


Clinical Development

Everolimus (RAD001)

Protocol Number CRAD001JIC06 / NCT03176238

A phase IIIb, multi-center, open-label study of EVERolimus (RAD001) in combination with EXemestane in post-menopausal women with EStrogen receptor positive, human epidermal growth factor receptor 2 negative locally advanced or metastatic breast cancer EVEREXES

Authors	
Document type	Amended Protocol Version
EUDRACT number	Not applicable
Development phase	IIIb
Version number	02 (Clean)
Document status	Final
Release date	07-Jul-2014

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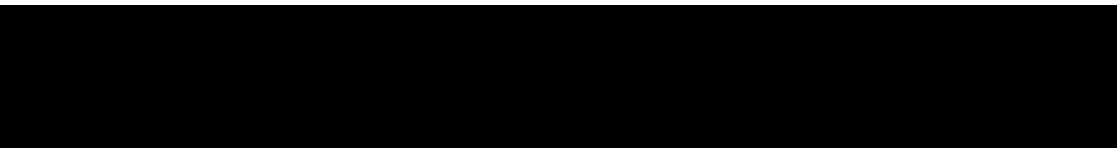
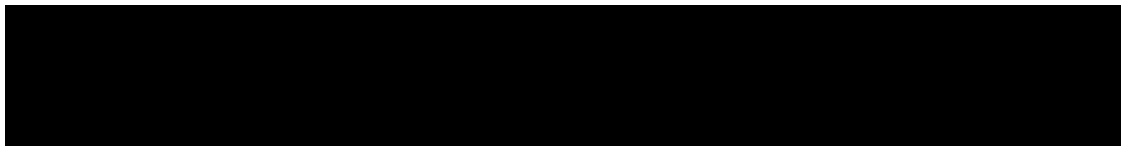
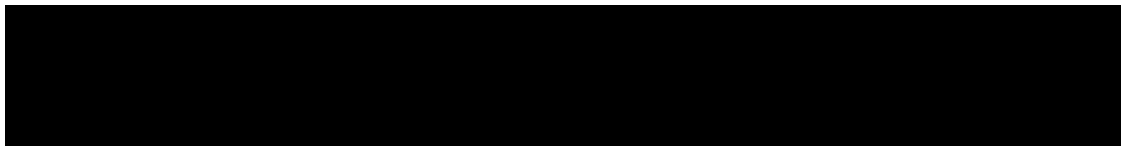


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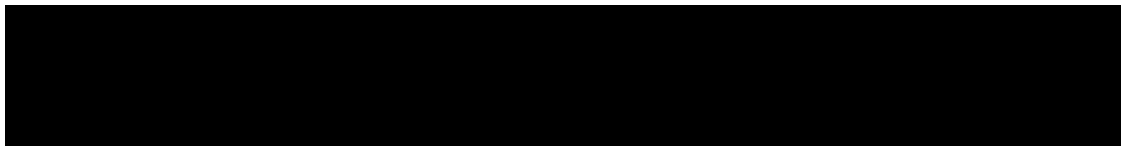
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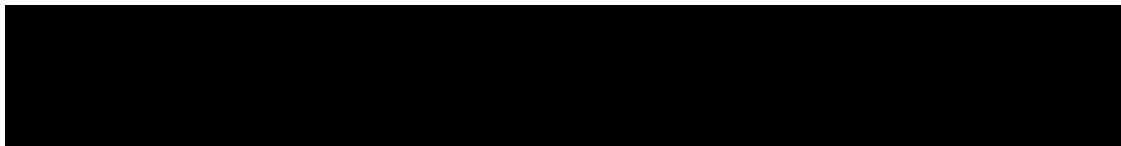
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List of abbreviations

Ab	Antibody
ABC	Advanced Breast Cancer: locally advanced, recurrent or metastatic breast cancer
ADL	Activities of Daily Living
ADR	Adverse Drug Reaction
AE	Adverse Event
Ag	Antigen
AI	Aromatase Inhibitor
AKT / PKB	Protein Kinase B (a component of the phosphatidylinositol 3-kinase signaling pathway)
AL(A)T	Alanine Aminotransferase/Glutamic Pyruvic Transaminase/SGPT
ALP	Alkaline Phosphatase
ANC	Absolute Neutrophil Count
aPTT	Activated Partial Thromboplastin Time
AS(A)T	Aspartate Aminotransferase/Glutamic Oxaloacetic Transaminase/SGOT
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the [concentration time] Curve
b.i.d.	bis in diem/twice a day
BAL	Broncho-Alveolar Lavage
█	█
BC	Breast Cancer
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CBR	Clinical Benefit Rate
CFR	Code of Federal Regulation
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C _{max}	Maximum Blood Concentration
CNS	Central Nervous System
CR	Complete Response
CRF	Case Report/Record Form
CRO	Contract Research Organization
CT	Computed Tomography
CTC	Common Terminology Criteria
CTCAE	Common Terminology Criteria for Adverse Events
█	█
CYP	Cytochrome P450
CYP3A4	Cytochrome P450 3A4 isoenzyme
DLT	Dose Limiting Toxicity
DNA	Deoxyribonucleic acid
E2	17β-estradiol
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report/record Form
EDC	Electronic Data Capture
EGM	Emergent Growth Market
EMA	European Medicines Agency

EOT	End Of Treatment
EPAR	European public assessment report
ER	Estrogen Receptor
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration (USA)
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
GI	Gastrointestinal
GM-CSF	Granulocyte Macrophage Colony Stimulating Factor
Hb	Hemoglobin
HBcAb	Hepatitis B core antibodies
HBs Ab	Hepatitis B surface antibodies
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
Hct	Hematocrit
HCV	Hepatitis C virus
Hep B	Hepatitis B
Hep C	Hepatitis C
HER2	Human Epidermal Growth Factor Receptor 2
HIV	Human Immunodeficiency Virus
HMG-CoA	3-Hydroxy-3Methyl-Glutaryl Coenzyme A
HR	Hazard ratio
HR	Hormone Receptor
HRT	Hormone Replacement Therapy
HUVECs	Human Umbilical Vein Endothelial Cells
i.v.	Intravenous
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IHC	ImmunoHistoChemistry
IMS	Integrated Medical Safety
IN	Investigator Notification
INR	International Normalized Ratio
IRB	Institutional Review Board
ITT	Intent-To-Treat
IVRS/IWRS	Interactive Voice Response System/Interactive Web Response System
LDH	Lactate Dehydrogenase
LLN	Lower Limit of Normal
LMWH	Low Molecular Weight Heparin
MBC	Metastatic Breast Cancer
MRI	Magnetic Resonance Imaging
MRP	Mutual Recognition Procedure (EU)
mTOR	mammalian Target of Rapamycin
mTORC1	mTOR-raptor (regulatory-associated protein of mTOR, Raptor) signal transduction complex 1
NCI	National Cancer Institute
NDA	New Drug Application

NSAI	Non-Steroidal Aromatase Inhibitors
o.d.	omnia die/once a day
O2	Oxygen
ORR	Objective Response Rate
OS	Overall Survival
p.o.	per os / by mouth / orally / by oral route of administration
PCR	Polymerase Chain Reaction
PD	Progressive Disease
PFS	Progression Free Survival
PFT	Pulmonary Function Test
P-gp	P-glycoprotein
PgR	Progesterone Receptor
PHI	Protected Health Information
PI3K	Phosphatidylinositol 3-Kinase (upstream effector of the mTOR signaling pathway)
PJP	Pneumocystis jirovecii pneumonia
pNET	Primitive Neuroectodermal Tumor(s)
PR	Partial Response
PS	Performance Status
Pt	Patient
Raptor	Regulatory-Associated Protein of mTOR
RBC	Red Blood Cell Count
REB	Research Ethics Board
RECIST	Response Evaluation Criteria In Solid Tumors
RNA	Ribonucleic acid
S6K1	serine / threonine kinase p70S6 kinaseS6 Kinase 1
SAE	Serious Adverse Events
SD	Stable Disease
SEGA	Subependymal giant cell astrocytoma
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
t _{1/2}	Half Life
t _{max}	Time to Maximum Concentration
TSC	Tuberous Sclerosis Complex
TTP	Time to Progression
ULN	Upper Limit of Normal
UNK	Unknown
UTI	Urinary Tract Infection
VEGF(R)	Vascular Endothelial Growth Factor (Receptor)
WBC	Total White Blood Cell Count
WHO	World Health Organization
Wks	Weeks

Glossary of terms

Assessment	A procedure used to generate data required by the study.
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 testing 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 and not included in the investigational treatment.
Subject Number (Subject No.)	A unique identifying number assigned to each patient/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 safety, 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, where applicable. Study treatment in this case refers to the investigational and non-investigational treatments used 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.

Amendment 2

Rationale for Amendment 2

Everolimus has been approved in the US and in the European Union for the treatment of advanced breast cancer in combination with exemestane in July 2012,

This study was initiated in 2012 with the aim of confirming safety and efficacy data and facilitate treatment access to everolimus plus exemestane for HR-positive/Her-2-negative advanced breast cancer until commercial availability in participating countries and estimated to end by 31st December 2014. After that date, should the study drug not be accessible to patients in the respective country, Novartis should have implemented local transition or exit plan in order to ensure that all on-going patients will still have access to the study medication without any delay in their treatment

As of June 30th 2014, 198 patients have been enrolled into the study.

At this stage we deem appropriate to change the end of study “until everolimus is locally reimbursed or commercialized for this indication or until all patients have been discontinued from investigational treatment due to disease progression, unacceptable toxicity, death, consent withdrawal or any other reason”, in order to:

- Facilitate treatment continuation at the single patient level in all participating countries
- Continue data collection and further strengthen the final safety and efficacy data set

The statistical plan was revised accordingly to take into account prolonged study duration and to ensure data will be analyzed will be mature enough to derive conclusive results. with primary efficacy and safety/tolerability analysis now planned at 15 months of median follow up time, i.e. at approximately two times the median PFS observed in the BOLERO-2 study.

On the other hand, as the investigational drug will be commercially available in the majority of the participating countries by the end of 2014, recruitment will end in any case in all participating countries no later than on 31st of October 2014.

Moreover, as substantial updates were included in the [Investigator’s Brochure] (version 13) recently released, relevant sessions of the protocol have been amendment accordingly, although this does not imply major changes in study implementation and conduction.

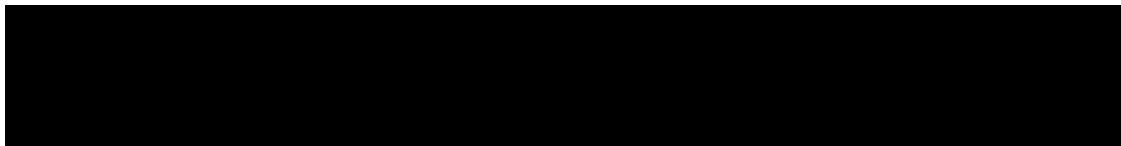
Additional minor changes were included to amend negligible inconsistencies in the previous version,

Changes to the background session:

- Updated information about everolimus clinical efficacy and safety profile have been included.

Changes to study design:

- It is specified that enrollment will end in all participating countries by the time of registration/commercial availability of everolimus in the investigational indication and in any case no later than October 31st 2014.



- End of study has been amended to be in each participating country when everolimus is locally reimbursed or commercialized for this indication or when all patients have been discontinued from investigational treatment due to disease progression, unacceptable toxicity, death, consent withdrawal or any other reason. In those countries in which patients will be transitioned to locally reimbursed or commercialized drug supply, Novartis will have a local transition plan in order to ensure that all on-going patients will still have access to the study medication without

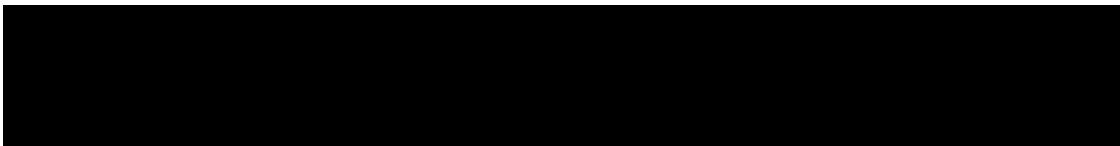
Changes to dose references:

- Publication from Yardley D. et al. 2014 is now included

IRB/IEC

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

The changes described in this amended protocol require IRB/IEC approval/favorable opinion and any applicable health authority authorization prior to implementation. In addition, if the changes herein affect the Informed Consent, sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this amended protocol.



Amendment 1

Amendment rationale

As of November 18th 2013, 114 patients have been enrolled into the study.

Need for more clarity about the phase IIIb nature vs ‘expanded treatment program’ of this study has been raised in multiple occasions during discussions with Health Authorities and for internal purposes.

We thus deemed appropriate to bring more clarity about this aspect standardizing the relevant sessions of the protocol in line with the phase IIIb nature of this study, with the aim of confirming the safety and efficacy of everolimus plus exemestane for the treatment of HR-positive/Her-2-negative advanced breast cancer in Emerging Growth Markets.

Moreover, the management of selected adverse events will be updated and aligned across the everolimus program and with the last [Investigator’s Brochure] (version 12), specifically for the window of time permitted for temporary discontinuation of the treatment with everolimus upon the development of Grade 2 noninfectious pneumonitis (4 weeks in the original protocol, 3 weeks in the amended version).

Additional changes in inclusion/exclusion criteria include the removal of previous treatment with exemestane from exclusion criteria, in line with product SmPC, and the exclusion of patients with leptomeningeal metastasis, as evidence of efficacy of the investigational therapy in this patients is missing, being these patients excluded from the phase III registration study.

Minor changes were introduced in the guidelines for screening and follow-up of bone disease to better standardize study procedures and correct some discrepancies in the original protocol.

ER (endocrine receptor) has been amended with HR (hormone receptor) along the whole protocol for better consistency with inclusion criteria (admitting patients with both ER and/or PgR positive tumors)

Changes to the title:

- The term ‘expanded access’ has been removed from the title and along the whole document, in order to avoid confusion given the phase IIIb study design

Changes to the rationale and study design:

- Safety and tolerability is confirmed to be the primary endpoint of the study (no changes vs previous version). The objective of providing early access to the treatment before local registration/reimbursement has been moved to the end of the secondary endpoint list.

Change to the inclusion – exclusion criteria:

- Previous treatment with exemestane has been removed from exclusion criteria, in line with product SmPC
- The exclusion of patients with leptomeningeal metastasis has been added, due to the lack of any evidence of efficacy of the investigational therapy in these patient subgroup


- It has been specified regarding HBV testing that all patients who currently live in (or have lived in) Asia, Africa, Central and South America, Eastern Europe, Spain, Portugal, and Greece for more than 6 months should be tested for hepatitis B viral load and serologic markers.

Changes to the treatment session:

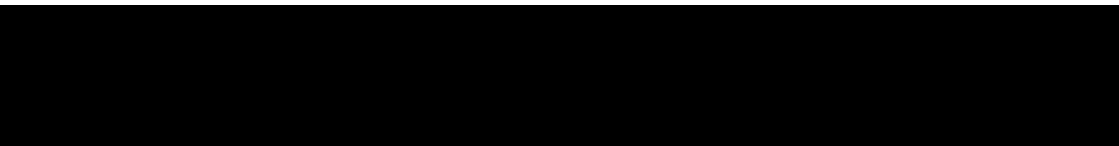
- It is now specified that enough tablets should be provided to cover administration until next scheduled visit
- In the actions recommended base on hepatitis B screening results it is clarified that prophylaxis treatment, when needed, should be started at least 1 week prior to first dose of study drug
- List of inhibitors or inducers of the isoenzyme CYP3A to be avoided during treatment with investigational drug has been updated, according to IB version 12.
- It has been added that the storage temperature must be recorded at least 3 times per week in the temperature log, as per recent Novartis standard operating procedure updates.

Changes to visit schedule and assessments:

- MRI has been added as an alternative of CT when applicable
- Regarding bone assessments, it has been clarified that bone scan/X-ray should be performed at screening and every 10 weeks if bone metastases are present at baseline. If bone metastases are not identified at baseline, bone scans will be performed as clinically indicated. In addition, CT/MRI will be required every 10 weeks until progression. If bone metastases are not identified at baseline, bone CT/MRI will be performed only to confirm potential findings identified by bone scans/X-rays.
- The window of time to complete screening imaging assessments has been standardized to 21 days along the whole document. For bone assessments this window has been now limited to 6 weeks prior to the Baseline visit/Treatment Day 1.

- 
- A typo in the definition of measurable lesions has been amended, confirming that all patients should have at least one lesion that can be accurately measured in at least one dimension ≥ 20 mm with conventional imaging techniques or ≥ 10 mm with spiral CT as per RECIST 1.1 criteria
 - Table 7-2 has been added to better specify the imaging collection plan, including CT or MRI for any site of disease different than chest, abdomen, pelvis, bone and brain and skin color photography for skin lesions

Changes to safety monitoring and reporting:

- Hypophosphatemia, hypersensitivity, wound healing complications, increased creatinine/renal failure/proteinuria, cardiac failure have been added to the list of adverse events with special interest, in line with the most updated version of the risk management plan
- 

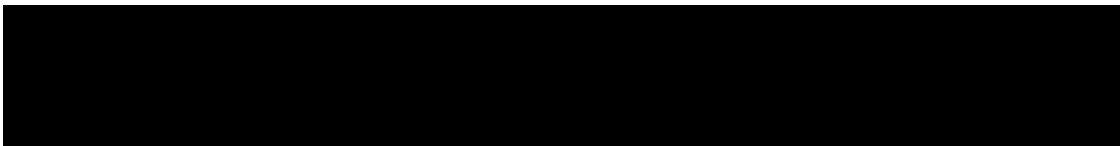
Changes to Appendices:

- Appendix 1 (Guidelines for response, duration of overall response, TTF, TTP, progression-free survival and overall survival (based on RECIST 1.1)) has been updated with the most recent version of the document (version 3.1).

IRB/IEC

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

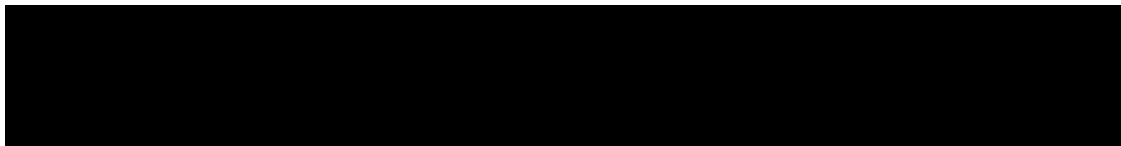
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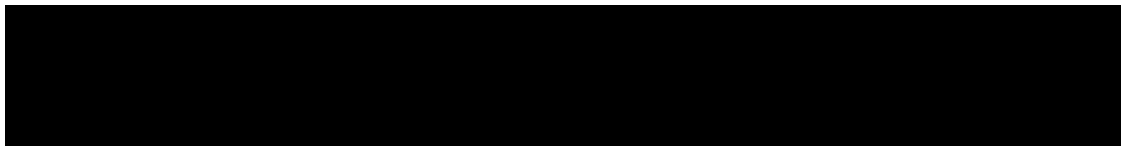
Protocol summary

Protocol number	CRAD001JIC06
Title	A phase IIIb, multicenter, open-label, study of everolimus (RAD001) in combination with exemestane in post-menopausal women with estrogen receptor positive, human epidermal growth factor receptor 2 negative locally advanced or metastatic breast cancer
Brief title	EVEREXES
Sponsor and Clinical Phase	Novartis Phase IIIb
Investigation type	Drug
Study type	Phase IIIb
Purpose and rationale	<p>The present international, multi-center, open-label, single-arm study aims at collecting clinical safety, tolerability and efficacy data with the use of everolimus combined with exemestane in the Novartis Oncology EGM countries for the treatment of post-menopausal women with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative locally advanced or metastatic breast cancer after documented recurrence or progression following a non-steroidal aromatase inhibitor (NSAI) therapy.</p> <p>The dose of everolimus is 10 mg daily orally and the recommended daily dose of exemestane is 25 mg via oral administration. Both drugs were shown to be safe and effective in the respective dose and regimens.</p> <p>The BOLERO-2 trial has demonstrated significant efficacy of the combinatorial treatment of everolimus and exemestane compared to an exemestane monotherapy in ER positive, HER2 negative women after failure of prior NSAI therapy.</p>
Primary Objective(s)	<p>To evaluate the safety and tolerability profile of everolimus in post-menopausal women with ER positive, HER2 negative locally advanced or metastatic breast cancer after documented recurrence or progression following a non-steroidal aromatase inhibitor therapy in EGM countries.</p> <p>The primary endpoints are safety and tolerability evaluations, assessed according to the Common Terminology Criteria (CTCAE), version 4.03. This includes the incidence of adverse events (AEs) by grade, incidence of serious adverse events (SAEs), changes from baseline in vital signs, as well as changes from baseline in laboratory results (hematology, blood chemistry, lipid profile, viral markers) qualifying as AEs.</p>
Secondary Objectives	<ul style="list-style-type: none"> ● To evaluate the efficacy of everolimus in post-menopausal women with ER positive, HER2 negative locally advanced or metastatic breast cancer after documented recurrence or progression following a non-steroidal aromatase inhibitor therapy in EGM countries. Efficacy will be assessed by the overall response rate (ORR), progression-free survival (PFS) rate and clinical benefit rate (CBR) as evaluated by RECIST 1.1 criteria over the study period. Efficacy endpoints will be derived using local (treating center's) radiologist's/ investigator's assessment. ● Additionally, changes from baseline in Eastern Cooperative Oncology Group (ECOG) performance status will be assessed. ● To provide early access to everolimus for patients in post-menopausal women with ER positive, HER2 negative locally advanced or metastatic breast cancer after documented recurrence or progression following a non-steroidal aromatase inhibitor therapy in EGM countries.

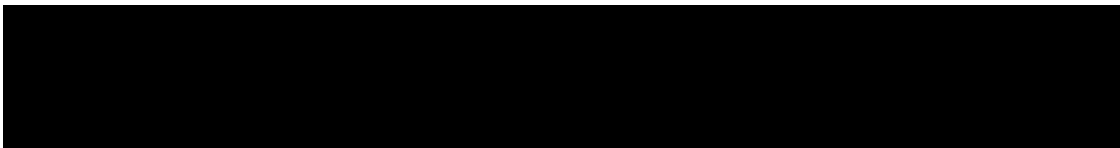
Study design	<p>This is an international, multi-center, open-label, single arm, study designed to collect clinical safety, tolerability and efficacy data with the use of everolimus combined with exemestane in the Novartis Oncology EGM countries in post-menopausal women with HR positive, HER2 negative locally advanced or metastatic breast cancer after documented recurrence or progression following a non-steroidal aromatase inhibitor therapy. It is anticipated that up to 400 patients will be enrolled.</p> <p>The study comprises two periods:</p> <ul style="list-style-type: none">● Screening phase: Patients will grant informed consent to participate in the study. After eligibility is confirmed (all inclusion/exclusion criteria verified), patients can be enrolled. All screening evaluations should be completed within 21 days prior to Treatment Day 1.● Treatment phase: Patients will start study treatment on Day 1 with everolimus 10 mg daily p.o. (either 2 x 5 mg or 1 x 10 mg tablets) in combination with exemestane 25 mg daily p.o. (25 mg tablets). Dose adjustment (reduction or interruption) will be allowed according to safety findings and dose adjustment guidelines. Study treatment will continue until progression, unacceptable toxicity or consent withdrawal. Further treatment after progression will be at the investigator's discretion. <p>During the study, visits will be performed at Screening, Baseline/Treatment Day 1 (Treatment start), Week 4 (\pm 1 week), Week 10 (\pm 2 weeks), and then every 10 weekly (\pm 2 weeks). Tumor evaluations through CT scan will be performed for Screening, at Week 10 (\pm 2 weeks) and thereafter every 10 weekly (\pm 2 weeks). All radiological evaluations and laboratory assessments will be performed locally, at the investigator's facilities. Patients will be followed up for safety for 30 days (\pm 2 days) after the last dose of everolimus. AEs/SAEs with a suspected causality to the study drug must be reported beyond this 30 days safety interval.</p> <p>Patients will continue to be treated per protocol until documentation of disease progression, unacceptable toxicity, death, discontinuation due to any other reason. The present study will continue in each participating country until everolimus is locally reimbursed or commercialized for this indication or until all patients have been discontinued from investigational treatment due to disease progression, unacceptable toxicity, death, consent withdrawal or any other reason.</p> <p>In those countries in which patients will be transitioned to locally reimbursed or commercialized drug supplies, Novartis will have a local transition plan in order to ensure that all on-going patients will still have access to the study medication without any delay in their treatment.</p>
Population	<p>Eligible patients are postmenopausal women with hormone receptor positive locally advanced or metastatic breast cancer progressing following prior NSAI therapy as defined by:</p> <ul style="list-style-type: none">● Recurrence while on or after completion of an adjuvant treatment including letrozole or anastrozole, or● Progression while on or following the completion of letrozole or anastrozole treatment for locally advanced or metastatic breast cancer. <p>Except for prior use of mTOR inhibitors, there are no restrictions as to the last anticancer treatment prior to enrolment. Patients must have documented evidence of recurrence or progression on last therapy prior to enrolment.</p>



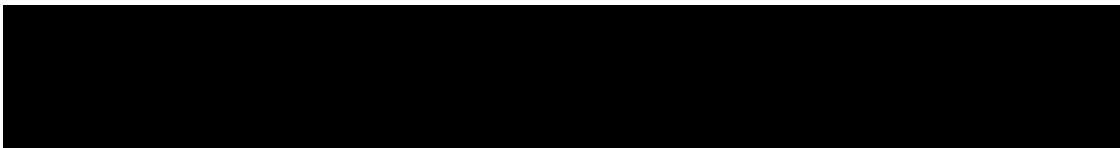
<p>Main inclusion criteria</p>	<ul style="list-style-type: none"> ● Postmenopausal women with metastatic, recurrent or locally advanced breast cancer not amenable to curative treatment by surgery or radiotherapy. ● Histological or cytological confirmation of hormone-receptor positive (HR+)breast cancer. ● Disease refractory to non-steroidal aromatase inhibitors, defined as: <ul style="list-style-type: none"> ● Recurrence while on, or within 12 months (365 days) of completion of adjuvant therapy with letrozole or anastrozole, or ● Progression while on, or within one month (30 days) of completion of letrozole or anastrozole treatment for locally advanced or metastatic breast cancer (ABC). <p>Note: letrozole or anastrozole do not have to be the last treatment prior to inclusion in the study. Patients may have received one prior chemotherapy line for ABC, or have received other endocrine treatments such as tamoxifen, or fulvestrant.</p> <ul style="list-style-type: none"> ● Radiological or objective evidence of recurrence or progression on or after the last systemic therapy prior to enrolment. <p>Note: the last line of therapy may be any other treatment than mTOR inhibitors. Patients must have recovered to grade 1 or better from any adverse events (except alopecia) related to any previous therapy prior to enrolment.</p> <ul style="list-style-type: none"> ● Patients must have: <ul style="list-style-type: none"> ● At least one lesion that can be accurately measured in at least one dimension ≥ 20 mm with conventional imaging techniques or ≥ 10 mm with spiral CT or MRI, or ● Bone lesions: lytic or mixed (lytic + blastic) in the absence of measurable disease as defined above. ● Patients must have adequate bone marrow, coagulation, liver and renal function.
<p>Main exclusion criteria</p>	<ul style="list-style-type: none"> ● Patients overexpressing HER2 by local laboratory testing (IHC 3+ staining or in situ hybridization positive). Patients with IHC 2+ must have a negative in situ hybridization test. ● Patients with only non-measurable lesions other than bone metastasis (e.g. pleural effusion, ascites). ● Patients with more than one prior chemotherapy line for ABC. A chemotherapy line is an anticancer regimen(s) that contains at least 1 cytotoxic chemotherapy agent, given for a minimum of 21 days. ● Previous treatment with mTOR inhibitors. ● Known hypersensitivity to mTOR inhibitors, e.g. Sirolimus (rapamycin). ● Patients with a known history of HIV seropositivity. Screening for HIV infection at baseline is not required. ● Patient being treated with drugs recognized as being strong inhibitors or inducers of the isoenzyme CYP3A ● History of brain or other CNS metastases, including leptomeningeal metastasis.
<p>Investigational drugs</p>	<p>All patients will receive everolimus 10 mg/day once daily + exemestane 25 mg/day once daily by oral route.</p>



<p>Efficacy assessments</p>	<ul style="list-style-type: none"> ● Overall Response Rate (ORR) over the study period, defined as the proportion of patients with best overall response of either complete response (CR) or partial response (PR) according to RECIST (version 1.1). ● Progression Free Survival (PFS) rate over the study period, defined as the proportion of patients who have not had any documented progression or death due to any cause, according to RECIST (version 1.1). ● Clinical Benefit Rate (CBR) over the study period, defined as the proportion of patients with best overall response of complete response (CR), partial response (PR) or stable disease (SD), with duration of 24 weeks or longer, according to RECIST (version 1.1). <p>Efficacy endpoints based on radiological assessments of tumor burden will be derived using local radiologist's/ investigator's assessment.</p>
<p>Safety and tolerability assessments</p>	<ul style="list-style-type: none"> ● Incidence of adverse events (AEs) by grade, assessed according to the Common Terminology Criteria (CTCAE), version 4.03 ● Incidence of serious adverse events (SAEs), assessed according to the Common Terminology Criteria (CTCAE), version 4.03 ● Changes from baseline in laboratory results (hematology, blood chemistry, lipid profile, viral markers) qualifying as AEs ● Changes from baseline in vital signs.
<p>Other assessments</p>	<ul style="list-style-type: none"> ● Time to deterioration of ECOG performance status, from baseline
<p>Data analysis</p>	<p>Analysis populations: The Full Analysis Set (FAS) consists of all patients to whom treatment was assigned and who received at least one dose of study drug.</p> <p>The Per-protocol Set (PP) consists of a subset of patients of the FAS who did not show major deviations from the protocol procedures that may have an impact on the study outcome.</p> <p>The Safety Set consists of all patients who received at least one dose of study drug and had at least one post-baseline safety assessment. The statement that a patient had no adverse events (on the Adverse Event CRF) constitutes a safety assessment. Patients who have received at least one dose of study drug but who have no post-treatment safety data of any kind would be excluded from the safety population.</p> <p>Sample size: The proposed sample size (up to 400 patients) is a convenience sample. The data will be summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, and safety/tolerability observations and measurements. Primary efficacy and safety/tolerability analysis will be conducted at 15 months of median follow up time, i.e. at approximately two times the median PFS reported in the BOLERO-2 study .</p> <p>Statistical methods: Demographic and other baseline characteristics will be summarized for the Full Analysis Set (FAS). Baseline characteristics include prior medication, past/current medical conditions and disease history. Concomitant medications and significant non-drug therapies prior to and after the start of the study drug will be coded according to the WHO Drug Reference List, and</p>



	<p>summarized by ATC class and preferred term using frequency distributions. Duration (days) of exposure to study drugs will be summarized using descriptive statistics separately for everolimus and exemestane.</p> <p>Safety and tolerability</p> <ul style="list-style-type: none">• Data collected by AE CRFs will be coded using the MedDRA dictionary. The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by MedDRA system organ class and preferred term using frequency distributions. Additionally, AE will be summarized by maximum severity (based on CTCAE grades), and for AE with suspected drug relation, serious AE (SAE), and AE leading to permanent discontinuation of study drug. All information pertaining to AE noted during the study will be listed by patient, detailing the verbatim term given by the investigator, MedDRA preferred term and system organ class, start/end dates, severity, seriousness, relationship to study drug and action taken.• The AE onset will also be shown relative (in number of days) to the date of initial dose. AE starting more than 30 days after discontinuation of study drug will not be considered as treatment-emergent and will not be included in AE summary tables but listed only.• Data from other tests (e.g., electrocardiogram or vital signs) will be summarized descriptively as appropriate. Notable values will be flagged, and any other information collected will be listed as appropriate. <p>Efficacy</p> <ul style="list-style-type: none">• Disease progression will be assessed based on radiological assessments of tumor burden will be derived using local radiologist's/ investigator's assessment. If a patient has not had an event at end of the study, his or her data will be censored at the date of last adequate tumor assessment.• The best overall response rate (ORR, according to RECIST 1.1) as well as individual response categories (CR, PR, SD, PD or unknown) will be summarized using frequency tables together with their associated two-sided exact 95% confidence intervals (Clopper-Pearson method).• The clinical benefit rate (CBR) is defined as the proportion of patients with best overall response of complete response (CR), partial response (PR) or stable disease (SD), with duration of 24 weeks or longer. The duration of best overall response is assessed as such: the start date is the date of first documented response (CR or PR) and the end date is the date of event defined as first documented progression disease or death due to underlying cancer. The CBR will be summarized using frequency tables together with its associated two-sided exact 95% confidence intervals (Clopper-Pearson method).• The progression-free survival (PFS) rate is defined as the proportion of patients who have not had any documented progression or death due to any cause, according to RECIST (version 1.1). If a patient has not had an event, progression-free survival is censored at the date of last adequate tumor assessment. PFS will be summarized using the Kaplan-Meier method. Percentiles (25%, median, 75%) of the event time distribution will be presented along with their two-sided 95% confidence interval. The Kaplan-Meier curve will be displayed graphically. <p>Other assessments</p> <ul style="list-style-type: none">• The ECOG Performance Status will be summarized using frequency distributions by visit. Shifts from baseline value to worst post-baseline value will be summarized using frequency distributions. <p>[REDACTED]</p>
Key words	Everolimus, Exemestane, mTor inhibitor, Advanced Breast Cancer, Metastatic Breast Cancer



1 Background

1.1 Epidemiology, pathogenesis, and current treatments of advanced breast cancer

Breast cancer is the most common form of malignancy in women, accounting globally for 23% of all cancers in women and 14% of cancer deaths (Jemal 2011). Of the estimated 12.7 million new cancer cases worldwide in 2008, 1.38 million were estimated to be new cases of breast cancer (Ferlay 2010). It was the most common cancer in women both in developed and developing regions with around 690,000 new cases estimated in each region (population ratio 1:4) (GLOBOCAN 2008), and the most frequent cause of cancer death in women in both developing (269 000 deaths, 12.7% of total) and developed regions, where the estimated 189 000 deaths is almost equal to the estimated number of deaths from lung cancer (188 000 deaths). The incidence rates varied from 19.3 per 100,000 women in Eastern Africa to 89.7 per 100,000 women in Western Europe, and were high (greater than 80 per 100,000) in developed regions of the world (except Japan) (GLOBOCAN 2008, Cancer Fact Sheet). However, although breast cancer is thought to be a disease of the developed world, a majority (69%) of all breast cancer deaths occurs in developing countries (WHO Global Burden of Disease 2004).

The differences in breast cancer incidence between developed and developing countries can partly be explained by dietary effects combined with later first childbirth, lower parity, and shorter breastfeeding. The increasing adoption of western life-style in low- and middle-income countries is an important determinant in the increase of breast cancer incidence in these countries (WHO Breast cancer risk factors).

Approximately 40% of patients treated for early stage breast will eventually develop metastatic breast cancer (MBC). Median life expectancy after recurrence is between 24 to 30 months or less (O'Shaughnessy 2005). Treatment goals for advanced breast cancer (ABC) are palliative in nature, primarily focused at reducing tumor size, slowing progression and metastasis and reducing complications such as fatigue, bone fracture and hypercalcemia.

A number of breast carcinomas are dependent for their proliferation on 17 beta-oestradiol (E2), which can be synthesized from androstenedione through the action of aromatase, an enzyme of the cytochrome P450 superfamily. In premenopausal women, the expression of aromatase is found in the granulosa cells of ovarian follicles while in post-menopausal women, the expression of aromatase is in general derived from non-glandular tissue, such as subcutaneous fat. In breast carcinoma tissue of post-menopausal women, the concentration of estradiol is approximately 10 fold the concentration found in plasma (Thijssen 1989).

The presence of estrogen receptor (ER) and/or progesterone receptor (PgR) is one of the most important predictive and prognostic markers in human breast cancers. Approximately 70% of all invasive breast cancers are positive for ER and/or PgR expressions at the time of diagnosis. Consequently, anti-estrogen therapies that antagonize ER functions (such as tamoxifen) or inhibit estrogen production (e.g. aromatase inhibitors (AIs)) have been extensively developed in oncology (Smith 2003, Jensen 2003). Deprivation of estrogenic signaling with the anti-estrogen tamoxifen has been the main form of hormonal treatment for over 30 years. Besides tamoxifen, progesterone analogues or progestins have been used for the treatment of breast cancer for almost 50 years. Although the exact mechanism of action of progestins has not been established, their effect on estrogen levels is thought to play a role.

While therapies interfering with ER functions such as tamoxifen have significantly contributed to mortality reduction in advanced breast cancer patients, at best 50-60% of ER positive patients respond to anti-estrogen therapy. Aromatase inhibitors (AI) are a class of compounds that reduce peripheral estrogen synthesis by blocking the conversion of androgens to estrogens, which is the primary way estrogens are produced in post-menopausal women. Aminoglutethimide was the first non-steroidal (reversible-competitive) inhibitor of aromatase evaluated clinically for the treatment of ABC. More selective, less toxic, reversible AIs have been developed thereafter (Buzdar 2003, Mokbel 2002, Gligorov 2007), and the third generation AIs anastrozole, exemestane and letrozole are in current use in postmenopausal women with hormone receptor positive BC.

Third-generation AIs can be broadly classified into two groups: non-steroidal aromatase inhibitors (NSAI), mainly letrozole (Femara[®]) and anastrozole (Arimidex[®]), and steroidal aromatase inactivators, represented by exemestane (Aromasin[®]).

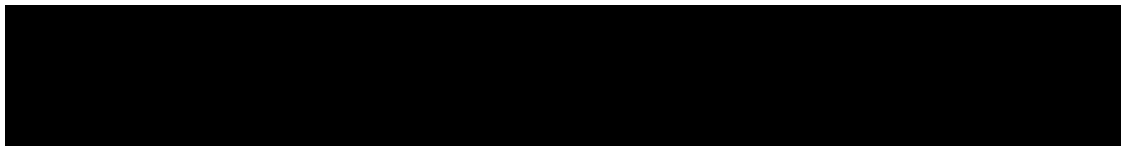
Letrozole and Anastrozole are both approved for use in the adjuvant setting and in the advanced breast cancer setting, based on comparisons to tamoxifen or megestrol acetate.

Letrozole (Femara[®], 2.5 mg tablets) has been approved for the following indications:

- Adjuvant setting:
 - Adjuvant treatment (following surgery) of postmenopausal women with hormone receptor-positive early stage breast cancer.
 - Extended adjuvant treatment of postmenopausal women with early breast cancer who have received prior standard (5 years) adjuvant tamoxifen therapy.
- ABC setting:
 - First-line treatment of postmenopausal women with hormone receptor-positive or unknown locally advanced or metastatic breast cancer.
 - Second-line treatment of postmenopausal women with hormone receptor-positive or unknown advanced breast cancer that is progressing after anti-estrogen therapy.

The approved indications for anastrozole (Arimidex[®], 1 mg tablets) are as follows:

- Adjuvant setting:
 - Adjuvant treatment of hormone receptor-positive early invasive breast cancer in postmenopausal women.
 - Adjuvant treatment of hormone receptor-positive early invasive breast cancer in postmenopausal women who have received 2 to 3 years of adjuvant tamoxifen.



- ABC setting:
 - First-line treatment of hormone receptor-positive advanced breast cancer in postmenopausal women. Superiority was shown for anastrozole vs. tamoxifen in the ITT population for disease free survival.
 - In the USA, it is also indicated for the treatment of advanced breast cancer in postmenopausal women with disease progression following tamoxifen therapy.

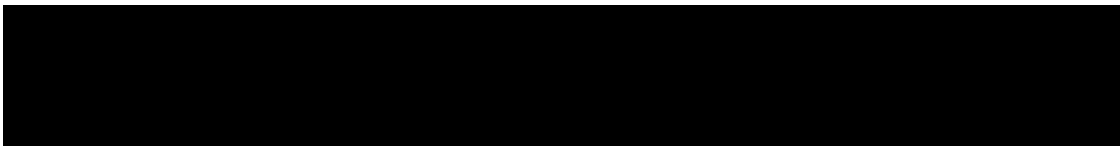
NSAI (letrozole or anastrozole) are generally the treatment of choice for postmenopausal women with ER positive breast cancer. Following recurrence or progression on letrozole or anastrozole, the most commonly subsequent treatment includes exemestane and fulvestrant. In clinical practice, the use of chemotherapy is usually reserved for patients with high tumor burden or for patients that demonstrate an aggressive disease progression or symptomatic visceral disease.

Exemestane (Aromasin®) is an irreversible steroidal aromatase inactivator that has demonstrated efficacy in the treatment of postmenopausal patients with advanced breast cancer. It is indicated for adjuvant treatment of postmenopausal women with ER positive early BC who have received two to three years of tamoxifen and are switched to exemestane for completion of a total of five consecutive years of adjuvant hormonal therapy (HR 0.76 for disease-free survival in favor of exemestane vs. tamoxifen, 95% CI 0.66 to 0.88, $p = 0.0001$, 4727 patients) (Coombes 2007). Exemestane is also indicated for the treatment of ABC in postmenopausal women whose disease has progressed following tamoxifen therapy (in the USA) or following antiestrogen therapy (in Europe).

Fulvestrant (Faslodex®) an estrogen receptor antagonist, is also approved in this same setting, i.e., for the treatment of hormone receptor positive MBC in postmenopausal women with disease progression following antiestrogen therapy. In a clinical study comparing fulvestrant to anastrozole in treatment of ABC in patients whose disease progresses on prior endocrine treatment, there was no significant difference for time to progression between the two treatment groups (HR, 0.92; 95% CI 0.74 to 1.14; $p = 0.43$) (Osborne 2002).

There are currently no treatments specifically approved for postmenopausal women with ER positive breast cancer after recurrence or progression on a NSAI (letrozole or anastrozole). To date, treatment of these patients remains an area of unmet medical need.

The activity of exemestane in MBC after failure of NSAI was evaluated in a phase II trial. Exemestane 25 mg once daily was demonstrated to be safe and effective in postmenopausal patients with MBC following progression after treatment with a NSAI. Exemestane produced an objective clinical benefit rate (defined as CR+PR+SD for 24 weeks or longer) of 24.3 % in a population where 98 % of the patients received exemestane as a third or fourth line hormonal treatment (Lønning 2000).



Another trial assessed the efficacy and tolerability of exemestane administered as third-line hormonal therapy to postmenopausal women with metastatic breast cancer refractory to NSAI. Sixty postmenopausal women with stage IV hormone receptor positive breast cancer were enrolled. All patients had received two prior hormonal manipulations and had measurable or assessable disease. Objective tumor response was achieved in 12 (20%) patients (95% CI, 9.6-30.4). The overall clinical benefit was 38.3% (95% CI, 21.2-49.3), and the median duration of objective tumor response was 20 months (range, 9-26). The median survival was 17.4 months (95% CI, 16.14-18.66) ([Gennatas 2006](#)).

Fulvestrant and exemestane were compared in a double blind placebo controlled phase III trial in 693 postmenopausal women with ER+ BC after recurrence or progression on a NSAI ([Chia 2008](#)). Fulvestrant was administered with a loading dose (500 mg d0, 250 mg d14 and d28) followed by the standard dose of 250 mg every 28 days. No differences were observed in terms of progression-free survival (3.7 month on both arms), response rate (7.4% vs. 6.7%, respectively) or disease control rate (32.2% vs. 31.5%, respectively). This modest level of activity emphasizes the need for new treatment options that are not solely targeting the estrogen receptor pathway.

1.2 Overview of investigational treatments

1.2.1 Overview of Everolimus

Everolimus has been in clinical development since 1996 as immunosuppressant in solid organ transplantation. Everolimus is approved in Europe and other global markets (trade name: Certican®) for cardiac and renal transplantation, and in the United States (trade name: Zortress®) for the prevention of organ rejection of kidney transplantation.

Everolimus was also developed in oncology as Afinitor®. From 2009, Afinitor has been approved for advanced renal cell carcinoma (RCC) worldwide. In 2010, Afinitor received US approval for patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis (TS). Everolimus is also available as Votubia® in the EU for patients with SEGA associated with TS. Afinitor® was approved for advanced PNET in 2011 in various countries, including the US and the EU. In July 2012, Afinitor® in combination with exemestane was approved for Advanced Breast Cancer in the US and in the EU.

The following is a brief summary of the main characteristics of everolimus. More detailed information can be obtained from the everolimus Investigator's Brochure.

Everolimus is a derivative of rapamycin. It is a selective mTOR inhibitor drug class, specifically targeting the mTOR-raptor (regulatory-associated protein of mTOR, Raptor) signal transduction complex 1 (mTORC1). Both rapamycin and everolimus potently inhibit proliferation of endothelial cells ([Francesc 1999](#), [Yu 1999](#), [Lane 2009](#)) and have antiangiogenic activity in vivo ([Guba 2002](#), [Tsutsumi 2004](#), [Mabuchi 2007](#), [Lane 2009](#)).

Everolimus exerts its activity through high affinity interaction with the intracellular receptor protein FKBP12. The FKBP12/everolimus complex binds to mTORC1, inhibiting its signaling capacity. mTORC1 signaling is effected through modulation of the phosphorylation of downstream effectors, the best characterized of which are the translational regulators S6 ribosomal protein kinase (S6K1) and eukaryotic elongation factor 4E-binding protein (4E-BP).

Disruption of S6K1 and 4E-BP1 function, as a consequence of mTORC1 inhibition, interferes with the translation of mRNAs encoding pivotal proteins involved in cell cycle regulation, glycolysis and adaptation to low oxygen conditions (hypoxia). This inhibits tumor growth and expression of Hypoxia-induced factors (e.g. HIF-1 transcription factors); the latter resulting in reduced expression of factors involved in the potentiation of tumor angiogenic processes (e.g. the vascular endothelial growth factor VEGF).

Everolimus is a potent inhibitor of the growth and proliferation of tumor cells, endothelial cells, fibroblasts and blood vessel-associated smooth muscle cells. Consistent with the central regulatory role of mTORC1, everolimus has been shown to reduce tumor cell proliferation, glycolysis and angiogenesis in solid tumors in vivo, and thus provides two independent mechanisms for inhibiting tumor growth: direct antitumor cell activity and inhibition of the tumor stromal compartment.

1.2.1.1 Non-clinical experience

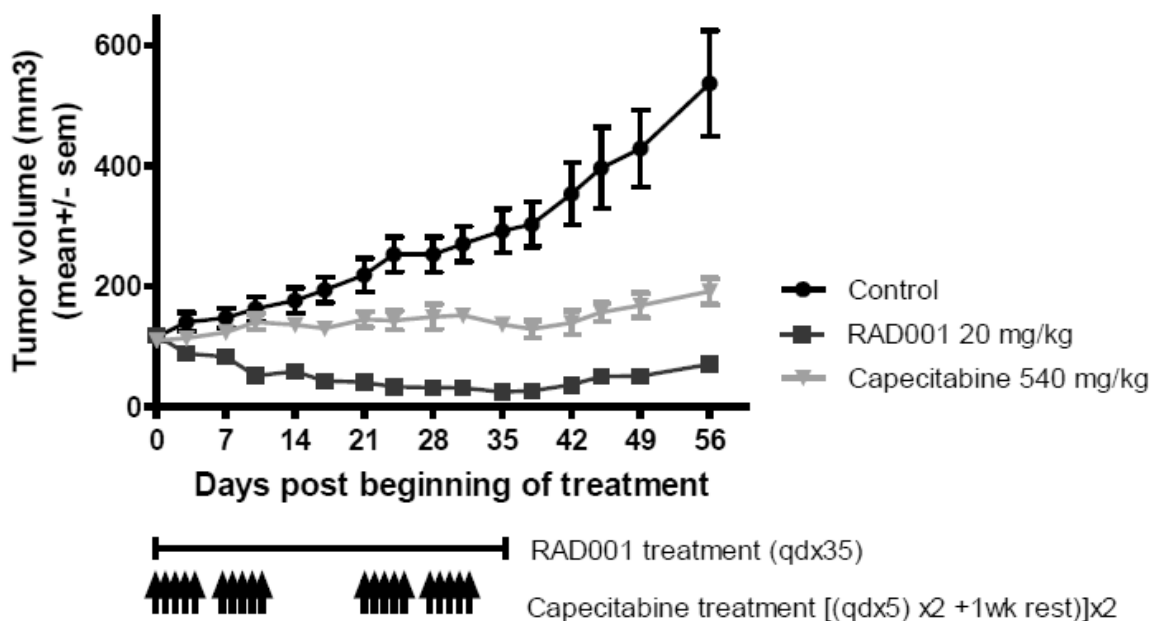
Everolimus inhibits the proliferation of a range of human tumor cell lines in vitro including lines originating from lung, breast, prostate, colon, melanoma and glioblastoma. IC50s range from sub/low nM to μ M. Everolimus also inhibits the proliferation of human umbilical vein endothelial cells (HUVECS) in vitro, with particular potency against VEGF-induced proliferation suggesting that everolimus may also act as an antiangiogenic agent. The antiangiogenic 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 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.

In breast cancer antitumor efficacy of everolimus was compared to other compounds in a panel of six breast cancer xenograft models established after direct transplantation of patients' tumors onto nude mice (Report RD-2011-50492) including an ER+ model, HBCx-3 (XTS-181) (Marangoni 2007). Everolimus given daily by oral gavage for 21 to 35 days at 20 mg/kg was well tolerated with no significant mean body weight loss. In all breast cancer models tested, tumor growth was significantly inhibited, while in HBCx-3 (XTS-181) this effect was particularly evident (Figure 1-1) with 9/10 partial tumor regressions (-13.5% mean tumor volume regression, $p < 0.001$).

Figure 1-1 Tumor Growth Changes in the HBCx-3 Breast Xenograft Model



Significant tumor growth delay with everolimus administered daily p.o. at 10mg/kg was also documented in other four estrogen-dependent breast cancer models: ZR75-1 (ER+, PTENmut), UACC812 (ER+, HER2+), MDA361 (ER+, HER2+) and KPL-1 (ER+, PTENwt) (Report RD-2011-50447).

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 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 [Investigator's Brochure].

1.2.1.2 Clinical experience

1.2.1.2.1 Everolimus Pharmacokinetics

Everolimus is rapidly absorbed with a median t_{max} of one to two hours. The steady-state $AUC_{0-\tau}$ is dose-proportional over the dose range between 5 to 70 mg in the weekly regimen and 5 and 10 mg in the daily regimen. Steady-state was achieved within two weeks with the daily dosing regimen. C_{max} is dose-proportional between 5 and 10 mg for both the weekly and daily regimens. At doses of 20 mg/week and higher, the increase in C_{max} is less than dose-proportional (amended [Study C2102 CP report]).

In healthy patients, high fat meals reduced systemic exposure to everolimus 10 mg (as measured by AUC) by 22% and the peak plasma concentration C_{max} by 54%. Light fat meals reduced AUC by 32% and C_{max} by 42%. Food, however, had no apparent effect on the post absorption phase concentration-time profile ([Study C2120]).

The blood-to-plasma ratio of everolimus, which is concentration-dependent over the range of 5 to 5,000 ng/mL, is 17% to 73%. The amount of everolimus confined to the plasma is approximately 20% at blood concentrations observed in cancer patients given everolimus 10 mg/day ([Study 303-044]). Plasma protein binding is approximately 74% both in healthy patients and in patients with moderate hepatic impairment ([Study A2303]).

The major and nearly exclusive enzyme responsible for the metabolism of everolimus in man was CYP3A4 ([DMPK(US)1998/005]; [DMPK(CH) R99-2448], (Kuhn 2001). Other CYP isoenzymes either do not metabolize everolimus or do so at very low rates. Everolimus is also a moderate inhibitor of P-glycoprotein-like mediated efflux systems, although the compound has a high intrinsic permeability when P-glycoprotein is inhibited (Crowe and Lemaire 1998, Laplante 2002, [DMPK(CH) 1997/417]). Following oral administration, everolimus is the main circulating component in human blood and is considered to contribute the majority of the overall pharmacologic activity ([Study W107]).

No specific excretion studies have been undertaken in cancer patients; however, data available from the transplantation setting found the drug to be mainly eliminated through the feces.

1.2.1.2.2 Everolimus in hormone receptor positive (HR+) breast cancer

Several randomized trials evaluated everolimus in HR+ breast cancer and showed evidence of efficacy of everolimus in this patient population.

Everolimus monotherapy

In a multicenter, randomized phase II study, a daily dose of everolimus (10 mg) was evaluated in patients with mostly HR + advanced breast cancer (ABC) who had received prior hormonal therapy. In this trial, 19 of the 49 patients enrolled were ER-positive/HER2-negative; one complete response, 2 partial responses, 3 stable disease for longer than 6 months, and 6 stable diseases for less than 6 months were reported in this subgroup. Median progression-free survival (PFS) in this subset of 19 patients was 3.5 months (95% C.I.: 1.9 – 5.5 months, data source: NCI-Canada). An additional partial response was reported in a patient with ER-positive HER2-unknown tumor (Ellard 2009).

Everolimus in combination with endocrine therapy

The combination of everolimus with hormonal therapy has been assessed in different disease settings.

In newly diagnosed patients with HR+ early BC, a neoadjuvant randomized 270-patient phase II study compared the combination of everolimus and letrozole to letrozole alone. The overall response rate in the everolimus arm was higher than that with letrozole alone arm (68% vs. 59% (palpation, $p = 0.062$) and 58% vs. 47% (ultrasound, $p = 0.021$) respectively. Additionally, there was a greater antiproliferative response, with a decrease of the Ki67 proliferation index to < 1 in 57% of patients in the everolimus arm and in 30% of patients in the placebo arm ($p < 0.01$). This reduction in Ki67 was observed only two weeks after initiation of trial therapy (Baselga 2009).

In a randomized phase III, double-blind, placebo-controlled study ([BOLERO-2 Study]), everolimus in combination with exemestane was compared with exemestane alone in 724 postmenopausal women with HR+ and HER2- breast cancer who had a recurrence or progression on letrozole or anastrozole (Baselga 2012). The study met its primary objective at the time of interim PFS analysis demonstrating 57% risk reduction in favor of treatment with everolimus plus exemestane (HR: 0.43; 95% CI: 0.35, 0.54; $p < 0.0001$). The median PFS duration and corresponding 95% CI were 6.93 months (6.44, 8.05) for everolimus + exemestane and 2.83 months (2.76, 4.14) for placebo + exemestane arms respectively. The final PFS results were consistent with the interim analysis result (HR: 0.45; 95% CI: 0.38, 0.54; $p < 0.0001$). PFS medians were 7.82 and 3.19 months for everolimus + exemestane and placebo + exemestane arms respectively. All secondary efficacy endpoints (CBR, ORR, duration of response) as well as PFS analysis based on the central radiology review were supportive of the primary efficacy endpoint. This significant improvement was consistent across major demographic and prognostic subgroups.

Results from the final OS analysis is also supportive of the clinical benefit demonstrated at the interim and final PFS analyses. Although the final analysis of OS was not statistically significant (results did not cross the boundary to declare statistical significance; one-sided pvalue from stratified log-rank test $p = 0.1426$, HR from stratified Cox proportional hazard model: 0.89; 95% CI: 0.73, 1.10), the median OS showed a 4.43 months difference in favor of the everolimus arm. Median OS was 30.98 months (95% CI: 27.96, 34.56) in the everolimus plus exemestane arm and 26.55 months (95% CI: 22.57, 33.08) in the placebo plus exemestane arm. This 4.43-month median OS prolongation is consistent with the 4.6-month improvement seen in PFS, and is considered to be clinically meaningful.

In a 111-patient randomized phase II study in postmenopausal women with ER+ ABC previously pretreated with aromatase inhibitors, the combination of everolimus and tamoxifen showed a significant improvement in progression-free survival (8.6 months vs. 4.5 months, $p = 0.0021$) and overall survival (median not reached vs. 24.4 months, $p = 0.0137$) relative to tamoxifen alone (Bachelot 2012). Although the results of this phase II trial are encouraging, the small sample size may limit the impact of these results on clinical practice.

Safety profile of everolimus

Overall, safety data available from completed, controlled and uncontrolled studies indicate that everolimus is generally well tolerated at weekly or daily dose schedules. The safety profile is characterized by manageable adverse events (AEs); mostly of grade 1 and 2 severity.

These AEs are generally reversible and non-cumulative.

The following adverse events are considered to be the class-effects of the mTOR inhibitors: stomatitis/oral mucositis/ulcers, infections and infestations, rash and similar events, cytopenia, hemorrhages, non-infectious pneumonitis, hyperglycemia/new-onset diabetes mellitus, renal events, and thromboembolism. The more common metabolic side effects reported with mTOR inhibitors result from inhibitory effects on mTOR-regulated lipid and glucose pathways, while infections stem from the immunosuppressive properties of these agents. Virtually all of the side effects associated with mTOR inhibitors can be managed effectively with dose modification and/or supportive intervention.

The safety profile of everolimus observed in the BOLERO-2 phase III study (Study Y2301) is consistent with prior experience in the oncology setting; events continue to be predominantly low grade (grade 1 or 2). An increased risk of non-infectious pneumonitis, infection, and stomatitis in the everolimus plus exemestane arm relative to the control arm (exemestane + placebo) was observed, although each of these events can be effectively managed in this setting.

The most common adverse events (AEs) suspected to be related to treatment from the pooled of safety data were (in decreasing order), with an incidence $\geq 10\%$, reported in association with everolimus plus exemestane therapy (see Table 1-1) were consistent with what was previously reported: stomatitis, rash, fatigue, decreased appetite, diarrhea, infections, dysgeusia, nausea, pneumonitis, weight decreased, anemia, epistaxis, hyperglycemia, thrombocytopenia, pruritus, asthenia, peripheral edema, hypercholesterolemia, epistaxis and headache.

The most common grade 3/4 ADRs (incidence $\geq 1/100$ to $< 1/10$ and suspected to be related to treatment by the investigator) were stomatitis, anemia, hyperglycemia, infections, fatigue, infections, pneumonitis, diarrhea, asthenia, thrombocytopenia, neutropenia, dyspnea, lymphopenia, proteinuria, hemorrhage, hypophosphatemia, rash, hypertension, aspartate aminotransferase (AST) increased, and alanine aminotransferase (ALT) increased, and pneumonia.

Further details related to everolimus safety can be found in the everolimus [Investigator's Brochure].

In clinical trials and post-marketing spontaneous reports, everolimus has been associated with serious cases of the following:

- hepatitis B reactivation, including fatal outcome. Reactivation of infections is an expected event during periods of immunosuppression.
- renal failure events (including fatal ones) and proteinuria. Monitoring of renal function is recommended.
- amenorrhea (including secondary amenorrhea).

- pneumocystis jirovecii pneumonia (PJP), some with a fatal outcome.
- angioedema has been reported with and without concomitant use of everolimus mTOR and ACE inhibitors.

Table 1-1 Study Y2301 (BOLERO-2): Most common Adverse Events (equal or greater than 10% of patients)

AE preferred term	Everolimus + Exemestane (n=482), %					Placebo + Exemestane (n=238), %				
	All	1	2	3	4	All	1	2	3	4
Stomatitis	59	29	22	8	0	12	9	2	1	0
Rash	39	29	9	1	0	7	5	2	0	0
Fatigue	37	18	14	4	< 1	27	16	10	1	0
Diarrhea	34	26	6	2	< 1	19	14	4	1	0
Nausea	31	21	9	< 1	< 1	29	21	7	1	0
Decreased appetite	31	19	10	2	0	13	8	4	1	0
Weight decreased	28	10	16	2	0	7	3	5	0	0
Cough	26	21	4	1	0	12	8	3	0	0
Dysgeusia	22	18	4	0	0	6	6	0	0	0
Dyspnea	22	10	6	5	< 1	11	8	2	1	< 1
Headache	23	17	6	< 1	0	15	13	2	0	0
Arthralgia	21	15	5	1	0	17	11	6	< 1	0
Peripheral edema	21	14	6	1	0	6	5	1	< 1	0
Anemia	21	4	10	7	1	5	2	2	< 1	< 1
Back pain	15	10	5	< 1	0	11	6	3	2	0
Epistaxis	17	16	2	0	0	1	1	0	0	0
Vomiting	17	11	6	1	< 1	13	9	3	1	0
Pyrexia	16	13	3	< 1	0	7	6	1	< 1	0
Pneumonitis	16	7	6	3	0	0	0	0	0	0
Constipation	15	11	3	1	0	13	8	5	< 1	0
Back pain	15	10	5	< 1	0	11	6	3	2	0
Pruritus	14	11	3	< 1	0	7	5	2	0	0
Insomnia	14	10	4	< 1	0	8	6	3	0	0
Asthenia	14	7	6	2	< 1	4	3	1	< 1	0
AST increased	14	6	5	3	< 1	6	2	2	1	0
Hyperglycemia	14	4	5	5	< 1	2	1	1	< 1	0
ALT increased	12	5	4	3	< 1	5	1	2	2	0
Dry mouth	11	10	1	0	0	7	7	< 1	0	0
Alopecia	11	9	1	0	0	12	12	0	0	0
Nasopharyngitis	10	9	1	0	0	9	7	2	0	0
Pain in extremity	10	6	3	< 1	0	12	5	5	2	0
UTI	10	3	7	< 1	0	2	< 1	2	0	0
GGT increase	10	2	2	5	2	9	1	1	5	2

AST: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma glutamyltransferase; UTI: urinary tract infection

1.2.2 Potential role of mTOR inhibition in the treatment of bone metastases

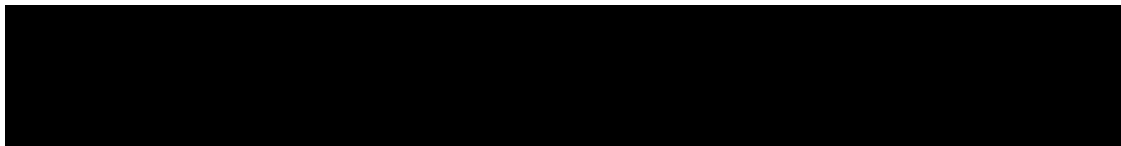
The most common site of first cancer relapse is bone as more than 50% of the patients will develop bone metastases at time of first recurrence. About 80% of these bone metastases are osteolytic tumors leading to complication such as pathological fracture and hypercalcemia. Histological analyses of osteolytic primary and secondary bone tumors reveal that bone destruction is mediated by osteoclasts rather than by tumor cells themselves.

Rapamycin and derivatives also influence bone tissues. Indeed, mTOR appears as an essential signaling pathway engaged in the stimulation of osteoclast survival and affects osteoblast differentiation (Ory 2007). Using primary osteoclast cultures, Kneissel et al have demonstrated that everolimus is a potent inhibitor of osteoclast formation and activity. Treatment of mouse osteoclast cultures with everolimus (0.3–100 nM) resulted in a concentration-dependent inhibition of osteoclast formation and activity. In human osteoclasts cultures, osteoclast formation and activity were completely inhibited at 30 and 10 nM, respectively. Everolimus appeared also to directly inhibit bone resorption, detected by the inhibition of mRNA and protein expression of cathepsin K; the main collagen-degrading protease in osteoclasts. In vivo data suggest that the overall impact of everolimus on bone in a classical model of bone loss is dominated by osteoclast inhibitory activity. Everolimus directly inhibits bone resorption by osteoclasts and thus could at least be neutral or protective for bone in vivo (Kneissel 2004).

1.2.3 Overview of Exemestane

Exemestane is an irreversible steroidal aromatase inactivator that has demonstrated efficacy in the treatment of postmenopausal patients with ABC. It is indicated for adjuvant treatment of postmenopausal women with ER+ early breast cancer who have received two to three years of tamoxifen and are switched to exemestane for completion of a total of five consecutive years of adjuvant hormonal therapy. It is also indicated for the treatment of advanced breast cancer (ABC) in postmenopausal women whose disease has progressed following tamoxifen therapy (in the USA) or following antiestrogen therapy (in Europe).

Exemestane is initially recognized by the aromatase enzyme as a false substrate and then transformed through an NADPH-dependent mechanism to an intermediate that binds irreversibly to the enzyme causing inactivation. Exemestane significantly lowers circulating estrogen concentrations (estradiol, estrone and estrone sulfate) but has no detectable effect on adrenal biosynthesis of corticosteroids or aldosterone (Aromasin prescribing information, Pfizer-Pharmacia, 2011).



The recommended daily dose of exemestane is 25 mg via oral administration. Exemestane is rapidly absorbed from the gastrointestinal tract. Its bioavailability is limited by first-pass metabolism, but is increased when taken with food. Exemestane is widely distributed, and is extensively bound to plasma proteins. It appears to be more rapidly absorbed in women with breast cancer (t_{\max} of 1.2 hours) than in healthy women (t_{\max} of 2.9 hours). The terminal half-life for exemestane is 18-24 hours. The time needed to reach maximal E2 suppression is 7 days (Demers 1993, Plourde 1995, Buzdar 2003). Exemestane is metabolized by CYP3A4 and aldoketoreductases. It does not inhibit any of the major CYP isoenzymes, including CYP 1A2, 2C9, 2D6, 2E1 and 3A4. Although no formal drug-drug interaction studies have been conducted, significant effects on exemestane clearance by CYP isoenzyme inhibitors appear unlikely (Aromasin® prescribing information, Pfizer-Pharmacia, 2011, Hutson 2005, Buzdar 2003).

The most frequently reported adverse effects for exemestane are gastrointestinal disturbances, hot flushes, arthralgia, myalgia, sweating, fatigue, and dizziness. Other reported effects include headache, insomnia, somnolence, depression, skin rashes, alopecia, asthenia, and peripheral and leg edema. Thrombocytopenia and leucopenia have been reported occasionally. Reductions in bone mineral density can occur with long-term use of exemestane.

A total of 1058 patients were treated with exemestane 25 mg once daily in the clinical trials program. Exemestane was generally well tolerated, and adverse events were usually mild to moderate. Adverse events occurring in greater than 10% of patients include hot flushes (14%), nausea (11.9%), insomnia, headache, increased sweating, joint and musculoskeletal pain, and fatigue (USPI; Aromasin SmPC August 2008 (UK as RMS for EU MRP)). Androgenic effects were reported in a limited number of patients (4.3%) (Buzdar 2003).

Refer to the package insert of the local supply of exemestane for more details.

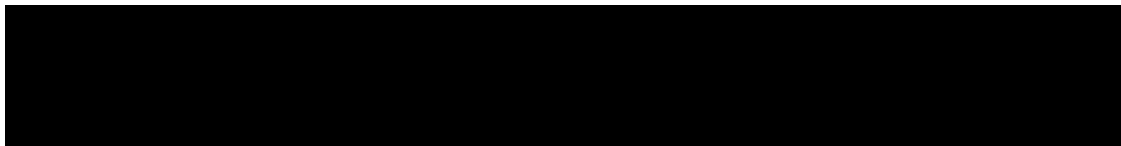
2 Rationale

2.1 Study rationale and purpose

This study is proposed in the light of the need for new treatment options, such as everolimus, in emergent growth market (EGM) countries until it is approved or reimbursed. Therefore, the study is conducted to collect clinical safety, tolerability and efficacy data with the use of everolimus combined with exemestane in the Novartis Oncology EGM countries.

2.2 Rationale for the study design

The present international, multi-center, open-label, single-arm study aims at collecting clinical safety, tolerability and efficacy data with the use of everolimus combined with exemestane in post-menopausal women with HR positive, HER2 negative locally advanced or metastatic breast cancer after documented recurrence or progression following a non-steroidal aromatase inhibitor therapy, in EGM countries.



Everolimus in combination of exemestane has been approved in the US and in the European Union in July 2012 for the treatment of post-menopausal women with advanced hormone receptor-positive, HER2-negative breast cancer (advanced HR+ BC) after failure of treatment with a non-steroidal aromatase inhibitor therapy. Novartis has also filed a NDA in many EGM countries. This study is proposed in the light of the need for new treatment options, such as everolimus, in EGM countries until it is approved or reimbursed.

2.3 Rationale for dose and regimen selection

The dose of everolimus is 10 mg daily orally and the recommended daily dose of exemestane is 25 mg via oral administration. Both drugs were shown to be safe and effective in the respective dose and regimens.

Exemestane is indicated for adjuvant treatment of postmenopausal women with hormone receptor positive (HR+) early BC who have received two to three years of tamoxifen and are switched to exemestane for completion of a total of five consecutive years of adjuvant hormonal therapy. It is also indicated for the treatment of advanced breast cancer (ABC) in postmenopausal women whose disease has progressed following tamoxifen therapy (in the USA) or following antiestrogen therapy (in Europe).

The BOLERO-2 trial (Study Y2301) has demonstrated significant efficacy (improvement of the PFS) of the combinatorial treatment of everolimus and exemestane compared to placebo plus exemestane in ER positive HER2 negative women after failure of prior NSAI therapy. Thus the benefit of the combination treatment versus exemestane monotherapy was shown in a defined patient population under controlled conditions.

3 Objectives and endpoints

3.1 Primary objectives

To evaluate the safety and tolerability profile of everolimus in post-menopausal women with HR positive, HER2 negative locally advanced or metastatic breast cancer after documented recurrence or progression following a non-steroidal aromatase inhibitor therapy in Novartis Oncology EGM countries.

3.1.1 Primary endpoints

The primary endpoints are safety and tolerability evaluations, assessed according to the Common Terminology Criteria (CTCAE), version 4.03. This includes the incidence of adverse events (AEs) by grade, incidence of serious adverse events (SAEs), changes from baseline in vital signs, as well as changes from baseline in laboratory results (hematology, blood chemistry, lipid profile, viral markers) qualifying as AEs.

3.2 Secondary objectives

- To evaluate the efficacy of everolimus in post-menopausal women with HR positive, HER2 negative locally advanced or metastatic breast cancer after documented recurrence or progression following a non-steroidal aromatase inhibitor therapy in EGM countries.

- To assess changes from baseline in Eastern Cooperative Oncology Group (ECOG) performance status during treatment with everolimus plus exemestane
- To provide early access to everolimus for post-menopausal women with HR positive, HER2 negative locally advanced or metastatic breast cancer after documented recurrence or progression following a non-steroidal aromatase inhibitor therapy in EGM countries.

3.2.1 Secondary endpoints

Efficacy endpoints based on radiological (and photographic when applicable) assessments of tumor burden will be derived using local (treating center's) radiologist's/ investigator's assessment.

For patients without event at the end of the study, data will be censored at the date of last adequate tumor assessment.

- Overall Response Rate (ORR) over the study period:
 - Overall response rate (ORR) is defined as the proportion of patients with best overall response of either complete response (CR) or partial response (PR) according to RECIST (version 1.1).
- Progression Free Survival (PFS) rate over the study period:
 - PFS rate is defined as the proportion of patients who have not had any documented progression or death due to any cause, according to RECIST (version 1.1).
- Clinical Benefit Rate (CBR) over the study period:
 - CBR rate is defined as the proportion of patients with best overall response of complete response (CR), partial response (PR) or stable disease (SD), with duration of 24 weeks or longer, according to RECIST (version 1.1).

For these three outcomes, in patients with non-measurable disease (bone metastases), the following is considered a disease progression: appearance of one or more new bone lytic lesions; appearance of one or more lesions outside of bone; unequivocal progression of existing bone lesions. Pathological fracture, new compression fracture, or complications of bone metastases will not be considered as evidence of disease progression unless one of the above criteria is fulfilled.

Changes from baseline in ECOG performance status will be described. Time to deterioration of ECOG performance status, from baseline will be assessed.

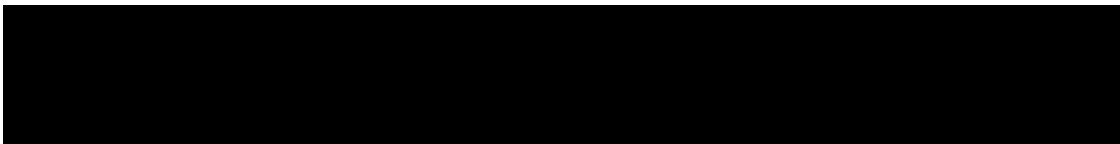
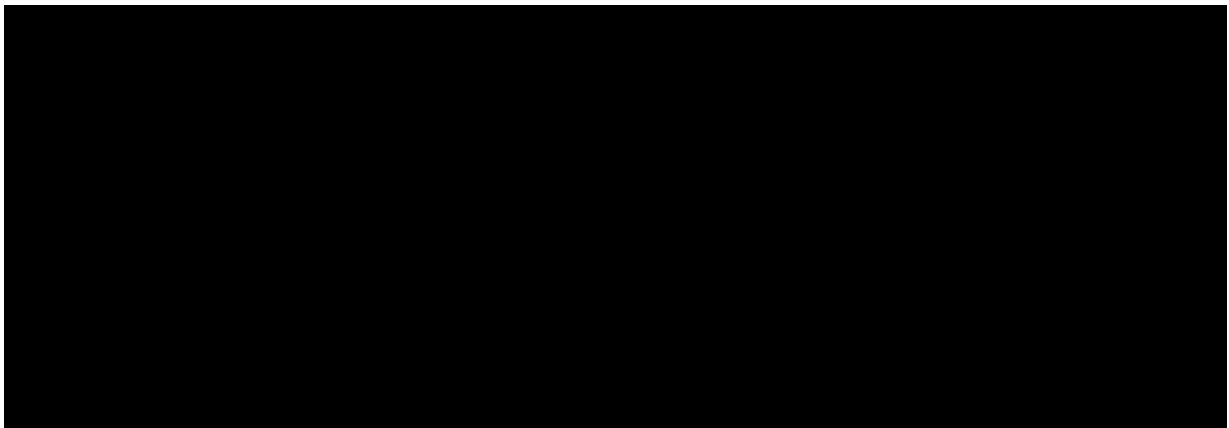
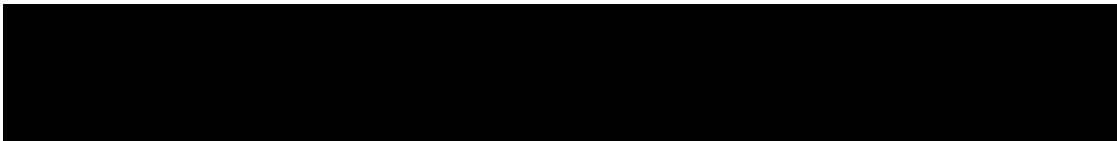
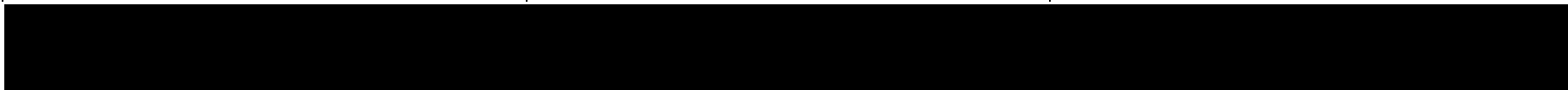


Table 3-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		
To evaluate the safety and tolerability profile of everolimus in post-menopausal women with HR positive, HER2 negative locally advanced or metastatic breast cancer after documented recurrence or progression following a non-steroidal aromatase inhibitor therapy in Novartis Oncology EGM countries.	Incidence of adverse events (AEs) by grade, serious adverse events (SAEs), changes from baseline in vital signs and laboratory results (hematology, blood chemistry, lipid profile) qualifying as AEs. All AEs will be assessed according to the Common Terminology Criteria (CTCAE), version 4.03.	Refer to Section 10.5
Key secondary		
- To evaluate the efficacy of everolimus in post-menopausal women with HR positive, HER2 negative locally advanced or metastatic breast cancer after documented recurrence or progression following a non-steroidal aromatase inhibitor therapy in EGM countries.	<ul style="list-style-type: none"> • ORR • PFS rate • CBR 	
Other secondary		
<p>- To assess changes from baseline in Eastern Cooperative Oncology Group (ECOG) performance status over the study period.</p> <p>- To evaluate the efficacy of provide early access to everolimus infor post-menopausal women with HR positive, HER2 negative locally advanced or metastatic breast cancer after documented recurrence or progression following a non-steroidal aromatase inhibitor therapy in EGM countries.</p>	<ul style="list-style-type: none"> • Time to deterioration of ECOG performance status, from baseline • Number of patients enrolled per study and per country 	Refer to Section 10.6.1



4 Study design

4.1 Description of study design

This is an international, multi-center, open-label, single arm, phase IIIb study designed to collect clinical safety, tolerability and efficacy data with the use of everolimus combined with exemestane in post-menopausal women with HR positive, HER2 negative locally advanced or metastatic breast cancer after documented recurrence or progression following a non-steroidal aromatase inhibitor therapy, with no prior treatment by mTOR inhibitors, in the EGM countries. Enrollment will end in all participating countries by the time of registration/commercial availability of everolimus for the investigational indication or in any case no later than October 31st 2014. It is anticipated that up to 400 patients will be enrolled from a set of EGM countries of Novartis Oncology by this date.

In each participating country, the study will start after approvals are being obtained from the respective local authority and IRB and will end when everolimus is locally reimbursed or commercialized for this indication or when all patients have been discontinued from investigational treatment due to disease progression, unacceptable toxicity, death, consent withdrawal or any other reason.

In those countries in which patients will be transitioned to locally reimbursed or commercialized drug supply, Novartis will have a local transition plan in order to ensure that all on-going patients will still have access to the study medication without any delay in their treatment.

Data derived from the study will be collected, according to ICH GCP and any international and local regulations, to evaluate the safety, tolerability and efficacy of the combination of everolimus (10 mg daily) and exemestane (25 mg daily) in eligible patients.

The study comprises two periods:

Screening phase

Written informed consent must be obtained before any study specific medical procedures are performed. The investigator or his/her authorized designee will assign a unique number to patients being considered for the study. Each patient is uniquely identified by a 9-digit patient identifier (consisting of a 4-digit center number and 5-digit patient number). Once assigned, the patient numbers for patients will not be reused.

After eligibility is confirmed (all inclusion/exclusion criteria verified), patients can be enrolled. All screening evaluations (including screening for hepatitis B and C) should be completed within 21 days prior to the first dose of the study drugs (Treatment Day 1).

Screening for hepatitis B

During the screening period, the following three categories of patients should be tested for hepatitis B viral load and serologic markers, that is, HBV-DNA, HBsAg, HBsAb, and HBcAb:

1. All patients who currently live in (or have lived in) Asia, Africa, Central and South America, Eastern Europe, Spain, Portugal, and Greece for more than 6 months.

2. Patients with any of the following risk factors:
 - Known or suspected past hepatitis B infection,
 - Blood transfusion(s) prior to 1990,
 - Current or prior IV drug users,
 - Current or prior dialysis,
 - Household contact with hepatitis B infected patient(s),
 - Current or prior high-risk sexual activity,
 - Body piercing or tattoos,
 - Mother known to have hepatitis B,
 - History suggestive of hepatitis B infection, e.g., dark urine, jaundice, right upper quadrant pain.
3. Additional patients at the discretion of the investigator.

Patients with positive HBV-DNA or HBsAg at screening must initiate prophylaxis with appropriate antiviral medication at least one week prior to treatment start (Treatment Day 1). The management guidelines are provided according to the results of the baseline assessment of viral load and serological markers for hepatitis B (see [Section 6.3.3.1](#)).

Screening for hepatitis C

Patients with any of the following risk factors for hepatitis C should be tested using quantitative RNA-PCR

- Known or suspected past hepatitis C infection (including patients with past interferon ‘curative’ treatment),
- Blood transfusions prior to 1990,
- Current or prior IV drug users,
- Current or prior dialysis,
- Household contact of hepatitis C infected patient(s),
- Current or prior high-risk sexual activity,
- Body piercing or tattoos,
- Additional patients at the discretion of the investigator.

The management guidelines are provided according to the results of the baseline assessment of hepatitis C viral load (see [Section 6.3.3.2](#)).

Enrolment in the study will be confirmed by completing the Enrolment form on the electronic case report form (eCRF). Information collected for screening failures include date of informed consent, inclusion/exclusion criteria, and serious adverse events (SAE) where relevant.

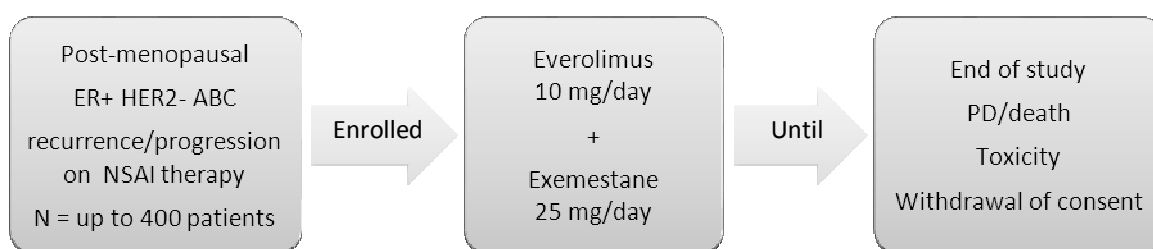
Treatment phase

Patients will start study treatment on Day 1 with everolimus 10 mg daily p.o. (either 2 x 5 mg or 1 x 10 mg tablets) in combination with exemestane 25 mg daily p.o. (25 mg tablets). Dose adjustment (reduction or interruption) will be allowed according to safety findings and dose adjustment guidelines. Study treatment will continue until disease progression, unacceptable toxicity, death, consent withdrawal or any other reason. Further treatment after progression will be at the investigator's discretion.

During the study, visits will be performed at Screening, Baseline/Treatment Day 1 (Treatment start), Week 4 (\pm 1 week), Week 10 (\pm 2 weeks), and then every 10-weekly (\pm 2 weeks) till end of treatment.

Tumor evaluations through CT scan/MRI will be performed for Screening, at Week 10, and 10 weekly thereafter. All radiological evaluations and laboratory assessments will be performed locally, at the center level. Patients will be followed up for safety for 30 days (\pm 2 days) after the last dose of everolimus. AEs/SAEs with a suspected causality to the study drug must be reported beyond this 30 days safety interval.

Figure 4-1 Study design



4.2 Definition of end of the study

In each participating country, the study will start after approvals are being obtained from the respective local authority and IRB and will end when everolimus is locally reimbursed or commercialized for this indication or when all patients have been discontinued from investigational treatment due to disease progression, unacceptable toxicity, death, consent withdrawal or any other reason.

In those countries in which patients will be transitioned to locally reimbursed or commercialized drug supplies, Novartis will have a local transition plan in order to ensure that all on-going patients will still have access to the study medication without any delay in their treatment.

Patients will be followed up for safety purposes for 30 days (\pm 2 days) after the last dose of study drug. At the end of the study, the progression status of all participating patients will be updated and recorded in the electronic case report form (eCRF).

4.3 Early study termination

Novartis can terminate the study at any time for reasons stipulated in the clinical trial agreement. Should this be necessary, the patient should be seen as soon as possible for the final visit and the same assessments should be performed as planned 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 the IRBs and/or Ethic Committees of the early termination of the trial.

5 Population

Enrollment will end in all participating countries by the time of registration/commercial availability of everolimus for this investigational indication or in any case no later than October 31st 2014. It is anticipated that up to 400 patients will be enrolled from a set of EGM countries of Novartis Oncology by this date.

Eligible patients are postmenopausal women with HR positive, HER2 negative locally advanced or metastatic breast cancer progressing following prior therapy with nonsteroidal aromatase inhibitors (NSAI) as defined by either of the following:

- Recurrence while on or after completion of an adjuvant treatment including letrozole or anastrozole, **or**
- Progression while on or following the completion of letrozole or anastrozole treatment for locally advanced or metastatic breast cancer.

Patients must not have been treated by mTOR inhibitors prior to enrolment. With this exception, there are no restrictions as to the last anticancer treatment prior to enrolment. Patients must have documented evidence of recurrence or progression on last therapy prior to enrolment.

Written informed consent must be obtained prior to any screening procedures. The investigator or designee must ensure that only patients who meet all the following inclusion and none of the exclusion criteria are offered enrolment in the study.

5.1 Inclusion criteria

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

1. Adult women (≥ 18 years of age) with metastatic, recurrent or locally advanced breast cancer not amenable to curative treatment by surgery or radiotherapy.
2. Histological or cytological confirmation of hormone receptor positive (HR+) breast cancer.
3. Postmenopausal women. Ovarian radiation or treatment with a luteinizing hormone-releasing hormone (LHRH) agonist (goserelin acetate or leuprolide acetate) does not satisfy this inclusion criterion. Postmenopausal status is defined by one of the following:
 - Age ≥ 55 years and one year or more of amenorrhea
 - Age < 55 years and one year or more of amenorrhea, with estradiol assay < 20 pg/ml and/or post-menopausal levels of FSH and LH per local institutional standards

- Prior hysterectomy, with estradiol assay < 20 pg/ml and/or post-menopausal levels of FSH and LH per local institutional standards
 - Surgical menopause with bilateral oophorectomy.
4. Disease refractory to non-steroidal aromatase inhibitors (NSAI), defined as:
- Recurrence while on, or within 12 months (365 days) of completion of adjuvant therapy with letrozole or anastrozole,
or
 - Progression while on, or within one month (30 days) of completion of letrozole or anastrozole treatment for ABC.
 - Notes: Letrozole or anastrozole do not have to be the last treatment prior to study baseline. Patients may have received one prior chemotherapy line for ABC, or have received other endocrine treatments such as tamoxifen, or fulvestrant and including exemestane monotherapy.
5. Radiological or objective evidence of recurrence or progression on or after the last systemic therapy prior to enrolment.
- Notes: The last line of therapy may be any other treatment than mTOR inhibitors. Patients must have recovered to grade 1 or better from any adverse events related to previous therapy (except alopecia) prior to enrolment.
6. Patients must have:
- Measurable disease defined as at least one lesion that can be accurately measured in at least one dimension ≥ 20 mm with conventional imaging techniques or ≥ 10 mm with spiral CT or MRI,
or
 - Bone lesions: lytic or mixed (lytic + blastic) in the absence of measurable disease as defined above.
- Note: Lymph nodes must be ≥ 15 mm in the short axis to be considered measurable
Patients with bone lesions and at least one measurable lesion are considered as having measurable disease
If bone lesions have been previously irradiated, at least one lesion must have clearly progressed since the radiotherapy by CT, MRI or X-ray for trial entry (in the absence of measurable disease).
7. Adequate bone marrow and coagulation function as shown by:
- Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9/L$
 - Platelets $\geq 100 \times 10^9/L$
 - Hemoglobin (Hgb) ≥ 9.0 g/dL
 - INR ≤ 2 .
8. Adequate liver function as shown by:
- Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 ULN (or ≤ 5 if hepatic metastases are present)
 - Total serum bilirubin $\leq 1.5 \times$ ULN ($\leq 3 \times$ ULN for patients known to have Gilbert Syndrome).
9. Adequate renal function as shown by serum creatinine $\leq 1.5 \times$ ULN.

10. Fasting serum cholesterol ≤ 300 mg/dl or 7.75 mmol/L and fasting triglycerides $\leq 2.5 \times$ ULN. Treatment with statins may be initiated or adjusted as needed to meet these values before enrolment.
11. ECOG Performance Status ≤ 2 .
12. Adequate organ function at the discretion of the investigator.
13. Patients with positive HBV-DNA and/or HBsAg at screening must initiate prophylaxis with appropriate antiviral medication at least one week prior to treatment start.
14. Signed informed consent obtained before any trial related activity and according to local guidelines.

5.2 Exclusion criteria

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

1. Patients overexpressing HER2 by local laboratory testing (IHC 3+ staining or in situ hybridization positive), based on the most recent test. Patients with IHC 2+ must have a negative in situ hybridization test.
2. Patients with only non-measurable lesions other than bone metastasis (e.g. pleural effusion, ascites).
3. Patients with more than one prior chemotherapy line for treating metastatic breast cancer. A chemotherapy line is an anticancer regimen(s) that contains at least 1 cytotoxic chemotherapy agent, given for a minimum of 21 days. A cytotoxic chemotherapy regimen that lasted less than 21 days and was discontinued for a reason other than disease progression is not accounted as a "prior line of chemotherapy".
4. Previous treatment with mTOR inhibitors.
5. Known hypersensitivity to mTOR inhibitors, e.g. Sirolimus (rapamycin).
6. Any other malignancy within 5 years prior to enrolment, with the exception of adequately treated in-situ carcinoma of the cervix uteri, basal or squamous skin cell carcinoma, or non-melanoma skin cancer.
7. Radiotherapy within four weeks prior to enrolment, except radiotherapy to the bone for analgesic purpose or for lytic lesions at risk of fracture. Patients must have recovered from radiotherapy toxicities prior to enrolment.
8. Patient receiving hormone replacement therapy (HRT). Patient may be enrolled after discontinuation of HRT.
9. History of brain or other CNS metastases, including leptomeningeal metastasis.

10. Treatment with immunosuppressive agents or chronic corticosteroids, with the following exceptions:
 - Patients on stable low dose of systemic corticosteroids for at least two weeks before enrolment
 - Corticosteroids used in topical applications (e.g. cream), inhaled sprays, eye drops or local (e.g. intra-articular) injections.
11. Bilateral diffuse lymphangitic carcinomatosis.
12. Patients with a known history of HIV seropositivity. Screening for HIV infection at baseline is not required.
13. Active, bleeding diathesis. Patients treated with anti-vitamin K medication, LMWH, or anti-platelet medication must have an INR ≤ 2.0 .
14. Any severe and / or uncontrolled medical conditions such as:
 - a. Unstable angina pectoris, symptomatic congestive heart failure, myocardial infarction ≤ 6 months prior to enrolment, serious uncontrolled cardiac arrhythmia
 - b. Uncontrolled diabetes as defined by fasting serum glucose $> 1.5 \times$ ULN
 - c. Acute and chronic, active infectious disorders (except for Hep B and Hep C positive patients) and non-malignant medical illnesses that are uncontrolled or whose control may be jeopardized by the complications of this study therapy
 - d. Impairment of gastrointestinal function or who have gastrointestinal disease that may significantly alter the absorption of study drugs (e.g., ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome)
 - e. Active skin, mucosa, ocular or gastro-intestinal disorders of Grade > 1
 - f. Significant symptomatic deterioration of lung function. If clinically indicated, pulmonary function tests including measures of predicted lung volumes, DLco, O2 saturation at rest on room air should be considered to exclude restrictive pulmonary disease, pneumonitis or pulmonary infiltrates.
15. Patients being treated with drugs recognized as being strong inhibitors or inducers of the isoenzyme CYP3A at enrolment (rifabutin, rifampicin, clarithromycin, ketoconazole, itraconazole, letrozole, voriconazole, ritonavir, telithromycin) continuously for at least 7 days during any time period in the last 2 weeks prior to enrolment (clinically relevant drug interaction are listed in [Section 6.4.1](#)).
16. Patients unwilling to or unable to comply with the protocol.
17. Patients enrolled in another investigational drug or device study.
18. Patients who have discontinued this study may not be re-enrolled.

6 Treatments

6.1 Study treatments

This is a non-randomized, single-arm, open-label study. The investigational drugs used in the course of this trial are everolimus in combination with exemestane. All patients will be assigned to treatment with everolimus and exemestane.

6.1.1 Everolimus

Everolimus is formulated as tablets of 10 and 5 mg strength for oral administration. The dose is 10 mg once daily (as one tablet of 10 mg or two tablets of 5 mg at a time) per oral route.

6.1.2 Exemestane

Commercially available exemestane will be supplied as tablets of 25 mg strength for oral administration. The dose is 25 mg once daily (one tablet) per oral route.

Complete guidelines for management and administration of exemestane can be found in the package insert.

6.1.3 Dosing regimen

All patients will receive everolimus + exemestane. All patients will take everolimus 10 mg orally per day. All patients will also take one 25 mg tablet of exemestane once daily (Table 6-1).

Table 6-1 Starting dose and treatment schedule

Study drugs	Pharmaceutical form, route of administration	Dose	Frequency
Everolimus (RAD0001)	Tablets for oral use	1 tablet of 10 mg or 2 tablets of 5 mg*	Daily
Exemestane	Tablets for oral use	25 mg	Daily

*: Choice will be made at each participating country level

Patients will be provided with study treatment for self administration at home, starting on Treatment Day 1. Enough tablets should be provided to cover administration until next scheduled visit.

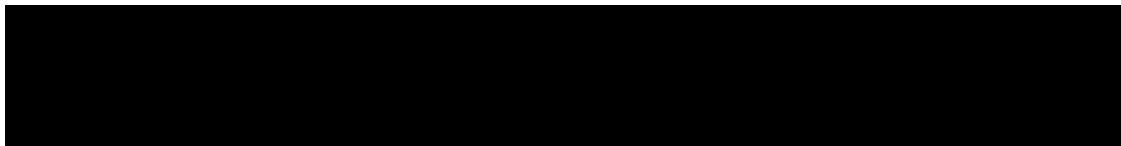
Everolimus and exemestane will be dosed starting on Treatment Day 1 (Visit 2).

Patients will be instructed to take one 10 mg tablet of everolimus or 2 tablets of 5 mg at a time per oral route with a large glass of water at the same time every day with or without food. The tablets should not be chewed or crushed.

Similarly, patients will be instructed to take one 25 mg tablet of exemestane orally with a large glass of water at the same time every day. Package insert instructions should be followed.

Everolimus should be swallowed whole with a glass of water and the tablets should not be chewed or crushed and grapefruit or citrus juices must be avoided for everolimus administration. If the tablets cannot be swallowed, the tablets should be disintegrated in approximately 30 ml of water. Immediately prior to administration, the contents should be stirred gently until the tablets have disintegrated into a suspension. The patient should then drink the contents. Afterwards, the glass should be rinsed with an additional 30 ml of liquid and drunk by the patient. If vomiting occurs no attempt should be made to replace the dose.

Everolimus and exemestane will be taken daily from Visit 2, Day 1 until disease progression, unacceptable toxicity, death, and withdrawal from the study for any other reason.



The End of Treatment (EOT) is defined as the last date that the patient has taken the study drug everolimus, excluding an everolimus interruption for < 4 weeks. A Follow-up visit 30 days (\pm 2 days) after the last date that the patient has taken the study drug will be conducted to report any adverse events during this period.

The investigator should promote compliance by instructing the patient to take the study drugs exactly as prescribed and by stating that compliance is necessary for the patient's safety and the validity of the study. The patient should be instructed to contact the investigator if she is unable for any reason to take the study drug as prescribed.

All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record CRF.

6.1.4 Treatment duration

Patients will be treated with everolimus and exemestane until progression of disease, unacceptable toxicity, death, consent withdrawal, or discontinuation for any other reason.

6.2 Dose modifications

6.2.1 Dose adjustment and interruption

Treatment with everolimus and exemestane should continue as long as clinical benefit is observed or until unacceptable toxicity occurs. The management of severe and/or intolerable suspected adverse events may require temporary dose interruption (with or without dose reduction) or discontinuation of everolimus therapy.

Dose adjustments are permitted for any adverse event suspected to be related to everolimus in those patients unable to tolerate their individual once daily oral dose. If dose reduction is required, the suggested dose is approximately 50% lower than the daily dose previously administered (see Table 6-2).

If administration of everolimus must be interrupted because of unacceptable toxicity, everolimus dosing should be interrupted or modified according to the guidelines presented in Table 6-2, [Table 6-3](#), and [Table 6-4](#).

Table 6-2 Everolimus dose reduction steps

Dose level	Dose and schedule
0 = starting dose	10 mg daily
-1 dose level	5 mg daily
-2 dose level	5 mg every other day

In addition, if any surgery is planned, everolimus dosing should be interrupted one week prior to surgery and should be re-started as soon as possible after wound healing.

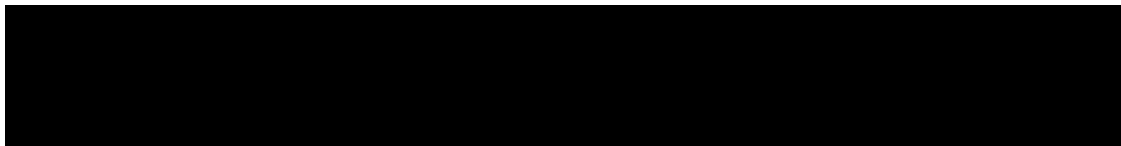


Table 6-3 and Table 6-4 provide the procedure to be followed in the event of toxicities suspected to be related to the everolimus treatment. Included are also instructions for re-initiation of everolimus dosing once sufficient recovery of toxicity is seen. If everolimus dosing is interrupted due to toxicity, everolimus should not be resumed unless recovery to grade ≤ 1 is achieved in less than 4 weeks. Then everolimus could be reintroduced at the initial dose or a lower dose level depending on the toxicity type and grade (see Table 6-3 and Table 6-4).

If a patient has already decreased everolimus intake by 2 dose levels, no further dose reduction is permitted. Patients requiring an additional everolimus dose reduction will be required to discontinue study treatment. Patients who interrupt everolimus therapy for more than 4 weeks must be discontinued from the study.

All study drugs, i.e. everolimus and exemestane, interruptions or dose modifications must be recorded on the Dosage Administration Record page of the CRF.

Table 6-3 Everolimus: dose modification guidelines for hematologic toxicities

Toxicity	Actions
Thrombocytopenia / Platelet count	$\geq 75000/\text{mm}^3$: No change $50000/\text{mm}^3$ to $75000/\text{mm}^3$ Hold everolimus treatment until recovery to $\geq 75000/\text{mm}^3$. Reintroduce everolimus at the same dose level $< 50000/\text{mm}^3$ Hold everolimus treatment until recovery to $\geq 75000/\text{mm}^3$. Reintroduce everolimus at the next lower dose level, if available.
Absolute neutrophil count (ANC)	$\geq 1000/\text{mm}^3$: No change $500/\text{mm}^3$ to $1000/\text{mm}^3$ Hold everolimus treatment until recovery to $\geq 1000/\text{mm}^3$. Reintroduce everolimus at the same dose level $< 500/\text{mm}^3$ Hold until recovery to $\geq 1000/\text{mm}^3$. Reintroduce everolimus (at the next lowest dose level, if available.
Febrile neutropenia	Hold further dosing until $\text{ANC} \geq 1250/\text{mm}^3$ and no fever. Then resume dosing at the next lower dose level, if available.
Toxicity requiring interruption for > 4 weeks	Permanently discontinue treatment.
Physicians should always manage patients according to their medical judgment based on the particular clinical circumstances.	

Table 6-4 Everolimus: dose modification guidelines for non-hematologic toxicities

Adverse drug reaction	Severity	Everolimus dose adjustment 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	Consider interruption of therapy, rule out infection and consider treatment with corticosteroids until symptoms improve to \leq grade 1. Re-initiate everolimus at a lower dose. Discontinue treatment if failure to recover within 4 weeks.
	Grade 3 Symptomatic, interfering with ADL; O ₂ indicated	Interrupt everolimus until symptoms resolve to \leq 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 Consider treatment with corticosteroids.
Stomatitis ^a	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 \leq 1. Re-initiate everolimus at the same dose. If stomatitis recurs at grade 2, interrupt dose until recovery to grade \leq 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).
	Grade 3 Symptomatic and unable to adequately eat or hydrate orally	Temporary dose interruption until recovery to grade \leq 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)
	Grade 4 Symptoms associated with life-threatening consequences	Discontinue everolimus and treat with appropriate medical therapy.
Other non-hematologic 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 \leq 1. Re-initiate everolimus at the same dose. If toxicity recurs at grade 2, interrupt everolimus until recovery to grade \leq 1. Re-initiate everolimus at a lower dose.

Adverse drug reaction	Severity	Everolimus dose adjustment and management recommendations
	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.
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.
Toxicity requiring interruption for > 4 weeks		Permanently discontinue treatment
ADL: activities of daily living O2: oxygen ^a : Avoid using agents containing hydrogen peroxide, iodine, and thyme derivatives in management of stomatitis as they may worsen mouth ulcers. Severity grade description: 1 = mild symptoms; 2 = moderate symptoms; 3 = severe symptoms; 4 = life-threatening symptoms. If dose reduction is required, the suggested dose is approximately 50% lower than the dose previously administered.		

6.2.2 Follow-up for toxicities

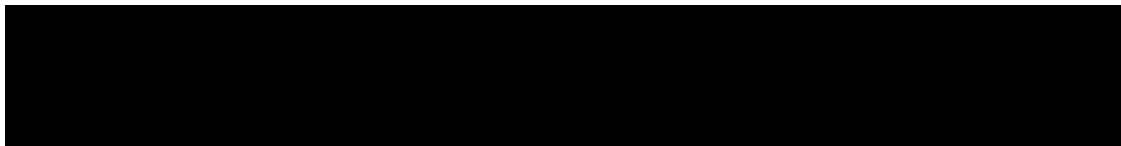
Patients whose everolimus treatment is interrupted or permanently discontinued due to an adverse event or abnormal laboratory value suspected to be related to study treatment must be followed at least weekly until the adverse event or abnormal laboratory values resolves or returns to grade 1.

If a patient requires a dose delay of > 4 weeks from the intended day of the next scheduled dose for either everolimus or exemestane, then the patient must be discontinued from the study.

6.3 Known undesirable effects of the study drugs

The most frequently observed adverse events (AEs) with everolimus are rash, stomatitis /oral mucositis, non-infectious pneumonitis, fatigue, headache, anorexia, nausea, vomiting, diarrhea, and infections. Overall, the most frequently observed laboratory abnormalities include neutropenia, thrombocytopenia, hypercholesterolemia, and/or hypertriglyceridemia. The majority of these AEs have been of mild to moderate severity (NCI CTC grade 1-2).

Recommendations for dose adjustments, should any of these treatment-related adverse events occur, are given in [Table 6-2](#), [Table 6-3](#), and [Table 6-4](#).



The most frequently reported adverse effects for exemestane are gastrointestinal disturbances, hot flushes, arthralgia, myalgia, sweating, fatigue and dizziness. Other reported effects include headache, insomnia, somnolence, depression, skin rashes, alopecia, asthenia and leg oedema. Thrombocytopenia and leucopenia have been reported occasionally. Reductions in bone mineral density can occur with long-term use of exemestane ([Motzer 2008](#)).

Please refer to the package insert of the local supply of exemestane for more details.

6.3.1 Non-infectious pneumonitis

Non-infectious pneumonitis is a class effect of rapamycin derivatives. Cases of non-infectious pneumonitis (including interstitial lung disease) have also been described in patients taking everolimus. Some of these have been severe and on rare occasions, a fatal outcome was observed.

A diagnosis of non-infectious pneumonitis should be considered in patients presenting with non-specific respiratory signs and symptoms such as hypoxia, pleural effusion, cough or dyspnea, and in whom infectious, neoplastic and other non-medicinal causes have been excluded by means of appropriate investigations. Opportunistic infections such as PJP should be considered ruled out in the differential diagnosis of non-infectious pneumonitis. Patients should be advised to report promptly any new or worsening respiratory symptoms.

Patients who develop radiological changes suggestive of non-infectious pneumonitis and have few or no symptoms may continue everolimus therapy without dose alteration. If symptoms are moderate (grade 2), consideration should be given to interruption of therapy until symptoms improve. The use of corticosteroids may be indicated. Everolimus may be reintroduced at a daily dose approximately 50% lower than the dose previously administered.

For cases of grade 3 non-infectious pneumonitis, interrupt everolimus until resolution to less than or equal to grade 1. Everolimus may be re-initiated at a daily dose approximately 50% lower than the dose previously administered depending on the individual clinical circumstances. If toxicity recurs at grade 3, consider discontinuation of everolimus. For cases of grade 4 noninfectious pneumonitis, everolimus therapy should be discontinued. Corticosteroids may be indicated until clinical symptoms resolve.

For patients who require use of corticosteroids for treatment of non-infectious pneumonitis, prophylaxis for pneumocystis jirovecii pneumonia (PJP) may be considered.

Guidelines for management of non-infectious pneumonitis suspected to be associated with everolimus and dose modification instructions have been provided in [Table 6-4](#).

6.3.2 Infections

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

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

Patients with positive results of HBV-DNA and/or HBsAg at screening should begin a prophylaxis treatment for 1-2 week prior to beginning everolimus therapy. Patients should have HBV-DNA monitored frequently throughout the course of everolimus therapy for signs of hepatitis reactivation.

If a diagnosis of invasive systemic fungal infection is made, discontinue everolimus and treat with appropriate antifungal therapy.

Cases of *Pneumocystis jirovecii* pneumonia (PJP), some with a fatal outcome, have been reported in patients who received everolimus. PJP may be associated with concomitant use of corticosteroids or other immunosuppressive agents. Prophylaxis for PJP should be considered when concomitant use of corticosteroids or other immunosuppressive agents are required.

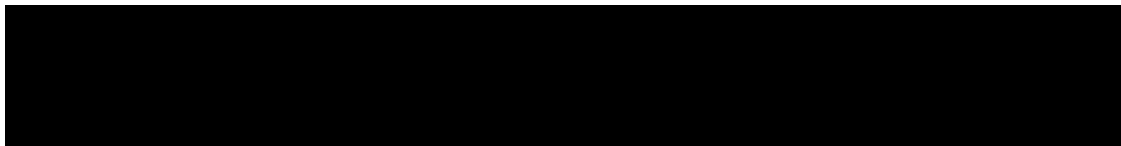
6.3.3 Management of Hepatitis reactivation/flare

6.3.3.1 Monitoring and prophylactic treatment for hepatitis B reactivation

Table 6-5 provides details of monitoring and prophylactic therapy according to the screening results of viral load and serologic markers testing. If the patient is already known to have a chronic infection with HBV and is taking anti-HBV medication, the site does not have to wait for the screening HBV results prior to enrolment in the study.

Table 6-5 Actions recommended base on hepatitis B screening results

	Result				
HBV-DNA	+	+ or -	-	-	-
HBsAg	+ or -	-	-	-	-
HBsAb	+ or -	+ or -	+ and no prior HBV vaccination	+ or -	- or + with prior HBV vaccination
HBcAb			+ or -	+	-
Recommendation	Prophylaxis treatment should be started at least 1 week prior to first dose of study drug. Monitor HBV-DNA approximately every 6 weeks (from Visit 2 and onwards)		No prophylaxis Monitor HBV-DNA approximately every 3 weeks (from Visit 2 and onwards)		No specific action



Antiviral prophylaxis therapy should continue for at least 4 weeks after last dose of study drug. The first HBV-DNA result would be regarded as screen visit.

For hepatitis B reactivation, definition and management guidelines, see [Table 6-6](#) Guidelines for management of hepatitis B.

Table 6-6 Guidelines for management of hepatitis B

HBV reactivation (with or without clinical signs and symptoms)*	
<p>For patients with baseline results: Positive HBV-DNA OR Positive HBsAg</p> <p>-----</p> <p>Reactivation is defined as: [Increase of 1 log in HBV-DNA relative to baseline HBV-DNA value OR new appearance of measurable HBV-DNA]</p>	<p>Treat: Start a second antiviral AND Interrupt study drug administration until resolution: - ≤ baseline HBV-DNA levels</p> <p>If resolution occurs within 28 days, study drug should be re-started at one dose lower, if available. (see Table 6-2- Study drug dose reductions) If the patient is already receiving the lowest dose of study drug according to the protocol, the patient should restart at the same dose after resolution. Both antiviral therapies should continue at least 4 weeks after last dose of study drug. If resolution occurs > 28 days, patients should discontinue study drug but continue both antiviral therapies at least 4 weeks after last dose of study drug.</p>
<p>For patients with baseline results: Negative HBV-DNA and HBsAg AND [Positive HBs Ab (with no prior history of vaccination against HBV), OR positive HBc Ab]</p> <p>-----</p> <p>reactivation is defined as: New appearance of measurable HBV-DNA</p>	<p>Treat Start first antiviral medication AND Interrupt study drug administration until resolution: ≤ undetectable (negative) HBV-DNA levels If resolution occurs within 28 days, study drug should be re-started at one dose lower, if available. (see Table 6-7 - Study drug dose reductions) If the patient is already receiving the lowest dose of study drug according to the protocol, the patient should restart at the same dose after resolution. Antiviral therapy should continue at least 4 weeks after last dose of study drug. If resolution occurs > 28 days, patients should discontinue study drug but continue antiviral therapy at least 4 weeks after last dose of study drug.</p>
<p>* All reactivations of hepatitis B are to be recorded as grade 3 (CTCAE v 3.0 Metabolic Laboratory/Other: Viral Re-activation), unless considered life threatening by the investigator; in which case they should be recorded as grade 4 (CTCAE v 3.0 Metabolic Laboratory/Other: Viral Re-activation). Date of viral reactivation is the date on which the rise or reappearance of HBV- DNA was recorded.</p>	

6.3.3.2 Monitoring for hepatitis C flare

The following two categories of patients should be monitored every 6 weeks for HCV flare:

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

For definition of HCV flare and the management guidelines, see [Table 6-7](#).

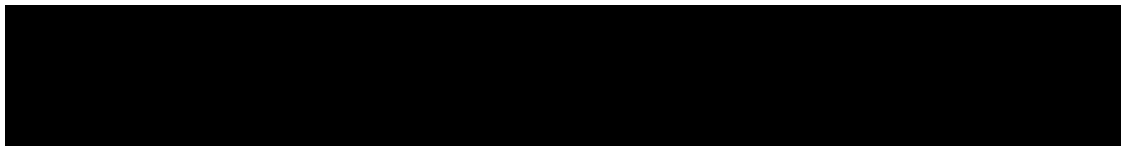


Table 6-7 Guidelines for management of hepatitis C

HCV flare *	
<p>For patients with baseline results: Detectable HCV-RNA, HCV flare is defined as: > 2 log₁₀IU/mL increase in HCV-RNA AND ALT elevation > 5 x ULN OR 3 x baseline level, whichever is higher</p>	Discontinue study drug
<p>For patients with baseline results: Knowledge of past hepatitis C infection with no detectable HCV-RNA, HCV flare is defined as: New appearance of detectable HCV-RNA AND ALT elevation > 5 x ULN OR 3 x baseline level, whichever is higher</p>	Discontinue study drug
<p>*All flares of hepatitis C are to be recorded as grade 3 (CTCAE v 3.0 Metabolic Laboratory/Other: Viral Flare), unless considered life threatening by the investigator; in which case they should be recorded as grade 4 (CTCAE v 3.0 Metabolic Laboratory/Other: Viral Re-activation). Date of viral flare is the date on which both the clinical criteria described above were met (e.g., for a patient whose HCV-RNA increased by 2 logs on 01 JAN 2011 and whose ALT reached > 5 x ULN on 22 JAN 2011), the date of viral flare is 22 JAN 2011.</p>	

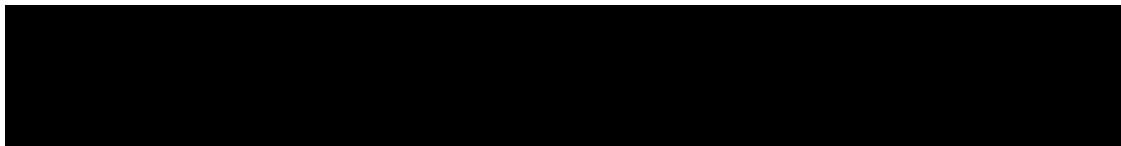
6.4 Concomitant medication

In addition to receiving everolimus and exemestane, all patients should receive best supportive care (BSC), as per standard local practice for the treatment of pre-existing medical conditions or adverse events that may arise during the study. BSC is defined as drug or nondrug therapies, nutritional support, physical therapy or any other treatment alternative that the investigator believes to be in the patient’s best interest, but excluding other antineoplastic treatments.

All medications and non-drug therapies taken within 30 days prior to starting the study treatment should be reported on the Concomitant Medication/Significant Non-drug Therapy Prior to Start of Study Drug CRF. The patient should notify the investigational site about any new medications (including over-the-counter products and herbal/alternative medications) taken during the study. All medications (other than study drug) and significant non-drug therapies (including physical therapy and blood transfusions) administered during the study and for up to 30 days after study drug discontinuation must be listed on the Concomitant Medications or the Procedures and Significant Non-Drug Therapies CRF pages, respectively.

The use of live vaccines and close contact with those who have received 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.

Information regarding drug-to-drug interactions for everolimus is provided in [Section 6.4.1](#).



6.4.1 Prohibited concomitant therapy

Local radiotherapy for analgesic purpose or for lytic lesions at risk of fracture should have been completed two weeks prior to enrolment. Patients must have recovered from radiotherapy toxicities prior to enrolment in the study.

Everolimus may affect the response to vaccinations making it less effective. Live vaccines must be avoided during treatment with everolimus. Examples of live vaccines are: intranasal influenza, measles, mumps, rubella, oral polio, BCG (Bacillus Calmette-Guérin), yellow fever, varicella, and TY21a typhoid vaccines.

Administration of the following treatments is prohibited during the study period:

- Investigational or commercial anticancer agents, such as chemotherapy, immunotherapy, targeted therapy, biological response modifiers, or endocrine therapy other than exemestane (including steroids)
- Hormone replacement therapy, topical estrogens (including any intra-vaginal preparations), megestrol acetate and selective estrogen-receptor modulators (e.g. raloxifene).

Treatment with topical applications (e.g. rash), inhaled sprays (e.g. obstructive airways diseases), eye drops or local injections (e.g. intra-articular) of corticosteroids is allowed. Chronic low dose therapy with systemic corticosteroids, i.e. ≤ 10 mg/day prednisolone equivalent, is also allowed.

Hematopoietic growth factors (e.g. erythropoietin, G-CSF and GM-CSF) are not to be administered prophylactically. Their use must be reserved to cases of Grade 3 or 4 neutropenia and anemia as per the labeling of these agents.

Where possible, it is recommended to avoid drugs or substances known to be inhibitors or inducers of the isoenzyme CYP3A as systemic therapy in association with everolimus as these can alter its metabolism:

- Co-administration of everolimus with strong CYP3A inhibitors (e.g. ketoconazole, itraconazole, ritonavir, clarithromycin and telithromycin), and strong inducers (e.g. rifampin, rifabutin) should be avoided.
- Co-administration of everolimus with moderate CYP3A inhibitors (e.g. erythromycin, fluconazole, calcium channel blockers, benzodiazepines, verapamil, diltiazem, amprenavir, fosamprenavir or aprepitant) and PgP inhibitors should also be used with caution (e.g. increased frequency of safety monitoring).
- Co-administration of everolimus with strong CYP3A4 inducers (e.g. phenytoin, carbamazepin, rifampin, rifabutin, Phenobarbital, St John's wort) should be avoided.
- Sevilla orange, grapefruit and grapefruit juice affect cytochrome P450 and PgP activity and must therefore be avoided during study drug intake.

Clinically relevant inducers, inhibitors and substrates of CYP3A and PgP are listed in [Table 6-8](#) and [Table 6-9](#).

Table 6-8 Clinically relevant drug interactions: inducers, and inhibitors of isoenzyme CYP3A

Inducers

Strong inducers:

avasimibe, carbamazepine, mitotane, phenobarbital, phenytoin, rifabutin, rifampin (rifampicin), St. John's wort

(hypericum perforatum)

Moderate inducers:

bosentan, efavirenz, etravirine, genistein, modafinil, nafcillin, ritonavir, [talviraline], thioridazine, tipranavir

Weak inducers:

amprenavir, aprepitant, armodafinil (R-modafinil), bexarotene, clobazam, danshen, dexamethasone, Echinacea,

garlic (allium sativum), ginkgo (ginkgo biloba), glycyrrhizin, methylprednisolone, nevirapine, oxcarbazepine,

pioglitazone, prednisone, [pleconaril], primidone, raltegravir, rufinamide, sorafenib, telaprevir, terbinafine,

topiramate, [troglitazone] , vinblastine

Inhibitors

Strong inhibitors:

boceprevir, clarithromycin, cobicistat, conivaptan, elvitegravir, indinavir, itraconazole, ketoconazole, lopinavir,

mibefradil, nefazodone, nelfinavir, posaconazole (Krishna et al 2009), ritonavir, saquinavir, telaprevir, telithromycin, tipranavir, troleandomycin, voriconazole

Moderate inhibitors:

Amprenavir, aprepitant, atazanavir, casopitant, cimetidine, ciprofloxacin, cyclosporine, darunavir, diltiazem,

dronedarone, erythromycin, fluconazole, fosamprenavir, grapefruit juice (citrus parasidi fruit juice), imatinib,

schisandra sphenanthera, tofisopam, verapamil

Table 6-9 Clinically relevant drug interactions: substrates, inducers, inhibitors of PgP and PgP/CYP3A dual inhibitors

Substrates
colchicine, digoxin, fexofenadine, indinavir, paclitaxel, talinolol, topotecan, vincristine, everolimus
Inducers
rifampin, St John's wort
PgP Inhibitors and PgP/CYP3A Dual Inhibitors
amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, diltiazem, dronedarone, elacridar, erythromycin, felodipine, fexofenadine, fluvoxamine, ginkgo (ginkgo biloba), indinavir, itraconazole, lopinavir, mibefradil, milk thistle (silybum marianum), nelfinavir, nifedipine, nitrendipine, paroxetine, quercetin, quinidine, ranolazine, rifampin, ritonavir, saquinavir, Schisandra chinensis, St John's wort (hypericum perforatum), talinolol, Telaprevir, telmisartan, ticagrelor, tipranavir, tolvaptan, valsopodar, verapamil
Reference: Internal Clinical Pharmacology Drug-drug interaction (DDI) memo, updated Oct. 2, 2011,29-Oct-2012 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.

6.5 Discontinuation of the study drugs

Study drug interruption refers to a patient stopping either study drug during the course of the study, but then re-starting it at a later time in the study. If either everolimus or exemestane are interrupted for more than 4 weeks, the patient will be permanently discontinued from the study.

If the administration of everolimus must be interrupted because of an unacceptable toxicity, everolimus dosing will be interrupted or modified according to rules described in [Section 6.2.1](#). All study drug interruptions must be recorded on the appropriate Dosage Administration CRF.

A patient who requires everolimus dose interruption (regardless of the reason for the interruption) lasting >28 days (counting from the first day when a dose was missed) must discontinue everolimus.

Study discontinuation refers to a patient's withdrawal from everolimus. The reason for discontinuation from treatment must be recorded on the End of treatment CRF.

Everolimus will be discontinued for any of the following reasons:

- Disease progression
- Consent withdrawal
- Unacceptable adverse events
- Everolimus dose interruption of >4 weeks
- Intercurrent illness that prevent further administration of everolimus treatment
- Need for any other types of anticancer therapy, except for palliative radiotherapy for bone lesions
- General or specific changes in the patient's condition which render the patient unacceptable for further everolimus treatment at the discretion of the investigator

- Death.

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

Patients who discontinue everolimus should be scheduled for an End of Treatment Visit, as soon as possible, after discontinuing everolimus, at which time all of the assessments listed for the End of Treatment Visit will be performed. The date and reason for stopping the study everolimus treatment should be recorded on the CRF.

If everolimus is permanently discontinued, the patient will be considered to have completed study treatment. All patients must have safety evaluations for 30 days (± 2 days) after the last dose of everolimus. Once the last dose of everolimus is taken, no further AEs/SAEs will be collected on this protocol beyond the 30 days follow-up safety interval.

After discontinuation of everolimus, the patient will be treated at the investigator's discretion.

6.6 Patient numbering

Each patient is uniquely identified in the study by a combination of her center number and patient number in the center. The center number is assigned by Novartis to the investigative site. Upon signing the informed consent form, the patient is assigned a patient number by the investigator; patients are numbered consecutively, starting with patient 1. Patient numbers will not be re-used. If the patient fails to be started on treatment for any reason, the reason for not being started on treatment will be entered on the Screening Log.

6.7 Study drug preparation and dispensation

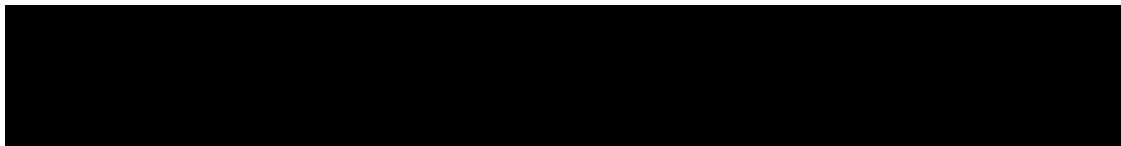
6.7.1 Packaging and labeling

All study medication will be packaged into blister packs. The blisters should be opened only at the time of administration, as the drugs are both hygroscopic and light sensitive. All blisters will conform to all local regulatory requirements.

Everolimus will be supplied to study sites by Novartis as commercial drug re-labeled for clinical trial use. 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.

6.7.2 Drug supply and storage

Everolimus and exemestane tablets including instructions for administration will be dispensed by the pharmacist or other authorized site personnel at the investigator's institution on an outpatient basis.



Study drugs must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated assistants have access. Upon receipt, the study drug should be stored according to the instructions specified on the drug labels. As long as both drugs are supplied by Novartis, they are to be stored below 30°C room temperature in dry and secured space. The storage temperature must be recorded at least 3 times per week in the temperature log.

An authorized person at the investigator's site throughout the entire study must record receipt and dispensing of supplied study drugs. Clinical supplies are to be dispensed only in accordance with the protocol.

In each participating country, everolimus and exemestane will be provided to participating centers by Novartis until everolimus is locally reimbursed or commercialized for this indication or when all patients have been discontinued from investigational treatment due to disease progression, unacceptable toxicity, death, consent withdrawal or any other reason.

In those countries in which patients will be transitioned to locally reimbursed or commercialized drug supplies, Novartis will have a local transition plan in order to ensure that all on-going patients will still have access to the study medication without any delay in their treatment.

6.7.3 Study drug compliance

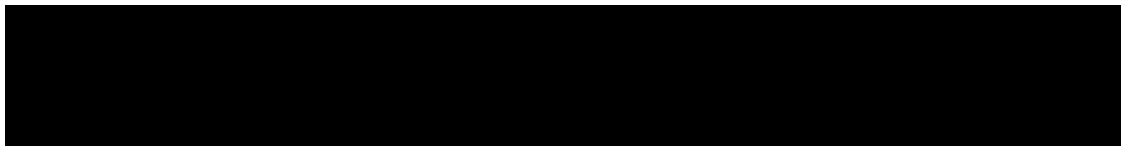
The investigator and/or study personnel will assess compliance at each patient visit. To accurately determine the patient's drug exposure throughout the study, the following information must be reported on the Drug Administration Record CRF for both everolimus and exemestane pages and in the source document:

- Planned dose administration
- Actual total daily dose administered
- Start and end date of drug administration
- Dose change (no or yes)
- Reason for dose change (e.g. adverse event, dosing error, lab test abnormality etc.).

6.7.4 Study drug accountability

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

In those countries in which patients will be transitioned to locally reimbursed or commercialized drug supplies, the investigator will return all used and unused Novartis supplied everolimus and exemestane 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.



6.7.5 Disposal and destruction

The drug supply can be destroyed at the local Novartis facility, Drug Supply group or third party, as appropriate. Destruction at the site is allowed only if permitted by local regulations and authorized by Novartis.

7 Visit schedule and assessments

7.1 Study flow and visits schedule

[Table 7-1](#) lists all study assessments by visit. All data obtained from these assessments must be supported in the patient's source documentation. All assessments will be captured in the CRF, with the only exception of safety laboratory tests and ECG, which will remain only in the patient's source documents.

Tests, procedures and visits should occur on schedule as far as possible.

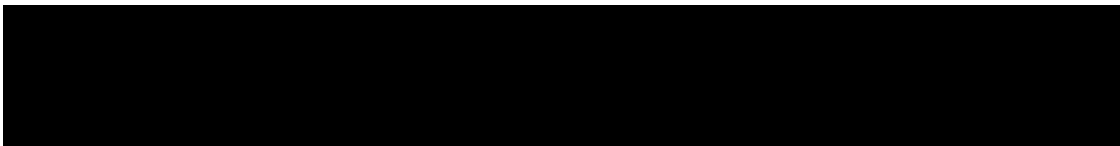
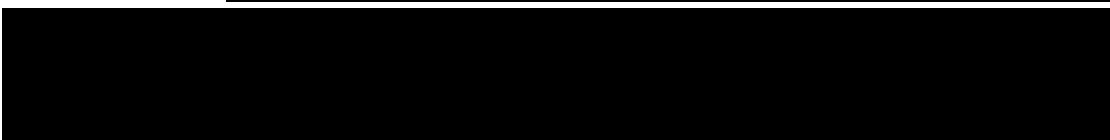
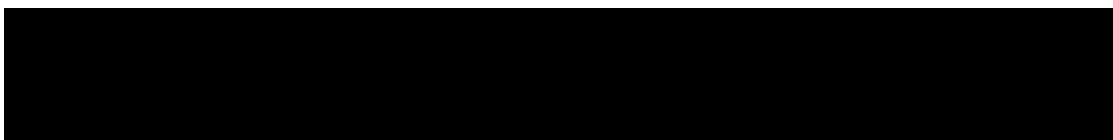


Table 7-1 Schedule of assessments

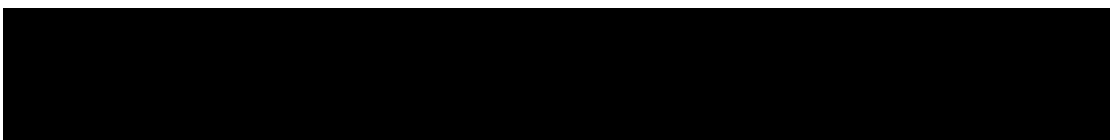
	Screening Day -21 to -1	Baseline Day 1	Week 4 ± 1 week	Week 10 ± 2 weeks	Week 20 ± 2 weeks	Week 30 ± 2 weeks	Week 40 ± 2 weeks	Week 50 ± 2 weeks/ EOT	Following visits (each 10 ± 2 weeks)	EOT	Follow-up EOT + 30 days (± 2 days)
Visit N°	1	2	3	4	5	6	7	8	N	EOT	F-up
Informed consent	X										
Demographics	X										
Eligibility criteria	X	X									
Medical history, current medical conditions	X										
Diagnosis and extent of breast cancer	X										
Prior antineoplastic therapies	X										
Height, weight	X										
Physical examination	X	X	X	X	X	X	X	X	X	X	
Vital signs, ECOG status	X	X	X	X	X	X	X	X	X	X	
Prior medications	X										
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X
Study drugs dispensation		X	X	X	X	X	X	X	X		
CT scan/MRI chest, abdomen,	X			X	X	X	X	X	X	X	



	Screening Day -21 to -1	Baseline Day 1	Week 4 ± 1 week	Week 10 ± 2 weeks	Week 20 ± 2 weeks	Week 30 ± 2 weeks	Week 40 ± 2 weeks	Week 50 ± 2 weeks/ EOT	Following visits (each 10 ± 2 weeks)	EOT	Follow-up EOT + 30 days (± 2 days)
Visit N°	1	2	3	4	5	6	7	8	N	EOT	F-up
pelvis (1)											
Brain CT scan or MRI (2)	X	As clinically indicated									
Bone scan/ X-ray (3)	X	If bone metastases are present at baseline, a bone scan or skeletal survey is required every 10 weeks. If bone metastases are not identified at baseline, bone scans will be performed as clinically indicated									
Bone CT/MRI (3)	X	If bone metastases are present at baseline, a bone scan or skeletal survey is required every 10 weeks. If bone metastases are not identified at baseline, bone CT/MRI will be performed only to confirm potential findings identified by bone scans/X-rays.									
Hematology, chemistry, lipid profile (5)	X	X	X	X	X	X	X	X	X	X	
Hepatitis B viral load and markers	X	Monitor approximately every 3-6 weeks when required.									
Hepatitis C viral load and markers	X	Monitor approximately every 6 weeks when required.									
ECG, coagulation, urinalysis	X	As clinically indicated									
BAL and pulmonary		As clinically indicated									



	Screening Day -21 to -1	Baseline Day 1	Week 4 ± 1 week	Week 10 ± 2 weeks	Week 20 ± 2 weeks	Week 30 ± 2 weeks	Week 40 ± 2 weeks	Week 50 ± 2 weeks/ EOT	Following visits (each 10 ± 2 weeks)	EOT	Follow-up EOT + 30 days (± 2 days)
Visit N°	1	2	3	4	5	6	7	8	N	EOT	F-up
function tests											
Final progression status											X
<p>(1): A RECIST evaluation must be performed and documented in the CRF for CT scans/MRI, including those performed routinely outside the study schedule.</p> <p>(2): A brain CT scan or MRI will be performed at baseline ≤ 21 days prior to the first dose of the study treatment, and as clinically indicated if the patient develops symptoms or signs of CNS involvement.</p> <p>(3): A bone scan or a skeletal survey will be performed at baseline ≤ 21 days prior to the first dose of the treatment. If clinically indicated, any abnormalities (i.e. hotspots) identified on the bone scan/X-rays must be confirmed by CT scan or MRI. Bone lesions (non-target) identified at baseline by CT scan or MRI will be followed using the same method according to radiological assessment schedule. If there are not bone metastases identified at baseline, additional bone scans or skeletal surveys should be performed as clinically indicated until disease progression or discontinuation from study treatment for any other reason. Abnormalities found on subsequent bone scans may also be confirmed by CT scan or MRI.</p> <p>[REDACTED]</p> <p>(5): Safety laboratory tests are performed according to routine clinical practice, and at least for each safety visit. Safety laboratory tests include hematology (complete blood count, white blood count, differential count, red blood cell count, hemoglobin, hematocrit, platelet count), serum chemistry (urea/BUN, uric acid, creatinine, electrolytes, total protein, LDH, total bilirubin, gamma-GT, albumin, alkaline phosphatase, AST and ALT, fasting glucose), and serum fasting lipid profile (total cholesterol and triglycerides).</p>											



7.1.1 Screening period

The baseline visit/Treatment Day 1 will occur no later than 21 days after the screening visit. All assessments requested at the screening visit should be completed before Treatment Day 1.

The following assessments and procedures will be performed at the screening visit or requested at the screening visit to be completed within the screening period:

- Obtain patient's written informed consent form prior to any study-specific assessment
- General demographics including age and gender
- Medical history/current medical conditions (including prior concomitant medications within the last 4 weeks prior to Day 1)
- History and current disease status (including staging, diagnosis information, previous anticancer treatments and sites of disease). The following information must be collected for all previous anticancer therapies: date start, date end, setting (neoadjuvant, adjuvant, metastatic), best response, reason for treatment discontinuation.
- Physical examination, height and weight
- Vital signs including blood pressure and heart rate
- ECOG performance status
- Hepatitis B viral load and markers, hepatitis C viral load (see [Section 6.3.3.1](#) and [Section 6.3.3.2](#)).

The other safety laboratory assessments, including hematology, biochemistry, serum lipid profile, coagulation and urinalysis should be performed locally at the investigator's discretion and are not captured on the CRF. However, laboratory results that are out of range and clinically significant should be captured on the medical history/current medical conditions CRF.

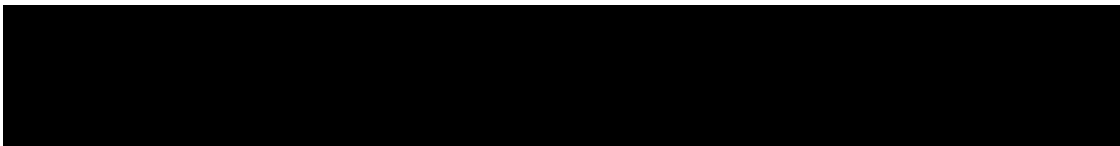
The following radiological tumor assessments should be performed within the 21-day screening period prior to the start of study treatment:

- CT scan/MRI for chest, abdomen, and pelvis. CT scan/MRI with contrast media should be used except for patients who are allergic/sensitive to the radiographic contrast media.
- Brain: CT or MRI if CNS metastases are present
- Bone Scan and CT or X-ray to confirm existing bone lesions (according to local practice), unless performed within 6 weeks prior to the Baseline visit/Treatment Day 1.

Patients eligible to the study with positive HBV-DNA or HBsAg at screening must initiate prophylaxis with appropriate antiviral medication at least one week prior to treatment start (Treatment Day 1).

7.1.1.1 Screening failures

Patient must provide a signed Informed Consent Form (ICF) prior to any study specific screening evaluations. The investigator must review inclusion/exclusion criteria and document the patient's eligibility in the patient record. Patients who do not meet all entry criteria will be considered to be screening failures. The reason for not being started will be entered in the site's screening failure log.



The following data will be collected for all screening failures:

- Date of informed consent signature
- Inclusion/exclusion criteria
- SAE data (where applicable).

7.1.1.2 Enrolment in the study

Enrolment in the study will be confirmed by completion of the Enrolment form on the eCRF.

7.1.2 Treatment period

Patients will start study treatment on Baseline/Treatment Day 1 with everolimus 10 mg daily p.o. (either 2 x 5 mg or 1 x 10 mg tablets) in combination with exemestane 25 mg daily p.o. (25 mg tablets). Dose adjustment (reduction or interruption) will be allowed according to safety findings and dose adjustment guidelines. Study treatment will continue until disease progression, unacceptable toxicity, death, consent withdrawal or any other reason. Further treatment after progression will be at the investigator's discretion.

During the treatment period, visits will be performed at Week 4 (\pm 1 week), and then on weeks 10 (\pm 2 weeks), 20 (\pm 2 weeks), 30 (\pm 2 weeks), 40 (\pm 2 weeks), and Week 50/End of treatment (\pm 2 weeks).

Tumor evaluations through CT scan/MRI will be performed for Screening, at Week 10, Week 20, Week 30, Week 40 and Week 50/EOT visits. All radiological evaluations and laboratory assessments will be performed locally, at the center level. Patients will be followed up for safety for 30 days (\pm 2 days) after the last dose of everolimus. AEs/SAEs with a suspected causality to the study drug must be reported beyond this 30 days safety interval.

7.1.3 Treatment exposure and compliance

Compliance with the study treatments will be assessed by the investigator and/or study personnel at each visit using pill counts and information provided by the patient or caregiver. This information should be captured in the source document at each visit for both drugs (everolimus and exemestane).

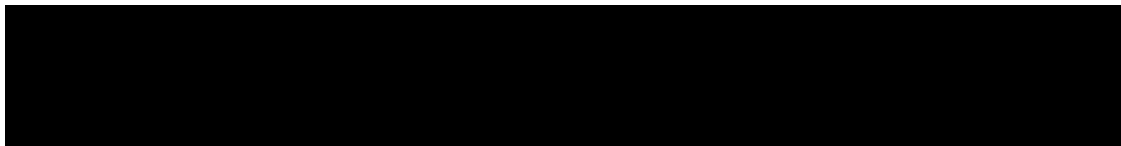
To accurately record the administration of study treatments, the following information must be recorded on the DAR CRF throughout the study:

- Planned dose administration
- Actual total dose administered
- Regimen
- Start/End date of drug administration
- Dose change or delay and reason for modification.

7.1.4 Discontinuation of the study drugs

Study discontinuation refers to a patient's withdrawal from everolimus. The reason for discontinuation from treatment must be recorded on the End of treatment CRF.

Everolimus will be discontinued for any of the following reasons:



- Disease progression
- Consent withdrawal
- Unacceptable adverse events
- Everolimus dose interruption of > 4 weeks
- Intercurrent illness that prevent further administration of everolimus treatment
- Need for any other types of anticancer therapy, except for palliative radiotherapy for bone lesions
- General or specific changes in the patient's condition which render the patient unacceptable for further everolimus treatment at the discretion of the investigator
- Death.

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

If everolimus or exemestane is permanently discontinued, the patient will be considered to have completed study treatment. All patients must have safety evaluations for 30 days (\pm 2 days) after the last dose of everolimus.

Patients who discontinue everolimus should be scheduled for an End of Treatment Visit, as soon as possible, after discontinuing everolimus, at which time all of the assessments listed for the End of Treatment Visit will be performed. The date and reason for stopping the study everolimus treatment should be recorded on the CRF.

Once the last dose of everolimus is taken, no further AEs/SAEs will be collected on this protocol beyond the 30 day follow-up safety interval.

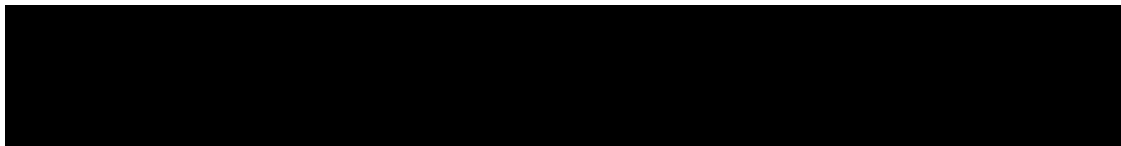
7.1.5 End of the study

In each participating country, the study will end when everolimus is locally reimbursed or commercialized for this indication or when all patients have been discontinued from investigational treatment due to disease progression, unacceptable toxicity, death, consent withdrawal or any other reason.

Patients will be followed up for safety purposes for 30 days (\pm 2 days) after the last dose of study drug.

At the end of the study, the progression status of all participating patients will be updated and recorded in the CRF.

In those countries in which patients will be transitioned to locally reimbursed or commercialized drug supplies, Novartis will have a local transition plan in order to ensure that all on-going patients will still have access to the study medication without any delay in their treatment.



7.2 Safety and tolerability assessments

Safety and tolerability will be monitored by assessing all adverse events, including serious adverse events, the regular monitoring of hematology, blood chemistry, lipid profile, hepatitis B and C markers, vital signs, ECOG performance status and physical examination. Adverse events will be evaluated continuously throughout the study period. The other assessments should be performed based on the scheduled day of assessment (Refer to [Table 7-1](#)).

Toxicity will be assessed using the NCI-CTCAE Common Terminology Criteria for Adverse Events, version 4.03 (CTCAEv4.03). AE/SAE collection and reporting is detailed in [Section 8](#).

7.2.1 Physical examination, height and weight

Physical examination must comprise a total body examination (general appearance, skin, neck, including thyroid, eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes and extremities).

Physical examination will be performed at screening, on treatment Day 1 (prior to administration of the study drug, unless physical examination in screening was done less than 7 days before Day 1), as well as at Week 4, Week 10, Week 20, Week 30, Week 40, and Week 50 or End of treatment visit.

Information for all physical examinations must be included in the source documentation at the study site. Significant findings that are present prior to the start of study drug must be documented on the Medical History / Current medical Conditions CRF. Significant findings made after the start of study drug, which meet the definition of an adverse event, must be recorded on the Adverse Event CRF.

Height and weight will be measured at the screening visit.

7.2.2 Vital signs

Vital signs will be recorded on the appropriate CRF pages at each visit. Heart rate and blood pressure will be measured according to normal medical practice.

The particular clinical findings seen before taking study drug must be documented in the Relevant Medical History CRF. The findings that are compatible with adverse events after taking study drug must be documented in the Adverse Event CRF.

7.2.3 Laboratory evaluations

Laboratory evaluations should be performed locally at every protocol required visit ([Table 7-1](#)) or as frequently as clinically indicated. The patient should be in a fasting state for 12 hours at the time of blood sampling.

All scheduled laboratory evaluations must be obtained according to the specified visit window in [Table 7.1](#), whether or not study treatment is administered. Screening examinations performed ≤ 7 days of the first dose of study treatment do not need to be repeated on Day 1.

Laboratory values will be recorded in the patient's source documents and must not be documented in the CRF. However, any particular clinically significant findings seen before taking study drugs must be documented in the Relevant Medical History/Current Medical Conditions CRF.

Abnormal laboratory parameters that are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy (e.g. hematologic abnormality that requires transfusion or hematological stem cell support), or require changes in study treatment, or require changes in study drug(s) constitute adverse events in their own right and must 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 AE (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 and is still, by definition, an adverse event.

7.2.3.1 Hematology

Hematology tests include a complete blood count (CBC): a total white blood cell count (WBC), differential count, red blood cell count (RBC), hemoglobin (Hb), hematocrit and a platelet count.

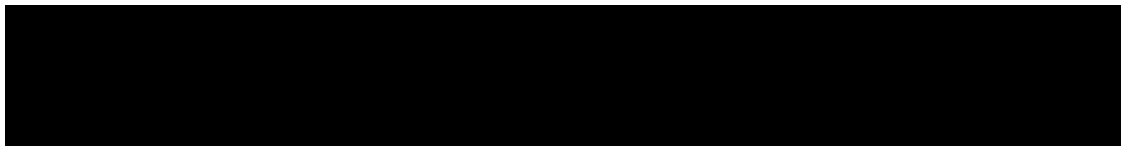
Hematological tests will be performed at screening, on Day 1 (repeated prior to administration of the study drug, if performed more than 7 days prior to Day 1), Week 4, Week 10, Week 20, Week 30, Week 40, and Week 50 or End of treatment visit.

In the event of Grade 2, Grade 3 or Grade 4 hematological toxicities that require study drug dose modifications or interruptions, hematological tests should be repeated weekly until recovery to the baseline value or Grade 1.

7.2.3.2 Blood chemistry

Serum chemistry tests should include urea/BUN, creatinine, LDH, total protein, electrolytes (sodium, potassium and calcium), total bilirubin, GGT, albumin, alkaline phosphatase, AST/SGOT, ALT/SGPT, uric acid and fasting glucose. Patients should fast for 12 hours prior to blood sampling.

Serum chemistry should be performed at screening, on Day 1 (repeated prior to administration of the study drug, if performed more than 7 days prior to Day 1), Week 4, Week 10, Week 20, Week 30, Week 40, and Week 50 or End of treatment visit.



In the event of Grade 2, Grade 3 or Grade 4 non-hematological toxicities that require study drug dose modifications or interruptions, biochemistry tests should be repeated weekly until recovery to the baseline value or Grade 1.

7.2.3.3 Serum lipid profile

A serum lipid profile assessment should be performed at screening, on Day 1 (repeated prior to administration of the study drug, if performed more than 7 days prior to Day 1), Week 4, Week 10, Week 20, Week 30, Week 40, and Week 50 or End of treatment visit. Patients should fast for 12 hours prior to blood sampling.

In the event of Grade 2, Grade 3 or Grade 4 toxicities serum lipid tests should be repeated weekly until recovery to the baseline value or Grade 1.

7.2.3.4 Other laboratory tests

Coagulation assessments such as international normalized ratio (INR) or activated partial thromboplastin time (aPTT) should be performed at screening/baseline and repeated if clinically indicated.

A urinalysis assessment according to local routine will be performed only at screening/baseline.

7.2.3.5 Hepatitis B viral load and markers, hepatitis C viral load

HBV-DNA, HBsAg, HBsAb, HBcAb and HCV-RNA will be measured at screening. Significant findings must be recorded as Relevant Medical History / Current Medical Conditions.

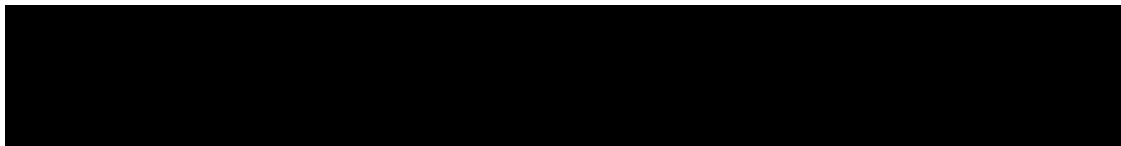
These assessments will be repeated every 3-6 weeks during the treatment period when required. Results will be recorded in the CRF. Hepatitis reactivation or flare will be managed according to guidelines presented in [Section 6.3.3](#), and will be recorded on the Adverse Events CRF.

7.2.3.6 ECG

A standard 12-lead ECG should be performed at screening/baseline. Tracings must be dated and signed by the investigator (or his/her designee) and filed with the patient's source documentation. Significant findings must be recorded as Relevant Medical History / Current Medical Conditions (if present before treatment). ECG may be repeated at the discretion of the investigator at any time during the study and as clinically indicated; any clinically relevant findings should be recorded on the Adverse Events CRF.

7.2.4 Pulmonary function tests (PFTs)

Pneumonitis is a known adverse event associated with the use of rapamycin and its analogues. Bronchoscopy with biopsy, broncho-alveolar lavage (BAL) and pulmonary function tests (PFTs) should be performed during the trial if clinically indicated and if warranted to exclude or manage non-infection pneumonitis. Significant findings must be recorded on the Adverse Events CRF.



7.3 Efficacy assessments

Tumor assessments are summarized in [Table 7-2](#).

Tumor response will be evaluated according to RECIST (Version 1.1) (See [Appendix 1](#)).

All patients should have at least one lesion that can be accurately measured in at least one dimension ≥ 20 mm with conventional imaging techniques or ≥ 10 mm with spiral CT as per RECIST 1.1 criteria, or in the absence of measurable disease have at least one lytic or mixed (lytic + blastic) bone lesion.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline for each study tumor assessment after start of study treatment.

For patients with measurable disease at baseline, tumor progression will be evaluated at each assessment according to the RECIST 1.1 criteria (see [Appendix 1](#) for details). All patients being discontinued from the study for disease progression must have their progression documented using the RECIST 1.1 criteria.

A CT scan/MRI of the chest, abdomen and pelvis will be performed at screening and repeated at Week 10, Week 20, Week 30, Week 40, and Week 50/EOT. CT scan with contrast media should be used except for patients who are allergic/sensitive to the radiographic contrast media. Response will be assessed by local radiology review. The decision regarding patient management will remain with the local investigator. The same radiologist/physician should perform the evaluation for the entire duration of the study.

Bone scans/skeletal survey by X-ray must be performed at baseline within 6 weeks before enrolment. Positive areas on bone scans/X-ray must be assessed by MRI or CT scan with bone windows, prior to enrolment and should continue to be assessed using the same modality (MRI or CT scan) at Weeks 10, 20, 30, 40, and Week 50 or End of Treatment. Additional bone scans/X-ray should be performed if clinically indicated. Abnormalities found on subsequent bone scans/X-ray must be confirmed by MRI or CT scan.

In the absence of measurable disease at baseline, the following will be considered progression among patients with lytic or mixed (lytic + blastic) bone lesions:

- Appearance of one or more new lytic lesions in bone
- Appearance of one or more new lesions outside of bone
- Unequivocal progression of existing bone lesions.

Note: Pathologic fracture, new compression fracture, or complications of bone metastases will not be considered as evidence of disease progression, unless one of the above-mentioned criteria is fulfilled.

Table 7-2 Imaging collection plan

Procedure	Screening: Day -21 to -1	Treatment phase	End of treatment
CT or MRI (chest, abdomen, pelvis)	Mandated	Every 10 weeks from treatment start until progression or end of study	Mandated
CT or MRI for any site of disease	Mandated if suspected lesion at screening	If lesion at screening: every 10 weeks from treatment start until progression or end of study	Mandated if lesion at screening
Brain CT or MRI	Mandated at screening only if existing or suspected brain metastases	As clinically indicated	As clinically indicated
Bone scan/X-ray	Mandated	As clinically indicated	As clinically indicated
Bone CT or MRI	Mandated at screening only if skeletal abnormalities identified by bone scan/X-ray at screening	If bone lesion at screening: every 10 weeks from treatment start until progression or end of study	Mandated only if bone lesion at screening
Skin color photography	Mandated if skin lesions at screening	If skin lesions at screening: every 10 weeks from treatment start until progression or end of study	Mandated if skin lesions at screening

7.4 ECOG Performance Status

The performance status will be scored using the ECOG Performance Status Scale (Oken, 1982), as described in [Table 7-3](#).

ECOG Performance Status will be assessed and recorded at screening, on Day 1, and at each follow-up visit. Assessment of ECOG Performance Status should be performed on the scheduled day, even if study medication is being held. Time to deterioration of ECOG performance status, from baseline will be assessed

Table 7-3 ECOG Performance Status

Score	Performance status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

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 drug(s).

Except for screening failures, 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/Current Medical Conditions CRF. Adverse event monitoring should be continued for at least 30 days (\pm 2 days) following the last dose of everolimus. Adverse events (including laboratory 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 through 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 during the screening process or between visits, or through physical examination, laboratory test, or other assessments.

Progression of malignancy (including fatal outcomes), if documented by use of RECIST (version 1.1) will 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 study drugs.

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 or Ongoing at End of Study)
3. Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes)
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. Whether it is serious, where a serious adverse event (SAE) is defined as in [Section 8.2.1](#)

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.

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

The adverse events of special interest associated with mTOR inhibition include:

- Stomatitis
- Non-infectious pneumonitis
- Infections
- Hyperglycemia
- Hyperlipidemia
- Hypophosphatemia
- Skin Rash
- Hypersensitivity
- Wound healing complications
- Increased creatinine/renal failure/proteinuria
- Cardiac failure

8.2 Serious adverse events

8.2.1 Definitions

A serious adverse event (SAE) is defined as one which:

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- 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: 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, if any
 - 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: 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

Every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until 30 days after the patient has stopped study treatment/participation must be reported to Novartis within 24 hours of learning of its occurrence.

Any SAE experienced after this 30-day period should only be reported to Novartis if the investigator suspects a causal relationship to the study drug.

Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all 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 drug, complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours to the oncology Novartis Drug Safety and Epidemiology (DS&E) department.

The telephone and telefax number of the contact persons in the local department of Drug Safety and Epidemiology (DS&E), specific to the site, are listed in the investigator folder provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site.

Follow-up information is sent to the same contact(s) to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the patient continued the study or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the Novartis study drug, an oncology Novartis Drug Safety and Epidemiology (DS&E) 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 European Directive 2001/20/EC or as per national regulatory requirements in participating countries.

8.3 Emergency unblinding of treatment assignment

Not applicable, this is an open label study.

8.4 Pregnancies

Not applicable; this study will enroll post-menopausal women only.

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 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.

9 Data collection and management

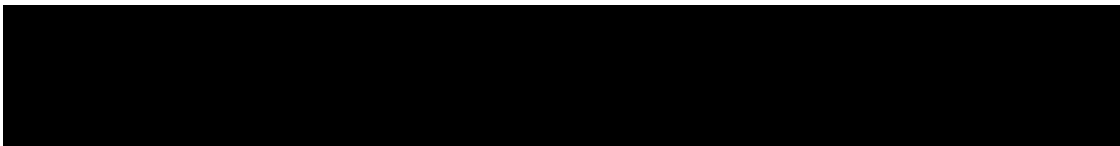
9.1 Data confidentiality

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

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

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the eCRF 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 eCRFs are performed according to the study-specific monitoring plan.

9.3 Data collection

Novartis will supply the investigator site with an Electronic Data Capture (EDC) system that has been fully validated and conforms to 21 CFR Part 11 requirements.

Novartis (or designated CRO) will train designated investigator site staff on the EDC system. Investigator site staff will not be given access to the EDC system until they have been trained.

The investigator will notify Novartis and the CRO of any changes in study personnel responsible for entering study related data into the EDC system. Once notified, Novartis (or designated CRO) will ensure that the new site personnel are adequately trained, understand the study protocol requirements and can properly use the EDC system.

Designated investigator staff will enter the data required by the protocol into the eCRFs through the EDC system. Automatic validation programs check for data discrepancies in the eCRFs and, by generating appropriate error messages, allow modification or verification of the entered data by the investigator staff before transfer to Novartis via a secure Virtual Private Network. If applicable, the investigator must certify that the data are complete and accurate by signing a memo prior to database lock.

The principal investigator is responsible for assuring that the data entered into the eCRF is complete, accurate, and that entries and updates are performed in a timely manner.

After database lock, the investigator will receive a CD-ROM or paper copies of the patient data for archiving at the investigational site.

9.4 Database management and quality control

Data recorded on the eCRFs will be reviewed by a designated CRO staff for completeness and accuracy following their own internal standard operating procedures that have been reviewed and approved by Novartis.

Site personnel will be instructed to make any required corrections or additions. Obvious errors are corrected by CRO Data Management staff. Queries are sent to the investigational site using an electronic data query system. The designated investigator site staff is required to respond to the query and make any necessary changes to the data within a reasonable timeframe. If the electronic query system is not used, a paper Data Query Form will be faxed to the site. Site personnel will complete and sign the faxed copy. This copy will then be faxed back to the CRO Data Management staff that will make the correction to the database. The signed copy of the Data Query Form is kept at the investigator site.

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

Samples and/or data may be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

At the conclusion of the study, the occurrence of any emergency code breaks will be determined after return of all code break reports and unused drug supplies to Novartis (or designated CRO). The occurrence of any protocol violations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, the database will be locked and made available for data analysis. Any changes to the database after that time can only be made by joint written agreement between the Global Head of Biostatistics and Statistical Reporting and the Global Therapeutic Area Head.

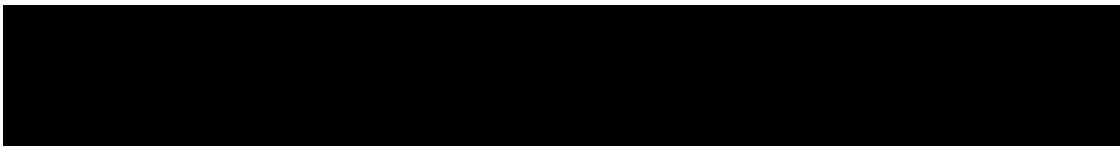
10 Statistical methods and data analysis

The study is designed as an open-label, single-arm, phase IIIB trial to assess the safety, tolerability and efficacy of everolimus plus exemestane in postmenopausal women with hormone receptor positive breast cancer progressing following prior therapy with non-steroidal aromatase inhibitors.

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

10.1 Analysis sets

The Full Analysis Set (FAS) consists of all patients to whom treatment was assigned and who received at least one dose of study drug.



The Per-protocol Set (PP) consists of a subset of patients of the FAS who did not show major deviations from the protocol procedures that may have an impact on the study outcome. Criteria that are assumed to have such an impact will be defined in the Protocol Deviations Module of the Validation and Planning (VAP) documentation, and assessed before database lock during the blinded review meeting.

The Safety Set consists of all patients who received at least one dose of study drug and had at least one post-baseline safety assessment. The statement that a patient had no adverse events (on the Adverse Event CRF) constitutes a safety assessment. Patients who have received at least one dose of study drug but who have no post-treatment safety data of any kind would be excluded from the safety population.

10.2 General statistical methods

The data will be summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, and safety observations and measurements. Primary efficacy and safety/tolerability analysis will be conducted at 15 months of median follow up time, i.e. at approximately two times the median PFS reported in the BOLERO-2 study (Baselga et al. 2012; Yardley D. et al. 2014). Categorical variables will be summarized by absolute and relative frequencies. Continuous variables will be summarized by descriptive statistics (number of valid and missing observations, mean, standard deviation, median, minimum, and maximum).

Time to event data including rates of affected patients will be assessed using the Kaplan-Meier method. Two-sided 95% confidence intervals will be provided for the main statistical estimators.

10.3 Patient demographics and baseline characteristics

Demographic and other baseline characteristics will be summarized for the Full Analysis Set (FAS). Baseline characteristics include prior medication, past/current medical conditions and disease history.

Medical history will be coded using MedDRA and will be presented by MedDRA system organ class, preferred term and treatment group. Separate tables will be provided for past medical conditions and current medical conditions. Prior medications and significant non-drug therapies will be coded according to the WHO Drug Reference List, and summarized by ATC class and preferred term using frequency distributions.

10.4 Treatments (study drugs, concomitant therapies)

Duration (days) of drug exposure will be summarized using descriptive statistics separately for everolimus and exemestane.

Duration of drug exposure will be calculated as the difference between the last and first day of drug application +1. Dosage averages will be calculated including and excluding zero doses for periods of temporary interruption of treatment, regardless of whether this was due to safety/tolerability reasons or patients' non-compliance. Average daily dose levels will be summarized descriptively. Frequencies of the number of patients with any dose reduction (including temporary dose interruption) as well as the number of dose reductions by reason will be given. These analyses will be performed on the Safety Set.

Concomitant medications and significant non-drug therapies prior to and after the start of the study drug will be coded according to the WHO Drug Reference List, and summarized by ATC class and preferred term using frequency distributions.

10.5 Primary objective

The primary objective is to evaluate the safety and tolerability profile of everolimus in post-menopausal women with ER positive, HER2 negative locally advanced or metastatic breast cancer after documented recurrence or progression following a non-steroidal aromatase inhibitor therapy in emergent growth markets (EGM).

The assessment of safety and tolerability will be based mainly on the frequency of adverse events, including the laboratory values that qualify as adverse events. Other safety data (e.g. vital signs, and special tests) will be considered as appropriate. The analysis will be descriptive. For all safety/tolerability analyses, the safety set will be used.

Data collected by AE CRFs will be coded using the MedDRA dictionary. The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by MedDRA system organ class and preferred term using frequency distributions. Additionally, AE will be summarized by maximum severity (based on CTCAE grades), and for AE with suspected drug relation, serious AE (SAE), and AE leading to permanent discontinuation of study drug. All information pertaining to AE noted during the study will be listed by patient, detailing the verbatim term given by the investigator, MedDRA preferred term and system organ class, start/end dates, severity, seriousness, relationship to study drug and action taken.

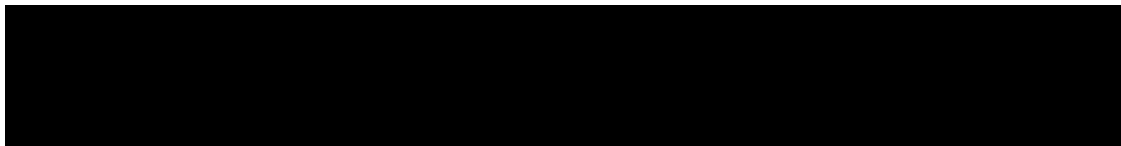
The AE onset will also be shown relative (in number of days) to the date of initial dose. AE starting more than 30 days after discontinuation of study drug will not be considered as treatment-emergent and will not be included in AE summary tables but listed only.

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

10.6 Secondary objectives

10.6.1 Efficacy endpoints

Efficacy endpoints will be analyzed on the Full Analysis Set (primary analysis) and on the Per Protocol Set (supportive analysis).



Efficacy endpoints based on radiological assessments of tumor burden will be derived using local radiologist's/ investigator's assessment. If a patient has not had an event before exiting the study, his or her data will be censored at the date of last adequate tumor assessment.

10.6.1.1 Overall response rate

The Overall response rate (ORR) will be provided over the study period. The ORR is the proportion of patients with a best overall response of confirmed complete (CR) or partial (PR) response at those time points. The best overall response for each patient is determined from the sequence of investigator overall lesion responses according to RECIST 1.1. To be assigned a best overall response of CR at least two determinations of CR at least 4 weeks apart before progression are required. To be assigned a best overall response of PR at least two determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR) are required.

The ORR (best overall response of CR or PR) as well as individual response categories (CR, PR, SD, PD or unknown) measured at approximately week 20 and week 50 will be summarized using frequency tables together with their associated two-sided exact 95% confidence intervals (Clopper-Pearson method).

10.6.1.2 Clinical benefit rate

The clinical benefit rate (CBR) will be provided over the study period. CBR rate is defined as the proportion of patients with best overall response of complete response (CR), partial response (PR) or stable disease (SD), with duration of 24 weeks or longer, according to RECIST 1.1. The best overall response for each patient is determined from the sequence of investigator overall lesion responses according to RECIST 1.1. To be assigned a best overall response of CR or PR, two determinations of CR at least 4 weeks apart before progression are required.

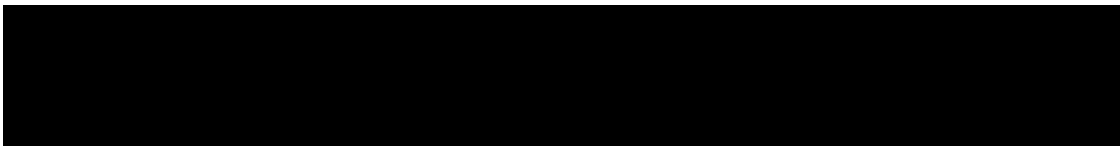
The duration of best overall response is assessed as such: the start date is the date of first documented response (CR or PR) and the end date is the date of event defined as first documented progression disease or death due to underlying cancer.

The CBR measured at approximately week 20 and week 50 will be summarized using frequency tables together with its associated two-sided exact 95% confidence intervals (Clopper-Pearson method).

10.6.1.3 Progression-free survival

Progression-free survival (PFS) is the time from date of 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.

Disease progression will be assessed using the local (treating center's radiologist's) investigator's tumor assessment. PFS will be summarized using the Kaplan-Meier method. Percentiles (25%, median, 75%) of the event time distribution will be presented along with their two-sided 95% confidence interval. The Kaplan-Meier curve will be displayed graphically.



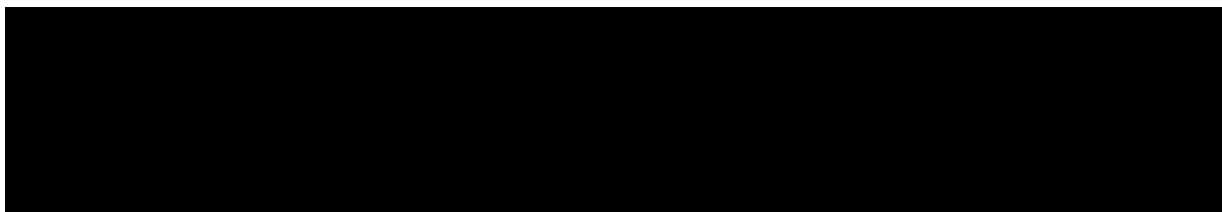
10.6.1.4 Handling of missing data

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 (see Post-text supplement 1). 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. Patients with a best overall response assessment of unknown (UNK) will not be regarded as 'responders' but will be included in the denominator for the calculation of the ORR for the FAS.

10.6.2 Other endpoints

10.6.2.1 ECOG Performance Status

The ECOG Performance Status will be summarized using frequency distributions by visit. Shifts from baseline value to worst post-baseline value will be summarized using frequency distributions.



10.7 Sample size calculation

No hypothesis testing will be performed in this study, which is descriptive in purpose.

The proposed sample size is up to 400 patients. The study recruitment will be globally competitive and end by October 31st 2014 at latest.

The actual sample size may differ from this plan.

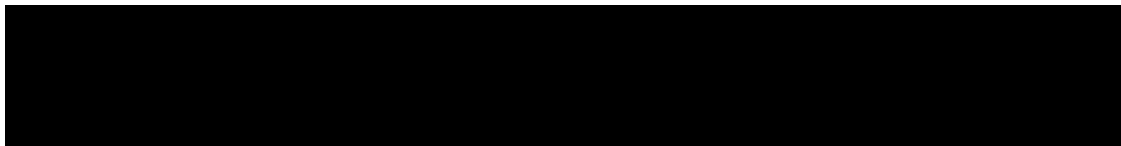
11 Ethical considerations and administrative procedures

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, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents. The date when a subject's Informed Consent was actually obtained will be captured in their eCRFs.

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.

11.4 Discontinuation of the study

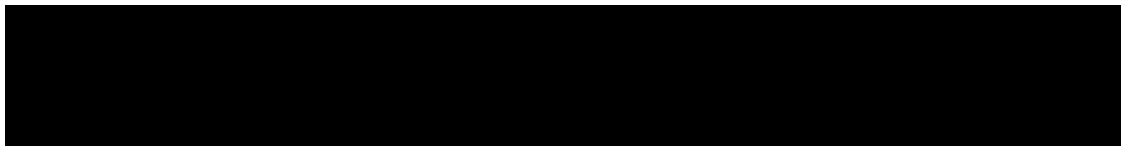
Novartis reserves the right to discontinue this study under the conditions specified in the clinical trial agreement. Specific conditions for terminating the study are outlined in [Section 4.3](#).

11.5 Publication of study protocol and results

Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this study will be either submitted for publication and/or posted in a publicly accessible database of clinical study results.

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 enrolment 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.

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 trial 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/REB at/of the study site should be informed according to local regulations, but not later than 10 working days.

13 References (available upon request)

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14 Appendices

14.1 Appendix 1: Guidelines for response, duration of overall response, TTF, TTP, progression-free survival and overall survival (based on RECIST 1.1)

Harmonization of efficacy analysis of solid tumor studies RECIST version 1.1.

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

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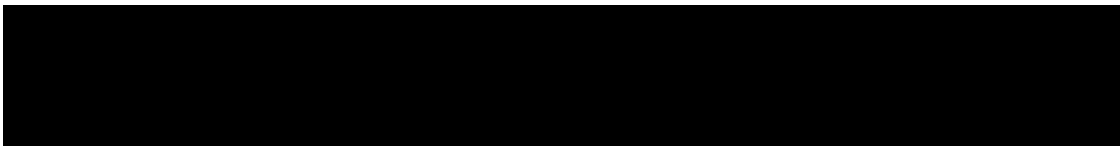
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Glossary

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
LPLV	Last patient last visit
MRI	Magnetic resonance imaging
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 14.1.16 are based on the RECIST 1.1 criteria but also give more detailed instructions and rules for determination of best response. [Section 14.1.17](#) 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 14.1.27](#) 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

14.1.3.1 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 14.1.25](#).

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.

14.1.4 Eligibility based on measurable disease

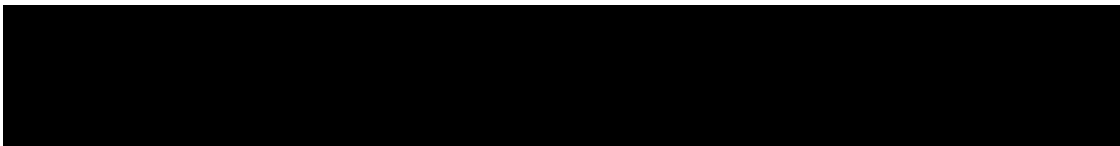
If no measurable lesions are identified at baseline, the patient may be allowed to enter the study in some situations (e.g. in Phase III studies where PFS is the primary endpoint).

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 14.1.25](#).

14.1.5 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 followup.

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.

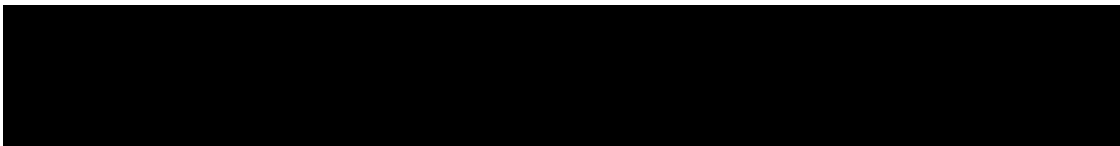
14.1.6 Baseline documentation of target and non-target lesions

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 14.1.3.1](#).
- **Nodal target:** See [Section 14.1.3.1](#).



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 e-CRF.

14.1.7 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.

14.1.8 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.

14.1.9 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.

14.1.10 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.

14.1.11 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 14.1.5 .	

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.

14.1.12 Determination of non-target lesion response

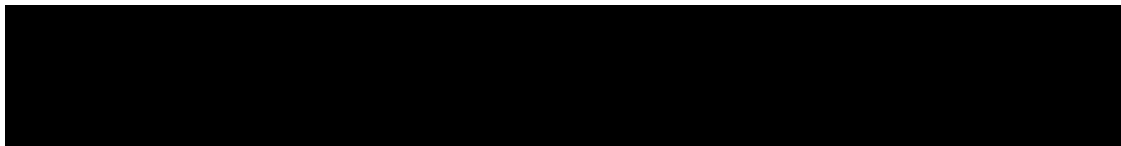
Table 14-2 Response criteria for non-target lesions

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)
Partial Response (PR):	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 14.1.11](#) for assigning PD following a CR for the non-target lesion response in the presence of non-target lesions nodal lesions should be applied.

14.1.13 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 14.1.14](#)).
- 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 14.1.5](#).

14.1.14 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 14.1.7](#).

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.

14.1.15 Efficacy definitions

The following definitions primarily relate to patients who have measurable disease at baseline.

[Section 14.1.25](#) outlines the special considerations that need to be given to patients with no measurable disease at baseline in order to apply the same concepts.

14.1.16 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

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 ($\geq 30\%$ reduction of tumor burden compared to baseline) at one assessment, followed by a $< 30\%$ reduction from baseline at the next assessment (but not $\geq 20\%$ 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 \pm 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).

14.1.17 Time to event variables

14.1.18 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.

14.1.19 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.

14.1.20 Time to progression

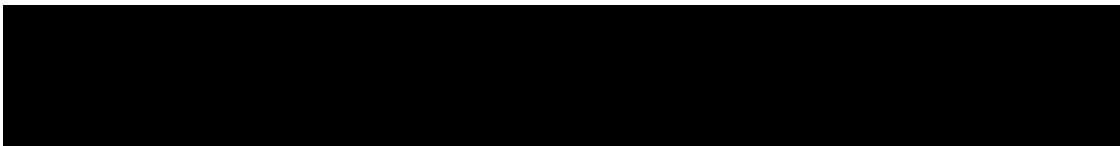
Some studies might consider only death related to underlying cancer as an event which indicates progression. In this case the variable “Time to progression” might be used. TTP is defined as PFS except for death unrelated to underlying cancer.

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.

14.1.21 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.



14.1.22 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 rate

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.

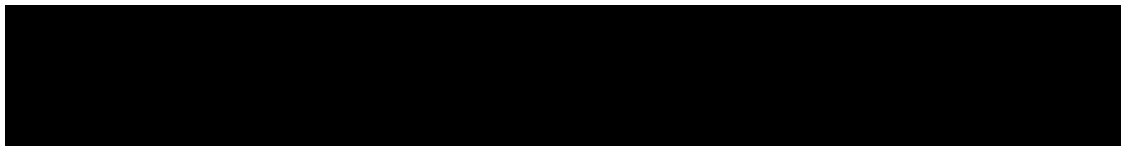
The following two durations might be calculated in addition for a large Phase III study in which a reasonable number of responders is seen.

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.

14.1.23 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 14.4.22. 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.

14.1.24 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

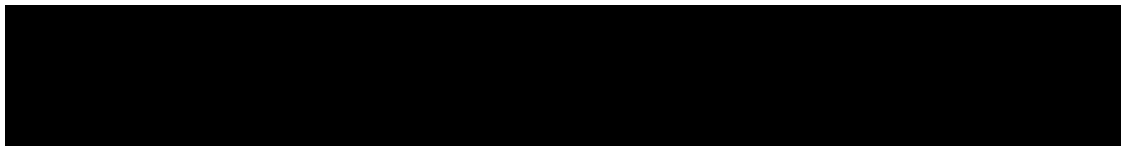
For all “time to event” variables, other than duration of response, the randomization/ date of treatment start will be used as the start date.

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 postbaseline 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 14.1.25](#)).

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.

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

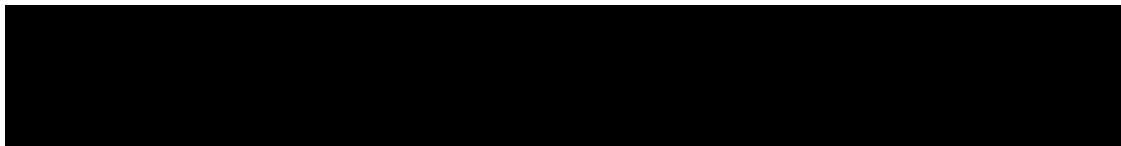
It is possible that patients with only non-measurable disease present at baseline are entered into the study, either because of a protocol violation or by design (e.g. in Phase III studies with PFS as the primary endpoint). In such cases the handling of the response data requires special consideration 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 14.1.7 .		

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 nonmeasurable disease.

14.1.26 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 14.1.24](#), 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:

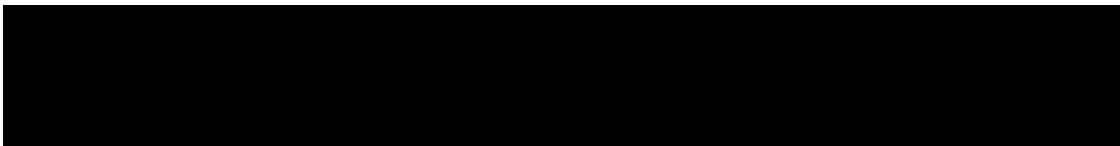


Table 14-5 Options for event dates used in PFS, TTP, duration of response

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 14.1.24](#)
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.

14.1.27 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).

14.1.28 Study/project specific decisions

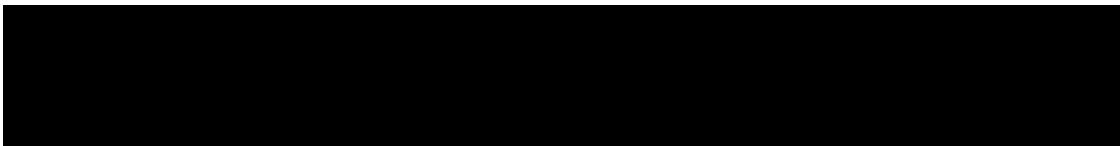
For each study (or project) various issues need to be addressed and specified in the protocol or RAP documentation. Any deviations from protocol must be discussed and defined at the latest in the RAP documentation.

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).

14.1.29 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)

14.1.30 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

14.1.31 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.

14.1.32 Programming rules

The following should be used for programming of efficacy results:

14.1.33 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.

14.1.34 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 14.1.24](#)). 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.

14.1.35 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.

14.1.36 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)’.

14.1.37 Study/project specific programming

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

14.1.38 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 14.1.24](#). 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 anticancer 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.

14.1.39 References (available upon request)

Dent S, Zee (2001) application of a new multinomial phase II stopping rule using response and early progression, *J Clin Oncol*; 19: 785-791

Eisenhauer E, et al (2009) New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). *European Journal of Cancer*, Vol.45: 228-47

Ellis S, et al (2008) Analysis of duration of response in oncology trials. *Contemp Clin Trials* 2008; 29: 456-465

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Therasse P, Arbuck S, Eisenhauer E, et al (2000) New Guidelines to Evaluate the Response to Treatment in Solid Tumors, *Journal of National Cancer Institute*, Vol. 92; 205-16