics (safety population, N=25)

Category	Mean (SD)	Median (Min-Max)
Age at screening [years]	34.5 (9.21)	33.0 (21-58)
Age at first histological diagnosis [years]	29.6 (7.30)	30.0 (20-45)
Weight [kg]	75.12 (11.66)	72.00 (58.0-95.0)
Height [cm]	178.6 (7.03)	178.0 (167-195)
Body mass index [kg/m^2]	23.57 (3.47)	23.51 (18.51-29.40)

SD=Standard deviation

Source: Table 14.1.3, Table 14.1.4 and Listing 16.2.4.2

Patients were screened at baseline for a number of viral infections by testing for the presence of Hbs-Ag, anti-Hbs, anti-Hbc and anti-HCV. All patients were negative for Hbs-Ag, anti-Hbc and anti-HCV (see Listing 16.2.4.5 for details).

11.2.2 Germ cell cancer history

Details on the general medical history of the study patients are given in Listing 16.2.4. The individual germ cell cancer history is displayed in Listing 16.2.4.2. A general overview on germ cell cancer history of the patients included in this study is given in Table 12.

Table 12: History of germ cell cancer (safety population, N=25)

Category	n (%)
Primary site	
Mediastinum	9 (36)
Retroperitoneum	11 (44)
Testis	12 (48)
Other	9 (36)
Histology	
Non-seminoma	25 (100)
Seminoma	2 (8)
Therapy	
High-dose chemotherapy with autologous stem cell transplantation	18[a] (72)
Chemotherapy	25 (100)
Radiotherapy	12 (48)
Surgery	24 (96)
Other	3 (12)

Note: The CRF (case report form) allowed multiple answers for histology and therapy. Although multiple answers for primary site were not allowed, more than one primary site was documented.

[a]This is the number of patients receiving autologous stem cell transplantations in connection to germ cell cancer treatment. The number of patients receiving autologous stem cell transplantations for antineoplastic therapies in general is higher (see Listing 16.2.4.3).

Source: Table 14.1.5

11.2.3 Prior antineoplastic therapies

Details of previous antineoplastic therapies of the patients participating in this study are given in Listing 16.2.4.3. An overview on the number of prior antineoplastic therapies per patient (thus, comprising all therapies the patient received, not only those directed to the patient's germ cell cancer) is displayed in Table 13.

Table 13: Number of antineoplastic therapies per patient – frequency by category of therapy (safety population, N=25)

Category	Number of therapies	n (%)
Chemotherapy	2	1 (4)
	3	2 (8)
	4	3 (12)
	5	7 (28)
	6	4 (16)
	7	2 (8)
	8	5 (20)
	10	1 (4)
Radiotherapy	1	8 (32)
	2	4 (16)
	3	2 (8)
Surgery	1	6 (24)
	2	1 (4)
	3	4 (16)
	4	3 (12)
	5	3 (12)
	6	6 (24)
	8	2 (8)

Note: Some patients received the same therapy more than once.
Source: Table 14.1.6.

The most frequently used chemotherapies were HD-CE (high-dose carboplatin and etoposide chemotherapy) with 22 patients (88%) receiving this treatment, followed by 17 patients (68%) each, receiving BEP/PEB (bleomycin, etoposide and cisplatin chemotherapy) and GOP treatment, respectively. 16 patients (64%) received VIP/PEI (etoposide, ifosfamide, and cisplatin chemotherapy) treatment (Source: Table 14.1.7). Radiotherapy and surgery were administered in a highly individualised manner concerning the corporeal location of the treatment (for details see Table 14.1.7 and for individual listings see Listing 16.2.4.3).

11.3 Measurement of Treatment Compliance

The study drug everolimus was formulated as tablets of 5 mg for oral administration. Patients were instructed to take everolimus orally at a dose of 10 mg. If vomiting occurred no attempt was to be made to replace the dose. Patients were required to bring their fully used medication, including empty packaging to the clinic at each visit. The investigator or his/her designee was to assess compliance at each visit using pill counts. The investigator or his/her designee was instructed to keep documentation (overall drug accountability for the study as well as individual study drug accountability for each patient) of tablets administered, tablets used, dose changes, and dates dispensed. The by-patient listing of study drug administration is displayed in Listing 16.2.5.1.

11.4 Efficacy Results and Tabulations of Individual Patient Data

11.4.1 Analysis of Efficacy

The following paragraphs present the results of the efficacy analysis for the ITT population. Similar results were obtained for the PP population. Details can be found in Section 14 (Tables 4.2.2 and 14.2.4 and Figures 14.2.5.2, 14.2.5.4 and 14.2.5.6).

11.4.1.1 Primary efficacy endpoint

The primary efficacy endpoint was the progression free survival rate after treatment duration of 12 weeks. The tumor response was assessed using CT scan or MRI of chest/abdomen using the RECIST criteria (version 1.1) and by tumor marker measurements.

Table 14: Response rates (ITT population, N=22)

Category	Response rate	80% confidence interval	
		Lower confidence limit	Upper confidence limit
Progression free survival rate after 12 weeks	0.000	0.0000	0.0695
Disease control rate	0.045	0.0137	0.1404
Objective response rate	0.000	0.0000	0.0695

Note: disease control rate – ratio of patients who achieved stable disease, partial response or complete response at least once
Objective response rate – ratio of patients who achieved partial response or complete response at least once
Source: Table 14.2.1

Progression free survival after 12 weeks of treatment was not achieved in any of the 22 patients of the ITT analysis set. Thus, the progression free survival rate after 12 weeks of treatment was 0.000 in the ITT population (Table 14).

11.4.1.2 Secondary efficacy endpoints

The secondary efficacy endpoint of objective response rate (partial response + complete response) was found to be 0.000, as none of the patients of the ITT population achieved partial response or complete response during the study treatment (Table 14).

The secondary efficacy endpoint of disease control rate (stable disease + partial remission + complete remission) was found to be 0.045 in the ITT population (Table 14). This was due to one patient (Patient number 19), who was reported with stable disease in cycle 3 of the study treatment (see Listing 16.2.6.3).

The median of the secondary efficacy endpoint progression-free survival as estimated for the ITT population by using the Kaplan-Meier method was 6.714 weeks (lower confidence limit:

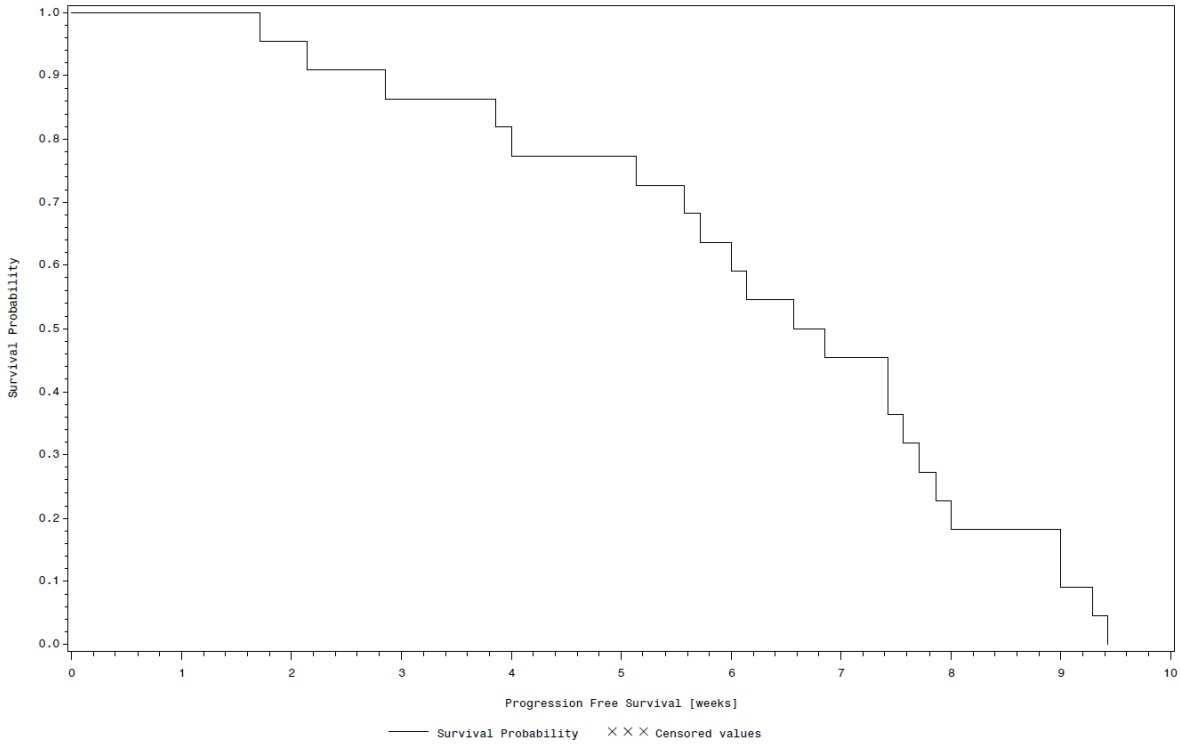


Figure 1: Progression-free survival [weeks] – Kaplan-Meier curve (ITT population)
Source: Figure 14.2.5.1

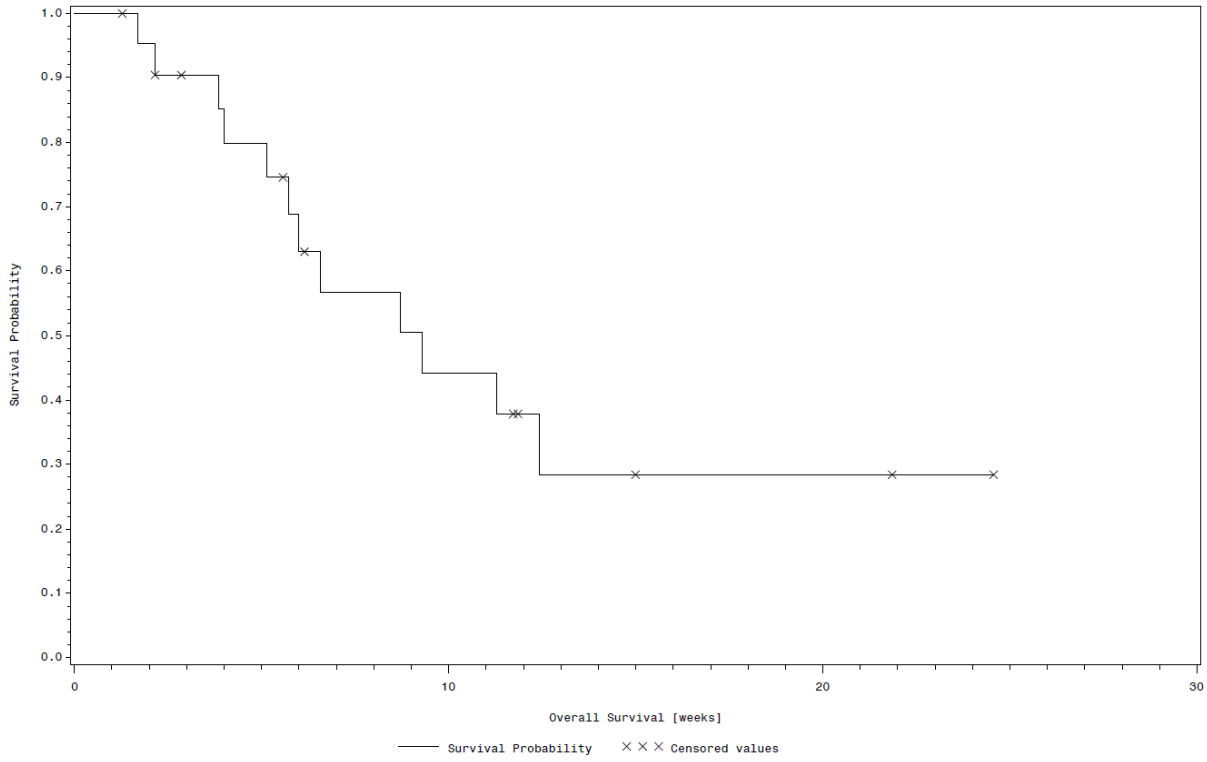
5.714, upper confidence limit: 7.429). The corresponding Kaplan-Meier curve is displayed in Figure 1. See Table 14.2.3 for details of the time to event descriptive statistics of the Kaplan Meier method.

The median Kaplan-Meier estimate of time-to-progression was 7.571 weeks (median value; lower confidence limit: 7.429, upper confidence limit: 7.857).

To clarify the differences between progression-free survival and time- to-progression, it should be remembered that the definition of progression-free survival considers both, the time to progression or the time to death (if progression was not observed) as relevant events whereas time to death is not included in the definition of time-to-progression.

The secondary efficacy endpoint of overall survival was reported with 9.286 weeks (median value; lower confidence limit: 6.000, upper confidence limit: 12.429) in the ITT population. The Kaplan-Meier curve for overall survival is displayed in Figure 2. See Table 14.2.3 for details of the descriptive statistics of the Kaplan Meier method.

Figure 2: Overall survival [weeks] – Kaplan-Meier curve (ITT population)
Source: Figure 14.2.5.3



The secondary endpoint of the safety profile of the study drug is presented in the safety evaluation Section 12.

11.4.2 Statistical/Analytical Issues

11.4.2.1 Adjustments for Covariates

Not applicable.

11.4.2.2 Handling of Dropouts or Missing Data

In studies collecting time-to-event data, the endpoint (progression or death) may not have occurred in all patients when the analysis is performed and may never occur during the study. These data are censored. Survival analysis using the Kaplan-Meier method is the standard approach to accommodate censored data.

11.4.2.3 Interim Analyses and Data Monitoring

The protocol of the study reported here stipulated an interim analysis (see Section 9.7.2) which was to be performed after 13 patients had been observed for 6 weeks. It was the aim to stop the trial for futility, if amongst these 13 patients not at least one patient had achieved a progression-free survival of at least 6 weeks. The interim analysis showed one patient (Patient number 12) with progression-free survival of at least 6 weeks (see Appendix 16). Therefore, the study did not have to be stopped for futility.

The type-1-error was not adjusted for this interim analysis as the sole purpose was to stop the trial for futility and definitely no positive conclusions could have been taken from the trial at this point in time.

11.4.2.4 Multicenter Studies

Patients were enrolled at 6 study centers, all of which were hospitals in Germany. Individual center results are not presented due to the rather small sample sizes.

11.4.2.5 Multiple Comparisons/Multiplicity

One primary efficacy endpoint was defined for this single arm trial. No confirmatory testing was performed. Multiplicity was therefore not an issue.

11.4.2.6 Use of an "Efficacy Subset" of Patients

Analysis of efficacy was performed on the ITT population and the PP population. No particular efficacy subset of patients was defined.

11.4.2.7 Active-Control Studies Intended to Show Equivalence

Not applicable.

11.4.2.8 Examination of Subgroups

Not applicable.

11.4.3 Tabulation of Individual Response Data

The individual response data of the patients are available in Listing 16.2.6.1 for tumor assessment of lesions, in Listing 16.2.6.2 for tumor marker results, and in Listing 16.2.6.3 for overall tumor assessment. Listing 16.2.6.4 displays a by-patient listing of individual event

dates with the corresponding censoring status. The data for progression-free survival were censored to the date of the last assessment, if necessary. The data for overall survival were either censored to the date of the last assessment, or to the date of the last contact, as applicable. The data for time-to-progression were censored to the date of the last assessment, if necessary.

11.4.4 Drug Dose, Drug Concentration, and Relationships to Response

Not applicable.

11.4.5 Drug-Drug and Drug-Disease Interactions

Not applicable.

11.4.6 By-Patient Displays

Not applicable.

11.4.7 Efficacy Conclusions

- Primary efficacy: progression-free survival rate after 12 weeks of treatment was 0.000 in the ITT population.
- Objective response rate was 0.000 in the ITT population
- Disease control rate was 0.054 in the ITT population
- Progression-free survival was 6.714 weeks (median value; lower confidence limit: 5.7143, upper confidence limit: 7.429) in the ITT population
- Overall survival was 9.286 weeks (median value; lower confidence limit: 6.000, upper confidence limit: 12.429) in the ITT population
- The efficacy conclusions based on the PP population are similar to those based on the ITT population

12. SAFETY EVALUATION

12.1 Extent of Exposure

All 25 patients enrolled received the study drug at least once (the safety population, see Section 11.1). See Listing 16.2.5.1 for detailed information on study drug administration to the patients.

12.2 Adverse Events

Information on AEs is provided in Listing 16.2.7.1 and Listing 16.2.7.2 and is summarised in Table 14.3.1.1 to Table 14.3.1.5.

12.2.1 Brief Summary of Adverse Events

A brief summary of AEs is given in Table 15 below. Overall, 16 of all 25 patients (64%) of the safety set experienced a total number of 86 treatment-emergent adverse events (TEAEs) after treatment with the study drug.

A total of 10 patients (40%) experienced 39 TEAEs that were assessed as possibly or probably related by the investigator.

A total of 13 patients (52%) experienced 34 serious TEAEs.

Table 15: Adverse Events - summary table (safety set, N=25)

	n (%) E
Any TEAE	16 (64.00) 86
Any related TEAE	10 (40.00) 39
Any serious TEAE	13 (52.00) 34
Any severe TEAE	14 (56.00) 38
Any TEAE leading to withdrawal of the study drug	1 (4.00) 7

E=number of events, n=number of subjects, N=number of subjects at risk, TEAE=treatment emergent adverse events
Note: %=n/N×100. Only TEAEs are displayed. Any adverse event that is probably or possibly related is treated as a related TEAE.
Any adverse event of CTCAE grade 3, 4 or 5 counts as a severe adverse event.
Source: Table 14.3.1.1

12.2.2 Display of Adverse Events

The incidence of TEAEs is summarised in Table 16, which displays all events reported in 8% of the safety population, i.e. at least 2 patients.

Table 16: Adverse events with an incidence ≥5% - frequency table by system organ class and preferred term (safety set, N=25)

System organ class	Preferred Term	n (%) E
General disorders and administration site conditions		
	Pain	5 (20.00) 6
	Disease progression	3 (12.00) 3
	Mucosal inflammation	3 (12.00) 3
	Fatigue	2 (8.00) 2
	General physical health deterioration	2 (8.00) 2
Respiratory, thoracic and mediastinal disorders		
	Dyspnoea	6 (24.00) 7
	Cough	2 (8.00) 2
Blood and lymphatic system disorders		
	Anaemia	5 (20.00) 6
	Thrombocytopenia	2 (8.00) 2
Gastrointestinal disorders		
	Ascites	2 (8.00) 2
	Constipation	2 (8.00) 2
	Vomiting	2 (8.00) 2
Skin and subcutaneous tissue disorders		
	Rash	2 (8.00) 3
Metabolism and nutrition disorders		
	Decreased appetite	2 (8.00) 2
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Tumor pain	2 (8.00) 2

E=number of events, n=number of subjects, N=number of subjects at risk, TEAE=treatment emergent adverse event
Note: %=n/N×100. Only TEAEs are displayed.
Coding was done using MedDRA (Medical Dictionary for Regulatory Activities) 17.1.
Source: Table 14.3.1.2

The most commonly reported AEs were dyspnoea (24%, 6 patients), pain (20%, 5 patients) and anaemia (20%, 5 patients). The system organ classes for which most frequently AEs were reported are: ‘general disorders and administration site conditions’ ‘respiratory, thoracic and mediastinal disorders’ and ‘blood and lymphatic system disorders’.

The relationship between AE and treatment with the study drug is displayed in Table 14.3.1.3. The most frequently reported AEs, considered to be probably or possibly related to the study drug, were dyspnoea (16%, 4 patients) and mucosal inflammation (12%, 3 patients). At a frequency of 8% (2 patients) the following AEs were considered to be related: ascites, disease progression, pain, tumor pain and rash. Other AEs reported as related were documented solely in single patients.

TEAEs by CTCAE grade are displayed in Section 14.3.1.4. The number of patients with AEs of CTCAE Grade 3, 4 and 5 (=severe TEAEs) is given in Table 17. Pain was most commonly reported as CTCAE Grade 3, 4 or 5 (5 patients in total), followed by dyspnea reported by 3 patients in total and disease progression, reported by 3 patients (with CTCAE Grade 5).

Table 17: Patients reporting treatment-emergent adverse events of CTCAE Grade 3, 4 or 5 (safety set, N=25)

System organ class Preferred term	Grade 3	Grade 4	Grade 5
Blood and lymphatic system disorders			
Anaemia	2 (8.0%)		
Thrombocytopenia	2 (8.0%)		
Gastrointestinal disorders			
Abdominal distension	1 (4.0%)		
Ascites	1 (4.0%)		
Constipation	1 (4.0%)		
Nausea	1 (4.0%)		
Subileus	1 (4.0%)		
Vomiting		1 (4.0%)	
General disorders and administration site conditions			
Asthenia	1 (4.0%)		
Death			1 (4.0%)
Disease progression			3 (12.0%)
General physical health deterioration			1 (4.0%)
Pain	2 (8.0%)	2 (8.0%)	1 (4.0%)
Pyrexia	1 (4.0%)		
Hepatobiliary disorders			
Hepatic failure			1 (4.0%)
Hepatomegaly	1 (4.0%)		
Investigations			
ECOG performance status worsened	1 (4.0%)		
Neoplasms benign, malignant and unspecified			
Metastases to liver	1 (4.0%)		
Neoplasm progression		1 (4.0%)	
Tumor pain	2 (8.0%)		
Renal and urinary disorders			
Dysuria	1 (4.0%)		
Renal failure	1 (4.0%)		
Urinary retention	1 (4.0%)		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea	1 (4.0%)		2 (8.0%)
Vascular disorders			
Haemorrhage	1 (4.0%)		
Lymphoedema	1 (4.0%)		

CTCAE=Common terminology criteria of AEs, ECOG=Eastern cooperative oncology group performance status.
Note: %=n/N×100. N=25. Only TEAEs are displayed.
Grade 3=Severe or medically significant but not immediately life-threatening, Grade 4=Life-threatening consequences, Grade 5=Death related to AE. Coding was done using MedDRA 17.1.
Source: Table 14.3.1.4

12.2.3 Analysis of Adverse Events

A total number of 86 AEs were reported by 25 patients in this study. AEs deemed to be related to the study medication by the investigator correspond to the known safety profile of everolimus as described in the current investigator's brochure, with dyspnoea and mucosal inflammation as the most frequently reported AEs to be at least possibly related in the present study.

No unexpected pattern emerged, concerning the administration of the study treatments and the occurrence of AEs in the present study.

12.2.4 Listing of Adverse Events by Patient

All AEs are listed by patient in Appendix 16, Listing 16.2.7.1.

12.3 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

12.3.1 Listing of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

A listing of SAEs and AEs leading to death or withdrawal is provided in Listing 16.2.7.2.

12.3.1.1 Deaths

Serious TEAEs with fatal outcome were reported for 9 patients (Patient number 1, 2, 5, 7, 11, 12, 14, 17 and 22), see Table 18 for an overview (for additional details, please refer to Listing 16.2.7.2). None of these TEAEs were reported as related to the study drug administration.

Table 18: Serious TEAEs with fatal outcome

Patient number	Preferred term	CTCAE Grade	Relatedness to study medication
1	Disease progression	5	Unlikely
	Pain	4	Unlikely
	General physical health deterioration	5	Unlikely
2	Death	5	Unrelated
5	Disease progression	5	Unlikely
7	Pain	4	Unrelated
	Pain	5	Unlikely
	Dyspnoea	5	Unlikely
11	Disease progression	5	Unrelated
12	Ascites	3	Unlikely
14	Disease progression	4	Unrelated
17	Dyspnoea	5	Unrelated
22	Hepatic failure	5	Unrelated

Any adverse event that is probably or possibly related is treated as a related TEAE. Any adverse event of CTCAE grade 3, 4 or 5 counts as a severe adverse event.
Source: Listing 16.2.7.2

12.3.1.2 Other Serious Adverse Events

A total number of 34 serious TEAEs were reported in13 patients (52%). Of these, 2 SAEs were deemed to be probably related to the study drug by the investigator (see Listing 16.2.7.2):

- In one patient (Patient number 4) renal failure was reported as probably related (CTCAE Grade 3), leading to hospitalisation, study drug discontinuation and withdrawal of the patient

- In one patient (Patient number 20) dyspnoea was reported as probably related (CTCAE Grade 2), leading to study drug dose reduction (to 5 mg daily)

Haematological SAEs were reported in 2 patients:

- In one patient (Patient number 11) anaemia was reported (CTCAE Grade 4), deemed to be unrelated to the study medication, the patient was hospitalised in the course of this event and received erythrocytes as concomitant medication

- In one patient (Patient number 17) anaemia and thrombocytopenia were reported (CTCAE Grade 4 and 3, respectively), deemed to be unrelated to the study medication, the patient was hospitalised in the course of these events and received erythrocytes as concomitant medication for the anaemia

12.3.1.3 Other Significant Adverse Events

Withdrawal from the study due to TEAEs (confer to Listing 16.2.7.2) was reported in one patient (Patient number 4 with the reported SAE renal failure, see above). For this patient, 6 non-serious TEAEs leading to withdrawal were documented (fatigue, stomatitis, bronchitis, dyspnoea, cough and chest pain), as well as one serious TEAE leading to withdrawal (renal failure).

12.3.2 Narratives of Deaths, Other Serious Adverse Events, and Certain Other Significant Adverse Events

No AEs of special interest were defined, narratives are not available. Only suspected unexpected serious adverse reactions (SUSARs) were explicitly planned to be described. Overall, none of the SAEs with a suspected relationship to study drug (at least 'possibly related') were unexpected: there were no SUSARs reported throughout the observation period (see the DSUR of the RADIT study No.4, 29 September 2014).

12.3.3 Analysis and Discussion of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

In the severely ill study population all patients (apart from Patient number 13, who was continued to be treated in an external hospital, see Listing 16.2.1.3) discontinued the study drug due to disease progression or death. See Table 19 for an overview.

Table 19: Study termination by patient

Patient number[a]	Primary reason for discontinuation	Specification of primary reason
1	Disease progression	
2	Disease progression	
4	Adverse event	Primary reason for discontinuation: disease progression was also reported
5	Disease progression	Also due to an adverse event
6	Death	
7	Death	
8	Disease progression	
9	Disease progression	
10	Disease progression	
11	Death	
12	Disease progression	
13	-	Not done, Patient was treated in an external hospital
14	Death	
15	Disease progression	
16	Disease progression	
17	Death	
18	Disease progression	
19	Disease progression	
20	Disease progression	
21	Disease progression	
22	Disease progression	
23	Disease progression	
24	Disease progression	
25	Disease progression	
26	Disease progression	

[a]Patient number 3 was allocated to a patient who did not sign an informed consent and was not included in the study due to a positive disease prognosis (exclusion criterion)
Source: Listing 16.2.1.3

It is to be noted that all serious TEAEs with fatal outcome were deemed to be unrelated to the study medication (see Table 18). Renal failure and dyspnoea, both reported as probably related serious TEAEs in one patient each (see Section 12.3.1.2) belong to the group of events to be expected from the known safety profile of everolimus. No previously unsuspected important adverse effect (SUSAR) of the study medication was detected during this study.

12.4 Clinical Laboratory Evaluation

Summary tables are available for serum chemistry (Table 14.3.5.1), haematology (Table 14.3.5.3), coagulation (Table 14.3.5.5) and urinalysis (Table 14.3.5.7).

12.4.1 Listing of Individual Laboratory Measurements by Patient

By-patient listings of all laboratory test results (quantitative variables) are given in Listing 16.2.8.1 for serum chemistry, in Listing 16.2.8.2 for haematology, in Listing 16.2.8.3 for coagulation and in Listing 16.2.8.4 for urinalysis results. A by-patient listing of abnormal laboratory parameters evaluated as clinically significant is displayed in Listing 16.2.8.5.

12.4.2 Evaluation of Each Laboratory Parameter

Evaluation of clinical safety laboratory parameters included:

- Serum biochemistry: AST, ALT, albumin, alkaline phosphatase, bilirubin, calcium, cholesterol, creatinine, GGT, glucose, HDL, LDH, LDL, magnesium, phosphate, potassium, protein, sodium, triglycerides, urea and uric acid.
- Haematology: haemoglobin, neutrophils, platelet count, white blood cell count
- Coagulation: partial thromboplastin time and prothrombin time

Urinalysis (Table 14.3.5.7) by dipstick test was only performed at screening and the majority of evaluable patients had normal results with the exception of proteinuria which was detected in 4 patients (and in 1 patient trace amounts of protein were detected).

Other laboratory parameters were analysed for each treatment cycle. Summary statistics for each parameter per treatment cycle are given in Table 14.3.5.1 (serum chemistry), Table 14.3.5.3 (haematology) and Table 14.3.5.5 (coagulation). The number of patients with laboratory data decreased over the treatment cycles because patients with disease progression discontinued from treatment or patients died.

12.4.2.1 Laboratory Values Over Time

Overall, most patients had laboratory values which were either normal or not considered to be clinically significant by the investigator (for those values see Section 12.4.2.3). These summary tables do not support any conclusion of an unexpected drug-related effect, as changes of laboratory values were generally as previously reported under treatment with everolimus.

12.4.2.2 Individual Patient Changes

Shift tables for clinical safety laboratory parameters (serum chemistry, haematology and coagulation) were not created, since no reference ranges were included in the database.

12.4.2.3 Individual Clinically Significant Abnormalities

Laboratory test results were evaluated in terms of clinical significance by the investigator. Abnormal clinically significant laboratory values were reported for 7 patients (see Listing 16.2.8.5). For most patients these values were detected already at screening and they were mainly limited to low haemoglobin and elevated liver enzymes.

12.5 Vital Signs, Physical Findings and Other Observations Related to Safety

Vital signs of the patients (systolic and diastolic blood pressure, heart rate, body temperature and ECOG score) were collected at screening and during treatment cycles. The change from baseline (screening) was assessed for each treatment cycle (for a by-patient listing of change from baseline see Listing 16.2.9.1). In Table 14.3.6.2 the descriptive statistics for change from baseline are given. In general, the number of patients with vital sign data decreased over the treatment cycles as patients were discontinued from treatment or died. In the course of the study, an increase of the ECOG score of patients (i.e. Cycle 3 and end of treatment: +1 change from baseline) could be observed, which corresponds with the deterioration of the condition of the severely ill study population. Overall, there was no indication of clinically significant changes in vital signs over time.

The frequency of concomitant medication use of the patients is displayed in Table 14.3.6.3. More than half of the patients were treated with pyrazolones (68%, 17 patients), proton pump inhibitors (60%, 15 patients) and natural opium alkaloids (60%, 15 patients) corresponding to the (cancer) pain relief and gastrointestinal disorder treatment required for the study patients.

12.6 Safety Conclusions

- Of 25 patients treated with everolimus, treatment-emergent AEs were reported for 16 patients (64%); 10 patients (40%) experienced AEs that were considered at least possibly related to the study drug
- The most common AE was dyspnoea (reported by 24% of the patients), followed by anaemia (20%) and pain (20.0%). The most common AEs assessed as at least possibly related were dyspnoea (37.5%) and anaemia (22.5%), nausea (17.5%), and rash (15.0%).
- No SUSARs were reported during the study
- There was no indication of unexpected, clinically significant changes in laboratory parameters or vital signs during treatment
- Overall, the safety profile observed in this study is consistent with the safety data already known for everolimus

13. DISCUSSION AND CONCLUSIONS

Preclinical data from many tumor models, including germ cell tumors, suggest that everolimus could play a role in inhibiting tumor cell proliferation in germ cell cancer. Moreover, everolimus also inhibits angiogenesis and therefore tumor growth indirectly. Given the paucity of therapeutic alternatives for patients with relapsed/refractory metastatic germ cell cancer, a prospective study with 25 patients treated with several cycles of everolimus as monotherapy was performed to evaluate this option.

Efficacy

The primary efficacy endpoint to evaluate everolimus as monotherapy in patients with metastatic germ cell cancer was the progression-free survival rate after 12 weeks of treatment. The rate was found to be 0.000 in the ITT population, thus all patients either showed disease progression or died during this time. As for the secondary efficacy endpoint of objective response rate the same value of 0.000 was found (in the ITT population; 22 patients). The disease control rate (in the ITT population) was 0.054 due to one patient displaying stable disease during the 12-week treatment phase. The median progression-free survival was 6.714 weeks (in the ITT population) and median overall survival was 9.286 weeks (in the ITT population).

Safety

Of 25 patients (the safety population) treated with everolimus, treatment-emergent AEs were reported for 16 patients (64%); 10 patients (40%) experienced AEs that were considered at least possibly related to the study drug. The most common AE was dyspnoea (24% of patients), followed by anaemia (20%) and pain (20.0%). The most common AEs assessed as at least possibly related were dyspnoea (37.5%) and anaemia (22.5%), nausea (17.5%), and rash (15.0%). No SUSARs were reported during the study. There was no indication of unexpected, clinically significant, changes in laboratory parameters or vital signs during treatment. Overall, the safety profile observed in this study is consistent with the safety data already known for everolimus.

Administration of everolimus in metastatic germ cell cancer resulted in a 0% progression-free survival of patients after 12 weeks of treatment. The safety profile did not reveal unexpected events apart from the known safety profile of everolimus.

14. LIST OF TABLES AND FIGURES REFERRED TO IN THE TEXT

Section 14 is provided in a separate file.

15. REFERENCE LIST

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16. APPENDICES

The appendices to this Clinical Study Report are included in a separate file.