Protocol

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Protocol for: Yao JC, Shah MH, Ito T, et al. Everolimus for advanced pancreatic neuroendocrine tumors. N Engl J Med 2011;364:514-23.

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Clinical Development & Medical Affairs

RAD001 (everolimus)

Clinical Trial Protocol CRAD001C2324

A randomized double-blind phase III study of RAD001 10 mg/d plus best supportive care versus placebo plus best supportive care in the treatment of patients with advanced pancreatic neuroendocrine tumor (NET)

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Document type	Working Copy of the Clinical Trial Protocol (WP) Clean
EUDRACT number	2006-006819-75
Version number	01 (incorporating changes from Amendment 1)
Development phase	III
Document status	Final
Release date	22-Jan-2010

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Ab	Antibodies
ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
ANC	Absolute neutrophil count
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
ASAP	As soon as possible
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
ATC	Anatomical Therapeutic Code
AUC	Area under the curve
BAL	Bronchoalveolar Lavage
bFGF	Basic fibroblast growth factor
BSC	Best supportive care
b.i.d.	bis in diem/twice a day
BUN	Blood urea nitrogen
CGA	Chromogranin A
CPK	Creatine phosphokinase
CPO	Country Pharmaceutical Organization
CR	Complete response
CRF	Case Report/Record Form
CRD	Clinical Research and Development
CRO	Contract Research Organization
CS&E	Clinical Safety and Epidemiology
CT	Computer Tomography
CTC	Common Toxicity Criteria
CTL	Clinical trial leader
CV	Coefficient of variation
DLCO	Carbon monoxide diffusion capacity
DLT	Dose limiting toxicity
DNA	Deoxyribonucleic Acid
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic data capture
EDTA	Ethylenediaminetetraacetic acid
EKG	Electrocardiogram
FGF	Fibroblast Growth Factor
FPFV	First Patient First Visit
FSH	Follicle stimulating hormone
FU	Follow up
GI	Gastrointestinal
HBV	hepatitis B virus
HBcAb	hepatitis B core antibodies

HBsAb	hepatitis B surface antibodies
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HDL	High density lipoprotein
HIV	Human immunodeficiency virus
HUVECS	Human umbilical endothelial cells
IAC	Independent Adjudication Committee
IB	Investigator's Brochure
ICH	International Conference on Harmonization
ICT	Islet cell tumors
IEC	Independent Ethics Committee
IGF-1	Insulin-like growth factor
IHC	Immunohistochemistry
IRC	Independent Review Committee
i.v.	intravenous(ly)
i.m.	Intramuscular
IDMC	Independent Data Monitoring Committee
IND	Investigational new drug
INR	International normalized ratio
IRB	Institutional Review Board
ITT	Intent to treat
IUD	Intrauterine device
IVRS	Interactive Voice Response System
LDH	Lactate dehydrogenase
LDL	Low density lipoprotein
LFTs	liver function tests
LLOQ	Lower level of quantification
LPLV	Last patient last visit
MDACC	MD Anderson Cancer Center
mg/d	Milligrams per day
MPD	Molecular pharmacodynamic
MRC	Mutual recognition procedure
MRI	Magnetic Resonance Imaging
MTD	Maximum tolerated dose
mTOR	Mammalian target of Rapamycin
NET	Neuroendocrine Tumor
o.d.	omnia die/once a day
ORR	Overall response rate
OS	Overall survival
p.o.	per os/by mouth/orally
PCR	Polymerase Chain Reaction
PGP	P-glycoprotein
PFS	Progression free survival

PFT	Pulmonary function test
PI3K	Phosphatidylinositol 3-kinase
PK	Pharmacokinetic
PLGF	Placental growth factor
PP	Pancreatic polypeptide
PR	Partial response
REB	Research Ethics Board
RECIST	Response evaluation criteria in solid tumors
RNA	Ribonucleic acid
SAE	Serious adverse event
SD	Stable disease
SOP	Standard Operating Procedure
SS	Steady state
STI	Signal transduction inhibitor
sVEGFR1	Soluble vascular endothelial growth factor receptor 1
sVEGFR2	Soluble vascular endothelial growth factor receptor 2
TSC	Tuberous sclerosis complex
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
VEGF	Vascular endothelial growth factor
VIP	Vasoactive intestinal polypeptide
WBC	White blood cells
WDHA	Watery diarrhea hypokalemia achlorhydria
WHO	World Health Organization

Oncology clinical study protocol synopsis

Investigational drug	RAD001 (everolimus)
Protocol no.	CRAD001C2324
Study phase	III
Study title	A randomized double-blind phase III study of RAD001 10 mg/d plus best supportive care versus placebo plus best supportive care in the treatment of patients with advanced pancreatic neuroendocrine tumor (NET).
Background	RAD001 (everolimus) is a derivative of rapamycin which acts as a signal transduction inhibitor. Its target is mTOR (mammalian target of rapamycin), a key protein kinase regulating cell growth, proliferation and survival. The mTOR pathway activity is modulated by the PI3K/AKT pathway, a pathway known to be dysregulated in numerous human cancers. Pancreatic neuroendocrine tumors (also called pancreatic endocrine tumors or islet cell tumors (ICT) comprise 1-2% of all pancreatic tumors and less than 50% of all neuroendocrine tumors. A wide range of response rates to chemotherapy are reported in the literature and the value of cytotoxic chemotherapy in treatment of pancreatic neuroendocrine tumors are open to question. No randomized studies have shown an improvement in progression free survival due to cytotoxic chemotherapy. In an investigator-sponsored trial at MD Anderson Cancer Center (MDACC), two partial responses were observed among thirteen patients with pancreatic neuroendocrine tumors treated with RAD001 5 mg/d plus Sandostatin LAR 30 mg IM q 28 days. Thirty additional patients with carcinoid and islet cell tumors have been enrolled and treated with RAD001 10 mg/d plus Sandostatin LAR 30 mg IM q 28 days. Safety and efficacy data is expected to be reported at ASCO 2007. The phase II and III monotherapy dose of RAD001 in other treatment settings including carcinoid and pancreatic neuroendocrine tumors is 10 mg/d. A phase II open label, stratified, single-arm study of RAD001 10mg/d in patients with advanced pancreatic neuroendocrine tumor after failure of cytotoxic chemotherapy, [CRAD001C2239], is currently ongoing. As of November 2006, 25 of 144 planned patients have been enrolled. Final primary analysis is planned for end of 2007.
Purpose/rationale	This study will evaluate the antitumor activity of RAD001 plus best supportive care versus placebo plus best supportive care in patients with Advanced Pancreatic Neuroendocrine Tumor.

Objectives	**Primary Objective:** To determine whether treatment with RAD001 10 mg/d plus best supportive care prolongs progression free survival (PFS) compared to treatment with best supportive care alone in patients with advanced pancreatic neuroendocrine tumor. **Secondary Objectives:** • To evaluate the effect of RAD001 on other tumor endpoints: objective response rate (CR, PR), response duration • To compare overall survival (OS) between the study arms • To compare changes from baseline in chromogranin A (CgA) and assess the effect of RAD001 on changes from baseline for other biochemical tumor markers in serum e.g. neuron specific enolase, pancreatic polypeptide, gastrin, glucagons and VIP. Insulin, proinsulin and c-peptide will be obtained in patients with insulinomas. • To determine the safety and tolerability of RAD001 (10 mg/d) in patients with advanced pancreatic neuroendocrine (NET). • To characterize the pharmacokinetics of RAD001 in patients with advanced pancreatic NET. • To determine the effects of RAD001 on plasma angiogenic molecules e.g. VEGF, basic FGF, PLGF, sVEGFR1, and sVEGFR2. • To characterize pre-treatment tumor samples by immunohistochemical and genetic analyses indicating activation of the mTOR pathway • To assess the relationship between RAD001 steady state levels, tumor response, and chromogranin A response (50% decrease from baseline) • **Exploratory Objectives:** Not applicable for this study.
Endpoints (efficacy, safety)	**Efficacy endpoints** The primary endpoint is progression free survival (PFS) assessed by local investigator assessment according to RECIST. Secondary endpoints will include objective response rate (CR or PR), response duration and overall survival. **Safety endpoints** Safety assessments will consist of monitoring and recording all adverse events, including serious adverse events, the regular monitoring of vital signs, physical condition, hematology and blood chemistry, and body weight. In order to monitor for non-infectious pneumonitis, chest X-Rays or chest CT Scans will be performed at screening, at regular intervals during efficacy assessments and as clinically indicated and at the end of the study. Additional workup including pulmonary function tests (PFTs) and bronchoscopy with BAL and/or biopsy will be performed per the discretion of the investigator if there is evidence of non-infectious pneumonitis. For additional detailed information on management of pneumonitis see Table 6-1. Hematology and serum blood chemistry assessment will be done at 2 and 4 weeks and then every cycle.

Study design	This is a prospective, double-blind, randomized, parallel group, placebo-controlled, multicenter phase III study of treatment with RAD001 10 mg p.o. qd plus best supportive care versus placebo plus best supportive care in 392 patients with advanced pancreatic NET. This trial will be supported by IVRS for the randomization and the study medication management. The randomization ratio is 1:1. Randomization and efficacy analyses will be stratified by whether or not patients have received prior cytotoxic chemotherapy, and by WHO performance status (0 vs. 1-2) at baseline. The final primary analysis will be performed when approximately 282 PFS events (per local investigator assessment) are observed in the intent-to-treat (ITT) population. An independent central radiology review committee will be established to review radiology studies as provided by investigational sites. All CT scans and MRIs obtained at baseline and post-baseline will be sent to the independent central radiologist. Independent central radiology review includes radiology assessments by an Independent Review Committee (IRC) and an Independent Adjudication Committee (IAC). • The IRC is constituted by teams of two board-certified independent radiologists who review radiological images from investigational sites on an ongoing basis. Discrepancies between the two central readers are adjudicated. • The IAC is constituted by a board certified radiologist and an oncologist with experience in NETs. The IAC adjudicates PFS discrepancies between local and IRC determination. The adjudication is performed in a blinded manner so that the committee members have no knowledge of treatment assignment or origin of RECIST evaluations (local or central). The data used in the sensitivity analysis of the primary endpoint will be comprised of data from IAC assessment for patients where adjudication is required and data from IRC assessment for patients where no adjudication is required. The process for IRC and the IAC review is specified within the Independent Review Charter. **Duration of Treatment:** Patients will be treated with blinded study treatment (RAD001 or Matching Placebo) until tumor progression is documented per RECIST (as per the investigator) or until any other reasons for treatment discontinuation as outlined within the protocol. During the blinded portion of the study, tumor assessments will be performed and sent for central review until patient starts on a new anti-tumor therapy. Once radiological disease progression has been documented (at the investigative site) during the blinded randomized portion of the study the treating oncologist may proceed to unblind the patient. It is required that RECIST eCRF pages be reviewed with the Novartis clinical trial leader prior to unblinding. Patients receiving placebo may be offered open-label treatment with RAD001 if the treating oncologist believes the patient could benefit from this therapy. For the open label phase of the study, tumor assessments will be required to be done locally and will ***not*** be sent in for central review. Patient unblinding information will not be disclosed to either the IRC or the IAC. All patients receiving open-label treatment with RAD001 will continue having safety and efficacy assessments as in the blinded portion of

	the trial. **Follow-Up:** Patients who have not progressed at the time of discontinuation of study treatment will be followed with tumor assessments. During this follow up period the site will continue to send radiological studies for central review. In addition, radiological studies should continue to be sent for central review for patients who have disease progression as assessed by the local investigator and have not started on new anti-tumor therapy (including open label RAD001). In addition, patients will be followed for safety until at least 28 days after study treatment discontinuation and for survival until the final analysis of overall survival. **Extension phase:** At the time of the final primary analysis (i.e. when approximately 282 events have been observed), all patients who are on-going blinded study treatment or treatment with open-label RAD001 as well as those who are being followed for post-treatment tumor evaluations and those in survival follow-up will complete the core phase of the study. After analysis, and as appropriate, a decision will be made to roll-over patients into the extension phase of the study.
Population	Eligible patients will have histologically proven advanced (unresectable or metastatic) pancreatic NET with measurable disease at baseline which has progressed in the past 12 months. Patients with poorly differentiated tumors are excluded. This multicenter international trial will enroll a total of 392 patients over a period of approximately 17 months.

Inclusion/exclusion criteria	Key Inclusion criteria: 1. Advanced (unresectable or metastatic) biopsy-proven pancreatic NET patients. 2. Patients must have confirmed low-grade or intermediate-grade neuroendocrine carcinoma. 3. Patients must have radiological documentation of progression of disease within 12 months prior to randomization. If patients received anti-tumor therapy during the past 12 months, they must have radiological documentation of progression of disease while on or after receiving the therapy. 4. Measurable disease per RECIST criteria using Triphasic Computed Tomography (CT) scan or multiphasic MRI for radiologic assessment. 5. Adequate bone marrow function as shown by: ANC ≥ 1.5 x 10^9/L, Platelets ≥ 100 x 10^9/L, Hemoglobin >9 g/dL. 6. Adequate liver function as shown by: • Serum bilirubin ≤ 1.5 x ULN. • INR < 1.3 (INR < 3 in patients treated with anticoagulants) • ALT and AST ≤ 2.5 x ULN (≤ 5x ULN in patients with liver metastases). 7. Adequate renal function: serum creatinine ≤ 1.5 x ULN. 8. Fasting serum cholesterol ≤ 300 mg/dL OR ≤ 7.75 mmol/L AND fasting triglycerides ≤ 2.5 x ULN. NOTE: In case one or both of these thresholds are exceeded, the patient can only be included after initiation of appropriate lipid lowering medication. 9. Performance Status 0-2 on the WHO scale. 10. Adult male or female patients ≥ 18 years of age. 11. Women of childbearing potential must have a negative serum pregnancy test within 14 days of enrollment and /or urine pregnancy test 48 hours prior to the administration of the first study treatment. 12. Patients who give a written informed consent obtained according to local guidelines. **Key Exclusion criteria :** 1. Patients with poorly differentiated neuroendocrine carcinoma, high-grade neuroendocrine carcinoma, adenocarcinoid, goblet cell carcinoid and small cell carcinoma are not eligible. 2. Cytotoxic chemotherapy, immunotherapy or radiotherapy within 4 weeks prior to randomization. 3. Hepatic artery embolization within the last 6 months (1 month if there are other sites of measurable disease), or cryoablation/ radiofrequency ablation of hepatic metastasis within 2 months of enrollment. 4. Prior therapy with mTOR inhibitors (sirolimus, temsirolimus, everolimus). 5. Uncontrolled diabetes mellitus as defined by fasting serum glucose > 1.5 x ULN.

	6. Patients who have any severe and/or uncontrolled medical conditions such as: • unstable angina pectoris, symptomatic congestive heart failure, myocardial infarction ≤ 6 months prior to randomization, serious uncontrolled cardiac arrhythmia. • active or uncontrolled severe infection. • cirrhosis, chronic active hepatitis or chronic persistent hepatitis. • severely impaired lung function (spirometry and DLCO 50% or less of normal and O_2 saturation 88% or less at rest on room air). • active, bleeding diathesis 7. Patients receiving chronic treatment with corticosteroids or another immunosuppressive agent. 8. Patients with a known history of HIV seropositivity. 9. No other prior or concurrent malignancy is allowed except for the following: adequately treated basal cell or squamous cell skin cancer, or other adequately treated in situ cancer, or any other cancer from which the patient has been disease free for ≥ 3 years. 10. Female patients who are pregnant or nursing (lactating), or adults of reproductive potential who are not using effective birth control methods. If barrier contraceptives are being used, these must be continued throughout the trial by both sexes.
Patient numbering	Each patient in the study is uniquely identified by a 9 digit patient number which is a combination of his/her 4-digit center number and 5-digit subject number. The center number is assigned by Novartis to the investigative site.
Investigational and control drugs	Study Drug = Study treatment = RAD001 10 mg or matching placebo
Dose, regimen, treatment cycle	In arm 1, RAD001 will be given at 10 mg (two 5 mg tablets) po qd by continuous daily dosing. In arm 2, matching placebo will be given po qd (two tablets) by continuous daily dosing. A treatment cycle is defined as 28 days of consecutive daily treatment with RAD001 or matching placebo. RAD001 daily administration should be timed so that it will precede by 24 hours the times (generally scheduled visits) at which blood is drawn for drug level measurement. RAD001 dose should be held and taken after PK sampling at the clinic on days of PK sampling.
Supply, preparation, and administration	RAD001 is formulated as tablets of 5 mg strength dosed on a daily basis. The blisters for RAD001 tablets should be opened only at the time of administration as drug is both hygroscopic and light-sensitive. Placebo will be formulated to be indistinguishable from the 5 mg RAD001 tablets. RAD001 will be provided and supplied centrally by Novartis.
Visit schedule and	Refer to Table 7-1.

assessments	
Efficacy assessment(s)	Triphasic CT or multiphase MRI will be performed at baseline and every 3 cycles (from the date of randomization) thereafter. Tumor progression and response will be assessed per RECIST criteria. If an initial observation of partial or complete response is made, a confirmation scan should be obtained no sooner than 4 weeks and not more than 6 weeks after the initial observation. All digital radiological files or copies of films to be submitted for Central Review must be made at the time of the radiological scan.
Special safety assessment(s)	Not applicable for this study
Patient reported outcomes	Not applicable for this study
Pharmacokinetics	Full pharmacokinetic profile assessments are planned to be performed in **a total of 40 patients at three preselected investigational sites,** in order to obtain approximately 20 full steady state profiles in the RAD001 arm. RAD PK profiles should be collected in patients who do not take Sandostatin LAR® Depot, chronic Sandostatin® injection or other long acting somatostatin analogs during the study as concomitant medication. • RAD001 full steady-state pharmacokinetic profile assessment on Cycle 2 Day 1 as follows: Pre-dose, 0.5, 1, 2, 5 and 24 hours post-dose. RAD001 blood samples for trough levels will be collected from all the patients at all sites. The sampling schedule is as follows: RAD001 trough level determination will be collected as a pre-dose sample on Cycle 1 Day 15, Cycle 2 Day 1, and every Cycle Day 1, thereafter until end of blinded study drug period. Patients will be advised to fast on the days of sampling for RAD001 over the 2hr sampling period. Patients are allowed to consume water during this time. A light breakfast may be taken after this point; however patients should be advised to avoid fatty meals.
Biochemical tumor markers	Biochemical tumor markers: Serum samples will be tested for levels of Chromogranin A (CgA), neuron specific enolase, pancreatic polypeptide, gastrin, glucagon, and VIP. Insulin, pro insulin, and c-peptide will be obtained in patients with insulinomas. Chromogranin A and any other markers elevated at baseline will be followed every cycle during subsequent visits.
Biomarker assessments	Plasma collection at pre-treatment, Day 1 on cycle 2, 3, and 4 and end of treatment: Plasma samples (10 mL) will be examined for RAD001 effects on angiogenesis markers, e.g. basic FGF, VEGF, PLGF, sVEGFR1, and sVEGFR2.

Biomarker pharmacodynamic studies involving tumor samples	• Available Ki 67 assessments are to be recorded in the eCRFs. • Ki 67 will be assessed when tumor blocks are available. Tumor samples: Archival tumor blocks will be collected from all patients if available. These samples will be analyzed by immunohistochemical and genetic methods for activation of the mTOR pathway and proliferative markers e.g. pAKT, pS6, PTEN expression, Ki 67, and PI3 kinase mutation. Additional markers may be added to this list if suggested by internal or external data. The purpose of these studies will be to provide information for future trials of RAD001, such as potentially testing RAD001 in a subset of patients whose tumors have an activated mTOR pathway. No post-treatment tumor biopsy samples are planned for this study.
Optional Biomarker studies on additional or remaining samples	Not applicable for this study
IDMC	The Independent Data Monitoring Committee (IDMC) is an independent (external) group consisting of at least 2 clinicians and 1 statistician. The IDMC will be constituted prior to the randomization of the first patient. Reviews of safety data will be ongoing.. A study steering committee will also be consulted in evaluating the conduct of the study and making any necessary recommendations as needed. It will be comprised of an independent/delegated committee comprising of key opinion leaders within this indication. The study steering committee will also include a Novartis physician and statistician.
Statistical methods and data analysis	**Populations** The intent-to-treat (ITT) population will consist of all randomized patients. The patients in the ITT population will be analyzed in the treatment group and stratum they were assigned to at randomization. Patients who were screened but not randomized will be listed, but not included in the ITT population. The safety population will consist of all patients who received any study drug and had at least one post-baseline safety assessment. Patients will be analyzed according to treatment received. Please note: the statement that a patient had no adverse events (on the Adverse Event eCRF) constitutes a safety assessment. The per protocol population will consist of all patients from the ITT population who are evaluable for efficacy without any major protocol deviation and who either have completed a minimum exposure requirement or discontinued for early disease progression (i.e. within the first 12 weeks of treatment). The pharmacokinetic analyses will be performed in safety population using all available PK samples **Primary analysis** The primary objective of the study is to compare the progression-free survival, between RAD001 10mg qd plus best supportive care and placebo plus best supportive care. The primary efficacy variable, progression-free survival, will be analyzed on ITT population using local investigator assessments. The final primary analysis will be performed when a total of about 282 PFS events (assessed by local investigator review) are observed in the ITT population.

	Randomization and efficacy analyses will be stratified by whether or not patients have received prior cytotoxic chemotherapy, and by WHO performance status (0 vs. 1-2) at baseline. Stratified log-rank test will be used to test the difference in PFS between the two treatment arms. **Sample size and power considerations** Using a unstratified log-rank test at the one-sided 2.5% significance level, a total of 282 events would allow 92.6% power to demonstrate a 33% risk reduction (hazard ratio for RAD/placebo of about 0.67, as calculated from an anticipated 50% increase in median PFS, from 6 months in placebo arm to 9 months in the RAD001 arm). With a uniform accrual of approximately 23 patients per month over 74 weeks and a minimum follow up of 39 weeks, a total of 352 patients would be required to obtain 282 PFS events, assuming an exponential progression-free survival distribution with a median of 6 months in the Placebo arm and of 9 months in RAD001 arm. With an estimated 10% lost to follow up patients, a total sample size of 392 patients should be randomized.

1 Background

1.1 Overview of pancreatic neuroendocrine tumors (NET)

Pancreatic neuroendocrine tumors (NET), or islet cell tumors of the pancreas (ICT), comprise only 1-2% of all pancreatic tumors and less than 50% of all neuroendocrine tumors (Barakat 2004). The annual incidence of pancreatic NET is approximately 3.5 to 4 per million population (Barakat 2004). The peak incidence of occurrence is between ages 40 to 60 (Eriksson 1990). The hormones secreted by pancreatic NET depend upon the cell of origin and are physiologically involved in a network of autocrine, paracrine, endocrine and neurotransmitter communication (Barakat 2004). While hormone secretion is not observed in all cases of pancreatic NET, the apparently "nonfunctioning" (i.e., non-secreting) pancreatic NET tend to be more aggressive and present with symptoms of tumor bulk (Barakat 2004). Nonfunctioning tumors account for 15-30% of pancreatic NET (Warner 2005).

Table 1-1 Characteristics of Endocrine Tumors of the Pancreas

Tumor (origin)	Major Clinical Symptom	Predominant Hormone	Other features
Insulinoma (beta cells of pancreatic islets)	Hypoglycemia	Insulin	Catecholamine excess, 42-50% of all cases
Gastrinoma (Gastrin secreting cells)	Recurrent peptic ulcer	Gastrin	Diarrhea , steatorrhea, 26-50% of all cases
VIPoma (VIP secreting cells of GI tract and nervous system)	Watery diarrhea, hypokalemia, achlorhydria (WDHA syndrome)	Vasoactive intestinal polypeptide (VIP)	Metabolic acidosis, Hyperglycemia, Hypercalcemia, Flushing
Ppoma (PP secreting cells of GI tract and head of pancreas)	Hepatomegaly, Abdominal pain	Pancreatic polypeptide (PP)	Occasional watery diarrhea
Glucagonoma (alpha cells of pancreatic islets)	Diabetes mellitus, Migratory necrolytic erythema	Glucagon	Panhypoaminoaciduria, Thromboembolism, Weight loss
Somatostatinoma (delta cells of GI tract)	Diabetes mellitus, Diarrhea / steatorrhea	Somatostatin	Hypochlorhydria, Weight loss, Gall bladder disease
Source: (Skarin 2003 and Delcore 1994)			

Although pancreatic NET are sometimes considered to be indolent, patients with unresectable or metastatic tumors have a lethal disease: All pancreatic NET, with the exception of 90% of insulinomas, have long-term metastatic potential. Often morbidity is from the secreted hormone rather than tumor bulk (Barakat 2004).

Because of their relative rarity among cancers, there is no routine screening for pancreatic NET, and patients tend to present for treatment at a late stage. Most pancreatic NET are overtly malignant at the time of diagnosis, and 60% or more present with liver metastases. The most common cause of death from pancreatic NET is hepatic failure (Warner 2005).

In a study of 83 patients with pancreatic NET, median survival from time of diagnosis was about 7.5 years for all patients, and about 4 years for patients presenting with liver metastases. The 5-year survival rate for patients in this study was 55.3% (Tomassetti 2005). In recent

studies of patients receiving chemotherapy for pancreatic NET, the median survival was estimated to be 2 to 3 years (Kouvaraki 2004, McCollum 2004).

Patients with malignant neuroendocrine tumors of the pancreas frequently present with liver metastases. Surgical excision offers the only hope for curative therapy and is also the optimal palliative treatment. Hepatic regional therapy, including arterial embolization and chemoembolization is recommended for patients with major symptoms who have not responded to more conservative therapy and who are not surgical candidates (NCCN 2006).

Before excision, however, any symptoms of hormonal excess must be treated. For insulinomas, the NCCN advises stabilizing glucose levels with diet and/or octreotide and/or diazoxide. For gastrinomas, Gastrin hypersecretion may be treated with histamine H2-receptor antagonists or with proton pump inhibitors (e.g., omeprazole or lansoprazole). Somatostatin analogs are frequently used as initial treatment for hypersecretion syndromes associated with functioning pancreatic NET (Warner 2005).

Literature reports vary regarding the value of chemotherapy for treatment of pancreatic NET (Cheng 1999, Ramanathan 2001, Bajetta 2003, Kouvaraki 2004, McCollum 2004). In the 1980s and early 1990s, regimens containing streptozocin plus doxorubicin were accepted as standard based on a response rate of 69% reported by Moertel (Moertel 1980, Moertel 1992). Recent reports provide conflicting results. Two small studies of streptozocin and doxorubicin (Cheng 1999, McCollum 2004) reported response rates of <10%. However, a recent report from MD Anderson Cancer Center (MDACC) reported an overall response rate (ORR) of 39% in 84 patients with locally advanced and metastatic disease who were consecutively treated with a 3-drug combination of 5-fluorouracil, streptozocin, and doxorubicin (Kouvaraki 2004). For painful bony metastases, radiotherapy or interferon are recommended (NCCN 2006). These results suggest a potential role for cytotoxic chemotherapy for first-line treatment of pancreatic NET. The role of second-line chemotherapy for pancreatic NET is unclear, and no drugs have been approved by regulatory authorities for this indication.

Clinical trial is another option for all patients with symptomatic unresectable distant metastases (NCCN 2006).

1.2 Overview of RAD001

1.2.1 RAD001

RAD001 (everolimus) is a novel derivative of rapamycin. RAD001 has been in clinical development since 1996 as an immunosuppressant in solid organ transplantation. Since 2003, RAD001 is approved in Europe (trade name: Certican®) via the Mutual Recognition Procedure (MRP) for the prevention of organ rejection in patients with renal and cardiac transplantation. Certican® is also approved in Australia, South Africa, the Middle East, Central and South America, the Caribbean and some Asian countries.

RAD001 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 VEGF production and VEGF-induced proliferation of endothelial cells)

1.2.2 mTOR pathway and cancer

The target of RAD001 is mTOR (mammalian target of rapamycin), a serine-threonine kinase implicated in the PI3/AKT pathway known to be active in numerous neoplastic conditions. Driven largely by growth factors acting upstream, the PI3K/AKT/mTOR pathway modifies downstream signaling events involved in the regulation of cell-cycling, cell growth and cell survival mechanisms.

An important aspect of the antitumor effect of RAD001 is its potential to act on both tumor cells directly (to inhibit growth) and indirectly (by inhibiting angiogenesis). The observation of *in vivo* sensitivity of xenografts comprised of cells demonstrating resistance to RAD001 *in vitro* is attributed to the drug's potential to act on the vascular component of the supporting peritumoral stroma. The antiangiogenic property of RAD001 has been confirmed through experiments demonstrating the effect of RAD001 in countering VEGF-induced proliferation of human umbilical endothelial cells (HUVECs) *in vitro*, VEGF-driven angiogenesis in a chamber implant murine model and neovascularization in a murine orthotopic melanoma model.

At the cellular and molecular level, RAD001 acts as a signal transduction inhibitor. The target of RAD001 is mTOR (mammalian target of rapamycin), a serine-threonine kinase which is a member of the larger PI3K (phosphatidylinositol 3-kinase) family and present in all cells. RAD001 selectively inhibits mTOR which regulates cell growth, proliferation and survival. The mTOR kinase is mainly activated via the phosphatidylinositol 3-kinase (PI3K) pathway through AKT/PKB and the tuberous sclerosis complex (TSC1/2). Mutations in these components or in PTEN, a negative regulator of PI3 kinase, may result in their dysregulation. Abnormal functioning of various components of the signaling pathways contributes to the pathophysiology of numerous human cancers. Various preclinical models have confirmed the role of this pathway in tumor development (Cohen 2005).

The main known functions of mTOR include (Bjornsti 2004):

- mTOR functions as a sensor of mitogens, growth factors, energy and nutrient levels, facilitating cell-cycle progression from G1 - S phase in appropriate growth conditions.
- The PI3K (mTOR) pathway itself is frequently deregulated in many human cancers, and oncogenic transformation may sensitize tumor cells to mTOR inhibitors.
- The mTOR pathway is involved in the production of pro-angiogenic factors (e.g. VEGF) and in endothelial cell growth and proliferation.
- Through inactivating eukaryotic initiation factor 4E binding proteins and activating the 40S ribosomal S6 kinases (e.g. p70S6K1), mTOR regulates protein translation.

The regulation of mTOR signaling is complex and involves positive regulators, such as AKT, that phosphorylate and inactivate negative regulators such as the Tuberous Sclerosis Complex (TSC1/TSC2).

The PI3K/AKT/mTOR pathway is known to be dysregulated in numerous proliferative disorders including cancer. Molecular epidemiological studies have also shown that activation of the PI3K/AKT/mTOR pathway is frequently associated with worsening prognosis through resistance to treatment, disease extension and disease progression. A variety of preclinical models have confirmed the role of this pathway in tumor development. It has also been

demonstrated that constitutional activation of kinases such as AKT can lead to inexorable development of cancers resembling those which in patients are characterized by frequent activation of the same kinases. This is complemented by the demonstration of the antitumor activity of kinase inhibitors acting on the pathway in *vitro* and *in vivo* preclinical models.

Table 1-2 Drug substance

Chemical name:	(1R,9S,12S,15R,16E,18R,19R,21R,23S,24E,26E,28E,30S,32S,35R)-1,18-dihydroxy-12-(1R)-2-[(1S,3R,4R)-4-(2-hydroxyethoxy)-3-methoxycyclohexyl]-1-methylethyl}-19,30-dimethoxy-15,17,21,23,29,35-hexamethyl-11,36-dioxa-4-aza-tricyclo[30.3.1.$0^{4,9}$]hexatriaconta-16,24, 26,28-tetraene-2,3,10,14,20-pentaone
International non-proprietary name	Everolimus

1.3 Overview of comparator/combination drugs

1.3.1 Preclinical studies of RAD001

RAD001 inhibits the proliferation of a range of human tumor cell lines *in vitro* including lines originating from lung, breast, prostate, colon, melanoma and glioblastoma. RAD001 also inhibits the proliferation of human umbilical vein endothelial cells (HUVECS) *in vitro*, with particular potency against VEGF-induced proliferation suggesting that RAD001 may also act as an anti-angiogenic agent. The anti-angiogenic activity of RAD001 was confirmed *in vivo*. RAD001 selectively inhibited VEGF-dependent angiogenic response at well tolerated doses. Mice with primary and metastatic tumors treated with RAD001 showed a significant reduction in blood vessel density when compared to controls.

RAD001 administered daily p.o. was a potent inhibitor of tumor growth, at well tolerated doses, in 11 different mouse xenograft models (including pancreatic, colon, epidermoid, lung and melanoma) and two syngeneic models (rat pancreatic, mouse orthotopic melanoma). These models included tumor lines considered sensitive and "relatively resistant" *in vitro*. In general, RAD001 was better tolerated in mouse xenograft models than standard cytotoxic agents (i.e., doxorubicin and 5-fluorouracil), while possessing similar anti-tumor activity. Additionally, activity in a VEGF-impregnated s.c. implant model of angiogenesis and reduced vascularity (vessel density) of RAD001-treated tumors (murine melanoma) provided evidence of *in vivo* effects of angiogenesis.

In vivo studies investigating the antitumor activity of RAD001 against experimental animal tumor models showed that RAD001 monotherapy typically reduced tumor cell growth rates rather than producing regressions or stable disease. These effects occurred within the dose range of 2.5 to 10 mg/kg p.o. daily.

All significant adverse events observed in toxicology studies with RAD001 in mice, rats, monkeys and mini-pigs were consistent with its anticipated pharmacological action as an anti-proliferative and immunosuppressant and at least in part reversible after a 2 or 4-week recovery period with the exception of the changes in male reproductive organs, most notably testes.

1.3.2 RAD001 pharmacokinetics

The pharmacokinetic characteristics of RAD001 have been extensively investigated in the context of the drug's development as an immunosuppressant in solid organ transplantation where RAD001 was administered twice daily as a part of an immunosuppressant, multi-drug regimen consistently including cyclosporin A and glucocorticoids. Recent Phase I studies provide steady-state pharmacokinetics for both the weekly and daily schedules at varying dose levels in patients with advanced cancers.

RAD001 is rapidly absorbed after oral administration, with a median time to peak blood levels (t_{max}) of 1-2 hours postdose. The extent of absorption is estimated at above 11%. The area under the blood concentration-time curve (AUC) is dose-proportional over the dose range 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. Inter-patient variability is moderate with the coefficient of variation (CV) of approximately 50%. A high-fat meal altered the absorption of RAD001 with 1.3 hour delay in $t_{max,}$ a 60% reduction in C_{max} and a 16% reduction in AUC. In whole blood, approximately 80% of RAD001 is contained in red blood cells. Of the fraction of drug contained in plasma, 74% is protein-bound. The apparent distribution volume (Vz/F) after a single dose was 4.7 L/kg. RAD001 is eliminated by metabolism, mainly by hydroxylation, then excreted into the feces >80%.

RAD001 is mainly metabolized by CYP3A4 in the liver and to some extent in the intestinal wall. RAD001 is also a substrate of P-glycoprotein (P-gp). Therefore, absorption and subsequent elimination of systematically absorbed RAD001 may be influenced by medicinal products that interact with CYP3A4 and/or P-glycoprotein. *In vitro* studies showed that RAD001 is a competitive inhibitor of CYP3A4 and of CYP2D6 substrates, potentially increasing the concentrations of medicinal products eliminated by these enzymes. In two phase III clinical trials in patients following kidney transplantation, strong inhibitors of CYP3A4 (azoles, antifungals, cyclosporine, erythromycin) have been shown to reduce the clearance of RAD001 therapy thereby increasing RAD001 blood levels. Similarly, Rifampin, a strong inducer of CYP3A4, increases the clearance of RAD001 thereby reducing RAD001 blood levels. Caution should be exercised when co-administering RAD001 with CYP3A4 inhibitors or inducers.

Pharmacokinetic drug to drug interactions with cancer agents have been evaluated in phase Ib studies. Based on currently available results, gemcitabine ([study 2101] part 2) and paclitaxel ([study 2104]) did not alter RAD001 pharmacokinetics to a clinically relevant extent whereas imatinib notably increased RAD001 exposure with a mean increase in AUC by a multiple of 3.7 for RAD001 administered weekly and two-fold for RAD001 administered daily [study 2206]. Exposure to RAD001 in the presence of letrozole did not exceed that in monotherapy [study 2108]. Co-administration of RAD001 did not influence pharmacokinetics of gemcitabine, imatinib or letrozole. Exposure to paclitaxel in the presence of RAD001 was slightly decreased (average by 23%). RAD001 pharmacokinetics in transplant patients was investigated in special populations such as subjects with hepatic or renal impairment, various ethnic groups and pediatric renal transplant patients. In subjects with mild–moderate hepatic impairment, mean AUC to RAD001 is increased by 2-fold whilst renal impairment does not affect the pharmacokinetics of RAD001. Age, weight (both over the adult range) and gender

do not affect the pharmacokinetics of RAD001 to a clinically relevant extent. Also, pharmacokinetics does not alter in Asian patients whereas black patients have 21% higher clearance compared to nonblacks. A single, escalating-dose study in Japanese subjects did not show a significant difference in dose normalized systemic exposure.

The pharmacokinetic parameters derived for RAD001 given daily are summarized in Table 1-3.

Table 1-3 Steady-state RAD001 pharmacokinetics (daily dosing)

Parameter	5 mg	10 mg
N	4	6
t_{max} (h)	1 (1)	1 (1-6)
C_{min}^{ss} (ng/mL)	5.4 ± 1.8	13.2 ± 7.9
C_{max}^{ss} (ng/mL)	32 ± 9	61 ± 17
C_{max}^{ss}/Dose (ng/mL/mg)	6.4 ± 1.8	6.1 ± 1.7
$AUC\tau^{ss}$ (ng·h/mL)	238 ± 77	514 ± 231
$AUC\tau^{ss}$/Dose (ng·h/mL/mg)	48 ± 15	51 ± 23
C_{avg}^{ss} (ng/mL)	9.9 ± 3.2	21.4 ± 9.6

Values are median (range) for tmax and mean ± standard deviation for all others.
Dose-normalized parameters are per mg. τ is 24 h

Pharmacodynamic studies

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. Furthermore, molecular pharmacodynamic (MPD) studies using IHC in biopsied tumor tissue assessed the degree of inhibition and its duration (for p-S6, p-4E-BP1 and p-Akt expression) with the daily and weekly dosing. The pathologist was blinded for the biopsy sequence. There was almost complete inhibition of p-S6 at all doses and schedules studied (p=0.001). Preliminary results suggest a dose-related decrease in p-4E-BP1 and increase in p-Akt expression with maximal effect at 10 mg daily and ≥ 50 mg weekly.

In [study C2107], molecular changes in tumor were subsequently investigated through serial biopsying of patients before and while on treatment (Tabernero, et al 2005). Biopsying of patients on treatment took place in week 4 (pharmacokinetic steady-state). All patients underwent a 24-hr post-dose biopsy. Patients following the weekly regimen had a further biopsy on Day 4-5 during the same week.

Molecular activity was measured by immunohistochemistry. In the absence of a reliable technique for measuring mTOR phosphorylation itself, the phosphorylation status of downstream markers S6 and eIF4G, for which reliable antibodies exist, was selected as reflecting the immediate pharmacodynamic effect of RAD001. Also measured were changes in the phosphorylation status of upstream AKT and the proliferation index Ki67. The daily regimen was associated with a high inhibition of p-S6 and p-eIF4G at 5mg/d which was complete at 10mg/d. In patients on the weekly schedule, p-S6 inhibition was complete and sustained at all dose levels while that of p-eIF4G was complete and sustained at 50mg/d but not at 20mg/wk. On both regimens numerous patients demonstrated apparent up-regulation of

AKT which tended, however, not to persevere in the patients at 50mg/wk. The proliferation index was reduced in most patients, recovering in some of those on the 50mg/wk regimen.

1.3.3 Phase I and II oncology studies

Data are available from phase I clinical studies of RAD001 given as a single agent to 147 patients with advanced solid tumors. Such studies included various doses and schedules (weekly dosing, range 5-70 mg and daily dosing 5-10 mg). Approximately, 46% of patients reported rash or erythema and 40% of the patients presented with stomatitis/ mucositis. The most frequent adverse events suspected to be drug-related observed in three studies using RAD001 as a single agent are listed in Table 1-4.

Table 1-4 Adverse events suspected to be drug-related in greater or equal to 10% of patients with advance cancer reported in Phase I RAD001 monotherapy [Study C2101, C2102, C2107]

	Weekly			Daily		
	5-30 mg n=30	50 mg n=18	70 mg n=38	5mg n=16	10 mg n=45	Total n=147
No. Pts with AEs						
Any event	23 (1)	17 (2)	38 (10)	14 (1)	43 (14)	135 (28)
By event						
Rash	5	8	18	10	27 (1)	68 (1)
Stomatitis/mucositis	6	8 (2)	16 (2)	6 (1)	23 (3)	59 (8)
Fatigue	8	7 (1)	14 (1)	1	17 (1)	47 (3)
Nausea	5	4	8	2	18 (1)	37 (1)
Anorexia	1	6	10	3	15	35
Diarrhea	1	7	7	-	9	24
Vomiting	4	5	5	-	10	24
Headache	7	4	6	6	4	20
Pruritus	2	1	6	3	4	16
Infections[1]	1	3	3 (1)	1	6 (2)	14 (3)
Constipation	-	1	2	2	9	14

The numbers of patients (by dose level and dose schedule) who have reported grade ≥3[1] toxicities is given in brackets.

[1]. events included in brackets reached no more than grade 3 severity

[2] Infections noted as drug-related included:

Herpes simplex:	5 pts (1 at 50 mg/wk; 1 at 5mg/d; 3 at 10 mg/d)
Oral candidiasis:	5 pts (1 at 50 mg/wk; 3 at 70 mg/wk, 1 at 10 mg/d)
Pneumonia (gr3)	1 pt (10 mg/d)
Pustular rash	1 pt (20 mg/wk)
Rhinitis	2 pts (50 mg/wk)
URT Infection	1 pt (50 mg/wk)
Urinary Tract Infect	1 pt (50 mg/wk)

Source: [Studies C2101], [C2102], [C2107]

Reduced blood cell counts at the initiation of treatment are frequent but remain mostly within the normal range or limited to grade 1 however a grade 3 neutropenia was a DLT in one patient. In addition a grade 3 thrombocytopenia was observed in a patient receiving RAD001

with letrozole where pharmacodynamic interaction is unlikely. This suggest that some patients may be particularly sensitive to the myelosuppressive effect of RAD001 making it necessary to monitor carefully blood cell counts at initiation of treatment.

Metabolic changes (hyperlipidemia and hyperglycemia) may be observed during treatment with RAD001. Both events may be medically managed. Hyperlipidemia has been reported as an ADR in 10% of patients although review of the laboratory values suggests that as many as a quarter of patients develop grade 1-2 hyperlipidemia on treatment, mostly hypercholesterolemia. Hyperglycemia has been reported as an adverse event in 7% of patients. Grade 3 hyperglycemia has been observed, especially in diabetics receiving RAD001 treatment. Therefore, patients with diabetes should have their blood glucose monitored carefully and their medications adjusted, as needed, to maintain adequate control of their blood glucose levels.

Outside the particular context of hemorrhagic gastritis in advanced GIST patients treated with RAD001 and imatinib, serious, suspected drug-related hemorrhages have been exceptional. Nevertheless, RAD001 should be considered as predisposing patients to hemorrhage, potentially fatal, should they develop severe drug-related thrombocytopenia. Platelet counts should be monitored. Patients with on-going thrombocytopenic or with a known bleeding diathesis should be subject to careful evaluation and more frequent monitoring. Imatinib (Glivec ® / Gleevec ^{TM}), a 3A4 and Pgp substrate, has been shown to increase the AUC of RAD001 more than threefold, most probably the consequence of competitive inhibition.

Non-infectious pneumonitis is a known side effect of rapamycin analogues. Clinically significant pneumonitis is typically accompanied by non-specific symptoms including dyspnea, nonproductive cough, fatigue, and fever. Diagnosis is generally suspected in individuals receiving mTOR inhibitors who develop these symptoms or in asymptomatic individuals in whom a routine chest CT scan reveals a new ground glass or alveolar infiltrate. The frequency of symptomatic pulmonary toxicity (all grades) was approximately 13% in a phase III study of RAD001 in patients with metastatic renal cell carcinoma ([CRAD001C2240]). Severe (CTC grade 3) pneumonitis occurred in 4% of patients. Fatal outcomes have been observed. The lung toxicity was partly or completely reversible in the majority of cases with interventions including drug interruption, discontinuation and the use of corticosteroids. For more details, see Section 6.1.1.

In addition, the dosage of RAD001 used in the treatment of cancer patients is substantially higher than that given routinely in the organ transplant setting. Everolimus (RAD001) is approved in many regions of the world for renal and cardiac transplantation at a daily dose of 0.75 mg twice a day guided by therapeutic drug monitoring (3-8 ng/mL) in combination with cyclosporine microemulsion. In phase 3 trials investigating everolimus in renal and cardiac transplantation, the overall reported rate of pneumonitis ranged from 0.0 to 1.4%. The spontaneous reporting rate for pneumonitis following exposure to commercially available everolimus in transplantation is very low (0.08% or 84.4 events/100,000 patient-years). Refer to the latest version of the RAD001 Investigator Brochure and safety letters (Investigator Notifications) for the most up to date information available.

1.3.4 RAD001 Phase 2 study in NET

In pancreatic NET cells, mTOR is activated in response to signalling by IGF-1 (von Wichert 2000, Van Gompel 2004,). Interruption of this signalling pathway through treatment with RAD001 in combination with a somatostatin analog was the goal of a recent phase 2 investigator sponsored clinical trial conducted by J. Yao at the MD Anderson Cancer Center (Yao 2006). This single-arm study evaluated treatment with RAD001 5 mg/day and RAD001 10 mg/d plus depot octreotide (Sandostatin LAR® Depot) 30 mg IM every 28 days in patients with metastatic or unresectable, well-differentiated, neuroendocrine carcinoma. Sixty evaluable patients have been enrolled, thirty patients treated with RAD001 5 mg/d and thirty patients treated with RAD001 10mg/d. The thirty patients treated with RAD001 5 mg/d were classified as follows: 17 with carcinoid, 13 with islet cell tumor. All were evaluable for response. Four patients were reported to have partial response (3 verified by independent radiologic review), 22 with stable disease (SD) and 4 with progressive disease (PD) per RECIST. Responses appeared to be durable; at last analysis responses were ongoing in 3 patients at 12, 9, and 6 months on treatment and the fourth patient progressed at 9 months on treatment. Partial responses were reported in 2 patients with carcinoid tumors and 2 with islet cell tumors. Of the 17 patients whose tumors had documented progression prior to study entry, 13 (76%) and 11 (65%) patients were progression free at 12- and 24- weeks respectively. Nineteen of the 30 evaluable patients had elevated chromogranin A (CgA) at baseline. Eleven (37% of all patients or 58% of those with elevated CgA at baseline) had >50% reduction in CgA.

The combination of RAD001 5 mg/day and Sandostatin LAR® Depot 30 mg q 28 days appears to have been well tolerated. The most common toxicities reported were aphthous ulceration, AST elevation, hyperglycemia, and nausea. CTC Grade 3/4 toxicities reported included (anemia, hyperbilirubinemia, thrombocytopenia, aphthous ulcer, diarrhea, edema, fatigue, hypoglycemia, nausea, pain, and rash). Only one patient discontinued treatment because of drug-related toxicity (grade 3 granulocytopenia). One patient was hospitalized due to grade 4 liver failure, which the investigator assessed as unlikely to be related to the study drugs. When grade 3 toxicities occurred, RAD001 was held until toxicity resolved to grade 1 and RAD001 was resumed at the initial dose of 5 mg/d.

The safety and efficacy data of the additional thirty patients with carcinoid and islet cell tumors treated with RAD001 10 mg/d plus Sandostatin LAR 30 mg IM q 28 days will be presented at ASCO 2007.

1.3.5 RAD001 Phase 2 study in advanced pancreatic NET

A phase II open label, stratified, single-arm study of RAD001 10mg/d in patients with advanced pancreatic neuroendocrine tumor after failure of cytotoxic chemotherapy, [CRAD001C2239], is currently ongoing. As of November 2006, 25 of 144 planned patients have been enrolled. A summary of the most frequent adverse events, with number of subjects, thus far include: rash (11 patients), constipation (3), abdominal pain (2), bone pain (2), osteolysis (1), eyelid pain (1), dysgeusia (1) and food deficit (1). One patient had discontinued and three patients have died due to disease progression.

Final primary analysis is planned for end 2007.

1.4 History of amendments

Amendment 1 was implemented to change the data source of the primary endpoint from PFS by central radiology review to PFS by local investigator review. Also, adjudication of discrepancies between local and central radiology was added and the interim analysis was canceled. The exploratory biomarker section has been updated to indicate that analyses may be performed to further address scientific questions as new information with regard to the disease or the study drug becomes available. Screening and management guidelines for patients with Hepatitis B and Hepatitis C were added. Other changes were made for clarification and the following updates were also made: management of hyperglycemia, update on pneumonitis, duration of adequate contraceptive usage after the end of trial therapy, use of cytochrome P450 (CYP) 3A4 and/or P-glycoprotein (PgP) induces or inhibitors, timing of administration of RAD001 with respect to food intake.

2 Study rationale/purpose

The purpose of this study is to assess the efficacy and safety of RAD001 10 mg/day plus best supportive care vs. matching placebo plus best supportive care in the treatment of advanced Pancreatic Neuroendocrine tumor. The primary objective is to compare the progression-free survival between RAD001 10 mg qd plus best supportive care and placebo plus best supportive care.

The rationale for this study is based on both preclinical and clinical considerations. IGF-1 is a known autocrine regulator of CgA secretion and cell growth in human neuroendocrine tumor cells (von Wichert 2000, Wulbrand 2000, Van Gompel 2004). A role for RAD001 as monotherapy in carcinoid and pancreatic NET is suggested by the regulatory role of mTOR in cell growth, metabolism and protein translation (Fingar 2004, Vignot 2005) and the observation that the PI3K/AKT/mTOR pathway is activated by IGF-1 in carcinoid and pancreatic NET cells (von Wichert 2000, Van Gompel 2004,).

Antitumor activity of RAD001 was observed in a clinical study of RAD001 plus Sandostatin (Yao 2006)

The proposed RAD001 dosage regimen is 10 mg/day in both monotherapy and combination therapy settings. This regimen is based both on Novartis Phase I/II studies and on results from an investigator-sponsored study in NET. Initial Phase I studies of the RAD001 10 mg/day schedule demonstrated dose limiting toxicities in 2 of 12 patients. Tolerability of this schedule was verified in a total of 33 patients in Phase 1 studies as well as in 12 breast cancer patients treated with letrozole 2.5 mg plus RAD001 10 mg/day. Pharmacodynamic modeling indicates that downstream effectors of mTOR are completely suppressed by RAD001 at the 10 mg/day dose. The investigator-sponsored study in NET, toxicity observed with RAD001 5 mg/day was similar to that observed for RAD001 5 mg/day alone in Phase 1 studies. (Yao 2006). Therefore a dose of RAD001 10 mg/day will be evaluated in this study.

3 Objectives

3.1 Primary objectives

To determine whether treatment with RAD001 10 mg/d plus best supportive care prolongs the progression free survival (PFS) compared to treatment with Placebo plus best supportive care in patients with advanced pancreatic neuroendocrine tumor.

3.2 Secondary objectives

- To evaluate the effect of RAD001 on other tumor endpoints: objective response rate (CR or PR), response duration
- To compare overall survival (OS) between the study arms
- To determine the safety and tolerability of RAD001 (10 mg/d) in patients with advanced Pancreatic Neuroendocrine Tumor
- To characterize the pharmacokinetics of RAD001 in Pancreatic NET indications
- To compare changes from baseline in chromogranin A (CgA) and follow other biochemical tumor markers produced by the tumor that are elevated at baseline, during subsequent visits. e.g., neuron specific enolase, pancreatic polypeptide, gastrin, glucagon, and VIP. Insulin, pro insulin, and c-peptide in patients with insulinomas.
- To characterize pre-treatment tumor samples by immunohistochemical and genetic analyses indicating activation of the mTOR pathway.
- To assess the relationship between RAD001 steady state levels, tumor response, and chromogranin A response (50% decrease from baseline)
- To determine the effects of RAD001 on plasma antigenic molecules e.g. VEGF, basic FGF, PLGF, sVEGFR1, and sVEGFR2.

3.3 Exploratory objectives

Not applicable for this study.

4 Study design

This is a prospective, double-blind, randomized, parallel group, placebo-controlled, multicenter phase III study of treatment with RAD001 10 mg p.o. qd plus best supportive care versus placebo plus best supportive care in 392 patients with advanced pancreatic NET.

Patients are permitted to remain on Sandostatin LAR Depot or other long acting somatostatin analog during the study, as concomitant medication.

The final primary analysis will be performed when approximately 282 PFS events (per local investigator assessment) are observed in the intent-to-treat (ITT) population.

Patients who meet the study eligibility criteria will be randomized to receive RAD001 or matching placebo. The randomization ratio is 1:1, with one patient being randomly assigned to RAD001 for every one patient randomly assigned to Matching placebo. Randomization and efficacy analyses will be stratified by whether or not they have received prior cytotoxic

chemotherapy and by WHO performance status (0 vs. 1-2) at baseline. This study will be supported by IVRS for the randomization and the study medication management.

Study drug refers to RAD001 or Matching Placebo. Study treatment refers to RAD001or Matching Placebo.

For each patient there will be up to four separate phases in the study: pre-treatment (screening & baseline), blinded treatment, open-label and follow-up. Each of these phases is described in detail below.

Pre-treatment phase (Screening & Baseline)

Pre-treatment phase: Screening

At screening, the investigator or his/her designee will assign a unique number (refer to Section 6.3) to patients being considered for the study. The patient should provide a signed Informed Consent Form prior to any study screening evaluations being performed. Once the patient provides a signed informed consent form, the investigator or his/her designee will register the patient using an Interactive Voice Response System (IVRS), a central patient screening/randomization system. Refer **to** Section 6.3, Section 6.3.1 and Section 6.4 for complete details.

Every patient must complete all screening evaluations up to 4 weeks prior to the date of randomization. During screening the disease must be staged. The tumor assessment made during the screening phase will provide the baseline tumor measurements. Tumor assessments should be conducted within 4 weeks prior to start of treatment. (Post text supplement 1)

Screening evaluations include: administration of informed consent, demography, inclusion/exclusion criteria, relevant medical history/current medical conditions, confirmation of Advanced Pancreatic Neuroendocrine Tumor, diagnosis and extent of cancer (sites of metastatic disease), prior antineoplastic therapy, radiotherapy and/or surgery, a physical examination (including a neurological examination), vital signs and other additional study entry evaluations. A complete list of screening evaluations is provided in schedule of evaluations (Table 7-1).

Radiological progression of disease, within 12 months prior to randomization, should be documented in the eCRFs. Progression of disease is demonstrated if there is an unequivocal increase in size of tumors assessed by radiological studies.

Pre-treatment phase: Baseline

Baseline evaluations (visit 1) will be performed within 2 weeks of the first dose of the study drug with the first date of study treatment administration to occur (visit 2). At or prior to Visit 2 the investigator or his/her designee will call the IVRS (after verifying that the patient fulfills all the inclusion/exclusion criteria) to randomize the patient. Patients should receive their study drug treatment within one week of randomization. Baseline evaluations include: vital signs, physical examination, WHO performance status, EKG, laboratory tests, chest x-ray, biochemical and biomarker evaluations and documentation of any prior somatostatin analogs.

Blinded treatment phase

This study does not have fixed treatment duration. Each study Cycle has 28 days. Patients will have their first daily dose of RAD001 or Matching Placebo at Visit 2 (Day 1, Cycle 1). The first dose of the study drug defines Day 1 of the Cycle; therefore the last day of a complete Cycle is Day 28. If unforeseen circumstances (i.e., unexpected personal reasons) impede the patient to comply with the established visit schedule, the site can re-schedule the visit (within 7 days). The reason(s) for any visit or treatment delays will be documented in the Comments eCRF for the appropriate cycle.

On Day 1, Cycle 1, 2 tablets of RAD001 5 mg or 2 tablets of Matching Placebo will be self-administered p.o. (by mouth). All doses taken by the patient and all dose changes during the study must be recorded on the Dosage Administration Record eCRF. All patients will continue to be treated with RAD001 or Matching Placebo daily until determination of objective tumor progression by the local radiologist (using the RECIST criteria), unacceptable toxicity, death or discontinuation from the study for any other reason.

Safety evaluations are routinely performed on Day 1 of every treatment Cycle or as frequently as necessary. Patient must be in a fasting state (at least 12 hours) at the time of blood sampling for all laboratory evaluations including the lipid profile. Hematology evaluations will be performed twice, on Day 1 and Day 15, during the first cycle; then on Day 1 of every treatment Cycle and at discontinuation from the study drug (≤ 2 weeks). All blood samples obtained at each Cycle during the study will be sent to a Central Laboratory for analysis. If laboratory results are requested on an urgent basis, the attending oncologist will use the local laboratory results for treatment decisions. Complete details regarding all study required safety assessments are provided on Section 7.5.

Screening for hepatitis B

In cancer patients with hepatitis B, whether carriers or in chronic state, use of antivirals during anticancer therapy has been shown to reduce the risk of hepatitis B virus (HBV) reactivation and associated HBV morbidity and mortality (Loomba et al. 2008).

The following three categories of patients should be tested for hepatitis B viral load and serologic markers, that is, HBV-DNA, HBsAg, HBs Ab, and HBc Ab:

1. All patients who currently live in (or have lived in) Asia, Africa, Central and South America, Eastern Europe, Spain, Portugal, and Greece. [http://wwwnc.cdc.gov/travel/yellowbook/2010/chapter-2/hepatitis-b.aspx#849]
2. Patients with any of the following risk factors:
    - known or suspected past hepatitis B infection,
    - blood transfusion(s) prior to 1990,
    - current or prior IV drug users,
    - current or prior dialysis,
    - household contact with hepatitis B infected patient(s),
    - current or prior high-risk sexual activity,
    - body piercing or tattoos,

- mother known to have hepatitis B
- history suggestive of hepatitis B infection, e.g., dark urine, jaundice, right upper quadrant pain.

3. Additional patients at the discretion of the investigator

The management guidelines, in Section 6, are provided according to the results of the baseline assessment of viral load and serological markers for hepatitis B.

Screening for hepatitis C

Patients with any of the following risk factors for hepatitis C should be tested using quantitative RNA-PCR

- known or suspected past hepatitis C infection (including patients with past interferon 'curative' treatment),
- blood transfusions prior to 1990,
- current or prior IV drug users,
- current or prior dialysis,
- household contact of hepatitis C infected patient(s),
- current or prior high-risk sexual activity,
- body piercing or tattoos,

At the discretion of the investigator, additional patients may also be tested for hepatitis C.

The management guidelines, in Section 6, are provided according to the results of the baseline assessment of hepatitis C viral load.

Radiologic assessments (CT scan, MRI) will be done every 12 weeks (± 1 week) from the date of randomization. The local radiologist will determine the objective tumor response. Complete or partial responses require a repeat radiological confirmation between 4-6 weeks from its initial observation. Clinical suspicion of disease progression at any time requires a physical examination and radiological confirmation to be performed promptly rather than waiting for the next scheduled radiological assessment. All CT Scans and MRIs obtained at baseline and post-baseline will be transmitted to the central review facility. Additionally, an Independent Adjudication Committee (IAC) will be established to review discrepant cases based on pre-specified criteria between local (investigator) and IRC radiological assessments. Independent central radiology review includes radiology assessments by an Independent Review Committee (IRC) and an Independent Adjudication Committee (IAC). The IRC is constituted by teams of two board-certified independent radiologists who review radiological images from investigational sites on an ongoing basis. Discrepancies between the two central readers are adjudicated. The IAC is constituted by a board certified radiologist and an oncologist with experience in NETs. The IAC adjudicates PFS discrepancies between local and IRC determination. The adjudication is performed in a blinded manner so that the committee members have no knowledge of treatment assignment or origin of RECIST evaluations (local or central). The data used in the sensitivity analysis of the primary endpoint will be comprised of data from IAC assessment for patients where adjudication is required

and data from IRC assessment for patients where no adjudication is required. The process for IRC and the IAC review is specified within the Independent Review Charter.

Complete details are provided on Section 7.4. Tumor assessments, during the blinded phase of the study, are performed until documented disease progression by RECIST criteria as assessed by the local investigator.

Pharmacokinetic assessments will be performed according to the Blood Collection Plan provided in Section 7.9. Full pharmacokinetic profile assessments are planned to be performed in **a total of 40 patients at three pre-specified investigational sites** on Day 1 of Cycle 2 as follows: Pre-dose, 0.5, 1, 2, 5 and 24 hours post-dose, in order to obtain approximately 20 full steady-state profiles in the RAD001 arm. RAD001 PK profiles should be collected in patients who do not take Sandostatin LAR Depot or other long acting somatostatin analogs during the study as concomitant medication. Trough levels will be collected **for all patients in all study centers** as a pre-dose sample on Cycle 1 Day 15, Cycle 2 Day 1 and Day 1 of every Cycle thereafter until end of blinded study drug period.

Biochemical assessments will be performed according to the Blood Collection Plan provided in Table 7-1 Assessments will be performed at baseline and if elevated at Day 1 Cycle2 and at Day 1 of subsequent cycles. Biomarker research studies will be performed as according to the blood collection plan provided in Section 7.10. Patients who consent to the studies will be asked to donate 10 mL of blood for plasma at screening and at Cycle 2 Day 1, Cycle 3 Day 1 and Cycle 4 Day 1 and end of treatment. On-treatment specimens will be compared to baseline samples for RAD001 effects on plasma angiogenic molecules, e.g., VEGF, basic FGF, PLGF, sVEGFR1, and sVEGFR2.

Open-label RAD001 phase

Patients who have disease progression which has been documented by the investigative site may be unblinded. RECIST assessment eCRF must be completed prior to unblinding and reviewed with the global Novartis clinical trial leader. Patients who had received placebo may be offered open-label treatment with RAD001 if the treating oncologist believes the patient could benefit from this therapy. For the open label phase of the study (including the follow-up phase), tumor assessments will be required to be done locally and will ***not*** be sent in for central review. The investigator or his/her designee will not disclose patient unblinding information to the central radiology reviewers. Due to the unblinding of a subset of patients at progression, members of the Novartis clinical trial team may become unblinded to individual patient's treatment during the conduct of the trial including team members involved in the cleaning of patient data. The blinding of the central radiology review will be maintained. despite the planned unblinding.

All patients receiving open-label treatment with RAD001 will continue to have safety and efficacy assessments as described in the Visit Evaluation Schedule provided in Table 7-1. Biomarker assessments and pharmacokinetic assessments will not be performed in the open-label phase. Open-label treatment with RAD001 continues until the patient again presents with disease progression (2^{nd} occurrence) which is radiologically documented by the investigator. At this point, patients will be discontinued from the study and will enter the follow-up phase.

Follow-Up phase

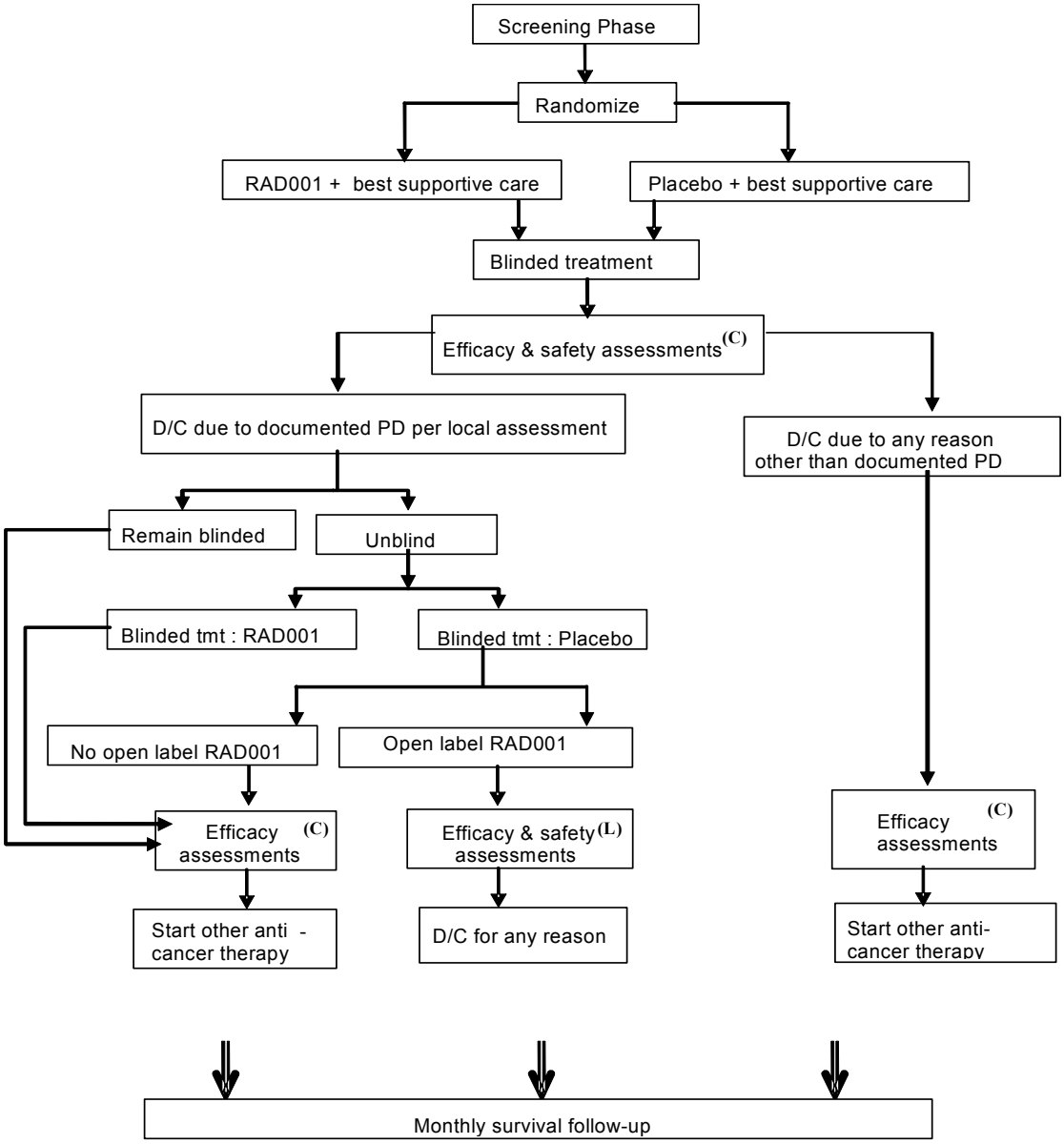
All patients will have a follow-up visit scheduled 28 days after the last dose of the study treatment to follow for AEs and SAEs that may have occurred after discontinuation from the study treatment.

Patients who have not progressed at the time of discontinuation of study treatment will be followed with tumor assessments until the start of other anti-cancer therapy. During this follow up period the site will continue to send radiological studies for central review. In addition, radiological studies should continue to be sent for central review for patients who have disease progression as assessed by the local investigator and have ***not*** started on new anti-tumor therapy (including open label RAD001). The investigator or his/her designee will continue collecting information on the initiation of additional anti-neoplastic therapies. Cancer medications/therapies given to the patient after the last dose of the study treatment must be recorded on the eCRFs designated to record antineoplastic therapies since discontinuation of the study treatment.

In addition, after discontinuation from the study treatment, all patients will have monthly survival assessments. The investigator or his/her designee will obtain monthly survival information on all patients until final survival analysis.

Figure 4-1 presents a schematic summary of the study design

Figure 4-1 Schematic study design



L: Films will be assessed locally only **; C:** Films should be sent to central radiology during this period .

PD refers to progressive disease; ***tmt*** refers to treatment., ***D/C*** refers to discontinuation, ***FU*** refers to Follow-up.

There are 2 distinct parts to the study: the core and the extension phase as described below.

Core Phase

The core phase is from the start of the trial up to the time when the required number (approximately 282) of PFS events for the final primary analysis has been observed. After analysis, and as appropriate, a decision will be made to roll-over patients into the extension phase of the study. At the time of datacut, data will be retrieved and cleaned for the final primary analysis of safety and efficacy.

Extension Phase

After analysis, and as appropriate, a decision will be made to roll-over patients into the extension phase of the study. Patients will continue into the extension phase on the same dose and regimen of blinded study drug or on open-label RAD001 that they were receiving in the core phase. Patients who are being followed for post-treatment evaluation or for survival will complete the core phase of the study and will transition to the extension phase of the study in order to provide additional data on efficacy and safety.

Patients in the extension phase will continue to have the same safety and efficacy assessments as in the core phase until disease progression, except for pharmacokinetics, biomarker, and biochemical tumor marker assessments.

Once the results of the final primary analysis are disclosed, all patients in the extension phase will be advised to stop or to continue treatment with RAD001. If the study results are favorable, treatment with RAD001 may continue. RAD001 will be provided at no charge until such time when:

- the patient has to stop treatment with RAD001 because of adverse event(s), abnormal laboratory value(s), unsatisfactory therapeutic effect, patient's condition no longer requires RAD001 therapy, withdrawal of consent, lost to follow-up, death, etc., or
- RAD001 becomes commercially available or Novartis discontinues development of RAD001 for patients with advanced neuroendocrine tumors.

5 Population

The target population is comprised of adult patients with histologically-confirmed, advanced pancreatic neuroendocrine tumor (NET) who have progressed within 12 months prior to randomization. If patient received anti-tumor therapy during the past 12 months, they must have radiological documentation of progression of disease while on or after receiving the therapy.

It is anticipated that approximately 440 subjects will need to be screened to enroll at least 392 patients. Subjects will be recruited from approximately 80-100 sites worldwide.

Inclusion/exclusion criteria

The investigator or his/her designee must ensure that all patients who meet the following inclusion and exclusion criteria during screening are offered enrollment in the study.

No additional exclusions can be applied by the investigator, in order that the study population will be representative of all eligible patients.

Patients must have screening evaluations performed to ensure potential patients being considered by the investigator meet all inclusion and exclusion criteria. Results of all screening evaluations, which assure that all inclusion and exclusion criteria have been satisfied, must be reviewed by the Principal Investigator, or his/her designee, prior to randomization of that patient into the study. Only laboratory results from the Central Laboratory will be used to determine patient eligibility for the study.

All study patients must be thoroughly informed about all aspects of the study, including the study visit schedule and required evaluations and all regulatory requirements for informed consent. The written informed consent must be obtained prior to the performance of any screening evaluations. If the patient is unable to read an impartial witness should be present during the entire informed consent discussion. The following criteria apply to all patients enrolled onto the study.

5.1 Inclusion criteria

1. Patients must have advanced (unresectable or metastatic) biopsy-proven pancreatic NET
2. Patients must have confirmed low-grade or intermediate-grade neuroendocrine carcinoma
3. Patients must have radiological documentation of progression of disease within 12 months prior to randomization. If patient received anti-tumor therapy during the past 12 months, he/she must have radiological documentation of progression of disease while on or after receiving the therapy
4. Measurable disease per RECIST criteria using Triphasic Computed Tomography (CT) scan or multiphase MRI for radiologic assessment
5. Adequate bone marrow function as shown by: ANC $\geq 1.5 \times 10^9$/L, Platelets $\geq 100 \times 10^9$/L, Hemoglobin >9 g/dL
6. Adequate liver function as shown by:
   - Serum bilirubin $\leq$ 1.5 x ULN
   - INR < 1.3 (INR < 3 in patients treated with anticoagulants)
   - ALT and AST $\leq$ 2.5 x ULN ($\leq$ 5x ULN in patients with liver metastases)
7. Adequate renal function: serum creatinine $\leq$ 1.5 x ULN
8. Fasting serum cholesterol $\leq$ 300 mg/dL OR $\leq$ 7.75 mmol/L AND fasting triglycerides $\leq$ 2.5 x ULN. NOTE: In case one or both of these thresholds are exceeded, the patient can only be included after initiation of appropriate lipid lowering medication
9. Performance Status 0-2 on the WHO scale
10. Adult male or female patients $\geq$ 18 years of age
11. Women of childbearing potential must have a negative serum pregnancy test within 14 days of enrollment and /or urine pregnancy test 48 hours prior to the administration of the first study treatment
12. Written informed consent from patients must be obtained in accordance to local guidelines

5.2 Exclusion criteria

1. Patients with poorly differentiated neuroendocrine carcinoma, high-grade neuroendocrine carcinoma, adenocarcinoid, goblet cell carcinoid and small cell carcinoma are not eligible

2. Cytotoxic chemotherapy, immunotherapy or radiotherapy within 4 weeks prior to randomization
3. Hepatic artery embolization within the last 6 months (1 month if there are other sites of measurable disease), or cryoablation/ radiofrequency ablation of hepatic metastasis within 2 months of enrollment
4. Prior therapy with mTOR inhibitors (sirolimus, temsirolimus, everolimus).
5. Uncontrolled diabetes mellitus as defined by fasting serum glucose > 1.5 x ULN
6. Patients who have any severe and/or uncontrolled medical conditions such as:
   - unstable angina pectoris, symptomatic congestive heart failure, myocardial infarction ≤ 6 months prior to randomization, serious uncontrolled cardiac arrhythmia
   - active or uncontrolled severe infection
   - cirrhosis, chronic active hepatitis or chronic persistent hepatitis
   - severely impaired lung function (spirometry and DLCO 50% or less of normal and O_2 saturation 88% or less at rest on room air).
   - active, bleeding diathesis
7. Patients receiving chronic treatment with corticosteroids or another immunosuppressive agent
8. Patients with a known history of HIV seropositivity
9. No other prior or concurrent malignancy is allowed except for the following: adequately treated basal cell or squamous cell skin cancer, or other adequately treated in situ cancer, or any other cancer from which the patient has been disease free for ≥ 3 years.□
10. Female patients who are pregnant or nursing (lactating), or adults of reproductive potential who are not using effective birth control methods. If barrier contraceptives are being used, these must be continued throughout the trial by both sexes

6 Treatment

6.1 Investigational and control drugs

The investigational drug used in the course of this trial is RAD001 (everolimus). The control drug used in this trial is matching placebo.

Definition of terms:

- Study treatment = Study drug = RAD001 or Matching Placebo

In both treatment arms, the study drug will be given by continuous oral daily dosing of two tablets.

Medication labels for RAD001 will comply with the legal requirements of each country and be printed in local language. They will supply no information about the patient. The storage conditions for study drug will be described on the medication label.

6.1.1 Known undesirable effects of study drug/treatment

Adverse events most frequently observed with RAD001 are rash, stomatitis / oral mucositis, fatigue, headache, anorexia, nausea, vomiting, diarrhea, and infections. Overall, the most frequently observed laboratory abnormalities include neutropenia, thrombocytopenia, hypercholesterolemia, and/or hypertriglyceridemia. The majority of these AEs have been of mild to moderate severity (CTC grade 1-2).

Management of stomatitis/oral mucositis/mouth ulcers

Stomatitis/oral mucositis/mouth ulcers due to RAD001 should be treated using local supportive care. Please note that investigators in earlier trials have described the oral toxicities associated with RAD001 as mouth ulcers, rather than mucositis or stomatitis. If your examination reveals mouth ulcers rather than a more general inflammation of the mouth, please classify the adverse event as such. Please follow the paradigm below for treatment of stomatitis/oral mucositis/mouth ulcers:

1. For mild toxicity (grade 1), use conservative measures such as **non-alcoholic mouth wash or salt water (0.9%) mouth wash** several times a day until resolution.
2. For more severe toxicity (grade 2 in which case patients have pain but are able to maintain adequate oral alimentation, or grade 3 in which case patients cannot maintain adequate oral alimentation), the suggested treatments are **topical analgesic mouth treatments (i.e., local anesthetics such as benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol, or phenol)** with or without **topical corticosteroids,** such as triamcinolone oral paste 0.1% (Kenalog in Orabase®).
3. Agents containing hydrogen peroxide, iodine, and thyme derivatives may tend to worsen mouth ulcers. It is preferable to avoid these agents.
4. Antifungal agents must be avoided unless a fungal infection is diagnosed. In particular, systemic imidazole antifungal agents (ketoconazole, fluconazole, itraconazole, etc.) should be avoided in all patients due to their strong inhibition of RAD001 metabolism, therefore leading to higher RAD001 exposures. Therefore, topical antifungal agents are preferred if an infection is diagnosed. Similarly, antiviral agents such as acyclovir should be avoided unless a viral infection is diagnosed.

Management of hyperlipidemia and hyperglycemia

Treatment of hyperlipidemia should take into account the pre-treatment status and dietary habits. Blood tests to monitor hyperlipidemia must be taken in the fasting state. Grade 2 hypercholesterolemia (> 300 mg/dL or 7.75 mmol/L) or grade 2 hypertriglyceridemia (>2.5 x upper normal limit) should be treated with a 3-hydroxy-3-methyl-glutaryl (HMG)-CoA reductase inhibitor (e.g. atorvastatin, pravastatin) or appropriate lipid-lowering medication, in addition to diet. Patients should be monitored clinically and through serum biochemistry for the development of rhabdomyolysis and other adverse events as required in the product label/data sheets for HMG-CoA reductase inhibitors.

Note: Concomitant therapy with fibrates and an HMG-CoA reductase inhibitor is associated with an increased risk of a rare but serious skeletal muscle toxicity manifested by rhabdomyolysis, markedly elevated creatine kinase (CPK) levels and myoglobinuria, acute

renal failure and sometimes death. The risk versus benefit of using this therapy should be determined for individual patients based on their risk of cardiovascular complications of hyperlipidemia.

Hyperglycemia has been observed in patients receiving RAD001 therapy. Based on this finding, it is suggested that optimal glucose control should be achieved before starting a patient on RAD001 and should be monitored during RAD001 therapy.

Management of diarrhea

Appearance of diarrhea attributed to RAD001 toxicity may be treated with loperamide. Other medications for diarrhea may be used as needed such as pancrealipase for the management of steatorrhea due to use of somatostatin analogs or cholestyramine for the management of diarrhea due to short gut syndrome.

In the event of an acute episode of increased disease symptoms resulting from tumor secretory products, short acting Sandostatin® (octreotide acetate) is recommended in place of increasing or initiating Sandostatin LAR® Depot therapy. Short acting Sandostatin® should be administered according to the approved product package insert and report dose administered and frequency appropriately on the Concomitant Medication/Significant Non-drug Therapy eCRF.

Management of non-infectious pneumonitis

Both asymptomatic radiological changes (grade 1= radiological lung changes only) and symptomatic non-infectious pneumonitis (grade 2 = not interfering with activities of daily living or grade 3 = interfering with activities of daily living and oxygen indicated) have been noted in patients receiving RAD001 therapy. Non-infectious pneumonitis has been associated with RAD001 and other mTOR inhibitors (Atkins, 2004). In order to monitor for asymptomatic (grade 1) pulmonary infiltrates, a chest X-ray is required if a CT scan of chest is not used for every three (3) cycle disease evaluation assessments. Additional chest X-rays/CT scans may be done, when clinically necessary. If non-infectious pneumonitis develop, consultation with a pulmonologist is recommended. Management of non-infectious pneumonitis suspected to be associated with RAD001 and dose modification instructions are provided in Table 6-1 and Table 6-5.

Table 6-1 Management of non-infectious pneumonitis

Worst Grade Pneumonitis	Required Investigations	Management of Pneumonitis	RAD001 Dose Adjustment
Grade 1	CT scans with lung windows. Repeat at least every three cycles until return to within normal limits.	No specific therapy is required	Administer 100% of RAD001 dose.
Grade 2	CT scan with lung windows. Consider pulmonary function testing includes: spirometry, DLCO, and room air O_2 saturation at rest. Repeat at least every three cycles until return to within normal limits. Consider a bronchoscopy with biopsy and/or BAL.	Symptomatic only. Consider corticosteroids if symptoms are troublesome.	Reduce RAD001 dose by 1 dose level (see Table 6-5) until recovery to ≤ grade 1. RAD001 may also be interrupted if symptoms are troublesome. Patients will be withdrawn from the study if they fail to recover to ≤ grade 1 within 3 weeks.
Grade 3	CT scan with lung windows and pulmonary function testing includes: spirometry, DLCO, and room air O_2 saturation at rest. Repeat at least every two cycles until return to within normal limits. Bronchoscopy with biopsy and/or BAL is recommended.	Consider corticosteroids if infective origin is ruled out. Taper as medically indicated.	Hold treatment until recovery to ≤ grade 1. May restart protocol treatment within 3 weeks at a reduced dose (by one level) if evidence of clinical benefit.
Grade 4	CT scan with lung windows and required pulmonary function testing, if possible, includes: spirometry, DLCO, and room air O_2 saturation at rest. Repeat at least every two cycles until return to within normal limits. Bronchoscopy with biopsy and/or BAL is recommended if possible.	Consider corticosteroids if infective origin is ruled out. Taper as medically indicated.	Discontinue treatment.

Management of Hepatitis reactivation

Monitoring and prophylactic treatment for hepatitis B reactivation

Table 6-2 provides details of monitoring and prophylactic therapy according to the results of viral load and serologic markers testing.

Table 6-2 Action to be taken for positive baseline hepatitis B results

Test	Result	Result	Result	Result	Result
HBV-DNA	+	+ or -	-	-	-
HBs Ag	+ or -	+	-	-	-
HBs Ab	+ or -	+ or -	+ and no prior HBV vaccination	+ or -	- or + with prior HBV vaccination
HBc Ab	+ or -	+ or -	+ or -	+	-
Recommendation	Prophylaxis treatment should be started 1-2 weeks prior to first dose of study drug Monitor HBV-DNA approximately every 4 weeks		No prophylaxis Monitor HBV-DNA approximately every 4 weeks		No specific action

Antiviral prophylaxis therapy should continue for at least 4 weeks after last dose of study drug.

For patients who have already been randomized and received study drug prior to the implementation of these guidelines, the same process should be followed at the patient's next visit. The first HBV-DNA result would be regarded as baseline.

For hepatitis B reactivation, definition and management guidelines, see Table 6-3 Guidelines for management of hepatitis B.

Table 6-3 Guidelines for management of hepatitis B

HBV reactivation (with or without clinical signs and symptoms)*	
For patients with baseline results: Positive HBV-DNA **OR** positive HBs Ag **reactivation is defined as:** [Increase of 1 log in HBV-DNA relative to baseline HBV-DNA value **OR** new appearance of measurable HBV-DNA] **AND** ALT elevation x 5 ULN	**Treat**: Start a second antiviral AND Interrupt study drug administration until resolution: • ≤ grade 1 ALT (or baseline ALT, if > grade 1) and • ≤ baseline HBV-DNA levels **If resolution occurs within ≤ 28 days** study drug should be re-started at one dose lower, if available. (see Table 6-2 – Study drug dose reductions) If the patient is already receiving the lowest dose of study drug according to the protocol, the patient should restart at the same dose after resolution. Both antiviral therapies should continue at least 4 weeks after last dose of study drug. **If resolution occurs > 28 days** Patients should discontinue study drug but continue both antiviral therapies at least 4 weeks after last dose of study drug.
For patients with baseline results: Negative HBV-DNA **and** HBsAg **AND** [Positive HBs Ab (with no prior history of vaccination against HBV), **OR** positive HBc Ab] **reactivation is defined as:** New appearance of measurable HBV-DNA	**Treat** : Start first antiviral medication AND **Interrupt** study drug administration until resolution: • ≤ baseline HBV-DNA levels **If resolution occurs within ≤ 28 days** study drug should be re-started at one dose lower, if available. (see Table 6-2 – Study drug dose reductions) If the patient is already receiving the lowest dose of study drug according to the protocol, the patient should restart at the same dose after resolution. Antiviral therapy should continue at least 4 weeks after last dose of study drug. **If resolution occurs > 28 days** Patients should discontinue study drug but continue antiviral therapy at least 4 weeks after last dose of study drug.
* All reactivations of hepatitis B are to be recorded as grade 3 (CTCAE v 3.0 Metabolic Laboratory/Other: Viral Re-activation), unless considered life threatening by the investigator; in which case they should be recorded as grade 4 (CTCAE v 3.0 Metabolic Laboratory/Other: Viral Re-activation). Date of viral reactivation is the date on which **both** DNA (or RNA) and ALT criteria were met (e.g. for a patient who was HBV-DNA positive on 01-JAN-10 and whose ALT reached ≥ 5 × ULN on 01-APR-10, the date of viral reactivation is 01-APR-10).	

Monitoring for hepatitis C

The following two categories of patients should be monitored every 4 weeks for HCV reactivation:

- Patients with detectable HCV RNA-PCR test at baseline.
- Patients known to have a history of HCV infection, despite a negative viral load test at baseline (including those that were treated and are considered 'cured')

For definition of hepatitis C reactivation and the management guidelines, see Table 6-4 Guidelines for management of hepatitis C.

Table 6-4 Guidelines for management of hepatitis C

HCV reactivation*	
For patients with baseline results: Detectable HCV-RNA, **reactivation is defined as:** ALT elevation x 5 ULN	Discontinue study drug
For patients with baseline results: Knowledge of past hepatitis C infection with no detectable HCV-RNA, **reactivation is defined as:** New appearance of detectable HCV-RNA	Discontinue study drug
* All reactivations of hepatitis C are to be recorded as grade 3 (CTCAE v 3.0 Metabolic Laboratory/Other: Viral Re-activation), unless considered life threatening by the investigator; in which case they should be recorded as grade 4 (CTCAE v 3.0 Metabolic Laboratory/Other: Viral Re-activation).	

6.1.1.1 Study drug

The study drug is RAD001 or matching placebo.

RAD001 is formulated as tablets of 5 mg strength, blister-packed under aluminum foil in units of 10 tablets and dosed on a daily basis. RAD001 or matching placebo tablets should be opened only at the time of administration as drug is both hygroscopic and light-sensitive.

Each study site will be supplied by Novartis with study drug in identically-appearing packaging. One component of the packaging has a 2-part label. Each part of this label contains a medication number corresponding to one of the 2 treatment groups. Investigator staff will identify the study drug package to dispense to the patient by calling the IVRS and obtaining the medication number. Immediately before dispensing the package to the patient, investigator staff will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) containing that patient's unique patient number.

6.1.1.2 Study combination

Not applicable for this study.

6.1.2 How Supplied

For the duration of the trial, RAD001 or matching placebo will be supplied by Novartis at no charge to each study site.

6.1.3 Preparation and storage

RAD001 is formulated as tablets of 5 mg strength, blister-packed under aluminum foil in units of 10 tablets and dosed on a daily basis. RAD001 or matching placebo tablets should be opened only at the time of administration as drug is both hygroscopic and light-sensitive.

6.1.3.1 Active control

Not applicable for this study.

6.2 Treatment arms

Two treatment arms: RAD001 plus Best Supportive Care (BSC) or Matching Placebo plus BSC.

Best Supportive Care includes all care provided to patients deemed necessary by the treating physician, such as, the use of somatostatin analogs; PPI for gastrinoma; diazoxide, short course of steroid, or feeding tube for insulinoma; Pancrealipase (lipase, protease, and amylase) for patients with pancreatic exocrine insufficiency; and non-specific anti-diarrheals, such as, imodium or lomotil (containing loperamide), opiates, etc.

Best Supportive Care excludes the use of anti-tumor therapies such as interferon, tumor ablative procedures, and radiation and/or concurrent chemotherapy. The optimal care of the patient is based on the treating physician's best medical judgment**.**

6.3 Patient numbering

Each patient in the study is uniquely identified by a **9 digit patient number** which is a combination of his/her **4-digit center number** and **5-digit subject number**. The center number is assigned by Novartis to the investigative site.

When the patient has signed the informed consent form, the investigator or his/her staff will telephone the IVRS and provide the requested identifying information including the patient number for the patient. The assigned 5-digit subject number alone (excluding the leading zeros) should be entered in the field labeled “Subject ID” on the EDC data entry screen. Once assigned to a patient, the patient number will not be reused. If the patient fails to be randomized, the IVRS must be notified why the patient was not randomized as soon as possible. In addition, the Screening Log should be completed for these patients.

Informed consent must be obtained before any testing is performed to determine a patient’s eligibility.

6.3.1 IVRS procedure

User Acceptance Testing of the IVRS based on test data will be performed by the project team prior to its implementation. IVRS will provide contact information and detailed instructions on registration and randomization procedures to each study site.

- At visit 1 the investigator will call to register the patient with IVRS.
- At or prior to visit 2 the investigator will again call IVRS to randomize all eligible patients to one of the two treatment arms.
- The investigator or his/her designee will call IVRS as close as possible to the initiation of therapy (Day 1, Cycle 1). This will avoid randomization of patients who ultimately decide not to participate in the trial.
- Patients should receive the study treatment within 1 week of randomization.

- If the screened patient fails to be randomized, the IVRS must be notified as soon as possible.
- The investigator or his/her designee will notify IVRS immediately of patient discontinuation from study.
- The investigator or his/her designee will call IVRS for patient unblinding (concerning patients who are candidates for open-label RAD001 therapy).
- No study medication should be dispensed without calling the IVRS.
- Re-supply of blinded medication will occur at 2-month (28 days/month) intervals. Medication will be assigned for scheduled visits via the IVRS.
- During the trial, IVRS will report the occurrence of any emergency code breaks immediately to the Clinical Trial Leader (CTL) and the site assigned clinical monitor.
- Unblinding may occur after documented disease progression during the blinded treatment phase – this is to enable patients randomized to placebo to switch to open-label RAD001. Unblinding may also occur in the case of medical emergencies when the treating oncologist believes that the knowledge of the blinded treatment is essential. Complete details are provided in Section 6.6.6 for Emergency unblinding of treatment assignment.

6.4 Treatment assignment

At or prior to Visit 2 the investigator or his/her designee will call the IVRS (after verifying that the patient fulfills all eligibility criteria) to randomize the patient. The IVRS will assign a randomization number to the patient, which will be used to link the patient to one of the two treatments, and will specify a unique medication number for the first package of study drug to be dispensed to the patient. The medication number appears on the study medication pack that will be dispensed to the patient. The randomization number will not be communicated to the caller. The randomization will be stratified by whether or not they have received prior cytotoxic chemotherapy and by WHO performance status (0 vs. 1-2) at baseline.

6.5 Treatment blinding

This is a double-blind study. The study design allows patient unblinding in very precise circumstances. The clinical personnel at the Central Laboratory and at the Central Radiology facility, including the Independent Adjudication Committee, will remain blinded to the identity of the treatment from the time of randomization until final database lock.

Randomization will be performed using the following procedures to ensure that treatment assignment is unbiased and concealed as best possible from all individuals involved in the study: 1) randomization data are kept strictly confidential until the time of unblinding at progression of disease and at time of final analyses, and will not be accessible to anyone involved in the conduct of the study with the exception of the IDMC who will perform an ongoing safety review and, 2) the identity of the treatments will be concealed by the use of study drugs (RAD001 and Matching Placebo) that are all identical in packaging, labeling, schedule of administration and in appearance.

The randomization list will be generated by the IVRS provider using a validated system that automates the random assignment of patient numbers to randomization numbers. The

randomization numbers are linked to the two different treatment arms, which in turn are linked to medication numbers. The randomization scheme for patients will be reviewed and approved by a member of the Biostatistics Quality Assurance Group and will be locked and kept by them after its approval.

Quarterly safety analyses will be performed by a team independent of the project team who interacts with IDMC. Decisions concerning the future conduct of the trial based on the IDMC recommendations (i.e. that it is ethical to continue the trial until final analysis) will be communicated to the project team without providing any details about the results of these safety analyses.

At the conclusion of the study, when the study data have been verified, and the protocol deviations have been determined and the database locked, the assigned blinded drug codes can be broken and made available to the sponsor for the final analysis of the study data.

6.6 Treating the patient

6.6.1 Study drug administration

RAD001 or matching placebo will be dispensed by the study center personnel on an outpatient basis. Patients will be provided with an adequate supply of RAD001 or matching placebo for self-administration at home. On the days of PK sampling, RAD001 or matching placebo will be administered by the investigator (or his/her designee). Patients who enter the open label phase of the study will be provided with an adequate supply of RAD001 for self-administration at home.

The investigator should instruct the patient to take the study drug exactly as prescribed (promote compliance). All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record eCRF.

RAD001 or matching placebo will be dosed starting on Cycle 1 Day 1. Patients will be instructed to take two tablets of RAD001 or matching placebo orally with a glass of water, once daily at the same time each day immediately after a meal. RAD001 or matching placebo should be swallowed whole and the tablets should not be chewed or crushed. Any dietary habits around the time of RAD001 or Matching Placebo intake should be as consistent as possible throughout the study, and in particular, during those periods when samples are being taken for pharmacokinetic analyses. If vomiting occurs, no attempt should be made to replace the vomited dose.

At visits, when blood work will be drawn, patients should ***not*** take the daily study drug dose ***until after*** blood work is drawn so that an accurate trough level of RAD001 can be obtained. In absence of any other reason for holding study drug, study drug may be continued for up to 5 days while awaiting central lab results, which may be used to determine a modification of the dosing regimen.

Patients should be requested to bring their unused study drug, including the empty blister packs, to the clinic at each visit. Compliance should be verified by the investigator's staff through counting the number of tablets consumed between visits. The investigator (or his/her designee) will document dosage administration and all dose changes during the study in the eCRF. The site must maintain an overall drug accountability log for the study, as well as

individual accountability records for each patient. The dose, amount dispensed, amount received, and amount remaining unused must be recorded in the source document. Drug accountability will be noted by the field monitor during site visits and at the completion of the study. The patient will be asked to return all unused RAD001 at the end of the study.

Patients will receive treatment with study drug until progression of tumor, the occurrence of unacceptable toxicity, or until the investigator or patient decides that continuation is not in the best interest of the patient. Interruption for toxicity should follow the instructions in Table 6-5 and Table 6-6.

6.6.2 Permitted study drug adjustments

For patients who are unable to tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to keep the patient on study drug. The guidelines set forth in Table 6-1, Table 6-5 and Table 6-6 should be followed:

If treatment is interrupted due to toxicity, RAD001 should not be resumed until recovery to grade ≤1, then reintroduce RAD001 at the initial dose or lower dose level depending on toxicity type and Grade (Table 6-6). These changes must be recorded on the Dosage Administration Record eCRF.

Table 6-5 RAD001 dose levels for dose adjustment

Dose level	Dose and schedule
0 = starting dose	10 mg daily
-1 dose level	5 mg daily
-2 dose level	5 mg every other day

If a patient has already decreased 2 dose levels, no further dose reduction is permitted. Patients requiring a third dose reduction will be required to discontinue study treatment.

Table 6-6 provides the procedure to be followed for dose modification and re-initiation of RAD001 in the event of toxicities suspected to be related to the study drug.

6.6.2.1 Dosing modifications

Table 6-6 Criteria for dose-modification in case of suspected RAD001 toxicity and re-initiation of RAD001 treatment.

Toxicity	Actions
Non-hematological toxicity	
Grade 2 (except pneumonitis – refer to Table 6-1)	If the toxicity is tolerable to the patient, maintain the same dose. If the toxicity is intolerable to patient, interrupt RAD001 until recovery to grade ≤1. Then reintroduce RAD001 at same dose. If event returns to grade 2, then interrupt RAD001 until recovery to grade ≤1. Then reintroduce RAD001 at the lower dose level.
Grade 3 (except hyperlipidemia*)	Interrupt RAD001 until recovery to grade ≤1. Then reintroduce RAD001 at the lower dose level. For pneumonitis consider the use of a short course of corticosteroids.
Grade 4	Discontinue RAD001.
Hematological toxicity	
Grade 2 Thrombocytopenia (platelets <75, ≥ 50x10^9/L)	Interrupt RAD001 until recovery to grade ≤1 (>75 x10^9/L). Then reintroduce RAD001 at initial dose. If thrombocytopenia again returns to grade 2, interrupt RAD001 until recovery to grade ≤1. Then reintroduce RAD001 at the lower dose level.
Grade 3 Thrombocytopenia (platelets <50, ≥ 25 x109/L)	Interrupt RAD001 until recovery to grade ≤1 (platelets ≥ 75 x10^9/L). Then resume RAD001 at one dose level lower. If grade 3 thrombocytopenia recurs, discontinue RAD001.
Grade 4 Thrombocytopenia (platelets < 25 x10^9/L)	Discontinue RAD001.
Grade 3 Neutropenia (neutrophils <1, ≥0.5 x10^9/L)	Interrupt RAD001 until recovery to grade ≤1 (neutrophils ≥ 1.5 x 10^9/L). Then resume RAD001 at the initial dose. If ANC again returns to Grade 3, hold RAD001 until the ANC ≥ 1.5 x 10^9/L. Then resume RAD001 dosing at the lower dose level. Discontinue patient from study therapy for a third episode of grade 3 neutropenia.
Grade 4 Neutropenia (neutrophils < 0.5 x10^9/L)	Interrupt RAD001 until recovery to grade ≤ 1 (neutrophils ≥ 1.5 x 10^9/L). Then resume RAD001 at the lower dose level. If grade 3 or grade 4 neutropenia occurs despite this dose reduction, discontinue RAD001.
Grade 3 febrile neutropenia (not life-threatening)	Interrupt RAD001 until resolution of fever and neutropenia to grade ≤ 1. Hold further RAD001 until the ANC ≥ 1,500/mm^3 and fever has resolved. Then resume RAD001 at the lower dose level. If febrile neutropenia recurs, discontinue RAD001.
Grade 4 febrile neutropenia (life-threatening)	Discontinue RAD001.
Any hematological or non-hematological toxicity requiring interruption for ≥ 3 weeks	Discontinue RAD001
*Grade 3 hyperlipidemia (hypercholesterolemia and/or hypertriglyceridemia) should be managed using medical therapies.	

6.6.2.2 Follow-up for toxicities

Patients whose treatment is interrupted or permanently discontinued due to an adverse event or abnormal laboratory value suspected to be related to RAD001 must be followed at least weekly until the adverse event or abnormal laboratory resolves or returns to grade 1. If a patient requires a dose delay of ≥ 3 weeks from the intended day of the next scheduled dose, then the patient must be discontinued from the study.

All patients will be followed for adverse events and serious adverse events for 28 days following the last dose of study drug.

6.6.3 Other concomitant medications

Patients must be instructed not to take any additional medications (over-the-counter or other products) during the study without prior consultation with the investigator. All medications taken within 30 days of starting study treatment should be reported on the Concomitant Medication/Significant Non-drug Therapy Prior to Start of Study Drug eCRF. The following concomitant treatments are not allowed during the study:

- Investigational or commercial anticancer agents other than RAD001
- Drugs or substances known to be inhibitors, inducers or substrates of the isoenzyme CYP3A unless use of the drug is essential and no substitute is available:
- Co-administration with strong CYP3A inhibitors (e.g. ketoconazole, itraconazole, ritonavir) or P-glycoprotein (PgP) should be avoided.
- Co-administration with moderate CYP3A inhibitors (e.g. erythromycin, fluconazole) or PgP inhibitors should be used with caution. If patient requires co-administration of moderate CYP3A4 inhibitors or PgP inhibitors, reduce the dose of everolimus to half the currently used dose. Additional dose reductions to every other day may be required to manage toxicities. If the inhibitor is discontinued the RAD001 or matching placebo dose should be returned to the dose used prior to initiation of the moderate CYP3A/PgP inhibitor.
- Seville orange, star fruit, grapefruit and their juices affect cytochrome P450 and PgP activity and should therefore be avoided.

Inducers of CYP3A4 and/or PgP

Avoid the use of strong CYP3A4 inducers. If patient requires co-administration of strong CYP3A4 inducers (i.e., phenytoin, carbamazepine, rifampin, rifabutin, phenobarbital, St. John's wort), an increase in the dose of RAD001 or matching placebo up to twice the currently used daily dose should be considered using 5mg increments. Enzyme induction usually occurs within 7-10 days, therefore RAD001 or matching placebo dose should be increased by one increment 7 days after the start of the inducer therapy. If no safety concerns are seen within the next 7 days, the dose can be increased again one additional increment up to a maximum of twice the daily dose used prior to initiation of the strong CYP3A4 inducer.

This dose adjustment of RAD001 or matching placebo is intended to achieve similar AUC to the range observed without inducers. However, there are no clinical data with this dose adjustment in patients receiving strong CYP3A4 inducers. If the strong inducer is

discontinued the RAD001 or matching placebo dose should be returned to the dose used prior to initiation of the strong CYP3A/PgP inducer.

Table 6-7 lists clinically relevant CYP3A inhibitors, inducers and the definition of strong, and moderate inhibitors/inducers.

RAD001 may affect the response to vaccinations making the response to the vaccination less effective. Live vaccines should be avoided while a patient is treated with RAD001.

Otherwise, the use of other concomitant medication/therapy deemed necessary for the care of the patient is allowed. The investigator should instruct the patient to notify the study site about any new medications he/she takes after the start of the study drug. All medications (other than study drug) and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient starts RAD001 must be listed on the Concomitant medications/Significant non-drug therapies after start of study drug eCRF.

The investigator should instruct the patient to notify the study site about any new medications he/she takes after the start of the study drug. All medications (other than study drug) and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient starts treatment with study drug must be listed on the Concomitant medications/Significant non-drug therapies after start of study drug eCRF.

Table 6-7 Clinically relevant drug interactions: substrates, inducers and inhibitors of isoenzyme CYP3A.

INDUCERS
Barbiturates, carbamazepine, glucocorticoids, modafinil, oxcarbazepine, phenobarbital, phenytoin, pioglitazone, rifabutin, rifampin, St. John's wort, troglitazone, efavirenz, nevirapine, topiramate
INHIBITORS
Strong inhibitors: clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, lopinavir, mibefradil, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandamycin, voriconazole, Posaconazole (Krishna et al, 2009) **Moderate inhibitors:** aprepitant, atazanavir, cimetidine, ciprofloxacin, darunavir, diltiazem, erythromycin, fluconazole, grapefruit juice, imatinib, tofisopam, verapamil,

Table 6-8 Clinically relevant drug interactions mediated by PgP

PgP Substrates	PgP Inhibitors in vivo	PgP Inducers
digoxin, fexofenadine, indinavir, vincristine, colchicine, topotecan, paclitaxel	amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, cyclosporine, diltiazem, elacridar, erythromycin, felodipine, (GF120918), itraconazole, ketocoanzole, lopinavir, (LY335979), mibefradil, nifedipine, nitrendipine, (PSC833), quinidine, ranolazine, ritonavir, talinolol, valspodar, verapamil	rifampin, St John's wort

Reference:

Internal Clinical Pharmacology Drug-drug interaction (DDI) memo, updated Dec. 2, 2009, which summarizes DDI data from three sources including the FDA's "Guidance for Industry, Drug Interaction Studies, the University of Washington's Drug Interaction Database, and Indiana University School of Medicine's Drug Interaction Table."

This list of clinically relevant drug interactions is updated as of December 02, 2009

6.6.4 Study drug interruption or discontinuation

The term "interruption" refers to a patient stopping the study medication during the course of the study, but then re-starting it at a later time in the study.

The term "discontinuation" refers to a patient's premature withdrawal from the study treatment. The reason for discontinuation from treatment will be recorded. The patient may discontinue participation in the study for any of the following reasons:

1. adverse event(s)
2. abnormal laboratory value(s)
3. abnormal test procedure result(s)
4. disease progression
5. protocol deviation
6. subject withdrew consent
7. lost to follow-up
8. administrative problems
9. death

If a patient has discontinued the study drug due to an unacceptable adverse drug reaction or an abnormal laboratory value, he/she should not have withdrawal of consent recorded as the reason for discontinuation. Instead, the reason for discontinuation must be recorded as due to adverse drug reaction or an abnormal laboratory value.

Patients who discontinue the study drug regardless of the reason must have end of study treatment evaluations (Refer to Table 7-1, Final Visit) on the Day of study treatment discontinuation or within 1 week of study treatment discontinuation. The investigator or his/her designee will proceed as follows:

- Notify IVRS immediately of patient discontinuation.
- Complete the end of study treatment evaluations and complete the End of Treatment eCRF indicating the date and reason for stopping the study drug. Additional details are provided in Table 7-1.
- All patients will have a follow-up visit 28 days after the last dose of the study treatment. During this visit, AEs and SAE information will be collected and recorded in the appropriate eCRFs. If the patient is unable to return to the clinic, the investigator or his/her designee will contact the patient or caregiver to collect this information.
- All patients who are discontinued from study treatment for any reason will continue to have tumor assessments until the start of other anti-cancer therapy. Radiological studies will be sent for central review during this follow-up period. The investigator or his/her

designee will collect information on the initiation of additional anticancer therapies every month. This information may be obtained during a telephone call and will be recorded in the source documents as well as in the appropriate eCRFs

- Collect survival information on all patients monthly until the final survival analysis. Survival information may be obtained during a telephone call and will be recorded in the source documents as well as in the appropriate eCRF. The sponsor will immediately notify the investigative sites when the final analysis date is reached.
- If patients refuse to return to the clinic for follow–up assessments or are unable to do so, the investigator or his/her designee will make every effort to contact the patient or a close relative or caretaker by telephone to collect survival information. The investigator or his/her designee should show "due diligence" by documenting in the source documents steps taken to contact the patient, i.e., dates of telephone calls, registered letters, etc.

All patients must have evaluations for 28 days after the last dose of study treatment. Patients lost to follow up should be recorded as such on the eCRF. Patients who discontinue study drug before completing the study should be scheduled for a visit as soon as possible, at which time all of the assessments listed for End of Treatment visit will be performed. At a minimum, all patients who discontinue study treatment, including those who refuse to return for a final visit, will be contacted for safety evaluations during the 28 days following the last dose of study drug.

6.6.5 Withdrawal from the study and Study evaluation completion

Patients **may** voluntarily withdraw from the study or be dropped from it at the discretion of the investigator at any time.

As a general rule, if a patient discontinues study drug and later is withdrawn from the study, the reasons for study evaluation completion may include the following:

- Protocol deviation
- Subject withdrew consent
- Lost to follow-up
- Death
- New cancer therapy
- Disease progression

For patients who are lost to follow-up, the investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

6.6.6 Emergency unblinding of treatment assignment

In general, circumstances that might lead to emergency unblinding are very rare. Most often, study drug discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study patient who presents with an emergency condition. One unusual circumstance in which unblinding might be necessary is when a patient requires emergency surgery and the anesthesiologist needs to know all medications that the patient has been exposed to in order to make proper decisions about treatment and support during the surgery.

Emergency unblinding should only be done when necessary in order to treat the patient. Emergency code breaks are performed using the IVRS. When the investigator telephones the system to unblind a patient, he/she must provide the requested patient identifying information. The investigator will then receive details of the drug treatment for the specified patient and a fax confirming this information. The system will automatically inform the Novartis monitor for the site and the Clinical Trial Leader that the code has been broken.

It is the investigator's responsibility to ensure that there is a procedure in place to allow access to the IVRS in case of emergency. The investigator will inform the patient how to contact his/her backup in cases of emergency when he/she is unavailable. The protocol number, study drug name if available, patient number and instructions for contacting the local Novartis CPO (or any entity to which it has delegated responsibility for emergency code breaks) will be provided to the patient in case emergency unblinding is required at a time when the investigator and backup are unavailable.

Study drug must be discontinued after emergency unblinding. The investigator is not allowed to place emergency unblinded patients into open-label RAD001 therapy.

6.6.7 Treatment Compliance

Compliance will be assessed by the investigator or his/her designee at each visit using pill counts. This information should be captured in the source document at each visit.

- Patients will be requested to bring their unused medication including empty packaging to the clinic at each visit.
- All doses taken by the patient and all dose changes during the study must be recorded on the Dosage Administration Record eCRF.
- The investigator or his/her designee must keep documentation (overall drug accountability log for the study as well as individual study drug accountability records for each patient) of tablets administered, tablets used, dose changes, dates dispensed and intervals between visits.
- Drug accountability will be monitored by the field monitor during site visits and at the completion of the study.

7 Visit schedule and assessments

Table 7-1 lists all of the assessments and indicates with an "X" the visits when they are performed. All data obtained from these assessments must be supported in the patient's source documentation. The table indicates which data are entered into the database (D) or remain in source documents only (S). Assessments that generate data for database entry and are recorded on eCRFs are listed using the eCRF name. Assessments that are transferred to the database electronically (e.g., laboratory data) are listed by test name.

Tests, procedures and visits should occur on schedule whenever possible. However, tests, procedures, and visits that occur up to 7 days before or after scheduled date will not constitute protocol deviation.

Table 7-1 Visit evaluation schedule

Assessment	Pre-Treatment (screening/ baseline)	Cycle 1		Cycle 2	Cycle 3	Cycle 4	Subsequent Cycles	End of study treatment	Post- treatment Evaluations & Survival Follow Up
Visit no.	1	2	3	4	5	6	N	Last	
Time point (days)	-14 to -1	1	15	1	1	1	1	Last	
Screening [a]	X [a]								
Vital signs (D) (Height at baseline only)	X	X	X	X	X	X	X	X	
Physical Exam [b] (S)	X [b]	X [b]	X [b]	X [b]	X [b]	X [b]	X [b]	X [b]	
WHO performance status (D)	X	X		X	X	X	X	X	
EKG [c] (S)	X [c]								
Hematology [d] (D)	X [d]	X [d]	X [d]	X [d]	X [d]	X [d]	X [d]	X [d]	
Coagulation Studies (PT/INR) (D)	X					X	Every 3 Cycles	X	
Serum Blood Chemistry [e] (D)	X [e]	X [e]	X [e]	X [e]	X [e]	X [e]	X [e]	X [e]	
Urinalysis [f] (D)	X [f]	X [f]		X [f]	X [f]	X [f]	X [f]	X [f]	
Urine or Serum pregnancy test (S) [o]	X [o]	X [o]		X [o]	X [o]	X [o]	X [o]	X [o]	
Serum Lipid Profile [g] (D)	X [g]					X [g]	Every 3 Cycles [g]		
HBV-DNA, HbsAg, HBs Ab, HBc Ab, HCV-RNA-PCR [r]							X	X	
Thyroid function test (TSH, free T4) & B12 (Patients receiving long acting somatostatin only) (D)	X						Every 6 Cycles		
Prior/concomitant medications (D)	X	Continuous							
Adverse events (D)	X	Continuous							
Radiologic tumor evaluation [h] (D)	X [h]					X [h]	Every 3 Cycles [h]	X [h]	

Assessment	Pre-Treatment (screening/ baseline)	Cycle 1		Cycle 2	Cycle 3	Cycle 4	Subsequent Cycles	End of study treatment	Post- treatment Evaluations & Survival Follow Up
Visit no.	1	2	3	4	5	6	N	Last	
Time point (days)	-14 to -1	1	15	1	1	1	1	Last	
Biochemical tumor markers [i]	X [i]	X [i]		X [i]	X [i]	X [i]	X [i]	X [i]	
Archival Tissue for correlative studies [j]	X [j]								
Whole blood DNA [q]			X [q]						
RAD001 dosing (D)		Daily ----------							
PK trough blood sampling [k] (D)			X [k]	X [k]	X [k]	X [k]	X [k]	X [k]	
PK: RAD PK profile assessments blood sampling [l] (D)				X [l]					
Plasma for angiogenesis [m] (D)	X [m]			X [m]	X [m]	X [m]		X [m]	
Study Completion (D)								X	
Follow-Up and Survival [n] (D)									X [n]
Chest X-ray and PFT [p] (D)	X [p]					X [p]	Every 3 Cycles [p]		

[a] Screening evaluations include: administration of informed consent, demography, inclusion/exclusion criteria, relevant medical history/current medical conditions, confirmation of Advanced Pancreatic Neuroendocrine Tumor, diagnosis and extent of cancer (sites of metastatic disease), prior antineoplastic therapy, radiotherapy and/or surgery, a physical examination (including a neurological examination), and vital signs

[b] Significant findings from Physical Exam will be noted in the Relevant Medical history pages or Adverse Events pages.

[c] Baseline EKG is a standard 12 lead and must be performed within 14 days of first dose for patients enrolled and may be repeated at the investigator's discretion if there are signs and symptoms of cardiotoxicity. Significant findings will be noted in the Relevant Medical history pages or Adverse Events pages.

[d] Hematology must include: hemoglobin, hematocrit, platelets, red blood cell count (RBC), total white blood cell count (WBC), & differential.

[e] Serum Blood Chemistry must include: sodium, potassium, chloride, bicarbonate, creatinine, albumin, total protein, SGOT (AST), SGPT (ALT), total bilirubin, alkaline phosphatase, uric acid, BUN, calcium, magnesium, phosphate, total LDH, and fasting glucose.

[f] Standard urinalysis assessment must include: pH, protein, glucose, blood, ketones, and leukocytes and should be performed at the central laboratory during screening. At subsequent visits, urine dipstick will be performed routinely at Day 1 of each cycle. This must be supplemented with central laboratory quantification of any potentially relevant abnormalities.

[g] Serum Lipid profile must include: total cholesterol, triglycerides, LDL, and HDL. Assessment should be repeated every 3 cycles.

[h] Repeat scans (multiphase MRI or triphasic CT) at baseline and every 12 weeks thereafter. The same type of scan should be used at baseline and follow-up. If an initial

Assessment	Pre-Treatment (screening/ baseline)	Cycle 1		Cycle 2	Cycle 3	Cycle 4	Subsequent Cycles	End of study treatment	Post- treatment Evaluations & Survival Follow Up
Visit no.	1	2	3	4	5	6	N	Last	
Time point (days)	-14 to -1	1	15	1	1	1	1	Last	

observation of partial or complete response is made, a confirmation scan should be obtained no sooner than 4 weeks and not more than 6 weeks after the initial observation...

[i] Pre-study Chromogranin A (CgA), neuron specific enolase, pancreatic polypeptide, gastrin, glucagon, and VIP will be assessed at baseline in all patients & repeated every cycle if elevated. Insulin, pro insulin, and c-peptide will be assessed at baseline in patients with insulinomas and repeated every cycle if elevated.

[j] Only in patients for whom tissue is available. (See protocol section 7.10.2.)

[k] RAD001 blood samples for trough levels will be collected from all the patients at all sites as a pre-dose sample at Cycle 1 Day 15, Cycle 2 Day 1, and every Cycle Day 1 thereafter until end of blinded study-drug period.

[l] RAD001 blood samples for full PK profile will be collected from **40 patients at three specific investigational sites**. RAD PK profiles should be collected in patients who do not take Sandostatin LAR® Depot, chronic Sandostatin® injection or other long acting somatostatin analog during the study as concomitant medication. The sampling schedule on Day 1 of Cycle 2 is Pre-dose, 0.5, 1, 2, 5 & 24 hrs post-dose.

[m] Plasma collection at pre-treatment, cycles 2 through 4 and end of treatment visits: 10 mL plasma samples will be examined for RAD001 effects on angiogenesis markers, e.g. basic FGF, VEGF, PLGF, sVEGFR1and sVEGFR2.

[n] Follow-up evaluation to include review of: Antineoplastic therapies since discontinuation of study drug and monthly survival data collection.

[o] All females of childbearing potential should have a negative serum pregnancy within the 14 day window prior to the first the dose of RAD001 or matching placebo and/or a urine pregnancy test 48 hours prior to the administration of the first study treatment. Monthly (if necessary) and End of Treatment Visit (required) tests can be urine pregnancy tests.

[P] Chest X-ray (or Chest CT) must be performed at screening and repeated every 3 cycles. Pulmonary function test and bronchoscopy with biopsy (or BAL) will be performed when medically necessary. See section 7.5.6.

[q] Whole blood sample is required only for patients who have archival tumor tissue available.

[r] Patients should be screened for hepatitis risk factors and any past illnesses of hepatitis B and hepatitis C. Patients on antiviral prophylaxis treatment or positive HBV antibodies, should be tested for HBV-DNA approximately every 4 weeks. Patients with positive HCV-RNA PCR or a history of past infection, even if treated and considered 'cured' – should be followed by HCV-RNA PCR approximately every 4 weeks. Antiviral treatment should continue throughout the entire study period and for at least 4 weeks after the last dose of study drug.

NOTE: Crossover (Open label phase of the study only): Assessments for safety and efficacy would occur at the same intervals as for blinded phase of trial. However, PK and Biomarker Pharmacodynamic studies will NOT be performed during the open-label phase. Radiologic tumor evaluations will not be sent for central review.

7.1 Information to be collected on screening failures

Patients who complete the informed consent process and do **not** meet all entry criteria and therefore who do not receive RAD001 or matching placebo will be considered screen failures. The screening failure data will be entered in the clinical database.

7.2 Patient demographics/other baseline characteristics

Data will be collected on patient characteristics including demographic information (age, sex, race, weight) and other background or relevant medical history (cancer history and extent of cancer, prior anticancer therapies) and any other assessments that are done for the purpose of determining eligibility for inclusion in the study (i.e., WHO Performance Status, complete physical examination including a neurological assessment, vital signs, hematology, blood chemistries including coagulation studies and a serum lipid profile, urinalysis, pregnancy test only required for women of childbearing potential, MRI, ECG, Chest X-ray). Urinalysis and the pregnancy test are only performed at either screening or baseline for eligibility but are not repeated after the patient has started study drug or at discontinuation from the study.

7.2.1 Baseline tumor assessment and chest X-rays

Tumor assessments are to be performed for screening purposes and are needed to determine the eligibility of the patient. Results of scans performed within 28 days prior to first dose of study drug will also be used as baseline values. Negative scans at screening need not be repeated unless warranted by signs and symptoms suggesting disease progression.

The following tumor assessments are to be performed and assessed prior to enrollment:

- Abdominal and pelvic triphasic CT or multiphase MRI;
- Chest X-ray (and/or chest CT if disease is present in chest).

To determine eligibility, measurable and non-measurable lesions must be assessed and target lesions identified prior to enrollment. For definition of measurable and target lesions please refer to the [Post-text supplement 1].

7.2.2 Recording historical tumor and chemotherapy information

If the patient has undergone somatostatin receptor scintigraphy, results of the most recent test should be recorded.

7.2.2.1 Documenting the diagnosis of Pancreatic NET:

Patients must have confirmed low-grade or intermediate-grade neuroendocrine carcinoma.

The radiologic, operative or pathology reports should document a pancreatic location of tumor at some point in the patient's history.

The pathology report should state one of the following: islet cell carcinoma, pancreatic endocrine tumor, low-grade or well-differentiated neuroendocrine carcinoma, intermediate-grade or moderately differentiated neuroendocrine carcinoma.

NOTE: Patients with poorly differentiated neuroendocrine carcinoma, high-grade neuroendocrine carcinoma, adenocarcinoid, goblet cell carcinoid and small cell carcinoma are not eligible.

7.3 Treatments

This study does not have a fixed treatment duration. Patients should start study treatment on Cycle 1 Day 1 and continue to be treated per protocol until documentation of disease progression as per local radiologist by RECIST criteria. However, study treatment may prematurely be discontinued for other reasons as well. Please refer to Section 6.6.4.

Compliance will be assessed by the investigator and/or study personnel at each visit using pill counts and information provided by the caregiver. This information should be captured in the source document at each visit.

7.4 Efficacy

7.4.1 Radiologic evaluation

For instruction regarding baseline tumor assessments, please refer to Table 7-1 and Section 7.2.1.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and after every 3 cycles while on-study.

Each center must have a designated radiologist or other physician who is responsible for the interpretation of X-rays and triphasic CT scans or multiphase MRI and the response evaluation according to RECIST criteria. The same radiologist/physician should perform the evaluation for the entire duration of the study. All radiology evaluations will be performed initially by the local radiologist. All scans will be reviewed by Independent Central Radiology Review as specified within the Independent Review Charter.

Independent central radiology review includes radiology assessments by an Independent Review Committee (IRC) and an Independent Adjudication Committee (IAC).

- The IRC is constituted by teams of two board-certified independent radiologists who review radiological images from investigational sites on an ongoing basis. Discrepancies between two central readers are adjudicated.
- The IAC is constituted by a board certified radiologist and an oncologist with experience in NETs. The IAC adjudicates PFS discrepancies between local and IRC determination. The adjudication is performed in a blinded manner so that the committee members have no knowledge of treatment assignment or origin of RECIST evaluations (local or central).

The data used in the sensitivity analysis of the primary endpoint will be comprised of data from IAC assessment for patients where adjudication is required and data from IRC assessment for patients where no adjudication is required. The process for IRC and the IAC review is specified within the Independent Review Charter. If an initial observation of partial or complete response is made, a confirmation scan should be obtained between 4-6 weeks after the initial observation.

All patients being discontinued from the study for progressive disease must have their disease progression documented by the investigator or local radiologist/physician using RECIST criteria.

7.4.2 Response evaluation by RECIST

Response and progression evaluation will be performed according to the RECIST criteria as described in detail in Post-text supplement 1. A few points from this document are emphasized below.

Baseline requirement:

All patients should have at least one measurable disease lesion by triphasic CT or multiphase MRI. Triphasic CT refers to a multi-phase CT scan done at 3 specific time-points: pre-contrast, arterial, and finally portal venous phase. In the event that contrast is contra-indicated for a patient, a multiphase MRI is acceptable in place. Measurable disease lesions must be accurately measured in at least one dimension with longest diameter ≥ 20 mm using conventional techniques or ≥ 10 mm with spiral CT scan (with minimum lesion size no less than double the slice thickness).

Measurement technique:

All measurements should be taken and recorded in metric notation, using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 28 days before the beginning of the treatment.

Target lesions:

All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements. A sum of the longest diameter for all target lesions will be calculated and reported as the baseline sum of the longest diameter. The baseline sum of the longest diameter will be used as reference by which to characterize the objective tumor response.

Response assessment:

Details of response assessment are provided in post-text supplement 1, and are based exclusively on radiological findings obtained at tumor assessments.

Partial response (PR) requires at least a 30% decrease in the sum of the longest diameter of all target lesions, taking as reference the baseline sum of the longest diameters. Complete response (CR) requires disappearance of all target and non-target lesions. To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed between 4-6 weeks after the criteria for response are first met.

Progression is either; 1) a 20% increase in the sum of the longest diameter of all target lesions, taking as reference the smallest sum of longest diameter of all target lesions recorded at or

after baseline or; 2) the appearance of a new lesion or; 3) the unequivocal progression of non-target lesions.

7.4.3 Exploratory analyses

Not applicable for this study.

7.5 Safety

Safety assessments will consist of monitoring and recording all adverse events, including serious adverse events, the regular monitoring of hematology and blood chemistry, regular monitoring of vital signs and physical condition.

These assessments should be performed within 7 days of the scheduled day of assessment (Table 7-1) except for adverse events that will be evaluated continuously through the study.

7.5.1 Adverse events

An adverse event for the purposes of this protocol is the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) occurring after signing the informed consent even if the event is not considered to be related to the study drug(s). Please refer to Section 6.1 for the protocol-specific definitions of study drug and study treatment.

Adverse events will be assessed according to the Common Toxicity Criteria for Adverse Events (CTCAE) version 3.0. If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, corresponding to grades 1 - 4, will be used. CTCAE grade 5 (death) will not be used in this study; rather, this information will be collected in the End of Treatment, Study Evaluation Completion or Survival Information eCRF pages. Adverse event monitoring should be continued for at least 28 days following the last dose of study treatment.

Adverse events (but not serious adverse events) occurring before starting study treatment but after signing the informed consent form are recorded on the Medical History/Current Medical Conditions Electronic Case Report Form. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant or require therapy (e.g., any hematologic abnormality that requires transfusion or cytokine treatment); and should be recorded on the Adverse Events eCRF under the signs, symptoms or diagnosis associated with them. In addition, isolated abnormal laboratory values that are considered clinically significant (e.g., cause study discontinuation or constitutes in and of itself a Serious Adverse Event) should be recorded on the Adverse Events eCRF. SAEs occurring after signing the Informed Consent are recorded on the Adverse Event eCRF.

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. The severity grade CTCAE grade 1-4
2. Its relationship to each study drug (suspected/not suspected)
3. Its duration (start and end dates or if continuing at final exam)

4. Action taken (no action taken; study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication taken; non-drug therapy given; hospitalization/prolonged hospitalization)
5. Whether it is serious, where a serious adverse event (SAE) is defined as one which:
    - Is fatal or life-threatening
    - Results in persistent or significant disability/incapacity
    - Constitutes a congenital anomaly/birth defect
    - Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
        - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
        - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
        - Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
        - Social reasons and respite care in the absence of any deterioration in the patient's general condition
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements; see Section 8.1.

All adverse events should be treated appropriately. Such treatment may include changes in study drug treatment including possible interruption or discontinuation, starting or stopping concomitant treatments, changes in the frequency or nature of assessments, hospitalization, or any other medically required intervention. Once an adverse event is detected, it should be followed until its resolution, an assessment should be made at each visit (or more frequently, if necessary) of any changes in its severity, its suspected relationship to the study drug(s), any of the interventions required to treat it, and its outcome.

Information about common side effects already known about the investigational drug can be found in the [Investigator's Brochure] or will be communicated between IB updates in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

7.5.2 Physical examination

Physical examination must include a total body examination (general appearance, skin, neck, including thyroid, eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities and basic nervous system). Significant findings must be recorded either as Relevant Medical History / Current Medical Conditions (if present before treatment) or as Adverse Events (if newly occurring or worsening since starting treatment).

7.5.3 Vital signs

Pulse, respiration rate, blood pressure and temperature, height (screening visit only) and weight will be measured as indicated in the Assessment schedule (Table 7-1) and will be recorded on source documents, repeated at each visit and entered in CRF pages. Weight will be recorded on the case report form at each visit. Other vital signs will be recorded on the eCRF if they represent an adverse event.

Blood pressure, pulse and respiration rate should be measured on patients after at least 3 minutes in the sitting position.

7.5.4 WHO performance status and scale

WHO performance status will be recorded during screening and repeated during each cycle thereafter.

Performance Status WHO grade:

Grade 0: Able to carry out all activity without restriction

Grade 1: Restricted in physically strenuous activity but ambulatory and able to do light work

Grade 2: Ambulatory and capable of all self-care but unable to carry out any work. Up and about more than 50% of waking hours.

Grade 3: Capable of only limited self-care, confirmed to bed or chair more than 50% of waking hours.

Grade 4: Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

7.5.5 Laboratory evaluations

All standard clinical laboratory analyses described below are to be performed by the central laboratory, according to the Visit Schedule outlined in Table 7-1. The name of the central laboratory can be found in the investigator binder supplied to the site. Details about all central laboratory procedures including collection, shipment of samples, reporting of results and alerting of extreme values are given in the Manual provided by the central laboratory. Notable values will be documented in the [Laboratory Manual].

For clinically relevant laboratory values from local labs, please record actual laboratory value and provide local lab ranges on the eCRF as appropriate. Unscheduled abnormal laboratory evaluations which are clinically relevant (e.g. require dose modification and/or interruption of study drug, indicate changes in previously abnormal values) must be recorded on the adverse event eCRF.

7.5.5.1 Hematology

Hematology tests are to be performed at each scheduled visit (± 7 days) as indicated in Table 7-1. These must include: hemoglobin, hematocrit, platelets, red blood cell count (RBC), total white blood cell count (WBC) absolute & differential including neutrophils, lymphocytes, monocytes, eosinophils, basophils). Absolute Neutrophil Count (ANC) will be calculated by the laboratory.

7.5.5.2 Coagulation

Prothrombin time will be determined at screening and repeated every 3 cycles; it will be reported as international normalized ratio (INR).

7.5.5.3 Biochemistry, lipid profile, thyroid function tests, and LDH

The following tests will be performed at each scheduled visit (± 7 days) as indicated in Table 7-1: and will include sodium, potassium, chloride, bicarbonate, creatinine, albumin, total protein, SGOT (AST), SGPT (ALT), total bilirubin, alkaline phosphatase, uric acid, BUN, calcium, magnesium, phosphate, total LDH, and fasting glucose.

A lipid profile (cholesterol, triglycerides, LDL, HDL) will be determined at screening and repeated after every 3 cycles while receiving study drug. The patient must be in a fasting state at the time of blood sampling for this evaluation.

Thyroid function tests (TSH, free T4) and Vitamin B12 will be collected at screening and repeated after every 6 cycles for patients who are receiving Sandostatin LAR® Depot, chronic Sandostatin® injection or other long acting somatostatin analog.

7.5.5.4 Cardiac enzymes

Not applicable for this study.

7.5.5.5 Urinalysis

During screening, a standard urinalysis assessment (pH, protein, glucose, blood, ketones, and leukocytes) should be performed and submitted to the central laboratory. Urine dipstick will be performed routinely at Day 1 of each cycle. This must be supplemented with central laboratory quantification of any potentially relevant abnormalities.

7.5.5.6 Pregnancy test

All females of childbearing potential should have a negative serum pregnancy within the 14 day window prior to the first the dose of RAD001 or matching placebo and/or a urine pregnancy test 48 hours prior to the administration of the first study treatment. Urine pregnancy tests may be used for monthly (if necessary) and End of Treatment Visit (required). It is recommended that postmenopausal women be amenorrheic for at least 12 months or have a serum FSH >40 mIU/ml to be considered “of non-childbearing potential” or 6 weeks post surgical bilateral oophorectomy with or without hysterectomy.

Acceptable contraception includes surgical sterilization (e.g., bilateral tubal ligation, vasectomy), hormonal contraception (implantable, patch, oral), and double-barrier methods (any double combination of: IUD, male or female condom with spermicidal gel, diaphragm, sponge, cervical cap).

Acceptable contraception must be used on-study and for 8 weeks after last dose of RAD001.

To ensure patient safety, each pregnancy in a patient on study drug must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth,

and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the local Novartis Clinical Safety & Epidemiology Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the Novartis study drug of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

7.5.5.7 HBV testing

The categories of patients listed in Section 4 should be tested for hepatitis B serologic markers and viral load: HBV-DNA HBsAg, HBc Ab, and HBs Ab.

HBV DNA monitoring should be done depending on results from serologic markers and viral load as listed in Table 6-5.

7.5.5.8 HCV testing

Patients with hepatitis C risk factors and additional patients at the discretion of the investigator should be tested for HCV RNA-PCR test at baseline. For a list of hepatitis C risk factors, refer to Section 4.

Follow-up testing will be performed, as per the visit schedule, only if the patient has a history or is positive at baseline, or both.

7.5.5.9 Biochemical tumor markers

Tumor marker evaluations will be conducted as noted in Table 7-1. Pre-study Chromogranin A (CgA), neuron specific enolase, pancreatic polypeptide, gastrin, glucagon, and VIP will be done at screening and, if elevated, repeated at every cycle. Insulin, pro insulin, and c-peptide will be assessed at baseline in patients with insulinomas and, if elevated, repeated at every cycle.

7.5.5.10 Whole blood DNA

Whole blood DNA sample will be collected to help identify whether the targets analyzed in the tumor represent an alteration from what is normally present in the patient. Whole blood DNA sample is required only for patients who have archival tumor tissue available.

7.5.6 Chest X-rays and pulmonary function tests

A Chest X-ray (and/or if disease is present in chest, then a chest CT) must be performed at screening for all patients. Repeat chest X-ray during study drug administration (after every 3 cycles) unless a CT scan of the chest is used for disease evaluation assessments.

Chest X-ray is to be repeated at the investigator's discretion if there is suspicion of non-infectious pneumonitis.

Pulmonary Function Tests (spirometry, DLCO and room air O_2 saturation at rest) will be performed as medically necessary if there is evidence of non-infectious pneumonitis.

A bronchoscopy with biopsy and/or a BAL will be performed only when medically necessary for ensuring patient care (details are provided in Tables 6-1 and 6-3). If non-infectious pneumonitis is diagnosed, consultation with a pulmonologist should be considered.

7.5.7 Cardiac assessments

7.5.7.1 Electrocardiogram (ECG)

A standard 12 lead ECG is to be performed during screening. Tracings must be dated and signed by the investigator (or his/her designee) and filed with the subject's source documentation. Significant findings must be recorded as Relevant Medical History / Current Medical Conditions (if present before treatment). ECG may be repeated at the discretion of the investigator at any time during the study and as clinically indicated, any clinically relevant findings should be added to the Adverse Event eCRF.

7.5.7.2 Cardiac enzymes

Not applicable for this study.

7.5.7.3 Cardiac imaging -- MUGA (multiple gated acquisition) scan or echocardiogram

Not applicable for this study.

7.6 Tolerability

Not applicable for this study.

7.7 Resource utilization

Not applicable for this study.

7.8 Patient-reported outcomes

Not applicable for this study.

7.9 Pharmacokinetics

Biofluid concentrations will be expressed in mass per volume units. All concentrations below the limit of quantitation or missing data will be labeled as such in the concentration data listings. Concentrations below the limit of quantitation will be treated as zero in summary statistics.

Patients will be advised to fast on the days of sampling for RAD001 over the 2 hr sampling period (note: patients are allowed to consume water during this time).

7.9.1 Pharmacokinetic blood sample collection and handling

Full pharmacokinetic profile assessments are planned to be performed in **a total of 40 patients at three pre-selected investigational sites,** on Day 1 of Cycle 2, in order to obtain approximately 20 full steady state profiles in the RAD001 arm. RAD PK profiles should be collected in patients who do not take Sandostatin LAR® Depot, chronic Sandostatin® injection, or other long acting somatostatin analogs during the study as concomitant medication.

Trough levels will be collected **for all patients in all study centers** on Cycle 1, Day 15, Cycle 2, Day 1 and Day 1 of every subsequent Cycle. Trough blood samples will be collected in both treatment arms during regularly scheduled visits by either direct venipuncture or an inserted indwelling cannula:

RAD001 samples:

RAD001 blood samples for full PK profile will be collected from 40 patients at three specific investigational sites. The sampling schedule is as follows:

- RAD001 full steady-state pharmacokinetic profile assessment on Day 1 of Cycle 2 as follows: Pre-dose, 0.5, 1, 2, 5 and 24 hours post-dose.
- RAD001 blood samples for trough levels will be collected from all the patients at all sites. The sampling schedule is as follows: As a pre-dose sample at Cycle 1 Day 15, Cycle 2 Day 1, and every Cycle Day 1 thereafter until end of blinded study-drug period.

RAD001 blood sample collection

Two mL of venous blood samples will be drawn for RAD001 blood concentration determination from a forearm vein into the tubes containing EDTA. The tube will be inverted several times to mix contents (e.g anti-coagulant) of the tube immediately after collection of the blood sample. Prolonged contact must be avoided with rubber stopper. The whole blood sample will be transferred to a labeled polypropylene screw cap tube and freeze at - 20°C or below within 60 minutes of venipuncture.

Sample collection handling:

The actual collection time of all samples must be documented on the PK Blood Collection eCRFs pages. **In addition, the date and actual time drug is taken for RAD001 and date and actual time blood sample is obtained must be entered**. Any sampling problems (i.e., patient took study drug before a trough [pre-dose]) must be noted in the comments section of the eCRF.

In order to assure compliance with sampling procedures, **on days of drug level and PK assessment, drug administration should be supervised by study center personnel.**

If the patient vomits within the first 4 hours following study-drug administration on the day of pharmacokinetic blood sampling, the time (using the 24-hour clock) of vomiting should be recorded on the Blood Collection / Vomiting Log eCRF and AE eCRFs (procedure applies only to patients providing full PK). For other patients, it should be recorded only on the AE

eCRFs. No additional study drug should be taken that day in an effort to replace the material that has been vomited.

7.9.2 Analytical method

RAD001 blood concentrations in whole blood will be determined by a LC-MS method following liquid extraction. The method has a LLOQ of 0.300ng/mL.

Placebo will not be analyzed. The bioanalyst will be provided the randomization list and will be unblinded during the study.

7.10 Biomarkers

Biomarker studies are proposed using patient plasma samples. These studies will focus on the anti-angiogenic effects of RAD001. Pancreatic NET is known to be a heavily vascularized tumor. RAD001 has been demonstrated to have anti-angiogenic effects *in vivo* and *in vitro* (Section 1.3.1). Biomarker studies are proposed to examine the effects on RAD001 on soluble markers of angiogenesis in this study. Data from these studies will be used to formulate hypotheses for future studies of RAD001 as an anti-angiogenic agent.

Patients who consent to the biomarker studies will be asked to donate 10 mL of blood for plasma at screening and at Cycle 2 Day 1, Cycle 3 Day 1 and at Cycle 4 Day 1 and end of treatment. On-treatment specimens will be compared to baseline samples for RAD001 effects on plasma angiogenic molecules, e.g., basic FGF, VEGF, PLGF, sVEGFR1,and sVEGFR2. Analysis will be performed using commercially available ELISA kits following manufacturers' specifications.

7.10.1 RAD001 pharmacodynamic biomarker assessments

See above.

7.10.2 Tumor characterizations

RAD001 effects on tumor proliferation are due to inhibition of the mTOR pathway. Certain protein and genetic alterations are known to activate this pathway, such as amplification of growth factor receptors, loss of tumor suppressor proteins, and activating mutations of kinases upstream of mTOR (see section 1.2). Patient tumor biopsy samples are requested when available. These samples will be analyzed by immunohistochemical and genetic methods for activation of the mTOR pathway and proliferative markers e.g. pAKT, pS6, PTEN expression, Ki 67, and PI3 kinase mutation. Additional markers may be added to this list if suggested by internal or external data. The purpose of these studies will be to provide information for future trials of RAD001, such as potentially testing RAD001 in a subset of patients whose tumors have an activated mTOR pathway.

7.10.3 Pharmacogenetics

Not applicable for this study.

7.10.4 Specialized (non-standard) imaging

Not applicable for this study.

8 Safety monitoring

8.1 Serious adverse event reporting

To ensure patient safety, every SAE, **regardless of suspected causality**, occurring after the patient has provided informed consent and until 4 weeks after the patient has stopped study treatment/participation must be reported to Novartis within 24 hours of learning of its occurrence. Any SAEs experienced after this 4-week period should only be reported to Novartis if the investigator suspects a causal relationship to the study drug. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form. The investigator must assess and record the relationship of each SAE to each specific study drug (if there is more than one study drug), complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours to the local Novartis Clinical Safety and Epidemiology Department.

The telephone and telefax number of the contact persons in the local department of Clinical Safety and Epidemiology, specific to the site, are listed in the investigator folder provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site.

Follow-up information is sent to the same person to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the [Investigator's Brochure] or Package Insert (new occurrence) and is thought to be related to the Novartis study drug, a Clinical Safety and Epidemiology Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported.

8.2 Pregnancies

To ensure patient safety, each pregnancy in a patient on study drug must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the local Novartis Clinical Safety and Epidemiology Department. Pregnancy

follow-up should be recorded on the same form and should include an assessment of the possible relationship to the Novartis study drug of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

8.3 Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) will be established prior to the randomization of the first patient. The IDMC is an external independent group including at least 2 oncologists and 1 statistician. The IDMC will perform an ongoing review of safety data.

The responsibilities of the IDMC include:

- minimize the exposure of patients to an unsafe therapy or dose
- make recommendations for changes in study processes where appropriate
- advise on the need for dose adjustments because of safety issues
- endorse continuation of the study

It will also be the responsibility of the IDMC to review the safety results and to make recommendations to continue, modify or stop the study based on these results.

Details on the membership, responsibilities and working procedures of the IDMC are described in the Independent Data Monitoring Committee charter.

8.4 Steering Committee

The general role of the steering committee is to provide guidance on study conduct and to help ensure delivery of study data. The steering committee will support the Novartis clinical team on a continuous basis when questions arise in the trial. The steering committee will monitor and supervise the progress of the trial towards its objectives. The committee will be appointed by Novartis and comprised of investigators, Novartis staff and may include clinical experts not directly involved in the clinical trial. The committee will be chaired by an external (non-Novartis) expert.

The steering committee chair will play a specific role in controlling the flow of the trial information, in being the primary contact to receive the recommendations from the IDMC at any safety data review, and in further communicating this information as appropriate, as described in the IDMC charter.

9 Data review and data management

9.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and eCRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the eCRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study drug is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on eCRFs must be traceable to these source documents in the patient's file. The investigator must also keep the original informed consent form signed by patient (a copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the eCRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety variables. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients will be disclosed.

9.2 Data collection

Novartis will supply the investigator site with a computer loaded with Electronic Data Capture (EDC) software that has been fully validated and conforms to 21 CFR Part 11 requirements. Novartis personnel will train designated investigator site staff on the EDC system. Investigator site staff will not be given access to the EDC system until they have been trained. Designated investigator staff will enter the data required by the protocol into the Novartis eCRFs using the Novartis-supplied computer. Automatic validation programs check for data discrepancies in the eCRFs and, by generating appropriate error messages, allow modification or verification of the entered data by the investigator staff before transfer to Novartis via a secure Virtual Private Network. The investigator must certify that the data are complete and accurate by signing a memo that will be sent to him by Novartis personnel after the last transfer of the data prior to analysis. After database lock, the investigator will receive a CD-ROM or paper copies of the patient data for archiving at the investigational site.

Blood samples for laboratory data and biomarkers will be collected by sites and sent to a Central laboratory for processing. The Laboratory results will be sent electronically to Novartis (or a designated CRO).

Local films or digital radiological data will be forwarded by the site for Central Review. The name of the Central Review facility can be found in the investigator binder supplied to the

site. Details about all radiologic Central Review procedures including collection, shipment and reporting of results are given in the Manual provided by the Central Review facility.

9.3 Database management and quality control

Novartis staff review the eCRFs entered by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Obvious errors are corrected by Novartis personnel. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff are required to respond to the query and make any necessary changes to the data. If the electronic query system is not used, a paper Data Query Form will be faxed to the site. Site personnel will complete and sign the faxed copy and fax it back to Novartis staff who will make the correction to the database. The signed copy of the Data Query Form is kept at the investigator site.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Laboratory samples will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

Randomization codes and data about all study drug dispensed to the patient will be tracked using IVRS. The system will be supplied by a vendor, who will also manage the database. The database will be sent electronically to Novartis.

PK blood samples collected by sites will be shipped to Novartis for processing. The PK blood collection times will be entered by sites in the eCRFs. The PK blood sample results will be merged with the eCRF PK blood collection times and analyzed by Novartis and in accordance with internal Novartis procedures.

Blood samples for biochemical tumor markers and biomarkers will be collected and sent to a central laboratory for processing. The results will be sent electronically to Novartis.

At the conclusion of the study, the occurrence of any emergency code breaks will be determined after return of all code break reports and unused drug supplies to Novartis. The occurrence of any protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded and made available for data analysis. Any changes to the database after that time can only be made by joint written agreement between the Global Head of Biostatistics and Statistical Reporting and the Global Therapeutic Area Head.

10 Statistical methods and data analysis

The data will be analyzed by Novartis. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

It is planned that the data from all centers that participate in this protocol will be used, so that an adequate number of patients will be available for analysis.

Final primary analysis will be performed at the time when approximately 282 PFS events are observed. The final update on safety and survival will be based on the additional data collected in the extension phase of the study.

10.1 Populations for analysis

The **intent-to-treat (ITT) population** will consist of all randomized patients. The patients in the ITT population will be analyzed in the treatment group and stratum assigned by randomization. Patients who were screened but not randomized will be listed, but not included in the ITT population.

The ITT population will be the primary population for efficacy analyses.

The **safety population** will consist of all patients that received any study drug and had at least one post-baseline safety assessment. Patients will be analyzed according to treatment received. Please note: the statement that a patient had no adverse events (on the Adverse Event eCRF) constitutes a safety assessment.

The safety population will be used for all safety analyses.

The **per protocol population** will consist of all patients from the ITT population who are evaluable for efficacy without any major protocol deviation, and who either completed a minimum exposure requirement or who progressed before this minimum exposure requirement could be met.

Patients will be evaluable for efficacy if they have a best overall response assessment different from 'Unknown' according to the RECIST criteria. The minimum exposure requirement is defined as having received a minimum dose intensity corresponding to 50% of the planned doses of study drug over the first 12 weeks (i.e. a relative dose intensity of 50%).

The pharmacokinetic analyses will be performed in safety population using all available PK samples.

10.2 Patient demographics/other baseline characteristics

Demographic and other baseline characteristics including age, gender, height, weight, body surface area, tumor type, medical conditions, etc. will be listed individually by patient, and summarized using descriptive statistics as mean, standard deviation, median, 25^{th} and 75^{th} percentiles, minimum, and maximum for continuous data or contingency tables presenting frequencies and percentages for categorical data. The ITT population will be used.

10.3 Treatments (study drug, concomitant therapies, compliance)

Duration of study drug exposure, cumulative dose, and dose intensity will be summarized by treatment group. The actual daily doses and reasons for dose change will be listed.

Concomitant medications and significant non-drug therapies prior and after the start of the study drug will be listed by patient and summarized by ATC term and treatment group using contingency tables.

10.4 Primary objective

The primary objective is to determine whether treatment with RAD001 10 mg/d plus best supportive care prolongs progression free survival (based on the local investigator assessments) compared to treatment with best supportive care alone in patients with advanced Pancreatic Neuroendocrine Tumor.

10.4.1 Variable

The primary endpoint of this study, progression-free survival (PFS), is defined as the time from the date of randomization to the date of the first documented disease progression or death due to any cause. If a patient has not progressed or died at the date of the analysis cut-off or when he/she receives any further anti-cancer therapy, PFS is censored at the time of the last tumor assessment before the cut-off date or the other anti-cancer therapy date. For the primary analysis, progression-free survival will be based on the data using local investigator assessments according to the RECIST criteria.

Definitions and further details can be found in Post-text Supplement 1.

10.4.2 Statistical hypothesis, model, and method of analysis

In the primary analysis, a stratified log rank test will be used to test the difference in PFS between the two treatment arms. There are two stratification factors: 1. prior cytotoxic chemotherapy (yes/no); 2. WHO performance status at baseline (0 vs. 1-2).

Kaplan-Meier estimates of the progression free survival (PFS) as well as the median PFS and the according 95% confidence intervals will be displayed per treatment group.

The primary analysis will be performed in the ITT population.

10.4.3 Handling of missing values/censoring/discontinuations

By default, if disease progression or death is documented after one single missing tumor assessment the actual event date of disease progression/death will be used for the PFS event date. If disease progression is documented after two or more missing tumor assessments the PFS time of these patients will be censored at the date of the last tumor assessment with overall lesion response of CR, PR or SD.

Additionally sensitivity analyses will be performed, where:

1. the actual event date of disease progression/death will be used for the PFS event date, irrespective of whether it is preceded by missing tumor assessments
2. in case of a documented progression/death after one or more missing tumor assessments, disease progression is considered to have occurred at the next scheduled tumor assessment after the date of the last tumor assessment with overall lesion response of CR, PR or SD

Other missing data will simply be noted as missing on appropriate tables/listings.

10.4.4 Supportive analyses

The treatment effect estimate, i.e. hazard ratio with 95% confidence interval, for the primary analysis based on local investigator assessments will be obtained from unadjusted proportional hazard Cox model.

Supportive analyses, stratified by whether or not patients have received prior cytotoxic chemotherapy, and by WHO performance status (0 vs. 1-2) at baseline and adjusting the treatment difference for key potential prognostic factors will be performed using a Cox proportional hazard model.

In addition, an analysis of central IRC PFS data will be applied adjusting for informative censoring.

For sensitivity reasons, the primary analysis and the Cox model will be repeated:

- using the local investigator assessment on the per protocol population using the same conventions as primary analysis
- using the **independent central adjudicated** assessments on the ITT population and using the same conventions as for the primary analysis
- For completeness, PFS analysis based on the data from central radiology review will be provided based on the ITT population and using the same conventions as the primary analysis.

10.5 Secondary objectives

Additional analyses on other tumor endpoints, overall survival and other tumor markers will be conducted as appropriate toward the achievement of secondary objectives.

10.5.1 Efficacy (secondary)

Secondary efficacy variables include overall response rate (CR or PR), the duration of overall response (CR or PR), overall survival and other efficacy markers.

The analyses of all secondary efficacy endpoints will be performed in the ITT population.

Best overall response

The best overall tumor response will be assessed by RECIST criteria. Definitions and details on RECIST can be found in Post-text supplement 1. Since the first tumor assessment is performed 12 weeks after randomization, the standard definition of a best overall response evaluation of 'progressive disease' or 'unknown' given in Post-text supplement 1 requires an adjustment. In this protocol, the following definitions will be used:

- any progression ≤ 18 weeks after randomization (and not qualifying for CR, PR or SD) will lead to a best overall response evaluation of 'progressive disease'
- UNK = all other cases (i.e. not qualifying for confirmed CR or PR and without SD after more than 6 weeks or early progression within the first 18 weeks)

The overall response rate is defined as the proportion of patients with complete response (CR) or partial response (PR) and will be summarized in terms of percentage rates with 95% confidence intervals for each treatment group.

The primary comparison of the overall response rate between the treatment arms will be performed in the ITT population and based on the local investigator data. Supportive analyses will be performed using data from adjudicated central radiology review.

Response duration

The duration of overall response (CR or PR) will be analyzed in patients with best overall response CR or PR. The duration is defined by its start and end date. The start date is the date of first documented response (CR or PR) and the end date is defined as the first documented progression or death due to underlying cancer. If a patient has not had an event, duration of response is censored at the date of last adequate tumor assessment.

Overall survival (OS)

Overall survival is defined as the time from date of randomization to date of death due to any cause. If the patient is not known to have died, survival will be censored at the date of the last contact.

The Kaplan-Meier product-limit method will be used to describe the overall survival in each treatment group (median, 95% confidence intervals, and plots).

In addition, an exploratory analysis will be performed using rank-preserving structural failure time method to correct for confounding introduced by cross-over.

Other efficacy markers

The analysis of other efficacy markers is described in Section 10.5.7.

10.5.2 Safety

The assessment of safety will be based mainly on the frequency of adverse events and on the number of laboratory values that fall outside of pre-determined ranges. Other safety data (e.g., electrocardiogram, vital signs, pulmonary function test) will be considered as appropriate. All safety data will be listed.

For all safety analyses, the safety population will be used.

10.5.2.1 Adverse events (AE)

All adverse events recorded during the study will be summarized. The incidence of adverse events will be summarized by body system, severity (based on CTCAE grades), type of adverse event, and relation to the study drug. Deaths reportable as SAEs and non-fatal serious adverse events will be listed by patient and type of adverse event.

Adverse events will be summarized by presenting the number and percentage of patients having any adverse event in each body system and having each individual adverse event. Any other information collected (e.g. severity or relatedness to study medication) will be listed as appropriate.

In addition, adverse events of related nature may be analyzed by categories regrouping the relevant preferred terms, as appropriate.

10.5.2.2 Laboratory abnormalities

All laboratory values will be converted into SI units and the severity grade calculated using appropriate common toxicity criteria for adverse events (CTCAE, version 3.0) unless otherwise indicated.

A listing of laboratory values will be provided by laboratory parameter and by patient. The frequency of notable lab abnormalities will be displayed by parameter.

Similarly, the frequency of all laboratory abnormalities will be displayed by parameter and worst CTCAE grade experienced.

10.5.2.3 Other safety data

Data from other tests (e.g., electrocardiogram or vital signs) will be listed, notable values flagged, and any other information collected will be listed as appropriate. Any statistical tests performed to explore the data will be used only to highlight any interesting comparisons that may warrant further consideration.

10.5.3 Tolerability

Not applicable for this study.

10.5.4 Resource utilization

Not applicable for this study.

10.5.5 Patient-reported outcomes

Not applicable for this study.

10.5.6 Pharmacokinetics

The primary pharmacokinetic analyses will include all patients from the safety population and all available blood samples (trough levels, PK profiles).

A sensitivity analysis will be performed where the PK data collected from patients during and after a period of receiving drugs or substances known to be inhibitors, inducers, or substrates of the isoenzyme CYP3A4 (see Table 6-7) and P-glycoprotein (see Table 6-8) will be excluded from the analysis. PK data collected prior to the use of prohibited medications will be included in the analysis. The results between the primary and the sensitivity analysis will be compared to assess an impact of concomitant drugs on the PK assessments. Trough concentrations of RAD001 will be graphed versus time (days). Pharmacokinetics parameters will be calculated for the steady-state profiles and the individual and summary profiles will be graphed versus time (hours).

RAD001 blood concentrations in whole blood will be determined by a LC-MS method following liquid extraction. Values below the lower limit of quantification (LLOQ) of 0.368ng/mL will be reported as 0.00 ng/mL. Missing values will be labeled accordingly.

As part of the pharmacokinetic analyses, the impact of RAD001 blood trough levels on efficacy and safety endpoints may be explored using conventional repeated measurement analysis methods.

Furthermore, the RAD001 trough levels and pharmacokinetic parameters obtained from steady-state full profiles will be summarized by means of descriptive statistics at each visit and used in future analysis along with RAD001 trough levels from other studies.

This analysis will be performed in a separate report.

10.5.7 Biomarkers

10.5.7.1 RAD001 pharmacodynamic biomarker analyses

The effect of RAD001 on biochemical tumor markers and on angiogenesis markers (e.g., VEGF basic FGF, PLGF, sVEGFR1 and sVEGFR2) will be analyzed using summary statistics for raw data and changes from baseline and also using longitudinal models.

Relationship between RAD001 steady state levels, tumor response, and chromogranin A response (50% decrease from baseline) will be assessed.

10.5.7.2 Tumor characterizations

Pre-treatment tumor samples will be characterized by immunohistochemical and genetic analyses indicating activation of the mTOR pathway and data will be summarized. If sufficient data is collected relationship with tumor response will be investigated.

10.5.7.3 Exploratory biomarker analysis

Exploratory biomarker analyses may be performed to further address scientific questions as new information with regard to the disease or the study drug becomes available. These exploratory analyses will be limited in scope to RAD001 or cancer, and will only be performed on samples for which specific consent for long term storage and use has been obtained.

10.5.8 Progression free survival (PFS)

No interim analysis will be performed for the primary efficacy endpoint PFS.

10.5.9 Overall survival (OS)

This study will use a two stage group design for OS (1st OS look at the time of final PFS analysis and the final 2nd look at a later point). Group sequential plan for the overall survival will use alpha spending function. The testing strategy for OS will be detailed in the analysis plan.

10.6 Sample size calculation

Using a unstratified log-rank test at the one-sided 2.5% significance level, a total of 282 PFS events would allow 92.6% power to demonstrate a 33% risk reduction (hazard ratio for RAD/placebo of about 0.67, as calculated from an anticipated 50% increase in median PFS, from 6 to 9 months in the RAD001 arm compared to the placebo arm).

With a uniform accrual of approximately 23 patients per month over 74 weeks and a minimum follow up of 39 weeks, a total of 352 patients would be required to obtain 282 PFS events, assuming an exponential progression-free survival distribution with a median of 6 months in the Placebo arm and of 9 months in RAD001 arm. With an estimated 10% lost to follow up patients, a total sample size of 392 patients should be randomized.

11 Administrative procedures

Regulatory and ethical compliance

This clinical study was designed and shall be implemented and reported in accordance with the protocol, the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

Responsibilities of the investigator and IRB/IEC/REB

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) before study start. A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC/REB must be given to Novartis before study initiation. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with

these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs and regulatory authorities as required.

Informed consent

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC/REB-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. Informed consent must be obtained before conducting any study-specific procedures (i.e., all of the procedures described in the protocol). In cases where the subject's legally acceptable representative gives consent, the subject (e.g., minors, patients with severe dementia), should be informed about the trial to the extent compatible with the subject's understanding and if capable, the subject should assent, sign and personally date the written informed consent. The process of obtaining informed consent should be documented in the patient source documents. In emergency situations when prior consent of the subject is not possible and the subject's legally acceptable representative is not available, enrollment of the subject should require measures described in the protocol with documented favorable opinion of the IRB/IEC/REB. The subject or the subject's legally appointed representative should be informed about the trial as soon as possible and consent to continue and other consent as appropriate should be requested.

A proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study is provided to each site. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC/REB, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC/REB approval.

Amendments to the protocol

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC/REB. Only amendments that are required for patient safety may be implemented prior to IRB/IEC/REB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC/REB at the study site should be informed within 10 working days.

Discontinuation of the study

Novartis reserves the right to discontinue this study under the conditions specified in the clinical trial agreement.

Study drug supply and resupply, storage, and tracking/drug accountability

Study drugs must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated assistants have access. Upon receipt, the RAD001 should be stored according to the instructions specified on the drug labels. Clinical supplies are to be dispensed only in accordance with the protocol.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the drug and the medication number but no information about the patient.

The investigator must maintain an accurate record of the shipment and dispensing of study drug in a drug accountability ledger. Drug accountability will be noted by the field monitor during site visits and at the completion of the trial. Patients will be asked to return all unused study drug and packaging at the end of the study or at the time of study drug discontinuation.

At the conclusion of the study, and, as appropriate during the course of the study, the investigator will return all used and unused study drug, packaging, drug labels, and a copy of the completed drug accountability ledger to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

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NOVARTIS

Clinical Development

RAD001/Everolimus

RAD001C2324

A randomized double-blind phase III study of RAD001 10 mg/d plus best supportive care versus placebo plus best supportive care in the treatment of patients with advanced pancreatic neuroendocrine tumor (NET)

RAP Module 3 – Detailed Statistical Methodology

Author:	Lincy J., Trial Statistician ; Sachs C., Clinical Trial Head

Document type:	RAP Documentation
Document status:	Final 2.0
Release date:	May 18, 2010

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AE	Adverse Event
ATC	Anatomic Therapeutic Chemical (Classification)
BOR	Best Overall Response
CMH	Cochran-Mantel-Haenszel
CI	Confidence Interval
CR	Complete Response
CTC	Common Terminology Criteria
DAR	Dosage Administration Record
DCR	Disease Control Rate
DI	Dose Intensity
IAC	Independent Adjudication Committee
IDMC	Independent Data Monitoring Committee
eCRF	Electronic Case Report/Record Form
FAS	Full Analysis Set
HR	Hazard Ratio
IR	Incomplete Response
ITT	Intent-To-Treat
IVR	Interactive Voice Response
KM	Kaplan-Meier
LLOQ	Lower Limit of Quantification
M&S	Modeling & Simulation
NET	Neuroendocrine Tumors
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease
PDI	Planned Dose Intensity
PFS	Progression Free Survival
PNET	Pancreatic Neuroendocrine Tumors
PP	Per-protocol
PR	Partial Response
PS	Performance Status
RAP	Report Analysis Plan
RDI	Relative Dose Intensity
RR	Response Rate
SAE	Serious Adverse Event
SD	Stable Disease
SYE	Subject Years Exposure
TA	Tumor Assessment
VAP	Validation and Planning

1 Introduction

This Reporting and Analysis Plan (RAP) Module 3 incorporates the latest project standards. It documents in details the statistical methods and analysis conventions to be used in the report of study CRAD001C2324.

RAD001C2324 is a prospective, double-blind, randomized, parallel group, placebo-controlled, multicenter phase III study of treatment with Everolimus 10 mg p.o. qd plus best supportive care versus placebo plus best supportive care in patients with advanced pancreatic NET.

Patients are permitted to remain on long-acting somatostatin analog during the study, as concomitant medication.

Patients who meet the study eligibility criteria will be randomized to receive Everolimus 10 mg or matching placebo. The randomization ratio is 1:1, with one patient being randomly assigned to Everolimus 10 mg for every one patient randomly assigned to matching placebo. Randomization and efficacy analyses will be stratified by whether or not they have received prior cytotoxic chemotherapy and by WHO performance status (0 vs. 1-2) at baseline.

The primary objective of this study is to determine whether treatment with Everolimus 10 mg/d plus best supportive care prolongs the progression-free survival (PFS) compared to treatment with Placebo plus best supportive care in patients with advanced pancreatic neuroendocrine tumor.

The data will be analyzed by Novartis. It is planned that the data from all centers that participate in this protocol will be used, so that an adequate number of patients will be available for analysis.

1.1 Summary of changes from the study protocol

The following items represent a brief summary of the key changes in the statistical analysis plan compared to the [Study Protocol Amendment 01]:

- Change in the name of the ITT population (see Section 2.1.9)
- Change in the Per-protocol Population definition (see Section 2.1.9)

The following analyses are not described in the study protocol:

- Rank-preserving structural failure time method (RPSFT) (see Section 2.6.5.1.1)
- Marginal Structural Cox Proportional Hazards Model using the Inverse Probability of Censoring Weighting (see Section 2.6.5.1.2)
- Time-to event methodology adjusting for dependent (informative) censoring (see Section 2.6.5.2)

Further details are given in the sections below.

2 Definitions, general considerations and statistical methodology

2.1 Definitions

2.1.1 Study drug

As described in the study protocol, ***study drug*** refers to Everolimus 10 mg or matching placebo.

2.1.2 Date of first administration of study drug

The date of first administration of study drug is derived as the first date when a nonzero dose of study drug was administered and recorded on DAR eCRF. For the sake of simplicity, the date of first administration of study drug will also be referred as **start of study drug**.

For the analyses referring to the open-label period the date of the first administration of open-label Everolimus will be considered as the start of that period.

2.1.3 Date of last administration of study drug

The date of last administration of study drug is defined as the last date before or on the data cut-off date when a nonzero dose of study drug was administered and recorded on DAR eCRF page.

For the analyses referring to the open-label period the date of the last administration of open-label Everolimus will be considered.

2.1.4 Study day

Double-blind period

The study day ***for safety assessments*** (e.g. adverse event onset, laboratory abnormality occurrence, vital sign measurement, dose interruption etc.) will be calculated using the start date of double-blind study drug as the origin, i.e. the study day will be calculated as (date of safety assessment) – (start date of study drug) + 1. Then study day 1 will be the first day of study drug. (For example, if an adverse event starts 3 days before the start of study drug the study day displayed on the listing will be negative).

The study day ***for all other, i.e. non-safety assessments*** (tumor assessment, death, disease progression (PD), tumor response, performance status) will be calculated using the randomization date as the origin, i.e. the study day will be calculated as (date of non-safety assessment) – (date of randomization) + 1. Then study day 1 will be the day of randomization.

Unless specified otherwise, the study day will be displayed in the data listings.

Open-label period

The study day ***for safety assessments*** in the open-label period will be calculated, in a similar way as in the double-blind period using the start date of open-label Everolimus treatment as the origin, i.e. the study day will be calculated as (date of safety assessment) – (start date of

open-label Everolimus treatment) + 1. Then study day 1 will be the first day of open-label treatment.

2.1.5 Baseline

For ***efficacy evaluations***, the last available assessment before or at date of randomization is taken as 'baseline' value or 'baseline' assessment. In the context of baseline definition, the efficacy evaluations include also WHO performance status and measures included in the stratification.

For ***safety evaluations*** (i.e. laboratory assessments and vital signs), the last available assessment before or at date of start of double-blind study drug is taken as 'baseline' assessment for the double-blind study period

If patients have no value as defined above, the baseline result will be missing.

Open-label baseline will be defined when appropriate as the last available assessment before or at the date of first non-zero dose of open-label Everolimus.

2.1.6 On-treatment assessment/event

Safety summaries and selected summaries of deaths will summarize only on-treatment assessments/events. On-treatment assessment/event is defined as any assessment/event obtained in the time interval (including the lower and upper limits):

<date of first administration of study drug; date of last administration of study drug +28 days or start of open-label>.

2.1.7 Last contact date

The last contact date will be derived for patients not known to have died at the analysis cut-off date using the latest complete date among the following data:

- All assessment dates (e.g. vital signs assessment, performance status assessment, and also assessment date in third-party data such as tumor imaging, central laboratory, etc.), excluding PK collection dates from the BCL eCRF page.
- Medication dates including study medication, concomitant medications, antineoplastic therapies administered after study treatment discontinuation.
- Adverse events dates
- Last contact date collected on the 'Survival information' eCRF
- Randomization date

The last contact date will be used for censoring of patients in the analysis of overall survival. This date is to be derived considering patient's assessments/events from the date of randomization on, irrespective of the fact that an assessment/event has occurred during the double-blind period or during the open-label period.

2.1.8 Time windows

In order to summarize the WHO performance status, PK, biomarker and tumor assessments data over time, assessments will be time-slotted using the following time windows.

Table 2-1, 2-2 and 2-3 show how to define the time windows for WHO performance status, biomarker, Everolimus through levels and tumor assessments.

Table 2-1 Time windows for WHO PS and Biomarker

Time Window	Planned Visit Timing	Time Window Definition
Baseline	On or before Study Day -2	≤ Study Day 1
Cycle 2 Day 1	Study Day 29	[2; 42]
Cycle 3 Day 1	Study Day 57	[43; 70]
Cycle k Day 1	Study Day ((k-1)*28)+1	[(k-1)*28-13; (k-1)*28+14] for k>2
Study Day 1 = Randomization date		

Table 2-2 Time windows for Everolimus trough levels

Time Window	Planned Visit Timing	Time Window Definition
Cycle 1 Day 15	Study Day 15	[10; 22]
Cycle 2 Day 1	Study Day 29	[23; 42]
Cycle 3 Day 1	Study Day 57	[43; 70]
Cycle k Day 1	Study Day ((k-1)*28)+1	[(k-1)*28-13; (k-1)*28+14] for k>2
Study Day 1 = Randomization date		

Table 2-3 Time windows for tumor assessments

	Planned Visit Timing	Time Window Definition
Cycle 4 Day 1	Study Day 85(Week 12)	]0; 126] days[or0; 18 (weeks)
Cycle 7 Day 1	Study Day 169(Week 24)	]126; 210] days[or[18; 30 (weeks)
Cycle 10 Day 1	Study Day 253(Week 36)	]210; 294] daysor[30; 42](weeks
Cycle k Day 1	Study Day x(Week y)	]x-42; x+42]daysor]y-6; y+6](weeks
	x= (k-1)*28+1 ; y=(k-1)*4	x= (k-1)*28; y=(k-1)*4
Study Day 1 = Randomization date		

2.1.9 Definitions of analysis populations

This section defines standard analysis sets and their use in the statistical analyses.

Full Analysis Set (FAS)

Full Analysis Set (FAS) is defined according to the Intention to Treat (ITT) principle.

The FAS consists of all randomized patients. Following the intent-to-treat principle patients are analyzed according to the drug and stratum they were assigned to at randomization.

The name of FAS replaces the formerly used term “ITT population” used in the protocols finalized before the standard oncology definition of analysis populations was issued (and this applies to the RAD001C2324 protocol), however the definition of the two populations is identical.

Safety set

The safety set includes all patients who received at least one dose of the double-blind study medication with a valid post-baseline assessment. Patients will be analyzed according to the treatment they actually received. If patient took at least one dose of the treatment to which he/she was randomized then the treatment actually received is the randomized treatment.

The statement that a patient has no AE constitutes a valid safety assessment. Occurrence of a death constitutes a valid safety assessment as well. Patients with no post-baseline safety assessment will be listed.

Open-label set

The open-label set will be used to summarize the safety analyses performed on data collected in the open-label phase of the study: the open-label set will include only patients who received at least one dose of open-label Everolimus 10 mg (at least one nonzero dose recorded on the open-label Everolimus 10 mg dose administration eCRF) and had at least one safety assessment during the open-label phase of the study.

Per-protocol (PP) Set

The names 'Per-protocol set' and 'Per-protocol population' will be used interchangeably.

The Per-protocol Set will consist of all patients from the FAS without any major protocol deviation (see Section 2.3), who are evaluable for efficacy and who have completed a minimum exposure requirement. However, if a patient progressed as per investigator radiology data, discontinued for adverse event or died before the minimum exposure requirement could be met, or before he/she could become evaluable for efficacy, that patient will still be included in the Per-protocol Set.

Patients will be evaluable for efficacy if they have a best overall response assessment from investigator data different from 'Unknown' according to RECIST.

The minimum exposure requirement is defined as having received a minimum dose intensity corresponding to 50% of the planned doses of double-blind study medication over the first 12 weeks (i.e. a relative dose intensity of 50%). For the calculation of this minimum exposure, the dose intensity (DI) for patients with non-zero duration of exposure will therefore be defined as : DI (dosing unit / unit of time) = Cumulative dose (dosing unit) $_{\text{over the first 12 weeks}}$ / 12 weeks (or 84 days).

This definition of Per-protocol Set represents a change from the Per-protocol definition given in the C2324 protocol. The new definition is part of new standard definitions (introduced after finalization of the C2324 protocol) to be used across all trials in Novartis Oncology.

The Per-protocol Set will be used for final sensitivity analyses of primary efficacy.

Pharmacokinetic set

The pharmacokinetic analyses will be performed in the safety set using all available PK samples.

Further details are given in Section 3.13.

2.2 General considerations

2.2.1 Data included in the analysis

The core phase is from the start of the trial up to the time of the final primary analysis (cut-off date of February 28th 2010 when approximately 282 local events is expected to be observed). After this final primary analysis, and as appropriate, a decision will be made to roll-over patients into the extension phase of the study.

Only data with an assessment date or event start date (e.g. vital sign assessment date or start date of an adverse event) prior to or on the cut-off date will be included in the final primary analysis. (Example: If cut-off date is 28FEB2010 then an AE starting on 13FEB2010 will be reported, whereas an AE with start date on 01MAR2010 will not be reported in the core phase. The latter AE will be reported in the extension).

All events with a start date before or on the cut-off date and with an end date after the cut-off date will be reported as 'continuing at the cut-off date'. The same rule will be applied to events starting before or on the cut-off date and not having documented end date. This approach applies, in particular, to adverse event and concomitant medication reports. For these events, the cut-off date will not be imputed and therefore will not appear in the listings.

If it is required to impute an end date to be able to perform a specific analysis (e.g. for a dose administration record with missing end date or end date after the cut-off date, the cut-off date needs to be imputed as an end date to allow for calculation of drug exposure duration and dose intensity), the imputed date will be displayed and flagged in the listings.

Blinded and open-label treatment phase

The primary statistical analyses will be performed using the data of the blinded treatment period of the core phase. Data collected in patients who have been unblinded and switched to the Everolimus 10 mg open-label treatment will be reported separately for the open-label treatment period. This open-label phase analysis will focus on safety.

2.2.2 Subject Classification

Patients are excluded from the analysis populations defined above based on the protocol deviations entered in the database and/or on specific subject classification rules defined in Table 2-4 below. All protocol deviations will be finalized before database lock. Protocol deviations and reasons for exclusion from populations will be tabulated by treatment arm for the double-blind period only.

Table 2-4 Subject classification rules

Analysis Population	Protocol deviation severity codes leading to exclusion	Additional subject classification rules leading to exclusion
Full Analysis Set		Not randomized
Safety Set		(i) Not randomized OR (ii) No post-baseline safety assessment during the double-blind period OR (iii) No nonzero dose of the double-blind study medication recorded on the DAR eCRF
Open-label Set		(i) No safety assessment during the open-label phase OR (ii) No nonzero dose of the open-label study medication recorded on the DAR eCRF
Per-protocol Set	1	(i) Not evaluable for efficacy, defined as having a best overall response assessment (per investigator) 'Unknown' according to RECIST OR (ii) insufficient drug exposure (except if a patient progressed as per investigator, discontinued for adverse event or died before the minimum exposure requirement could be met, or before he could become evaluable for efficacy).
Severity code: 1=exclude from Per-protocol analysis		

2.3 Major protocol deviations

The following protocol deviations are considered major and will lead to exclusion of patients from the PP Set:

- Incomplete documentation of an advanced (unresectable or metastatic) biopsy-proven pancreatic NET
- No radiological documentation of progression of disease within 12 months of randomization
- No measurable lesion at baseline (per RECIST)
- WHO performance status > 2
- Low-grade or intermediate-grade neuroendocrine carcinoma not confirmed
- Prior therapy with mTOR inhibitors (sirolimus, temsirolimus, Everolimus)
- Patient with chronic treatment of corticosteroids or another immunosuppressive agent.

Other protocol deviations will also be identified, summarized and listed (see Section 3.5). However, patients will not be excluded from the Per-protocol set based on these other deviations.

2.4 Concomitant medications with specific impact on the analysis

2.4.1 Inducers and inhibitors of CYP3A4 and PgP

As per study protocol:

- Co-administration with ***strong inhibitors of CYP3A4*** (e.g., ketoconazole, itraconazole, ritonavir) ***or P-glycoprotein (PgP)*** should be avoided.
- Co-administration with ***moderate CYP3A4 inhibitors*** (e.g., erythromycin, fluconazole) ***or PgP inhibitors*** should be used with caution. If a patient requires co-administration of moderate CYP3A4 inhibitors or PgP inhibitors, reduce the dose of Everolimus to half the currently used dose. Additional dose reductions to every other day may be required to manage toxicities. If the inhibitor is discontinued the Everolimus dose should be returned to the dose used prior to initiation of the moderate CYP3A4/PgP inhibitor.
- Seville orange, star fruit, grapefruit and their juices affect P450 and PgP activity. Concomitant use should be avoided.
- Avoid the use of ***strong CYP3A4 inducers***. If patient requires co-administration of strong CYP3A4 inducers (i.e., phenytoin, carbamazepine, rifampin, rifabutin, phenobarbital, St. John's wort), an increase in the dose of Everolimus up to twice the currently used daily dose should be considered, using 2.5mg - 5mg increments. Enzyme induction usually occurs within 7-10 days, therefore Everolimus dose should be increased by one increment 7 days after the start of the inducer therapy. If no safety concerns are seen within the next 7 days, the dose can be increased again one additional increment up to a maximum of twice the daily dose used prior to initiation of the strong CYP3A4 inducer.

This dose adjustment of Everolimus is intended to achieve similar AUC to the range observed without inducers. However, there are no clinical data with this dose adjustment in patients receiving strong CYP3A4 inducers. If the strong inducer is discontinued the Everolimus dose should be returned to the dose used prior to initiation of the strong CYP3A4/PgP inducer.

The following will be tabulated and summarized:

- Substrates, inducers, and inhibitors of isoenzyme CYP3A
- List of clinically relevant drug interactions mediated by PgP substrates
- List of clinically relevant drug interactions mediated by PgP inhibitors
- List of clinically relevant drug interactions mediated by PgP inducers

Despite the fact that some of these drugs should be avoided completely and some used with caution, there will be patients who took these drugs during the study and therefore these concomitant medications will be identified and classified by a Clinical Pharmacologist and then tabulated and/or listed in the Clinical Study Report. Further details on how the PK analyses account for administration these drugs is provided in Section 3.13.5.

2.4.2 Further anti-neoplastic therapy

As per the study protocol, the administration of anti-neoplastic drugs (apart from study drug) and other investigational drugs is not allowed during study treatment and within 4 weeks prior to treatment start. In addition, their efficacy data (other than overall survival) will be censored so that tumor assessments made after the intake of anti-neoplastic and/or investigational drugs

are not included in analyses. In efficacy analyses, administration of open-label Everolimus will be considered further anti-neoplastic therapy and will lead to censoring of efficacy data (other than overall survival). [See RAP module 3 - Post-text supplement 1] for details on the censoring rules.

Clinical review of individual study data will be performed in order to identify those anti-neoplastic medications which are considered disallowed.

2.5 Implementation of RECIST

Response and progression evaluation will be performed according to the RECIST guideline version 2 (as described in detail in the [RAP module 3 - Post-text supplement 1]).

The sections below provide more detailed instructions and rules to provide further details needed for programming.

2.5.1 Disease progression

Progressive disease (PD) will only be assigned if it is documented as per RECIST by an objective assessment method (e.g. radiological scan).

If a new lesion is detected using an objective assessment method other than radiological scan then it should also be entered on the 'New lesion' RECIST eCRF with appropriate method (or method='Other') and the objective documentation should be sent to the central radiology review committee.

In particular, a discontinuation due to disease progression or death due to progressive disease, without supporting objective evidence (as defined above), will not be considered as progressive disease (in the best overall response determination and in the analysis of progression-free survival).

2.5.2 Best overall response

The best overall response (BOR) will be derived using RECIST criteria based on the overall lesion responses. The definitions and the details on the derivation are given in [RAP Module 3 Post-text supplement 1].

Only tumor assessments performed before the start of any further anti-neoplastic therapies (i.e. any additional secondary anti-neoplastic therapy or surgery or initiation of open-label Everolimus) will be considered in the assessment of best overall response. Further anti-neoplastic therapies will be identified via protocol deviations (see Section 2.4.2), from the data collected on 'Antineoplastic therapies since discontinuation of study drug' eCRF and from the data collected on the open-label Everolimus dose administration eCRF.

Since in this study the tumor assessments are performed every 12 weeks after randomization, the standard definition of a BOR evaluation of 'progressive disease' or 'unknown' given in the [RAP module 3 - Post-text supplement 1] requires an adjustment. The following definitions will be used:

- The determination of complete response (CR), partial response (PR) and stable disease (SD) remains the same as stated in the [RAP module 3 - Post-text supplement 1]

- any progression ≤ 18 weeks after randomization (and not qualifying for CR, PR or SD) will lead to a best overall response evaluation of 'progressive disease'
- UNK = all other cases (i.e. not qualifying for confirmed CR or PR and without SD after more than 6 weeks or early progression within the first 18 weeks).

Patients with best overall response 'unknown' will be summarized by reason for having unknown status. The following reasons will be used:

- No valid post-baseline assessment
- All post-baseline assessments have overall response UNK
- New anti-neoplastic therapy started before first post-baseline assessment
- SD too early
- PD too late.

Special (and rare) cases where BOR is 'unknown' due to both early SD and late PD will be classified as 'SD too early'.

2.5.3 Change in imaging modality

Per RECIST, the imaging method used at baseline should be matched at all subsequent assessment, but, for a number of reasons such as site error (e.g. switch from MRI to CT) or renal dysfunction (making contrast a risk), this will not always be done. A strict implementation of RECIST would mean that any change in the imaging method compared to one used at baseline should lead to unknown overall response at any given assessment. However, a change in the use of contrast does not necessarily represent a change in precision since for many tumor types, the assessment can be done despite the fact that contrast has changed.

Therefore, in the calculation of overall response (see Source 3 in Table 3-1 in Section 3.10.1) the methods/modalities listed under the same bullet point will be considered the same:

- 'CT with contrast' and 'CT without contrast'
- 'Spiral CT with contrast' and 'spiral CT without contrast'
- 'MRI with contrast', 'MRI without contrast', 'Dynamic contrast – enhanced MRI' and 'GD-MRI'.

However, the following needs to be emphasized: For primary analysis of progression-free survival (PFS) and BOR based on investigator/local radiology assessments, the overall lesion response as provided by investigator (see Source 1 in Table 3-1 in Section 3.10.1) will be taken regardless of the change in imaging modality. Similarly, for the analysis of PFS and BOR based on central radiology assessments, the overall lesion response as provided by central radiologist (see Source 4 in Table 3-1 in Section 3.10.1) will be taken regardless of the change in imaging modality. Potential discrepancies between the modality used and overall lesion response (e.g. change in modality but response different from 'Unknown') for Sources 1 and 4 will be queried during the data validation process.

2.5.4 Determination of missing adequate tumor assessments (TAs)

In this section, the 'missing adequate TA' is defined as TA not done or TA with overall lesion response equal to 'Unknown'. For the sake of simplicity, the 'missing adequate TA' will also be referred as 'missing TA'.

As detailed in Section 3.10.2 below and in the [RAP module 3 - Post-text supplement 1], the PFS censoring and event date options depend on the presence and the number of missing TAs. For example:

- in the primary analysis of PFS, an event occurring after two or more missing TAs is censored at the last adequate TA
- in one of the sensitivity analyses of PFS, an event occurring after one or more missing TAs is backdated to the date of next scheduled assessment.

An exact rule to determine whether there is none, one or two missing TAs is therefore needed. This rule will be based on the distance between the last adequate TA date and the event date.

If the distance is larger than threshold D1=12+2=14 weeks or D2=(2*12)+2=26 weeks then the analysis will assume one or two missing TAs, respectively. The threshold D1 is defined as the protocol specified interval between the TAs plus the protocol-allowed window around the assessments. Similarly, the threshold D2 is defined as two times the protocol specified interval between the TAs plus the protocol allowed window around the assessments.

Therefore, using the D2 definition above, the censoring of an event occurring after ≥2 missing TAs (in primary PFS analysis) can be refined as follows: if the distance between the last adequate TA date and the PFS event date is larger than D2 then the patient will be censored and the censoring reason will be 'Event documented after two or more missing tumor assessments'.

The same definition of D2 will be used to determine other PFS censoring reasons (see the conventions for the PFS censoring reasons provided below).

1. analysis cut-off date
2. start date of further anti-neoplastic therapy (see Section 2.4.2)
3. date of discontinuation due to consent withdrawal
4. date of discontinuation due to loss to follow-up

2.5.5 No measurable disease at baseline

As specified in the [RAP module 3 - Post-text supplement 1], using RECIST criteria implies that only patients with measurable disease at baseline should be included in the study. However, it can still happen that a patient without measurable disease is present in the data. One reason might be a simple violation of inclusion criteria. Furthermore, in central radiology data, another reason for having a patient without target lesions is coming from the fact that the eligibility is assessed by investigator (i.e. there are some target lesions seen locally but not centrally). Therefore, a rule needs to be specified on how to handle these cases.

Target lesion response will always be unknown (UNK) due to missing baseline measurements. Therefore, a complete response, partial response or stable disease can never be

assigned as an overall lesion response. However, a PD can still be determined from non-target lesions or from new lesions.

As a result, the overall lesion responses will always be UNK until PD occurs. The BOR will either be UNK or PD depending on the timing of PD (see Section 2.5.2). The PFS censoring and event date options will depend on how many UNKs precede the PD (see Sections 2.5.4 and 3.10).

2.5.6 No baseline tumor assessments

If there is no baseline tumor assessment, all post-baseline overall lesion responses will be UNK.

As specified in [Table 3-1 in Section 3.1.8 of the RAP module 3 - Post-text supplement 1], since the timing of PD cannot be determined for patients with missing baseline tumor assessment these patients are censored in the PFS analysis at the date of randomization. This rule however only applies to the "progressive disease component" of the PFS assessment.

Patients without baseline tumor assessment who die within D2 distance (see Section 2.5.4 for definition) from randomization will be counted as having an event in the primary analysis of PFS. (Of note: since the overall survival analysis obviously does not use the information about the baseline tumor assessment all deaths will be counted in the overall survival analysis regardless of presence or absence of the baseline tumor assessment.)

2.5.7 Construction of waterfall graphs

The waterfall graphs will be used to depict the anti-tumor activity. These plots will display the best percentage change from baseline in the sum of the longest diameter of all target lesions for each patient. The proportions of patients with various degrees of tumor shrinkage or growth which can be read directly from the graph can then represent a useful efficacy metric.

However, a caution needs to be paid to the assessments where an occurrence of a new lesion or worsening in non-target lesions (resulting in PD as an overall lesion response at given assessment) contradicts the measurements obtained on target lesions. These assessments will not be displayed as bars in the graph. If such a "contradicting" assessment represents the only post-baseline assessment for a patient then the patient will be represented by a special symbol (e.g. ✶) in the waterfall graph.

The assessments with unknown target response and also assessments with unknown overall response will be excluded. Patients without any valid assessments will be completely excluded from the graphs. Patients without any target lesions at baseline will be excluded as well.

The total number of patients displayed in the graph needs to be shown and this number will be used as a denominator when calculating the percentages of patients with tumor shrinkage and tumor growth. Footnote will explain the reason for excluding some patients (due to absence of any valid assessment).

All possible assessment scenarios are described in Table 2-5.

Table 2-5 Inclusion/exclusion of assessments used in waterfall graph

	Criteria for inclusion/exclusion			Possible sources of contradictions	
case	Target response	Overall lesion response	Include in waterfall?	Non-target response	New lesion?
1	CR/PR/SD	PD	Yes but as ✶ only	PD	any
2	CR/PR/SD	PD	Yes but as ✶ only	any	Yes
3	UNK	UNK or PD	No	any	any
4	CR/PR/SD	UNK	No	UNK	No
5	CR/PR/SD	CR/PR/SD	Yes as a bar	SD/IR	No
6	PD	PD	Yes as a bar	any	any

Therefore, the following algorithm will be used to construct the graph:

1. Select "valid" post-baseline assessments to be included, i.e. for each patient and each assessment repeat the following four steps.
   1.1. Check the target lesion response and overall lesion response at each assessment. If at least one of them is UNK then exclude the whole assessment. Otherwise, go to step 1.2.
   1.2. Check the overall lesion response. If it is PD then go to step 1.3. Otherwise go to step 1.4.
   1.3. Check target response. If it's PD then go to step 1.4. Otherwise flag the assessment with ✶ .
   1.4. Calculate the % change from baseline in target lesions.
2. For each patient, go through all valid assessments identified in Step 1 and find the assessment with best % change from baseline in target lesions. The "best" means best for the patient, i.e. the largest shrinkage or if a patient only has assessments with tumor growth take the assessment where the growth is minimal. (*Example 1*: Patient 1 has the following % changes from baseline at assessments 1, 2, 3, 4 and 5, respectively: -10%; -25%; -13%; -4% and +6%. His/her best % change is then -25%. *Example 2*: Patient 2 has the following % changes from baseline at assessments 1, 2 and 3, respectively: +5%; +18% and +35%. His/her best % change is then +5%.
3. Construct the waterfall graph displaying the best % change from baseline for each patient. Patients having only ✶ flagged assessment(s) will be displayed separately.

The graph will use the investigator reported overall lesion responses (see Source 1 in Table 3-1) and will be repeated using the adjudicated central radiology data (Source 2 in Table 3-1) and using the central radiology data (Source 4 in Table 3-1).

The display from left to right is the following:

1. Bars above the horizontal axis representing tumor growth

2. Bars under the horizontal axis representing tumor shrinkage

3. "Zero" bars with ✶ symbol representing patients with contradiction.

4. Patients with 0 changed will be graphically denoted using with • symbol.

For each of the 4 categories above, n (%) (where % uses the total number of patients displayed in the graph) will be displayed.

2.6 General statistical methodology

2.6.1 Stratification

A stratified analysis method will be used to test the difference between the treatment groups and to obtain the treatment effect estimates.

The strata are defined by the use of prior cytotoxic chemotherapy (Yes vs. No) and by the WHO performance status (0 vs. 1-2) at baseline.

The primary analyses of efficacy will be based on the stratification factors as declared at the time of randomization, i.e. the factors needed to perform the stratified randomization and collected via the Interactive Voice Response (IVR) system.

The primary analysis of PFS (i.e. PFS by investigator) will also be repeated based on the stratification factors as reported by investigator on eCRFs. Discrepancies between randomization stratification factors and baseline stratification factors collected on eCRFs will be tabulated and listed.

2.6.2 Center pooling

All study centers will be combined for the analysis. Due to expected small size of centers, no center effect will be assessed.

However, protocol deviations, number of patients in analysis populations and discontinuations from study treatment will be summarized by center.

2.6.3 One-sided vs. two-sided test

Since RAD001C2324 is a placebo-controlled study where the primary objective is clearly directional, one-sided tests at 2.5% significance level will be used to test the primary endpoint (PFS) and also in the test of Overall Survival (OS) and Time to definitive worsening of WHO PS..

The 95% confidence intervals will not be used for decision making and will only be used for estimation and will therefore always be two-sided.

2.6.4 Standard time-to-event analyses

The following sections present a general methodology used to analyze progression-free survival and overall survival.

2.6.4.1 Analysis of time-to-event data with ties

In general, analysis of discrete events becomes complicated in the presence of ties, i.e. events that occurred at exactly the same time or events that are recorded with exactly the same times (e.g. due to discrete assessment schedule). Note: censored observations that occurred at the same time are not counted as ties.

In the PHREG procedure, SAS software offers several methods to handle ties (specified by TIES=*method* option in the MODEL statement): BRESLOW, EFRON, EXACT and DISCRETE methods. If there are no ties, all four options give identical results. However, when the number of ties is large, relative to the number at risk, different methods yield

different results and possibly lead to different conclusions (Allison 1995; Dmitrienko et al 2005). Since the number of ties in this study is expected to be rather large (due to the discrete tumor assessment scheme), a careful consideration needs to be made in terms of the choice of the method.

The Breslow approximation should be avoided since when there are many ties (relative to the number at risk), it performs poorly (Farewell and Prentice 1980; Hsieh 1995). In particular, the Breslow method will break down when the number of ties is large, and then tends to yield estimates of coefficients (in the Cox proportional hazards model) which are biased toward 0.

Since in the presence of ties the log-rank test produced by LIFETEST procedure with TEST statement gives results equivalent to the Breslow method, the STRATA statement in LIFETEST procedure will be used instead.

Cox proportional hazards model will be implemented using PHREG procedure with option TIES= EXACT. It assumes that there is a true but unknown ordering for the tied event times (as contrasted to option TIES=DISCRETE which assumes that the events in fact occurred at exactly the same time (Collett 1994).

Note: Ideally, the ties handling method used in LIFETEST and PHREG procedures should be consistent. However, since the main purpose of employing the PHREG procedure is to produce a hazard ratio with confidence interval and this cannot be obtained in a way consistent with log-rank based p-value produced by LIFETEST (see further details in Section 2.6.4.2), the decision was made that as a project standard the PHREG procedure should use a ties handling method which is considered optimal in given setting regardless of the consistency between LIFETEST and PHREG procedures.

2.6.4.2 Hypothesis and test statistic

The null hypothesis stating that survival distributions of the two treatment groups are equivalent will be tested against a one-sided alternative. The significance level of 2.5% will be used.

Suppose that $S_E(t)$ and $S_P(t)$ are the survival functions in Everolimus 10 mg and Placebo groups, respectively.

The null hypothesis

H_0: $S_E(t) = S_P(t)$

will be tested against the one-sided alternative hypothesis

H_{a1}: $S_E(t) > S_P(t)$.

Stratified log-rank test adjusting for the strata used in the randomization will be used to test the difference between the treatment arms and will be implemented as follows: In each of the 4 strata (1. prior cytotoxic chemotherapy & WHO=0; 2. prior cytotoxic chemotherapy & WHO>0; 3. no prior cytotoxic chemotherapy & WHO=0; 4. no prior cytotoxic chemotherapy & WHO>0) separately, the LIFETEST procedure with STRATA statement including only the treatment group variable and with the TIME statement as shown below will be used to obtain the rank statistic S_k and variance $var(S_k)$ where k=1, 2, …, *4*.

```
PROC LIFETEST data=dataset  METHOD=KM CONFTYPE=LOGLOG;
      BY stratum;
      TIME survtime*censor(1);
      STRATA trt;
RUN;
/* stratum represents stratum variable (to be included for stratified
   analysis only;
   survtime represents variable containing event/censor times;
   censor represents censoring variable (1=censored, 0=event);
   trt represents treatment group variable; */
```

The final test statistics will then be reconstructed as follows:

$Z=[S_1 +\ldots+ S_4]/\sqrt{[var(S_1) +\ldots+ var(S_4)]}$.

One-sided p-value will be obtained using the Z statistic (under the null hypothesis, the test statistic Z is approximately normally distributed).

2.6.4.3 Kaplan-Meier estimates

An estimate of the survival function in each treatment group will be constructed using ***Kaplan-Meier (product-limit) method*** as implemented in PROC LIFETEST with METHOD=KM option (see examples above).

Median survival for each treatment group will be obtained along with 95% confidence intervals calculated from PROC LIFETEST output using the method of (Brookmeyer and Crowley 1982).

Kaplan-Meier estimates of the survival function with 95% confidence intervals at specific time points will be summarized. The standard error of the Kaplan-Meier estimate will be calculated using Greenwood's formula (Collett 1994).

The PROC LIFETEST statement will use the option CONFTYPE=LOGLOG. The CONFTYPE option specifies the transformation applied to the survival function to obtain the pointwise confidence intervals and the confidence intervals for the quartiles of the survival times. The LOGLOG keyword specifies the complementary log-log transformation (Collett 1994; Lachin 2000) g(x)=log(-log(x)) which ensures that the pointwise confidence intervals are always within interval [0,1]. Although the LOGLOG is the default option in SAS v 9.1 it should be explicitly shown in the code.

The Kaplan-Meier curves, medians and Kaplan-Meier estimates with 95% confidence intervals at specific time points will also by displayed by stratum.

The survival time for both PFS and overall survival (OS) will be expressed in months and one month is defined as (365.25 / 12)=30.4375 days (which is not equal to 4 weeks).

The Kaplan-Meier graphs will be constructed using Splus software. The statistics (test statistics, p-value, hazard ratio etc.) to be displayed on the graph will, however, be obtained from the SAS software.

2.6.4.4 Hazard ratio

Hazard ratio as a treatment effect measure will be derived from the ***Cox proportional hazards model*** using SAS procedure PHREG (with TIES=EXACT option in the MODEL statement).

A ***stratified unadjusted Cox model*** will be used (where the baseline hazard function is allowed to vary across strata) for the primary analysis, i.e. the MODEL statement will include the treatment group variable as the only covariate and the STRATA statement will include stratification variable(s).

```
PROC PHREG data=dataset;
      MODEL survtime*censor(1)=trt / TIES=EXACT;
      STRATA stratum1 .. <stratum 4>;
RUN;
/* survtime represents variable containing event/censor times;
   censor represents censoring variable (1=censored, 0=event);
   trt represents treatment group variable;
   stratum1 to stratum 4 represent stratification variables */
```

Hazard ratio with two-sided 95% confidence interval will be based on ***Wald test***.

Note: Ideally, the hazard ratio and the confidence interval should be derived by a method consistent with the p-value calculation, i.e. in this case with log-rank test (see Section 2.6.4.2). This requirement would lead to the ***score test*** based intervals. However, since these intervals are not available in the SAS procedure PHREG, Wald test based intervals will be used instead.

For secondary sensitivity analyses, ***stratified Cox model adjusted for covariates*** will be used.

```
PROC PHREG data=dataset;
      MODEL survtime*censor(1)=trt cov1..<covk>;/TIES=EXACT;
      STRATA stratum1 .. <stratum k>;
RUN;
/* survtime represents variable containing event/censor times;
   censor represents censoring variable (1=censored, 0=event);
   trt represents treatment group variable;
   cov1 to covk represent covariates;
   stratum1 to stratumk represent stratification variables */
```

2.6.5 Additional time-to-event analyses accounting for treatment crossover and informative censoring

2.6.5.1 Supportive analyses of overall survival (OS)

Patients who progressed on placebo are allowed to cross-over to open-label Everolimus. Despite the cross-over design, the primary analysis of OS will use the strict intention-to-treat (ITT) approach, i.e. 'analyze as randomized' and ignore the treatment switch following progression (and ignore additional anticancer therapies administered after study treatment discontinuation). This approach represents a gold standard. However, placebo patients who switch to Everolimus after they progress are likely to benefit from the delayed administration of Everolimus and, therefore, the survival treatment estimate becomes confounded. Under such circumstances, the statistical test of the treatment effect is known to be biased towards the null hypothesis of no difference (Robins and Tsiatis 1991; Korhonen et al 1999; Greenland et al 2008). Therefore, the following modeling approaches will be used to obtain an estimate of survival treatment effect corrected for treatment cross-over: 'Rank-preserving structural failure time method' and 'Cox model with Inverse Probability of Censoring Weighting'. More details are provided in sections below.

2.6.5.1.1 RPSFT approach

The OS will also be analyzed using ***rank-preserving structural failure time method (RPSFT)*** to correct for confounding introduced by the change of treatment (Robins and Tsiatis 1991; Korhonen et al 1999). The use of RPSFT method allows to estimate the survival time gained by anyone receiving Everolimus (i.e. either as randomized to Everolimus or after cross-over from placebo to open-label Everolimus). The RPSFT model is based on an accelerated failure time model (Kalbfleisch and Prentice 1980) and uses a structural assumption of time-proportionality instead of a proportional hazards assumption as used in the Cox model. The widely used Cox model measures drug effect on the hazard ratio scale, whereas the accelerated failure time model measures drug effect on the survival time ratio scale.

Notation

We follow (Korhonen et al 1999) for the notation. The treatment assignment indicator is denoted by R_i and takes the value 0 if allocated to placebo and 1 if allocated to active drug (Everolimus 10 mg). $Strata_i$ stands to baseline stratification factors. Each individual is followed from the time of randomization (DR_i) until death or the date of last contact (EOF_i) and the fixed closing date (CD_i) which ever comes first. The censoring time $C_i = min(EOF_i - DR_i, CD_i - DR_i)$, is measured in days and is assumed to be independent of the treatment assignment. (Note: in a sensitivity analysis, censoring time $C_i = EOF_i - DR_i$ will also be considered). Time to death (T_i) is the time from randomization to death which is also measured in days. We can only observe $X_i = \min(T_i, C_i)$ with $\delta_i = 1$ if $X_i = T_i$ and $\delta_i = 0$ otherwise. Some of the subjects randomized to the placebo arm switch to the active drug at some point after randomization. There may be several different periods when active drug has been received instead of the randomized placebo. The total time on active drug after randomization is denoted as A_i which is measured in days. If no switch occurs in the placebo arm then $A_i = 0$. Similarly, some subjects randomized to the active treatment arm may stop taking their randomized drug and therefore it is possible that $A_i \leq X_i$ for them. Switching to the

active drug is potentially related to the patient's prognosis and thus cannot be assumed independent of the death time.

Thus the observed data for each subject *i* are $\{R_i, Strata_i, C_i, X_i, \delta_i, A_i\}$.

Model

For subject *i,* we denote U_i as the potential survival time had no active drug with Everolimus been received. U_i is a concept that is defined for each subject at the time of the randomization and U_i may depend on the value of the baseline risk factor. U_i will be observed only for those subjects who will never receive active drug during the study and die before $min(EOF_i, CD_i)$.

For a given time on active drug A_i the drug-free survival time U_i is linked to the death time T_i through a structural model

$$U_i = \int_0^{T_i} e^{\psi A_i(s)} ds$$

where $A_i(t) = 1$ if subject *i* is on active drug at time *t* and 0 otherwise. For a fixed value of the parameter ψ the above model can be written as

$$U_i(\psi) = \int_0^{A_i} e^{\psi \times 1} ds + \int_0^{T_i - A_i} e^{\psi \times 0} ds = A_i e^{\psi} + (T_i - A_i).$$

If $A_i(t) = 0$ for all *t* then $U_i = T_i$. If, on the other hand $A_i(t) = 1$ for all *t* then $U_i = T_i e^{\psi}$. Thus the parameter ψ has the following interpretation: $e^{-\psi}$ expresses how much the survival time is increased or decreased on relative scale if on active drug versus if not on active drug.

Therefore, we can see that the main assumption of this method is that the total duration of survival time for each patient is the sum of two distinct parts:

- potential survival time, had no drug been received, and
- time added from multiplying the duration on active drug by an unknown factor.

For the estimation of the parameter ψ it needs to be assumed that:

1. the above model correctly captures the drug action
2. no other factor than the amount of the active drug received, A_i, induces a difference in survival experience for an individual *i* under different treatment arm assignments
3. the drug-free survival time U_i for an individual *i* is unaffected by the drug assignment or by the survival experience of other individuals
4. the censoring time C_i is independent of the randomization mechanism R_i

Estimation algorithm for parameter ψ

Randomization guarantees that any variable measured at baseline will on average be balanced with respect to the drug assignment. In particular, $U_i \coprod R_i$ where $\coprod$ denotes statistical independence. This holds also within each of the *k* strata of the baseline risk factor. It follows that

$$\Pr(U_i(\psi) \le x \mid R_i = 0, Strata_i = z) = \Pr(U_i(\psi) \le x \mid R_i = 1, Strata_i = z), \quad z = 1,2,..,k.$$

In other words, the drug free survival time is independent of the randomization within the different strata of the baseline risk factor. Therefore, a procedure for estimating the parameter ψ can be based on computing $U_i(\psi)$ for various values of ψ and finding a value $\hat{\psi}$ where $U_i(\hat{\psi}) \coprod R_i \mid Strata_i$. We use the stratified log-rank test statistic for a device to estimate the parameter ψ. The stratified log-rank test statistic is obtained from PROC PHREG procedure in SAS. The stratified log-rank test has an asymptotic chi-squared distribution with one degree of freedom under the hypothesis $\psi = \psi_0$ where ψ_0 denotes the true parameter value. From a grid of values for ψ we choose as $\hat{\psi}$ where the stratified log-rank test statistic has its minimum value. The approximate lower and upper 95% confidence limits are obtained as those values where the stratified log-rank test statistic is close to 3.84. In reality the stratified log-rank test statistic is a step function in ψ and therefore there might be several values where the minimum is obtained and also the upper and lower confidence limits need to be chosen as the point for ψ where the value of the stratified log-rank test statistic changes from less than 3.84 to greater than 3.84.

Complication due to censoring in the estimation algorithm

One complication arises from the fact that due to censoring $U_i(\psi)$ cannot always be computed from the observed data using the above model. One cannot simply replace T_i by X_i in the above model and calculate the respective value, say $U_i^x(\hat{\psi})$ from the model because then $U_i^x(\hat{\psi})$ would not be independent of R_i and the assumptions for the estimation would not hold. Instead the censoring is handled as follows.

i) If $\delta_i = 1$ then calculate
$$C_i(\psi) = \min(C_i, C_i e^{\psi})$$
$$X_i(\psi) = \min(U_i(\psi), C_i(\psi))$$
$$\delta_i(\psi) = I(X_i(\psi) = U_i(\psi))$$

ii) If $\delta_i = 0$ then calculate
$$C_i(\psi) = \min(C_i, C_i e^{\psi})$$
$$X_i(\psi) = C_i(\psi)$$
$$\delta_i(\psi) = 0$$

By these definitions, $C_i(\psi)$ is independent of $U_i(\psi)$ and R_i. The new censoring time $C_i(\psi)$ can be interpreted as the maximum $U_i(\psi)$ that can be calculated which is smaller than C_i no matter how long individual i is on the randomized active drug. Both $X_i(\psi)$ and $\delta_i(\psi)$ can be calculated based on observed data and furthermore $\{X_i(\psi), \delta_i(\psi)\} \coprod R_i \mid Strata_i$. Thus the estimation can be performed by calculating $X_i(\psi)$ and $\delta_i(\psi)$ for the various values of ψ within the different strata of the baseline risk factor and proceed as described in the estimation section.

This way of dealing with censoring was introduced by Robins and Tsiatis 1991. Note that some extra censoring will occur due to nature of handling the censoring times in this estimation procedure. This causes some loss of power.

Summary of the method and interpretation

Drug effect is obtained by estimating the multiplicative factor; which would be interpreted as either a relative increase or decrease in survival if one took active drug (Everolimus) compared to taking placebo. The multiplicative factor is determined by repeatedly reconstructing the anticipated survival duration of all patients by varying degrees of the factor, until both survival curves (Everolimus arm and Placebo) can no longer be distinguished, i.e. as if all patients only received placebo.

This method maintains the original randomized-group definitions and thus preserves the validity of between group comparison. It provides a randomization based estimate of drug effect corrected for the bias due to crossover (under the assumption that the effect is multiplicative in time). This estimate is valid even in presence of outcome dependent drug change. Of note, this method requires extra censoring (i.e. some events become censored) which impacts the precision of the drug effect estimate.

2.6.5.1.2 Marginal Structural Cox Proportional Hazards Model using the Inverse Probability of Censoring Weighting (IPCW)

The Marginal Structural Cox Proportional Hazards Model using the Inverse Probability of Censoring Weighting (IPCW) will also be considered (Hernan et al 2000) to account for the treatment cross-over.

We follow Hernan et al 2000 and Korhonen et al 1999 for the notation. The treatment assignment indicator is denoted by R_i and takes the value 0 if allocated to placebo and 1 if allocated to active treatment (Everolimus). The baseline covariates to be included in the model are jointly denoted as matrix V_i. We will consider two time-dependent covariates: WHO performance status and investigators assessment of disease progression which are collectively denoted as matrix L_i.

Each individual is followed from the time of randomization (DR_i) until death or the last date of contact (EOF_i) and the fixed closing date (CD_i) which ever comes first. The censoring time, $C_i = min(EOF_i - DR_i, CD_i - DR_i)$, is measured in days and is assumed to be independent of the treatment assignment and also from the death time. Time to death (T_i) is the time from randomization to death which is also measured in days. We can only observe $X_i = \min(T_i, C_i)$ with $\delta_i = 1$ if $X_i = T_i$ and $\delta_i = 0$ otherwise. The follow-up time is divided in to intervals $k=0, 1, 2,..., K$ where 0 denotes the baseline. The length of the intervals after baseline may vary but the same intervals are used for each individual. Some of the subjects randomized to the placebo arm switch to the active treatment at some point after randomization. Switching to the active treatment is potentially related to the patient's prognosis and thus cannot be assumed independent of the death time. The time to switching to the active treatment is denoted by S_i and for subjects who do not switch to the active treatment arm we define $S_i = X_i$. We denote $A_i(k) = 0$, if the subject did not receive active treatment during the time interval k and $A_i(k) = 1$, if the subject received active treatment during the time interval k. For subjects

randomized to the active treatment arm $A_i(k)=1$ for all k until X_i. Similarly, for subjects randomized to the placebo arm $A_i(k)=0$ for all time intervals k prior to S_i and $A_i(k)=1$ thereafter for all k until X_i. With these notations we call $A_i(X_i)=\{A_i(u);0\le u\le X_i\}$ subjects observed active treatment until the end of follow-up and $\overline{A}_i(k)=\{A_i(u);u=0,1,...,k-1\}$ a subject's active treatment history until the start of the k^{th} time interval. The time-dependent covariate history is similarly denoted by $\overline{L}_i(k)=\{L_i(u);u=0,1,...,k-1\}$ and subjects observed time-dependent covariates until the end of follow-up as $L_i(X_i)=\{L_i(u);0\le u\le X_i\}$.

Thus the observed data for each subject i are $\{R_i, V_i, L_i(X_i), C_i, X_i, \delta_i, A_i(X_i)\}$.

The usual ITT approach for estimating the treatment effect concerning overall survival is likely to be biased towards zero due to considerable amount of switching to the active treatment in the placebo arm. In order to trying to estimate the treatment effect one might think of estimating the time varying effect of treatment received on overall survival possibly using Cox's proportional hazards model to model the death risk as a function of the treatment history $\overline{A}_i(k)=\{A_i(u);u=0,1,...,k-1\}$. This approach is likely to be biased whenever there is a time-dependent covariate that is (i) both a risk factor for mortality and (ii) which also predicts subsequent treatment $A_i(u)$ and (iii) at the same time the treatment history $\overline{A}_i(k)$ predicts the subsequent level of the time-dependent covariate $L_i(u)$. In this study the WHO performance status after baseline and investigator's assessment of disease progression are such time-dependent covariates.

One approach trying to finding an unbiased estimate of the treatment effect is to use the marginal structural Cox proportional hazards model where the death risk is modeled using a conventional Cox's proportional hazards model using time-dependent case weights for those who did not switch to active treatment but continue to remain on their original randomized treatment.

The marginal structural Cox model is specified as follows:

$$\lambda(t\mid \overline{A}(t),V)=\lambda_0(t)\exp(\gamma_1 A_i(t)+\gamma_2 V_i);t\le S_i$$

where a subject stays at risk for death until (s)he switches to the active treatment. Thus, the whole follow-up experience from randomization to X_i = min(T_i, C_i) is used from subjects randomized to the active treatment arm. But, in the placebo arm only the follow-up experience from randomization to min(S_i, X_i) is used in the marginal structural Cox model. This means in practice that in the placebo arm the data after switching to the open label active treatment is discarded. Each subject is given in this model the case weight indicating the cumulative probability of not switching to the active treatment at time t. Unfortunately, the PROC PHREG procedure does not allow to specify time-dependent weights. Therefore one needs to divide the follow-up time into discrete time intervals and fit the above model using the PROC GENMOD procedure which allows time-dependent weights.

The case weights are estimated using the IPCW scheme for the probability of switching in the placebo arm. In the IPCW, the probability of not switching is modeled using two separate logistic regression models as follows:

$$sw_i(k) = \prod_{u=0}^{k} \frac{\Pr(A_i(u) = a_i(u) \mid \overline{A}_i(u) = (0,...,0)^T, V_i)}{\Pr(A_i(u) = a_i(u) \mid \overline{A}_i(u) = (0,...,0)^T, V_i, \overline{L}_i(u))}$$

$$a_i(u) = \begin{cases} 1 & \text{if subject crossed - over at time k} \\ 0 & \text{if subject did not crossed - over at time k} \end{cases}$$

The first logistic regression model (i.e. the nominator model) uses only the baseline covariate information to describe the probability of switching. The second logistic regression model (i.e. the denominator model) uses both baseline covariate information and time-dependent covariate information. The estimation of these stabilized weights can easily be done with the PROC LOGISTIC procedure in SAS.

Note that the estimation of the stabilized weights is only needed in the placebo arm. In the active treatment arm we set the stabilized weights to 1 for all subjects and for all discrete time periods.

This type of weighting effectively creates, for a risk set at time t, a pseudo-population in which $L_i(u)$ no longer predicts the receipt of active treatment at time t (that is, $L_i(u)$ is not a confounder). If we can be comfortable assuming that after having modeled the dependence of the subsequent treatment $A_i(u)$ with the stabilized weights then under this assumption of no unmeasured confounders, the coefficient γ_1 of $A_i(u)$ in the marginal structural Cox model represents the causal association between the receipt of active treatment and mortality on the log-hazard ratio scale.

Note: For the estimation of the stabilized weights and the discrete version of the marginal structural Cox model one has to model the time-dependent intercepts using either a smooth function of time, such as a cubic spline or by combining time intervals. Otherwise the estimation may not be possible and also the asymptotic theory may break down.

2.6.5.2 Time-to event methodology adjusting for dependent (informative) censoring for PFS

Censoring is informative if the probability of censoring depends on the outcome the patient would have had in the absence of censoring. This type of censoring can arise when there are some covariates affecting both outcome (time-to-event variable) and probability of censoring. In this trial, PFS based on central review is affected by informative censoring when a local progression cannot be confirmed centrally and the patient is censored due to absence of radiological imaging after local progression or to initiation of another anticancer therapy(including open-label Everolimus).

In general, this type of informative censoring will make the affected PFS curve appear more favorable than it is in truth. In addition, there is a loss of 'central' events and eventually the trial may never reach the number of events targeted in its original design. Fleming et al 2009 points out that informative censoring will likely lead to "significant bias as well as increased variability in the evaluation of treatment effects."

A modified IPCW methodology (described in Section 2.6.5.1.2) will be used to estimate the treatment effect for centrally (IRC) assessed PFS adjusted for informative censoring. In Section 2.6.5.1.2, logistic regressions were used to model the probability of not crossing-over.

Here, we will model censoring rather than cross-over (although these two are very similar: for many placebo patients the informative censoring arises when a local progression cannot be confirmed centrally and the patient is censored due to cross-over to another anti-cancer therapy, i.e. due to initiation of open-label Everolimus).

2.6.6 Between group comparisons – categorical variables

2.6.6.1 Comparison of response rates

The exact Cochran-Mantel-Haenszel test (implemented via SAS procedure MULTTEST) will be used to test the difference in response rates between the two arms. The Cochran-Mantel-Haenszel strategy potentially removes the confounding influence of the explanatory variables that comprise the stratification and so can provide increased power for detecting association by comparing like subjects with like subjects (Stokes et al 2000).

The test is performed by running a stratified version of the Cochran-Armitage permutation test (see for example Dmitrienko et al 2005 for more details).

The following SAS code will be used:

```
PROC MULTTEST data=dataset;

      CLASS trt;

      STRATUM stratum;

      TEST CA(response/ PERMUTATION=number options);

RUN;

/* trt represents treatment group variable; stratum represents stratum variable;
response represents response variable; number should be greater than or equal to
the number of patients in the largest stratum, so as to ensure that the p-value is
exact; options include UPPERTAILED and LOWERTAILED to obtain one-sided p-
values */
```

2.6.7 Confidence interval for response rate

Responses will be summarized in terms of percentage rates with 95% confidence intervals.

As a standard, an ***exact binomial confidence interval*** (implemented using SAS procedure FREQ with EXACT statement for one-way tables) will be calculated (Clopper and Pearson 1934).

3 Statistical methods used in reporting

3.1 Introduction

Statistical methods used in reporting for both efficacy and safety are described below.

3.2 General presentation of descriptive summaries

Qualitative data (e.g., gender, race, etc.) will be summarized by means of contingency tables by drug group; a missing category will be included as applicable. Percentages will be calculated using the number of patients in the relevant population or subgroup as the denominator.

Quantitative data (e.g., age, body weight, etc.) will be summarized by appropriate descriptive statistics (i.e. mean, standard deviation, median, minimum, and maximum) by drug group.

3.3 Enrollment status

Number of patients screened and enrolled (i.e. randomized and, therefore, in the FAS) will be summarized by country, center and drug group.

3.4 Background and demographic characteristics

The FAS will be used for all baseline and demographic summaries and listings.

3.4.1 Basic demographic and background data

All demographic and background data will be summarized (see Section 3.2) by treatment arm and will be listed in detail.

3.4.2 Stratification factors

The baseline stratification factors collected on the eCRFs will be cross-classified, tabulated and listed against the stratification factors actually used to randomize patients (contained in the IVR dataset).

3.4.3 Protocol eligibility criteria

Protocol eligibility criteria as per eCRFs will be summarized and listed.

3.4.4 Diagnosis and extent of cancer

Summary statistics will be tabulated for diagnosis and extent of cancer, according to the data collected on the eCRF. This analysis will include the following: primary site of cancer, details of tumor histology/cytology, histological grade, time since initial diagnosis, time between discontinuation of previous treatment and PD before study start, time between PD before study start and randomization, type of lesion (target/non-target), number and type of organs involved.

The numbers and percentages of patients in categories defined by the following variables: ‘type of lesion (target/non-target)’, ‘number of organs involved’ and ‘organ types involved’ will be based on the data collected on the investigator RECIST eCRFs, in particular, on the individual target and non-target lesion codes.

Time since initial diagnosis, time between discontinuation of previous treatment and PD before study start, time between PD before study start and randomization will be calculated in months (1 month = 365.25 / 12 = 30.4375 days) and categorized into time intervals.

Frequency counts and percentages will be presented for the number of patients in each interval.

3.4.5 Medical history

Medical history and ongoing conditions, including cancer-related conditions and symptoms will be summarized and listed. Separate summaries will be presented for ongoing and historical medical conditions. The summaries will be presented by primary system organ class and preferred term. (Medical history/current medical conditions are coded using the Medical dictionary for regulatory activities MedDRA terminology.)

3.4.6 Prior anti-neoplastic therapy

Prior anti-neoplastic therapy will be listed in three separate listings: 1. medications, 2. radiotherapy, 3. surgery.

The number and percentage of patients recording any prior anti-neoplastic medications, prior anti-neoplastic radiotherapy and prior anti-neoplastic surgery will be summarized by drug.

Prior anti-neoplastic medications will be summarized by therapy type (chemotherapy, hormonal therapy, immunotherapy, targeted therapy, and other), ATC class, preferred term and drug.

3.4.7 History of prior long-acting somatostatin analog

The history of prior long-acting somatostatin analog therapy will be summarized by arm.

3.4.8 Other

All data collected at baseline, including source of subject referral, child bearing potential, pregnancy test results, and exploratory biomarker informed consent, will be listed.

3.5 Protocol deviation summaries

The number and percentage of patients in the FAS with any protocol deviation will be tabulated by the deviation category (as specified in the VAP documents) and by drug group.

The protocol deviations will also be summarized by center.

Protocol deviations leading to the exclusion from the analysis populations will be tabulated separately by drug group.

All protocol deviations will be listed.

3.6 Groupings for Analysis

The number and percentage of patients in each analysis population (definitions are provided in Section 2.1.9) will be summarized by drug group. The distribution of patients in screening and in selected analysis populations will also be summarized by country, center and drug.

3.7 Patient disposition

The FAS will primarily be used for the patient disposition summary tables and listings. However, the disposition table summarizing the reasons for discontinuation from the study drug will also be repeated on the Safety set to allow for creation of a patient flow chart and also on the open-label set.

Based on the two eCRF pages 'End of Treatment' and 'Study Evaluation Completion' there will be one combined by-drug summary showing:

1. Number (%) of patients who are still on-drug (based on the absence of the 'End of Treatment' page);
2. Number (%) of patients who discontinued the study drug (based on the 'End of Treatment' page)
3. Reasons for study drug discontinuation (based on 'End of Treatment' page).

Discontinuations from the study drug will also be summarized by country and center.

3.8 Study drug

Duration of study drug exposure, cumulative dose, dose intensity (DI) and relative dose intensity (RDI) will be summarized by drug. In addition, the duration of exposure to study drug will be categorized into time intervals; frequency counts and percentages will be presented for the number of patients in each interval. The number of patients who have dose reductions or interruptions, and the reasons, will be summarized by drug.

Listings of all doses of the study drug along with dose change reasons will be produced.

The safety set will be used for all summaries and listings of study drug.

3.8.1 Duration of study drug exposure

The following algorithm will be used to calculate the duration of double-blind study drug exposure for patients who took at least one dose of the study drug:

Duration of exposure (days) = (date of last administration of study drug) – (date of first administration of study drug) + 1.

The duration includes the periods of temporary interruption. 'Date of last administration of study drug' and 'date of first administration of study drug' are defined in Section 2.1.2 and Section 2.1.3.

The categorical summaries of exposure will use weeks or days and the continuous summaries (i.e. mean, standard deviation etc.) will use days.

The time to cross-over to open-label Everolimus will be analyzed in Placebo patients using Kaplan-Meier method.

3.8.2 Cumulative dose

Cumulative dose is defined as the total dose given during the study drug exposure and will be summarized.

3.8.3 Dose intensity and relative dose intensity

Dose intensity (DI) for patients with non-zero duration of exposure is defined as follows:

DI (dosing unit / unit of time) = Cumulative dose (dosing unit) / Duration of exposure (unit of time).

Planned dose intensity (PDI) is the assigned dose by unit of time planned to be given to patients as Per-protocol in the same dose unit and unit of time as that of the Dose Intensity.

Relative dose intensity (RDI) is defined as follows:

RDI = DI (dosing unit / unit of time) / PDI (dosing unit / unit of time).

3.8.4 Dose reductions or interruptions

The number of patients who have dose reductions or interruptions, and the reasons, will be summarized separately.

Interruption: An interruption is defined as a 0 mg/0 tablets dose given on one or more days.

Reduction: A reduction is defined as a decrease in dose from the protocol-planned dose or a decrease from the previous non-zero dose, even if this decrease has been directly preceded by an interruption. For example, in the sequence 10mg – 0mg – 5mg, the 5mg dose will be counted as a reduction. A decrease in frequency of administration which results in a lower cumulative dose is also counted as a reduction, e.g. in the sequence 10mg od – 5mg od – 5mg qod, two reductions will be counted.

If a patient moves from a higher-than-protocol-planned dose down to the planned dose then this is not be counted as a reduction, however if they move directly from a higher-than-planned dose down to a lower-than-protocol-planned dose or the planned dose on a less frequent regimen, then this is counted as a reduction.

The number of dose reductions and interruptions per patient will be tabulated both separately and combined. The reasons for reductions/interruptions will also be summarized. Dose escalations should not be counted in these summaries.

Missing data : If dose is recorded but regimen is missing or entered as ‘none’, it is assumed that the study drug was taken as per-protocol.

3.9 Concomitant therapy

Concomitant therapy is defined as all interventions (therapeutic treatments and procedures) besides the study drug that were administered to a subject preceding or coinciding with the study assessment period.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List to allow for categorization by preferred term. In addition to categorizing medication data by preferred term, drugs are classified according to their ATC classification in order to present and compare how they are being utilized. The ATC classification allows to summarize medications by a high-level common drug class.

Concomitant medications and significant non-drug therapies taken concurrently with the study drug will be listed and summarized by ATC class, preferred term and treatment arm by means

of frequency counts and percentages. These summaries will include medications starting on or after the start of study drug or medications starting prior to the start of study drug and continuing after the start of study drug.

Any prior concomitant medications or significant non-drug therapies starting and ending prior to the start of study drug will be listed.

The safety set will be used for all above mentioned concomitant medication tables.

Concomitant medications with a specific impact on some analyses (e.g. PK or efficacy analyses) will be identified prior to database lock and summarized:

- Inhibitors, inducers and/or substrates of CYP3A and PgP will be identified, classified and listed (see Section 2.4.1). Those that may lead to the exclusion of PK samples from PK sensitivity analysis (i.e. strong and moderate inhibitors of CYP3A, inhibitors of PgP and inducers of CYP3A and/or PgP) will be tabulated by ATC code.
- Further anti-neoplastic therapies administered concomitantly with study treatment will be listed based on their identification (by the method given in Section 2.4.2) by the protocol deviation process.
- Anti-neoplastic therapies since discontinuation of study drug will be listed and tabulated by ATC class, preferred term and treatment arm by means of frequency counts and percentages in separate summaries using the FAS.

3.10 Efficacy evaluation

The efficacy endpoints based on the tumor assessments (as well as the overall survival) will be derived according to the RECIST guideline version 2 (see the [RAP module 3 - Post-text supplement 1] for details).

The primary endpoint is PFS based on the investigator assessment according to RECIST. PFS based on adjudicated central radiology assessments and PFS based on central radiology assessments will be used for sensitivity analysis of the primary endpoint. All tests will be performed at the 2.5% significance level.

The key secondary endpoint is overall survival (OS): a hierarchical testing procedure has been defined to address the multiplicity issue in testing PFS and OS together with the timing of primary overall survival test (see Section 3.15.1.1).

The other secondary endpoints are objective response rate and response duration.

With the exception of OS where the final analysis will be performed at a later point (see Section 3.15), the final analyses on all other efficacy endpoints will be performed using the 28th of February , 2010 cut off date.

3.10.1 Sources for overall lesions response

The tumor endpoints derivation is based on the sequence of overall lesion responses at each assessment/time point. However, the overall lesion response at a given assessment/time point may be provided from different sources as illustrated in Table 3-1.

Table 3-1 Sources for overall lesion response

Source 1	Investigator (local radiology) reported overall lesion response
Source 2	Adjudicated central radiology chosen overall lesion response
Source 3	Calculated overall lesion response based on raw (i.e. individual lesion) measurements from Investigator (local radiology)
Source 4	Final central radiology reported overall lesion response
* Source 2 comprises Source 1 and Source 4 depending on the choice of the IAC and Source 4 for patients where no adjudication is required.	

Source 1 data will be used for the primary endpoint derivation, i.e. PFS by local radiology, and will also be used for primary analyses of other tumor related endpoints.

In particular, the investigator reported visit response for each assessment/evaluation point collected on the summary page "RECIST Overall Response" of the local radiology assessment will be used to derive the efficacy endpoints. These data reflect the best opinion of the investigator based on the most complete information available. However, the assessment/time point date will be derived using the dates of the individual lesion measurements.

Source 2 data will be used for sensitivity analysis of the primary endpoint, i.e. PFS by adjudicated central radiology: The adjudicated central radiology review data will also be used to repeat the analyses of critical tumor endpoints as sensitivity analyses. As above, the dates of the individual lesion measurements will be used to derive the assessment/time point date.

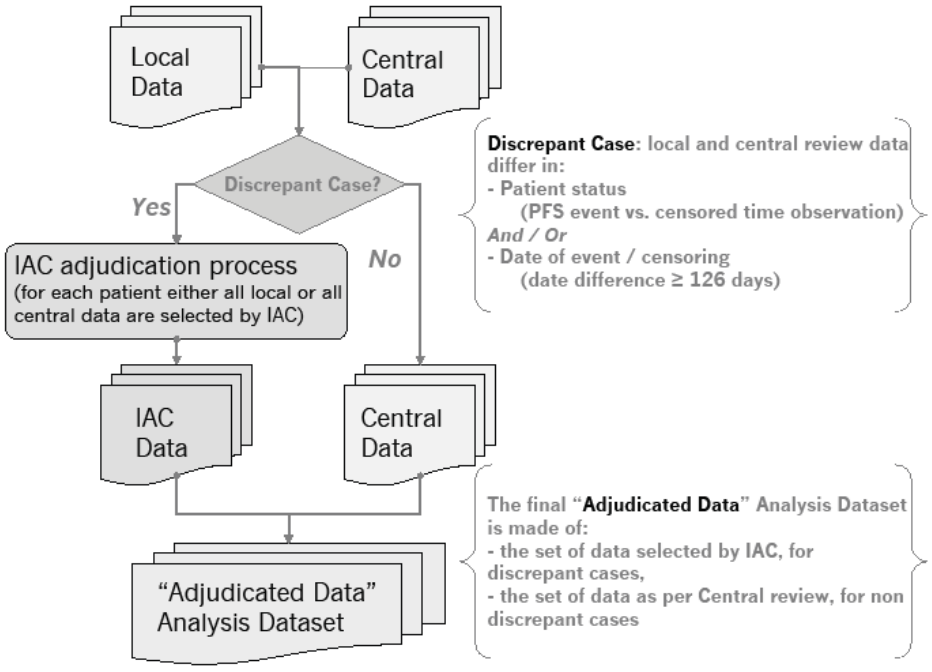
The adjudication between the local (Source 1) and central (Source 4) radiology assessment will be performed by the Independent Adjudication Committee (IAC) in a blinded manner (i.e. without knowing the source of the data) and will be required for patients where the PFS per local assessment differs from PFS per central radiology assessment. For selected patients (see Figure 3-1 for the selection rules), the IAC will be asked to choose which assessment, i.e. the one provided by the investigator or that of the central review, better represents the tumors evolution based on their review of the radiological studies and their expert knowledge. The final adjudicated (See Figure 3-1) central radiology data will be composed of:

- data from the IAC assessment for patients requiring the adjudication
- data from the central radiology assessment for patients where no adjudication was required.

The number of patients requiring adjudication will be summarized by treatment arm and by reason for adjudication.

For adjudicated patients, the IAC choice (i.e. investigator assessment vs. central radiology assessment) will be summarized by treatment arm.

Figure 3-1 PFS based on adjudicated central radiology data



Source 3 data will be derived programmatically based on raw data collected on "RECIST target lesion measurements", "RECIST non-target lesion evaluations" and "RECIST new lesion" pages. The derive overall responses will not be used for derivation of efficacy endpoint and and will only be listed against source 1.

PFS analysis based on **Source 4** data will be performed for completeness as a secondary supportive analysis. The listing of central radiology assessments will also display the calculated (derived) overall lesion response based on raw measurements from Central Radiology

3.10.2 Progression-free survival (PFS)

The primary endpoint of this study is **progression-free survival (PFS)**.

PFS is defined as the time from the date of randomization to the date of the first documented PD or death due to any cause. If a patient has not progressed or died at the date of the analysis cut-off or when he/she receives any further anti-neoplastic therapy (including open-label Everolimus), PFS is censored at the time of the last tumor assessment before the cut-off date or the anti-neoplastic therapy date. The further anti-neoplastic therapies will be identified via protocol deviations (see Section 2.4.2), from the data collected on 'Antineoplastic therapies since discontinuation of study drug' eCRF and from 'Dose administration record RAD001 unblinded' eCRF.

Definitions and further details on PFS can be found in the [RAP module 3 - Post-text supplement 1].

The derivation of PFS will only be based on the RECIST data. In particular, discontinuation due to disease progression (recorded on "End of Treatment" and/or "Study Evaluation Completion" eCRFs) without supporting data collected on RECIST pages will not be considered as progressive disease in the analysis of progression-free survival. See also Section 2.5.1.

3.10.2.1 Primary analysis

The primary analysis of PFS will be based on the investigator assessments (Source 1 in Table 3-1), will be performed using the FAS and will use the default censoring and event date options from [Table 3-1 in Section 3.1.8 of the RAP module 3 - Post-text supplement 1], i.e. A(1), B(1), C1(1), C2(1), D(1), E(1), and F(1). In particular, the PFS will be censored at the last adequate tumor assessment if one of the following occurs: absence of event; the event occurred after a new anticancer therapy (including open-label Everolimus) is given; the event occurred after two or more missing tumor assessments (see Section 2.5.4). PFS will not be censored for any other reason without supportive evidence collected on RECIST pages, in particular not for a discontinuation from the study treatment (for any reason).

The following will be applied for the rare cases of missing baseline tumor assessment: a death occurring within the D2 period (see Section 2.5.6) from randomization will be considered a PFS event.

3.10.2.2 Hypothesis and test statistic

Suppose that $S_E(t)$ and $S_P(t)$ are the PFS survival functions in Everolimus 10 mg and Placebo drug groups, respectively. The null hypothesis

H_0: $S_E(t) = S_P(t)$

will be tested at 2.5% significance level against the one-sided alternative hypothesis

H_{a1}: $S_E(t) > S_P(t)$.

A stratified one sided log-rank test will be used to test the null hypothesis. However, for the PFS analyses performed in the Japanese subgroup of patients, unstratified log-rank test will be used.

The details on methodology are given in Section 2.6.4.

3.10.2.3 Kaplan-Meier (K-M) estimates

In each drug group, the Kaplan-Meier estimate of the PFS survival function will be constructed. The Kaplan-Meier curves will also be displayed by stratum. The plots will display the number of patients at risk at given points.

Median PFS for each drug group will be obtained along with 95% confidence intervals. 25% and 75% percentiles will be calculated as well.

K-M estimates with 95% confidence intervals at the following time points will be summarized as well: 3, 6, 9, 12, 15 and 18 months (time points of the estimates may be updated).

3.10.2.4 Hazard ratio

Hazard ratio with two-sided 95% confidence interval will be derived from the stratified Cox proportional hazards model (except in the Japanese subgroup of patients where the unstratified Cox proportional hazards model will be used).

3.10.2.5 Sensitivity and other supportive analyses of PFS

Supportive analyses of PFS (using local investigator radiology assessments) adjusting the treatment difference for the key potential prognostic factors, including age, sex and WHO PS status (see Table 3-3) will be performed in the *FAS* using a multivariate Cox proportional hazard model.

The key PFS analyses, i.e. stratified log-rank test, Kaplan-Meier curves, median with 95% confidence interval, and hazard ratio, will be repeated:

- using the adjudicated central radiology assessments (Source 2 in Table 3-1) on the FAS and using the same conventions as for the primary analysis
- using the investigator assessments (Source 1 in Table 3-1) on the FAS and using the following options from [Table 3-1 in Section 3.1.8 of the RAP module 3 - Post-text supplement 1]: A(1), B(1), C1(1), **C2(3)**, D(1), E(1), and F(1), i.e. taking the event whenever it occurs even after two or more missing tumor assessments (see Section 2.5.4). In the summary tables, this approach is referred as 'actual event PFS analysis'.
- using the investigator assessments (Source 1 in Table 3-1) on the FAS and using the following options from [Table 3-1 in Section 3.1.8 of the RAP module 3 - Post-text supplement 1]: A(1), B(1), **C1(2)**, **C2(2)**, D(1), E(1), and F(1), i.e. backdating of events occurring after missing tumor assessments. In the summary tables, this approach is referred as 'backdating PFS analysis'.
- using the investigator assessments (Source 1 in Table 3-1) on the **PP Set** and using the same conventions as for the primary analysis
- using the central radiology assessments (Source 4 in Table 3-1) on the FAS and using the same conventions as for the primary analysis
- using the central radiology assessments (Source 4 in Table 3-1) on the FAS, using the same conventions as for the primary analysis and using the modeling approach correcting for informative censoring (see Section 2.6.5.2)

Further supportive analyses will be performed using the FAS only and will include:

- Number of patients and number of events by treatment arm and the hazard ratio for drug difference with confidence interval will be calculated within each stratum.
- Stratified Cox proportional hazard model using investigator assessments adjusting the drug difference for important baseline covariates: age (<65 years, ≥ 65years), gender (Male, Female), region (Europe, America, Asia), Prior long-acting somatostatin analog (Yes, No).
- Cross-tabulation of 'PFS by adjudicated central radiology review' vs. 'PFS by investigator' by PFS event/censor type and by drug will be constructed (more details are provided in Section 3.10.2.7 below)

- Cross-tabulation of 'PFS by central radiology review' vs. 'PFS by investigator' by PFS event/censor type and by drug will be constructed (more details are provided in Section 3.10.2.7 below).
- Comparison of PFS event type/censor and date between adjudicated central radiology and investigator
- Comparison of PFS event type/censor and date between central radiology and investigator
- Summary for the difference in days to progression as per central radiology review and as per investigator
- Timing of all tumor assessments will be depicted graphically for investigator and displayed by treatment arm
- Summary of missing tumor assessments by both investigator and adjudicated central radiology review (more details below)
- Time to 1st /2nd tumor assessment for investigator (more details in Section 3.10.2.9 and 3.10.2.10 below).
- Subgroup analyses of PFS by following baseline characteristics: age (<65 years, ≥ 65years), gender (Male, Female), WHO performance status (0, 1-2), region (Europe, America, Asia), liver involvement at baseline (patient with at least one baseline target or non-target lesion in liver as per investigator: Yes, No), tumor grades (well differentiated, moderately differentiated, poorly differentiated), use of prior long-acting somatostatin analog (Yes, No), Race (Caucasian, Asian, Other), Japanese patients (Japanse, non-Japanese) and Prior chemotherapy (Yes, No) will be performed to explore the homogeneity of the treatment effect across relevant patient subsets, using investigator data only.

3.10.2.6 PFS censoring reasons

The number of patients with a PFS event and number of patients censored for the PFS analysis will be summarized for PFS based on the investigator, adjudicated central radiology review and central radiology review (on FAS only). In addition, a summary of reasons for PFS censoring will be provided by treatment arm. The following categories will be used as appropriate:

- Ongoing without event
- Lost to follow-up
- Withdrew consent
- Adequate assessment no longer available (when follow-up for progression is stopped at a certain time or interrupted for a certain time period before cut-off or any other censoring reason)
- New cancer therapy added
- Event documented after two or more missing tumor assessments (for primary analysis only, i.e. the analysis the C2(1) option from [Table 3-1 in Section 3.1.8 of the RAP module 3 - Post-text supplement 1] based on the distance D2 defined in Section 2.5.4.

The categories will be determined using the treatment completion page, the study evaluation completion page and the survival page. The distance D2 defined in Section 2.5.4 will also be

used to determine other PFS censoring reasons. If the distance between the last adequate TA date and one of the following dates:

1. analysis cut-off date
2. start date of further anti-neoplastic therapy (see Section 2.4.2)
3. date of discontinuation due to consent withdrawal
4. date of discontinuation due to lost to follow-up

is smaller or equal to D2, then the censoring reason will be 1.'Ongoing', 2. 'New cancer therapy added', 3. 'Withdrew consent' or 4. 'Lost to follow-up', respectively. However, if this distance is larger than D2 then the censoring reason will be 'Adequate assessment no longer available'.

For patients censored at the date of randomization/start of treatment due to missing baseline tumor assessment (see Section 2.5.6), the censoring reason will be "Adequate assessment no longer available".

Summary will present central, local and adjudicated radiology data to compare the pattern not only between the treatment arms but also between the three sources of assessment.

3.10.2.7 Comparison of PFS assessments between central radiology and investigator

Cross-tabulation of 'PFS by central radiology' vs. 'PFS by investigator' (and of 'PFS by adjudicated central radiology' vs. 'PFS by investigator') by PFS event type (i.e. 'death', 'PD', 'censor' for each of the two sources resulting in a 3-by-3 table) and by drug will be constructed to investigate discordance between the two sources on patient-by-patient basis. The resulting 3-by-3 table example for 'PFS by central radiology' vs. 'PFS by investigator' is presented in Table 3-2.

Table 3-2 Comparison of PFS between central radiology and investigator

Investigator PFS result	Central radiology PFS result		
	Death	PD	Censor
Death	n_{11}	n_{12}	n_{13}
PD	n_{21}	n_{22}	n_{23}
Censor	n_{31}	n_{32}	n_{33}

Separately in each treatment arm, a ***discrepancy rate*** (or more precisely overall rate of disagreement on censoring status) will be calculated and presented as % as follows:

$$100 \times (n_{13} + n_{23} + n_{31} + n_{32})/ N$$

where N represents the total number of patients in the FAS.

3.10.2.8 Missing tumor assessments (TAs)

This analysis should provide an insight as to whether the TAs have been carried out in accordance with the protocol and whether any discrepancies exist between the pattern of missing assessments between local and central reviews and between treatment arms with each of the two sources.

Disjoint time-windows will be considered to determine whether a TA was present or missing and will be defined based on the per-protocol grid. The following time-windows (in weeks) will be constructed: [0, 18],]18, 30],]30, 42], etc. for each patient, where '0' is the patient's date of randomization. Every time-window (with the exception of the initial, broader one) is centered at the scheduled time of TA, i.e., around week 24, week 36 for second and third window, respectively, etc. A patient is considered 'at risk' of missing his/her TA for any one of these time-windows if he/she either:

- was 'on study' for at least the first 6 weeks of the time-window (12 weeks for the first time-window), i.e., if the patient is ongoing at the time of the scheduled TA, or
- discontinued drug due to documented PD within the specific time-window.

For the purpose of this analysis, 'unknown' TAs (i.e., evaluations with an overall lesion response of 'unknown') will be considered to be missing. However, a clear distinction between 'truly missing' and 'present but unknown' needs to be done in the derived dataset to allow for both combined, i.e. missing and unknown treated the same, and separate analyses.

TAs performed after a documented PD will not be considered. In other words, the final time-window for which a patient would be at risk of a missing/unknown scan would be that during which the documented PD occurred.

For patients without documented PD, all TAs are considered up to the earliest of the following dates: death, the analysis cut-off, start of new anticancer therapy, discontinuation for either PD, withdrawal of consent or lost to follow-up.

The results will be presented by treatment arm and separately for central radiology review and investigator. Number of patients with at least one missing/unknown TA will be presented together with the following break down categories: number of patients with 1, 2,..,5 missing/unknown TAs.

Since the two treatment arms are expected to differ in the follow-up "tails" the following summaries will be displayed in addition: number of patients with at least one missing/unknown TA between the last adequate TA and PFS event or cut-off, number of patients with at least one missing TA after the study drug discontinuation.

3.10.2.9 Time to 1st tumor assessment (TA)

In order to investigate whether there are systematic differences between treatment arms in the timing of the first TA, an analysis of time to 1st TA will be performed using assessments from the investigator only.

Distinct TAs are identified by different evaluation numbers. If the TAs within one evaluation are done over more than one day, the date of TA will be the first day.

Time to 1st TA will be calculated from randomization (date of 1st TA - date of randomization + 1), i.e. only post-randomization TAs will be considered. The nominal numbering of evaluations will be ignored. The identification of the first TA will instead be based on the calendar dates.

Patients with no 1st TA will be censored at the earliest date of the following dates:

- Death

- Start of a new antineoplastic therapy
- Last contact (see Section 2.1.7 for definition)
- Analysis cut-off.

The analysis will include all patients from the FAS. Patients with no TA will be censored at the date of last contact (See Section 2.1.7 for definition).

Ascending Kaplan-Meier (KM) curves will be constructed by treatment arm. KM medians with 95% confidence intervals will be presented. Hazard ratio with 95% confidence interval will be obtained from the Cox proportional hazards model. A p-value from the (unstratified and 2-sided) log-rank test will be provided.

The following will be summarized by drug group: number of patients with a first TA, number of patients censored, median time to 1st assessment (in days).

3.10.2.10 Time to 2nd tumor assessment (TA)

This analysis will include all patients from the FAS who had a 1st TA corresponding to an overall lesion response different from PD and will be performed using assessments from investigator only.

Distinct TAs are identified by different evaluation number. If the TAs within one evaluation are done over more than one day, the date of TA will be the first day.

Time to 2nd TA will be calculated from randomization (date of 2nd TA - date of randomization + 1), i.e. only post-randomization TAs will be considered.

TAs done after PD or after further anti-neoplastic therapy or after the analysis cut-off date will be excluded.

Patients with no 2nd TA will be censored at the earliest date of the following dates:

- Death
- Start of a new antineoplastic therapy
- Last contact (see Section 2.1.7 for definition)
- Analysis cut-off.

Ascending Kaplan-Meier (KM) curves will be constructed by treatment arm. KM medians with 95% confidence intervals will be presented. Hazard ratio with 95% confidence interval will be obtained from the Cox proportional hazard model. A p-value from the (unstratified and 2-sided) log-rank test will be provided.

The following will be summarized by drug group: number of patients with 2nd TA, number of censored, median time to 2nd TA (in days).

If one of the analyses (time to 1st TA and time to 2nd TA) or both show a significant difference between the treatment arms a sensitivity analysis will be performed to address the impact of bias introduced by different timing.

3.10.3 Overall survival (OS)

The key secondary endpoint of this study is **overall survival (OS)**.

OS is defined as the time from date of randomization to date of death due to any cause. If a patient is not known to have died, survival will be censored at the date of last contact, (see Section 2.1.7 for definition).

The analysis of overall survival will include all deaths in the FAS up to the analysis cut-off date, regardless of whether they were observed during the blinded-drug phase, during the post-drug evaluations, during survival follow-up or during the treatment with open-label Everolimus.

Survival time, survival status, reason for censoring and death cause will be listed.

3.10.3.1 Hypothesis and test statistic

See Section 3.10.2.2.

3.10.3.2 Kaplan-Meier (K-M) estimates

See Section 3.10.2.3.

3.10.3.3 Hazard ratio

See Section 3.10.2.4.

3.10.3.4 Sensitivity and other supportive analyses of OS

If the OS interim analysis shows significant results then it will be considered as the final analysis.

The following supportive analyses will be performed (on FAS only) at the OS final analysis only:

- Stratified Cox proportional hazard model adjusting the drug difference for important baseline covariates (See Section 3.10.2.5 for details on important baseline covariates)
- Subgroup analyses of OS by baseline characteristics (See Section 3.10.2.5 for details on baseline characteristics)

The following supportive analyses will be performed (on FAS only) at the OS interim and final analyses:

- Rank-preserving structural failure time method (RPSFT) to correct for confounding introduced by cross-over (see Section 2.6.5.1.1).
- Marginal Structural Cox Proportional Hazards Model using the Inverse Probability of Censoring Weighting (see Section 2.6.5.1.2).

3.10.3.5 OS censoring reasons

Censoring reasons (‘alive’ or ‘lost-to-follow-up’) will also be summarized by treatment arm. Patients not known to have died will be censored for ‘Lost-to-follow-up’ if the time between their last contact date and the analysis cut-off date is longer than 44 days (per study protocol: all patients are expected to have monthly survival assessments after discontinuation from the study drug; 2 weeks window is added).

3.10.4 Best Overall Response (BOR)

BOR will be summarized by category (CR, PR, SD, PD, UNK) and by treatment arm (see also Section 2.5.2). The primary summary of BOR will be based on investigator data (see Source 1 in Table 3-1, Section 3.10.1). Supportive analysis of BOR will be based on adjudicated central radiology review (see Source 2 in Table 3-1, Section 3.10.1). BOR based on central radiology review (see Source 4 in Table 3-1, Section 3.10.1) will also be summarized.

3.10.5 Objective response rate (ORR)

ORR is defined as the proportion of patients with best overall response of complete response (CR) or partial response (PR). See [RAP module 3 - Post-text supplement 1] for details.

The primary analysis of ORR will be based on overall lesions responses per investigator (see Source 1 in Table 3-1) and will be performed on FAS. Supportive analysis of ORR will be based on adjudicated central radiology review (see Source 2 in Table 3-1). Patients with best overall response of 'Unknown' will be treated as non-responders in the calculation of the ORR in the FAS.

Responses will be summarized in terms of percentage rates with 95% confidence intervals.

3.10.6 Response duration / time to response

Response duration / time to response analyses will include only responders

Duration of response (CR or PR) applies only to patients whose best overall response was CR or PR. The start date is the date of first documented response (CR or PR) and the end date is the date of event defined as the first documented PD or death due to underlying cancer. In other words, the start date should be determined using the time the response was first determined and not using the time the response was confirmed. If a patient has not had an event, duration is censored at the date of last adequate tumor assessment.

Time to overall response (CR or PR) is the time between date of randomization/start of drug until first documented response (CR or PR).

Since a low number of responses is expected duration of response and time to response will be listed only. Confirmed responses will be flagged in the listing. The listing will be produced for investigator only.

3.10.7 Schema of Efficacy Analyses

The following tables provide summary of planned PFS analyses and analyses of secondary efficacy endpoints. The 'X' marks indicate the planned analyses.

Table 3-3 Schema of Efficacy Analyses for PFS

Endpoint	Analysis	Local radiology review (Investigator)	Independent adjudicated commitee (IAC)	Independent radiology commitee (IRC)
PFS	PFS primary analysis (KM, log-rank, HR (stratified unadjusted Cox PH model)) and summary of censoring reasons	X (+ PP set)	X	X

Endpoint	Analysis	Local radiology review (Investigator)	Independent adjudicated commitee (IAC)	Independent radiology commitee (IRC)
PFS	Stratified Cox PH model adjusting the drug difference for important baseline covariates	X		
PFS	Subgroup analyses of PFS by baseline characteristics (Cox PH model)	X		
PFS	PFS by strata	X		
PFS	PFS sensitivity analyses (actual event , backdating)	X		
PFS	Analysis to correct for informative censoring using central radiology review only			X
PFS	Cross-tabulation of 'PFS by X' vs. 'PFS by investigator' by PFS event type and by treatment		X	X
PFS	Comparison of PFS event type/censor between investigator and X		X	X
PFS	Comparison of PFS event type/censor and PFS date between investigator and X		X	X
PFS	PFS event type/censor time disagreement between investigator and X		X	X
PFS	Summary for the difference in days to progression as per central radiology review and as per investigator	X		X
PFS	Timing of tumor assessments	X		
PFS	Summary of missing tumor assessments	X		
PFS	Time to 1st and 2nd tumor assessment	X		
PFS	Comparison with overall lesion response as calculated by programs	X (listing only)		

PFS= Progression Free Survival

The patient population for all the analyses is the FAS (additional patient populations are specified in the table)

Table 3-4 Schema of Efficacy Analyses for other secondary efficacy endpoints

Endpoint	Analysis	Local Review (Investigator)	Adjudicated Central Review (IAC)	Central Review (IRC)
BOR	Frequency distribution	X (+ PP set)	X	X
BOR	Reasons for BOR=UNK	X	X	X
ORR	Shown in the BOR table	X (+ PP set)	X	X
DOR/TTR	Listings only	X		
Best % change	Waterfall plots	X	X	X

BOR= Best Overall response, ORR= Objective response rate
DOR= Duration Of Response, TTR= Time To Response
Best % change refers to measurements of target lesions

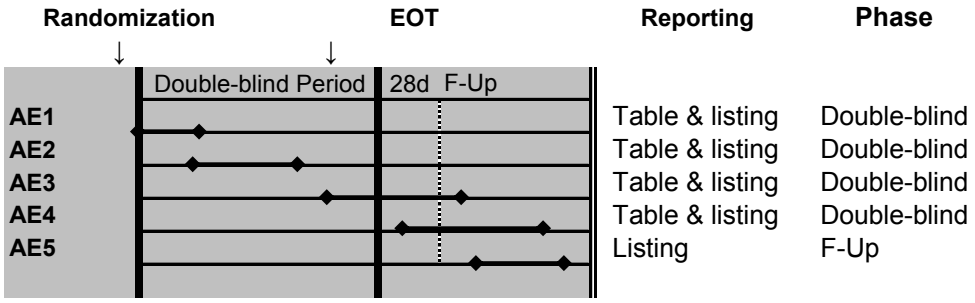
3.11 Safety evaluation

The assessment of safety will be based mainly on the frequency of adverse event summaries and on the number of laboratory values that fall outside of pre-determined ranges. Other safety data (e.g. pneumonitis, vital signs) will be considered as appropriate.

There will be two types of safety summaries (first one being the primary source of safety assessment):

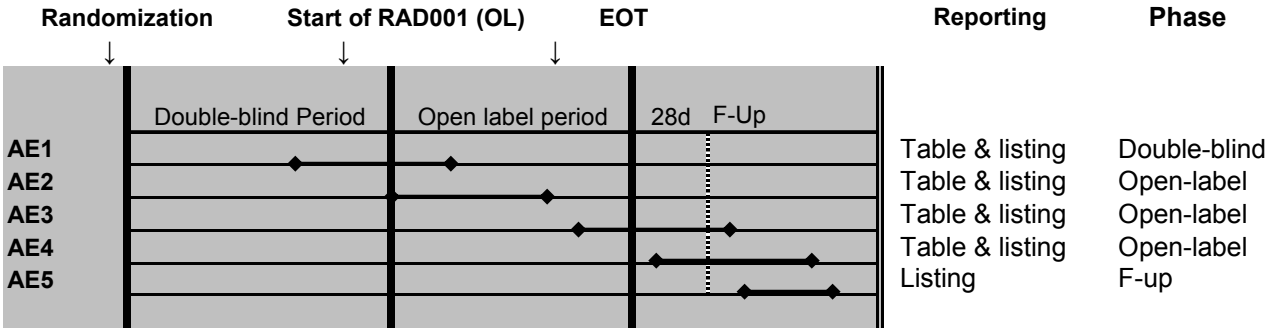
1. Safety summaries and listings based on assessments collected in the **double-blind phase** of the study. These outputs will use the Safety set (see Section 2.1.9 for definition). The safety summary tables will include only assessments collected no later than 28 days after double-blind study drug discontinuation and collected before cross-over to open-label Everolimus (i.e. before the first dose of open-label Everolimus was administered). All safety assessments collected before the cross-over will be listed and those collected later than 28 days after study drug discontinuation will be flagged.
2. Safety summaries and listings based on assessments collected in the **open-label phase** of the study. These outputs will use the open-label set (see Section 2.1.9 for definition). The summary tables will include only the safety assessments collected no later than 28 days after discontinuation of the open-label Everolimus. Any events after 28 days of the discontinuation of the open-label Everolimus will be listed (and flagged) only.

Figure 3-2 Reporting of AEs for patients not entering into the open-label phase



EOT=End of Treatment; OL=Open-label, 28d=28 days

Figure 3-3 Reporting of AEs for patients crossing-over to Everolimus 10 mg open-label



EOT=End of Drug; OL=Open-label, 28d=28 days

3.11.1 Adverse events data

3.11.1.1 Coding of AEs

Adverse events are coded using the Medical dictionary for regulatory activities (MedDRA version 13.0) terminology.

3.11.1.2 Grading of AEs

AEs will be assessed according to the [Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 (http://ctep.cancer.gov/forms/CTCAEv3.pdf)]. In case of an update of the CTC criteria and for legacy studies using an older version of CTC some mapping may be necessary when data need to be pooled.

The CTCAE represents a comprehensive grading system for reporting the acute and late effects of cancer treatments. CTCAE v3.0 grading is by definition a 5-point scale generally corresponding to mild, moderate, severe, life threatening, and death. This grading system inherently places a value on the importance of an event, although there is not necessarily proportionality among grades (a Grade 2 is not necessarily twice as bad as a Grade 1).

If CTCAE grading does not exist for an adverse event, Grades 1 – 4 corresponding to the severity of mild, moderate, severe, and life-threatening will be used. CTCAE Grade 5 (death) will not be used in this project; rather, this information will be collected on the "End of Treatment", "Study Completion Evaluation" or "Survival Information" eCRF pages.

3.11.1.3 General rules for AE Reporting

AE summaries will include all AEs starting on or after study day 1 (i.e. on or after the day of the first intake of study drug) and starting no later than 28 days after the last drug/exposure date (see Section 2.1.6). All AEs will be listed. AEs starting prior to study day 1 and AEs starting later than 28 days after the last drug/exposure date will be flagged in the listings.

AEs will be summarized by presenting the number and percentage of patients having at least one AE, and having at least one AE in each body system/primary system organ class (SOC_TXT), and for each preferred term (PT_TXT) using MedDRA coding. A subject with multiple occurrences of an AE will be counted only once in the AE category.

Separate AE summaries will be presented by primary system organ class, preferred term, and maximum CTC grade (AEVGRD1C). A patient with multiple CTC grades for an AE will be summarized under the maximum CTC grade recorded for the event. In the summaries presented by grade, all AEs will be pooled regardless of whether they are CTC gradable or not, i.e. regardless of whether the question "CTC AE" (variable CTIAEV1C) on the Adverse Events eCRF is answered 'Yes' or 'No'.

The frequency of CTC Grade 3 and 4 AEs will be summarized separately.

Any information collected (e.g. CTC grades, relatedness to study drug, action taken etc.) will be listed as appropriate.

In addition, a listing of adverse events occurring between the randomization and the first intake of study drug will be produced.

3.11.1.4 AE summaries

The following adverse event summaries will be produced:

- Adverse events, regardless of study drug relationship by primary system organ class and preferred term
- Adverse events with suspected relationship to study drug by primary system organ class, preferred term
- Adverse events, regardless of study drug relationship by primary system organ class, preferred term and maximum CTC
- Adverse events with suspected study drug relationship by primary system organ class, preferred term and maximum CTC
- CTC Grade 3 or 4 adverse events, regardless of study drug relationship by primary system organ class and preferred term
- CTC Grade 3 or 4 adverse events with suspected study drug relationship by primary system organ class and preferred term
- Deaths, by primary system organ class and preferred term
- Serious adverse events, regardless of study drug relationship, by primary system organ class and preferred term
- Serious adverse events with suspected study drug relationship, by primary system organ class and preferred term
- Adverse events leading to study drug discontinuation, regardless of study drug relationship, by primary system organ class and preferred term
- Adverse events requiring dose adjustment or study-drug interruption, regardless of study drug relationship, by primary system organ class and preferred term
- Adverse events requiring additional therapy, regardless of study drug relationship, by primary system organ class and preferred term.

3.11.1.5 Grouping of clinically notable AEs

Specific groupings of clinically notable adverse events will be considered and the number of patients with at least one event in each grouping will be reported. Such groups consist of

adverse events for which there is a specific clinical interest in connection with Everolimus 10 mg or adverse events which are similar in nature (although not identical). The groups are defined according to the criteria described in the following Table 3-5.

All notable adverse event groupings are defined through the use of Preferred Terms (PT), High Level Terms (HLT) or System Organ Classes (SOC) or through a combination of these three components. Details can be found in [RAP module 3 – Post-text Supplement 2]. Note that certain adverse events may be reported within multiple groupings.

Table 3-5 Clinically notable adverse event groupings

Clinically notable adverse event grouping	Source
Bleeding / Thromboembolic events	PT / HLT / PT+SOC
Pulmonary events	PT
Rash and similar events	SOC+HLT / PT
Renal events	PT / PT+SOC
Stomatitis /Oral Mucositis / Ulcers	PT
Haematopoiesis decreased / Cytopenias	PT / PT+HLT / HLT
Hepatic events	PT
Metabolic events	PT+HLT / PT
Infection and infestation	SOC

3.11.1.6 Grouping of indication-related adverse events

Indication-specific groupings of Intestinal obstruction or ileus adverse events will be considered and the number of patients with at least one event in that grouping will be reported. This group consist of adverse events for which there is a specific clinical interest in connection within the indication. The Intestinal obstruction or ileus group is defined through the use of Preferred Terms as shown in Table 3-6.

Table 3-6 Intestinal obstruction or ileus

Preferred term		
Abdominal adhesions	Gastrointestinal necrosis	Obstruction gastric
Acute abdomen	Gastrointestinal obstruction	Oesophageal hypomotility
Colonic atony	Gastrointestinal stenosis	Oesophageal stenosis
Colonic obstruction	Ileal stenosis	Peritoneal adhesions
Colonic pseudo-obstruction	Ileus	Peritoneal fibrosis
Colonic stenosis	Ileus paralytic	Peritonitis sclerosing
Distal ileal obstruction syndrome	Ileus spastic	Prepyloric stenosis
Distal intestinal obstruction syndrome	Impaired gastric emptying	Proctoparalysis
Duodenal obstruction	Intestinal dilatation	Pylorospasm
Duodenal scarring	Intestinal obstruction	Pylorus dilatation
Duodenal stenosis	Intestinal stenosis	Rectal obstruction
Fibrosing colonopathy	Intestinal strangulation	Rectal spasm
Gastric atony	Jejunal stenosis	Rectal stenosis
Gastric dilatation	Large intestinal obstruction	Small intestinal obstruction
Gastric ileus	Mechanical ileus	Small intestinal stenosis

Preferred term		
Gastric stenosis	Megacolon	Subileus
Gastrointestinal mucosal necrosis	Neurogenic bowel	Toxic dilatation of intestine

3.11.1.7 AEs adjusted for subject years exposure (SYE)

In order to account for differences in exposure of the Everolimus 10 mg arm relative to the placebo arm, incidence rates of selected adverse events will be presented as adjusted for number of subject years exposure (SYE).

SYE is the sum of each patient's exposure in days, divided by 365.25. The adjusted rate for a given AEs is calculated as number of events per 100 subject year exposure (=[n/SYE]*100).

3.11.1.8 Time to first onset of specific AEs

For selected AEs (or groups of AEs), the following analysis of time to first occurrence will be considered:

All AEs of interest occurring between the start of study drug and min(last drug/exposure date+28 days; start date of a new anticancer therapy) will be taken into account.

Time to first occurrence of an AE is defined as time from start of study drug to the date of first occurrence of an adverse event within the grouping, i.e. time in days is calculated as (start date of first occurrence of AE) – (date of first dose of study drug) +1.

A patient will be censored for time to first occurrence if:

- the patient dies with no event
- the patient receives a new anticancer therapy (including open-label Everolimus) with no event or before the event has occurred
- the patient discontinues from the study drug with no event (up to 28 days after study treatment discontinuation)
- the patient is still on-going at the cut-off with no event

In the absence of an event, the censoring date applied will be the earliest from the following dates: end of double-blind study drug + 28 days, analysis cut-off, new anti cancer therapy start, death and last contact date (see Section 2.1.7 for definition).

For the event of radiological pneumonitis (which is not captured on AE page), events will again be counted if they occur between start of drug and last drug/exposure date +28 days, unless the patient commenced a new anticancer therapy (including open-label Everolimus) prior to the event, in which case the event will be censored at the last CT scan where radiological changes of pneumonitis were evaluated by central review before the start date of the new anticancer therapy. All patients without an event will be censored at the last CT scan (where radiological evidence of pneumonitis was evaluated by central review) before the earliest date between end of double-blind study drug + 28 days, last visit, death, date of cut-off for analysis or new anticancer therapy start.

Ascending Kaplan-Meier curves will be constructed by treatment arm.

The following AE groupings (see the [RAP Module 3 – Post-text Supplement 2] for definition of the groups) will be considered:

- (non-infectious) pneumonitis, as defined by the 'Pulmonary events' AE grouping
- 'Stomatitis/oral mucositis and ulcers', as defined by the corresponding AE grouping
- Infections as defined by the SOC (MedDRA) 'Infections and Infestations'
- 'Renal events', as defined by the corresponding AE grouping
- 'Intestinal obstruction/ileus' as defined by AE grouping provided in Table 3-6 above.

3.11.2 Laboratory data

On analyzing laboratory assessments, data from all sources (central and local laboratories) will be combined. The summaries will include all laboratory assessments collected no later then 28 days after the last drug/exposure date (see Section 2.1.6).and before the start of the open-label drug. All laboratory assessments will be listed and those collected later then 28 days after the last drug/exposure date will be flagged in the listings.

Laboratory data will be classified (by biostatistics/SAS programming) into CTC grades according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) v3.0. A severity grade of 0 will be assigned when the value is within normal limits. (In the case when a local laboratory normal range overlaps into the higher (i.e. non-zero) CTC grade, the laboratory value will still be taken as within normal limits and assigned a CTC grade of zero.)

The following summaries will be produced for the laboratory data (by laboratory parameter):

- Number and percentage of patients with worst post-baseline CTC grade (regardless of the baseline status). Each patient will be counted only for the worst grade observed post-baseline.
- Shift tables using CTC grades to compare baseline to the worst post-baseline value will be produced for hematology and biochemistry laboratory parameters with CTC grades.
- For laboratory parameters where CTC grades are not defined, shift tables to the worst post-baseline value will be produced using the low/normal/high classifications based on laboratory reference ranges.

3.11.2.1 Time to first abnormal laboratory values

For given laboratory parameters or defined groups of laboratory parameters, the time-to abnormal laboratory value is defined as the time from start of drug to the date of the event, defined as any abnormal new or worsening (from baseline CTC grades) laboratory values. If a group of laboratory parameters is considered, the time to the earliest event will be used in the analysis. Abnormal laboratory values are considered up to 28 days after study drug discontinuation.

Patients with no new or worsening post-baseline laboratory values are censored at the date of the last laboratory value available (or, when considering a group of laboratory parameters, the earliest of the last available laboratory values) collected before the earliest of the following dates:

- Study drug discontinuation + 28 days
- death
- new anti-neoplastic therapy start

- analysis cut-off date.

Patients without any laboratory value at the time of the analysis cut-off will be censored at study day 1.

The following events (based on laboratory measurements) will be considered:

- Clinically significant liver impairment (AST, ALT, bilirubin), i.e. newly occurring or worsening CTC Grade 3 or above.
- Hyperglycemia defined using abnormal glucose increase laboratory values.

  Time-to abnormal glucose increase analysis will be performed using all CTC grades and will be repeated for CTC grades ≥ 3.

3.11.2.2 Listing of laboratory values

The following listings will be produced for the laboratory data:

- Listing of patients with laboratory values outside the laboratory reference ranges with values flagged to show the corresponding CTC grades and the classifications relative to the laboratory reference ranges
- Listing of all laboratory data with values flagged to show the corresponding CTC grades and the classifications relative to the laboratory reference ranges.

3.11.3 Vital signs

Vital sign assessments are performed in order to characterize basic body function. The parameters collected are the following: height (cm), weight (kg), body temperature (°C), heart rate (beats per minute), systolic and diastolic blood pressure (BP) (mmHg), and respiration rate (breaths per minute).

The criteria for clinically notable abnormalities are defined as follows:

Clinically notable elevated values

- Systolic BP: ≥ 180 mmHg and an increase ≥ 20 mmHg from baseline
- Diastolic BP: ≥ 105 mmHg and an increase ≥ 15 mmHg from baseline.
- Body temperature: ≥ 39.1°C
- Weight: Increase from baseline of ≥ 10%
- Heart rate: ≥ 120 bpm with increase from baseline of ≥15 bpm

Clinically notable below normal values

- Systolic BP: ≤ 90 mmHg and a decrease ≥ 20 mmHg from baseline
- Diastolic BP: ≤ 50 mmHg and a decrease ≥ 15 mmHg from baseline
- Body temperature: ≤ 35°C
- Weight: decrease from baseline of ≥ 10%
- Heart rate: ≤ 50 bpm with decrease from baseline of ≥ 15 bpm

The following summaries will be produced for each vital sign parameter for both the double-blind and the open-label phases of the study:

- Summary statistics for change from baseline to the worst post-baseline value (in both directions, i.e. from baseline to highest post baseline and from baseline to lowest post-baseline value)
- Number and percentage of patients with at least one post-baseline vital sign abnormality (in both directions, i.e. both elevated and below normal values).

In addition, the following two listings will be produced by drug group for both the double-blind and the open-label phase of the study:

- Patients with clinically notable vital sign abnormalities.
- All vital sign assessments will be listed by patient and vital sign parameter.

In both listings, the clinically notable values will be flagged as will the assessments collected later than 28 days after the last drug/exposure date.

3.11.4 Pneumonitis

3.11.4.1 Central radiology review

The statistical analysis will be based on the central radiological review of chest CT scans/X-Rays. All analyses conducted will be descriptive in nature.

Treatment arms will be compared with respect to the number (%) of patients with evidence of pneumonitis at baseline, post baseline and newly occurred or worsened cases. If both, central radiology review of chest CT scans and chest X-rays are performed, the correlation between the detection of non-infectious pneumonitis by chest X-ray vs. chest CT Scans will be investigated.

If both X-Rays and Chest CT scans are performed on the same day, only results from CT scans will be used for the summaries.

Since a separate listing organized by clinically notable AE groupings (see Table 3-5) will be produced, all pulmonary adverse events (i.e. AEs assigned to the group “Pulmonary events”) can easily be identified.

3.11.5 Other safety data

Data from other tests (e.g. pulmonary function tests, bronchoscopy) will be listed, notable values will be flagged, and any other information collected will be listed as appropriate.

All assessments collected later than 28 days after the last drug/exposure date (see Section 2.1.6) will be flagged in the listings.

Any statistical tests performed to explore the data will be used only to highlight any interesting comparisons that may warrant further consideration.

3.12 Other test data

3.12.1 WHO performance status

The WHO performance scale is an instrument designed by the World Health Organisation and used by doctors to describe the physical health of patients, ranging from 0 (most active) to 4 (least active):

Table 3-7 WHO Performance Scale

Score	Description
0	Able to carry out all activity without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to do light work.
2	Ambulatory and capable of all self-care but unable to carry out any work. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confirmed to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

The patient performance status will be summarized by time windows (see Section 2.1.8) and treatment arm using numbers (%) of patients in each score category.

Time to definitive deterioration of WHO performance status will be analyzed and compared between the treatment arms.

Definitive deterioration is defined as a definitive increase in performance status from a baseline of 0 or 1 to WHO ≥ 2, or, from a baseline value of 2 to WHO ≥ 3. Deterioration is considered definitive if no later decrease below the defined threshold is observed within the course of the study. A single measure reporting an increase in WHO performance status is sufficient to consider it as definitive only if it is the last one available for this patient.

(Example 1: if the score is 1 at baseline and then 1 – 2 – 1 – 2 – 3 at study days 28 – 57 – 83 – 115 – 150, respectively, then the time to definitive deterioration is 115 days, Example 2: if the score is 1 at baseline and then 1 – 1 – 2 at study days 28 – 57 – 83, respectively, with no assessment after day 83 then the time to definitive worsening is 83 days).

The time to definitive deterioration is calculated from the date of randomization. Baseline is the last available assessment on or before date of randomization.

In addition, death is considered as a worsening of WHO performance status if it occurs close to the last available assessment, where “close” is defined as twice the planned period between two assessments (i.e. 2×cycle length+2 weeks=10 weeks=70 days). This avoids overestimating the time to definitive worsening in patients dying after an irregular assessment scheme. Patients who die after more than twice the planned period between two assessments are censored at the date of their last available assessment of WHO performance status.

Patients receiving any further anti-neoplastic therapy (including open-label Everolimus) before definitive deterioration will be censored at the date of their last assessment before

starting this therapy. Patients that have not worsened as of the cutoff date will be censored at the date of their last assessment before the cutoff.

Patients who discontinued the study drug prior to the analysis data cut off will be censored at the date of their last assessment before study discontinuation.

Last, patients with no baseline score will be censored at study day 1.

Kaplan-Meier estimates will be constructed for each treatment arm. Median for each drug group will be obtained along with 95% confidence intervals.

Stratified one-sided log-rank test will be used to test the difference in time to definitive worsening of WHO performance status between the treatment arms. **Stratified** Cox proportional hazard model will be used to obtain the hazard ratio (with 95% confidence interval).

3.13 Pharmacokinetic analyses

3.13.1 Analysis set used for pharmacokinetic analyses

The PK analyses will be performed in the safety set using all valid PK samples. All analyses will be performed by actual dose for PK parameters and by "leading dose" for pre-dose concentrations (definition see below). Patients not at steady state will be excluded from the analysis of PK parameters and pre-dose concentrations.

Steady state for daily dosing refers to the state after continuous 4 days dosing at the same dose and dosing scheme.

3.13.2 Pharmacokinetic parameters

Table 3-8 PK parameters

$AUC_{(0\text{-}tlast)}$	The area under the blood concentration-time curve from time zero to the last quantifiable concentration [ng x h x mL^{-1}]
AUC_{τ}	The area under the blood concentration-time curve during a dosing interval (τ) [ng x h x mL^{-1}]
C_{max}	The maximum (peak) blood concentration after single dose administration [ng x mL^{-1}]
C_{min}	The minimum (pre-dose) blood drug concentration in the dosing interval (τ) [ng x mL^{-1}]
CL/F	The total apparent body clearance of drug from the blood [L x h^{-1}] or [L x h^{-1} x m^{-2}] or [L x h^{-1} x kg^{-1}]
t	Time after drug administration [h]
t_{max}	The time to reach peak or maximum concentration following drug administration [h]
τ	Dosage interval [h]

Apparent clearance CL/F will be derived from actual dose and AUC_{τ} . However, if AUC_{τ} cannot be reliably estimated, CL/F will be derived from actual dose and AUC(0-tlast). These values will be flagged in the individual PK parameter listing.

For body surface normalization, the Gehan and George formula is used:

$$BSA\left[m^2\right] = 0.0235 \cdot Height\left[cm\right]^{0.42246} \cdot Weight\left[kg\right]^{0.51456}$$

3.13.3 PK analyses

This section describes the standard PK analyses. Additional sensitivity analyses can be found in Section 3.13.4.

Only confirmed pre-dose C_{min} values collected 20-28 hours after the last dose in the daily dosed patients and 44-52 hours for patients dosed every other day are considered valid and will be included in the standard analysis for pre-dose concentrations.

All valid PK parameters will be included into standard analysis.

Descriptive statistics of concentrations and PK parameters will include n, arithmetic mean, geometric mean, median, SD, coefficient of variation CV (%), geometric CV (%), minimum and maximum. For t_{max}, only median, minimum and maximum will be calculated.

In general, geometric mean and the geometric CV (%) will be derived from non-zero Cmin values.

Coefficient of variation CV (%) is calculated as follows: 100*(SD/arithmetic mean).

Geometric CV (%) is calculated as follows:

$$CV(\%) = 100 \cdot \sqrt{\exp\left(\hat{\sigma}^2\right) - 1} \qquad (1)$$

where σ^2 denotes the variance of the log-transformed values.

Concentration-time profiles will be presented individually and by tabulating and plotting summary statistics over time showing mean (SD) concentrations at each time point. Summary of concentration-time profiles are shown in a linear and a semi-logarithmic view. Concentration-time profiles for Japanese patients will be summarized separately if 3 or more Japanese patients with an evaluable profile are available.

PK parameters, given in Table 3-8, will be summarized for patients who have taken the same actual dose. Summary statistics will be produced if the sample size for each dose group is greater or equal 3 or listed only otherwise.

PK parameters given in Table 3-8 and BSA and weight normalized CL/F will be summarized in the same way for Japanese patients and compared to non-Japanese patients if 3 or more Japanese patients with evaluable PK parameters are available.

Pre-dose values are summarized by time point and are graphically represented by showing box plots at all sampling time points with sufficient number of values (≥3 samples).

In particular, 3 dose levels are planned for this trial, 10mg o.d., 5mg o.d. and 5mg every other day. Consequently, patients are at steady state if they have taken 10mg or 5mg for four days prior to pre-dose sampling respectively or 5mg on day -4 and -2 before pre-dose sampling for 5mg dose every other day.

Pre-dose concentrations are also summarized by time point for Japanese patients and compared to non-Japanese patients.

Pre-dose concentrations are also summarized by time point for patients with and without comedication with sandostatin.

All summaries and figures of pre-dose concentrations will be presented by "leading dose" which is the dose given at steady state conditions before pre-dose sampling. Samples taken from patients who are not at steady state or from patients who have vomited within 4 hours of taking a Everolimus dose on the day (before collection of PK sample) will be excluded from the summaries and listed only.

3.13.4 Sensitivity Analyses

In addition to the standard PK analyses, further sensitivity analyses will be performed. The following criteria apply in addition to the criteria for the standard PK analysis detailed in section before.

For any sensitivity analysis the following PK samples will be excluded:

- PK parameters from patients who vomited within 4 hours of the last dose
- As for the standard analysis for PK, PK parameters not taken at steady state
- The RAD001 pre-dose samples (C_{min}) collected on a given day, when the patient is known to be taking a concomitant medication that is a substrate or inhibitor of CYP3A4 and/or P-glycoprotein (PgP) on any one of the 4 days prior to collection of the pre-dose samples.
- The RAD001 pre-dose samples (C_{min}) collected on a given day, when the patients is known to be taking a concomitant medication that is known to be an inducer of CYP3A4 and/or PgP continuously over a 7 day period prior to collection of the pre-dose samples. Any pre-dose samples collected prior to use of these medications will be included in the analysis

3.13.5 Summary statistics for PK samples obtained from patients taking concomitant medication

Summary statistics for confirmed C_{min} samples obtained from patients taking concomitant medication will be provided for the following categories:

- when patient is taking a concomitant medication known to be a **substrate of CYP3A4 and/or PgP** on any one of the 4 days prior to collection of these PK samples
- when patient is taking a concomitant medication known to be a **weak inhibitor of CYP3A4** on any one of the 4 days prior to collection of these PK samples
- when patient is taking a concomitant medication known to be a **moderate inhibitor of CYP3A4** on any one of the 4 days prior to collection of these PK samples
- when patient is taking a concomitant medication known to be a **strong inhibitor of CYP3A4** on any one of the 4 days prior to collection of these PK samples
- when patient is concomitantly taking an **inducer of CYP3A4 and/or PgP continuously** over the previous 7 days
- when patient is taking a concomitant medication known to be an **inhibitor of PgP** on any one of the 4 days prior to collection of these PK samples

In case of co-medications of more than one inhibitor and substrate (CYP3A4 or PgP), patients will be assigned to the group of the stronger inhibitor. In case of co-medication of both inducer and weak, moderate or strong inhibitor then patients will not be assigned to any subgroup. In case of co-medication of substrate and inducer patients will be assigned to the subgroup of inducers.

3.13.6 Handling missing and invalid values

Missing concentrations or PK parameters will not be imputed. Concentrations below the Lower Limit of Quantification (LLOQ) are automatically replaced by zero when transferred from the bio-analytical data base (Watson Lims).

Invalid concentrations or PK parameters will be flagged in the PK concentration data set and the PK parameter data set by the pharmacokineticist after the merge of clinical and bio-analytical data has taken place. Flagged values will not be included into summaries but listed only.

3.13.7 Analysis of relationship between Everolimus 10 mg blood levels and efficacy/safety endpoints.

3.13.7.1 Analyses of the relationship between Everolimus blood levels and safety endpoints

The relationship between RAD001 exposure and time to first adverse events will be investigated for the clinically notable adverse events, as defined in Table 3-1, Section 3.10.1. However, since very low number of events are expected for the notable adverse event group "Bleeding / Thromboembolic events", this category will not be analyzed.

For the time to first notable adverse event, a Cox regression model will be fitted including the log-transformed time-normalized Cmin as a covariate. Further covariates might be included if appropriate.

The time-normalized C_{min} ($C_{min,TN}$) is defined as:

$$C_{min,TN} = AUCC_{(0\text{-}t)}/t$$

Where $AUCC_{(0\text{-}t)}$ denotes the area under the pre-dose concentration-time curve from study start to the start date of the respective adverse event.

For derivation of $C_{min,TN}$ the following procedure will be applied. The $AUCC_{(0\text{-}t)}$ is calculated by trapezoidal formula. For this calculation, C_{min} at study start is assumed to be zero. From study day 5 onwards, C_{min} is considered to be the same as observed on cycle 1 day 15 (first observation carried backwards). This procedure is justified by the observation that steady-state concentration is achieved within 4 days of once daily treatment with RAD001.

C_{min} might not be estimated at the start date of the adverse event. If no pre-dose concentration is available at the start of the adverse event, the calculation of $AUCC_{(0\text{-}t)}$ will include pre-dose concentrations that are sampled within a time-window of +/- 4 days around the start date. If there is no sample taken within this time window of +/- 4 days the last C_{min} will be carried forward to the start date of the adverse event. In case of dose changes without available concentrations, the following assumptions are made: a) during dose interruptions C_{min} is

assumed to be zero and C_{min} at the start of new treatment period is considered to be the same as the first observed C_{min} after dose interruption, b) for 5mg daily C_{min} is assumed to be ½ of the last observed C_{min} under 10mg daily dose before the change of the dose, c) for 5mg every other day, C_{min} is assumed to be ¼ of the last observed C_{min} before the change of the dose.

Additionally, a subgroup analysis will be done in the same way as detailed above to compare Japanese and non-Japanese patients.

Total billirubin and albumin will separately be related to C_{min} by correlating individuals geometric mean of pre-dose concentrations preceding the laboratory assessments at time t with the individuals results for total bilirubin at time t. A table will report Pearsons and Neymans coefficient of correlation together with number of subjects included for every time point starting with cycle 1 day 15. Correlations will only be given if the number of patients is greater or equal three at a respective time point.

In addition, a scatter plot will show individual's geometric mean of pre-dose concentrations preceding an assessment at time t versus the results of total bilirubin and albumin separately. This figure will include all results from different time points.

Censoring mechanisms for adverse events are detailed in Section 3.11.1.8.

3.13.7.2 Analyses of the relationship between Everolimus blood levels and efficacy endpoints

The relationship between RAD001 exposure and PFS will be investigated by a Cox regression model including the log-transformed covariate time-normalized C_{min} as defined above, history of sandostatin treatment (Y/N) and comedication with sandostatin (Y/N) as separate covariates. Further covariates might be included if appropriate.

The analyses will be repeated comparing Japanese and non-Japanese patients.

In addition, tumor size, expressed as the individuals sum of longest diameters of all target lesions at time t, will be investigated by a linear mixed model including the covariate Cmin, represented by the log-transformed individual's geometric mean of pre-dose concentrations of the preceeding three cycles, and a random subject term for the intercept and the slope parameter for Cmin and history of sandostatin treatment (Y/N) and co-medication with sandostatin (Y/N) as separate covariates. Further covariates might be included if appropriate.

However, caution needs to be paid to the assessments where an occurrence of a new lesion or worsening in non-target lesions (resulting in PD as an overall lesion response at given assessment) contradicts the measurements obtained on target lesions. These assessments will not be used for the analysis. Patients without any valid assessments will be excluded from the analysis. Patients without any target lesions at baseline will be excluded as well (see also Section 2.5.6).

Tumor size, expressed as the mean of individual's sum of longest diameters of all target lesions at time t, will be shown in a figure together with SD by Cmin, represented by the individuals geometric mean of pre-dose concentrations of the preceding three cycles of time t.

Mean change of tumor size from baseline and its SD will be shown graphically by Cmin, represented by the individual's geometric mean of pre-dose concentrations of the preceding three cycles of time t.

3.14 Biomarkers

Only biomarkers collected in the clinical database will be analyzed by Novartis Oncology Biostatistics and Statistical Reporting group.

All the analyses will use patients from the FAS with available data for the biomarker considered. These analyses will be treated as exploratory.

As per the study protocol, the following biomarkers are collected in the study:

- Biochemical tumor markers (collected monthly if elevated at baseline): chromogranin A (CgA), neuron specific enolase (NSE), pancreatic polypeptide, gastrin, glucagon, and VIP. Insulin, pro insulin, c-peptide which will be analysed in patients with insulinoma only ;
- Angiogenesis markers (collected for patients consenting to exploratory studies, samples collected at baseline, and monthly for the first 3 months only): basic FGF, VEGF, PLGF, sVEGFR1 and sVEGFR2;
- Activation of the mTOR pathway and proliferative markers assessed by immunohistochemical and genetic analyses in patients for whom tumor biopsy sample is available: Cyclin D1, phosphoserine 240-S6 ribosomal protein (pS6), Tumor protein 53 (p53), Ki 67 proliferation antigen,. These markers will be analyzed if available at the time of core database lock. Other markers collected will be listed only.

The biomarkers will be analyzed using summary statistics for raw data and changes from baseline.

All these analyses will be treated as exploratory.

Analysis of Chromogranin A (CgA)and Neuron Specific Enolase (NSE)

These two soluble biomarkers CgA and NSE, are of particular interest in this study. Data from a phase II study (RADIANT-1) in pancreatic NET patients treated with Everolimus 10 mg with or without Sandostatin LAR (RADIANT-1) suggests that these two biomarkers may be correlated with clinical outcomes.

CgA and NSE baseline levels will be categorized using the upper limit of normal range (ULN) as follows and summarized by means of contingency tables, by treatment group:

- CgA: '≤ 2 xULN' vs. > '2xULN'
- NSE: '≤ ULN' vs. > 'ULN'

CgA and NSE responses to treatment will be investigated. For each parameter, early response, response at each cycle and best response are defined as follows:

1. **Early response** is defined for patients with elevated level at baseline:
   - Early response: change from baseline to cycle 2 day 1 ≤ -30% (i.e. at least 30% decrease) or normalization at cycle 2 day 1
   - Non-early response: change from baseline to cycle 2 day 1 > -30% without normalization.
2. **Response at cycle k** is defined for patients with elevated level at baseline as a 3-category variable:

- Response: change from baseline to cycle k day 1 ≤ -50% (i.e. at least 50% decrease) or normalization at cycle k day 1
- Stable: change from baseline to cycle k day 1 > -50% and < 100% without normalization
- Progression at cycle k: Increase from baseline >= 100%

3. **Best response** is defined as the best response observed over all cycles.

If more than one biomarker assessment fall within the time window corresponding to a given cycle, the minimum value will be considered for the derivation of early response and response at that cycle e.g. if reported CgA levels are 53 ng/ml at Day 25 and 41 ng/ml at Day 38, both being within the time window for cycle 2 day 1 ([23-42]), then 41 ng/ml will be used for the assessment of response.

CgA and NSE early response and best response will be summarized by means of contingency tables, by treatment group.

The relationship between clinical outcomes (tumor shrinkage as per local assessment, PFS per local assessment and OS) and these two biomarkers will be explored further, as described below.

1. Scatter plots of PFS times (event or censor) as per local investigator by baseline level of the biomarker considered, by treatment group. Different symbols will be used for censored and uncensored events. Considering the expected wide range of values and skewed distribution, the biomarker values will be displayed on the log-scale;
2. Kaplan-Meier plots of estimates of the PFS survival function will be constructed, for each treatment group, within each biomarker baseline category. Median PFS will be displayed along with 95% confidence intervals. The hazard ratio (Everolimus / Placebo) and its 95% confidence interval will be obtained from a stratified Cox model within each baseline category. The strata are defined by the use of prior cytotoxic chemotherapy (Yes vs. No) and by the WHO performance status (0 vs. 1-2) at baseline. The treatment groups will also be compared, within each category, by means of a stratified log-rank test adjusting for the same stratification factors;
3. The above analysis will be repeated for early response;
4. Kaplan-Meier plots of estimates of the PFS survival function will be constructed for each baseline category, regardless of the treatment group. Median PFS will be displayed along with 95% confidence intervals. The hazard ratio (and its 95% confidence interval) of low vs. high baseline will be obtained from a stratified Cox model with treatment, prior cytotoxic chemotherapy (yes/no) and WHO performance status (0 vs. 1-2) at baseline as the stratification factors; The two subgroups will also be compared by means of a stratified log-rank test adjusting for the same stratification factors;
5. The above analysis will be repeated for early response;
6. All the above analyses will be repeated for OS;
7. Waterfall plots of the best tumor shrinkage as per local assessment, by treatment group, within each baseline category as defined above;
8. Waterfall plots displaying the best tumor shrinkage as per local assessment, by treatment group, for early responders and non-responders separately;

Analysis of Ki 67

Ki 67 is known to be a proliferative marker of neuroendocrine tumor. Ki 67 is assessed by immunohistochemistry from archival tissue. Baseline Ki 67 will be categorized as follows and summarized by means of contingency tables, by treatment group:

- ≤ 2 % ,
- 2 < to ≤5 %,
- > 5 %

The relationship between clinical outcomes (tumor shrinkage per local assessment, PFS per local assessment and OS) and Ki 67 will be explored further, as described below.

1. Scatter plots of PFS as per investigator by Ki 67 level, by treatment group. Different symbols will be used for censored and uncensored events. Depending on the range of values, the log-scale might be used for displaying Ki 67 values;
2. Kaplan-Meier plots of estimates of the PFS survival function will be constructed, for each treatment group, within each Ki 67 category. Median PFS will be displayed along with 95% confidence intervals. The hazard ratio and its 95% confidence interval of Everolimus 10 mg to placebo will be obtained from a stratified Cox model within each baseline category and with prior cytotoxic chemotherapy (yes/no) and WHO performance status (0 vs. 1-2) at baseline as the stratification factors; The treatment groups will also be compared, within each category, by means of a stratified log-rank test adjusting for the same stratification factors;
3. Kaplan-Meier plots of estimates of the PFS survival function will be constructed for each baseline category, regardless of the treatment group. Median PFS will be displayed along with 95% confidence intervals.
4. All the above analyses will be repeated for OS;
5. Waterfall plots of the best tumor shrinkage as per local assessment, by treatment group, within each Ki 67 category as defined above;

Analysis of angiogenesis markers

Angiogenesis effect of Everolimus 10 mg will be investigated on the angiogenesis markers using longitudinal models.

Models will be fitted on change from baseline (after log-transformation for relative changes defined as the ratio of post-baseline value over baseline value) with baseline (also log-transformed as appropriate), treatment, cycle, prior cytotoxic chemotherapy (yes/no), WHO performance status (0 vs. 1-2) and the interaction term treatment by cycle as fixed effect. The time variable cycle will use the time window derived variable defined in Section 2.1.8. Only data collected from baseline through Cycle 4 Day 1 will be included in the model. Unscheduled data, if any, collected beyond Cycle 4 Day 1 will not be included in the model.

Values below the lower limit of quantification (LLOQ) are reported as 0. To allow the above data transformation, these values will be replaced by 0.5*LLOQ and if the later is not known at the time of the core database lock, then nil values will be replaced by 0.5*{Min(values > 0) -1}.

To account for correlated repeated measures within patients an unstructured variance-covariance matrix will be used.

Relevant adjusted means and associated confidence intervals will be derived.

The following SAS code will be used:

```
PROC MIXED DATA=myData;
    CLASS treat subjid visit;
    MODEL response=baseline treat p_cyttox who_cat  visit treat*visit / SOLUTION DDFM=KR;
    REPEATED visit / SUBJECT=subjid   TYPE=UN R RCORR;
    LSMEANS treat*visit / CL   ALPHA=0.05;
    ESTIMATE 'Everolimus vs. Placebo @ C2-D1'   treat -1 1   treat*visit  -1  0  0  1  0  0/ CL ALPHA=0.05;
    ESTIMATE 'Everolimus vs. Placebo @ C3-D1'   treat -1 1   treat*visit   0 -1  0  0  1  0/ CL ALPHA=0.05;
    ESTIMATE 'Everolimus vs. Placebo @ C4-D1'   treat -1 1   treat*visit   0  0 -1  0  0  1/ CL ALPHA=0.05;
RUN;
```

3.15 Interim analysis for overall survival

In this study, PFS per local investigator assessment is the primary endpoint and OS is the key secondary endpoint. However, since the study was not powered to detect a difference in OS the number of deaths expected at the time of final PFS analysis is expected not to be sufficient to have at least reasonable chance (i.e. statistical power) to achieve statistical significance for this key secondary endpoint. Therefore, the formal final analysis of OS will be performed at a later time point, when sufficient survival events have been observed (see Table 3-9). It should also be noted that the analysis of OS is likely to be confounded due to treatment cross-over.

We consider the following two time points $s_1 < s_2$ (note: these are meant as time points on the time axis and not information fractions):

- s_1 = time of final analysis of PFS when targeted number of local PFS events is expected to be observed
- s_2 = time of final analysis of OS when sufficient number of deaths is expected to be observed.

3.15.1 Group sequential design for overall survival

The statistical methodology for analyzing the OS will be based on a two-stage group sequential design with one interim analysis performed at s_1 and final analysis performed at s_2.

The alpha-spending function described in Lan and DeMets (Lan and DeMets 1983) for one-sided test has the following functional form:

$$\alpha(t) = 2 - 2\phi(Z_{\alpha/2} / \sqrt{t})$$

This function generates stopping boundaries that closely resemble the O'Brien-Fleming boundaries (O'Brien and Fleming 1979). As pre-specified in the study protocol, the calculations will use α=0.025.

3.15.1.1 Testing strategy with PFS as a primary endpoint and overall survival as a key secondary endpoint

PFS per local investigator assessment is the primary endpoint and OS is the key secondary endpoint, for which a control of the Type I error rate is required.

By pre-specifying the OS as a key secondary endpoint, a hierarchical testing procedure which allows the testing of OS if PFS is statistically significant is meant to be adopted. This statistical testing approach is consistent with the strategy of seeking inclusion of OS results in the drug label, in the situation where the primary endpoint PFS achieves statistical significance and a formal statistical testing of OS shows benefit in favor of Everolimus 10 mg.

There are 2 questions that need to be addressed:

1. How to maintain the control of the family-wise Type I error probability (associated with testing the two endpoints PFS and OS) in the situation where the timing of OS interim analysis is driven by the primary endpoint PFS (considering that OS events are observed after PFS events)?
2. When to perform the final analysis of secondary endpoint OS, in the situation where the timing of OS interim analysis and OS final analysis is driven by the primary endpoint PFS (considering that OS events are observed after PFS events) ?

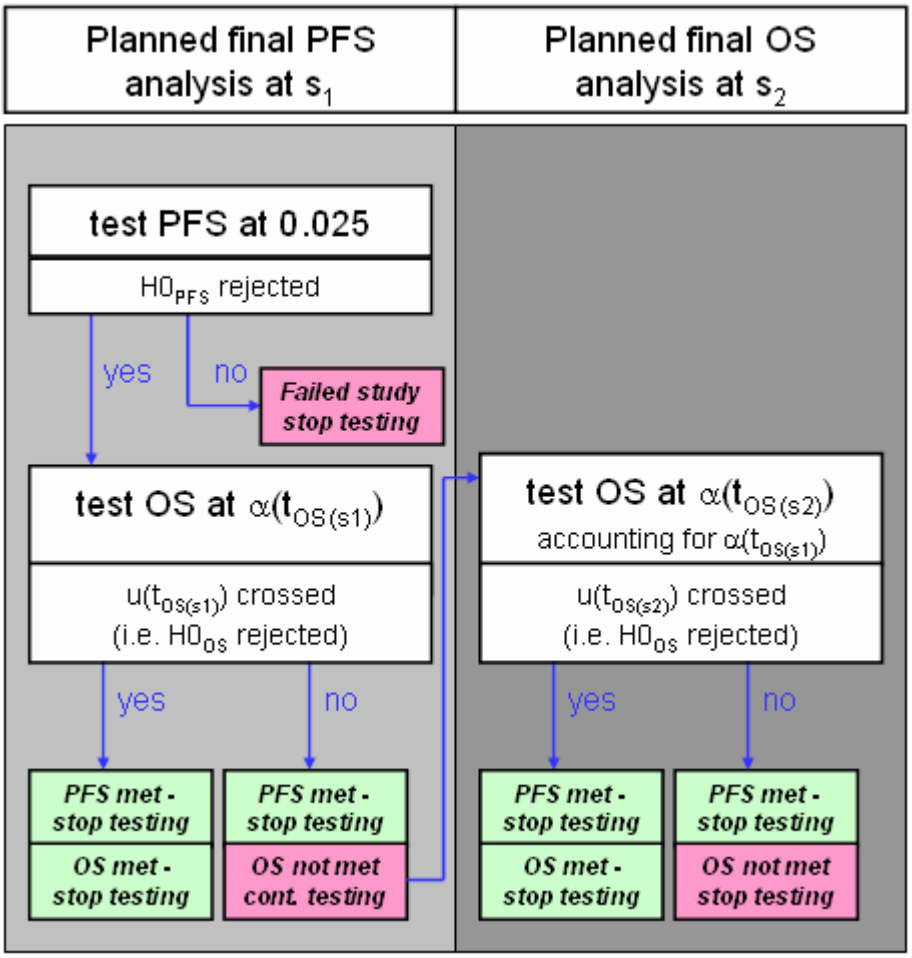
An intuitive hierarchical testing strategy to address the first question might be to test for OS only conditionally to PFS being found significant, using the same level of significance α that was used to test for the primary endpoint PFS. It has, however, been shown recently (Hung et al 2007) that this conventional hierarchical strategy when applied in a group sequential design does not control the overall Type I error rate (or the family-wise type I error probability) in the strong sense. It has been demonstrated that the correlation between the two endpoints and the effect size of the primary endpoint are two nuisance parameters that determine the level of the Type I error probability of falsely concluding a positive effect on the secondary endpoint.

The testing strategy for OS will be implemented by the use of one alpha spending functions α(t) for OS as described in Figure 3-4. Notation used in the figure is defined as follows:

- $H0_{PFS}$ and $H0_{OS}$ are the null hypotheses for testing PFS and OS, respectively.
- α(t) is the alpha-spending function for OS.
- s_1, s_2 are time points for planned final analysis of PFS when targeted number of PFS events is expected to be observed and planned final analysis of OS. (Note: these are time points on the time axis and not information fractions).
- $t_{OS(s1)}$, $t_{OS(s2)}$, represent information fractions for OS at time points s_1, s_2, respectively.
- $u(t_k)$ is the efficacy stopping boundary for OS at information fraction t_k.

The testing strategy for overall survival has been defined after the finalization of the study protocol but before the database lock. Calculation of spending and corresponding critical values will be done as described in the Table 3-9. This testing strategy controls the overall Type I error rate.

Figure 3-4 Testing of PFS (primary) and OS (key secondary)



The study was not originally sample sized for the overall survival endpoint. Calculations shown below were performed prior to the database lock.

Using a log-rank test at the one-sided 2.5% significance level, a total of 250 survival events would allow for at least 80% power to demonstrate a 30% risk reduction (assuming that the overall survival follows the exponential distribution with median of 24 and 34.3 months for Placebo and RAD respectively, i.e. hazard ratio= 0.70), in a design with 1:1 randomization.

Table 3-9 Design properties of the proposed two stage group sequential design for OS

	First interim at s_0 (Final PFS analysis)	**Final analysis at s_2** (Final OS analysis)
Information fraction (%)	47.2	100
Number of events	118	250
Patients accrued	392	392
Boundaries		
Efficacy (reject H0)		
Z-scale	3.0679	1.9661
p-scale	0.001078	0.024644
Cumulative Stopping probability (%)[2]		
Under H0 for activity[2]	0.10%	2.39%
Under Ha for activity[2]	12.57%	80.09%

[2] results obtained by simulations. Probabilities are reported as if OS was tested alone, regardless of the testing strategy with PFS. The true probabilities should take into account the probability of PFS at each look.

At OS interim analysis, information fraction will be computed as the ratio of the number of events actually observed relative to the number targeted for the final analysis. The critical value for the final analysis will be calculated using the exact number of observed events at the final cut-off date, and considering the α-levels spent at interim analysis (analyses), in order to achieve a cumulative type I error smaller than 2.5% for one-sided test.

3.16 Subgroup analyses

Japanese patients:

In addition to the efficacy subgroup analyses defined in Section 3.10.2.5, the following subgroup analyses will be also performed for Japanese patients (Japanese patients are defined as Japanese patients randomized in the Japanese center). The following summary tables will be repeated:

- Patient disposition by treatment
- Protocol deviations by category
- Analysis populations
- Demographic characteristics
- Patient and disease characteristics at baseline
- RECIST tumor-specific characteristics at baseline
- History of prior long-acting somatostatin analog

- Prior antineoplastic therapy

Definition of Regions

Subgroups analysis will be performed by regions as detailed in Section 3.10.2.5. Europe, America and Asia have been defined as detailed in Table 3-10.

Table 3-10 Definition of regions used for the subgroup efficacy analyses

Region	Countries (number of randomized patients)	Total randomized
Europe	Belgium (15), Switzerland (2), Germany (18), Spain (16), France (52), Great Britain (9), Greece (3), Italy (30), Nederland (7), Slovakia (3), Sweden (1)	156
America	Brazil (1), USA (165), CAN (19)	185
ASIA	Japan (40), Korea (9), Taiwan (18), Thailand (2)	69

3.16.1 Safety

The key summary outputs for adverse events will be repeated for Japanese patients.

3.16.2 Efficacy

The following outputs will be repeated for Japanese patients:

- Analysis of PFS using Kaplan-Meier and Cox's Proportional Hazard model (tables and figures) as per investigator, adjudicated central radiology review and central radiology review: Hazard ratio with 95% CI will be calculated and the unstratified log-rank test and unstratified Cox model will be used.
- Analysis of OS using Kaplan-Meier and Cox's Proportional Hazard model (tables and figure): Hazard ratio with 95% CI will be calculated and the unstratified log-rank test and unstratified Cox model will be used
- Best overall response as per investigator, adjudicated central radiology review and central radiology review (table)
- Best percentage change from baseline in sum of longest diameters as per investigator, adjudicated central radiology review and central radiology review (figure)
- Analysis of time to definitive deterioration of WHO performance status using Kaplan-Meier and Cox's Proportional Hazard model (tables and figure)

All analyses will be performed using the FAS. In addition, analyses of PFS using the investigator radiology review will be repeated using the PP set.

3.17 Median follow-up of the study

Median study follow-up (in months) will be calculated as follows:

([analysis cut-off date] - [median randomization date] + 1) / 30.4375

Median randomization date is obtained by first sorting all patients in the FAS by the randomization dates and then taking the date of the median patient (i.e. patient in the middle of the sorted list in case of odd number of patients or the average between the two patients in the middle of the sorted list in case of even number of patients).

3.18 Sample size calculation

This section presents the sample size considerations as presented in the study protocol.

Using an unstratified log-rank test at the one-sided 2.5% significance level, a total of 282 events would allow for 92.6% power to demonstrate a 33% risk reduction (hazard ratio for RAD/placebo of about 0.67, as calculated from an anticipated 50% increase in median PFS, from 6 to 9 months in the Everolimus 10 mg arm compared to the placebo arm).

With a uniform accrual of approximately 23 patients per month over 74 weeks and a minimum follow up of 39 weeks, a total of 352 patients would be required to obtain 282 PFS events. With an estimated 10% lost to follow up patients, a total sample size of 392 patients should be randomized.

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