NOVARTIS

Oncology Clinical Development

RAD001 (everolimus)

Clinical Trial Protocol CRAD001Y2201 (BOLERO-6) / NCT01783444

A three-arm, randomized, open label, phase II study of everolimus in combination with exemestane versus everolimus alone versus capecitabine in the treatment of postmenopausal women with estrogen receptor positive, locally advanced, recurrent, or metastatic breast cancer after recurrence or progression on prior letrozole or anastrozole

Authors [redacted]

Document type	Amended Protocol Version
EUDRACT number	2012-003757-28
Version number	03 (Clean)
Development phase	II
Document status	Final
Release date	18-Apr-2017

[redacted]

Table of contents

[redacted]

[redacted]

[redacted]

[redacted]

List of appendices

List of figures

List of tables

[redacted]

List of abbreviations

Ab	Antibodies
(e)CRF	(electronic) Case Report / Record Form
(eIF) 4E-BP1	eukaryotic translation initiation factor (eIF) 4E-binding proteins 1
(s)VEGF(R)	(soluble) Vascular Endothelial Growth Factor (Receptor)
ABC	Locally Advanced, recurrent or metastatic Breast Cancer: Advanced Breast Cancer
ADR	Adverse Drug Reaction
AE	Adverse Event
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
ALT	alanine aminotransferase/glutamic pyruvic transaminase/GPT
ANC	Absolute Neutrophil Count
AS(A)T	Aspartate Aminotransferase / Glutamic Oxaloacetic Transaminase / sGOT
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
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
BAP	Bone Alkaline Phosphatase
BC	Breast Cancer
bFGF	Basic Fibroblast Growth Factor
BP	Blood Pressure
bpm	beats per minute
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CBR	Clinical Benefit Rate
CFR	Code of Federal Regulation
CI	Confidence Interval
CL/F	Oral Clearance
C_{max}	Maximum blood concentration
CMC	Chemistry / Manufacturing / Controls
C_{min}	Minimum blood concentration
CNS	Central Nervous System
CPK	Creatine Phosphokinase
CPO	Country Pharma Organization
CR	Complete Response
CRD	Clinical Research and Development
CRF	Case Report/Record Form
CRO	Contract Research Organization
CSR	Clinical Study Report
CT	Computed Tomography
CTA	Clinical Trials Application

[redacted]

CTC	Common Terminology Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CTX	C-terminal cross linking telopeptide of type I collagen
CV	Coefficient of Variation
CYP	Cytochrome P450
CYP3A4	Cytochrome P450 3A4 isoenzyme
DCR	Disease Control Rate
DDI	Drug-Drug Interaction
DLCO	Diffusing Capacity for Carbon Monoxide
DNA	Deoxyribonucleic Acid
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
EDTA	ethylenediaminetetraacetic acid
EGFR	Epidermal Growth Factor Receptor
ELISA	Enzyme Linked ImmunoSorbent Assay
EMA	European Medicines Agency
EORTC	European Organization for Research and Treatment of Cancer
EOT	End Of Treatment
ER	Estrogen Receptor
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration (USA)
FEV1	Forced Expiratory Volume in one second
FKBP12	FK506-binding protein
GCP	Good Clinical Practice
GGT	Gamma-Glutamyltransferase
GI	Gastrointestinal
GM-CSF	Granulocyte Macrophage Colony Stimulating Factor
GTP	Guanosine Triphosphate
HBcAb	hepatitis B core antibodies
HBs Ab	hepatitis B surface antibodies
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HBV-DNA	Hepatitis B virus deoxyribonucleic acid
HCV	hepatitis C virus
HDL	High-Density Lipoprotein
Hep B	Hepatitis B
Hep C	Hepatitis C
HER2	Human Epidermal Growth Factor Receptor 2
Hgb	Hemoglobin
HIF	Hypoxia-Inducible Factor
HIV	Human Immunodeficiency Virus
HMG-CoA	3-Hydroxy-3methyl-glutaryl coenzyme A
HPLC	High Performance Liquid Chromatography
HR	Hazard Ratio
HR	Hormone Receptor

[redacted]

IB	Investigator's Brochure
IC50	Inhibitory Concentration at 50%
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
IMS	Integrated Medical Safety
IND	Investigational New Drug Application (USA)
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT (IWRS)	Interactive Response Technology (that includes Interactive Web Response System)
ITT	Intent-To-Treat
LDH	Lactate Dehydrogenase
LDL	Low-Density Lipoprotein
LH-RH	Luteinizing hormone-releasing hormone
LLN	Lower Limit of Normal
LLOQ	Lower Limit Of Quantification
LMWH	Low Molecular Weight Heparin
LS/MS	Liquid Chromatography / Mass Spectrometry
MBC	Metastatic Breast Cancer
MPD	Molecular Pharmacodynamics
MRI	Magnetic Resonance Imaging
MRP	Mutual Recognition Procedure (EU)
mTOR	mammalian Target of Rapamycin
NADPH	Nicotinamide Adenine Dinucleotide Phosphate
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NDA	New Drug Application (USA)
NSAI	Non-steroidal Aromatase Inhibitors
NSCLC	Non-Small Cell Lung Cancer
o.d.	omnia die/once a day
ORR	Objective Response Rate
OS	Overall Survival
p.o.	per os / by mouth / orally
PCR	Polymerase Chain Reaction
PD	Progressive Disease
PFS	Progression Free Survival
PFT	Pulmonary Function Test
P-gp	P-glycoprotein
PgR	Progesterone Receptor
PI3K	Phosphatidylinositol 3-Kinase (upstream effector of the mTOR signaling pathway)
PINP	Procollagen type I N-terminal Propeptide
PK	Pharmacokinetics
PLGF	Placental Growth Factor
PR	Partial Response
PRO	Patient Reported Outcome
PS	Performance Status

[redacted]

PTEN	Phosphatase and Tensin Homolog (deleted on chromosome 10)
QoL	Quality of Life
RAPTOR	Regulatory Associated Protein of mTOR
RBC	Red Blood Cell Count
REB	Research Ethics Board
RECIST	Response Evaluation Criteria In Solid Tumors
RIA	Radioimmunoassay
RICTOR	Rapamycin-Insensitive Companion of mTOR
RMS	Reference Member State (EU)
RNA	Ribonucleic acid
S6K1	serine / threonine kinase p70S6 kinaseS6 Kinase 1
SAE	Serious Adverse Events
SD	Stable Disease
SEC	Study Evaluation Completion
SmPC	Summary of Product Characteristics
SNPs	Single Nucleotide Polymorphisms
SOP	Standard Operating Procedure
SPA	Special Protocol Assessment
SSC	Study Steering Committee
SST	Serum Separator Tube
t1/2	Half Life
T-Bil	Total bilirubin
TKI	Tyrosine Kinase Inhibitor
t_{max}	Time to Maximum Concentration
TSQM	Treatment Satisfaction Questionnaire for Medication
TTP	Time to Progression
ULN	Upper Limit of Normal
UNK	Unknown
WBC	Total White Blood Cell Count
WHO	World Health Organization
Wks	Weeks

[redacted]

Amendment 3 (18-Apr-2017)

Study status

At the time of this amendment, the study is fully recruited with 309 patients and 11 patients are still receiving treatment. The last patient was randomized on 24-Nov-2014.

Amendment rationale

This study is a post-approval commitment with the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) and the clinical study report (CSR) must be provided to these Agencies. Per protocol, the final PFS analysis is to be performed after at least 150 PFS events have been documented for each of the following comparisons: (i) everolimus + exemestane versus everolimus monotherapy (primary objective) and (ii) everolimus + exemestane versus capecitabine monotherapy (key secondary objective). Overall survival (OS) is a secondary objective and currently the OS analyses are to be conducted with two data cut-off dates; 2 years after the last patient's randomization ~~a~~nd at the time of the final PFS analysis.

Based on the current number of observed PFS events, the required 150 PFS events have been reached in one comparison and 146 PFS events have been observed in the other comparison. In the latter comparison, there is a high risk of not reaching the events over extended time due to long lasting stable disease status in the remaining patients. From a statistical perspective, loss of precision in the HR estimate with ≤ 4 events short of the required 150 is considered minimal (details described in section 10.7). The OS analyses will be amended: only one OS analysis will be performed and the timing for the final OS will be changed. The final OS analysis will be performed at the same time as the final PFS analysis using the same data cut-off date.

In order to meet regulatory commitment for submitting the CSR without affecting the scientific objective of the study, the current amendment proposes to:

1. Perform the final PFS analysis after *approximately* (instead of *at least*) 150 PFS events have been documented for each comparison.
2. Perform the final OS analysis at the same time as the final PFS analysis using same cut-off date and only one OS analysis will be completed.

This amendment is considered "non-substantial" as it does not affect patient management nor the statistical analyses of the study data.

Changes to the protocol

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

1. Section 4.1.2: Replaced "at least" with "approximately".
2. Section 4.1.3.1: Survival follow-up data collection will be stopped at the time of the final PFS analysis. The final PFS and OS analyses will use the same data cut-off date.
3. Section 4.3: Replaced "at least" with "approximately".

[redacted]

4. Section 7.1.3.1: Survival follow-up data collection will be stopped at the time of the final PFS analysis.
5. Section 7.1.5: Survival follow-up data collection will be stopped at the time of the final PFS analysis. Final PFS and OS analyses will use the same data cut-off date and only one OS analysis will be performed.
6. Section 7.2.1.1: Replaced “at least” with “approximately”.
7. Section 10.4.3: Replaced “at least” with “approximately”.
8. Section 10.5.2.1: The final OS analysis will be conducted at the same time as the final PFS analysis using the same data cut-off date.
9. Section 10.7: Updated Table 10-1 to include hazard ratio (HR) estimates for 146 and 150 PFS events. Clarifications on the analysis precision were added.

IRB/IEC

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

The changes described in this protocol amendment are non-substantial and do not require IRB/IEC approval prior to implementation.

[redacted]

Amendment 2

Amendment rationale

At the time of this amendment, 10-Feb-2014, 119 patients have been randomized.

The original protocol design included one final analysis for PFS, when approximately 150 PFS events were expected in each of the two following groups: (i) everolimus + exemestane arm plus everolimus monotherapy arm, and (ii) everolimus + exemestane arm plus capecitabine monotherapy arm. In order to allow early termination of the everolimus monotherapy arm, in case the efficacy in the everolimus monotherapy arm is far inferior to the everolimus + exemestane combination arm, Novartis plans to perform an interim PFS analysis when approximately 75 PFS events have been observed as per local tumor assessment, across the following 2 arms: everolimus monotherapy and everolimus + exemestane combination arm. This approach was endorsed by the DMC and Study Steering Committee.

Since Capecitabine had been approved by the regulatory authorities for breast cancer indication as part of Standard of Care, treatment with capecitabine for patients in this study will be followed per its local label. Therefore, capecitabine treatment will not be terminated early and no interim analysis between capecitabine monotherapy arm and everolimus + exemestane combination therapy is deemed necessary.

In addition, instructions for missed dosing, re-screening and some administrative updates for clarification and consistency have been made, across the different sections of the protocol and across the everolimus program level. Also typographical errors were corrected throughout the protocol.

Changes to the protocol

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

1. Protocol summary: Interim Analysis recommendation added to study design and objectives adapted to match endpoints
2. Section 3 Table 3-1 objectives adapted to match endpoints
3. Section 4.1.2 Randomization ratio clarified based on the Interim Analysis recommendation
4. Section 4.2 Addition of Interim analysis to allow for the early termination of the everolimus monotherapy arm
5. Section 5.2 Calculation of Creatinine clearance by the Cockroft-Gault formula was added
6. Section 6.1 Instructions on early termination of the everolimus monotherapy arm and possible transition onto the everolimus + exemestane combination arm were added
7. Section 6.1.1 Instructions for missed dosing were added: if the missed dose for everolimus or/and exemestane is **within 6 hours** following the scheduled dosing time point, the missed dose of the study medication(s) should be taken. If patients realize they missed a dose **more than 6 hours** following the scheduled dosing time point, then patients should skip the missed dose(s). Also clarification was added to state that Everolimus 10 mg (2 x 5 mg) and exemestane 25 mg should be taken together at the same time every day.

[redacted]

8. Section 6.2.1 Dose modifications in the management of adverse reactions have been clarified
9. Section 6.2.1.1 Wording for dose reductions was updated, Table 6-5 was corrected for typographical errors and clarification was added on the dose adjustments
10. Section 6.2.1.2 Capecitabine section updated with the reference to local product information and Table 6-7 clarification added to FDA USA label use according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.
11. Section 6.3.1 Denosumab used for the management of bone lesions was adapted
12. Section 6.3.1.1 A note was added that provides further insight into capecitabine co-administered with CYP2C9 substrates: co-administration of CYP2C9 substrates should be exercised with caution (in line with Xeloda label) and should be monitored closely
13. Section 7.1.1.1 Process and eligibility for re-screening was included: patients, who met all inclusion exclusion criteria, however were not able to be randomized within the screening window due to administrative issues, will be allowed to be re-screened for re-randomization. This was added due to time issues and constrains within the logistics of the site set and vendor.
14. Section 7.1.1.2. Screening failure definition was clarified
15. Table 7-4 Typographic corrections on the timing of the HBV-DNA prophylaxis monitoring recommendations were synchronized
16. Section 8.6 Information on efficacy interim analysis and DMC recommendations were added
17. Section 10 Clarification on the use of independent statistician and independent programmer for the interim analysis has been added.
18. Section 10.1.2 Clarification on safety analysis for the patients who receive everolimus monotherapy that may cross over to everolimus and exemestane upon the interim analysis has been added.
19. Section 10.4.4 The supportive analysis for hypothesis testing and providing *p*-value was deleted
20. Section 10.5.2.1 Clarified completion of the final OS analysis to be consistent with section 4.1.3.1
21. Section 10.6 Interim Analysis section was added to describe early termination guideline of the everolimus monotherapy arm
22. Section 13 Reference has been added Wei L.J. (2007)

IRB/IEC

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

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

[redacted]

Final draft version of the Protocol Amendment 2 was already reviewed and commonly endorsed by FDA and EMA.

[redacted]

Amendment 1

Amendment rationale

At the time of this amendment, 07-Jun-2013, 4 patients were randomized, 6 patients were in screening and 1 subject was discontinued due to disease progression.

The rationale of this amendment is as follows:

- Significant drug-drug interaction between sorivudine and 5-FU leads to increased fluoropyrimidine toxicity, which is potentially fatal (EU SmPC for Xeloda®). Sorivudine pertains to a class of antiviral drugs for the treatment of Herpes simplex infection. Therefore, capecitabine must not be administered concomitantly with sorivudine or its chemically related analogues, such as brivudine (EU SmPC for Xeloda®). Accordingly, a new exclusion criteria (re-numbered as #19) was added to exclude subjects who are being treated with sorivudine or its chemically related analogues (e.g. brivudine) or to have at least 4 weeks period between end of treatment with such drugs and randomization date.
- Altered coagulation parameters and/or bleeding have been reported in patients taking capecitabine concomitantly with coumarin-derivative anticoagulants such as warfarin and phenprocoumon. These events occurred within several days and up to several months after initiating capecitabine therapy in patients with and without liver metastases (EU SmPC and US PI for Xeloda®). Therefore, to be consistent with exclusion criterion #20 (re-numbered as #18 after amendment), which excludes patients under coumarin-derivate anticoagulants, the exclusion criterion #15 was updated to also exclude patients under low dose warfarin treatment.
- As everolimus is a mixed inhibitor of CYP2D6 in vitro and capecitabine is presumed to inhibit CYP2C9 in vitro, the original protocol had a conservative approach to limit intake of drugs recognized as being strong or moderate inhibitors of these isoenzymes within the last five days prior to randomization. However, the mean steady-state of everolimus Cmax with an oral dose of 10 mg daily is more than 36-fold below the Ki-values of the in vitro inhibition. An effect of everolimus on the metabolism of CYP2D6 substrates was therefore considered to be unlikely (US PI for Afinitor®). Furthermore, a drug interaction study of capecitabine with single-dose warfarin administration showed a significant increase in the mean AUC (+57%) of S-warfarin. These results suggest an interaction, probably due to an inhibition of the cytochrome P450 2C9 isoenzyme system by capecitabine. Other than warfarin, no formal drug-drug interaction studies between capecitabine and other CYP2C9 substrates have been conducted (EU SmPC and US PI for Xeloda®). Therefore, the exclusion criteria #18 and 19 were removed with the amendment.
- The primary and key secondary analyses aim to assess the PFS treatment effect via stratified Cox models. To assess the impact of stratification, a sensitivity analysis using unstratified Cox models will be conducted. Because significance testing is not an objective of these analyses, the computation of the one-sided unstratified log-rank test p-value was removed in the amendment. Furthermore, besides the pre-specified final OS analysis, it is desirable to assess the treatment effect on overall survival at the time of the pre-specified final PFS analysis. This supplementary OS analysis is added in the amendment. No

[redacted]

multiple testing considerations are needed because hypothesis testing is not part of either OS analysis.

In addition to the above, some administrative updates for clarification have been made for consistency across the different sections of the protocol and also across the program level. Also typographical errors were corrected throughout the document.

Changes to the protocol

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

The changes to the protocol are as follows:

1. List of abbreviations: Typographic corrections
2. Sections 1.1.1, 1.2.3 and 2.5.2: Typographic corrections
3. Section 4.1.1: Wording for capecitabine and exemestane central supply where applicable was added. Clarification for monitoring patients with hepatitis C positive at baseline was made.
4. Sections 4.1.2 and 7.2.1.1: The wording for additional confirmatory scan after initial observation of tumor response was updated for clarity
5. Section 5.2:
   a. Inclusion criterion #4 was updated to specify that recurrence or progression should occur while on or after adjuvant treatment with letrozole or anastrozole, instead of aromatase inhibitors in general, for clarity
   b. To insure adequate renal function at study entry, creatinine clearance > 60 ml/min was added to inclusion criterion #9
6. Section 5.3:
   a. Wording “low dose warfarin” was removed from the exception scenarios in exclusion criterion #15
   b. “*e.g.*” was added before the list of CYP3A modifiers in exclusion criterion #17 to clarify these drugs as examples
   c. Exclusion criteria #18 and #19 were removed
   d. A new exclusion criterion numbered as 19 was added
7. Sections 6.1.1 and 6.1.2: Wording for local supply of commercially available exemestane and capecitabine was removed and a note for central supply of these drugs where applicable was added
8. Section 6.3.1:
   a. A note was added on bisphosphonate therapy, which is not allowed during the study for chronic prevention of bone metastases
   b. Section 6.3.1.1: This section was reworded for clarity, and a note was added for guidance on the classification of P-glycoprotein modifiers if not found in the table 6-9. Tables 6-8 and 6-9 were updated according to the most recent references available.
9. Table 7-1: The word “visit” under “Treatments” for clarity and missing word “twice” for capecitabine dosing were added

10. Section 7.1.1.2 and 7.1.1.3: Wording on screen failure definition was updated for clarity, and randomization was added to replace first drug treatment
11. Section 7.1.2: Clarification was made to include an initial dosing window upon randomization
12. Section 7.2.1.1: Lost to follow up was added for clarity
13. Section 7.2.2:
    a. ECG added to the list of safety monitoring assessments
    b. Section 7.2.2.2: Informed consent was added to replace start of study drug
    c. Section 7.2.2.5: Missing hepatitis B screening results information was added, and typographic corrections were made in Table 7-4
    d. Section 7.2.2.7.2: "(if present before treatment)" was removed
14. Section 8.6: Clarification was made to define the first DMC data review meeting
15. Section 9: Randomization codes and IRT data will be available for everolimus treatment only
16. Section 10:
    a. Designated CRO was deleted as Novartis will perform all statistical analyses
    b. Section 10.4.4: The computation of the one-sided unstratified log-rank test p-value was removed from the sensitivity analysis
    c. Section 10.5.2.1: Additional OS analysis at the time of the pre-specified final PFS analysis was added
    d. Section 10.5.3.5: The example list of other safety data was updated for consistency with the eCRFs.

IRB/IEC

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

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

[redacted]

Protocol summary:

Protocol number	CRAD001Y2201
Title	A three-arm, randomized, open label, phase II study of everolimus in combination with exemestane versus everolimus alone versus capecitabine in the treatment of postmenopausal women with estrogen receptor positive, locally advanced, recurrent, or metastatic breast cancer after recurrence or progression on prior letrozole or anastrozole
Brief title	A study of everolimus plus exemestane versus everolimus versus capecitabine in postmenopausal women with estrogen receptor positive, locally advanced, recurrent, or metastatic breast cancer after recurrence or progression on prior letrozole or anastrozole
Sponsor and Clinical Phase	Novartis Phase II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	This study is a post-approval commitment to the FDA and EMA. It is aimed to estimate the hazard ratio of progression free survival for everolimus plus exemestane versus everolimus monotherapy versus capecitabine monotherapy in postmenopausal women with estrogen receptor positive (ER+), human epidermal growth factor receptor 2 negative (HER2-), locally advanced, recurrent, or metastatic breast cancer (ABC) after recurrence or progression on non-steroidal aromatase inhibitors. The rationale of this study is based on the following: ● Everolimus activity in breast cancer, both as monotherapy and in combination with endocrine therapy ● Positive efficacy data of everolimus in combination with exemestane in a similar patient population ● Capecitabine monotherapy has shown similar efficacy results to everolimus plus exemestane in estrogen receptor positive patients in terms of median progression free survival. Taking into account a different safety profile of chemotherapy compared to everolimus in combination with endocrine treatment, the evaluation of two treatment approaches in the randomized setting is of interest
Primary Objective and Key Secondary Objective	**Primary Objective**: To estimate the hazard ratio of progression free survival for everolimus plus exemestane versus everolimus alone in postmenopausal women with ER+, HER2-, ABC after recurrence or progression on letrozole or anastrozole. **Key Secondary Objective**: To estimate the hazard ratio of progression free survival for everolimus plus exemestane versus capecitabine alone in postmenopausal women with ER+ HER2-, ABC after recurrence or progression on letrozole or anastrozole.

[redacted]

Secondary Objectives	To evaluate the treatment groups with respect to: ● Overall survival ● Overall response rate ● Clinical benefit rate ● Safety ● Time to ECOG performance deterioration ● Time to Quality of Life (QoL) deterioration ● Treatment satisfaction using Treatment Satisfaction Questionnaire for Medication (TSQM)
Study design	This is a three-arm, randomized, open label, multi-center phase II study investigating the combination of everolimus with exemestane versus everolimus versus capecitabine monotherapy in patients with ER+ HER2-, ABC after recurrence or progression on letrozole or anastrozole. A total of 300 patients will be randomized in 1:1:1 ratio to one of the three arms. Treatment assignment will be stratified by the presence of visceral disease (yes vs. no). Based on the interim analysis results, the everolimus monotherapy arm might be stopped early. Under this scenario no additional patients will be randomized into everolimus monotherapy arm.
Population	Postmenopausal women with ER+ HER2-, ABC, recurrent or metastatic breast cancer after recurrence or progression on prior letrozole or anastrozole.
Inclusion criteria	1. Women with locally advanced, recurrent, or metastatic breast cancer. Locally advanced breast cancer is not amenable to curative treatment by surgery or radiotherapy. 2. Histological or cytological confirmation of ER+ breast cancer 3. Postmenopausal women. Postmenopausal status is defined either by: ● Age ≥ 18 with prior bilateral oophorectomy ● Age ≥ 60 years ● Age <60 years with amenorrhea for at least 12 months and both follicle-stimulating hormone (FSH) and estradiol levels are in postmenopausal range (according to the local laboratory) **Note**: Ovarian radiation or treatment with a luteinizing hormone-releasing hormone (LHRH) agonist (goserelin acetate or leuprolide acetate) does not satisfy this inclusion criterion. 4. Recurrence or progression on prior NSAIs is defined as: ● Recurrence while on, or within one year (365 days) of end of adjuvant treatment with letrozole or anastrozole OR ● Progression while on, or within one month (30 days) of the end of, prior treatment with letrozole or anastrozole for ABC **Notes**: ● Letrozole or anastrozole do not have to be the last treatment prior to randomization ● Patients must have recovered to grade 1 or better from any adverse events (except alopecia) related to previous therapy prior to randomization

[redacted]

	5. Radiological or objective evidence of recurrence or progression on or after the last systemic therapy prior to randomization 6. Patients must have either: ● Measurable disease defined as at least one lesion ≥ 10 mm by CT or MRI that can be accurately measured in at least one dimension (CT scan slice thickness ≤ 5 mm) OR ● Bone lesions: lytic or mixed (lytic + blastic) in the absence of measurable disease as defined above **Notes**: ● Lymph nodes have to be ≥ 15 mm in short axis to be considered measurable ● 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 absence of measurable disease)
Exclusion criteria	1. HER2-overexpressing patients by local laboratory testing (IHC 3+ staining or in situ hybridization positive), based on the most recent test. Note: Patients with IHC 2+ must have a negative in situ hybridization test 2. Patients who received more than one chemotherapy line for ABC **Note**: A chemotherapy line in advanced disease is an anticancer regimen that contains at least one chemotherapy agent and is given for 21 days or longer. If a cytotoxic chemotherapy regimen was discontinued for a reason other than disease progression and lasted less than 21 days, then this regimen does not count as a "prior line of chemotherapy". Chemotherapy regimens composed of more than one drug are considered as one line of therapy. 3. Patients with only non-measurable lesions other than lytic or mixed (lytic and blastic) bone metastasis (e.g. pleural effusion, ascites etc.) 4. Patients being treated with drugs recognized as being strong inhibitors or inducers of the isoenzyme CYP3A (e.g. Rifabutin, Rifampicin, Clarithromycin, Ketoconazole, Itraconazole, Voriconazole, Ritonavir, Telithromycin) continuously for at least 7 days during any time period in the last 2 weeks prior to randomization 5. Patients under treatment with sorivudine or its chemically related analogues, such as brivudine, or those who discontinue this treatment less than 4 weeks prior to randomization.
Investigational and reference therapy	Study treatment is defined as everolimus plus exemestane (10 mg/day + 25 mg/day), everolimus monotherapy (10 mg/day) and capecitabine monotherapy (1250 mg/m2 twice daily for 2 weeks followed by one week rest).
Efficacy assessments	Efficacy assessments (overall tumor response and progression) will be evaluated every 6 weeks. Tumor response will be based on radiological tumor measurements. The evaluation of overall tumor response will be performed according to RECIST 1.1.

[redacted]

Safety assessments	The assessment of safety will be based mainly on the frequency of adverse events and on the number of laboratory values that fall outside of pre-determined ranges. The overall observation period will be divided into three mutually exclusive segments: 1. pre-treatment period: from day of patient's informed consent to the day before first dose of study medication 2. on-treatment period: from day of first dose of study medication to 30 days after last dose of study medication 3. post-treatment period: starting on day 31 after last dose of study medication.
Other assessments	Assessment of overall survival (OS), overall response rate (ORR), clinical benefit rate (CBR), deterioration in the ECOG performance status, changes in quality of life scores over time and patient satisfaction are planned in the trial.
Data analysis	The Full Analysis Set (FAS) comprises all patients to whom study treatment has been assigned by randomization. All primary analyses will be conducted using data from this population according to the intent-to-treat (ITT) principle, i.e., patients will be analyzed according to the treatment and stratum they have been assigned to during the randomization procedure. For the comparison of everolimus + exemestane versus everolimus alone (primary objective) as well as the comparison of everolimus + exemestane versus capecitabine alone (key secondary objective), stratified Cox regression models will be used to estimate the hazard ratios of a PFS event, along with associated 90% confidence intervals, where the stratification information will be obtained through IRT. For each of the three treatment arms, distribution of PFS will be assessed using the Kaplan-Meier estimation method. The estimated median PFS and probability of not experiencing a PFS event by 2, 4, 6, and 9 months, along with 90% confidence intervals, will be presented.
Keywords	Postmenopausal woman, Advanced breast cancer, Endocrine therapy, Aromatase inhibitors

[redacted]

1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatment

1.1.1 Epidemiology of breast cancer

Breast cancer is the most frequently diagnosed cancer in women accounting for 23% (1.38 million) of all new cancer cases and is the leading cause of cancer related deaths in females worldwide causing more than 400,000 deaths yearly (Jemal et al 2011). The presence of hormone receptor (HR) (estrogen receptor (ER) and/or progesterone receptor (PgR)) is one of the most important prognostic factors detected in approximately 70% of all invasive breast cancers. Endocrine therapy is the core treatment modality in patients with HR+ advanced breast cancer (ABC).

1.1.2 Treatment options for Hormone Receptor positive Advanced Breast Cancer

Endocrine therapy options for postmenopausal women with ER+ ABC include selective nonsteroidal aromatase inhibitors (NSAI; anastrozole and letrozole), steroidal aromatase inhibitors (exemestane), estrogen receptor antagonist (fulvestrant), and selective estrogen receptor modulator (SERM; tamoxifen). Blocking of estrogenic signaling with tamoxifen has been the main approach in treatment for ER positive breast cancer for over 30 years. Tamoxifen is indicated for the treatment across the whole continuum of breast cancer, ranging from risk reduction in women with high risk of developing breast cancer to treatment in multiple lines of metastatic disease. Aromatase inhibitors (AI) reduce peripheral estrogen synthesis by blocking the conversion of androgens to estrogens, which is the primary way estrogens are produced in postmenopausal women. Aromatase inhibitors are generally prescribed as the first line of therapy for the treatment of postmenopausal women with ER+ breast cancer (Beslija et al 2009, Cardoso et al 2011, NCCN 2011.2).

Despite broad spectrum of available options of endocrine therapy for the patients with ER+ ABC, all patients will eventually develop resistance to initial treatment.

An emerging mechanism of endocrine resistance is aberrant signaling via the phosphatidylinositol 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) signaling pathway (Burstein 2011, Johnston 2006, Schiff et al 2004). Also, hyperactivation of the PI3K/mTOR pathway is observed in endocrine-resistant breast cancer cells, and treatment with mTOR inhibitors, including rapamycin analogs, reverses this resistance (Miller 2010). In addition, growing evidence supports a close interaction of the mTOR pathway with ER signaling. A substrate of mTOR Complex 1 (mTORC1), S6 kinase-1 (S6K1), phosphorylates the activation domain AF-1 of the ER, responsible for ligand-independent receptor activation (Yamnik et al 2009; Yamnik and Holz 2010).

Everolimus is a rapamycin derivative that inhibits mTOR through allosteric binding to mTORC1 but not mTORC2 (Efeyan and Sabatini 2010). Everolimus combined with AIs in preclinical models of ER-positive (ER+), hormone-sensitive and hormone-resistant breast

[redacted]

cancer, results in G1 arrest and enhanced apoptosis (Boulay et al 2005). In the clinic, everolimus monotherapy demonstrated clinical activity in patients with advanced breast cancer who had mostly ER+ tumors and had received previous endocrine therapy (Ellard et al 2009). In this trial, 19 of the 49 patients enrolled were ER+/human epidermal growth factor receptor 2 negative (HER2-); 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 et al 2009).

More recently, the combination of everolimus with exemestane showed significant improvement in efficacy, in terms of PFS, response rate, and clinical benefit rate, relative to exemestane monotherapy (Baselga et al 2011). The median progression-free survival (PFS) by local assessment was 7.8 months for everolimus + exemestane versus 3.2 months for exemestane (HR = 0.45; 95% CI: 0.38-0.54; P<.0001). Overall response rate (12.6 % vs 1.7%; P<.0001) and clinical benefit rate (51.3% vs 26.4%; P<.0001) were superior in the everolimus + exemestane arm versus exemestane + placebo. Analyses by central assessment showed a median progression-free survival of 11 months with everolimus versus 4.1 months with placebo (HR = 0.38; 95% CI: 0.31 – 0.48; P <.0001) confirming the results of the primary PFS analysis (Piccart et al 2012, Baselga et al 2012). The combination of everolimus and exemestane has received a marketing authorization in the USA, EU and many other countries based on the results of this study.

In patients with a significant tumor burden and symptomatic visceral disease, the indication of chemotherapy is supported by the perception of a more rapid and higher response rate. Endocrine responsive patients with liver or lung metastasis and no or few clinical symptoms do have both chemotherapy and endocrine therapy as therapeutic alternatives (Barrios et al 2009).

The evolution of clinical practice in early breast cancer in the last decade has resulted in extensive use of anthracyclines and taxanes as adjuvant treatment. Capecitabine monotherapy has become an important and frequently used option for the first-line cytotoxic treatment. Capecitabine is also the choice for the patients without previous exposure to taxanes or anthracyclines based on its generally mild safety profile and convenience of oral administration. Several clinical studies investigated capecitabine monotherapy in this setting and showed PFS between 4.1 and 7.9 months, and OS between 18.6 and 29.4 months (O'Shaughnessy et al 2012, Stocker et al 2007, Jaeger et al 2010, Kaufmann et al 2010, Robert et al 2011). Single agent capecitabine is therefore included in the NCCN and other national guidelines as a reasonable option for a first line treatment in patients with advanced BC (ABC: locally advanced, recurrent, or metastatic BC). The use of capecitabine monotherapy in this patient population is estimated to be up to 20% in the EU (Verma et al 2011) and 8-16% in the US (market research data).

[redacted]

1.1.3 Role of Mammalian Target of Rapamycin in ER+ ABC

The mammalian target of rapamycin (mTOR), a key protein kinase, acts as a nutrient sensor and monitor of the cellular metabolic state regulating protein synthesis and ultimately cell growth, proliferation, and survival. mTOR serves a key role in normal mammalian cell physiology, and is centrally involved in tumor-cell physiology, (for example, facilitating cell-cycle progression from G1-S phase) and consequently inhibition of this target has received considerable attention as an anti-cancer approach, as reviewed by (Bjornsti and Houghton 2004; Abraham and Gibbons 2007). mTOR regulates global mRNA translation (Beuvink 2005). Indeed, downstream from mTOR is the serine / threonine kinase p70S6 kinase (S6K). S6K phosphorylates key residues on the ribosomal protein S6, permitting its activation and full function as a protein involved in ribosomal biogenesis. The mTOR kinase also modulates phosphorylation of 4E-BP1, releasing its inhibition of eIF-4E and consequently permitting efficient cap-dependent translation (Bjornsti and Houghton 2004).

Activation of the mTOR pathway is a key adaptive change driving endocrine resistance. Research into the mechanisms of resistance has shown that various signal transduction pathways are activated to escape the effect of endocrine therapy. For example, the PI3 kinase/Akt/mTOR pathway is constitutively activated in aromatase inhibitor resistant and long-term estrogen deprivation BC cells (Tokunaga et al 2006; Santen et al 2005; Campbell et al 2001). Selective inhibitor of mTOR, sirolimus or rapamycin, demonstrated a significant growth inhibition particularly in long-term estrogen deprivation BC cells (Yue et al 2007). Rapamycin and its analogues partially inhibit mTOR through allosteric binding to mTORC1 but not mTORC2 (Efeyan and Sabatini 2010). However, prolonged exposure to rapamycin also results in mTORC2 inhibition (Sarbassov et al 2006).

In addition, there is a growing evidence supports a close interaction between the mTOR pathway and ER signaling. A substrate of mTOR complex 1 (mTORC1), called S6 kinase 1, phosphorylates the activation function domain 1 of the ER, which is responsible for ligand-independent receptor activation (Yamnik et al 2009; Yamnik and Holz 2010)

1.2 Introduction to control arm and investigational treatments

In the context of this clinical trial, the combination arm of everolimus and exemestane is the considered control arm and the everolimus monotherapy and capecitabine monotherapy arms are considered investigational treatments.

Everolimus has been in clinical development since 1996 as an 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®. Afinitor was approved for advanced renal cell carcinoma (RCC) in 2009. In 2010, Afinitor received US approval for patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC). 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, Canada and the EU. In April 2012, Afinitor was approved for the treatment of patients

[redacted]

with TSC who have angiomyolipoma and subsequently in the EU in November 2012 and various other countries. In July 2012, Afinitor in combination with exemestane was approved for the treatment of postmenopausal women with ER+, HER2-, advanced breast cancer after failure of treatment with letrozole or anastrozole in the US and EU as well as in various countries.

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

1.2.1 Overview of Everolimus

Everolimus (Afinitor®; RAD001) 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 (Yu and Sato 1999, Lane et al 2009) and have antiangiogenic activity in vivo (Guba et al 2002, Tsutsumi et al 2004, Mabuchi et al 2007, Lane et al 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 µM. Everolimus also inhibits the proliferation of human umbilical vein endothelial cells (HUVECS) in vitro, with particular potency against VEGF-induced proliferation suggesting that everolimus may also act as an anti-angiogenic agent. The 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

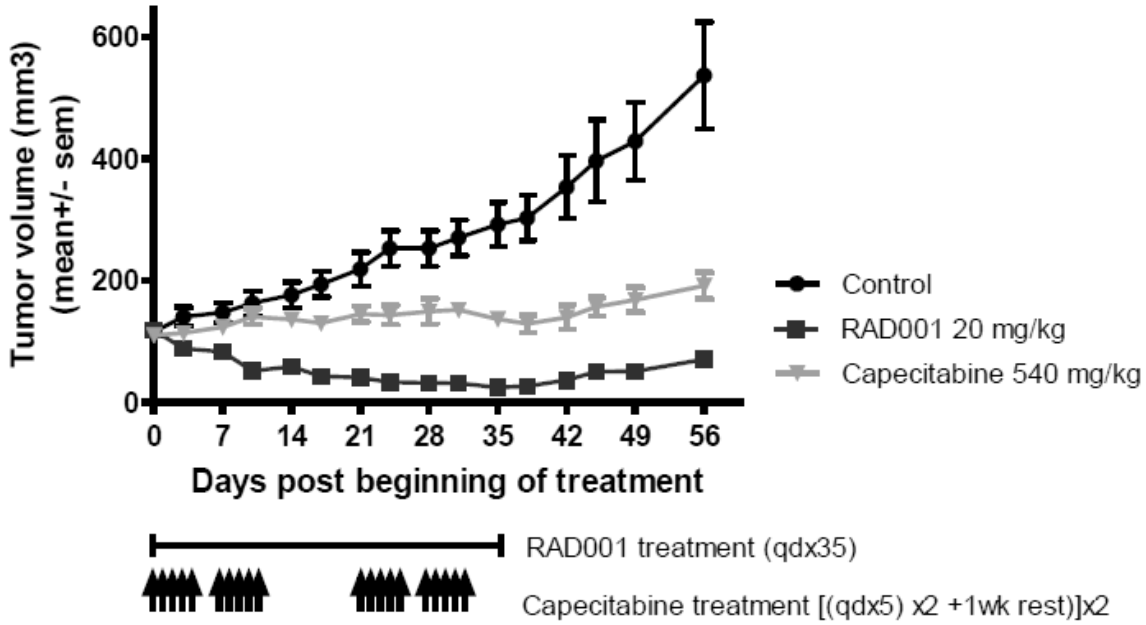
[redacted]

xenograft model, and demonstrating high tumor penetration in a rat pancreatic tumor model. The pharmacokinetic profile of everolimus indicates sufficient tumor penetration, above that needed to inhibit the proliferation of endothelial cells and tumor cell lines deemed sensitive to everolimus in vitro.

Everolimus administered orally daily was a potent inhibitor of tumor growth, at well tolerated doses, in 11 different mouse xenograft models (including pancreatic, colon, epidermoid, lung and melanoma) and two syngeneic models (rat pancreatic, mouse orthotopic melanoma). These models included tumor lines considered sensitive and "relatively resistant" in vitro. In general, everolimus was better tolerated in mouse xenograft models than standard cytotoxic agents (i.e., doxorubicin and 5-fluorouracil), while possessing similar anti-tumor activity.

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 et al 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].

[redacted]

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 et al 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 et al 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.

[redacted]

1.2.1.2.2 Clinical experience of Everolimus in hormone receptor positive breast cancer (HR+ BC)

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 + ABC who had received prior endocrine therapy. In this trial, 19 of the 49 patients enrolled were ER-positive/human epidermal growth factor receptor 2 (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 et al 2009).

Everolimus in combination with endocrine therapy

The combination of everolimus with endocrine 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 et al 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+ ABC who had a recurrence or progression on letrozole or anastrozole. The median duration of the follow-up of the patients was 18 months. Median PFS was 7.8 months for everolimus plus exemestane versus 3.2 months for placebo plus exemestane (HR, 0.45; 95% CI, 0.38 to 0.54; P < .0001). Centrally assessed PFS analyses showed a median PFS duration of 11.0 months for the everolimus plus exemestane arm versus 4.1 months for the placebo plus exemestane arm (HR, 0.38; 95% CI, 0.31 to 0.48; P < .0001). Subgroup analyses showed consistent PFS benefit with combination therapy across all patient subsets. By local assessment, three complete responses (CRs, 0.6%) and 58 partial responses (PRs, 12%) were reported for the everolimus plus exemestane arm, versus only four PRs (1.7%) for the placebo plus exemestane arm. The CBR also was increased with everolimus plus exemestane therapy versus placebo plus exemestane (51.3% vs 26.4%; P < .0001). These differences in ORR and CBR were also supported by central radiology review (Piccart et al 2012).

[redacted]

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 et al 2012). Although the results of the phase II trial are encouraging, the small sample size may limit the impact of these results on clinical practice.

Safety profile of everolimus

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 phase III study (BOLERO-2) 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, with an incidence $\geq$ 10%, reported in association with everolimus plus exemestane therapy were consistent with what was previously reported: stomatitis, rash, fatigue, decreased appetite, diarrhea, dysgeusia, nausea, pneumonitis, weight decreased, anemia, epistaxis, hyperglycemia, thrombocytopenia, and pruritus. The most common grade 3-4 AEs suspected to be related to treatment with an incidence of $\geq$ 2% were: stomatitis, hyperglycemia, anemia, pneumonitis, fatigue, elevated alanine and aspartate transaminase concentrations, elevated γ-glutamyltransferase concentrations, dyspnea, neutropenia, and thrombocytopenia. No new safety concerns have emerged compared to previous experience with everolimus monotherapy or combination therapy.

[redacted]

Table 1-1 BOLERO-2 Study: Most common Adverse Events (equal or greater than 10 percent of Patients)

	EVE + EXE (n = 482), %					PBO + EXE (n = 238), %				
		Grade					Grade			
AE (preferred term)	**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
Urinary tract infection	10	3	7	<1	0	2	<1	2	0	0
GGT increase	10	2	2	5	2	9	1	1	5	2

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; EVE, everolimus; EXE, exemestane; GGT, gamma glutamyltransferase; PBO, placebo.

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

[redacted]

1.2.2 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 estrogen receptor positive (ER+) 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 endocrine therapy. It is also indicated for the treatment of ABC in postmenopausal women whose disease has progressed following tamoxifen therapy (in the USA) or following anti-oestrogen 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, 2005).

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 E_2 suppression is 7 days (Demers et al 1993, Plourde et al 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 et al 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.

1.2.3 Overview of Capecitabine

Capecitabine is a fluoropyrimidine carbamate with antineoplastic activity, which functions as an orally administered precursor of the cytotoxic moiety 5-fluorouracil (5-FU). Capecitabine is activated via several enzymatic steps. The enzyme involved in the final conversion to 5-FU,

[redacted]

thymidine phosphorylase (ThyPase), is found in tumor tissues, but also in normal tissues, albeit usually at lower levels (US PI for Xeloda®)

Capecitabine is indicated in combination with docetaxel for the treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy that included an antracycline. Capecitabine is also indicated as monotherapy for the treatment of patients with locally advanced or metastatic breast cancer after failure of taxanes and an anthracycline-containing chemotherapy regimen or for whom further anthracycline therapy is not indicated. The dose of capecitabine approved by the U.S. Food and Drug Administration (FDA) for patients with locally advanced or metastatic breast cancer is 1,250 mg/m^2 twice daily (bid), given intermittently for 14 days on a 21-day cycle. Capecitabine has a favorable safety profile, with adverse events (AEs) readily managed by dose modification, and it offers the additional benefit of convenient oral dosing. Capecitabine is suitable for long-term administration and generally lacks cumulative toxicity with prolonged use. (O'Shaughnessy et al 2012)

As a monotherapy, capecitabine was extensively evaluated in the first line metastatic breast cancer in phase II and phase III clinical trials. The ORR shown in these studies was in a range of 21 to 30% and PFS between 2.8 to 7.1 months in patients with metastatic breast cancer unselected for ER status (O'Shaughnessy et al 2012). The two phase III studies were conducted in unselected by ER status patients with metastatic breast cancer. Stocker et al reported (ANZBCTG0001) study where patients with first-line mBC unsuited for more intensive chemotherapy were randomized to receive capecitabine monotherapy or cyclophosphamide, methotrexate and 5-fluorouracil (CMF). 323 patients were enrolled in this study. All patients had to have a relapse-free survival interval for at least 6 months following adjuvant chemotherapy and 80% of patients had received adjuvant endocrine therapy. The primary endpoint PFS was similar between two treatment arms HR= 0.86; (95%CI 0.67–1.10). Patients enrolled in the capecitabine arm had a median PFS of 7 months and median OS of 22 months, compared to median PFS of 6 months and OS of 18 months in patients randomized to CMF arm. The OS difference was statistically significant in favor of capecitabine arm (HR=0.72; 95% CI, 0.55– 0.94; log-rank p=0.02). Another randomized Phase III study compared the efficacy and safety of first-line capecitabine with pegylated liposomal doxorubicin (PLD) in patients with mBC (Jäger et al 2010).The primary endpoint of time to progression (TTP) was similar with capecitabine and PLD (median TTP, 7.1 months versus 6.2 months, respectively; HR, 1.21; 95% CI, 0.84 –1.75; p=0.31). Capecitabine also had efficacy similar to that of PLD in terms of OS (median OS time, 29.4 months versus 22.4 months, respectively; HR=1.17; 95% CI, 0.79 –1.74; p=0.44).

Robert et al, reported a PFS of 6.2 months in ER-positive HER2 –negative breast cancer patients receiving capecitabine monotherapy (Robert et al 2011).

Diarrhea, hand-foot syndrome (HFS), nausea, vomiting and stomatitis are common adverse reaction attributed to capecitabine treatment. Across the phase II/III breast cancer trials, HFS and diarrhea were the most frequently reported grade 3 or 4 AEs; alopecia and myelosuppression were rare (O'Shaughnessy et al 2012). Refer to US PI for Xeloda® for more details.

[redacted]

2 Rationale

2.1 Study rationale and purpose

This study aims at estimating the hazard ratios of PFS for everolimus plus exemestane versus everolimus alone and versus capecitabine alone, in postmenopausal women with ER+ ABC after recurrence or progression on aromatase inhibitors. The study is a post-approval commitment to the FDA and EMA.

The rationale of this study is based on the following:

- Everolimus activity in breast cancer, both as monotherapy (Ellard et al 2009) and in combination with endocrine therapy (Baselga et al 2009; Bachelot et al 2012)
- Positive efficacy data of everolimus in combination with exemestane in a similar patient population (Piccart et al 2012)
- Capecitabine monotherapy has shown similar efficacy results to everolimus plus exemestane in ER+ patients in terms of median PFS (Robert et al 2011). Taking into account different safety profile of chemotherapy compared to everolimus in combination with endocrine treatment, the evaluation of two treatment approaches in the randomized setting is of interest

In preclinical models of ER-positive hormone-sensitive and hormone-resistant breast cancer, everolimus combined with AIs results in G1 arrest and enhanced apoptosis (Bouly et al 2005). The combination of everolimus with endocrine therapy for the treatment of ER+ ABC after progression on an AI has been supported in phase II trials (Baselga et al 2009; Bachelot et al 2012). Exemestane is commonly used after failure of prior therapy with letrozole or anastrozole. In a Phase-II clinical setting, exemestane 25 mg once daily has been demonstrated to be both safe and effective in postmenopausal patients with metastatic breast cancer following progression on treatment with a NSAI (Lønning et al 2000). In this particular study, exemestane was associated with a 24.3% clinical benefit rate (defined as CR+PR+SD $\geq$ 24 weeks) in a population who received exemestane as a third- or fourth-line endocrine therapy. Results from a double-blind, placebo-controlled Phase-III trial comparing exemestane to fulvestrant in 693 postmenopausal women with ER-positive breast cancer after recurrence or progression on a NSAI demonstrated no difference between treatment arms in terms of TTP/PFS (median 3.7 months in both arms), ORR (7.4% versus 6.7%, respectively), or clinical benefit rate (32.2% versus 31.5%, respectively) (Chia et al 2008). Exemestane was therefore considered to be an appropriate combination strategy for the phase III clinical trial. In the trial the combination of everolimus and exemestane has shown superiority in terms of PFS compared to exemestane alone (Baselga et al 2011; Piccart 2012).

Everolimus monotherapy demonstrated clinical activity in patients with advanced breast cancer who had mostly ER+ tumors and had received previous endocrine therapy (Ellard et al 2009).

In metastatic setting combinations of cytotoxic agents might provide a greater objective response rate and longer PFS compared to single agent therapy. However, the increase in side effects and overlapping toxicity are limiting wide use of these approaches. Therefore, sequential single agent cytotoxic therapy remains a frequent strategy in the first line treatment of metastatic or locally recurrent breast cancer (Sledge 2003). Capecitabine monotherapy is

[redacted]

used successfully as the first line therapy in patients with ER+ HER-2 negative breast cancer with median PFS of 6.2 months (Robert et al 2011).

2.2 Rationale for the study design

This is a phase II randomized, open label, international multicenter study. This study design is well-established for the estimation of the efficacy and tolerability of everolimus and capecitabine monotherapies compared to everolimus/exemestane combination.

2.3 Rationale for dose and regimen selection

The selection of the 10-mg continuous daily dose for everolimus is based on a pharmacodynamic model (Tanaka et al 2008), which was supported by results from a clinical pharmacodynamic study in patients with solid tumors (Tabernero et al 2008). These results showed that the 10-mg daily dose produced a more profound, sustained suppression of mTOR activity than could be achieved with weekly dosing. Also, the 10 mg daily dose of everolimus was favored over a 5 mg daily dose in Study C2108, a Phase 1 study combining everolimus with letrozole in postmenopausal patients with advanced breast cancer (Awada et al 2008). This was further corroborated by results from a randomized Phase 2 study conducted by the National Cancer Institute of Canada, where a daily regimen of 10 mg everolimus was more efficacious than a 70 mg weekly regimen (Ellard et al 2009). The same 10-mg dose was used effectively in the BOLERO-2 study (Piccart et al 2012).

The approved dose of everolimus in combination with exemestane in the treatment of postmenopausal women with HR+ HER2- and ABC is 10 mg daily via oral administration.

The recommended daily dose of exemestane is 25 mg via oral administration and this dose will be used in this study.

The approved dose of capecitabine for patients with LABC or MBC is 1250 mg/m^2 twice daily (bid), given intermittently for 14 days on a 21-day cycle. This dose will be used in the study.

2.4 Rationale for choice of combination therapy as a control arm

The rationale for assigning the combination of everolimus with exemestane as the control arm in this trial is based on significant improvement in efficacy, in terms of PFS, response rate, and clinical benefit rate, relative to exemestane monotherapy in patients resistant to NSAI (Baselga et al 2011; Piccart et al 2012). Everolimus in combination with exemestane as the control arm in the trial is also based on the approval by FDA and EMA in July 2012 for the combination therapy in the treatment of postmenopausal women with HR+ HER2- and ABC. In addition, there is a regulatory requirement to compare efficacy and safety of the approved therapy with everolimus and capecitabine monotherapy.

[redacted]

2.5 Rationale for choice of comparators drugs

2.5.1 Rationale for choice of Everolimus

Everolimus monotherapy demonstrated clinical activity in patients with advanced breast cancer who had mostly ER+ tumors and had received previous endocrine therapy (Ellard et al 2009). In this trial, 19 of the 49 patients enrolled were ER-positive/human epidermal growth factor receptor 2 (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 et al 2009).

2.5.2 Rationale for choice of Capecitabine

Capecitabine monotherapy has become an important and frequently used option for the first-line chemotherapy treatment particularly in patients with residual toxicity after adjuvant therapy or high cumulative dose of anthracyclines. Capecitabine is also the choice for the patients without previous exposure to taxanes or anthracyclines based on its generally mild safety profile and convenience of oral administration. Capecitabine monotherapy as first line treatment demonstrated efficacy in phase III studies in unselected patients and in patients with ER+ ABC (Stocker et al 2007; Jäger et al 2010; Robert et al 2011). Single agent capecitabine is therefore included in the NCCN and other national guidelines as a reasonable option for a first line treatment in patients with ABC.

Capecitabine is indicated as monotherapy for the treatment of patients with locally advanced breast cancer (LABC) or MBC after failure of taxanes and an anthracycline-containing regimen and in patients for whom further anthracycline therapy is not indicated (US PI for Xeloda®)

3 Objectives and endpoints

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

[redacted]

Table 3-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		Refer to Section 10.4
To estimate the hazard ratio of PFS for everolimus plus exemestane versus everolimus alone in postmenopausal women with ER positive, HER2 negative, advanced breast cancer after recurrence or progression on letrozole or anastrozole.	Progression free survival (PFS) based on the local radiologist/investigator's tumor assessment (RECIST 1.1)	
Key secondary		Refer to Section 10.5.1
To estimate the hazard ratio of PFS for everolimus plus exemestane versus capecitabine in postmenopausal women with ER positive, HER2 negative, advanced breast cancer after recurrence or progression on letrozole or anastrozole	Progression free survival (PFS) based on the local radiologist/investigator's tumor assessment (RECIST 1.1)	
Other secondary		Refer to Section 10.5.2
To evaluate the treatment groups with respect to:		
- Overall survival	Overall survival (OS)	
- Overall response rate	Overall response rate (ORR)) based on the local radiologist/investigator's tumor assessment (RECIST 1.1)	
- Clinical benefit rate	Clinical benefit rate (CBR)	
- Safety	Safety: Incidence of adverse events, serious adverse events, changes from baseline in vital signs and laboratory results (hematology, blood chemistry)	
- Time to ECOG performance deterioration	Time to ECOG performance deterioration	
- Time to Quality Of Life (QoL) deterioration	Time to Quality Of Life (QoL) deterioration	
- Treatment satisfaction using Treatment Satisfaction Questionnaire for Medication (TSQM) version 1.4	TSQM score	

[redacted]

4 Study design

4.1 Description of study design

This is a three-arm, randomized, open label, multi-center phase II study investigating the combination of everolimus (10mg daily) with exemestane (25mg daily) versus everolimus (10mg daily) versus capecitabine (1250mg/m^2 twice daily for 14 days, 3-week cycle) in patients with estrogen-receptor positive, HER2 negative, advanced breast cancer after recurrence or progression on letrozole or anastrozole.

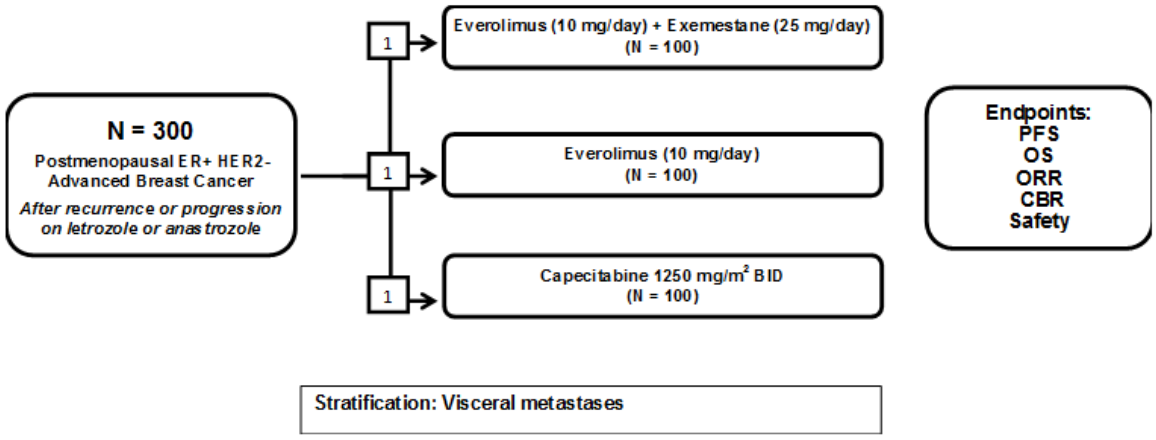
The reference therapy (control arm) used in the course of this trial is the combination arm of everolimus plus exemestane. The investigational therapies in the context of this study are everolimus monotherapy and capecitabine monotherapy. All treatments will be taken orally until disease progression, intolerable toxicity or withdrawal of patient's informed consent.

Patients will be randomly assigned with equal allocation to one of the treatment arms:

a. Exemestane (25mg daily) in combination with everolimus (10mg daily)
b. Everolimus (10mg daily)
c. Capecitabine (1250mg/m^2 twice daily) orally for two weeks, followed by a one week rest period in 3-weeks cycles.

Treatment assignment will be stratified by the presence of visceral disease (yes vs. no). Visceral refers to lung, liver, heart, ovary, spleen, kidney, adrenal gland, malignant pleural or pericardial effusion or malignant ascites.

Figure 4-1 Study Design



4.1.1 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.

The study will use Interactive Response Technology (IRT), a central patient screening/ randomization system for screening, randomization and for management of everolimus drug supply. Other study medications (capecitabine and exemestane) will be supplied locally in accordance with local regulations in participating countries, or centrally supplied by Novartis where applicable.

After the patient signs the informed consent and prior to randomization, a patient's pre-randomization form, which includes key eligibility criteria, will be completed by the site and sent to Novartis for review and approval. Patients who do not meet the eligibility criteria will not be randomized. All screening assessments to confirm eligibility must be performed within maximum 28 days prior to the first dose of study drug (Table 7-1 and Section 7.1.1).

Screening for hepatitis B

In cancer patients with hepatitis B, whether carriers or in chronic state, use of antivirals during anticancer therapy has been shown to reduce the risk of hepatitis B virus (HBV) reactivation and associated HBV morbidity and mortality (Loomba et al. 2008).

Prior to randomization, the following three categories of patients should be tested for hepatitis B viral load and serologic markers, that is, HBV-DNA, HBsAg, HBs Ab, and HBc Ab:

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

The management guidelines, in Section 7.2.2.5, are provided according to the results of the baseline assessment of viral load and serological markers for hepatitis B.

[redacted]

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,

At the discretion of the investigator, additional patients may also be tested for hepatitis C.

The management guidelines, in Section 7.2.2.5, are provided according to the results of the baseline assessment of hepatitis C viral load.

All screening evaluations will be performed within 28 days prior to Treatment Day 1. Patients with positive baseline hepatitis B results have to start prophylactic treatment of 1 to 2 weeks prior to randomization. Patients with detectable HCV-RNA results should be monitored every 6 weeks.

4.1.2 Randomization and treatment phase

At Visit 3 all eligible patients will be randomized via IRT to one of the treatment arms. Randomization will be performed using a randomization list produced by the IRT vendor. A randomization number will be assigned to the patient, which will be used to link the patient to a treatment arm.

A total of 300 patients will be randomized in 1:1:1 ratio to receive everolimus (10mg daily oral tablets) in combination with exemestane (25 mg daily oral tablets), everolimus (10mg daily oral tablets) or capecitabine monotherapy (1250mg/m^2 twice daily orally for two weeks followed by a one week rest period in 3-weeks cycles). Assignment will be stratified by the presence of visceral disease (yes vs. no). Visceral refers to lung, liver, heart, ovary, spleen, kidney, adrenal gland, malignant pleural or pericardial effusion or malignant ascites.

After randomization, study treatment will start and continue until progression, intolerable toxicity or consent withdrawal. Further treatment after progression and study treatment discontinuation will be at the investigator's discretion. Dose adjustment (reduction, interruption) according to safety findings will be allowed. Regular safety and efficacy reviews by Data Monitoring Committee (DMC) will be performed.

Tumor assessments will be performed every 6 weeks until disease progression. If an initial observation of response is made, a confirmation scan (or photography for measurable skin lesions) should be obtained at least 4 weeks after the initial observation. After approximately 150 PFS events have been documented per RECIST 1.1 by local assessment in each of the two following groups: (i) everolimus + exemestane arm plus everolimus monotherapy arm,

[redacted]

and (ii) everolimus + exemestane arm plus capecitabine monotherapy arm, the frequency of tumor assessments will be changed to every 12 weeks or as clinically indicated.

Based on the interim analysis results and DMC recommendation, the everolimus monotherapy arm might be stopped early. If this scenario happens before all patients are randomized, the ratio of 1:1:1 randomization will no longer be kept. The remaining patients will be randomized in 1:1 ratio to receive everolimus in combination with exemestane or capecitabine monotherapy.

4.1.3 Follow-up phase

Patients will be followed for safety for 30 days after study treatment discontinuation. If a patient did not discontinue study treatment due to disease progression, lost to follow-up or consent withdrawal, then tumor assessments should continue to be performed every 6 weeks until disease progression, death, lost to follow-up or investigator decision in patient best interest.

4.1.3.1 Survival data collection

All patients will be followed for survival status at least every 3 months regardless of treatment discontinuation reason. Survival follow-up data collection will be stopped at the time of the final PFS analysis. The final PFS and OS analyses will use the same data cut-off date. Survival information can be obtained via phone and information will be documented in the source documents and eCRF. Additional survival follow-up may be performed more frequently if a survival update is required for reporting the results or to meet safety or regulatory needs.

4.2 Interim analysis

One efficacy interim analysis will be conducted, which will allow early termination of the everolimus monotherapy arm, in case of far inferior efficacy as compared to the everolimus + exemestane combination treatment arm. A general guidance is to stop everolimus monotherapy arm if the observed hazard ratio is less than 0.20. The efficacy interim analysis is planned after 75 PFS events have been observed as per local tumor assessment, across the following 2 arms: everolimus monotherapy and everolimus + exemestane combination arm. Please refer to Section 10 for more details. Capecitabine has been approved by the regulatory authorities for breast cancer indication as part of Standard of Care, and treatment with capecitabine for patients in this study will be followed per its local label. Therefore, capecitabine treatment will not be terminated early and no interim analysis between capecitabine monotherapy arm and everolimus + exemestane combination therapy is warranted. Following review of the efficacy results at the interim analysis, DMC might recommend to stop the monotherapy everolimus arm early. In that case, patients on the everolimus arm will have the option to receive everolimus + exemestane combination treatment at investigator's discretion in patient best interest. No further efficacy assessments will be required for those patients. However, safety, end of treatment, and safety follow up visits will be conducted, as per protocol.

[redacted]

4.3 Timing of final primary analysis

The study will be analyzed for PFS related objectives when approximately 150 PFS events per local tumor assessment have been documented in each of the two following groups:

a. the everolimus + exemestane arm combination arm plus the everolimus monotherapy arm, and
b. the everolimus + exemestane arm combination arm plus the capecitabine monotherapy arm.

The expected time to observing 150 PFS events in each of the two groups (a. and b.) is about 28 months after randomization of the first patient (see Section 10 for further details).

4.4 Definition of end of the study

The definition of the end of the study will be the date of the last visit of the last patient.

4.5 Early study termination

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

5 Population

5.1 Patient population

Postmenopausal women with ER+ HER2- locally advanced, recurrent, or metastatic breast cancer after recurrence or progression on prior letrozole or anastrozole.

Patients enrolled in this study are not permitted to participate in additional parallel investigational drug or device studies. Patients who have discontinued this study may not be re-enrolled.

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

5.2 Inclusion criteria

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

1. Women with locally advanced, recurrent, or metastatic breast cancer. Locally advanced breast cancer is not amenable to curative treatment by surgery or radiotherapy.
2. Histological or cytological confirmation of estrogen-receptor positive (ER+) breast cancer

[redacted]

3. Postmenopausal women. Postmenopausal status is defined either by:
   - Age ≥ 18 with prior bilateral oophorectomy
   - Age ≥ 60 years
   - Age <60 years with amenorrhea for at least 12 months and both follicle-stimulating hormone (FSH) and estradiol levels are in postmenopausal range (according to the local laboratory)

   Note: Ovarian radiation or treatment with a luteinizing hormone-releasing hormone (LHRH) agonist (goserelin acetate or leuprolide acetate) does not satisfy this inclusion criterion.
4. Recurrence or progression on prior NSAIs is defined as:
   - Recurrence while on, or within one year (365 days) of end of adjuvant treatment with letrozole or anastrozole

   OR
   - Progression while on, or within one month (30 days) of the end of, prior treatment with letrozole or anastrozole-for ABC

   Notes:
   - Letrozole or anastrozole do not have to be the last treatment prior to randomization
   - Patients must have recovered to grade 1 or better from any adverse events (except alopecia) related to previous therapy prior to randomization
5. Radiological or objective evidence of recurrence or progression on or after the last systemic therapy prior to randomization
6. Patients must have either:
   - Measurable disease defined as at least one lesion ≥ 10 mm by CT or MRI that can be accurately measured in at least one dimension (CT scan slice thickness ≤ 5 mm)

   OR
   - Bone lesions: lytic or mixed (lytic + blastic) in the absence of measurable disease as defined above

   Notes:
   - Lymph nodes have to be ≥15 mm in short axis to be considered measurable
   - 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 absence of measurable disease)
7. Adequate bone marrow and coagulation function as shown by:
   - Absolute neutrophil count (ANC) ≥ 1.5 10^9/L
   - Platelets ≥ 100 $\times 10^9$/L
   - Hemoglobin (Hgb) ≥ 9.0 g/dL
   - INR ≤ 2

[redacted]

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 ≤ 1.5 × ULN (≤ 3 × ULN for patients known to have Gilbert Syndrome)
9. Adequate renal function as shown by serum creatinine ≤ 1.5 × ULN and creatinine clearance > 60 ml/min. Creatinine clearance will be calculated using the Cockroft-Gault formula.
10. Fasting serum cholesterol ≤ 300 mg/dl and fasting triglycerides ≤ 2.5 x ULN
11. ECOG Performance Status ≤ 2
12. Left ventricular ejection fraction assessment (echocardiogram or MUGA scan) performed within 4 weeks prior to randomization, showing a LVEF value ≥ LLN
13. Signed written informed consent must be obtained before any screening procedure or study related activities are performed and according to local guidelines.

5.3 Exclusion criteria

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

1. HER2-overexpressing patients by local laboratory testing (IHC 3+ staining or in situ hybridization positive), based on the most recent test. Note: Patients with IHC 2+ must have a negative in situ hybridization test
2. Patients who received more than one chemotherapy line for ABC

   Note: A chemotherapy line in advanced disease is an anticancer regimen that contains at least one chemotherapy agent and is given for 21 days or longer. If a cytotoxic chemotherapy regimen was discontinued for a reason other than disease progression and lasted less than 21 days, then this regimen does not count as a "prior line of chemotherapy". Chemotherapy regimens composed of more than one drug are considered as one line of therapy.
3. Patients with only non-measurable lesions other than lytic or mixed (lytic and blastic) bone metastasis (e.g. pleural effusion, ascites etc.)
4. Previous treatment with exemestane, mTOR inhibitors, PI3K inhibitors or AKT inhibitors.
5. Patients who received a fluoropyrimidine-containing regimen as a prior chemotherapy treatment within 24 weeks prior to randomization
6. Known hypersensitivity to mTOR inhibitors, e.g. sirolimus (rapamycin) or known hypersensitivity to capecitabine or to any of its components or to 5-fluorouracil
7. Patients with known rare hereditary problems of galactose intolerance, the lapp lactase deficiency, glucose-galactose malabsorption or dihydropyrimidine dehydrogenase (DPD) deficiency.
8. Another malignancy within 5 years prior to randomization, with the exception of adequately treated: in-situ carcinoma of the cervix uteri, basal or squamous cell carcinoma, non-melanomatous cancer of skin or history of stage IA melanoma that has been cured.
9. Radiotherapy within four weeks prior to randomization except in case of localized palliative radiotherapy (for analgesic purpose) or for lytic lesions at risk of fracture which

[redacted]

was completed at least two weeks prior to randomization. Patients must have recovered from radiotherapy toxicities.

Note: Lesions in previously irradiated areas should not be considered measurable, unless they have clearly progressed since the radiotherapy. If lesions in previously irradiated areas have not progressed since the radiotherapy, they should be considered non-measurable and followed as non-target lesions

10. Currently receiving any hormone replacement therapy, unless discontinued prior to randomization.
11. Current or history of CNS metastases. Patients with symptoms suggestive of CNS metastases should have a CT/MRI to rule out CNS metastasis prior to randomization to be eligible.
12. Patients receiving concomitant immunosuppressive agents or chronic corticosteroids use at the time of study entry except topical applications, inhaled sprays, eye drops or local injections.
13. Bilateral diffuse lymphangitic carcinomatosis
14. Patients with a known history of HIV seropositivity. Screening for HIV infection at baseline is not required.
15. Active, bleeding diathesis, or on oral anti-vitamin K medication (except LMWH and acetylsalicylic acid or equivalent, as long as the INR is $\leq$2).
16. Any severe and / or uncontrolled medical conditions.
17. Patients being treated with drugs recognized as being strong inhibitors or inducers of the isoenzyme CYP3A (e.g. Rifabutin, Rifampicin, Clarithromycin, Ketoconazole, Itraconazole, Voriconazole, Ritonavir, Telithromycin) continuously for at least 7 days during any time period in the last 2 weeks prior to randomization
18. Patients being treated with coumarin-derivate anticoagulants such as warfarin and phenprocoumon
19. Patients under treatment with sorivudine or its chemically related analogues, such as brivudine, or those who discontinue this treatment less than 4 weeks prior to randomization
20. History of noncompliance to medical regimens
21. Patients unwilling to or unable to comply with the protocol

[redacted]

6 Treatment

6.1 Study treatment

The investigational therapies in the context of this study are everolimus monotherapy and capecitabine monotherapy. The control therapy is everolimus + exemestane combination therapy.

Study treatment is defined as everolimus + exemestane, everolimus monotherapy or capecitabine monotherapy. All study drugs are open label and defined as everolimus, exemestane and capecitabine.

Patients who terminated everolimus monotherapy early, per DMC recommendation based on the efficacy interim analysis results (if applicable), will be provided with an option to receive the everolimus + exemestane combination treatment at investigator's discretion in patient best interest. No further efficacy assessments will be required for those patients. However, safety, end of treatment, and safety follow up visits will be conducted, as per protocol.

6.1.1 Dosing regimen

Patients will be randomly assigned with equal allocation to one of the treatment arms below:

a. Everolimus in combination with exemestane
b. Everolimus monotherapy
c. Capecitabine monotherapy

Table 6-1 Dose and treatment schedule

Study drugs	Pharmaceutical form and route of administration	Dose	Frequency and/or Regimen
Everolimus	Tablets for oral use	10 mg (2 × 5 mg)	Daily
Exemestane	Tablets for oral use	25 mg	Daily
Capecitabine	Tablets for oral use	1250 mg/m^2	Twice daily for 2 weeks followed by one week rest (3-week cycle)

Everolimus (RAD001) will be self-administered by continuous oral daily dosing of 2 × 5 mg tablets. Everolimus should be taken at the same time every day. Everolimus tablets should be swallowed whole with a glass of water once daily, either consistently with food or consistently without food. Tablets should not be chewed or crushed.

Capecitabine and exemestane will be self-administered as described in Table 6-1 in accordance with the local label in participating countries.

Everolimus 10 mg (2 x 5 mg) and exemestane 25 mg should be taken together at the same time every day.

If patients realize they missed a dose of study medications (everolimus, exemestane) **within 6 hours** following the scheduled dosing time point, they should take the missed dose of the study medication(s). If patients realize they missed a dose **more than 6 hours** following the

[redacted]

scheduled dosing time point, then patients should skip the missed dose(s). For missing dose of capecitabine, please refer to the local product information.

6.1.2 Study drug supply

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

Everolimus is formulated as tablets of 5 mg strength and will be provided centrally by Novartis. Medication label for everolimus will comply with the legal requirements of each country and be printed in local language. The storage conditions for study drug will be described on the medication label.

Commercially available exemestane and capecitabine will be supplied locally in accordance with local regulations in participating countries, or centrally supplied by Novartis where applicable.

Table 6-2 Packaging and labeling

Study drug	Packaging	Labeling (and dosing frequency)
Everolimus	Tablets in blister packs	Labeled as Everolimus; 2× 5 mg tablets to be taken orally
Exemestane	Refer to local product information[1]	25 mg tablets to be taken orally. Refer to local product information
Capecitabine	Refer to local product information[1]	1250 mg/m^2 tablet to be taken orally. Refer to local product information[1]

[1] Commercially available exemestane and capecitabine may be centrally supplied by Novartis in case the product is not available locally.

Study drugs must be received by designated personnel at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, the study treatment should be stored according to the instructions specified on the drug labels.

Table 6-3 Supply and storage of study drugs

Study drug	Supply	Storage
Everolimus	Centrally supplied by Novartis	Refer to the study drug label
Exemestane	Locally supplied	Refer to local product information
Capecitabine	Locally supplied	Refer to local product information[1]

[1] Commercially available exemestane and capecitabine may be centrally supplied by Novartis in case the product is not available locally.

[redacted]

6.1.3 Treatment duration

Eligible patients will receive either: everolimus monotherapy, capecitabine monotherapy or everolimus in combination with exemestane. All treatments will be open label. Patients will start taking their first dose of medication at Day1, and continue to receive study treatment until disease progression, intolerable toxicity, withdrawal of consent or investigator decision in patient's best interest.

6.2 Dose modifications

6.2.1 Dose modifications in the management of adverse reactions

For patients who do not tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to allow the patient to continue the study treatment, refer to the Section 6.2.1.1, Section 6.2.1.2, and Section 6.2.1.3.

Note: If the study medication in either everolimus or capecitabine monotherapy arm is discontinued for more than 4 consecutive weeks due to treatment related toxicities, the patient will permanently discontinue that study medication. If either one of the study medications in the everolimus + exemestane arm is discontinued for more than 4 consecutive weeks due to treatment related toxicities, the patient will permanently discontinue that study medication, and should continue with the another one until disease progression, intolerable toxicity or withdrawal of patient consent.

6.2.1.1 Everolimus

Management of severe or intolerable adverse reactions may require temporary dose reduction and/or interruption of everolimus therapy. If dose reduction is required, the suggested dose is approximately 50% lower than the daily dose previously administered.

If a patient already had 2 levels of dose reduction, no further dose reduction is permitted.

Patients who interrupt study treatment for more than 4 weeks must discontinue from the study or the study medication (in combination arm if applicable).

Recommendations for dose reduction, interruption or discontinuation of everolimus in the management of adverse reactions are summarized in Table 6-4, Table 6-5 and Table 6-6.

Table 6-4 Recommendation of everolimus dose reductions

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

[redacted]

Table 6-5 Everolimus dose adjustment and management recommendation for adverse reactions

Adverse Drug Reaction	Severity[a]	Everolimus Dose Adjustment[b] and Management Recommendations
Non-infectious pneumonitis	Grade 1 Asymptomatic, radiographic findings only	No dose adjustment required. Initiate appropriate monitoring.
	Grade 2 Symptomatic, not interfering with ADL[c]	Consider interruption of therapy, rule out infection and consider treatment with corticosteroids until symptoms improve to ≤ grade 1. Re-initiate everolimus at a lower dose. Discontinue treatment if failure to recover within 4 wks.
	Grade 3 Symptomatic, interfering with ADL[c]; O_2 indicated	Interrupt everolimus until symptoms resolve to ≤ grade1. Rule out infection, and consider treatment with corticosteroids. Consider re-initiating everolimus at a lower dose. If toxicity recurs at grade 3, consider discontinuation.
	Grade 4 Life-threatening, ventilatory support indicated	Discontinue everolimus, rule out infection, and consider treatment with corticosteroids.
Stomatitis	Grade 1 Minimal symptoms, normal diet	No dose adjustment required. Manage with non-alcoholic or salt water (0.9%) mouth wash several times a day.
	Grade 2 Symptomatic but can eat and swallow modified diet	Temporary dose interruption until recovery to grade ≤1. Re-initiate everolimus at the same dose. If stomatitis recurs at grade 2, interrupt dose until recovery to grade ≤1. Re-initiate everolimus at a lower dose. Manage with topical analgesic mouth treatments (e.g. benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol or phenol) with or without topical corticosteroids (i.e. triamcinolone oral paste).[d]
	Grade 3 Symptomatic and unable to adequately eat or hydrate orally	Temporary dose interruption until recovery to grade ≤1. Re-initiate everolimus at a lower dose. Manage with topical analgesic mouth treatments (i.e. benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol or phenol) with or without topical corticosteroids (i.e. triamcinolone oral paste).[d]
	Grade 4 Symptoms associated with life-threatening consequences	Discontinue everolimus and treat with appropriate medical therapy.

[redacted]

Adverse Drug Reaction	Severity[a]	Everolimus Dose Adjustment[b] and Management Recommendations
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 ≤1. Re-initiate everolimus at the same dose. If toxicity recurs at grade 2, interrupt everolimus until recovery to grade ≤1. Re-initiate everolimus at a lower dose.
	Grade 3	Temporary dose interruption until recovery to grade ≤1. Initiate appropriate medical therapy and monitor. Consider re-initiating everolimus at a lower dose. If toxicity recurs at grade 3, consider discontinuation.
	Grade 4	Discontinue everolimus and treat with appropriate medical therapy.
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 Afinitor at a lower dose. Manage with appropriate medical therapy and monitor.
	Grade 4	Discontinue everolimus and treat with appropriate medical therapy.

[a] Severity grade description: 1 = mild symptoms; 2 = moderate symptoms; 3 = severe symptoms; 4 = life-threatening symptoms.
[b] If dose reduction is required, the suggested dose is approximately 50% lower than the dose previously administered.
[c] Activities of daily living (ADL)
[d] Avoid using agents containing alcohol, hydrogen peroxide, iodine, and thyme derivatives in management of stomatitis as they may worsen mouth ulcers.

[redacted]

Table 6-6 Dose modification guidelines for hematologic toxicities

Toxicity	Actions
Thrombocytopenia Platelet count	≥ 75000/mm3: No change 50000/ mm3 to 75000/ mm3 Hold everolimus treatment until recovery to ≥ 75000/mm3 Reintroduce everolimus at the same dose level < 50000/ mm3 Hold everolimus treatment until recovery to ≥ 75000/mm3 Reintroduce everolimus at the next lower dose level, if available.
Absolute Neutrophil count (ANC)	≥ 1000/ mm3: No change 500/ mm3 to 1000/ mm3 Hold everolimus treatment until recovery to ≥ 1000/ mm3 Reintroduce everolimus at the same dose level < 500/ mm3 Hold until recovery to ≥ 1000/ mm3. Reintroduce everolimus at the next lowest dose level, if available.
Febrile neutropenia	Hold further dosing until ANC ≥ 1250/mm3 and no fever. Then resume dosing at the next lower dose level if available.
Toxicity requiring interruption for > 4 weeks	Permanently discontinue everolimus treatment
Physicians should always manage patients according to their medical judgment based on the particular clinical circumstances.	

Management of skin toxicity

For patients with grade 1 toxicity, no specific supportive care is usually needed or indicated. Rash must be reported as an AE. Patients with grade 2 or higher toxicity may be treated with the following suggested supportive measures at the discretion of the investigator: oral minocycline, topical tetracycline, topical clindamycin, topical silver sulfadiazine, diphenphydramine, oral prednisolone (short course) topical corticosteroids or pimecrolimus.

6.2.1.2 Capecitabine

Local label should be used for capecitabine dose modifications for the management of adverse reactions or as described in Table 6-7.

[redacted]

Table 6-7 Recommended Dose Modifications of Capecitabine

Toxicity*	During a course of therapy	Dose adjustment for next treatment (% of starting dose)
Grade 1	Maintain dose level.	Maintain dose level.
Grade 2		
1st appearance	Interrupt until resolved to grade 0-1.	100%
2nd appearance		75%
3rd appearance		50%
4th appearance	Discontinue treatment permanently.	-
Grade 3		
1st appearance	Interrupt until resolved to grade 0-1.	75%
2nd appearance		50%
3rd appearance	Discontinue permanently.	-
Grade 4		
1st appearance	Discontinue permanently OR If physician deems it to be in the patient's best interest to continue, interrupt until resolved to grade 0-1.	50%

* Common Terminology Criteria for adverse events v4.0 or toxicity management per local label was used, except for the hand-and-foot syndrome

6.2.1.2.1 Adjustment of Starting Dose in Special Populations

Renal Impairment

No adjustment to the starting dose of capecitabine is recommended in patients with mild renal impairment (creatinine clearance = 51 to 80 mL/min [Cockroft and Gault, as shown below]). Dose reduction should be made if grade 2 to 4 adverse events occurred, Table 6-7.

Cockroft and Gault Equation:

$$\text{Creatinine clearance for males} = \frac{(140 - \text{age [yrs]})\ (\text{body wt [kg]})}{(72)\ (\text{serum creatinine [mg/dL]})}$$

Creatinine clearance for females = 0.85 × male value

Elderly

For capecitabine monotherapy, no adjustment in starting dose is needed. However, sever Grade 3 or 4 treatment-related adverse events were more frequent in patients ≥ 60 years old compared to younger patients. Careful monitoring of elderly patients is advisable.

Hepatic Impairment due to Liver metastasis

Patients with mild or moderate hepatic impairment due to liver metastasis should be monitored carefully while administered capecitabine. No starting dose reduction is necessary.

[redacted]

6.2.1.3 Exemestane

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.

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.

6.2.2 Follow-up for toxicities

Patients whose treatment is interrupted or permanently discontinued due to an adverse event or abnormal laboratory value must be followed at least once a week for 4 weeks, and subsequently at 4-week intervals, until resolution or stabilization of the event. All patients will be followed for onset of any new serious adverse events for 30 days following the last dose of study treatment.

6.3 Concomitant medications

All medications and non-drug therapies taken within 30 days prior to starting study treatment should be reported on the Concomitant Medication/Significant Non-drug Therapy eCRF. The investigator should instruct the patient to notify the study site about any new medications (including over-the-counter drugs and herbal/alternative medications) he/she takes after the start of study treatment. Patients must be instructed not to take any additional medications (including over-the-counter products and herbal/alternative medications) during the trial without prior consultation with the investigator. All medications (other than study treatments) and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient starts study treatment must be listed on the Concomitant medications/Significant non-drug therapy eCRF.

6.3.1 Prohibited concomitant therapy and concomitant therapy requiring caution and/or action

The following concomitant treatments are not allowed during the study:

- Investigational or commercial anticancer agents, such as chemotherapy, immunotherapy, targeted therapy, biological response modifiers, or endocrine therapy other than exemestane (including steroids) should not be given to patients.
- Hormone replacement therapy, topical estrogens (including any intra-vaginal preparations), megestrol acetate and selective estrogen-receptor modulators (e.g. raloxifene) are prohibited.

[redacted]

- Prolonged systemic corticosteroid treatment, except for topical applications (e.g. rash), inhaled sprays (e.g. obstructive airways diseases), eye drops or local injections (e.g. intra-articular) should not be given. A short duration (<2 weeks) of systemic corticosteroids is allowed (e.g. chronic obstructive pulmonary disease, anti-emetic).
- Hematopoietic growth factors (e.g. erythropoietins, G-CSF and GM-CSF) are not to be administered prophylactically. Use of these should be reserved to cases of severe neutropenia and anemia as per the labeling of these agents.
- Oral coumarin-derivate anticoagulants such as warfarin and phenprocoumon should be avoided in patients receiving capecitabine as study treatment. If patient needs to take coumarin-derivate anticoagulants anticoagulant response (INR or protrombin time) should be monitored frequently in order to adjust the anticoagulant dose based on Xeloda prescribing information. Altered coagulation parameters and / or bleeding, including deaths have been reported during concomitant use.
- Aluminium hydroxide- and magnesium hydroxide-containing antacid (such as Maalox) should not be administrated immediately after capecitabine because of their effect on the pharmacokinetics of capecitabine.

It is to be noted that:

- Use of bisphosphonate or denosumab for osteoporosis and management of bone metastases are allowed for approved indications as per local label. Chronic concomitant bisphosphonate therapy for the prevention of bone metastases are not permitted during the study. Please refer to prescribing information for details of administration. If bisphosphonate therapy is initiated after randomization, the reason for its use must be clearly documented.
- Local radiotherapy for analgesic purposes or for lytic lesions at risk of fracture may be carried out if required. Whenever possible, these patients should have a tumor assessment of the lesion(s) before they actually receive the radiotherapy. No dose modification of study treatment is needed during radiotherapy.
- Everolimus may affect the response to vaccinations making it less effective. Live vaccines should be avoided while a patient is treated with everolimus.
- The level of phenytoin should be carefully monitored in patients receiving capecitabine and phenytoin dose may need to be reduced based on Xeloda prescribing information.

6.3.1.1 CYP3A4, CYP2C9 and P-glycoprotein inhibitors/inducers/substrates

Everolimus is metabolized by CYP3A4 in the liver and to some extent in the intestinal wall. Capecitabine and its metabolites do not inhibit the metabolism of CYP3A4 substrates but capecitabine and/or its metabolites may inhibit the metabolism of CYP2C9 substrates.

Therefore:

- Co-administration of CYP2C9 substrates (e.g. Irbesartan, Losartan, Phenytoin, Cyclophosphamide) should be exercised with caution and monitored closely per capecitabine local label.
- Co-administration with strong inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, ritonavir) or should be avoided.

[redacted]

- Co-administration with moderate CYP3A4 inhibitors (e.g., erythromycin, fluconazole) or PgP inhibitors should be used with caution.
- Seville orange, star fruit, grapefruit and their juices affect CYP3A4 and PgP activity. Concomitant use should be avoided.
- Avoid the use of strong CYP3A4 inducers such as phenytoin, carbamazepine, rifampin, rifabutin, phenobarbital, St. John's wort), Please refer to Table 6-8 listing relevant inducers and inhibitors of CYP3A and to Table 6-9 for a list of relevant substrates, inducers, and inhibitors of PgP.

Note: Most of PgP inhibitors/inducers are also inhibitors/inducers of CYP3A4. In case the drug is not listed on Table 6-9 below, refer to the list of CYP3A modifiers (Table 6-8) and apply the same classification specified therein to the concerned PgP inhibitor/inducer. In the rare case the PgP inhibitor/inducer cannot be found in either Table 6-8 or Table 6-9, then consider the drug as a strong PgP inhibitor and follow the guidance as per the stated above.

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

Inducers
Strong inducers: avasimibe, carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin (rifampicin), St. John's wort (*Hypericum perforatum*)
Moderate inducers: bosentan, efavirenz, etravirine, genistein, modafinil, nafcillin, ritonavir, talviraline, thioridazine, tipranavir
Inhibitors
Strong inhibitors: boceprevir, clarithromycin, cobicistat, conivaptan, elvitegravir, indinavir, itraconazole, ketoconazole, lopinavir, mibefradil, nefazodone, nelfinavir, posaconazole (Krishna et al 2009), ritonavir, saquinavir, saquinavir, telaprevir, telithromycin, tipranavir, troleandamycin, 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
Reference: Internal Clinical Pharmacology Drug-drug interaction (DDI) memo, updated Oct 2, 2011, 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.

[redacted]

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
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, ritonavir, saquinavir, *Schisandra chinensis*, St John's wort (*Hypericum perforatum*), talinolol, telaprevir, telmisartan, ticagrelor, tipranavir, tolvaptan, valspodar, verapamil
Reference: Internal Clinical Pharmacology Drug-drug interaction (DDI) memo, updated Oct. 2, 2011, 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.

6.3.2 Study drug compliance and accountability

6.3.2.1 Study drug compliance

Records of study drug administration will be kept at the study and recorded in the Dosage Administration Record eCRF(s).

Compliance 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 study drugs (everolimus, exemestane and capecitabine).

To accurately record the administration of study treatments, the following information must be recorded in the Dosage Administration Record eCRF page throughout the study:

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

6.3.2.2 Study drug accountability

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

[redacted]

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

6.3.3 Disposal and destruction

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

7 Visit schedule and assessments

7.1 Study flow and visit schedule

Table 7-1 lists all of the assessments and indicates with an "X", the visits when they are performed. All data obtained from these assessments must be supported in the patient's source documentation. The table indicates which data are entered into the database (D) or remain in source documents only (S). Assessments that generate data for database entry and which are recorded on eCRFs are listed using the eCRF name. Assessments that are transferred to the database electronically (e.g., laboratory data) are listed by test name.

No CRF will be used as a source document.

[redacted]

Table 7-1 Visit evaluation schedule

	Category	Protocol Section	Screening	Baseline	Day 1	3 wks	6 wks	12 wks	Every 6 wks	End of treatment (EOT)	Post-treatment Evaluation		Study Evaluation Completion (SEC)	Survival follow up Every 3 months
											EOT+30 days	FU		
Visit Window						**±7 Days**				**+14 days after ending study drug**				
Visit no.			**1**	**2**	**3**	**4**	**5**	**6**	**7, 8, etc**	**777**	**501**	**502, 503 etc**	**778**	
Treatment days			**-28 to -1**	**-7 to -1**	**1**	**21**	**42**	**84**						
Screening														
Obtain Informed Consent	D	7.1.1, 11.3	X											
IRT Registration (after ICF signed)		7.1.1	X											
Patient history														
Demography	D	7.1.1.3	X											
Inclusion/exclusion criteria	D,S	5.2 / 5.3		X										
Relevant Medical history/current medical conditions	D	7.1.1.3	X											
ECG	D	7.2.2.7.1	X	Only performed if clinically indicated										
Cardiac Imaging (MUGA/ECHO)	D	7.2.2.7.2	X	Only performed if clinically indicated										
Diagnosis and extent of cancer	D	7.1.1.3	X											
HER2 and HR status	D	5.2	X											
Smoking history	D	7.1.1.3	X											

[redacted]

	Category	Protocol Section	Screening	Baseline	Day 1	3 wks	6 wks	12 wks	Every 6 wks	End of treatment (EOT)	Post-treatment Evaluation		Study Evaluation Completion (SEC)	Survival follow up Every 3 months
											EOT+30 days	FU		
Visit Window						**±7 Days**				**+14 days after ending study drug**				
Visit no.			**1**	**2**	**3**	**4**	**5**	**6**	**7, 8, etc**	**777**	**501**	**502, 503 etc**	**778**	
Treatment days			**-28 to -1**	**-7 to -1**	**1**	**21**	**42**	**84**						
Prior antineoplastic therapy (surgery, radiotherapy, medications)	D	7.1.1.3	X											
Prior/concomitant medications	D	7.1.1.3	X	X	X	X	X	X	X	X	X			
Screening log	D	7.1.1.2 7.1.1.3		X										
Pre-randomization Form	S	7.1.1.1		X										
Randomization														
IRT - Randomization		7.1.1.4			X									
Physical examination	S	7.2.2.2		X	X	X	X	X	X	X				
Weight	D	7.2.2.2		X	X	X	X	X	X	X				
Height	D	7.2.2.2		X										
Vital signs	D	7.2.2.3		X	X	X	X	X	X	X				
ECOG Performance status	D	7.2.2.4		X	X		X	X	X	X		X		
Laboratory assessments														
Hematology	D	7.2.2.6		X		X	X	X	X	X				
Chemistry	D	7.2.2.6		X		X	X	X	X	X				
Lipid Panel	D	7.2.2.6		X			X	X	X	X				
Coagulation	D	7.2.2.6		X										

[redacted]

	Category	Protocol Section	Screening	Baseline	Day 1	3 wks	6 wks	12 wks	Every 6 wks	End of treatment (EOT)	Post-treatment Evaluation		Study Evaluation Completion (SEC)	Survival follow up Every 3 months
											EOT+30 days	FU		
Visit Window						**±7 Days**				**+14 days after ending study drug**				
Visit no.			**1**	**2**	**3**	**4**	**5**	**6**	**7, 8, etc**	**777**	**501**	**502, 503 etc**	**778**	
Treatment days			**-28 to -1**	**-7 to -1**	**1**	**21**	**42**	**84**						
Urinalysis	D	7.2.2.6		X										
Hepatitis B and C screening/monitoring (if applicable)	D	4.1.1 7.2.2.5	X				X	X	X	X				
Tumor assessments	D	7.2.1	X				X	X	X	X		X		
Safety														
Adverse events	D	7.2.2.1	X	X	X	X	X	X	X	X	X			
Pulmonary Function Tests (PFTs)	D	7.2.2.8	**Not mandatory** - can be performed at screening or baseline (prior to administration of first dose), during the trial if clinically indicated, and if warranted to exclude or manage non-infection pneumonitis											
[redacted]														
Patient Reported Outcome (PRO)														
EORTC (QLQ-C30)	D	7.2.4		X			X	X	X	X		X		
EORTC module (BR23)	D	7.2.4		X			X	X	X	X		X		
TSQM	D	7.2.4				X	X	X		X				

[redacted]

	Category	Protocol Section	Screening	Baseline	Day 1	3 wks	6 wks	12 wks	Every 6 wks	End of treatment (EOT)	Post-treatment Evaluation		Study Evaluation Completion (SEC)	Survival follow up Every 3 months
											EOT+30 days	FU		
Visit Window						**±7 Days**				**+14 days after ending study drug**				
Visit no.			**1**	**2**	**3**	**4**	**5**	**6**	**7, 8, etc**	**777**	**501**	**502, 503 etc**	**778**	
Treatment days			**-28 to -1**	**-7 to -1**	**1**	**21**	**42**	**84**						
Treatments (First dose within 7 days after baseline visit)														
Everolimus + Exemestane OR Everolimus OR Capecitabine	D	6.1.1			10 mg daily + 25 mg daily									
	D	6.1.1			10 mg									
	D	6.1.1			1250 mg/m^2 twice daily for 2 weeks and 1 week rest									
Discontinuation														
IRT - Progression/ discontinuation/ Death		7.1.3								X				
Antineoplastic therapies since discontinuation of study treatment	D	7.1.4									X			
Survival Follow-up - At least every 3 months (may be via phone contact)	D	7.1.5												X

[redacted]

7.1.1 Screening and baseline

Written informed consent must be obtained before any study specific medical procedures are performed.

The investigator is obliged to give the patient thorough information about the study and the study related assessments and she should be given ample time to consider her participation. If a patient is unable to read, an impartial witness should present during the entire informed consent discussion. The original signed informed consent should be kept in the patient's source records and a photocopy of the signed consent should be provided to the patient.

For details on the screening assessments please refer to Table 7-1.

Patient Number:

Each patient in the study is uniquely identified by a **9 digit patient number** which is a combination of his/her **4-digit center number** and **5-digit subject number**. 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. At each site, the first patient is assigned patient number 1, and subsequent patients are assigned consecutive numbers (e.g. the second patient is assigned patient number 2; the third patient is assigned patient number 3). The investigator or his/her staff will access the IRT and provide the requested identifying information for the patient to register them into the IRT. Once assigned to a patient, the patient number will not be reused. If the patient fails to be randomized, the IRT must be notified within 2 days why the patient was not randomized.

To enter a patient into study:

- Obtain written consent and complete all the screening and baseline evaluations
- Pre-randomization form must be completed by site and sent to Novartis for approval prior to randomizing patient via IRT.
- Assign a 9-digit patient identifier (consisting of a 4-digit center number and 5-digit patient number).
- Contact and provide the IRT with the patient information for registration purposes.

7.1.1.1 Eligibility screening

Patient eligibility will be checked by the Sponsor once all screening and baseline procedures are completed. The Patient Pre-randomization Form will be sent from the site to the Sponsor via email for evaluation. Upon confirmation of eligibility, the Sponsor will return the signed form to the site via email. The investigator site will then be allowed to randomize the patient to the study via IRT.

Re-screening is allowed, only, for patients who meet all of the inclusion/exclusion criteria, but were not randomized due to one of the following administrative reasons:

[redacted]

- CT /MRI results have expired (>28 days prior to randomization) due to unexpected administrative issues
- Delays in sample processing, damage to the shipped samples and other administrative lab related issues.
- Unexpected drug supply issues.

Procedure for re-screening is as follows:

- Site must register the patient as a screen failure in IWRS
- Site is to send a re-screening request to the CRA within **7 days** of the screen failure date
- Patient number will be the same as the initial screening
- Informed consent doesn't need to be resigned.
- Lab assessments needs to be to performed -7 or -1 days before randomization
- 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 Relevant Medical History/Current Medical Conditions CRF.
- CRA is to review and confirm patient's eligibility for re-screening with the site.
- CRA will forward the request to the global study team using the BOLERO-6 email address [redacted] for review/approval
- CTH/CM will assess the request and provide an approval for randomization, if all eligibility criteria are met, by providing a rescreening-code (4 numbers) to the site.

Patients may be re-screened only once and must be randomized within 28 days after the recorded rescreening date. All evaluations including original assessments and repeated assessments must be collected on the eCRF.

7.1.1.2 Information to be collected on screening failures

Patients who sign an informed consent but are not randomized for any reason will be considered a screen failure. The reason for not being randomized will be entered into the Screening Log. The demographic information must also be completed for screen failure patients.

If the patient fails to be randomized, the IRT must be notified within 2 days that the patient was not randomized.

7.1.1.3 Patient demographics and other baseline characteristics

Screening assessments to confirm eligibility must be performed within **28 days** prior to randomization. The following patient demographic and baseline characteristics will be collected on the eCRF:

- Demographic information (age, sex, race etc.);
- Medical history/current active conditions;
- Smoking history

[redacted]

- 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 therapy: Date start, date end, setting (neoadjuvant vs. adjuvant vs. therapeutic), best response, reason for treatment discontinuation;
- Prior/concomitant medications;
- Additionally, the following assessments will be performed:
  a. Tumor assessment (Table 7-2);
  b. ECG;
  c. Left ventricular ejection fraction (LVEF) via ECHO or MUGA
  d. Laboratory assessments: HBV and HCV test to be performed by central laboratory.
  e. At screening visit, patients listed in Section 4.1.1 should be tested for hepatitis B (HBV DNA HBsAg, HBc Ab, and HBs Ab) and HCV RNA-PCR. If the patient is already known to have a chronic infection with HBV or HCV and is taking anti-HBV medication, the site does not have to wait for the screening HBV or HCV results from the central laboratory prior to randomization.

HBV and HCV monitoring should be done as listed in Table 7-4, Table 7-5 and Table 7-6.

Baseline assessments to confirm eligibility must be performed within 7 **days** prior to the first dose of study treatment. Baseline assessments in the study include:

- Complete physical examination/neurological exam, vital signs;
- ECOG performance status;
- Laboratory assessments will be performed by either central or local laboratory : hematology, blood chemistries, coagulation, fasting serum lipid profile, urinalysis;
- Patient reported outcome (PRO): EORTC QLQ-C30 and QLQ-BR23

In addition, the Screening Log should be completed after screening/baseline assessments are performed.

7.1.1.4 Randomization

At Visit 3 (Day 1 visit), all eligible patients will be randomized via IRT to one of the treatment arms prior to the first dose of study treatment.

The investigator or his/her delegate will log on to the IRT System after confirming that the patient fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the patient, which will be used to link the patient to a treatment arm and will specify a unique medication number for the first package of everolimus to be dispensed to the patient. The randomization number will not be communicated to the caller.

Assignment will be stratified by:

- the presence of visceral disease (yes vs. no)

A patient randomization list, produced by Novartis, will be provided by the IRT provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment groups, which in turn are linked to the study medication numbers. A separate medication

[redacted]

randomization listing will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of the study medication numbers to each of the study drugs. The randomization scheme for patients will be reviewed and approved by a member of the Biostatistics Quality Assurance Group.

Specific website information and instructions for IRT will be provided separately to each study site.

[redacted] All assessment required at Day 1 must be performed prior to dispending the study medication(s) instructed by the IRT to the patient. The first dose of study treatment should be administered on the same day as randomization.

7.1.2 Treatment period

Patients will start the study treatment as soon as possible, but not later than 7 days after being randomized, and continue to be treated per protocol until documentation of disease progression, intolerable toxicity or withdrawal of consent. However, study treatment may prematurely be discontinued for other reasons as well. Please refer to Section 7.1.3.2.

For details of assessments required for the treatment period, refer to Table 7-1.

During study treatment, the site personnel must assess study drug (everolimus, exemestane and capecitabine) compliance using pill counts at each visit. This information should be captured in the source documents. All doses taken by the patient and all dose changes during the study must be recorded on the Dosage Administration Record eCRF.

7.1.3 End of treatment visit including study completion and premature withdrawal

At the time patients discontinue the study treatment, a visit should be scheduled as soon as possible, but not later than 14 days from the last day of study medication, at which time all of the assessments listed for the End of Treatment (EOT) visit will be performed. An End of Treatment CRF page should be completed, giving the date and reason for stopping the study treatment.

7.1.3.1 Study drug discontinuation

The term “discontinuation” refers to a patient’s withdrawal from study treatment (everolimus plus exemestane, everolimus or capecitabine).

Patients who receive treatment with everolimus plus exemestane and discontinue everolimus for any reason other than progression may continue exemestane as part of the trial therapy and should follow the protocol safety and efficacy assessments as scheduled in Section 7.1. In rare cases, patients who discontinue exemestane for any reason other than progression may continue everolimus as part of the trial therapy and should follow the protocol safety and efficacy assessments as scheduled.

The patient may discontinue the study treatment for any of the following reasons:

[redacted]

- Adverse event(s)
- Disease progression, defined in Section 7.2.1
- Protocol deviation
- Subject withdrew consent
- Lost to follow-up
- Administrative problems
- Death
- Investigator decision in patient best interest

Patients who discontinue study treatment regardless of the reason must have end of treatment evaluation (Refer to Table 7-1, EOT) on the day or within 14 days after the last day of study treatment discontinuation. The investigator or his/her designee will proceed as outlined below:

- Complete the end of treatment evaluations (additional details are provided in Table 7-1) and complete the End of Treatment eCRF page indicating the date and reason for stopping the study drug.
- Update IRT immediately with everolimus discontinuation and report disease progression and/or deaths accordingly.

After the end of treatment visit, there will be additional follow-up on the patient. See Section 7.1.4 and Section 7.1.5 for further details.

- Post-treatment safety follow-up (for 30 days after last dose of study treatment);
- Patients who have discontinued study treatment and have not progressed will be followed for tumor assessments, ECOG and PRO QLQ-C30 and BR23 every 6 weeks until disease progression.
- Patients will be followed for overall survival every 3 months Survival follow-up data collection will be stopped at the time of the final PFS analysis.If patients who discontinue treatment due to “Subject withdrew consent” agree to be followed for progression and/or survival, additional data will be collected.

7.1.3.2 Premature withdrawal and study evaluation completion

Patients **may** voluntarily withdraw from the study treatment or be taken off study treatment at the discretion of the investigator at any time.

As a general rule, if a patient discontinues from the study treatment and later is withdrawn from the study, the reasons for study evaluation completion may include the following:

- Subject withdrew consent
- Lost to follow-up
- Death
- New cancer therapy
- Disease progression

[redacted]

For patients who are lost to follow-up, the investigator 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 investigator must determine the primary reason for a patient's premature withdrawal from the study and record this information on the Study Evaluation Completion eCRF.

7.1.4 Follow-up

All patients should be followed up to and including 30 days for safety after study treatment discontinuation. Adverse events and SAE information will be collected and recorded in the appropriate eCRFs. Record all concomitant medications or therapies used/taken to treat the SAEs.

If patients discontinue study treatment for any reason other than progression, lost to follow-up or consent withdrawal, the tumor assessments, ECOG performance status and EORTC QLQ C30 and BR23 will continue to be performed every 6 weeks until progression, lost to follow-up, consent withdrawal or investigator decision in patient best interest.

The first antineoplastic medications/therapies given to a patient after the last dose of study treatment must be recorded on the eCRF.

7.1.5 Survival follow-up

All patients will be followed for survival status (i.e., phone contacts, visit) at least every 3 months regardless of treatment discontinuation reason. Survival follow-up data collection will be stopped at the time of the final PFS analysis. Final PFS and OS analyses will use the same data cut-off date and only one OS analysis will be performed. Survival information will be documented in the source documents and eCRF. Additional survival follow up may be performed more frequently if a survival update is required for reporting the results or to meet safety or regulatory needs.

7.2 Assessment types

7.2.1 Efficacy assessments

7.2.1.1 Tumor assessments

Tumor response will be based on radiological tumor measurements and evaluated locally using RECIST Criteria (refer to RECIST 1.1) as described in Appendix 1.

Tumor assessments will occur every 6 weeks after randomization until disease progression with a visit window of ±7 days. All patients who discontinue from study drug(s) for any reason other than disease progression, lost to follow up and withdrawal of consent from the study will continue to have tumor assessments every 6 weeks and until the patient has documented disease progression determined by the local radiologist and/or the investigator. After approximately 150 PFS events have been documented per RECIST 1.1 by local assessment in the combination of the everolimus + exemestane and everolimus alone arms as well as in the combination of the everolimus + exemestane and capecitabine alone arms, the frequency of tumor assessments will be changed to every 12 weeks or as clinically indicated.

[redacted]

Patients must meet the following RECIST 1.1 conditions at study entry:

- The minimum size of measurable lesions at baseline should be twice the slice thickness of the baseline scans
- Measurable disease defined as at least one lesion ≥ 10 mm by CT or MRI that can be accurately measured in at least one dimension (CT scan slice thickness ≤ 5 mm)

OR

- Bone lesions: lytic or mixed (lytic + blastic) in the absence of measurable disease as defined above

Notes:

- Lymph nodes have to be ≥15 mm in short axis to be considered measurable
- 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 absence of measurable disease)

Clinical lesions (i.e., skin nodules and palpable lymph nodes) will only be considered measurable when they are superficial. For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, should not be considered as a measurable lesion in this trial. Blastic bone lesions are non-measurable. These lesions should be captured as non-target lesions on the appropriate eCRF page(s).

In the absence of measurable disease at baseline, patients with bone only lesions (lytic + blastic) will be allowed to enter the study and the following will be considered disease progression among these patients:

- the appearance of one or more new lytic lesions in bone
- the appearance of one or more new lesions outside of bone
- unequivocal progression of existing bone lesions.

Please refer to Appendix 1 for details regarding the evaluation of response criteria.

Note: If an initial observation of response is made, a confirmation scan (or photography for measurable skin lesions) should be obtained at least 4 weeks after the initial observation.

[redacted]

Table 7-2 Imaging/RECIST Assessment Collection Plan

Procedure	Screening/Baseline	During Treatment/Follow-up
CT or MRI (Chest, Abdomen, Pelvis)	Mandated	Mandated, every 6 weeks (+/- 7 days).
Whole body bone scan or skeletal survey	Mandated	If clinically indicated
Brain CT or MRI (e.g. Brain)	Mandated if symptoms suggestive of CNS metastases present	If clinically indicated
Bone X-ray (or CT / MRI)	Mandated during screening period for any hot spot or positive finding identified by bone scan/skeletal survey to confirm bone lesion(s)	Mandated for any confirmed bone lesion at screening every 6 weeks (+/- 7 days). The same method used at screening (for confirmation) should be used at each evaluation. Mandated for any hotspot or positive finding identified by bone scan/skeletal survey during treatment/follow up.
Color photography (with a ruler)	Mandated for any skin lesions at screening	Mandated for any skin lesions identified at screening every 6 weeks

7.2.1.2 Radiology procedure

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

- All lesions identified at screening (target and non-target) will be reassessed using the same method (CT scan with contrast or MRI with contrast etc.) and technique (i.e. for scans, the use of contrast, slice thickness etc.) throughout the course of the study so that the basis of measurement remains consistent for accurate comparison and determination of disease status.
- Regarding the use of contrast, at screening (≤ 4 weeks prior to randomization), all patients should have a CT scan with contrast or MRI with contrast of the chest, abdominal and pelvic area. CT scan without contrast or MRI without contrast may be used for patients who are allergic/sensitive to the radiographic contrast media used in CT scans or MRI. Ultrasound scans cannot be used to measure tumor lesions.
- All CT scans and MRIs obtained on all patients enrolled at the center should be reviewed by the local radiologist who together with the investigator will determine the local assessment of response and progression. The same radiologist/physician should perform the evaluation for the entire duration of the study if possible. All radiology evaluations will be performed by the local radiologist. All bone scans and bone imaging (X-ray, CT or MRI) obtained from the patient with bone metastases at baseline also should be reviewed similarly.

[redacted]

7.2.2 Safety and tolerability assessments

Safety assessments will consist of monitoring and recording all adverse events (AEs), including serious adverse events (SAEs), the regular monitoring of hematology, serum chemistry, coagulation, urinalysis, routine monitoring of vital signs (heart rate, blood pressure, and body temperature), weight, ECOG performance status, CT scans of the chest, abdominal, and pelvic area, physical examinations, cardiac assessments (MUGA scan/ECHO), ECG and pulmonary function tests (PFTs) if clinically indicated.

These assessments should be performed ± 7 days of the scheduled day of assessment (Table 7-1) except for adverse events and concomitant medications that will be evaluated and recorded continuously throughout the study.

Significant findings of any safety evaluation must be recorded either on the Relevant Medical History/Current Medical Conditions eCRF (if present before signing informed consent) or on the Adverse Events eCRF (if newly occurring or worsening since signing informed consent).

7.2.2.1 Adverse events

An adverse event for the purposes of this protocol is the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) occurring after signing the informed consent even if the event is not considered to be related to the study drug(s). Please refer to Section 6.1 for the protocol-specific definitions of study drug and study treatment.

Adverse events will be assessed according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, or grades 1 - 4, will be used. CTCAE grade 5 (death) will not be used in this study; rather, death information will be collected on a separate eCRF page. Adverse event monitoring should be continued for at least 30 days following the last dose of study treatment.

Adverse events that begin or worsen after informed consent should be recorded in the Adverse Events CRF. Conditions that were already present at the time of informed consent should be recorded in the Medical History page of the patient's CRF. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, or require therapy (e.g., any hematologic abnormality that requires transfusion or cytokine treatment); and should be recorded on the Adverse Events eCRF under the signs, symptoms or diagnosis associated with them. In addition, isolated abnormal laboratory values that cause study discontinuation or constitutes in and of itself a Serious Adverse Event should be recorded on the Adverse Events eCRF

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

[redacted]

1. The severity grade CTCAE grade 1-4
2. Its relationship to each study drug (suspected/not suspected)
3. Its duration (start and end dates or if continuing at final exam)
4. Action taken (no action taken; study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication taken; non-drug therapy given; hospitalization/prolonged hospitalization)
5. Whether it is serious, where 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
    - Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
        - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (specify what this includes)
        - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
        - Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
        - Social reasons and respite care in the absence of any deterioration in the patient's general condition
    - Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above

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

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

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

7.2.2.2 Physical examination, weight and height

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

[redacted]

Physical examination and weight check will be performed at the following visits:

- Baseline (≤ 7 days prior to administration of the study drugs)
- Day 1 (prior to administration of the study drugs);
- Week 3, week 6 and then every 6 weeks
- End of Treatment

Height is measured only at Baseline visit.

Significant findings that are present prior to informed consent must be included in the Relevant Medical History / Current Medical Conditions eCRF. Significant findings made after the start of study drug which meet the definition of an adverse event must be recorded on the Adverse Event eCRF.

7.2.2.3 Vital signs

Body temperature, respiration rate, sitting pulse rate and sitting blood pressure will be routinely measured.

- Baseline (≤ 7 days prior to administration of the study drugs)
- Day 1 (prior to administration of the study drugs)
- Week 3, week 6, and every 6 weeks
- End of Treatment

7.2.2.4 Performance status

The ECOG performance status Scale Index allows patients to be classified as to their functional impairment, the definition of scores in relation to the PS is given in Table 7-2.

ECOG PS will be evaluated at the following visits:

- Baseline (≤ 7 days prior to administration of the study drugs)
- Day 1 (prior to administration of the study drugs)
- Every 6 weeks
- End of treatment

Table 7-3 ECOG Performance Status Scale

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

[redacted]

7.2.2.5 Management of Hepatitis reactivation/flare

Monitoring and prophylactic treatment for hepatitis B reactivation

Table 7-4 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 from the central laboratory prior to randomization.

Table 7-4 Action to be taken based on Hepatitis B Screening Results

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

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

For hepatitis B reactivation, definition and management guidelines see Table 7-5.

Table 7-5 Guidelines for management of hepatitis B

HBV reactivation (with or without clinical signs and symptoms)*	
For patients with baseline results: Positive HBV-DNA OR Positive HBsAg --- Reactivation is defined as: [Increase of 1 log in HBV-DNA relative to baseline HBV-DNA value OR new appearance of measurable HBV-DNA]	Treat: Start a second antiviral AND Interrupt study drug administration until resolution: - ≤ baseline HBV-DNA levels If resolution occurs within 28 days, study drug should be re-started at one dose lower, if available. (see Table 6-4- 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.

[redacted]

HBV reactivation (with or without clinical signs and symptoms)*	
For patients with baseline results: Negative HBV-DNA and HBsAg AND [Positive HBs Ab (with no prior history of vaccination against HBV), OR positive HBc Ab] ---------- reactivation is defined as: New appearance of measurable HBV-DNA	Treat: Start first antiviral medication AND Interrupt study drug administration until resolution: ≤ 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.
* All reactivations of hepatitis B are to be recorded as grade 3 (CTCAE v4.0 Metabolic Laboratory/Other: Viral Re-activation), unless considered life threatening by the investigator; in which case they should be recorded as grade 4 (CTCAE v4.0 Metabolic Laboratory/Other: Viral Re-activation). Date of viral reactivation is the date on which the rise or reappearance of HBV- DNA was recorded.	

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 7-6 Guidelines for management of hepatitis C. If the patient is already known to have a chronic infection with HCV, the site does not have to wait for the screening HCV results from the central laboratory prior to randomization.

Table 7-6 Guidelines for management of hepatitis C flare

HCV flare *	
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	Discontinue study drug
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	Discontinue study drug
*All flares of hepatitis C are to be recorded as grade 3 (CTCAE v 4.0 Metabolic Laboratory/Other: Viral Flare), unless considered life threatening by the investigator; in which case they should be recorded as grade 4 (CTCAE v 4.0 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.	

[redacted]

7.2.2.6 Laboratory evaluations

The standard clinical laboratory analyses described below are to be performed by a central laboratory according to the Visit Schedule, outlined in Table 7-1.

Local laboratories may be used during the screening period to determine the eligibility criteria for a patient or during study treatment if necessary, although the use of the central laboratory is recommended. If local laboratories are used, the following items must be completed:

- Local laboratory data must be entered on the appropriate eCRF
- The lab normal ranges for each parameter analyzed must be provided to Novartis via the lab normal range (LNR) form
- A copy of the local laboratory certificate must be provided to Novartis

In addition, if at any time a patient has laboratory parameters obtained from a different outside laboratory, Novartis must be provided with a copy of the certification and a tabulation of the normal ranges for that laboratory.

Abnormal laboratory parameters which are clinically relevant (e.g., require dose modification and/or interruption of study drug, lead to clinical symptoms or signs or require therapeutic intervention), whether specifically requested in the protocol or not, must be recorded in the eCRF. When abnormal laboratory values or test results constitute an adverse event (Section 7.2.2) it must be recorded on the eCRF Adverse Events page.

The frequency of the assessments is indicated in Table 7-1 and repeated if clinically indicated. Dose modifications for abnormal laboratory values are found in Table 6-4, Table 6-5, Table 6-6 and Table 6-7.

Table 7-7 Clinical laboratory parameters collection plan

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Platelets, Red blood cells, White blood cells with Differential (including Neutrophil count., Basophils count, Eosinophils, Lymphocytes, Monocytes)
Chemistry	Fasting Glucose, Albumin, Total protein, Alkaline phosphatase, ALT (SGPT), AST (SGOT), GGT, Sodium, Potassium, Calcium, Creatinine, , Uric Acid, Total Bilirubin, Lipid profile: Total Cholesterol, LDL, HDL, Triglycerides, Blood Urea Nitrogen (BUN) or Urea
Urinalysis	Dipstick test: Bilirubin, Blood, Glucose, Ketones, Leukocytes esterase, Protein.
Coagulation	International normalized ratio [INR])
Hepatitis markers	HBV-DNA, HbsAg, HbsAb, HbcAb, HCV RNA-PCR

7.2.2.7 Cardiac assessments

7.2.2.7.1 Electrocardiogram (ECG)

A standard 12-lead ECG is to be performed at screening and if clinically indicated during the study. Tracings must be dated and signed by the investigator (or his/her designee) and filed with the subject's source documentation. Results from 12-lead ECG should be captured on the ECG Evaluation eCRF. Significant findings must be recorded as Relevant Medical History /Current Medical Conditions (if present before signing informed consent). 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 added to the Adverse Event eCRF.

[redacted]

7.2.2.7.2 Cardiac Imaging – MUGA (multiple gated acquisition) scan or echocardiogram

MUGA scan or echocardiogram (ECHO) to assess LVEF will be performed at screening. Significant findings must be recorded as Relevant Medical History / Current Medical Conditions.

If clinically indicated, a post-baseline LVEF assessment may be performed at the discretion of the investigator. Any clinically relevant findings should be added to the Adverse Event eCRF. The same method (MUGA or ECHO) should be used throughout the course of the study so that the basis of assessment remains consistent for accurate comparison.

7.2.2.8 Monitoring for pneumonitis (pulmonary function tests)

Pulmonary function tests can be performed only if clinically indicated. During study treatment, all pulmonary function tests (Spirometry, Room air O2 saturation at rest, DLCO) must be performed if the patient develops non-infectious pneumonitis according to the management guidelines addressed in Table 6-5.

When needed, PFTs must be performed under supervision of trained personnel. Potential lung radiological changes can be detected by the Chest CT scans that are performed on all patients every 6 weeks for tumor assessment according to the schedule of events (Table 7-1). A bronchoscopy with biopsy and/or a bronchoalveolar lavage (BAL) will be performed only when medically necessary for ensuring patient care. When non-infectious pneumonitis is diagnosed, consultation with a pulmonologist should be considered.

Further details are provided in Section 6.2.1 and Table 6-5.

[redacted]

[redacted]

[redacted]

7.2.4 Patient reported outcomes

Patient reported outcomes (PRO) will be evaluated using the EORTC QLQ-C30, the breast module BR23 questionnaire and Treatment Satisfaction Questionnaire for Medication (TSQM) version 1.4. The EORTC QLQ-C30 and the module BR23 were developed to assess the quality of life of breast cancer patients, while TSQM is to assess patient's satisfaction with the study treatment. Completion of the PRO questionnaires will be dependent on the availability of EORTC QLQ-C30, BR23 and TSQM in the local language.

EORTC QLQ-C30 and BR29 will be performed at the following visits:

- Baseline
- Every 6 weeks during the study treatment
- EOT
- Every 6 weeks during post-treatment follow-up

TSQM will be performed at the following visits:

- Week 3
- Week 6
- Week 12
- EOT

Samples of these questionnaires can be found on the website of the EORTC and PROQOLID groups for research into Quality of Lifethe PRO:

http://groups.eortc.be/qol/downloads/modules/specimen_20qlq_c30.pdf (version present as of January 2009)

http://groups.eortc.be/qol/downloads/modules/specimen_20qlq_br23.pdf (version present as of January 2009)

proqolid.org/instruments/treatment_satisfaction_questionnaire_for_medication_tsqm (version present as of May 2012)

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,

[redacted]

require therapy (e.g., hematologic abnormality that requires transfusion or hematological stem cell support), or require changes in study medication(s).

Except 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 Relevant Medical History/Current Medical Conditions CRF. Adverse event monitoring should be continued for at least 30 days following the last dose of study treatment. Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate Adverse Event.

Adverse events will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

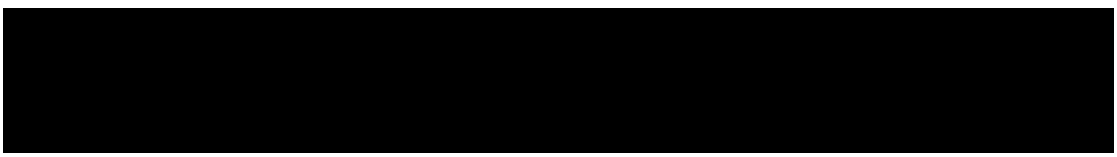
If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, corresponding to Grades 1 - 4, will be used. CTCAE Grade 5 (death) will not be used in this study; rather, information about deaths will be collected on the Death form or EOT/SEC/Survival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

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

1. The severity grade (CTCAE Grade 1-4)
2. Its duration (Start and end dates, or ongoing at End of Study)
3. Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes)
   or
   Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes, investigational treatment, Yes, the study treatment (non-investigational), Yes, both and/or indistinguishable)
4. Action taken (none, study drug dosage adjusted/temporarily interrupted, study drug permanently discontinued due to this adverse event, hospitalization/prolonged hospitalization, unknown)
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.



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

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

8.1.2 Laboratory test abnormalities

8.1.2.1 Definitions and reporting

Laboratory abnormalities that constitute an Adverse event in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the Adverse Events CRF. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g. anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for Adverse Events should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported adverse event, it is not necessary to separately record the lab/test result as an additional event.

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

8.1.3 Adverse events of special interest

8.1.3.1 Definition

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

- Stomatitis
- Infections & Infestations
- Rash
- Non-infectious pneumonitis
- Hyperglycemia

In the BOLERO-2 study of postmenopausal women with estrogen receptor positive, locally advanced or metastatic breast cancer who were refractory to letrozole or anastrazole, patients experienced the following adverse events of special interest in the everolimus + exemestane arm of the study:

[redacted]

Table 8-1 AEs of special interest

Adverse Event	Everolimus + Exemestane (n=482), %		
	All Grades	Grade 3	Grade 4
Stomatitis	67	8	0
Infections & Infestations	50	4	2
Rash	44	2	<1
Non-infectious pneumonitis	19	4	<1
Hyperglycemia	15	5	<1

Source: Summary of Clinical Safety (cut-off date: 08-Jul-2011)

For details for the management of the AEs of special interest, please refer to Section 6.2.

8.2 Serious adverse events

8.2.1 Definitions

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

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Note that hospitalizations for the following reasons should not be reported as serious adverse events:
  - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - Social reasons and respite care in the absence of any deterioration in the patient's general condition
- Note that treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE given above is not a serious adverse event.

8.2.2 Reporting

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

Any SAEs experienced after this 30 days period should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment. Recurrent episodes,

[redacted]

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 treatment (if there is more than one study treatment), 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, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the Novartis study treatment, 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 Directive 2001/20/EC or as per national regulatory requirements in participating countries.

8.3 Emergency unblinding of treatment assignment

This is an open label study.

8.4 Pregnancies

Not applicable.

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.

[redacted]

8.6 Data Monitoring Committee

Data Monitoring Committee (DMC) will be constituted. The DMC will be responsible for the overall risk/benefit assessment of the study by reviewing the efficacy results from the interim analysis as well as accumulating safety data at regular intervals and being provided access to additional efficacy data as requested.

The DMC will consist of at least two oncologists and one biostatistician and will be formed prior to randomization of the first patient. Detailed recruitment status and interim safety reports will be provided to the DMC on a regular basis. The first DMC meeting will be held prior to randomization of the first patient. The first data review will be held when at least one month data are available for the first 30 randomized patients. Subsequent data reviews will occur every six months unless otherwise requested by the Chairman of the DMC. The DMC role will continue until the final analysis of PFS is performed.

The DMC will provide recommendations to the Head of Oncology Global Development at Novartis.

The DMC recommendations will include, but not limited to:

- No safety or efficacy issues, ethical to continue the trial as planned
- Ethical to continue the study but recommend an amendment to the protocol (e.g., incorporate an additional safety interim analysis before the next scheduled analysis)
- Serious safety concerns precluding further study treatment, regardless of efficacy

In case the DMC recommends continuing the study as planned with the everolimus monotherapy arm based on the efficacy interim analysis, the results of this efficacy interim analysis will not be revealed until the final analysis.

Further information detailing the membership and operational aspects of the DMC are provided in the DMC charter.

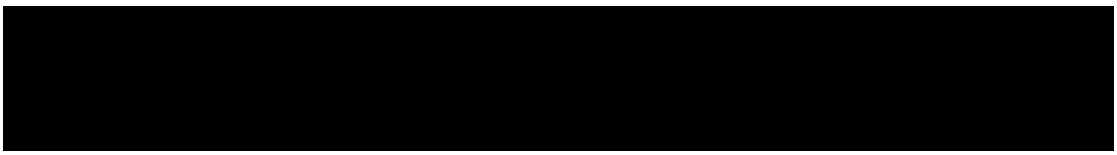
8.7 Steering Committee

A Study Steering Committee (SSC) will also be constituted for overseeing the conduct of the study and making any necessary recommendations as needed. The SSC will include at least four main investigators. Other members may be added after consultation with the SSC members. The SSC will also include two Novartis physicians, a statistician and the clinical trial head. The details of the role of the Steering Committee will be defined in a Steering Committee charter.

9 Data collection and management

9.1 Data confidentiality

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



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

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

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

9.2 Site monitoring

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

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

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

For studies using Electronic Data Capture (EDC), the designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs and, allow modification or verification of the entered data by the investigator staff.

The Principal Investigator is responsible for assuring that the data entered into eCRF is complete, accurate, and that entry and updates are performed in a timely manner.

[redacted]

The study sites will collect the protocol required laboratory samples and will send these samples to a Central Laboratory for analysis. Laboratory samples will be processed centrally and the results will be transmitted to the investigative staff, to Novartis (or to the designated CRO). As needed, blood work done at local laboratories will be collected as unscheduled assessments. Documentation (such as certifications and normal ranges) for all local laboratories used must be collected for data management. Please refer to the [Central Laboratory Manual] for detailed instructions on central laboratory sample collection and analysis.

9.3 Database management and quality control

For studies using eCRFs, Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff is required to respond promptly to queries and to make any necessary changes to the data.

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

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

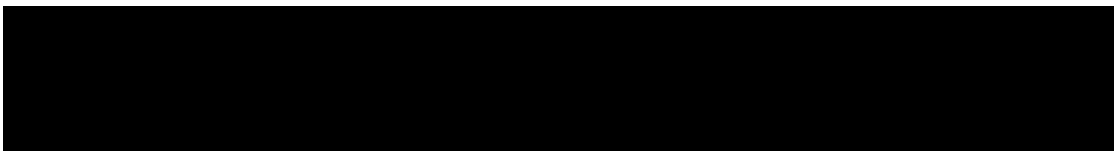
Randomization codes and data about everolimus treatment dispensed to the patient will be tracked using an Interactive Response Technology. The system will be supplied by a vendor(s), who will also manage the database. The data will be sent electronically to Novartis personnel (or designated CRO).

Authorization is required prior to making any database changes to locked data, by joint written agreement between the Global Head of Biostatistics and Data Management and the Global Head of Clinical Development.

Since this is EDC study, the investigator will receive a CD-ROM or paper copies of the patient data after the database lock for archiving at the investigational site.

10 Statistical methods and data analysis

It is planned that the data from all centers participating in the trial will be combined, so that an adequate number of patients is available for analysis. Novartis will perform all the analyses. The efficacy interim analysis and safety analyses for the DMC meetings will be performed by the independent statistician and independent programmer. Any data analyses performed independently by any investigator should be submitted to Novartis before publication or presentation.



10.1 Analysis sets

10.1.1 Full Analysis Set

The Full Analysis Set (FAS) comprises all patients to whom study treatment has been assigned by randomization. All primary analyses will be conducted using data from this population according to the intent-to-treat (ITT) principle, i.e., patients will be analyzed according to the treatment and stratum they have been assigned to during the randomization procedure.

10.1.2 Safety Set

The Safety Set includes all patients who received at least one dose of study medication and have at least one post-baseline safety evaluation. Patients will be analyzed according to the study treatment (regimen) they actually received.

Note: the statement that a patient had no adverse events (on the adverse event eCRF) constitutes a safety assessment.

The safety analysis for patients who received everolimus monotherapy arm that cross over to everolimus + exemestane combination arm (second line medication) will be performed on the subset of Safety set patients receiving at least one dose of second line medication. This subset will be referred to as Safety set 2nd line (Safety-2L).

10.1.3 Per-protocol Set

Not Applicable

10.1.4 Dose-determining analysis set

Not Applicable

10.2 Patient demographics/other baseline characteristics

Baseline demographic and disease characteristics data will be listed and summarized by treatment group using the FAS. Qualitative data such as sex, race, etc. will be presented using frequency tables (counts and proportions by category). Relevant descriptive statistics (mean, median, minimum, maximum and standard deviation in most cases) will be used to present quantitative data.

10.3 Treatments (study treatment, concomitant therapies, compliance)

10.3.1 Study treatment

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

[redacted]

10.3.2 Concomitant therapies

Concomitant medications and relevant non-drug therapies taken concurrently with the study drugs will be listed and summarized by Anatomical Therapeutic Chemical Classification System (ATC) term, preferred term and treatment arm by means of frequency counts and proportions. These summaries will include medications starting on or after the start of study treatment or medications starting prior to the start of study treatment and continuing after the start of study treatment.

Any prior concomitant medications or relevant non-drug therapies starting and ending prior to the start of study treatment will be listed.

The safety set will be used for all aforementioned concomitant medication tables and listings.

10.4 Primary objective

The primary objective of this study is to estimate the hazard ratio of a progression-free survival event comparing the everolimus + exemestane combination therapy with the everolimus monotherapy in postmenopausal women with ER-positive, HER2-negative, advanced breast cancer (ABC) after recurrence or progression on letrozole or anastrozole.

10.4.1 Variable

The primary endpoint in this study is progression-free survival (PFS), defined as the time from the date of randomization to the date of first documented progression or death due to any cause. If a patient has not had an event, PFS will be censored at the date of the last adequate tumor assessment (see RECIST 1.1 in Appendix 1). Disease progression for primary endpoint derivation will be assessed using the local (treating center's) investigator's/radiologist's tumor assessment.

10.4.2 Statistical model and method of analysis

The primary endpoint, PFS, as determined based on the local tumor assessment, will be analyzed using data from the FAS following the ITT principle, i.e., patients will be analyzed according to the treatment group they were randomized and the stratum they were assigned to at the baseline. Distribution of PFS will be assessed using the Kaplan-Meier estimation method. The estimated median PFS and probability of not experiencing a PFS event by 2, 4, 6 and 9 months, along with 90% confidence intervals, will be presented by the two treatment groups. The stratified Cox regression model will be used to estimate the hazard ratio (HR) of a PFS event, along with the associated 90% confidence interval, comparing the everolimus + exemestane combination therapy with everolimus monotherapy where the stratification information will be obtained through IRT.

10.4.3 Handling of missing values/censoring/discontinuations

This is an event-driven trial and the final PFS analysis will be performed after approximately 150 PFS events have been documented in each of the two following groups: (i) the everolimus + exemestane plus the everolimus monotherapy arm, and (ii) the everolimus + exemestane arm plus the capecitabine monotherapy arm. A database cut-off date will be established after approximately 150 PFS events have been documented in both (i) and (ii) defined above. For

[redacted]

the final analysis, PFS will be censored on the cut-off date if no PFS event is observed before or on the cut-off date, or on the date a new anti-neoplastic therapy, whichever occurs earlier. The censoring date will be the date of the last adequate tumor assessment before either of those two dates. If a PFS event is observed after two or more missing or non-adequate tumor assessments, then the date of progression will be censored at the date of the last adequate tumor assessment. If a PFS event is observed after a single missing or non-adequate tumor assessment, the actual date of event will be used.

10.4.4 Supportive analyses

A sensitivity analysis will be performed to assess the PFS treatment effect using the unstratified Cox regression model yielding the hazard ratio estimate of a PFS event along with the 90% confidence interval.

Other sensitivity analyses will be performed that will additionally include PFS events recorded after two or more missed or non-adequate tumor assessments with the PFS event date defined as (i) the actual event date [actual event PFS analysis], and (ii) the date of the next scheduled tumor assessment [backdating PFS analysis].

Descriptive analyses within subgroups defined by the single stratification factor will be performed: the analyses will include Kaplan-Meier PFS summaries, hazard ratio point and interval estimates from unstratified Cox regression models.

A Cox regression model will be used to evaluate the effect of baseline demographic and disease characteristics on PFS. The robustness of the PFS hazard ratio estimate to the adjustment for various prognostic factors in the Cox model including prior chemotherapy (yes vs. no), performance status (0 vs. 1 or 2), patients with bone lesions only at baseline (yes vs. no), time since first diagnosis of metastasis/recurrence to randomization (<= 6 months vs. > 6 months), non-steroidal aromatase inhibitor (NSAI) (letrozole or anastrozole) use (adjuvant vs. metastatic setting), number of organs involved (1 vs. 2 vs. ≥ 3), and PgR status (positive vs. negative) will be assessed. The strata will be based on stratification information obtained through IRT.

10.5 Secondary objectives

10.5.1 Key secondary objective

The key secondary objective of this study is to estimate the hazard ratio of a PFS using local investigator's/radiologist's tumor assessments comparing the everolimus + exemestane combination therapy with the capecitabine therapy in postmenopausal women with ER-positive, HER2-negative, advanced breast cancer after recurrence or progression on letrozole or anastrozole.

Distribution of PFS will be assessed using the Kaplan-Meier estimation method. The estimated median PFS and probability of not experiencing a PFS event by 2, 4, 6 and 9 months, along with 90% confidence intervals, will be presented by the two treatment groups. The stratified Cox regression model will be used to estimate the hazard ratio (HR) of a PFS event, along with the associated 90% confidence interval, comparing the everolimus + exemestane combination therapy with the capecitabine therapy where the stratification

[redacted]

information will be obtained through IRT. The confidence interval for the HR will not be adjusted for multiple comparisons. The same missing value/censoring rules as in Section 10.4.3 will apply.

10.5.2 Other secondary objectives

Other secondary objectives of this study are to evaluate each of everolimus + exemestane versus everolimus monotherapy and everolimus + exemestane versus capecitabine monotherapy with respect to overall survival (OS), overall response rate (ORR), clinical benefit rate (CBR), deterioration in the ECOG performance status, changes in quality of life scores over time, and safety.

10.5.2.1 Overall Survival (OS)

Overall survival (OS) is defined as the time from the date of randomization to the date of death due to any cause. The final OS analysis will be conducted at the same time as the final PFS analysis using the same data cut-off date. If death has not been observed by the analysis cut-off date, then OS will be censored at the date of last contact.

The OS analysis will be based on data from the FAS on the ITT basis, i.e., according to the treatment group patients are randomized to at baseline. Distribution of OS in each of the three treatment arms will be assessed using the Kaplan-Meier estimation method. The estimated median OS and probability of surviving at the estimated median OS, along with 90% confidence intervals, will be presented for the three treatment arms. Stratified Cox regression models will be used to estimate the hazard ratio (HR) of death from any cause, along with the associated 90% confidence interval, comparing (i) the everolimus + exemestane combination therapy with everolimus monotherapy, and (ii) the everolimus + exemestane combination therapy with capecitabine monotherapy where the stratification information will be obtained through IRT.

10.5.2.2 Overall Response Rate (ORR)

Overall response rate (ORR) is defined as the proportion of patients with best overall response of complete response (CR) or partial response (PR) according to RECIST 1.1 (Appendix 1). ORR will be calculated based on the FAS according to the ITT principle, using local radiologist's/investigator's tumor assessment. Patients with bone lesions only at baseline will be included in the numerator if they achieve a complete response. ORR estimates will be presented by treatment group along with exact 90% confidence intervals (Clopper and Pearson 1934). The estimation procedure will be repeated based on data for a subset of patients in the FAS with measurable disease only at baseline.

10.5.2.3 Clinical Benefit Rate (CBR)

Clinical Benefit Rate (CBR) is defined as the proportion of patients with best overall response of CR, PR or stable disease (SD) with duration of 24 weeks or longer. A patient will be considered to have a SD for 24 weeks or longer if SD is recorded at 24 weeks or later after randomization. Taking into account the allowed time window for tumor assessment visits, the SD response has to be recorded at 23 weeks or later after randomization to be included in the CBR calculation. CR, PR and SD are defined according to RECIST 1.1 (see Appendix 1).

[redacted]

CBR will be calculated based on the FAS according to the ITT principle, using local radiologist's/investigator's tumor assessment. Patients with non-measurable disease only at baseline will be included in the numerator if they achieve a complete response. CBR will be summarized for the three treatment groups using descriptive statistics.

10.5.2.4 ECOG Performance Status

ECOG performance status (PS) scale as described in Table 7-3 will be used to assess physical health of patients. An analysis of the time to definitive deterioration of the ECOG PS by at least one category of the score from baseline will be performed. A deterioration is considered definitive if no improvements in the ECOG PS are observed at subsequent measurement times during the treatment period following the time point at which the deterioration is observed.

Death will be considered as worsening of the ECOG PS if it occurs close to the last available assessment, where "close" is defined as being within twice the planned period between two assessments. Patients who die after more than twice the planned period between two assessments will be censored at the date of their last assessment before the cut-off.

Patients receiving any further anti-neoplastic therapy prior to definitive worsening will be censored at their date of last assessment prior to the start of therapy. Patients that have not worsened at the data cut-off point will be censored at the date of last assessment prior to the cutoff.

The Kaplan-Meier estimation method will be used to assess the distribution of time to definitive worsening in the ECOG PS score, stratified by treatment. The estimated treatment-specific median times to definitive worsening will be presented along with 90% confidence intervals.

10.5.2.5 Patient-reported outcomes (PRO)

The FAS will be used for all PRO summaries and listings.

Quality of life questionnaire (QLQ)

The EORTC QLQ-C30 questionnaire along with the breast module (BR23) will be used to collect patients' quality of life (QoL) data. Raw QoL data will be scored according to the EORTC scoring manual. The global health status/QoL scale score is identified as the primary QoL variable of interest. Physical functioning, emotional functioning and social functioning scale scores are identified as secondary QoL variables of interest.

The number of patients providing QoL data and the number of patients missing/expected to have QoL assessments will be summarized by each treatment group for scheduled assessment time points.

Descriptive statistics (count, mean, median, standard deviation, first and third quartile) will be used to summarize individual item and multi-item scale scores at each scheduled assessment time. Patients will be included if they completed at least one questionnaire item. Additionally, change from baseline in the scale scores at the time of each assessment will be summarized.

Time to definitive 10% deterioration in the global health status / QoL, and in each of the three secondary scales, will be examined for the three treatment arms. In addition, time to definitive

[redacted]

5-point deterioration in the global health status / QoL score will be explored for each treatment arm. The assessed distributions will be presented descriptively using Kaplan-Meier curves. Summary statistics based on Kaplan-Meier distributions will be presented, including the estimated median time to definitive 10% (5-point) deterioration and the probability of not experiencing definitive 10% (5-point) deterioration by 12 and 24 weeks. Both point estimates and 90% confidence intervals will be presented.

Definitive 10% (5-point) deterioration is defined as a decrease in score by at least 10% (5-points) compared to baseline, with no later increase above this threshold observed during the course of the study. A single-item measure reporting a decrease of at least 10% (5-point) is considered definitive only if it is the last one available for the patient. Baseline is defined as the latest available assessment made on or before the date of randomization. Time to definitive deterioration is the number of days between the date of randomization and the date of the assessment at which definitive deterioration is seen.

Death will be considered as deterioration of symptoms/QoL if it occurs close to the last available assessment where "close" is defined as twice the planned period between two assessments. This avoids overestimating the time to definitive worsening in patients dying after an irregular assessment scheme. Patients who die after more than twice the planned period between two assessments since the last assessment will be censored at the date of their last available questionnaire.

Patients receiving any further anti-neoplastic therapy before definitive worsening will be censored at the date of their last assessment before starting this therapy. Patients that have not worsened as of the cut-off date for the analysis will be censored at the date of their last assessment (questionnaire) before the cut-off.

Treatment satisfaction questionnaire for medication (TSQM)

Patients' self-reported satisfaction or dissatisfaction with the study treatment will be measured using the Treatment Satisfaction Questionnaire for Medication (TSQM) version 1.4. Patients will provide assessments of treatment satisfaction at week 3, 6, 12, and the end-of-treatment (EOT)visit. The questionnaire will be administered in the patients' local language in a quiet setting.

TSQM items will be divided into four scales: side effects, effectiveness, convenience, and global satisfaction. Raw TSQM data will be scored according to the scoring manual

Descriptive statistics (count, mean, median, standard deviation, first and third quartile) will be used to summarize individual item and multi-item scale scores by treatment group and assessment time point (week 3, week 12, and EOT). For weeks 3 and 12, differences in mean scale scores along with 90% confidence intervals comparing treatment satisfaction with everolimus + exemestane versus everolimus alone, and everolimus + exemestane versus capecitabine alone will be reported (no significance testing will be performed).

[redacted]

10.5.3 Safety objectives

10.5.3.1 Analysis set and grouping for the analyses

For all safety analyses, the safety set will be used. The assessment of safety will be based mainly on the frequency of adverse events and on the number of laboratory values that fall outside of pre-determined ranges. All safety data will be listed.

The overall observation period will be divided into three mutually exclusive segments:

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

10.5.3.2 Adverse events (AEs)

All adverse events recorded during the study will be summarized. The incidence of treatment-emergent AEs, i.e., AEs that started or worsened during the on-treatment period, will be summarized by system organ class, preferred term, severity (based on CTCAE grades), type of adverse event and relation to the study drug by treatment group. Deaths reportable as severe adverse events (SAEs) and non-fatal SAEs will be listed by patient and tabulated by type of adverse event and treatment group. All AEs (including those from the pre- and post-treatment periods) will be listed and those collected during the pre- and post-treatment period will be flagged.

Adverse events will be summarized by presenting the number and percentage of patients having any adverse event in each body system and having each individual adverse event. Any other information collected (e.g., severity or relatedness to study medication) will be listed as appropriate.

In addition, adverse events of related nature and/or for which there is a specific clinical interest in connection with the study treatments may be analyzed by categories regrouping the relevant preferred terms, as appropriate. For each such category, the number and percentage of patients with at least one AE belonging to the category will be reported.

10.5.3.3 Laboratory abnormalities

All laboratory values will be converted into SI units and the severity grade calculated using appropriate common toxicity criteria (CTCAE).

A listing of laboratory values will be provided by laboratory parameter, patient, and treatment group. A separate listing will display notable laboratory abnormalities (i.e., newly occurring CTCAE grade 3 or 4 laboratory toxicities). The frequency of laboratory abnormalities will be displayed by parameter and treatment group.

Laboratory data will be classified into CTC grades according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) v4.0. A severity grade of 0 will be assigned when the value is within normal limits. In the unlikely case when a laboratory

[redacted]

normal range overlaps into the higher (i.e. non-zero) CTC grade, the laboratory value will still be taken as within normal limits and assigned a CTC grade of zero.

Besides listings, the following summaries will be produced for the laboratory data (by laboratory parameter and treatment):

- Number and percentage of patients with worst post-baseline CTC grade (regardless of the baseline status). Each patient will be counted only for the worst grade observed post-baseline.
- Shift tables using CTC grades to compare baseline to the worst post-baseline value will be produced for hematology and biochemistry laboratory parameters with CTC grades.

For laboratory parameters where CTC grades are not defined, shift tables to the worst post-baseline value will be produced using the low/normal/high classifications based on laboratory reference ranges.

10.5.3.4 Vital signs

Vital sign assessments will be performed in order to characterize basic body function. The parameters expected to be collected include: height (cm), weight (kg), body temperature (°C), heart rate (beats per minute), systolic and diastolic blood pressure (mmHg), and respiration rate (breaths per minute).

The criteria for clinically notable abnormalities are defined as follows:

Clinically notable elevated values

- systolic BP: ≥ 180 mmHg and an increase ≥ 20 mmHg from baseline
- diastolic BP: ≥ 105 mmHg and an increase ≥ 15 mmHg from baseline
- body temperature: ≥ 39.1°C
- weight: increase from baseline of ≥ 10%
- heart rate: ≥ 120 bpm with increase from baseline of ≥15 bpm

Clinically notable below normal values

- systolic BP: ≤ 90 mmHg and a decrease ≥ 20 mmHg from baseline
- diastolic BP: ≤ 50 mmHg and a decrease ≥ 15 mmHg from baseline
- body temperature: ≤ 35°C
- weight: decrease from baseline of ≥ 10%
- heart rate: ≤ 50 bpm with decrease from baseline of ≥ 15 bpm.

The following summaries will be produced for each vital sign parameter:

- summary statistics for change from baseline to the worst post-baseline value (in both directions, i.e., from baseline to the highest post-baseline and from baseline to the lowest post-baseline value)
- number and percentage of patients with at least one post-baseline vital sign abnormality (in both directions, i.e., both elevated and below normal values).

In addition, the following two listings will be produced by treatment group:

[redacted]

- patients with clinically notable vital sign abnormalities
- all vital sign assessments will be listed by patient and vital sign parameter.

In both listings, the clinically notable values will be flagged and also the assessments collected later than 30 days after the last treatment/exposure date will be flagged.

10.5.3.5 Other safety data

Data from other tests (e.g. electrocardiogram, pulmonary function tests, LVEF) will be listed, notable values will be flagged, and any other information collected will be listed as appropriate.

All assessments collected later than 30 days after the last treatment/exposure date will be flagged in the listings.

Any statistical tests performed to explore the data will be used only to identify any interesting comparisons that may warrant further consideration.

10.6 Interim analysis

An efficacy interim analysis will be conducted to allow early termination of the everolimus monotherapy arm, in case the efficacy in the everolimus monotherapy arm is by far inferior compared to the everolimus + exemestane combination arm. This efficacy interim analysis is planned after 75 PFS events have been reached across the following 2 arms: everolimus monotherapy and everolimus + exemestane combination treatment.

At the time of interim analysis, the observed hazard ratio along with the 90% confidence interval will be provided for decision making. A general guidance is to stop everolimus monotherapy arm if the observed hazard ratio is less than 0.20 (i.e., if the everolimus monotherapy arm is far inferior when compared to the everolimus + exemestane combination arm).

In addition, simulation (Wei L.J. 2007) will also be carried out to predict the hazard ratio and 90% confidence interval at the final analysis conditional on the data observed at interim.

In summary, only the observed hazard ratio along with its 90% confidence interval will be used for decision making. However, the predicted hazard ratio along with its 90% confidence interval will be provided as complementary information.

10.7 Sample size calculation

The primary objective of this study is to estimate the hazard ratio of PFS comparing everolimus + exemestane versus everolimus alone with approximately 150 PFS events. For this number of PFS events, the precision of HR estimation is illustrated by tabulating the approximate 90% confidence intervals (Jennison and Turnbull 1999) for the hazard ratio (HR) (see Table 10-1) under different point estimates for the HR.

[redacted]

Table 10-1 Approximate* 90 percent CI bounds for HR

	Assuming 146 observed PFS events		Assuming 150 observed PFS events	
Estimated HR	**Lower bound of approximate 90% CI for HR**	**Upper bound of approximate 90% CI for HR**	**Lower bound of approximate 90% CI for HR**	**Upper bound of approximate 90% CI for HR**
0.55	0.419	0.722	0.420	0.719
0.60	0.457	0.788	0.459	0.785
0.65	0.495	0.853	0.497	0.850
0.70	0.533	0.919	0.535	0.916
0.75	0.571	0.985	0.573	0.981
* Jennison and Turnbull (1999)				

A total of 300 patients are planned to be recruited at a uniform rate over an 18-month enrollment period and randomized with equal allocation to one of the three treatment arms. Assuming the median PFS time to be 7 months in the everolimus + exemestane arm (Baselga et al 2012), 4 months in the everolimus monotherapy arm (NCI-Canada), and 6 months in the capecitabine monotherapy arm (O'Shaughnessy et al 2012, Stocker et al 2007, Jäger et al 2010, Kaufmann et al 2010, Robert 2011), the expected time to observe 150 PFS events in each of the two pairwise treatment comparisons is about 28 months after the randomization date of the first patient in the study, assuming that about 10% of the patients will be lost to follow-up or withdraw consent.

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.

[redacted]

11.3 Informed consent procedures

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

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

Novartis will provide to investigators, in a separate document, a proposed informed consent form (ICF) that is considered appropriate for this study and complies with the ICH GCP guideline and regulatory requirements. Any changes to this ICF suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC/REB, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC/REB approval.

11.4 Discontinuation of the study

Novartis reserves the right to discontinue this study under the conditions specified in the clinical study agreement. Specific conditions for terminating the study are outlined in Section 4.5.

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.

[redacted]

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

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

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

11.7 Confidentiality of study documents and patient records

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

11.8 Audits and inspections

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

11.9 Financial disclosures

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

[redacted]

12 Protocol adherence

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

12.1 Amendments to the protocol

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

[redacted]

13 References (available upon request)

Abraham RT, Gibbons JJ. (2007) The Mammalian Target of Rapamycin Signaling Pathway: Twists and Turns in the Road to Cancer Therapy. Clin Cancer Res 13; 3109-3114.

Awada A, Cardoso F, Fontaine C, et al. (2008) The oral mTOR inhibitor RAD001 (everolimus) in combination with letrozole in patients with advanced breast cancer: results of a phase I study with pharmacokinetics. Eur J Cancer. 44(1):84-91.

Bachelot T, Bourgier C, Cropet C. et al (2012) Randomized Phase II Trial of Everolimus in Combination With Tamoxifen in Patients With Hormone Receptor–Positive, Human Epidermal Growth Factor Receptor 2–Negative Metastatic Breast Cancer With Prior Exposure to Aromatase Inhibitors: A GINECO Study. J Clin Oncol. 30(22):2718-24

Baselga J, Semiglazov V, van Dam P, et al. (2009) Phase II randomized study of neoadjuvant everolimus plus letrozole compared with placebo plus letrozole in patients with estrogen receptor-positive breast cancer. J Clin Oncol. 27(16):2630-7.

Baselga J, Campone M, Piccart-Gebhart MJ, et al (2011) Everolimus in combination with exemestane in the treatment of postmenopausal women with estrogen receptor-positive metastatic breast cancer who are refractory to letrozole or anastrozole: Preliminary results of the BOLERO-2 trial. J Clin Oncol 29: 2011 (suppl; abstr e11058)

Baselga J, Campone M, Piccart M, et al. (2012) Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. N Engl J Med. 366:520-9.

Barrios CH, Sampaio C, Vinholes J, et al. (2009) What is the role of chemotherapy in estrogen receptor-positive, advanced breast cancer? Ann Oncol. 20:1157-62.

Beslija S, Bonneterre J, Burstein HJ, Cocquyt V, et al. (2009) Third consensus on medical treatment of metastatic breast cancer. Ann Oncol. 20:1771-85.

Beuvink I, Boulay A, Fumagalli S et al. (2005). The mTOR Inhibitor RAD001 Sensitizes Tumor Cells to DNA-Damaged Induced Apoptosis through Inhibition of p21 Translation; Cell. 120: 747-759.

Bjornsti M-A, Houghton PJ. (2004) The TOR pathway: A target for cancer chemotherapy. Nature Reviews Cancer 4:335-48.

Boulay A, Rudloff J, Ye J, et al. (2005) Dual inhibition of mTOR and estrogen receptor signaling in vitro induces cell death in models of breast cancer. Clin Cancer Res. 11 :5319-28

Burstein HJ. (2011) Introduction: Current and future approaches to chemotherapy in patients with resistant breast cancer. Semin Oncol. 38 Suppl 2:S1-2.

Buzdar A. (2003) Pharmacology and Pharmacokinetics of the Newer Generation Aromatase Inhibitors. Clinical Cancer Research 9, 468s-472s, (Suppl.)

Campbell RA, Bhat-Nakshatri P, Patel NM, et al. (2001). Phosphatidylinositol 3-kinase /AKTmediated activation of estrogen receptor alpha: a new model for anti-estrogen resistance. J Biol Chem; 276:9817–9824

Cardoso F, Fallowfield L, Costa A, et al (2011) Locally recurrent or metastatic breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 22 Suppl 6:vi25-30.

[redacted]

Clopper C, Pearson S (1934) The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika 26: 404-413.

Crowe A, Lemaire M. (1998) In vitro and in situ absorption of SDZ-RAD using a human intestinal cell line (Caco-2) and a single pass perfusion model in rats: comparison with rapamycin. Pharm Res. 15(11):1666-72.

Demers, L M, Lipton A, Harvey H A et al. (1993). The efficacy of CGS 20267 in suppressing estrogen biosynthesis in patients with advanced stage breast cancer. J Steroid Biochem Mol Biol 44: 687–691.

Efeyan A, Sabatini DM. (2010) mTOR and cancer: many loops in one pathway. Curr Opin Cell Biol. 22:169-76.

Ellard S, Clemons M, Gelmon K et al (2009) A randomized phase II study comparing two schedules of everolimus in patients with recurring/metastatic breast cancer: National Cancer Institute of Canada Clinical Trials Group IND.163. J Clin Oncol. 27:4536-41.

Guba M, von Breitenbuch P, Steinbauer M, et al. (2002) Rapamycin inhibits primary and metastatic tumor growth by antiangiogenesis: involvement of vascular endothelial growth factor. Nat Med. 8(2):128-35

Hutson P R, Love R, Havighurst T et al. (2005). Effect of Exemestane on Tamoxifen Pharmacokinetics in Postmenopausal Women Treated for Breast Cancer; Clin Cancer Res 2005;11(24) 8722-8727

Jäger E, Al-Batran S, Saupe S, et al. (2010) A randomized phase III study evaluating pegylated liposomal doxorubicin (PLD) versus capecitabine (CAP) as first-line therapy for metastatic breast cancer (MBC): Results of the PELICAN study. J Clin Oncol 28:15s (suppl; abstr 1022).

Jemal A, Bray F, Center MM, et al. (2011) Global cancer statistics. CA Cancer J Clin. 61:69-90.

Jennison C, Turnbull BW, (1999) Group Sequential Methods: Applications to Clinical Trials. (Book)

Johnston SR. (2006) Targeting downstream effectors of epidermal growth factor receptor/HER2 in breast cancer with either farnesyltransferase inhibitors or mTOR antagonists. Int J Gynecol Cancer. 16 Suppl 2:543-8.

Kaufmann M, Maass N, Costa SD, et al (2010) First-line therapy with moderate dose capecitabine in metastatic breast cancer is safe and active: results of the MONICA trial. Eur J Cancer. 46:3184-91.

Kuhn B, Jacobsen W, Christians U, et al (2001) Metabolism of sirolimus and its derivative everolimus by cytochrome P450 3A4: insights from docking, molecular dynamics, and quantum chemical calculations. J Med Chem. 44(12):2027-34.

Lane HA, Wood JM, McSheehy PM, et al. (2009) mTOR inhibitor RAD001 (everolimus) has antiangiogenic/vascular properties distinct from a VEGFR tyrosine kinase inhibitor. Clin Cancer Res. 15(5):1612-22

Laplante A, Demeule M, Murphy GF, et al (2002) Interaction of immunosuppressive agents rapamycin and its analogue sdz-rad with endothelial p-gp. Transplant Proc. 34:3393-5.

[redacted]

Loomba R, Rowley A, Wesley R, et al (2008). Systematic review: the effect of preventive lamivudine on hepatitis B reactivation during chemotherapy. Ann Intern Med 148(7): 519-28.

Lønning P, Bajetta E, Murray R et al. (2000) Activity of Exemestane in Metastatic Breast Cancer after failure of Nonsteroidal Aromatase Inhibitors: A phase II trial, J Clin Onc 18: 2234-2244

Mabuchi S, Altomare DA, Connolly DC, et al (2007a) RAD001 (Everolimus) delays tumor onset and progression in a transgenic mouse model of ovarian cancer. Cancer Res 67: 2408-2413.

Marangoni E, Vincent-Salomon A, Auger N, et al. (2007) A new model of patient tumor-derived breast cancer xenografts for preclinical assays. Clin Cancer Res. 13(13):3989-98.

Miller WR. (2010) Aromatase inhibitors: prediction of response and nature of resistance. Expert Opin Pharmacother. 11(11):1873-87.

NCCN. (2012) Clinical Practice Guidelines for NSCLC Version 2.

O'Shaughnessy JA, Kaufmann M, Siedentopf F, et al. (2012) Capecitabine monotherapy: review of studies in first-line HER-2-negative metastatic breast cancer. Oncologist. 17:476-84.

Piccart-Gebhart MJ, Noguchi S,. Pritchard, KI et al. (2012) Everolimus for postmenopausal women with advanced breast cancer: Updated results of the BOLERO-2 phase III trial. J Clin Oncol 30: (suppl; abstr 559).

Plourde PV, Dyroff M, Dowsett M et al. (1995). ARIMIDEX: a new oral, once-a-day aromatase inhibitor. J Steroid Biochem Mol Biol 53*:* 175–179.

Robert NJ, Diéras V, Glaspy J, et al (2011) RIBBON-1: randomized, double-blind, placebo-controlled, phase III trial of chemotherapy with or without bevacizumab for first-line treatment of human epidermal growth factor receptor 2-negative, locally recurrent or metastatic breast cancer. J Clin Oncol. 29(10):1252-60.

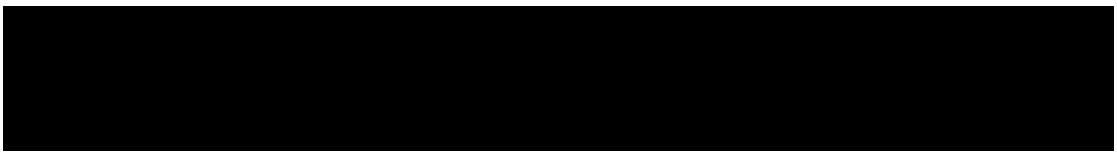
Santen RJ, Song RX, Zhang Z et al. (2005). Adaptive hypersensitivity to estrogen: mechanisms and clinical relevance to aromatase inhibitor therapy in breast cancer treatment. J Steroid Biochem Mol Biol 95:155–165

Sarbassov DD, Ali SM, Sengupta S, et al. (2006) Prolonged rapamycin treatment inhibits mTORC2 assembly and Akt/PKB. Mol Cell. 22:159-68.

Schiff R, Massarweh SA, Shou J, et al. (2004) Cross-talk between estrogen receptor and growth factor pathways as a molecular target for overcoming endocrine resistance. Clin Cancer Res. 10(1 Pt 2):331S-6S.

Sledge GW, Neuberg D, Bernardo P, et al. (2003) Phase III trial of doxorubicin, paclitaxel, and the combination of doxorubicin and paclitaxel as front-line chemotherapy for metastatic breast cancer: an intergroup trial (E1193). J Clin Oncol. 21(4):588-92.

Stockler M, Sourjina T, Grimison P, et al (2007) A randomized trial of capecitabine (C) given intermittently (IC) rather than continuously (CC) compared to classical CMF as first-line chemotherapy for advanced breast cancer (ABC). J Clin Oncol, 25:18s (2007 ASCO Annual Meeting Proceedings Part I., 2007: 1031)



Tabernero J, Rojo F, Calvo E, et al. (2008) Dose- and schedule-dependent inhibition of the mammalian target of rapamycin pathway with everolimus: a phase I tumor pharmacodynamics study in patients with advanced solid tumors. J Clin Oncol 26:1603-1610

Tanaka C, O'Reilly T, Kovarik JM, et al (2008) Identifying optimal biologic doses of everolimus (RAD001) in patients with cancer based on the modeling of preclinical and clinical pharmacokinetic and pharmacodynamic data. J Clin Oncol 26: 1596-1602

Tokunaga E, Kimura Y, Oki E, et al. (2006). Akt is frequently activated in HER2/neu-positive breast cancers and associated with poor prognosis among hormone-treated patients. Int J Cancer. 118:284–289.

Tsutsumi N, Yonemitsu Y, Shikada Y, et al. (2004) Essential role of PDGFRalpha-p70S6K signaling in mesenchymal cells during therapeutic and tumor angiogenesis in vivo: role of PDGFRalpha during angiogenesis. Circ Res. 94(9):1186-94.

Verma S, McLeod D, Batist G, et al. (2011) In the end what matters most? A review of clinical endpoints in advanced breast cancer. Oncologist .16:25–35

Wei L.J. (2007). “Data Monitoring in Clinical Trials Using Prediction”, Drug Information Journal 2007 41: 733

Yamnik RL, Digilova A, Davis DC, et al. (2009) S6 kinase 1 regulates estrogen receptor alpha in control of breast cancer cell proliferation. J. Biol. Chem. 284:6361-9.

Yamnik RL, Holz MK. (2010) mTOR/S6K1 and MAPK/RSK signaling pathways coordinately regulate estrogen receptor alpha serine 167 phosphorylation. FEBS Lett. 584:124-8. Epub .

Yu Y, Sato JD (1999) MAP kinases, phosphatidylinositol 3-kinase, and p70 S6 kinase mediate the mitogenic response of human endothelial cells to vascular endothelial growth factor. J Cell Physiol 178: 235–246

Yue W, Fan P, Wang J, et al. (2007) Mechanisms of acquired resistance to endocrine therapy in hormone-dependent breast cancer cells. J Steroid Biochem Mol Biol; 106:102-110

[redacted]

14 Appendices

14.1 Appendix 1

Harmonization of Efficacy Analysis of Solid Tumor Studies

Guidelines for Response, Duration of Overall Response, TTF, TTP, Progression-Free Survival and Overall Survival (based on RECIST 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

Authors (Version 3.1): [redacted]

Authors (Version 3): [redacted]

Authors (Version 2): [redacted]

Authors (Version 1): [redacted]

[redacted]

Glossary

CR	Complete response
CRF	Case Report Form
CSR	Clinical Study Report
CT	Computed tomography
DFS	Disease-free survival
eCRF	Electronic Case Report Form
FPFV	First patient first visit
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
[redacted]	[redacted]
TTP	Time to progression
UNK	Unknown

[redacted]

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

14.1.2 Efficacy assessments

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

14.1.3 Definitions

14.1.4 Disease measurability

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

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

For patients without measurable disease see Section 14.1.26

Measurable lesions (both nodal and non-nodal)

- Measurable non-nodal - As a rule of thumb, the minimum size of a measurable non-nodal target lesion at baseline should be no less than double the slice thickness or 10mm whichever is greater - e.g. the minimum non-nodal lesion size for CT/MRI with 5mm cuts will be 10 mm, for 8 mm contiguous cuts the minimum size will be 16 mm.
- Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components, that can be evaluated by CT/MRI, can be considered as measurable lesions, if the soft tissue component meets the definition of measurability.

[redacted]

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

14.1.5 Eligibility based on measurable disease

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

14.1.6 Methods of tumor measurement - general guidelines

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

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

- All measurements should be taken and recorded in metric notation (mm), using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.
- Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

[redacted]

- For optimal evaluation of patients, the same methods of assessment and technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Contrast-enhanced CT of chest, abdomen and pelvis should preferably be performed using a 5 mm slice thickness with a contiguous reconstruction algorithm. CT/MRI scan slice thickness should not exceed 8 mm cuts using a contiguous reconstruction algorithm. If, at baseline, a patient is known to have a medical contraindication to CT contrast or develops a contraindication during the trial, the following change in imaging modality will be accepted for follow up: a non-contrast CT of chest (MRI not recommended due to respiratory artifacts) plus contrast-enhanced MRI of abdomen and pelvis.
- A change in methodology can be defined as either a change in contrast use (e.g. keeping the same technique, like CT, but switching from with to without contrast use or vice-versa, regardless of the justification for the change) or a change in technique (e.g. from CT to MRI, or vice-versa), or a change in any other imaging modality. A change in methodology will result by default in a UNK overall lesion response assessment. However, another response assessment than the Novartis calculated UNK response may be accepted from the investigator or the central blinded reviewer if a definitive response assessment can be justified, based on the available information.
- **FDG-PET**: can complement CT scans in assessing progression (particularly possible for 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:
  - Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
  - No FDG-PET at baseline with a positive FDG-PET at follow-up:
- If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.
- If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT are needed to determine if there is truly progression occurring at that Site (if so, the date of PD will be the date of the initial abnormal CT scan).
- If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
- **Chest x-ray**: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- **Ultrasound**: When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

[redacted]

- **Endoscopy and laparoscopy**: The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.
- **Tumor markers**: Tumor markers alone cannot be used to assess response. However, some disease specific and more validated tumor markers (e.g. CA-125 for ovarian cancer, PSA for prostate cancer, alpha-FP, LDH and Beta-hCG for testicular cancer) can be integrated as non-target disease. If markers are initially above the upper normal limit they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.
- **Cytology and histology**: Cytology and histology can be used to differentiate between PR and CR in rare cases (i.e., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors). Cytologic confirmation of neoplastic nature of any effusion that appears or worsens during treatment is required when the measurable tumor has met the criteria for response or stable disease. Under such circumstances, the cytologic examination of the fluid collected will permit differentiation between response and stable disease (an effusion may be a side effect of the treatment) or progressive disease (if the neoplastic origin of the fluid is confirmed).
- **Clinical examination**: Clinical lesions will only be considered measurable when they are superficial (i.e., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

14.1.7 Baseline documentation of target and non-target lesions

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

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

Minimum target lesion size at baseline

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

[redacted]

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

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

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

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

14.1.9 Follow-up and recording of lesions

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

14.1.10 Non-nodal lesions

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

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

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

[redacted]

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

14.1.11 Nodal lesions

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

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

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

14.1.12 Determination of target lesion response

Table 14-1 Response criteria for target lesions

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

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

Notes on target lesion response

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

[redacted]

- 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.

[redacted]

- Since lesions less than 10 mm are considered normal, a CR for target lesion response should be assigned when all nodal target lesions shrink to less than 10 mm and all non-nodal target lesions have disappeared.
- Once a CR target lesion response has been assigned a CR will continue to be appropriate (in the absence of missing data) until progression of target lesions.
- Following a CR, a PD can subsequently only be assigned for target lesion response if either a non-nodal target lesion "reappears" or if any single nodal lesion is at least 10 mm and there is at least 20% increase in sum of the diameters of all nodal target lesions relative to nadir with at least 5 mm increase in the absolute sum of the diameters.

14.1.13 Determination of non-target lesion response

Table 14-2 Response criteria for non-target lesions

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

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

Notes on non-target lesion response

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

[redacted]

14.1.14 New lesions

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

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

14.1.15 Evaluation of overall lesion response

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

Table 14-3 Overall lesion response at each assessment

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

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

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

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

[redacted]

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

14.1.16 Efficacy definitions

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

14.1.17 Best overall response

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

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

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

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

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

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

- CR = at least two determinations of CR at least 4 weeks apart before progression where confirmation required or one determination of CR prior to progression where confirmation not required
- PR = at least two determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR) where confirmation required or one determination of PR prior to progression where confirmation not required

[redacted]

- SD = at least one SD assessment (or better) > 6 weeks after randomization/start of treatment (and not qualifying for CR or PR).
- PD = progression ≤ 12 weeks after randomization/ start of treatment (and not qualifying for CR, PR or SD).
- UNK = all other cases (i.e. not qualifying for confirmed CR or PR and without SD after more than 6 weeks or early progression within the first 12 weeks)

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

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

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

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

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

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

- Investigator overall lesion response
- Novartis calculated overall lesion response (based on measurements from Investigator)

The primary analysis of the best overall response will be based on the sequence of investigator's overall lesion responses.

[redacted]

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

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

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

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

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

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

14.1.18 Time to event variables

14.1.19 Progression-free survival

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

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

14.1.20 Overall survival

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

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

[redacted]

14.1.21 Time to progression

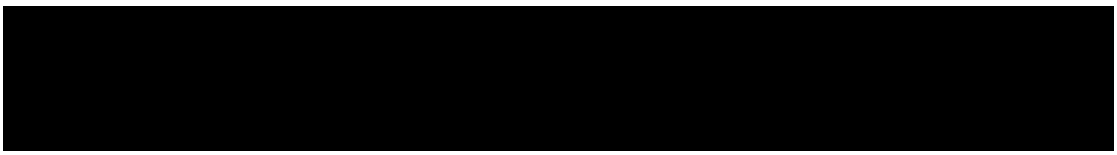
Some studies might consider only death related to underlying cancer as an event which indicates progression. In this case the variable "Time to progression" might be used. TTP is defined as PFS except for death unrelated to underlying cancer.

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

14.1.23 Duration of response

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

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



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

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

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

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

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

14.1.24 Time to response

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

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

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

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

[redacted]

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

Assessment date

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

Start dates

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

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

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

End dates

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

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

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

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

[redacted]

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

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

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

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

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

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

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

[1] As defined in Section 14.1.8.

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

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

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

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

[redacted]

14.1.27 Sensitivity analyses

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

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

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

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

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

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

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

[redacted]

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

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

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

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

Additional suggestions for sensitivity analyses

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

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

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

14.1.28 Data handling and programming rules

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

14.1.29 Study/project specific decisions

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

[redacted]

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

14.1.30 End of treatment phase completion

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

The end of treatment visit and its associated assessments should occur within 14 days of the last study treatment.

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

- Adverse event(s)
- Lost to follow-up
- Investigator decision in patient best interest
- Protocol deviation
- Administrative problems
- Subject withdrew consent
- Death
- Progressive disease

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

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

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

- Adverse event
- Subject withdrew consent
- Lost to follow-up
- Protocol deviation
- Administrative problems
- Death
- New cancer therapy
- Progressive disease
- Follow-up phase completed as per protocol

14.1.32 Medical validation of programmed overall lesion response

As RECIST is very strict regarding measurement methods (i.e. any assessment with more or less sensitive method than the one used to assess the lesion at baseline is considered UNK) and not available evaluations (i.e. if any target or non-target lesion was not evaluated the

[redacted]

whole overall lesion response is UNK unless remaining lesions qualified for PD), these UNK assessments may be re-evaluated by clinicians at Novartis or external experts. In addition, data review reports will be available to identify assessments for which the investigators' or central reader's opinion does not match the programmed calculated response based on RECIST criteria. This may be queried for clarification. However, the investigator or central reader's response assessment will never be overruled.

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

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

14.1.33 Programming rules

The following should be used for programming of efficacy results:

14.1.34 Calculation of 'time to event' variables

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

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

14.1.35 Incomplete assessment dates

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

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

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

14.1.36 Incomplete dates for last known date patient alive or death

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

[redacted]

14.1.37 Non-target lesion response

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

14.1.38 Study/project specific programming

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

14.1.39 Censoring reason

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

For survival the following censoring reasons are possible:

- Alive
- Lost to follow-up

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

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

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

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

[redacted]

14.1.40 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

FDA Guidelines: 2005 Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, April 2005

FDA Guidelines: 2007 Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, May 2007

Morgan TM (1988) Analysis of duration of response: a problem of oncology trials. Cont Clin Trials; 9: 11-18

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

[redacted]