NOVARTIS

Clinical Development

RAD001

CRAD001C24114 / NCT00767819

Multicenter, triple-arm, single-stage, phase II trial to determine the preliminary efficacy and safety of RAD001 in patients with histological evidence of progressive or metastatic bone or soft tissue sarcomas

Author(s): [redacted]

Document type: Amended Protocol Version

EUDRACT number : 2007-005294-60

Development phase: II

Version No. 07 Amended Protocol Version

Release date: 2013-08-27

Novartis approval signatures for:

Amendment No. 7 to Clinical Study Protocol CRAD001C24114

[redacted]	Signature	Date
[redacted]	Signature	Date
[redacted]	Signature	Date

Investigator approval signatures for:

Amendment No. 7 to Clinical Study Protocol CRAD001C24114

Investigator signature

I have read the protocol amendment and agree to conduct this trial in accordance with all stipulations of the protocol as amended, with applicable laws and regulations and in accordance with the ethical principles outlined in the Declaration of Helsinki.

Investigator	Signature	Date

Affiliation:

Table of contents

List of tables

List of abbreviations

AE	adverse event
ALT / GPT	alanine aminotransferase / glutamic pyruvic transaminase
ASPS	alveolar soft part sarcoma
AST / GOT	aspartate aminotransferase / glutamic oxaloacetic transaminase
AUC	area under the curve; area under the drug concentration time curve
b.i.d.	bis in die / twice a day
CRF	case report/record form
Cmax	maximum concentration
CNS	central nervous system
CS&E	clinical safety and epidemiology
CR	complete response
CRO	contract research organization
CT	computer tomography
CTC	Common Toxicity Criteria
CYP	human cytochrome P450
ECG	electrocardiogram
CRF	case report/record form
EGF	epidermal growth factor
GI	gastrointestinal
GRF	growth hormone releasing factor
Hb	hemoglobin
HIV	human immunodeficiency virus
ICH	International Conference on Harmonization of technical requirements for registration of pharmaceuticals for human use
IEC	Independent Ethics Committee
i.v.	intravenous(ly)
IGF-1	insulin-like growth factor 1
i.m.	intramuscular
IRB	Institutional Review Board
IVRS	interactive voice response system
mTOR	mammalian target of rapamycin
NET(s)	neuroendocrine tumor(s)
ORR	objective response rate
OS	overall survival
PBMC(s)	peripheral blood mononuclear cell(s)
PI3K	phosphatidylinositol 3-kinase
p.o.	per os / by mouth (orally)
PD	pharmacodynamics (or progressive disease in the context of tumor response)
PFS	progression free survival
PK	pharmacokinetics
PR	partial response
q.d.	quaque die / once a day

REB	Research Ethics Board
RECIST	response evaluation criteria in solid tumors
SD	stable disease
SAE	serious adverse event
SOP	standard operating procedure
STI	signal transduction inhibitors
STS	Soft Tissue Sarcoma
TTP	time to progression
ULN	upper limit of normal
VEGF	vascular endothelial growth factor
VIP	vasoactive intestinal peptide

Amendment 7

Amendment rationale

This study was designed as a three-armed phase II trial to evaluate the preliminary efficacy and safety of RAD001 in patients with advanced bone or soft tissue sarcomas. Enrollment of patients with progressive or metastatic bone or soft tissue sarcomas [except gastrointestinal stromal tumors (GIST) and alveolar soft part sarcoma (ASPS)] in arm I, enrollment of patients with progressive GIST after failure of prior imatinib and sunitinib treatment in arm II and enrollment of patients with progressive or metastatic alveolar soft part sarcoma (ASPS) in arm III were already completed.

As on 23 July 2013, one patient in arm II and one patient in arm III are ongoing and receive study drug. To ensure drug supply to both patients with RAD001 (everolimus), this amendment implements the use of Afinitor® (everolimus) as study drug.

Changes to the protocol

Additions to the study protocol are shown in red and deletions are shown in ~~strike-out mode~~. Comments and instructions for changes are shown in *italics*.

Changes to Section 6 Treatment

The section was amended as follows:

6.2 Investigational drug

RAD001 is formulated as tablets of 5mg strength, blister-packed under aluminum foil in units of 10 tablets. In addition RAD001 will also be delivered as Afinitor® (everolimus) tablets formulated as tablets of 5 mg strength, blister-packed in units of 30 tablets per pack. RAD001/everolimus are dosed on a daily basis.

6.3.5 Other concomitant medications

Inducers of CYP3A4 and/or PgP

If patient requires co-administration of strong CYP3A4 inducers (i.e., phenytoin, carbamazepine, rifampin, rifabutin, phenobarbital, St. John's worth), an increase in the dose of everolimus up to twice the currently used daily dose should be considered, using 5 mg increments every other day 5 mg increments daily.

IRB/IEC/REB Approval

A copy of this amendment will be sent to the Institutional Review Board (IRB) / Independent Ethics Committee (IEC) / Research Ethics Board (REB).

The changes described in this amendment require IRB/IEC/REB approval prior to implementation. In addition, sites are required to update and submit for approval a revised informed consent that takes into account the changes to the protocol described herein.

1 Background and introduction

1.1 Soft tissue sarcomas

Soft tissue sarcomas (STS) are rare tumours with an incidence of 2-3/100.000. Overall, STS account for approximately 1% of all malignancies, while they give rise to 2% of the total cancer-related mortality. Sarcomas constitute a heterogeneous group of rare tumours arising from cells of connective tissues (Clark MA et al, 2005). The gender distribution is equal. STS arise from mesodermal or ectodermal tissues and therefore occur at any site of the extremities, trunk, retroperitoneum or head and neck. There are multiple histological subtypes of STS. At present all these subtypes are usually grouped under the heading of STS for the purpose of treatment, although an increasing number of new treatment options are expected to be directed more specifically at individual histological subtypes.

Currently, more than half of all patients die within 5 years of primary diagnosis, mostly due to metastatic disease involving the lungs. About 10% of the patients present with metastatic disease at the time of diagnosis, whereas 40-60% of patients with localized, high-grade soft tissue sarcoma will develop metastases, predominantly in the lungs, despite local control of the tumour. Median survival from the time of diagnosis of metastatic disease is 8 to 12 months. According to the EUROCARE data (Ref.) the 5-year survival in Europe of adult STS (excluding visceral ones) averages 60%, with substantial geographic variations. Thus further improvements in the treatment outcome of these rare tumours are needed.

1.1.1 Treatment

Local surgery is usually the first line of management. Standard treatment is generally a wide surgical excision of the primary tumour combined with adjuvant radiotherapy, whenever feasible, or in some cases radical surgery, i.e. compartmental resection or amputation of the extremity.

Partly because of the presence of a misleading pseudo membrane and a multifocal origin of the tumour, surgery was initially followed by a very high incidence of local recurrence. Nowadays, the addition of post-operative radiotherapy appears to reduce the rate of local recurrence significantly. However, even an optimal local treatment does not prevent the occurrence of distant metastases in some of the patients – especially those with high-grade tumours. Although the effect adjuvant chemotherapy has been studied by several groups, they did not allow any final conclusions. A recent international meta-analysis indicated an effect on progression free survival but no effect on overall survival.

STS metastasise primarily to the lungs but also to bone, liver and other organs depending on the subtype. The median survival is generally less than 12 months, though long term survival may follow optimal response to chemotherapy in a limited number of patients. Chemotherapy is widely used in the treatment of advanced disease, basically with a palliative intent, but with the present knowledge its effect is clearly inadequate.

Only few drugs have shown single-agent activity above 15% with the most active being doxorubicin, epirubicin and ifosfamide resulting in response rates of 18-29% in first-line treatment. Combination chemotherapy consisting of anthracyclines and ifosfamide results in

response rates of 40-50% with up to 10% complete remissions, however at the cost of increased toxicity. Whereas complete remissions lead to prolonged survival, sometimes even cure, overall survival superiority of combination chemotherapy over single-agent doxorubicin has not been established yet.

In second-line treatment after anthracycline failure, ifosfamide plays a major role with response rates of up to 30%. Even after pre-treatment with standard doses of ifosfamide, high-dose ifosfamide represents an active treatment option.

Based on the understanding of molecular mechanisms and experience from clinical trials, it has become increasingly clear that distinct histological subtypes have a completely different clinical behaviour and response to systemic therapy. Hormonal therapy is very active in low-grade endometrial stromal tumours. Taxanes have shown interesting activity in angiosarcomas, though being inactive in soft tissue sarcoma in general. Topoisomerase I – inhibitors lead to response rates of 0 to 10% with some additional proportion of disease stabilisation in leiomyosarcomas. Gemcitabine was used in several trials and responses were reported in up to 18% of patients. The combination of Gemcitabine and Docetaxel resulted in a response rate of 53%, predominantly in uterine leiomyosarcomas. This combination was found to be significantly superior to Gemcitabine alone for progression-free survival and overall survival, being the first trial at all, to show superiority in overall survival.

There is a wide variety of DNA alternations observed in sarcoma, including translocations, gene amplifications, kinase mutation, gene deletion, loss of p53 and/or Rb and gross chromosomal rearrangements, often define nosological entities (e.g. Ewing sarcoma, synovial sarcoma and GIST). The proteins encoded by these mutated genes differ vary between histological sub-types, ranging from transcription factor. IN recent years, systemic treatment of sarcomas have evolved from a relatively uniform approach (doxorubicin + ifosfamide regiments) towards individualized strategies selecting cytotoxics and targeted treatment for specific histotypes and molecular subtypes (Cassier et al. 2007)

1.1.2 Active drugs

Doxorubicin appears to be the most active drug in the treatment of STS. During the last decade more than a thousand patients have been treated with the drug in connection with several reported studies. The cumulative response rate in non-pre-treated patients is 23%. Activity has also been noted in pre-treated patients in an EORTC trial. Doxorubicin treatment is limited because of cumulative cardiotoxicity, but unfortunately none of the tested anthracycline analogs has shown superiority or comparability to doxorubicin in terms of therapeutic activity with less toxicity.

A second active drug in the treatment of STS is ifosfamide. The initial non-randomized studies had shown response rates of 38-67%. The EORTC Soft Tissue and Bone Sarcoma Group (STBSG) performed a randomized phase II trial comparing cyclophosphamide with ifosfamide. In this trial the activity of ifosfamide was confirmed with a 25% response rate in non-pre-treated patients. In a recent study also by the EORTC STBSG, ifosfamide $3g/m^2$, given over 4 hours on 3 consecutive days showed better activity than ifosfamide $5g/m^2$ over 24 hours schedule.

The third drug with known moderate activity is DTIC (Dacarbazine), which achieved a response rate of 17% in 53 patients. Because the response rate of the combination of doxorubicin plus DTIC was much higher as compared with either one of these two drugs alone, DTIC was not studied further as a single agent, until the EORTC STBSG confirmed the activity of the drug in second line.

Doxorubicin and ifosfamide have been studied in second line treatment after pre-treatment with the respective other drug. Activity was comparable to first line therapy. After pre-treatment with the combination of doxorubicin and ifosfamide, there is currently no standard treatment available.

Therefore, there is a need to identify other active agents against this disease.

1.2 mTOR pathway and cancer

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. The main known functions of mTOR include (Bjornsti and Houghton, 2004):

- mTOR functions as a sensor of mitogens, growth factors, energy and nutrient levels, facilitating cell-cycle progression from G1 to 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 inhibits endothelial cell growth and proliferation directly.
- 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 pathway is known to be deregulated in numerous proliferate disorders including cancer. Molecular epidemiological studies have also shown that activation of the PI3/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 antitumour activity of kinase inhibitors acting on the pathway in *in vitro* and *in vivo* preclinical models.

1.3 Overview of RAD001

RAD001 (everolimus) is a derivative of rapamycin. It is commercialized as Certican® as an immunosuppressant in solid organ transplantation.

1.3.1 Preclinical studies of RAD001

At the cellular and molecular level RAD001 acts by selectively inhibiting mTOR (mammalian target of rapamycin). Various *in vitro* and *in vivo* experiments were performed in order to identify the cell signaling pathways through which RAD001 acts in cancer and identify molecular markers which may predict cellular response. A significant positive correlation was observed between the antiproliferative activity of RAD001 and levels of phosphorylated AKT (Serine 473) and phosphorylated S6 (Serines 240 and 244). Hence, phospho-AKT/phospho-S6 levels may be useful indicators of pathway activation and sensitivity to RAD001. [Investigators' Brochure, 2006]

In vivo studies investigating the antitumour 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 2.5-10mg/kg p.o. daily.

The antiangiogenic activity of RAD001 was also confirmed in animal experiments. RAD001 selectively inhibited VEGF-dependent angiogenic response at doses that were well tolerated (see IB 4.1.2.6.), and both primary and metastatic tumors from RAD001-treated mice demonstrated a significant reduction in blood vessel density compared to controls.

In humans, studies suggested that 70S6K1 level in peripheral blood mononuclear cells (PBMCs) could be a useful pharmacodynamic marker of RAD001 inhibitory effects on the mTOR pathway. Preclinical and clinical studies have been (and are being) conducted to further evaluate which are the best indications and combination partners for RAD001, and which potential molecular markers can predict response to treatment.

Based on findings of safety pharmacology studies, the potential of RAD001 to affect vital functions in patients is considered to be low. All significant adverse effects observed in preclinical toxicology studies of RAD001 in mice, rats, monkeys and minipigs were consistent with its anticipated pharmacological action as an antiproliferative and immunosuppressive agent and were 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. [Investigators' Brochure, 2006]

1.3.2 RAD001 pharmacokinetics

RAD001 is formulated for oral administration. It is rapidly absorbed with a median t_{max} of 1-2 hours and a bioavailability estimated at 11% or more. The AUC is dose-proportional over the range of doses tested while C_{max} becomes less than dose-proportional at doses above 20mg. The coefficient of variation between patients is approximately 50%. In whole blood, approximately 80% of the drug is sequestered in cells. Of the remaining 20% in plasma, approximately a quarter is unbound. Metabolism and excretion are essentially hepatic. *In vitro* studies showed that RAD001 is a competitive inhibitor of CYP3A4, P-gp and CYP2D6 substrates, potentially increasing the concentrations of medicinal products eliminated by these enzymes. Thus, caution should be exercised when co-administering RAD001 with CYP3A4 and CYP2D6 substrates with a narrow therapeutic index. The elimination half-life is approximately 30 hours. [Investigators' Brochure, 2006]

1.3.3 RAD001 Phase I Studies

RAD001 has been evaluated in phase I studies involving 147 patients with advanced cancers using both a weekly regimen (up to 70mg/wk) and a daily regimen (10mg/d) [Investigators' Brochure, 2006]. The most frequent adverse drug reactions in the oncology setting have been rash, stomatitis, fatigue and, to a lesser extent, gastrointestinal disorders (nausea, anorexia, diarrhea, vomiting) and headache. The adverse events are mild-moderate (CTC grade 1-2) in the majority of patients. Severe (grade 3), suspected drug-related, dose-limiting events occurred in 19% of patients, mainly stomatitis (often apthous ulcers), and occasionally severe fatigue, hyperglycemia and neutropenia. Reduced blood counts, hyperlipidemia (mainly hypercholesterolemia) and hyperglycemia are relatively frequent laboratory findings. Infections have not been frequent.

The dose and schedule of 10mg p.o. q.d. has been selected for most phase II studies based on assessment of both pharmacodynamic and safety studies. Molecular pharmacodynamic studies using immunohistochemistry assays on tumor biopsies have shown target inhibition at both daily dosage (5-10mg) and weekly dosage (50-70mg) with satisfactory tolerability in most patients.

Conventional cytotoxic agents were empirically evaluated in *in vitro* and *in vivo* pharmacology studies as combination partners for RAD001 and have shown that RAD001 is additive or synergistic in combination with other anticancer agents, including cytotoxics and other signal transduction inhibitors (STIs) as well as endocrine therapy. In many cases, a potentiation of cell death by the drug combination was observed. RAD001 has also been evaluated in several phase I studies in combination with other anticancer drugs. Interactions have required dose reduction of RAD001 when given in combination with some drugs (e.g. Gleevec, Xeloda) but not others (e.g. paclitaxel, letrozole). Please refer to Investigator Brochure for more information.

1.3.4 RAD001 Phase II / III Studies

RAD001 is currently investigated in different Phase III trials in renal cell carcinoma (Jac et al., ASCO 2007, abstract 5107), in neuroendocrine tumors (Yao et al., ASCO 2007, abstract 4503), and in lymphoma.

Phase II trials are ongoing in many different tumor entities, such as breast cancer (Ellard et al., ASCO 2007, abstract 3513), non small lung cancer, small lung cancer, colorectal cancer, lymphoma (Johnston et al., ASCO 2007, abstract 8055), GIST (van Oosterom et al., ASCO 2005, abstract 9033), and melanoma (Rao et al., ASCO 2007, abstract 8530).

In a Phase II study with the mTOR inhibitor CCI-779 in patients with soft tissue sarcoma it was shown that this concept of treatment has acceptable toxicity profile (Okuna et al, 2006).

1.4 Rationale

The systemic treatment of locally advanced or metastatic soft tissue sarcoma (STS) is unsatisfactory with few drugs showing signs of activity. Treatment is toxic, yet usually given with palliative intent.

PET responses and improvement of symptoms have been described in sarcoma patients with AP23573, an intravenous mTOR inhibitor ([redacted]) tested in a phase II trial (Sankhala et al., ASCO 2005, abstract 9028).

Recent data with this mTOR inhibitor AP23573 demonstrate a single-agent activity in a broad range of sarcoma tumor types in a phase I/II trial. In this trial the patients were enrolled according to their histological subtype of the tumor. Totally, 212 patients were enrolled of which over 90% had a progression at the time of study entry. 79% had 2 prior chemotherapies. The overall clinical benefit rate was 29% and the median OS was 40,1 weeks. In the subset of patients achieving a clinical benefit response, the OS was 67,6 weeks. (Chawla, ASCO 2007, abstract 10076).

The experiences with this mTOR inhibitor are a rational to test RAD001 in patients with soft tissue and bone sarcoma.

RAD001 is a macrolide, a new derivative of rapamycin. It is orally available and acts as an mTOR inhibitor. TOR is a ubiquitous protein kinase implicated in cell cycle control and specifically in the progression of cells from the G1 to S phase. It is considered to be downstream of PI3-AKT. RAD001 is being developed as an antiproliferative drug with applications as an immunosuppressant and anticancer agent. It is already registered in the transplantation setting as Certican®.

In a phase I study in 33 patients with advanced solid tumors, RAD001 has been given at doses of 20mg, 50mg and 70mg weekly, or 5mg and 10mg daily. Dose limiting toxicities have been stomatitis, neutropenia and hyperglycemia. The recommended dose for further phase II evaluation is 10mg daily (Tabernero et al., ASCO 2005, abstract 3007).

2 Study purpose

The purpose of this multicenter, triple-arm, exact binomial single-stage, phase II trial is to determine the preliminary efficacy and safety of RAD001 in patients with histological evidence of progressive or metastatic bone or soft tissue sarcoma.

3 Objectives

Primary objective

- To evaluate preliminary efficacy of RAD001 in progressive or metastatic bone and soft tissue sarcoma (except for GIST). Efficacy is defined as the proportion of patients showing complete response, partial response or stable disease at 16 weeks.
- To evaluate preliminary efficacy of RAD001 in patients with gastrointestinal stromal tumor (GIST) after failure or intolerance of treatment with imatinib or sunitinib in 1st and 2nd line. Efficacy is defined as the proportion of patients showing complete response, partial response or stable disease at 16 weeks.
- To evaluate preliminary efficacy of RAD001 in progressive or metastatic alveolar soft part sarcoma (ASPS). Efficacy is defined as the proportion of patients showing complete response, partial response or stable disease at 16 weeks.

Secondary objective(s)

The following secondary objectives will be evaluated in three arms separately:

- To evaluate the tolerability and safety profile of RAD001 in these patient populations.
- To evaluate the objective tumor response rate based on RECIST-criteria (complete response [CR] and partial response [PR]) at 16 weeks.
- To evaluate duration of response.
- To evaluate progression-free survival (PFS) at 16 weeks.
- To evaluate overall survival (OS).
- To evaluate PFS at month 12 for patients with data available from follow-up observation (optional).
- To evaluate OS at 12 months for patients with data available from follow-up observation (optional).

4 Study design

This is a non-randomized, multicenter, triple-arm, phase II trial evaluating the treatment of RAD001 in the following three arms: in patients with progressive or metastatic bone or soft tissue sarcoma (except for GIST), in patients with progressive or metastatic GIST after failure or intolerance of treatment with imatinib or sunitinib in 1st and 2nd line and in patients with progressive or metastatic alveolar soft part sarcoma (ASPS) (see Table 4-1).

It is anticipated to achieve an estimated total sample size of 10 subjects in arm III. No interim analysis is planned.

A 12-month recruitment phase is anticipated to achieve an estimated total sample size of 36 subjects in arm I, a total sample size of 24 subjects in arm II and in arm III, respectively, in a single stage. No interim analysis is planned. All 5 patients with alveolar soft part sarcoma (ASPS) included in the arm I of the study will be transferred to and analyzed in the arm III.

Table 4-1 Schematic of study design

Arm I:	**Patients with progressive or metastatic bone or soft tissue sarcoma (except for GIST)**
	Starting dose: RAD001 10 mg/day
	36 patients to be accrued in a single stage
Arm II:	**Patients with progressive GIST after failure or intolerance of treatment with imatinib or sunitinib in 1st and 2nd line**
	Starting dose: RAD001 10 mg/day
	24 patients to be accrued in a single stage
Arm III:	**Patients with progressive or metastatic alveolar soft part sarcoma (ASPS)**
	Starting dose: RAD001 10 mg/day
	10 patients to be accrued in a single stage

Studies with other mTOR-inhibitors have shown a significant clinical benefit in patients with soft tissue sarcoma. Therefore, the 10mg daily dose of RAD001 has been selected as the treatment regimen for this study.

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).

Screening for hepatitis B

Prior to starting study drug 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 6.3.3, 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 6.3.3, are provided according to the results of the baseline assessment of hepatitis C viral load.

5 Population

The study population will consist of adult patients with bone and soft tissue sarcoma.

In phase II trials of novel cytotoxics, it has been usual practice to include patients who have received 2 lines of single agent chemotherapy or 1 line of combination treatment. Given the novel mechanism of action of this agent, such a restriction is illogical. Therefore, there will be no restriction on the number of lines of prior chemotherapy, provided the patients have adequate performance status and organ function and have failed standard treatment.

5.1 Inclusion/exclusion criteria

The investigator must ensure that all patients who meet the following inclusion and exclusion criteria are offered enrollment in the study. No additional exclusion parameters can be applied by the investigator, in order that the study population will be representative of all eligible patients.

Inclusion criteria

- Histological evidence of progressive or metastatic bone or soft tissue sarcoma.
  The following tumor types are included:
  - alveolar soft part sarcoma (ASPS)
  - malignant fibrous histiocytoma;
  - liposarcoma;
  - synovial sarcoma;
  - malignant paraganglioma;
  - fibrosarcoma;
  - leiomyosarcoma;
  - angiosarcoma including haemangiopericytoma;
  - malignant peripheral nerve sheath tumor;
  - STS, not otherwise specified;
  - miscellaneous sarcoma including mixed mesodermal tumors of the uterus;
  - osteosarcoma;
  - Ewing's sarcoma;
  - rhabdomyosarcoma;

- gastrointestinal stromal tumor (only after failure or intolerance of imatinib or sunitinib in 1st and 2nd line)

Objective progression of disease may be documented by RECIST criteria. Any of the following would be sufficient according to RECIST:

- a 20% increase in the sum of unidimensionally measured target lesions;
- a new lesion;
- unequivocal increase in non-measurable disease.

- At baseline, a CT or MRI scan must demonstrate measurable disease by RECIST criteria, i.e. the presence of at least one measurable lesion. Measurable disease lesions must be accurately measured in at least one dimension with longest diameter ≥ 20mm using conventional techniques or ≥ 10mm with spiral CT scan (with minimum lesion size no less than double the slice thickness). (see post-text supplement 1).
- At least one measurable lesion outside of the field of any prior radiation therapy (according to RECIST criteria). Prior radiotherapy to a single index lesion is not allowed.
- Adult male or female patients (≥18 years of age). In countries outside Germany patients at the age of ≥ 16 can also be included into the trial.
- Patients must have disease not amenable to surgery, radiation, or combined modality therapy with curative intent.
- Adequate bone marrow function as shown by: absolute neutrophil count (ANC) > 1,500/µl, Platelets ≥ 100,000/µl, Hb > 9g/dL.
- Adequate renal function as shown by: a serum creatinine value < 1.5 x upper limit of normal (ULN).
- Adequate liver function as shown by:
  - serum bilirubin ≤ 1.5 x ULN;
  - INR < 1.3 x ULN (or < 3 on anticoagulants);
  - ALT and AST ≤ 2.5x ULN (≤ 5x ULN in patients with liver metastases).
- ECOG performance status 0 – 2.
- Fully recovered from any previous surgery, prior chemotherapy or radiation therapy (at least 4 weeks since major surgery or prior myelosuppressive chemotherapy). Prior radiotherapy to a single index lesion is not allowed. With the exception of alopecia, patients must have resolution of all acute toxic effects of any prior surgery, radiotherapy, or chemotherapy to NCI CTC (Version 3.0) grade ≤ 1.
- Signed informed consent to participate in the study must be obtained from patients after they have been fully informed of the nature and potential risks by the investigator (or his/her designee) with the aid of written information.

Exclusion criteria

- Anticancer therapy within 3 weeks of enrollment including chemotherapy, hormonal therapy, immunotherapy, or radiotherapy.
- The following tumor types will not be included:

  - gastrointestinal stromal tumor (except for patients after treatment with imatinib or sunitinib in 1st and 2nd line);
  - chondrosarcoma;
  - malignant mesothelioma;
  - neuroblastoma.
- Prior therapy with RAD001 (everolimus) or other rapamycins (sirolimus, temsirolimus).
- neurotoxicity ≥ grade 2 CTC.
- Radiation of the lung.
- Patients taking drugs known to inhibit or induce isoenzyme CYP3A (Table 6-4) are excluded unless the drugs are medically necessary and no substitutes are available. If there are no acceptable substitutes, special precautions should be taken in these patients (section 6.3.5).
- Patients with any concurrent major medical condition liable to compromise the patient's participation in the study (e.g. known HIV infection, uncontrolled diabetes, serious cardiac dysrhythmia or condition, New York Heart Association classification of III or IV, congestive cardiac failure, myocardial infarction within 6 months, unstable angina, chronic or acute renal or liver disease, uncontrolled serious infections including abscess or fistulae, etc.).
- Patients with a history of another malignancy prior to study entry, except curatively treated non-melanotic skin cancer or carcinoma in-situ cervical cancer unless in complete remission or no evidence of disease and off all therapy for that disease for a minimum of 5 years.
- No symptomatic brain metastasis. Patients with asymptomatic brain metastases can be entered, if this is deemed to be in the best interest of the patient by the responsible physician. Previously radiated brain lesions will be defined non evaluable for response.
- Use of other investigational drugs at the time of enrollment, or within 30 days or 5 half-lives of enrollment, whichever is longer.
- History of hypersensitivity to any of the study drugs or to drugs with similar chemical structures.
- Patients committed to an institution by order of the authorities or court decision.
- Female patients who are pregnant or breast feeding or patients of reproductive potential not employing an effective method of birth control. Because oral, implantable or injectable contraceptives may be affected by cytochrome P450 interactions, an appropriate method of birth control should be used throughout the trial in both sexes. Women of childbearing potential (WOCBP) must have a negative serum pregnancy test within 48 hours prior to the administration of study medication.

  Definition of women of child-bearing potential (WOCBP): all women physiologically capable of becoming pregnant, including women whose career, lifestyle, or sexual orientation precludes intercourse with a male partner and women whose partners have been sterilized by vasectomy or other means, UNLESS they meet the following definition of post-menopausal: 12 months of natural (spontaneous) amenorrhea or 6 months of spontaneous amenorrhea with serum FSH levels > 40mIU/m or 6 weeks post surgical bilateral oophorectomy with or without hysterectomy OR are using one or more of the following acceptable methods of contraception: Acceptable

methods of contraception may include total abstinence at the discretion of the investigator in cases where the age, career, lifestyle, or sexual orientation of the patient ensures compliance. Appropriate contraception is defined as 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).Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. Reliable contraception should be maintained throughout the study and for 30 days after study drug discontinuation.

5.2 Premature patient withdrawal

Patients must be withdrawn from the study for any of the following reasons:

- Withdrawal of informed consent
- Pregnancy
- Study drug discontinuation
- Progression of tumor
- Unacceptable toxicity
- Patients also should be withdrawn at any time if the investigator concludes that it would be in the patient's best interest for any reason.

The reason for premature patient withdrawal from the study must be recorded on the Study Completion CRF.

Protocol violations should not lead to patient withdrawal unless they indicate a significant risk to the patient's safety.

Patients may voluntarily withdraw from the study for any reason at any time. They may be considered withdrawn if they state an intention to withdraw, or fail to return for visits, or become lost to follow up for any other reason.

For patients who are lost to follow-up (i.e. those patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), 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.

Patients who are prematurely withdrawn from the core study will be replaced by an equal number of newly enrolled patients.

6 Treatment

6.1 Treatment assignment

Each patient is uniquely identified in the study by a combination of his/her center number and patient number. The center number is assigned by the sponsor to the investigative site. Upon signing the informed consent form, the patient is assigned a patient number by the investigator. At each site the first patient is assigned patient number 1, and subsequent patients are assigned consecutive numbers (e.g. the second patient is assigned patient number 2, the third patient is assigned patient number 3). Once assigned to a patient, a patient number

will not be reused. If the patient fails to be started on treatment for any reason, the reason for not being treated will be entered on the Screening Log.

6.2 Investigational drug

RAD001 is formulated as tablets of 5 mg strength, blister-packed under aluminum foil in units of 10 tablets. In addition RAD001 will also be delivered as Afinitor® (everolimus) tablets formulated as tablets of 5 mg strength, blister-packed in units of 30 tablets per pack. RAD001/everolimus are dosed on a daily basis.

6.3 Treating the patient

6.3.1 Instructions for prescribing and taking the study drug

RAD001 will be dispensed by the study center personnel on an outpatient basis. Patients will be provided with an adequate supply of RAD001 for self-administration at home.

RAD0001 will be dosed starting on Week 1 Day 1. Patients will be instructed to take two tablets of RAD001 orally with a glass of water, once daily at the same time each day, in a fasting state or after no more than a light, fat-free meal. If vomiting occurs, no attempt should be made to replace the vomited dose. Patients should be requested to bring their unused medication, 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 CRF. 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 study treatment.

Patients will be treated with RAD001 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 6.2.

6.3.2 RAD001 dose adjustments

For patients who are unable to tolerate the protocol-specified RAD001 dosing schedule, dose-adjustment guidelines are given below. Three RAD001 dose levels are defined for dose adjustment: 10mg daily, 5mg daily, and 5mg every other day. (Table – 1)

Table 6-1 RAD001 Dose levels for dose adjustment

Dose level	Dose and schedule
0 (starting dose)	10mg daily
Decrease 1 dose level	5mg daily
Decrease 2 dose levels	5mg every other day

Toxicity will be assessed using the NCI-CTC for Adverse Events, version 3.0 (CTCAE v3.0,

(http://ctep.cancer.gov/forms/CTCAEv3.pdf)).

6.3.3 Management of RAD001 toxicities

Known Undesirable Side Effects of RAD001

Adverse events most frequently observed with RAD001 are rash, stomatitis/oral mucositis, fatigue, headache, anorexia, nausea, vomiting, diarrhea, ocular toxicity and infections. Non-infectious pneumonitis has also been observed. 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).

Table 6-2 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 6.3)	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, 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 (see table 6.3).
Grade 3 hyperlipidemia (hypercholesterolemia and/or hypertriglyceridemia)	Should be managed using standard medical therapies.
Grade 4	Discontinue RAD001.
Hematological toxicity Grade 2 Thrombocytopenia (platelets < 75, ≥ $50x10^9$/L)	Interrupt RAD001 until recovery to grade ≤ 1 (platelets ≥ $75x10^9$/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, ≥ $25x10^9$/L)	Interrupt RAD001 until recovery to grade ≤ 1 (platelets ≥ $75x10^9$/L). Then resume RAD001 at one dose level lower. If grade 3 thrombocytopenia recurs, discontinue RAD001.
Grade 4 Thrombocytopenia (platelets < $25x10^9$/L)	Discontinue RAD001.

Grade 3 Neutropenia (neutrophils (< 1, ≥ 0.5x10^9/L)	Interrupt RAD001 until recovery to grade ≤ 1 (neutrophils ≥ 1.5x10^9/L). Then resume RAD001 at the initial dose. If ANC again returns to Grade 3, hold RAD001 until the ANC ≥ 1.5x10^9/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 (< 0.5x10^9/L)	Interrupt RAD001 until recovery to grade ≤ 1 (neutrophils ≥ 1.5x10^9/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.

Monitoring of RAD001 suspected 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 via telephone until the adverse event or abnormal laboratory value resolves or returns to grade 1. If a patient requires a dose delay of > 21 days from the intended day of the next scheduled dose, then the patient must be discontinued from the study.

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, thus 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.

Note: Stomatitis/oral mucositis should be appropriately graded using the functional grading given on the NCI-CTC for Adverse Events, version 3.0.

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 or higher hypercholesterolemia (> 300mg/dL or 7.75mmol/L) or grade 2 or higher hypertriglyceridemia (> 2.5 x ULN) should be treated with a statin 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.

Grade 3 hyperglycemia has been observed in patients receiving RAD001 therapy. In many cases the affected patients had an abnormal fasting glucose at baseline. Based on this finding, it is recommended that optimal glucose control is achieved before starting a patient on RAD001. Study patients should have their glucose levels monitored during RAD001 therapy.

Management of skin disorders

In prior phase I clinical studies with RAD001 alone, rash and/or erythema was the most frequent AE experienced by approximately 40% of patients. For patients with grade 1 toxicity, no specific supportive care is usually needed or indicated. The rash should be reported as an AE. Patients with grade 2 supportive toxicity may be treated with supportive measures, including the following at the discretion of the investigator: oral minocycline, topical tetracycline, topical clindamycin, topical silver sulfadiazine, diphenhydramine, oral predinisolone (short course) or pimecrolimus.

Management of gastrointestinal disorders

Nausea, vomiting and diarrhea have been seen in approximately 15-55% of patients treated with RAD001. The symptoms have in general been mild to moderate (CTC grade 2). Appearance of grade 1-2 diarrhea should lead to supportive care such as loperamide, initiated at the earliest onset (4mg orally followed by 2mg orally every 2 hours until resolution of diarrhea). In patients who have emesis and are unable to retain the medication, every attempt should be made to control symptoms of nausea and vomiting with the best available supportive care. However, no attempt should be made to replace the vomited dose. Patients experiencing diarrhea leading to hospitalisation will have their drug administration interrupted or changed according to the procedures described in table 6.2.

Management of non-infectious pneumonitis

Both asymptomatic radiological changes (grade 1) 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.

Since disease control for tumor measurement includes bimonthly CT of the lung or chest x-ray, no additional CT/x-ray is required to monitor for asymptomatic (grade 1) non-infectious pneumonitis.

Additional chest x-rays or CT scans may be performed when clinically necessary. If non-infectious pneumonitis develops, a consultation with a pulmonologist should be considered. If the patient develops grade 3 pneumonitis, treatment with RAD001 should be interrupted and the patient should be treated as medically indicated (short course corticosteroids, oxygen, etc). Management of non-infectious pneumonitis suspected to be associated with RAD001 and dose modifications instructions are provided in Table 6.3.

Table 6-3 Management of non-infectious pneumonitis

Worst Grade Pneumonitis	Required Investigations	Management of Pneumonitis	RAD001 Dose Adjustment
Grade 1	CT scans with lung windows and required pulmonary function testing includes: spirometry, DLCO, and room air O_2 saturation at rest. Repeat a chest x-ray/CT scan every 2 cycles until return to baseline.	No specific therapy is required.	Administer 100% of RAD001 dose.
Grade 2	CT scan with lung windows and pulmonary function testing includes: spirometry, DLCO, and room air O_2 saturation at rest. Repeat each subsequent cycle until return to baseline. Consider a bronchoscopy.	Symptomatic only. Prescribe corticosteroids if cough is troublesome.	Reduce RAD001 dose 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 each subsequent cycle until return to baseline. Bronchoscopy is required	Prescribe corticosteroids if infective origin is ruled out. Taper as medically indicated.	Hold treatment until recovery to < grade 1. May restart protocol treatment within 2 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 includes: spirometry, DLCO, and room air O_2 saturation at rest. Repeat each subsequent cycle until return to baseline. Bronchoscopy is required.	Prescribe corticosteroids if infective origin is ruled out. Taper as medically indicated.	Discontinue treatment.

The investigator should promote compliance by instructing the patient to take the study drug exactly as prescribed and by stating that compliance is necessary for the patient's safety and the validity of the study. The patient should be instructed to contact the investigator if he/she is unable for any reason to take the study drug as prescribed.
All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record CRF.

Management of Hepatitis reactivation

Monitoring and prophylactic treatment for hepatitis B reactivation
Table 4 provides details of monitoring and prophylactic therapy according to the baseline results of viral load and serologic markers testing.

Table 6-4 Action to be taken for positive baseline hepatitis B results

Test	Result	Result	Result	Result	Result
HBV-DNA	+	+ or -	-	-	-
HBsAg	+ or -	+	-	-	-
HBs Ab	+ or -	+ or -	+ and no prior HBV vaccination	+ or -	- or + with prior HBV vaccination
HBc Ab	+ or -	+ or -	+ or -	+	-

Test	Result	Result	Result	Result	Result
Recommendation	Prophylaxis treatment should be started 1-2 weeks prior to first dose of study drug Monitor HBV-DNA approximately every 4-8 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 approval of the amendment, 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 5 Guidelines for management of hepatitis B.

Table 6-5 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 HBsAg --- 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 1 – 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	**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 1 – 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

Ab] --- reactivation is defined as: New appearance of measurable HBV-DNA	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 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 4–8 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 Guidelines for management of hepatitis C.

Table 6-6 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).

6.3.4 Follow-up for toxicities while receiving RAD001

Patients who interrupt or permanently discontinue RAD001 due to an adverse event or abnormal laboratory value must be followed at least weekly via telephone for 28 days after the last dose of RAD001, and subsequently at monthly intervals until resolution or stabilization of the event, whichever comes first. If a patient requires a RAD001 dose delay of > 21 days from the intended day of the next scheduled dose, then the patient should 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 RAD001.

6.3.5 Other concomitant medications

Inhibitors of CYP3A4 and/or PgP

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 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.

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 worth), an increase in the dose of everolimus up to twice the currently used daily dose should be considered, using 5 mg increments every other day – 5 mg increments daily. 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 CYP3A/PgP inducer.

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),	rifampin, St John's wort

PgP Substrates	PgP Inhibitors in vivo	PgP Inducers
	itraconazole, ketocoanzole, lopinavir, (LY335979), mibefradil, nifedipine, nitrendipine, (PSC833), quinidine, ranolazine, ritonavir, talinolol, valspodar, verapamil	

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*****

6.3.6 Study drug discontinuation

Study drug must be discontinued for a given patient if the investigator determines that continuing it would result in a significant safety risk for that patient. Patients who, in the opinion of the investigator, require alternative medical therapy, will be discontinued from the study. Patients with a progression will be discontinued from the study. Patients who become pregnant during the study must be withdrawn. If the treatment has to be interrupted for more than 21 consecutive days for any reason, the patient will be discontinued from the study unless otherwise discussed with the study coordinator. In case of patient's discontinuation, the end of study evaluation will be completed as soon as possible. End of study evaluations will include adverse events, concomitant medications and therapies, physical examination, vital signs, ECOG performance status, biochemistry, hematology and tumor measurement.

Patients who discontinue prematurely due to significant AE should continue to be followed-up until resolution of the AE, and the relevant sections of the CRF should be completed as appropriate. Patients who are discontinued due to clinically significant abnormalities in clinical laboratory results should continue to be evaluated until the abnormality resolves or is judged to be permanent.

It will be documented whether or not each patient completed the clinical study. If, for any patient, the study treatment was discontinued the reason will be recorded. Reasons that a patient may discontinue participation in a clinical study are considered to constitute one of the following:

1. Adverse event(s)
2. Abnormal laboratory value(s)
3. Abnormal test procedure result(s)
4. Unsatisfactory therapeutic effect
5. Subject's condition no longer requires study treatment

6. Protocol violation which affect the safety of the patient
7. Subject withdraws consent
8. Lost to follow-up
9. Administrative problems
10. Death

Progressive disease is defined as unsatisfactory therapeutic effect.

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.

It is agreed that for reasonable cause, either the investigator or Novartis may terminate this study, provided a written notice is submitted at a reasonable time in advance of the intended termination.

A Study Drug Discontinuation form should be completed, giving the date and primary reason for stopping the study drug.

Study treatment will be continued until progression. Patients will be followed until progression.

The overall survival will be documented on the survival information page for all patients except for those who withdrew consent or are lost to follow-up.

7 Visit schedule and assessments

7.1 Information to be collected on screening failures

Information on screening failures will be kept in the Novartis Screening Failure Log. No CRF has is needed for screening failures.

All data obtained from the assessments listed in Table 1 and described in detail in the subsections below must be supported in the patient's source documentation. Assessments that generate data for database entry and which are recorded on CRFs are listed using the CRF name. Assessments that are transferred to the database electronically (e.g. laboratory data) are listed by test name.

The final examination (visit 6 respectively EOS) will be performed for all patients included in this trial (i.e. who signed an informed consent form and received study treatment), whether they discontinued study treatment prematurely or completed the study treatment. Patients who discontinue study drug before completing the core study, and those who prematurely withdraw from the core study for any reason, should be scheduled for the End-of-study-visit as soon as possible, at which time all of the assessments listed for the EOS-visit will be performed.

During the follow-up period, the treatment regimen as taken during the study should be maintained. However, changes in the regimen based on each patient's clinical needs and the investigators' experience and discretion will be possible at any time. In the Follow-Up-Phase

the End-of-Follow-Up-Visit is the corresponding visit to the End-of-Study-Visit in the Core Phase.

For all visits of the Core Study a tolerance of 3 days in both directions is acceptable. For all visits of the Follow Up Phase a tolerance of 1 week in both directions is acceptable.

Table 7-1 Assessment schedule

	Base-line[1]	Core study						Follow-up[12]				
Visit No.	1	2	3	4	5	6	EOS					End of FUP
								FUP 1 - X				
Day	-14	1										
Week			4	8	12	16		28	40	52	X	
Demographics[1]	x											
Informed consent	x											
In-/exclusion criteria	x											
HBV-DNA, HBsAg, HBs Ab, HBc Ab, HCV-RNA-PCR[X]	x											
HBV DNA, HCV RNA-PCR[XX]		X	X	X	X	X	X	X	X	X	X	X
Pregnancy test [5]	x											
Medical history	x											
Extent of cancer	x											
Prior anti-neoplastic treatment	x											
Vital signs [2]	x	x	x	x	x	x	x	x	x	x	x	x
Height	x											
Weight	x	x	x	x	x	x	x	x	x	x	x	x
ECG [6]	x						x					x
Physical examination [1]	x	x	x	x	x	x	x	x	x	x	x	x
ECOG PS [3]	x	x	x	x	x	x	x	x	x	x	x	x
Hematology [4]	x	x	x	x	x	x	x	x	x	x	x	x
Biochemistry [4]	x	x	x	x	x	x	x	x	x	x	x	x
Urinanalysis [4]	x	x	x	x	x	x	x	x	x	x	x	x
CT / MRI	x			x		x	x	x	x	x	x	
Chest x-ray [9]	x			x		x		x	x	x	x	
PET optional (not in Germany) [7]	x		x									

	Base-line[1]	Core study						Follow-up[12]				
Visit No.	1	2	3	4	5	6	EOS					End of FUP
								FUP 1 - X				
Day	-14	1										
Week			4	8	12	16		28	40	52	X	
Tumor evaluation (RECIST)[7]	x			x		x	x	x	x	x	x	
Study drug administration		x	x	x	x	x		x	x	x	x	
Adverse events[8]	x	ongoing data capture						ongoing data capture				
Prior medication	x											
Concomitant medication	x	ongoing data capture						ongoing data capture				
Survival-information[10]												x
Comments		ongoing data capture						ongoing data capture				

[1]Described in Section 7.2; 7.5.2
[2]Described in Section 7.5.3
[3]Described in Section 7.5.4
[4]Described in Section 7.5.5
[5]Described in Section 7.5.7; 8.2
[6]Described in Section 7.5.6
[7]Described in Section 7.4
[8]Described in Section 8.1.1
[9]Chest x-ray only in cases where no CT/MRI thorax is available
[10]Survival information for patients who discontinued earlier
[11] Baseline assessment can be done between day-14 and day 1 together with visit 2
[12] During the follow up period patients will continues to be followed every 3 months until progression
[X] All patients should be screened for hepatitis risk factors and any past illnesses of hepatitis B and hepatitis C. It is highly recommended that patients positive HBV-DNA or HBsAg are treated prophylactically with an antiviral for 1-2 weeks prior to receiving study drug. The antiviral treatment should continue throughout the entire study period and for at least 4 weeks after the last dose of study drug. Patients with viral hepatitis C risk factors should be screened for HCV RNA-PCR.
[XX] Patients on antiviral prophylaxis treatment or positive HBV antibodies should be tested for HBV-DNA according to study visit schedule. 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 according to visit schedule.

7.2 Patient demographics/other baseline characteristics

Demographic data include: Date of birth, sex, and race.
Baseline characteristics include: Medical history/current medical condition, prior medication, tumor history, baseline tumor assessment, relevant prior tumor therapy, ECOG, vital signs (height, weight, blood pressure, pulse), result of pregnancy test, hematology and biochemistry.

HBV testing

Prior to starting study drug, the categories of patients listed in Section 4 Changes to Study design 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 4.

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 Changes to Study design.
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.

7.3 Treatments

Study drug administration will be documented. Dose modifications and interruptions will be documented ongoing.

7.4 Efficacy

Tumor evaluation

Disease status will be based on CT/MRI scans and/or chest x-ray performed maximum ca. 2 weeks before baseline, thereafter after week 8, 16, 28, 40, 52 and X, respectively at final visit. If medically indicated, unscheduled CT/MRI examinations and/or chest x-ray will be performed at the investigator's discretion. Response status will be evaluated using RECIST criteria (please see Post-text supplement 1). The evaluation of the central radiologist will be used.

At baseline and 1st comparative FDG-PET assessment at visit 5 can be carried out optional in non-German-centers in order to provide this additional perspective on changes in tumor activity induced by the therapy and give data on correlation of PET as an indicator for progression or response. Although ^{18}FDG-PET functional imaging may be valuable as a complement to standard anatomical imaging (CT or MRI) in any tumor assessment (identification of new lesions or of newly active foci in otherwise inactive lesions), the primary variable for efficacy assessment will be that obtained by standard anatomical imaging.

7.5 Safety

7.5.1 Adverse events

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after date of signed informed consent even if the event is not considered to be related to study drug. Study drug includes the investigational drug under evaluation that is given during any phase of the trial. Medical conditions/diseases present before date of signed informed consent are only considered adverse events if they worsen

after date of signed informed consent. 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). In addition, abnormal laboratory values that cause study discontinuation or constitutes in and of itself a Serious Adverse Event (SAE) should be recorded on the Adverse Events CRF.

Adverse events will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 (http://ctep.cancer.gov/forms/CTCAEv3.pdf). If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, OR 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 or Survival Information CRF page.** Adverse event monitoring should be continued for at least 4 weeks following the last dose of study drug.

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) or mild, moderate, severe, life-threatening if CTCAE grading does not exist for an adverse event,
2. its relationship to the study drug(s) (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), and
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 (specify what this includes)
        - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
        - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of an 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

In contrast to routine safety assessments, SAE are monitored continuously and have special reporting requirements; see Section 8.1 "Serious adverse event reporting".

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, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the 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 form and should be discussed with the patient during the study as needed.

7.5.2 Physical examination

A routine physical examination will be performed according to the visit schedule.

A full physical examination is to be performed once a month during the first five months of the study and every two months thereafter. It should comprise 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).

Information about the physical examination must be present in the source documentation at the study site. Significant findings that are present prior to signing informed consent (or therapy) must be included in the Relevant Medical History / Current Medical Conditions CRF. Significant findings made after signing informed consent which meet the definition of an adverse event must be recorded on the Adverse Event CRF.

7.5.3 Vital signs

Pulse, blood pressure (measured after at least 3 minutes in the sitting position), temperature and weight will be measured at every visit. Height will be measured at baseline only.

Patients should be weighed and monitored regularly for signs and symptoms of fluid retention. An unexpected rapid weight gain should be carefully investigated and appropriate treatment provided.

7.5.4 Performance status

The patient's performance status should be estimated using the ECOG scale / Karnofsky scale, and recorded in the CRF. Post-text supplement 2 shows the grading scale for reference (Karnofsky, 1948).

7.5.5 Laboratory evaluations

Blood and urine samples will be analyzed in the local laboratory. The laboratory details will be provided in writing to Novartis prior to the screening of the first patient at the site. In particular, the name, address and contact details of the lab must be provided, together with the lab normal ranges, and a copy of the latest lab certificate. Unless prior agreement is given by

Novartis to the site, the site must use the same lab(s) for all samples from a given patient, and all patients at that site.

The following assessments should be made:

Hematology

Total white blood cell (WBC (total)), red blood cells (RBC), Hemoglobin, Hematocrit, platelets.

Differential counts of the following should be made also: neutrophils, lymphocytes, eosinophils, basophils, monocytes. Results should be provided as absolute or percentage values (not both). The same units used for the screening visit assessment should be used for all samples for a particular patient.

Blood chemistry

Urea or BUN (depending on what is commonly used at the site), creatinine, sodium, potassium, glucose, uric acid, LDH, total protein, albumin, total bilirubin, SGOT, SGPT, alkaline phosphatase, cholesterol, triglycerides y-GT, Lipase, CRP, Quick, PTT.
.

Urine measurements

Glucose, protein, bilirubin, ketones, leukocytes, erythrocytes, specific gravity, pH, microscopic analysis.

7.5.6 ECG

A standard 12 lead ECG must be carried out at baseline for screening purposes and to provide a pretreatment comparison for an on-treatment ECG performed at the End of Study visit and at the end of follow-up.

7.5.7 Pregnancy test

Any pregnancy that occurs during study participation should be reported using a Clinical Trial Pregnancy Form. To ensure patient safety each pregnancy must also 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 birth, and the presence or absence of any birth defects, congenital abnormalities or maternal and newborn complications. Instructions about completing initial and follow-up Clinical Trial Pregnancy Forms and sending them to Novartis are given in Section 8.2. “Instructions for rapid notification of pregnancies”.

8 Safety monitoring

8.1 Serious adverse event reporting

8.1.1 Safety assessments

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 participation (end of treatment) must be reported to Novartis within 24 hours of learning of its occurrence. Any SAE 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 SAE is collected and recorded on the Serious Adverse Event Report Form. The investigator must assess the relationship to 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 & 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 CRF 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, 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 & 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.

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

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

If the father is taking the study drug, informed consent to report information regarding pregnancy outcome needs to be obtained from the mother.

9 Data review and database 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 CRFs 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 CRFs, 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 CRFs must be traceable to these source documents in the patient's file. Data not requiring a separate written record will be defined before study start and will be recorded directly on the CRFs, which will be documented as being the source data. The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAE, 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 CRFs 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

Designated investigator staff must enter the information required by the protocol onto the Novartis CRFs that are printed on 3-part, non-carbon-required paper. Field monitors will review the CRFs for completeness and accuracy and instruct site personnel to make any required corrections or additions. The CRFs are forwarded to the Data Management of Novartis or to the designated CRO by field monitors, one copy being retained at the investigational site; a further copy may be used as a working copy for the field monitors.

Once the CRFs are received by Novartis, their receipt is recorded and they are forwarded for data entry.

9.3 Database management and quality control

Data from the CRFs are entered into the study database using double data entry with electronic verification. Text items (e.g. comments) are entered once and checked manually against the CRF.

Subsequently, the entered data are systematically checked by Data Management staff, using error messages printed from validation programs and database listings. Obvious errors are corrected by Novartis personnel. Other errors or omissions are entered on Data Query Forms, which are returned to the investigational site for resolution. The signed original and resolved Data Query Forms are kept with the CRFs at the investigator site, and a copy is sent to Novartis so the resolutions can be entered into the database. Quality control audits of all key safety and efficacy data in the database are made prior to locking the database.

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.

10 Data analysis

This is a non-randomized, multicenter, triple-arm, phase II trial evaluating the treatment of RAD001 in the following three arms: in patients with progressive or metastatic bone or soft tissue sarcoma (except for GIST), in patients with progressive or metastatic GIST after failure or intolerance of treatment with imatinib or sunitinib, and in patients with progressive or metastatic alveolar soft part sarcoma (ASPS) respectively.

The study is designed to assess the activity, safety, and tolerability of the therapy with RAD001 in progressive bone or soft tissue sarcoma in the three arms each.

The data will be analyzed by Novartis and/or by the designated CRO. Any data analysis carried out independently by the investigator(s) should be submitted to Novartis before publication or presentation. It is planned that the data from participating centers in this protocol will be combined within each of the arms, so that an adequate number of patients will be available for analysis.

Data will be summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, safety observations and measurements, and pharmacokinetic measurements. Categorical data will be presented as absolute frequencies and percentages. For continuous data, N, mean, standard deviation, median, minimum, and maximum will be presented.

It is planned that the data of each arm will be analyzed independently of the other arm once the number of patients needed for analysis was reached.

For simplification, populations for analysis, and the analysis of patient demographics/other baseline characteristics, treatment, primary and secondary efficacy variables, and safety will

be described without referring to a specific arm. As mentioned above, the methods of analysis will be applied to each arm separately.

In a period of 46 months, so far 8 patients have been enrolled in arm III of this trial. It is deemed very unlikely, that a further extension of the enrollment period will result in the required number of patients in arm III of this trial. Therefore, enrollment in arm III will be stopped. However, patients already enrolled into arm III will continue to be treated and observed as foreseen by the protocol. The final analysis of arm III will be done when all patients have completed the study or discontinued prematurely. Since the sample size required for the decision algorithm will not be reached, data for arm III will be summarized descriptively, and results will be interpreted purely exploratively.

10.1 Populations for analysis

The Safety Population will consist of all patients who received at least one dose of study drug and had at least one post-baseline safety assessment. Patients will be analyzed according to treatment received. Of note, the statement that a patient had no adverse events also constitutes a safety assessment.

The intent-to-treat (ITT) population will consist of all patients who received at least one dose of study drug and have at least one post-baseline assessment of the primary efficacy variable (assessment according to RECIST). Patients without any post-baseline assessment of tumor will be included if they are defined as progressive disease based on clinical evaluation.

The per-protocol (PP) population (i.e. the efficacy-analyzable population) consists of all patients of the intent-to-treat population who show no major protocol violations. As major protocol violations are considered those that may have an impact on the study outcome. Criteria that are assumed to have such an impact will be defined in a Review Meeting before database lock.

10.2 Patient demographics/other baseline characteristics

Demographic and background information will be summarized for the safety, the ITT, and the PP population, using frequency distributions for categorical variables and descriptive statistics of mean, standard deviation, minimum, median and maximum for continuous variables. Background information includes prior medication, past/current medical conditions, diagnosis and extent of cancer, ECOG performance status and tumor evaluation at baseline.

Medical history will be coded using MedDRA and will be presented by system organ class, MedDRA preferred term and treatment group. Separate tables will be provided for past medical condition and current medical condition. Prior medication will be coded according to WHO Drug Reference List.

10.3 Treatments (study drug, rescue medication, other concomitant therapies, compliance)

Duration (days) of application of study medication will be summarized descriptively. Dosage averages will be calculated including and excluding zero doses for periods of temporary interruption of treatment regardless of whether this was due to safety reasons or patients' non-compliance. Daily dose levels will be summarized descriptively. Frequency of dose reduction

(including temporary dose interruption) for safety reasons as per protocol guidelines as well as average daily dose will be presented by visit. Reasons for dose adjustments (including temporary dose interruption) will be presented by frequency distribution. Permanent treatment discontinuations will be analyzed by frequencies. These analyses will be performed for the ITT and the PP population.

10.4 Analysis of the primary objective(s)

10.4.1 Variable

The primary variable is defined as the proportion of patients in whom a complete (CR) or partial (PR) response or stable disease (SD) was observed at 16 weeks according to RECIST.

10.4.2 Statistical hypothesis, model, and method of analysis

Response rate will be presented with the appropriate 95% confidence interval for the PP population. The absolute number of patients showing a response will be determined to conclude preliminary activity or non-activity of the study drugs in this patient population according to the rules outlined in section 10.2.

10.4.3 Handling of missing values/censoring/discontinuations

Not applicable, only efficacy-analyzable patients (PP population) will be analyzed.

10.4.4 Supportive analyses

Additionally, absolute and relative frequencies together with their appropriate 95% confidence interval will be presented for each category (CR/PR/SD/PD/UNK) for PP population.

10.5 Analysis of secondary objectives

10.5.1 Efficacy (secondary)

Objective response rate (ORR) is defined as the proportion of patients in whom a complete (CR) or partial (PR) response was observed at week 12 according to RECIST. Absolute and relative frequencies of patients in whom an objective response (CR/PR) was observed at week 12 will be presented together with the 95% confidence interval for the ITT and PP population.

Duration of response is defined as the time from onset of response (CR/PR) to progression or death from any cause. Patients, not experiencing progression or death at 16 weeks will be censored with the date of their last assessment. Duration of response will be explored graphically by presenting the Kaplan-Meier curve.

Progression-free survival (PFS) is defined as the time from first study drug administration to objective tumor progression or death from any cause. Observations from patients not experiencing tumor progression or death at 16 weeks will be censored with the date of their last assessment. PFS will be explored graphically by presenting the Kaplan-Meier curve. Additionally, the Kaplan-Meier curve will be presented for PFS at 12 months.

Overall survival (OS) is defined as the time from first study drug administration to death from any cause. Patients, not experiencing death at 16 weeks will be censored with the date of their last assessment. OS will be explored graphically by presenting the Kaplan-Meier curve.

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, and special tests) will be considered as appropriate.

10.5.2.1 Adverse events

Adverse events will be summarized by presenting for the safety population the number and percentage of patients having any adverse event, having an 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.

10.5.2.2 Laboratory values

Laboratory data will be summarized by presenting shift tables using extended normal ranges (baseline to most extreme post-baseline value), by presenting summary statistics of raw data and change from baseline values (means, medians, standard deviations, ranges) and by the flagging of notable values in data listings.

Data from other tests (e.g. electrocardiogram or vital signs) will be listed, notable values will be 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.

10.5.4 Resource utilization

Not applicable.

10.6 Sample size calculation

The study follows an exact binomial single-stage design in each arm. (A'Hern 2001). Values of P_0 and P_1 follow the recommendation of the EORTC Soft Tissue and Bone Sarcoma Group previous publication evaluating PFS in STS patients treated with 2nd line active and inactive compounds. In arm I (patients with bone and soft tissue sarcoma except for GIST), the study requires 36 evaluable subjects to decide whether the proportion responding, P, is less than or equal to $P_0 = 20\%$ or greater than or equal to $P_1 = 40\%$ (Table 10-1). In arm II or III (patients with GIST after failure or intolerance of 1st and 2nd line treatment with imatinib or sunitinib, and patients with progressive or metastatic alveolar soft part sarcoma (ASPS), respectively), the study requires 24 evaluable subjects to decide whether the proportion responding, P, is less than or equal to $P_0 = 20\%$ or greater than or equal to $P_1 = 40\%$.

If the number of responses in arm I is 11 or more, the hypothesis that P is less than or equal to 20% is rejected with a target type I error rate of 10% and an actual error rate of 8.9% (Table 10-1). If the number of responses in arm I is 10 or less, the hypothesis that P is greater than or equal to 40% is rejected with a target type II error rate of 10% and an actual error rate of 9%.

If the number of responses in arm II or arm III, respectively, is 8 or more, the hypothesis that P is less than or equal to 20% is rejected with a target type I error rate of 10% and an actual error rate of 8.9%. If the number of responses in arm II is 7 or less, the hypothesis that P is greater than or equal to 40% is rejected with a target type II error of 20% and an actual error rate of 19.2%.

The designs were estimated with NCSS Trial and PASS 2002.

Table 10-1 Design features for exact binomial single-stage designs

	Arm I	Arm II	Arm III
P_0 (maximum response proportion of an inactive drug)	20%	20%	20%
P_1 (minimum response proportion of an active drug	40%	40%	40%
Type I error (one-sided test)	10%	10%	10%
Type II error (one-sided test)	10%	20%	20%
Sample size	36	24	24
Accept inactivity at the end if	≤ 10 responders	≤ 7 responders	≤ 7 responders
Reject inactivity at the end if	≥ 11 responders	≥ 8 responders	≥ 8 responders
Actual type I error level	8.9%	8.9%	8.9%
Actual type II error level	9.0%	19.2%	19.2%

The type I error is the probability of rejecting that P is lower or equal to P_0 when this is true. **The type II error** is the probability of rejecting that P is greater or equal to P_1 when this is true.

10.7 Power for analysis of critical secondary variables

Not applicable.

11 References

A'Hern, RP: Sample size tables for exact single-stage phase II designs. Statist. Med. 2001; 20:859 – 866

Bjornsti MA, Houghton PJ, The TOR pathway: a target for cancer therapy. Nat Rev Cancer. 2004 May;4(5):335-48.

Cassier PA, Dufresne A, Fayette J, Alberti L, Ranchere D, Ray-Coquard I Blay JY Emergine drungs for the treatment of soft tissue sarcomas. Expert opin Emerg Drugs. 2007; 12(1): 139-53.

Clark MA, Fisher C, Judson I, Thomas JM: Soft tissue sarcoma in adults. N Engl J Med. 2005; 353:701-11.

Investigators' Brochure RAD001, Edition 5. 2006

Jac J, Giessinger S, Khan M et al: A phase II trial of RAD001 in patients (Pts) with metastatic renal cell carcinoma (MRCC). Journal of Clinical Oncology. ASCO Annual Meeting Proceedings Part I. 2007; Vol 25, No. 18S (June 20 Supplement): 5107

Yao JC, Phan A, Chang DZ et al., Phase II study of RAD001 (everolimus) and depot octreotide (sandostatin LAR) in advanced low grade neuroendocrine carcinoma (LGNET).

Journal of Clinical Oncology, ASCO Annual Meeting Proceedings Part I. 2007: Vol 25, No. 18S (June 20 Supplement): 4503

Ellard S, Gelmon KA, Chia S et al: A randomized phase II study of two different schedules of RAD001C in patients with recurrent/metastatic breast cancer. Journal of Clinical Oncology, 2007: ASCO Annual Meeting Proceedings Part I. Vol 25, No. 18S (June 20 Supplement): 3513

Johnston PB, Ansell SM, Colgan JP et al: Phase II trial of the oral mTOR inhibitor everolimus (RAD001) for patients with relapsed or refractory lymphoma, Journal of Clinical Oncology, 2007 ASCO Annual Meeting Proceedings Part I. Vol 25, No. 18S (June 20 Supplement): 8055

van Oosterom A, Reichardt P, Blay JY et al.: A phase I/II trial of the oral mTOR-inhibitor Everolimus (E) and Imatinib Mesylate (IM) in patients (pts) with gastrointestinal stromal tumor (GIST) refractory to IM: Study update. Journal of Clinical Oncology, 2005 ASCO Annual Meeting Proceedings. Vol 23, No. 16S, Part I of II (June 1 Supplement): 9033

Rao RD, Allred JB, Windschitl HE et al: N0377: Results of NCCTG phase II trial of the mTOR inhibitor RAD-001 in metastatic melanoma. Journal of Clinical Oncology, 2007 ASCO Annual Meeting Proceedings Part I. Vol 25, No. 18S (June 20 Supplement): 8530

Sankhala KK, Chawla SP, Iagaru A et al: Early response evaluation of therapy with AP23573 (an mTOR inhibitor) in sarcoma using [18F]2-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET) scan; Journal of Clinical Oncology, 2005 ASCO Annual Meeting Proceedings. Vol 23, No. 16S, Part I of II (June 1 Supplement), 2005: 9028

Chawla SP, Tolcher AW, Staddon AP et al: Survival results with AP23573, a novel mTOR inhibitor, in patients (pts) with advanced soft tissue or bone sarcomas: Update of phase II trial. Journal of Clinical Oncology, 2007 ASCO Annual Meeting Proceedings Part I. Vol 25, No. 18S (June 20 Supplement), 2007: 10076

Okuno SH, Mahoney MR, Bailey HH et al (2006) A multicenter phase 2 consortium (P2C) study of mTOR inhibitor in advanced soft tissue sarcomas (STS). Journal of Clinical Oncology, 2006 ASCO Annual Meeting Proceedings Part I. 2006; 24: 9504

Tabernero J., Rojo F., Burris H., et al: A phase I study with tumor molecular pharmacodynamic (MPD) evaluation of dose and schedule of the oral mTOR-inhibitor Everolimus (RAD001) in patients (pts) with advanced solid tumors Journal of Clinical Oncology, 2005 ASCO Annual Meeting Proceedings. Vol 23, No. 16S, Part I of II (June 1 Supplement), 2005: 3007

Oken, MM et al, Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649-655.

Karnofsky DA, Abelmann WH, Craver LF, et al, Cancer 1948; 1:634-656.

Loomba R, Rowley A, Wesley R, et al (2008). Systematic review: the effect of preventive lamivudine on hepatitis B reactivation during chemotherapy. *Ann Intern Med* 148(7): 519-28.

Krishna G, Moton A, Lei Ma L, Savant I, Martinho M, Seiberling M, McLeod J. Effects of oral posaconazole on the pharmacokinetic properties of oral and intravenous midazolam: A phase I, randomized, open-label, crossover study in healthy volunteers. Clinical Therapeutics, 2009; 31: 286-98.

Appendix 1: Administrative procedures

Regulatory and ethical compliance

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), 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 monitors, auditors, Clinical Quality Assurance representatives, IRBs/IECs/REBs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

Informed consent

Eligible patients may only be included in the study after providing written, 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. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. 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.

Study drug supply and resupply, storage, and tracking

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, all study drugs 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 German or in the local language and comply with the legal requirements of Germany or the respective country. They will include storage conditions for the drug, but no information about the patient except for the randomization number.

The investigator must maintain an accurate record of the shipment and dispensing of study drug in a drug accountability ledger. Monitoring of drug accountability will be performed by the field monitor during site visits and at the completion of the trial. Patients must 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 Novartis.

Post-text supplement 1: Response Evaluation Criteria in Solid Tumors (RECIST)

RECIST criteria for evaluation of tumor response

Eligibility

Only patients with measurable disease at baseline should be included in the study:

- **Measurable disease** - the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.
- **Measurable lesions** - lesions that can be accurately measured in at least one dimension with longest diameter ≥ 20mm using conventional techniques or ≥ 10mm with spiral CT scan (with minimum lesion size no less than double the slice thickness).
- **Non-measurable lesions** - all other lesions, including small lesions (longest diameter < 20mm with conventional techniques or < 10mm with spiral CT scan), i.e. bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal masses that are not confirmed and followed by imaging techniques, and cystic lesions.

Methods of tumor measurement

The following considerations are to be made when evaluating the tumor:

- 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 14 days before the beginning of the treatment.
- The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.
- Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.
- **CT and MRI**: CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10mm or less in slice thickness contiguously. Spiral CT should be performed using a 5-8mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen and pelvis.
- **Chest x-ray**: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- **Ultrasound**: When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

- **Endoscopy and laparoscopy**: The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.
- **Cytology and histology**: Cytology and histology can be used to differentiate between PR and CR in rare cases (i.e. after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors). Cytologic confirmation of neoplastic nature of any effusion that appears or worsens during treatment is required when the measurable tumor has met the criteria for response or stable disease. Under such circumstances, the cytologic examination of the fluid collected will permit differentiation between response or stable disease (an effusion may be a side effect of the treatment) or progressive disease (if the neoplastic origin of the fluid is confirmed).
- **Clinical examination**: Clinical lesions will only be considered measurable when they are superficial (i.e. skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Baseline documentation of target and non-target lesions

For the evaluation of lesions at baseline and throughout the study, the lesions are classified at baseline as either target or non-target lesions:

- **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 (either by imaging techniques or clinically). 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.
- **Non-target lesions**: All other lesions are considered non-target lesions, i.e. lesions not fulfilling the criteria for target lesions at baseline. Measurements of these lesions are not required, but the presence or absence or worsening of each should be noted throughout the study.

Evaluation of target and non-target lesions

To assess tumor response, the sum of the longest diameter for all target lesions will be calculated (at baseline and throughout the study). At each assessment response is evaluated first separately for target (Table 1) and non-target lesions (Table 2). These evaluations are then used to calculate the overall lesion response considering both, the target and non-target lesions together (Table 3).

Table Appendix 1: Response criteria for target lesions

Response Criteria	Evaluation of target lesions
Complete Response (CR):	Disappearance of all target lesions
Partial Response (PR):	At least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum longest diameter.
Progressive Disease (PD):	At least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum of longest diameter recorded since the treatment started or the appearance of one or more new lesions.
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of the longest diameter since the treatment started.
Unknown (UNK)	Progression has not been documented and one or more target lesions have not been assessed or have been assessed using a less sensitive method than baseline.

Table Appendix 2: Response criteria for non-target lesions

Response Criteria	Evaluation of non-target lesions
Complete Response (CR):	Disappearance of all non-target lesions
Incomplete Response/ Stable Disease (SD):	Persistence of one or more non-target lesion(s)
Progressive Disease (PD):	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.[1]
Unknown (UNK)	Progression has not been documented and one or more non-target lesions have not been assessed or have been assessed using a less sensitive method than baseline.

Although a clear progression of “non target” lesions only is exceptional, in such circumstances, the opinion of the treating physician does prevail and the progression status should be confirmed later on by the review panel (or study chair).

The response for non-target lesions is CR only if all non-target lesions which were evaluated at baseline are now all absent. If any of the non-target lesions is still present, the response can only be ‘Incomplete response/Stable disease’ unless any of the lesions was not assessed (in which case response is UNK) or worsened (in which case response is PD).

Evaluation of overall lesion response

The evaluation of overall lesion response at each assessment is a composite of the target lesion response, non-target lesion response and presence of new lesions as shown below in Table 3.

Table Appendix 3: Overall lesion response at each assessment

Target lesions	Non-target lesions	New Lesions	Overall lesion response
CR	CR	No	CR[1]
CR	Incomplete response/SD	No	PR
CR, PR, SD	UNK	No	UNK
PR	Non-PD and not UNK	No	PR[1]
SD	Non-PD and not UNK	No	SD[1, 2]
UNK	Non-PD or UNK	No	UNK[1]
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

[1] This overall lesion response also applies when there are no non-target lesions at baseline

[2] Once confirmed PR was achieved, all these assessments are considered PR.

If the evaluation of any of the target or non-target lesions identified at baseline could not be made during follow-up, the overall status must be 'unknown' unless progression was seen.

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the CR.

Best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed not less than 4 weeks after the criteria for response are first met.

The best overall response for each patient is determined from the sequence of overall (lesion) responses according to the following rules:

- CR = at least two determinations of CR at least 4 weeks apart before progression.
- PR = at least two determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR).
- SD = at least one SD assessment > 6 weeks after start of treatment (and not qualifying for CR or PR).
- PD = progression or death due to underlying cancer ≤ 16 weeks after start of treatment (and not qualifying for CR, PR or SD). Patients with symptoms of rapidly progressing disease without radiologic evidence will be classified as progression only when clear evidence of clinical deterioration is available and patient discontinued due to 'Disease progression'.
- 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 16 weeks)

Overall lesion responses of CR must stay the same until progression sets in, with the exception of a UNK status. A patient who had a CR can not subsequently have a lower status, e.g. PR or SD, as this would imply that one or more lesions reappeared, in which case the status would become a PD.

Overall lesion responses of PR must stay the same or improve over time until progression sets in, with the exception of a UNK status. However, if a patient has a PR (≥ 30% reduction of tumor burden compared to baseline) at one assessment, followed by a < 30% reduction from baseline at the next assessment (but not > 20% increase from previous smallest sum), the objective status at that assessment should be SD. Once a confirmed PR was seen, the overall lesion response should be considered PR (or UNK) until progression is documented.

If the patient progressed but continues study medication, further assessments are not considered for the determination of best overall response.

The best overall response for each patient will be determined based on investigator assessments ('Investigator best overall lesion response').

Post-text supplement 2: ECOG Performance Status Scale

Criteria for Estimation of Performance Status

GRADE	SCALE
0	Fully active, able to carry out all pre-disease performance without restriction. (Karnofsky 90-100%)
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light housework, office work. (Karnofsky 70-80%)
2	Ambulatory and capable of all self-care, but unable to carry out work activities. Up and about more than 50% of waking hours (Karnofsky 50-60%)
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. (Karnofsky 30-40%)
4	Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair. (Karnofsky 10-20%)
5	Dead (Karnofsky 0%)

Sources:
Oken, MM et al, Am J Clin Oncol 5:649-655, 1982
Karnofsky, DA et al, Cancer 1:634-656, 1948