Official Protocol Title:	An Extension Trial of Deforolimus (AP23573; MK-8669), an mTOR Inhibitor, for Patients with Advanced Cancer
NCT number:	NCT00836927
Document Date:	01-October-2008

An Extension Trial of Deforolimus (AP23573; MK-8669), an mTOR Inhibitor, for Patients with Advanced Cancer

ARIAD protocol number: AP23573-08-901
IND Reference Numbers: 72,003 (oral)
65,630 (Intravenous)

Date of Protocol: Original: 1 October 2008

Sponsor:
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1. CONTACTS

1.1 Serious Adverse Events (SAEs)

Any death or serious adverse event (SAE) experienced by the patient from the time that the patient signs the informed consent form to 30 days after receiving study drugs or through the date of the post-treatment discontinuation visit (i.e., approximately 30 ± 7 days following the last dose of study drug; unless the patient begins alternate anti-cancer treatment in this time window), or any death or SAE believed to be study drug-related that occurs at anytime thereafter, must be promptly reported (within 24 hours of learning of the event) by telephone or telefax to the Sponsor or the Sponsor's designee.

1.2 Contact for Emergencies and Study-related Issues

A list of the Sponsor's study personnel and their contact information will be provided in the Investigator's Notebook. Additional contacts are:

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2. APPROVAL

The protocol must be read before signing.

2.1 Investigator Signature

I have read the protocol and agree that it contains all necessary details for carrying out the trial as described. I will conduct this protocol as outlined therein, including all statements regarding confidentiality. I will make a reasonable effort to complete the trial within the time designated. I will provide copies of the protocol and access to all information furnished by the Sponsor to study personnel under my supervision. I will discuss this material with them to ensure they are fully informed about the drug and the trial. I understand that the study may be terminated or enrollment suspended at any time by the Sponsor, with or without cause, or by me if it becomes necessary to protect the best interests of the study patients.

I agree to conduct this trial in full accordance with all applicable regulations.

_____ _____

Investigator's Signature Date (dd-mmm-yyyy)

_____

Investigator's Name (print)

2.2 Sponsor Representative Signature

ARIAD Pharmaceuticals, Inc. has approved of this protocol and assures that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality.

_____ _____

Sponsor Representative's Signature Date (dd-mmm-yyyy)

_____

Sponsor Representative's Name (print)

3. INSTITUTIONAL REVIEW BOARD / ETHICS COMMITTEE

The Institutional Review Board or Ethics Committee and its affiliation and address for *each site* implementing this protocol shall be identified below or on the FDA Form 1572.

IRB/EC: _____

Affiliation: _____

Address: _____

_____

_____

4. DISCLOSURE STATEMENT

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This document contains information that is confidential and proprietary to the Sponsor. This information is being provided to you solely for the purpose of evaluation and/or conducting a clinical trial for the Sponsor. For this purpose, you may disclose the contents of this document only to study personnel under your supervision, IRBs/ECs, or duly authorized representatives of regulatory agencies under the condition that they maintain confidentiality. The contents of this document may not be used in any other clinical trial, disclosed to any other person or entity, and/or published without the prior written permission of the Sponsor. The foregoing shall not apply to disclosure required by any regulation; however, you will give prompt notice to the Sponsor of any such disclosure.

Any information that may be added to this document also is confidential and proprietary to the Sponsor and must be kept in confidence in the same manner as the contents of this document.

The ARIAD protocol number for this trial is AP23573-08-901.

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5. LIST OF ABBREVIATIONS

Abbreviation	Term
4E-BP1	eukaryotic mutation factor 4E binding protein 1
ADR	adverse drug reaction
AE	adverse event
ALT	alanine aminotransferase
ARIAD	ARIAD Pharmaceuticals, Inc.
AST	aspartate aminotransferase
AUC	area under the concentration curve
ß-HCG	beta human chorionic gonadotropin
BUN	blood urea nitrogen
C_{max}	maximum concentration
CBC	complete blood count
CI	confidence interval
CL/F	apparent total blood clearance
CR	complete response
CRF	case report form
CTC	circulating tumor cells
CTCAE	Common Terminology Criteria for Adverse Events (version 3)
CYP3A	cytochrome P450, family 3, subfamily A
DLT	dose-limiting toxicity
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
EMEA	European Agency for the Evaluation of Medicinal Products
FDA	Food and Drug Administration (United States)
FKBP	FK506-binding protein (12 kDa)
GCP	Good Clinical Practice
HC	Health Canada
IGF-1R	insulin-like growth factor receptor-1
IMP	investigational medicinal product
IRB	Institutional Review Board
IV	intravenous
K	potassium
kg	kilogram
MedDRA	Medical Dictionary for Regulatory Activities
min	minute(s)
mL	milliliter
mg	milligram
mRNA	messenger ribonucleic acid

MTD .....maximum tolerated dose
mTOR .....mammalian target of rapamycin
Na.....sodium
NCI .....National Cancer Institute (of the United States)
OTC .....over the counter
OS .....overall survival
PBMCs.....peripheral blood mononuclear cells
PD .....progressive disease (in context of tumor response assessment)
PFS.....progression-free survival
PI3K……..phosphoinositide 3 kinase
PR .....partial response
PTEN .....phosphatase and tensin homologue deleted on chromosome 10
QD.....every day
QDx4.....once daily for 4 consecutive days
QDx5.....once daily for 5 consecutive days
QDx5/week .....once daily for 5 consecutive days every week
QDx21.....once daily for 21 consecutive days
QDx28.....once daily for 28 consecutive days
QW.....once weekly
RECIST.....Response Evaluation Criteria in Solid Tumors
S6K .....S6 ribosomal protein kinase
SAE.....serious adverse event
SD .....stable disease
SSAR .....suspected serious adverse reaction
SUSAR .....suspected unexpected serious adverse reaction
$t_{1/2}$.....terminal half life
$t_{1/2\beta}$ .....terminal elimination half life
t_{lag}.....mean absorption lag time
V_{ss} .....volume of distribution

6. DEFINITION OF TERMS

Term	Definition
Adverse Drug Reaction	Any adverse event that is deemed to be at least possibly related to the study drug.
Clinical Benefit Response	A clinical benefit response includes patients who achieve a complete response (CR), a partial response (PR), or stable disease (SD) for ≥ 16 weeks.
End-of-Trial	The end-of-trial (completion) date is up to 6 months after the last patient has discontinued from the study (including follow-up).
Enrolled Patient	An enrolled patient is a patient who has signed the informed consent form, completed all screening evaluations and has been deemed eligible for the trial by the investigator.
Ethics Committee	The term "ethics committee" refers to all appropriate properly constituted committees or boards recognized by the appropriate regulatory agencies for approving clinical studies. These include independent ethics committees and institutional review boards.
Follow-Up Period	The follow-up period begins at the one-month post-treatment discontinuation visit and continues until the patient dies or is lost to follow-up.
Institutional Review Board	Throughout this document the term institutional review board (IRB) refers to all appropriate properly constituted committees or boards recognized by the appropriate regulatory agencies for approving clinical studies. These include independent ethics committees and institutional review boards.
Parent Trial	Any other trial investigating single-agent or combination deforolimus.
Patient	The term patient refers to a patient in a clinical research trial.
Regulation	The term "regulation" refers to all appropriate regulations, laws, and guidelines. This trial will be conducted according to all appropriate regulations. The regulations may be international, national, or local and may include but not be limited to the Code of Federal Regulations (United States), the

	Good Clinical Practice: Consolidated Guideline (Canada), the International Conference on Harmonization Guideline for Good Clinical Practice, the Therapeutic Goods Administration Annotated International Conference on Harmonization Guidelines (Australia), and the World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Patients.
Regulatory Agency	The term "regulatory agency" refers to all appropriate health and regulatory authorities. These may be international, national, or local and may include but not be limited to the Health Canada (HC), the European Agency for the Evaluation of Medicinal Products (EMEA), and the United States Food and Drug Administration (FDA).
Screening Period	The screening period begins when the patient signs the Informed Consent Form and continues until first dose of study drug is administered as part of this trial.
Sponsor	The term Sponsor refers to ARIAD Pharmaceuticals, Inc.
Study Drug	The agent(s) used in the Sponsor's clinical research and development trial.
Study Start Date	Date of signature of first informed consent form for this trial.
Treatment Period	The time period that extends from administration of the first dose of study drug and continues through to the end of the one month post-treatment discontinuation visit, or to the start of another anti-cancer therapy if it occurs before the one-month post-treatment visit.

7. SYNOPSIS

Study Title	An Extension Trial of Deforolimus (AP23573; MK-8669), an mTOR Inhibitor, for Patients with Advanced Cancer
Clinical Phase	Extension Trial
Study Rationale	Mammalian target of rapamycin (mTOR) The mammalian target of rapamycin (mTOR) is a serine-threonine kinase that functions as a central regulator of multiple signaling pathways that control cell growth, division, metabolism, and angiogenesis. mTOR is activated in response to environmental and nutritional conditions and plays a critical role in the transduction of proliferative signals mediated through the PI3K/Akt pathway by activating two key downstream proteins: the p70 S6 kinase (S6K) and the eukaryotic initiation factor 4E binding protein 1 (4E-BP1). Deregulation of the PI3K/Akt pathway has been linked to oncogenesis in many human cancers. Deforolimus Deforolimus (AP23573; MK-8669) is a non-prodrug analog of rapamycin that has been shown to inhibit mTOR activity, as evidenced by reduced phosphorylation of 4E-BP1 and S6. Deforolimus also inhibits the proliferation of multiple tumor cell lines *in vitro* and *in vivo*, including tumors of breast, colon, lung, prostate, pancreas and glial cells. Deforolimus has been investigated in 16 clinical trials involving approximately 700 patients with advanced cancer. These trials have demonstrated that deforolimus has a favorable safety profile and has anti-tumor activity in a broad range of cancers. Single-agent oral deforolimus is being studied in a randomized, placebo-controlled, pivotal Phase 3 trial in patients with metastatic soft-tissue or bone sarcomas. Other indications under investigations include endometrial, breast, non-small-cell lung cancer, and prostate cancer. Combinations of deforolimus with other agents are being investigated. Clinical trials are often designed for a finite period of time, based on the average outcome of the investigated populations. However, some patients, even in populations of patients with advanced cancer, experience a long-term benefit from the investigational treatment well beyond the finite period of the trial. Because clinical protocols are not designed for long-term collection of safety and efficacy data, this information is often lost. For those patients who have a long-term benefit from deforolimus treatment, the standard protocol procedure with frequent assessments of safety and efficacy may constitute an undue burden for patients with limited additional scientific information. An abbreviated, less-frequent follow-up would be appropriate to collect sufficient information while ensuring patient safety. Summary The specific purpose of the present trial is to collect long-term safety and efficacy data from patients for whom a clinical benefit has been established in a prior clinical trial with deforolimus and/or in those who remain in long-term follow-up. These other trials are collectively designated as “parent trials”.
Study Objective(s)	Primary Objective: • To describe the long-term safety of deforolimus in patients for whom a clinical benefit has been established in a prior parent trial with the deforolimus and/or in those who remain in long-term follow-up.

	Secondary Objectives • To describe the long term efficacy of deforolimus in patients for whom a clinical benefit has been established in a prior parent trial with deforolimus and/or in those who remain in long-term follow-up. • To evaluate progressive-free survival and overall survival.
Trial Design	Open-label, non-randomized, multicenter trial for the evaluation of the long-term efficacy and safety of deforolimus in patients for whom a clinical benefit has been established in a prior parent trial with the drug or for those who are continuing on for long-term follow-up. The patients will continue the treatment planned in the parent protocol, with a simplified follow-up. Treatment will continue as long as the investigator believes the patient is deriving benefit. After the treatment period ends, patients will continue to be followed until death, they withdraw consent, or they are removed from study.
Study Endpoints	Primary Endpoint: • Safety and tolerability of long-term deforolimus Secondary Endpoints: • Progression-free survival, defined as the time from the date of enrollment in the prior parent trial to the date of documented progressive disease (as defined by the parent protocol or the investigator), recurrence or death (whichever occurs first). • Overall survival • Duration of objective response
Diagnosis and Main Criteria for Inclusion	• Any patient enrolled in this extension trial must have been enrolled on a Deforolimus parent trial • Any patient enrolled in this extension trial must have derived a clinical benefit from the parent trial, as assessed by the parent trial investigator, or be in long-term follow-up. • ECOG performance status: ≤ 2 (see Attachment B) if the patient is scheduled to received treatment with deforolimus and/or comparators; no requirement if the patient is included for follow-up purpose only. • Patient is not on any other cancer-directed therapy (with the exception of agents included in the parent protocol regimen)
Approximate Number of Patients	Approximately 50 patients
Approximate Duration of Patient Participation	The actual duration of each patient's participation will vary because patients may continue to receive study drug as long as they continue to derive benefit from the treatment. Once study drug is discontinued, follow up will continue until death, withdrawal of consent, or removal from study for other reasons..
Approximate Number of Study Centers	Not applicable
Approximate Duration of Study	Not applicable
Study Drug	Oral or IV deforolimus. If the parent protocol involves a combination of deforolimus with one or several additional drugs, the additional drug(s) may be continued as described in the parent protocol.

	Patients will remain on the same study medication (including other agents) and dose schedule in this extension trial as in the parent trial in which they had been enrolled.
Reference Therapy	None
Dosage and Administration	Deforolimus (and other study drugs) should be provided and administered as described in the parent trials but investigators will need to take into account individual dose reductions and schedule modifications that have been made over the course of that prior trial. In cases of where the Parent Trial is not clear for long-term oral or IV dosing. The following dosing and administration schedules can be used as guidelines for patients ≥ 13 years of age: • For single-agent oral deforolimus trials, the standard administration is 40 mg once daily for 5 consecutive days per week (QDx5/week). The oral formulation consists of 10mg enteric-coated tablets. • For single-agent IV deforolimus trials, the standard administration is an IV infusion over 30 minutes on days 1-5 of each 14-day treatment course. • Each treatment cycle will be 4 weeks (28 days) in duration Dose modifications will be permitted for management of adverse events as stipulated in the subject's Parent Trial. Additional Dosage and schedule modifications, beyond what is stipulated in the parent trial, may be considered by investigators after approval from the Sponsor.
Concomitant Treatment	Palliation and supportive care are permitted during the course of the study for underlying conditions. The following concurrent medications are prohibited: • Any other anticancer treatment (unless such therapy was part of the parent protocol), including chemotherapy, immunotherapy, biological response modifiers (excluding hematopoietic growth factors), radiation therapy, and systemic hormonal therapy administered as anti-cancer treatment • Use of any other investigational drug or device • Medications that strongly induce or inhibit CYP3A, such as ketoconazole and erythromycin, are prohibited unless required for urgent medical care. • Herbal preparations or related over-the-counter preparations containing herbal ingredients (e.g., St. John's Wort, Blue Cohash, Estroven) Concomitant treatments with medications that are metabolized by CYP3A are allowed (e.g., atorvastatin or simvastatin)
Efficacy Evaluation	Efficacy endpoint variables include: duration of objective response; progression-free survival; and overall survival.
Safety Evaluation	Safety assessments will include routine physical examinations, laboratory evaluations, and interim history. Adverse events will be graded according to U.S. NCI Common Terminology Criteria for Adverse Events (CTCAE), version 3.
Pharmacokinetics	None for this trial
Pharmacodynamics	None for this trial
Biomarkers/ Pharmacogenomics	None for this trial
Quality of Life	No specific assessments for this trial

Statistical Analysis	Summary statistics and analyses for safety will be provided along with information concerning patient demographics. The adverse event incidence rates and the frequency of study drug related adverse events, categorized by severity grades will be described. Listings of applicable laboratory test results collected during the study will be generated. Safety and efficacy analyses will be conducted every 6 months during the life time of the trial. Endpoints that will be analyzed include: progression-free survival and overall survival. Progression-free survival and overall survival will be estimated using the Kaplan-Meier procedure
Rationale for Number of Patients	Not Applicable for this trial

8. STUDY FLOWCHARTS (SCHEDULE OF EVENTS)

Procedure	Screening [a] / Baseline	Frequency of assessment	Post-treatment Discontinuation Visit[l]	Post-treatment Follow-up
Informed Consent [b]	X			
Reference of parent trial (including trial and patient identification)	X			
Performance Status (ECOG; Attachment B)	X	every month	X	
Disease Assessment	X	every 3 months	X	
Directed physical examination [d]		every month	X	
Hematology [e]	X	every month	X	
Chemistry [f]	X	every month	X	
Serum cholesterol and Triglycerides	X	every month		
Additional safety assessment for concomitant anticancer drug [g]	X [g]	X [g]	X [g]	
Serum β-HCG	X [h]	every 6 months		
Study drug administration[i]		every month	X	
Adverse Events [j, k]		To be recorded throughout study		
Concomitant Medication [k]	X	To be recorded throughout study		
Survival follow-up[m]				every 3 months

Table 8-1: Key

a Screening procedures are to be performed within 14 days prior to first dose of study drug on this extension trial, unless otherwise specified.

b Written consent must be obtained prior to performing any protocol-related procedure. Results of a test performed as part of routine clinical management or were required as part of the parent protocols is acceptable.

d Directed physical examination includes interim history, weight and a detailed physical examination as clinically indicated.

e Hematology assessments include complete blood count (CBC) with differential and platelet counts.

f Chemistry assessments include Sodium (Na), Potassium (K), Chloride (Cl), bicarbonate, blood urea nitrogen (BUN), creatinine, glucose, cholesterol, total bilirubin (direct and indirect), AST, ALT, alkaline phosphatase, calcium (Ca), phosphorous (PO_4), albumin, and total protein, in addition to the other laboratory tests listed in the table above.

g Patients receiving deforolimus in combination with other anticancer drugs should continue any additional safety assessments as required for these other drugs per the parent protocol or standards of care (e.g., cardiac monitoring for patients treated with deforolimus + doxorubicin)

h Serum pregnancy test for women of child-bearing potential is to be performed within 7 days prior to first dose of study drug received as part of this extension trail.

i For oral administration, patients and/or a caregiver will be trained for home administration of the study medication. Training must include the use of the Patient Diary (provided separately), study drug storage, management of missed doses, and emergency contact information. In addition, patients should be instructed to administer all doses at approximately the same time daily (± 2 hours) and not less than 2 hours following or preceding meals. Oral deforolimus may be self-administered by the patient throughout this trial. IV deforolimus will be administered in the clinic.

j All SAE and study drug-related adverse events must be followed to resolution or until another anti-cancer treatment is instituted.

k Adverse events and concomitant medications are to be collected through the Post-treatment Discontinuation visit.

l 30 days (± 7 days) after last dose of deforolimus.

m. Patients followed for survival should be contacted by telephone every 3 months from the date of treatment discontinuation visit or from the last time they were contacted until death or they end participation in the study.

9. INTRODUCTION

9.1 Mammalian target of rapamycin (mTOR)

The mammalian target of rapamycin (mTOR) is a serine-threonine kinase that functions as a central regulator of multiple signaling pathways that control cell growth, division, metabolism, and angiogenesis (Bjornsti and Houghton, 2004; Faivre et al., 2006; Brown et al., 1994; Schmelzle and Hall, 2000). mTOR is activated in response to environmental and nutritional conditions and plays a critical role in the transduction of proliferative signals mediated through the PI3K/Akt pathway by activating two key downstream proteins, the p70 S6 kinase (S6K) and the eukaryotic initiation factor 4E binding protein 1 (4E-BP1) (Janus et al., 2005). Both of these downstream proteins are involved in ribosomal biosynthesis and translation of specific mRNAs required for cell-cycle regulation (Brown et al., 1994; Schmelzle and Hall, 2000; Mamene et al., 2006). Dysregulation of the PI3K/Akt pathway has been linked to oncogenesis in many human cancers. Mechanisms underlying aberrant PI3K/Akt pathway activation include mutation and silencing of the PTEN tumor suppressor gene, activating mutations in the PI3K catalytic subunit, and Akt amplification (Chan, 2004; Hennessy et al., 2005).

9.2 Deforolimus

Deforolimus (also known as AP23573; MK-8669) is a nonprodrug analog of rapamycin that has been shown to inhibit mTOR activity, as evidenced by reduced phosphorylation of 4E-BP1 and S6 (Rivera et al., 2005; Rivera et al., 2004). Deforolimus also inhibits the proliferation of multiple tumor cell lines *in vitro* and *in vivo*, including tumors of breast, colon, lung, prostate, pancreas, and glial cells.

Deforolimus is currently in clinical development as a potential treatment for patients with advanced malignancies in 16 clinical trials (8 Phase 1 and 7 Phase 2 trials and 1 ongoing Phase 3 trial) by both the intravenous and oral routes of administration either as a single-agent or in combination therapy. Of these, 10 trials were with intravenous administration and 6 trials were with oral administration.

9.2.1 Single-agent, Intravenous Deforolimus

Two schedules for intravenous administration of deforolimus have been investigated: once weekly (Protocol AP23573-02-101, hereafter Trial 101), and once daily for 5 days every 2 weeks (QDx5, IV) (Protocol AP23573-02-102, hereafter Trial 102).

The safety profile of escalating dose levels of QDx5, IV deforolimus was established in Trial 102, which was a Phase 1, accelerated-titration, dose-escalation trial in adult patients (≥ 18 years of age) with refractory or advanced solid tumors. A total of 32 patients were treated at doses ranging from 3 to 28 mg daily. The maximum tolerated dose level was

determined to be 18.75 mg QDx5, IV. Frequent (≥ 20%) adverse reactions were mucosal inflammation, stomatitis, fatigue, rash, anemia, leukopenia, neutropenia, thrombocytopenia, diarrhea, constipation, vomiting, nausea, hyperglycemia, hypercholesterolemia, and hypertriglyceridemia.

Based on these Phase 1 results, the dosage of 12.5 mg QDx5, IV was recommended for further investigations of intravenous deforolimus.

Additionally, a Multi-center Phase 1 study of intravenous Deforolimus is currently ongoing in pediatric patients with advanced solid tumors. IV Deforolimus is being given (QDx5) x 2 weeks followed by a two week rest. One cycle is defined as 4 weeks. The starting dose level was 8 mg/m2 (10 mg maximum) and the MTD has yet to be determined.

9.2.2 Single-agent, Oral Deforolimus

The recommended dose schedule of oral deforolimus chosen is 40 mg daily for 5 consecutive days each week (QDx5/week). This dose schedule is being utilized in an ongoing randomized, placebo-controlled, blinded pivotal Phase 3 trial in sarcoma patients. This dose and schedule appear to provide a balance of the potential benefit of deforolimus treatment with the risk of adverse effects that are generally mild or moderate and manageable. This dose of oral deforolimus is supported by the preliminary data from the Phase 1 trial of single-agent oral deforolimus in patients with refractory or advanced malignancies in which 147 patients were enrolled and treated (Protocol AP23573-05-106; Trial 106). Trial 106 was designed to assess the safety, tolerability, and MTD of several dosing schedules of oral deforolimus, and found that a short holiday from dosing each week enhances tolerability and allows for substantially higher sustained cumulative doses. The main dose-limiting toxicity (DLT) for all schedules of oral deforolimus was mouth sores. The MTD for the QDx5/week schedule was 40 mg daily. This study further demonstrated that oral deforolimus has anti-tumor activity in patients with advanced cancers, has inhibitory activity on molecular targets, as assessed by pharmacodynamic assays, and has acceptable absolute bioavailability. The oral dose schedule selected from Trial 106 for use in future studies was 40 mg QDx5/week. This dosage schedule would provide an expected cumulative dose of 800 mg over 4 weeks, which is greater than the cumulative doses expected from continuous oral dosing schedules that have lower maximum tolerated doses.

9.2.3 Combination Trials

Four deforolimus combination trials with paclitaxel, capecitabine, doxorubicin, and trastuzumab have recently completed or are still ongoing. Maximum tolerated dose levels include:

(i) 37.5 mg deforolimus (IV) + 60 mg/m^2 paclitaxel or 12.5 mg deforolimus (IV) + 80 mg/m^2 paclitaxel when both agents are administered once weekly for 3 weeks of a 4 week cycle;

(ii) 75 mg deforolimus (IV) + 1650 mg/m^2 capecitabine, with deforolimus administered once weekly for 3 weeks of a 4 week cycle, and capecitabine administered orally in 2 divided daily doses for 14 consecutive days beginning on Day 1 of the cycle; and

(iii) 40 mg deforolimus administered orally on a QDx4 schedule in combination with 75 mg/m^2 doxorubicin (IV, every-3-weeks).

(iv) 40 mg deforolimus administered orally on a QDx5 schedule in combination with 4 mg/kg trastuzumab (IV, Loading dose week 1), followed by 2 mg/kg (IV, weekly).

Other combination trials are ongoing or will be initiated soon, in particular deforolimus + bevacizumab, deforolimus + MK-0646 (an inhibitor of IGF-1R), deforolimus + erlotinib, and others. These trials are Phase 1 and Phase 2 studies aimed at defining the early safety and efficacy of these combinations. It is anticipated that recommended doses for further investigations in specific indications will be identified in the future; it is possible that some patients who derive a benefit from the treatment will be candidate for an extension protocol, assessing the long-term safety and efficacy of deforolimus in these combinations.

9.2.4 Pharmacokinetic Studies with Deforolimus

Pharmacokinetic (PK) data following IV administration have revealed rapid tissue distribution and a slower elimination phase. Inter-individual variation in model-predicted PK parameters was modest within each dose cohort. Following weekly IV administration, the median terminal elimination half-life ($t_{1/2}$) was 48 hours, and the mean for each cohort ranged from 45 to 57 hours. Following QDx5 IV administration, the median $t_{1/2}$ was 61 hours, and the mean for each cohort ranged from 56 to 74 hours. The AUC and C_{max} increased less than proportionately with dose, particularly at dose levels above 50 mg QW and 15 mg QDx5, IV. This might be attributable to an increase in clearance with dose, and is consistent with saturation of distribution sites, such as red blood cells. The volume of distribution (V_{ss}) also increased with dose, which could be attributed to saturation of red blood cells which might allow for deeper penetration of deforolimus to other tissues.

The pharmacokinetics of deforolimus after oral administration was best characterized by a 2-compartment, oral absorption model consisting of central blood and peripheral tissue compartments with an additional absorption compartment representing the gastrointestinal tract. The compartments accounted for rapid exponential decline in blood concentrations followed by a slower exponential phase with linear elimination out of the body.

The mean (median) terminal elimination half-life ($t_{1/2\beta}$) of deforolimus across all doses following oral administration was 63.2 (42.6) hours. The terminal half life for different dose schedules, ranged from 31 to 110 hours. With terminal half-lives in this range, steady state would not be expected to be achieved until after 9 to 18 days of dosing. Mean absorption lag time (t_{lag}) ranged from 1.2 to 3 hours across all dosing regimens. Based on IV data from the

prior studies (Protocol AP23573-02-101 and AP23573-02-102) and oral data from this study (Protocol AP23573-05-106), the absolute bioavailability was estimated to be 18% to 21%.

The AUC and apparent total blood clearance (CL/F) were nonlinearly related to dose. Doses greater than 40 to 50 mg (up to 100 mg) across all schedules had similar mean parameter estimates, which suggests that there would be little benefit from administration of higher doses. Mean terminal half-life in the blood following oral administration of deforolimus at doses of 10 to 100 mg ranged from 41 to 90 hours, which was similar to that following IV administration.

9.2.5 Pharmacodynamic Studies with Deforolimus

Pharmacodynamic (PD) studies using peripheral blood mononuclear cells (PBMCs) as surrogate tissue have demonstrated *in vivo* mTOR inhibition following all IV and oral dose levels tested.

In Phase 1 clinical trials, mouth sores[1] have been the dose-limiting toxicity with most dose schedules tested, and the maximum tolerated doses (MTDs) for the IV dosing were 75 mg for the QW schedule and 18.75 mg for the QDx5 schedule. The MTDs for oral dosing were 50 mg for the QDx4 schedule, 40 mg for the QDx5 schedule, 15 mg for the QDx21 schedule, and 10 mg for the QDx28 schedule. Unlike chemotherapy-induced mucositis, mouth sores caused by deforolimus are similar to aphthous ulcers and can, depending on the specific location, cause significant discomfort.

9.2.6 Current Safety Information on Deforolimus

Deforolimus adverse drug reactions that have been commonly reported within any given trial include asthenia, fatigue, anorexia, mouth sores, rash, anemia, diarrhea, leukopenia/neutropenia, nausea, hypercholesterolemia, hypertriglyceridemia, vomiting, thrombocytopenia, and dysgeusia. Less frequent, treatment-related AEs include headache, fever, weight loss, paresthesia, alopecia, hyperglycemia, constipation, increased liver enzyme levels, hyponatremia, hypokalemia, hypophosphatemia, and nail disorders (discoloration and brittleness). These side effects were mostly mild or moderate in severity and were reversible. Other less frequent treatment-related AEs, including hypersensitivity reactions, have also been reported and are tabulated in the Clinical Investigator's Brochure. Notable, treatment-related serious adverse events resulting in hospitalizations include mouth sores, renal failure, tumor hemorrhage, and pneumonitis.

[1] Usually reported as mucositis. Other MedDRA preferred terms included under 'mouth sores' are aphthous stomatitis, gingival pain, gingival ulceration, glossitis, mouth ulceration, oral discomfort, oral pain, stomatitis and mucosal inflammation.

Please refer to the current edition of the deforolimus Clinical Investigator's Brochure for a complete description of all available safety information reported during the deforolimus clinical and non-clinical studies.

9.2.7 Current Efficacy Information on Deforolimus

Indications of antitumor activity in a broad range of tumor types have been reported in Phase 1 clinical trials, including partial and/or minor responses in patients with transitional cell carcinoma of the bladder, mesothelioma, malignant mixed mullerian carcinosarcoma, renal cell carcinoma, anaplastic large cell lymphoma, large cell carcinoma, non-small cell lung cancer, gastrointestinal stromal tumor, thyroid carcinoma, Ewing's sarcoma, and liposarcoma. In addition, prolonged periods of stable disease lasting ≥4 months have also been observed. These results support the continued study and development of deforolimus for the treatment of advanced malignancies. Towards this end, efficacy assessments and analyses are ongoing in Phase 2 trials of single-agent deforolimus in patients with hematological malignancies, prostate cancer, endometrial cancer, and soft-tissue and bone sarcomas.

9.3 Long-term Benefit from Deforolimus Treatment

As of 26 August 2008, 9 patients were continuing to receive deforolimus long-term (more than 24 months) on one of several parent trials (Table 9-1). All of these patients were either from the Phase 1 or 2 program. No patients were from the Phase 3 trial because of the recent activation of this trial in September 2007.

Table 9-2 Patients Currently Receiving Long-Term Deforolimus on Parent Clinical Trials

Protocol Number	Protocol Title / Short Description	No. Patients Enrolled [a]	No. Patients on deforolimus > 24 months
Intravenous Administration			
AP23573-02-101	Phase I dose escalation trial to determine the safety, tolerability, and maximum tolerated dose of weekly administration of AP23573 (QW) in patients with refractory or advanced malignancies	46	0
AP23573-02-102	Phase I dose escalation trial to determine the safety, tolerability, and MTD of dailyx5 administration of AP23573 (QDx5, IV) in patients with refractory or advanced malignancies	32	1
AP23573-04-103	Phase I sequential ascending dose trial of AP23573 (QDx5, IV) in patients with progressive or recurrent glioma	10	0
AP23573-04-104	Phase Ib pharmacokinetic and pharmacodynamic study to define the optimal dose for combining AP23573 (QW) with paclitaxel	29	~~0~~
AP23573-04-105	Phase Ib pharmacokinetic and pharmacodynamic study to define the optimal dose for combining AP23573 (QW) with capecitabine	32	0
AP23573-04-201	Phase II trial of AP23573 (QDx5, IV) in patients with relapsed or refractory hematologic malignancies	57	0

AP23573-04-202	Phase II trial of AP23573 (QDx5, IV) in patients with advanced sarcoma	212	0
AP23573-04-203	Phase II trial of AP23573 (QDx5, IV) in female adult patients with recurrent or metastatic endometrial cancer	45	0
AP23573-04-204	Phase II study of the efficacy and safety of AP23573 (QW) in patients with taxane-resistant androgen-independent prostate cancer	38	0
AP23573-07-110	Phase I study of IV Deforolimus administered QDX5 every other week in pediatric patients with advanced solid tumors	1	0
Oral Administration			
AP23573-05-106	Phase I/IIa dose escalation trial to determine the safety, tolerability and maximum tolerated dose of AP23573 when administered orally in patients with refractory or advanced malignancies (QDx4, QDx5, QDx6, QDx21, QDx28, BIDx4)	147	7
AP23573-05-107	Phase Ib dose escalation trial to determine the safety, tolerability, and maximum tolerated dose of oral AP2373 (QDx4, QDx14) in combination with doxorubicin (every 3 weeks)	37	1
AP23573-07-205	Randomized Phase II trial of oral Deforolimus (QDx5/Week) compared to IV progestin (QWeek) in women with advanced endometrial carcinoma following one line of chemotherapy	0	0
AP23573-08-206i	Phase II study of oral Deforolimus (QDx5/Week) in patients with metastatic and/or locally advanced recurrent endometrial cancer	0	0
AP23573-08-207	Phase II trial of oral Deforolimus (QDx5/Week) in combination with Trastuzumab for patients with HER-positive Trastuzumab-refractory metastatic breast cancer	2	0
AP23573-07-302	A Pivotal Trial to Determine the Efficacy and Safety of AP23573 when Administered as Maintenance Therapy to Patients with Metastatic Soft-Tissue or Bone Sarcomas	83	0

a: Number of patients receiving at least 1 dose of study treatment and with data in the study database as of August 2008.

Patients continuing on deforolimus parent protocols long-term are presumably deriving a clinical benefit from treatment. Patients benefiting from long-term deforolimus treatment have an undue burden of needing to comply with all of the follow-up procedures as described in the initial protocol if they want to continue on deforolimus treatment. Whereas the extensive or aggressive follow-up procedures are fully justified in the early phases of these trials that are designed to detect any efficacy and safety signals in short-term exposures, the procedures in the long-term follow up may not be needed in the later phases of clinical research and may have to be adapted for the long-term exposures.

- In long-term follow-up, the efficacy parameters are not expected to change substantially initially; however, long-term assessments should focus on the duration of response, progression-free survival, overall survival, and other long-term efficacy parameters
- In long-term follow-up, the probability of newly emergent acute or sub-acute adverse events is low. The focus should shift towards the detection of less frequent, chronic adverse events

A reduced, less intense follow-up would appear sufficient to detect, collect and analyze the long term efficacy and safety of deforolimus.

Summary

Many patients derive clinical benefit from treatment with deforolimus. An intense long-term follow-up of these patients is not required to detect the long-term efficacy and safety of deforolimus. An intense long term follow-up procedure as would be required if the patient were to remain on the parent trial would clearly represent an undue burden for these patients. The specific purpose of the present trial is to collect long-term safety and efficacy data from patients for whom a clinical benefit has been established in a prior clinical trial ("parent trial") with deforolimus, through simplified follow-up procedures.

10. STUDY OBJECTIVES

Primary objective

- To describe the long-term safety of deforolimus in patients for whom a clinical benefit has been established in a prior ("parent") clinical trial with deforolimus, as assessed by the parent trial investigator, and/or in those who continue in long-term follow-up.

Secondary objectives

- To describe the long-term efficacy of deforolimus in patients for whom a clinical benefit has been established in a prior ("parent") clinical trial with deforolimus, as assessed by the parent trial investigator, and/or in those who continue in long-term follow-up.
- To evaluate progressive-free survival and overall survival.

11. TRIAL DESIGN

11.1 Description of Trial Design

This is an open-label, non-randomized, single-arm, extension trial designed for the long-term evaluation of the efficacy and safety of deforolimus, in patients who have derived a clinical benefit from treatment with deforolimus, given either as single agent or in combination, in a prior parent protocol and for patients who continue in long-term follow-up. The patients will continue the treatment planned in the parent protocol, with a reduced and simplified follow-up. Treatment will continue as long as the investigator believes the patient is deriving benefit. After the treatment period ends, patients will continued to be followed until death, they withdraw consent, or they are removed from study for other reasons.

11.2 Selection of Trial Endpoints

Primary Endpoint

- Safety and tolerability of long-term deforolimus

Secondary Endpoints

- Progression-free survival, defined as the time from the date of enrollment in the prior parent trial to the date of documented progressive disease, recurrence or death (whichever occurs first)
- Overall survival
- Duration of objective response

11.3 Patient Population

This trial will evaluate the efficacy and safety of deforolimus in patients with advanced cancers who have derived a clinical benefit from therapy with deforolimus in a prior parent trial. The clinical benefit will have been assessed by the investigator in the prior parent trial. This trial will also evaluate progressive-free survival and overall survival among patients who have finished treatment with deforolimus.

11.4 Deforolimus Doses and Schedules

Patients will remain on the same dose and schedule of deforolimus (including other concomitant study medications) in this extension trial as in the parent trial at s/he is coming from.

In cases of where the parent trial is not clear for long-term oral or IV dosing, dosing and administration schedule guidelines will be based on current oral and IV dosage and administration schedules.

Dose modifications will be permitted for management of adverse events as stipulated in the subject's parent trial and reiterated in this protocol. Additional dosage and schedule modifications, beyond what is stipulated in the parent trial, may be considered by investigators after approval from the Sponsor.

11.5 Duration of Trial

Due to the nature of this extension trial, the trial duration and the estimated duration of each patient's participation in the trial cannot be specified. In the treatment portion of the trial, patients may stay on treatment as long as the risk benefit ratio is deemed to be positive by the investigator.

The overall risk benefit ratio for the entire patient population enrolled in this study will be assessed at least every 6 months. This assessment will serve as a basis to continue this extension study without modification or to amend, suspend or discontinue the study protocol.

For those patients who are in the follow-up portion of the trial, they will remain on trial until they are no longer eligible to continue, consent is withdrawn, death, or the sponsor decides to end the trial.

12. STUDY POPULATION

Patients will be eligible for this extension study if they have participated in a prior deforolimus trial and are continuing to receive deforolimus under the parent protocol or if they are being followed for overall survival (OS) under the parent protocol.

All patients must take part in the informed consent process for this protocol. During the consent process, the person obtaining consent must inform the patient of all elements of informed consent. Adequate time must be allowed for questions and for the patient to make a voluntary decision. No protocol specific procedures are to be performed until the patient has signed and dated an IRB/EC approved informed consent form. Each patient's participation in the trial begins with the signing and dating of the informed consent form. Patients must meet the inclusion and exclusion criteria to be enrolled in the trial.

12.1 Inclusion Criteria

Patients must meet <u>each</u> of the following criteria to be eligible for participation in this trial:

1. To be considered for enrollment in this extension trial, patients must have participated on a deforolimus parent trial.
2. Patients enrolled in this extension trial must have derived a clinical benefit from the parent trial, as assessed by the parent trial investigator, or continue to be in long-term follow-up for a deforolimus parent trial.
3. Patient is not on any other anti-cancer treatment(s) unless that therapy was allowed in the parent protocol. This includes chemotherapy, immunotherapy, biological response modifiers (excluding hematopoietic growth factors), or systemic hormonal therapy (see section 15.2 for more detailed list of exceptions)
4. ECOG performance status: ≤ 2 (see Attachment B) if the patient is scheduled to receive treatment with deforolimus; no requirement if the patient is included for follow-up purpose only.
5. Patients who are of childbearing potential and will be receiving study drug must have a negative serum pregnancy test within 7 days prior to screening evaluation and must use an approved contraceptive method as appropriate from time of study screening until 30 days after the last dose of study drug. Non-hormonal methods must be used in this trial. Approved contraceptive methods include, for example, intra-uterine device, diaphragm with spermicide, cervical cap with spermicide or female condom with spermicide. (Spermicides alone are not an acceptable method of contraception.)
6. Signed informed consent document stating that the patient understands the investigational nature of the proposed treatment.

12.2 Exclusion Criteria

- Has not participated on a parent trial.
- Women who are to receive study drug who are pregnant or lactating.
- Any condition in the Investigator's judgment that renders the patient unable to fully understand and provide informed consent and/or comply with the protocol

12.3 Number of Patients

Approximately 50 patients will be enrolled

12.4 Screening Failures

Not applicable.

12.5 Replacements

Not applicable.

13. STUDY PROCEDURES

Procedures to be performed during the study period for those patients who are on deforolimus are listed in Section 8: Schedule of Events.

13.1 Patient Enrollment

Patients in long term treatment and/or follow-up on a parent protocol, will be enrolled in the extension study using a procedure established by the Sponsor. Ideally, the off-treatment evaluations for the parent protocol will be used as the screening and baseline evaluations for this extension study.

13.2 Study Drug Administration

In this extension trial, patients will remain on the same study medication(s) (including other agents) with the same dose and schedule of deforolimus as the patient was on during the parent trial taking into account individual dose reductions and schedule modifications that have been made over the course of that prior trial.

In cases of where the Parent Trial is not clear for long-term oral or IV dosing. The following dosing and administration schedules can be used as guidelines for patients ≥ 13 years old:

- For single-agent oral deforolimus trials, the standard administration is 40 mg once daily for 5 consecutive days per week (QDx5/week). The oral formulation consists of 10mg enteric-coated tablets.
- For single-agent IV deforolimus trials, the standard administration is an IV infusion over 30 minutes on days 1-5 of each 14-day treatment course.
- Each treatment cycle will be 4 weeks (28 days) in duration

Dose modifications will be permitted for management of adverse events as stipulated in the subject's Parent Trial and Section 14.2 in this protocol. Additional Dosage and schedule modifications, beyond what is stipulated in the parent trial, may be considered by investigators after approval from the Sponsor.

13.2.1 Management of Missed Doses of Study Drug

Oral Study Drug: Patients who forget to take their scheduled dose of oral deforolimus will be instructed not to make up the missed dose. Missed doses will be recorded in an appropriate source record (e.g., clinic chart) and on the Patient Diary Card, if applicable.

IV Study Drug: Under certain circumstances, it may be necessary to adjust the dosing schedule for any given patient. Every attempt should be made to adjust the dosing schedule such that the patient receives all doses. If a dose is missed, the dose may be administered by extending the cycle by one day, if possible. For example, if a dose scheduled on a Monday was missed, the patient should be dosed for a 5-day course from Tuesday through Saturday. The following course of dosing should begin as scheduled on a Monday.

13.3 Treatment Discontinuation Visit

A Post-Treatment Discontinuation Visit will be conducted approximately one month (30 days ± 7 days) after the last dose of study drug for safety evaluations. Patients with ongoing, study drug-related adverse events at this follow-up visit should be followed until the AE has resolved, stabilized or returned to baseline status or another anti-cancer therapy is instituted.

13.4 Follow-up for Survival

Patients being followed for survival should be contacted by telephone every three months from the date of Treatment Discontinuation Visit or from the last time the patient was contacted in the parent trial until death, loss to follow-up, or unless otherwise informed by the Sponsor to discontinue further follow up visits.

13.5 Removal of Patients from Study Drug Administration or Assessment

In the event that a patient is withdrawn from the study, every effort will be made by the Investigator to document and report the reasons for withdrawal as thoroughly as possible. The reason(s) for termination must be clearly reported on the appropriate page of the patient's CRF. A CRF must be completed for any patient who has been enrolled.

If a patient on active treatment is prematurely discontinued from the trial for any reason, every effort must be made to perform all clinical and laboratory procedures as scheduled for the post-treatment discontinuation visit. In the event that the patient fails to return for the necessary visit(s), an effort must be made to contact the patient to determine the reason and this information should be documented in the appropriate source record for the patient.

13.6 Criteria for Discontinuation

Patients will be discontinued from further study drug administration in the event of any of the following:

- Intolerable adverse drug reaction, either to deforolimus single agent or to a deforolimus combination
- Documented disease progression
- Significant deviation from the protocol or eligibility criteria. Such patients will be considered to have protocol violations and will be removed from study.
- Noncompliance with study or follow-up procedures
- Patient decision (election to discontinue study treatment versus further study participation)
  - Patients choosing to discontinue study treatment (without full withdrawal of consent to study participation) should be encouraged to continue participation in follow-up procedures; continued survival follow-up should be strongly encouraged.
- Termination of the study by the Sponsor
- Any other reason which, in the opinion of the Investigator, would justify removing the patient from the study.

14. STUDY DRUG

14.1 Study Drug Administration

Study drug will be administered only to eligible enrolled patients at a center listed on the FDA Form 1572. Once study treatment has been initiated, study drug administration may continue until such time that the discontinuation criteria have been met (see Section 13.6: Criteria for Discontinuation).

14.1.1 Single-agent Intravenous Deforolimus

Deforolimus will be administered at the investigational site. Prior to the infusion of study drug, the study staff should ensure that the intravenous access established for the patient is adequate for infusion of study drug over the specified period. Study drug solution will be delivered via a central venous catheter or port (if available) or a peripheral vein. The access device should be flushed with normal saline or water for injection prior to and following study drug administration. The study drug should not be co-administered with other drugs in the same infusion line.

Patients will receive deforolimus at the dosage and schedule defined in the parent trial. If the deforolimus dosage had been adjusted in the parent trial, the patient will start the extension trial at the adjusted dosage. Study drug solution will be administered, at a constant rate, over a 30 ± 5 minute period using an automatic dispensing pump (or timed infusion pump).

In cases of where the Parent Trial is not clear for long-term IV dosing. The following dosing and administration schedules can be used as guidelines for patients ≥ 13 years of age:

- For single-agent IV deforolimus trials, the standard administration is an IV infusion over 30 minutes on days 1-5 of each 14-day treatment course.
- Each treatment cycle will be 4 weeks (28 days) in duration

Dose modifications will be permitted for management of adverse events as stipulated in the subject's Parent Trial. Additional dosage and schedule modifications for deforolimus, beyond what may be stipulated in the parent trial, are described in Section 14.2. Any further dose reductions or delays may be considered by investigators after approval from the Sponsor.

Qualified medical personnel will carefully monitor intravenous infusions of study drug. Such personnel must be available throughout the course of study drug administration to evaluate and treat any adverse event(s), as well as to evaluate whether continued participation of the patient in the study is warranted or advisable. If clinical symptomatology suggests a rate of infusion-related toxicity or hypersensitivity reaction, the infusion will be interrupted and appropriate medical therapy instituted and/or modification to study drug infusion will be made (see Section 14.2.3.1).

14.1.2 Single-agent Oral Deforolimus

Oral deforolimus may be self-administered by the patient. Patients will continue on the dose and schedule defined in the parent trial.

If the deforolimus dosage had been adjusted in the parent trial, the patient will start the extension trial at the adjusted dosage.

In cases of where the Parent Trial is not clear for long-term oral dosing. The following dosing and administration schedules can be used as guidelines for patients ≥ 13 years of age:

- For single-agent oral deforolimus trials, the standard administration is 40 mg once daily for 5 consecutive days per week (QDx5/week). The oral formulation consists of 10mg enteric-coated tablets.
- Each treatment cycle will be 4 weeks (28 days) in duration

Dose modifications will be permitted for management of adverse events as stipulated in the subject's Parent Trial. Additional dosage and schedule modifications for deforolimus, beyond what may be stipulated in the parent trial, are described in Section 14.2. Any further dose reductions or delays may be considered by investigators after approval from the Sponsor.

14.1.3 Deforolimus in Combination

Deforolimus and combination drugs will be administered at the dosages defined in the parent trial. If the dosage of deforolimus and/or combination drugs had been adjusted in the parent trial, the patient will start the extension trial at the adjusted dosages.
Further dose reductions or delays of treatment due to drug-related adverse events for deforolimus are described in Section 14.2.

14.2 Management of Adverse Drug Reactions - Deforolimus

14.2.1 General Adverse Drug Reactions and Dose Modifications for Oral Deforolimus

Comprehensive assessments of any study drug-related adverse events (adverse drug reactions) including any serious adverse events experienced by the patient will be performed throughout the course of the study. Anticipated adverse drug reactions that may be experienced are described below, and in the Clinical Investigator's Brochure. Appropriate management of the patient for any adverse event experienced while participating in this trial will be determined by the severity of the event and the clinical judgment of the investigator and medical monitor.

The dosage modification rules for the majority of adverse drug reactions for oral deforolimus are detailed in Table 14.2-1. This table outlines the recommended dose modification steps of deforolimus in the event a patient has ≥ Grade 2 adverse event (other than pneumonitis or mouth sores) believed to be related to deforolimus. Occurrence refers to a specific, repeating adverse event. That is, "second" means the second episode of the event following resolution of the first episode to ≤ Grade 1. For purposes of the example, it is assumed that patients are taking the drug on a Monday-to-Friday schedule.

See Table 14.2-2 for additional guidance on management of mouth sores.

Table 14.2-1: Management of Oral Deforolimus Dose Modifications for All Adverse Drug Reactions, Except Mouth Sores and Pneumonitis

Occurrence*	Action until Friday	Sat/Sun	Action during next week	Sat/Sun	Action during second week or more
First	Decrease dose to 10 mg (1 tablet)	No drug	If AE ≤ Grade 1 (resolved) on Monday may increase dose to 40 mg; otherwise continue at 10 mg through Friday	No drug	If AE resolved on Monday, may increase dose to 40 mg; otherwise stop drug until resolution and resume at 40 mg
Second	Decrease dose to 10 mg (1 tablet)	No drug	If AE resolved on Monday may increase dose to 30 mg for remainder of study; otherwise continue at 10 mg through Friday	No drug	If AE resolved on Monday may increase dose to 30 mg for remainder of study; otherwise stop drug until resolution and resume at 30 mg
Third	Decrease dose to 10 mg (1 tablet)	No drug	If AE resolved on Monday may increase dose to 20 mg for remainder of study; otherwise continue at 10 mg through Friday	No drug	If AE resolved on Monday may increase dose to 20 mg for remainder of study; otherwise stop drug until resolution and resume at 20 mg
Fourth	Decrease dose to 10 mg (1 tablet)	No drug	Continue drug at 10 mg through Friday	No drug	If AE resolved on Monday may continue on drug at 10 mg; otherwise stop drug until resolution and resume at 10 mg or consider withdrawal of patient
* should include adverse events that occurred in the parent protocol in addition to the extension protocol.					

14.2.2 Mouth Sores for Oral Deforolimus

Mouth sores were commonly reported among patients who received deforolimus. Terms for mouth sores or "mucositis" included aphthous stomatitis, gingival pain, gingival ulceration, glossitis, mucositis, mouth ulceration, oral discomfort, oral pain, stomatitis, and mucosal inflammation. The sores associated with deforolimus are distinct punctuate ulcers that most closely resemble aphthous ulcers. They are usually painful and can be up to 1 cm in widest diameter. The onset of mouth sores following the first dose of deforolimus may occur as early as during the first week of treatment and usually resolves during regularly scheduled treatment holidays or following dose reductions and/or delays.

Treatment of mouth sores should include dose modifications as described in Table 14.2-2, as well as palliative pain management with the type and strength of the analgesia escalating in parallel with the severity of the mouth sore pain. Topical analgesics may be employed if felt to be beneficial. The following treatment plan is suggested:

- Bicarbonate rinses 4 times a day every day if there are *any* oral mucosal symptoms or signs. (There do not have to be actual ulcers to institute this prophylactic measure.)
- At the appearance of mouth sores, use topical analgesics such as Orajel® Medicated Mouth Sore Swabs, or equivalent, as needed to achieve pain relief and allow normal eating.
- Use other agents such as Gelclair® or anesthetic mouth washes only if dose reduction and application of topical analgesics do not result in pain control.

Table 14.2-2: Dose Modifications of Oral Deforolimus for Mouth Sores[a]

NCI CTCAE Grade [b]	Dose Delay and or Reduction Required
GRADE 1	Continue treatment without dose interruption or reduction. Begin symptomatic treatment and prophylaxis.
GRADE 2 or higher	First episode [c] ➢ Reduce dose to 10 mg per day for remainder of week. • Resume 40 mg per day after the two-day break if improvement to Grade 1 or less • If Grade 2 or higher, dose 10 mg per day for additional week Second episode [c] ➢ Reduce dose to 10 mg per day for remainder of week. • Resume 30 mg per day after the two-day break if improvement to Grade 1 or less • If Grade 2 or higher, dose 10 mg per day for additional week Third episode [c] ➢ Reduce dose to 10 mg per day for remainder of week. • Resume 20 mg per day after the two-day break if improvement to Grade 1 or less • If Grade 2 or higher, dose 10 mg per day for additional week Fourth episode or greater [c] ➢ Stop treatment until improved to ≤ Grade 1 ➢ Improvement occurs in ≤ 2 weeks • Resume at 10 mg per day ➢ Improvement occurs in > 2 weeks • Contact Medical Monitor and consider permanently discontinuing study treatment

a: Mouth sores refers to the following terms: aphthous stomatitis, gingival pain, gingival ulceration, glossitis, mouth ulceration, oral discomfort, oral pain, stomatitis, and mucosal inflammation.

b: NCI CTCAE Grade (version 3) based on functional/symptomatic criteria described for mucositis /stomatitis

c: This should include adverse events that occurred in the parent protocol in addition to the extension protocol.

14.2.3 Management of Hypersensitivity and Other Reactions During IV Administration of Deforolimus

14.2.3.1 Pre-Medications/Therapy for Infusion Site or Hypersensitivity Reactions

As of March 25, 2008, there have been no reports of infusion site reactions related to deforolimus in any of the past or ongoing clinical trials.

1. If clinical symptomatology suggests a hypersensitivity reaction, the infusion will be interrupted and appropriate medical therapy instituted.
2. Patients with demonstrated Grade 1 or 2 hypersensitivity reactions will be premedicated in advance of future study drug administration. The following

premedications, including H_2-receptor antagonists and/or corticosteroid therapy, may be administered:

- Recommended dose of diphenhydramine, 25-50 mg, IV, 30 minutes prior to study drug infusion
- Recommended doses of H_2-receptor antagonists, 30 minutes prior to infusion, are as follows: IV; ranitidine, 50 mg, IV; or famotidine, 20 mg, IV
- Recommended corticosteroid regimen of dexamethasone, 8 mg, po, bid x 3 days (starting one day prior to AP23573 dosing)

3. Patients who experience a Grade 3 or 4 hypersensitivity reaction will be discontinued from further study drug administration.

Any medications administered for either prophylaxis or therapy of symptoms considered to be associated with study drug administration should be documented on the appropriate page of the patient's CRF.

14.2.3.2 Study Drug Infusion Modifications

If clinical symptomatology suggests a ***rate of infusion-related adverse event***, or if clinically significant changes in vital signs occur, the ***infusion will be interrupted*** for approximately 30 minutes in order to allow for amelioration or resolution of the potential rate-related toxicity. The infusion may be resumed at a slower rate such that the infusion will be complete within a longer time period (approximately 2 hours). Such modifications must be carefully documented on the patient's CRF.

In the event of an unacceptable $\geq$ Grade 3 adverse drug reaction, or significant clinical symptomatology that is not controlled by optimal supportive care, the Investigator ***will discontinue*** the study drug infusion prior to delivery of the full dose.

14.2.4 General Adverse Drug Reactions and Dose Modifications for IV Deforolimus

Dose Delays and Reductions

Dose delays and/or reductions will be implemented for patients who experience adverse drug reactions as indicated in following sections

Starting Dose Level	First Reduction*	Second Reduction*
Dose Level 1 (12.5 mg)	10 mg	7.5 mg

* should include adverse events that occurred in the parent protocol in addition to the extension protocol.

Once reduced, patients will continue study drug administration at the reduced dose level throughout the remainder of the active study period. If an adverse drug reaction is not adequately controlled following two dose reductions, further dose reductions should be discussed with the Sponsor or the patient should be discontinued from the study. If the patient is on a different starting IV dose level other than 12.5mg, dose reductions should be discussed with the Sponsor.

14.2.4.1 Dose Delay and/or Reduction for Grade 1 or 2 Adverse Drug Reactions

In the event of a Grade 1 or 2 adverse drug reaction that is not controlled by optimal supportive care, or is intolerable due to symptomatology or interference with normal daily activities, the patient may be managed by extending the interval between two scheduled doses for up to two weeks to allow for amelioration or resolution of the event. In these cases, subsequent study drug administration must be at the reduced dose level according to the above schedule. If a delay is required following two dose reductions, the patient should be discontinued from further study drug administration.

14.2.4.2 Dose Reduction With /Without Dose Delay for Grade 3 or 4 Adverse Drug Reactions

In the event of a Grade 3 or 4 adverse drug reaction, the patient may be managed by either dose reduction according to the above schedule, or a decision may be made to discontinue the patient from further study drug administration. Study drug administration (at the reduced dose level) may be delayed for up to two weeks to allow for amelioration or resolution of the event. If a delay is required following two dose reductions, further dose reductions should be discussed with the Sponsor, or the patient should be discontinued from further study drug administration.

Patients with stable disease or response may continue on study without a dose reduction and in the presence of a Grade 3 or 4 adverse drug reaction at the discretion of the Principal Investigator and following discussion with the Sponsor.

14.2.5 Dose Re-escalation

Once a patient has undergone a dose reduction, re-escalation will not be allowed.

14.2.6 Dose Modifications for Oral or IV Deforolimus in case of Pneumonitis and/or Hypertriglyceridemia/Hypercholesterolemia

14.2.6.1 Pneumonitis

Interstitial pneumonitis or bronchiolitis obliterans and/or organizing pneumonia have been observed in patients receiving rapamycin and rapamycin analogs, including deforolimus (Hidalgo, 2004; Champion et al., 2006; Duran et al., 2006; Nashan et al., 2004). Pneumonitis may be asymptomatic or may be associated with symptoms such as dyspnea, cough, hemoptysis and fever. Pulmonary opacities noted on thoracic radiographs need to be distinguished from progressive metastatic disease.

Across all clinical trials, pneumonitis has been reported for approximately 2% to 4% of the more than 650 patients who had been treated with deforolimus as of March 2008. Several of these patients experienced additional prolonged stable disease after resumption of treatment following dose interruption or steroid treatment. Patients receiving the IV formulation of deforolimus have resumed treatment for as long as 18 months. Among the 147 patients enrolled and treated in the Phase 1 oral deforolimus trial (Trial 106), pneumonitis was reported for 10 patients (6.8%).

Patients participating in this trial may have a diagnosis of pneumonitis under two circumstances: 1) as the result of the investigation of respiratory symptoms or 2) detection by scheduled tumor assessment scans for this trial. While reviewing patient scans for tumor progression, the clinician and radiologist should consider pneumonitis as a cause for a pulmonary lesion. What follows are guidelines for the treatment of patients diagnosed with pneumonitis deemed related to deforolimus.

The treatment of symptomatic patients differs from asymptomatic patients. Patients with symptomatic pneumonitis should immediately stop receiving study drug and have an evaluation to rule out other causes, such as infection. If the diagnosis is study drug-associated (deforolimus) pneumonitis, the following recommended treatment plan should be applied.

Recommended treatment for patients with symptomatic pneumonitis:

- If ≤ Grade 2: Dose interruption and steroid intervention with option to return to treatment if improvement to Grade 1 or resolution within 4 weeks
  - Patients should begin a regimen of steroids (prednisone 60-80 mg QD 1-2 weeks) tapering over 1-4 weeks. Study drug may be resumed after clinical improvement is observed

- If ≥ Grade 3: Immediate discontinuation

After improvement of the pneumonitis to ≤ Grade 1, the following rules should apply for those on oral deforolimus (for IV recommendations call the sponsor):

- First episode of pneumonitis (including any parent trial episodes)
  - Improvement occurs in ≤ 2 weeks – Resume full dose
  - Improvement occurs in > 2 weeks – Resume at 10 mg lower than starting dose
- Second episode of pneumonitis (including any parent trial episodes)
  - Permanently discontinue study treatment if upon study drug rechallenge patient develops pneumonitis ≥ Grade 2

Recommended treatment for patients with asymptomatic pneumonitis:
Patients who are asymptomatic but have findings of pneumonitis should stop study drug for one week and during that week receive steroids (60 mg prednisone). If there is no improvement in the signs of pneumonitis, additional diagnostic procedures should be considered, such as bronchoscopy, to confirm the diagnosis. If there is improvement in the pneumonitis, the patient may resume treatment with study drug while undergoing a 1-2 week taper of the steroids. The patient should be followed every 2-4 months by chest x-ray to monitor for recurrence of the pneumonitis.

14.2.6.2 Hypertriglyceridemia/Hypercholesterolemia

Hyperlipidemia is a common adverse reaction associated with rapamycin analogs. Clinically significant elevations above baseline levels of cholesterol and/or triglyceride levels should be immediately managed with respect to the patient's overall condition; both statins and fibrate agents have been used in patients receiving AP23573. In principle, no dose interruptions or reductions should occur. However, for patients with persistent hypercholesterolemia despite therapy with statins or fibrates, dose reduction or interruption may be considered.

14.3 Dose Modification for Unrelated Adverse Events

Dosage interruptions are permitted in the case of medical/surgical events (e.g., elective surgery, unrelated medical events) not related to study drug administration. The reason for the interruption must be documented in the patient's chart.

14.4 Other dose Modifications

Investigators may consider dose modifications other than those described in sections 14.1 to 14.3: for example, long-term therapy could be administered at a reduced frequency while maintaining the overall benefit for the patient (e.g., administering IV deforolimus for

5 consecutive days every 3 weeks instead of every 2 weeks). These dose modifications must be discussed with and approved by the Sponsor.

14.5 Formulation, Packaging, and Labeling – Deforolimus

Oral deforolimus
Deforolimus tablets are manufactured as enteric-coated tablets for delayed release. One tablet strength (i.e., 10 mg) will be used for this study. Each tablet contains 10 mg of deforolimus active pharmaceutical ingredient and typical pharmaceutical excipients. The study drug is packaged in a child-resistant aluminum blister pack and will be removed from the blister packs by the patient at the time of administration.

Intravenous deforolimus
Deforolimus vials contain deforolimus drug product (62.5 mg/mL in 2 mL 100% ethanol). In addition, a second vial, that contains deforolimus diluent (5.2 % propylene glycol, 5.2 % polysorbate 80 [Tween 80], in Water for Injection; 9.6 mL) will be provided. Vial Labels will bear the appropriate label text as required by governing regulatory agencies.

The study drug is light sensitive and must be protected from direct and indirect light during preparation and administration.

Study drug is to be prepared as described in the Directions For Use insert provided with each drug shipment. Briefly, 0.4 mL of deforolimus drug product Vial 1 is to be transferred into the Diluent Vial, yielding a stock solution containing the following: 2.5 mg/mL study drug stock solution (25 mg in 10.0 mL total volume) in 4% ethanol, 5% propylene glycol, 5% polysorbate 80 (Tween), in water for injection.

The stock solution should be used within 2 hours following preparation, stored at room temperature, and protected from light.

The study drug dosing solution is then prepared by transferring the appropriate volume of stock solution into a glass bottle or non-PVC bag containing approximately 250 mL of Normal Saline.

Gently invert the infusion bottle or bag several times to ensure that the dosing solution is well mixed.

The dosing solution should be stored at room temperature, protected from light, and administered within six hours following preparation (study drug contains no preservative or bacteriostatic agents). Only non-PVC infusion sets must be used. In-line filters must not be used.

14.6 Storage and Stability – Deforolimus

Oral deforolimus
The recommended storage condition for deforolimus tablets is refrigerated at 2ºC to 8°C (36°F to 46°F). Formal ICH stability studies are ongoing to determine the shelf life of the product. Currently, the stability period for deforolimus tablets is at least 18 months under refrigeration.

Intravenous deforolimus
The recommended storage condition for deforolimus drug product (vial 1) is ≤ -20ºC. The recommended storage condition for deforolimus diluent (vial 2) is 2ºC to 8ºC. Formal ICH stability studies are ongoing to determine the shelf-life of the product. Currently, the retest period for deforolimus drug product is 26 months and deforolimus diluent is at least 36 months.

14.7 Drug Accountability – Deforolimus

14.7.1 Dispensing of Study Drug and Dosing Compliance

The study pharmacist at the site will be responsible for handling study drug and completion of associated paperwork.

Supplies are shipped to the investigational site at appropriate intervals, depending on patient accrual. The site must use an appropriate dispensing log/accountability form provided by the Sponsor or an acceptable substitute approved by the Sponsor. Each time a kit is dispensed for a patient the following information must be recorded: patient initials, patient study number, the kit number dispensed with their corresponding lot number, and the initials of the person dispensing the dose. These logs are to be maintained by the study pharmacist in the pharmacy throughout the duration of the study and will be periodically verified by a representative of the Sponsor.

14.7.2 Disposition of Used Supplies

Use of deforolimus tablets or IV product outside the scope of this trial is NOT authorized by the Sponsor. The Principal Investigator or his/her designee will be responsible for the appropriate handling and disposition of any remaining unused study drug and containers.

14.7.3 Inventory of Unused Supplies

During the trial and at termination, patients must return all unused oral drug supplies to the investigational site and this must be recorded. These returned supplies must not be redispensed.

Periodically throughout and at the conclusion of the trial, a representative of the Sponsor will conduct an inventory of unused study drug. At the completion of the trial, a final drug accountability review will be conducted. Any discrepancies must be investigated and all unused study drug MUST be returned to the Sponsor, or designee, with the appropriate forms unless otherwise authorized in writing by the Sponsor.

15. CONCOMITANT TREATMENTS

All concomitant medications administered during the active study period are to be reported on the appropriate case report forms for each patient.

15.1 Permitted Treatment

Palliative and supportive care will be provided during this trial, as clinically indicated, and in accordance with the standard practices of the institution. Clinical judgment should be utilized in the treatment of any adverse event experienced by the patient.

Information on all concomitant medications, blood products administered, as well as interventions occurring during the study period must be recorded on the patient's case report form.

15.2 Prohibited Treatment

Surgery or radiotherapy for tumor control is not permitted while patients are on treatment.

The following drugs and other treatments are not permitted:

- Anti-cancer treatments including chemotherapy, immunotherapy, biological response modifiers (excluding hematopoietic growth factors), and systemic hormonal therapy
  Exceptions:
  - When the agent was allowed during the parent protocol
  - hormonal therapy (e.g., Megace) for appetite stimulation
  - nasal, ophthalmic, and topical glucocorticoid preparations
  - a stable dose of corticosteroids for at least two weeks
  - low dose maintenance steroid therapy for other conditions
  - physiologic hormone replacement therapy (e.g., thyroid supplementation for thyroid deficiency or oral replacement glucocorticoid therapy for adrenal insufficiency)

- Herbal preparations or related OTC preparations containing herbal ingredients that are known to affect CYP3A isoenzymes (e.g., St. John's Wort)
- Elective use of recombinant hematopoietic growth during study treatment

15.3 Potential Drug Interactions

Caution should be used when administering concomitant medications that induce, inhibit, or are metabolized by cytochrome P450 (CYP3A). Deforolimus is extensively metabolized by CYP3A. As a result, the potential for drug-drug interactions should be considered. Concomitant administration of products that interfere with P450 enzyme systems (see Attachment C) will be clearly documented in the CRF. The use of such agents should be avoided whenever possible.

Caution should also be used when administering concomitant medications, such as warfarin, propranolol, phenytoin, and diazepam, which are extensively bound to plasma protein. *In vitro*, deforolimus was found to be 96.8% bound to plasma proteins. *In vivo*, it is likely that most deforolimus will be bound to FKBP in red blood cells because of the high affinity of deforolimus for FKBP. Thus, it is anticipated that a very small amount of deforolimus will be in plasma at any given time. Nevertheless, drugs that are extensively bound to plasma proteins may displace deforolimus from binding sites in plasma. Concomitant administration of products that are bound to plasma proteins must be clearly documented in the CRF.

16. MEASURES TO MINIMIZE/AVOID BIAS

As this is an open label study, bias minimization is not applicable.

17. INTERIM SAFETY AND EFFICACY ANALYSIS

Safety and efficacy analyses will be conducted and the overall risk benefit ratio of long-term deforolimus treatment will be assessed every 6 months during the trial. The available data will be reviewed by a team comprised of the Sponsor's representatives, including at least the Sponsor's medical monitor, 20% of principal investigators of the sites with enrolled patients, and any other individuals deemed appropriate by the Sponsor.

18. SAFETY

18.1 Safety Assessment

Safety will be assessed by physical examination, interim history, and laboratory assessments. Severity of adverse events will be graded according to the NCI Common

Terminology Criteria for Adverse Events (CTCAE), Version 3.0 (provided with the study administration documents).

18.2 Safety Assessment Methods

Patients who did not receive any protocol treatment during the extension this trial will not be included in the safety analysis. All patients who received any study treatment on this extension protocol will be included in the safety analysis according to their actual treatment. Patients will be monitored for the occurrence of adverse events (AEs) from the time of signing informed consent through the post-treatment discontinuation visit.

Safety evaluations will be based on the incidence, intensity, and type of adverse events, and clinically significant changes in the patient's physical examination findings, vital signs and clinical laboratory results. Safety variables will be tabulated and presented for all patients who receive any amount of study medication.

The incidence of adverse events will be evaluated. Patients are to be followed for adverse events through the post-treatment discontinuation visit. All study drug-related adverse events and all serious adverse events will be followed until resolution or until administration of another anti-cancer therapy. All safety assessments will be recorded on the CRF.

Serum pregnancy tests (ß-HCG) in women of child-bearing potential will be performed according to the Schedule of Events (see Section 8: Schedule of Events).

19. STATISTICAL ANALYSIS

19.1 Study Overview

Patients will be eligible for the extension study if they have participated in a prior deforolimus trial and are continuing to receive deforolimus under the parent protocol or if they are being followed for overall survival (OS) under the parent protocol.
Patients may continue to receive deforolimus and/or be followed for overall survival (OS) during the extension study.

19.2 Endpoints

Primary Endpoint
- Safety and tolerability of long-term deforolimus

Secondary Endpoints
- Progressive Disease (PD) will be assessed by the investigator as determined by the parent protocol. For consistency, the RECIST guidelines are used in most cases, when applicable.
- Overall survival, defined as the time from the date of first dose of study drug in the parent trial to the date of death,

Progression-free survival (PFS), overall survival (OS), and duration of response will be evaluated using the Kaplan-Meier method and graphed as in the parent protocols. Progression free survival, overall survival, and duration of response at fixed time points (e.g., 6 months, 12 months, and 2 years), will be estimated using the Kaplan-Meier method. Confidence intervals for PFS, OS, and duration of response will be computed and graphed.

20. CONTRAINDICATIONS, PRECAUTIONS, AND WARNINGS

20.1 Precautions Regarding Procreation

Deforolimus does not induce microbial or mammalian cell gene mutations *in vitro*, and does not produce chromosomal aberrations *in vitro* or *in vivo*. Reproductive effects have not been studied in women. Reproductive effects of deforolimus were seen in repeat-dose studies in rats. In repeat-dose toxicity studies with IV deforolimus, deforolimus was associated with testicular degeneration with decreased epididymal spermatogenesis. In preliminary results from the dose-ranging portion of a fetal development study in female rats, the incidence of early fetal resorption was 100% for all doses of deforolimus tested (i.e., 10, 25, 50, and 100 mg/kg/day). Early embryonic or fetal mortality is a class effect that has been reported with other mTOR inhibitors.

Women of childbearing potential will be informed as to the potential risk of procreation while participating in this trial and will be advised that they must use approved contraceptive method as appropriate from time of study screening until 30 days after the last dose of study drug. Non-hormonal methods must be used in this trial. Approved contraceptive methods include, for example, intra-uterine device, diaphragm with spermicide, cervical cap with spermicide or female condom with spermicide. (Spermicides alone are not an acceptable method of contraception.). A pregnancy test will be performed on each pre-menopausal female of childbearing potential immediately prior to entry into the study (at the time of Baseline for this study), every 6 months while on study, and at the post-treatment discontinuation visit.

If a patient is confirmed to be pregnant during the trial, study drug administration must be discontinued immediately. Any pregnancy occurring during this study is to be reported as an SAE. The Investigator must immediately notify the medical monitor about the pregnancy and record it as a Serious Adverse Event on the SAE Form as well as on the adverse event page of the CRF (or other CRF specifically provided for this purpose). In addition, the Investigator must report follow-up information to the Sponsor regarding the course of the pregnancy, including perinatal and neonatal outcome, regardless of whether the patient has discontinued participation in the study, unless the patient has received other anti-cancer therapy.

Once the newborn is determined to be healthy, additional follow-up will no longer be required.

20.2 Additional Precautions

Caution should be used when administering concomitant medications that induce, inhibit, or are metabolized by cytochrome P450 or that are extensively protein bound (see Section 15.4: Potential Drug Interactions).

Caution should also be used when administering concomitant medications, such as warfarin, propranolol, phenytoin, and diazepam, which are extensively bound to plasma protein. *In vitro*, deforolimus was found to be 96.8% bound to plasma proteins. *In vivo*, it is likely that most deforolimus will be bound to FKBP in red blood cells because of the high affinity of deforolimus for FKBP. Thus, it is anticipated that a very small amount of deforolimus will be in plasma at any given time. Nevertheless, drugs that are extensively bound to plasma proteins may displace deforolimus from binding sites in plasma.

Please refer to the current edition of the deforolimus Clinical Investigator's Brochure for a complete description of all available safety information reported during the deforolimus clinical and non-clinical studies.

21. ADVERSE EVENTS

21.1 Adverse Event Definition

An adverse event (AE) is defined as any unintended or undesirable, noxious, or pathological change, compared to pre-existing conditions, experienced by a patient during a clinical study or the follow-up period, regardless of relationship to study drug. Adverse events include:

- Suspected adverse drug reactions
- Reactions from drug overdose, abuse, withdrawal, sensitivity, or toxicity
- Significant changes or abnormalities, when compared to baseline, in structure (sign), function (symptom), clinical laboratory results, or physiological testing. This

includes any worsening of a pre-existing condition temporally associated with the use of study drug
- Other medical events, regardless of their relationship to the study drug, such as injury, surgery, accidents, extensions of symptomatology, or apparently unrelated illnesses

21.2 Evaluating Adverse Events

21.2.1 Determination of Seriousness

The Investigator will determine the seriousness of an adverse event based on the following definitions:

1. Serious Adverse Events (SAEs)

   An SAE is any adverse event occurring at any dose that:
   - Results in death
   - Is life-threatening or places the patient, in the view of the investigator, at immediate risk of death as the event occurred (note: this does not include an adverse event that had it occurred in a more severe form, might have caused death).
   - Results in in-patient hospitalization or prolongation of existing hospitalization
   - Is a persistent or significant disability/incapacity
   - Is a congenital anomaly/birth defect (in offspring of a patient who is taking or has taken study medication)
   - Is a new cancer (does not include metastasis or progression of primary cancer unless the metastasis or progression meets one of the 5 serious criteria stated above)
   - Is an overdose (accidental or intentional)
   - Other important medical events that may not result in death, not be life threatening, or not require or prolong hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above

Hospitalization refers to admission of a patient into a hospital for any length of time.
A prescheduled or elective procedure or routinely scheduled treatment will not be considered an SAE, even if the patient is hospitalized, provided the study site stipulates:

- The prescheduled elective procedure or routinely scheduled treatment was scheduled (or was on a waiting list to be scheduled) prior to obtaining the patient's consent to participate in the study.
- The condition requiring the prescheduled elective procedure or routinely scheduled treatment was present before and did not worsen or progress between the patient's consent

The term "life-threatening" describes any adverse event or experience, suspected to be drug related that places the patient or subject in the view of the investigator, at immediate risk of death at the time of the event. This does not include events that may have caused death had they been more severe.

Persistent or significant disability refers to a significant disruption of a person's ability to conduct life functions.

A congenital anomaly/birth defect refers to a fixed, permanent impairment established at or before birth.

For the purposes of this protocol, a deforolimus overdose is defined as:

(a) Oral formulation:
- A single dose in excess of 100 mg
- A cumulative 28-day dose of greater than 800 mg for daily or intermittent dosing schedules

(b) Intravenous formulation:
- A single dose in excess of 100 mg
- A cumulative 28-day dose of greater than 200 mg for daily or intermittent dosing schedules.

2. Non-serious Adverse Events

All other adverse events, not fulfilling the previous definitions, are classified as non-serious adverse events.

21.2.2 Determination of Severity

The severity of AEs will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0. If the AE is not defined in the CTCAE, the Investigator will determine the severity of an adverse event based on the following definitions:

- Mild (Grade 1): The AE is noticeable to the patient but does not interfere with routine activity. The AE does not require discontinuing administration or reducing the dose of the study drug.
- Moderate (Grade 2): The AE interferes with routine activity but responds to symptomatic therapy or rest. The AE may require reducing the dose but not discontinuing administration of the study drug.

- Severe (Grade 3): The AE significantly limits the patient's ability to perform routine activities despite symptomatic therapy. In addition, the AE leads to discontinuing administration or reducing the dose of the study drug.
- Life-Threatening (Grade 4): The AE requires discontinuing administration of the study drug. The patient is at immediate risk of death.

21.2.3 Definitions for Categories of Relatedness

The Investigator will determine the relatedness of an adverse event with the study drug based on the following definitions:

A. Definitely related to test drug (drug related):
- There is evidence of exposure to the test drug.
- The temporal sequence of the AE onset relative to administration of the test drug is reasonable.
- The AE is more likely explained by the test drug than by another cause.
- Dechallenge is positive.
- Rechallenge (if feasible) is positive.
- The AE shows a pattern consistent with previous knowledge of the test drug or test drug class

B. Probably related to test drug (drug related):
- There is evidence of exposure to the test drug.
- The temporal sequence of the AE onset relative to administration of the test drug is reasonable.
- The AE is more likely explained by the test drug than by another cause.
- Dechallenge (if performed) is positive.

C. Possibly related to test drug (drug related):
- There is evidence of exposure to the test drug.
- The temporal sequence of the AE onset relative to administration of the test drug is reasonable.
- The AE could have been due to another equally likely cause.
- Dechallenge (if performed) is positive.

D. Probably not related to test drug (not drug related):
- There is evidence of exposure to the test drug.
- There is another more likely cause of the AE.
- Dechallenge (if performed) is negative or ambiguous.

- Rechallenge (if performed) is negative or ambiguous

E. Definitely not related to test drug (not drug related):

- The patient did not receive the test drug.

OR

- Temporal sequence of the AE onset relative to administration of the test drug is not reasonable.

OR

- There is another obvious cause of the AE.

Note: Not all criteria in each category of relatedness need to be present.

21.3 Documenting Adverse Events

All adverse events (including SAEs) are to be accurately recorded on the Adverse Event page of the patient's case report form from the time the patient signs the informed consent until the post-treatment discontinuation visit. Each event will be graded for severity, intensity, and relatedness (see Section 21.2: Evaluating Adverse Events). The date of onset as well as the duration of the event will be recorded. In addition, the method used to treat the adverse event and the outcome of the adverse event will also be noted.

21.4 Reporting SAEs and Patient Deaths

21.4.1 Time-frame for Reporting

Any death or serious adverse event experienced by the patient from the time the patient signs informed consent to 30 days after receiving study drugs or through the date of the post-treatment discontinuation visit (i.e., approximately 30 ± 7 days following the last dose of study drugs), or any death or SAE believed to be study drug-related that occurs at anytime thereafter, must be reported within 24 hours of learning of the event by telephone or telefax to the Sponsor or the Sponsor's designee.

21.4.2 Information to be provided by the Investigator

Within 24 hours of learning about the SAE or patient death, the Investigator must notify the Sponsor or designee and transmit information to the Sponsor or designee. The Sponsor or designee will require of the following information:

1. Patient identification code, sex, age or date of birth
2. Investigator/reporter information – name, site number, contact information

3. Description of suspect medication (study drug(s) - including dose and frequency of study drug administered, data of administration if available
4. Description of event
5. Date of death (if applicable)

In addition to the above information, the Sponsor will require the Investigator's assessment of the following:

1. Severity of the adverse event
2. Relationship of the adverse event to the study drug
3. Outcome of the adverse event

21.4.3 Follow-up Information on an SAE

Appropriate diagnostic tests should be performed and therapeutic measures, if indicated, should be instituted. Appropriate consultation and follow-up evaluations should be carried out until the event has resolved or is otherwise explained by the Principal Investigator.

Follow-up data concerning the SAE (e.g., diagnostic test reports, physician's summaries, etc.) must also be submitted to the Sponsor within 24 hours of the study site becoming aware of new information. Should the FDA or National Regulatory Authorities require that the Sponsor submit additional data on the event, the Investigator will be asked to provide those data to the Sponsor in a timely fashion.

21.5 Review of an SAE by the Sponsor and Determination of Further Action

Based in part on the Investigator's assessment of the adverse event, the Sponsor will determine regulatory reportability of the SAE.

21.5.1 Suspected Unexpected Serious Adverse Drug Reactions (SUSAR)

SUSARs are SAEs that are unexpected and judged by the Investigator or the Sponsor to be related to study drug. In accordance with applicable regulations, SUSARs will be submitted by the Sponsor (or designee) to appropriate regulatory authorities, ethics committees and Investigators.

If the discovery of a new adverse event related to study drug raises concern over the safety of its continued administration to patients, the Sponsor may take further action which may include the following:

- Alteration of the existing research program by modification of the protocol

- Discontinuation or suspension of the trial
- Alteration of the informed consent process by modification of the existing consent form and informing current study participants of new findings

21.6 Required Follow-up for SAEs

There should be routine follow-up for 30 days after study drug discontinuation in all patients in order to monitor for the occurrence of serious adverse events. In addition, limited follow-up at three and six months after the end of the last dosing cycle will be conducted to evaluate for cessation of any adverse drug reaction that may have arisen during the trial, unless the patient has received another anti-cancer agent. The Medical Monitor may specify a longer period of time, if required to ensure the safety of the patient.

22. DATA QUALITY ASSURANCE

The Sponsor will perform quality control and assurance checks on all clinical studies that it sponsors. Before enrolling any patients into this trial, Sponsor personnel and the Investigator will review the protocol, the Clinical Investigator's Brochure, the CRFs and instructions for their completion, the procedure for obtaining informed consent, and the procedure for reporting AEs. A qualified representative of the Sponsor will monitor the conduct of the trial by visiting the site and by contacting the site by telephone. During the visits, information recorded on the CRFs will be verified against source documents. If paper CRFs are used, those data are entered into the database using a double data entry procedure (or other quality assurance procedure). The Sponsor's medical monitor will review the data for safety information. The Sponsor's clinical data associates will review the data for legibility, completeness, and logical consistency. Additionally, the Sponsor clinical data associates will use automated validation programs to help identify missing data, selected protocol violations, out-of-range data, and other data inconsistencies. Requests for data clarification or correction will be forwarded to the investigational site for resolution. A sample set of records from the final database will be fully audited against the corresponding CRFs.

23. INVESTIGATOR'S REGULATORY OBLIGATIONS

23.1 Institutional Review Board (IRB) / Ethics Committee (EC) Approval

This extension protocol and the informed consent document, as well as the parent protocol(s) and informed consent document(s) justifying enrollment into this extension protocol must have the initial and at least annual (when required) approval of an IRB/EC. The signed IRB/EC approval letter must identify the documents approved (i.e., list the Investigator's name, the protocol number and title, the date of the protocol and informed consent document, and the date of approval of the protocol and the informed consent

document). The Sponsor will not ship clinical supplies until a signed approval letter from the IRB/EC has been received and a contractual agreement has been signed by the Sponsor and the clinical site.

23.2 Prestudy Documentation

The Investigator must provide the Sponsor with the following documents BEFORE enrolling any patients:

- Completed and signed FDA Form 1572
- All applicable country specific regulatory forms
- Current curricula vitae for the Investigator and all subinvestigators
- Copy of the IRB/EC approval letter for the protocol and informed consent.
- Copy of the IRB/EC-approved informed consent document to be used
- When applicable, a list of the IRB/EC members or a statement of compliance with regulations
- Copy of the protocol signature page signed by the Investigator
- Fully executed clinical trial agreement
- Certification or accreditation with the name of the laboratory at which protocol required tests are performed. To be provided for all laboratories listed on the 1572.
- List of normal reference ranges for all laboratories performing tests required by the protocol. The name of the laboratory and effective dates should be specified. To be provided for all laboratories listed on the 1572.

23.3 Informed Consent

Regulatory agencies have issued regulations to provide protection for human patients in clinical investigations and to describe the general requirements for informed consent.

A copy of your proposed informed consent document should be submitted to the Sponsor for review and comment before submission to your IRB/EC. The trial should not begin until the document has been reviewed by the Sponsor and must not begin until the document has been approved by the IRB/EC. In some instances the trial must not begin until the document has been approved by a regulatory agency.

The informed consent document shall contain all of the elements of informed consent specified in the regulations. Some regulations may require the disclosure of additional information to the patient and/or inclusion of additional information in an informed consent document.

23.4 Declaration of Helsinki

This trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with GCP and the applicable regulatory requirements.

23.5 Case Report Forms

1. All data will be reported on CRFs provided by the Sponsor

2. If paper CRFs are used, the originals must be returned to the Sponsor; the Investigator must retain a copy for his/her files. If an Electronic Data Capture system is used, an electronic copy of the CRFs will be provided to the Investigator for retention in the study files

3. CRFs and other pertinent records are to be submitted to the Sponsor during and/or at completion or termination of the trial

4. The Investigator also must submit all incomplete CRFs that document patient experience with the study drug, including retrievable data on patients who withdraw before completion of the trial

All study information should be recorded in an appropriate source document (e.g., clinic chart).

23.6 Adverse Event Reporting

The Investigator agrees to report all AEs to the Sponsor as described in the Adverse Event section (see Section 21.4: Reporting SAEs and Patient Deaths). Furthermore, the Investigator is responsible for ensuring that any coinvestigator or subinvestigator promptly brings AEs to the attention of the Investigator. If applicable, the Investigator also is responsible for informing the participating IRB/EC of any SAEs.

23.7 Review of Source Records

The Investigator agrees that qualified representatives of the Sponsor and regulatory agencies will have the right, both during and after this trial, to conduct inspections and to audit and review medical records pertinent to the clinical study as permitted by the regulations. Patients will not be identified by name, and confidentiality of information in medical records

will be preserved. The confidentiality of the patient will be maintained unless disclosure is required by regulations. Accordingly, the following statement (or similar statement) that permits the release of the patient's medical records will be included in the informed consent document:

Representatives of regulatory agencies, IRB/EC, the Sponsor, and your personal physician may review your medical records and all information related to this trial as permitted by law. The Sponsor will not know your identity. Your identity will remain confidential unless disclosure is required by law.

23.8 Monitoring of the Study

This trial is monitored by a representative of the Sponsor. Site visits are made before the trial begins, at regular intervals during the study, and at the study closeout. Communication by telephone, mail and e-mail may be used as needed to supplement site visits. The Investigator and study personnel will cooperate with the Sponsor, provide all appropriate documentation, and be available to discuss the trial. The purpose of the site visits is to verify:

1. Adherence to the protocol (The Investigator should document and explain any deviation from the approved protocol)

2. The completeness and accuracy of the CRFs and the dispensing and inventory record (Adequate time and space for these visits should be allocated by the Investigator)

3. Compliance with regulations. The verification will require comparison of the source documents to the CRFs

23.9 Protocol Amendments

Any significant change in the study protocol will require an amendment. The Investigator and the appropriate Sponsor medical monitor indicate their approval by signing the approval page of the amendment. Once a protocol amendment has received approval from the Sponsor, the Investigator submits it to the IRB/EC for written approval. The approval letter, signed by the IRB/EC chair, must refer specifically to the investigator, the Sponsor protocol number, the protocol title, the protocol amendment number, and the date of the protocol amendment. The Sponsor submits a copy of the protocol amendment to the appropriate regulatory agency/agencies. A protocol amendment may be implemented after it has been approved by the IRB/EC.

A protocol change intended to eliminate an apparent immediate hazard to patients may be implemented immediately, but the change must then be documented in an amendment and reported to the IRB/EC within 5 working days.

23.10 Change in Investigator

If any investigator retires, relocates, or otherwise withdraws from conducting a trial, the responsibility for maintaining records may be transferred to another person (Sponsor, IRB/EC, other investigators) who will accept the responsibility. The Sponsor must be notified of and agree to the change. An updated FDA Form 1572 will be filed with the Sponsor and the FDA for any changes in the study personnel reported in the current FDA Form 1572.

23.11 Termination of Study

23.11.1 Termination by the Sponsor

The Sponsor may terminate the trial at anytime for any of the following reasons:

1. Failure to enroll patients
2. Protocol violations
3. Inaccurate or incomplete data
4. Unsafe or unethical practices
5. Questionable safety of the study drug
6. Suspected lack of efficacy of the study drug
7. Administrative decision

23.11.2 Termination of Investigator

If the Investigator terminates participation in the trial prematurely, the Investigator does the following:

1. Return all study drugs, CRFs, and related study materials to the Sponsor
2. Provide a written statement describing why the trial was terminated prematurely

23.12 Final Study Report

The Investigator must complete a report notifying the IRB/EC of the conclusion of the clinical trial. This report should be made within 3 months of completion or termination of the trial.

The final report sent to the IRB/EC is also sent to the Sponsor and, along with the completed CRFs, constitutes the final summary to the Sponsor, thereby fulfilling the Investigator's regulatory responsibility.

23.13 Confidentiality

All unpublished information that the Sponsor gives to the Investigator shall be kept confidential and shall not be published or disclosed to a third party without the prior written consent of the Sponsor.

When the Sponsor generates reports for presentations to regulatory agencies, 1 or more of the investigators who have contributed significantly to the trial will be asked to endorse the final report. The endorsement is required by some regulatory agencies.

The investigator shall not make a patent application based on the results of this trial and shall not assist any third party in making such an application without the written authorization of the Sponsor.

23.14 Records Retention

All correspondence related to this clinical trial should be kept in appropriate study files. Record of patients, source documents, CRFs, drug inventory, and IRB/EC and Sponsor correspondence pertaining to the trial must be kept on file. All original patient, laboratory, and drug inventory records relating to the trial are retained for not less than 5 years after notification by the Sponsor that all studies using the study drug have been discontinued or that a regulatory agency has approved an application for the marketing of the study drug. Thereafter, records will not be destroyed without giving the Sponsor prior written notice and the opportunity to further store such records, at the Sponsor's cost and expense.

24. REFERENCES

Atabai K, Ishigaki M, Geiser T, et al. Keratinocyte growth factor can enhance alveolar epithelial repair by nonmitogenic mechanisms. Am. J. Physiol. Lung Cell. Mol. Physiol. 2002; 283:163–9.

Bjornsti MA, Houghton PJ. The TOR pathway: A target for cancer therapy. Nat Rev Cancer 2004;4:335-348.

Brown EJ, Albers MW, Shin TB, et al. A mammalian protein targeted by G1-arresting rapamycin-receptor complex. Nature 1994;369:756-758.

Champion L, Stern M, Israel-Biet D, et al. Brief communication: sirolimus-associated pneumonitis: 24 cases in renal transplant recipients. Ann Int Med 2006;144: 505-509.

Chan S. Targeting the mammalian target of rapamycin (mTOR): a new approach to treating cancer. Br J Cancer 2004;91:1420-1424.

Duran I, Siu LL, Oza AM, et al. Characterisation of the lung toxicity of the cell cycle inhibitor temsirolimus. Eur J Cancer 2006;42: 1875–18.

Faivre S, Kroemer G, Raymond E. Current development of mTOR inhibitors as anticancer agents. Nat Rev Drug Discov 2006;5:671-688.

Ferlay J, Autier P, Boniol M, et al. Estimates of the cancer incidence and mortality in Europe in 2006. Ann Oncol 2007;18:581-592.

Hennessy BT, Smith DL, Ram PT, et al. Exploiting the PI3K/AKT pathway for cancer drug discovery. Nat Rev Drug Discov 2005;4:988-1004.

Hidalgo M. New target, new drug, old paradigm. J Clin Oncol, 2004;22(12):2270-222.

http::\\www.cancer.org. Breast cancer. Accessed February 3, 2008.

Jemal A, Siegel R, Ward E, et al. Cancer statistics 2007. CA Cancer J Clin 2007;57:43-66.

Janus A, Robak T, Smolewski P. The mammalian target of the rapamycin (mTOR) kinase pathway: its role in tumourigenesis and targeted antitumour therapy. Cell Mol Biol Lett 2005;10:479-498.

Karakas B, Bachman KE, Park BH. Mutation of the PIK3CA oncogene in human cancers. Br J Cancer 2006;94:455–459.

Mamane Y, Petroulakis E, LeBacquer O, et al. MTOR, translation initiation and cancer. Oncogene 2006;25:6416-6422.

Miettinen PJ, Warburton D, Bu D et al. Impaired lung branching morphogenesis in the absence of functional EGF receptor. Dev Biol 1997;186:224–36.

Nashan B, Curtis J, Ponticelli C, et al. Everolimus and reduced-exposure cyclosporine in de novo renal-transplant recipients: a three-year phase II, randomized, multicenter, open-label study. Transplantation 2004;74:1332-1340.

Rivera VM, Berk L, Mita M, et al. Pharmacodynamic evaluation of the mTOR inhibitor AP23573 in phase 1 clinical trials. Eur J Cancer 2004;2 (Abstract 123).

Rivera V, Kreisberg J, Mita M, et al. Pharmacodynamic study of skin biopsy specimens in patients (pts) with refractory or advanced malignancies following administration of AP23573, an mTOR inhibitor. J Clin Oncol 2005;23:200s (suppl; abstract 3033).

Saal LH, Holm K, Maurer M, et al. PIK3CA mutations correlate with hormone receptors, node metastasis, and ERBB2, and are mutually exclusive with PTEN loss in human breast carcinoma. Cancer Res 2005;65:2554–2559.

Schmelzle T, Hall MN. TOR, a central controller of cell growth. Cell 2000;103:253-262.

Shaw RJ, Cantley LC. Ras, PI(3)K and mTOR signalling controls tumour cell growth. Nature 2006;441:424-430.

Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. J Nat Cancer Inst 2000;92:205-216.

25. ATTACHMENTS

Attachment A: ECOG Performance Status Evaluation

Attachment B: Inhibitors and Inducers of CYP3A

Attachment A: ECOG Performance Status Evaluation

Level	ECOG
0	Normal activity
1	Symptoms but ambulatory
2	In bed < 50% of time
3	In bed > 50 % of time
4	100 % bedridden
5	Death

Oken M, Creech RH, Tormey DC, Horton J, Davis TE, McFadden E, and Carbone PP. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol (CCT) 1982, 5:649-655.

Attachment B: Inhibitors and Inducers of CYP3A

EXAMPLES OF CYTOCHROME P450 ISOENZYME INHIBITORS AND INDUCERS			
Inhibitors		**Inducers**	
amiodarone	indinavir	barbiturates	phenobarbital
cimetidine	itraconazole	carbamazepine	phenytoin
ciprofloxacin	ketoconazole	efavirenz	rifampin
clarithromycin	mibefradil	glucocorticoids	St. John's Wort
delaviridine	mifepristone	modafinil	troglitazone
diltiazem	nefazodone	nevirapine	
erythromycin	nelfinavir		
fluconazole	norfloxacin		
fluvoxamine	ritonavir		
gestodene	saquinavir		
grapefruit juice	troleandomycin		

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