Pasireotide (SOM230C) and Everolimus (RAD001)

Clinical Trial Protocol CSOM230CUS18T

A 3-Arm Randomized Phase II Trial Evaluating Single Agent and Combined Efficacy of Pasireotide and Everolimus in Adult Patients with Radioiodine-Refractory Differentiated and Medullary Thyroid Cancer

List of changes to protocol version 6, dated 03-09-2014

Pages 6-8: Update list of investigators and participating sites
Page 21: Delete "Table and Figures Error"
Page 36: Clarify and update the follow-up schedule for study subjects
Page 37: Update criteria for iodine refractory thyroid cancer
Page 43: Clarify acceptable interval between screening and initiation of treatment
Page 45: Delete "Table and Figures error"
Page 47: Correct wrong references in Table 6-3 as follows:

- Grade 3 pneumonitis reference to Table 3-2 changed to Table 6-5;
- Grade 2 and 3 Mucositis reference to section 4.4.4 changed to section on "Management of stomatitis/oral Mucositis/mouth ulcers "
- Grade 3 Hyperlipidemia reference to section 4.4.5 for management changed to section on "Management Guidelines for Hyperlipidemia and Hyperglycemia"
- Grade 3 Hyperglycemia section 4.4.6 changed to section; "Management Guidelines for Hyperlipidemia and Hyperglycemia"

Page 54: Changed reference to Table 3-7 to Table 6-8 for management guidelines for Hep C.
Page 54: Change CTCAE v 3.0 v 4.0 in the footnote to Table 6-8
Page 55: Clarify recommendations for Blood Glucose monitoring
Page 65: Specify the +/- 2 day window allowed for scheduled assessments
Page 66: Added title header to table of Schedule of Events
Page 68: Correct footnote reference to Hepatitis Screening section" on page 62 and change reference to table 3-3 and 3-4 to 6-7 and 6-8.
Page 79: Update contact information for study regulatory specialists
Page 81: Section 7.5.7 – Electrocardiogram; clarify the schedule of EKG testing to match Table 7-1 and footnote.
Page 83: Section 8.1: clarified that adverse event reporting schedule should follow IRB guidance
Page 99: APPENDIX B - clarify that samples are to be collected through end of cycle 6 only
Page 99: Added detailed sampled preparation for PBMC and serum

List of changes to protocol version 5 dated 10-29-2012 (page number according to the tracked version):

Pages 3 -6: Update to study staff and participating sites

Page 35: Update patient assignment schema to include Arms A1 and B1 designation for patients who progressed and started 2-drug combination

Page 38: Update the QTcF requirement from 450ms to 470ms for exclusion #11 according to the guidance letter from Novartis study team dated September 13, 2012.

Patient 42: Add arms A1 and B1 as designation for patients switching from single agent therapy to 2-drug combination at the time of progression.

Page 43, section 6-4: corrected time frame within which to initiate treatment following registration and screening

Page 43, section 6-5: include further clarification for Arms A1 and B1 designation for patients who switch to 2-drug therapy following progression on single agent therapy.

Page 53, last paragraph: Additional information on hyperglycemia management guidelines included.

Page 60; section 6-9: update the criteria for subject withdrawal due to treatment delay resulting from treatment-emergent toxicity

Page 62-64: update the treatment schedule table

Page 74, section 7.5.1.4: Update the contact information for AE reporting to the coordinating center at the Winship Cancer Institute

Page 75; section 7.5.4: Update details and frequency of SOC and research related blood tests

Page 7.7, section 7.7.1: clarify that PBMC collection is optional

List of changes to protocol version 4 dated 01-05-2012:

Pages 3 -5: Update to study staff and participating sites

Page 35: Update inclusion criteria #10 regarding modified LFT criteria

Pages 36 & 37: update exclusion criteria 9 and 13

Pages 53-54: Include details of the SOM230 Management Guidelines for Suspected Hepatic Toxicity

Pages 60-62: Update study schema to incorporate additional required LFT tests on C1D22 and C2D22

Pages 71 & 72: Update Novartis contact Fax number for SAE reporting

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Version number: 6.0 (modified protocol)

Original Version Release date: March 15, 2010

Current Version Release Date March 08, 2014

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Table of Contents

List of abbreviations

AE	Adverse Event
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT

b.i.d.	*bis in diem*/twice a day
CRF	Case Report/Record Form
CS&E	Clinical Safety and Epidemiology
CRD	Clinical Research and Development
CRO	Contract Research Organization
CT	Computer Tomography
CTCAE	Common Toxicity Criteria for Adverse Events
DM	Diabetes Mellitus
ECG	Electrocardiogram
HBcAb	hepatitis B core antibodies
HBs Ab	hepatitis B surface antibodies
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
hsst	Human somatostatin receptor
IB	Investigator's Brochure
ICH	International Conference on Harmonization
ITT	Intent to Treat
i.v.	intravenous(ly)
IRB	Institutional Review Board
IVRS	Interactive Voice Response System
LAR	Long Acting Release
LFTs	liver function tests
MRI	Magnetic Resonance Imaging
MTD	Maximum tolerated dose
o.d.	*omnia die*/once a day
PCR	Polymerase Chain Reaction
PK/PD	Pharmacokinetic/Pharmacodynamic
p.o.	*per os*/by mouth/orally
PT	Prothrombin time
PTT	Partial thromboplastin time
q.d.	Once a day
RNA	Ribonucleic acid
SAE	Serious Adverse Event
s.c.	Subcutaneous
SOP	Standard Operating Procedure
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit Normal
US	Ultrasound

List of tables

1 Introduction

1.1 Overview of thyroid cancer

Thyroid cancer is the most common endocrine cancer worldwide representing approximately 1% of all cancers and responsible for 0.5% of all cancer related deaths. The worldwide incidence of thyroid cancers has however, increased significantly in the last 2 decades with a near doubling of the incidence rate.[1-5] A review of the US population cancer surveillance database showed that the incidence of thyroid cancer increased from 3.6 per 100,000 in 1973 to 8.7 per 100,000 in 2002.[5] This increase cuts across racial groups with a 150% in the US Caucasian population and a 73% increase in African Americans.[6] Approximately 40,000 new cases of thyroid cancers were diagnosed in the US in 2008. Whereas a large majority of patients with thyroid cancers present with localized disease and therefore achieve disease control with surgical resection, there is a substantial rate of disease relapse in up to a third of patients. Half of such relapses occur at distant sites with mortality approaching 50% at 5 years with currently available systemic treatment options. Radioactive iodine has been the mainstay of systemic therapy for metastatic differentiated thyroid cancers.[7] However, alternative treatment options are warranted due to the limitations imposed by radiation exposure limits, and the histologic progression with loss of differentiation and impaired uptake of radioiodine which can occur in up to 70% of patients with original diagnosis of papillary thyroid carcinoma. The use of biologic agents targeting cellular pathways in thyroid cancer has shown some promise. Multi-targeted tyrosine kinase inhibitors such as sorafenib, sunitinib, axitinib and motesanib have produced encouraging clinical benefit with objective responses (mainly partial responses) observed in approximately 15 - 30% of patients with iodine refractory disease. Majority of the patients experienced disease stabilization with a median progression free survival ranging between 40 and 80 weeks.[8-10]

Medullary thyroid Cancer: Vandetanib is a multi-targeted tyrosine kinase inhibitor with predominant activity against EGFR and VEGFR kinase enzyme activity. This drug received approval from the U. S. Food and Drug Administration for the treatment of symptomatic or progressive locally advanced, or metastatic medullary thyroid cancer patients. The drug was evaluated in an international, multicenter, double-blind trial that randomized MTC patients in a 2:1 ratio to receive either Vandetanib or placebo. The study met its primary objective of a PFS improvement in patients treated with Vandetanib (HR=0.35; 95% CI: 0.24, 0.53; $p<0.0001$). At the primary PFS analysis, 15% of the patients had died and no significant OS difference was noted. The overall response rate was 44% versus 1% in favor of patients randomized to receive Vandetanib.
The most common adverse events included diarrhea/colitis, rash, dermatitis acneiform, nausea, hypertension, headache, fatigue, decreased appetite, and abdominal pain, decreased

calcium, increased ALT, and decreased glucose. Frequent grade 3-4 adverse reactions were diarrhea/colitis, hypertension and hypertensive crisis, QT prolongation, fatigue, and rash. Adverse reactions resulting in death in patients receiving vandetanib (n=5) were respiratory failure, respiratory arrest, aspiration pneumonia, cardiac failure with arrhythmia, and sepsis. In addition, two deaths in patients receiving vandetanib (one sudden death and one death from cardiopulmonary arrest) were noted after data cut-off. QT prolongation, torsades de pointes, and sudden death are included in a boxed warning. Due to the toxicity profile of this agent, a mandatory Risk Evaluation Mitigation Strategy Program and a restricted distribution program was required at the time of its approval in April 2011. While this is a great therapeutic advancement in this patient population, the adverse event profile of this agent makes it unsuitable for a significant number of patients either with slowly progressive disease, limited symptoms or preexisting cardiac disorder. More effective and better tolerated agents will be needed for this patient group.

As characteristic of other endocrine tumors, somatostatin receptor expression has been demonstrated in various histologic types of thyroid cancer.[11-13] While the role of somatostatin receptor signaling in regulating hormone secretion has been well established, it is only more recently that its important role as an endogenous inhibitor of cellular proliferation and activator of apoptosis is becoming recognized. This antiproliferative effect of somatostatin receptor activation has been shown to be both a direct effect as well as off target result of its activation of phosphotyrosine phosphatases that subsequently inhibit the activity of non-somatostatin receptors such as the Insulin-like Growth Factor (IGF) and Epidermal Growth Factor (EGF) Receptors, which play key role in cellular proliferation and survival. Tyrosine phosphorylation of endogenous proteins such as ERK and Akt induced by the somatostatin isoform, SS-14, was clearly shown to result in inhibition of growth hormone and IGF1 mRNA expression.[14] In addition, somatostatin receptor activation using octreotide, potently disrupts downstream signaling through the phosphatidyl inositol 3 (PI3) kinase and the mitogen activated protein kinase (MAPK) pathways.[15] Particularly important is the inhibition of PI3 kinase activity due to the dissociation and dephosphorylation of its p85 subunit following somatostatin receptor 2 activation. It is clear from the preceding summary that preclinical studies have provided substantial evidence linking somatostatin receptor inhibitory activity on cellular proliferation to its modulation of the PI3 kinase/Akt/mTOR pathway.

Thyroid stimulating hormone is the key driver of proliferation in normal and neoplastic thyroid epithelial cells. This effect is mediated by convergence of signaling on the AKT/mTOR pathway.[16] Indeed, upstream stimulation of mTOR signaling induced by PTEN haploinsufficiency in mice harboring a dominant-negative mutant thyroid hormone receptor beta (TRbeta(PV/PV) mice) significantly increased the rate of progression of spontaneously formed thyroid tumor and occurrence of lung metastasis leading to reduced survival as compared with PTEN haplosufficent TRbeta(PV/PV)Pten(+/+) mice.[17] Furthermore, a potent and specific inhibitor of the PI3 kinase signaling, LY294002, inhibited downstream mTOR signaling and resulted in reduced thyroid tumor growth and metastasis.[18] The available preclinical evidence demonstrating the important roles of somatostatin receptor and mTOR pathway signaling in thyroid cancer development and progression provides a justification and

a strong rationale for a systematic evaluation of agents targeting these pathways in patients with thyroid cancer. We therefore propose to evaluate the efficacy of everolimus, pasireotide and their combinations in patients with radioiodine refractory thyroid cancers.

1.2 Somatostatin analogs in the treatment of patients with thyroid cancer

There is to date no published report of a prospective trial evaluating somatostatin analogue therapy in thyroid cancer. There is, however, a limited number of case series and case reports showing a variable outcome when patients with radiorefractory or medullary thyroid cancer were treated with somatostatin analogue.

Robbins et al. reported the result in two patients with progressive metastatic papillary thyroid cancer no longer responsive to high doses of ^{131}I or showing lack of uptake on ^{131}I scintigraphy. Pretreatment ^{111}In-pentetreotide scans confirmed the expression of somatostatin receptors by the metastatic deposits. Following approximately 4 months of therapy with long acting octreotide (Sandostatin LAR Depot) therapy, significant reduction was observed in tumor volume and standard uptake values between baseline and restaging ^{18}F-FDG-PET scans.[19]

A case series of 8 patients with symptomatic metastatic medullary thyroid carcinoma treated with short acting octreotide in combination with recombinant interferon alpha-2b was reported by Lupoli et al. Octreotide was given at a single daily dose of 150 micrograms for 6 months followed by a daily dose of 300 micrograms for an additional 6 months. Interfreon was administered at a dose of 5.000.000 IU intramuscularly 3 times a week for 12 months. Two patients discontinued therapy due to treatment associated toxicities. Although no anatomic response was observed in the tumor deposits, there was symptomatic improvement in five patients. Biochemical response was recorded with significant reduction in serum calcitonin and carcinoembryonic antigen levels within 3 months of starting treatment.[20]

Long acting octreotide therapy was also shown to be associated with durable biochemical response lasting up to 17 months in three patients with metastatic medullary thyroid carcinoma, two of whom had MEN IIa syndrome. Similar to the case series by Lupoli et al. maximal biochemical response was achieved within 3 months with maximal percent decrease in mean serum calcitonin of 47, 52 and 81% compared to basal values and 45, 60 and 63% in carcinoembryonic antigen (CEA) levels. Response was not durable in the patient with the sporadic form of disease and anatomic correlate of the biochemical response was not reported.[21]

Lanreotide is a cyclic octapeptide somatostatin analogue with affinity for type 2 and type 5 somatostatin receptor subtypes. Vitale et al. combined the long acting form of this agent with recombinant interferon alpha-2b in seven patients with medullary thyroid carcinoma. There

was symptomatic improvement in nearly all patients with associated biochemical response while 5 out of 7 patients achieved disease stabilization.[22]

The use of somatostatin analogue therapy for poorly differentiated follicular or papillary thyroid showed poor disease control in part because toxicity limited prolonged treatment. In a series of twelve patients with somatostatin receptor expression confirmed by scintigraphy, only three patients were able to tolerate long term treatment lasting one year or more. All three showed disease progression on FDG PET scan.[23]

Overall, experience with somatostatin analogue therapy in thyroid cancer is limited. Available published data suggest that this class of drugs have some efficacy in well differentiated thyroid cancer but little or no anticancer activity in poorly differentiated or anaplastic tumors.

1.3 Pasireotide (SOM230)

Pasireotide is an injectable somatostatin analogue. It is a novel cyclohexapeptide with the following chemical name: (2-Aminoethyl)carbamic acid (2R,5S,8S,11S,14R,17S,19aS)-11-(4-aminobutyl)-5-benzyl-8-(4-benzyloxybenzyl)-14-(1H-indol-3-ylmethyl)-4,7,10,13,16,19-hexaoxo-17-phenyloctadecahydro-3a,6,9,12,15,18-hexaazacyclopentacyclooctadecen-2-yl ester, di[(S)-2-aminosuccinic acid] salt.

Like natural somatostatin and other somatostatin analogues (SRIFa), pasireotide exerts its pharmacological activity via binding to somatostatin receptors (sst). There are five known somatostatin receptors: sst 1, 2, 3, 4 and 5. Somatostatin receptors are expressed in different tissues under normal physiological conditions. Somatostatin analogues activate these receptors with different potencies[24] and this activation results in a reduced cellular activity and inhibition of hormone secretion. Somatostatin receptors are strongly expressed in many solid tumors, especially in neuroendocrine tumors where hormones are excessively secreted e.g. acromegaly,[25] GEP/NET[26] and Cushing's disease.[27]

The somatastatin analogues currently approved for clinical use (octreotide and lanreotide) have a high affinity to sst subtype 2 (sst2), with moderate or no affinity to the remaining subtypes. Pasireotide is a novel cyclohexapeptide somatostatin analogue that exhibits a unique binding profile, binding with high affinity to four of the five known human somatostatin receptors. (Table 1-1) Compared to Sandostatin® (octreotide acetate), pasireotide exhibits a binding affinity which is 30-40 times higher for human sst1 and sst5, 5 times higher for human sst3, and similar to the affinity for sst2 receptors. A detailed summary of available preclinical data is provided in the [Investigator's Brochure].

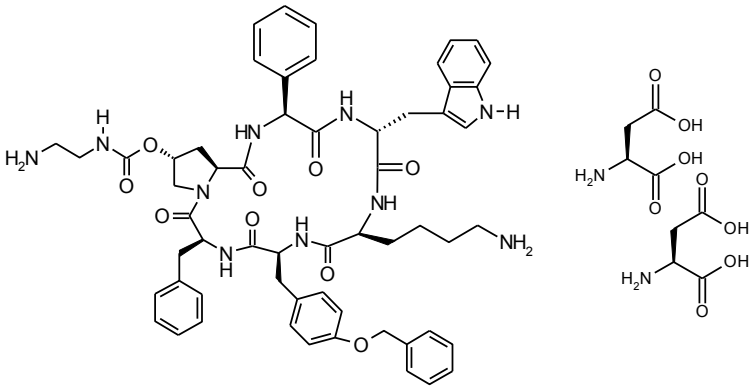
Table 1-1 Binding profile for octreotide and pasireotide at hsst1-5 (IC_{50}, M)

Compound	**sst 1**	**sst2**	**sst3**	**sst4**	**sst5**
octreotide acetate (SMS)	$2.8x10^{-7}$	$3.8x10^{-10}$	$7.1x10^{-9}$	$>10^{-6}$	$6.3x10^{-9}$
Pasireotide (SOM230)	$9.3x10^{-9}$	$1.0x10^{-9}$	$1.5x10^{-9}$	$>10^{-6}$	$1.6x10^{-10}$
Ratio of IC_{50}: octreotide/ pasireotide	30	0.4	5	--	40

Chemical name

Chemical name: (2-Aminoethyl)carbamic acid (2R,5S,8S,11S,14R,17S,19aS)-11-(4-aminobutyl)-5-benzyl-8-(4-benzyloxybenzyl)-14-(1H-indol-3-ylmethyl)-4,7,10,13,16,19-hexaoxo-17-phenyloctadecahydro-3a,6,9,12,15,18-hexaazacyclopentacyclooctadecen-2-yl ester, di[(S)-2-aminosuccinic acid] salt

Chemical structure



Mechanism of action

SOM230 is a novel cyclohexapeptide somatostatin analogue that exhibits a unique binding profile with high affinity to four of the five known human somatostatin receptors. As compared to Sandostatin®, SOM230 exhibits a binding affinity, which is 30-40 times higher for human sst1 and sst5, 5 times higher for human sst3, and 2.5 times lower for human sst2. In preclinical experiments, SOM230 showed, in comparison to Sandostatin®, a more pronounced IGF-1 suppression in four species and a longer biological presence leading to slower elimination.

Human experience

Pasireotide s.c.

Pasireotide when given subcutaneously (s.c.) was well-tolerated at doses up to 600 µg b.i.d., 900 µg b.i.d. and 1200 µg b.i.d by acromegalic, Cushing's disease and carcinoid tumor patients, respectively. For all indications the most frequently reported adverse events were gastrointestinal, predominantly diarrhea, nausea and abdominal pain. Generally these events were mild, transient and only occasionally caused patients to discontinue treatment.

Hyperglycemia was also observed for some patients in the different indications. When hyperglycemia occurred, it was most common in patients with impaired fasting glucose or diabetes mellitus at baseline. However hyperglycemia in these patients was responsive to appropriate diabetic management such as adjustments in oral antidiabetic treatment, or in some cases the addition of insulin. Occasionally laboratory abnormalities in liver function tests and pancreatic enzymes have been observed at higher doses of pasireotide. These events however have been transient.

Overall the safety profile of pasireotide is comparable to that of currently available somatostatin analogues. However as pasireotide has a broader binding profile (binds to 4 of the 5 sst), and thus more closely resembles natural somatostatin, it may impact secretion of hormones by the pancreas, pituitary, thyroid, adrenals and the gastrointestinal tract. Hence parameters of glucose metabolism (fasting blood glucose, HbA1C), pituitary function (GH, IGF-1, prolactin, ACTH), thyroid function (free T4, TSH) and the adrenals (serum cortisol) will be monitored in this study.

Preliminary safety data are available from a Phase II study [CSOM230B2202] in 45 patients with symptomatic metastatic carcinoid disease inadequately controlled by octreotide LAR who received pasireotide s.c. doses from 300 µg s.c. b.i.d. up to 1200 µg b.i.d. for a mean of 20 weeks. Pasireotide s.c. has been found to be generally well-tolerated by these patients, with the most common adverse events being mild diarrhea, nausea and abdominal pain. Blood glucose increases occurred in some patients, particularly in those with preexisting DM or impaired fasting glucose, but were moderate and manageable by adjustment in oral hypoglycemic medications in most cases. Weight loss was also observed in 18 patients. Maximum weight loss occurred within 4 to 6 months on the study drug, with a stabilization of effect after approximately 6 months. There was no apparent relationship between the weight loss and pasireotide dose.

Preliminary efficacy data from this study also supports that pasireotide is active in patients refractory/resistant to Sandostatin LAR, as partial or complete symptom control was observed in 12 of 44 patients (27%). Complete response was achieved in two patients at the pasireotide 600 µg s.c. b.i.d. dose and one patient at the 900 µg s.c. b.i.d. dose. Nine patients achieved partial response to treatment, three at each of the following doses: 600, 750, and 900 µg s.c. b.i.d.

The mean pasireotide plasma concentration versus time profiles are shown in Figure 1-1. The mean PK parameters of C_{min}, C_{max} and $AUC_{0\text{-}6hr}$ for pasireotide are listed in Table 1-2. Since there is no biomarker available for clinical response in carcinoid patients and since clinical response was observed with similar frequency at doses of 600 to 900 □g s.c. b.i.d., the target pasireotide concentration for symptom control was estimated as approximately 10 ng/mL from the mean C_{min} value at these doses (Table 1-2), assuming that a constant drug level is required for pharmacological activity.

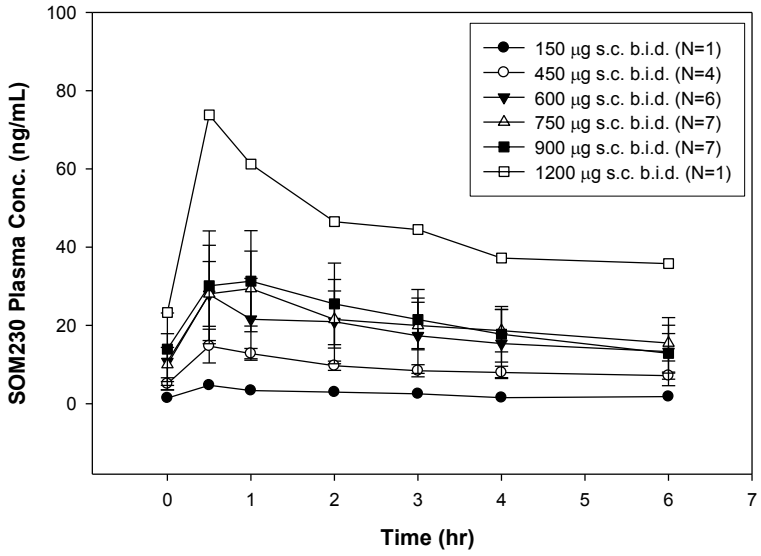
Further details on pasireotide s.c. can be found in the [Pasireotide s.c. Investigator's Brochure].

Table 1-2 **Pasireotide s.c.: Number (%) of patients with most frequent AEs (greater than or equal to 8% for any dose group) regardless of relationship to study drug [CSOM230B2202]**

	Pasireotide sc						
Adverse event (preferred term)	300-≤600µg (N=45) n (CTC≥ **grade3**)	>600-≤900µg (N=39) n (CTC≥ **grade3**)	>900-≤1200µg (N=42) n (CTC≥ **grade3**)	>1200-≤1500µg (N=35) n (CTC≥ **grade3**)	>1500-≤1800µg (N=31) n (CTC≥ **grade3**)	>1800-≤2400µg (N=10) n (CTC≥ **grade3**)	Any dose (N=45) n (%) n (CTC≥ **grade3**)
Weight decreased	6	1	5	1	5	1	19 (42.2)
Abdominal pain	6 **(2)**	3	4	4	2	0	15 (33.3) **(2)**
Nausea	6 **(1)**	2	5	2	3 **(1)**	0	13 (28.9) **(1)**
Fatigue	4	1	1	1	6	0	12 (26.7)
Diarrhea	1	1	3 **(1)**	1	6 **(2)**	0	11 (24.4) **(3)**
Hyperglycemia	1	1	0	2 **(2)**	2 **(1)**	1	7 (15.6) **(3)**
Peripheral edema	1	0	1	2	3	0	7 (15.6)
Flatulence	2	1	1	2	1	0	5 (11.1)
Diabetes mellitus	1	0	0	2 **(1)**	0	1	4 (8.9) **(1)**
Vertigo	1	2	0	0	1	0	4 (8.9)
Dizziness	2	1	0	1	0	0	4 (8.9)
Vomiting	2 **(1)**	1	2	0	2 **(1)**	0	4 (8.9) **(1)**
Dysgeusia	0	1	0	1	2	0	4 (8.9)
Nasopharyngitis	0	1	1	1	1	0	4 (8.9)
Dyspnea	1	1	2 **(1)**	0	1	0	4 (8.9) **(1)**
Hypokalemia	1	1	1	0	0	1	4 (8.9)
Arthralgia	0	0	2	0	2	0	4 (8.9)

Source: [CSOM230B2202]

Figure 1 Error! No text of specified style in document.-1 **Mean (SD) plasma concentration versus time profiles of pasireotide in carcinoid patients (N=26) at week 4 following b.i.d. doses of pasireotide s.c. [CSOM230B2202]**



Source: [CSOM230B2202]

Table 1-3 Mean (SD) pharmacokinetic parameters of pasireotide in carcinoid patients (N=26) following s.c. b.i.d. doses of pasireotide [CSOM230B2202]

Dose (s.c.)	C_{min} (ng/mL)	C_{max} (ng/mL)	$AUC_{(0\text{-}6hr)}$ (ng·hr/mL)
150 □g bid (N=1)	1.4	4.7	14.8
450 □g bid (N=4)	5.1 (1.6)	15.2 (3.9)	58.5 (9.5)
600 □g bid (N=6)	10.7 (7.2)	27.9 (12.6)	108 (56.8)
750 □g bid (N=7)	10.5 (4.1)	32.5 (10.2)	130 (37.1)
900 □g bid (N=7)	13.9 (9.2)	32.4 (12.5)	124 (49.7)
1200 □g bid (N=1)	23.3	73.8	271
Source: [CSOM230B2202]			

Pasireotide long acting release formulation

Pasireotide LAR in healthy volunteers

Preliminary data from a healthy volunteer [study CSOMC2101] which assessed single i.m. doses of pasireotide LAR up to 60 mg (N=5 per cohort) show that pasireotide LAR was well-tolerated, and that the adverse events observed are comparable with those observed with octreotide LAR. Diarrhea was the most common adverse event which was sometimes associated with abdominal

pain and/or flatulence. The gastrointestinal events were mild or moderate in severity. About half of the subjects reported transient mild injection site pain. Two volunteers on the 60 mg dose had mild increases in fasting blood glucose (< 123 mg/dL) with all values returning to normal within 28 days after the LAR injection.

The exposure of pasireotide was dose-proportional with C_{max} of the extended release phase as 9.6 ± 5.1 ng/mL and 15.8 ± 3.3 ng/mL for 40 mg and 60 mg doses, respectively. Multiple dose simulation suggested that this LAR formulation is suitable for monthly (q 28 d) dosing. The simulated trough concentrations ($C_{trough.ss}$) at steady state were 5.5 and 11.5 ng/mL for the 40 and 60 mg doses, respectively.

Further details on the safety and PK of pasireotide LAR in healthy volunteers can be found in the [Pasireotide LAR Investigators' Brochure].

Pasireotide LAR in carcinoid patients

Safety

Preliminary safety data are available from 20 carcinoid patients inadequately controlled by somatostatin analogues treated with pasireotide LAR in an ongoing study [CSOM230C2110] (Table 1-4). These patients were under treatment with pasireotide LAR i.m. depot injections at doses of 20 mg, 40 mg or 60 mg for up to six weeks at the time of the safety summary. Pasireotide LAR was generally well-tolerated. The most commonly reported AEs were gastrointestinal, however, most of these events were considered unrelated to study drug.

Table 1-4 **Pasireotide LAR: Number (%) of patients with most frequent AEs (> 5% for any dose group) regardless of relationship to study drug (preliminary data from study SOM230C2110)**

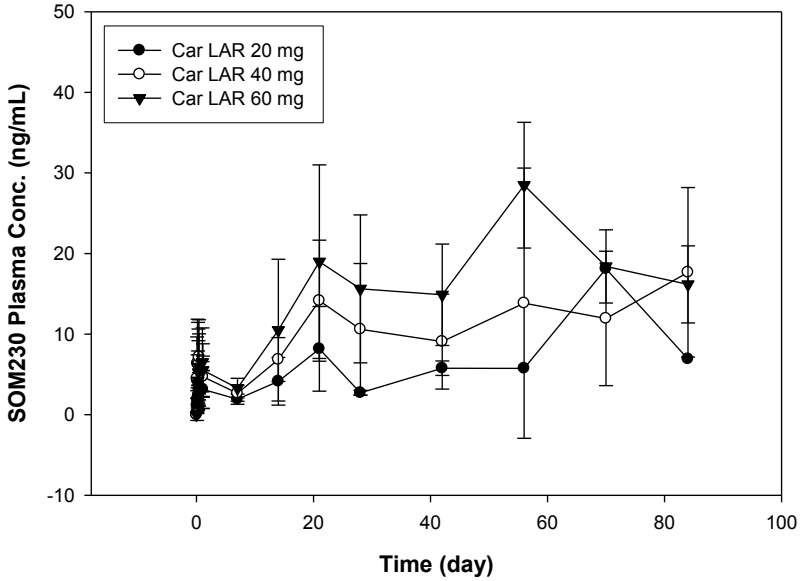
Adverse Event (Preferred term)	Pasireotide LAR 20mg (N=5) n (CTC= **grade3**)	Pasireotide LAR 40mg (N=7) n (CTC= **grade3**)	Pasireotide LAR 60mg (N=8) n (CTC= **grade3**)	Pasireotide LAR Any dose (N=20)n (%) (n=CTC grade3)
Diarrhea	1	2	2	5 (25.0%)
Fatigue	1	2 (1)	1	4(20.0%) (1)
Dyspnea	1	2 (1)	1	4 (20.0%) (1)
Flushing	1	1 (1)	1 (1)	3 (15.0%) (2)
Back Pain	1	1	1	3 (15.0%)
Nausea	1	1	0	2 (10.0%)
Palpitations	0	2	0	2 (10.0%)
Abdominal Pain	1	1	0	2 (10.0%)
Steatorrhea	1	1	0	2 (10.0%)
Asthenia	1	1	0	2 (10.0%)
Headache	0	1	1	2 (10.0%)
Anorexia	0	1	1	2 (10.0%)
Hyperglycemia	0	1 (1)	1	2 (10.0%) (1)
Odema Peripheral	0	1	0	1 (5.0%)
Erythema	1	0	0	1 (5.0%)

Source: [SOM230C2110]

Pharmacokinetics

Interim PK analysis has shown that a steady state appeared to be achieved following three monthly i.m. injections of 20 mg (N=5), 40 mg (N=7) or 60 mg (N=8) pasireotide LAR in carcinoid patients. The mean (SD) concentration versus time profiles of pasireotide are shown in Figure 1-2. The median (mean ± SD) trough plasma concentrations of pasireotide on days 28, 56 and 84 are shown in Table 1-3. The release pattern of pasireotide from the first injection of 40 and 60 mg LAR in carcinoid patients (Figure 1-2) was very similar to that of a single-dose of 40 and 60 mg LAR in healthy volunteers. PK exposures to pasireotide on day 84 at steady state in carcinoid patients (Table 1-3) were roughly 2-fold higher than the simulated concentrations at steady state following multiple doses in healthy volunteers (Section 1.3.2.1).

Figure 1 Error! No text of specified style in document.**-2 Mean (SD) plasma concentration versus time profiles of pasireotide in carcinoid patients following three monthly i.m. injections of 20 mg (N=5), 40 mg (N=7), or 60 mg (N=8) pasireotide LAR [CSOM230C2110]**



Source: [SOM230C2110]

Table 1-5 Median (Mean plus or minus SD) trough plasma concentrations of pasireotide on days 28, 56 and 84 in carcinoid patients following three monthly i.m. injections of 20 mg (N=5), 40 mg (N=7) or 60 mg (N=8) pasireotide LAR [CSOM230C2110]

Dose (mg)	Day 28 (ng/mL)	Day 56 (ng/mL)	Day 84 (ng/mL)
20 (N=5)	2.7 (N=2)	5.7 (N=1)	6.9 (N=1)
40 (N=7)	7.2 (10.6 ± 8.2) (N=6)	5.9 (13.8 ± 16.8) (N=3)	12.0 (17.7 ± 10.5) (N=3)
60 (N=8)	14.2 (15.6 ± 9.2) (N=8)	28.2 (28.5 ± 7.8) (N=4)	16.9 (16.2 ± 4.8) (N=4)
Source: [SOM230C2110]			

1.4 RAD001 (everolimus)

RAD001 (everolimus) is a novel oral derivative of rapamycin.

RAD001 has been in clinical development since 1996 as an immunosuppressant in solid organ transplantation and has obtained marketing authorization (Certican®) for prophylaxis of rejection in renal and cardiac transplantation in a number of countries, including the majority of the European Union. RAD001 has been in development for patients with various malignancies since 2002.

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 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.

At weekly and daily schedules and at various doses explored, RAD0001 is generally well tolerated. The most frequent adverse events (rash, mucositis, fatigue and headache) associated with RAD001 therapy are manageable. Non-infectious pneumonitis has been reported with mTOR inhibitors but is commonly low-grade and reversible.

mTOR pathway and mechanism of action

At cellular and molecular level RAD001 acts as a signal transduction inhibitor. RAD001 selectively inhibits mTOR (mammalian target of rapamycin), a key and a highly conservative serine-threonine kinase, which is present in all cells and is a central regulator of protein synthesis and ultimately cell growth, cell proliferation, angiogenesis and cell survival. mTOR is the only currently known target of RAD001.[28]

mTOR is downstream of PI3K/AKT pathway, a pathway known to be dysregulated in a wide spectrum of human cancers (e.g. through loss/mutation of the PTEN negative regulator; through PI3K mutation/amplification; through AKT/PKB overexpression/overactivation; through modulation of TSC1/TSC2 tumor suppressors). In addition, activation of the PI3K/AKT/mTOR pathway is frequently a characteristic of worsening prognosis through increased aggressiveness, resistance to treatment and progression.

The main known functions of mTOR include the following:[28, 29]

- mTOR functions as a sensor of mitogens, growth factors and energy and nutrient levels, facilitating cell-cycle progression from G1 to S phase in appropriate growth conditions.
- The PI3K-mTOR pathway itself is frequently activated in many human cancers, and oncogenic transformation may sensitize tumor cells to mTOR inhibitors.
- Through inactivating eukaryotic initiation factor 4E binding proteins (4E-BP1) and activating the 40S ribosomal S6 kinases (i.e., p70S6K1), mTOR regulates translation of important massages, including those encoding the HIF-1 proteins, c-myc, ornithine decarboxylase, and cyclin D1, as well as ribosomal proteins themselves.
- The activation of mTOR pathway leads to the increased production of pro-angiogenic factors (i.e., VEGF) in tumors and to tumor, endothelial and smooth muscle cell growth and proliferation.
- The regulation of mTOR signaling is complex and involves positive regulators, such as AKT that phosphorylate and inactivate negative regulators such as the Tuberous Sclerosis Complex (TSC1/TSC2).

mTOR is represented by two structurally and functionally distinct multiprotein signaling complexes, mTORC1 (mTOR complex 1, rapamycin sensitive) and mTORC2 (mTOR complex 2, rapamycin insensitive).[30]

mTORC1 is mainly activated via the PI3 kinase pathway through AKT (also known as PKB, protein kinase B) and the tuberous sclerosis complex (TSC1/TSC2).[29] Activated AKT phosphorylates TSC2, which lead to the dissociation of TSC1/TSC2 complex, thus inhibiting the ability of TSC2 to act as a GTPase activating protein. This allows Rheb, a small G-protein, to remain in a GTP bound state and to activate mTORC1. AKT can also activate mTORC1 by PRAS40 phosphorylation, thereby relieving the PRAS40-mediated inhibition of mTORC1.[31, 32]

mTORC2 (mTOR complex 2) is activated through a currently unknown mechanism, possibly by receptor tyrosine kinase (RTK) signalling.[31] It has been suggested that mTORC2 phosphorylates and activates a different pool of AKT that is not upstream of mTORC1. PHLPP phosphatase plays a role of a negative regulator. mTORC2 is rapamycin insensitive and is required for the organization of the actin cytoskeleton.[30]

mTORC1-mediated signaling is subject to modulation by the macrocyclic lactone rapamycin and its derivatives, such as RAD001. Once these agents bind to the 12 kDa cytosolic FK506-binding protein immunophilin FKBP12, the resulting rapamycin-FKBP12 complexes bind to a specific site near the catalytic domain of mTORC1 and inhibit phosphorylation of mTOR substrates. As a consequence, downstream signaling events involved in regulation of the G1 to S-phase transition are inhibited. This mechanism is thought to be responsible for the immunosuppressive effects of rapamycin as well as its putative antineoplastic activity.[33] As many cancers are characterized by dysregulation of G1 transit (for example, overexpression of cyclin or cyclin-dependent kinases), inhibition of mTOR becomes an intriguing target for inducing cytostasis.[29]

Preclinical studies

Pre-clinical investigations have demonstrated that RAD001 is a potent inhibitor of the proliferation of a range of human tumor cell lines *in-vitro* with IC50s ranging from sub/low nM to μM concentrations, concentrations capable of being reached in patients at the doses used in clinical trials.

RAD001 was shown to have activity in human tumor cell lines originating from lung, breast, prostate, colon, kidney, melanoma and glioblastoma. RAD001 was also shown to have activity in human pancreatic neuroendocrine cells, where induction of apoptosis was reported,[34] as well as in acute myeloid leukemia cells,[35] adult T-cell leukemia cells,[36] diffuse large B cell lymphoma cells (DLBCL;[37] pancreatic tumor cells,[38] ovarian cancer cells[39-41] and hepatocellular carcinoma cells.[42]

As a single agent, RAD001 inhibited proliferation in three mantle cell lymphoma cell lines (Jeko1, SP49 and NCEB1) approximately 40–65% compared to control cells. This was associated with G1 cell-cycle arrest and reduced phosphorylation of the mTOR downstream target, 4E-BP1.[43]

In a clonogenic assay using cells derived from 81 patient-derived tumor xenografts never cultured *in vitro* (11 human tumor types with 3 to 24 tumors each: bladder, colon, gastric, NSCLC [adeno, squamous epithelium and large cell], SCLC, breast, ovary, pancreatic, renal,

melanoma, and pleural mesothelioma), RAD001 inhibited colony formation in a concentration-dependent manner. In addition, normal hematopoetic stem cells were insensitive to RAD001, with an IC50 about 15 fold higher than the tumor lines.

RAD001 also inhibits the proliferation of human umbilical vein endothelial cells (HUVECS), with particular potency against VEGF-induced proliferation. The inhibition of endothelial proliferation and antiangiogenic activity of RAD001 was confirmed *in vivo*, as RAD001 selectively inhibited VEGF-dependent angiogenic response. Mice with primary and metastatic tumors treated with RAD001 showed a significant reduction in blood vessel density when compared to controls at well tolerated doses. Additionally, activity in a VEGF-impregnated s.c. implant model of angiogenesis and reduced vascularity (vessel density) of RAD001-treated tumors (murine melanoma) provided evidence of *in vivo* effects of angiogenesis.

RAD001 also inhibits tumor growth *in-vivo* in xenografted, syngeneic and orthotopic animal models, residing longer in tumor tissue than in plasma and demonstrating high tumor penetration in a rat pancreatic tumor model. These effects occurred within the dose range of 2.5 to 10 mg/kg p.o. daily. Typically, the antitumor activity of RAD001 monotherapy was that of reduction of tumor growth rates rather than producing regressions or stable disease.

RAD001, administered p.o., was a potent inhibitor of tumor growth and well tolerated in:

- s.c. mouse xenograft model, established from a variety of tumor cell lines of diverse histotypes (NSCLC, pancreatic, colon, melanoma, epidermoid), including a Pgp170 overexpressing multi-drug resistant tumor line
- in a series of low-passage tumor xenografts established directly from human tumor material, maintained only *in vivo* and considered highly predictive of therapeutic outcome in patients. These included breast (5 lines), colorectal (9 lines), gastric (3 lines), lung (22 lines including adenocarcinomas, epidermoid cell, large cell and small cell histotypes), melanoma (6 lines), ovarian (4 lines), pancreatic (3 lines) and renal (6 lines)
- in two syngeneic models (CA20948 rat pancreatic, B16/Bl6 mouse orthotopic melanoma)

Taken together, these data indicate the broad antiproliferative potential of RAD001.

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. PTEN status alone may not be predictive of RAD001 relative *in vitro* sensitivity, however in some cases (i.e., GBM) there is also a correlation with PTEN status.

In preclinical models, the administration of RAD001 is associated with reduction of protein phosphorylation in target proteins downstream of mTOR, notably phosphorylated S6 (pS6) and p4E-BP1, and occasionally with an increase in phosphorylation AKT (pAKT).

Pre-clinical safety

In safety pharmacology studies, RAD001 was devoid of relevant effects on vital functions including the cardiovascular, respiratory and nervous systems. RAD001 had no influence on QT interval prolongation. Furthermore, RAD001 showed no antigenic potential. Although RAD001 passes the blood-brain barrier, there was no indication of relevant changes in the behavior of

rodents, even after single oral doses up to 2000mg/kg or after repeated administration at up to 40 mg/kg/day. Based on these findings, the potential of RAD001 to affect vital functions in patients is considered to be low.

RAD001 is considered to have no genotoxicity or carcinogenicity potential. All significant adverse events observed in preclinical toxicology studies with RAD001 in mice, rats, monkeys and minipigs were consistent with its anticipated pharmacologic action as an antiproliferative and immunosuppressant and at least in part reversible after a 2- or 4-week recovery period with the exception of the changes in male reproductive organs, most notably testes. Ocular effects (lenticular disorders) observed in rats were not observed in any other species and are considered to be a species-specific disorder.

More pre-clinical information is provided in the [Investigator's Brochure].

Clinical experience

RAD001 Pharmacokinetics

RAD001 is rapidly absorbed with a median t_{max} of 1-2 hours. The bioavailability of the drug is believed to be 11% or greater. The $AUC_{0-\tau}$ is dose-proportional over the dose range between 5 to 70 mg in the weekly regimen and 5 and 10 mg in the daily regimen. C_{max} is dose-proportional between 5 and 10 mg for both the weekly and daily regimens. At doses of 20 mg/week and higher, the increase in C_{max} is less than dose-proportional. The coefficient of variation between patients is approximately 50%.

Trough levels (24 hour post-dose) correlate well with $AUC_{0-\tau}$ at steady-state during daily administration.

In whole blood, at a daily dose of 10 mg, about 20% of RAD001 is confined in plasma with 26% being unbound. The remaining 80% is sequestered in blood cells.

RAD001 is extensively metabolized in the liver and eliminated in the bile. Major metabolites are inactive. Elimination half-life is approximately 30 hours. The clearance of RAD001 is approximately halved in patients with mild-moderate hepatic impairment (Child-Pugh Class A or B), while renal impairment has little or no impact on the pharmacokinetics of RAD001.

Age, weight and gender in the adult population do not affect the pharmacokinetics of RAD001 to a clinically relevant extent. The clearance of RAD001 is reduced in children.

Pharmacokinetic characteristics are not notably different between Caucasian and Japanese subjects, whereas in Black patients population pharmacokinetic studies have shown an average 20% higher clearance.

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.

RAD001 is a substrate of CYP3A4 and a substrate and a moderate inhibitor of the multi-drug efflux pump P-glycoprotein (P-gP, MDR1, ABCB1). Hence, its metabolism is sensitive to drugs which modify these enzymes (substrates, inducers, or inhibitors of these enzymes). Competitive inhibition could occur when RAD001 is combined with drugs which are also CYP3A4 or P-glycoprotein substrates

Table 6-9 (Section 6-8) lists examples of clinically relevant CYP3A inhibitors and inducers.

Please refer to Section 6-8 for more information on the concomitant use of CYP3A4 inhibitors/inducers and other medications.

More information on RAD001 pharmacokinetics is provided in the [Investigator's Brochure].

RAD001 Pharmacodynamic studies

Pharmacokinetic/pharmacodynamic modeling based on inhibition of the biomarker p70S6 kinase 1 [S6K1] in peripheral blood mononuclear cells [PBMC]) suggests that 5-10 mg daily should be an adequate dose to produce a high-degree of sustained target inhibition ([Study C2101] / [Study 2102].[44] Furthermore, molecular pharmacodynamic (MPD) studies, using immunocytochemistry (IHC) in biopsied tumor tissue, assessed the degree of inhibition and its duration for pS6, p4E-BP1 and pAKT expression with the daily and weekly dosing. There was high inhibition of the downstream markers S6K1 and 4E-BP1 at 5mg/day, which was complete at 10 mg/day, while preliminary results suggest increase in pAKT expression with maximal effect at 10 mg daily ([Study C2107].[45]

More information is provided in the [Investigator's Brochure].

Clinical experience with RAD001

RAD001 has been investigated as a component of multi-drug immunosuppression in solid organ transplantation since 1996 and was approved for the indication of prophylaxis of organ rejection in adult patients receiving an allogeneic renal or cardiac transplant on 8 Jul 2003 by the European Union under the trade name of Certican®. The most frequent adverse drug reactions in this context are highly specific to the transplant context. However, certain events are generalizable, most notably myelosuppression, skin disorders and increases in blood lipid levels.

RAD001 (everolimus) was approved by the United States Food and Drug Administration in March 2009 for the treatment of advanced renal cell carcinoma for patients with advanced renal cell carcinoma (RCC) after failure of treatment with sunitinib or sorafenib.

RAD001 has been in development for patients with cancer since 2002. Approximately 4000 patients with various malignancies have been treated in either Novartis sponsored or non-Novartis sponsored, and 3 healthy volunteer clinical studies as of 31 Aug 2008. Overall, Novartis sponsored a total of 28 studies of RAD001 administered either as single-agent (n=13), or in combination with other anti-tumor agents (n=15). Ongoing or completed Investigator sponsored studies also enrolled over 1000 patients globally.

Eight single-agent Novartis sponsored trials have or are being conducted in various advanced malignancies. Five Phase I studies evaluated several escalating doses with either weekly or daily administration (Studies C2101/02, C2106, C2107, C1101) of RAD001 with the objective to identify an optimal regimen and dosage, based on safety, pharmacokinetics and knowledge of the drug's molecular effects on various tumors. The 10 mg/day and 50-70 mg/week dosages were proposed for further studies, when using RAD001 as a single agent, and as a target maximum dose in combination studies. In addition the Phase I studies, conducted in prostate cancer (Study

C2106) and in Japanese patients with advanced cancers (Study C1101), evaluated the safety and the molecular changes in tumor, associated with the administration of RAD001.

Two Phase II monotherapy studies were designed to evaluate the safety and efficacy of a single dose of 10 mg administered daily including Study C2235 in advanced NSCLC (n=81) and Study C2239 in advanced pancreatic neuroendocrine tumors (n=160).

A Phase III, randomized, double blind, placebo controlled study in patients with mRCC who progressed on a VEGFr TKI demonstrated that everolimus, administered daily at an oral dose of 10 mg administered provides positive clinical benefit (Motzer, 2008). Median progression free survival (PFS) was prolonged from 1.87 months for patients receiving placebo to 4.01 months for everolimus treated patients, assessed by central independent review blinded to clinical data (hazard ratio 0.30, 95% CI 0.22-0.40, p<0·0001).

Updated results presented at the American Society of Clinical Oncology 2009 Genitourinary Cancers Symposium (Kay et al, 2009) demonstrated everolimus as having even greater superiority to placebo in the primary endpoint of PFS. Median PFS was prolonged from 1.9 months for patients receiving placebo to 4.9 months for everolimus-treated patients, assessed by central independent review blinded to clinical data (hazard ratio 0.33, 95% CI 0.25-0.43, p<0.001).

Overall, the most frequent adverse effects suspected to be related to RAD001 have been stomatitis, rash, anemia, fatigue, asthenia, diarrhea, anorexia, nausea, hypercholesterolemia, mucosal inflammation, vomiting, hypertriglyceridemia, cough, peripheral edema, dry skin, epistaxis, pruritus and dyspnea. The most common Grade 3 or 4 adverse reactions suspected to be related to treatment were anemia, infections, hyperglycemia, stomatitis, fatigue, lymphopenia, hypercholesterolemia, pneumonitis, and elevated gammaglutamyltransferase concentrations.

Non-infectious low-Grade (Grade 1/2) pneumonitis has led to development of treatment guidelines for the disorder (Table 6-5). The primary DLT has been severe (Grade 3) stomatitis, and occasionally fatigue, hyperglycemia, and neutropenia. For more information on known undesirable effects of RAD001 refer to Section 6-7.

Further detailed information regarding RAD001 clinical development, safety and efficacy is provided in the [Investigator's Brochure].

2 Study rationale/purpose

Preclinical data in non small cell lung cancer cell lines and cell lines from other tumor types have clearly established that isolated inhibition of the mTOR pathway through downstream blockade with rapamycin analogues engenders a compensatory activation of survival pathway response with increased signaling through AKT, MEK/ERK and EGFR (Figure 1).[46-48] Dual blockade of the mTOR and the alternative survival pathways however results in increased efficacy (Figure 2 and 3).[46-49] It remains unclear, however, whether initial mTOR inhibitor therapy to induce cellular addiction to the survival pathway is superior to the reverse schedule of blocking the survival pathway prior to mTOR inhibition. Also, superiority of any these schedules over simultaneous inhibition with combined mTOR and for instance a PI3/Akt inhibitor is yet to be

established. Further, despite the implicated role for somatostatin receptor activity in thyroid proliferation, anecdotal reports of treatment with somatostatin analogues, octreotide and lanreotide, in differentiated thyroid cancer showed mixed result of efficacy. Although majority of patients derived symptomatic benefit, objective tumor responses as assessed by functional and anatomic imaging were very limited. The promise with this class of drugs in thyroid cancer is probably best achieved either by the use of more potent somatostatin analogues or in combination with other targeted agents. Pasireotide is a new generation somatostatin analogue that targets four of the five known isoforms of the somatostatin receptor. It is anticipated that this broad activity will result in greater antitumor effect compared to the highly selective somatostatin analogues. By combining Pasireotide and Everolimus, we anticipate greater antitumor efficacy without compromising the expected symptomatic improvement. We therefore seek to establish the activity of each agent alone as well as determine whether maximal pathway inhibition using both drugs together will result in improved clinical outcome in this 3-arm phase II trial. To provide some insight into the question of the optimal sequence of administration of the two agents, patients on the single agent arm of the trial will be allowed to receive the second agent in combination at the time of disease progression.

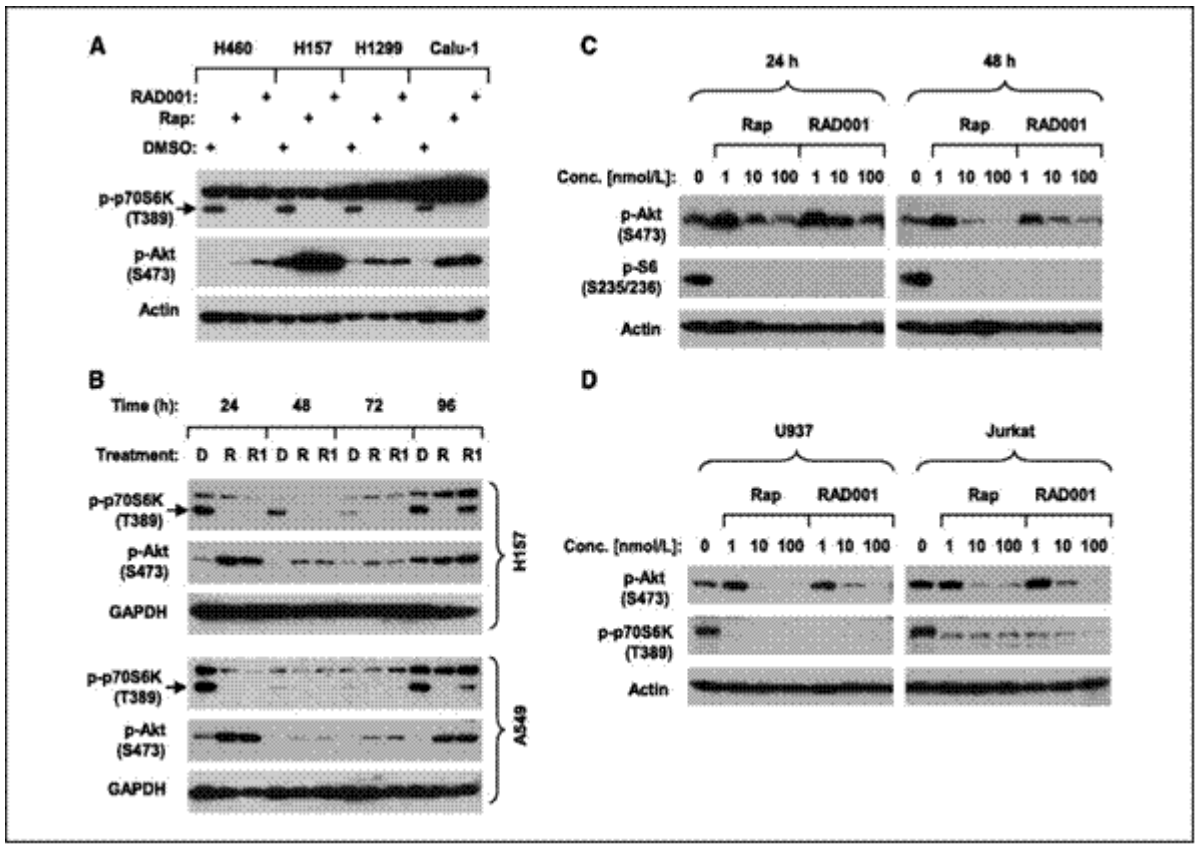


Figure 2-1: Effects of prolonged treatment with mTOR inhibitors on Akt phosphorylation. A, the indicated cell lines were treated with DMSO and 10 nmol/L rapamycin (Rap) or RAD001 for 24 h. B, the indicated cell lines were treated with DMSO (D), 1 nmol/L rapamycin (R), or RAD001 (R1) for the given times. GAPDH, glyceraldehyde-3-phosphate dehydrogenase. C, PC-

3 cells were treated with the given concentrations of rapamycin or RAD001 for the indicated times. D, U937 or Jurkat cells were treated with the given concentrations of rapamycin or RAD001 for 24 h. The cells were then harvested from the aforementioned treatments for preparation of whole-cell protein lysates and subsequent Western blot analysis.[48]

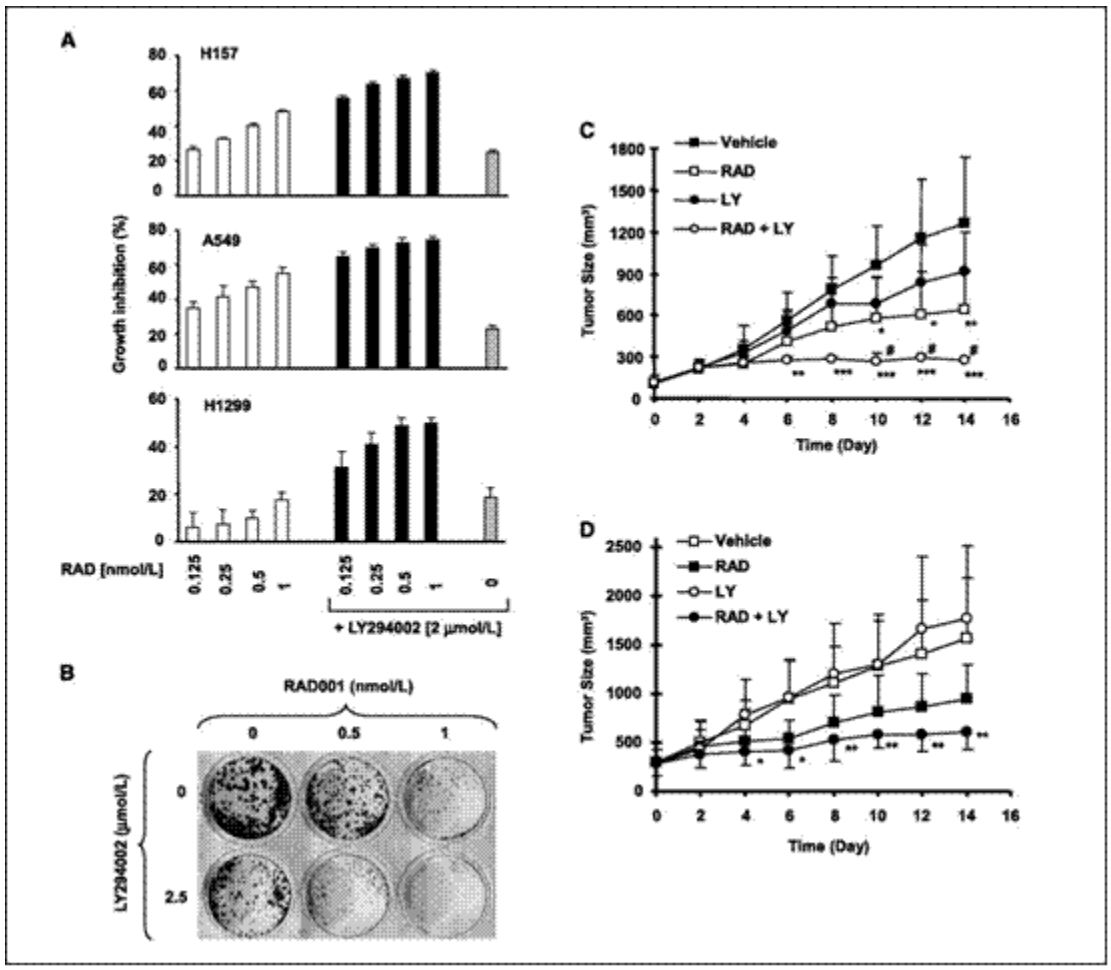


Figure 2-2: Combination of RAD001 and LY294002 augments growth inhibition of lung cancer cells in cell culture (A and B) and in nude mice (C and D). A, the individual cell lines, as indicated, were seeded in 96-well plates. On the second day, they were treated with the indicated concentrations of RAD001 (RAD) alone, 2 μmol/L LY294002 alone, and their respective combinations. After 3 d, plates were subjected to determination of cell number using a SRB assay. Columns, mean of four replicate determinations; bars, SD. B, H460 cells at a density of 250 per well were seeded in 12-well plates. On the second day, cells were treated with the indicated concentrations of RAD001 alone, 2.5 μmol/L LY294002 alone, and their respective combinations. The same treatments were repeated every 3 d. After 10 d, the plates were stained for the formation of cell colonies with crystal violet dye. The picture of the colonies was then taken using a digital camera. C and D, four groups of mice with either A549 (C) or H460 (D) xenografts were treated with vehicle control, RAD001 alone, LY294002 (LY) alone, and RAD001 plus LY294002 on the same day after grouping. After 14 d, the mice were sacrificed

and the tumors were removed. Tumor sizes were measured once every 2 d. Points, mean (n = 6); bars, SD. *, P < 0.05; **, P < 0.01; and ***, P < 0.001, compared with vehicle control; #, P < 0.05, compared with RAD001 treatment.[47]

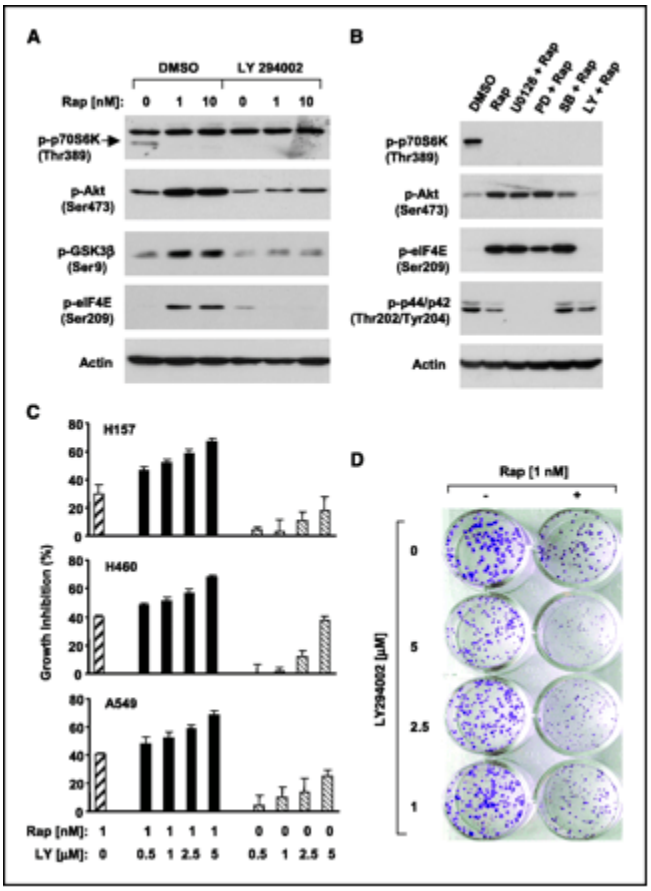


Figure 2-3: Involvement of PI3K in rapamycin-mediated increase of Akt and eIF4E phosphorylation (A and B) and enhancement of rapamycin-mediated growth inhibitor effects by LY294002 in NSCLC cells (C and D). A, H157 cells were pretreated with 5 μmol/L LY294002 for 30 minutes and then cotreated with the indicated concentrations of rapamycin (Rap) for 3 hours. The cells were subjected to preparation of whole cell protein lysates for detection of the indicated proteins using Western blotting. B, H157 cells were pretreated with 20 μmol/L U0126, PD98059 (PD), and SB203580 (SB), respectively, and 10 μmol/L LY294002 (LY) for 30 minutes, and then cotreated with 10 nmol/L rapamycin. After 3 hours, the cells were subjected to preparation of whole cell protein lysates for detection of the indicated proteins using Western blot analysis. C, the individual cell lines, as indicated, were seeded in 96-well plates. On the second day, they were treated with the indicated concentrations of LY294002 alone, 1 nmol/L rapamycin alone, and their respective combinations. After 3 days, plates were subjected to determination of cell number using a SRB assay. Columns, means of four replicate determinations; bars, ±SD. D, H460 cells at a density of 250 cells per well were seeded in 12-well plates. On the second day, cells were treated with the indicated concentrations of LY294002 alone, 1 nmol/L rapamycin alone, and their respective combinations. The same treatments were repeated every 3 days. After 10 days, the plates were stained for the formation of cell colonies with SRB dye. The picture of the colonies was then taken using a digital camera.[47]

2.1 Selection of doses

Everolimus will be dosed at the once daily dose of 10 mg orally continuously. This is the maximum tolerated dose of the drug when dosed on daily continuous schedule. This dose is also the efficacious anticancer dose approved for the treatment of patients with renal cell cancer. The planned dose of Pasireotide LAR is 60 mg intramuscular injection to be given approximately once every 4 weeks. A company-sponsored phase I study of this combination has already determined the proposed doses of 60mg Pasireotide LAR in combination with everolimus 10 mg once daily, to be safe and tolerable.[50] The study is currently enrolling more patients into an

expansion cohort to obtain additional safety and toxicity data. The final result of this phase I trial is awaited within the next 6 months in time for any dose adjustment for Pasireotide in the current study.

3 Objectives

3.1 Primary objectives

To determine the Response Rate [(complete response (RR) + partial response (PR)] of everolimus, pasireotide and the combination of both agents in the therapy of radioiodine refractory differentiated and medullary thyroid cancer.

To establish the progression free survival associated with everolimus, pasireotide and the combination of both agents in radioiodine refractory differentiated and medullary thyroid cancer.

3.2 Secondary objectives

To determine the clinical benefit rate (CBR: CR + PR + SD)of everolimus, pasireotide and the combination of both agents when used as the frontline treatment for radioiodine refractory differentiated and medullary thyroid cancer.

Determine the Time to Treatment Failure (TTF) for each arm of the study

Assess the rate of and time to biochemical response using changes in serum concentrations of thyroglobulin, carcinoembryonic antigen (CEA), chromogranin A and calcitonin

To obtain additional safety data regarding concurrent and sequential administration of Everolimus and pasireotide

3.3 Exploratory objectives

Correlate the level of expression of mTOR pathway signaling proteins in archival tumor tissue with the clinical activity of everolimus

Correlate the level of expression of somatostatin receptor expression and IGF1-R in archival tumor tissue with clinical efficacy of Pasireotide

Exploratory analysis of disease response based on histology and FDG PET uptake

4 Study design

This is an open-label, 3-arm, non comparative phase II clinical trial to study the single agent and combined efficacy of pasireotide and everolimus in patients with iodine refractory, differentiated (papillary, follicular and their variants) and medullary thyroid cancer. Patients will be randomly assigned to one of three arms to receive single agent pasireotide, everolimus or the combination of both drugs (Figure 4). Patient randomization will be stratified by histology, (medullary versus non medullary thyroid cancer). In order to explore the optimal schedule of administration,

patients who were initially randomized to the single agent arm will be allowed to receive the second agent at the time of disease progression. Such patients, however, may only proceed with the trial if they achieve disease stabilization or objective response at the end of the first 2 cycles of 2-drug combination and without experiencing any grade ≥ 4 hematologic or grade ≥ 3 non-hematologic toxicities. Everolimus will be administered once daily continuously on days 1 to 28; pasireotide will be administered as a long acting intramuscular depot injection given once every 4 weeks. One cycle will be defined as 4 weeks with response assessment with cross sectional imaging planned for the end of every even numbered cycle. Biochemical response will be assessed using serum-based tumor markers (Thyroglobulin, CEA, calcitonin) specific or informative for the histologic subtype of thyroid cancer. Patients will be evaluated at the end of cycle 1 and cycle 2, and subsequently after every 2 cycles along with restaging scans.

The study design for this Phase II trial is a randomized screening design with multiple arms. A simple winner arm is selected only from the arms shown to be superior to the historical control. Between arms: Eligible patients will be randomly assigned to one of three arms to receive single agent pasireotide, everolimus or the combination of both drugs. Randomization is conducted with a block of 3 patients in order to balance the enrollment in each arm (The first of the 3 patients entered consecutively is randomly assigned to any of the 3 arms; the second patient is randomly assigned to one of the remaining 2 arms and the third patient to the last arm).

Within arms: Within each of the 3 arms, a Simon's 2-stage MinMax design is used. Eighteen evaluable patients will be enrolled into stage I. At least one objective response is required to proceed to stage II accrual of 10 additional patients for a total of 28 patients per arm. At least 3 patients must achieve objective response for the particular treatment arm to be considered worthy of further clinical evaluation in this disease.

Between Arms: Any treatment arm closed to accrual after the first stage interim analysis will be considered an inferior arm and will be excluded from comparison for the winner of trials.
The arm with the best overall RR at the end of full enrolment will be adjudged the winner to be considered for further development. In the event of identical RR between the arms or if none of the arms met the RR criterion (less than 3 objective responses after full patient enrolment), the 1-yr PFS rate will be employed to determine a winner. Based on recent clinical trials of targeted agents in similar patient population, 90% of patients were alive at 1 year and median progression free survival ranged between 9 and 18 months.[8-10] We assume a conservative estimate that only 20% of the patients will be progression free at 1 year if the treatment is ineffective while 50% or more of the patients will be progression free at the same time point with an effective regimen. For this purpose, a 1-year PFS rate of 50% or greater will be considered sufficient activity to justify further evaluation of the treatment in this disease. Assuming a 20% or lower 1-year PFS rate with an inactive regimen and a 50% or greater rate with an active regimen, 28 patients enrolled onto each arm will classify the treatment as having sufficient activity for further evaluation with a probability of 0.95 (power against the alternative hypothesis $p = 0.05$). In this respect, the arm with the highest 1-yr PFS rate will be judged the winner. In the event of a tie between the arms for both the RR and 1-yr PFS rate, the arm with the best profile in terms of safety and tolerability will be considered the overall winner to be selected for further evaluation in this disease. The power calculation for PFS assessment assumes full enrolment of 28 patients

to the treatment arm, therefore any arm closed to further accrual following the initial interim analysis will not be considered for PFS endpoint assessment.

Figure 4-1: Statistical Consideration for Power and Sample Size

Primary Efficacy Decision Using Simon's MinMax Design Based on RR: P0 = 5% vs. P1 = 15% Power = 80%; α = 0.20	
First Stage Sample Size Upper Limit for First Stage Rejection of Drug	18 0
Maximum Sample Size Upper Limit for Second Stage Rejection of Drug	28 2
Secondary Efficacy Decision Based on 1-Year PFS Rate Endpoint at the End of Complete Enrolment; Total enrolment of 28 patients per arm Duration of enrolment: 30 months Additional follow-up time: None 1-year PFS Rate	
P0 **P1**	20% 50%
Power	95%
2-sided α	0.05

4.1 Treatment

Everolimus (10mg) orally continuously day 1-28

Pasireotide LAR 60 mg i.m. day 1 of each cycle

Safety and efficacy will be assessed throughout the treatment period.

4.2 Follow-up

Patients will remain on treatment and be followed at regularly scheduled office visit until treatment discontinuation due to progression, withdrawal of consent, or intolerable toxicity. Patients who discontinued therapy for reason of toxicity will be monitored at least monthly via phone or office visit until resolution of the adverse event. "All patients will be contacted for survival follow-up at least monthly via phone or office visit until death or the completion of the trial (LPLV + 30 days).

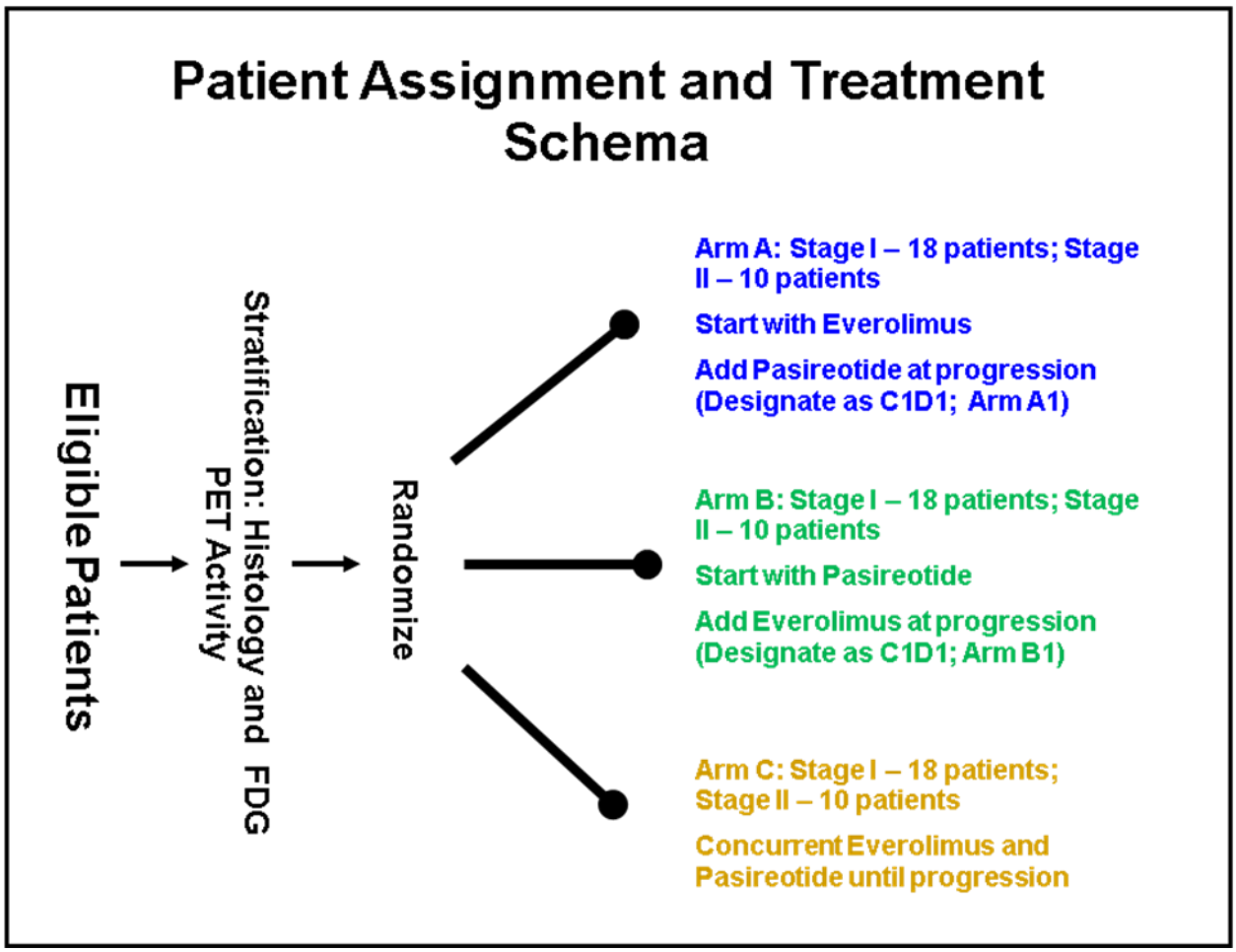


Figure 4-2: Flow diagram of the study schema, screening, stratification and randomization to one of 3 arms.

5 Population

Ninety adult patients with pathologically confirmed medullary or differentiated thyroid cancer who no longer benefit from or are intolerant of radioiodine therapy will be enrolled in the study. Patients will be enrolled across all participating sites in order of registration into the study. Patients who meet the eligibility and screening requirement will be stratified by histology,for the purposes of randomization to one of the 3 treatment arms. Patients will be randomly assigned to one of three treatment arm as described in the statistics section for a total of thirty patients in each arm.

Inclusion/exclusion criteria

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

5.1 Inclusion criteria

1. Histologic or cytologic confirmation of thyroid cancer (papillary, follicular, medullary); histologic variants such as Hurthle and tall cell variants are allowed.
2. Biochemical or radiologic documentation of disease progression within the last 12 months prior to enrollment.
3. Presence of at least one site of measurable disease according to RECIST criteria version 1.1
4. Patient must have radioiodine refractory disease as defined by one or more of the following conditions:
   - All cases of medullary thyroid carcinoma
   - No iodine-uptake on a post- radioactive iodine treatment scan (in presence of low iodine diet and thyroid stimulating hormone (TSH) suppression) in an anatomically defined lesion that qualifies as target lesion by RECIST criteria

     OR
   - If there is demonstrable iodine-uptake: the last radioiodine therapy of (≥ 100 mCi) was given within the last 16 months OR if given more than 16 months before enrollment, there is evidence of disease progression after each of the last two radioiodine treatment performed within 16 months of each other (each dose should be ≥ 100mCi)

     OR
   - If the patient has received the maximum cumulative life time dose of radioactive iodine treatments of at least 600 mCi
   - If the patient declines or is intolerant of radioiodine therapy or if with progressive disease that is, in the opinion of the treating physician, likely to benefit from biologic therapy rather than further iodine therapy e.g. patient with heavy burden of disease
5. Age ≥ 18 years.
6. Minimum of four weeks since any major surgery or since completion of radiation (patients should have adequately recovered from the acute toxicities of any prior therapy).
7. ECOG performance status ≤ 2.
8. Life expectancy of at least 6 months.
9. Adequate bone marrow function as shown by: ANC ≥ 1.5 x 10^9/L, Platelets ≥ 100 x 10^9/L, Hgb > 9 g/dL.
10. Adequate liver function as shown by: serum bilirubin ≤ 1.5 x upper limit of normal (ULN), and serum transaminases activity ≤ 3 x ULN,.
11. Adequate renal function as shown by serum creatinine ≤ 1.5 x ULN or GFR of 60cc/ml using the formula of Cockroft and Gault.
12. Fasting serum cholesterol ≤300 mg/dL OR ≤7.75 mmol/L AND fasting triglycerides ≤ 2.5 x ULN. NOTE: In case one or both of these thresholds are exceeded, the patient can only be included after initiation of appropriate lipid lowering medication.
13. Women of childbearing potential must have a negative serum pregnancy test within 7 days of the administration of the first study treatment. Women must not be lactating. Both men and

women of childbearing potential must be advised of the importance of using effective birth control measures during the course of the study.

14. Signed informed consent to participate in the study must be obtained from patients after they have been fully informed of the nature and potential risks by the investigator (or his/her designee) with the aid of written information.
15. INR and PTT ≤1.5 x ULN. (Anticoagulation is allowed if target INR ≤ 1.5 on a stable dose of warfarin or on a stable dose of LMW heparin for >2 weeks at time of randomization.)

5.2 Exclusion criteria

1. Prior treatment with not more than 1 systemic agent (including chemotherapy or biologic agent e.g. vandetanib for patients with medullary thyroid cancer)
2. Patients who have undergone major surgery within 4 weeks prior to study enrollment (tracheotomy, feeding tube or vascular access catheter placement and interventional procedures such as bronchoscopy, upper GI endoscopy or colonoscopy are not considered major surgery).
3. Chronic treatment with systemic steroids or another immunosuppressive agent.
4. Patients should not receive immunization with attenuated live vaccines during study period or within 1 week of study entry. Close contact with those who have received attenuated live vaccines should be avoided during treatment with everolimus. Examples of live vaccines include intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella and TY21a typhoid vaccines.
5. Uncontrolled brain or leptomeningeal metastases, including patients who continue to require glucocorticoids for brain or leptomeningeal metastases.
6. Patients with prior or concurrent malignancy except for the following: adequately treated basal cell or squamous cell skin cancer, or other adequately treated in situ cancer, or any other cancer from which the patient has been disease free for five years.
7. Patients with uncontrolled diabetes mellitus or a fasting plasma glucose > 1.5 ULN. Note: Optimal glycemic control should be achieved before starting trial therapy. At the principal investigator's discretion, non-eligible patients can be re-screened after adequate medical therapy has been instituted.
8. Patients with symptomatic cholelithiasis (asymptomatic gall stone discovered on screening US should be reviewed by the PI but will not lead to automatic exclusion)
9. Liver disease such as cirrhosis or severe hepatic impairment (Child-Pugh class C).
   - History of liver disease, such as cirrhosis or chronic active hepatitis B and C.
   - Presence of Hepatitis B surface antigen (HbsAg)
   - Presence of Hepatitis C antibody test (anti-HCV)

   Note: A detailed assessment of Hepatitis B/C medical history and risk factors must be done at screening for all patients. HBV DNA and HCV RNA PCR testing are required at screening for all patients with a positive medical history based on risk factors and/or confirmation of prior HBV/HCV infection.

10. Patients who have congestive heart failure (NYHA Class III or IV), unstable angina, sustained ventricular tachycardia, ventricular fibrillation, clinically significant bradycardia, advanced heart block or a history of acute myocardial infarction within the six months preceding enrollment
11. QT related exclusion criteria
    - QTcF at screening > 470 msec.
    - History of syncope or family history of idiopathic sudden death.
    - Sustained or clinically significant cardiac arrhythmias.
    - Risk factors for Torsades de Pointes such as hypokalemia, hypomagnesemia, cardiac failure, clinically significant/symptomatic bradycardia, or high-grade AV block.
    - Concomitant disease(s) that could prolong QT such as autonomic neuropathy (caused by diabetes, or Parkinson's disease), HIV, cirrhosis, uncontrolled hypothyroidism or cardiac failure
    - Concomitant medication(s) known to increase the QT interval.
12. Patients with the presence of active or suspected acute or chronic uncontrolled infection or with a history of immunocompromise, including a positive HIV test result (ELISA and Western blot).
13. Patients who have any severe and/or uncontrolled medical conditions or other conditions that could affect their participation in the study such as:
    - Severely impaired lung function (as defined as spirometry and DLCO that is 50% of the normal predicted value and/or 0_2 saturation that is 88% or less at rest on room air)
    - Any active (acute or chronic) or uncontrolled infection/ disorders.
    - Nonmalignant medical illnesses that are uncontrolled or whose control may be jeopardized by the treatment with the study therapy
    - Impairment of gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of RAD001
    - Patients who have a history of drug abuse in the 6 month period prior to receiving treatment with pasireotide or RAD001
    - History of, or current alcohol misuse/abuse within the past 12 months
    - Acute or chronic pancreatitis
14. Women who are pregnant or breast feeding, or women/men of reproductive potential who are not using and unwilling to practice an effective method of birth control. (Women of childbearing potential must have a negative serum pregnancy test within 7 days prior to administration of pasireotide and RAD001).
15. Male patient whose sexual partner(s) are WOCBP who are not willing to use adequate contraception, during the study and for 8 weeks after the end of treatment
16. Patients with a known hypersensitivity to RAD001 (everolimus) or other rapamycins (sirolimus, temsirolimus) or to its excipients
17. Known hypersensitivity to somatostatin analogues or any component of the pasireotide or octreotide LAR formulations
18. History of noncompliance to medical regimens

19. Patients unwilling to or unable to comply with the protocol
20. Patients taking medications known to be strong CYP3A inhibitors (Table 6-5).

6 Treatment

6.1 Investigational and control drugs

Known undesirable effects of study drug/treatment

For information on Pasireotide and Everolimus, please refer to Section 1, Human experience, and the Investigator Brochure.

6.2 Study drugs

SOM230C

Study drug: pasireotide LAR (long-acting release) i.m. depot injection

Inactive ingredients of pasireotide LAR include: mannitol, carmellose sodium (carboxymethylcellulose sodium), poloxamer 188 and water for injection. Inactive ingredients of pasireotide s.c. include: mannitol, tartaric acid, sodium hydroxide and water for injection.

For detailed information on pasireotide, please refer to Sections 1.3 and 1.4 or the pasireotide Investigator Brochures.

How supplied

Study drug, Pasireotide LAR i.m. depot injections will be supplied in open-label packaging by Novartis as a powder in vials containing 20 mg and 40 mg labeled as SOM230 LAR, with ampoules containing 2 mL of vehicle (for reconstitution). No syringes or needles will be provided with the pasireotide study drug supplies.

Preparation and storage

Prior to reconstitution, vials should be brought to room temperature. Pasireotide LAR should then be prepared as follows:

Table 6-1 Handling and preparation of pasireotide LAR dose

Dose	Volume to be injected
20 mg	1 x 20 mg vial + 2 mL vehicle; whole volume to be injected
40 mg	1 x 40 mg vial + 2 mL vehicle: whole volume to be injected
60 mg	1 x 20 mg vial + 1 x 40 mg vial + 2 mL vehicle; whole volume to be injected

Doses should be prepared and administered immediately after preparation.

Novartis will supply pasireotide LAR as long as the patient remains on study, shows continuous benefit from treatment, and there are no safety concerns. Medication labels will

comply with the legal requirements of the U.S. and will be printed in English. The storage conditions for pasireotide LAR will be described on the medication label. Bottles must be stored in a safe, secure location.

All study medication will be supplied to each site directly by Novartis. Under the responsibility of each site's lead investigator, drug supplies must be kept in an appropriate, secure area (e.g. locked cabinet) and stored in accordance with the conditions specified on the drug labels. The investigator must maintain an accurate record of the shipment and dispensing of the study drug in a drug accountability ledger. An accurate record of the date and amount of study drug dispensed to each subject must be available for inspection at any time.

All drug supplies are to be used only for this protocol and not for any other purpose. Unless specifically instructed by Novartis, the investigator must not destroy any drug labels, or any unused drug supply.

The storage condition for the study drug will be described on the medication label.

Administration

Pasireotide LAR will be administered i.m., intragluteally, every 4 weeks. The starting dose will be 60 mg. The reconstitution has to be performed just prior to administration of the suspension. A minimal standing time can be tolerated for the reconstituted suspension in the vial. Prior to administration, the reconstituted suspension in the vial should be shaken again before withdrawal in the syringe. The i.m. injection must be given immediately after withdrawal of the reconstituted suspension from the vial to the syringe.

RAD001 Administration

The study drug RAD001 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. RAD001 will be administered orally as once daily dose of 10 mg continuously from study day 1 until progression of disease or unacceptable toxicity. Patients will be instructed to take RAD001 in the morning, at the same time each day.

RAD001 may be taken by the patient with or without food. However, dietary habits around the time of RAD001 intake should be as consistent as possible throughout the study.

If vomiting occurs, no attempt should be made to replace the vomited dose.

All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded.

Medication labels will comply with US legal requirements and be printed in English. They will supply no information about the patient. The storage conditions for study drug will be described on the medication label.

RAD001 will be provided by Novartis. RAD001 is formulated as tablets for oral administration of 2.5mg, 5mg and 10mg strengths. Tablets are blister-packed under aluminum foil in units of 10 tablets, which should be opened only at the time of administration as drug is both hygroscopic and light-sensitive.

6.3 Treatment arms

Arm A: Everolimus 10 mg daily continuously (switch to 2-drug combination at progression if no intolerable toxicity)

Arm A1: Patient switching from single agent everolimus to 2-drug combination will be re-registered as Arm A1

Arm B: Pasireotide LAR 60mg i.m. once every 4 weeks (switch to 2-drug combination at progression if no intolerable toxicity)

Arm B1: Patient switching from pasireotide LAR single agent to 2-drug combination will be re-registered as Arm B1

Arm C: Everolimus 10 mg daily continuously together with Pasireotide LAR 60mg i.m. once every 4 weeks

6.4 Patient Registration and Numbering

Each enrolled patient will be assigned a composite number consisting of the three letter abbreviation for the study, a single digit for the center, a 3 digit number representing the next higher number serially from 1 – 90 followed by a single letter representing the arm to which the patient was randomized e.g. "PEC/1/001/C" meaning Pasireotide, Everolimus or combination study, Emory center, patient number 1, randomized to the combination arm.

Eligible patients will be entered on study centrally at the Emory University Winship Cancer Institute by the Study Coordinator. To verify slot availability, all sites should call the Study Coordinator:

Jacene R. Myrie, CCRC

Phone: 404-778-4383

Fax: 404-778-4389

PIC#: 64576

Email:jacene.myrie@emory.edu

Before an investigator may enroll patients, a signed IRB approval letter and approved consent form must be on file with the coordinating center at Emory WINSHIP CANCER INSTITUTE.

Prior to discussing protocol entry with a patient, call or e-mail to verify slot availability.

Once it is confirmed that a slot is available, call and fax a completed eligibility checklist, required laboratory tests and signed consent form to the coordinator at (404-778-4389) between 9 a.m. and 4 p.m. ET, Monday through Friday.

At the time of registration, WINSHIP CANCER INSTITUTE coordinating center will verify the following:

- IRB approval at the registering institution
- Patient eligibility
- Existence of a signed consent form
- Existence of a signed authorization for use and disclosure of protected health information.
- Patient consent for tumor biopsy or special studies (if applicable)

After verifying eligibility, the Emory WINSHIP CANCER INSTITUTE Clinical Research Coordinator will contact the study statistician, Zhengjia (Nelson) Chen, PhD; (Research Assistant Professor, Department of Biostatistics and Bioinformatics, Rollins School of Public Health & Biostatistics Shared Core Resource; 1365 Clifton Road NE, Building B, Room B4110; Tel: 404-778-2017; Fax: 404-778-5016. Email: zchen38@emory.edu) to randomize patient, assign a study number and a dose. The coordinator is expected to fax a confirmation back to the registering site within 24 hours.

Treatment on this protocol cannot begin prior to registration and must be administered at each site under the supervision of a medical oncologist.
All screening procedures should be completed within 14 days prior to treatment unless otherwise specified in the Study Calendar or specific sections of this protocol. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Study Coordinator and or the study PI should be notified of cancellations as soon as possible.
Investigational agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded to the study regulatory specialist at the Emory University WINSHIP CANCER INSTITUTE.

6.5 Treatment assignment

Eligible patients will be randomly assigned to one of three arms to receive single agent Everolimus (Arm A), Pasireotide (Arm B) or the combination of both drugs (Arm C).
Randomization is conducted with a block of 3 patients in order to balance the enrollment in each arm (The first of the 3 patients entered consecutively is randomly assigned to any of the 3 arms; the second patient is randomly assigned to one of the remaining 2 arms and the third patient to the last arm).
Patients who progress while on single agent therapy (Arms A or B) and proceed with the 2-drug combination will be re-registered into Arm A1 and Arm B1 respectively for everolimus and pasireotide arms.

6.6 Treatment blinding

This is an unblinded randomized trial. Both the investigator and the patient will be aware of treatment assignment at the time of enrolment.

6.7 Treating the patient

Study drug administration

Everolimus is an oral drug to be self-administered by the patient with or without food and preferably around the same time every day.

Pasireotide is parenterally administered. The long acting formulation of Pasireotide will be administered intramuscularly by trained Oncology nurse at the beginning of each cycle. All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded.

The investigational study drugs used in the course of this trial are pasireotide (SOM230) and everolimus (RAD001). Novartis will supply pasireotide and everolimus free of charge for study participants.

Permitted study drug adjustments

Toxicity will be assessed using the NCI-CTC for Adverse Events, version 4.0 (CTCAEv4.0, (http://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcaev4.pdf)). For patients who are unable to tolerate the protocol-specified SOM230C and RAD001 dosing schedule, dose-adjustment guidelines are given below.

The following dose modification schedules will be used where dose adjustment is necessitated by treatment related adverse events. The listed starting dose of Pasireotide may change if the ongoing phase I study established that higher doses of Pasireotide can be safely combined with the established dose of Everolimus.

Table Error! No text of specified style in document.6-2 SOM230C + RAD001 Dose Levels

Pasireotide LAR	
Dose level	Dose and schedule
0 (starting dose)	60 mg i.m. Q 4 weeks
Decrease 1 dose level	40 mg i.m. Q 4weeks
Decrease 2 dose levels	20 mg i.m. Q 4 weeks
Everolimus	
Dose level	Dose and schedule
0 (starting dose)	10 mg daily day 1 - 28

Decrease 1 dose levels	5 mg daily day 1 - 28
Decrease 2 dose levels	5 mg daily days 1 - 21 of a 28-day cycle
Decrease 3 dose levels	5 mg every other day for a 28-day cycle

Table 6-3-Criteria for dose-modification in case of suspected SOM230 and RAD001 toxicity for non-hematologic toxicity

Toxicity	Actions
Grade 2 (except pneumonitis [refer to Table 6-5] and mucositis)	If the toxicity is tolerable to the patient, maintain the same dose. If the toxicity is intolerable to patient, interrupt RAD001 and pasireotide until recovery to grade ≤1. Then reintroduce RAD001 and pasireotide at one lower dose level.
Grade 2 mucositis	If the toxicity is tolerable to the patient, maintain the same dose. If the toxicity is intolerable to patient, interrupt RAD001 and pasireotide until recovery to grade ≤1. Then reintroduce RAD001 and pasireotide at one lower dose level. See Management of stomatitis/oral Mucositis/mouth ulcers for further details.
Grade 3 (except hyperlipidemia and hyperglycemia and mucositis and pneumonitis)	Interrupt RAD001 and pasireotide until recovery to grade ≤1. Then reintroduce RAD001 and pasireotide at one lower dose level. If the same toxicity recurs at CTC grade ≥3 SOM230 and RAD001 will be discontinued.
Grade 3 hyperlipidemia	Grade 3 hyperlipidemia (hypercholesterolemia and/or hypertriglyceridemia) should be managed using medical therapies, see Management Guidelines for Hyperlipidemia and Hyperglycemia. Dose reduction of RAD001 and pasireotide can be considered but is not required.
Grade 3 hyperglycemia	Grade 3 hyperglycemia should be managed using medical therapies, see Management Guidelines for Hyperlipidemia and Hyperglycemia. Dose reduction of RAD001 or pasireotide can be considered but is not required.
Grade 3 mucositis	For Grade 3 mucositis, interrupt RAD001 until recovery to grade ≤1. Then reintroduce RAD001 and pasireotide at one lower dose level See Management of stomatitis/oral Mucositis/mouth ulcers for further details.
Grade 3 pneumonitis	Please refer to Table 6-5
Grade 4	Discontinue pasireotide and RAD001.

Any non-hematological toxicity requiring interruption for > 3 weeks	Discontinue pasireotide and RAD001.

Table 6-4Criteria for dose-modification in case of suspected SOM230 and RAD001 for hematologic toxicity

Toxicity	Actions
Hematological toxicity	
Grade 2 Thrombocytopenia (platelets <75, ≥ 50x10^9/L)	Interrupt RAD001 until recovery to grade ≤1 (>75 x10^9/L). Then reintroduce RAD001 at initial dose. If thrombocytopenia again returns to grade 2, interrupt RAD001 until recovery to grade ≤1. Then reintroduce RAD001 at the lower dose level.
Grade 3 Thrombocytopenia (platelets <50, ≥ 25 x10^9/L)	Interrupt RAD001 until recovery to grade ≤1 (platelets ≥ 75 x10^9/L). Then resume RAD001 at one dose level lower. If grade 3 thrombocytopenia recurs, discontinue RAD001.
Grade 4 Thrombocytopenia (platelets < 25 x10^9/L)	Discontinue RAD001.
Grade 3 Neutropenia (neutrophils <1, ≥0.5 x10^9/L)	Interrupt RAD001 until recovery to grade ≤1 (neutrophils ≥ 1.5 x 10^9/L). Then resume RAD001 at the initial dose. If ANC again returns to Grade 3, hold RAD001 until the ANC ≥ 1.5 x 10^9/L. Then resume RAD001 dosing at the lower dose level. Discontinue patient from study therapy for a third episode of grade 3 neutropenia. If clinically indicated, patient with prolonged neutropenia may be treated with growth factors.
Grade 4 Neutropenia (neutrophils < 0.5 x10^9/L)	Interrupt RAD001 until recovery to grade (1 (neutrophils ≥ 1.5 x 109/L). Then resume RAD001 at the lower dose level. If grade 3 or grade 4 neutropenia occurs despite this dose reduction, discontinue RAD001. . If clinically indicated, patient with prolonged neutropenia may be treated with growth factors.
Grade 3 febrile neutropenia (not life-threatening)	Interrupt RAD001 until resolution of fever and neutropenia to grade ≤ 1. Hold further RAD001 until the ANC ≥ 1,500/mm3 and fever has resolved. Then resume RAD001 at the lower dose level. If febrile neutropenia recurs, discontinue RAD001. If clinically indicated, patient with prolonged neutropenia may be treated with growth factors.
Grade 4 febrile neutropenia (life-threatening)	Discontinue RAD001.
Any hematological or non-hematological toxicity requiring interruption for ≥ 3 weeks	Discontinue RAD001

*Grade 3 hyperlipidemia (hypercholesterolemia and/or hypertriglyceridemia) should be managed using medical therapies (see Sec. 3.2.5.2).

Management of non-infectious pneumonitis

Both asymptomatic radiological changes (grade 1) and symptomatic non-infectious pneumonitis (grade 2 = not interfering with activities of daily living or grade 3 = interfering with activities of daily living and oxygen indicated) have been noted in patients receiving RAD001 therapy. Non-infectious pneumonitis has been associated with RAD001 and other mTOR inhibitors (Atkins 2004). In order to monitor for asymptomatic (grade 1) pulmonary infiltrates, a chest X-ray is required if a CT scan of chest is not used for bi-monthly disease evaluations. Additional chest CT scans may be performed, when clinically necessary. If non-infectious pneumonitis develops, a consultation with a pulmonologist should be considered. If the patient develops grade 3 pneumonitis, treatment with RAD001 should be interrupted and the patient should be treated as medically indicated (short course corticosteroids, oxygen, etc).

Management of non-infectious pneumonitis suspected to be associated with RAD001 and dose modifications instructions are provided in Table 6-2 and Table 6-3, respectively.

Table 6-5 Management of non-infectious pneumonitis

Worst Grade Pneumonitis	Required Investigations	Management of Pneumonitis	RAD001 Dose Adjustment
Grade 1	CT scans with lung windows and pulmonary function testing including: spirometry, DLCO, and room air O_2 saturation at rest. Repeat chest x-ray/CT scan every 2 Cycles until return to baseline.	No specific therapy is required	Administer 100% of RAD001 dose.
Grade 2	CT scan with lung windows and pulmonary function testing including: spirometry, DLCO, and room air O_2 saturation at rest. Repeat each subsequent Cycle until return to baseline. Consider bronchoscopy *	Symptomatic only. Prescribe corticosteroids if cough is troublesome.	Reduce RAD001 dose until recovery to ≤ Grade 1. RAD001 may also be interrupted if symptoms are troublesome. Patients will be withdrawn from the study if they fail to recover to ≤ Grade 1 within 3 weeks.
Grade 3	CT scan with lung windows and pulmonary function testing including: spirometry, DLCO, and room air O_2 saturation at rest.; Repeat each subsequent Cycle until return to baseline. Bronchoscopy is recommended *	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. Patients will be withdrawn from the study if they fail to recover to ≤ Grade 1 within 2 weeks.
Grade 4	CT scan with lung windows and required pulmonary function testing includes: spirometry, DLCO, and room air O_2 saturation at rest. Repeat each subsequent Cycle until return to baseline. Bronchoscopy is recommended *.	Prescribe corticosteroids if infective origin is ruled out. Taper as medically indicated.	Discontinue treatment.

*A bronchoscopy with biopsy and/or bronchoalveolar lavage is recommended.

Other Known Undesirable Side Effects of everolimus

The data described below reflect exposure to everolimus (n=274) and placebo (n=137) in a randomized phase III study for the treatment of metastatic renal cell carcinoma. In total, 165 patients were exposed to everolimus 10 mg/day for ≥4 months. The median age of patients was 61 years (range 27 to 85). The most common adverse reactions (incidence ≥10%) were stomatitis, rash, fatigue, asthenia, diarrhea, anorexia, nausea, mucosal inflammation, vomiting, cough, peripheral edema, infections, dry skin, epistaxis, pruritus, and dyspnea. The most common grade 3-4 adverse reactions (incidence ≥2%) were infections, stomatitis, fatigue, and pneumonitis.

The median duration of blinded study treatment was 141 days (range 19 to 451) for patients receiving everolimus and 60 days (range 21 to 295) for those receiving placebo. The rates of treatment-emergent adverse reactions resulting in permanent discontinuation were 7% and 0% for the everolimus and placebo treatment groups, respectively. Most treatment-emergent adverse reactions were grade 1 or 2 in severity. Grade 3 or 4 treatment-emergent adverse reactions were reported in 39% versus 7% of patients receiving everolimus and placebo, respectively. Deaths due to acute respiratory failure (0.7%), infection (0.7%), and acute renal failure (0.4%) were observed on the everolimus arm.

Everolimus has immunosuppressive properties and may predispose patients to bacterial, fungal, viral or protozoan infections, including infections with opportunistic pathogens. Localized and systemic infections, including pneumonia, other bacterial infections, invasive fungal infections, such as aspergillosis or candidiasis and viral infections including reactivation of hepatitis B virus, have been described in patients taking everolimus. Some of these infections have been severe (e.g. leading to respiratory or hepatic failure) and occasionally have had a fatal outcome.

Physicians and patients should be aware of the increased risk of infection with everolimus. Treat pre-existing infections prior to starting treatment with everolimus. While taking everolimus, be vigilant for symptoms and signs of infection; if a diagnosis of infection is made, institute appropriate treatment promptly and consider interruption or discontinuation of everolimus. If a diagnosis of invasive systemic fungal infection is made, discontinue everolimus and treat with appropriate antifungal therapy.

Reactivation of Hepatitis B (HBV) has been observed in patients with cancer receiving chemotherapy (Yeo 2004). Sporadic cases of Hepatitis B reactivation have also been seen in this setting with everolimus. Use of antivirals during anti-cancer therapy has been shown to reduce the risk of Hepatitis B virus reactivation and associated morbidity and mortality (Loomba 2008). A detailed assessment of Hepatitis B/C medical history and risk factors must be done for all patients at screening, with testing performed prior to the first dose of everolimus.

Hypersensitivity reactions manifested by symptoms including, but not limited to, anaphylaxis, dyspnea, flushing, chest pain or angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) have been observed with everolimus.
Hyperglycemia has been reported in clinical trials. Monitoring of fasting serum glucose is recommended prior to the start of everolimus therapy and periodically thereafter. Optimal glycemic control should be achieved before starting a patient on everolimus. Mouth ulcers,

stomatitis and oral mucositis have been seen in patients treated with everolimus. In such cases topical treatments are recommended, but alcohol- or peroxide-containing mouthwashes should be avoided as they may exacerbate the condition. Antifungal agents should not be used unless fungal infection has been diagnosed.

Elevations of serum creatinine, usually mild, have been reported in clinical trials. Monitoring of renal function, including measurement of blood urea nitrogen (BUN) or serum creatinine, is recommended prior to the start of everolimus therapy and periodically thereafter.

Decreased hemoglobin, lymphocytes, platelets and neutrophils have been reported in clinical trials. Monitoring of complete blood count is recommended prior to the start of everolimus therapy and periodically thereafter.

Everolimus is not recommended in patients with severe hepatic impairment, (Child-Pugh class C).

The use of live vaccines and close contact with those who have received live vaccines should be avoided during treatment with everolimus.

Hypophosphatemia, hypomagnesemia, hyponatremia and hypocalcemia have been reported as serious adverse reactions. Electrolytes should be monitored in patients treated with everolimus.

More detailed information regarding everolimus reported suspected toxicities and individual cases is provided in the [Investigator's Brochure].

Management of Hepatitis reactivation

In cancer patients with hepatitis B, whether carriers or in chronic state, use of antivirals during anticancer therapy has been shown to reduce the risk of hepatitis B virus (HBV) reactivation and associated HBV morbidity and mortality.[51]

Monitoring and prophylactic treatment for hepatitis B reactivation

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

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

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

Test	Result	Result	Result	Result	Result
	Monitor HBV-DNA approximately every 4 weeks		every 4 weeks		

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

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

For hepatitis B reactivation, definition and management guidelines, see Table 6-7 Guidelines for management of hepatitis B.

Table 6-7 Guidelines for management of hepatitis B

HBV reactivation (with or without clinical signs and symptoms)*	
For patients with baseline results: Positive HBV-DNA OR positive HBsAg --- reactivation is defined as: [Increase of 1 log in HBV-DNA relative to baseline HBV-DNA value OR new appearance of measurable HBV-DNA] AND ALT elevation x 5 ULN	Treat: Start a second antiviral AND Interrupt study drug administration until resolution: ≤ grade 1 ALT (or baseline ALT, if > grade 1) and ≤ baseline HBV-DNA levels If resolution occurs within ≤ 28 days study drug should be re-started at one dose lower, if available. If the patient is already receiving the lowest dose of study drug according to the protocol, the patient should restart at the same dose after resolution. Both antiviral therapies should continue at least 4 weeks after last dose of study drug. If resolution occurs > 28 days Patients should discontinue study drug but continue both antiviral therapies at least 4 weeks after last dose of study drug.
For patients with baseline results: Negative HBV-DNA and HBsAg AND [Positive HBs Ab (with no prior history of vaccination against HBV), OR positive HBc Ab] --- reactivation is defined as: New appearance of measurable HBV-DNA	Treat : Start first antiviral medication AND Interrupt study drug administration until resolution: ≤ baseline HBV-DNA levels If resolution occurs within ≤ 28 days study drug should be re-started at one dose lower, if available. If the patient is already receiving the lowest dose of study drug according to the protocol, the patient should restart at the same dose after resolution. Antiviral therapy should continue at least 4 weeks after last dose of study drug. If resolution occurs > 28 days Patients should discontinue study drug but continue antiviral therapy at least 4 weeks after last dose of study drug.

* All reactivations of hepatitis B are to be recorded as grade 3 (CTCAE v 4.0 Metabolic Laboratory/Other: Viral Re-activation), unless considered life threatening by the investigator; in which case they should be recorded as grade 4 (CTCAE v 4.0 Metabolic Laboratory/Other: Viral Re-activation). Date of viral reactivation is the date on which **both** DNA and ALT criteria were met (e.g. for a patient who was HBV-DNA positive on 01-JAN-10 and whose ALT reached ≥ 5 × ULN on 01-APR-10, the date of viral reactivation is 01-APR-10).

Monitoring for hepatitis C

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

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

For definition of hepatitis C reactivation and the management guidelines, see Table 6-8 Guidelines for management of hepatitis C.

Table 6-8 Guidelines for management of hepatitis C

HCV reactivation*	
For patients with baseline results: Detectable HCV-RNA, reactivation is defined as: ALT elevation x 5 ULN	Discontinue study drug
For patients with baseline results: Knowledge of past hepatitis C infection with no detectable HCV-RNA, reactivation is defined as: New appearance of detectable HCV-RNA	Discontinue study drug

* All reactivations of hepatitis C are to be recorded as grade 3 (CTCAE v4.0 Metabolic Laboratory/Other: Viral Re-activation), unless considered life threatening by the investigator; in which case they should be recorded as grade 4 (CTCAE v 4.0 Metabolic Laboratory/Other: Viral Re-activation).

Management of stomatitis/oral mucositis/mouth ulcers

Stomatitis/oral mucositis/mouth ulcers due to everolimus should be treated using local supportive care. Please note that investigators in earlier trials have described the oral toxicities associated with everolimus as mouth ulcers, rather than mucositis or stomatitis. If your examination reveals mouth ulcers rather than a more general inflammation of the mouth, please

classify the adverse event as such. Please follow the paradigm below for treatment of stomatitis/oral mucositis/mouth ulcers:

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

Note: Stomatitis/oral mucositis should be appropriately graded using the functional grading given on the NCI-CTC for adverse events, version 4.0.

Management Guidelines for Hyperlipidemia and Hyperglycemia

Treatment of hyperlipidemia should take into account the pre-treatment status and dietary habits. Blood tests to monitor hyperlipidemia must be taken in the fasting state.. Hyperlipidemia and hypertriglyceridemia should be treated according to local best clinical practice. Patients should be monitored clinically and through serum chemistry for the development of rhabdomyolysis and other adverse events as required in the product label/data sheets for HMG-CoA reductase inhibitors.

Hyperglycemia has been reported in clinical trials. Monitoring of fasting serum glucose is recommended prior to the start of everolimus therapy and periodically thereafter. Optimal glycemic control should be achieved before starting trial therapy.

Hyperglycemia is known to be associated with the treatment with somatostatin analogues (SSA). Clinical studies of pasireotide in healthy volunteers and in patients with Cushing's disease, acromegaly or carcinoid syndrome have reported transient, asymptomatic increases in fasting and postprandial glucose levels. Novartis has conducted 2 clinical studies ([sSOM230B2216] and [SOM230B2124) to further understand the mechanism of pasireotide-induced hyperglycemia and to evaluate the clinical utilotiy of anti-diabetes agents in the management of pasreiotide-induced hyperglycemia. Preliminary results suggest that pasireotide induces insulin suppression particularly in the postprandial period, as being the key mechanistic driver of hyperglycemia. Based on the mechanisms of pasireotide-induced hyperglycemia and findings from the [SOM230B2124] study, appropriate management for the pasireotide-induced hyperglycemia includes the use of oral anti-diabetic agents for mild to moderate hyperglycemia,

such as incretin enhancers (e.g. GLP-1 analogues or DPP4 inhibitors or insulin secretagogues). Metformin is not recommended. Insulin should be used for moderate to sever hyperglycemia.

Clinical monitoring and self-monitoring of blood glucose level

In addition to the laboratory evaluation of blood glucose level at the regularly scheduled visits, patients are recommended to self-monitor their blood glucose (fasting and postprandial assessment) using a home glucometer. This self-monitoring guidance is to provide adequate and proactive monitoring so that pasireotide-induced hyperglycemia can be adequately managed and treated.

Patients with the history of increased blood glucose level in the past are recommended to self-monitor blood glucose twice a day (fasting and two hours after a meal). Patients with normal blood glucose level without history of elevated blood glucose levels in the past should be recommended to measure blood glucose level every other day. Patients should be instructed to record the blood glucose value in a glucose diary and contact the study site immediately, if the glucose level rises beyond 130mg/dL in a fasting state or 180 mg/dL after a meal.

During the study, all patients with HbA1c = 7 % and or fasting plasma glucose (FPG) > 130 mg/dL (7.2 mmol/L), or 2-hour post-prandial capillary glucose (PPG) = 180 mg/dL (10 mmol/L) on two consecutive measurements that are within 14 days, should be considered for the following:

- Referral to a diabetes specialist for evaluation and appropriate management
- Provided information and receive teaching on diabetes disease management
- Monitoring of blood glucose by fingerstick twice daily (fasting morning blood glucose and 2-hour post-meal) if not already done. Patients, who monitor blood glucose should keep a diary of their glucose values and present the collected data to their physician/ diabetes specialist for evaluation and appropriate management.

Management Guidelines for ECG Monitoring for Prolonged QT

ECG frequency for SOM230 LAR studies:

ECG monitoring is recommended at the following time points:

- Baseline (before SOM230 LAR injection)
- 21 days after 1st SOM230 LAR injection
- 21 days after 3rd SOM230 LAR injection
- Cycle 6 (before SOM230 LAR injection)
- Every 3 cycles after Cycle 6
- ECG should be done at any time when clinically indicated

ECG procedures in the event of prolonged QTc

- If at any visit a QTcF>480 msec is observed, the following steps need to be taken:
    - A cardiology consultation must be sought as soon as practicable but within 7 days of the initial abnormal ECG and the cardiologist must re-evaluate the ECG (this can be done by the central cardiologist if the trial has one).
    - If a QTcF>480msec is NOT confirmed, no further action needs to be taken.

- If a QTcF>480msec is confirmed, a cardiologist must perform a thorough examination (such as reviewing baseline ECG, concurrent medications and performing a cardiovascular examination (including at least a cardiac auscultation)) to assess the patient for cardiovascular risk factors.

- If based upon the assessment by the cardiologist, the investigator considers that there is an acute cardiovascular safety risk and that the patient should not continue with study medication, the patient needs to be discontinued immediately (discontinuation criteria to be followed).

- If following the examination by the cardiologist, the investigator considers that there is not an acute cardiovascular safety risk and that the patient could continue to receive study medication, a Holter ECG (24hr) must be recorded soon as practicable but within 7 days after the initial abnormal ECG or at the next SOM230 LAR injection. The Holter-ECG must be started 30min prior to an injection of study medication.

- The results of the ECGs, cardiac examination, Holter-ECGs and the recommendation by the cardiologist must be evaluated by the investigator to determine whether the patient should continue in the trial or not (discontinuation criteria to be followed).

- **C_{max} drug concentration visit**: If at a Day 21 visit (day 21 after any injection of Pasireotide/Octreotide LAR) a C_{max} QTcF>480 msec is observed for the first time for a patient at a given dose level, the following steps need to be taken:
  - A cardiology consultation as described in the preceding section must be sought as soon as practicable but within 7 days after the initial abnormal ECG and prior to the next Pasireotide/ Octreotide LAR injection.
  - All steps described in the preceding section must be followed, however if a Holter ECG is required, a 24hour Holter ECG must be recorded when the patient receives the next scheduled Pasireotide/ Octreotide LAR injection. The Holter ECG should be started 30min prior to the injection.

- **Trough concentration visit e.g. day 1 of a new cycle:** If at any visit a trough level QTcF>480 msec is observed for the first time for a patient at a given dose level, the following steps need to be taken:
  - A cardiology consultation as described in the preceding section must be sought as soon as practicable but within 7 days after the initial abnormal ECG and prior to the next Pasireotide/Octreotide LAR injection.
  - All steps described in the preceding section must be followed; however if a Holter-ECG is required, a 24hour Holter-ECG must be recorded and evaluated prior to the next injection of Pasireotide/Octreotide LAR. The Pasireotide/Octreotide injection must be postponed until the Holter-ECG results are available with a maximal permissible delay of 7 days. If the outcome of the cardiac evaluation is that the patient may receive a further dose of Pasireotide/ Octreotide LAR, then a second 24hr Holter-ECG must be done on the day of the LAR injection.

- This Holter ECG should be started 30min prior to the injection.

Table 6-8a: Guidelines for dose modification for QT prolongation while on SOM230

Adverse event	Action
*Grade ≤ 2	No study drug adjustments
*Grade ≥ 3 and judged as at least possibly drug related	· Further injections should be held for at least 7 days and until toxicity improves to ≤ Grade 1. · If toxicity improves to grade ≤ 1 within 7 days, no dose reduction is required. · If toxicity improves to grade ≤ 1 in 8-14 days, resume treatment with a single dose level reduction. · If toxicity improves to grade ≤ 1 in 15-28 days, resume treatment with two dose level reductions. · If toxicity fails to improve to grade ≤ 1 within 28 days, study treatment must be discontinued unless there is clear evidence of therapeutic benefit from the study regimen, in which case continued treatment is left to the discretion of the Overall Principal Investigator. · If any toxicity recurs at CTCAE grade ≥ 3, treatment must be discontinued.
QTc CTC grade 1 (≤ 480 msec)	· No study drug adjustments
QTc CTC grade 2 (> 480 or ≤ 500 msec) either drug related or drug unrelated	Patient is to be referred to a cardiologist for evaluation and appropriate management, and the patient can remain in the study · Patient's study drug dose will be reduced to 1 dose level down
QTc CTC grade ≥ 3 (> 500 msec)	Discontinue study drug Follow patient for safety[A]

SOM230 Management Guidelines for Suspected Hepatic Toxicity

In case of suspected SOM230-related hepatic injury manifesting as abnormal LFTs, the following steps should be followed within 72 hours of awareness of abnormal liver function tests:

- Liver-directed medical history and physical examination (i.e. assess occupational hazards, concomitant medications including OTC meds, intercurrent illness, etc)
- Liver chemistry tests: ALT, AST, total bilirubin, (fractionate to direct/indirect bilirubin if total bilirubin is > 2.0x ULN), Alb, PT (INR), ALP, and GGT
- Hepatitis screen:
  - anti-HAV, IgM (to confirm acute hepatitis A)
  - HbsAg, Anti-HBc
  - anti-HCV (if positive, PCR viral load should be assessed),
  - Anti-HEV
  - ANA antibodies, anti-smooth muscle anti-bodies, CMV, EBV
- Perform abdominal ultrasound (liver and biliary tree)

Liver chemistry tests should be monitored every 3-4 days until resolution or return to baseline status.

- For ALT or AST > 5x ULN and ≤ 8x ULN:
    - Study medication should be temporarily interrupted and liver chemistry tests monitored every 3-4 days until resolution or return to baseline
    - If resolution or return to baseline does not occur after 2 weeks, the patient should be discontinued.
    - If ALT or AST returns to less than 5x ULN, study drug can be resumed and patient can continue study per protocol
    - If ALT or AST rises above 5x ULN anytime after study drug is resumed, then study drug should be discontinued immediately.

Follow-up LFT monitoring will take place at 3-4 day intervals (Table 2).

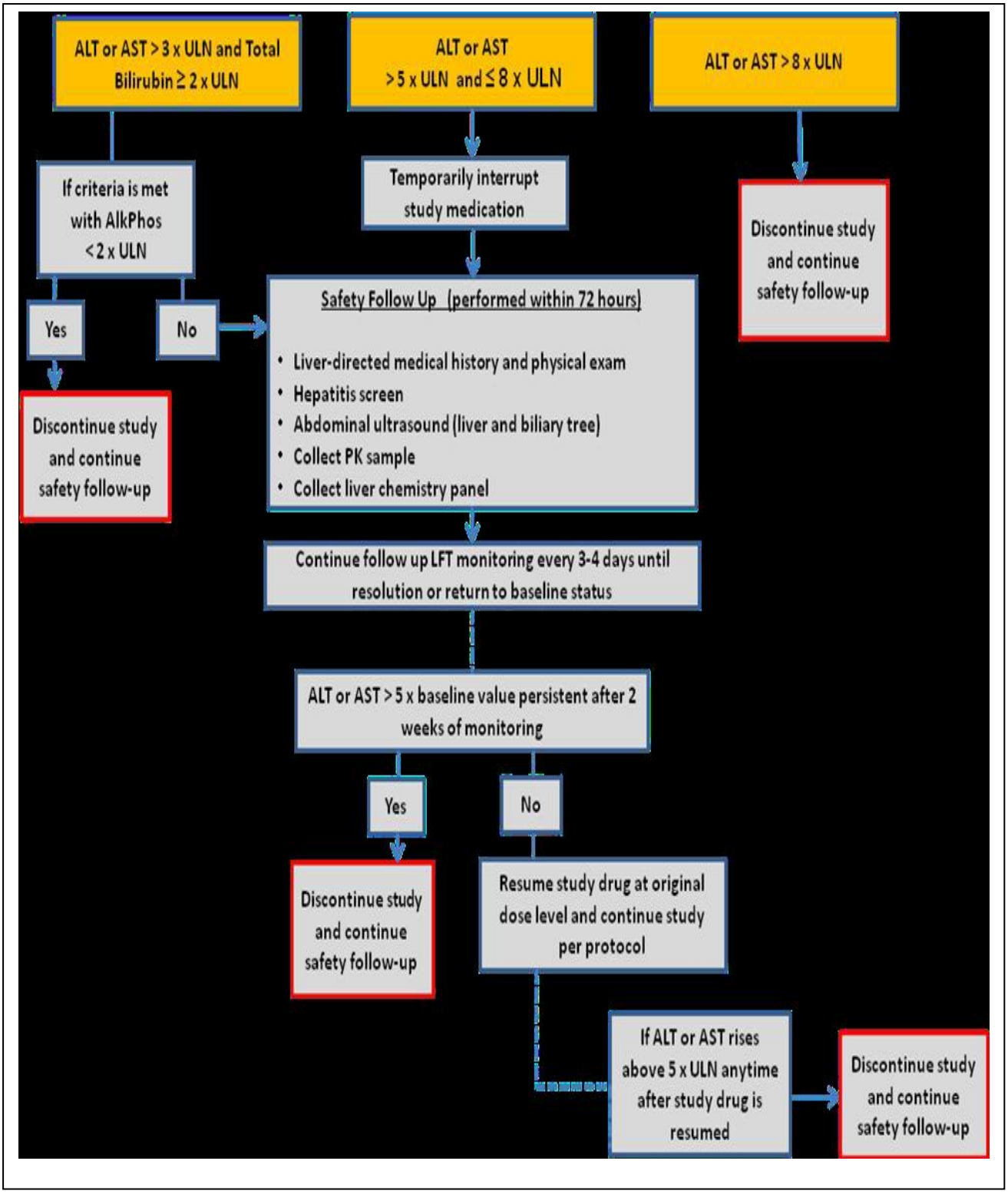
SOM230 Hepatic-related discontinuation criteria

Study medication should be discontinued immediately if any of the discontinuation criteria below are met:

- ALT or AST > 3x ULN and Total Bilirubin > 2x ULN and ALP < 2x ULN
- ALT or AST > 5x ULN and ≤ 8x ULN persistent for more than 2 weeks
- ALT or AST > 8x ULN

Re-challenge of study medication is prohibited once discontinuation criteria are met.

SOM230 LFT Management Algorithm



Follow-up for toxicities

Patients who interrupt or permanently discontinue SOM230 and RAD001 due to an adverse event or abnormal laboratory value should be followed at least weekly for 28 days after the last dose of SOM230 and RAD001, and subsequently at monthly intervals until resolution or stabilization of the event, whichever comes first. If a patient requires a SOM230 and RAD001 dose delay of > 21 days from the intended day of the next scheduled dose, then the patient should be discontinued from the study.
All patients will be followed for adverse events and serious adverse events for 28 days following the last dose of SOM230 and RAD001.

6.8 Other concomitant medications

Concomitant therapy

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 Concomitant medications/Significant non-drug therapies taken ≤ 30 days prior to start and after start of study drug, including physical therapy and blood transfusions, should be recorded.

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 medication should be given to patients. If such agents are required for a patient then the patient must first be withdrawn from the study.
- Co-administration with strong inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, ritonavir) or P-glycoprotein (PgP) should be avoided
- Seville orange, star fruit, grapefruit and their juices affect P450 and PgP activity. Concomitant use should be avoided
- Co-administration with moderate CYP3A4 inhibitors (e.g., erythromycin, fluconazole) or PgP inhibitors should be used with caution. If patient requires co-administration of moderate CYP3A4 inhibitors or PgP inhibitors, reduce the dose of RAD001 to 5 mg daily. Additional dose reductions to 5 mg every other day may be required to manage toxicities. If the inhibitor is discontinued the RAD001 dose should be returned to the dose used prior to initiation of the moderate CYP3A4/PgP inhibitor.
- Avoid the use of strong CYP3A4 inducers. If patient requires co-administration of strong CYP3A4 inducers (i.e., phenytoin, carbamazepine, rifampin, rifabutin, Phenobarbital, St. John's wort)**, the patient should be monitored as per protocol and discontinued from study treatment if progression occurs.** An increase in the dose of RAD001 from 10 mg up to 20 mg daily should be considered, using 5 mg increments. Enzyme induction usually occurs within 7-10 days, therefore RAD001 dose should be increased to 15 mg daily, 7 days

after the start of the inducer therapy. If no safety concerns are seen within the next 7 days, the dose can be increased again to 20 mg daily. This dose of RAD001 is intended to achieve similar AUC to the range observed without inducers. However, there are no clinical data with this dose adjustment in patients receiving strong CYP3A4 inducers. If the strong inducer is discontinued the RAD001 dose should be returned to the dose used prior to initiation of the strong CYP3A4/PgP inducer.

- No chronic treatment with systemic steroids or another immunosuppressive agents (at a dose equivalent of greater than 20 mg prednisone per day) or other immunosuppressive agents). Topical or inhaled corticosteroids are allowed.
- RAD001 may affect the response to vaccinations making the response to the vaccination less effective. Live vaccines should be avoided while a patient is treated with RAD001.
- QT prolonging medication - the use of concomitant medications that might lead to QT prolongation is prohibited and requires the discontinuation of the patient prior to starting the respective QT prolonging medication.

Oral anticoagulants such as warfarin are CYP2C9 substrates and, as such, no interaction with RAD001 is expected. However, drug-drug interaction studies between macrolide antibiotics and warfarin have produced mixed outcomes and the disparity in these findings has led to the conclusion that multiple factors may alter the clearance of warfarin. The co-administration of RAD001 and oral anticoagulants is possible but should be subject to verification of coagulation (INR) once steady state is reached (after one week's treatment).

Examples are provided in Table 6-9. A comprehensive list of cytochrome P450 isoenzymes and CYP3A4 inhibitors, inducers, and substrates can be found at http://medicine.iupui.edu/flockhart. This website is continually revised and should be checked frequently for updates.

Table 6-9 Examples of clinically relevant drug interaction: substrates, inducers and inhibitors of isoenzyme CYP3A.

Substrates (competitive inhibition)	
Antibiotics[1]: **clarithromycin*** **erythromycin** **telithromycin*** **Anti-arrhythmics:** **quinidine** **Benzodiazepines:** **alprazolam** **diazepam** **midazolam** **triazolam** **Immune Modulators:** **cyclosporine** **tacrolimus (FK506)** **HIV Protease Inhibitors:** **indinavir*** **ritonavir*** **saquinavir*** **Prokinetic:** **cisapride** **Antihistamines:** **astemizole** **chlorpheniramine61**	**Calcium Channel Blockers:** **amlodipine** **diltiazem** **felodipine** **nifedipine** **nisoldipine** **nitrendipine** **verapamil** **HMG CoA Reductase Inhibitors[2]:** **atorvastatin** **cerivastatin** **lovastatin** **simvastatin** **Miscellaneous:** **aprepitant** **buspirone** **haloperidol** **methadone** **pimozide** **quinine** **sildenafil** **tamoxifen** **trazodone** **vincristine**
Inducers	
Carbamazepine **Phenobarbital** **Phenytoin*** **Rifabutin***	**Rifampin*** **St John's wort** **Troglitazone**
Inhibitors	
Amiodarone **Cimetidine** **Clarithromycin** **Delaviridine** **Diltiazem** **Erythromycin** **Fluvoxamine*** **Grapefruit juice** **Sevilla orange**	**Indinavir** **Itraconazole*** **Ketoconazole*** **Voriconazole*** **Posaconazole*** **Mibefradil** **Nefazodone*** **Nelfinavir*** **Troleandomycin** **Verapamil**

Based on: Ingelman-Sundberg M, Human drug metabolising cytochrome P450 enzymes: properties and polymorphisms, Naunyn Schmiedebergs Arch Pharmacol. 2004 Jan;369(1):89-104. and [http://www.medicine.iupui.edu/flockhart/clinlist.htm as of July 13, 2006]

*** asterisk denotes strong inhibition/ induction**

Please note:

- **strong inhibitor implies that it can cause ≥5-fold increase in 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 50-80% decrease in clearance of sensitive CYP substrates.**

  (Distinction is not always categorical as interaction can vary according to conditions).

1. **Macrolide antibiotics: Azithromycin is not a CYP3A substrate. It may therefore be employed where**

antibiotherapy with a macrolide is desirable in a patient being treated with RAD001

2. **Statins: Atorvastatin and pravastatin may be associated with RAD001, since a PK interaction study has shown that there is no relevant PK interaction.**

6.9 Study drug discontinuation

Patients experiencing unacceptable toxicity (AE grade 3 or higher) that the investigator considers directly attributable to the study drug should have their dose adjusted as per dose modification guidelines in Table 6-2. If a patient has already decreased 2 dose levels, no further dose reduction is permitted, and the patient will be permanently discontinued from treatment. A delay of more than 21 days in resuming study drug due to treatment-emergent adverse event will result in the withdrawal of the patient from the study (non-treatment related delay of more than 21 days but no more than 28 consecutive days may be allowed to resume therapy after discussion with the overall PI). Patient so withdrawn should undergo the required end of study procedures follow-up post treatment discontinuation.

Premature patient withdrawal/End of treatment

Patients **may** voluntarily withdraw from the study or be dropped from it at the discretion of the investigator at any time. Patients may be withdrawn from the study if any of the following occur:

- Disease progression or lack of efficacy
- Uncontrolled diabetes mellitus (DM)
- Pregnancy
- Adverse event(s)
- Abnormal laboratory value(s)
- Abnormal test procedure result(s)

QT-related discontinuation criteria

  - Confirmed QTcF >480msec and discontinuation recommended by a cardiologist
  - New occurrence of clinically significant/symptomatic bradycardia
  - Increased risk of QT prolongation by use of QT prolonging medication
  - Hypokalemia (<3.5 mmol/L) or hypomagnesaemia (<0.7 mmol/L) confirmed by repeat testing that is either a new finding or accompanied by vomiting or diarrhea and not corrected by treatment
- Protocol violation
- Subject withdrew consent
- Lost to follow-up
- Administrative problems
- Death
- Disease progression
- Treatment duration completed as per protocol

7 Visit schedule and assessments

Table 7-1 lists all of the assessments and indicates the visits at which they are to be performed with an "X". All data obtained from these assessments must be supported in the patient's source documentation. To accommodate scheduling challenges, the required assessments may be performed within +/- 2 days of the specified scheduled dates.

Hepatitis Screening

A detailed assessment of hepatitis B/C medical history and risk factors must be done for all patients at screening. Patients with positive hepatitis B and/or hepatitis C test results are ineligible for the study. Testing for hepatitis B viral load and serologic markers: HBV-DNA, HBsAg, HBs Ab, and HBc Ab and HCV RNA PCR are required at screening for all patients in the following risk categories:

o All patients who currently live in (or have lived in) Asia, Africa, Central and South America, Eastern Europe, Spain, Portugal, and Greece.
[http://wwwnc.cdc.gov/travel/yellowbook/2010/chapter-2/hepatitis-b.aspx#849]

o Patients with any of the following risk factors:

- known or suspected past hepatitis B infection,
- blood transfusion(s) prior to 1990,
- current or prior IV drug users,
- current or prior dialysis,
- household contact with hepatitis B infected patient(s),
- current or prior high-risk sexual activity,
- body piercing or tattoos,
- mother known to have hepatitis B
- history suggestive of hepatitis B infection, e.g., dark urine, jaundice, right upper quadrant pain.

o Additional patients at the discretion of the investigator

Testing for hepatitis C should be performed using quantitative RNA-PCR at screening for all patients in the following risk categories:

o known or suspected past hepatitis C infection (including patients with past interferon 'curative' treatment),
o blood transfusions prior to 1990,
o current or prior IV drug users,
o current or prior dialysis,
o household contact of hepatitis C infected patient(s),
o current or prior high-risk sexual activity,
o body piercing or tattoos,
o At the discretion of the investigator, additional patients may also be tested for hepatitis C.

Table 7-1 Schedule of Events and Assessments

Patient assessments and the visits at which they are to be performed are indicated with an "X". All data obtained from these assessments must be supported in the patient's source documentation.

In order to accommodate scheduling challenges, the required assessments may be performed within +/- 2 days of the specified scheduled dates.

Examination	**Screening/ Baseline**		**Pasireotide i.m. Everolimus p.o**									**End of Study**	**Follow-up**
Visit number	1	C1D1	C1D22*	C2D1	C2D22*	C3D1	C3D22*	C4D1	C5D1	C6D1	C7D1[$]		
Informed consent	X												
Demography	X												
History/ current medical conditions	X	X	X	X		X	X	X	X	X	X[#]	X	X
Inclusion and exclusion criteria	X												
Diagnosis and stage of cancer	X												
Prior and ongoing therapy	X[a]												X
Randomization	X												
Physical exam	X	X		X		X		X	X	X	X[#]	X	
Vital signs	X	X	X	X		X	X	X	X	X	X[#]	X	
ECG	X*	X	X*				X*			X*			
Gallbladder ultrasound	X[b]												
Performance Status	X	X		X		X		X	X	X	X[#]	X	
Hematology	X	X[&]		X		X		X	X	X	X[#]	X	
Glycosylated hemoglobin	X[c]	X[&]											
PT, PTT	X	X[&]											
CMP including fasting cholesterol and triglyceride[@]	X	X[&]		X		X		X	X	X	X[#]	X	

Table 7-1 Schedule of Events and Assessments

Patient assessments and the visits at which they are to be performed are indicated with an "X". All data obtained from these assessments must be supported in the patient's source documentation.

In order to accommodate scheduling challenges, the required assessments may be performed within +/- 2 days of the specified scheduled dates.

Examination	**Screening/ Baseline**		**Pasireotide i.m. Everolimus p.o**									**End of Study**	**Follow-up**
LFT assessment[+]	X	X	X	X	X	X		X	X	X	X[#]	X	
Hepatitis screening	X[%]												
Tumor Markers: Medullary: Free T4, TSH, CEA, Calcitonin and chromogranin A; Differentiated: TSH, free T4, thyroglobulin, thyroglobulin antibodies.	X					X			X		X[#]		
Biomarker Samples (IGF-1, optional PBMC)	X[d]					X			X		X		
Urinalysis	X	X[&]											
Pregnancy test	X	X[&]											
Archival tissue collection	X[e]												
MRI/CT Scan	X[f]					X			X		X		
Study Drug Administration		X		X		X		X	X	X	X		
Response Assessment						X			X		X		
Adverse events	X	X		X		X		X	X	X	X	X	X
Concomitant medications	X	X		X		X		X	X	X	X	X	

[$] cycle 7 and beyond

[&] need not be repeated if within normal institutional reference limits and obtained within 7 days of C1D1

[@] Albumin, alkaline phosphatase, total bilirubin, calcium, chloride, creatinine, magnesium, potassium, total protein, SGOT, SGPT, sodium, bicarbonate, total protein, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, urea/BUN γ-GT, fasting blood glucose, phosphorous, [at screening and as clinically indicated: CPK, HbA1c, LDH lipase, α-amylase and uric acid]. If the total bilirubin concentration is increased above 1.5 times the upper normal limit (UNL), total bilirubin should be differentiated into the direct and indirect reacting bilirubin (patient may be treated if direct bilirubin is < 1.5 x ULN)

[#] repeat visit every other cycle until progression or withdrawal from study; cholesterol and triglyceride only for patients on everolimus

* Day 22 assessments only applicable to patients on pasireotide; EKG to be obtained only for patients on pasireotide at the following timepoints

- Baseline (before pasireotide LAR injection)
- 21 days after 1st pasireotide LAR injection
- 21 days after 3rd pasireotide LAR injection
- Cycle 6 (before pasireotide LAR injection)
- Every 3 cycles after Cycle 6
- ECG should be done at any time when clinically indicated

[%] All patients should be screened for hepatitis risk factors and any past illnesses of hepatitis B and hepatitis C infection using clinical history as detailed in the subsection on hepatitis screening. Patients with viral hepatitis C risk factors should be screened for HCV RNA-PCR. Patients on antiviral prophylaxis treatment or positive HBV antibodies should be tested for HBV-DNA on Cycle 1 Day 1 and Day 1 of all subsequent cycles (every 28 days) to monitor for re-activation. If re-activation is confirmed, everolimus must be interrupted or discontinued according to the guidance in Tables 6-7 and 6-8. Patients with positive HCV RNA-PCR results at screening and/or a history of past infection (even if treated and considered 'cured') should have HCV RNA-PCR testing performed on Cycle 1 Day 1 and Day 1 of all subsequent cycles (every 28 days) to monitor for reactivation. Everolimus must be discontinued if HCV reactivation is confirmed according to the guidance in Table 3-4.

+: For patients receiving pasireotide, liver function tests [ALT, AST, total bilirubin, (fractionate to direct/indirect bilirubin if total bilirubin is > 2.0x ULN), Alb, PT (INR), Alkaline Phosphatase, and GGT] must be assessed at screening, baseline (C1D1), Day 22 (C1D22) after the first injection, Day 29 (C2D1), Day 50 (C2D22), Day 57 (C3D1) and Day 85 (C4D1). After Day 85, monitoring should follow the regular CMP schedule. The Day 22 and Day 50 LFTs must be available and assessed prior to dosing on Day 29 (2nd injection) and Day 57 (3rd LAR injection).

a: not more than 1 prior systemic therapy for patients's current cancer allowed; prior radiation therapy is allowed.

b: obtain only if clinically indicated; patient found with symptomatic gallstones are excluded; patients with asymptomatic incidental gall stone may be allowed at the discretion of the PI

c: repeat as necessary if patient is a known diabetic or if baseline values elevated

d: obtain peripheral blood sample for IGF-1 at the end of every even number cycle (up to end of cycle 6) as part of restaging evaluation

e: if archival tissue cannot be obtained, upto-20 unstained slides may be collected if available.

f: same modality should be used for each restaging; other imaging studies may be obtained in addition as necessary for clinical management. **Baseline scan must be obtained not later 30 days of initiation of drug administration.**

7.1 Information to be collected on screening failures

All clinical information and results of study related procedures should be collected in the CRF for all patients who signed informed consent but later found ineligible at screening.

7.2 Patient demographics/other baseline characteristics

The study will be open to adult patients of all ethnicities, race, gender or social status who meet the eligibility criteria set forth in the protocol. Patient demographic information will be entered in the CRF at the time of enrolment.

7.3 Treatments

All current medication used to treat diabetes mellitus should be documented.

All medications, including over-the-counter medication, taken prior to study drug administration and which continue during the course of the study must be documented

Compliance will be assessed by the investigator and/or study personnel at each visit. Records of study medication used, treatment administered, and intervals between visits will be kept during the study. Drug accountability will be noted. Patients will be asked to return all used medication ampoules at each visit and the end of the study.

7.4 Efficacy

Primary efficacy assessment

The primary endpoints of this study are response rate (RR) and progression free survival (PFS). Interim analysis for the RR primary endpoint will be performed after 18 evaluable patients have been enrolled for each arm of treatment. Any arm not meeting the pre-specified efficacy RR (specified in Section 10.1 under statistical analysis) will be closed to further accrual. Tumor response assessment will be performed after every two cycles of therapy using cross-sectional imaging according to the RECIST 1.1 criteria.

All patients who completed at least 2 cycles of therapy will be deemed evaluable for the efficacy endpoint. In the event of study discontinuation prior to completing two treatment cycles for reasons other than disease progression, the affected subject will be considered inevaluable for efficacy and will be replaced by another subject (comparable as per stratification criteria) to be enrolled on the same arm of the study.
Patients who discontinue treatment due to drug-related toxicity prior to obtaining a restaging scan would be considered inevaluable and would be replaced.
Patients who discontinue treatment for symptomatic disease progression prior to a restaging scan would be deemed to have progressed as of the time of treatment discontinuation and will not be replaced.
Patients who are lost to follow-up will be censored as of the last official contact date for efficacy and survival outcome analysis. If the event occured prior to the first restaging scan such patients will be deemed inevaluable for RR efficacy endpoint and will therefore be replaced by another

patient. They will, however, remain evaluable for overall safety assessment provided they have received at least one dose of the study drug..

Secondary efficacy assessments

Assessment for other secondary and exploratory endpoint will be performed at study conclusion.

Patient will be evaluable for overall toxicity and safety endpoint determination if they received any dose of the investigational agent.
Any patient deemed inevaluable for efficacy assessment as a result of treatment discontinuation due to treatment-related toxicity may still be evaluated for overall safety profile assessment. Notwithstanding this provision, however, only patients who are evaluable for the primary efficacy endpoint may be included in the safety assessment conducted for the sole of picking a winning arm for the trial.

The investigational agents in this trial have not been previously studied in thyroid cancer, therefore we are unable to accurately determine the patient drop-off rate. Nonethelss, we have estimated that approximately 5% of all enrolled patients will be deemed inevaluable for safety and or efficacy assessment due to various factors listed above.

Tumor response

Response assessment will be based on the RECIST 1.1 criteria. Only patients with measurable disease at baseline should be included in the study.

Definitions

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; and:

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.

- Since clinical benefit rate is one of the primary endpoints of the study, ultrasound (US) should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

• The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.

• 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 two lesions per organ and 5 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) or/and 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 (1)

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.

Table 7-2: Response Assessment by RECIST

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 complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response 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.

Response Review

For trials 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. A central review of all responses is planned for the end of the study. Nonetheless, decision regarding treatment continuation will be based on the treating physician's assessment with the concurrence of the PI in cases where there is differences of opinion.

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) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 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.

7.5 Safety

Safety assessments will consist of monitoring and recording all adverse events and serious adverse events, the regular monitoring of hematology, blood chemistry and urine values, regular measurement of vital signs and the performance of physical examinations.

These assessments should be performed within ±2 days of the scheduled day of assessment except for adverse events that will be evaluated continuously through the study. Safety and tolerability will be assessed according to the NIH/NCI CTCAE version 4.0 http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev4.pdf.

7.5.1 Adverse events

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded and followed as appropriate.

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is not considered to be related to study drug. Medical conditions/diseases present before starting study drug are only considered adverse events if they worsen after starting study drug. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

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

1. the severity grade (mild, moderate, severe) or (grade 1-4)
2. its relationship to the study drug(s) (suspected/not suspected)
3. its duration (start and end dates or if continuing at final exam)
4. action taken (no action taken; study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication taken; non-drug therapy given; hospitalization/prolonged hospitalization)
5. whether it constitutes a serious adverse event (SAE)

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

Information about common side effects already known about the investigational drug can be found in the [Investigators' Brochure]. This information should be included in the patient informed consent and should be discussed with the patient during the study as needed.

7.5.1.1 Serious adverse events

A serious adverse event is an undesirable sign, symptom or medical condition which:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (specify what this includes)
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
  - social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above

To ensure patient safety, every SAE, **regardless of suspected causality**, occurring

- after the patient has provided informed consent and until 4 weeks after the patient has stopped study treatment/participation
- after the patient is randomized and until 4 weeks after the patient has stopped study treatment

- after the patient begins taking study drug and until 4 weeks after the patient has stopped study treatment
- after protocol-specified procedures begin (e.g., placebo run-in, washout period, double-blind treatment, etc.) and until 4 weeks after the patient has stopped study treatment
- after the start of any period in which the study protocol interferes with the standard medical treatment given to a patient (e.g., treatment withdrawal during washout period, change in treatment to a fixed dose of concomitant medication) and until 4 weeks after the patient has stopped study treatment

must be reported to Novartis within 24 hours of learning of its occurrence. Any SAEs experienced after this 4-week period should only be reported to Novartis if the investigator suspects a causal relationship to the study drug. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

The investigator must assess and record the relationship of each SAE to each specific study drug (if there is more than one study drug), complete the SAE Report in English, and send the completed, signed form by fax (**1-877-778-9739**) within 24 hours to the Novartis Clinical Safety and Epidemiology Department.

The original copy of the SAE Report and the fax confirmation sheet must be kept within the Trial Master File at the study site.

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

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

7.5.1.2 Novartis instructions for rapid notification of serious adverse events

The principal investigator has the obligation to report all serious adverse events to the FDA, IRB, and Novartis Pharmaceuticals Clinical Safety and Epidemiology Department (CS&E).

All events reported to the FDA by the investigator are to be filed utilizing the Form FDA 3500A (MedWatch Form).

All events must be reported, by FAX (1-877-778-9739), to Novartis Pharmaceuticals CS&E Department within 24 hours of learning of its occurrence. This includes serious, related, labeled (expected) and serious, related, unlabeled (unexpected) adverse experiences. All deaths during treatment or within 30 days following completion of active protocol therapy must be reported within 24 hours of learning of the occurrence.

Any serious adverse event occurring after the patient has provided informed consent and until 4 weeks after the patient has stopped study participation must be reported. This includes the period in which the study protocol interferes with the standard medical treatment given to a patient (e.g. treatment withdrawal during washout period, change in treatment to a fixed dose of concomitant medication).

Serious adverse events occurring more than 4 weeks after study discontinuation need only be reported if a relationship to the Novartis study drug (or therapy) is suspected.

For Comparator Drugs/Secondary Suspects (Concomitant Medications), all serious adverse experiences will be forwarded to the product manufacturer by the investigator.

7.5.1.3 Pregnancies

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

7.5.1.4 Adverse Event and Serious Adverse Event reporting from other participating sites

The coordinating center at Emory University WINSHIP CANCER INSTITUTE would ultimately be responsible for reporting AEs and SAEs to the study supporter, NOVARTIS and the FDA as outlined above. All other participating sites are required to transmit details of any suspected AE and SAE at their centers to the coordinating center for the attention of:

Vanessa H. Phelan, BS

Regulatory & Compliance Specialist

Winship Cancer Institute-Emory University

1256 Briarcliff Road, Bldg. A, 421W-A

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Kim T. Nguyen

Assistant Director of Regulatory Affairs

Clinical Trials Office

Emory University/Winship Cancer Institute

1256 Briarcliff Road, Room 423W

Atlanta GA, 30306

404-778-5680(p)

404-778-4004 (f)

kim.t.nguyen@emory.eduThe Emory sponsor-investigator will review the adverse events and determine whether it meets Serious Adverse Event reporting requirements based on expectedness, relatedness, frequency, severity and outcome.

7.5.2 Vital signs

Body weight, body temperature, supine blood pressure, and supine pulse rate will be assessed. Height will be noted during the screening/baseline period.

7.5.3 Performance status

Performance status will be assessed and graded using the ECOG scale at screening and prior to initiation of every new cycle (See appendix A).

7.5.4 Laboratory evaluations

Patients are to fast overnight for 8 hours prior to all biochemistry samples being taken. Blood samples are to be taken as early in the day as possible. Water is allowed during this time. Laboratory samples will be analyzed locally at the clinical sites, unless indicated otherwise.

Albumin, alkaline phosphatase, total bilirubin, calcium, chloride, creatinine, magnesium, potassium, total protein, SGOT, SGPT, sodium, bicarbonate, total protein, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, urea/BUN γ-GT, fasting blood glucose, phosphorous. [at screening and as clinically indicated: CPK, HbA1c, LDH lipase, α-amylase and uric acid]. If the total bilirubin concentration is increased above 1.5 times the upper normal limit (UNL), total bilirubin should be differentiated into the direct and indirect reacting bilirubin (patient may be treated if direct bilirubin is < 1.5 x ULN)

7.5.4.1 Thyroid function tests

Free T4 and TSH will be assessed.

7.5.4.2 Hormone assessments

IGF-1 will be assessed.

7.5.4.3 Urinalysis

Specific gravity, pH, glucose, protein, bilirubin, ketones, leukocytes and blood will be assessed.

7.5.4.4 Hepatitis B Virus testing

Prior to randomization (or starting study drug in non-randomized trials), the categories of patients listed in Section 7 should be tested for hepatitis B serologic markers and viral load: HBV-DNA HBsAg, HBc Ab, and HBs Ab.

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

7.5.4.4.Hepatitis C Virus testing

Patients with hepatitis C risk factors and additional patients at the discretion of the investigator should be tested for HCV RNA-PCR test at baseline. For a list of hepatitis C risk factors, refer to Section 7.

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

7.5.5 Pregnancy test

Study drug treatment should be withdrawn in the event of pregnancy. To ensure patient safety each pregnancy must also be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects, congenital abnormalities or maternal and newborn complications. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

7.5.6 Gallbladder ultrasound

A gallbladder ultrasound will be performed as clinically indicated at baseline and during the course of the study. Patients with a history of symptomatic cholelithiasis are excluded from participating in the study.

7.5.7 Electrocardiogram (ECG)

A 12-lead electrocardiogram (ECG) and rhythm strip will be performed at baseline for all enrolled patients. Due to concern with prolonged QT interval, all patients treated with pasireotide will have repeat EKGs performed as follows:

- Baseline (before pasireotide LAR injection)
- 21 days after 1st pasireotide LAR injection
- 21 days after 3rd pasireotide LAR injection
- Cycle 6 (before pasireotide LAR injection)

- Every 3 cycles after Cycle 6

Note that ECG may be done at any time when clinically indicated

If a clinically significant abnormality is detected, the electrocardiogram will be repeated at the discretion of the Investigator until the abnormality has been resolved.

7.6 Pharmacokinetics

Pharmacokinetic analysis will not be performed during this study.

7.7 Exploratory biomarker assessments

7.7.1 Sample collection

Refer appendix B for details of sample collection, handling, preservation and shipping

Blood Sample Collection:

Blood samples will be collected at the indicated times into heparinized green top tubes (7 mls for PBMC collection - optional), red top tube (7 mls to obtain serum sample for ELISA assay). PBMC will be purified using standard Ficoll-Paque gradient centrifugation according to the instructions of the manufacturer (Amersham Pharmacia, Uppsala, Sweden). All samples must be stored away within 2 hours of collection by refrigeration at -70 to -80^{o}C until ready for assay.

Paraffin-Embedded Tissue

Archival paraffin embedded tissue collected at the time of patient screening will be shipped to the lab of Shi-Yong Sun, PhD at the Winship Cancer Institute. If the entire paraffin block cannot be submitted, 15-20 slides of 4-5 micron sections cut from the block should be submitted. The patient ID # should be provided with the specimens.

ELISA Assay

ELISA detection and quantification of the cytokines of interest will be performed using previously published methods. Samples will be loaded onto a 96-well microtiter plate coated with monoclonal antibody specific for the cytokine of interest. After a blocking step, samples will be diluted into a buffer and incubated with the primary antibody. After a washing step, antisera specific for the cytokine is added followed by additional incubation. Another washing step will be performed to be followed by the addition of peroxidase-conjugated secondary antibody. The concentrations of the respective cytokines will be determined in triplicate for each serum samples using an ELISA plate reader. A set of calibrators and assay controls will be run with each assay.

Immunohistochemistry (IHC) for mTOR pathway proteins and somatostatin receptor expression

Immunohistochemical detection of the mTOR pathway proteins will be carried out with the avidin-biotin technique using specific monoclonal antibodies targeting the proteins of interest. The IHC will be performed in collaboration with, Shi-Yong Sun, PhD and on a fee-for-service basis using the personnel and resources provided by the Pathology Core facility at Emory Winship Cancer Institute. Semiquantitative scoring of protein expression will be performed by Dr. Owonikoko (prior pathology training) in collaboration with Anthony Gal, MD a staff anatomic pathologist with Emory University Hospital.

8 Data Review and Data Management

8.1 Data Monitoring Committee

The institution data safety monitoring committee will review the outcome of the study at regular intervals as mandated by institutional policy or more frequently if deemed necessary by the Principal Investigator. The Data Monitoring Committee (DMC) will be composed of medical, ethics and statistical experts and will meet to review the efficacy and safety data and determine a risk/benefit analysis in this subject population. The purpose of the DMC is to advise on serious safety considerations, lack of efficacy and any other considerations within the charge to the Committee. The DMC may request additional meetings or safety reports as deemed necessary upon discussion with Novartis and its representatives. The DMC may stop the study following review of results from each interim analysis. Appropriate efficacy and safety data summaries will be provided to the DMC after each interim analysis.

In addition, the principal investigator will review the toxicities as they occur and/or are reported. The approval of the principal investigator or designee is necessary for accrual of all patients.

The Data Coordinating Center will review responses and toxicity and report these to the regularly scheduled meetings of the Data Safety Monitoring Committee of the Emory Winship Cancer Institute

Each participating site is expected to have its own data monitoring and safety plan (DMSP) with regard to forwarding information to their IRBs. If the data reveals a change in the risk/benefit ratio, the investigator will notify the IRB and the PI. The principal investigator and co-investigators will review the data and forward any changes or protocol amendments to the IRBs. All serious adverse events will be reported promptly or periodically to the IRB according to the requirements specified in the IRB policy and guidelines. All study participant information will be kept in a confidential manner by the assigning of a random number to each study participant. All data will be kept confidential as per institutional guidelines and policies. Any breach of confidentiality is a serious matter and conflicts with institutional policies and will be reported to the IRB. A cumulative summary of all adverse events occurring on this study and a report of the

data safety and monitoring plan will be submitted to the IRBs with the annual renewal reports. Enter information concerning the data monitoring board

8.2 Data Collection and Management

Investigator responsibilities are set out in the ICH guideline for Good Clinical Practice (GCP) and in the US Code of Federal Regulations.

Investigators must enter study data onto CRFs or other data collection system. The Investigator will permit study-related audits by Novartis or its representatives, IRB/EC review, and regulatory inspection(s) (e.g., FDA, EMEA, TPP), providing direct access to the facilities where the study took place, to source documents, to CRFs, and to all other study documents.

The Investigator, or a designated member of the Investigator's staff, must be available at some time during audits to review data and resolve any queries and to allow direct access to the subject's records (e.g., medical records, office charts, hospital charts, and study related charts) for source data verification. The data collection must be completed prior to each visit and be made available to the Novartis representative so that the accuracy and completeness may be checked.

8.3 Overall Study Monitoring for Collaborating Sites

The coordinating center for this multicenter study is the Clinical Trials Office of the Winship Cancer Institute of Emory University. Monitoring plan for this study will therefore follow the established Data Safety and Monitoring Plan for all investigator-initiated phase II trials at the Winship. The Emory University WINSHIP CANCER INSTITUTE monitoring team will have primary responsibility to coordinate, conduct and/or oversee all study auditing. The study will be audited at least annually in addition to the reporting requirement established by the IRB. If the Monitoring Committee determined that an external audit should be conducted, the committee shall be responsible for appointing the external auditors. The scope and conduct of the audit will be established by the committee and support for the audit will be provided by the Emory WINSHIP CANCER INSTITUTE Monitoring Office.

Monitoring Committee: The committee members shall consist of faculty members, a research nurse, the Clinical Trials Director and/or Associate Director, the Medical Director of Clinical Trials, the Director of the Phase I program and the Regulatory and Compliance Manager. The Monitoring Committee reviews all auditing, DSMB composition and reports, and recommends corrective action if needed to the PI.

The committee will:

Review all SAEs from all sites at the time of report to the WINSHIP CANCER INSTITUTE

Review risk/benefit ratio and report to Emory IRB at the time of continuing review

Review the protocol, amendments, informed consent documents and IRB submissions

Meet with the PI for clarification of objectives and collection tools for these objectives.

The Monitoring Office: This office consists of auditors and support staff and is administered by the Regulatory and Compliance Manager. The Clinical Trials Medical Director is available for ongoing consultation. Auditing will be performed by a qualified auditor who has access to the Medical Director of Clinical Trials, or a designee if he is involved in the study, for guidance and resolution of medical questions. The Emory WINSHIP CANCER INSTITUTE Monitoring Office will audit data integrity and safety information for all participating sites according to the approved schedule in the Winship DSMC Standard Operating Procedures and Policies.

The following will be inspected during the monitoring visit

i. Review of data integrity

ii. Documentation of the qualifications, training and experience of the PI and other study staff

iii. Eligibility of consented/enrolled patients

iv. Informed consent document and process

v. Verification that the local PI and staff are performing trial functions in accordance with protocol

vi. Accuracy, completeness and timeliness of data

vii. Accuracy and completeness of all source documentation

viii. Response evaluation: verify that responses are identified according to the protocol definition of response for any response that is a major endpoint

ix. Toxicity

x. Appropriate reporting of all AEs and SAEs as required by GCP, the protocol, IRB regulations, sponsor's SOPs and other regulatory requirements

The monitor shall meet with RN/Coordinator assigned to the trial to:

provide an itemized review of the deficiencies to the RN/Coordinator and remove items from itemized review which are corrected during this meeting

review and document corrections; the RN/coordinator should indicate any remaining deficiencies and provide corrective action plan for resolution

prepare summary report for PI and Monitoring Committee to include summary of systematic deficiencies, significant protocol deviations, summary of remaining deficiencies and RN/coordinator corrective action plan, recommendations for data collection, protocol revision for clarity

The Monitor shall meet with the overall PI to discuss the report and document the PI's responses prior to submitting final report to the Monitoring Committee

The final Monitoring Committee review of audit report and PI response and PI summary of protocol to date will be included in the annual renewal submission.

Egregious data insufficiencies that may impact the scientific integrity of the trial are reported to the Medical Director and Clinical Trial Review Committee.

Please see the attached supplementary Emory University WINSHIP CANCER INSTITUTE data safety monitoring plan policy document for a complete detail of the monitoring plan.

9 Statistical methods and data analysis

All treated subjects will be included in the analysis of efficacy and safety.

Demographic and baseline characteristics will be summarized using descriptive statistics. The toxicities will be tabulated by organ system. Time to disease progression and overall survival will be evaluated using the Kaplan-Meier method.

Correlative analysis will be exploratory in the context of this Phase II screening trial.

Post treatment correlatives will be collected on a limited number of patients who progress on the single agent arm. These will allow us to explore whether biological mechanisms postulated to be specific to the investigational agents is involved, and if dynamic changes in putative targets distinguish between responders and non-responders in this limited subset of patients.

Analysis of baseline measurements obtained on all patients: Three types of analysis are planned: (a) Conditional analysis: does the correlate have an impact on response rate if the patient is treated with the specific investigational agent? (b) Marginal analysis: does the correlate have an impact when combining the two agents? and (c) Interaction: does the correlate have an impact differing by the treatment arm?

Due to the variability in the baseline expression of correlative endpoints such as somatostatin receptor and mTOR protein, the limited sample-size and response rate, and pre-determined sample-size, no formal power calculation is presented for this exploratory research.

9.1 Objective RR and PFS as endpoints

Within Arm: Using a Simon's 2-stage MinMax design, 18 patients will be enrolled into stage I. At least one objective response is required to proceed to stage II accrual of 10 additional patients for a total of 28 patients per arm. If 3 or more patients achieve objective response following total

accrual, the particular treatment arm will be deemed worthy of further clinical evaluation in this disease. For response determination, any patient who progress prior to satisfying the objective response criteria will not be replaced but will be deemed evaluable for response evaluation and classified as a non-responder.

Between Arms: Any treatment arm closed to accrual after the first stage interim analysis will be considered an inferior arm and will be excluded from comparison for the winner of trials.
The arm with the best overall RR at the end of full enrolment will be adjudged the winner to be considered for further development provided there are at least 3 objective responses. Only in the event of identical RR between 2 or more arms or if none of the arms met the RR criterion (less than 3 objective responses after full patient enrolment) would the 1-yr PFS rate be employed to determine a winner. Based on recent clinical trials of targeted agents in similar patient population, 90% of patients were alive at 1 year and median progression free survival ranged between 9 and 18 months.[8-10] We assume a conservative estimate that only 20% of the patients will be progression free at 1 year if the treatment is ineffective while 50% or more of the patients will be progression free at the same time point with an effective regimen. For this purpose, a 1-year PFS rate of 50% or greater will be considered sufficient activity to justify further evaluation of the treatment in this disease. Assuming a 20% or lower 1-year PFS rate with an inactive regimen and a 50% or greater rate with an active regimen, 28 patients enrolled onto each arm will classify the treatment as having sufficient activity for further evaluation with a probability of 0.95 (power against the alternative hypothesis $p = 0.05$).In this respect, the arm with the highest 1-yr PFS rate will be judged the winner. In the event of a tie between the arms for both the RR and 1-yr PFS rate, the arm with the best profile in terms of safety and tolerability will be considered the overall winner to be selected for further evaluation in this disease. The power calculation for PFS assessment assumes full enrolment of 28 patients to the treatment arm, therefore any arm closed to further accrual following the initial interim analysis will not be eligible for the PFS endpoint assessment. The investigational agents in this trial have not been previously studied in thyroid cancer; therefore we are unable to accurately determine the drop-off rate. Nonetheless, all patients

9.2 CBR as endpoints

Any treatment arm that was closed to accrual after the first stage analysis will be considered to be an inferior arm. The CBR rates of all arms with complete accrual of 28 evaluable patients will be estimated and used as additional reference for the determination of the winner arm to be considered for further study.

9.3 Other Endpoints:

Preclinical evidence show that mTOR inhibitor resistance may be due to increased survival pathway signaling activity with resultant addiction of the tumor cells to this pathway. The trial will explore the potential benefit of sequential versus concurrent initiation of mTOR inhibitor and Pasireotide. For this purpose, patients randomized to the single agent arms will be allowed to receive the 2-drug combination at the time of disease progression. Such patients may, however, remain on treatment only if they achieve disease stabilization or objective response at the end of

the first 2 cycles of 2-drug combination using the last imaging scan obtained while on the single agent therapy as the new baseline.

9.4 Correlative Study Analyses:

The expression of somatostatin receptor and mTOR pathway protein (S6, pS6, 4E-BP1, p-4E-BP1, eIF4e, Akt, pAkt, raptor, rictor, PRAS40, mSin1, FKBP38, IGF-R, IRS-1 and HIF1-α) in archival tissue and in fresh tumor biopsy obtained at the time of progression will be determined by immunohistochemistry and quantified by immunoscore as previously described.[52] Differences in mean expression between the 3 treatment arms will be compared with ANOVA or Chi-Square test. Longitudinal analyses will also be conducted to investigate the association between the treatment arm and changes in circulating IGF-1 using ELISA assay and immunoscore of the listed proteins in progressing patients. The MIXED procedure of SAS will be used for the analyses.

10 Protocol amendments, or changes in study conduct

10.1 Declaration of Helsinki

The investigator must conduct the trial in accordance with the principles of the Declaration of Helsinki. Copies of the Declaration of Helsinki and amendments will be provided upon request or can be accessed via the website of the World Medical Association at http://www.wma.net/e/policy/17-c_e.html.

10.2 Ethics and Good Clinical Practice

This study must be carried out in compliance with the protocol and the principles of Good Clinical Practice, as described in Novartis standard operating procedures and:

ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996.

Directive 91/507/EEC, The Rules Governing Medicinal Products in the European Community.

US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations).

Declaration of Helsinki and amendments, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects).

The investigator agrees to adhere to the instructions and procedures described in it and thereby to adhere to the principles of Good Clinical Practice that it conforms to.

10.3 Protocol Modification

Any change or addition (excluding administrative) to this protocol requires a written protocol amendment that must be reviewed by Novartis and the investigator before implementation. Amendments significantly affecting the safety of subjects, the scope of the investigation or the scientific quality of the study require additional approval by the IRB at each study center. A

copy of the written approval of the IRB must be provided to Novartis. Examples of amendments requiring such approval are:

1. increases in drug dose or duration of exposure of subjects,
2. significant changes in the study design (e.g. addition or deletion of a control group),
3. increases in the number of invasive procedures,
4. addition or deletions of a test procedure required for monitoring of safety.

These requirements for approval should in no way prevent any immediate action from being taken by the investigator or by Novartis in the interests of preserving the safety of all patients included in the trial. If an immediate change to the protocol is felt to be necessary by the investigator and is implemented for safety reasons Novartis must be notified and the IRB at the center must be informed immediately. Amendments affecting only administrative aspects of the study do not require formal protocol amendments or IRB approval but the IRB must be kept informed of such administrative changes. Examples of administrative changes not requiring formal protocol amendments and IRB approval include:

1. changes in the staff used to monitor trials
2. minor changes in the packaging or labeling of study drug.

11 Regulatory Considerations

11.1 Institutional Review Board/Ethics Committee approval

The protocol for this study has been designed in accordance with the general ethical principles outlined in the Declaration of Helsinki. The review of this protocol by the IRB/EC and the performance of all aspects of the study, including the methods used for obtaining informed consent, must also be in accordance with principles enunciated in the declaration, as well as ICH Guidelines, Title 21 of the Code of Federal Regulations (CFR), Part 50 Protection of Human Subjects and Part 56 Institutional Review Boards.

Before implementing this study, the protocol, the proposed informed consent form and other information to subjects, must be reviewed by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB). 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. Any amendments to the protocol, other than administrative ones, must be reviewed by Novartis approved by this committee.

The Investigator will be responsible for preparing documents for submission to the relevant IRB/EC and obtaining written approval for this study. The approval will be obtained prior to the initiation of the study.

The approval for both the protocol and informed consent must specify the date of approval, protocol number and version, or amendment number.

Any amendments to the protocol after receipt of IRB/EC approval must be submitted by the Investigator to the IRB/EC for approval. The Investigator is also responsible for notifying the

IRB/EC of any serious deviations from the protocol, or anything else that may involve added risk to subjects.

Any advertisements used to recruit subjects for the study must be reviewed and approved by the IRB/EC prior to use.

11.2 Informed consent

The Investigator must obtain informed consent of a subject or his/her designee prior to any study related procedures as per GCPs as set forth in the CFR and ICH guidelines.

Documentation that informed consent occurred prior to the subject's entry into the study and the informed consent process should be recorded in the subject's source documents. The original consent form signed and dated by the subject and by the person consenting the subject prior to the subject's entry into the study, must be maintained in the Investigator's study files.

The investigator must explain to each subject (or legally authorized representative) the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in non-technical language. The subject should read and consider the statement before signing and dating it, and should be given a copy of the signed document. If the subject cannot read or sign the documents, oral presentation may be made or signature given by the subject's legally appointed representative, if witnessed by a person not involved in the study, mentioning that the patient could not read or sign the documents. No patient can enter the study before his/her informed consent has been obtained.

The informed consent form is considered to be part of the protocol, and must be submitted by the investigator with it for IRB/IEC/REB approval.

11.3 Subject confidentiality

Novartis affirms the subject's right to protection against invasion of privacy. In compliance with United States federal regulations, Novartis requires the Investigator to permit representatives of the sponsor and, when necessary, representatives of the FDA or other regulatory authorities to review and/or copy any medical records relevant to the study in accordance with local laws.

Should direct access to medical records require a waiver or authorization separate from the subject's statement of informed consent, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

11.4 Disclosure and confidentiality

The investigator agrees to keep all information provided by Novartis in strict confidence and to request similar confidentiality from his/her staff and the IRB/IEC/REB. Study documents provided by Novartis (investigators' brochures and other material) will be stored appropriately to ensure their confidentiality. The information provided by Novartis to the investigator may not be disclosed to others without direct written authorization from Novartis, except to the extent necessary to obtain informed consent from patients who wish to participate in the trial.

11.5 Study records requirements

The Investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the protocol therapy, that is copies of CRFs and source documents (original documents, data, and records [e.g., hospital records; clinical and office charts; laboratory notes; memoranda; subject's diaries or evaluation checklists; SAE reports, pharmacy dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiches; photographic negatives, microfilm, or magnetic media; x-rays; subject files; and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical study; documents regarding subject treatment and drug accountability; original signed informed consents, etc.]) be retained by the Investigator for as long as needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the last marketing approval). The Investigator agrees to adhere to the document/records retention procedures by signing the protocol.

11.6 Publication of results

Any formal presentation or publication of data from this trial may be published after review and comment by Novartis and prior to any outside submission. Novartis must receive copies of any intended communication in advance of publication (at least fifteen working days for presentational materials and abstracts and thirty working days for manuscripts). These requirements acknowledge Novartis' responsibility to provide peer input regarding the scientific content and conclusions of such publications or presentations. Principal Investigation/Institution shall have the final authority to determine the scope and content of its publications, provided such authority shall be exercised with reasonable regard for the interests of Novartis and, in accord with the trial contract and shall not permit disclosure of Novartis confidential or proprietary information.

11.7 Premature discontinuation of study

The Principal Investigator, institution and Novartis have the right to discontinue this study at any time for reasonable medical or administrative reasons. Possible reasons for termination of the study could be but are not limited to:

Unsatisfactory enrollment with respect to quantity or quality.

Inaccurate or incomplete data collection.

Falsification of records.

Failure to adhere to the study protocol.

Any possible premature discontinuation would be documented adequately with reasons being stated, and information would have to be issued according to local requirements (e.g., IRB/EC, regulatory authorities, etc.).

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13 APPENDICES

13.1 APPENDIX A- Performance Status Criteria

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

13.2 APPENDIX B – Blood sample collection and processing

Pharmacodynamic Studies

Plasma samples will be obtained in green-topped vacutainer tubes; PBMCs will be prepared and stored for future use at each time for which blood is sampled.

Sample collection and processing

Careful attention should be paid to the types of tubes required for each day's sample acquisition. Samples for pharmacodynamic and PBMC preparation will be performed at the beginning of each odd numbered cycle 1, 3, 5 through the end of cycle 6. Does not need to be repeated with cycle 1 if already collected as part of screening.

Venous blood will be collected in 4-ml heparinized green-topped vacutainer tubes. When obtained, each tube should be inverted several times to mix the heparin anticoagulant with blood. All samples will be sent to Dr. Owonikoko's lab in batches to attention, Guojing Zhang. Lab should be notified prior to sample packaging and shipping.

Sample Processing

Microtainer tubes shall be inverted several times to mix blood with heparin and then centrifuged at approximately 300 x g in a refrigerated tabletop centrifuge so as to produce plasma. The resulting plasma should be aspirated from the tubes, placed into appropriately-labeled microcentrifuge tubes, and stored at -70°C. Blood samples for IGF-1 ELISA should be collected in red topped tubes to obtain the serum.

PBMC - Collect blood in CPT or heparinized tube. Centrifuge at 1500g (approximately 2800rpm) for 30 minutes. Discard supernatant (plasma). Remove the thin white layer of WBC (Buffy coat and transfer to a clean 15 ml centrifuge tube. Wash cells by filling the tube with PBS. Centrifuge at 300g (approximately1200rpm) for 5 minutes. Discard supernatant, resuspend cells in small quantity of PBS and transfer into two cryotubes tubes. Store at -70oC until ready for shipment.

Serum: Collect whole blood in SST tube. Allow to clot by leaving it undisturbed at room temperature for 15-30 minutes. Centrifuge at 1500 g (approximately 2800rpm) for 10 minutes in a refrigerated centrifuge. Immediately transfer the supernatant serum into clean cryotubes and store as 0.5 - 1 ml aliquots at –70°C until ready for shipment.

13.3 APPENDIX C - Medication Diary

Study Title	A 3-Arm Randomized Phase II Trial Evaluating Single Agent and Combined Efficacy of Pasireotide and Everolimus in Adult Patients with Radioiodine-Refractory Differentiated and Medullary Thyroid Cancer	
Medication Diary		
Subject Initials		
Subject ID		
Cycle #		
Research Coordinator Name: Phone: Pager: e-mail:		
Cohort#	Original Everolimus Dose ……	Original Pasireotide Dose …….
# of Dose Reductions	Current Everolimus Dose: ……..	Current Pasireotide Dose: ……

Instructions:
1. Please take the prescribed medications as instructed

2. Please record the date and time you take your medications. On visit days, medications should be taken in the clinic unless otherwise instructed

3. Please bring medication and pill diary to each study visit.

Day	Date	Everolimus (Y/N)	Pasireotide (Y/N)	Comments
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
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15				

16				
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23				
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25				
26				
27				
28				
Patient Signature		……		Date:
This section to be completed by a Research Personnel (Investigator, Research Nurse/Coordinator)				
Dosing Cycle Start Date:		Dosing Cycle End Date:		
Everolimus Lot Number: ……	# of Bottles / # of Tablets Dispensed : ____5mg ____10mg			Any Interruptions? (Yes/No)
Pasireotide Lot Number ……	# of Bottles / # of Injections Dispensed : ____			Any Interruptions? (Yes/No)
Length of Dose Interruption: Everolimus ……			Pasireotide …….	
Reason for Interruption				
Reason for Dose Reduction				
Additional Comments:				

13.4 Attached Supplement – Emory Winship DSMP Policy

Emory Winship Cancer Institute Data Safety Monitoring Plan Policy attached as a supplement