NOVARTIS

RAD001, Everolimus

Amendment 1 to Clinical Trial Protocol CRAD001LIC01 / NCT01206764

An Open-Label, Multi-Center Phase 2 Study to Evaluate Everolimus as Monotherapy Treatment for Patients with Metastatic Recurrent and/or Unresectable Renal Cell Carcinoma (EVERMORE)

Authors	[redacted]

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List of Abbreviations

ADR	apparent drug reactions
AE	adverse event
AKT/PKB	Protein Kinase B (a component of PI3K signaling pathway)
ALT	alanine aminotransferase/glutamic pyruvic transaminase/GPT
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
ATC	Anatomical Therapeutic Chemical classification system
AUC	area under the blood-concentration time curve
CI	confidence interval
C_{max}	maximum plasma concentration
CNS	central nervous system
CR	complete response
CRF	case report form
CRO	Contract Research Organization
CT	computerized tomography
CTC	Common Toxicity Criteria
CTCAE	Common Toxicity Criteria for Adverse Events
CV	coefficient of variation
CYP	cytochrome P450
DLCO	diffusion capacity of carbon monoxide
DLT	dose limiting toxicity
DSMB	Drug Safety Monitoring Board
ECG	electrocardiogram
EDC	electronic data capture
FDA	Food and Drug Administration
FAS	Full Analysis Set
GCP	Good Clinical Practice
GGT	gamma-glutamyl-transferase
Hb	hemoglobin
HIF	hypoxia-inducible factor
HMG CoA	high mobility group co-enzyme A
IB	Investigator‟s Brochure
IC_{50}	inhibitory concentration at 50%

ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IFN	interferon
IMS	Integrated Medical Safety
IND	Investigational New Drug
INR	international normal ratio
IRB	Institutional Review Board
ITT	Intent-to-Treat
iv	intravenous(ly)
IVRS	Interactive Voice Response System
LD	longest diameter
LDH	lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MPD	molecular pharmacodynamic
MRCC	metastatic renal cell carcinoma
MRI	magnetic resonance imaging
MSKCC	Memorial Sloan-Kettering Cancer Center
mTOR	mammalian target of rapamycin
NCI	National Cancer Institute
NIH	National Institutes of Health
ORR	objective response rate
OS	overall survival
p-4E-BP1	eukaryotic initiation factor 4E binding protein-1
p-AKT	phospho-AKT
PBMCs	peripheral blood mononuclear cells
PD	progressive disease
PFS	progression-free survival
P-gp	P-glycoprotein
PI	principle investigator
PI3K	phosphatidylinositol 3-kinase (mTOR pathway)
PK	pharmacokinetics
PKB	protein kinase B
po	*per os*/by mouth/orally
PR	partial response
PT	prothrombin time
PTEN	phosphatase and tensin homolog deleted on chromosome 10

RBC	red blood cells
RCC	renal cell carcinoma
REB	Research Ethics Board
RECIST	Response Evaluation Criteria in Solid Tumors
S6K1	S6 kinase 1
SAE	serious adverse event
SAP	Statistical Analysis Plan
sc	subcutaneous
SD	stable disease
SOC	System Organ Class
SUSARS	Suspected Unexpected Serious Adverse Reactions
t_{max}	time to reach maximum plasma concentration
TTP	time to progression
TSC	tuberous sclerosis complex
ULN	upper limit of normal
US	United States
VEGF	vascular endothelial growth factor
VHL	Von Hippel-Lindau
WBC	total white blood cell count
WHO	World Health Organization

Oncology Clinical Study Protocol Synopsis

Investigational drug	RAD001 (everolimus)
Protocol no.	CRAD001LIC01
Study phase	Phase 2
Study title	An open-label, multi-center phase 2 study to evaluate everolimus as monotherapy treatment for patients with metastatic recurrent and/or unresectable renal cell carcinoma (EVERMORE)
Background	Renal cell carcinoma (RCC) accounts for more than 200,000 new cases of cancer and over 100,000 cancer deaths annually in the World (Ferlay, et al., 2004). It is estimated that there were about 15,000 new cases of RCC in the region that excludes the Americas, European Union and Japan. Renal cell carcinomas arise from the proximal tubal epithelium are more common in males than in females with an overall lifetime risk of 1 in 75 and a median age of diagnosis of 65 years. The past 10 years have seen a dramatic expansion of therapeutic options in the treatment of metastatic renal cell carcinoma (MRCC). Cytokine-based immunotherapy, the introduction of vascular endothelial growth factor (VEGF) targeted therapies, such as sorafenib, sunitinib, bevacizumab, and the mammalian target of rapamycin (mTOR) inhibitor temsirolimus have completely changed the treatment paradigm, with another mTOR inhibitor, everolimus (Afinitor®), approved in the US and Europe. Despite this progress, MRCC still remains a fatal disease; therefore, the development of new treatments is needed to help improve the outcome for these patients. Everolimus (Certican®) has been approved since 2003 in more than 60 countries for the prevention of organ rejection in patients with renal and cardiac transplantation. Everolimus (RAD001) is a derivative of rapamycin, which acts as a signal transduction inhibitor. It targets mTOR, a key protein kinase regulating cell growth, proliferation, and survival. The mTOR pathway activity is modulated by the phosphatidylinositol-3-kinase (PI3K)/protein kinase B AKT (AKT) pathway, a pathway known to be deregulated in numerous human cancers. RAD001 (Afinitor®) has been investigated as an anticancer agent based on its potential to act: • directly on the tumor cells by inhibiting tumor cell growth and proliferation; • indirectly by inhibiting angiogenesis leading to reduced tumor vascularity (via potent inhibition of tumor cell hypoxia-inducible factor 1 (HIF-1) activity, VEGF production, and VEGF-induced proliferation of endothelial cells). The role of angiogenesis in the maintenance of solid tumor growth is well established, and the mTOR pathway has been implicated in the regulation of tumor production of proangiogenic factors as well as modulation of VEGFR signaling in endothelial cells. This activity has recently been confirmed in a Phase 3 study (RECORD-1), which was stopped at its interim analysis by an Independent Data Monitoring Committee for outstanding efficacy observed at the second interim analysis. The results indicated a significant difference in efficacy between the RAD001

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	group and placebo group (hazard ratio 0.30 [95% confidence interval (CI): 0.22, 0.40], p<0.0001). The progression-free survival (PFS) showed in favor of RAD001 with a median PFS of 4.0 months (95% CI: 3.7, 5.5) versus 1.9 months (CI: 1.8, 1.9) for the placebo group (Motzer, et al, 2008). The probability of being progression-free at 6 months was 26% (95% CI: 14, 37) for patients receiving RAD001 compared with 2% (CI: 0, 6) for patients in the placebo group. The medium overall survival (OS) had not been reached for the RAD001 group and was 8.8 months (95% CI: 7.9, ASCO2009) for the placebo group. There was no significant difference between the groups in terms of OS (hazard ratio 0.83; 95% CI: 0.50, 1.37; p=0.23) (Motzer et al, 2008). Results from a further analysis in the RECORD-1 study, indicated a significant prolongation in PFS for the RAD001 group compared with the placebo group (hazard ratio 0.33; 95% CI: 0.25, 0.43; p<0.001) (Escudier, et al., 2008). The PFS showed in favor of RAD001 with a median PFS of 4.9 months versus 1.87 months for the placebo group. The median OS was not reached for RAD001, (hazard ratio 0.82; 95% CI: 0.57, 1.17; p<0.137) versus 13 months for the placebo group. RAD0001 is generally well tolerated at a dose of 10mg administered daily. The most frequent adverse events associated with RAD001 therapy (stomatitis, anemia, asthenia, fatigue, rash, mucosal inflammation, hypercholesterolemia, and headache) are effectively managed with drug and non-drug therapies or dietary interventions. Non-infectious pneumonitis has been reported with mTOR inhibitors but is commonly low-grade and reversible. A Phase 2 study reported promising information in 41 metastatic renal cell cancer patients (majority were previously-treated with cytokine therapy), who were treated with RAD001, 10 mg orally (po) daily (Amato, et al., 2009). The reported response rate was 32% (12 partial responses [PRs]), the median time to tumor progression was 11.17 months (2.00 months to >31.53 months) and OS in 39 patients was 24.17+ months. The intravenous mTOR inhibitor, temsirolimus (Torisel), has been reported to have a PFS and OS advantage over interferon (IFN) alpha in Memorial Sloan-Kettering Cancer Center (MSKCC) poor prognosis MRCC patients treated in the first-line setting. The median survival in the temsirolimus arm was prolonged to 10.9 months versus 7.3 months for interferon alpha (p=0.0069). Planned and post-hoc analyses have been performed to assess the influence of tumor histology (clear cell versus others) on survival in patients treated with temsirolimus or IFN (Dutcher, et al., 2007). The “other” subgroup category included non-clear cell and indeterminate histologies. The HR analysis for OS suggested an advantage for temsirolimus over IFN in this sub-group category (11.6 months versus 4.3 months, p=0.00095), even if the group analyzed is small and thus the confidence interval broader. It is clear that novel therapies are needed for patients with advanced RCC, including those with metastatic disease and those whose tumors are not amenable to surgical resection. Although sunitinib and temsirolimus have improved PFS or OS, in comparison with IFN, and the addition of

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	bevacizumab to IFN has led to improved results in comparison with single-agent IFN, in some countries IFN remains the only available treatment option for patients with advanced RCC. This trial will therefore explore the use of once daily oral RAD001 in patients with advanced kidney cancer of clear and non-clear cell histology and all MSKCC prognosis.
Purpose/rationale	The purpose of this study is to demonstrate the safety and efficacy of RAD001 (everolimus), an mTOR inhibitor, as monotherapy in patients with metastatic carcinoma of the kidney who have not received prior systemic treatment, other than cytokine therapy. The proposed dose and schedule (10 mg/day) is based on various Phase 1, Phase 2 studies (monotherapy and combination therapy) in advanced cancers, including RCC, and a large controlled Phase 3 study (RECORD-1). Current standard therapies (chemotherapies and cytokine-based therapies) have produced few and short-lived tumor responses, and are associated with severe toxicities. The efficacy of RAD001 as monotherapy in patients who were previously treated with cytokine therapy (Amato et al., 2009), and whose disease had progressed on VEGF-tyrosine kinase inhibitor therapy (Motzer et a., 2008l) were recently reported.
Objectives	Primary: To evaluate the PFS rate over time. Secondary: • To evaluate the disease control rate (stable disease [SD] + partial response [PR] + complete response [CR]); • To evaluate the objective response rate (ORR; where ORR = CR + PR) and duration; • To evaluate Overall Survival (OS) • To describe the safety profile of RAD001.
Study design	This is an open-label, multi-center, single arm Phase 2 study to evaluate the safety and efficacy of RAD001 as monotherapy in patients with any MSKCC prognosis metastatic recurrent and/or unresectable clear cell or non-clear cell carcinoma of the kidney. Patients who have received prior cytokine therapy are permitted to participate in the study. Patients will self-administer orally, 10 mg RAD001 per day. Tumor assessments will be performed at 8 weeks to evaluate for inadequate response (progressive disease [PD]). The visit at which PD is documented will be deemed the End-of-Treatment Visit. In the absence of PD, assessments will continue every 12 weeks (±1 week) until the start of new anticancer therapy and at End-of-Treatment Visit (within 1 week of stopping treatment) or until death. A partial or complete response warrants confirmation no sooner than 4 weeks. Follow-up phase: All patients will have a follow-up visit scheduled 28 days after the End-of-Treatment Visit to follow for AEs and SAEs that may have

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	occurred after discontinuation from the study. No Data Safety Monitoring Board (DSMB) is planned.
Population	Adult patients who have any MSKCC prognosis metastatic recurrent and/or unresectable clear cell or non-clear cell carcinoma of the kidney are eligible for enrollment in this study. Previous cytokine therapy is permitted. Patients must have histological or cytological confirmation of clear cell or non-clear cell renal carcinoma or a component of these histologies.
Inclusion/exclusion criteria	Inclusion criteria: Patients may be entered in the study only if they meet all of the following criteria: • Age ≥18 years old; • Patients with advanced renal cell carcinoma with confirmed clear or non-clear cell histology, with or without nephrectomy, and with any MSKCC prognosis; • Prior cytokine therapy is permitted; • Patients with at least one measurable lesion at baseline as per the Response Evaluation Criteria in Solid Tumors (RECIST) criteria. If skin lesions are reported as target lesions, they must be documented (at baseline and at every physical exam) using color photography and a measuring device (such as a caliper) in clear focus to allow the size of the lesion(s) to be determined from the photograph; • Life expectancy ≥3 months. Life expectancy should be judged in relation to other determining patient eligibility factors such as laboratory results, Karnofsky Performance Status, etc.; • Patients with a Karnofsky Performance Status ≥70%; • Adequate bone marrow function as shown by: absolute neutrophil count (ANC) ≥1.5 x 10^9/L, platelets ≥100 x 10^9/L, hemoglobin (Hb) >9 g/dL; • Adequate liver function: serum bilirubin ≤1.5 x upper limit of normal (ULN), alanine transaminase (ALT), and aspartate transaminase (AST) ≤2.5 x ULN. Patients with known liver metastases: AST and ALT ≤5 x ULN; • Adequate renal function: serum creatinine ≤1.5 x ULN; • Females of childbearing potential must have had a negative serum or urine pregnancy test 7 days prior to the administration of the study treatment start; • Patients who give a written informed consent obtained according to local guidelines.

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	Exclusion criteria: Patients may not be entered into the study if they meet any of the following criteria: • Patients within 2 weeks post-minor surgery (e.g., herniorrhaphy), 4 weeks post-major surgery (e.g., intra-thoracic, intra-abdominal, or intra-pelvic) to avoid wound healing complications. Percutaneous biopsies require no waiting time prior to study entry; • Patients with a recent history of hemoptysis, ≥0.5 teaspoon of red blood; • Patients who have received prior systemic treatment for their metastatic RCC other than with cytokine therapy; • Patients who received prior therapy with a VEGF pathway inhibitor, such as sunitinib, sorafenib, and bevacizumab; • Patients who have previously received mTOR inhibitors (sirolimus, temsirolimus, everolimus, deferolimus); • History or clinical evidence of central nervous system (CNS) metastases. Note: Subjects who have previously-treated CNS metastases (surgery±radiotherapy, radiosurgery, or gamma knife) and meet all 3 of the following criteria are eligible: ▪ Are asymptomatic; ▪ Have had no evidence of active CNS metastases for ≥ 6 months prior to enrollment and; ▪ Have no requirement for steroids or enzyme-inducing anticonvulsants (EIAC); • Clinically significant gastrointestinal abnormalities including, but not limited to: ▪ Malabsorption syndrome; ▪ Major resection of the stomach or small bowel that could affect the absorption of study drug; ▪ Active peptic ulcer disease; ▪ Inflammatory bowel disease; ▪ Ulcerative colitis, or other gastrointestinal conditions with increased risk of perforation; ▪ History of abdominal fistula, gastrointestinal perforation, or intra abdominal abscess within 28 days prior to beginning of study treatment;

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	• Patients receiving chronic systemic treatment with corticosteroids (dose of ≥10 mg/day methylprednisone equivalent) or another immune-suppressive agent. Inhaled and topical steroids are acceptable, as well as opotherapy after bilateral adrenal gland removal; • Patients with a known history of human immunodeficiency virus seropositivity; • Patients with autoimmune hepatitis; • Patients with an active, bleeding diathesis. Patients may use coumadin or heparin preparations; • Patients who have any severe and/or uncontrolled medical conditions or other conditions that could affect their participation in the study; • Patients who have a history of another primary malignancy ≤3 years, with the exception of non-melanoma skin cancer and carcinoma in situ of uterine; • Female patients who are pregnant or breastfeeding, or adults of reproductive potential who are not using effective birth control methods. If barrier contraceptives are being used, these must be continued throughout the study by both sexes. **Oral contraceptives are not acceptable as the only contraception method. However they can be used in combination with other methods such as barrier contraceptives**; • Patients who are using other investigational agents or who had received investigational drugs ≤4 weeks prior to study treatment start; • Patients unwilling or unable to comply with the protocol.
Patient numbering	The patient number is a 9-digit number. The first part is the site number (first 4 digits) and the second part (last 5 digits) is one of a series of numbers allocated to patients at that site. The site number is assigned by Novartis. There will be no Interactive Voice Response System (IVRS) used.
Investigational and control drugs	Study drug refers to any Novartis investigational drug(s) or any Novartis marketed drug(s) being used for an unapproved indication. The investigational drug used in this study is RAD001. The study drug will be self-administered (by the patients themselves). The investigator will instruct the patient to take the study drug exactly as specified in the protocol.
Dose, regimen, treatment cycle	Patients will be instructed to take two 5 mg RAD001 tablets (one tablet after another) orally, with a glass of water at the same time each day in a fasting state or with a light fat-free meal. RAD001 will be taken daily from Visit 2 (Day 1) until disease progression, unacceptable toxicity, or death or discontinuation from the study for any other reason.

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	Each treatment cycle is 28 days.
Supply, preparation, and administration	RAD001 will be provided by Novartis. RAD001 is formulated as tablets of 5 mg strength for oral administration. The starting dose for Cycle 1 is 10 mg/day. Tablets should be opened only at the time of administration, as the drug is both hygroscopic and light sensitive. Patients will be supplied with enough tablets for a complete 28-day cycle. Tablets should be stored in a secure, dry, light-proof medicine cabinet.
Visit schedule and assessments	Patients will present to the clinic on Day 1 and Day 15 of treatment Cycles 1, 2, and 3 and Day 1 of each subsequent treatment cycle for assessments. Please see Section 7 and Table 9 for details of assessments.
Efficacy assessment(s)	Tumor response, SD, and progression will be assessed using the RECIST criteria. A computerized tomography (CT) scan or magnetic resonance image (MRI) of the chest/abdomen and pelvis will be obtained at screening (≤35 days) prior to the first dose of RAD001. Tumor response will be assessed at 8 weeks (±1 week), and every 12 weeks (±1 week) thereafter, until determination of disease progression (by the local radiologist) and at the end of the study. The same imaging modality used at screening must be used for all subsequent follow-up assessments. **Ultrasound scans cannot be used to measure tumor lesions.**
Special safety assessment(s)	Safety assessments will consist of monitoring and recording all AEs, including SAEs, the regular monitoring of hematology, serum chemistry, routine monitoring of vital signs (heart rate, blood pressure, and body temperature), and chest x- rays, electrocardiograms, and physical condition. Toxicity will be assessed using the National Institutes of Health (NIH)-National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 3.0. During the screening period, ALL patients must be screened for HBV and HCV (current or past history of infection). Careful medical history must be taken for all patients to look for risk factors (family history of HBV and HCV, intravenous drug abuse, unprotected sex, dialysis, blood transfusions, etc), and any past or present HBV symptoms (e.g., jaundice, dark urine, light-colored stools, right upper quadrant pain). In addition, ALL patients will be tested at screening for: • HBV-DNA levels • Hepatitis B surface antigen (HBsAg) • Hepatitis B core antibody (HBcAb) • Hepatitis B surface antibody (HBsAb) Based on the results of the screening HBV tests, the patients may be given prophylactic antiviral treatment and will be monitored throughout the study according to Table 6-5. ALL patients will be tested for quantitative HCV RNA-PCR at the screening

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	visit. Monitoring for HCV RNA-PCR levels every six weeks is required for: • patients known to have a history of HCV infection, despite a negative viral load test at screening (including those that were treated and are considered „cured") • patients positive for viral load on HCV RNA-PCR test at screening.
Patient reported outcomes	There are no patient reported outcomes.
Pharmacokinetics	Not applicable.
DSMB	No Data Safety Monitoring Board is planned for this study.
Statistical methods and data analysis	Study Populations The Full Analysis Set (FAS) consists of all patients treated with RAD001. Following the intent-to-treat (ITT) principle, patients are analyzed according to the treatment and stratum they were in at the start of the study. The Safety population consists of all patients who received at least one dose of the study drug and who have at least one post-baseline safety assessment. Patients are analyzed according to the treatment received Efficacy: The primary endpoint of this study, PFS, is defined as the time from the date of the start of RAD001 treatment to the date of the first documented disease progression or death due to any cause. A patient who has not progressed or died at the date of the analysis cut-off, or when he/she receives any further anticancer therapy, would have his/her PFS censored at the time of the last tumor assessment, before the first of the cut-off date or the anticancer therapy date. The primary analysis, PFS, will be based on the review by the local radiologist and/or the investigator, who will determine tumor response and progression according to the RECIST criteria. Secondary endpoints include OS, disease control rate, duration of response, ORR, and frequency of AEs and SAEs. The disease control rate will be based on the data as per radiological review, following the RECIST criteria. The disease control rate is defined as the proportion of patients with CR, PR, or SD. The disease control rate (CR + PR + SD) will be summarized in terms of percentage with a 95% confidence interval (CI). The overall response rate is defined as the proportion of patients with CR or PR. The overall response rate (CR + PR) will be summarized in terms of percentage with a 95% CI. The sample size for this study will be determined with reference to estimating a CI for the PFS rate at 10 months, assuming (for simplicity) the use of the

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	normal approximation to the binomial distribution and assuming that a CI for a proportion is based on this normal approximation. To be able to estimate a 95% CI for the PFS rate, centered at 0.50, and having an expected total interval width of approximately 0.27, requires a sample size of 55 patients in each cohort (first- and second-line). With 95% confidence, the expected total interval width is approximately 0.19 for all 110 patients (both cohorts combined).	
Study Recruitment and duration	Recruitment: Approximately 18 months. Treatment period: Patients will receive study treatment until: (a) there is evidence of disease progression; (b) the patient develops unacceptable toxicity; or (c) the patient withdraws informed consent. Follow-up: 28 days	
Key dates	FPFV: 31 July 2009	LPLV: 30 January 2012
Number of patients, sites and location	Total number of patients: 110 Number of sites: 25 Location of sites: Algeria, Morocco, Tunisia, Egypt, Saudi Arabia, Thailand, Jordan, Lebanon, India, Russia, and South Africa.	

1 Background

1.1 Overview of Metastatic Renal Cell Carcinoma

Renal cell carcinoma (RCC) accounts for more than 200,000 new cases of cancer and over 100,000 cancer deaths annually in the World (Ferlay, et al., 2004). It is estimated that there were about 15,000 new cases of RCC in the region that excludes the Americas, European Union and Japan.

Renal cell carcinomas arise from the tubular epithelium. Alternatively known as clear-cell cancer or renal adenocarcinoma, RCC is characterized by a distinct clear or granular cell appearance visible by light microscopy (Amato, 2000; George and Kaelin, 2003). Renal cell carcinoma can occur in different cellular types (Storkel and van den Berg, 1995):

- conventional RCC (also known as clear cell) (75% of cases);
- RCC of papillary cell type (also known as chromophilic) (10% of cases);
- chromophobe cell carcinoma (5% of cases);
- Others (10% of cases).

The most common molecular abnormality in clear cell RCC is loss of Von Hippel-Lindau (VHL), which is found in about 50%-70% of sporadic cases (Kim and Kaelin, 2004). Sporadic somatic and hereditary germ cell mutations cause the loss of the VHL protein (Gnarra and Dressler, 1995) and VHL negatively regulates hypoxia inducible genes, such as those encoding hypoxia inducible factor-1 alpha (HIF 1-alpha), vascular endothelial growth factor (VEGF), and platelet-derived growth factor B and the glucose transporter GLUT-1 (Iliopoulus, et al., 1996). An animal model of VHL-deficient tumors showed increased uptake of the positron emission tomography tracer fluorodeoxyglucose in an mTOR dependent manner (Thomas, et al., 2006).

As with clear cell cancers, papillary tumors originate from the tubular epithelium, but they are morphologically and genetically distinct malignancies. Multiple genetic abnormalities have been described. Among 29 malignant papillary RCCs, for example, trisomy 16 was present in 20 tumors, and trisomy 12 and trisomy 20 were each identified in 8 cases (Kovacs, et al., 1989). No tumor had an abnormality in 3p, which is the typical finding in clear cell carcinomas. While inherited papillary RCCs have been associated with mutations in the c-met oncogene, such mutations have not been routinely detected in sporadic cases.

Papillary carcinomas have been subdivided into two subtypes, based upon histologic criteria and distinctive gene expression profiles (Delahunt and Eble, 1997). Type 1 tumors tend to be low-grade and have a better prognosis, while type 2 lesions generally are high-grade and have a poorer prognosis. An analysis of 130 cases of papillary carcinomas at a median follow-up of 48 months found that patients with type 1 tumors had a significantly better overall and disease-free survival than patients with type 2 tumors (89% and 92% versus 55% and 44%, respectively; Pignot, et al., 2007).

Approximately 25% of the patients present with advanced disease at the time of diagnosis, including locally invasive or metastatic renal cell carcinoma, and 50% of the patients

undergoing curative surgery can be expected to experience relapse at distant sites (Figlin, 1999; Linehan, 2001). Median survival for patients with metastatic disease is about 13 months (Cohen and McGovern, 2005).

Renal cell carcinoma is characterized by a high degree of resistance to chemotherapy. Interferon-α and interleukin-2 were for many years standard therapies for patients with metastatic RCC (MRCC). Both achieve complete plus partial responses in 10% to 20% of patients. Only a minority of patients achieve long-term survival. Recently developed VEGF targeted therapies, both receptor tyrosine kinase inhibitors (sunitinib, sorafenib) and VEGF-A ligand antibodies (bevacizumab), have demonstrated activity in clear-cell MRCC (Motzer, et al., 2007; Awada, et al., 2005; Escudier, et al., 2007; Yang, et al., 2003); however, there is limited data regarding their efficacy in papillary RCC.

The mammalian target of rapamycin (mTOR) inhibitor, temsirolimus, reported both a PFS and overall survival (OS) advantage over interferon alpha in Memorial Sloan-Kettering Cancer Center (MSKCC) poor prognosis MRCC patients treated in the first-line setting (Hudes, et al., 2006). This study demonstrated a statistically significant improvement in PFS (3.7 months) for patients who received 25 mg intravenous (iv) temsirolimus on a weekly schedule versus 1.9 months for patients who received interferon alpha (p=0.0001). The median survival in the temsirolimus arm was prolonged to 10.9 months versus 7.3 months for interferon alpha (p=0.0069). Planned and post-hoc analyses have been performed to assess the influence of tumor histology (clear cell versus others) on survival in patients treated with temsirolimus or interferon (IFN) (Dutcher, et al., 2007). The "other" subgroup category included non-clear cell and indeterminate histologies. The HR analysis for OS suggested an advantage for temsirolimus over IFN in this sub-group category (11.6 months versus 4.3 months, p=0.00095), even if the group analyzed was small and thus the confidence interval broader (Dutcher, et al., 2007).

It is clear that novel therapies are needed for patients with advanced RCC, including those with metastatic disease and those whose tumors are not amenable to surgical resection. Although sunitinib and temsirolimus have improved PFS or OS, in comparison with IFN, and the addition of bevacizumab to IFN has led to improved results in comparison with single-agent IFN, in some countries IFN remains as the only available treatment option for patients with advanced RCC. This trial will therefore explore the use of oral RAD001 daily in both clear cell and non-clear cell carcinoma of the kidney.

1.2 Overview of RAD001

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

RAD001 is being investigated as an anticancer agent based on its potential to act:

- directly on the tumor cells by inhibiting tumor cell growth and proliferation;

- indirectly, by inhibiting angiogenesis leading to reduced tumor vascularity (via potent inhibition of tumor cell VEGF production and VEGF-induced proliferation of endothelial cells).

1.2.1 mTor Pathway and Cancer

At the cellular and molecular level, RAD001 acts as a signal transduction inhibitor. RAD001 selectively inhibits mTOR, a key protein kinase present in all cells, which regulates cell growth, proliferation, and survival. mTOR is mainly activated via the phosphatidylinositol 3-kinase (P13K) pathway through AKT/protein kinase B (PKB) and the tuberous sclerosis complex (TSC1/2). Mutations in these components, or in PTEN (phosphatase and tensin homolog deleted on chromosome 10), a negative regulator of PI3K, may result in their dysregulation. Abnormal functioning of various components of the signaling pathways contributes to the pathophysiology of numerous human cancers. Various preclinical models have confirmed the role of this pathway in tumor development.

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

- mTOR functions as a sensor of mitogens, growth factors, and energy and nutrient levels, facilitating cell-cycle progression from G1-S phase in appropriate growth conditions;
- The PI3K (mTOR) pathway itself is frequently dysregulated 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 (i.e., VEGF) and inhibition of endothelial cell growth and proliferation;
- Through inactivating eukaryotic initiation factor 4E binding proteins and activating the 40S ribosomal S6 kinases (i.e., p70S6K1), mTOR regulates protein translation, including the HIF-1 proteins. Inhibition of mTOR is expected to lead to decreased expression of HIF-1.

1.2.2 Preclinical Studies

RAD001 inhibits the proliferation of a range of human tumor cell lines in vitro, including lines originating from lung, breast, prostate, colon, melanoma, and glioblastoma. The 50% inhibitory concentration (IC_{50}) ranges from sub/low nM to μM. RAD001 also inhibits the proliferation of human umbilical vein endothelial cells in vitro, with particular potency against VEGF-induced proliferation, suggesting that RAD001 may also act as an antiangiogenic agent.

The antiangiogenic activity of RAD001 was confirmed in vivo. RAD001 selectively inhibited VEGF-dependent angiogenic responses at well tolerated doses. Mice with primary and metastatic tumors treated with RAD001 showed a significant reduction in blood vessel density when compared with controls.

The potential of RAD001 as an anticancer agent was shown in rodent models. RAD001 is orally bioavailable, residing longer in tumor tissue than in plasma in a subcutaneous (sc) mouse xenograft model, and demonstrating high tumor penetration in a rat pancreatic tumor model. The pharmacokinetic (PK) profile of RAD001 indicates sufficient tumor penetration,

above that needed to inhibit the proliferation of endothelial cells and tumor cell lines deemed sensitive to RAD001 in vitro.

RAD001 administered daily orally (po) was a potent inhibitor of tumor growth, at well-tolerated doses, in 11 different mouse xenograft models (including pancreatic, colon, epidermoid, lung, and melanoma) and two syngeneic models (rat pancreatic, mouse orthotopic melanoma). These models included tumor lines considered sensitive and "relatively resistant" in vitro. In general, RAD001 was better tolerated in mouse xenograft models than standard cytotoxic agents (i.e., doxorubicin and 5-fluorouracil), while possessing similar antitumor activity. Additionally, in a VEGF-impregnated sc implant model of angiogenesis, RAD001 antiangiogenic activity was demonstrated by reduced vascularity in RAD001-treated tumors (murine melanoma).

It is not clear which molecular determinants predict responsiveness of tumor cells to RAD001. Molecular analysis has revealed that relative sensitivity to RAD001 in vitro correlates with the degree of phosphorylation (activation) of the AKT/PKB protein kinase and the S6 ribosomal protein; in some cases (i.e., glioblastoma multiforme) there is also a correlation with PTEN status.

In vivo studies investigating the antitumor activity of RAD001 in experimental animal tumor models showed that RAD001 monotherapy typically reduced tumor cell growth rates rather than regression or stable disease. These effects occurred within the dose range of 2.5 mg/kg to 10 mg/kg, po once a day.

In preclinical models, the administration of RAD001 was associated with reduction of protein phosphorylation in target proteins downstream of mTOR, notably phosphorylated S6 (p-S6) and eukaryotic initiation factor 4E binding protein-1 (p-4E-BP1), and occasionally with an increase in phosphorylation of AKT, a protein upstream of mTOR in the signaling pathway. Study CRAD001A2107 explored molecular pharmacodynamic (MPD) changes in tumors at different doses and schedules of RAD001 (weekly 20, 50, and 70 mg or daily 5 and 10 mg).

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

Thomas, et al. (2006), have published on the preclinical rationale for using mTOR inhibitors in kidney cancer. Their work showed that HIF mutants rescue growth suppression caused by treatment of CCI-779, a rapamycin prodrug, in mice, and supports that the effect of mTOR inhibitors in renal cell carcinoma are mediated primarily via direct effects on tumor cells. However, the effect of mTOR inhibitors on the carcinoma‟s microenvironment requires further study. The mTOR inhibitors have a distinct mechanism of action from the VEGF pathway inhibitors such as VEGF receptor tyrosine kinase inhibitors (sunitinib and sorafenib) and VEGF ligand antibodies (bevacizumab). Therefore, resistance to VEGF inhibitors does not imply resistance to mTOR inhibitors.

1.2.3 Clinical Experience

1.2.3.1 RAD001 Pharmacokinetics

The PK characteristics of RAD001 have been extensively investigated in the context of the drug‟s development as an immunosuppressant in solid organ transplantation, where RAD001 was administered twice daily as a part of an immunosuppressant, multi-drug regimen, consistently including cyclosporin A and glucocorticoids.

Recent Phase 1 studies provide steady-state PK for both the weekly and daily schedules at varying dose levels in patients with advanced cancers. RAD001 is rapidly absorbed after oral administration, with a median time to peak plasma levels (t_{max}) of 1-2 hours postdose. The extent of absorption is estimated at above 11%.

The area under the blood concentration-time curve (AUC) is dose-proportional over the dose range tested, while maximum blood concentration (C_{max}) appears to plateau at dose levels higher than 20 mg. The terminal half-life in cancer patients averaged 30 hours, which is similar to that in healthy subjects. Inter-patient variability is moderate with the coefficient of variation (CV) of approximately 50%. A high-fat meal altered the absorption of RAD001 with 1.3 hour delay in t_{max}, a 60% reduction in C_{max}, and a 16% reduction in AUC. In whole blood, approximately 80% of RAD001 is contained in red blood cells (RBC).

Of the fraction of drug contained in plasma, 74% is protein-bound. The apparent distribution volume after a single dose was 4.7 L/kg. RAD001 is eliminated by metabolism, mainly by hydroxylation, then excreted into the feces (>80%). RAD001 is mainly metabolized by cytochrome P450 (CYP) 3A4 isoenzyme in the liver and to some extent in the intestinal wall.

RAD001 is also a substrate of P-glycoprotein (P-gp). Therefore, absorption and subsequent elimination of systematically absorbed RAD001 may be influenced by medicinal products that interact with CYP3A4 and/or P-gp. In vitro studies showed that RAD001 is a competitive inhibitor of CYP3A4 and of CYP2D6 substrates, potentially increasing the concentrations of medicinal products eliminated by these enzymes.

In two Phase 3 clinical studies in patients following kidney transplantation, strong inhibitors of CYP3A4 (azoles, antifungals, cyclosporine, erythromycin) have been shown to reduce the clearance of RAD001, thereby increasing RAD001 blood levels. Similarly, rifampin, a strong inducer of CYP3A4, increases the clearance of RAD001, thereby reducing RAD001 blood levels. Caution should be exercised when co-administering RAD001 with CYP3A4 inhibitors or inducers.

Pharmacokinetic drug to drug interactions with cancer agents are being evaluated in ongoing Phase 1b studies. Based on currently available results, gemcitabine (Study 2101 part 2) and paclitaxel (Study 2104) did not alter RAD001 PK to a clinically relevant extent, whereas imatinib notably increased RAD001 exposure with a mean increase in AUC by a multiple of 3.7 for RAD001 administered weekly and 2-fold for RAD001 administered daily (Study 2206). Exposure to RAD001 in the presence of letrozole did not exceed that in monotherapy (Study 2108).

Co-administration of RAD001 did not influence the PK of gemcitabine, imatinib, or letrozole. Exposure to paclitaxel in the presence of RAD001 was slightly decreased (average by 23%).

RAD001 PK in transplant patients were investigated in special populations, such as patients with hepatic or renal impairment, various ethnic groups, and pediatric renal transplant patients. In patients with mild to moderate hepatic impairment, mean AUC for RAD001 was increased by 2-fold whilst renal impairment did not affect the PK of RAD001. Age, weight (both over the adult range), and gender did not affect the PK of RAD001 to a clinically relevant extent. Also, the PK were not altered in Asian patients, whereas black patients had 21% higher clearance compared with non-blacks.

A single, escalating-dose study in Japanese subjects did not show a significant difference in systemic exposure relative to the Caucasian population.

1.2.3.2 Pharmacodynamic Studies

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

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

In the first part of Study C2101/C2102, the inhibition of S6K1 activity in PBMCs was measured in patients on a weekly regimen (5, 10, 20, and 30 mg) by radioimmunoassay (Lane, et al., 2003). Subsequently, PK/pharmacodynamic modeling was carried out, extrapolating from preclinical findings in order to predict the likely inhibitory effect of RAD001 on its known target in the tumor of patients at these doses in the weekly regimen, as given, at postulated higher weekly doses, and in a postulated daily regimen. For the weekly regimen, the modeling suggested 20 mg/week as a minimum inhibitory dose, but with a decline of inhibition (over 50%) between administrations, which was only marginally improved by increasing the dose. The model indicated that a greater degree of sustained inhibition should be obtained with a daily regimen at comparable total drug consumption.

A daily regimen of RAD001 (5 mg/day) was associated with a high inhibition of p-S6 and p-eIF4G, which was complete at 10 mg daily. In patients on the weekly schedule, p-S6 inhibition was complete and sustained at all dose levels, while that of p-eIF4G was complete and sustained at 50 mg weekly, but not at 20 mg weekly. On both regimens, numerous patients demonstrated apparent up-regulation of AKT, which tended not to persevere in the patients at 50 mg weekly. The proliferation index was reduced in most patients, recovering in some of those on the 50 mg weekly regimen. Please refer to the Investigator"s Brochure (IB) for further details.

1.2.3.3 Phase 1 Oncology Studies

Data are available from Phase 1 clinical studies of RAD001 given as a single agent to 147 patients with advanced solid tumors. Such studies included various doses and schedules (weekly dosing, range 5 mg to 70 mg and daily dosing 5 mg to 10 mg). Approximately 46%

of patients reported rash or erythema and 40% of the patients presented with stomatitis/mucositis. The most frequent AEs suspected to be drug-related observed in 3 studies using RAD001 as a single-agent are listed in Table 1.

Table 1 Adverse Events Suspected to be Drug-Related in ≥10% of Patients with Advanced Cancers Reported in Phase 1 RAD001 Monotherapy Studies (C2101, C2102, and C2107)

	Weekly			Daily		
	5-30 mg n=30	50 mg n=18	70 mg n=38	5 mg n=16	10 mg n=45	Total n=147
Number of Patients with Adverse Event						
Any event	23 (1)	17 (2)	38 (10)	14 (1)	43 (14)	135 (28)
By event						
Rash	5	8	18	10	27 (1)	68 (1)
Stomatitis/mucositis	6	8 (2)	16 (2)	6 (1)	23 (3)	59 (8)
Fatigue	8	7 (1)	14 (1)	1	17 (1)	47 (3)
Nausea	5	4	8	2	18 (1)	37 (1)
Anorexia	1	6	10	3	15	35
Diarrhea	1	7	7	-	9	24
Vomiting	4	5	5	-	10	24
Headache	7	4	6	6	4	20
Pruritis	2	1	6	3	4	16
Infections	1	3	2	1	4 (1)	14 (1)
Constipation	-	1	2	2	9	14

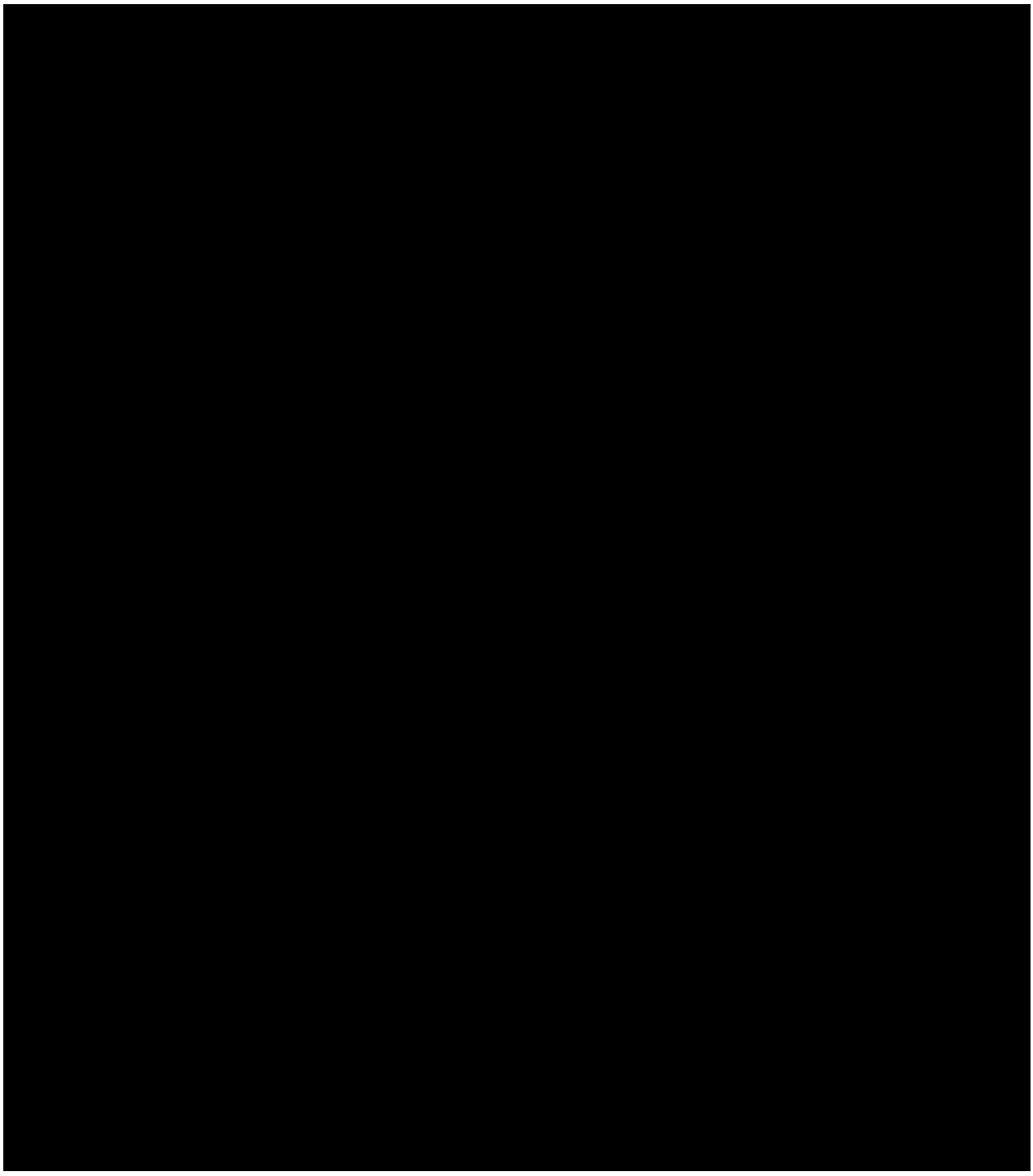
The number of patients (by dose level and dose schedule) who have reported grade ≥3 toxicities is given in brackets. There were no RAD001 suspected grade 4 adverse events.

Infections noted as drug-related included:

Herpes simplex	4 patients (1 at 50 mg/week; 1 at 5 mg/day; 2 at 10 mg/day)
Oral candidiasis	5 patients (1 at 20 mg/week; 1 at 50 mg/week; 2 at 70 mg/week; 1 at 10 mg/day)
Pneumonia (grade 3)	1 patient (10 mg/day)
Rhinitis	2 patients (50 mg/week)
Upper respiratory tract infection	1 patient (50 mg/week)
Urinary tract infection	1 patient (50 mg/week)

Reduced blood cell counts at the initiation of treatment are frequent, but remain mostly within the normal range or limited to grade 1, although a grade 3 neutropenia was a dose-limiting toxicity (DLT) in one patient, as was a grade 3 thrombocytopenia in a patient receiving RAD001 with letrozole, where pharmacodynamic interaction is unlikely. This suggests that some patients may be particularly sensitive to the myelosuppressive effect of RAD001, making it necessary to carefully monitor blood cell counts at the initiation of treatment.

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



1.2.3.4 Clinical Studies with RAD001 in MRCC Patients

RAD001 has shown single agent responses in patients with MRCC. Porter, et al. (2006), reported data from 12 RCC patients enrolled in two Phase 1 studies who received RAD001 on a weekly or a daily schedule. Seven patients received doses ranging from 20 mg to 70 mg po weekly and 5 patients received 10 mg po daily. Ten of the 12 patients had

received prior treatment (7 patients had received bevacizumab and erlotinib, 2 patients had received IL-2, and 1 patient received other drugs).

The results of tumor assessments using Response Evaluation Criteria in Solid Tumors (RECIST) showed one confirmed and one unconfirmed partial response (PR), the latter having progressed on bevacizumab therapy. Overall, 6 patients had stable disease (SD) for ≥6 months and 4 patients were progression-free beyond 12 months (maximum 20 months). Two of the latter patients had previously received bevacizumab therapy.

In a Phase 2 study (Amato, et al., 2006) of RAD001 in patients with MRCC involving no more than 1 prior therapy, an oral daily dose of 10 mg without an interruption (28-day cycle) and response rate determined using RECIST criteria with re-assessment every 3 cycles, RAD001 had promising anti-tumor activity as demonstrated by a 33% PR rate. Anti-tumor activity was further suggested by prolonged time to progression (TTP) of ≥3 months for 86% of patients. The antitumor effect was also demonstrated when RAD001 was used as a second-line therapy.

In a second Phase 2 study, RAD001 (10 mg po daily) demonstrated promising anti-tumor activity in 41 previously-treated patients with metastatic RCC. The reported response rate was 32% (12 PRs), the median TTP was 11.17 months (2.00 months to >31.53 months) and OS in 39 patients was >24.17+ months (Amato, et al., 2009).

This activity has recently been confirmed in a Phase 3 study, RECORD-1, which was stopped at its interim analysis by an Independent Data Monitoring Committee for outstanding efficacy observed at the second interim analysis. The results indicated a significant difference in efficacy between the RAD001 group and placebo group (hazard ratio 0.30 [95% confidence interval (CI): 0.22, 0.40], p<0.0001). The progression-free survival (PFS) showed in favor of RAD001 with a median PFS of 4.0 months (95% CI: 3.7, 5.5) versus 1.9 months (CI: 1.8, 1.9) for the placebo group (Motzer, et al, 2007). The probability of being progression-free at 6 months was 26% (95% CI: 14, 37) for patients receiving RAD001 compared with 2% (CI: 0, 6) for patients in the placebo group. The medium OS had not been reached for the RAD001 group and was 8.8 months (95% CI: 7.9, not available) for the placebo group. There was no significant difference between the groups in terms of OS (hazard ratio 0.83; 95% CI: 0.50, 1.37; p=0.23) (Motzer et al, 2008). Results from a further analysis in the RECORD-1 study, indicated a significant prolongation in PFS for the RAD001 group compared with the placebo group (hazard ratio 0.33; 95% CI: 0.25, 0.43; p<0.001) (Kay, et al., 2008). The PFS showed in favor of RAD001 with a median PFS of 4.9 months versus 1.87 months for the placebo group. The median overall survival was not reached for RAD001, (hazard ratio 0.82; 95% CI: 0.57, 1.17; p<0.137) versus 13 months for the placebo group.

RAD001 (Afinitor) was recently approved by the US FDA for the treatment of patients with advanced renal cell cancer after failure of treatment with sunitinib or sorafenib.

It is clear that novel therapies are needed for patients with advanced RCC, including those with metastatic disease and those whose tumors are not amenable to surgical resection. Although sunitinib (Motzer, et al., 2007) and temsirolimus (Hudes, et al., 2007) have improved PFS or OS, in comparison with IFN, and the addition of bevacizumab to IFN has led to improved results in comparison with single-agent IFN (Escudier, et al., 2007), in some countries IFN remains the only available treatment option for patients with advanced RCC.

This trial will therefore explore the use of oral RAD001 daily in clear and non-clear cell advanced kidney cancer.

1.3 History of Amendments

Changes in paragraphs:

1. Section 4: Hepatitis B and C Screeening.
2. Section 5.2: Exclusion Criteria # 14.
3. Table 3: Criteria for Dose Modification in Case of Suspected RAD001 Toxicity.
4. Table 5: Action to be taken based on Screening Hepatitis B Results.
5. Table 6: Guidelines for the management of Hepatitis B reactivation.
6. Table 9: Visits Evaluation Schedule:

   CT scan or MRI of chest, abdomen, and pelvis- If the CT scan was performed during the screening (in the range of 35 days) it does not need to be performed again at baseline.

   Pulmonary Function Test- will be peformed at screening per investigator discretion.
7. Section 7.5.1: Radiological Assessment of Tumor(s).
8. Section 7.6.5.8: Chest X-Ray/Chest Computed Scans/Pulmonary Function Tests.
9. Section 10.5.1.3: Overall Survival Definition.
10. Table 10: Updated country, # of patients, and #of sites.
11. Section 10.1: Population for Analysis.
12. Section 10.5.1.3: Overall Survival.

2 Study Rationale

Current standard therapies (chemotherapies and cytokine-based therapies) have produced few and short-lived tumor responses, and are associated with severe toxicities. It is clear that novel therapies are needed for patients with advanced RCC, including those with metastatic disease and those whose tumors are not amenable to surgical resection. Although sunitinib and temsirolimus have improved PFS or OS, in comparison with IFN, and the addition of bevacizumab to IFN has led to improved results in comparison with single-agent IFN, in some countries IFN remains the only available treatment option for patients with advanced RCC.

A smaller sub-group analysis of patients with “other” subgroup category (non-clear and indeterminate histologies), the HR analysis for OS suggested an advantage for temsirolimus (an iv mTOR inhibitor) over IFN (Dutcher, at al., 2007).

The oral formulation of RAD001 presents an improvement in the delivery of anticancer therapy, with direct impact on the patient and the health care delivery system. RAD001 is generally well tolerated at 10 mg daily doses (see Table 1).

RAD001 has been studied extensively in solid organ transplantation (renal and cardiac) where over 1000 patients have received RAD001 for ≥3 years, with the drug being given as a constituent of an immunosuppressive regimen, which included cyclosporine (a CYP3A4 inhibitor) and glucocorticoids.

Pharmacodynamic modeling indicates that downstream effectors of mTOR are completely suppressed by RAD001 at the 10 mg/day. Preliminary results of MPD studies in biopsied tumor tissue suggest a dose-related decrease in p-4E-BP1 and increase in p-AKT expression, with maximal effect at 10 mg daily.

The proposed dose and schedule (10 mg/day) is based on various Phase 1 and Phase 2 studies (monotherapy and combination therapy) in advanced cancers, including RCC. This dose and schedule also showed significant efficacy in a large placebo-controlled Phase 3 study in patients with MRCC who previously progressed on anti-VEGF targeted therapy.

The purpose of this open-label, multi-center, Phase 2 study is to demonstrate the safety and efficacy of RAD001 10 mg po daily dose, as monotherapy, in patients with metastatic carcinoma of the kidney with clear cell and non-clear cell histology and all MSKCC prognosis, who have not received prior systemic treatment other than cytokine therapy.

3 Objectives

3.1 Primary Objective

The primary objective of the study is to evaluate the PFS rate over time.

3.1.1 Endpoint for Primary Objective

The primary efficacy endpoint is PFS (i.e., remaining free from disease progression and death).

3.2 Secondary Objectives

The secondary objectives of the study are:

1. To evaluate the disease control rate (stable disease [SD] + partial response [PR] + complete response [CR]) (SD + PR + CR);
2. To evaluate the objective response rate (ORR; where ORR = CR + PR);
3. To evaluate duration of response;
4. To evaluate OS;
5. To describe the safety profile of RAD001.

3.2.1 Endpoints for Secondary Objectives

Secondary endpoints include:

- Disease control rate (SD + PR + CR);
- ORR;

- Response duration;
- OS;
- Safety will be assessed using CTCAE version 3.0. Safety parameters include AEs, laboratory , and other safety parameters as appropriate.

4 Study Design

This is an open-label, multi-center, single arm Phase 2 study to evaluate the safety and efficacy of RAD001 as monotherapy in patients with any MSKCC prognosis metastatic recurrent and/or unresectable clear cell or non-clear cell carcinoma of the kidney. Patients who have received prior cytokine therapy are permitted to participate in the study.

Tumor assessments will be performed at 8 weeks to evaluate for inadequate response (progressive disease [PD]). The visit at which PD is documented will be deemed the End-of-Treatment Visit.

In the absence of PD, assessments will continue every 12 weeks (±1 week) until the start of new anticancer therapy and at the End-of-Treatment Visit (within 1 week of stopping treatment) or until death. A PR or CR warrants confirmation no sooner than 4 weeks.

Follow-up phase: All patients will have a follow-up visit scheduled 28 days after the End-of-Treatment Visit to follow for AEs and SAEs that may have occurred after discontinuation from the study. Any patient who is discontinued from study treatment for any reason will continue to have tumor assessments every 12 weeks (±1 week) until the patient is switched to another anticancer therapy or until death. The investigator or his/her designee will continue collecting information on the initiation of additional anticancer therapies until the date of data cutoff for the final analysis (see Section 10.6). All new anticancer therapies after the last dose of study treatment will be recorded on the appropriate case report form (CRF) page.

Study drug refers to RAD001. All patients who meet the study entry criteria will receive RAD001. It is anticipated that approximately 110 patients will be enrolled in the study.

Hepatitis B and C Screening

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 HBV reactivation and associated HBV morbidity and mortality (Loomba et al. 2008; Sorrell et al. 2009).

During the screening period, ALL patients must be screened for HBV and HCV (current or past history of infection). Careful medical history must be taken for all patients to look for risk factors (family history of HBV and HCV, intravenous drug abuse, unprotected sex, dialysis, blood transfusions, etc), and any past or present HBV symptoms (e.g., jaundice, dark urine, light-colored stools, right upper quadrant pain). All patients will be tested for HBV-DNA and serological markers, and HCV viral load by quantitative RNA-PCR. It is highly recommended that patients at risk of HBV reactivation are treated prophylactically with antivirals for 1-2 weeks prior to receiving study drug and for at least 4 weeks after last dose of study drug. The management guidelines, in Section 6.1.4.4, are provided according to the results of the screening assessment of viral load and serological markers for HBV and HCV.

5 Population

Adult patients who have metastatic recurrent and/or unresectable renal cell carcinoma are eligible for enrollment in this study. Previous cytokine therapy is permitted. Patients must have histological or cytological confirmation of clear cell or non-clear cell renal carcinoma or a component of these histologies. The treating oncologist is advised to consider biopsy of lesions to establish the diagnosis of MRCC if there is substantial clinical ambiguity regarding the nature or source of primary disease.

Inclusion/exclusion criteria

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

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

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

5.1 Inclusion Criteria

Patients may be entered in the study only if they meet all of the following criteria:

1. Age ≥18 years old;
2. Patients with advanced renal cell carcinoma with confirmed clear or non-clear cell histology, with or without nephrectomy, and with any MSKCC prognosis;
3. Prior cytokine therapy is permitted;
4. Patients with at least one measurable lesion at baseline as per the RECIST criteria. If skin lesions are reported as target lesions, they must be documented (at baseline and at every physical exam) using color photography and a measuring device (such as a caliper) in clear focus to allow the size of the lesion(s) to be determined from the photograph;

5. Life expectancy ≥3 months. Life expectancy should be judged in relation to other determining patient eligibility factors such as laboratory results, Performance Status, etc.;
6. Patients with a Karnofsky Performance Status ≥70%;
7. Adequate bone marrow function as shown by: absolute neutrophil count (ANC) ≥1.5 x 10^9/L, platelets ≥100 x 10^9/L, hemoglobin (Hb) >9 g/dL;
8. Adequate liver function: serum bilirubin ≤1.5 x upper limit of normal (ULN), alanine transaminase (ALT) and aspartate transaminase (AST) ≤2.5 x ULN. Patients with known liver metastases: AST and ALT ≤5 x ULN;
9. Adequate renal function: serum creatinine ≤1.5 x ULN;
10. Females of childbearing potential must have had a negative serum or urine pregnancy test 7 days prior to the administration of the study treatment start;
11. Patients who give a written informed consent obtained according to local guidelines.

5.2 Exclusion Criteria

Patients may not be entered into the study if they meet any of the following criteria:

1. Patients within 2 weeks post-minor surgery (e.g., herniorrhaphy), 4 weeks post-major surgery (e.g., intra-thoracic, intra-abdominal, or intra-pelvic) to avoid wound healing complications. Percutaneous biopsies require no waiting time prior to study entry;
2. Patients with a recent history of hemoptysis, ≥0.5 teaspoon of red blood;
3. Patients who have received prior systemic treatment for their metastatic RCC other than cytokine therapy;
4. Patients who received prior therapy with a VEGF pathway inhibitor, such as sunitinib, sorafenib, and bevacizumab;
5. Patients who have previously received mTOR inhibitors (sirolimus, temsirolimus, everolimus, deferolimus);
6. History or clinical evidence of central nervous system (CNS) metastases. Note: Subjects who have previously-treated CNS metastases (surgery±radiotherapy, radiosurgery, or gamma knife) and meet all 3 of the following criteria are eligible:
    - Are asymptomatic;
    - Have had no evidence of active CNS metastases for ≥ 6 months prior to enrollment and;
    - Have no requirement for steroids or enzyme-inducing anticonvulsants (EIAC);
7. Clinically significant gastrointestinal abnormalities including, but not limited to:
    - Malabsorption syndrome;
    - Major resection of the stomach or small bowel that could affect the absorption of study drug;

- Active peptic ulcer disease;
- Inflammatory bowel disease;
- Ulcerative colitis, or other gastrointestinal conditions with increased risk of perforation;
- History of abdominal fistula, gastrointestinal perforation, or intra abdominal abscess within 28 days prior to beginning of study treatment;

8. Patients receiving chronic systemic treatment with corticosteroids or another immunosuppressive agent. Inhaled and topical steroids are acceptable;
9. Patients with a known history of human immunodeficiency virus seropositivity;
10. Patients with autoimmune hepatitis;
11. Patients with an active, bleeding diathesis. Patients may use coumadin or heparin preparations;
12. Patients who have any severe and/or uncontrolled medical conditions or other conditions that could affect their participation in the study such as:
    - unstable angina pectoris, symptomatic congestive heart failure, myocardial infarction ≤6 months prior to first study treatment, serious uncontrolled cardiac arrhythmia;
    - uncontrolled diabetes as defined by fasting serum glucose >1.5 x ULN;
    - any active (acute or chronic) or uncontrolled infection/disorders that impair the ability to evaluate the patient or for the patient to complete the study;
    - non-malignant medical illnesses that are uncontrolled or whose control may be jeopardized by the study treatment, such as severe hypertension that is not controlled with medical management and thyroid abnormalities whose thyroid function cannot be maintained in the normal range by medication;
    - liver disease such as cirrhosis, decompensated liver disease, chronic active hepatitis, or chronic persistent hepatitis;
    - fatal or life-threatening autoimmune and ischemic disorders;
13. Patients who have a history of another primary malignancy ≤3 years, with the exception of non-melanoma skin cancer and carcinoma in situ of uterine;
14. Female patients who are pregnant or breastfeeding, or adults of reproductive potential who are not using effective birth control methods. If barrier contraceptives are being used, these must be continued throughout the study by both sexes. Oral contraceptives are not acceptable as the only contraception method. However they can be used in combination with other methods such as barrier contraceptives;
15. Patients who are using other investigational agents or who had received investigational drugs ≤4 weeks prior to study treatment start;
16. Patients unwilling or unable to comply with the protocol.

6 Treatment

6.1 Investigational and Control Drugs

6.1.1 Study Drug

The investigational drug used in this study is RAD001. The study drug will be self-administered (by the patients themselves). The investigator will instruct the patient to take the study drug exactly as specified in the protocol.

Patients will be instructed to take two 5 mg RAD001 tablets (one tablet after another) orally, with a glass of water at the same time each day, in a fasting state or with a light fat-free meal.

If vomiting occurs, no attempt should be made to replace the vomited dose. Any dietary habits around the time of RAD001 intake should be as consistent as possible throughout the study.

RAD001 will be taken daily from Visit 2 (Day 1) until disease progression, unacceptable toxicity, or death or discontinuation from the study for any other reason.

6.1.2 Known Undesirable 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 as indicated in Section 1.2.3.3.

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 to grade 2). Refer to Table 3 for management of laboratory abnormalities.

6.1.3 RAD001 Dose Level Modification/Interruption Guidelines in Case of Suspected Toxicity

Dose adjustments are permitted in those patients who are unable to tolerate the protocol-specified dosing schedule. If administration of RAD001 must be interrupted because of unacceptable toxicity, drug dosing will be interrupted or modified according to rules described in Table 2, Table 3, and Table 4.

If the toxicity is tolerable to the patient, the initial dose should be maintained. If the toxicity is intolerable to the patient, RAD001 treatment is to be interrupted until recovery to grade ≤1, then reintroduced at the initial dose or a lower dose level, depending on toxicity type and grade (see Table 3). All interruptions or dose modifications must be recorded on the Dosage Administration Record CRF.

Table 2 RAD001 Dose Level Modification Guidelines

Dose Level	Dose Schedule
0	10 mg daily
1	5 mg daily
2	5 mg every other day

Table 3 provides the procedure to be followed for dose modification and re-initiation of RAD001 in the event of toxicities suspected to be related to the study drug.

Table 3 Criteria for Dose Modification in Case of Suspected RAD001 Toxicity

Toxicity	Actions
Non-hematological toxicity	
Grade 1	No dose modification.
Grade 2 (except pneumonitis):	If the toxicity is tolerable to the patient, maintain the same dose. If toxicity is intolerable to the patient, interrupt RAD001 until recovery to grade ≤1, then re-introduce RAD001 at the same dose. If the event returns to grade 2, interrupt RAD001 until recovery to grade ≤1, then re-introduce at the lower dose level.
Grade 3 (except hyperlipidemia):	Interrupt RAD001 until recovery to grade ≤1, then re-introduce at the lower dose level. For pneumonitis, consider the use of a short course of corticosteroids.
Grade 3 hyperlipidemia (hypercholesterolemia and/or hypertriglyceridemia):	Should be managed using standard medical therapies.
Grade 4:	Discontinue RAD001.
Reactivation of HBV or HCV	Please refer to Tables 6 and 7.
Hematological toxicity	
Grade 1	No dose modification.
Grade 2 thrombocytopenia (platelets <75 x 10^9/L, ≥50 x 10^9/L):	Interrupt RAD001 until recovery to grade ≤1 (platelets ≥75 x 10^9/L), then re-introduce RAD001 at the initial dose. If thrombocytopenia returns to grade 2, interrupt RAD001 until recovery to grade ≤1, then re-introduce at the lower dose level.
Grade 3 thrombocytopenia (platelets <50 x 10^9/L, ≥25 x 10^9/L):	Interrupt RAD001 until recovery to grade ≤1 (platelets ≥75 x 10^9/L), then resume RAD001 at 1 dose level lower. If grade 3 thrombocytopenia recurs, discontinue RAD001.
Grade 4 thrombocytopenia (platelets <25 x 10^9/L):	Discontinue RAD001.
Grade 3 neutropenia (neutrophils <1 x 10^9/L, ≥0.5 x 10^9/L):	Interrupt RAD001 until recovery to grade ≤1 (neutrophils ≥1.5 x 10^9/L), then resume RAD001 at initial dose. If absolute neutrophil count (ANC) returns to grade 3, hold RAD001 until recovery to grade 1 (ANC ≥0.5 x 10^9/L), then resume RAD001 at the lower dose level. Discontinue patient from study therapy for a third episode of grade 3 neutropenia.
Grade 4 neutropenia (neutrophils <0.5 x 10^9/L):	Interrupt RAD001 until recovery to grade ≤1 (neutrophils ≥1.5 x 10^9/L), then resume RAD001 at the lower dose level. If grade 3 or grade 4 neutropenia occurs despite this dose reduction, discontinue RAD001.
Grade 3 febrile neutropenia (not life-threatening):	Interrupt RAD001 until resolution of fever and neutropenia to grade ≤1. Hold further RAD001 until the ANC ≥1500/mm^3 and fever has resolved. 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	Discontinue RAD001.

requiring interruption for ≥3 weeks:

6.1.4 Monitoring of RAD001 Suspected Toxicities

Patients whose treatment is interrupted or permanently discontinued due to an AE or abnormal laboratory value suspected to be related to RAD001 must be followed at least weekly until the AE 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.

6.1.4.1 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 studies have described the oral toxicities associated with RAD001 as mouth ulcers, rather than mucositis or stomatitis.

If examination reveals mouth ulcers rather than a more general inflammation of the mouth, the AE should be classified as such. Please follow the paradigm below for the treatment of stomatitis/oral mucositis/mouth ulcers:

1. For mild toxicity (grade 1), conservative measures such as non-alcoholic mouth wash or salt water (0.9%) mouth wash several times a day until resolution should be used.
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, 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 National Cancer Institute- (NCI) CTC for Adverse Events (CTCAE), version 3.0.

6.1.4.2 Management of Hyperlipidemia and Hyperglycemia

Treatment of hyperlipidemia should take into account the pre-treatment status and dietary habits of the patient. Blood tests to monitor hyperlipidemia must be taken in the fasting state.

Grade 2 or higher hypercholesterolemia (>300 mg/dL or 7.75 mmol/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 AEs 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 phosphokinase 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 in Study RAD001C2222, the affected patients had an abnormal fasting glucose at baseline. Based on this finding, it is recommended that optimal glucose control be achieved before starting a patient on RAD001. Study patients should have their glucose levels monitored during RAD001 therapy.

6.1.4.3 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 (Atkins, et al., 2004).

In order to monitor for asymptomatic (grade 1) non-infectious pneumonitis, a chest x-ray or CT scan is required in addition to the 3-monthly CT or magnetic resonance imaging (MRI) tumor examinations.

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.).

Chest x-ray/chest CT scans obtained during the study should be readily accessible at the site and must be kept with the patient‟s source documents.

Dose modification instructions and Management of non-infectious pneumonitis suspected to be associated with RAD001 and are provided in Table 3 and Table 4.

Table 4 Management of Non-Infectious Pneumonitis

Worst Grade Pneumonitis	Required Investigations	Management of Pneumonitis	RAD001 Dose Adjustment
Grade 1	CT scans with lung windows. Repeat every 3 cycles until return to within normal limits.	No specific therapy is required.	Administer 100% of RAD001 dose.
Grade 2	CT scans 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. Consider a bonchoscopy.[a]	Symptomatic only. Prescribe cortico-steroids if cough is troublesome.	Reduce RAD001 dose until recovery to ≤ grade 1. RAD001 may also be interrupted if symptoms are troublesome. Patients should be withdrawn from the study if they fail to recover to ≤ grade 1 within 3 weeks.
Grade 3	CT scans 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. Bonchoscopy[a] 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 scans 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. Bonchoscopy[a] is required.	Prescribe corticosteroids if infective origin is ruled out. Taper as medically indicated.	Discontinue treatment.

[a] A bronchoscopy with a biopsy and/or broncheoalveolar lavage is required.
Abbreviations: CT = computerized tomography; DLCO = diffusion capacity of carbon monoxide.

6.1.4.4 Management of hepatitis reactivation

Monitoring and Prophylactic Treatment for Hepatitis B Reactivation

Table 5 provides details of monitoring and prophylactic therapy according to the screening results of viral load and serologic markers testing.

Test	Result	Result	Result	Result	Result
HBV-DNA	+	+ or -	-	-	-
HBsAg	+ or -	+	-	-	-
HBsAb	+ or -	+ or -	+ and no prior HBV vaccination	+ or -	or + with prior HBV vaccination

HBcAb	+ or -	+ or -	+ or -	+	-
Recommendation	Prophylactic antiviral treatment should be started 1-2 weeks prior to first dose of study drug. Monitor HBV-DNA every 6 weeks		No prophylaxis Monitor HBV-DNA every 3 weeks		No specific action

Table 5 Action to be taken based on Screening Hepatitis B Results

Antiviral prophylaxis therapy should continue for at least 4 weeks after last dose of study drug. For HBV reactivation definition and management guidelines, see Table 6.

Table 6 Guidelines for the management of Hepatitis B reactivation

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 6-1 for dose levels available). 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 HBsAb (with no prior history of vaccination against HBV), **OR** positive HBcAb**]** --- **reactivation is defined as**: New appearance of measurable HBV-DNA	**Treat** : Start first antiviral medication AND **Interrupt** study drug administration until resolution: • ≤ baseline HBV-DNA levels **If resolution occurs within ≤ 28 days,** study drug should be re-started at one dose lower, if available (see Table 6-1 for dose levels available). If the patient is already receiving the lowest dose of study drug according to the protocol, the patient should restart at the same dose after resolution. Antiviral therapy should continue at least 4 weeks after last dose of study drug. **If resolution occurs > 28 days** Patients should discontinue study drug but continue antiviral therapy at least 4 weeks after last dose of study drug.
** All reactivations of HBV are to be recorded as grade 3 (CTCAE Version 3.0 – Metabolic Laboratory/Other: Viral Reactivation), unless considered life threatening by the investigator, in which case they should be recorded as grade 4. Date of viral reactivation is the date on which 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 Reactivation

The following two categories of patients should be monitored every 6 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 definitions of HBV or HCV reactivation and actions to be taken in the event of reactivation, please refer to Table 7.

Table 6 Guidelines for the management of Hepatitis C reactivation

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 HCV are to be recorded as grade 3 (CTCAE Version 3.0 – Metabolic Laboratory /Other: Viral Reactivation), unless considered life threatening by the investigator; in which case they should be recorded as grade 4.*	

6.1.5 How Supplied

6.1.5.1 Study Drug

RAD001 will be provided by Novartis at no charge to the study site. RAD001 is formulated as tablets of 5 mg strength for oral administration. Tablets should be opened only at the time of administration, as the drug is both hygroscopic and light sensitive.

Medication labels will comply with the legal requirements of each country and are printed in the local language. The labels do not contain information about the patient. The storage conditions for the study drug will be described on the study drug label.

Each study site will receive the study drug (RAD001). After a final drug accountability/ reconciliation review has been performed by the study monitor, unused, used, and empty study drug packaging and any unused tablets will be destroyed at the end of the study according to local regulatory procedures. All local regulatory procedures must be followed.

6.1.6 Preparation and Storage

6.1.6.1 Study Drug

RAD001 is supplied as 5 mg tablets. Patients will be supplied with enough tablets for a complete 28-day cycle. Tablets should be stored in a secure, dry, light-proof medicine cabinet.

6.2 Treatment Arms

One treatment arm: RAD001.

6.3 Patient Numbering

Patient informed consent must be obtained before any screening testing is performed to determine the patient‟s eligibility. At screening (Visit 1), upon signing the informed consent form, the patient is assigned a unique patient number by the investigator or his/her designee.

The patient number is a 9-digit number. The first part is the site number (first 4 digits) and the second part (last 5 digits) is one of a series of numbers allocated to patients at that site. The site number is assigned by Novartis. The patient identification numbers will be assigned in a sequential manner. Once assigned, the patient identification number will not be reused. At screening (Visit 1), the investigator or his/her designee will record the patient identification number appropriately on the CRFs.

6.4 Treatment Assignment

This is a single arm study with one dose of study drug. All patients will initiate treatment with 10 mg/day RAD001.

6.5 Treatment Blinding

This is an open-label study.

6.6 Treating the Patient

6.6.1 Commencing Treatment

At Visit 1 (Screening, Visit 1a) and Visit 2 (Baseline, Visit 1b), the investigator or his/her designee will verify that the patient fulfills all the inclusion/exclusion criteria to commence RAD001 treatment. The Baseline Visit should be no sooner than 28 days and no later than 35 days after the Screening Visit. Study treatment can commence (Visit 2) immediately after the Baseline Visit.

Patient stratification will be based on previous cytokine therapy.

6.6.2 Study Drug Administration

The study drug will be self-administered (by the patients themselves). The investigator will instruct the patient to take the study drug exactly as specified in the protocol.

Patients will be instructed to take RAD001 (two 5 mg tablets at once, ie., one tablet after another) orally daily with a glass of water, at the same time each day in a fasting state or with a light fat-free meal.

If vomiting occurs, no attempt should be made to replace the vomited dose. Any dietary habits around the time of RAD001 intake should be as consistent as possible throughout the study.

RAD001 will be taken daily from Visit 2 (Day 1) until disease progression, unacceptable toxicity, death, or discontinuation from the study for any other reason.

6.6.3 Permitted Study Drug Adjustments

Dose adjustments are permitted in those patients who are unable to tolerate the protocol-specified dosing schedule. If administration of RAD001 must be interrupted because of unacceptable toxicity, drug dosing will be interrupted or modified according to the rules described in Section 6.1.3.

6.6.3.1 Follow-Up for Toxicities

Patients whose treatment is interrupted or permanently discontinued due to an AE or abnormal laboratory value suspected to be related to RAD001 must be followed at least weekly until the AE 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.

6.6.4 Concomitant Medications

Patients will be instructed not to take any additional medications (including over-the-counter products) during the course of the study without prior consultation with the investigator.

At each visit, the investigator will ask the patient about any new medications he/she is or has taken after the start of the study drug. All medications taken ≤30 days prior to study entry should be recorded on the Concomitant Medications/Significant Non-Drug Therapies Prior to Start of Study Drug CRF page. All medications (other than the study drug) and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient starts treatment with study drug must be listed on the Concomitant Medications/Significant Non-Drug Therapies CRF. Prior and concomitant medications will be coded to indication-specific Anatomic Therapeutic Chemical classification (ATC) and preferred name using the World Health Organization (WHO) Drug Dictionary (latest version).

Permitted treatments during the study include:

- Bisphosphonate therapy for treatment of bone metastases. This therapy should be initiated before the patient is enrolled into the study;
- Pain medication to allow the patient to be as comfortable as possible;
- Localized radiotherapy, for the treatment of pre-existing, painful bone metastases is allowed during the study only if evidence of radiological progression is not present. Radiotherapy for brain metastases is not permitted during the course of the study (the need for CNS radiation will constitute disease progression);

- Nutritional support as recommended by the investigator;
- Megesterol acetate may be prescribed during the course of the study as an appetite stimulant;
- Oxygen therapy and blood transfusions.

The following restrictions apply during the entire duration of the study:

- No other investigational therapy should be given to patients;
- No anticancer agents other than the study drug (RAD001) should be given to patients. If such agents are required for a patient, then the patient must first be withdrawn from the study;
- Leukocyte growth factors (e.g., colony-stimulating factor and granulocyte-macrophage colony-stimulating factor) are not to be administered prophylactically, but may be prescribed by the investigator for severe neutropenia if this is thought to be appropriate;

Drugs or substances known to be inhibitors or inducers or substrates of the isoenzyme CYP3A4 should be avoided in association with RAD001 because these can alter the metabolism of RAD001. In addition, patients should refrain from grapefruit juice, which is a potent CYP3A4-inhibitor. Complete details are provided in Table 8.

Table 8 Clinically Relevant Drug Interaction: Substrates, Inducers, and Inhibitors of Isoenzyme CYP3A

Substrates (competitive inhibition)	
Antibiotics[a]:	Calcium channel blockers:
clarithromycin*	amlodipine
erythromycin	diltiazem
telithromycin*	felodipine
Anti-arrhythmics:	nifedipine
quinidine	nisoldipine
Benzodiazepines:	nitrendipine
alprazolam	verapamil
diazepam	HMG -CoA reductase inhibitors[b]:
midazolam	cerivastatin
triazolam	lovastatin
Human immunodeficiency virus protease	simvastin
inhibitors:	Miscellaneous:
indinavir*	aprepitant
ritonavir*	buspirone
saquinavir*	haloperidol
Prokinetic:	methadone
cisapride	pimozide
Antihistamines:	quinine
astemizole	sildenafil
chlorpheniramine	tamoxifen
	trazodone
	vincristine
Inducers	

Carbamazepine	Rifampin*
Phenobarbitol	St. John‟s wort
Phenytoin*	Troglitazone
Rifabutin*	
Inhibitors	
Amiodarone	Indinavir
Cimetidine	Itraconazole*
Clarithromycin	Ketoconazole*
Delaviridine	Voriconazole*
Diltiazem	Posaconazole*
Erythromycin	Mibefradil
Fluvoxamine*	Nefazodone*
Grapefruit juice	Nelfinavir*
Sevilla orange	Troleandomycin
	Verapamil

Base on: Ingelman-Sundberg M. Human drug metabolising cytochrome P450 enzymes: Properties and polymorphisms. Naunyn Schmiedebergs Arch Pharmacol 2004;369:89-104 (http://www.medicine.iupui.edu/flockhart/clinlist.htm).
* Denotes strong inhibition/induction. Please note:

- Strong inhibitor implies that it can cause ≥5-fold increase in area under the concentration curve (AUC) or ≥80% decrease in clearance of sensitive CYP substrates;
- Moderate inhibitor implies that it can cause 2 to 5-fold increase in AUC values or 50% to 80% decrease in clearance of sensitive CYP substrates.

(Distinction is not always categorical as interaction can vary depending on conditions).
[a] Macrolide antibiotics: Azithromycin is not a CYP3A substrate. It may therefore be employed where antibiotic therapy with a macrolide is desirable in a patient being treated with RAD001.
[b] Statins: Pravastatin may be taken with RAD001 since a pharmacokinetic interaction study has shown that there is no relevant pharmacokinetic interaction.

6.6.5 Interruption or Discontinuation of Study Drug

The term “interruption” refers to a patient stopping all study drug during the course of the study, but then re-starting it at a later time in the study. If treatment has to be interrupted for more than 14 days for any reason other than toxicities suspected to be related to RAD001, the patient will be discontinued from the study. If treatment has to be interrupted for more than 21 days due to suspected study drug-related toxicity, the patient will be discontinued from the study.

Tumor evaluations will continue until the start of new anticancer therapies. The term “discontinuation” refers to a patient‟s premature withdrawal from the study treatment. In accordance with the current revision of the Declaration of Helsinki and current US Food and Drug law, a patient has the right to withdraw from the study at any time for any reason without prejudice to his/her future medical care by the physician or at the institution.

The reason for discontinuation from treatment will be recorded on the appropriate CRF page. The patient may discontinue participation in the study for any of the following reasons:

1. Adverse event(s);
2. Abnormal laboratory value(s);
3. Abnormal test procedure result(s);
4. Disease progression;
5. Protocol violation;

6. Patient withdrew consent;
7. Lost to follow-up;
8. Administrative problems;
9. Death.

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

6.6.6 Patient Withdrawal

6.6.6.1 End of Treatment

All cancer medications/therapies given to a patient ≤4 weeks after the last dose of study treatment must be recorded on the CRF.

Patients who discontinue the study regardless of the reason must have end-of-study treatment evaluations (see Table 9) on the day of study drug discontinuation or within 2 weeks of study drug discontinuation. The investigator or his/her designee will proceed as follows:

- Notify clinical team immediately of patient discontinuation;
- Complete the end of study assessments and complete the End-of-Treatment CRF page indicating the date and reason for stopping the study drug. Additional details are provided in Table 9;
- All patients will have a follow-up visit 28 days after the last dose of the study drug. During this visit, AE and SAE information will be collected and recorded on the appropriate CRF pages. If the patient is unable to return to the clinic, the investigator or his/her designee will contact the patient or caregiver to collect this information;
- All patients who are discontinued from the study drug for any reason (i.e., documented disease progression by the investigator, an AE or SAE, administrative reasons, etc.) will continue to have tumor assessments at 12-week intervals until the initiation of new anticancer therapy. This information will be recorded on the appropriate CRF pages;
- If patients refuse to return to the clinic for follow-up assessments or are unable to do so, the investigator or his/her designee will make every effort to contact the patient, a close relative, or caretaker by telephone to collect survival information. The investigator or his/her designee should show “due diligence” by documenting on the source documents steps taken to contact the patient, i.e., dates of telephone calls, registered letters, etc.

6.6.7 Emergency Unblinding of Treatment Assignment

Not applicable to this open-label study.

7 Visit Schedule and Assessments

Table 9 lists all of the assessments and indicates the visits with an "X" and when they are to be performed. All data obtained from these assessments must be supported in the patient"s source documentation.

Table 9 Visit Evaluation Schedule

	Screening - 35	Baseline -7 to -1	Cycle 1 (28 days)		Cycle 2 (28 days)		Cycle 3 (28 days)		Subsequent Cycles (28 days)	End-of-Study Treatment	Endpoint Follow-Up[a]
Visit number	**1a**	**1b**	**2**	**3**	**4**	**5**	**6**	**7**	**8, 9**	**Last visit**	
Day of cycle			**1**	**15**	**1**	**15**	**1**	**15**	**1**	**Last day**	
Demography/informed consent	X										
Inclusion/exclusion criteria	X		X								
Medical history/current medical conditions	X		X								
Diagnosis and extent of cancer	X										
Prior antineoplastic therapy	X										
Vital signs[a]	X	X	X		X		X		X	X	
Height, weight	X										
Physical examination/neurological assessment[b]	X		X		X		X		X	X	
Karnofsky Performance Status	X	X	X		X		X		X	X	
Hematology[c]	X	X	X	X[c]	X	X[c]	X	X[c]	X	X	
Coagulation[d]	X				X						
Serum chemistry[e]	X	X	X		X		X		X	X	
Serum lipid profile[f]	X	X	X		X		X		X	X	
Urinalysis[g]	X	X									
Serum pregnancy test[h]	X	X									
HBV-DNA & serology, HCV RNA-PCR [r]	X		X		X		X	X	X		X
CT scan or MRI of chest, abdomen, and pelvis[i] **If the CT Scan was performed during the screenig (in the range of 35 days) it does not need to be performed again at baseline**	X	X					X			Every 12 weeks after Visit 6	X
Brain MRI/brain CT scan[k]	X	X	As described in footnote[k]								
Bone scan[l]	X	X	As described in footnote[l]								
Electrocardiogram[m]	Electrocardiograms are to be performed at the investigator"s discretion as clinically indicated										
Pulmonary function tests[n]	X	X	Pulmonary function tests to be performed as described in footnote[n]								

Table 9 Visit Evaluation Schedule

	Screening - 35	Baseline -7 to -1	Cycle 1 (28 days)		Cycle 2 (28 days)		Cycle 3 (28 days)		Subsequent Cycles (28 days)	End-of-Study Treatment	Endpoint Follow-Up[a]
Visit number	**1a**	**1b**	**2**	**3**	**4**	**5**	**6**	**7**	**8, 9**	**Last visit**	
Day of cycle			**1**	**15**	**1**	**15**	**1**	**15**	**1**	**Last day**	
Concomitant medications[o]	X	X	X	X	X	X	X		X	X	X	X
Adverse event[p]	X	X	X	X	X	X	X		X	X	X	X
Imaging for tumor evaluation[q]							X			Every 12 weeks after Visit 6	X	
RAD001 administration[r]			Daily administration									
Study completion[s]											X	
Follow-up and survival[t]												X
Post-discontinuation antineoplastic therapies[u]												X

[a] Vital signs will be collected at screening and repeated on Day 1 of every treatment cycle and at the end of-the-study (within ≤2 weeks).

[b] A complete physical examination includes a neurological examination. All significant findings will be noted on the Relevant Medical History pages or Adverse Event pages of the case report form (CRF). If a skin lesion or lesions are selected as target lesions, they must be clearly photographed and measured with a measuring device (a caliper or ruler) in clear focus to allow the size of the lesion(s) to be determined from the photograph. Serial photographs from the skin lesion(s) must be performed at every physical exam visit. Copies of the serial photographs must be submitted with the radiological assessments for radiology review.

[c] Hematology tests must include: hemoglobin, hematocrit, platelets, total white blood count (WBC), and differential. Hematological tests will be performed at screening and on Day 1 (prior to administration of the study drug) of each treatment cycle. Hematological tests may also be performed on Day 15 of the first 3 treatment cycles at the investigator"s discretion and according to local practice. Subsequently, on Day 1 (of every treatment cycle) or as medically necessary and at discontinuation from the study drug (within ≤2 weeks).

[d] The prothrombin time will be performed at screening and on Day 1 of Cycle 2. Prothrombin time will be repeated as clinically indicated and will be reported as international normalized ratio (INR).

[e] Serum blood chemistry evaluations must include: lactate dehydrogenase (LDH), fasting glucose, magnesium, sodium, potassium, chloride, creatinine, blood urea nitrogen, albumin, total protein, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, gamma-glutamyl-transferase (GGT), alkaline phosphatase, urea, uric acid, serum calcium, and serum corrected calcium (measured at screening only). These assessments will be performed at screening and on Day 1 of every treatment cycle and at the time of discontinuation from the study drug (within ≤2 weeks).

[f] Serum lipid profile includes: total cholesterol, trigycerides, low-density lipoprotein, and high-density lipoprotein. These assessments will be performed at screening and on Day 1 of every treatment cycle and at the time of discontinuation from the study drug (within ≤2 weeks).

[g] Urine analysis assessments include: gross or a microscopic urine exams. A dipstick assessment includes: specific gravity, pH, protein, glucose, bilirubin, ketones, blood cells, and leukocytes. The urinalysis will be performed at screening and as clinically indicated. Urine specimens will be sent to the local laboratory for analysis.

[h] Serum urine pregnancy test. Females of childbearing potential must have a serum or urine pregnancy test performed within 7 days prior to the first dose of study drug.

[i] A computerized tomography (CT) scan or magnetic resonance image (MRI) of the chest/abdomen and pelvis will be performed at screening (≤35 days) prior to the first dose of study drug and at 8 weeks (±1 week). Thereafter, a CT scan or MRI of the chest/abdomen and pelvis will be performed every 12 weeks (±1 week), and at the time of discontinuation of the study drug (within 2 weeks).

[j] A chest x-ray can be performed at the investigator"s discretion, if there is a suspicion of non-infectious pneumonitis.

[k] A brain MRI or brain CT scan will be obtained within 2 weeks of the first dose of study drug and as clinically indicated if the patient develops signs or symptoms of central nervous system (CNS) involvement. If brain metastases are present at baseline, brain MRI/brain CT scan will be performed every 8 weeks during the study.

[l] A bone scan will be obtained at screening (within 3 weeks of the first dose of study drug) and as clinically indicated if the patient develops signs or symptoms of bone disease. If bone metastases are present at baseline, the bone scans will be performed every 12 weeks (±1 week) during the study.

[m] Standard 12-lead electrocardiograms are to be performed at the investigator"s discretion according to local practice, or if there are signs and symptoms of cardiotoxicity. Any significant findings will be noted

Table 9 Visit Evaluation Schedule

	Screening - 35	Baseline -7 to -1	Cycle 1 (28 days)		Cycle 2 (28 days)		Cycle 3 (28 days)		Subsequent Cycles (28 days)	End-of-Study Treatment	Endpoint Follow-Up[a]
Visit number	**1a**	**1b**	**2**	**3**	**4**	**5**	**6**	**7**	**8, 9**	**Last visit**	
Day of cycle			**1**	**15**	**1**	**15**	**1**	**15**	**1**	**Last day**	

on the Relevant Medical History or Adverse Event pages of the CRF.

[n] Pulmonary function tests (including spirometry, diffusion capacity of carbon monoxide, and room air O_2 saturation at rest) will be performed at screening per investigator discretion, and at the end of the study (≤2 weeks) and as medically necessary if there is evidence of non-infectious pneumonitis. A bronchoscopy with a biopsy and/or brancheoalveolar lavage will be performed when medically necessary for decisions regarding patient care. The results will be recorded on the appropriate CRF page.

[o] Record all medications given ≤30 days prior to study entry on the Concomitant Medications/Significant Non-Drug Therapies Prior to the Start of the Study CRF page. After the start of the study, concomitant medications must be recorded on the Concomitant Medications/Significant Non-Drug Therapies CRF page.

[p] All adverse events (AEs) occurring after the start of the study, even if the event is not considered to be related to the study drug, must be documented on the Adverse Event CRF page.

[q] Information on all target tumor and non-target lesions will be collected at screening. Subsequently, radiological assessments (to follow the target and non-target lesions identified at baseline) will be performed at 8 weeks (±1 week). In the absence of progressive disease, assessments will continue every 12 weeks (±1 week) until the start of new anticancer therapy and at the End-of-Study Visit (within 1 week of stopping treatment) or until death. Observation of tumor response (partial or complete response) warrants a confirmation no sooner than 4 weeks. The same type of scan (CT or MRI) used at screening must be used for all subsequent follow-up assessments.

[r] RAD001 10 mg daily dosing will begin on Day 1 of Cycle 1. Treatment with the study drug will continue until disease progression, unacceptable toxicity, withdrawal of consent, death, etc.

[s] Patients who discontinue the study drug will have end-of-study evaluations performed on that day or within 2 weeks of discontinuation of the study drug.

[t] All patients will have a follow-up visit 28 days after the last dose of RAD001. During this visit, AE and serious adverse event information occurring since the last dose of study drug will be collected and recorded on the appropriate CRF pages. All patients who are discontinued from the study drug for any reason will continue to have tumor assessments until the start of any new anticancer therapy.

[u] After discontinuation of the study drug, the investigator or his/her designee will collect information on the initiation of new anticancer therapies given after the last dose of study drug.

[r] All patients will be screened for HBV-DNA, HBV serologic markers and HCV RNA-PCR. It is highly recommended that patients positive for HBV-DNA or HBsAg receive prophylactic antivirals 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. Monitoring for HBV reactivation, according to Table 6-5, will only require the measurement of HBV-DNA from Visit 2 onwards. Patients who are HBV-DNA / HBsAg positive at screening will be monitored every cycle. Patients who are HBV-DNA and HBsAg negative at screening (and not receiving prophylaxis) but HBsAb or HBcAb positive will be monitored every cycle. Follow-up testing for HCV RNA-PCR will be performed every cycle only if the patient has a history of HCV or is positive at baseline, or both. If there is no history of HCV and HCV RNA-PCR test is negative at baseline, no follow-up testing is required.

7.1 Visit Windows

For Cycles 1, 2, and 3, visits will be on the 1st and 15th day (±5 days) of each 28-day cycle. For each subsequent cycle, patients will return to the site on the 1st day (±5 days) of each 28-day cycle.

7.2 Information to be Collected on Screening Failures

Patients who are screened and do not meet all entry criteria will not receive the first dose of RAD001. Such patients are considered to be screen failures. The reason for not being started on RAD001 will be entered on the Screening Log CRFs. Screen failures are not entered into the clinical data base.

7.3 Patient Demographics/Other Baseline Characteristics

Data will be collected on patient characteristics, including demographic information (age, sex, race, weight) and other background or relevant medical history (cancer history and extent of cancer, prior anticancer therapies) and any other assessments that are done for the purpose of determining eligibility for inclusion in the study (i.e., Karnofsky Performance Status, complete physical examination including a neurological assessment, vital signs, hematology, blood chemistries including coagulation studies and a serum lipid profile, urinalysis, pregnancy test [only required for females of childbearing potential], a brain MRI or a brain CT scan, electrocardiogram [ECG]).

Urinalysis and the pregnancy test are only performed at either screening or baseline for eligibility, but are not repeated after the patient has started the study drug or at discontinuation from the study.

The patient population will be stratified by prior cytokine therapy.

7.4 Treatments

RAD001 10 mg daily dosing will begin on Day 1 of Cycle 1. This study does not have a fixed treatment duration. Patients will receive study treatment until disease progression or until unacceptable toxicity is observed. Information on drug exposure will be collected on the Dosage Administration Record CRF page. Concomitant medications/significant non-drug therapies prior to start (≤30 days) and after the start of study treatment will be recorded on the appropriate CRF pages. Patient screening and randomization data will be stored on the appropriate CRF pages.

7.5 Efficacy

The primary efficacy endpoint is PFS as defined in Section 10.4.1. Secondary efficacy endpoints are OS, disease control rate (SD + PR + CR), the ORR (CR + PR) as defined in Section 10.5.1, as well as response duration.

7.5.1 Radiological Assessment of Tumor(s)

Tumor response, stable disease, and progression, will be assessed using the RECIST criteria (see Post-Text Supplement 1 for complete details). A CT scan or MRI of the chest/abdomen

and pelvis will be obtained at screening (≤35 days) prior to the first dose of RAD001 and periodically as indicated in Table 9. Tumor response will be assessed at 8 weeks (±1 week) and every 12 weeks (±1 week) thereafter until determination of disease progression (by the local radiologist) and at the end of the study.

All patients who are discontinued from RAD001 for any reason (i.e., documented disease progression by the investigator, an AE or SAE, or administrative reasons, etc.) will continue to have tumor assessments until the start of new anticancer therapy.

At screening (≤35 days prior to the first dose of RAD001), all patients must have a CT scan with contrast or MRI with contrast of the chest, abdominal, and pelvic area. Patients who are allergic/sensitive to the radiographic contrast media used in CT scans and MRIs may have a CT scan of the chest without contrast and a MRI of the abdomen and pelvis without contrast. The same imaging modality used at screening must be used for all subsequent follow-up assessments.

Ultrasound scans cannot be used to measure tumor lesions.

All patients should have at least one measurable disease lesion by CT scan or MRI or by physical exam. Physical examination findings, such as skin lesions, must be photographed (color photography) using a digital camera. Subcutaneous nodules will be measured with a caliper or a ruler. If skin lesions are used for assessment of disease, at least one skin lesion should be biopsied to establish the malignant nature of the lesions. The site must document on the Tumor Assessment Comments CRF page that a biopsy of at least one skin lesion confirming the presence of metastatic disease has been obtained or was available for this purpose.

Measurable disease lesions must be accurately measured in at least one dimension with the longest diameter ≥20 mm using conventional techniques, or ≥10 mm with spiral CT scan (with a minimum lesion size no less than double the slice thickness). Conventional CT and MRI should be performed with contiguous cuts of 7.5 mm or less in slice thickness. Spiral CT should be performed using a 5 mm or less contiguous reconstruction algorithm (this specification applies to tumors of the chest, abdomen, and pelvis).

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. The target lesions will be measured and recorded at baseline and during the course of the study. The target lesions should be selected on the basis of their size (lesions with the longest diameters) and suitability for accurate repeated measurements. A sum of the longest diameter for all target lesions will be calculated and reported as the baseline sum of the longest diameter.

If a very small lesion cannot be reliably measured because of its size, it is recommended to enter the minimum lesion size (i.e., 5 mm for spiral CT). In other cases where the lesion cannot be reliably measured for reasons other than its size (i.e., borders of the lesion are confounded by neighboring anatomical structures), no measurement should be entered and the lesion cannot be evaluated.

A target lesion that resolves from baseline must be assigned a size of 0 mm when documenting on the patient"s RECIST CRF page. Refer to Supplement 1 for additional target and non-target lesion reporting guidelines.

Partial response requires at least a 30% decrease in the sum of the longest diameters of all target lesions, taking as reference the baseline sum of the longest diameters.

Complete response requires a disappearance of all target and non-target lesions. If an initial observation of partial or complete response is made, a confirmation scan is required no sooner than 4 weeks.

In case of an unscheduled or delayed tumor assessment (i.e., to confirm a PR/CR or due to any other reason), subsequent tumor assessments must be performed according to the originally planned scheme from baseline, i.e., every 12 weeks from the time of the second assessment at 8 weeks.

Disease progression is either 1) a 20% increase in the sum of the longest diameter of all target lesions, taking as reference the smallest sum of the longest diameters of all target lesions recorded at or after baseline, or 2) the appearance of a new lesion, or 3) the unequivocal progression of non-target lesions overall. Patients who had suspected clinical symptoms of disease progression should be immediately evaluated with a physical examination and imaging (CT scan or MRI) assessment for objective evidence of disease progression.

7.5.2 Imaging Procedures

To ensure a valid comparison of tumor data and uniformity in the assessment of tumor response during the study, the following procedure must be implemented at the study site:

- All lesions identified at baseline (target and non-target) will be reassessed using the same method (CT scan with contrast or MRI) throughout the course of the study;
- All CT scans, MRIs, bone scans, and chest x-rays obtained on all patients enrolled at the site should be reviewed by the local radiologist who, together with the investigator, will determine the local assessment of response and progression;
- If skin lesions are used for tumor assessment, the corresponding photos must also be transmitted/delivered to the local radiologists.

7.6 Safety

Safety assessments will consist of monitoring and recording all AEs, including SAEs, the regular monitoring of hematology, serum chemistry, routine monitoring of vital signs (heart rate, blood pressure, and body temperature), and chest x- rays, ECGs, and physical condition.

Toxicity will be assessed using the National Institutes of Health (NIH) NCI-CTCAE, version 3.0 (CTCAE v3.0, [http://ctep.cancer.gov/forms/CTCAEv3.pdf]).

7.6.1 Adverse Events

An AE, for the purposes of this protocol, is the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) occurring after signing the informed consent, even if the event is not considered to be related to the study drug (study drug refers to the drug under evaluation [RAD001], and study treatment also refers to RAD001).

Adverse events will be assessed according to the CTCAE, version 3.0. If CTCAE grading does not exist for a particular AE, the severity of mild, moderate, severe, and life-threatening, or grades 1 to 4, will be used. The CTCAE grade 5 (death) will not be used in this study; rather, this information will be collected on the End of Treatment or Survival Information CRF page. All AEs will be coded by System Organ Class (SOC) and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA), latest version.

Adverse event monitoring should be continued for at least 4 weeks following the last dose of study treatment. Adverse events (but not SAEs) occurring before starting study treatment, but after signing the informed consent form, are recorded on the Medical History/Current Medical Conditions CRF pages. Abnormal laboratory values or test results constitute an AE only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy (e.g., any hematological abnormality that requires transfusion or cytokine treatment); and should be recorded on the Adverse Events CRF page under the signs, symptoms, or diagnosis associated with them. In addition, isolated abnormal laboratory values that are considered clinically significant (e.g., cause study discontinuation or constitutes in and of itself a SAE) should be recorded on the Adverse Events CRF page. Serious AEs occurring after signing the Informed Consent are recorded on the Adverse Event CRF page.

The occurrence of AEs should be sought by non-directive questioning of the patient at each visit during the study. Adverse events may also 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 AE should be evaluated to determine:

1. The severity grade (CTCAE grades 1 to 4);
2. Its relationship to study drug (suspected/not suspected);
3. Its duration (start and end dates or if continuing at final exam);
4. Action taken (no action taken; study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this AE; concomitant medication taken; non-drug therapy given; hospitalization/prolonged hospitalization);
5. Whether it is serious, where a 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:
        a) Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (specify what this includes);
        b) Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent;

c) Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission;

d) Social reasons and respite care in the absence of any deterioration in the patient"s general condition.

- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above.

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

All AEs should be treated appropriately. Such treatment may include changes in the 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 AE is detected, it should be followed until its resolution, an assessment should be made of any changes in its severity at each visit (or more frequently, if necessary), its suspected relationship to the study drug, any of the interventions required to treat it, and its outcome.

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

7.6.2 Physical Examination, Including a Neurological Examination

A complete physical examination includes a major review of body systems (general appearance, skin, neck including thyroid, eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, and a neurological examination). Significant findings must be recorded either as relevant medical history/current medical conditions, if present before the start of study treatment, or as an AE, if newly occurring or worsening since start of treatment.

A physical examination must be performed at screening, on Day 1 of each study treatment cycle (≤1 week), and at completion/discontinuation from study treatment (≤2 weeks).

7.6.3 Vital Signs

Body temperature, sitting pulse rate, and sitting blood pressure will be routinely measured. Blood pressure will be measured according to the NIH, National Heart, Lung, and Blood Institute Guidelines (NIH, 1997) with the following standardized techniques:

- Patients are seated in a chair; blood pressure measurement begins after at least 5 minutes of rest;
- The appropriate cuff size is used to ensure accurate measurement.

Vital signs will be performed at screening, on Day 1 of each cycle (≤1 week), and at the completion/discontinuation from the study drug (≤2 weeks). Height and weight will be measured and recorded at screening only.

7.6.4 Karnofsky Performance Status

The baseline Karnofsky Performance Status will be assessed and recorded at baseline (within 1 week of the first dose of the study drug), on Day 1 of every subsequent treatment cycle, and at discontinuation from the study drug (within 1 week). The Karnofsky Performance Scale Index allows patients to be classified as to their functional impairment. The definition of scores in relation to the performance status is given in Table 7.

Table 7 Karnofsky Performance Scale

Score (%)	Performance Status
100	Normal, no complaints; no evidence of disease
90	Able to carry out normal activity; minor symptoms
80	Normal activity with effort; some symptoms
70	Cares for self; unable to carry out normal activities
60	Requires occasional assistance; cares for most needs
50	Requires considerable assistance and frequent care
40	Disabled: requires special care and assistance
30	Severely disabled: Hospitalized, but death not imminent
20	Very sick: active supportive care needed
10	Moribund: fatal processes are progressing rapidly
0	Dead

7.6.5 Laboratory Evaluations

All standard clinical laboratory analyses described below are performed by local laboratories. The frequency of the assessments is indicated in Table 9. All laboratory procedures including collection of samples, shipment, reporting of results, alerting of extreme values, and notable values are provided in the Laboratory Manual. The local laboratory will provide the sponsor with a copy of the laboratory certification and tabulation of the reference ranges.

Abnormal laboratory values that are clinically relevant (i.e., require a dose modification, interruption, or indicate changes in previously abnormal values) must be recorded on the Adverse Events CRF page. For clinically relevant values from local laboratories, record actual laboratory abnormality value and grade on the local laboratory CRF page only if the severity grade is different from the severity grade reported by the local laboratory.

If a local laboratory value is recorded on the local laboratory CRF page, the site will provide the local laboratory reference range attached to the local laboratory CRF page.

All laboratory results must be available at the time the patient sees his/her attending oncologist.

7.6.5.1 Hematology

Hematological tests include a complete blood count, a total white blood cell (WBC), neutrophil count (including bands), lymphocyte, monocyte, eosinophil, basophil counts, Hb, hematocrit, and a platelet count.

Hematological tests will be performed at screening, on Day 1 (prior to administration of the study drug) of each treatment cycle. Hematological tests may also be performed on Day 15 of the first 3 treatment cycles at the investigator‟s discretion and according to local practice. Subsequently, these tests will be performed on Day 1 (of every treatment cycle), or as medically necessary, and at discontinuation from study treatment (≤2 weeks). In the event of grade 2, grade 3, or grade 4 hematological toxicities that require study drug dose modifications or interruptions, hematological tests must be repeated until recovery to the baseline value or grade 1.

7.6.5.2 Coagulation

The prothrombin time (PT) will be performed at screening and on Day 1, Cycle 2. Prothrombin time will be repeated as clinically indicated and will be reported as international normalized ratio (INR).

7.6.5.3 Biochemistry

Serum chemistry tests include urea, blood urea nitrogen, creatinine, lactate dehydrogenase, total protein, fasting glucose, phosphorus, serum corrected calcium (calculated at baseline only), electrolytes (sodium, magnesium, chloride, and potassium), total bilirubin, gamma-glutamyl-transferase, albumin, alkaline phosphatase, ALT, AST, and uric acid. The patient must be in a fasting state (at least 12 hours) at the time of blood sampling for this evaluation. Serum chemistries must be performed at screening and on Day 1 of each treatment cycle and at discontinuation from study treatment (≤2 weeks). In the event of grade 2, grade 3, or grade 4 non-hematological toxicities that require study drug dose modifications or interruptions, biochemistry tests must be repeated until recovery to the baseline value or grade 1.

7.6.5.4 Serum Lipid Profile

A serum lipid profile includes: total cholesterol, triglycerides, low-density lipoprotein, and high-density lipoprotein. This assessment will be performed at screening and on Day 1 of every treatment cycle and at the time of discontinuation from the study drug (within 2 weeks). The patient must be in a fasting state (at least 12 hours) at the time of blood sampling for this evaluation. In the event of grade 2, grade 3, or grade 4 toxicities that require study drug dose modifications or interruptions, serum lipid tests must be repeated until recovery to the baseline value or grade 1.

7.6.5.5 Urinalysis

Urine analysis includes gross or microscopic urine exams. Gross (dipstick) urine examination includes: specific gravity, pH, protein, glucose, bilirubin, ketones, blood cells, and leukocytes.

The microscopic examination includes: WBC/high-powered field, RBC/high-powered field, and casts. A dipstick analysis will be done locally, if its results are abnormal, a urine specimen will be sent to the local laboratory for microscopy analysis. The urinalysis test is required only at screening.

7.6.5.6 Pregnancy Test

Females of childbearing potential will have a serum or urine pregnancy test that must be performed within 7 days prior to the administration of study drug.

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. Any patient who becomes pregnant must be discontinued from study drug immediately. 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 oncology Novartis Integrated Medical Safety (IMS) Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the Novartis study drug of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Pregnancy outcomes must be collected for the female partners of any males who took study drug in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

7.6.5.7 Electrocardiogram

Standard 12-lead ECGs are to be performed at the investigator"s discretion according to local practice, or if there are signs and symptoms of cardiotoxicity. Tracings must be dated and signed by the investigator or his/her designee and filed with the patient"s source documents.

Significant findings must be recorded as relevant medical/current medical conditions if present before treatment with study drug or as an AE (if newly occurring or worsening since start of treatment). An ECG must be performed at screening and as clinically indicated.

7.6.5.8 Chest X-Ray/Chest Computed Tomography Scans/Pulmonary Function Tests

A chest x-ray can be performed at the investigator"s discretion, if there is a suspicion of non-infectious pneumonitis

as indicated in Table 9. Chest x-rays will be used in this study solely for the purpose of detecting non-infectious pneumonitis. Chest x-rays will not be used to report tumor-related findings.

Pulmonary function tests (spirometry, diffusion capacity of carbon monoxide, and room air O_2 saturation at rest) will be performed as medically necessary if there is evidence of non-infectious pneumonitis per invistigator discretion..

A bronchoscopy with biopsy and/or broncheoalveolar lavage will be performed when medically necessary for decisions regarding patient care. The results will be recorded on the appropriate CRF page. Additional details are provided in Table 4.

8 Safety Monitoring

8.1 Serious Adverse Event Reporting

The investigator must fax each SAE or pregnancy (see below) to Novartis within 24 hours of learning of its occurrence, even if it is not felt to be treatment-related. Follow-up information about a previously reported SAE must also be faxed to Novartis within 24 hours of receipt. If the SAE is not documented in the IB (i.e., unexpected), and it is thought to be related to the Novartis investigational drug(s), central IMS may need to contact the investigator urgently in order to obtain further information prior to the submission of the reported event to the health authorities. If warranted, to fulfill the regulatory requirement, an Investigator Notification may be issued, to inform all investigators involved in any study with the same drug (or therapy) that this serious unexpected and suspected adverse reaction has been reported.

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until the patient has stopped study participation must be reported to Novartis within 24 hours of learning of its occurrence. Any SAEs experienced by the patient during the follow-up period beginning 4 weeks after study drug has been stopped 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. A 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.

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 investigator must complete the SAE Report Form in English, assess the relationship to the Novartis investigational drug(s) and send the completed, signed-off, form by fax within 24 hours to the local Novartis safety office (for trials monitored by Novartis) or to the relevant Contract Research Organization (CRO). The local Novartis safety office or CRO, after ensuring that the form is accurately and fully completed, must then fax it to the central Novartis IMS Department within 2 to 3 calendar days for deaths or life-threatening events and within 5 calendar days for other SAEs. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the CRFs at the study site. A copy of the SAE Report Form is forwarded to the monitor by the local Novartis safety office or CRO, to perform source data verification.

Follow-up information is always forwarded to the same person to whom the original SAE Report Form was sent. A new SAE Report Form should be sent stating that this is a follow-up. The follow-up should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not (in the case of a blinded study), and whether the patient continued or discontinued study participation. Where a SAE is followed by reports of recurrent episodes, complications or progression of the initial event, all such reports will be treated as follow-up to the original episode. If a new SAE occurring at a different time interval is considered completely non-associated to a previously reported one, a new SAE

Report Form should be submitted as an initial report. All forms and fax confirmation sheets must be retained by the study site.

If the SAE is not previously documented in the IB or Package Insert (new occurrence) and is thought to be related to the Novartis study drug, a Clinical Safety and Epidemiology Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant Ethics Committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

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. Any patient who becomes pregnant must be discontinued from study drug immediately. 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. An abortion is to be regarded always as a SAE and assessed as "other medically significant event" even if no other seriousness criterion is fulfilled.

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

Pregnancy outcomes must be collected for the female partners of any males who took study drug in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

8.3 Data Monitoring Board

Since this study has a single open-label treatment arm, a Data Monitoring Committee is not required.

9 Data Review and Data Management

9.1 Site Monitoring

Before study initiation, at a site initiation visit or at an investigator"s meeting, Novartis personnel (or designated CRO) 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. 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 SAEs, and the recording of data that will be used for all primary and safety variables. Additional checks of the consistency of the source data with the 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

For studies using paper CRFs, 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 Medical Documents Reception Center of Novartis and the designated CRO by field monitors or by the investigational site, with one copy being retained at the investigational site.

9.3 Auditing Procedures

The Quality Assurance unit in Novartis (sponsor of this study) conducts audits of clinical research activities in accordance with internal Standard operating Procedures to evaluate compliance with the principles of Good Clinical Practice. A regulatory authority may also wish to conduct and inspection (during the study or even after its completion). If an inspection is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

9.4 Database Management and Quality Control

Data will be entered into the study database by Novartis Data Management personnel (or designated CRO) for paper studies.

For studies using paper CRFs, the entered data are systematically checked by Novartis Data Management personnel (or designated CRO) using error messages printed from validation programs and database listings. Obvious errors are corrected by Novartis Data Management personnel (or designated CRO). 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) latest version terminology.

This is an open-label study; therefore, no Interactive Voice Randomization System (IVRS) will be used.

At the conclusion of the study, the occurrence of any protocol violations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and made available for data analysis. Any changes to the database after that time can only be made by joint written agreement between the Global Head of Biostatistics and Statistical Reporting and the Global Therapeutic Area Head.

10 Statistical Methods and Data Analysis

This is an open-label, multi-center, single arm Phase 2 study to evaluate the safety and efficacy of RAD001 as monotherapy in patients with any MSKCC prognosis metastatic recurrent and/or unresectable clear cell or non-clear cell carcinoma of the kidney, with or without prior cytokine therapy.

The data will be analyzed by Novartis and/or designated CRO. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation. It is planned that the data from participating centers in this protocol will be combined, so that an adequate number of patients will be available for analysis. The data will be summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, and safety observations and measurements. Categorical data will be presented as absolute frequencies and percentages. For continuous data, number (N), mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented. Time to event variables, Kaplan-Meier product-limit estimates will also be presented.

The final safety and efficacy analyses will be conducted at the time when approximately 110 patients have completed the study. There will be no interim analysis.

10.1 Populations for Analysis

The **Full Analysis Set (FAS)** consists of all patients treated with RAD001. Following the ITT principle, patients are analyzed according to the treatment and stratum they were in at the start of the study.

The **Safety population** consists of all patients who received at least one dose of the study drug and who have at least one post-baseline safety assessment. Patients are analyzed according to the treatment received.

> **Please note:** the statement that a patient had no AEs (on the Adverse Event CRF page) constitutes a safety assessment. Patients who have received at least one dose of study drug, but who have no post-treatment safety data of any kind, would be excluded from the Safety population.

10.2 Patient Demographics/Other Baseline Characteristics

Demographic and background information will be summarized for the Safety population and the FAS, using frequency distributions for categorical variables and descriptive statistics for continuous variables. Background information includes prior medication, past/current medical conditions, diagnosis and extent of cancer, Karnofsky Performance Status and tumor history at baseline. Medical history will be coded using MedDRA and will be presented by System Organ Class and MedDRA preferred term. Separate tables will be provided for past medical condition and current medical condition. Prior medication will be coded according to WHO Drug Dictionary (latest version).

10.3 Treatments (Study Drug, Concomitant Therapies, Compliance)

10.3.1 Study Drug

The study drug administration will be summarized. The number of treated patients and the duration of treatment will be presented.

10.3.2 Concomitant Therapies

Concomitant medications and significant non-drug therapies taken concurrently with the study drug will be listed and summarized by ATC class preferred term for the safety population by frequency tables. These summaries will include medications starting on or after the start of study treatment or medications starting prior to the start of study treatment and continuing after the start of study treatment.

10.4 Primary Objective

The primary objective of this study is to estimate the PFS over time in patients who receive RAD001 as monotherapy.

10.4.1 Variable: Progression-Free Survival

The primary endpoint of this study, PFS, is defined as the time from the date of the start of RAD001 treatment to the date of the first documented disease progression or death due to any cause.

A patient who has not progressed or died at the date of the analysis cut-off, or when he/she receives any further anticancer therapy, would have his/her PFS censored at the time of the last tumor assessment, before the first of the cut-off date or the anticancer therapy date.

For the primary analysis, PFS will be based on the review by the local radiologist who, together with the investigator, will determine the local assessment of response and progression according to the RECIST criteria.

10.4.2 Statistical Hypothesis, Model, and Method of Analysis

No statistical test of hypotheses will be performed in this study.

The primary analysis for this study is to estimate the PFS rate over time and its 95% CI by the method of Kaplan-Meier for:

1. All patients;
2. First-line patients (receiving RAD001 as their first treatment);
3. Second-line patients (patients who received cytokine therapy as first-line therapy).

Progression-free survival curves (graphing the PFS rate over time) will be displayed, overall and by strata, according to the Kaplan-Meier product-limit method. The PFS rate over time will also be tabulated. The resulting median PFS time will be given with 95% CIs.

The primary analysis will be performed on the Full Analysis Set (FAS). Consolidated summary results obtained from the local radiological review will be used for this analysis.

10.4.3 Handling of Missing Values/Censoring/Discontinuations

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

Additionally, sensitivity analyses will be performed where:

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

10.4.4 Supportive Analyses

The primary analysis will also be performed on all available events (progressions) as per local radiological review, as a supportive, secondary analysis.

All analyses will be fully described and document in the statistical analysis plan (SAP).

10.5 Secondary Objectives

10.5.1 Secondary Efficacy Evaluation

The analyses of all secondary efficacy endpoints will be performed on the FAS.

10.5.1.1 Disease Control Rate (SD + PR + CR)

The disease control rate will be based on the data as per local radiological review, following the RECIST criteria. The disease control rate is defined as the proportion of patients with CR,

PR, or SD. The disease control rate (CR + PR + SD) will be summarized in terms of percentage with 95% CIs.

10.5.1.2 Objective Response Rate and Duration

The overall tumor response will be based on the data as per local radiological review, following RECIST criteria. The ORR is defined as the proportion of patients with CR or PR. The ORR (CR + PR) will be summarized in terms of percentage with 95% CIs.

The duration of overall response (CR or PR) will also be calculated, and is defined as the time from the first occurrence of PR or CR (as per local radiological review) until the date of the first documented disease progression or death due to underlying cancer. If a patient has not had an event, or when he/she receives any further anticancer therapy, duration of overall response is censored at the date of the last adequate tumor assessment. In case of missing data, the same rules will be applied as for PFS (see Section 10.4.3).

Duration-of-response curves (graphing the proportion of patients remaining free from progression and death due to cancer) will be displayed, overall and by strata, according to the Kaplan-Meier product-limit method, for those patients who had an overall response. This proportion over time will also be tabulated. The resulting median duration of response will be given with 95% CIs.

10.5.1.3 Overall Survival

Overall survival is defined as the time from date of start of treatment to date of death due to any cause. If a patient is not known to have died, survival will be censored at the date of last contact. Overall survival will be analyzed for the FAS. The Kaplan Meier curve will be displayed. Median, 25th and 75th percentile of the Kaplan Meier estimator along with their 95% confidence intervals will be reported.

10.5.2 Safety Evaluation

For all safety analyses, the Safety population will be used. The assessment of safety will be based mainly on the frequency of AEs and on the number of laboratory values that fall outside of pre-determined ranges. Other safety data (i.e., ECG, vital signs) will be considered as appropriate.

For all safety analyses, the safety population will be used. The assessment of safety will be based mainly on the frequency of AEs and on the number of laboratory values that fall outside of pre-determined ranges. Other safety data (i.e., electrocardiogram, vital signs) will be considered as appropriate.

Adverse events will be summarized by presenting the number and percentage of patients having any AE, having an AE in each body system and having each individual AE. Any other information collected (e.g., CTC grades or relatedness to study drug) will be listed as appropriate. In addition, the incidence of pneumonitis AEs will be summarized by preferred term.

Deaths reportable as SAEs and non-fatal SAEs will be listed by patient and tabulated by the type of AE.

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

Data from other tests (e.g., electrocardiogram or vital signs) will be listed and any other information collected will be listed as appropriate.

10.5.3 Tolerability

Frequency and severity of all treatment-emergent AEs will be listed.

10.5.4 Resource Utilization

No resource utilization will be specifically collected in this study.

10.5.5 Patient-Reported Outcomes

No patient-reported outcomes are planned.

10.5.6 Pharmacokinetics

Not applicable.

10.5.7 Biomarkers

Not applicable.

10.6 Interim Analysis

No interim analysis is planned for this study.

10.7 Sample Size Calculation

By way of background, Hudes et al. (2006), for first-line poor-prognosis metastatic RCC patients, estimated at 3.8 months a PFS rate of 50% for temsirolimus treatment. Amato, et al. 2008 (draft manuscript), for mostly second-line RCC patients, observed at 11.2 months a PFS rate of 50% for everolimus (RAD001) treatment. How patients are selected (i.e., whether the selected patients are poor-prognosis patients or patients are selected irrespective of prognosis) may have a large impact on the observed median PFS.
The sample size for this study will be determined with reference to estimating a CI for the PFS rate at 10 months, assuming (for simplicity) the use of the normal approximation to the binomial distribution and assuming that a CI for a proportion is based on this normal approximation. To be able to estimate a 95% CI for the PFS rate, centered at 0.50, and having an expected total interval width of approximately 0.27, requires a sample size of 55 patients in each cohort (first- and second-line). With 95% confidence, the expected total interval width is approximately 0.19 for all 110 patients (both cohorts combined).

Some alternative sample size calculations, using different assumptions about the desired expected CI width, are as shown in Table 8.

Table 8 Number of Patients Required per Cohort Depending on Desired Width of

Confidence Interval (CI) for the 10-Month Progression-Free Survival Proportion

Expected CI Width for One Cohort	Number of Patients Required Per Cohort	Total Required Number of Patients	Expected CI Width for all Patients Combined
0.2	97	194	0.14
0.25	62	124	0.18
0.3	43	86	0.21
0.35	32	64	0.24
0.4	25	50	0.28

10.8 Power for Analysis of Critical Secondary Variables

Not applicable.

11 Administrative Procedures

11.1 Administrative Structure

Novartis, the sponsor for this study, is responsible for overseeing all activities conducted during the course of the study.

The study administrative structure is described in Table 9.

Table 9 Study Administrative Structure

Steering Committee: **Chair:** **Co-Chair:** **Country Representative:**	**Drug Safety Reporting:**
Clinical Study Supply Management:	**Data Management:**
Study Monitoring:	**Biostatistics:**
Medical Monitoring:	**Study Report Preparation:**
Clinical Laboratory:	

11.2 Regulatory and Ethical Compliance

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

11.3 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 (IRB)/Independent Ethics Committee (IEC)/Research Ethics Board (REB) before study initiation. A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC/REB must be given to Novartis before study initiation. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs, and regulatory authorities as required.

11.4 Informed Consent

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC/REB-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. 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 guidelines 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.

Females of childbearing potential should be informed that taking the study drug may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

11.5 Exploratory Biomarker Consent Form

Not applicable.

11.6 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.

11.7 Discontinuation of the Study

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

11.8 Study Drug Supply and Resupply, Storage, and Tracking/Drug Accountability

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

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

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

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

11.9 Study Duration/Timelines

The enrollment period for this study is expected to last approximately 18 months.

Table 10 Study Milestones

First patient, first visit:	31 July 2009
Last patient, last visit:	30 January 2012
Total number of patients:	110
Number of study sites:	25
Number of patients per study site:	4
Location of study sites:	Algeria, Morocco, Tunisia, Egypt, Saudi Arabia, Thailand, Jordan, Lebanon, India, Russia, and South Africa.

11.10 Publication

Novartis has sole ownership of all data, results, reports, and any other information collected and full rights of publication based on data from this trial and will maintain full access to the database.

Interim data cuts are planned and any formal presentation or publication of data from this trial will be considered as a joint publication by the physician(s) and appropriate Novartis personnel. Publications will be based on data from all centers, analyzed as stipulated in the protocol. Investigators agree not to present data gathered from one center or a small group of centers before the global publication, unless formally agreed to by all other investigators and

Novartis. Authorship will be determined by agreement with Novartis and the Scientific Steering Committee.

Regional and local publications are permitted once the global publication for each interim data summary or aggregate thereof has been published. Novartis and the Scientific Steering Committee must receive copies of any intended communication in advance of publication (at least 15 working days for an oral presentation and 45 working days for any other proposed publication). Novartis shall have the right to require amendments to any such proposed presentation or publication on reasonable grounds including without limitation:

a) To ensure the accuracy of the presentation or publication;

b) To ensure that proprietary information is not inadvertently divulged;

c) To enable intellectual property rights to be secured;

d) To enable relevant supplementary information to be provided.

12 Protocol Adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the study to request approval of a protocol deviation, as no authorized deviations are permitted. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC/REB, it cannot be implemented. All significant protocol deviations will be recorded and reported in the Clinical Study Report.

12.1 Signature Pages

Clinical Development & Medical Affairs

RAD001, Everolimus

Clinical Trial Protocol CRAD001LIC01

An Open-Label, Multi-Center Phase 2 Study to Evaluate Everolimus as Monotherapy Treatment for Patients with Metastatic Recurrent and/or Unresectable Renal Cell Carcinoma (EVERMORE)

Protocol Signature Page

Novartis approval signature for:

Clinical Study Protocol: CRAD001LIC01

Sr. Clinical Trial Head	Signature	Date
Study Statistician	Signature	Date
Medical Brand Leader	Signature	Date

INVESTIGATOR SIGNATURE PAGE

Protocol Title: An Open-Label, Multi-Center Phase 2 Study to Evaluate Everolimus as Monotherapy Treatment for Patients with Metastatic Recurrent and/or Unresectable Renal Cell Carcinoma (EVERMORE)

IMP: RAD001

Protocol Number: CRAD001LIC01

Version Date:

Amendment Number: 01

I have read and understood the protocol and agree to implement the study in accordance with the procedures set forth in the protocol and in accordance with the sponsor"s guidelines and all applicable government regulations and the International Conference on Harmonisation Good Clinical Practice Guidelines E6 (ICH-GCP), Good Clinical Practices (GCP) as described in the United States Code of Federal Regulations (CFR) – 21 CFR parts 50, 56, and 312, and the International Conference on Harmonisation (ICH) document "Guidance for Industry – E6 Good Clinical Practice: Consolidated Guidance" dated April 1996.

I will provide adequate protocol training to my associates, colleagues, and employees assisting in the conduct of the study.

I will obtain Institutional Biosafety Review Committee (or equivalent) and Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approval of the Protocol and Patient Informed Consent Form prior to enrollment of patients in the study. I understand that any modifications to the protocol made during the course of the study must first be approved by the Institutional Review Committee (or equivalent) and IRB/IEC except when such modification is made to remove an immediate hazard to the patient.

I will ensure that a fully executed Patient Informed Consent is obtained from each patient prior to initiation of any study procedures.

I will report (within 24 hours) any serious adverse event that occurs during the course of the study in accordance with the procedures described in Section 8.1 of the protocol.

I will allow the sponsor, Novartis and its agents, as well as the United States of America (USA) Food and Drug Administration (FDA) and other regulatory agencies, to inspect study facilities and pertinent records at reasonable times and in a reasonable manner, ensuring patient confidentiality.

Investigator"s Name	Signature	Date

STEERING COMMITTEE

Name and Affiliation

Name and Affiliation

Name and Affiliation

13 References (available upon request)

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14 Post-Text Supplements

Response Evaluation Criteria in Solid Tumors (RECIST) Quick Reference:

Eligibility

- Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint.

  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 ≥20 mm using conventional techniques or ≥10 mm with spiral CT scan.

  Non-measurable lesions – all other lesions, including small lesions (longest diameter <20 mm with conventional techniques or <10 mm with spiral CT scan), i.e., bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, and also abdominal masses that are not confirmed and followed by imaging techniques.

- 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 4 weeks 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.
- Clinical lesions will only be considered measurable when they are superficial (e.g., 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.

Methods of Measurement

- 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 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis. Head and neck tumors and those of extremities usually require specific protocols.
- Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung; however, CT is preferable.
- When the primary endpoint of the study is objective response evaluation, ultrasound 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. Ultrasound might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

- 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 sites. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized sites. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.
- Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.
- Cytology and histology can be used to differentiate between PR and CR in rare cases (e.g., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors).

Baseline documentation of "Target" and "Non-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 (LD) for *all target lesions* will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor.
- All other lesions (or sites of disease) should be identified as ***non-target lesions*** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

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 LD of target lesions, taking as reference the baseline sum LD.
- Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD 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 LD since the treatment started.

Evaluation of non-target lesions

- Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level.
- Incomplete Response/ Stable Disease (SD): Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
- Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.*

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

Evaluation of 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.

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

- Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.
- In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the CR status.

Confirmation

- The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.
- To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. Longer intervals as determined by the study protocol may also be appropriate.

- In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval (in general, not less than 6-8 weeks) that is defined in the study protocol.

Duration of overall response

- The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that recurrence or PD is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started.

Duration of stable disease

- SD is measured from the start of the treatment until the criteria for disease progression are met, taking as reference the smallest measurements recorded since the treatment started.
- The clinical relevance of the duration of SD varies for different tumor types and grades. Therefore, it is highly recommended that the protocol specify the minimal time interval required between two measurements for determination of SD. This time interval should take into account the expected clinical benefit that such a status may bring to the population under study.

Response review

- For studies where the response rate is the primary endpoint it is strongly recommended that all responses be reviewed by an expert(s) independent of the study at the study‟s completion. Simultaneous review of the patients‟ files and radiological images is the best approach.

Reporting of results

- All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) CR, 2)PR, 3) SD, 4) PD, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data).
- All of the patients who met the eligibility criteria should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered as failing to respond to treatment (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.
- All conclusions should be based on all eligible patients.
- Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported.
- The 95% confidence intervals should be provided.