Official Title: Phase IV, open-label, multi-center, single-arm study of the safety and efficacy of everolimus (Afinitor) in adult patients with locally advanced, unresectable or metastatic, well differentiated progressive pancreatic neuroendocrine tumors (pNET) in China.

NCT Number: NCT02842749

Document Date: Clinical Study Protocol Final Version 01: 31-May-2017

NOVARTIS

Clinical Development

Everolimus/ Afinitor

Oncology Clinical Protocol CRAD001PCN31

Phase IV, open-label, multi-center, single-arm study of the safety and efficacy of everolimus (Afinitor) in adult patients with locally advanced, unresectable or metastatic, well differentiated progressive pancreatic neuroendocrine tumors (pNET) in China

Authors	[redacted]
Document type	Amended Protocol Version
EUDRACT number	Not applicable
Version number	01 (Clean)
Development phase	IV
Document status	Final
Release date	31-May-2017

Template version 15-Jan-2017

Table of contents

List of appendices

List of figures

List of tables

List of abbreviations

AE	Adverse Event
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
CFDA	China Food and Drug Administration
CMO&PS	Chief Medical Office and Patient Safety
CRF	Case Report/Record Form; the term CRF can be applied to either EDC or Paper
CRO	Contract Research Organization
CSR	Clinical study report
CSR addendum	An addendum to Clinical Study Report (CSR) that captures all the additional information that is not included in the CSR
DLT	Dose Limiting Toxicity
ECG	Electrocardiogram
EDD	Estimated Deliver Date
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
PHI	Protected Health Information
PI	Package insert
RAP	The Report and Analysis Plan (RAP) is a regulatory document which provides evidence of preplanned analyses
REB	Research Ethics Board
SAE	Serious Adverse Event

Glossary of terms

Assessment	A procedure used to generate data required by the study
Control drug	A study treatment used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Dose level	The dose of drug given to the patient (total daily or weekly etc.)
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The study treatment whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug."
Investigational treatment	Drug whose properties are being tested in the study as well as their associated placebo and active treatment controls (when applicable). This also includes approved drugs used outside of their indication/approved dosage, or that are tested in a fixed combination. Investigational treatment generally does not include other study treatments administered as concomitant background therapy required or allowed by the protocol when used in within approved indication/dosage
Medication number	A unique identifier on the label of each study treatment package which is linked to one of the treatment groups of a study
Other study treatment	Any drug administered to the patient as part of the required study procedures that was not included in the investigational treatment
Patient Number (Patient No.)	A unique identifying number assigned to each patient/subject/healthy volunteer who enrolls in the study
Period	A subdivision of the study timeline; divides stages into smaller functional segments such as screening, baseline, titration, washout, etc.
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study treatment administration and/or assessments; at this time all study treatment administration is discontinued and no further assessments are planned, unless the patient will be followed for progression and/or survival
Stage in cancer	The extent of a cancer in the body. Staging is usually based on the size of the tumor, whether lymph nodes contain cancer, and whether the cancer has spread from the original site to other parts of the body
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study treatment was discontinued whichever is later
Study treatment	Includes any drug or combination of drugs in any study arm administered to the patient (subject) as part of the required study procedures, including placebo and active drug run-ins. In specific examples, it is important to judge investigational treatment component relationship relative to a study treatment combination; study treatment in this case refers to the investigational and non-investigational treatments in combination.
Study treatment discontinuation	Point/time when patient permanently stops taking study treatment for any reason; may or may not also be the point/time of premature patient withdrawal

Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points
Withdrawal of consent	Withdrawal of consent occurs only when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact

Protocol summary

Title	Phase IV, open-label, multi-center, single-arm study of the safety and efficacy of everolimus (Afinitor) in adult patients with locally advanced, unresectable or metastatic, well differentiated progressive pancreatic neuroendocrine tumors (pNET) in China.
Brief title	Phase IV study of the safety and efficacy of everolimus (Afinitor) in adult patients with progressive pancreatic neuroendocrine tumors (pNET) in China.
Sponsor and Clinical Phase	Novartis IV
Investigation type	Drug
Study type	Interventional
Purpose and rationale	To evaluate safety and efficacy of everolimus (Afinitor®) in Chinese adult patients with locally advanced, unresectable or metastatic, well differentiated progressive pancreatic neuroendocrine tumors.
Primary Objective(s) and Key Secondary Objective	Primary: To evaluate the safety of treatment with Afinitor in Chinese adult patients with well differentiated progressive p-NET. No key secondary objective
Secondary Objectives	Secondary: To evaluate the overall efficacy of treatment with Afinitor in Chinese patients with well differentiated progressive p-NET
Study design	Open-label, multi-center, single-arm study of the safety and efficacy of everolimus (Afinitor) in adult patients with locally advanced, unresectable or metastatic, well differentiated progressive pancreatic neuroendocrine tumors (pNET) in China.
Population	Chinese adult patients with unresectable, locally advanced, unresectable or metastatic, G1 or G2 progressive pancreatic neuroendocrine tumors (pNET) (WHO 2010).
Inclusion criteria	Patients eligible for inclusion in this study have to meet **all** of the following criteria: Written informed consent must be obtained prior to any screening procedures. 1. Chinese Adult patients ≥ 18 years of age 2. Patients must have histological confirmed G1 or G2 pancreatic neuroendocrine tumors(pNETs) (WHO 2010) 3. Patients must have radiological documentation of progression of disease per RECIST 1.1 within 12 months prior to enrollment. 4. Measurable disease per RECIST 1.1 criteria using triphasic computed tomography (CT) scan or multiphase MRI for radiologic assessment. 5. Afinitor treatment which is recommended by the treating physician.
Exclusion criteria	Patients eligible for this study must not meet **any** of the following criteria: 1. Hypersensitivity to everolimus, to other rapamycin derivatives, or to any of the excipients. 2. Inability to attend scheduled clinic visits or scheduled tests. 3. Patient who is unwilling to receive Afinitor treatment due to any reason. 4. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test. Women of child-bearing potential, who are or might become sexually active, must be informed of the need to prevent pregnancy during the study. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant (including female pediatric patients who are menarcheal or who become menarcheal during the study), must use highly effective contraception during study treatment and for8 weeks after stopping treatment. Highly effective contraception methods include:

	a. Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception b. Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment c. Male sterilization (at least 6 months prior to screening). The vasectomized male partner should be the sole partner for that subject with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate d. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/ vaginal suppository e. Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment. 5. Prior therapy with mTOR inhibitors (e.g. sirolimus, temsirolimus, everolimus). 6. Use of an investigational drug within the 30 days prior to enrollment 7. Any severe and/or uncontrolled medical conditions which could cause unacceptable safety risks or compromise compliance with the protocol, such as: Impairment of gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of study drug (e.g., ulcerative disease, uncontrolled nausea, vomiting, diarrhea, etc). 8. Known history of seropositivity for human immunodeficiency virus (HIV) 9. Any cause that the investigator considers will harm the patient's benefit if participate in this study and please specify.
Investigational and reference therapy	everolimus 10mg/day
Efficacy assessments	● Overall Survival： defined as time from study treatment to death due to any cause. ● Progression free survival：defined as time from first dose of study treatment to progression or death due to any cause
Safety assessments	Incidences of AEs, AE suspected to be related to Afinitor, Grade 3/4 AEs and SAEs
Other assessments	Not applicable to this study
Data analysis	Descriptive Statistics for safety variables and efficacy assessment, will be provided through tables and listings whereas applicable.
Key words	Everolimus (Afinitor®), locally advanced, unresectable or metastatic, well differentiated progressive pancreatic neuroendocrine tumors, safety, efficacy

Amendment 1 (31-May-2017)

Amendment rationale

The main purpose of the amendment is:

- To increase the sample size from approximately 30 to 60 patients to collect additional safety and efficacy data of everolimus in Chinese adult patients with pNET to meet the post-approval commitment request from CFDA.
- To update format according to new template.
- To fix wording, spelling and punctuation.

First patient first visit (FPFV) of this study was on 14-Mar-2016 and 31 patients had been enrolled by Nov 2016.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

The following changes have been implemented:

- Section 1.1, 2.1, 3, 5.1, 5.2, 10.8: To add “unresectable” to clearly identify population.Section 1.2.1 and 1.2.1.1: Update approved indication and registry study’s brief result.
- Section 1.2.1.1: Add non-clinical experience.
- Section 2.4, 2.5, 6.1.2, 6.1.3, 6.4.4, 7.1.1, 7.1.2.1, 7.1.3, 7.1.5.1, 7.1.7, 7.1.8, 7.2.2.6, 7.2.2.7, 7.2.2.8, 8.6, 8.7, 10.1.6, 10.2, 10.5.6, 10.5.7 and 10.6: Insert related sections according to new template and most are not applicable.
- Section 2.6: Replace original 6.3.3 section to section 2.6 risk and benefit according to new template.
- Section 4.1: Add sentences to emphasize commercial drug shifting has no impact on participation in the study.
- Section 4.2 and 10.7: To remove the license renewal specific date.
- Section 4.3: Clearly identify end of treatment (EOT).
- Section 5.1 and 10.7: The sample size has been increased to approximately 60 patients in total.
- Section 5.3: Update contraceptive text (highly effective methods)
- Section 6.1.1: Update dosing regimen according to new template.
- Section 6.3: Add dose adjustments guidance for QTcF.
- Section 6.3.2.1: Add drug-induced liver injury.
- Section 6.4: Add permitted and prohibited concomitant therapy.
- Section 7: Add a column for follow up on 30 day safety follow-up in Table 7-1
- Section 7.2.2.3: Add text to describe screening measurement of height and body weight.

- Section 8.1.1, 8.1.3 and 8.2.2: Update safety monitoring and reporting wording according to new template.
- Section 8.3 &10.5.3.2: Add 3 items of AESI
- Section 10.1.2: Update safety set definition according to new template.
- Section 10.5.3.2 and 10.5.3.3: Update description of AEs and laboratory abnormalities according to new template.
- Section 10.5.3.1: Corrected the post-treatment period from “starting at day 31+1 after last dose of study medication” to “starting at day 31 after last dose of study medication” for safety analyses.
- Section 10.7 Add text to describe interim analysis- both safety and efficacy.
- Section 2.2, 2.3, 5.1, 6.61, 7.2.2 8.2.2, 8.4 and 9.4: Spelling and punctuation has been corrected.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatment

Neuroendocrine tumors (NETs) are a genetically diverse group of rare malignant tumors that arise from neuroendocrine cells throughout the body, e.g. the pancreatic islet cells, neuroendocrine cells within the respiratory epithelium, parafollicular cells within the thyroid and from the diffuse neuroendocrine cells in the gastrointestinal (GI) tract. Their clinical course is often indolent but can also be highly aggressive and resistant to therapy (Yao 2008b). Historically, they have been referred to as carcinoid tumors (with the exception of pancreatic islet cell tumors) and classified according to their point of origin in embryonic development as foregut (e.g.,bronchial or gastric carcinoid), midgut (e.g., small intestine or appendiceal carcinoid), or hindgut (e.g., rectal carcinoid) NETs. More recently the WHO designation has gained acceptance in the literature as it appears to have better prognostic relevance. In this modern anatomic nomenclature, NETs are classified on the basis of primary tumor location (e.g. gastrointestinal (jejunum, ileum, appendix, etc.), lung, or pancreas), rather than the previous classification based on the embryonic origin of the organ. Well-differentiated neuroendocrine tumors of unknown origin are generally considered to be of gastrointestinal origin (Klöppel et al 2004).

The incidence of neuroendocrine tumors has been increasing over the past several decades. Results from the National Cancer Institute Surveillance, Epidemiology and End Results (SEER) database show that in 2004, there were 5.25 new patients with NETs per 100,000 people (age-adjusted US 2000 standard population), compared with the 1.09 new cases of NETs per 100,000 people in 1973 (Yao et al 2008a). NETs of the small intestine, lung and rectum are the most frequently diagnosed NETs in the US, and have had the greatest increase in incidence from 1973 to 2004 (Yao et al 2008a). Since most NETs are slow growing and the majority are not associated with characteristic symptoms associated with the secretion of peptides and other bioactive molecules, many NETs are discovered incidentally during routine colonoscopy or other endoscopic procedures, or during autopsy (Oberg and Jelic 2008). As such, commonly cited figures may underestimate the true incidence of NETs.

The majority of patients with NETs present with advanced disease at diagnosis, with regional spread or distant metastasis seen in 50% of patients (Yao et al 2008a). Up to 75% of patients who present with NETs of the mid- or hindgut region, and approximately 60% of patients with pNETs have liver metastases (Falconi et al 2006). Metastases usually develop initially in regional lymph nodes, later in the liver and subsequently in distant sites, such as bone (Metz and Jensen 2008).

pNET

Pancreatic neuroendocrine tumors (pNETs), or islet cell tumors of the pancreas (ICT), comprise only 1-2% of all pancreatic tumors and less than 10% of all neuroendocrine tumors (Yao 2008a). Pancreatic NETs constitute a distinct subgroup of NETs characterized by a different genetic profile, more aggressive clinical evolution, and a different pattern of

response to cytotoxic chemotherapy (Yao 2008a). The annual incidence of pancreatic NET is approximately 3.5 to 4 per million population (Barakat 2004). The peak age of occurrence is from 40 to 60 years. The polypeptide hormones secreted by pancreatic neuroendocrine tumors (pNETs) vary depending upon the cell type of origin within the pancreatic islet; these can include insulin (insulinoma), gastrin (gastrinoma), vasoactive intestinal peptide (VIPoma), and glucagon (glucagonoma) (Barakat 2004). The apparently "nonfunctioning" (i.e., non-secreting) pNETs tend to be more aggressive and present with symptoms of tumor bulk (Barakat 2004). Nonfunctioning tumors account for approximately 30% of all pancreatic neuroendocrine tumors (pNETs).

Although pancreatic neuroendocrine tumors (pNETs) are sometimes considered to be indolent, patients with unresectable or metastatic tumors have a lethal disease, and all pancreatic neuroendocrine tumors (pNETs), with the exception of 90% of insulinomas, have long-term metastatic potential. Morbidity can arise both from secreted hormones as well as tumor bulk (Barakat 2004). The median survival for pancreatic neuroendocrine tumors (pNETs) patients with metastatic disease is 27 months (Yao 2008a).

Gastrointestinal (GI) and Bronchopulmonary neuroendocrine tumors

GI NETs can arise from neuroendocrine cells throughout the gastrointestinal tract. The most frequent sites of origin include the small intestine, stomach, cecum, appendix, colon and rectum (Yao 2008a). Approximately 10% of patients with carcinoid tumors suffer from the classical symptoms of carcinoid syndrome, caused by elevated levels of serotonin ([Barak 2004]). While advanced GI NETs have a reputation for being slowly progressive compared with other tumor types (such as adenocarcinomas), the median survival for patients with metastatic GI NETs varies from 13 months for patients with a gastric primary to 65 months for NETs of small intestinal origin (Yao 2008a).

The bronchopulmonary tree represents another common site of origin of carcinoid tumors, with an annual incidence of approximately 1.4 cases per 100,000 (Yao 2008a). The median survival for patients with lung NETs following metastatic spread is 27 months (Yao 2008a).

Treatment of neuroendocrine tumors

The primary treatment goal for patients with neuroendocrine tumors (NETs) is complete resection of the tumor. If inoperable, the goal is to control tumor growth, to control symptoms if the tumor is functional, and to prolong survival time. Surgical resection represents the traditional first-line therapy of NETs (Plockinger and Wiedenmann 2007). The prognosis following complete surgical resection is generally favorable (Schurr et al 2007). However, curative surgery is often not possible because the majority of patients present with locally advanced, unresectable or metastatic disease. When radical surgery cannot be performed, debulking procedures and resection of metastases (i.e. in liver) may improve the outcome of patients. Guidelines state that surgical resection of liver metastases should be undertaken only if at least 90% of the tumor mass can be removed (Plockinger et al 2004; Eriksson et al 2008). Cytoreductive surgery (tumor debulking) may also render medical therapy more effective by decreasing the secretion of bioactive substances. In patients with jejuno-ileal NETs and liver metastases, the post-surgical 5-year survival rate is approximately 60% compare to 30% in those patients without surgical treatment (Eriksson et al 2008).

Biotherapy with somatostatin (SMS) analogs (SSAs) remains the mainstay of symptomatic therapy for neuroendocrine tumors (NETs). Most neuroendocrine tumors (NETs) highly express somatostatin receptors (SSTRs). In addition to its recognized antisecretory effects, octreotide appears to induce antiproliferative effects on the tumor. Direct effects are mediated through binding directly to the tumor cell, whereas indirect effects may occur via inhibition of growth factors and angiogenesis and through effects on the immune system. Subsequent to the approval of octreotide for the treatment of symptoms of functional GI NETS and pNETs, evidence of antitumor activity of octreotide was observed in small series of patients (Arnold et al 1993; Arnold et al 1996; Evers et al 1991; Pollak et al 1989; Arnold et al 1992). Subsequently, the PROMID trial, a randomized, double-blind, placebo-controlled, multicenter trial in patients with well differentiated inoperable or metastatic embryonic midgut NET showed significant delay in time to tumor progression (TTP) in patients treated with octreotide LAR 30 mg compared to placebo (Rinke et al 2009).

For patients who experience disease progression, therapeutic options are limited. For gastrointestinal (GI) NETs, despite the many chemotherapy trials that have been conducted, no regimen has demonstrated a response rate of more than 15% using the criterion of a 50% reduction of bidimensionally measurable disease (Schnirer Yao and Ajani 2003). Interferon has also been widely studied in this disease setting. Pooling the data from patients with carcinoid tumors involved in these trials, only 37 (12%) of 309 had objective tumor responses (Schnirer Yao and Ajani 2003).

Despite the approval of streptozocin in 1976 by the US FDA, the role of chemotherapy for patients with advanced neuroendocrine tumors continues to be debated. Clinical trials using streptozocin alone and in combination with agents such as doxorubicin have reported objective responses, but most studies did not use currently accepted methods such as cross-sectional radiological imaging in conjunction with RECIST or WHO criteria. Chemotherapeutic regimens used for treatment of pancreatic neuroendocrine tumors (pNETs) can be associated with significant toxicity, and no published data have documented improvements in progression-free or overall survival (Yao 2010a).

1.2 Introduction to investigational treatment

1.2.1 Overview of everolimus

Everolimus first entered clinical development for one of numerous oncology indications in 2002.

It was approved by the FDA on 30-Mar-2009 under the trade name Afinitor® for the treatment of patients with advanced renal cell carcinoma (RCC) after failure of treatment with sunitinib or sorafenib. The European Commission (EC) approved Afinitor® on 03-Aug-2009 for the treatment of patients with advanced RCC, whose disease has progressed on or after treatment with vascular endothelial growth factor (VEGF)-targeted therapy. Everolimus has been approved in 122 countries worldwide for the treatment of patients with advanced RCC.

On 05-May-2011, FDA approved Afinitor® for the treatment of progressive neuroendocrine tumors of pancreatic origin (pNET) in patients with unresectable, locally advanced or metastatic disease. The EC approved Afinitor® on 24-Aug-2011 for the treatment of unresectable or metastatic, well- or moderately-differentiated neuroendocrine tumors of

pancreatic origin in adults with progressive disease. Everolimus has been approved in 112 countries worldwide for the treatment of patients with advanced pNET/NET.

On 26-Feb-2016, FDA approved Afinitor® for advanced non-functional NET of gastrointestinal (GI) or lung origin based on the results of Phase III study T2302. On 20-Jul-2012, FDA approved Afinitor® for the treatment of postmenopausal women with advanced hormone receptor-positive (HR+), human epidermal growth factor receptor 2 negative (HER2-) breast cancer in combination with exemestane, after failure of treatment with letrozole or anastrozole. The EC approved Afinitor® on 23-Jul-2012 for the treatment of HR+, HER2- advanced breast cancer, in combination with exemestane, in postmenopausal women without symptomatic visceral disease after recurrence or progression following a non-steroidal aromatase inhibitor. Everolimus has been approved in 115 countries worldwide for the treatment of patients with advanced HR+, HER2- breast cancer.

Everolimus received accelerated approval from FDA on 29-Oct-2010 for the treatment of patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis that require therapeutic intervention but are not candidates for curative surgical resection. Subsequently on 26-Apr-2012, the indication was slightly revised by FDA to "Afinitor® is indicated for the treatment of adult and pediatric patients, 3 years of age or older, with SEGA associated with tuberous sclerosis complex (TSC) who require therapeutic intervention but are not candidates for curative surgical resection". The EC conditionally approved everolimus on 02-Sep-2011 under the trade name Votubia® for the treatment of patients aged 3 years and older with SEGA associated with TSC who require therapeutic intervention but are not amenable to surgery.

On 29-Aug-2012, FDA revised the indication to "Afinitor® Tablets and Afinitor® Disperz are indicated in pediatric and adult patients with TSC for the treatment of SEGA that requires therapeutic intervention but cannot be curatively resected".

Under the trade name of Votubia®, on 15-Nov-2013, based on M2301 study, the indication was revised with the removal of the age restriction to "Votubia is indicated for the treatment of patients with SEGA associate with TSC who require therapeutic intervention but are not amendable to surgery".

The follow-up data from studies C2485 and M2301 demonstrated sustained efficacy and safety of everolimus in this patient population. In 2015/2016, these data allowed the conversion of the conditional marketing authorization to full approval in the EU and fulfillment of post-marketing requirements by the FDA.

Everolimus has been approved in 100 countries worldwide for the treatment of patients with TSC who have SEGA.

Everolimus received accelerated approval from FDA on 26-Apr-2012 for the treatment of adult patients with renal angiomyolipoma and TSC, not requiring immediate surgery. On 31-Oct-2012, the EC granted a decision for Votubia® for the treatment of adult patients with renal angiomyolipoma associated with TSC who are at risk of complications (based on factors such as tumor size or presence of aneurysm, or presence of multiple or bilateral tumors) but who do not require immediate surgery.

Finally in 2017, everolimus received approval in Europe for the treatment of patients 2 years and older with refractory partial onset seizures associated with TSC.

In China, everolimus has received approval in the advanced RCC on 22 Jan 2013, advanced pNET and TSC-SEGA on 13 Feb 2014 and TSC-AML on 29 Nov 2016.

1.2.1.1 Non-clinical experience

Everolimus inhibits the proliferation of a range of human tumor cell lines *in vitro* including lines originating from lung, breast, prostate, colon, melanoma and glioblastoma. IC50s range from sub/low nM to µM. Everolimus also inhibits the proliferation of human umbilical vein endothelial cells (HUVECS) *in vitro*, with particular potency against VEGF-induced proliferation suggesting that everolimus may also act as an anti-angiogenic agent. The anti-angiogenic activity of everolimus was confirmed *in vivo*. Everolimus selectively inhibited VEGF-dependent angiogenic response at well tolerated doses. Mice with primary and metastatic tumors treated with everolimus showed a significant reduction in blood vessel density when compared to controls.

The potential of everolimus as an anti-cancer agent was shown in rodent models. Everolimus is orally bioavailable, residing longer in tumor tissue than in plasma in a subcutaneous mouse xenograft model, and demonstrating high tumor penetration in a rat pancreatic tumor model. The pharmacokinetic profile of everolimus indicates sufficient tumor penetration, above that needed to inhibit the proliferation of endothelial cells and tumor cell lines deemed sensitive to everolimus *in vitro*.

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

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

In vivo studies investigating the anti-tumor activity of everolimus in experimental animal tumor models showed that everolimus monotherapy typically reduced tumor cell growth rates rather than produced regressions. These effects occurred within the dose range of 2.5 mg to 10 mg/kg, orally once a day.

In preclinical models, the administration of everolimus is associated with reduction of protein phosphorylation in target proteins downstream of mTOR, notably phosphorylated S6 (p-S6) and p-4E-BP1, and occasionally with an increase in phosphorylated AKT, a protein upstream of mTOR signaling pathway.

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

Further details can be found in the [everolimus IB] and/or the locally approved prescribing information.

1.2.1.2 Clinical experience

Several lines of evidence suggest that the mTOR pathway is involved in the pathogenesis of NETs. For example, patients with defects in the TSC2 gene, whose protein product inhibits mTOR activation, develop pancreatic neuroendocrine tumours (pNETs). Loss of the NF1 gene, which also regulates mTOR activity, is associated with the development of GI NETs in patients with neurofibromatosis. Sporadic NETs have been shown to coexpress insulin-like growth factor (IGF-1) and the IGF1 receptor (IGF-1R). Activation of the IGF-1/IGF-1R pathway activates mTOR leading to increased cell proliferation (Yao 2008b). Lastly, gene expression profiling studies show inhibition of the TSC2 and PTEN genes, both of which act as negative regulators of the PI3K/Akt/mTOR pathway, in most tumor samples from patients with pNETs, with lower levels of expression being associated with shorter disease-free and overall survival (Missiaglia 2010).

Based on these observations, a phase II clinical trial conducted by J. Yao at the MD Anderson Cancer Center studied everolimus and octreotide LAR in advanced low grade neuroendocrine carcinoma (Yao 2008b). A total of 60 evaluable patients were treated in two cohorts; patients received either everolimus at 5mg/day or 10 mg/day. Out of the sixty treated patients, 30 had carcinoid, and 30 islet cell tumours. Sixty-five percent of the patients were in progression at the time of study entry. Overall, 12 (20%) patients were reported to have partial response (4 carcinoids and 8 islet cell tumours, respectively), 43 (72%) had stable disease (25 in carcinoids and 18 in islet cell, respectively) and 5 (8%) had progressive disease (1 in carcinoids and 4 in islet cell, respectively) per RECIST. Overall median progression free survival (PFS) was 59 weeks (64 weeks in carcinoids and 50 in islet cell tumours, respectively). Median overall survival (OS) was not reached, with a 2 yrs survival rate of 78%. The combination of everolimus and octreotide LAR 30 mg appears to have been well tolerated. The most common toxicity reported was mucositis. CTC Grade 3/4 toxicities reported included: anemia, thrombocytopenia, aphthous ulcer, diarrhea, edema, fatigue, hypoglycemia, nausea, pain, and rash.

Subsequently, a second phase II open label, parallel group study was conducted in patients with advanced pancreatic neuroendocrine tumors (pNETs). Patients received either everolimus 10 mg daily as monotherapy (stratum 1; n = 115) or everolimus 10 mg daily in combination with ≤30 mg octreotide LAR q 28 days (stratum 2; n = 45), based on prior octreotide LAR treatment (Yao 2010a). In stratum 1, there were 11 partial responses (9.6%), 78 patients with stable disease (67.8%), and 16 patients with progressive disease (13.9%); median progression-free survival was 9.7 months. In stratum 2, there were two partial responses (4.4%), 36 patients with stable disease (80%), and no patient with progressive disease. Median progression-free survival (PFS) was 16.7 months.

Two Phase III studies have recently provided additional evidence that everolimus has promising activity in patients with advanced neuroendocrine tumors.

[CRAD001C2324] is a phase III randomized double blind study of everolimus + best supportive care (BSC) vs. placebo + BSC in patients with pancreatic neuroendocrine tumors who have radiological documentation of disease progression within 12 months prior to randomization (Yao 2011). Patients were randomized 1:1 to receive either everolimus 10 mg once daily (n = 207) or placebo (n = 203). Patients in the placebo arm were allowed to crossover upon disease progression. Patients were stratified by prior cytotoxic chemotherapy and WHO performance status. The primary endpoint was progression free survival. Median progression free survival was 11.04 months for everolimus compared to 4.60 months for placebo (HR=0.35; 95% confidence interval, 0.27 to 0.45; p <0.0001). No statistically significant difference in overall survival between the two arms was seen. The most common adverse reactions (occurring > 20%) in the everolimus arm included: stomatitis (53.9%), rash (52.5%), diarrhea (46.6%), fatigue (43.6%), peripheral edema (35.8%), nausea (31.9%), headache (29.9%), pyrexia (29.4%), decreased appetite (28.9%), vomiting (28.4%), weight loss (27.9%), abdominal pain (23.5%), anemia (22.1%), cough (21.6%) and epistaxis (21.1%).

Study [CRAD001C2325] is a Phase III randomized double blind study of everolimus in combination with octreotide LAR versus placebo + octreotide LAR in patients with advanced low or intermediate grade NET with a history of secretory symptoms and radiological documentation of disease progression within 12 months prior to randomization (Pavel 2011). Patients were randomized 1:1 to receive either everolimus 10 mg once daily + octreotide LAR 30 mg once every 28 days (n = 216) or placebo + octreotide LAR 30 mg once every 28 days (n = 213). Patients in the placebo + octreotide LAR arm were allowed to crossover to treatment with open label everolimus + octreotide LAR upon disease progression. The primary endpoint was progression free survival (PFS) by central radiology review (adjudicated central review). Median progression free survival was 16.4 months for everolimus + octreotide LAR compared to 11.3 months for placebo + octreotide LAR (HR=0.77; 95% confidence interval, 0.59 to 1.00; p=0.026 vs. P=0.0246 pre-specified). Median PFS by investigator assessment was 12.0 months for everolimus + octreotide LAR compared to 8.6 months for placebo + octreotide LAR (HR=0.78; 95% confidence interval, 0.62 to 0.98; p=0.018). Adjusting for different censoring patterns, loss of power, and baseline imbalances between the two treatment arms, the Inverse Probability of Censoring Weights (IPCW) adjusted PFS, which was pre-specified in the study, demonstrated a consistent benefit in favor of everolimus + octreotide LAR (HR=0.60; 95% confidence interval, 0.44 to 0.84; p=0.0014). No statistically significant difference in overall survival between the two arms was seen. The most common adverse reactions (occurring ≥ 20%) in the everolimus + octreotide LAR arm included: stomatitis (62%), rash (37%), fatigue (31%), diarrhea (27%), nausea (20%) and infections (20%).

Study [CRAD001T2302] included patients with advanced, progressive non-functional NET of GI or lung origin. Everolimus demonstrated superiority over placebo in terms of PFS showing a 52% relative risk reduction of progression/death in favor of everolimus (HR: 0.48; 95% CI: 0.35, 0.67) (p<0.001) (Yao 2016)). Based on these results, submissions worldwide have led to marketing authorization of everolimus in progressive, nonfunctional NET of GI or lung origin in over 41 countries including the US, EU, Canada, and Japan.

2 Rationale

2.1 Study rationale and purpose

In China, everolimus (Afinitor®) has been approved for the treatment of patients with local advanced, unresectable or metastatic, well differentiated progressive pancreatic neuroendocrine tumors (pNET) without safety and efficacy data in Chinese patients.

Thus this study is a post-approval commitment to China CFDA's request to collect the safety and efficacy data of everolimus in Chinese adult patients within this indication.

2.2 Rationale for the study design

This is a single arm, open-label study. The inclusion and exclusion criteria, as well as the dosing and dose modification criteria are designed according to the approved Chinese Package Insert (PI).

The primary variable corresponding to the main objective of the study is the safety profile in terms of adverse events, serious adverse events, adverse events suspected to be related to study drug and Grade 3 and 4 AEs. In addition, the incidences of specific adverse events of non-infectious pneumonitis as requested by CDE will be determined. For a complete list of the adverse events of special interest refer to Section 8.1.3.

Efficacy endpoint will be the same as the primary endpoint in global phase 3 study CRAD001C2324, i.e. progression free survival (PFS), and the 5 year OS data as required by CDE in the approval letter.

This is an interventional study. In order to minimize the risk of low data quality, interval of visit schedule is relatively fixed. The population and dosing chosen for this study are all within label indication and the test are all suggested by approved Chinese PI for safety consideration.

2.3 Rationale for dose and regimen selection

Starting dose and dose adjustment will follow the approved Chinese Package Insert. The starting dose is 10 mg once daily. The subsequent dose levels are subject to change due to severe or intolerable adverse reactions, change of liver function, changes in concomitant drug use (refer to Section 6.3.1).

2.4 Rationale for choice of combination drugs

Not applicable

2.5 Rationale for choice of comparators drugs

Not applicable

2.6 Risks and benefits

Appropriate eligibility criteria as well as specific dose modification and stopping rules, are included in this protocol. Recommended guidelines for prophylactic or supportive management of study-drug induced adverse events are provided in Section 6.3.1. The risk to subjects in this trial may be minimized by compliance with the eligibility criteria and study procedures, as well as, close clinical monitoring and targeted follow up checklist use for specific adverse events. There may be unforeseen risks with study treatment which could be serious including: Onset of benign or malignant tumors; potential risks related to missing information for the specific study population, e.g. Patients with uncontrolled cardiac disease etc.

3 Objectives and endpoints

To evaluate safety and efficacy of everolimus (Afinitor®) in Chinese adult patients with local advanced, unresectable or metastatic, well differentiated progressive pancreatic neuroendocrine tumors.

Objectives and related endpoints are described in Table 3-1.

Table 3-1 Objectives and related endpoints

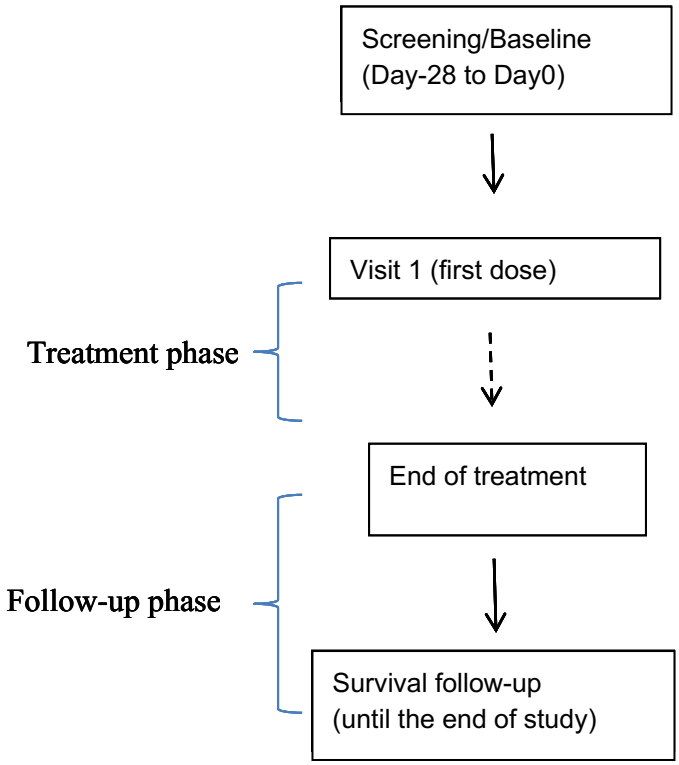
Objective	Endpoint	Analysis
Primary		Refer to Section 10.4
To evaluate the safety of treatment with Afinitor in Chinese adult patients with well differentiated progressive p-NET	Incidences of AEs, AE suspected to be related to Afinitor, Grade 3/4 AEs and SAEs Listing of AEs with special interest: Non-infectious pneumonitis	
Secondary		Refer to Section 10.5
To evaluate the overall efficacy of treatment with Afinitor in Chinese patients with well differentiated progressive p-NET	● **Overall Survival :** defined as time from study treatment to death due to any cause. ● **Progression free survival :** defined as time from first dose of study treatment to progression or death due to any cause	
Other secondary		
	Not applicable	Not applicable

4 Study design

4.1 Description of study design

Patient who are eligible will be provided with everolimus by sponsor to treat pNET and will follow the visit schedule in Table 7-1 to collect safety and efficacy data until disease progression, unacceptable toxicity, death, protocol deviation or other reason that may lead to discontinuation before the end of study. All patients will be followed-up for survival status every 6 months by the investigator until death, lost to follow-up, withdrawal of consent for survival or end of study. If the patient is still on treatment after 2 years, he/she will be shifted to commercial drug. However, this shift has no impact on participation in the study, all assessments will continue as before.

Figure 4-1 Study design



4.2 Timing of interim analyses and design adaptations

Interim analysis is planned for this study to provide a snapshot of data available to CFDA for license renewal. Based on the license renewal timeline, an interim analysis is planned in July 2017 with approximate 30 patients enrolled.

4.3 Definition of end of the study

The "End of study" is defined as either at least 75% of patients have completed survival follow up or all patients discontinued study treatment or the last patient finished 5-year survival follow up, whichever comes first. Final analysis will be conducted at the end of the study. Additional analyses between interim analyses (IA) and final analysis might be performed per Center for Drug Evaluation (CDE)'s request.

4.4 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible and the same assessments should be performed as described in Section 7 for a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing IRBs and/or ECs of the early termination of the trial.

5 Population

5.1 Patient population

The patient population includes Chinese adult patients with unresectable, locally advanced or metastatic, G1 or G2 progressive pancreatic neuroendocrine tumors (pNET) (WHO 2010). The planned sample size will be approximately 60patients with 30 additional patients enrolled after protocol amendment (v01).

The investigator or designee must ensure that only patients who meet all the following inclusion and none of the exclusion criteria are offered treatment in the study.

5.2 Inclusion criteria

Patients eligible for inclusion in this study have to meet **all** of the following criteria:

Written informed consent must be obtained prior to any screening procedures

1. Chinese Adult patients ≥ 18 years of age
2. Patients must have histological confirmed G1 or G2 locally advanced, unresectable pancreatic neuroendocrine tumors(pNETs) (WHO 2010)
3. Patients must have radiological documentation of progression of disease per RECIST 1.1 within 12 months prior to enrollment.
4. Measurable disease per RECIST 1.1 criteria using triphasic computed tomography (CT) scan or multiphase MRI for radiologic assessment.
5. Afinitor treatment which is recommended by the treating physician.

5.3 Exclusion criteria

Patients eligible for this study must not meet **any** of the following criteria:

1. Hypersensitivity to everolimus, to other rapamycin derivatives, or to any of the excipients.
2. Inability to attend scheduled clinic visits or scheduled tests.
3. Patient who is unwilling to receive Afinitor treatment due to any reason.
4. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.

   Women of child-bearing potential, who are or might become sexually active, must be informed of the need to prevent pregnancy during the study. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant (including female pediatric patients who are menarcheal or who become menarcheal during the study), must use highly effective contraception during study treatment and for 8 weeks after stopping treatment. Highly effective contraception methods include:

   - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
   - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
   - Male sterilization (at least 6 months prior to screening). The vasectomized male partner should be the sole partner for that subject with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate)
   - Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/ vaginal suppository
   - Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception

   In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.
5. Prior therapy with mTOR inhibitors (e.g. sirolimus, temsirolimus, everolimus).
6. Use of an investigational drug within the 30 days prior to enrollment.
7. Any severe and/or uncontrolled medical conditions which could cause unacceptable safety risks or compromise compliance with the protocol, such as: Impairment of gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of study drug (e.g., ulcerative disease, uncontrolled nausea, vomiting, diarrhea, etc).
8. Known history of seropositivity for human immunodeficiency virus (HIV)
9. Any cause that the investigator considers will harm the patient's benefit if participate in this study and please specify.

6 Treatment

6.1 Study treatment

This is a single arm, open-label study, and the investigational drug used in the course of this trial is Afinitor® (everolimus, 2.5 mg tablet, 5 mg tablet).

6.1.1 Dosing regimen

Everolimus will be dosed starting on Treatment Day 1 (Visit 1). Patients will be instructed to take Everolimus at a starting dose of 10 mg orally once daily. Everolimus should be administered orally once daily at the same time every day, either consistently with or consistently without food and be swallowed whole with a glass of water and should not be chewed or crushed. A change of dose might be required during the treatment, please refer to Section 6.3 and the Package Insert for more details.

If vomiting occurs, no attempt should be made to replace the vomited dose. Patients should be instructed that if they miss a dose on one day, they must not take any extra dose the next day, but instead to immediately contact the study center as soon as possible to ask for advice.

6.1.2 Ancillary treatments

Not applicable.

6.1.3 Rescue medication

Not applicable.

6.1.4 Treatment duration

Patient may continue treatment with the study drug until the patient experiences unacceptable toxicity, disease progression and/or treatment is discontinued at the discretion of the investigator or withdrawal of consent, if the patient is still on treatment after 2 years, he/she will be shifted to commercial drug.

6.2 Dose escalation guidelines

Not applicable.

6.3 Dose modifications

6.3.1 Dose modification and dose delay

For patients who do not tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to allow the patient to continue the study treatment.

These changes must be recorded on the Dosage Administration Record CRF.

Management of severe or intolerable adverse drug reactions (ADRs) may require temporary dose interruption (with or without dose reduction) or discontinuation of everolimus therapy. If dose reduction is required, the suggested dose is approximately 50% lower than the daily dose

previously administered. For dose reductions below the lowest available tablet strength, alternate day dosing should be considered.

If a patient has already decreased 2 dose levels, no further dose reduction is permitted. Patients who need an additional dose reduction will be required to discontinue everolimus/placebo or comparator drug.

Table 6-1 summarizes the recommendations for dose interruption, reduction, or discontinuation of everolimus in the management of ADRs. General management recommendations are also provided as applicable. Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

Table 6-1 Afinitor Dose Adjustment and Management Recommendation for Adverse Drug Reaction

Adverse Drug Reaction	Severity [a]	Everolimus Dose Adjustment [b] and Management Recommendations
Non-infectious pneumonitis	Grade 1 Asymptomatic, radiographic findings only	No dose adjustment required. Initiate appropriate monitoring.
	Grade 2 Symptomatic, not interfering with ADL[c]	Consider interruption of therapy, rule out infection and consider treatment with corticosteroids until symptoms improve to ≤ grade 1. Re-initiate Everolimus at a lower dose. Discontinue treatment if failure to recover within 4 weeks.
	Grade 3 Symptomatic, interfering with ADL[c]; O_2 indicated	Interrupt Everolimus until symptoms resolve to ≤ grade 1. Rule out infection, and consider treatment with corticosteroids. Consider re-initiating Everolimus at a lower dose. If toxicity recurs at grade 3, consider discontinuation.
	Grade 4 Life-threatening, ventilatory support indicated	Discontinue Everolimus, rule out infection, and consider treatment with corticosteroids.

Adverse Drug Reaction	Severity [a]	Everolimus Dose Adjustment [b] and Management Recommendations
Stomatitis	Grade 1 Minimal symptoms, normal diet	No dose adjustment required. Manage with non-alcoholic or salt water (0.9%) mouth wash several times a day.
	Grade 2 Symptomatic but can eat and swallow modified diet	Temporary dose interruption until recovery to grade ≤1. Re-initiate Everolimus at the same dose. If stomatitis recurs at grade 2, interrupt dose until recovery to grade ≤1. Re-initiate Everolimus at a lower dose. Manage with topical analgesic mouth treatments (e.g. benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol or phenol) with or without topical corticosteroids (i.e. triamcinolone oral paste).[d]
	Grade 3 Symptomatic and unable to adequately aliment or hydrate orally	Temporary dose interruption until recovery to grade ≤1. Re-initiate Everolimus at a lower dose. Manage with topical analgesic mouth treatments (i.e. benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol or phenol) with or without topical corticosteroids (i.e. triamcinolone oral paste).[d]
	Grade 4 Symptoms associated with life-threatening consequences	Discontinue Everolimus and treat with appropriate medical therapy.
Other nonhematologic toxicities (excluding metabolic events)	Grade 1	If toxicity is tolerable, no dose adjustment required. Initiate appropriate medical therapy and monitor.
	Grade 2	If toxicity is tolerable, no dose adjustment required. Initiate appropriate medical therapy and monitor. If toxicity becomes intolerable, temporary dose interruption until recovery to grade ≤1. Re-initiate Everolimus at the same dose. If toxicity recurs at grade 2, interrupt Everolimus until recovery to grade ≤1. Re-initiate Everolimus at a lower dose.
	Grade 3	Temporary dose interruption until recovery to grade ≤1. Initiate appropriate medical therapy and monitor. Consider re-initiating Everolimus at a lower dose. If toxicity recurs at grade 3, consider discontinuation.
	Grade 4	Discontinue Everolimus and treat with appropriate medical therapy.

Adverse Drug Reaction	Severity [a]	Everolimus Dose Adjustment [b] and Management Recommendations
Metabolic events (e.g. hyperglycemia, dyslipidemia)	Grade 1	No dose adjustment required. Initiate appropriate medical therapy and monitor
	Grade 2	No dose adjustment required. Manage with appropriate medical therapy and monitor
	Grade 3	Temporary dose interruption. Re-initiate Everolimus at a lower dose. Manage with appropriate medical therapy and monitor.
	Grade 4	Discontinue Everolimus and treat with appropriate medical therapy.
Physicians should always manage patients according to their medical judgment based on the particular clinical circumstances.		

[a] Severity grade description: 1 = mild symptoms; 2 = moderate symptoms; 3 = severe symptoms; 4 = life-threatening symptoms,

[b] If dose reduction is required, the suggested dose is approximately 50% lower than the dose previously administered.

[c] Activities of daily living (ADL)

[d] Avoid using agents containing hydrogen peroxide, iodine, and thyme derivatives in management of stomatitis as they may worsen mouth ulcers.

Renal Impairment

No clinical studies were conducted with everolimus in patients with decreased renal function. Renal impairment is not expected to influence drug exposure and no dosage adjustment of everolimus is recommended in patients with renal impairment.

Hepatic Impairment

Hepatic impairment will increase the exposure to everolimus. Dose adjustments are recommended:

- Mild hepatic impairment (Child-Pugh class A): The recommended dose is 7.5 mg daily; the dose may be decreased to 5mg if not well tolerated.
- Moderate hepatic impairment (Child-Pugh class B): The recommended dose is 5 mg daily; the dose may be decreased to 2.5 mg if not well tolerated.
- Severe hepatic impairment (Child-Pugh class C): If the desired benefit outweighs the risk, a dose of 2.5 mg daily maybe used but must not be exceeded.

Dose adjustments should be made if a patient's hepatic (Child-Pugh) status changes during treatment.

Dose adjustments for QTcF prolongation.

1. Assess the quality of the ECG recording and the QT value and repeat if needed
2. Interrupt study treatment
3. Determine the serum electrolyte levels (in particular hypokalemia, hypomagnesemia). If abnormal, correct abnormalities before resuming study drug treatment.
4. Review concomitant medication associated with QT prolongation, including drugs with a "Known", "Possible", or "Conditional risk of Torsade de Pointes", and drugs with the potential to increase the risk of study drug exposure related QT prolongation

5. Check study drug dosing schedule and treatment compliance
6. Consider collecting a time-matched PK sample, and record time and date of last study drug intake.

After confirming ECG reading at site, if QTcF > 500 msec

- Interrupt study treatment
- Repeat ECG and confirm ECG diagnosis by a cardiologist or central ECG lab
- If QTcF confirmed > 500 msec:
  - Correct electrolytes, eliminate culprit concomitant treatments, and identify and address clinical conditions that could potentially prolong the QT as per the ECG and QTc Clinical Safety Standards Guidelines Section 3.3.1.
  - Consult with a cardiologist (or qualified specialist)
  - Increase cardiac monitoring as indicated, until the QTcF returns to ≤ 480 msec.
- After resolution to ≤ 480 msec, consider re-introducing treatment at reduced dose, and increase ECG monitoring for the next treatment(s):
  - If QTcF remains ≤ 500 msec after dose reduction, continue planned ECG monitoring during subsequent treatment

If QTcF recurs > 500 msec after dose reduction, discontinue patient from trial.

6.3.2 Follow-up for toxicities

All patients will be followed for adverse events and serious adverse events for 30 days following the last dose of study drug. Beyond these 30 days, any serious adverse events that are suspected to be related to the study drug will also be collected.

6.3.2.1 Follow up on potential drug-induced liver injury (DILI) cases

Patients with transaminase increase combined with TBIL increase may be indicative of potential DILI, and should be considered as clinically important events.

The threshold for potential DILI may depend on the patient's baseline AST/ALT and TBIL value; patients meeting any of the following criteria will require further follow-up as outlined below:

- For patients with normal ALT and AST and TBIL value at baseline: AST or ALT > 3.0 x ULN combined with TBIL > 2.0 x ULN
- For patients with elevated AST or ALT or TBIL value at baseline: [AST or ALT > 2 x baseline AND > 3.0 x ULN] OR [AST or ALT > 8.0 x ULN], combined with [TBIL > 2 x baseline AND > 2.0 x ULN]

Medical review needs to ensure that liver test elevations are not caused by cholestasis, defined as ALP elevation > 2.0 x ULN with R value < 2 in patients without bone metastasis, or elevation of ALP liver fraction in patients with bone metastasis.

Note: (The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes whether the relative pattern of ALT and/or ALP elevation is due to cholestatic (R ≤ 2), hepatocellular (R ≥ 5), or mixed (R >2 and < 5) liver injury).

In the absence of cholestasis, these patients should be immediately discontinued from study drug treatment, and repeat LFT testing as soon as possible, preferably within 48 hours from the awareness of the abnormal results. The evaluation should include laboratory tests, detailed history, physical assessment and the possibility of liver metastasis or new liver lesions, obstructions/compressions, etc.

1. Laboratory tests should include ALT, AST, albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, GGT, prothrombin time (PT)/INR and alkaline phosphatase.
2. A detailed history, including relevant information, such as review of ethanol, concomitant medications, herbal remedies, supplement consumption, history of any pre-existing liver conditions or risk factors, should be collected.
3. Further testing for acute hepatitis A, B, C or E infection and liver imaging (e.g. biliary tract) may be warranted.
4. Obtain PK sample, as close as possible to last dose of study drug, if PK analysis is performed in the study.
5. Additional testing for other hepatotropic viral infection (CMV, EBV or HSV), autoimmune hepatitis or liver biopsy may be considered as clinically indicated or after consultation with specialist/hepatologist.

All cases confirmed on repeat testing meeting the laboratory criteria defined above, with no other alternative cause for LFT abnormalities identified should be considered as “medically significant”, thus, met the definition of SAE (Section 8.2.1) and reported as SAE using the term “potential drug-induced liver injury”. All events should be followed up with the outcome clearly documented

6.4 Concomitant medications

In clinical trials and post-marketing spontaneous reports, angioedema has been reported with and without concomitant use of angiotensin-converting-enzyme (ACE) inhibitors. The risk of angioedema events may be increased with concomitant administration of ACE inhibitors. Patients must be instructed not to take any additional medications (over-the-counter, herbal or other products) during the study without prior consultation with the investigator. All medications taken within 30 days of starting study treatment and during the study until the last dose should be reported on the Concomitant Medication/Significant Non-drug Therapy CRF. Co-administration with strong CYP3A4 inhibitors, strong CYP3A4 inducers, St. John’s Wort (Hypericum perforatum), and grapefruit, grapefruit juice, and other foods that are known to inhibit cytochrome P450 and PgP activity should be avoided during the treatment (refer to Package Insert for more details). Contraindications include hypersensitivity to the active substance, to other rapamycin derivatives, or to any of the excipients.

For concomitant medications deemed necessary for the care of the patient, dose modifications may be required and please refer to Section 6.3 and Package Insert for detailed instructions. The concomitant medications should be documented in CRF.

6.4.1 Permitted concomitant therapy

The patient must be told to notify the investigational site about any new medications he/she takes after the start of the study drug. All medications (other than study drug) and significant non-drug therapies (including physical therapy, herbal/natural medications and blood transfusions) administered during the study must be listed on the Concomitant Medications or the Procedures and Significant Non-Drug Therapies CRF.

6.4.2 Permitted concomitant therapy requiring caution and/or action

Cytochrome P450 and P-glycoprotein (PgP) inhibitors/inducers/substrates

Everolimus is metabolized by CYP3A4 in the liver and to some extent in the intestinal wall.

Therefore, the following are recommended:

Co-administration with strong inhibitors of CYP3A4/PgP should be avoided and may cause increased everolimus concentrations.Co-administration with moderate CYP3A4/PgP inhibitors should be used with caution. If a patient requires co-administration of moderate CYP3A4/PgP inhibitors, reduce the dose of study drug to half the currently used dose. Additional dose reductions may be required to manage toxicities. If the inhibitor is discontinued, consider a washout period of at least 2-3 days (average for the most commonly used moderate inhibitors), before the study drug dose is returned to the dose used prior to initiation of the moderate CYP3A4/PgP inhibitor.

If a patient requires co-administration of strong CYP3A4 inducer, an increase in the dose of study drug up to twice the currently used daily dose should be considered, using 5 mg increments or less. This dose adjustment of study drug is predicted to achieve similar AUC to the range observed without inducers. However, there are no clinical data with this dose adjustment in patients receiving strong CYP3A4 inducers. If the strong inducer is discontinued, consider a washout period of at least 3-5 days (reasonable time for significant enzyme de-induction), before the study drug dose is returned to the dose used prior to initiation of the strong CYP3A4/PgP inducer.

Please refer to Table 6-2 listing relevant inducers and inhibitors of CYP3A and to Table 6-3 for a list of relevant substrates, inducers, and inhibitors of PgP.

Table 6-2 Clinically relevant drug interactions: inducers, and inhibitors of isoenzyme CYP3A

Inducers
Strong inducers:
avasimibe, carbamazepine, phenytoin, rifampin, St. John's wort, rifabutin, phenobarbital, mitotane, enzalutamide
Moderate inducers:
bosentan, efavirenz, etravirine, modafinil, nafcillin, genistein, ritonavir, thioridazine, tipranavir, semagacestat, talviraline, lopinavir, lersivirine,
Weak inducers:
amprenavir, aprepitant, armodafinil bexarotene, clobazam, danshe, dexamethasone, echinacea, garlic , gingko (ginkgo biloba), glycyrrhizin, methylprednisolone, nevirapine, oxcarbazepine, pioglitazone, prednisone, pleconaril, primidone, raltegravir, rufinamide, sorafenib, telaprevir, terbinafine, topiramate, troglitazone, vinblastine, eslicarbazepine, ginseng, vemurafenib, boceprevir, sulfinpyrazone, ticagleror, vicriviroc/ritonavir, ritonavir, ticlopidine, brivacetam, Stribild (combo of elvitegravir, cobicistat, emtricitabine, and tenofovir), quercetin.
Inhibitors
Strong inhibitors:
boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, sequinavir/ritonavir, telaprevir, telithromycin, voriconazole, indinavir/ritonavir, tipranoavir/ritonavir, cobicistat, troleandomycin, danoprevir/ritonavir, eltegravir/ritonavir,
Moderate inhibitors:
amprenavir, aprepitant, atazanavir, ciprofloxacin, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice, nilotinib imatinib, tofisopam, cyclosporin, ciprofloxacin, verapamil, dronedarone, crizotinib, casopitant, amprenavir, atazanavir/ritonavir, duranavir, netupitant, schisandra sphenanthera , cimetidine, lomitapide
Weak inhibitors:
tabimorelin, ranolaxine, fosaprepritant, Seville orange, amlodipine, clozoxazone, fluvoxamine, ranitidine, goldenseal ,clotrimazole, tacrolimus, cilostazol, ticagrelor, ivacaftor, roxithromycin, propiverine, isoniazid, berberine, oral contraceptives, peppermint oil, delavirdine, simeprevir, atorvastatin, tolvaptan, almorexant, linagliptin, resveratrol, lacipidine, cranberry juice, nilotinib, pazopanib, evrolimus, blueberry juice, alprazolam, bicalutamide, sitaxentan, azithromycin, ginkgo, teriflunomide, alprazolam, amiodarone, amlodipine, bicalutamide, cilostazol, cimetidine, cyclosporine, fluoxetine, isoniazid, ranitidine, ranolazine, tipranavir/ritonavir, zileuton

Table 6-3 Clinically relevant drug interactions: substrates, inducers, inhibitors of PgP and PgP/CYP3A dual inhibitors

Substrates
digoxin, quinidine, paclitaxel, cyclosporine, sirolimus, tacrolimus, fentanyl, pphenytoin, aliskiren, ambrisentan, atorvastatin, atorvastatin acid, azithromycin, cerivastatin, colchicine, CP-481,715, cyclosporine, dabigatran, digoxin, docetaxel, domperidone, doxorubicin, fentanyl, fexofenadine, lapatinib, linezolid, loperamide, maraviroc, nevirapine, paclitaxel, proguanil, quinidine, ranolazine, ritonavir, saquinavir, simvastatin, sirolimus, sofosbuvir, tacrolimus, ticagrelor, voclosporin, afatinib, alfuzosin, aliskiren, alogliptin, ambrisentan, apixaban, apremilast, aprepitant, boceprevir, bosentan, carvedilol, carvedilol, caspofungin, ceritinib, citalopram, colchicine, cyclosporine, dabigatran, digoxin, doxepin, doxorubicin, eribulin, everolimus, fidaxomicin, fluvastatin, fosamprenavir, gatifloxacin, idelalisib, iloperidone, indacaterol, irbesartan, lacosamide, lapatinib, levetiracetam, levofloxacin, linagliptin, losartan, maraviroc, mirabegron, moxifloxacin, naloxegol, nateglinide, nintedanib, olodaterol, pantoprazole, paroxetine, pazopanib, posaconazole, pravastatin, quinine, ranolazine, riociguat, risperidone, rivaroxaban, saquinavir, silodosin, simeprevir, sirolimus, sitagliptin, sorafenib, telaprevir, tenofovir, ticagrelor, tipranavir, tolvaptan, topotecan, umeclidinium, valsartan, vardenafil, vincristine, voriconazole
Inducers
avasimibe, carbamazepine, efavirenz, genistein, phenytoin, quercetin, rifampin, St. John's wort extract
PgP Inhibitors and PgP/CYP3A Dual Inhibitors
PgP Inhibitors
alogliptin, canaglifozin, cremophor RH40, curcumin, ketoconazole, lapatinib, lopinavir/ritonavir, mirabegron, propafenone, simepravir, valspodar, vandetanib, voclosporin
PgP/CYP3A Dual Inhibitors
amiodarone, azithromycin,captopril, carvedilol, clarithromycin, conivaptan, diltiazem, dronedarone, elacridar, erythromycin, felodipine, fluvoxamine, ginko, indinavir, indinavir/ritonavir, itraconazole, mibefradil, milk thisle, nelfinavir, nifedipine, nitredipine, paroxetine, quercetin, quinidine, ranolazine, rifampin, ritonavir, sequinavir/ritonavir, schisandra chinesis extract, St. John's wort extract, talinolol, telaprevir, telmisartan, ticagrelor, tipranavir/ritonavir, tolvaptan, verapamil
Reference: Internal Clinical Pharmacology Drug-drug interaction (DDI) memo, updated April-2015 which summarizes DDI data from three sources including the FDA's "Guidance for Industry, Drug Interaction Studies", the University of Washington's Drug Interaction Database, and Indiana University School of Medicine's Drug Interaction Table.

Vaccinations

Immunosuppressants may affect the response to vaccination and vaccination during treatment with everolimus may therefore be less effective. The use of live vaccines should be avoided during treatment with everolimus. Examples of live vaccines are: intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines.

6.4.3 Prohibited concomitant therapy

Anti-neoplastic therapies

Treatment with systemic anticancer agents (chemotherapy, hormone therapy, targeted or biologic agents) other than the protocol treatment is not permitted until disease progression is documented per RECIST. Palliative radiotherapy or surgery may be allowed and should be discussed with Novartis prior to administration.

6.4.4 Use of Bisphosphonates (or other concomitant agents)

Not applicable.

6.5 Patient numbering, treatment assignment or randomization

6.5.1 Patient numbering

Each patient is identified in the study by a Subject Number (Subject No.), that is assigned when the patient is first enrolled for screening and is retained as the primary identifier for the patient throughout his/her entire participation in the trial. The Subject No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential patient number suffixed to it, so that each subject is numbered uniquely across the entire database. Upon signing the informed consent form, the patient is assigned to the next sequential Subject No. available to the investigator.

Once assigned to a patient, the Subject No. will not be reused.

6.5.2 Treatment assignment or randomization

6.5.3 Not applicable. Treatment blinding

This study is an open-label study, thus it is not applicable.

6.6 Study drug preparation and dispensation

The investigator or responsible site personnel must instruct the patient or caregiver to take the study drugs as per protocol. Study drug(s) will be dispensed to the patient by authorized site personnel only. All dosages prescribed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record CRF.

Table 6-4 Preparation and dispensing

Study treatments	Dispensing	Preparation
Afinitor	Tablets including instructions for administration are dispensed by study personnel on an outpatient basis. Patients will be provided with adequate supply of study treatment for self-administration at home until at least their next scheduled study visit.	Not applicable

6.6.1 Study drug packaging and labeling

Study treatment, [everolimus], will be sourced as local commercial supply (in the locally approved formulation and packaging configuration) and labeled in the country when possible.

The study medication packaging has a 2-part label. A unique medication number is printed on each part of this label which corresponds to the treatment arm and a specific visit. Responsible site personnel will identify the study treatment package(s) to dispense to the patient and obtaining the medication number(s). Site personnel will add the patient number on the label. Immediately before dispensing the package to the patient, site personnel will detach the outer

part of the label from the packaging and affix it to the source document (Drug Label Form) for that patient's unique patient number.

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

Everolimus tablet, 2.5mg/tablet, 5 mg/ tablet, 1 tablet per blister

6.6.2 Drug supply and storage

Everolimus tablet will be supplied by Novartis, and it must be received by designated personnel at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, the **study treatment** should be stored according to the instructions specified on the drug labels and in the Chinese PI.

6.6.3 Study drug compliance and accountability

6.6.3.1 Study drug compliance

Compliance will be assessed by the investigator and/or study personnel at each patient visit and information provided by the patient and/or caregiver will be captured in the Drug Accountability Form. This information must be captured in the source document at each patient visit.

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

6.6.3.2 Study drug accountability

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

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

6.6.3.3 Handling of other study treatment

Not applicable.

6.6.4 Disposal and destruction

The study drug supply can be destroyed at the local Novartis facility, Drug Supply group or third party, as appropriate.

7 Visit schedule and assessments

7.1 Study flow and visit schedule

Table 7-1 lists all of the assessments and indicates with an "X", the visits when they are performed. All data obtained from these assessments must be supported in the patient's source documentation.

No CRF will be used as a source document.

The table indicates which assessments produce data to be entered into the clinical database (D) or remain in source documents only (S) ("Category" column). Tests, procedures and visits should occur on schedule whenever possible. However, tests, procedures, and visits that occur outside the prescribed allowable windows indicated in Table 7-1 will not constitute protocol deviations.

Table 7-1 Visit evaluation schedule

	Category	Protocol Section 7.2	Screening/ Baseline (-28~0day)	Visit 1 (day1)	Visit 2 (day28±2d)	Visit 3 (week 12±1wk)	Subsequent visits (every 12wk±1wk)	End of study treatment (EOT)	30-day Safety Follow-up	Survival follow up (every 6 months)
Obtain Informed Consent	D		X							
Patient history	D		X							
Demography	D		X							
Inclusion/exclusion criteria	D		X							
Relevant medical history/current medical conditions	D		X							
Diagnosis of cancer	D		X							
Prior/concomitant medications	D		X	X	X	X	X	X		
Physical examination	S	7.2.2.1	X	X	X	X	X	X		
Vital signs	D	7.2.2.2	X	X	X	X	X	X		
Height/Weight	D	7.2.2.3	X							
Laboratory assessments		7.2.2.4								
Hematology [a]	D	7.2.2.4.1	X	X	X	X	X	X		
Liver function tests [b]	D	7.2.2.4.2	X		X	X	X	X		
Coagulation	S	7.2.2.4.3	X		X	X	X	X		
Other laboratory test [c]	S	7.2.2.4.6		Only to be done if clinically indicated						
Urinalysis [c]	S	7.2.2.4.4	X	Only to be done if clinically indicated						
Pregnancy test [d]	D	7.2.2.4.5	X					X		
Tumor evaluation(MRI or CT) [e]	D	7.2.1	X			X	X			X[f]
Pulmonary function tests, Chest CT[g]	D	7.2.2.5		Only to be done if clinically indicated						
Adverse events	D		X	Continuously					X	
Study Drug administration	D			X	X	X	X	X		

	Category	Protocol Section 7.2	Screening/ Baseline (-28~0day)	Visit 1 (day1)	Visit 2 (day28±2d)	Visit 3 (week 12±1wk)	Subsequent visits (every 12wk±1wk)	End of study treatment (EOT)	30-day Safety Follow-up	Survival follow up (every 6 months)
Reason for discontinuation/ withdrawal	D							X		
Survival Follow-up	D									X

a. Fasting hematology include: hemoglobin, hematocrit, platelets, red blood cell count (RBC) total white blood cell count (WBC) absolute & differential including neutrophils, lymphocytes, monocytes, eosinophils and basophils. Absolute Neutrophil Count (ANC) will be calculated by the laboratory.

b. Liver function tests include: AST, ALT, total bilirubin, alkaline phosphatase, serum albumin.

c. Clinically significant findings will be noted in the Medical history/ Current medical condition pages or Adverse Events pages. Urinalysis assessment could include but not limited to: pH, protein, glucose, blood, ketones, and leukocytes. Other laboratory test could include but not limited to: total LDH, GGT, fasting glucose, fasting serum lipid, sodium, magnesium, phosphate, potassium, chloride, bicarbonate, creatinine, BUN, total protein, uric acid, calcium.

d. A serum pregnancy test will be conducted locally at screening /baseline in all females of child-bearing potential, urine pregnancy test will be conducted at the end of treatment visit.

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

f. Efficacy assessment will be collected until progression of disease (PD).

g. If an investigator suspects a patient may be developing pneumonitis, investigations such as pulmonary function tests, CT chest and referral to a pulmonologist should be considered.

7.1.1 Molecular pre-screening

Not applicable.

7.1.2 Screening

Screening examination must include serum hCG laboratory test (Section 5.3 exclusion criteria-4), and confirmation of diagnosis according to inclusion criteria.

Informed consent must be signed prior to any screening procedure.

Re-screening is allowed for no more than 3 times within 6 months only when the previous severe and/or uncontrolled medical conditions mentioned in Section 5.3 Exclusion Criteria (except for bullet point 1, 5 and 8) has been resolved.

7.1.2.1 Eligibility screening

Not applicable.

7.1.2.2 Information to be collected on screening failures

Patients who sign an informed consent but fail to be started on treatment for any reason will be considered as screen failure. The reason for not being started on treatment will be entered on the Screening Phase Disposition Page. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for Screen Failure patients. No other data will be entered into the clinical database for patients who are screen failures, unless the patient experienced a Serious Adverse Event during the Screening Phase (see Section 8 for SAE reporting details).

7.1.2.3 Patient demographics and other baseline characteristics

Data will be collected on patient characteristics including demographic information (age, sex, race, weight, height) and other background or relevant medical history (disease history, family history of disease, prior anti-neoplastic therapies, and any other assessments that are done for the purpose of determining eligibility for inclusion in the study [i.e., complete physical examination, pregnancy test for women of child-bearing potential, CT/MRI].

Medical history will include family history of disease.

7.1.3 Run-in period

Not applicable.

7.1.4 Treatment period

Patients will start study treatment at Visit 1 (Treatment Day 1) and continue to be treated per protocol until documentation of disease progression, unacceptable toxicity, death, withdrawal of consent or sponsor decision to stop the study. However, study treatment may prematurely be discontinued for other reasons as well. Please refer to Section 7.1.5. And patients should follow the visit schedule in Table 7-1. If the patient is still on treatment after 2 years, he/she will be shifted to commercial drug.

7.1.5 Discontinuation of study treatment

Patients may voluntarily discontinue from the study treatment (everolimus) for any reason at any time. If a patient decides to discontinue from the study treatment (everolimus) the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for this decision and record this information in the patient's chart and on the appropriate CRF pages. They may be considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason.

The investigator may discontinue study treatment (everolimus) for a given patient if, he/she believes that continuation would be detrimental to the patient's well-being.

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

The term "discontinuation" refers to a patient's premature and permanent withdrawal from the study treatment. The reason for discontinuation from treatment will be recorded.

At the time patients discontinue study treatment, a visit should be scheduled as soon as possible, at which time all of the assessments listed for the End of Treatment (EOT) visit will be performed. An End of Treatment Phase Disposition CRF page should be completed, giving the date and reason for stopping the study treatment.

At a minimum, all patients who discontinue study treatment, including those who refuse to return for a final visit, will be contacted for safety evaluations during the 30 days following the last dose of study treatment.

For criteria for premature withdrawal refer to Section 7.1.6.

End of treatment/Premature withdrawal visit is not considered as the end of the study.

7.1.5.1 Replacement policy

Not applicable.

7.1.6 Withdrawal of consent

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

- pregnancy;
- discovery of patient ineligibility;

In addition to the general withdrawal criteria, the following study specific criteria will also require study treatment discontinuation:

- Any other protocol deviation that results in a significant risk for the patient's safety
- Subject withdrew consent
- Lost to follow-up
- Administrative problems
- Adverse events including laboratory abnormalities which required discontinuation of study treatment listed in Table 6-1;

- Compliance problems other than dose interruption as described above;
- Unsatisfactory therapeutic effect as the investigator consider the subject's condition no longer benefit from study treatment (be specified in the CRF)
- Use of prohibited treatment

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

7.1.7 Follow up for safety evaluations

All patients must have safety evaluations for 30 days after the last dose of study treatment.

Data collected should be added to the Adverse Events CRF and the Concomitant Medications CRF.

7.1.8 Lost to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw consent, the investigator should show "due diligence" by contacting the patient, family or family physician as agreed in the informed consent and by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc. A patient should not be considered lost to follow-up until due diligence has been completed. Patients lost to follow up should be recorded as such on the appropriate Disposition CRF.

7.2 Assessment types

7.2.1 Efficacy assessments

Tumor assessments are to be performed for screening purposes and are needed to determine the eligibility of the patient. Last available results of scans performed within 28 days prior to first dose of study drug will be used as baseline values. Negative scans at screening need not be repeated unless warranted by signs and symptoms suggesting disease progression. The assessment data will be collected until disease progression, unacceptable toxicity, death, protocol deviation or other reason that may leads to discontinuation or the end of study.

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

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

To determine eligibility, measurable and non-measurable lesions must be assessed and target lesions identified prior to enrollment. For definition of measurable and target lesions please refer to RECIST 1.1 (Appendix 1)

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and after every 12 weeks while on-study. All radiology evaluations will be performed initially by the local radiologist.

Details of response assessment are provided in full protocol based on RECIST1.1, and are based exclusively on radiological findings obtained at tumor assessments.

7.2.2 Safety and tolerability assessments

Safety will be monitored by assessing as well as collecting of the adverse events at every visit. For details on AE collection and reporting, refer to Section 8.

7.2.2.1 Physical examination

A complete physical examination will include the examination of general appearance, height and weight, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed.

A short physical exam will include the examination of general appearance and vital signs. A short physical exam will be at all visits starting from Visit 3 except where a complete physical examination is required (see above).

Significant findings that were present prior to the signing of informed consent must be included in the Medical History page on the patient's CRF. Significant new findings that begin or worsen after informed consent must be recorded on the Adverse Event page of the patient's CRF.

7.2.2.2 Vital signs

Pulse, respiration rate, blood pressure and temperature will be measured as indicated in the Assessment schedule (Table 7-1) and will be recorded on source documents, and entered on CRF pages.

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

7.2.2.3 Height and weight

Height and Body weight (in indoor clothing, but without shoes) will be measured at screening.

7.2.2.4 Laboratory evaluations

Local laboratory will be used for analysis of all specimens collected.

7.2.2.4.1 Hematology

Hemoglobin, hematocrit, white blood cell count with differential, and platelet count will be measured.

7.2.2.4.2 Liver function tests

Total bilirubin, AST, ALT, serum albumin and alkaline phosphatase will be measured.

7.2.2.4.3 Coagulation

Prothrombin time (PT) or International normalized ratio [INR]), Partial thromboplastin time (PTT), Activated partial thromboplastin time (APTT).

7.2.2.4.4 Urinalysis

During screening, a standard urinalysis assessment (pH, protein, glucose, blood), any significant findings on dipstick shall be followed up with a microscopic evaluation where WBC and RBC sediments should also be considered per the investigator's clinical practice routine.

7.2.2.4.5 Pregnancy and assessments of fertility

All females must have a negative serum pregnancy test at screening/baseline, while at the end of treatment visit urinary pregnancy tests are sufficient.

It is recommended that female before come to age of menarche or women considered at postmenopausal status by investigator's judgment according to local clinical practice or post-surgical bilateral oophorectomy or hysterectomy are to be considered "of non-childbearing potential".

Highly effective contraception, must be used on-study and for up to 8 weeks after ending treatment for those patients who considered as with childbearing potential (definition of highly effective contraception is detailed in Section 5.3.

Instruction in Section 8.4 should be followed when patients is confirmed of pregnancy.

7.2.2.4.6 Other laboratory tests

Other laboratory test should be done as clinically indicated, and could include but not limited to: total LDH, fasting glucose, fasting serum lipid, sodium, magnesium, phosphate, potassium, chloride, bicarbonate, creatinine, BUN, total protein, uric acid, calcium.

7.2.2.5 Radiological examinations (Pulmonary function tests)

Individuals participating in this trial will be questioned at each visit as to the presence of new or changed pulmonary symptoms consistent with lung toxicity. If an investigator suspects a patient may be developing pneumonitis investigations such as pulmonary function tests, CT chest and referral to a pulmonologist should be considered.

7.2.2.6 Cardiac assessments

Not applicable

7.2.2.7 Tolerability

Not applicable

7.2.3 Pharmacokinetics

Not applicable.

7.2.4 Biomarkers

Not applicable.

Other assessments

No additional tests will be performed on patients entered into this study.

7.2.5 Resource utilization

Not applicable.

7.2.6 Patient reported outcomes

Not applicable.

8 Safety monitoring and reporting

8.1 Adverse events

8.1.1 Definitions and reporting

An adverse event is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur after patient's signed informed consent has been obtained.

Abnormal laboratory values or test results occurring after informed consent constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, require therapy (e.g., hematologic abnormality that requires transfusion or hematological stem cell support), or require changes in study medication(s).

Adverse events that begin or worsen after informed consent should be recorded in the Adverse Events CRF. Conditions that were already present at the time of informed consent should be recorded in the Medical History page of the patient's CRF. Adverse event monitoring should be continued for at least 30 days (or 5 half-lives, whichever is longer) following the last dose of study treatment. Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate Adverse Event.

Adverse events will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, corresponding to Grades 1 - 4, will be used. CTCAE Grade 5 (death) will not be used in this study; rather, information about deaths will be collected though a Death form.

The occurrence of adverse events should be sought by non-directive questioning of the patient (subject) during the screening process after signing informed consent and at each visit during the study. Adverse events also may be detected when they are volunteered by the patient

(subject) during the screening process or between visits, or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. The severity grade (CTCAE Grade 1-4)
2. Its duration (Start and end dates)
3. Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes)
   or
   Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes, investigational treatment, Yes, the study treatment (non-investigational), Yes, both and/or indistinguishable)
4. Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
5. Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
6. Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequalae, fatal, unknown)
7. Whether it is serious, where a serious adverse event (SAE) is defined as in Section 8.2.1

If the event worsens the event should be reported a second time in the CRF noting the start date when the event worsens in toxicity. For grade 3 and 4 adverse events only, if improvement to a lower grade is determined a new entry for this event should be reported in the CRF noting the start date when the event improved from having been Grade 3 or Grade 4.

All adverse events should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded on the Adverse Event CRF.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (for example, as per RECIST criteria for solid tumors or as per Cheson's guidelines for hematological malignancies), should not be reported as a serious adverse event.

Adverse events separate from the progression of malignancy (example, deep vein thrombosis at the time of progression or hemoptysis concurrent with finding of disease progression) will be reported as per usual guidelines used for such events with proper attribution regarding relatedness to the drug.

8.1.2 Laboratory test abnormalities

8.1.2.1 Definitions and reporting

Laboratory abnormalities that constitute an Adverse event in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the Adverse Events CRF. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g. anemia

instead of low hemoglobin). Laboratory abnormalities that meet the criteria for Adverse Events should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported adverse event, it is not necessary to separately record the lab/test result as an additional event.

Laboratory abnormalities, that do not meet the definition of an adverse event, should not be reported as adverse events. A Grade 3 or 4 event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per investigator's discretion. A dose hold or medication for the lab abnormality may be required by the protocol in which case the lab abnormality would still, by definition, be an adverse event and must be reported as such.

8.1.3 Adverse events of special interest

Adverse events of special interest (AESI) are defined as events (serious or non-serious) which are ones of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor may be appropriate. Such events may require further investigation in order to characterize and understand them.

Adverse events of special interest are defined on the basis of an ongoing review of the safety data. AESIs are discussed in detail in the [Investigator Brochure].

As a result of observations during the conduct of earlier studies with everolimus, several groups of events were defined as adverse events of special interest, AESIs. These groups consist of AEs for which there is a specific clinical interest in association with everolimus treatment and/or with inhibition of mTOR signaling.

For this study the following adverse events are events of special interest:

- Stomatitis/ oral mucositis
- Reactivation of hepatitis B virus
- Cardiac disorders: Cardiac failure; ejection fraction decreased

Non-infectious pneumonitis.

8.2 Serious adverse events

8.2.1 Definitions

Serious adverse event (SAE) is defined as one of the following:

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- Requires inpatient hospitalization or prolongation of existing hospitalization,

- Note that hospitalizations for the following reasons should not be reported as serious adverse events:
  - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - Social reasons and respite care in the absence of any deterioration in the patient's general condition
- Note that treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE given above is not a serious adverse event

8.2.2 Reporting

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until at least 30 days after the patient has stopped study treatment must be reported to Novartis within 24 hours of learning of its occurrence.

Any SAEs experienced after this 30 days period should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Any SAEs experienced after the 30 day safety evaluation follow-up period should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and submit the completed form within 24 hours to Novartis. Detailed instructions regarding the SAE submission process and requirements for signatures are to be found in the investigator folder provided to each site Follow-up information is submitted in the same way as the original SAE Report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the patient continued or withdrew from study participation.

For Everolimus the following adverse events are the AE that Novartis has committed to perform targeted follow up, for example in the Risk Management Plan , including: 1.Non-infectious pneumonitis. 2. Severe Infections including Hepatitis Reactivation; 3. Hypersensitivity including Anaphylaxis; 4.Renal Impairment or Failure; 5. Acute and Congestive Heart Failure; 6. Female fertility (including secondary amenorrhea); 7. Reactivation, Aggravation, Exacerbation of Background Disease; 8. Postnatal developmental toxicity; 9. Pregnant or breast-feeding women; 10. Onset of benign or malignant tumors.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the Novartis study treatment, an oncology Chief Medical Office and Patient Safety (CMO&PS) department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

8.3 Emergency unblinding of treatment assignment

Not Applicable.

8.4 Pregnancies

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

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the oncology Novartis Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Preclinical data regarding reproductive toxicity is described in the most recent [Investigator Brochure]. The potential reproductive risk for humans is unknown. Women of childbearing potential should be advised to use highly effective contraception methods while they are receiving everolimus and up to 8 weeks after treatment has been stopped. If a pregnancy occurs while on study treatment, the newborn will be followed for at least 12 months.

The potential for everolimus to cause infertility in male and female patients is unknown. However, menstrual irregularities, secondary amenorrhea and associated luteinizing hormone (LH)/follicle stimulating hormone (FSH) imbalance has been observed. Blood levels of FSH and LH increased, blood levels of testosterone decreased, and azoospermia have been observed in male patients receiving everolimus.

Based on non-clinical and clinical findings, male and female fertility may be compromised by treatment.

It is not known whether everolimus is excreted in human breast milk. However, in animal studies everolimus and/or its metabolites readily passed into the milk of lactating rats at a concentration 3.5 times higher than in maternal serum. Women taking everolimus should therefore not breast-feed.

In case of pregnancy during study treatment

When pregnancy occurs in a patient in the study, as general rule the study drug must be discontinued. If a female patient or partner of a male patient become pregnant during the study they should immediately consult the study physician. Following appropriate medical advice the patient may stay in the study and follow the assessments, if she wishes to do so. However, any assessments that are considered as a risk during pregnancy must not be performed. The patient may continue all other protocol assessments. In exceptional cases, such as a woman responding to the lifesaving treatment, the study drug can be continued.

To ensure patient safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications according to the following schedule.

Timing of follow up attempt	**applicability**
EDD+1 month	Mandatory for all cases
EDD+2months	Mandatory if no answer is obtained after request at EDD+1 months
EDD+3 months	Mandatory for all cases of live birth
EDD+12months	Mandatory for all cases of live birth

8.5 Warnings and precautions

No evidence available at the time of the approval of this study protocol indicated that special warnings or precautions were appropriate, other than those noted in the provided Investigator Brochure. Additional safety information collected between IB updates and/or the locally approved prescribing information will be communicated in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

8.6 Data Monitoring Committee

Not applicable.

8.7 Steering Committee

Not applicable.

9 Data collection and management

9.1 Data confidentiality

Information about study subjects will be kept confidential and managed under the applicable laws and regulations. Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect follow-up safety information (e.g. has the subject experienced any new or worsened AEs) at the end of their scheduled study period.

The data collection system for this study uses built-in security features to encrypt all data for transmission in both directions, preventing unauthorized access to confidential participant information. Access to the system will be controlled by a sequence of individually assigned user identification codes and passwords, made available only to authorized personnel who have completed prerequisite training.

9.2 Site monitoring

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

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

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria and documentation of SAEs. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan.

9.3 Data collection

For studies using paper CRFs, designated investigator staff must record the information required by the protocol onto the Novartis CRFs that are printed on multi-part, non-carbon-required paper. Field monitors will review the CRFs for completeness and accuracy and instruct site personnel to make any required corrections or additions. The harvested CRFs will be forwarded to the Medical Documents Reception Center or applicable CRO Document receipt location by field monitors or by the investigational site, with one copy being retained at the investigational site.

The Principal Investigator is responsible for assuring that the data recorded on CRFs is complete, accurate, and that entry and updates are performed in a timely manner.

9.4 Database management and quality control

This study will use paper CRF, data will be entered into a fully validated study database by Novartis Data Management personnel (or designated CRO). Following entry from the CRFs, the data are systematically checked by Novartis Data Management personnel (or designated CRO) using programmed checks and data review tools/reports. Data Query Forms (DQF) are created for discrepancies or missing values and sent to the investigational site for resolution. Original signed responses to the DQFs must be returned to Novartis Data Management (or designated CRO) so that resolutions can be entered into the database. Copies of the resolved DQFs are kept with the CRFs at the investigator site.

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

10 Statistical methods and data analysis

The data from all participating centers in this protocol will be combined. Novartis and/or a designated CRO will perform all analyses. Any data analyses performed independently by any investigator should be submitted to Novartis before publication or presentation.

10.1 Analysis sets

10.1.1 Full Analysis Set

The **Full Analysis Set (FAS)** comprises all patients who receive at least one dose of study treatment. Patients will be analyzed according to the treatment they received. The FAS will be the primary population in the assessment of efficacy.

10.1.2 Safety Set

The **Safety Set** and the FAS are identical in this study**.** All safety analysis will be analyzed using the Safety Set.

10.1.3 Per-Protocol Set

Not applicable

10.1.4 Dose-determining analysis set

Not applicable.

10.1.5 Pharmacokinetic analysis set

Not applicable.

10.1.6 Other analysis sets

Not applicable

10.2 Patient demographics/other baseline characteristics

Demographic and other baseline characteristics will be listed and summarized using the FAS.

Qualitative data (e.g., gender, race) will be summarized by means of contingency tables, and quantitative data (e.g., age, body weight) will be summarized by appropriate descriptive statistics (mean, standard deviation, median, minimum and maximum).

Relevant medical histories and current medical at baseline will be summarized by system organ class, preferred term and by treatment group.

10.3 Treatments (study treatment, concomitant therapies, compliance)

Duration of study treatment exposure, cumulative dose and dose intensity will be summarized. The number of patients with dose changes/interruptions will be presented, along with reasons for the dose change.

Concomitant medications and significant non-drug therapies taken prior to and after the start of the study treatment will be listed and summarized according to the Anatomical Therapeutic Chemical (ATC) classification system.

The safety population will be used for all above-mentioned concomitant medication tables and listings.

10.4 Primary objective

The primary objective is to evaluate the safety of treatment with Afinitor in Chinese adult patients with well differentiated progressive p-NET

10.4.1 Variable

The primary variable is the safety profile in terms of adverse events, serious adverse events, adverse events suspected to be related to study drug and Grade 3 and 4 AEs.

10.4.2 Statistical hypothesis, model, and method of analysis

Please refer to Section 10.5.3.

10.4.3 Handling of missing values/censoring/discontinuations

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

10.4.4 Supportive and Sensitivity analyses

Not applicable

10.5 Secondary objectives

The secondary objective is to evaluate the overall efficacy of treatment with Afinitor in Chinese patients with well differentiated progressive p-NET. All efficacy analyses will be performed based on the FAS, unless otherwise specified.

The secondary variables include

- Overall Survival (OS), defined as time from study treatment to death due to any cause.
- Progression free survival (PFS), defined as time from first dose of study treatment to progression or death due to any cause.

10.5.1 Key secondary objective(s)

Not applicable.

10.5.2 Other secondary efficacy objectives

See the description in Section 10.5.

10.5.2.1 Endpoint and analysis for other secondary objective

Endpoints for other secondary objectives are Overall Survival (OS) and Progression free survival (PFS), as defined above,

OS and PFS will be described using Kaplan-Meier methods and appropriate summary statistics.

10.5.3 Safety objectives

10.5.3.1 Analysis set and grouping for the analyses

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

The overall observation period will be divided into three mutually exclusive segments, which all applicable listings and tables will be presented by:

1. pre-treatment period: from day of patient's informed consent to the day before first dose of study medication
2. on-treatment period: from day of first dose of study medication to 30 days after last dose of study medication
3. post-treatment period: starting at day 31 after last dose of study medication.

10.5.3.2 Adverse events (AEs)

Summary tables for adverse events (AEs) have to include only AEs that started or worsened during the on-treatment period, the ***treatment-emergent*** AEs. However, all safety data (including those from the pre and post-treatment periods) will be listed and those collected during the pre-treatment and post-treatment period are to be flagged.

The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by system organ class and or preferred term, severity (based on CTCAE grades), type of adverse event, relation to study treatment

Serious adverse events (SAE), non-serious adverse events and adverse events of special interest (AESI) during the on-treatment period will be tabulated

All death (on-treatment and post-treatment) will be summarized.

The adverse events of special interest (AESI) include the following categories

- Non-infectious pneumonitis
- Stomatitis/ oral mucositis
- Reactivation of hepatitis B virus
- Cardiac disorders: Cardiac failure; ejection fraction decreased

All AEs, deaths and serious adverse events (including those from the pre and post-treatment periods) will be listed and those collected during the pre-treatment and post-treatment period will be flagged

10.5.3.3 Laboratory abnormalities

All laboratory values will be converted into SI units and the severity grade calculated using appropriate common toxicity criteria for adverse events (CTCAE, version 4.03) unless otherwise indicated. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account. CTCAE Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used. For laboratory tests where grades are not defined by CTCAE version 4.03, results will be categorized as low/normal/high based on laboratory normal ranges.

A listing of all laboratory values will be provided by laboratory parameter and by patient. All notable lab abnormalities will be presented in a separate listing.

For laboratory tests where grades are defined by CTCAE version 4.03:

- Worst post-baseline CTCAE grade (regardless of the baseline status). Each patient will be counted only once for the worst grade observed post-baseline.
- Shift tables using CTCAE grades to compare baseline to the worst on-treatment value

For laboratory tests where grades are not defined by CTCAE version 4.03:

- Shift tables using the low/normal/high classification to compare baseline to the worst on-treatment value.

10.5.3.4 Other safety data

Safety data from other tests (e.g., vital signs) will be listed and summarized using descriptive statistics as appropriate. Notable values may be flagged. Notable/Abnormal values for safety data will be further specified in the analysis plan.

Analyses will be performed on the safety set.

10.5.3.5 Supportive analyses for secondary objectives

Not applicable.

10.5.3.6 Tolerability

Tolerability will be summarized in terms of dose reductions or drug interruption due to an AE.

10.5.4 Pharmacokinetics

Not applicable.

10.5.5 Biomarkers

Not applicable.

10.5.6 Resource utilization

Not applicable.

10.5.7 Patient-reported outcomes

Not applicable.

10.6 Exploratory objectives

Not applicable.

10.7 Interim analysis

Interim analysis is planned for this study for the purpose of providing a snapshot of available data to CDE for license renewal. An interim analysis will be performed in July 2017 with approximate 30 patients enrolled. This interim analysis will focus on safety and preliminary efficacy, including but not limited to:

- Safety: all adverse events observed by the data cutoff date will be summarized and listed. Separate summaries will be provided for SAE and death, respectively. Abnormal results on laboratory assessment and vital signs will be presented and listed in detail.
- Efficacy: OS and PFS observed by the data cutoff will be described using Kaplan-Meier methods and appropriate summary statistics.

Details of the analysis will be defined in statistical analysis plan (SAP).

10.8 Sample size calculation

Based on pre-marketing field survey, each year, approximately 6 to10 patients per site will be newly diagnosed as 'locally advanced, unresectable or metastatic, well differentiated progressive pNET', about 10% to 20% of diagnosed patients will be eligible and agree to participate the study. In order to speed up the enrollment, 5 major sites, where most patients are usually referred to, are selected. Approximately 30 patients were planned in the original protocol based on feasibility. Based on further evaluation after communication with CDE, the sample size was increased to approximately 60 patients to support license renewal. Due to the uncertainties during the enrollment, the actual number of patients may differ from estimations.

10.9 Power for analysis of key secondary variables

Not applicable.

11 Ethical considerations and administrative procedures

11.1 Regulatory and ethical compliance

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

11.2 Responsibilities of the investigator and IRB/IEC/REB

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) before study start. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs and regulatory authorities as required.

11.3 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC/REB-approved informed consent.

Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents. The date when a subject's Informed Consent was actually obtained will be captured in their CRFs.

Novartis will provide to investigators, in a separate document, a proposed informed consent form (ICF) that is considered appropriate for this study and complies with the ICH GCP guideline and regulatory requirements. Any changes to this ICF suggested by the investigator

must be agreed to by Novartis before submission to the IRB/IEC/REB, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC/REB approval.

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

Additional consent form

Not applicable

11.4 Discontinuation of the study

Novartis reserves the right to discontinue this study under the conditions specified in the clinical study agreement. Specific conditions for terminating the study are outlined in Section 4.4.

11.5 Publication of study protocol and results

Novartis is committed to following high ethical standards for reporting study results for its innovative medicine, including the timely communication and publication of clinical trial results, whatever their outcome. Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov before study start.

In addition, results of interventional clinical trials in adult patients are posted on www.novartisclinicaltrials.com, a publicly accessible database of clinical study results within 1 year of study completion (i.e., LPLV), those for interventional clinical trials involving pediatric patients within 6 months of study completion.

Novartis follows the ICMJE authorship guidelines (www.icmje.org) and other specific guidelines of the journal or congress to which the publication will be submitted

Authors will not receive remuneration for their writing of a publication, either directly from Novartis or through the professional medical writing agency. Author(s) may be requested to present poster or oral presentation at scientific congress; however, there will be no honorarium provided for such presentations.

As part of its commitment to full transparency in publications, Novartis supports the full disclosure of all funding sources for the study and publications, as well as any actual and potential conflicts of interest of financial and non-financial nature by all authors, including medical writing/editorial support, if applicable.

For the Novartis Guidelines for the Publication of Results from Novartis-sponsored Research, please refer to www.novartis.com.

11.6 Study documentation, record keeping and retention of documents

Each participating site will maintain appropriate medical and research records for this trial, in compliance with Section 4.9 of the ICH E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of subjects. As part of participating in a Novartis-sponsored study, each site will permit authorized representatives of the sponsor(s) and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Principal Investigator. The study case report form (CRF) is the primary data collection instrument for the study. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the CRFs and all other required reports. Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the CRF must be recorded. Any missing data must be explained. Any change or correction to a paper CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry. For electronic CRFs an audit trail will be maintained by the system. The investigator should retain records of the changes and corrections to paper CRFs.

The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by applicable regulations and/or guidelines. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents (written and electronic) should be retained for a period of not less than fifteen (15) years from the completion of the Clinical Trial unless Sponsor provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines

11.7 Confidentiality of study documents and patient records

The investigator must ensure anonymity of the patients; patients must not be identified by names in any documents submitted to Novartis. Signed informed consent forms and patient enrollment log must be kept strictly confidential to enable patient identification at the site.

11.8 Audits and inspections

Source data/documents must be available to inspections by Novartis or designee or Health Authorities.

11.9 Financial disclosures

Financial disclosures should be provided by study personnel who are directly involved in the treatment or evaluation of patients at the site - prior to study start.

12 Protocol adherence

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

12.1 Amendments to the protocol

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC/REB. Only amendments that are required for patient safety may be implemented prior to IRB/IEC/REB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations (e.g. UK requires the notification of urgent safety measures within 3 days) but not later than 10 working days.

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14 Appendices

14.1 Appendix 1: Response Evaluation Criteria in Solid Tumors (RECIST 1.1) Version 3.1 Guidelines for Response, Duration of Overall Response, TTF, TTP, Progression-Free Survival and Overall Survival

Document type: TA Specific Guideline

Document status: Version 3.1: 29-Nov-2011
Version 3:0: 19-Oct-2009
Version 2:0: 18-Jan-2007
Version 1:0: 13-Dec-2002

Release date: 29-Nov-2011

Authors (Version 3.1): [redacted]

Authors (Version 3): [redacted]

Authors (Version 2): [redacted]

Authors (Version 1): [redacted]

Glossary

CR	Complete response
CRF	Case Report Form
CSR	Clinical Study Report
CT	Computed tomography
DFS	Disease-free survival
eCRF	Electronic Case Report Form
FPFV	First patient first visit
GBM	Glioblastoma multiforme
MRI	Magnetic resonance imaging
LPLV	Last patient last visit
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
RAP	Reporting and Analysis Plan
RECIST	Response Evaluation Criteria in Solid Tumors
SD	Stable disease
SOD	Sum of Diameter
TTF	Time to treatment failure
TTP	Time to progression
UNK	Unknown

14.1.1 Introduction

The purpose of this document is to provide the working definitions and rules necessary for a consistent and efficient analysis of efficacy for oncology studies in solid tumors. This document is based on the RECIST criteria for tumor responses (Therasse et al 2000) and the revised RECIST 1.1 guidelines (Eisenhauer et al 2009).

The efficacy assessments described in Section 14.1.2 and the definition of best response in Section 14.1.17 are based on the RECIST 1.1 criteria but also give more detailed instructions and rules for determination of best response. Section 14.1.18 is summarizing the "time to event" variables and rules which are mainly derived from internal discussions and regulatory consultations, as the RECIST criteria do not define these variables in detail. Section 14.1.28 of this guideline describes data handling and programming rules. This section is to be referred to in the RAP (Reporting and Analysis Plan) to provide further details needed for programming.

14.1.2 Efficacy assessments

Tumor evaluations are made based on RECIST criteria (Therasse et al 2000), New Guidelines to Evaluate the Response to Treatment in Solid Tumors, Journal of National Cancer Institute, Vol. 92; 205-16 and revised RECIST guidelines (version 1.1) (Eisenhauer et al 2009) European Journal of Cancer; 45:228-247.

14.1.3 Definitions

14.1.4 Disease measurability

In order to evaluate tumors throughout a study, definitions of measurability are required in order to classify lesions appropriately at baseline. In defining measurability, a distinction also needs to be made between nodal lesions (pathological lymph nodes) and non-nodal lesions.

- **Measurable disease** - the presence of at least one measurable nodal or non-nodal lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

For patients without measurable disease see Section 14.1.26.

Measurable lesions (both nodal and non-nodal)

- Measurable non-nodal - As a rule of thumb, the minimum size of a measurable non-nodal target lesion at baseline should be no less than double the slice thickness or 10mm whichever is greater - e.g. the minimum non-nodal lesion size for CT/MRI with 5mm cuts will be 10 mm, for 8 mm contiguous cuts the minimum size will be 16 mm.
- Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components, that can be evaluated by CT/MRI, can be considered as measurable lesions, if the soft tissue component meets the definition of measurability.
- Measurable nodal lesions (i.e. lymph nodes) - Lymph nodes ≥15 mm in short axis can be considered for selection as target lesions. Lymph nodes measuring ≥10 mm and <15 mm are considered non-measurable. Lymph nodes smaller than 10 mm in short axis at baseline, regardless of the slice thickness, are normal and not considered indicative of disease.

- **Cystic lesions**:
  - Lesions that meet the criteria for radiographically defined simple cysts (i.e., spherical structure with a thin, non-irregular, non-nodular and non-enhancing wall, no septations, and low CT density [water-like] content) should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
  - 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred for selection as target lesions.
- Non-measurable lesions - all other lesions are considered non-measurable, including small lesions (e.g. longest diameter <10 mm with CT/MRI or pathological lymph nodes with ≥ 10 to < 15 mm short axis), as well as truly non-measurable lesions e.g., blastic bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

14.1.5 Eligibility based on measurable disease

If no measurable lesions are identified at baseline, the patient may be allowed to enter the study in some situations (e.g. in Phase III studies where PFS is the primary endpoint). However, it is recommended that patients be excluded from trials where the main focus is on the Overall Response Rate (ORR). Guidance on how patients with just non-measurable disease at baseline will be evaluated for response and also handled in the statistical analyses is given in Section 14.1.26.

14.1.6 Methods of tumor measurement - general guidelines

In this document, the term "contrast" refers to intravenous (i.v) contrast.

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

- All measurements should be taken and recorded in metric notation (mm), using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.
- Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.
- For optimal evaluation of patients, the same methods of assessment and technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Contrast-enhanced CT of chest, abdomen and pelvis should preferably be performed using a 5 mm slice thickness with a contiguous reconstruction algorithm. CT/MRI scan slice thickness should not exceed 8 mm cuts using a contiguous reconstruction algorithm. If, at baseline, a patient is known to have a medical contraindication to CT contrast or develops a contraindication during the trial, the following change in imaging modality will be accepted for follow up: a non-contrast CT of chest (MRI not recommended due to respiratory artifacts) plus contrast-enhanced MRI of abdomen and pelvis.

- A change in methodology can be defined as either a change in contrast use (e.g. keeping the same technique, like CT, but switching from with to without contrast use or vice-versa, regardless of the justification for the change) or a change in technique (e.g. from CT to MRI, or vice-versa), or a change in any other imaging modality. A change in methodology will result by default in a UNK overall lesion response assessment. However, another response assessment than the Novartis calculated UNK response may be accepted from the investigator or the central blinded reviewer if a definitive response assessment can be justified, based on the available information.
- **FDG-PET**: can complement CT scans in assessing progression (particularly possible for 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:
  - Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
  - No FDG-PET at baseline with a positive FDG-PET at follow-up:
- If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.
- If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT are needed to determine if there is truly progression occurring at that Site (if so, the date of PD will be the date of the initial abnormal CT scan).
- If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
- **Chest x-ray**: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- **Ultrasound**: When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
- **Endoscopy and laparoscopy**: The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.
- **Tumor markers**: Tumor markers alone cannot be used to assess response. However, some disease specific and more validated tumor markers (e.g. CA-125 for ovarian cancer, PSA for prostate cancer, alpha-FP, LDH and Beta-hCG for testicular cancer) can be integrated as non-target disease. If markers are initially above the upper normal limit they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.

- **Cytology and histology**: Cytology and histology can be used to differentiate between PR and CR in rare cases (i.e., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors). Cytologic confirmation of neoplastic nature of any effusion that appears or worsens during treatment is required when the measurable tumor has met the criteria for response or stable disease. Under such circumstances, the cytologic examination of the fluid collected will permit differentiation between response and stable disease (an effusion may be a side effect of the treatment) or progressive disease (if the neoplastic origin of the fluid is confirmed).
- **Clinical examination**: Clinical lesions will only be considered measurable when they are superficial (i.e., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

14.1.7 Baseline documentation of target and non-target lesions

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

- **Target lesions**: All measurable lesions (nodal and non-nodal) up to a maximum of five lesions in total (and a maximum of two lesions per organ), representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). Each target lesion must be uniquely and sequentially numbered on the CRF (even if it resides in the same organ).

Minimum target lesion size at baseline

- **Non-nodal target**: Non-nodal target lesions identified by methods for which slice thickness is not applicable (e.g. clinical examination, photography) should be at least 10 mm in longest diameter. See Section 14.1.4.
- **Nodal target**: See Section 14.1.4.

A sum of diameters (long axis for non-nodal lesions, short axis for nodal) for all target lesions will be calculated and reported as the baseline sum of diameters (SOD). The baseline sum of diameters will be used as reference by which to characterize the objective tumor response. Each target lesion identified at baseline must be followed at each subsequent evaluation and documented on eCRF.

- **Non-target lesions**: All other lesions are considered non-target lesions, i.e. lesions not fulfilling the criteria for target lesions at baseline. Presence or absence or worsening of non-target lesions should be assessed throughout the study; measurements of these lesions are not required. Multiple non-target lesions involved in the same organ can be assessed as a group and recorded as a single item (i.e. multiple liver metastases). Each non-target lesion identified at baseline must be followed at each subsequent evaluation and documented on eCRF.

14.1.8 Follow-up evaluation of target and non-target lesions

To assess tumor response, the sum of diameters for all target lesions will be calculated (at baseline and throughout the study). At each assessment response is evaluated first separately for the target (Table 14-1) and non-target lesions (Table 14-2) identified at baseline. These evaluations are then used to calculate the overall lesion response considering both the target and non-target lesions together (Table 14-3) as well as the presence or absence of new lesions.

14.1.9 Follow-up and recording of lesions

At each visit and for each lesion the actual date of the scan or procedure which was used for the evaluation of each specific lesion should be recorded. This applies to target and non-target lesions as well as new lesions that are detected. At the assessment visit all of the separate lesion evaluation data are examined by the investigator in order to derive the overall visit response. Therefore all such data applicable to a particular visit should be associated with the same assessment number.

14.1.10 Non-nodal lesions

Following treatment, lesions may have longest diameter measurements smaller than the image reconstruction interval. Lesions smaller than twice the reconstruction interval are subject to substantial “partial volume” effects (i.e., size may be underestimated because of the distance of the cut from the longest diameter; such lesions may appear to have responded or progressed on subsequent examinations, when, in fact, they remain the same size).

If the lesion has completely disappeared, the lesion size should be reported as 0 mm.

Measurements of non-nodal target lesions that become 5 mm or less in longest diameter are likely to be non-reproducible. Therefore, it is recommended to report a default value of 5 mm, instead of the actual measurement. This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). Actual measurement should be given for all lesions larger than 5 mm in longest diameter irrespective of slice thickness/reconstruction interval.

In other cases where the lesion cannot be reliably measured for reasons other than its size (e.g., borders of the lesion are confounded by neighboring anatomical structures), no measurement should be entered and the lesion cannot be evaluated.

14.1.11 Nodal lesions

A nodal lesion less than 10 mm in size by short axis is considered normal. Lymph nodes are not expected to disappear completely, so a “non-zero size” will always persist.

Measurements of nodal target lesions that become 5 mm or less in short axis are likely to be non-reproducible. Therefore, it is recommended to report a default value of 5 mm, instead of the actual measurement. This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness).Actual measurement should be given for all lesions larger than 5 mm in short axis irrespective of slice thickness/reconstruction interval.

However, once a target nodal lesion shrinks to less than 10 mm in its short axis, it will be considered normal for response purpose determination. The lymph node measurements will continue to be recorded to allow the values to be included in the sum of diameters for target lesions, which may be required subsequently for response determination.

14.1.12 Determination of target lesion response

Table 14-1 Response criteria for target lesions

Response Criteria	Evaluation of target lesions
Complete Response (CR):	Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm [1]
Partial Response (PR):	At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters.
Progressive Disease (PD):	At least a 20% increase in the sum of diameter of all measured target lesions, taking as reference the smallest sum of diameter of all target lesions recorded at or after baseline. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm[2].
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR or CR nor an increase in lesions which would qualify for PD.
Unknown (UNK)	Progression has not been documented and one or more target lesions have not been assessed or have been assessed using a different method than baseline.[3]

[1]. SOD for CR may not be zero when nodal lesions are part of target lesions
[2]. Following an initial CR, a PD cannot be assigned if all non-nodal target lesions are still not present and all nodal lesions are <10 mm in size. In this case, the target lesion response is CR
[3]. Methodology change See Section 14.1.6.

Notes on target lesion response

Reappearance of lesions: If the lesion appears at the same anatomical location where a target lesion had previously disappeared, it is advised that the time point of lesion disappearance (i.e., the "0 mm" recording) be re-evaluated to make sure that the lesion was not actually present and/or not visualized for technical reasons in this previous assessment. If it is not possible to change the 0 value, then the investigator/radiologist has to decide between the following three possibilities:

- The lesion is a new lesion, in which case the overall tumor assessment will be considered as progressive disease
- The lesion is clearly a reappearance of a previously disappeared lesion, in which case the size of the lesion has to be entered in the CRF and the tumor assessment will remain based on the sum of tumor measurements as presented in Table 14-1 above (i.e., a PD will be determined if there is at least 20% increase in the sum of diameters of **all** measured target lesions, taking as reference the smallest sum of diameters of all target lesions recorded at or after baseline with at least 5 mm increase in the absolute sum of the diameters). Proper documentation should be available to support this decision. This applies to patients who have not achieved target response of CR. For patients who have achieved CR, please refer to last bullet in this section.
- For those patients who have only one target lesion at baseline, the reappearance of the target lesion which disappeared previously, even if still small, is considered a PD.

- **Missing measurements**: In cases where measurements are missing for one or more target lesions it is sometimes still possible to assign PD based on the measurements of the remaining lesions. For example, if the sum of diameters for 5 target lesions at baseline is 100 mm at baseline and the sum of diameters for 3 of those lesions at a post-baseline visit is 140 mm (with data for 2 other lesions missing) then a PD should be assigned. However, in other cases where a PD cannot definitely be attributed, the target lesion response would be UNK.
- **Nodal lesion decrease to normal size**: When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size they should still have a measurement recorded on scans. This measurement should be reported even when the nodes are normal in order not to overstate progression should it be based on increase in the size of nodes.
- **Lesions split**: In some circumstances, disease that is measurable as a target lesion at baseline and appears to be one mass can split to become two or more smaller sub-lesions. When this occurs, the diameters (long axis - non-nodal lesion, short axis - nodal lesions) of the two split lesions should be added together and the sum recorded in the diameter field on the case report form under the original lesion number. This value will be included in the sum of diameters when deriving target lesion response. The individual split lesions will not be considered as new lesions, and will not automatically trigger a PD designation.
- **Lesions coalesced**: Conversely, it is also possible that two or more lesions which were distinctly separate at baseline become confluent at subsequent visits. When this occurs a plane between the original lesions may be maintained that would aid in obtaining diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the maximal diameters (long axis - non-nodal lesion, short axis - nodal lesions) of the "merged lesion" should be used when calculating the sum of diameters for target lesions. On the case report form, the diameter of the "merged lesion" should be recorded for the size of one of the original lesions while a size of "0"mm should be entered for the remaining lesion numbers which have coalesced.
- The **measurements for nodal lesions**, even if less than 10 mm in size, will contribute to the calculation of target lesion response in the usual way with slight modifications.
    - Since lesions less than 10 mm are considered normal, a CR for target lesion response should be assigned when all nodal target lesions shrink to less than 10 mm and all non-nodal target lesions have disappeared.
    - Once a CR target lesion response has been assigned a CR will continue to be appropriate (in the absence of missing data) until progression of target lesions.
    - Following a CR, a PD can subsequently only be assigned for target lesion response if either a non-nodal target lesion "reappears" or if any single nodal lesion is at least 10 mm and there is at least 20% increase in sum of the diameters of all nodal target lesions relative to nadir with at least 5 mm increase in the absolute sum of the diameters.

14.1.13 Determination of non-target lesion response

Table 14-2 Response criteria for non-target lesions

Response Criteria	Evaluation of non-target lesions
Complete Response (CR):	Disappearance of all non-target lesions. In addition, all lymph nodes assigned a non-target lesions must be non-pathological in size (< 10 mm short axis)
Progressive Disease (PD):	Unequivocal progression of existing non-target lesions.[1]
Non-CR/Non-PD:	Neither CR nor PD
Unknown (UNK)	Progression has not been documented and one or more non-target lesions have not been assessed or have been assessed using a different method than baseline.

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

Notes on non-target lesion response

- The response for non-target lesions is **CR** only if all non-target non-nodal lesions which were evaluated at baseline are now all absent and with all non-target nodal lesions returned to normal size (i.e. < 10 mm). If any of the non-target lesions are still present, or there are any abnormal nodal lesions (i.e. ≥ 10 mm) the response can only be '**Non-CR/Non-PD**' unless any of the lesions was not assessed (in which case response is **UNK**) or there is unequivocal progression of the non-target lesions (in which case response is **PD**).
- Unequivocal progression: To achieve "unequivocal progression" on the basis of non-target disease there must be an overall level of substantial worsening in non-target disease such that, even in presence of CR, PR or SD in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of CR, PR or SD of target disease is therefore expected to be rare. In order for a PD to be assigned on the basis of non-target lesions, the increase in the extent of the disease must be substantial even in cases where there is no measurable disease at baseline. If there is unequivocal progression of non-target lesion(s), then at least one of the non-target lesions must be assigned a status of "Worsened". Where possible, similar rules to those described in Section 14.1.12 for assigning PD following a CR for the non-target lesion response in the presence of non-target lesions nodal lesions should be applied.

14.1.14 New lesions

The appearance of a new lesion is always associated with Progressive Disease (PD) and has to be recorded as a new lesion in the New Lesion CRF page.

- If a new lesion is **equivocal**, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the first observation of the lesion.

- If new disease is observed in a region which was **not scanned at baseline** or where the particular baseline scan is not available for some reason, then this should be considered as a PD. The one exception to this is when there are no baseline scans at all available for a patient in which case the response should be UNK, as for any of this patient's assessment (see Section 14.1.15).
- A **lymph node is considered as a "new lesion"** and, therefore, indicative of progressive disease if the short axis increases in size to ≥ 10 mm for the first time in the study plus 5 mm absolute increase.
  FDG-PET: can complement CT scans in assessing progression (particularly possible for 'new' disease). See Section 14.1.6.

14.1.15 Evaluation of overall lesion response

The evaluation of overall lesion response at each assessment is a composite of the target lesion response, non-target lesion response and presence of new lesions as shown below in Table 14-3.

Table 14-3 Overall lesion response at each assessment

Target lesions	Non-target lesions	New Lesions	Overall lesion response
CR	CR	No	CR[1]
CR	Non-CR/Non-PD[3]	No	PR
CR, PR, SD	UNK	No	UNK
PR	Non-PD and not UNK	No	PR[1]
SD	Non-PD and not UNK	No	SD[1, 2]
UNK	Non-PD or UNK	No	UNK[1]
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

[1]. This overall lesion response also applies when there are no non-target lesions identified at baseline.
[2]. Once confirmed PR was achieved, all these assessments are considered PR.
[3]. As defined in Section 14.1.8.

If there are no baseline scans available at all, then the overall lesion response at each assessment should be considered Unknown (UNK).

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

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

14.1.16 Efficacy definitions

The following definitions primarily relate to patients who have measurable disease at baseline. Section 14.1.26 outlines the special considerations that need to be given to patients with no measurable disease at baseline in order to apply the same concepts.

14.1.17 Best overall response

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

The best overall response will usually be determined from response assessments undertaken while on treatment. However, if any assessments occur after treatment withdrawal the protocol should specifically describe if these will be included in the determination of best overall response and/or whether these additional assessments will be required for sensitivity or supportive analyses. As a default, any assessments taken more than 30 days after the last dose of study treatment will not be included in the best overall response derivation. If any alternative cancer therapy is taken while on study any subsequent assessments would ordinarily be excluded from the best overall response determination. If response assessments taken after withdrawal from study treatment and/or alternative therapy are to be included in the main endpoint determination, then this should be described and justified in the protocol.

Where a study requires confirmation of response (PR or CR), changes in tumor measurements must be confirmed by repeat assessments that should be performed not less than 4 weeks after the criteria for response are first met.

Longer intervals may also be appropriate. However, this must be clearly stated in the protocol. The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.

- -For non-randomized trials where response is the primary endpoint, confirmation is needed.
- -For trials intended to support accelerated approval, confirmation is needed
- For all other trials, confirmation of response may be considered optional.

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

- CR = at least two determinations of CR at least 4 weeks apart before progression where confirmation required or one determination of CR prior to progression where confirmation not required
- PR = at least two determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR) where confirmation required or one determination of PR prior to progression where confirmation not required
- SD = at least one SD assessment (or better) > 6 weeks after randomization/start of treatment (and not qualifying for CR or PR).
- PD = progression ≤ 12 weeks after randomization/ start of treatment (and not qualifying for CR, PR or SD).
- UNK = all other cases (i.e. not qualifying for confirmed CR or PR and without SD after more than 6 weeks or early progression within the first 12 weeks)

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

Once an overall lesion response of PR is observed (which may have to be a confirmed PR depending on the study) this assignment must stay the same or improve over time until progression sets in, with the exception of an UNK status. However, in studies where confirmation of response is required, if a patient has a single PR (≥30% reduction of tumor burden compared to baseline) at one assessment, followed by a <30% reduction from baseline at the next assessment (but not ≥20% increase from previous smallest sum), the objective status at that assessment should be SD. Once a confirmed PR was seen, the overall lesion response should be considered PR (or UNK) until progression is documented or the lesions totally disappear in which case a CR assignment is applicable. In studies where confirmation of response is not required after a single PR the overall lesion response should still be considered PR (or UNK) until progression is documented or the lesion totally disappears in which case a CR assignment is applicable.

Example: In a case where confirmation of response is required the sum of lesion diameters is 200 mm at baseline and then 140 mm - 150 mm - 140 mm - 160 mm - 160 mm at the subsequent visits. Assuming that non-target lesions did not progress, the overall lesion response would be PR - SD - PR - PR - PR. The second assessment with 140 mm confirms the PR for this patient. All subsequent assessments are considered PR even if tumor measurements decrease only by 20% compared to baseline (200 mm to 160 mm) at the following assessments.

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

Note: these cases may be described as a separate finding in the CSR but not included in the overall response or disease control rates.

The best overall response for a patient is always calculated, based on the sequence of overall lesion responses. However, the overall lesion response at a given assessment may be provided from different sources:

- Investigator overall lesion response
- Central Blinded Review overall lesion response
- Novartis calculated overall lesion response (based on measurements from either Investigator or Central Review)

The primary analysis of the best overall response will be based on the sequence of investigator/central blinded review/calculated (investigator)/calculated (central) overall lesion responses.

Based on the patients' best overall response during the study, the following rates are then calculated:

Overall response rate (ORR) is the proportion of patients with a best overall response of CR or PR. This is also referred to as 'Objective response rate' in some protocols or publications.

Disease control rate (DCR) is the proportion of patients with a best overall response of CR or PR or SD.

Another approach is to summarize the progression rate at a certain time point after baseline. In this case, the following definition is used:

Early progression rate (EPR) is the proportion of patients with progressive disease within 8 weeks of the start of treatment.

The protocol should define populations for which these will be calculated. The timepoint for EPR is study specific. EPR is used for the multinomial designs of Dent and Zee (2001) and counts all patients who at the specified assessment (in this example the assessment would be at 8 weeks ± window) do not have an overall lesion response of SD, PR or CR. Patients with an unknown (UNK) assessment at that time point and no PD before, will not be counted as early progressors in the analysis but may be included in the denominator of the EPR rate, depending on the analysis population used. Similarly when examining overall response and disease control, patients with a best overall response assessment of unknown (UNK) will not be regarded as "responders" but may be included in the denominator for ORR and DCR calculation depending on the analysis population (e.g. populations based on an ITT approach).

14.1.18 Time to event variables

The protocol should state which of the following variables is used in that study.

14.1.19 Progression-free survival

Usually in all Oncology studies, patients are followed for tumor progression after discontinuation of study medication for reasons other than progression or death. If this is not used, e.g. in Phase I or II studies, this should be clearly stated in the protocol. Note that randomized trials (preferably blinded) are recommended where PFS is to be the primary endpoint.

Progression-free survival (PFS) is the time from date of randomization/start of treatment to the date of event defined as the first documented progression or death due to any cause. If a patient has not had an event, progression-free survival is censored at the date of last adequate tumor assessment.

14.1.20 Overall survival

All patients should be followed until death or until patient has had adequate follow-up time as specified in the protocol whichever comes first. The follow-up data should contain the date the patient was last seen alive / last known date patient alive, the date of death and the reason of death ("Study indication" or "Other").

Overall survival (OS) is defined as the time from date of randomization/start of treatment to date of death due to any cause. If a patient is not known to have died, survival will be censored at the date of last known date patient alive.

14.1.21 Time to progression

Some studies might consider only death related to underlying cancer as an event which indicates progression. In this case the variable "Time to progression" might be used. TTP is defined as PFS except for death unrelated to underlying cancer.

Time to progression (TTP) is the time from date of randomization/start of treatment to the date of event defined as the first documented progression or death due to underlying cancer. If a patient has not had an event, time to progression is censored at the date of last adequate tumor assessment.

14.1.22 Time to treatment failure

This endpoint is often appropriate in studies of advanced disease where early discontinuation is typically related to intolerance of the study drug. In some protocols, time to treatment failure may be considered as a sensitivity analysis for time to progression. The list of discontinuation reasons to be considered or not as treatment failure may be adapted according to the specificities of the study or the disease.

Time to treatment failure (TTF) is the time from date of randomization/start of treatment to the earliest of date of progression, date of death due to any cause, or date of discontinuation due to reasons other than 'Protocol violation' or 'Administrative problems'. The time to treatment failure for patients who did not experience treatment failure will be censored at last adequate tumor assessment.

14.1.23 Duration of response

The analysis of the following variables should be performed with much caution when restricted to responders since treatment bias could have been introduced. There have been reports where a treatment with a significantly higher response rate had a significantly shorter duration of response but where this probably primarily reflected selection bias which is explained as follows: It is postulated that there are two groups of patients: a good risk group and a poor risk group. Good risk patients tend to get into response readily (and relatively quickly) and tend to remain in response after they have a response. Poor risk patients tend to be difficult to achieve a response, may have a longer time to respond, and tend to relapse quickly when they do respond. Potent agents induce a response in both good risk and poor risk patients. Less potent agents induce a response mainly in good risk patients only. This is described in more detail by Morgan (1988)

It is recommended that an analysis of all patients (both responders and non-responders) be performed whether or not a "responders only" descriptive analysis is presented. An analysis of responders should only be performed to provide descriptive statistics and even then interpreted with caution by evaluating the results in the context of the observed response rates. If an inferential comparison between treatments is required this should only be performed on all patients (i.e. not restricting to "responders" only) using appropriate statistical methods such as the techniques described in Ellis et al (2008). It should also be stated in the protocol if duration of response is to be calculated in addition for unconfirmed response.

For summary statistics on "responders" only the following definitions are appropriate. (Specific definitions for an all-patient analysis of these endpoints are not appropriate since the status of patients throughout the study is usually taken into account in the analysis).

Duration of overall response (CR or PR): For patients with a CR or PR (which may have to be confirmed the start date is the date of first documented response (CR or PR) and the end date and censoring is defined the same as that for time to progression.

The following two durations might be calculated in addition for a large Phase III study in which a reasonable number of responders is seen.

Duration of overall complete response (CR): For patients with a CR (which may have to be confirmed) the start date is the date of first documented CR and the end date and censoring is defined the same as that for time to progression.

Duration of stable disease (CR/PR/SD): For patients with a CR or PR (which may have to be confirmed) or SD the start and end date as well as censoring is defined the same as that for time to progression.

14.1.24 Time to response

Time to overall response (CR or PR) is the time between date of randomization/start of treatment until first documented response (CR or PR). The response may need to be confirmed depending on the type of study and its importance. Where the response needs to be confirmed then time to response is the time to the first CR or PR observed.

Although an analysis on the full population is preferred a descriptive analysis may be performed on the "responders" subset only, in which case the results should be interpreted with caution and in the context of the overall response rates, since the same kind of selection bias may be introduced as described for duration of response in Section 14.1.23. It is recommended that an analysis of all patients (both responders and non-responders) be performed whether or not a "responders only" descriptive analysis is presented. Where an inferential statistical comparison is required, then all patients should definitely be included in the analysis to ensure the statistical test is valid. For analysis including all patients, patients who did not achieve a response (which may have to be a confirmed response) will be censored using one of the following options.

- at maximum follow-up (i.e. FPFV to LPLV used for the analysis) for patients who had a PFS event (i.e. progressed or died due to any cause). In this case the PFS event is the worst possible outcome as it means the patient cannot subsequently respond. Since the statistical analysis usually makes use of the ranking of times to response it is sufficient to assign the worst possible censoring time which could be observed in the study which is equal to the maximum follow-up time (i.e. time from FPFV to LPLV)
- at last adequate tumor assessment date otherwise. In this case patients have not yet progressed so they theoretically still have a chance of responding

Time to overall complete response (CR) is the time between dates of randomization/start of treatment until first documented CR. Similar analysis considerations including (if appropriate) censoring rules apply for this endpoint described for the time to overall response endpoint.

14.1.25 Definition of start and end dates for time to event variables

Assessment date

For each assessment (i.e. evaluation number), the **assessment date** is calculated as the latest of all measurement dates (e.g. X-ray, CT-scan) if the overall lesion response at that assessment is CR/PR/SD/UNK. Otherwise - if overall lesion response is progression - the assessment date is calculated as the earliest date of all measurement dates at that evaluation number.

Start dates

For all "time to event" variables, other than duration of response, the randomization/ date of treatment start will be used as the start date.

For the calculation of duration of response the following start date should be used:

- Date of first documented response is the assessment date of the first overall lesion response of CR (for duration of overall complete response) or CR / PR (for duration of overall response) respectively, when this status is later confirmed.

End dates

The end dates which are used to calculate 'time to event' variables are defined as follows:

- Date of death (during treatment as recorded on the treatment completion page or during follow-up as recorded on the study evaluation completion page or the survival follow-up page).
- Date of progression is the first assessment date at which the overall lesion response was recorded as progressive disease.
- Date of last adequate tumor assessment is the date the last tumor assessment with overall lesion response of CR, PR or SD which was made before an event or a censoring reason occurred. In this case the last tumor evaluation date at that assessment is used. If no post-baseline assessments are available (before an event or a censoring reason occurred) the date of randomization/start of treatment is used.
- Date of next scheduled assessment is the date of the last adequate tumor assessment plus the protocol specified time interval for assessments. This date may be used if back-dating is considered when the event occurred beyond the acceptable time window for the next tumor assessment as per protocol (see Section 14.1.26).

Example (if protocol defined schedule of assessments is 3 months): tumor assessments at baseline - 3 months - 6 months - missing - missing - PD. Date of next scheduled assessment would then correspond to 9 months.

- Date of discontinuation is the date of the end of treatment visit.
- Date of last contact is defined as the last date the patient was known to be alive. This corresponds to the latest date for either the visit date, lab sample date or tumor assessment date. If available, the last known date patient alive from the survival follow-up page is used. If no survival follow-up is available, the date of discontinuation is used as last contact date.

- Date of secondary anti-cancer therapy is defined as the start date of any additional (secondary) antineoplastic therapy or surgery.

14.1.26 Handling of patients with non-measurable disease only at baseline

It is possible that patients with only non-measurable disease present at baseline are entered into the study, either because of a protocol violation or by design (e.g. in Phase III studies with PFS as the primary endpoint). In such cases the handling of the response data requires special consideration with respect to inclusion in any analysis of endpoints based on the overall response evaluations.

It is recommended that any patients with only non-measurable disease at baseline should be included in the main (ITT) analysis of each of these endpoints.

Although the text of the definitions described in the previous sections primarily relates to patients with measurable disease at baseline, patients without measurable disease should also be incorporated in an appropriate manner. The overall response for patients with measurable disease is derived slightly differently according to Table 14-4.

Table 14-4 Overall lesion response at each assessment: patients with non-target disease only

Non-target lesions	New Lesions	Overall lesion response
CR	No	CR
Non-CR/Non-PD[1]	No	Non-CR/non-PD
UNK	No	UNK
PD	Yes or No	PD
Any	Yes	PD

[1] As defined in Section 14.1.8.

In general, the **non-CR/non-PD response** for these patients is considered equivalent to an SD response in endpoint determination. In summary tables for best overall response patients with only non-measurable disease may be highlighted in an appropriate fashion e.g. in particular by displaying the specific numbers with the non-CR/non-PD category.

In considering how to incorporate data from these patients into the analysis the importance to each endpoint of being able to identify a PR and/or to determine the occurrence and timing of progression needs to be taken into account.

For ORR it is recommended that the main (ITT) analysis includes data from patients with only non-measurable disease at baseline, handling patients with a best response of CR as "responders" with respect to ORR and all other patients as "non-responders".

For PFS, it is again recommended that the main ITT analyses on these endpoints include all patients with only non-measurable disease at baseline, with possible sensitivity analyses which exclude these particular patients. Endpoints such as PFS which are reliant on the determination and/or timing of progression can incorporate data from patients with only non-measurable disease.

14.1.27 Sensitivity analyses

This section outlines the possible event and censoring dates for progression, as well as addresses the issues of missing tumor assessments during the study. For instance, if one or more assessment visits are missed prior to the progression event, to what date should the progression event be assigned? And should progression event be ignored if it occurred after a long period of a patient being lost to follow-up? It is important that the protocol and RAP specify the primary analysis in detail with respect to the definition of event and censoring dates and also include a description of one or more sensitivity analyses to be performed.

Based on definitions outlined in Section 14.1.25, and using the draft FDA guideline on endpoints (Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, April 2005) as a reference, the following analyses can be considered:

Table 14-5 Options for event dates used in PFS, TTP, duration of response

Situation		Options for end-date (progression or censoring)[1] **(1) = default unless specified differently in the protocol or RAP**	Outcome
A	No baseline assessment	(1) Date of randomization/start of treatment[3]	Censored
B	Progression at or before next scheduled assessment	(1) Date of progression (2) Date of next scheduled assessment[2]	Progressed Progressed
C1	Progression or death after **exactly one** missing assessment	(1) Date of progression (or death) (2) Date of next scheduled assessment[2]	Progressed Progressed
C2	Progression or death after **two or more** missing assessments	(1) Date of last adequate assessment[2] (2) Date of next scheduled assessment[2] (3) Date of progression (or death)	Censored Progressed Progressed
D	No progression	(1) Date of last adequate assessment	Censored
E	Treatment discontinuation due to 'Disease progression' without documented progression, i.e. clinical progression based on investigator claim	(1) N/A (2) Date of discontinuation (visit date at which clinical progression was determined)	Ignored Progressed
F	New anticancer therapy given	(1) Date of last adequate assessment (2) Date of secondary anti-cancer therapy (3) Date of secondary anti-cancer therapy (4) N/A	Censored Censored Event Ignored
G	Deaths due to reason other than deterioration of 'Study indication'	(1) Date of last adequate assessment	Censored (only TTP and duration of response)

[1].=Definitions can be found in Section 14.1.25
[2].=After the last adequate tumor assessment. "Date of next scheduled assessment" is defined in Section 14.1.25.
[3].=The rare exception to this is if the patient dies no later than the time of the second scheduled assessment as defined in the protocol in which case this is a PFS event at the date of death.

The primary analysis and the sensitivity analyses must be specified in the protocol. Clearly define if and why options (1) are not used for situations C, E and (if applicable) F.

Situations C (C1 and C2): Progression or death after one or more missing assessments: The primary analysis is usually using options (1) for situations C1 and C2, i.e.

- (C1) taking the actual progression or death date, in the case of only one missing assessment.
- (C2) censoring at the date of the last adequate assessment, in the case of two or more consecutive missing assessments.

In the case of two or missing assessments (situation C2), option (3) may be considered jointly with option (1) in situation C1 as sensitivity analysis. A variant of this sensitivity analysis consists of backdating the date of event to the next scheduled assessment as proposed with option (2) in situations C1 and C2.

Situation E: Treatment discontinuation due to 'Disease progression' without documented progression: By default, option (1) is used for situation E as patients without documented PD should be followed for progression after discontinuation of treatment. However, option (2) may be used as sensitivity analysis. If progression is claimed based on clinical deterioration instead of tumor assessment by e.g. CT-scan, option (2) may be used for indications with high early progression rate or difficulties to assess the tumor due to clinical deterioration.

Situation F: New cancer therapy given: the handling of this situation must be specified in detail in the protocol. However, option (1), i.e. censoring at last adequate assessment may be used as a default in this case.

Additional suggestions for sensitivity analyses

Other suggestions for additional sensitivity analyses may include analyses to check for potential bias in follow-up schedules for tumor assessments, e.g. by assigning the dates for censoring and events only at scheduled visit dates. The latter could be handled by replacing in Table 14-5 the "Date of last adequate assessment" by the "Date of previous scheduled assessment (from baseline)", with the following definition:

- **Date of previous scheduled assessment (from baseline)** is the date when a tumor assessment would have taken place, if the protocol assessment scheme was strictly followed from baseline, immediately before or on the date of the last adequate tumor assessment.

In addition, analyses could be repeated using the Investigators' assessments of response rather than the calculated response. The need for these types of sensitivity analyses will depend on the individual requirements for the specific study and disease area and have to be specified in the protocol or RAP documentation.

14.1.28 Data handling and programming rules

The following section should be used as guidance for development of the protocol, data handling procedures or programming requirements (e.g. on incomplete dates).

14.1.29 Study/project specific decisions

For each study (or project) various issues need to be addressed and specified in the protocol or RAP documentation. Any deviations from protocol must be discussed and defined at the latest in the RAP documentation.

The proposed primary analysis and potential sensitivity analyses should be discussed and agreed with the health authorities and documented in the protocol (or at the latest in the RAP documentation before database lock).

14.1.30 End of treatment phase completion

Patients **may** voluntarily withdraw from the study treatment or may be taken off the study treatment at the discretion of the investigator at any time. For patients who are lost to follow-up, the investigator or designee should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

The end of treatment visit and its associated assessments should occur within 7 days of the last study treatment.

Patients may discontinue study treatment for any of the following reasons:

- Adverse event(s)
- Lost to follow-up
- Physician decision
- Pregnancy
- Protocol deviation
- Technical problems
- Subject/guardian decision
- Death
- Progressive disease
- Study terminated by the sponsor
- Non-compliant with study treatment
- No longer requires treatment
- Treatment duration completed as per protocol (optional, to be used if only a fixed number of cycles is given)

14.1.31 End of post-treatment follow-up (study phase completion)

End of post-treatment follow-up visit will be completed after discontinuation of study treatment and post-treatment evaluations but prior to collecting survival follow-up.

Patients may provide study phase completion information for one of the following reasons:

- Adverse event
- Lost to follow-up
- Physician decision
- Pregnancy
- Protocol deviation
- Technical problems
- Subject/guardian decision

- Death
- New therapy for study indication
- Progressive disease
- Study terminated by the sponsor

14.1.32 Medical validation of programmed overall lesion response

As RECIST is very strict regarding measurement methods (i.e. any assessment with more or less sensitive method than the one used to assess the lesion at baseline is considered UNK) and not available evaluations (i.e. if any target or non-target lesion was not evaluated the whole overall lesion response is UNK unless remaining lesions qualified for PD), these UNK assessments may be re-evaluated by clinicians at Novartis or external experts. In addition, data review reports will be available to identify assessments for which the investigators' or central reader's opinion does not match the programmed calculated response based on RECIST criteria. This may be queried for clarification. However, the investigator or central reader's response assessment will never be overruled.

If Novartis elect to invalidate an overall lesion response as evaluated by the investigator or central reader upon internal or external review of the data, the calculated overall lesion response at that specific assessment is to be kept in a dataset. This must be clearly documented in the RAP documentation and agreed before database lock. This dataset should be created and stored as part of the 'raw' data.

Any discontinuation due to 'Disease progression' without documentation of progression by RECIST criteria should be carefully reviewed. Only patients with documented deterioration of symptoms indicative of progression of disease should have this reason for discontinuation of treatment or study evaluation.

14.1.33 Programming rules

The following should be used for programming of efficacy results:

14.1.34 Calculation of 'time to event' variables

Time to event = end date - start date + 1 (in days)

When no post-baseline tumor assessments are available, the date of randomization/start of treatment will be used as end date (duration = 1 day) when time is to be censored at last tumor assessment, i.e. time to event variables can never be negative.

14.1.35 Incomplete assessment dates

All investigation dates (e.g. X-ray, CT scan) must be completed with day, month and year.

If one or more investigation dates are incomplete but other investigation dates are available, this/these incomplete date(s) are not considered for calculation of the assessment date (and assessment date is calculated as outlined in Section 14.1.25). If all measurement dates have no day recorded, the 1st of the month is used.

If the month is not completed, for any of the investigations, the respective assessment will be considered to be at the date which is exactly between previous and following assessment. If a previous and following assessment is not available, this assessment will not be used for any calculation.

14.1.36 Incomplete dates for last known date patient alive or death

All dates must be completed with day, month and year. If the day is missing, the 15th of the month will be used for incomplete death dates or dates of last contact.

14.1.37 Non-target lesion response

If no non-target lesions are identified at baseline (and therefore not followed throughout the study), the non-target lesion response at each assessment will be considered 'not applicable (NA)'.

14.1.38 Study/project specific programming

The standard analysis programs need to be adapted for each study/project.

14.1.39 Censoring reason

In order to summarize the various reasons for censoring, the following categories will be calculated for each time to event variable based on the treatment completion page, the study evaluation completion page and the survival page.

For survival the following censoring reasons are possible:

- Alive
- Lost to follow-up

For PFS and TTP (and therefore duration of responses) the following censoring reasons are possible:

- Ongoing without event
- Lost to follow-up
- Withdrew consent
- Adequate assessment no longer available*
- Event documented after two or more missing tumor assessments (optional, see Table 14-5)
- Death due to reason other than underlying cancer *(only used for TTP and duration of response)*
- Initiation of new anti-cancer therapy

*Adequate assessment is defined in Section 14.1.25. This reason is applicable when adequate evaluations are missing for a specified period prior to data cut-off (or prior to any other censoring reason) corresponding to the unavailability of two or more planned tumor assessments prior to the cut-off date. The following clarifications concerning this reason should also be noted:

- This may be when there has been a definite decision to stop evaluation (e.g. reason="Sponsor decision" on study evaluation completion page), when patients are not followed for progression after treatment completion or when only UNK assessments are available just prior to data cut-off).
- The reason "Adequate assessment no longer available" also prevails in situations when another censoring reason (e.g. withdrawal of consent, loss to follow-up or alternative anti-cancer therapy) has occurred more than the specified period following the last adequate assessment.
- This reason will also be used to censor in case of no baseline assessment.

14.1.40 References (available upon request)

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