NOVARTIS

Clinical Development and Medical Affairs

RAD001/Everolimus

Protocol CRAD001Y24135 / NCT01698918

# An open-label, phase II, single-arm study of everolimus in combination with letrozole in the treatment of postmenopausal women with estrogen receptor positive HER2 negative metastatic or locally advanced breast cancer

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| Authors | [redacted] |
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## Table of contents



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[redacted]

## List of tables



[redacted]

## List of figures



[redacted]

## List of abbreviations

| | |
|---|---|
| ABC | Advanced Breast Cancer |
| AE | Adverse Event |
| AI | Aromatase Inhibitor |
| ALT | Alanine aminotransferase/glutamic pyruvic transaminase/GPT |
| ANC | Absolute Neutrophil Count |
| AST | Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT |
| AUC | Area Under the Curve |
| [redacted] | [redacted] |
| BC | Breast Cancer |
| BUN | Blood Urea Nitrogen |
| CBR | Clinical Benefit Rate |
| CDP | Clinical Development Plan |
| Cmax | Maximum blood concentration |
| CMO&PS | Chief Medical Office and Patient Safety |
| CPK | Creatine phosphokinase |
| CRF | Case Report/Record Form; the term CRF can be applied to either EDC or Paper |
| CRO | Contract Research Organization |
| CSR | Clinical study report |
| CSR addendum | An addendum to Clinical Study Report (CSR) that captures all the additional information that is not included in the CSR |
| [redacted] | [redacted] |
| CV | Coefficient of variation |
| CYP3A4 | Cytochrome P450 3A4 |
| ECG | Electrocardiogram |
| ER | Estrogen Receptor |
| FAS | Full Analysis Set |
| HER-2 | Human Epidermal Growth Factor Receptor 2 |
| HMG | 3-hydroxy-3-methyl-glutaryl |
| HR | Hormone Receptor |
| ICH | International Conference on Harmonization |
| IEC | Independent Ethics Committee |
| IHC | Immunohistochemistry |
| INR | International Normalized Ratio |
| IRB | Institutional Review Board |
| IRT | Interactive Response Technology that includes Interactive Voice Response System and Interactive Web Response System |
| IV | Intravenous(ly) |
| IVRS | Interactive Voice Response System |
| LHRH | Luteinizing hormone-release hormone |
| LLLT | Low Level Laser Therapy |
| MBC | Metastatic Breast Cancer |
| MTD | Maximum Tolerated Dose |

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| | |
|---|---|
| mTOR | mammalian Target Of Rapamycin |
| NCCN | National Comprehensive Cancer Network |
| NSAI | Non-steroidal Aromatase Inhibitor |
| ORR | Overall Response Rate |
| OS | Overall Survival |
| OSDQ | Oral Stomatitis Daily Questionnaire |
| PFS | Progression Free Survival |
| PgP | P-glycoprotein |
| PgR | Progesterone Receptor |
| PHI | Protected Health Information |
| [redacted] | [redacted] |
| pNET | Pancreatic Neuroendocrine Tumor |
| PRO | Patient Reported Outcome |
| PT | Prothrombin Time |
| PTT | Partial Thromboplastin Time |
| RAP | The Report and Analysis Plan (RAP) is a regulatory document which provides evidence of preplanned analyses |
| RCC | Renal Cell Carcinoma |
| REB | Research Ethics Board |
| S6K | S6 ribosomal protein kinase |
| SAE | Serious Adverse Event |
| SEGA | Subependymal Giant Cell Astrocytoma |
| SOC | Standard of Care |
| [redacted] | [redacted] |
| Tmax | Time to maximum concentration |
| TS | Tuberous Sclerosis |
| TSC | Tuberous Sclerosis Complex |
| TTP | Time To Progression |
| ULN | Upper Limit of Normal |
| VEGF | Vascular Endothelial Growth Factor |

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## Glossary of terms

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| Assessment | A procedure used to generate data required by the study |
| Cohort | A group of newly enrolled patients treated at a specific dose and regimen (i.e. treatment group) at the same time |
| Cycles | Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g.: q28 days) |
| Dose level | The dose of drug given to the patient (total daily or weekly etc.) |
| Enrollment | Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol) |
| First line setting | Everolimus plus letrozole as first line treatment for patients with metastatic or locally advanced unresectable breast cancer |
| Second line setting | Everolimus plus exemestane treatment following progression on first line therapy with everolimus plus letrozole |
| Investigational drug | The study treatment whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug.” |
| Investigational treatment | Drug whose properties are being tested in the study as well as their associated placebo and active treatment controls (when applicable). This also includes approved drugs used outside of their indication/approved dosage, or that are tested in a fixed combination. Investigational treatment generally does not include other study treatments administered as concomitant background therapy required or allowed by the protocol when used in within approved indication/dosage |
| Medication number | A unique identifier on the label of each study treatment package which is linked to one of the treatment groups of a study |
| Other study treatment | Any drug administered to the patient as part of the required study procedures that was not included in the investigational treatment |
| Patient No. | A unique identifying number assigned to each patient/subject/healthy volunteer who enrolls in the study |
| Period | A subdivision of the study timeline; divides stages into smaller functional segments such as screening, baseline, titration, washout, etc. |
| Premature patient withdrawal | Point/time when the patient exits from the study prior to the planned completion of all study treatment administration and/or assessments; at this time all study treatment administration is discontinued and no further assessments are planned, unless the patient will be followed for progression and/or survival |
| Randomization number | A unique treatment identification code assigned to each randomized patient, corresponding to a specific treatment arm assignment |
| Stage related to study timeline | A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc. |
| Stage in cancer | The extent of a cancer in the body. Staging is usually based on the size of the tumor, whether lymph nodes contain cancer, and whether the cancer has spread from the original site to other parts of the body |

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| Stop study participation | Point/time at which the patient came in for a final evaluation visit or when study treatment was discontinued whichever is later |
| Study treatment | Includes any drug or combination of drugs in any study arm administered to the patient (subject) as part of the required study procedures, including placebo and active drug run-ins.<br>In specific examples, it is important to judge investigational treatment component relationship relative to a study treatment combination; study treatment in this case refers to the investigational and non-investigational treatments in combination. |
| Study treatment discontinuation | Point/time when patient permanently stops taking study treatment for any reason; may or may not also be the point/time of premature patient withdrawal |
| Supportive treatment | Refers to any treatment required by the exposure to a study treatment, e.g. premedication of vitamin supplementation and corticosteroid for pemetrexed disodium. |
| Treatment group | A treatment group defines the dose and regimen or the combination, and may consist of 1 or more cohorts. Cohorts are not expanded, new cohorts are enrolled. |
| Variable | Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints |

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## Amendment 5 (14-Feb-2017)

### Amendment rationale

The main purpose of the amendment is to add an Extension Phase for up to three years to continue to monitor safety and provide access to treatment for patients who are continuing to benefit from treatment with everolimus following the overall survival cutoff which is 24 months post last patient first visit (LPFV) of the core study phase. The first line combination treatment (everolimus + letrozole) is not approved in label for any country and for the second line combination (everolimus + exemestane) some countries mandate that the treatment be provided without cost to patients and some countries have limited availability of supply. For these reasons, treatment will continue to be provided to patients receiving treatment at the time of implementation of this amendment. Treatment will be provided for the respective line of treatment (first or second) that the patients are currently receiving at the time of starting the Extension Phase. This new amendment will continue safety monitoring however supersede the previous amendment (Amendment 4) with regard to the method of access to treatment. In the previous amendment, the method of access to treatment was planned by offering patients participation in a rollover study, however the Novartis rollover studies are not approved for the combination therapies of this trial.

During the Extension Phase, patients will be evaluated as per institution's standard of care to determine clinical benefit and safety will continue to be monitored as per the protocol requirements. The purpose of the extension is to continue safety monitoring and provide access to treatment; the only efficacy assessment to be collected will be the physician's determination of whether or not the patient is continuing to clinically benefit from the study treatment. Note: Efficacy assessments will continue to be collected as per protocol until approval of this amendment and patients have transitioned to the Extension Phase.

To date, enrollment in the study is closed. LPFV was achieved on 17-Dec-2014. A total of two hundred and two patients were enrolled in the study. At the time of the data cut-off of the 17-Jun-2016 (18 months after the last patient's recruitment), 64 patients were ongoing in the 1$^{st}$ line treatment setting and 19 patients were ongoing in the 2$^{nd}$ line treatment setting. The study closure will occur once the last patient last visit (LPLV) in the study has been documented.

### 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:

| Section | Change |
|---|---|
| List of Abbreviations | Updated list of abbreviations to reflect those present in this protocol version |
| Protocol Summary | Added text in reference to Extension Phase |

[redacted]

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|---|---|
| Protocol Summary<br>4.1<br>6.1<br>6.1.2<br>7.1.3<br>7.1.4<br>7.1.5 | Throughout protocol made consistent the reference for the reasons for discontinuation. |
| 1.1 | Updated references and everolimus information |
| 1.2.1<br>1.2.1.1<br>6.1.3.1<br>6.2.1<br>6.2.2<br>6.2.2.1<br>6.2.2.2<br>6.2.2.5<br>6.2.2.6<br>6.2.2.10 | Updated text to current IB (27-Apr-2016) / Program standard language (Aug2016) |
| 1.2.1.4 | Updated references and everolimus information |
| 1.2.1.5<br>1.2.1.6<br>2.1<br>2.3<br>2.4 | Updated references |
| 3 | Added objectives for the Extension Phase under Secondary Objectives (Table 3-1) |
| 4.1 | Added text to describe the addition of the Extension Phase. Updated text to distinguish aspects that are different in the Extension phase compared to the Core Phase. Removed reference to the rollover study (from previous amendment, Amendment 4). Clarified the overall survival cutoff. Updated Study Design figure (Figure 4-1) to include Extension Phase |
| 4.3 (new) | Added Section Definition of end of study (not in previous version) to clarify end of study |
| 5.1 | Clarified that patients in the Core Phase that progress can be offered second line treatment |
| 6.1 | Clarified that when patients on first line treatment in the Extension Phase they will not be offered second line treatment and that the OSDQ will not be administered during the Extension Phase |
| 6.1.1<br>6.1.2 | Updated to reflect addition of Extension Phase |
| 6.3.2 | Added text regarding that during the Extension Phase, standard of care at the patient's site as recommended by the investigator to treat stomatitis will be followed |
| 7.1 | Updated the visit schedules as a result of adding the Extension Phase |

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| 7.1.3 | Clarified that when patients progress while on first line treatment in the Extension Phase they will not be offered second line treatment and clarified that "documented disease progression" refers to the image scan that determined disease progression |
| 7.1.4 (new) | Added new section to detail Extension Phase procedures |
| 7.1.5 (previously 7.1.4) | Clarified the EOT eCRFs that will be used in the main study phase and the Extension Phase. Removed reference to rollover (from previous amendment, Amendment 4) |
| 7.1.6<br>(previously 7.1.5)<br>7.1.6.1<br>(previously 7.1.5.1.1) | Removed reference to rollover (from previous amendment, Amendment 4) |
| 7.1.6.2 | Clarified cutoff for overall survival. |
| 7.2.1<br>7.2.2<br>7.2.2.1<br>7.2.2.2<br>7.2.2.3<br>7.2.2.4<br>7.2.2.6.1 | Add text regarding assessments not required during Extension Phase. |
| 7.2.6 | Clarified that OSDQ will not be administered during the Extension Phase. |
| 8.2.2 | [redacted] |
| 10.2<br>10.3.1<br>10.3.2<br>10.5<br>10.5.5.1<br>10.5.5.2<br>10.5.5.2.1<br>10.5.5.2.2<br>10.5.5.2.3<br>10.5.5.3 (new) | Updated statistical section to reflect changes made due to the addition of the Extension Phase. |
| 13 | Updated references |

## 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]

# Amendment 4

## Amendment rationale

The main purpose of the amendment is to clarify that patients who are benefiting from treatment with Afinitor at the time of overall survival analysis may discontinue this study and transition to commercial Afinitor or to a rollover study. The study closure will occur once the last patient last visit (LPLV) in the study has been documented.

A rollover study allows patients to continue to be treated from multiple protocols in one program spanning multiple indications. Patients will be evaluated as per institution's standards and safety will continue to be monitored as per rollover protocol requirements.

Several Novartis rollover studies are available such as the global rollover study: CRAD001C2X01B or local studies (e.g. CRAD001C1X01B in Japan, CRAD001C2XB in Thailand). Choice of rollover studies will be depending on the country/site location. These studies have reduced scheduled assessments for the patients, reduced data collection, queries and monitoring frequencies.

Patients may also transition to commercially available treatments, where possible as per local regulations. Patients will be evaluated as per institution's standards and safety will continue to be monitored as per prescribing information.

In addition, the amendment clarifies the timing of the analysis of progression free survival for second line treatment. This analysis will be performed 18 months after last patient first visit (LPFV) only if there is adequate number of patients in second line treatment at that time. Otherwise, the analysis will be performed 24 months after LPFV at the same time as the overall survival analysis.

To date, enrollment in the study is closed. Last patient first visit was achieved on 17$^{th}$ of December 2014. A total of two hundred and two patients were enrolled in the study. At the release date of this amendment, 127 patients were ongoing in the 1$^{st}$ line treatment setting and 11 patients were ongoing in the 2$^{nd}$ line treatment setting. A total of 20 patients were randomized in the stomatitis therapeutic intervention sub-study.

As mentioned in protocol Section 10.5.4, the overall survival analysis will be performed 24 months after LPFV which occurred on 17$^{th}$ of December 2014.

## 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:

- Section 4.1 Description of study design:

Specific language added indicating that patients still benefiting from Afinitor at time of overall survival analysis may discontinue the study and transition to a rollover study, where possible or to commercial supply of Afinitor. Only patients transitioning to a rollover study

[redacted]

will not need a 28 day follow up safety visit since their safety will be evaluated as part of the rollover study.

The end of study was defined by adding the following sentence: "The end of study is planned to be 24 months after last patient's recruitment when the overall survival analysis will be performed. Patients who are benefiting from treatment with Afinitor at that time may discontinue this study and transition to commercial Afinitor or to a rollover study. The study will be closed once the last patient last visit (LPLV) in the study has been documented".

Text was also added to clarify the timing of the analysis of progression free survival (PFS) for second line treatment. This analysis will be performed 18 months after the last patient's recruitment provided that the number of patients in second line treatment is adequate for a reliable PFS analysis. Otherwise, this analysis will be performed 24 months after the last patient's recruitment.

- Section 7.1.4 End of treatment visit including study completion and premature withdrawal:

Reason for end of treatment: "Treatment duration completed as per protocol" has been added. This reason will be chosen when patient ends treatment to transition to a rollover study or to commercial Afinitor. Language around the 28 days follow-up and study evaluation completion visit has been added.

- Section 7.1.5 Follow-up period:

Text added to mention that the 28-day follow-up is not applicable to the patients transitioning to the rollover study. Instead, these patients will have their safety follow-up performed and included in the study report of the rollover study.

- Section 7.1.5.1.1 Study evaluation completion:

Language added to indicate that patients transitioning to a rollover study or to commercial supply of Afinitor will not need to complete the Study Evaluation Completion visit.

- Section 10.4.3 Handling of missing values/censoring/discontinuations

Text added to clarify the timing of the analysis of progression free survival (PFS) for second line treatment. This analysis will be performed 18 months after the last patient's recruitment provided that the number of patients in second line treatment is adequate for a reliable PFS analysis. Otherwise, this analysis will be performed 24 months after the last patient's recruitment.

## 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]

## Amendment 3

### Amendment rationale

The main purpose of the amendment is to describe the process for implementing a centralized key eligibility check prior to enrollment of patients to the study.

The total number of patients that currently have been treated with everolimus, in either Novartis-sponsored clinical studies, individual patient supply programs or investigator sponsored clinical studies, as of 30-Sep-2013 was also updated.

The management of data from Oral Stomatitis Daily Questionnaires (OSDQ) has also been clarified since the data from the questionnaires are not being entered in a separate electronic database by a designated CRO. Indeed, the data from the OSDQ are being entered in the study database by the investigational staff.

In addition, the calculation of the clinical benefit rate was clarified to mention that patients with non-measurable disease only at baseline will be included into the numerator of CBR, if they achieve a complete response or stable disease lasting 24 weeks or longer. The wording used to describe the censoring rule for PFS was also clarified. These changes are only to add clarity and will not impact the statistical analysis.

As of 17$^{th}$ of March 2014, fifty six patients have been enrolled in the study.

The changes proposed by this amendment will not influence the population, design, treatment, assessments, safety monitoring, data review, statistical methods, or analysis of the primary endpoint of this study.

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.

### Changes to the protocol

The changes to the protocol are as follows:

- Section 1.2.1 Overview of everolimus and Section 6.2.1 Everolimus:

The total number of patients that currently have been treated with the study treatment as of 30-Sep-2013 has been updated to 30,582

- Section 7.1.1.1 Screening:

The eligibility checklist has been added.

- Table 7-1 Visit Evaluation Schedule (First-line treatment):
  - The eligibility checklist has been added.
- Section 9.4 Database management and quality control

The management of data from Oral Stomatitis Daily Questionnaires has been corrected to reflect the current practice.

- Section 10.4.3 Handling of missing values/censoring/discontinuations

[redacted]

The wording used to describe the censoring rule for PFS was clarified.

- Section 10.5.1 overall response rate and clinical benefit rate

Calculation of the clinical benefit rate was clarified to mention that patients with non-measurable disease only at baseline will be included into the numerator of CBR, if they achieve a complete response or stable disease lasting 24 weeks or longer.

## IRB/IEC

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

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

[redacted]

## Amendment 2

### Amendment rationale

The main purpose of the amendment is to clarify that the dexamethasone therapeutic investigation will only be conducted in countries where an alcohol-free 0.5mg/5ml dexamethasone solution is commercially available. The availability of alcohol-free dexamethasone solution at the dosage specified in the protocol is geographically limited and this clarification would allow all countries to participate in the trial to investigate the activity of everolimus in combination with letrozole in first line and in combination with exemestane in second line even though they cannot participate in the stomatitis assessment part.

The amendment also includes the following changes:

The title and other sections of the document were corrected to follow the patient population definition in the inclusion criteria.

The efficacy assessment radiologic specifications were amended to allow more flexibility in practice at study sites.

The definition of Clinical Benefit Rate (CBR) is provided

The start date to calculate progression-free survival in the first-line setting is clarified

The language to define study drug and investigational therapy is updated

Recent updates regarding Afinitor approvals and IB are included

### Changes to the protocol

The changes to the protocol are as follows:

- Locally advanced, HER2 negative breast cancer patients:
  - The title has been updated to include locally advanced, HER2 negative breast cancer patients as defined in inclusion criteria #1
  - Throughout the entire document, relevant sections have been updated to include HER2 negative, locally advanced breast cancer patients in line with inclusion criteria #1
- Objectives and endpoints:
  - Table 3-1 was updated to include ORR to be in line with secondary endpoints described in Section 10.5.3
- Radiology:
  - Table 7-1 was updated to include CT or MRI for brain as clinically indicated, during the study
  - Section 7.2.1 changed ‘Each center must have a designated radiologist who is responsible for the interpretation of CT or MRI’ to ‘If possible, each center should have a designated radiologist responsible for the interpretation of CT or MRI scans and the evaluation according to RECIST version 1.0 criteria (see Appendix 2 for details)’

[redacted]

  - Section 7.2.1: +/- 1 week was added as a window for tumor assessments
  - Table 7-3: +/- 1 week was added as a window for CT and MRI procedures and bone scan or skeletal surveys
  - Throughout the document references to RECIST have been updated to reflect RECIST version 1.0 used in this trial
- Visit assessment:
  - Visit assessment window of +/- 3 days has been added (except for on-study imaging assessments for which window is +/- 1 week)
- Clinical Benefit Rate:
  - The protocol summary section and Section 10.5.1 have been updated to include the definition of clinical benefit rate
  - CBR defined as the proportion of patients with best overall response of CR, PR or SD with a duration of 24 weeks or longer according to RECIST version 1.0
  - Sections 10.5.1 and 10.5.3 have been corrected to include CBR to be in line with secondary endpoints.
  - Section 10.5.3 has been updated to correct a typo to replace ‘median PFS’ by ‘ORR and CBR’
- Start date for progression Free Survival and Overall survival
  - In Section 10.4.1, starting date for PFS in the first-line setting has been corrected to ‘date of enrollment’ to be in line with the definition provided in the protocol summary and the definition of the Full Analysis Set
  - Similarly in Section 10.5.4, starting date for OS has been corrected to ‘date of enrollment’
- Dexamethasone therapeutic intervention:
  - Throughout the entire document clarification has been added to references to the dexamethasone therapeutic intervention to specify that it will only be conducted in countries where an alcohol-free 0.5mg/5ml dexamethasone oral solution is commercially available
- Study Drug:
  - Section 6 has been updated to clarify the source of study drug and study treatments
  - Section 6 has been updated to include the definition of study drug and investigational therapy for this trial
  - Section 7.1.2 has been updated to reflect all methods of study drug compliance
- Afinitor approvals:
  - Section 1.2.1 has been updated to include recent Afinitor approvals
  - Section 6.2.1 has been updated based on investigator brochure edition 11

Throughout the protocol typographical errors have been corrected. At the time of this amendment one patient has been enrolled to the study. 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.

[redacted]

## IRB/IEC

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# Amendment 1

## Amendment rationale

The purpose of the amendment is to correct the dosage strength of the oral dexamethasone mouth rinse to be administered in the stomatitis therapeutic intervention; to add that patients who discontinue study treatment for any reason other than disease progression or consent withdrawal will continue to have tumor assessments until disease progression or until new anti-cancer therapy is initiated; to add that the ratio for randomization in the stomatitis therapeutic intervention will be 1:1 and to remove progesterone receptor from the population description.

The changes to the protocol are as follows:

1. Concentration of dexamethasone
    a. The concentration of the dexamethasone oral solution has been corrected from 5% to 0.5mg/5ml throughout the document.
2. Schedule of tumor assessments
    a. All patients who discontinue study treatment for any reason (i.e., an adverse event, administrative reasons etc) other than disease progression or consent withdrawal will continue to have tumor assessments per the schedule until disease progression or until new anti-cancer therapy is initiated.
    b. The visit evaluation schedule has been updated to include additional Post treatment evaluations for consistency with the schedule of tumor assessments.
3. Proportions for randomization in the stomatitis substudy
    a. Patients who develop stomatitis will be randomized in a 1:1 ratio to receive either 0.5mg/5ml solution dexamethasone mouth rinse or standard of care at the patient's center.
4. Estrogen receptor positive patients
    a. The patient population includes estrogen receptor positive only. Reference to progesterone receptor has been removed.

This amendment will also correct typographical errors in the inclusion criteria numbering and throughout the document. The Local clinical lab parameters collection plan and the Guideline for hepatitis B reactivation tables have been updated for consistency with the eCRF and the global hepatitis guidance. There are also minor editorial changes throughout the document. At the time of this amendment, enrollment has not yet been initiated.

## Changes to the protocol

The following has been changed:

- Throughout the entire document 5% has been changed to 0.5mg/5ml
- Protocol Summary: Removed and/or progesterone receptor
- Section 5.1: Removed and/or progesterone receptor
- Section 7.2.6: Added the following: All patients who discontinue study treatment for any reason (i.e., an adverse event, administrative reasons etc) other than disease progression or

[redacted]

consent withdrawal will continue to have tumor assessments per the schedule until disease progression or until new anti-cancer therapy is initiated.

- Section 6.3.2 changed randomly assigned to randomized in 1:1 ratio
- Table 7-5 updated for consistency with Section 7.2.2.5
- Table 6-7 updated for consistency with global hepatitis guidance
- Table 7-1 and 7-2: added column for post treatment evaluations

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.

## IRB/IEC

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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.

## Protocol summary:

| | |
|---|---|
| **Protocol number** | CRAD001Y24135 |
| **Title** | An open-label, phase II, single-arm study of everolimus in combination with letrozole in the treatment of postmenopausal women with estrogen receptor positive HER2 negative metastatic or locally advanced breast cancer |
| **Brief title** | Study of efficacy and safety of everolimus and letrozole in estrogen receptor positive HER2 negative metastatic or locally advanced breast cancer patients. |
| **Sponsor and Clinical Phase** | Novartis<br>Phase II |
| **Investigation type** | Drug |
| **Study type** | Interventional |
| **Purpose and rationale** | There is growing evidence to support close interaction between the mTOR pathway and ER signaling. mTOR forms two different protein complexes, mTOR-raptor signal transduction complexes 1 and 2 (mTORC1 and mTORC2) (Guertin and Sabatini 2007). A substrate of mTORC1, p70 ribosomal S6 kinase (S9K1), directly phosphorylates the activation domain AF-1 of the ER, responsible for ligand-independent receptor activation (Yamnik et al 2009, Yamnik and Holz 2010). Preclinical studies suggest that in breast cancer cells with upregulated Akt signaling, sensitivity to hormonal therapy may be restored by treatment with everolimus or other mTOR inhibitors (Baselga 2009). mTOR inhibitors given in combination with aromatase inhibitors (AIs) in preclinical models result in synergistic inhibition of proliferation and induction of apoptosis (Boulay et al 2005).<br>This extensive preclinical work suggests that co-targeting the mTOR pathway and ER signaling may improve the effectiveness of endocrine therapy. In addition, endocrine-resistant breast cancer cells demonstrate hyperactivation of the PI3K/mTOR pathway, and treatment with mTOR inhibitors including rapamycin analogs reverses this resistance (Miller et al 2010).<br>Results from recent clinical studies support these findings. Combining everolimus with letrozole (Baselga et al 2009) in the neoadjuvant setting induced higher response rates than with letrozole alone in postmenopausal women with ER-positive breast cancer. The combination of everolimus with tamoxifen was also associated with prolonged PFS and improved overall survival (OS) in a phase II randomized study in patients progressing after prior AI treatment compared with tamoxifen alone (Bachelot et al 2012). An ongoing trial combining everolimus with fulvestrant in postmenopausal women with ER positive breast cancer has also shown encouraging activity (Badin et al 2010). In a recent pivotal phase III, randomized, double-blind, placebo-controlled trial, BOLERO-2, of everolimus plus exemestane versus exemestane plus placebo in ER positive postmenopausal women with locally advanced or metastatic disease refractory to letrozole or anastrozole, the addition of everolimus to exemestane prolonged median progression free survival from 3.2 to 7.8 months based on local assessment (hazard ratio, 0.45; 95% confidence interval 0.38-0.54; p< 0.0001) and 4.1 to 11 months based on central radiology review (hazard ratio, 0.38; 95% confidence interval 0.31-0.48; p< 0.0001) (Piccart-Gebhart et al 2012).<br>Taken together, the above data support the activity of everolimus both in |

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| | patients progressing after initial endocrine treatment and in patients who have not received prior treatment in the neoadjuvant setting. However, to date the efficacy of everolimus plus endocrine therapy has not been explored for first line therapy of patients with metastatic disease. Preclinical studies have shown that inhibition of the PI3K/mTOR pathway can prevent the emergence of hormone-independent cells, suggesting that early intervention with combined endocrine therapy and mTOR inhibition may prevent or delay endocrine resistance (Miller et al 2010). It is also of interest to investigate whether continued mTOR inhibition with sequential endocrine therapy may provide clinical benefit. The proposed trial will assess the efficacy of everolimus plus letrozole in the first line treatment of patients with metastatic or locally advanced breast cancer and explore the efficacy of continued treatment with everolimus plus exemestane after initial progression. |
| **Primary Objective** | The primary objective is to estimate progression-free survival in patients treated with everolimus + letrozole in the first line setting. |
| **Secondary Objectives** | Determine the overall response rate and clinical benefit rate of everolimus + letrozole in the first line setting<br>Determine the progression free survival and clinical benefit rate of everolimus + exemestane in the second line setting<br>Evaluate the safety of everolimus + letrozole in the first line setting<br>Evaluate the safety of everolimus + exemestane in the second line setting<br>Estimate the overall survival of patients treated with everolimus + letrozole in the first line setting<br>Evaluate a therapeutic intervention to reduce the severity and duration of stomatitis<br>Evaluate clinical benefit as assessed by the investigator during the Extension Phase<br>Evaluate long term safety data |
| [redacted] | |
| **Study design** | This is an open-label, phase II, multicenter, international, single-arm trial for patients with ER+, HER2- metastatic or locally advanced unresectable breast cancer. Patients will receive everolimus in combination with letrozole until disease progression (primary study endpoint).<br>The study will be comprised of 2 phases:<br>• Core Phase: from FPFV to 24 months after LPFV and upon approval of amendment 5; safety and efficacy data (including PROs in selected subset) will be collected.<br>• Extension Phase: from the end of the Core Phase (upon approval of amendment 5) to LPLV of the extension phase for patients that are still deriving benefit at the end of the Core Phase. Patients may be transitioned to the Extension Phase and continue to receive the drugs up to 3 years or until disease progression or for any other reason the patient may be discontinued (refer to Section 7.1.5). Note: Only safety and clinical benefit as assessed by investigator will be collected.<br>In the Core Phase, following initial progression, patients will be offered everolimus in combination with exemestane until disease progression (secondary study endpoint). In countries where the alcohol-free 0.5mg/5ml |

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| | dexamethasone oral solution is commercially available, patients developing oral stomatitis will be randomized to take a 0.5mg/5ml dexamethasone mouth rinse (3 times/day) or the best supportive care normally used at each participating center (secondary study endpoint).<br>Patients still benefiting from everolimus following the overall survival cutoff and following approval of Amendment 5 may continue treatment in an Extension Phase of the study up to 3 years. Patients may continue on their existing line of treatment (1st or 2nd) in the extension and they will participate in the study until disease progression as deemed by physician judgement or other reason the patient may be discontinued (refer to Section 7.1.5). Those patients entering the Extension Phase on 1st line setting will not be offered to move on to 2nd line treatment if deemed no longer clinically benefiting in that setting. Rather, these patients can start other standard treatment(s) or approved everolimus combination after exiting the study. |
| **Population** | Postmenopausal women with estrogen receptor positive HER2 negative metastatic or locally advanced unresectable breast cancer.<br>Patients enrolled in this study are not permitted to participate in additional parallel investigational drug or device studies. |
| **Number of Patients** | 200 |
| **Inclusion criteria** | Refer to Section 5.2 for the complete list and more details on inclusion criteria<br>Adult women (>18 years of age) with metastatic or locally advanced, unresectable breast cancer not amenable to curative treatment by surgery or radiotherapy<br>Histological or cytological confirmation of estrogen-receptor positive (ER+) human epidermal growth factor receptor 2 negative (HER2-) breast cancer<br>Postmenopausal women. Postmenopausal status is defined in Section 5.2.<br>No prior treatment for metastatic breast cancer<br>Patients must either have at least one lesion that can be accurately measured in at least one dimension >20mm with conventional imaging techniques or >10mm with spiral CT or MRI OR Bone lesions: lytic or mixed (lytic + sclerotic) in the absence of measurable disease as defined above.<br>Willingness to complete a daily diary quality-of- life questionnaire throughout the study |
| **Exclusion criteria** | Refer to Section 5.3 for complete list and more details on exclusion criteria<br>Patients with only non-measurable lesions other than bone metastases as defined above (e.g., pleural effusion, ascites, etc)<br>Patients who have received prior hormonal or any other systemic therapy for metastatic breast cancer.<br>Patients may have received prior neoadjuvant or adjuvant endocrine therapy. In the case of neoadjuvant or adjuvant NSAI (letrozole/anastrozole) therapy patients must have completed therapy at least 1 year prior to study enrollment.<br>Previous treatment with mTOR inhibitors.<br>Known hypersensitivity to mTOR inhibitors, e.g., sirolimus (rapamycin).<br>Currently receiving hormone replacement therapy, unless discontinued prior to enrollment.<br>Patients receiving chronic treatment with systemic immunosuppressive agents |

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| **Investigational and reference therapy** | Everolimus<br>Letrozole<br>Exemestane |
| **Efficacy assessments** | The primary endpoint in this study (Core Phase) is progression-free survival (PFS), defined as the time from date of enrollment to the date of first documented progression or death due to any cause in the first line treatment. If a patient has not had an event, PFS will be censored at the date of last adequate tumor assessment. See RECIST version 1.0 (Appendix 2). Disease progression for primary efficacy endpoint derivation will be based on the local radiologist's/investigator's tumor assessment. Overall response rate, a secondary endpoint in this study, is defined as the proportion of patients whose best overall response is either complete response (CR) or partial response (PR) according to RECIST. Clinical benefit rate (CBR), another secondary endpoint in this study, is defined as the proportion of patients with best overall response of CR, PR or stable disease (SD) with a duration of 24 weeks or longer according to RECIST version 1.0.<br>During the Extension Phase, there will be no efficacy assessments other than the physician's determination of whether or not the patient is continuing to clinically benefit from the study treatment. |
| **Safety assessments** | Safety assessments will consist of monitoring and recording all adverse (AEs), including serious adverse events (SAE), the regular monitoring of hematology, serum chemistry, routine monitoring of vital signs (heart rate, blood pressure, and body temperature), weight, ECOG performance status, chest CT scans and physical condition.<br>Toxicity will be assessed using the NCI-CTC Common Terminology Criteria for Adverse Events, version 4.0 (CTCAEv4.0).<br>In the Extension Phase, safety assessments will consist of monitoring and recording all adverse (AEs), including serious adverse events (SAE) |
| **Other assessments** | An assessment of Patient reported outcomes (PRO) is planned in this trial using Oral Stomatitis Daily Questionnaire (OSDQ); OSDQ questionnaires will not be administered during the Extension Phase. |
| **Data analysis** | The primary efficacy endpoint, PFS, will be analyzed based on the data from FAS. The median PFS as well as the $25^{th}$ and $75^{th}$ quartile will be estimated using the Kaplan-Meier method and presented along with 95% confidence intervals. |
| **Key words** | Estrogen receptor positive, HER-2 negative, metastatic or locally advanced breast cancer, everolimus in combination with letrozole, exemestane, oral stomatitis |

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# 1 Background

## 1.1 Overview of disease pathogenesis, epidemiology and current endocrine treatment options

Breast cancer is the most common form of malignancy occurring in women. In the US, it is estimated that approximately 231,840 new cases of invasive breast cancer (BC) were diagnosed in 2015. In that same year, about 40,290 women would die from their disease (American Cancer Society 2015-2016). Worldwide breast cancer was responsible for over 500,000 deaths in 2004. Approximately 30-40% of diagnosed breast cancer patients will eventually develop metastatic breast cancer (MBC) (American Cancer Society 2015-2016). Treatment for MBC is palliative and median life expectancy after recurrence is between 24 and 30 months or less (World Health Organization Facts and Figures 2007, Piccart 2014).

The presence of estrogen receptor (ER) and/or progesterone receptor (PgR) is one of the most important prognostic and predictive markers in human breast cancers. Patients with hormone receptor-positive disease have a more favorable prognosis compared with those who are hormone receptor-negative. In addition, hormone receptor positivity predicts for responsiveness to treatment with endocrine therapy (NCCN 2016). Approximately 70% of all invasive breast cancers are positive for ER and/or PgR expression at the time of diagnosis. Consequently, anti-estrogen therapies that antagonize ER function (such as tamoxifen) or inhibit estrogen production (e.g. aromatase inhibitors [AIs]) have been extensively developed in oncology (Smith and Dowsett 2003, Jensen and Jordan 2003). Deprivation of estrogenic signaling with the anti-estrogen tamoxifen has been the main form of hormonal treatment for 30 years. Tamoxifen is indicated for treatment across the whole continuum of breast cancer, ranging from risk reduction for women with increased risk of breast cancer, as an adjuvant treatment and also for metastatic disease. Besides tamoxifen, progesterone analogues or progestins have been used for the treatment of breast cancer for almost 50 years. Once the standard second-line therapy after tamoxifen, progestins are now mainly used for patients whose cancer does not respond well to other hormonal treatments (NCCN 2016).

While tamoxifen has significantly contributed to the mortality reduction in patients with early breast cancer, a significant number of patients experience relapse, and up to 50% of ER-positive patients with advanced breast cancer (ABC) do not respond to tamoxifen therapy. Consequently, new approaches have been investigated. A number of aromatase inhibitors (AIs) that reduce peripheral estrogen synthesis have been developed for the treatment of ABC. The AIs block the conversion of androgens to estrogen, which is the primary way estrogens are produced in postmenopausal women (Mouridsen et al 2003).

At present, third generation aromatase inhibitors are the accepted standard of care for adjuvant therapy in postmenopausal women and the accepted standard of care for first line treatment of metastatic disease in postmenopausal women. The third generation AIs can be broadly classified into two groups: non-steroidal aromatase inhibitors (NSAI), such as letrozole (Femara®) and anastrozole (Arimidex®) and the steroidal aromatase inactivator, exemestane (Aromasin®) (NCCN 2016).

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Letrozole (Femara®) is indicated for the adjuvant treatment of postmenopausal women with hormone receptor positive early breast cancer, for the extended adjuvant treatment of early breast cancer in postmenopausal women who have received 5 years of adjuvant tamoxifen therapy, for neoadjuvant use in Europe and for the first line treatment of postmenopausal women with hormone receptor positive locally advanced or metastatic breast cancer.

Anastrozole (Arimidex®) is indicated for adjuvant treatment of postmenopausal women with hormone receptor positive early breast cancer. In Europe it is indicated for adjuvant treatment of hormone receptor-positive early invasive breast cancer in postmenopausal women who have received 2 to 3 years of adjuvant tamoxifen. It is also indicated for the first line treatment of postmenopausal women with hormone receptor positive locally advanced or metastatic breast cancer and in the US for the treatment of advanced breast cancer in postmenopausal women with disease progression following tamoxifen therapy.

Exemestane (Aromasin®) is an irreversible steroidal aromatase inactivator that has demonstrated efficacy in the treatment of postmenopausal patients with advanced breast cancer. It is indicated for adjuvant treatment of postmenopausal women with estrogen receptor positive early breast cancer who have received two to three years of tamoxifen and are switched to exemestane for completion of adjuvant hormonal therapy and for the treatment of ABC in postmenopausal women whose disease has progressed following tamoxifen therapy (in US) or following anti-estrogen therapy (in Europe).

Fulvestrant (Faslodex®) an estrogen receptor antagonist, is indicated for the treatment of hormone receptor positive MBC as monotherapy or in combination with palbociclib (in US) in postmenopausal women with disease progression following antiestrogen therapy (AstraZeneca prescribing information, 2016) or for disease relapse on or after adjuvant anti-estrogen therapy, or disease progression on therapy with an anti-estrogen (in Europe 2016).

## 1.2 Introduction to investigational treatment(s) and other study treatment(s)

### 1.2.1 Overview of everolimus

#### Organ transplantation

Everolimus was initially developed for the prophylaxis of organ transplant rejection. It was originally approved in Europe on 3-Dec-2003 under the trade name Certican® for the prophylaxis of allograft rejection following renal or cardiac transplantation, in a combination immunosuppressive regimen with cyclosporine and corticosteroid therapy, and has since been granted approval in 106 countries worldwide. In the United States (US), everolimus was approved by the Food and Drug Administration (FDA) on 20-Apr-2010 under the trade name Zortress® (NDA 21-560) for prophylaxis of organ rejection in adult patients at low-moderate immunologic risk receiving a kidney transplant. Certican®/Zortress® is also approved for the prophylaxis of organ rejection in adult patients receiving a liver transplant in 78 countries worldwide (approval in Europe received 17-October-2012 and FDA approval on 15-February-2013). Additional registrations for use of Certican® in organ transplantation are pending in Africa, South America, Middle East, and Asia-Pacific region.

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## Oncology

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

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

On 05-May-2011, FDA approved Afinitor® for the treatment of progressive neuroendocrine tumors of pancreatic origin (pNET) in patients with unresectable, locally advanced or metastatic disease. The EC approved Afinitor® on 24-Aug-2011 for the treatment of unresectable or metastatic, well- or moderately-differentiated neuroendocrine tumors of pancreatic origin in adults with progressive disease. Everolimus has been approved in 112 countries worldwide for the treatment of patients with advanced pNET/NET.

On 26-Feb-2016, FDA approved Afinitor® for advanced non-functional NET of gastrointestinal (GI) or lung origin based on the results of Phase III study T2302. The EC approved Afinitor® on 26-May-2016 for the treatment of unresectable or metastatic, well-differentiated (Grade 1 or Grade 2) non-functional NET of GI or lung origin in adults with progressive disease. Other health authority reviews are ongoing.

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

## Tuberous sclerosis

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

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

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

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

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

Everolimus received accelerated approval from FDA on 26-Apr-2012 for the treatment of adult patients with renal angiomyolipoma and TSC, not requiring immediate surgery. On 31-Oct-2012, the EC granted a decision for Votubia® for the treatment of adult patients with renal angiomyolipoma associated with TSC who are at risk of complications (based on factors such as tumor size or presence of aneurysm, or presence of multiple or bilateral tumors) but who do not require immediate surgery. Everolimus has been approved in 95 countries for the treatment of renal angiomyolipoma associated with TSC.

Approximately 35801 patients (excluding those patients who received marketed Afinitor®/Votubia®, those on planned and roll over studies as well as investigator-sponsored studies) have been enrolled in studies with everolimus as of 31-Mar-216:

- 33761 patient in Novartis-sponsored clinical trials
- 2,040 patients in the individual patient program

The following is a brief summary of the main characteristics of Everolimus. More complete information can be obtained from the everolimus investigator's brochure (IB).

#### 1.2.1.1 Mechanism of action

Everolimus is a derivative of rapamycin that acts as a signal transduction inhibitor (Table 1-1, Figure 1-1). Everolimus selectively inhibits mammalian target of rapamycin (mTOR), specifically targeting the mTOR-raptor signal transduction complex. mTOR is a key serine-threonine kinase in the phosphoinositide 3-kinase/protein kinase B (PI3K/AKT) signaling cascade, which is known to be dysregulated in a wide spectrum of human cancers (Boulay and Lane 2007).

Everolimus is being investigated as an anticancer agent based on its potential to act

- directly tumor cells by inhibiting growth and proliferation
- indirectly by inhibiting angiogenesis leading to reduced tumor vascularity (via potent inhibition of tumor cell VEGF production and VEGF-induced proliferation of endothelial cells).

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**Table 1-1 Everolimus - Drug substance**

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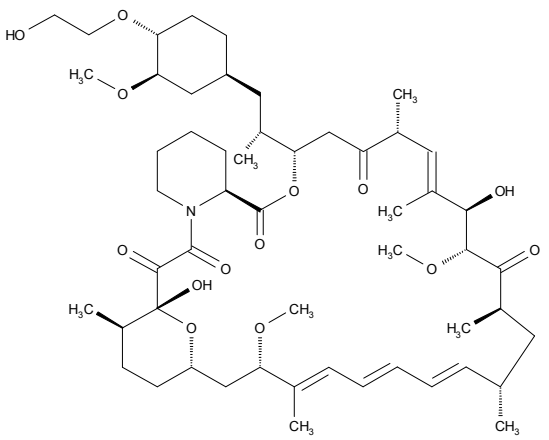
| Chemical name | (1R,9S,12S,15R,16E,18R,19R,21R,23S,24E,26E,28E,30S,32S,35R)-1,18-dihydroxy-12-{(1R)-2-[(1S,3R,4R)-4-(2-hydroxyethoxy)-3-methoxycyclohexyl]-1-methylethyl}-19,30-dimethoxy-15,17,21,23,29,35-hexamethyl-11,36-dioxa-4-aza-tricyclo[30.3.1.$0^{4,9}$]hexatriaconta-16,24, 26,28-tetraene-2,3,10,14,20-pentaone |
| International non-proprietary name | Everolimus |

**Figure 1-1 Chemical structure of everolimus**



### 1.2.1.2 Everolimus pharmacokinetics

Everolimus is rapidly absorbed after oral administration, with a median time to peak blood levels ($t_{max}$) of 1-2 hours post dose. The extent of absorptions is estimated at about 11%. The area under the blood concentration-time curve (AUC) is dose-proportional over the dose range tested with maximum blood concentration ($C_{max}$) appears to plateau at dose levels higher than 20mg. The elimination half-life in cancer patients averaged 30 hours, which is similar to that in healthy subjects. Inter-patient variability is moderate with the coefficient of variation (CV) of approximately 50%. In healthy subjects, high fat meals reduced systemic exposure to everolimus 10mg (as measured by AUC $_{0-\infty}$) by 22% and peak plasma concentration $C_{max}$ by 54%. Light fat meals reduced $AUC_{0-\infty}$ by 32% and $C_{max}$ by 42%. Food, however, had no apparent effect on the post absorption phase concentration-time profile (Everolimus (RAD001) Investigator Brochure, Clinical Study Report [RAD001C2120]).

Steady-state trough levels are highly predictive of AUC, with a coefficient of determination of 0.96, as has been reported in renal transplantation patients (Kovarik 2001).

Everolimus is mainly metabolized by the cytochrome P450 isoenzyme 3A4 (CYP3A4) in the liver and to some extent in the intestinal wall. Everolimus is also a substrate of P-glycoprotein (P-gp). Therefore, the absorption and subsequent elimination of systematically absorbed everolimus may be influenced by medicinal products that interact with CYP3A4 and/or P-gp. Strong CYP3A inhibitors (such as ketoconazole, itraconazole, ritonavir) and inducers (such as rifampicin, rifabutin) should be avoided. In study [RAD001C2108], everolimus, at a daily dose of either 5mg or 10mg, was added to the daily letrozole regimen of 2.5mg in breast

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cancer patients. Metabolism of letrozole is mainly mediated by CYP3A4 and CYP2A6 with minor contribution of renal clearance. Due to the low affinity of letrozole to CYP3A4, the potential for pharmacokinetic interaction is remote. Pharmacokinetic profiles of letrozole were investigated before addition of everolimus and after everolimus reached steady state (day 15). Data suggested that, indeed, co-administration of everolimus with 2.5mg/day letrozole did not influence the pharmacokinetics of letrozole. The exposure of everolimus in the presence of letrozole was similar to the historical data obtained from the amended study [C2102] CP report (Everolimus (RAD001) [Investigator Brochure], Clinical Study Report [RAD001C2102] and 2108).

#### 1.2.1.3 mTOR and breast cancer

Activation of the mTOR pathway is a key adaptive change driving endocrine resistance in patients with breast cancer. 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 (Campbell 2001, Santen 2005, Tokunaga 2006). The selective inhibitor of mTOR, sirolimus or rapamycin, demonstrated a significant growth inhibition particularly in long-term estrogen deprivation BC cells (Yue 2007).

#### 1.2.1.4 Everolimus in breast cancer

Everolimus was studied in a randomized phase II study comparing two schedules of everolimus (10mg daily and 70mg weekly) in patients with recurrent/metastatic breast cancer (Ellard 2009). The results demonstrated that in general, adverse effects were those predicted from preclinical and early clinical studies (O'Donnell 2008, Tabernero 2008) including hyperglycemia and hyperlipidemia (generally in patients with preexisting abnormalities), and were reversible. The most common grade 3 or 4 adverse events were fatigue, non-infectious pneumonitis and neutropenia. Pneumonitis occurred more frequently than anticipated, but was reversible in all affected patients and in general, manageable, although some patients required discontinuation. None of the 16 patients recruited to the weekly 70mg arm responded, with four patients with a stable disease. Among the 33 patients treated in the daily 10mg arm, response was evaluable in 30 patients; one patient had a complete response, three patients had a partial response and 15 patients had stable disease. The four responding patients were ER+ and the HER2 status was normal in 3 patients and unknown in one. Ellard et al. suggested that continuous daily dosing of everolimus, but not weekly dosing, has single agent activity in this disease setting. While ER positive and HER-2 normal status appeared to be predictive for response and/or prolonged stable disease, no associations were noted between molecular markers and efficacy (Ellard 2009).

There is growing evidence to support close interaction between the mTOR pathway and ER signaling. mTOR forms two different protein complexes, mTOR-raptor signal transduction complexes 1 and 2 (mTORC1 and mTORC2) (Guertin and Sabatini 2007). A substrate of mTORC1, p70 ribosomal S6 kinase (S6K1), directly phosphorylates the activation domain AF-1 of the ER, responsible for ligand-independent receptor activation (Yamnik et al 2009, Yamnik and Holz 2010). Preclinical studies suggest that sensitivity to hormonal therapy may

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be restored by treatment with everolimus or other mTOR inhibitors in breast cancer cells with upregulated Akt signaling (Baselga 2009). mTOR inhibitors given in combination with aromatase inhibitors (AIs) in preclinical models result in synergistic inhibition of proliferation and induction of apoptosis (Boulay et al 2005).

In particular, the combination of everolimus and letrozole synergistically inhibits proliferation in breast cancer cells (Miller et al 2010). This combination letrozole (2.5mg daily) and everolimus (10mg daily) (L-R) was evaluated in a randomized double blind phase II trial against letrozole + placebo (L-P) as a 4-month neoadjuvant treatment for postmenopausal women with early BC. 270 patients were enrolled in this trial (138 L-R vs. 132 L-P). Response rates on L-R and L-P were 68% vs. 59% (palpation, $p = 0.0062$) and 58% vs. 47% (ultrasound, $p = 0.0021$) respectively. Pharmacodynamic changes in each treatment arm were observed. Marked downregulation in progesterone receptor and cyclin D1 were seen in response to letrozole. Phospho-S6 levels showed dramatic down-regulation only in response to everolimus. Cell cycle response, as defined by the proportion of patients with < 2.7% $Ki67^+$ tumor cells at day 15, was also significantly higher in the everolimus + letrozole arm (57% everolimus treated patients vs. 30% placebo treated patients were cell cycle responder at day 15, $p<0.01$). Baselga et al concluded that everolimus significantly increased the efficacy of letrozole in newly diagnosed ER+ BC, with regard to both clinical and cell cycle response. The increased cell cycle response rate on everolimus was found in all subsets of tumors, including PTEN-positive PI3KCA wild-type tumors. The most common grade 3 / 4 adverse events in the L-R arm were hyperglycemia (5%), stomatitis (2%), pneumonitis (2%), and infections (2%). The trial demonstrated that mTOR inhibition provides additional efficacy to long term estrogen deprivation and has an acceptable level of tolerability in the neoadjuvant setting (Baselga 2008).

The Tamoxifen-RAD001 (TAMRAD) trial was designed to evaluate the role of everolimus in combination with endocrine therapy in patients with hormone resistant disease. It was a randomized, open-label phase II trial evaluating tamoxifen (20 mg daily) and the combination of tamoxifen (20 mg daily) plus everolimus (10 mg daily) in patients with progressive MBC who received prior aromatase inhibitor (AI) therapy. Additionally, patients had to be postmenopausal and have hormone-receptor (HR) positive and HER2 (-) disease. Prior AI therapy could have been in the adjuvant or metastatic setting. Prior adjuvant tamoxifen and prior chemotherapy, administered in the adjuvant or metastatic setting was allowed. Patients were stratified based on primary or secondary resistance to AI therapy. Primary resistance was defined as relapse during or within 6 months of stopping adjuvant AI therapy or disease progression within 6 months of starting AI therapy in the metastatic setting. Secondary resistance was defined as relapse occurring 6 months or later after stopping adjuvant AI therapy, or prior response of at least 6 months duration to an AI within the metastatic setting. No cross-over was planned or allowed. The primary study endpoint was the CBR at 6 months, defined as the total number of patients who had a complete response, partial response, or stable disease at 6 months. Secondary endpoints included TTP, OS, ORR, toxicity, as well as translational studies to evaluate PI3K/mTOR pathway biomarkers (Bachelot et al 2012).

One-hundred and eleven patients were randomized. The median follow-up duration was 22 months. Over 75% of patients had bone involvement while over 50% had visceral involvement. Prior adjuvant AI therapy had been given to 31% of the patients; 58% received

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an AI in the metastatic setting, and a small number (<10%) received an AI in both the adjuvant and metastatic settings. As per planned stratification, half of the patients had primary hormone resistance while the other half had secondary hormone resistance (Bachelot et al 2012).

In the intent-to-treat analysis, CBR in the tamoxifen alone group was 42% (95% CI, 29.1-55.9) and 61.1% (95% CI, 46.9-74.1%) in the combination arm, (*P*=0.045, exploratory analysis). Therefore, the requirement of 20% increase in CBR with the combination was met. Median TTP was 4.5 months in the tamoxifen arm and 8.6 months in the combination arm (HR=0.53, 95% CI, 0.35-0.81; *P*=0.0026). Exploratory analysis demonstrated a higher CBR with the combination versus tamoxifen alone across all subgroups. Addition of everolimus had a greater benefit in patients with secondary hormone resistance, where the TTP in the TAM + RAD group was 17.4 months vs. 5.0 months in the TAM group (HR, 0.38; 95% CI, 0.21-0.71). By contrast, the difference between groups in patients with primary hormone resistance was not as great (HR, 0.74; 95% CI, 0.42-1.3) (Bachelot et al 2012).

The number of patients who discontinued therapy due to an adverse event was comparable between treatment arms (tamoxifen, 7%; combination arm, 5.6%). More patients required a dose reduction due to an adverse event in the combination arm versus tamoxifen alone (28% versus 0%). Toxicities observed in the combination arm were consistent with those previously reported with everolimus. These included fatigue, stomatitis, rash, anorexia, and diarrhea. The majority of adverse events were of grade 1 or 2 in severity (Bachelot et al 2012).

The combination of everolimus and tamoxifen contributed to a higher CBR, longer median TTP, and longer OS compared to tamoxifen alone, in patients with MBC previously treated with an AI. The benefit of the combination appears to favor patients with secondary hormone resistance. Additionally, the combination was associated with a manageable toxicity profile despite the need for everolimus dose reduction in 28% of patients in the combination arm (Bachelot et al 2012).

Following these encouraging results everolimus was evaluated in a pivotal phase III trial. The BOLERO-2 trial is a phase III, double-blind, randomized, placebo-controlled study involving postmenopausal patients with ER-positive advanced breast cancer. Patients were required to have disease refractory to previous letrozole or anastrozole, defined as recurrence during or within 12 months of the end of adjuvant treatment or progression during or within one month of the end of treatment for advanced disease. Letrozole or anastrozole were not required to be the last treatment received prior to enrollment, but recurrence or progression on the last systemic therapy had to be documented before randomization. Seven-hundred twenty-four patients were randomized to the combination of everolimus (10 mg/day) and exemestane (25 mg/day) (n=485) or the combination of exemestane (25 mg/day) plus placebo (n=239). Randomization, (2:1 in favor of the combination therapy arm), was stratified according to presence of visceral metastasis and previous sensitivity to endocrine therapy. (Baselga et al 2012)

The PFS results after 18 months of median follow-up indicated that the addition of everolimus to exemestane prolonged median progression free survival from 3.2 to 7.8 months based on local assessment (hazard ratio, 0.45; 95% confidence interval 0.38-0.54; p< 0.0001) and 4.1 to 11 months based on central radiology review (hazard ratio, 0.38; 95% confidence interval

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0.31-0.48; p< 0.0001) (Yardley et al 2013). The analysis included 457 PFS events based on local radiology review and 282 PFS events based on central radiology review. A significant benefit in PFS with consistent magnitude was seen in both the local and central assessment. The most common grade 3 or 4 adverse events were stomatitis (8% in the everolimus-plus-exemestane group vs. 1% in the placebo-plus-exemestane group), anemia (6% vs. <1%), dyspnea (4% vs. 1%), hyperglycemia (4% vs. <1%), fatigue (4% vs. 1%), and pneumonitis (3% vs. 0%) (Piccart et al 2014).

Everolimus has also been evaluated in patients with HER2-overexpressing metastatic breast cancer in combination with trastuzumab and vinorelbine. In a phase I trial of daily and weekly everolimus in combination with weekly vinorelbine and trastuzumab in heavily pretreated patients with HER2-overexpressing MBC with prior resistance to trastuzumab, everolimus was well tolerated at doses of 5mg daily and 30mg weekly. A total of 50 patients were enrolled. Patients were extensively pretreated, having received a median of 4 prior regimens for advanced disease. Thirty-seven patients completed the Core Phase and 35 entered the Extension Phase. Of the 13 patients who did not complete the Core Phase, 9 discontinued therapy due to progressive disease, three discontinued therapy due to an adverse event, and 1 patient died. The ORR was 20% (n=6) in the 5 mg daily group versus 15% (n=3) in the 20 or 30 mg weekly group. The CBR (CR + PR + SD >24 weeks) was 50% (n=15) in the 5 mg daily group versus 60% (n=12) in the 20 or 30 mg weekly group. The median PFS for the entire patient population was 30.7 weeks (95% CI, 25.9-43) while it was 30.7 weeks (95% CI, 28-44.9) in the daily dosing arm and 27.1 weeks (95% CI, 25.6-NA) in the weekly dosing arm. The dose of everolimus selected for further development was 5mg daily (Jerusalem et al 2011).

In another phase I of daily and weekly everolimus in combination with weekly paclitaxel and trastuzumab in patients with HER2 overexpressing MBC with prior resistance to trastuzumab, everolimus was well tolerated at doses of 5mg and 10mg daily and 30mg weekly. The combination showed encouraging response in heavily pretreated patients including patients refractory to both taxanes and trastuzumab. As of the data cutoff of May 2009, 33 heavily pretreated patients were enrolled (5 mg daily n=6; 10 mg daily; n=17, and 30 mg weekly n=10). Twenty-nine patients had measurable disease and 27 were evaluable for response. The median duration of therapy was 28 weeks in the 5 mg and 10 mg daily cohorts and 33 weeks in the 30 mg weekly cohort. The ORR was higher in the 5 mg daily treatment group. The median PFS for the entire evaluable patient population was 34 weeks (95% CI, 29.1-40.7); while it was 40.7 weeks (95% CI, 30 to NA) for the weekly dosing arm and 33 weeks (95% CI, 23.7 to NA) for the daily dosing arm Twenty-nine patients had measurable disease and 27 were evaluable for response. The median duration of therapy was 28 weeks in the 5 mg and 10 mg daily cohorts and 33 weeks in the 30 mg weekly cohort (Andre et al 2010).

Results from these two early clinical studies supported the initiation of Phase III trials J2301 and W2301 to further evaluate the potential of everolimus in combination with trastuzumab (Herceptin®) and chemotherapy in HER2-positive metastatic breast cancer patients (Andre et al 2010, Jerusalem et al 2011). The PFS analysis and OS analysis for BOLERO-1 (J2301) (Hurvitz et al 2015) and for BOLERO-3 (W2301) (Andre et al 2014) have been completed and has been reported, details are also included in the IB.

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### 1.2.1.5 Overview of letrozole

Letrozole is an aromatase inhibitor indicated for the adjuvant treatment of postmenopausal women with hormone receptor positive early breast cancer. It is also indicated for the extended adjuvant treatment of early breast cancer in postmenopausal women who have received 5 years of adjuvant tamoxifen therapy and for neoadjuvant use in Europe. In the first line setting, letrozole is indicated for the treatment of postmenopausal women with hormone receptor positive, locally advanced or metastatic breast cancer and following anti-estrogen therapy for second-line treatment.

Letrozole is a nonsteroidal competitive inhibitor of the aromatase enzyme system; it inhibits the conversion of androgens to estrogens. Letrozole inhibits the aromatase enzyme by competitively binding to the heme of the cytochrome P450 subunit of the enzyme, resulting in a reduction of estrogen biosynthesis in all tissues (Femara prescribing information, Novartis Pharmaceuticals, 2014).

The recommended dose of letrozole is one 2.5mg tablet administered once a day. Letrozole is rapidly and completely absorbed from the gastrointestinal tract and absorption is not affected by food. It is metabolized slowly to an inactive metabolite whose glucuronide conjugate is excreted renally, representing the major clearance pathway. Letrozole's terminal elimination half-life is about 2 days and steady-state plasma concentration after daily 2.5mg dosing is reached in 2-6 weeks. Letrozole is metabolized by CYP3A4 to the carbinol metabolite while CYP2A6 formed both this metabolite and its ketone analog. Letrozole strongly inhibits CYP2A6 and moderately inhibits CYP2C19 (Femara prescribing information, Novartis Pharmaceuticals, 2014).

### 1.2.1.6 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 early BC who have received two to three years of tamoxifen and are switched to exemestane for completion of a total of five consecutive years of adjuvant hormonal therapy. It is also indicated for the treatment of advanced breast cancer in postmenopausal women whose disease has progressed following tamoxifen therapy (in the US) or following anti-estrogen 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, 2016).

The recommended daily dose of exemestane is 25mg via oral administration. Exemestane is rapidly absorbed from the gastrointestinal tract. Its bioavailability is limited by first-pass metabolism, but is increased when taken with food. Exemestane is widely distributed, and is extensively bound to plasma proteins. It appears to be more rapidly absorbed in women with breast cancer ($t_{max}$ of 1.2 hours) than in healthy women ($t_{max}$ of 2.9 hours). The terminal half-life for exemestane is 18-24 hours. The time needed to reach maximal E2 suppression is 7

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days (Demers 1993, Plourde 1995, Buzdar 2003). Exemestane is metabolized by CYP3A4 and aldeoketoreductases. It does not inhibit any of the major CYP isoenzymes, including CYP1A2, 2C9, 2D6, 2E1 and 3A4. Although no formal drug-drug interaction studies have been conducted, significant effects on exemestane clearance by CYP isoenzyme inhibitor appear unlikely (Aromasin prescribing information, Pfizer-Pharmacia, 2016, Hutson 2005, Buzdar 2002).

# 2 Rationale

## 2.1 Study rationale and purpose

There is growing evidence to support close interaction between the mTOR pathway and ER signaling. mTOR forms two different protein complexes, mTOR-raptor signal transduction complexes 1 and 2 (mTORC1 and mTORC2) (Guertin and Sabatini 2007). A substrate of mTORC1, p70 ribosomal S6 kinase (S9K1), directly phosphorylates the activation domain AF-1 of the ER, responsible for ligand-independent receptor activation (Yamnik et al 2009, Yamnik and Holz 2010). Preclinical studies suggest that sensitivity to hormonal therapy may be restored by treatment with everolimus or other mTOR inhibitors in breast cancer cells with upregulated Akt signaling (Baselga 2009). mTOR inhibitors given in combination with aromatase inhibitors (AIs) in preclinical models result in synergistic inhibition of proliferation and induction of apoptosis (Boulay et al 2005).

This extensive preclinical work suggests that co-targeting the mTOR pathway and ER signaling may improve the effectiveness of endocrine therapy. In addition, endocrine-resistant breast cancer cells demonstrate hyperactivation of the PI3K/mTOR pathway, and treatment with mTOR inhibitors including rapamycin analogs reverse this resistance (Miller et al 2010).

Results from recent clinical studies support these findings, as previously described in Section 1.2.1.4. Combining everolimus with letrozole (Baselga et al 2009) in the neoadjuvant setting induced higher response rates than with letrozole alone in postmenopausal women with ER-positive breast cancer. The combination of everolimus with tamoxifen was also associated with prolonged PFS and improved overall survival (OS) in a phase II randomized study in patients progressing after prior AI treatment compared with tamoxifen alone (Bachelot et al 2012). An ongoing trial combining everolimus with fulvestrant in postmenopausal women with ER positive breast cancer has also shown encouraging activity (Badin et al 2010). In a recent pivotal phase III, randomized, double-blind, placebo-controlled trial, BOLERO-2, of everolimus plus exemestane versus exemestane plus placebo in ER positive postmenopausal women with locally advanced or metastatic disease refractory to letrozole or anastrozole, the addition of everolimus to exemestane prolonged median progression free survival 3.2 to 7.8 months based on local assessment (hazard ratio, 0.45; 95% confidence interval 0.38-0.54; $p< 0.0001$) and 4.1 to 11 months based on central radiology review (hazard ratio, 0.38; 95% confidence interval 0.31-0.48; $p< 0.0001$) (Baselga et al 2012, Yardley et al 2013).

Taken together, the above data support the activity of everolimus both in patients progressing after initial endocrine treatment and in patients who have not received prior treatment in the neoadjuvant setting. However, to date the efficacy of everolimus plus endocrine therapy has not been explored for first line therapy of patients with metastatic disease. Preclinical studies

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have shown that inhibition of the PI3K/mTOR pathway can prevent the emergence of hormone-independent cells, suggesting that early intervention with combined endocrine therapy and mTOR inhibition may prevent or delay endocrine resistance (Miller et al 2010). It is also of interest to investigate whether continued mTOR inhibition with sequential endocrine therapy may provide clinical benefit. The proposed trial will assess the efficacy of everolimus plus letrozole in the first line treatment of patients with metastatic breast cancer and explore the efficacy of continued treatment with everolimus plus exemestane after initial progression.

## 2.2 Rationale for the study design

This trial is designed to assess the progression free survival of patients treated with everolimus in combination with letrozole in the first line setting (primary study endpoint). It is also designed to evaluate the efficacy of continued therapy with everolimus in combination with a second endocrine agent, exemestane, in patients progressing on first line treatment (secondary study endpoint). Allowing patients to continue everolimus in combination with exemestane after progression will assess the effectiveness of continued treatment with everolimus in this patient population, who have progressed following first line treatment with everolimus plus letrozole. The study design will be open-label, single arm and will enroll a sufficient number of patients to allow a robust estimate of PFS in the first line setting.

### 2.2.1 Stomatitis therapeutic intervention

Stomatitis, the inflammation of mucous membranes lining the mouth and throat, has been observed in approximately 44-64% of everolimus-treated patients (Afinitor PI). It is also a common adverse event associated with radiation and chemotherapy. Specific strategies to prevent and/or ameliorate the severity of everolimus-associated mucositis are not well documented. Caphosol is an oral mouth rinse indicated as an adjunct to standard oral care in the prevention and treatment of stomatitis caused by radiation or high dose chemotherapy. Low level laser therapy (LLLT) has also been suggested by the Multinational Association of Supportive Care in Cancer (MASCC) and the International Society for Oral Oncology (ISOO) to reduce the incidence of oral stomatitis and its associated pain in patients receiving high dose chemotherapy or chemo-radiotherapy (Keefe et al 2007). However, mTOR inhibitor-induced stomatitis is a different clinical entity, manifesting more frequently as discrete aphthous-like lesions rather than diffuse inflammation. A recent study evaluated the clinical presentation and management of stomatitis in 17 patients treated with an mTOR inhibitor. The majority of patients were treated with topical corticosteroids including an oral dexamethasone solution which was rinsed and expectorated. Clinical improvement was noted in over 85% of topical corticosteroid-treated patients (de Oliveira et al 2011). Additional reports from investigators indicate that an oral steroid rinse may help to ameliorate mTOR-induced stomatitis (Irene Ghobrial, personal communication, February, 2012 and Ingrid Mayer, personal communication, March 2012).

As a secondary endpoint, this trial will assess the effectiveness of treating stomatitis using an alcohol-free 0.5mg/5ml dexamethasone mouth rinse in countries where the solution is commercially available. At the onset of symptoms, enrolled patients will contact their physician. Based on preliminary confirmation of diagnosis, patients will be asked to visit the study site within 24 hours. Upon confirmation of the diagnosis of stomatitis the patient will be

[redacted]

randomly assigned to use either 0.5mg/5ml dexamethasone mouth rinse swished and expectorated 3 times per day or the standard of care normally used to treat stomatitis at the patient's center.

## 2.3 Rationale for dose and regimen selection

Letrozole has been selected for first line treatment in combination with everolimus and exemestane has been selected for second line treatment in combination with everolimus based on the following considerations:

- The activity of letrozole in the first line setting has been extensively documented (Mouridsen et al 2003; Park et al 2010, Baselga et al 2009, Krainich-Strobel et al 2008).
- The combination of everolimus and letrozole has been investigated and is generally well tolerated (Baselga et al 2009).
- Exemestane in the second line setting has been established as an effective treatment in combination with everolimus in BOLERO-2 (Baselga 2012, Yardley 2013).

Based on the current literature and product approvals, everolimus, letrozole and exemestane will all be given at the standard approved doses for first line and second line treatment in this patient population (Baselga et al 2009, Baselga et al 2012).

## 2.4 Rationale for choice of combination drugs

The activity of letrozole in the first line setting has been extensively documented (Mouridsen et al 2003; Park et al 2010, Baselga et al 2009, Krainich-Strobel et al 2008). Letrozole was chosen as the combination drug in the first line setting because of its approval in this setting and wide-spread use as first line endocrine therapy. Additionally, Baselga and colleagues combined everolimus 10mg daily and letrozole 2.5mg daily in the neoadjuvant setting and found that the combination induced higher response rates than letrozole alone in postmenopausal women with ER-positive breast cancer (Baselga et al 2009). The combination was well tolerated.

Exemestane in combination with everolimus has been established as an effective treatment in the second line setting. In phase III, randomized, double-blind, placebo-controlled trial, BOLERO-2, the combination of everolimus 10mg daily plus exemestane 25mg daily prolonged median progression free survival from 3.2 to 7.8 months based on local assessment (hazard ratio, 0.45; 95% confidence interval 0.38-0.54; $p< 0.0001$) and 4.1 to 11 months based on central radiology review (hazard ratio, 0.38; 95% confidence interval 0.31-0.48; $p< 0.0001$). The combination was generally well tolerated (Yardley et al 2013).

# 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:**<br>The primary objective is to estimate progression-free survival in patients treated with everolimus + letrozole in the first line setting. | PFS | Refer to Section 10.4. |
| **Secondary:**<br>Determine the overall response rate and clinical benefit rate of everolimus + letrozole in the first line setting | ORR, CBR | Refer to Section 10.5.1. |
| Determine the progression free survival, overall response rate and clinical benefit rate of everolimus + exemestane in second line population | PFS, ORR, CBR | Refer to Section 10.5.2 and Section 10.5.3. |
| Evaluate the safety of everolimus + letrozole in the first line setting | Incidence of Adverse events | Refer to Section 10.5.5.2. |
| Evaluate the safety of everolimus + exemestane in the second line setting | Incidence of Adverse events | Refer to Section 10.5.5.2. |
| Estimate the overall survival of patients treated with everolimus + letrozole in the first line setting | OS | Refer to Section 10.5.4. |
| Evaluate a therapeutic intervention to reduce the severity and duration of stomatitis | Oral Stomatitis Daily Questionnaire (OSDQ) data | Refer to Section 10.5.5.1. |
| Evaluate clinical benefit as assessed by the Investigator during the Extension Phase | Proportion of patients with clinical benefit as assessed by the Investigator at scheduled visits | Refer to Section 10.5.5.3. |
| Evaluate long term safety data | Frequency and severity of AEs/SAEs | Refer to Section 10.5.5.2. |

[redacted]

[redacted]

# 4 Study design

## 4.1 Description of study design

This is an open-label, phase II, multicenter, international, single-arm trial for patients with ER+, HER2- metastatic or locally advanced breast cancer. Enrolled patients will receive everolimus in combination with letrozole in the first line setting until disease progression or any other reason for which the patient may be discontinued (refer to Section 7.1.5). PFS in the first line setting is the primary study endpoint.

The study will be comprised of 2 phases:

- Core Phase: from FPFV to 24 months after LPFV and upon approval of amendment 5; safety and efficacy data (including PROs in selected subset) will be collected.
- Extension Phase: from the end of the Core Phase (upon approval of amendment 5) until LPLV of the Extension Phase for patients that are still deriving benefit at the end of the Core Phase. Patients may be transitioned to the Extension Phase and continue to receive the drugs up to 3 years or until progression or any other reason for which the patient may be discontinued (refer to Section 7.1.5); only safety and clinical benefit as assessed by investigator will be collected.

During the Core Phase following disease progression in the first line setting, patients will be offered everolimus in combination with exemestane. Patients who discontinue treatment in the first line setting due to unacceptable toxicity or due to withdrawal of consent will not be offered everolimus plus exemestane. Those patients treated in the second line setting will continue treatment until disease progression or any other reason for which the patient may be discontinued (refer to Section 7.1.5).

All patients who discontinue study treatment will have a 28 day follow up visit for safety and will be followed every 3 months thereafter for overall survival after completing treatment in either the first or second line treatment setting. Overall Survival will be followed until 24 months post LPFV.

At the first onset of symptoms suggestive of stomatitis patients will contact the study site. Upon confirmation of stomatitis, patients in countries where the alcohol-free 0.5mg/5ml dexamethasone oral solution is commercially available will be randomly assigned to take either 0.5mg/5ml dexamethasone mouth rinse or the standard of care used to treat stomatitis at the patient's center. The mouth rinse will be self-administered at a dose of 10ml 3 times per day. Patients will be instructed to swish and expectorate the mouth rinse. Patients will also be instructed to fill out the Oral Stomatitis Daily Questionnaire (OSDQ) at home every day until the patient recovers. For subsequent episodes of stomatitis patients will be instructed to contact the physician. Upon telephone confirmation, they will be instructed to utilize the same treatment they were assigned to after the first episode and complete the OSDQ booklet. **Note:** only those patients who develop symptoms suggestive of stomatitis and who have the diagnosis of stomatitis confirmed by the study site will participate in the investigation of the stomatitis intervention. OSDQ will not be administered during the Extension Phase.

[redacted]

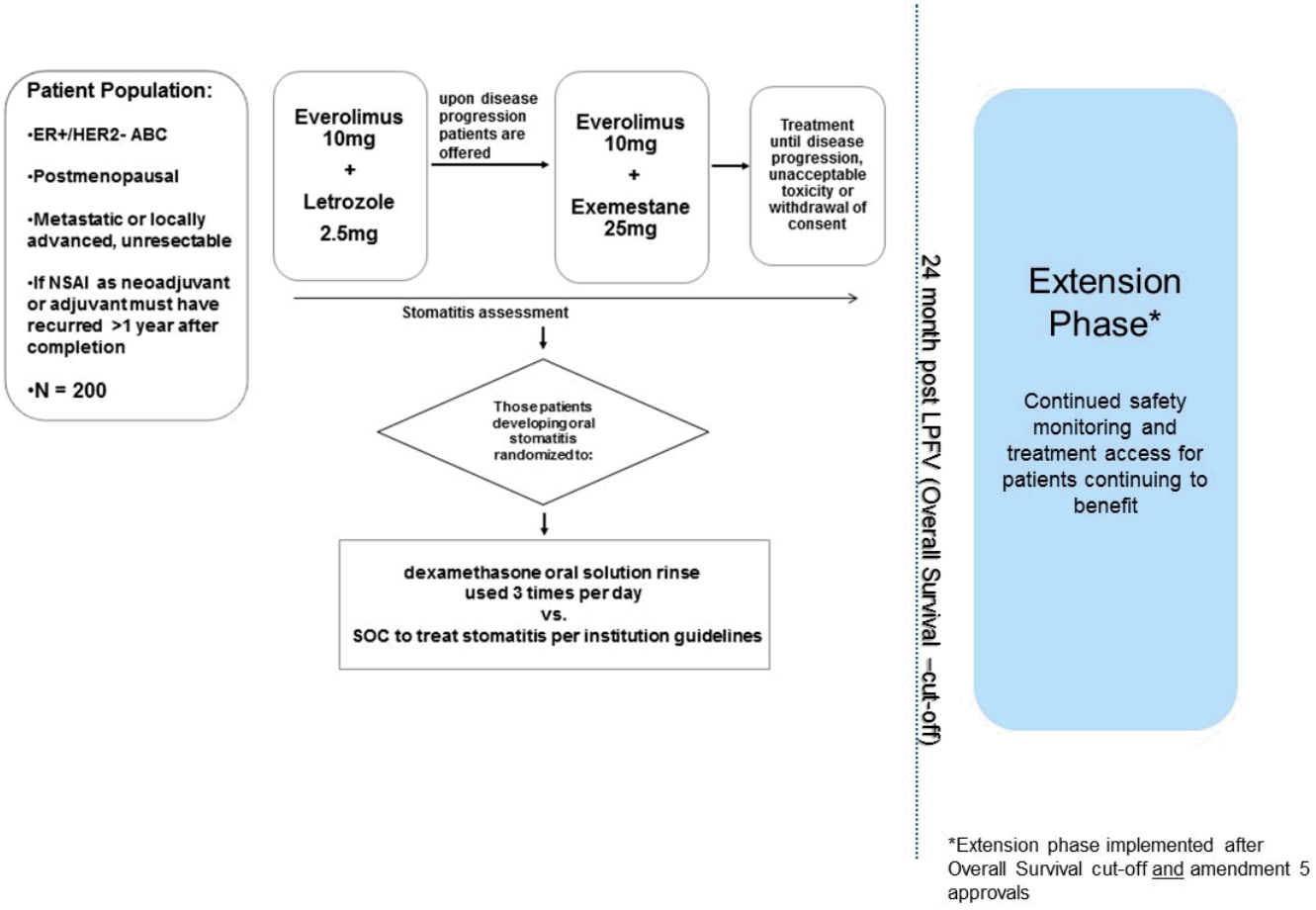
The primary analysis of PFS for first line treatment will be performed 12 months after the last patient's recruitment. The analysis of PFS for second line treatment will be performed 6 months later (18 months after the last patient's recruitment) provided that the number of patients in second line treatment is adequate for a reliable PFS analysis. Otherwise, this analysis will be performed 24 months after the last patient's recruitment. The overall survival analysis will be performed 24 months after the last patient's recruitment. Assuming an enrollment period of 18 months, the expected trial duration is therefore 42 months.

Patients still benefiting from everolimus following the overall survival cutoff and following approval of Amendment 5 may continue treatment in the Extension Phase of the study. Patients may continue on their existing line treatment ($1^{st}$ or $2^{nd}$) in the extension up to 3 years or until the following: disease progression as deemed by physician judgement or any other reason for which the patient may be discontinued (refer to Section 7.1.5). Patients entering the Extension Phase on $1^{st}$ line treatment and deemed to no longer be clinically benefiting will not be offered $2^{nd}$ line treatment in the context of the study. Rather, these patients can start other standard treatments available or approved everolimus combination after exiting the study.

The extension will include required safety evaluations and standard of care, per investigator discretion and in consultation with the Sponsor.

[redacted]

**Figure 4-1 Study design**

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## 4.2 Early study termination

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

## 4.3 Definition of end of study

The planned overall study duration of the Core Phase will from FPFV until 24 months post LPFV and approval and implementation of Amendment 5. At the end of the Core Phase, if patients are still deriving benefit, patient may be transitioned to the Extension Phase which will last a total of 3 years (end of study). The LPLV is when the last patient has discontinued treatment for any reason in the Extension Phase and has had the 28 day safety follow up visit. The study closure will occur once the LPLV of the Extension Phase of the study has been documented.

# 5 Population

## 5.1 Patient population

Two hundred postmenopausal women with estrogen receptor positive HER2 negative metastatic or locally advanced breast cancer will be enrolled in this study. Patients enrolled in this study are not permitted to participate in additional parallel investigational drug or device studies.

The investigator or designee must ensure that only patients who meet all the following inclusion (Section 5.2) and none of the exclusion (Section 5.3) criteria are offered enrollment in the study. Upon enrollment patients will initiate first line treatment with everolimus plus letrozole.

All required screening evaluations must be performed to protect the safety of the patients and to ensure all inclusion and exclusion criteria are met. The results of all screening evaluations must be reviewed by the Principal Investigator or designee prior to enrollment of that patient onto the study.

All patients must be thoroughly informed about all aspects of the study including the study visit schedule, required evaluations and all regulatory requirements for informed consent. The written informed consent must be obtained before any screening evaluations are performed. If the patient is unable to read, an impartial witness should be present during the entire informed consent discussion.

Prior to patients being offered second line treatment with everolimus plus exemestane in the Core Phase, investigators must re-examine specified inclusion criteria 6, 7, 8, 9, 10 and exclusion criteria 8, 10, 12, 13, 14 as described in Section 5.2 and Section 5.3 below. Refer to Section 7.1.3 for second line treatment procedures.

[redacted]

## 5.2 Inclusion criteria

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

Written informed consent must be obtained prior to any screening procedures

1. Adult women (>18 years of age) with metastatic or locally advanced breast cancer not amenable to curative treatment by surgery or radiotherapy.
2. Histological or cytological confirmation of estrogen-receptor positive (ER+) human epidermal growth factor receptor 2 negative (HER2-) breast cancer.
3. Postmenopausal women. Postmenopausal status is defined either by:
   a. Age ≥55 years and one year or more of amenorrhea
   b. Age < 55 years and one year or more of amenorrhea, with an estradiol assay <20pg/ml
   c. Surgical menopause with bilateral oophorectomy
   d. Note: Ovarian radiation or treatment with a luteinizing hormone-release hormone (LHRH) agonist (goserelin acetate or leuprolide acetate) is not permitted for induction of ovarian suppression.
4. No prior treatment for metastatic breast cancer
5. Patients must either have at least one lesion that can be accurately measured in at least one dimension >20mm with conventional imaging techniques or >10mm with spiral CT or MRI OR Bone lesions: lytic or mixed (lytic + sclerotic) in the absence of measurable disease as defined above
6. Adequate bone marrow and coagulation function as shown by:
   a. Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L
   b. Platelets $\geq 100 \times 10^9$/L
   c. Hemoglobin (Hgb) >9.0g/dL
   d. INR ≤2
7. Adequate liver function as shown by:
   a. Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5xULN (or ≤5 if hepatic metastases are present)
   b. Total serum bilirubin <1.5xULN (<3xULN for patients known to have Gilberts Syndrome)
8. Adequate renal function as shown by:
   a. Serum creatinine < 1.5xULN
9. Fasting serum cholesterol ≤300 mg/dL or 7.75 mmol/L and fasting triglycerides ≤2.5 x ULN.
10. ECOG Performance Status ≤2
11. Written informed consent obtained before any trial related activity and according to local guidelines.
12. Willingness to complete a daily stomatitis symptom questionnaire throughout each stomatitis event

[redacted]

## 5.3 Exclusion criteria

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

1. Patients with only non-measurable lesions other than bone metastasis as define above (e.g., pleural effusion, ascites, etc).
2. Patients who have received prior hormonal or any other systemic therapy for metastatic breast cancer.
   a. Patients may have received prior neoadjuvant or adjuvant endocrine therapy. In the case of neoadjuvant or adjuvant NSAI (letrozole/anastrozole) therapy patients must have completed therapy at least 1 year prior to study enrollment.
3. Previous treatment with mTOR inhibitors.
4. Known hypersensitivity to mTOR inhibitors, e.g., sirolimus (rapamycin).
5. Another malignancy within 5 years prior to enrollment with the exception of adequately treated in-situ carcinoma of the cervix uteri, basal or squamous cell carcinoma or non-melanomatous skin cancer
6. Radiotherapy within four weeks prior to randomization except in case of localized radiotherapy for analgesic purpose of lytic lesions at risk of fracture which can then be completed within two weeks prior to enrollment.
7. Currently receiving hormone replacement therapy, unless discontinued prior to enrollment.
8. History of brain or other CNS metastases.
9. Patients receiving chronic treatment with systemic immunosuppressive agents
10. Bilateral diffuse lymphangitic carcinomatosis.
11. Patients with a known history of HIV seropositivity. Screening for HIV infection at baseline is not required.
12. Active bleeding diathesis.
13. Any severe and/or uncontrolled medical conditions such as:
    a. Unstable angina pectoris, symptomatic congestive heart failure, myocardial infarction ≤6 months prior to enrollment, serious uncontrolled cardiac arrhythmia.
    b. Uncontrolled diabetes as defined by fasting serum glucose >1.5xULN.
    c. Acute and chronic, active infectious disorders (except for Hep B and Hep C positive patients) and nonmalignant medical illness that are uncontrolled or whose control may be jeopardized by the complications of this study therapy
    d. Impairment of gastrointestinal function or who have gastrointestinal disease that may significantly alter the absorption of study drugs (e.g., ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome)
    e. Active skin, mucosa, ocular or GI disorders of Grade >1
14. Significant symptomatic deterioration of lung function. If clinically indicated, pulmonary function tests including measures of predicted lung volumes, DLco, O2 saturation at rest on room air should be considered to exclude restrictive pulmonary disease, pneumonitis or pulmonary infiltrates.
15. Patients being treated with drugs recognized as being strong inhibitors or inducers of the isoenzyme CYP3A within the last 5 days prior to enrollment (see Section 6.1.3.1)
16. History of non-compliance to medical regimens.

[redacted]

17. Patients unwilling to or unable to comply with the protocol.

# 6 Treatment

## 6.1 Study treatment

### Definition of terms

The investigational therapy in the context of this study is everolimus

Study Treatment = Everolimus + Letrozole or Everolimus + Exemestane

Study Drug = Everolimus

Everolimus will be self-administered as a daily dose of 10mg (two 5mg tablets) taken orally continuously from study day 1 until progression of disease, unacceptable toxicity or withdrawal of consent. 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. Letrozole will be self-administered as a daily dose of 2.5mg continuously from study day 1 until disease progression or any other reason for which the patient may be discontinued (refer to Section 7.1.5) and should be taken at the same time every day, consistently with or without food. Everolimus and letrozole tablets should be taken together.

During the Core Phase of the study following disease progression on everolimus in combination with letrozole, patients will be offered everolimus in combination with exemestane. Exemestane will be self-administered as a daily dose of 25mg taken orally continuously until disease progression or any other reason for which the patient may be discontinued (refer to Section 7.1.5) and should be taken at the same time every day. Exemestane should be taken after a meal. Everolimus and exemestane tablets should be taken together.

During the Core Phase and at the onset of symptoms suggestive of stomatitis patients must contact the study site. Upon confirmation of stomatitis at the site, patients in countries where the alcohol-free 0.5mg/5ml dexamethasone oral solution is commercially available will be randomly assigned to take either 0.5mg/5ml dexamethasone mouth rinse or the standard of care used to treat stomatitis at the patient's center. The mouth rinse will be self-administered at a daily dose of 10ml 3 times per day. Patients will be instructed to swish and expectorate the mouth rinse. Patients will also be instructed to fill out the Oral Stomatitis Daily Questionnaire (OSDQ) at home every day until the patient recovers (see Section 10.5.5.1). During the Extension Phase, standard of care at the patient's site as recommended by the investigator to treat stomatitis will be followed and the OSDQ will not be administered when the patients are in the Extension Phase.

[redacted]

### 6.1.1 Dosing regimen

**Table 6-1 Dose and treatment schedule (first line setting & Extension Phase)**

| Study treatments | Pharmaceutical form and route of administration | Dose | Frequency and/or Regimen |
|---|---|---|---|
| Everolimus | Tablet for oral use | 10 mg(two 5mg tablets) | Daily (28 day cycles) |
| Letrozole | Tablet for oral use | 2.5mg | Daily (28 day cycles) |

**Table 6-2 Dose and treatment schedule (second line setting & Extension Phase)**

| Study treatments | Pharmaceutical form and route of administration | Dose | Frequency and/or Regimen |
|---|---|---|---|
| Everolimus | Tablet for oral use | 10 mg(two 5mg tablets) | Daily (28 day cycles) |
| Exemestane | Tablet for oral use | 25mg | Daily (28 day cycles) |

**Table 6-3 Dose and treatment schedule for oral stomatitis**

| Study treatments | Pharmaceutical form and route of administration | Dose | Frequency and/or Regimen |
|---|---|---|---|
| 0.5mg/5ml dexamethasone (for patients randomized to dexamethasone treatment) | Oral Solution | 10ml | Swish and expectorate 3 times/day |
| Standard of Care to treat oral stomatitis | See Section 6.2.2.1. | | |

### 6.1.2 Treatment duration

#### Core Phase

The study treatment refers to the administration of everolimus in combination with letrozole or exemestane to patients. A treatment cycle consists of 4 weeks (or 28 days). The first day of the open-label study medication begins at Visit 2 (Cycle 1 day 1). The patient must take the first dose of medication at the study center. Patients will receive everolimus 10mg orally daily in combination with letrozole until the occurrence of documented disease progression by RECIST 1.0 criteria or discontinuation due to unacceptable toxicity (with either study treatment) or withdrawal of consent (first line setting). After initial disease progression, patients will be offered everolimus in combination with exemestane according to the treating physician's clinical discretion (see Section 7.1.3). Patients will be treated in the second line until subsequent disease progression or any other reason for which the patient may be discontinued (refer to Section 7.1.5).

#### Extension Phase

In the Extension Phase, visits will be every 3 months instead of every 28 days hence patients will be completing approximately 3 treatment cycles between visits. Patients will continue treatment as described in the Core Phase until disease progression or any other reason for which the patient may be discontinued (refer to Section 7.1.5).

[redacted]

### 6.1.3 Prohibited concomitant therapy

Patients must be instructed not to take any additional medications (over-the-counter or other products) during the study without prior consultation with the investigator. All medications taken within 28 days of starting study treatment should be reported on the Concomitant Medication eCRF pages.

The following concomitant treatments are not allowed during the study:

- Chronic concomitant bisphosphonate therapy for the prevention of bone metastases are not permitted during the study. Bisphosphonate therapy for the treatment of osteopenia or osteoporosis is permitted during the study. Bisphosphonate or denosumab therapy for the management of bone metastases is recommended as standard of care. Please refer to prescribing information for details of administration. If bisphosphonate or denosumab therapy is initiated after enrollment, the reason for its use must be clearly documented.
- 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.
- 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. intraarticular) should not be given. A short duration (<2 weeks) of systemic corticosteroids is allowed (e.g. chronic obstructive pulmonary disease, anti-emetic). Please note, alcohol-free 0.5mg/5ml dexamethasone oral mouth rinse is allowed for patients randomized to receive it at the onset of stomatitis in countries where it is commercially available.
- 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.

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

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

Therefore, the following are recommended:

- Co-administration with strong inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, ritonavir) or P-glycoprotein (PgP) should be avoided and may cause increased everolimus concentrations.
- Co-administration with moderate CYP3A4 inhibitors (e.g., erythromycin, fluconazole) or PgP inhibitors should be used with caution. If a patient requires co-administration of moderate CYP3A4 inhibitors or PgP inhibitors, reduce the dose of everolimus to half the currently used dose (see Table 6-9 for everolimus dose modifications). Additional dose reductions may be required to manage toxicities. If the inhibitor is discontinued, consider a washout period of at least 2-3 days (average for the most commonly used moderate

[redacted]

inhibitors), before the study drug isreturned to the dose used prior to initiation of the moderate CYP3A4/PgP inhibitor.

- Co-administration with strong inducers of CYP3A4 should be avoided.
- If a patient requires co-administration of strong CYP3A4 inducers (i.e., phenytoin, carbamazepine, rifampin, rifabutin, phenobarbital, St. John's wort), an increase in the dose of everolimus up to twice the currently used daily dose should be considered, using 5mg increments or less (see Table 6-9 for everolimus dose modifications). This dose adjustment of everolimus is predicted to achieve similar AUC to the range observed without inducers. However, there are no clinical data with this dose adjustment in patients receiving strong CYP3A4 inducers. If the strong inducer is discontinued, consider a washout period of at least 3-5 days (reasonable time for significant enzyme de-induction), before the study drug dose is returned to the dose used prior to initiation of the strong CYP3A4/PgP inducer.

It is to be noted that:

- 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.
- Lipid-lowering drugs may be given in case of hyperlipidemia.

Otherwise, the use of other concomitant medication/therapy deemed necessary for the care of the patient is allowed. The investigator should instruct the patient to notify the study site about any new medications she takes after the start of the study drug. All medications (other than study drug) and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient starts study treatment and for up to 28 days after study drug discontinuation must be listed on the Concomitant medications/Significant Nondrug Therapy After Start of Study Drug eCRF. The first regimen of antineoplastic medication/treatments received after study treatment discontinuation must also be recorded in the antineoplastic treatment eCRF.

[redacted]

**Table 6-4 Clinically relevant drug interactions: inducers and inhibitors of isoenzyme CYP3A**

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

[redacted]

**Table 6-5 Clinically relevant drug interactions: substrates, inducers, inhibitors of PgP and PgP/CYP3A dual inhibitors**

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

## 6.2 Dose modifications and known undesirable effects of study drug/treatment

### 6.2.1 Everolimus

As of 31 March 2016 approximately 35,801 patients with various malignancies (excluding patients who received marketed Afinitor®/ Votubia®) have been treated with everolimus in either Novartis-sponsored clinical studies, individual patient supply programs or investigator sponsored clinical studies.

The most common adverse reactions (incidence ≥10% in at least one pivotal trial) were (by decreasing order) stomatitis, rash, fatigue, diarrhea, infections, nausea, decreased appetite, anemia, dysgeusia, pneumonitis, edema peripheral, hyperglycemia, asthenia, pruritus, weight decrease, hypercholesterolemia, epistaxis, cough, and headache, The most common grade 3-4 adverse reactions (incidence ≥2% in at least one pivotal trial), were stomatitis, anemia, hyperglycemia, fatigue, infections, pneumonitis, diarrhea, asthenia, thrombocytopenia, neutropenia, dyspnea, lymphopenia, proteinuria, hemorrhage, hypophosphatemia, rash,

[redacted]

hypertension, aspartate aminotransferase (AST) increased, alanine aminotransferase (ALT) increased, pneumonia and diabetes mellitus. For more details about clinically notable adverse events, refer to the most recent everolimus investigator brochure. Management of specific toxicities is described in Section 6.2.2.

#### 6.2.1.1 Letrozole

The most frequently reported adverse reactions (>20%) were hot flashes, arthralgia, flushing, asthenia, edema, arthralgia, headache, dizziness, hypercholesterolemia, sweating increased, bone pain and musculoskeletal pain. Use of letrozole can also cause decreases in bone mineral density. Increases in total cholesterol may occur. Letrozole may be taken with or without food. Refer to the package insert of the local supply of letrozole for management of toxicities and dose adjustments.

#### 6.2.1.2 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. 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 management of toxicities and dose adjustments.

### 6.2.2 Management of specific everolimus-related toxicities

Permitted everolimus (RAD001) dose adjustments are described in Table 6-7, Table 6-8, Table 6-9, Table 6-10, and Table 6-11.

#### 6.2.2.1 Management of stomatitis/oral mucositis/mouth ulcers

Patients with a clinical history of stomatitis/mucositis/mouth ulcers and those with gastrointestinal morbidity associated with mouth/dental infections, irritation of esophageal mucosa e.g. gastroesophageal reflux disease (GERD) and pre-existing stomatitis/mucositis must be monitored even more closely. Patients should be instructed to report the first onset of buccal mucosa irritation/reddening to their study physician immediately.

Stomatitis/oral mucositis/mouth ulcers due to study drug should be treated using local supportive care. Please note that investigators in earlier trials have described the oral toxicities associated with everolimus as mouth ulcers, rather than mucositis or stomatitis. If examination reveals mouth ulcers rather than a more general inflammation of the mouth, please classify the adverse event as such. As noted in Section 6.1, patients in countries where the alcohol-free 0.5mg/5ml dexamethasone oral solution is commercially available, randomized to dexamethasone will be prescribed a 0.5mg/5ml dexamethasone mouth rinse to swish and

[redacted]

expectorate 3 times per day. Treatment of stomatitis/oral mucositis/mouth ulcers for patients randomized to standard of care may include the following measures in conjunction with institutional standards:

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

Additional measures for management of stomatitis consistent with institutional standards should be utilized for patients randomized to standard of care.

#### 6.2.2.2 Management of hyperlipidemia and hyperglycemia

Treatment of hyperlipidemia should take into account the pre-treatment status and dietary habits. Grade 2 or higher hypercholesterolemia (>300 mg/dL or 7.75 mmol/L) or grade 2 hypertriglyceridemia or higher (>2.5x upper normal limit) should be treated with a 3-hyroxy-3-methyl-glutaryl (HMG)-CoA reductase inhibitor (e.g., atorvastatin, pravastatin, fluvastatin) or appropriate triglyceride-lowering medication, in addition to diet.

**Note:** Concomitant therapy with fibrates and an HMG-CoA reductase inhibitor is associated with an increased risk of a rare but serious skeletal muscle toxicity manifested by rhabdomyolysis, markedly elevated creatinine phosphokinase (CPK) levels and myoglobinuria, acute renal failure and sometimes death. The risk versus benefit of using this therapy should be determined for individual patients based on their risk of cardiovascular complications of hyperlipidemia.

Hyperglycemia has been reported in in patients taking everolimus. Monitoring of fasting serum glucose is recommended prior to the start of everolimus therapy and periodically thereafter. More frequent monitoring is recommended when everolimus is co-administered with other drugs that may induce hyperglycemia. Optimal glycemic control should be achieved before starting trial therapy.

#### 6.2.2.3 Management of hepatitis reactivation

Monitoring and prophylactic treatment for hepatitis B reactivation

[redacted]

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

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

| Test | Result | Result | Result | Result | Result |
|---|---|---|---|---|---|
| HBV-DNA | + | + or - | - | - | - |
| HBs Ag | + or - | + | - | - | - |
| HBsAb | + 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 treatment<br>Monitor HBV-DNA approximately every 4-8 weeks | | No prophylaxis<br>Monitor HBV-DNA approximately every 3-4 weeks | | No specific action |
| Antiviral prophylaxis therapy should continue for at least 4 weeks after last dose of study treatment. | | | | | |

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

[redacted]

**Table 6-7 Guidelines for management of hepatitis B reactivation**

| **HBV reactivation (with or without clinical signs and symptoms)*** | |
|---|---|
| For patients with baseline results:<br>Positive HBV-DNA<br>OR<br>positive HBs Ag<br>----------<br>reactivation is defined as:<br>[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<br>AND<br>Interrupt study drug administration until resolution:<br>≤ baseline HBV-DNA levels<br>If resolution occurs within ≤ 28 days study drug should be re-started at one dose lower, if available. (see Table 6-10 – 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 treatment.<br>If resolution occurs > 28 days Patients should discontinue study drug but continue both antiviral therapies at least 4 weeks after last dose of study treatment. |
| For patients with baseline results:<br>Negative HBV-DNA and HBsAg<br>AND<br>[Positive HBs Ab (with no prior history of vaccination against HBV), OR positive HBc Ab]<br>----------<br>reactivation is defined as:<br>New appearance of measurable HBV-DNA | Treat: Start first antiviral medication<br>AND<br>Interrupt study treatment administration until resolution:<br>≤ undetectable (negative) HBV-DNA levels<br>If resolution occurs within ≤ 28 days study drug should be re-started at one dose lower, if available. (see Table 6-10 – Study drug dose reductions) If the patient is already receiving the lowest dose of either study treatment 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 treatment.<br>If resolution occurs > 28 days Patients should discontinue study drug but continue antiviral therapy at least 4 weeks after last dose of study treatment. |
| * All reactivations of hepatitis B are to be recorded as grade 3 (CTCAE v 4.0 Metabolic Laboratory/Other: Viral Re-activation), unless considered life threatening by the investigator; in which case they should be recorded as grade 4 (CTCAE v 4.0 Metabolic Laboratory/Other: Viral Re-activation). Date of viral reactivation is the date on which the rise or reappearance of HBV-DNA was recorded. | |

## Monitoring for hepatitis C

The following two categories of patients should be monitored every 4–8 weeks for HCV reactivation:

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

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

[redacted]

**Table 6-8 Guidelines for management of hepatitis C flare**

| **HCV reactivation*** | |
|---|---|
| For patients with baseline results:<br>Detectable HCV-RNA<br>HCV flare definition:<br>>2 $log_{10}$ IU/mL increase in HCV-RNA<br>AND<br>ALT elevation x 5 ULN or 3 x baseline level, whichever is higher. | Discontinue study treatment |
| For patients with baseline results:<br>Knowledge of past hepatitis C infection with no detectable HCV-RNA<br>HCV flare definition:<br>New appearance of detectable HCV-RNA<br>AND<br>ALT elevation>5x ULN or 3x baseline level, whichever is higher. | Discontinue study treatment |
| * All reactivations of hepatitis C are to be recorded as grade 3 (CTCAE v 4.0 Metabolic Laboratory/Other: Viral Re-activation), unless considered life threatening by the investigator; in which case they should be recorded as grade 4 (CTCAE v 4.0 Metabolic Laboratory/Other: Viral Re-activation). Date of viral flare is the date on which both the clinical criteria described above were met. (e.g., for a patients whose HCV-RNA increased by 2 logs on 01JAN2011 and whose ALT reached >5 x ULN on 22JAN2011, the date of viral flare is 22JAN2011). | |

#### 6.2.2.4 Management of diarrhea

Appearance of grade 1-2 diarrhea attributed to study drug toxicity may be treated with supportive care such as loperamide, initiated at the earliest onset (e.g., 4mg orally followed by 2mg orally every 2 hours until resolution of diarrhea).

#### 6.2.2.5 Management of non-infectious pneumonitis

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

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

[redacted]

Patients who develop radiological changes suggestive of non-infectious pneumonitis and have few or no symptoms may continue everolimus therapy without dose alteration.

If symptoms are moderate (grade 2), consideration should be given to interruption of therapy until symptoms improve. The use of corticosteroids may be indicated. Everolimus may be reintroduced at a daily dose approximately 50% lower than the dose previously administered.

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

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

Individuals participating in this trial will be routinely questioned as to the presence of new or changed pulmonary symptoms consistent with lung toxicity. Moreover, potential lung radiological changes can be detected by chest CT/MRI scans that are performed on all patients every 8 weeks for tumor assessments according to the schedule of visits (Table 7-1). In addition, PFTs will be conducted, including spirometry, $D_LCO$, and room air $O_2$ saturation at rest should be performed. Bronchoscopy with biopsy and/or bronchoalveolar lavage (BAL), if clinically indicated to monitor for pneumonitis. If non-infectious pneumonitis develops, the guidelines in Table 6-10 should be followed. Dose modification instructions are also provided in Table 6-9. Consultation with a pulmonologist is recommended for any case of pneumonitis that develops during the study.

#### 6.2.2.6 Management of infections

Everolimus has immunosuppressive properties and may predispose patients to bacterial, fungal, viral or protozoan infections, including infections with opportunistic pathogens.

Localized and systemic infections, including pneumonia, other bacterial infections, invasive fungal infections, such as aspergillosis or candidiasis, PJP and viral infections including reactivation of hepatitis B virus, have been described in patients taking everolimus. Some of these infections have been severe (e.g. leading to respiratory or hepatic failure) and occasionally have had a fatal outcome. Physicians and patients should be aware of the increased risk of infection with everolimus. Treat pre-existing infections prior to starting treatment with everolimus. While taking everolimus, be vigilant for symptoms and signs of infection; if a diagnosis of infection is made, institute appropriate treatment promptly and consider interruption or discontinuation of everolimus. If a diagnosis of invasive systemic fungal infection is made, discontinue everolimus and treat with appropriate antifungal therapy.

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

[redacted]

Cases of PJP, some with fatal outcome, have been reported in patients who received everolimus. PJP may be associated with concomitant use of corticosteroids or other immunosuppressive agents. Prophylaxis for PJP should be considered when concomitant use of corticosteroids or other immunosuppressive agents is required.

#### 6.2.2.7 Management of hematologic toxicities

Patients' blood counts should be monitored regularly during treatment. Please refer to Table 6-11 for details.

#### 6.2.2.8 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.

#### 6.2.2.9 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 weekly until resolution or stabilization of the event, whichever comes first. The patient must be discontinued from the study if they require a dose delay of ≥ 28 days.

#### 6.2.2.10 Permitted study drug adjustments

For patients who may require dose adjustments because of concomitant medication, please refer to Section 6.1.3. For patients who are unable to tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to allow the patient to continue study drug. The following guidelines should be followed. These changes must be recorded on the Dosage Administration Record eCRF. If treatment is interrupted due to toxicity, study drug should not be resumed until recovery to Grade ≤ 1. Study drug can then be reintroduced at the initial dose or a lower dose level depending on the toxicity type and Grade (see Table 6-9, Table 6-10, Table 6-11).

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

**Table 6-9 Dose reduction steps for everolimus**

| **Dose reduction*** | | | |
|---|---|---|---|
| | Starting dose level | Dose level – 1 | Dose level - 2 |
| Everolimus | 10 mg daily | 5 mg daily | 5 mg every other day** |
| *Dose reduction should be based on the worst toxicity demonstrated at the last dose received.<br>**Dose reduction below 5 mg every other day is not allowed. Treatment must be discontinued. | | | |

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

[redacted]

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

Table 6-10 and Table 6-11 summarize the recommendations for dose interruption, reduction, or discontinuation of everolimus in the management of ADRs. General management recommendations are also provided as applicable. Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

**Table 6-10 Dosing guidelines for study drug-related non-hematologic toxicities**

| Adverse drug reaction | Severity[1] | Everolimus dose adjustment[2] and management recommendations |
|---|---|---|
| Non-infectious pneumonitis | Grade 1<br>Asymptomatic, radiographic findings only | No dose adjustment required.<br>Initiate appropriate monitoring. |
| | Grade 2<br>Symptomatic, not interfering with ADL[3] | Consider interruption of therapy, rule out infection and consider treatment with corticosteroids until symptoms improve to Grade ≤ 1.<br>Re-initiate everolimus at a lower dose.<br>Discontinue treatment if failure to recover within 4 weeks. |
| | Grade 3<br>Symptomatic, interfering with ADL[3]<br>$O_2$ indicated | Interrupt everolimus until symptoms resolve to Grade ≤ 1. Rule out infection and consider treatment with corticosteroids.<br>Consider re-initiating everolimus at a lower dose.<br>If toxicity recurs at Grade 3, consider discontinuation. |
| | Grade 4<br>Life-threatening, ventilatory support indicated | Discontinue everolimus, rule out infection, and consider treatment with corticosteroids. |

[redacted]

| Adverse drug reaction | Severity[1] | Everolimus dose adjustment[2] and management recommendations |
|---|---|---|
| Stomatitis | Grade 1<br>Minimal symptoms, normal diet | No dose adjustment required.<br>Manage with non-alcoholic or salt water (0.9%) mouthwash several times a day. |
| | Grade 2<br>Symptomatic but can eat and swallow modified diet | Temporary dose interruption until recovery to Grade ≤1.<br>Re-initiate everolimus at the same dose.<br>If stomatitis recurs at Grade 2, interrupt dose until recovery to Grade ≤1. Re-initiate everolimus at a lower dose.<br>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).[4] |
| | Grade 3<br>Symptomatic and unable to adequately eat or hydrate orally | Temporary dose interruption until recovery to Grade ≤1.<br>Re-initiate everolimus at a lower dose.<br>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).[4] |
| | Grade 4<br>Symptoms associated with life-threatening Consequences | Discontinue everolimus and treat with appropriate medical therapy. |
| Other non-hematologic toxicities (excluding metabolic events) | Grade 1 | If toxicity is tolerable, no dose adjustment required.<br>Initiate appropriate medical therapy and monitor. |
| | Grade 2 | If toxicity is tolerable, no dose adjustment required.<br>Initiate appropriate medical therapy and monitor.<br>If toxicity becomes intolerable, temporary dose interruption until recovery to Grade ≤1. Re-initiate everolimus at the same dose.<br>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.<br>Initiate appropriate medical therapy and monitor.<br>Consider re-initiating everolimus at a lower dose.<br>If toxicity recurs at Grade 3, consider discontinuation. |
| | Grade 4 | Discontinue everolimus and treat with appropriate medical therapy. |

[redacted]

| Adverse drug reaction | Severity[1] | Everolimus dose adjustment[2] and management recommendations |
|---|---|---|
| Metabolic events (e.g. hyper-glycemia, dys-lipidemia) | Grade 1 | No dose adjustment required.<br>Initiate appropriate medical therapy and monitor. |
| | Grade 2 | No dose adjustment required.<br>Manage with appropriate medical therapy and monitor. |
| | Grade 3 | Temporary dose interruption.<br>Re-initiate everolimus at a lower dose.<br>Manage with appropriate medical therapy and monitor. |
| | Grade 4 | Discontinue everolimus and treat with appropriate medical therapy. |

[1] Severity Grade description: 1 = mild symptoms; 2 = moderate symptoms; 3 = severe symptoms; 4 = life-threatening symptoms.

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

[3] Activities of daily living (ADL)

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

[redacted]

**Table 6-11 Dosing guidelines for study drug-related hematologic toxicities**

| Adverse event | Severity[1] | Everolimus Dose Adjustment |
|---|---|---|
| Platelet count decreased (Thrombocytopenia) | Grade 1 (<LLN-75.0x$10^9$/L) | No dose adjustment required. |
| | Grade 2 (<75.0-50.0x$10^9$/L) | Temporary dose interruption until recovery to Grade ≤1. Re-initiate everolimus at the same dose. |
| | Grade 3 (<50.0-25.0x$10^9$/L) | Temporary dose interruption until recovery to Grade ≤1. Re-initiate everolimus at a lower dose. |
| | Grade 4 (<25.0x$10^9$/L) | Temporary dose interruption until recovery to Grade ≤1. Re-initiate everolimus at a lower dose. |
| Neutrophil count decreased (Neutropenia) | Grade 1 (<LLN-1.5x$10^9$/L) | No dose adjustment required. |
| | Grade 2 (<1.5-1.0x$10^9$/L) | No dose adjustment required. |
| | Grade 3 (<1.0-0.5x$10^9$/L) | Temporary dose interruption until recovery to Grade ≤2 (ANC≥1.0x$10^9$/l). Re-initiate everolimus at the same dose. |
| | Grade 4 (<0.5x$10^9$/L) | Temporary dose interruption until recovery to Grade ≤2 (ANC≥1.0x$10^9$/l). Re-initiate everolimus at a lower dose. |
| Febrile neutropenia | Grade 3 (ANC<1.0x$10^9$/L with single temperature >38.3° C (101°F) or sustained temperature ≥38°C (100.4°F) for >1h) | Temporary dose interruption until recovery to Grade ≤2 (ANC≥1.25x$10^9$/l) and no fever. Re-initiate everolimus at a lower dose. |
| | Grade 4 (Life-threatening consequences; urgent intervention indicated) | Discontinue everolimus. |
| Any hematologic toxicity requiring study drug interruption for >28 days | | Discontinue everolimus. |

[1] Grading based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03

## 6.3 Patient numbering, treatment assignment or randomization

### 6.3.1 Patient numbering

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

[redacted]

### 6.3.2 Treatment assignment for oral stomatitis therapy

Upon diagnosis of stomatitis, patients in countries where the alcohol-free 0.5mg/5ml dexamethasone oral solution is commercially available, will be randomized in 1:1 ratio to take either 0.5mg/5ml dexamethasone mouth rinse or standard of care at the patient's center. The assignment of a patient to a particular cohort will be coordinated by the sponsor. A randomization list will be produced by or under the responsibility of Novartis Drug Supply Management and the Biostatistician. The randomization list will be reviewed by a Biostatistics Quality Assurance Group and locked by them after approval.

During the Extension Phase, standard of care at the patient's site as recommended by the investigator to treat stomatitis will be followed.

### 6.3.3 Treatment blinding

This is an open-label trial, treatment will not be blinded.

## 6.4 Study drug preparation and dispensation

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

**Table 6-12 Preparation and dispensing**

| Study treatments | Dispensing | Preparation |
|---|---|---|
| Everolimus (RAD001) | Tablets including instructions for administration are dispensed by study personnel on an outpatient basis. Patients will be provided with adequate supply of study treatment for self-administration at home until at least their next scheduled study visit. | Refer to local product information |
| Letrozole | Oral tablets | Refer to local product information |
| Exemestane | Oral tablets | Refer to local product information |
| dexamethasone | Oral solution | Refer to local product information |

### 6.4.1 Study drug packaging and labeling

Everolimus can be provided with locally available commercial material or centrally as needed. It will be supplied and labeled accordingly to comply with the legal requirements of local Health Authority regulations in each country. Medication labels for the centrally provided everolimus (RAD001), under the responsibility of Novartis DSM will comply with the legal regulations of each country and be printed in local language. Everolimus (RAD001) will be open-label to allow patients to take medication at home. For countries where the study medications are supplied by Novartis DSM, the supplies will be sent as open-label bulk supply. The storage conditions for study drug will be described on the medication label. Commercially available letrozole and exemestane will be supplied to sites or prescribed to

[redacted]

patients in accordance with local regulations in participating countries. The storage conditions will be described on the medication label.

**Table 6-13 Packaging and labeling**

| Study treatments | Packaging | Labeling (and dosing frequency) |
|---|---|---|
| Everolimus (RAD001) | Tablets in blister packs | Labeled as Everolimus (RAD001); 2-5mg tablets to be taken orally |
| Letrozole | Refer to local product information | 2.5mg tablets to be taken orally. Refer to local product information |
| Exemestane | Refer to local product information | 25mg tablet to be taken orally. Refer to local product information |
| dexamethasone (for patients randomized to dexamethasone treatment) | Refer to local product information | 0.5mg/5ml Oral solution to be swished and expectorated 3 times per day for duration of stomatitis. Refer to local product information for additional details |

### 6.4.2 Drug supply and storage

Study treatments 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 6-14 Supply and storage of study treatments**

| Study treatments | Supply | Storage |
|---|---|---|
| Everolimus (RAD001) | Locally or centrally supplied by Novartis as needed | Refer to study treatment label |
| Letrozole | Locally supplied by Novartis as needed or by prescription in applicable countries | Refer to local product information |
| Exemestane | Locally supplied by Novartis as needed or by prescription in applicable countries | Refer to local product information |
| 0.5mg/5ml dexamethasone | Supplied via prescription in countries where it is commercially available | Refer to local product information. |

### 6.4.3 Study drug compliance and accountability

#### 6.4.3.1 Study drug compliance

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

[redacted]

#### 6.4.3.2 Study drug accountability

The investigator or designee must maintain an accurate record of the shipment and dispensing of study drug 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 drug and packaging on a regular basis, at the end of the study or at the time of study treatment discontinuation.

At study close-out, and, as appropriate during the course of the study, the investigator will return all used and unused study drug, 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.

#### 6.4.3.3 Handling of other study treatment

Storage conditions for letrozole, exemestane and dexamethasone will be described on the medication label.

### 6.4.4 Disposal and destruction

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

# 7 Visit schedule and assessments

## 7.1 Study flow and visit schedule

Table 7-1, Table 7-2 and Table 7-3 lists all of the assessments and indicates with an “X”, the visits when they are performed. All data obtained from these assessments must be supported in the patient’s source documentation. No CRF will be used as a source document.

[redacted]

**Table 7-1 Visit evaluation schedule (Core Phase: First line treatment)**

| | Category | Reference to Section | Screening/ Baseline | Cycles 1 cycle = 28 days* | | | | End of treatment (EoT) for first line treatment | 28 Day Safety Follow up* | Study Evaluation completion* | Survival follow up** | Post Treatment Evaluations |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Cycle Number** | | | | **C1** | **C2** | **C3** | **Subsequent cycles** | | | | | |
| **Visit Number** | | | **1** | **2** | **3** | **4** | **5,6,7…** | **777** | **501** | **778** | | |
| **Day of cycle** | | | **-28 to -1** | **1** | **1** | **1** | **1** | **Last dose + ≤15 days** | **Last dose + 28 days** | | | |
| Obtain Informed Consent | D | 7.1.1.1. | X | | | | | | | | | |
| Eligibility checklist | S | 7.1.1.1. | X | | | | | | | | | |
| Patient history: | | | | | | | | | | | | |
| Demography | D | 7.1.1.4. | X | | | | | | | | | |
| Inclusion/exclusion criteria | S/D | 5.2. 5.3. | X | | | | | | | | | |
| Relevant medical history/current medical conditions | D | 7.1.1.4. | X | | | | | | | | | |
| Diagnosis and extent of cancer | D | 7.1.1.4. | X | | | | | | | | | |
| Prior antineoplastic therapy | D | 7.1.1.4. | X | | | | | | | | | |
| Prior/concomitant medications | D | 7.1.1.4. | X | Continuous during the study up to 28 days after last treatment | | | | | | | | |
| Physical examination: | | | | | | | | | | | | |
| Physical examination | S | 7.2.2.1. | X | X | X | X | Day 1 of subsequent cycles | X | | | | |

[redacted]

| | Category | Reference to Section | Screening/ Baseline | Cycles 1 cycle = 28 days* | | | | End of treatment (EoT) for first line treatment | 28 Day Safety Follow up* | Study Evaluation completion* | Survival follow up** | Post Treatment Evaluations |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Cycle Number** | | | | **C1** | **C2** | **C3** | **Subsequent cycles** | | | | | |
| **Visit Number** | | | **1** | **2** | **3** | **4** | **5,6,7…** | **777** | **501** | **778** | | |
| **Day of cycle** | | | **-28 to -1** | **1** | **1** | **1** | **1** | **Last dose + ≤15 days** | **Last dose + 28 days** | | | |
| ECOG Performance status | D | 7.2.2.4. | X | X | X | X | Day 1 of subsequent cycles | X | | | | |
| Height | D | 7.2.2.3. | X | | | | | | | | | |
| Weight | D | 7.2.2.3. | X | X | X | X | Day 1 of subsequent cycles | X | | | | |
| Vital signs | D | 7.2.2.2. | X | X | X | X | Day 1 of subsequent cycles | X | | | | |
| ECG | D | 7.2.2.6.1. | X | As clinically indicated | | | | | | | | |
| Pulmonary function test (PFTs) | D | 7.2.2.7. | As clinically indicated | | | | | | | | | |
| Laboratory assessments: | | 7.2.2.5. | | | | | | | | | | |
| Hematology | D | 7.2.2.5.1. | X | X | X | X | Day 1 of subsequent cycles | X | | | | |
| Chemistry | D | 7.2.2.5.2. | X | X | X | X | Day 1 of subsequent cycles | X | | | | |
| Coagulation | D | 7.2.2.5.3. | X | As clinically indicated | | | | | | | | |

[redacted]

| | Category | Reference to Section | Screening/ Baseline | Cycles 1 cycle = 28 days* | | | | End of treatment (EoT) for first line treatment | 28 Day Safety Follow up* | Study Evaluation completion* | Survival follow up** | Post Treatment Evaluations |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Cycle Number** | | | | **C1** | **C2** | **C3** | **Subsequent cycles** | | | | | |
| **Visit Number** | | | **1** | **2** | **3** | **4** | **5,6,7…** | **777** | **501** | **778** | | |
| **Day of cycle** | | | **-28 to -1** | **1** | **1** | **1** | **1** | **Last dose + ≤15 days** | **Last dose + 28 days** | | | |
| Hepatitis screening and monitoring (if applicable) | D | 7.2.2.5.4. 7.2.2.5.5. | X | | | | | | | | | |
| Urinalysis | D | 7.2.2.5.6. | X | As clinically indicated | | | | | | | | |
| Imaging: | | 7.2.1. | | | | | | | | | | |
| CT or MRI for chest, abdomen, pelvis | D | 7.2.1. | X | | | X | Every 8 weeks | X only for patients discontinuing for reasons other than documented PD, lost to follow up and death | | | | X |
| CT or MRI for Brain | D | 7.1.1.4. | X | As clinically indicated | | | | | | | | |
| Bone scan or skeletal survey | D | 7.2.1. | X | | | X | Every 8 weeks | | | | | |
| If baseline bone scan positive perform X-ray, CT or MRI | D | 7.2.1. | X | | | X | Every 8 weeks | X only for patients discontinuing for reasons other than documented PD, lost to follow up and death | | | | |

[redacted]

[redacted]

| | Category | Reference to Section | Screening/ Baseline | Cycles 1 cycle = 28 days* | | | | End of treatment (EoT) for first line treatment | 28 Day Safety Follow up* | Study Evaluation completion* | Survival follow up** | Post Treatment Evaluations |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Cycle Number** | | | | **C1** | **C2** | **C3** | **Subsequent cycles** | | | | | |
| **Visit Number** | | | **1** | **2** | **3** | **4** | **5,6,7…** | **777** | **501** | **778** | | |
| **Day of cycle** | | | **-28 to -1** | **1** | **1** | **1** | **1** | **Last dose + ≤15 days** | **Last dose + 28 days** | | | |
| [redacted] | | | | | | | | | | | | |
| Safety: | | 7.2.2. | | | | | | | | | | |
| Adverse events | D | 7.2.2. | | Continuous during the study, up to 28 days after the last treatment | | | | | X | | | |
| Patient reported Outcomes – OSDQ | | 7.2.6. | | Complete OSDQ daily during every episode of oral stomatitis. | | | | | | | | |
| Everolimus administration | D | 6.1. | | Daily dosing | | | | | | | | |
| Letrozole administration | D | 6.1. | | Daily dosing for FIRST LINE TREATMENT ONLY | | | | | | | | |
| Study Evaluation Completion | D | 7.1.6.1. | | | | | | | | X | | |
| Survival Follow-up | D | 7.1.6.2. | | | | | | | | | X | |
| Antineoplastic therapies since discontinuation of study treatment | D | 5. | | | | | | | X | | | X |

[redacted]

| | Category | Reference to Section | Screening/ Baseline | Cycles 1 cycle = 28 days* | | | | End of treatment (EoT) for first line treatment | 28 Day Safety Follow up* | Study Evaluation completion* | Survival follow up** | Post Treatment Evaluations |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Cycle Number** | | | | **C1** | **C2** | **C3** | **Subsequent cycles** | | | | | |
| **Visit Number** | | | **1** | **2** | **3** | **4** | **5,6,7…** | **777** | **501** | **778** | | |
| **Day of cycle** | | | **-28 to -1** | **1** | **1** | **1** | **1** | **Last dose + ≤15 days** | **Last dose + 28 days** | | | |

Category: 'S' indicates assessments that produce data that will remain in source documents only.

'D' indicates assessments that produce data that will be entered in the clinical database.

Visit assessment window is defined as +/- 3 days except for on-study imaging assessment: +/- 1 week

*Once the patient starts the Extension Phase those indicated will not be performed as part of the main study phase, refer to Table 7-3 for all that will be performed in the Extension Phase.

**Survival Follow-up will only be collected until 24 Months post LPFV (date of OS data cutoff)

[redacted]

**Table 7-2 Visit evaluation schedule (Core Phase: Second-line treatment)**

| | Category | Reference to Section | Cycles* 1 cycle = 28 days | | | | End of treatment (EoT) for second line treatment | 28 Day Safety Follow up* | Study Evaluation Completion* | Survival follow up** | Post Treatment Evaluations |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Cycle Number** | | | **Cycle 101** | **C102** | **C103** | **Subsequent cycles** | | | | | |
| **Visit Number** | | | **102** | **103** | **104** | **105, 106, 107…** | **779** | **501** | **778** | | |
| **Day of cycle** | | | **Day 1 of each cycle** | | | | **Last dose + ≤15 days** | **Last dose + 28 days** | | | |
| Inclusion/exclusion criteria re-examination | S/D | 7.1.3. | X | | | | | | | | |
| Concomitant medications | D | 7.1.1.4. | Continuous during the study up to 28 days after last treatment | | | | | | | | |
| Physical examination | S | 7.2.2.1. | Day 1 of each cycle | | | | X | | | | |
| ECOG Performance status | D | 7.2.2.4. | Day 1 of each cycle | | | | X | | | | |
| Weight | D | 7.2.2.3. | Day 1 of each cycle | | | | X | | | | |
| Vital signs | D | 7.2.2.2. | Day 1 of each cycle | | | | X | | | | |
| ECG | D | 7.2.2.6.1. | As clinically indicated | | | | | | | | |
| Pulmonary function test (PFTs) | D | 7.2.2.7. | As clinically indicated | | | | | | | | |
| Laboratory assessments: | | 7.2.2.5. | | | | | | | | | |
| Hematology | D | 7.2.2.5.1. | Day 1 of each cycle | | | | X | | | | |
| Chemistry | D | 7.2.2.5.2. | Day 1 of each cycle | | | | X | | | | |
| Coagulation | D | 7.2.2.5.3. | As clinically indicated | | | | | | | | |
| Urinalysis | D | 7.2.2.5.6. | As clinically indicated | | | | | | | | |

[redacted]

| | Category | Reference to Section | Cycles* 1 cycle = 28 days | | | | End of treatment (EoT) for second line treatment | 28 Day Safety Follow up* | Study Evaluation Completion* | Survival follow up** | Post Treatment Evaluations |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Cycle Number** | | | **Cycle 101** | **C102** | **C103** | **Subsequent cycles** | | | | | |
| **Visit Number** | | | **102** | **103** | **104** | **105, 106, 107…** | **779** | **501** | **778** | | |
| **Day of cycle** | | | **Day 1 of each cycle** | | | | **Last dose + ≤15 days** | **Last dose + 28 days** | | | |
| Hepatitis testing | D | 7.2.2.5.4. 7.2.2.5.5. | | | | | | | | | |
| Imaging: | | 7.2.1. | | | | | | | | | |
| CT or MRI for Brain | D | 7.1.1.4. | As clinically indicated | | | | | | | | |
| CT or MRI for chest, abdomen, pelvis | D | 7.2.1. | | | X | Every 8 weeks | X only for patients discontinuing for reasons other than documented PD, lost to follow up and death | | | | X |
| If bone scan positive perform X-ray, CT or MRI | D | 7.2.1. | | | X | Every 8 weeks | X only for patients discontinuing for reasons other than documented PD, lost to follow up and death | | | | |
| Safety: | | 7.2.2. | | | | | | | | | |
| Adverse events | D | 7.2.2. | Continuous during the study, up to 28 days after the last treatment | | | | | X | | | |
| Patient reported Outcomes – OSDQ | | 7.2.6. | Complete OSDQ daily during every episode of oral stomatitis. | | | | | | | | |
| Everolimus administration | D | 6.1. | Daily dosing | | | | | | | | |
| Exemestane administration | D | 6.1. | Daily dosing after initial progression for SECOND-LINE TREAMTENT ONLY | | | | | | | | |

[redacted]

| | Category | Reference to Section | Cycles* 1 cycle = 28 days | | | | End of treatment (EoT) for second line treatment | 28 Day Safety Follow up* | Study Evaluation Completion* | Survival follow up** | Post Treatment Evaluations |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Cycle Number** | | | **Cycle 101** | **C102** | **C103** | **Subsequent cycles** | | | | | |
| **Visit Number** | | | **102** | **103** | **104** | **105, 106, 107…** | **779** | **501** | **778** | | |
| **Day of cycle** | | | **Day 1 of each cycle** | | | | **Last dose + ≤15 days** | **Last dose + 28 days** | | | |
| Study Evaluation Completion | D | 7.1.6.1. | | | | | | | X | | |
| Survival Follow Up | D | 7.1.6.2. | | | | | | | | X | |
| Antineoplastic therapies since discontinuation of study treatment | D | 5. | | | | | | X | | | X |

Visit assessment window is defined as +/- 3 days except for on-study imaging assessment: +/- 1 week.

*Once the patient starts the Extension Phase those indicated will not be performed as part of the main study phase, refer to Table 7-3 for all that will be performed in the Extension Phase.

**Survival Follow-up will only be collected until 24 Months post LPFV (date of OS data cutoff).

[redacted]

**Table 7-3 Visit evaluation schedule (Extension Phase)**

| | Category | Reference to Section | Visits (every 12 weeks ±1 week) | | End of treatment (EoT) for extension | 28 Day Safety Follow up | Study Evaluation Completion |
|---|---|---|---|---|---|---|---|
| **Visit Number** | | | **EXT Visit 1** | **EXT Visit 2, EXT Visit 3,** | **780** | **501** | **778** |
| **Day of visit** | | | **Day 1 of each visit** | | **Last dose + ≤15 days** | **Last dose + 28 days** | |
| Re-consent | S | 7.1.4. | X | | | | |
| Adverse events | D | 7.2.2. | X | Continuous during the study, up to 28 days after the last treatment | | | |
| Everolimus administration | D | 6.1. | X | Daily dosing | | | |
| Letrozole administration | D | 6.1. | X if current treatment prior to entry in extension | Daily dosing | | | |
| Exemestane administration | D | 6.1. | X if current treatment prior to entry in extension | Daily dosing | | | |
| Confirmation of Clinical Benefit from investigator | D | 7.1.4. | X | At every visit | | | |
| Antineoplastic therapies since discontinuation of study treatment | D | 7.1.5. | | | | X | |
| Study Evaluation Completion | D | 7.1.6.1. | | | | | X |
| Hepatitis monitoring (if applicable) | S | 7.2.2.5.4. 7.2.2.5.5. | As clinically indicated | | | | |

[redacted]

### 7.1.1 Screening procedures

#### 7.1.1.1 Screening

Prior to performing any screening procedures, the patient must have signed and dated the informed consent document. 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. The investigator or designee must ensure that only patients who meet all of eligibility criteria are offered enrollment on the study. All data for the Inclusion/Exclusion criteria must be verifiable in the patient's source document.

In case the patient does not fulfill all eligibility criteria, the patient will be a screening failure. Re-screening of patients is only allowed once per patient within 28 days of the screening period. In the case of re-screening, the original patient number assigned to the patient will be used and the patient will be identified with the number throughout her entire participation in the study.

Patient eligibility will be checked by the Sponsor once all screening procedures are completed. The eligibility checklist form will be sent from the site to the Sponsor either via fax or email for evaluation. Upon confirmation of eligibility (Key criteria), the Sponsor will return the signed eligibility checklist via fax or email to the site. The investigator site will then be allowed to proceed with the enrollment of the patient into the trial, providing that all other Inclusion/Exclusion criteria are met.

Screening assessments must be done to confirm eligibility prior to the first dose of study drug. Laboratory baseline assessments (including hematology, chemistry, coagulation, and urinalysis), physical examination including performance status, ECG, height and weight must be performed within 28 days prior to first dose of study treatment. Radiological screening assessments performed within 28 days of baseline visit can be used for both study eligibility and baseline assessments. Screening evaluations performed ≤7 days before the date of the first dose of study treatment for all laboratory assessments and ECOG performance status can be used as baseline evaluations (i.e., need not be performed on Cycle 1 Day 1). Patients with potassium, sodium and/or calcium levels that are below the LLN at screening must have their potassium, sodium and/or calcium replenished through supplementation and the levels must be within normal limits prior to the first dose of study drug.

Information from procedures that may have been previously performed as part of the patient's routine disease care (prior to enrolling the trial) is allowed to be used to satisfy inclusion criteria as long as the procedures were performed within 28 days of study drug start.

[redacted]

#### 7.1.1.2 Information to be collected on screening failures

Patients who sign an informed consent but fail to be started on treatment for any reason will be considered a screen failure. The reason for not being started on treatment will be entered on the Screening Failure Log. The Demography CRF page must also be completed for all screen failures. No other data will be entered into the clinical database for subjects who are screen failures, unless the subject experienced a Serious Adverse Event during the Screening Phase (see Section 8 for SAE reporting details).

#### 7.1.1.3 Hepatitis screening/baseline

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).

##### 7.1.1.3.1 Screening for hepatitis B

Prior to starting trial therapy, 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. (http://nc.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 6.2.2.3, are provided according to the results of the baseline assessment of viral load and serological markers for hepatitis B.

##### 7.1.1.3.2 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,

[redacted]

- 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 6.2.2.3, are provided according to the results of the baseline assessment of hepatitis C viral load.

#### 7.1.1.4 Patient demographics and other baseline characteristics

The following patient demographic and baseline characteristics will be collected on the eCRF:

- General demography including age, gender, race, ethnic origin
- Medical history/current medical conditions (including prior and concomitant medications and prior antineoplastic therapies)
- History and current disease status (including staging, diagnosis information, hormonal receptor and HER2 status, previous anticancer treatments and sites of disease). The following information must be collected for all previous anticancer therapies: start date, end date, setting (neoadjuvant vs. adjuvant vs. therapeutic), best response, reason for treatment discontinuation.
- Physical/neurological examination, weight and height
- Vital signs including sitting blood pressure, pulse and temperature
- ECOG performance status
- ECG
- Safety laboratory assessments: chemistry, hematology, urinalysis coagulation
- HBV testing: prior to enrollment, the categories of patients listed in Section 7.1.1.3 should be tested for hepatitis B serologic markers and viral load: HBV-DNA HBsAg, HBcAb, and HBsAb. HBVDNA monitoring should be done depending on results from serologic markers and viral load as listed in Table 6-6.
- HCV testing: patients with hepatitis C risk factors and additional patients at the discretion of the investigator should be testing for HCV RNA-PCR test at baseline. For a list of hepatitis C risk factors, refer to Section 7.1.1.3. Follow-up testing will be performed, as per Section 6.2.2.3, only if the patient has a history or is positive at baseline or both.
- Bone scan or skeletal survey
- Radiological tumor assessment (CT or MRI for chest, abdomen, pelvis, brain and bone scan or skeletal survey); positive areas on bone scans must be assessed by X-ray, CT scan with bone windows or MRI

### 7.1.2 Treatment period

Patients will start study treatment at treatment 1 day 1 (cycle 1 day 1) and continue to be treated per protocol until documentation of disease progression or any other reason for which

[redacted]

the patient may be discontinued (refer to Section 7.1.5). However, study treatment may prematurely be discontinued for other reasons as well.

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

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

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

### 7.1.3 Second line treatment

Following disease progression in the first line setting, patients will be offered everolimus in combination with exemestane during the Core Phase, during the Extension Phase these patients will be discontinued from the study. Patients who discontinued first line treatment due to reasons other than disease progression are not eligible for second line treatment.

Informed consent will not be repeated for patients moving into the second line treatment period. However, specified inclusion / exclusion criteria must be re-examined (see Section 5.1) and collected on the eCRF.

At the determination of documented disease progression (e.g., image scan that determined the disease progression) in the first line treatment, the patient must begin second line treatment within 28 days.

A complete schedule of evaluations required for the second line treatment period are provided in Table 7-2.

The procedures for patients receiving second line treatment will proceed as follows:

- Re-examination of specified inclusion/exclusion criteria, see Section 5.1.
- ECOG Status
- Current concomitant medications
- Safety laboratory assessments: chemistry, hematology, urinalysis, coagulation
- HBV and HCV testing and monitoring should be continued only for those patients identified during enrollment on first line treatment. Testing should be performed as per Section 6.2.2.3.
- Tumor evaluations will follow the same schedule used in the first line treatment period. If the end of treatment tumor evaluations from the first line treatment period that lead to documentation of disease progression is <28 days prior to starting the second line treatment medication, then the end of treatment tumor evaluations from the first line will serve as Cycle 101 day 1 tumor evaluations for second line treatment period

[redacted]

- All continuing concomitant medications from the first line treatment period will be followed into the second line treatment period and will be recorded on the Concomitant Medications eCRF
- Treatment with everolimus and exemestane in the second line period continues until documented disease progression or any other reason for which the patient may be discontinued (refer to Section 7.1.5)
- When patients discontinue the second line treatment for any reason, an end of treatment visit following discontinuation of the second line medication will be performed. The 28 day follow up visit will also be performed to check on continuing AEs/SAEs or any new AEs/SAEs that may have occurred
- The first dose of open-label second line study medication begins at Cycle 101 day 1

### 7.1.4 Extension Phase

Following the overall survival cut-off (24 months post LPFV) and approval of Amendment 5, patients continuing to derive benefit from everolimus will be transitioned to an Extension Phase until disease progression or any other reason for which the patient may be discontinued (refer to Section 7.1.5).

Patients will be re-consented prior to starting the Extension Phase.

Patients must return to the study center on a quarterly basis (12 weeks ± 1 week) for resupply of medication at which time drug dispensing information and adverse event information will be collected.

A complete schedule of evaluations required for the Extension Phase is provided in Table 7-3.

The procedures for patients entering the Extension Phase will proceed as follows:

- Safety laboratory assessments: chemistry, hematology, urinalysis, coagulation will be done as clinically indicated
- HBV and HCV testing and monitoring should be continued only for those patients identified during enrollment on first line treatment. Testing should be performed as per Section 6.2.2.3.
- Treatment with everolimus and letrozole (1$^{st}$ line) or everolimus and exemestane (2$^{nd}$ line) until lack of clinical benefit as assessed by Investigator at the site or any other reason for which the patient may be discontinued (refer to Section 7.1.5) Patients entering the Extension Phase on 1$^{st}$ line treatment and deemed to no longer be clinically benefiting will not be offered 2$^{nd}$ line treatment in the context of this study)
- At every quarterly visit, the investigator is required to confirm that the patient continues to have clinical benefit and may continue receiving study treatment.
  Although formal assessment of efficacy is not required during the Extension Phase, confirmation of continued treatment benefit as per standard of care is mandatory.
- When patients discontinue the first or second line treatment for any reason, an end of treatment visit following discontinuation of the medication will be performed. The 28 day follow up visit will also be performed to check on continuing AEs/SAEs or any new AEs/SAEs that may have occurred

[redacted]

### 7.1.5 End of treatment visit including study completion and premature withdrawal

At the time patients discontinue study treatment (in the first line treatment or, if applicable, second line treatment and Extension Phase), a visit should be scheduled as soon as possible (within 2 weeks), at which time all of the assessments listed for the End of Treatment (EOT) visit will be performed. An End of Treatment eCRF page should be completed separately for both first and second line treatment for the core study phase, and an End of Treatment eCRF for the Extension Phase should be completed for those subjects ending treatment while in the Extension Phase. The EOT eCRF will provide the date and reason for stopping the study treatment.

If patients refuse to return for an end of treatment visit or are unable to do so, every effort should be made to contact them or a knowledgeable informant by telephone to determine the primary reason for premature withdrawal from the study and record this information on the End of Treatment eCRF page.

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

- Pregnancy
- Discovery of patient ineligibility
- Protocol violation or errors in treatment compliance [study treatment, other prescribed or non-prescribed medications]
- Missed/unscheduled/off-schedule/incomplete/incorrect assessments
- Adverse events (including abnormal laboratory value, abnormal test procedure result)
- Unacceptable toxicity
- Subject withdrew consent
- Lost to follow up
- Administrative problems
- Death
- New cancer therapy
- Disease progression
- Treatment duration completed as per protocol
- Discontinuation of everolimus development by Novartis

At a minimum, all patients who discontinue study treatment for any reason, including those who refuse to return for a final visit, will be contacted for safety evaluations during the 28 days following the last dose of study treatment. If patients begin second line treatment < 28 days after completion of first line treatment, safety evaluations should continue until second line treatment begins.

All patients who discontinue treatment due to disease progression should be scheduled for a visit as soon as possible (within 2 weeks), at which time all of the assessments listed for the End of Treatment visit will be performed. After the 28-day safety follow-up visit, the patient

will begin the survival follow up period. At the start of new antineoplastic therapy, the patient will complete the Study Evaluation Completion eCRF.

If a patient discontinues treatment for reasons other than progression of disease according to RECIST 1.0 (see Appendix 2) tumor imaging evaluations should be performed at the End of Treatment visit (along with EOT assessments) unless the last tumor imaging evaluation was performed ≤ 4 weeks earlier. This does not apply to the Extension Phase, once the patient enters the extension, tumor imaging is no longer required per the study schedule.

All information on the start of a new antineoplastic therapy should be obtained and must be recorded in the Antineoplastic Therapies Since Discontinuation of Study Drug eCRF. If patients refuse to return for these visits or are unable to do so, every effort should be made to contact them or a knowledgeable informant by telephone to determine the patient's disease status or any start of new antineoplastic therapy. The Study Evaluation Completion eCRF page should be completed upon the patient's completion of the study.

### 7.1.6 Follow up period

All patients must have safety evaluations for 28 days after the last dose of study treatment.

Patients lost to follow up should be recorded as such on the eCRF. 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 End of Treatment or Study Evaluation Completion eCRF as applicable.

#### 7.1.6.1 Study evaluation completion

The study evaluation completion eCRF will be completed once all study evaluations are completed and patients are only being followed for survival (if applicable).

#### 7.1.6.2 Survival follow up

All patients who discontinued study treatment, have started a new antineoplastic therapy, and/or are no longer followed radiologically will be contacted (via telephone) for survival information every 12 weeks from the patient's last visit (which can be the safety follow up visit), until death, lost to follow up or withdrawal of consent. The investigator or his designee will collect this survival information and any additional antineoplastic therapies for all patients until the final survival analysis.

Patients who withdraw consent from participation in study should be asked to consent for survival follow up. If applicable, information regarding the death should be captured in the eCRF.

Patients completing the Extension Phase will not be followed for survival.

[redacted]

## 7.2 Assessment types

### 7.2.1 Efficacy assessments

#### Core Phase

Patients should have either at least one lesion that can be measured as per RECIST 1.0 criteria OR have bone lesions: lytic or mixed (lytic + sclerotic) in the absence of measurable disease as defined above.

For patients with measurable disease at baseline (as per RECIST 1.0 criteria), efficacy (overall tumor response and progression) will be evaluated every 8 weeks (+/- 1 week) during the Core Phase according to the RECIST 1.0 criteria. 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. All patients being discontinued from the study for disease progression must have their progression documented using the criteria specified in Appendix 2. All patients who discontinue study treatment for any reason (i.e., an adverse event, administrative reasons etc) other than disease progression or consent withdrawal will continue to have tumor assessments per the schedule during the Core Phase until disease progression or until new anti-cancer therapy is initiated.

All primary and secondary endpoints based on radiological (and photographical when applicable) assessments of tumor burden will be derived using the local (treating centers) radiologist's / investigator's assessment.

A bone scan or a skeletal survey should be performed at baseline for all patients within 28 days of enrollment. Any abnormalities (i.e., hotspots) identified on the bone scan must be confirmed by X-ray, CT scan with bone windows or MRI. Bone lesions identified at baseline should follow the same assessment schedule as for measurable lesions. Additional bone scans or skeletal surveys should be performed if clinically indicated. Abnormalities found on subsequent bone scans must also be confirmed by X-ray, CT scan or MRI.

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

If possible, each center should have a designated radiologist responsible for the interpretation of CT or MRI scans and the evaluation according to RECIST 1.0 criteria (see Appendix 2 for details). The same radiologist/physician should perform the evaluation for the entire duration of the study. All radiology evaluations will be performed initially by the local radiologist.

[redacted]

**Table 7-4 Imaging collection plan during Core Phase**

| Procedure | Screening/Baseline | During Treatment/Follow-up |
|---|---|---|
| CT or MRI (Chest, Abdomen, Pelvis) | Mandated | Mandated, every 8 weeks (**+/- 1 week**) |
| CT or MRI (brain) | Mandated | As clinically indicated |
| Bone scan or Skeletal survey (X-ray, CT or MRI) | Mandated | Mandated, every 8 weeks if applicable (Section 7.2.1) (**+/- 1 week**) |

### Extension Phase

During the Extension Phase there will be no efficacy assessments other than physician's determination of whether or not the patient is continuing to derive clinical benefit from the study treatment.

## 7.2.2 Safety and tolerability assessments

### Core Phase

Safety assessments will consist of monitoring and recording all adverse events (AEs) including serious adverse events (SAEs), the regular monitoring of hematology, serum chemistry, routine monitoring of vital signs (heart rate, blood pressure and body temperature), weight, ECOG performance status, CT scans and physical conditions. For details on AE collection and reporting, refer to Section 8.

### Extension Phase

Safety assessments in the Extension Phase will consist of monitoring and recording all AEs) including SAEs, refer to Section 8.

### 7.2.2.1 Physical examination

A complete physical examination will be conducted at screening and day 1 (+/- 3 days) of every cycle and as clinically indicated during the Extension Phase. It will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed.

Significant findings that were present prior to the signing of informed consent for the Core Phase of the study must be included in the Relevant Medical History/Current Medical Conditions page on the patient's eCRF. The Relevant Medical History/Current Medical Conditions collected at the beginning of the study will serve as baseline for transition to the Extension Phase. Significant new findings that begin or worsen after informed consent must be recorded on the Adverse Event page of the patient's eCRF. This is applicable for the duration of patient participation including the Extension Phase.

[redacted]

#### 7.2.2.2 Vital signs

Vital signs will be assessed at screening and day 1 (+/- 3 days) of every cycle and as clinically indicated during the Extension Phase. Vital signs will include blood pressure, pulse measurements and body temperature. After the patient has been sitting for five minutes, with back supported and both feet placed on the floor, systolic and diastolic blood pressure will be measured three times using an automated validated device, e.g. OMRON, with an appropriately sized cuff. The repeat sitting measurements will be made at 1 - 2 minute intervals and the mean of the three measurements will be used. In case the cuff sizes available are not large enough for the patient's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used. Vital signs that may be assessed during the Extension Phase will not be collected in the eCRF.

#### 7.2.2.3 Height and weight

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured and as clinically indicated during the Extension Phase. (Note: eCRFs are designed to collect the data in the units they are measured in; e.g., height in cm or in and weight in kg or lb). Height and Weight that may be assessed during the Extension Phase will not be collected in the eCRF.

#### 7.2.2.4 Performance status

ECOG Performance Status will be assessed and recorded at screening or on Treatment Day 1 (prior to administration of the study drug unless PS in screening was done less than 7 days before Day 1), and every cycle thereafter until progression and as clinically indicated during the Extension Phase. ECOG performance status that may be assessed during the Extension Phase will not be collected in the eCRF.

Assessment of ECOG Performance Status will be performed on the scheduled day, even if study medication is being held. The ECOG performance status Scale Index (Oken 1982) allows patients to be classified as to their functional impairment, the definition of scores in relation to PS is given below:

**Table 7-5 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 confirmed to bed or chair. |
| 5 | Death |

[redacted]

### 7.2.2.5 Laboratory evaluations

**Table 7-6 Local clinical laboratory parameters collection plan**

| Test Category | Test Name |
|---|---|
| Hematology | Hematocrit, Hemoglobin, Platelets, Red blood cells, White blood cells, RBC Morphology with Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils) |
| Chemistry | Albumin, Alkaline phosphatase, ALT (SGPT), AST (SGOT), Bicarbonate, Calcium, Chloride, Creatinine, Creatine kinase, Direct Bilirubin, Indirect Bilirubin, Total Bilirubin, Total Cholesterol, LDL, HDL, Total Protein, Triglycerides, Blood Urea Nitrogen (BUN) or Urea, Uric Acid, Sodium, Potassium, Glucose, Phosphorous |
| Urinalysis | Standard Dipstick:Bilirubin, Blood, Glucose, Ketones, Leukocytes, pH, Protein, Specific Gravity |
| Coagulation | Prothrombin time (PT) or International normalized ratio [INR]), Partial thromboplastin time (PTT) |
| Hepatitis markers | HBV-DNA, HbsAg, HbsAb, HbcAb, HCV RNA-PCR |

The standard clinical laboratory analyses described below are to be performed by the local laboratory according to the Visit Schedule. All attempts should be made to obtain scheduled laboratory evaluations ≤ 48 hours of the specified time periods, whether or not study treatment is administered. More frequent examinations may be performed at the investigator's discretion if medically indicated; results should be recorded in the eCRFs. Laboratory evaluation that may be performed during the Extension Phase will not be collected in the eCRF.

#### 7.2.2.5.1 Hematology

Hemoglobin, hematocrit, platelet count, red blood cells (RBC) count, white blood cell (WBC) count with differential including lymphocytes, monocytes, neutrophils, eosinophils, basophils, neutrophils will be measured. Hematologic test will be performed at screening, treatment day 1 and day 1 (+/- 3 days) of all subsequent cycles. In the event of Grade 2, Grade 3 or Grade 4 hematological toxicities that require study drug dose modifications or interruptions, hematological test must be repeated weekly until recovery to the baseline value or Grade 1. Any particular clinical finding seen before ICF signature must be documented in the Relevant Medical History eCRF. Findings compatible with adverse events after ICF signature must be documented in the Adverse Event eCRF.

#### 7.2.2.5.2 Clinical chemistry

Blood urea nitrogen or urea, total bilirubin, direct bilirubin, indirect bilirubin, AST, ALT, alkaline phosphatase, sodium, albumin, creatinine, creatine kinase, potassium, bicarbonate, chloride, calcium, phosphorous, total protein, triglycerides, total cholesterol, LDL, HDL, glucose and uric acid will be measured. Serum chemistries must be performed at screening, treatment day 1 and day 1 (+/- 3 days) of all subsequent cycles. In the event of Grade 2, Grade 3, or Grade 4 non-hematological toxicities that require study drug dose modifications or interruptions, biochemistry tests must be repeated until recovery to the baseline value or Grade 1. Any particular clinical finding seen before taking ICF signature must be documented

in the Relevant Medical History eCRF. Findings compatible with adverse events after ICF signature must be documented in the Adverse Event eCRF.

#### 7.2.2.5.3 Coagulation

The prothrombin time (PT), international normalized ratio (INR), and partial thromboplastin time (PTT) will be performed at screening and as clinically indicated.

#### 7.2.2.5.4 HBV testing

Prior to enrollment, the categories of patients listed in Section 7.1.1.3 should be tested for hepatitis B serologic markers and viral load (local results are acceptable for screening only):

- HBV-DNA, HBsAg, HBc Ab, and HBs Ab.
- During the treatment period, HBV DNA monitoring should be done depending on results from serologic markers and viral load as listed in Table 6-6.
- The final monitoring visit for HBV will be at the 28-day safety follow-up.

#### 7.2.2.5.5 HCV testing

Patients with hepatitis C risk factors and at the discretion of the investigator should be tested for HCV RNA prior to enrollment (local results are acceptable for screening only). For a list of hepatitis C risk factors, refer to Section 7.1.1.3.

Follow-up testing will be performed, as per the visit schedule (see Section 6.2.2.3), only if the patient has a history of Hepatitis C. The final monitoring visit for HCV will be at the 28-day safety follow-up.

#### 7.2.2.5.6 Urinalysis

A urinalysis will be performed at screening and as clinically indicated. Urinalysis standard dipstick test (protein, glucose, blood, ketones,leucocytes, bilirubin, pH and specific gravity) to be supplemented with laboratory quantification of any potential laboratory abnormalities. Any particular clinical findings seen before ICF signature must be documented in the Relevant Medical History eCRF. Findings compatible with adverse events after ICF signature must be documented in the Adverse Event eCRF.

#### 7.2.2.5.7 Pregnancy and assessments of fertility

Women enrolled in this trial will be postmenopausal as defined in the inclusion criteria. Pregnancy testing will not be performed.

### 7.2.2.6 Cardiac assessments

#### 7.2.2.6.1 Electrocardiogram (ECG)

A standard 12 lead ECG will 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 subjects' source documentation. Results from 12-lead ECG should be captured on the ECG Evaluation eCRF. Significant findings must be recorded as Relevant Medical History (if present before ICF signature). 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. ECG that may be assessed during the Extension Phase will not be collected in the eCRF.

#### 7.2.2.7 Pulmonary function tests

Pulmonary function tests (DLCO and room air O2 saturation at rest) will be performed as medically necessary if there is evidence of non-infectious pneumonitis. Refer to Table 6-9 for management of non-infectious pneumonitis.

[redacted]

**Other assessments**

### 7.2.6 Patient reported outcomes

Patient reported outcome (PRO) and impact of oral stomatitis burden on patient's daily living will be evaluated using the Oral Stomatitis Daily Questionnaire (OSDQ). The PRO will be not be administered during the Extension Phase. Completion of the PRO questionnaire will be dependent on the availability of OSDQ in the local language. The OSDQ is a patient self-administered 6-item questionnaire with a 24-hour recall period. Sample of the questionnaires can be found in the Appendix 1.

The OSDQ is an oral stomatitis-specific exploratory questionnaire developed for the purpose of this study. It is based on prior work by Stiff et al (2006) who developed and validated the Oral Mucositis Daily Questionnaire (OMDQ) to assess impact of oral mucositis on pain and daily functioning in patients undergoing autologous hematopoietic stem cell transplantation (HSCT). Although the OMDQ is available in the public domain (personal communication with the author, March 2012), it does not readily meet the need of this study as it contains diarrhea items more sensitive in measuring the symptoms intrinsic to the HSCT setting.

At the first episode of stomatitis, an OSDQ booklet will be handed out to patients at the study site upon confirmation of an oral stomatitis diagnosis. The booklet will contain 28 copies of the OSDQ, marked from Day 1 to Day 28, to be filled out by the patient up to 28 consecutive days, as long as the episode continues. During first episode of oral stomatitis, Day 1 OSDQ should be filled out on site by the patient. The patient should be given sufficient space and

[redacted]

time to complete the questionnaire. The site personnel should check the OSDQ for completeness and ask the patient to complete any missing responses but should not guide them in any way in their responses. Patient's refusal to complete all or any part of the Day 1 OSDQ should be documented in the study data capture system and should not be captured as a protocol deviation.

Booklets should be returned to site by patient at next scheduled visit and site should remind the patient to bring booklet with her. Site personnel will then give the patient a new OSDQ booklet. For patients who withdraw from study because of an oral stomatitis adverse event, effort should be made by site to collect the OSDQ on day of exit visit and to collect the OSDQ booklet back from the patient. OSDQ should be completed in the language most familiar to the patient. The original OSDQ booklet will be kept with the patient's file as the source document. For subsequent episodes of stomatitis patients will be instructed to contact the physician. Upon telephone confirmation, they will be instructed to utilize the same treatment they were assigned to after the first episode and fill in the OSDQ booklet as above.

# 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. Please refer to Section 6.1 for the protocol specific definition of study treatment.

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

Except for screening failures, adverse events that begin or worsen after informed consent should be recorded in the Adverse Events CRF. Conditions that were already present at the time of informed consent should be recorded in the Relevant Medical History/Current Medical Conditions of the patient's CRF. Adverse event monitoring should be continued for at least 28 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 through End of Treatment eCRF, Study Evaluation Completion eCRF and/or Survival information.

[redacted]

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 with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
5. Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
6. Whether it is serious, where a serious adverse event (SAE) is defined as in Section 8.2.1.

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

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

Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (for example, as per RECIST 1.0 criteria for solid tumors), 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.

## 8.2 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 28 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 28 days period should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

[redacted]

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 Chief Medical Office and Patient Safety (CMO&PS) department.

The telephone and telefax number of the contact persons in the local department of CMO&PS, 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 CMO&PS department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

## 8.3 Pregnancies

Postmenopausal women will be enrolled in this trial, there will be no pregnancy testing for patients enrolled in this study. Women of child bearing potential are not permitted to enroll.

## 8.4 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.

## 8.5 Data Monitoring Committee

A Data Monitoring Committee will not be used for this trial.

[redacted]

## 8.6 Steering Committee

The steering committee will be established comprising investigators participating in the trial and Novartis representatives from the Clinical Trial Team.

The SC will ensure transparent management of the study according to the protocol through recommending and approving modifications as circumstances require. The SC will review protocol amendments as appropriate. Together with the clinical trial team, the SC will also develop recommendations for publications of study results including authorship rules. 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

[redacted]

assessments. All information recorded on CRFs must be traceable to source documents in the patient's file. The investigator must also keep the original signed informed consent form (a signed copy is given to the patient).

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

## 9.3 Data collection

For studies using 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.

## 9.4 Database management and quality control

For studies using eCRFs, Novartis personnel (or designated CRO) will review the data entered by investigational staff, including data from the Oral Stomatitis Daily Questionnaires, 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 are 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.

[redacted]

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

# 10 Statistical methods and data analysis

The data analysis will be performed by Novartis and/or a designated CRO. It is planned that the data from all centers participating in the trial will be combined, so that an adequate number of patients are available for analysis. Any data analyses performed independently by any investigator should be submitted to Novartis before publication or presentation.

[redacted]

## 10.1 Analysis sets

### 10.1.1 Full Analysis Set

The primary efficacy population is defined as the Full Analysis Set (FAS), which consists of all patients to whom the first line study treatment has been assigned. All primary efficacy analyses will be evaluated based on data from this population.

For second line efficacy analyses a subset of the FAS will be used and referred to as Full Analysis Set 2nd line (FAS-2L), which consists of all patients in the FAS who received at least one dose of 2nd line study medication.

### 10.1.2 Safety Set

The Safety Population includes all patients who received at least one dose of study medication and had at least one post-baseline safety assessment.

The safety analysis for the second line will be performed on the subset of patients receiving at least one dose of second line medication. This subset will be referred to as Safety Population 2nd line (Safety 2L). Note: the statement that a patient had no adverse events (on the adverse event eCRF), constitutes a safety assessment.

## 10.2 Patient demographics/other baseline characteristics

Baseline demographics and disease characteristics data will be listed and summarized for both first line and second line using the FAS and FAS-2L, as appropriate for the study and the Extension Phase. Qualitative data, such as gender, race, etc, will be presented by contingency type tables. Descriptive summary statistics (e.g. frequency, mean, median, range and standard deviation) will be used to present numeric data.

## 10.3 Treatments (study drug, concomitant therapies, compliance)

### 10.3.1 Study medication

Duration of study treatment exposure, cumulative dose and dose intensity will be summarized separately for each study treatment both in first line (everolimus and letrozole) and second line treatment (everolimus and exemestane), as appropriate for the core and the Extension Phase. The number of patients with dose changes/interruptions will be presented, along with reasons for the dose change.

### 10.3.2 Concomitant therapies

Concomitant medications and significant non-drug therapies taken concurrently with the study drugs will be listed and summarized by Anatomical Therapeutic Chemical Classification System (ATC) term and preferred term by means of frequency counts and percentages. 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. Concomitant medications will not be collected during the Extension Phase.

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

[redacted]

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

## 10.4 Primary objective

The primary objective is to estimate the progression-free survival in patients treated with everolimus + letrozole in the first line setting.

### 10.4.1 Variable

The primary efficacy endpoint in this study is PFS, defined as the time from the date of enrollment 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, Appendix 2. The primary efficacy endpoint will be assessed as per local radiological assessment.

### 10.4.2 Statistical hypothesis, model, and method of analysis

The primary efficacy endpoint, PFS, will be analyzed based on the data from FAS. The median PFS as well as the 25$^{th}$ and 75 quartile will be estimated using the Kaplan-Meier method and presented along with 95% confidence intervals.

### 10.4.3 Handling of missing values/censoring/discontinuations

In this study the primary analysis of PFS for first line treatment will be performed 12 months after the last patient's recruitment. The analysis of PFS for second line treatment will be performed 6 months later (18 months after the last patient's recruitment) provided that the number of patients in second line treatment is adequate for a reliable PFS analysis. Otherwise, this analysis will be performed 24 months after the last patient's recruitment. For the analyses, PFS will be censored on the date of last adequate tumor assessment, if no PFS event is observed before the cut-off date or before the date a new anti-neoplastic therapy or another investigational treatment for cancer is started, whichever occurs earlier. 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 latest occurring evaluable tumor assessment. If a PFS event is observed after a single missing or non-evaluable tumor assessment, the actual date of event will be used.

## 10.5 Secondary objectives

The secondary objective in this study is to determine the overall response rate and clinical benefit rate of everolimus + letrozole in the first line setting. Additionally, the median progression free survival and clinical benefit rate of everolimus + exemestane in 2nd line population will be evaluated. Additional secondary objectives are to evaluate the safety of everolimus + letrozole in the first line settingand to evaluate the safety of everolimus + exemestane in the second line setting. For the Extension Phase, the proportion of patients with clinical benefit will be reported and long term safety as assessed by the occurrence of AEs/SAEs will be evaluated.

The overall survival of patients treated with everolimus + letrozole in the first line setting will also be evaluated.

### 10.5.1 Overall response rate and clinical benefit rate in first line

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 version 1.0 (see Appendix 2). Clinical benefit rate (CBR) is defined as the proportion of patients with best overall response of CR, PR or stable disease (SD) with a duration of 24 weeks or longer according to RECIST. ORR and CBR will be calculated based on the FAS, using local radiologist's/investigator's tumor assessment.

Patients with only non-measurable disease at baseline will be included in the numerator for ORR if they achieve a complete response and in the numerator for CBR if they achieve a complete response or stable disease lasting 24 weeks or longer. Proportions of subjects with ORR and CBR will be presented along with exact 95% confidence intervals (Clopper and Pearson 1934). The above analyses will also be repeated based on the data from subset of patients with only measurable disease at baseline.

### 10.5.2 Progression free survival in second line

Progression-free survival in the second line (PFS-2L) is defined as the time interval between start of 2nd line treatment and documented disease progression or death due to any cause reported during or after second-line treatment. The median PFS in the second line will be estimated using the Kaplan-Meier method and presented along with 95% confidence intervals.

### 10.5.3 Overall response rate and clinical benefit rate in second line

The analysis described in Section 10.5.1 will be repeated on FAS-2L population to estimate the ORR and CBR of the second line study treatment.

### 10.5.4 Overall survival (OS)

The overall survival (OS) following first line treatment with Everolimus + Letrozole is defined as the time from the date enrollment to date of death due to any cause. The OS analysis will be performed 24 months after the last patient's recruitment. If a death has not been observed by the date of analysis cutoff, then OS will be censored at the date of last contact. The analysis for OS will be based on the data from FAS. The median OS as well as the $25^{th}$ and $75^{th}$ quartile will be estimated using the Kaplan-Meier method and presented along with 95% confidence intervals.

### 10.5.5 Other secondary objective

#### 10.5.5.1 Therapeutic intervention for stomatitis

The secondary objective, to evaluate a therapeutic intervention to reduce the severity and duration of stomatitis, will be performed using the PRO questionnaire OSDQ data from patients in FAS who had an incidence of stomatitis while on study and were enrolled in countries where the alcohol-free 0.5mg/5ml dexamethasone oral solution is commercially available. The analysis for this objective will be based on PRO data for the first incidence of

[redacted]

stomatitis AE. The mean, standard deviation and 95% confidence interval of each severity items in the questionnaire will be calculated at each day for the two therapeutic interventions for stomatitis groups and presented graphically. The duration of the first stomatitis incidence will be calculated using the dates reported in the PRO, the median duration with 95% confidence interval of the first stomatitis AE will be estimated using Kaplan-Meier method for the two therapeutic interventions for stomatitis groups. As supportive analysis, the median duration will also be estimated using the duration calculated from start dates and end dates reported in AE CRFs.

As an exploratory analysis, sensitivity analysis for duration and severity may be performed on PRO data from multiple occurrences on the same patient. In this analysis appropriate methods will be used to account for within patient correlation.

The PRO will be not be administered during the Extension Phase.

#### 10.5.5.2 Safety

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. Other safety data (e.g., electrocardiogram, vital signs) will be considered as appropriate. All safety data collected will be listed. For all safety analyses, the safety population will be used. The safety summary tables will include only assessments collected no later than 28 days after study drug discontinuation.

##### 10.5.5.2.1 Adverse events (AE)

All adverse events recorded during study the core study phase and cumulatively reporting core and Extension Phase will be summarized. The incidence of treatment emergent adverse events will be summarized by system organ class, severity (based on CTCAE grades), type of adverse event, relation to the study drug by treatment group. Deaths reportable as SAEs and non-fatal serious adverse events will be listed by patient and tabulated by type of adverse event and treatment group. 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 may be analyzed by categories regrouping the relevant preferred terms, as appropriate.

##### 10.5.5.2.2 Laboratory abnormalities

All laboratory values collected during the core study phase 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

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.

#### 10.5.5.2.3 Other safety data

Data from other tests (e.g. vital signs) collected during the Core Phase will be listed, notable values will be flagged, and any other information collected will be listed as appropriate. Any statistical tests performed to explore the data will be used only to highlight any interesting comparisons that may warrant further consideration.

### 10.5.5.3 Extension Phase

The secondary objective related to the Extension Phase of the study is to evaluate clinical benefit as assessed by the Investigator. Proportion of patients with clinical benefit as assessed by the Investigator will be summarized at scheduled visits.

[redacted]

## 10.7 Interim analysis

No formal interim analysis is planned.

[redacted]

## 10.8 Sample size calculation

The sample size is calculated based on an estimate of median PFS with reasonable accuracy (width of 95% confidence interval) for first line treatment with everolimus in combination with anastrozole or letrozole. The progression-free survival (PFS) for the population of patients treated with anastrozole or letrozole alone as first line therapy is approximately 9 months (Mouridsen et al 2003, Bonneterre et al 2001). Combining everolimus, the median PFS is expected to increase to 11 – 14 months. Considering a recruitment period of 18 months (1.5 years) and one year of follow up after the last patient is enrolled the expected 95% CIs for median PFS for 200 patients with 10% lost to follow-up, are provided in the table below for median PFSs of 11, 12, 13 and 14 months.

| Median PFS | Expected 95% CI | 95% CI width |
|---|---|---|
| 11 months | 9.32, 12.98 | 3.66 |
| 12 months | 10.13, 14.22 | 4.09 |
| 13 months | 10.93, 15.46 | 4.53 |
| 14 months | 11.73, 16.71 | 4.98 |

# 11 Ethical considerations and administrative procedures

## 11.1 Regulatory and ethical compliance

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

## 11.2 Responsibilities of the investigator and IRB/IEC/REB

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

## 11.3 Informed consent procedures

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

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

[redacted]

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 4.2.

## 11.5 Publication of study protocol and results

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

## 11.6 Study documentation, record keeping and retention of documents

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

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

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

entry. For electronic CRFs an audit trail will be maintained by the system. The investigator should retain records of the changes and corrections to paper CRFs.

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

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

### 11.7 Confidentiality of study documents and patient records

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

### 11.8 Audits and inspections

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

### 11.9 Financial disclosures

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

## 12 Protocol adherence

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

### 12.1 Amendments to the protocol

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC/REB. Only amendments that are required for patient safety may be implemented prior to IRB/IEC/REB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study

site should be informed according to local regulations (e.g. UK requires the notification of urgent safety measures within 3 days) but not later than 10 working days.

# 13 References (available upon request)

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# 14 Appendices

## 14.1 Appendix 1: Oral Stomatitis Daily Questionnaire (OSDQ)

### Oral Stomatitis Daily Questionnaire

The following questions ask about the effect of your mouth and throat soreness on your ability to perform regular daily activities. By mouth and throat soreness we mean any inflammation of the mouth and throat, with redness, irritation, and/or swelling or mouth ulcers. Think about the current episode of mouth and throat soreness only. This questionnaire includes 6 questions. Please reserve some time (5 minutes) for answering the questions. Answer every question by selecting the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can. Try to respond to questionnaire each day at same of the day.

**Table 14-1 Oral Stomatitis Daily Questionnaire**

| | |
|---|---|
| 1. What is the date today? | DD – MM – YYYY |
| 1b. When did you experience the first symptoms of mouth and throat soreness? (only ask this question on Day 1 of the questionnaire) | DD – MM – YYYY |

2. How would you rate your OVERALL HEALTH during the PAST 24 HOURS?

| | | | |
|---|---|---|---|
| Worst possible | Half-way between | Perfect health | worst possible and perfect health |

0 1 2 3 4 5 6 7 8 9 10
CIRCLE A NUMBER

3. During the PAST 24 HOURS, how much MOUTH AND THROAT SORENESS did you have?

| | |
|---|---|
| No soreness | 0 |
| A little soreness | 1 |
| Moderate soreness | 2 |
| Quite a lot of soreness | 3 |
| Extreme soreness | 4 |

If you circled 0, please skip to Question 5

CIRCLE A NUMBER

4. During the PAST 24 HOURS, how much did MOUTH AND THROAT SORENESS limit you in each of the following activities?

| | Not Limited | Limited A Little | Limited Some | Limited A Lot | Unable To Do |
|---|---|---|---|---|---|
| a. Swallowing | 0 | 1 | 2 | 3 | 4 |
| b. Drinking | 0 | 1 | 2 | 3 | 4 |
| c. Eating | 0 | 1 | 2 | 3 | 4 |
| d. Talking | 0 | 1 | 2 | 3 | 4 |
| e. Sleeping | 0 | 1 | 2 | 3 | 4 |

CIRCLE A NUMBER for each question

[redacted]

1. What is the date today? DD – MM – YYYY

5. During the PAST 24 HOURS, how severe was the PAIN in your MOUTH?

No pain at all Unbearable pain

0 1 2 3 4 5 6 7 8 9 10
CIRCLE A NUMBER

6. During the PAST 24 HOURS, how much did your MOUTH AND THROAT SORENESS affect your ability to do your regular daily activities?

By regular activities, we mean the usual activities you do, such as employment (working for pay), work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If MOUTH AND THROAT SORENESS affected your activities only a little, choose a low number. Choose a high number if MOUTH AND THROAT SORENESS affected your activities a great deal.

Consider only how much during the PAST 24 HOURS, MOUTH AND THROAT SORENESS affected your ability to do your regular daily activities.

Had no effect on my daily activities Completely prevented me from doing my daily activities

0 1 2 3 4 5 6 7 8 9 10
CIRCLE A NUMBER

[redacted]

## 14.2 Appendix 2: Guidelines for response, duration of overall response, TTF, TTP, progression-free survival and overall survival (based on RECIST version 1.0)

### Harmonization of efficacy analysis of solid tumor studies

Authors (Version 2): [redacted]

Authors (Version 1):

Document type: TA Specific Guideline

Document status: Final
Version 2: 18-Jan-2007
Version 1: 13-Dec-2002

[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 |
| MRI | Magnetic resonance imaging |
| LPLV | Last patient last visit |
| OS | Overall survival |
| PD | Progressive disease |
| PFS | Progression-free survival |
| PR | Partial response |
| RAP | Report Analysis Preparation |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| SD | Stable disease |
| TTF | Time to treatment failure |
| TTP | Time to progression |
| UNK | Unknown |

[redacted]

### 14.2.1 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).

The efficacy assessments described in Section 14.2.2 and the definition of best response (Section 14.2.9) are based on the RECIST criteria but also give more detailed instructions and rules for determination of best response. Section 14.2.10 is summarizing the "time to event" variables and rules which are mainly derived from internal discussions, as the RECIST criteria do not define these variables in detail. Section 14.2.19 of this guideline describes data handling and programming rules. This section may be used in the analysis plan(s) to provide further details needed for programming.

### 14.2.2 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).

It is assumed that all information which is considered for assessment of the tumor is captured in the RECIST eCRF, i.e. not merged from several sources.

### 14.2.3 Eligibility

Using RECIST criteria implies that only patients with measurable disease at baseline should be included in the study:

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

If patients without measurable disease are allowed to be included in the study (when the primary endpoint is not the objective tumor response), please adapt the sentence accordingly.

- **Measurable lesions** - lesions that can be accurately measured in at least one dimension with longest diameter ≥ 20 mm using conventional techniques or ≥ 10 mm with spiral CT scan (with minimum lesion size no less than double the slice thickness).
- **Non-measurable lesions** - all other lesions, including small lesions (longest diameter <20 mm with conventional techniques or <10 mm with spiral CT scan), i.e., bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal masses that are not confirmed and followed by imaging techniques, and cystic lesions.

If any of lesion should be handled differently, this must be clearly stated and justified in the protocol, e.g. tumor lesions that are situated in a previously irradiated area might or might not be considered measurable, and the conditions under which such lesions should be considered must be defined in the protocol when appropriate.

[redacted]

### 14.2.4 Methods of tumor measurement

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

- All measurements should be taken and recorded in metric notation, using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

If different window for baseline assessments is allowed in the protocol this must be justified in the protocol.

- The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.
- Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.
- **CT and MRI:** CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 7.5 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen and pelvis. To calculate the sum of all target lesions, their size must be entered throughout the study. Actual measurement of each lesion should be entered in the eCRF regardless of the size of the measurement. A size of 0 mm should only be entered if the lesion completely disappeared. If a very small lesion cannot be reliably measured because of its size, it is recommended to enter the minimum lesion size (e.g. 5 mm for spiral CT). 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.

If head and neck tumors and those of extremities are evaluated in the study, please specify the methods in detail in the protocol.

- **Chest x-ray:** Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- **Ultrasound:** When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
- **Endoscopy and laparoscopy:** The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.
- **Tumor markers:** Tumor markers alone cannot be used to assess response. 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.

[redacted]

If tumor markers are used in the study for the response assessment, the criteria must be clearly stated in the protocol and the presence of abnormality in tumor markers be entered in the eCRF page for RECIST evaluations (see also Section 14.2.6).

- **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).

When pathological response is being used, the protocol must clearly state details on how pathological responses are documented.

- **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.

If the protocol is considering specific symptoms as objective signs of clinical progression, e.g. bone pain or GI bleeding, then the criteria for clear worsening of these non-measurable 'lesions' indicative of PD should be clearly specified in the protocol. In that case, the protocol should clearly specify that additional criteria are used to complement RECIST criteria.

### 14.2.5 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 up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).
  A sum of the longest diameter for all target lesions will be calculated and reported as the baseline sum of the longest diameter. The baseline sum of the longest diameter will be used as reference by which to characterize the objective tumor response.
- **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.

If the protocol is considering specific symptoms for assessment of the tumor, e.g. bone pain or GI bleeding, then these symptoms are to be entered as non-target lesions with either presence or absence or as a new lesion (based on protocol specified criteria). In that case, the protocol should clearly specify that additional criteria are used to complement RECIST criteria.

For cancers which are known to metastasize in bone, the protocol should specify if and how bone lesions should be handled, e.g. if they are not identified only at baseline and end of study by scintigram but also followed throughout the study by bone X-ray or CT scan.

If no measurable lesions are identified at baseline, the patient is not evaluable for RECIST. Therefore, the Guideline leaves the decision to the study teams to determine how to handle time to event endpoints, e.g. in the metastatic setting non-target lesions could be followed for PFS/ TTP.

### 14.2.6 Evaluation of target and non-target lesions

To assess tumor response, the sum of the longest diameter 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 14-2) and non-target lesions (Table 14-3) identified at baseline. These evaluations are then used to calculate the overall lesion response considering both the target and non-target lesions together (Table 14-4) as well as the presence or absence of new lesions.

The response for non-target lesions is CR only if all non-target lesions which were evaluated at baseline are now all absent. If any of the non-target lesions is still present, the response can only be 'Incomplete response/Stable disease' 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).

If tumor markers are used as non-target lesions to evaluate response, please specify criteria for CR, SD and PD in the protocol, e.g. CR='Normalization of tumor marker level', PD='Elevation of tumor markers to certain level', SD='Not qualifying for CR or PD'. These criteria are indication and study specific. In that case, the protocol should clearly specify that additional criteria are used to complement RECIST criteria.

**Table 14-2 Response criteria for target lesions**

| Response Criteria | Evaluation of target lesions |
|---|---|
| Complete Response (CR): | Disappearance of all target lesions |
| Partial Response (PR): | At least a 30% decrease in the sum of the longest diameter of all target lesions, taking as reference the baseline sum of the longest diameters. |
| Progressive Disease (PD): | At least a 20% increase in the sum of the longest diameter of all measured target lesions, taking as reference the smallest sum of longest diameter of all target lesions recorded at or after baseline. |
| 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. |

[redacted]

**Table 14-3 Response criteria for non-target lesions**

| Response Criteria | Evaluation of non-target lesions |
|---|---|
| Complete Response (CR): | Disappearance of all non-target lesions |
| Progressive Disease (PD): | Unequivocal progression of existing non-target lesions.[1] |
| Incomplete Response/ Stable Disease (SD): | 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).

- The appearance of a new lesion is always associated with Progressive Disease (PD) and has to be recorded as a new lesion in the appropriate module of the CRF.
- If a 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 has not been possible to change the 0 value, then the investigator/radiologist has to decide between the following two possibilities:
  - The lesion is a new lesion, in which case the overall tumor assessment will be considered as progressive disease
  - The lesion is clearly a re-appearance 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 14-2 above (i.e., a PD will be determined if there is at least 20% increase in the sum of the longest diameter of **all** measured target lesions, taking as reference the smallest sum of longest diameter of all target lesions recorded at or after baseline). Proper documentation should be available to support this decision.
- For those patients who have only one target lesion at baseline, the reappearance of the target lesion, which disappeared previously, is considered a PD.

### 14.2.7 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 14-4.

[redacted]

**Table 14-4 Overall lesion response at each assessment**

| Target lesions | Non-target lesions | New Lesions | Overall lesion response |
|---|---|---|---|
| CR | CR | No | CR[1] |
| CR | Incomplete response/SD[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 14.2.6.

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

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

### 14.2.8 Efficacy definitions

### 14.2.9 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.

To be assigned a status of 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.

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.
- PR = at least two determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR).
- SD = at least one SD assessment (or better) > 6 weeks after randomization/start of treatment (and not qualifying for CR or PR).

[redacted]

The protocol should state if randomization or start of treatment is used as start date (baseline). This is then used in all definitions.

If a different minimum follow-up period is required to classify for overall response= 'stable disease', this must be specified in the protocol.

- PD = progression ≤ 12 weeks after randomization/ start of treatment (and not qualifying for CR, PR or SD).

If PD in a different follow-up period is considered overall response='progressive disease', this must be specified in the protocol.

The protocol should state if discontinuation due to 'Disease progression' or death due to study indication is considered PD even if this was not accompanied by documentation of PD based on tumor measurements. This depends on Phase of the study and the primary endpoint (e.g. Phase III studies in which progression-free survival is primary endpoint should consider only documented PD, whereas Phase I and II studies may consider all clinical deteriorations PD). The following sentence therefore is only applicable if this is specified in the protocol:

- Patients with symptoms of rapidly progressing disease without radiologic evidence will be classified as progression only when clear evidence of clinical deterioration is documented and/or patient discontinued due to 'Disease progression' or death due to study indication.
- 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 confirmed overall lesion responses of PR must stay the same or improve over time until progression sets in, with the exception of a UNK status. However, if a patient has a 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.

Example: The sum of lesion diameters is 20 cm at baseline and then 14 cm - 15 cm - 14 cm - 16 cm - 16 cm 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 14 cm confirms the PR for this patient. All subsequent assessments are considered PR even if tumor measurements decrease only by 20% compared to baseline (20 cm to 16 cm) at the following assessments.

If the patient progressed but continues study medication, 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 best overall response rate.

[redacted]

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

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

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

Specify which determination of best overall response will be considered primary (and delete the other terms in the text). If a central blinded review is used (e.g. in an open-label study in which response is the primary endpoint), the best overall response evaluated by the central blinded review will always be considered the primary response.

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. Time duration for EPR is study specific. EPR is used for the multinomial designs of Dent and Zee 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 unknown assessment at that time point and no PD before, are also considered PD.

### 14.2.10 Time to event variables

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

### 14.2.11 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.

**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.

### 14.2.12 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 contacted, 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 contact.

### 14.2.13 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.

### 14.2.14 Time to treatment failure

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

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

### 14.2.15 Duration of response

If the following variables are analyzed, it should be stated that this analysis might introduce a bias as it includes only responders. There have been reports where a treatment with a significantly higher response rate had a significantly shorter duration of response. The analysis of duration of responses should only be used as a descriptive analysis. If they are used as inferential comparison between treatments, clear justification must be given in the protocol. It should also be stated in the protocol if duration of response is to be calculated in addition for unconfirmed response.

**Duration of overall response (CR or PR)** applies only to patients whose best overall response was CR or PR. 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. Justification must be given in the protocol when these endpoints are used for any comparison between treatments.

**Duration of overall complete response (CR)** applies only to patients whose best overall response was CR. 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)** applies only to patients whose best overall response was SD, PR or CR. The start and end date as well as censoring is defined the same as that for time to progression.

### 14.2.16 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). This analysis will include all patients/responders. Patients who did not achieve a confirmed PR or CR will be censored at last adequate tumor assessment date when they did not progress (including deaths not due to underlying disease) or at maximum follow-up (i.e. FPFV to LPLV used for the analysis) when they had an event for progression-free survival.

**Time to overall complete response (CR)** is the time between date of randomization/start of treatment until first documented CR. This analysis will include all patients/responders. Patients who did not achieve a confirmed CR will be censored at last adequate tumor assessment date when they did not progress (including deaths not due to underlying disease) or at maximum follow-up (i.e. FPFV to LPLV used for the analysis) when they had an event for progression-free survival.

Indicate whether this analysis should include only the responder (in which case please delete 'patients/' and the sentence on patients who did not respond) or should estimate the time to response for the whole study population (in which case please delete '/responders'). If both methods should be used, please state that in the protocol.

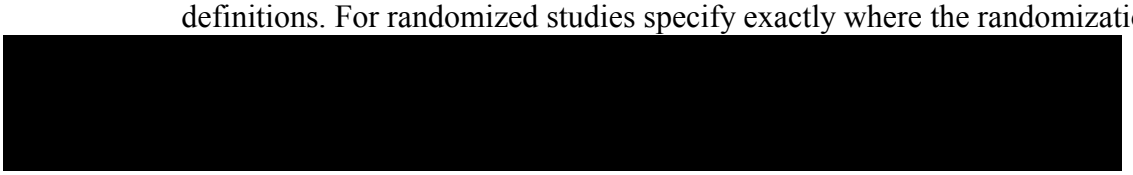
### 14.2.17 Definition of start and end dates for time to event variables

#### 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

State in the protocol if date of randomization or date of start of treatment is to be used for all definitions. For randomized studies specify exactly where the randomization date comes from,



e.g. from IVRS, or if start of treatment is used as randomization date. For non-randomized studies please specify which treatment start date is taken if more than one treatment is to be given.

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

For the calculation of duration of responses 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.

If applicable, if patients who discontinued due to 'Disease progression' are considered to be PD solely based on clinical deterioration, then add the following in the protocol:

> When there is no documentation of radiologic evidence of progression, and the patient discontinued for 'Disease progression' due to documented clinical deterioration of disease, the date of discontinuation is used as date of progression.

- **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 14.2.18).
  **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 corresponds 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 contact date from that survival follow-up page is used. If no survival follow-up is available, the date of discontinuation is used as last contact date.

In comparative studies with long follow-up period and therefore extended visit schedule, it may be useful to collect the survival status at a pre-specified cut-off within a limited timeframe for all patients with no documented death. In this case, this requires a contact to be

[redacted]

made with the patient or with any reliable source of information on the patient's status, but not requiring a specific visit to be scheduled

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

If this is applicable for the study, it should be specified in the protocol if new cancer therapy is considered an event or endpoints are censored.

### 14.2.18 Sensitivity analyses

This section outlines the possible event and censoring dates for progression, as well is addressing 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 analysis plan 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 14.2.17, 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)[1] (1) = default unless specified differently in the protocol or analysis plan | Outcome |
|---|---|---|---|
| A | No baseline assessment | (1) Date of randomization/start of treatment | Censored |
| B | Progression at or before next scheduled assessment | (1) Date of progression<br>(2) Date of next scheduled assessment[2] | Progressed<br>Progressed |
| C1 | Progression or death after **exactly one** missing assessment | (1) Date of progression (or death)<br>(2) Date of next scheduled assessment[2] | Progressed<br>Progressed |
| C2 | Progression or death after **two or more** missing assessments | (1) Date of last adequate assessment[2]<br>(2) Date of next scheduled assessment[2]<br>(3) Date of progression (or death) | Censored<br>Progressed<br>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<br>(2) Date of discontinuation (visit date at which clinical progression was determined) | Ignored<br>Progressed |
| F | New anticancer therapy given | (1) Date of last adequate assessment<br>(2) Date of secondary anti-cancer therapy | Censored<br>Censored |
| G | Deaths due to reason other than deterioration of 'Study indication' | (1) Date of last adequate assessment | Censored (only TTP) |

[1] = Definitions can be found in Section 14.2.17.

[2] = After the last adequate tumor assessment. "Date of next scheduled assessment" is defined in Section 14.2.17.

[redacted]

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

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

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

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

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

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

### Additional suggestions for sensitivity analyses

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

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

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

## 14.2.19 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).

[redacted]

### 14.2.20 Study/project specific decisions

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

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

### 14.2.21 Treatment and study completion CRFs

If study drug is discontinued, the **treatment completion page** is to be completed with a visit date reflecting the date the discontinuation decision was made, and with the 'Last known date subject took study drug' and one of the following reasons:

- Adverse event(s)
- Abnormal laboratory value(s)
- Abnormal test procedure results(s)
- Protocol violation
- Subject withdrew consent
- Lost to follow-up
- Administrative problems
- Death
- Disease progression
- Treatment duration completed as per protocol (optional, to be used if only a fixed number of cycles is given)

For reasons other than progression (and death) it should be checked if this was not in fact progression (especially reasons Adverse Events, Abnormal laboratory value (s), Abnormal test procedure result and subject withdrew consent). Also it should be checked if patient withdrew consent because of safety issues, in which case reasons Adverse Events, Abnormal laboratory value (s), Abnormal test procedure result should be used.

All patients who discontinued study drug for reasons other than documented progression, death or lost to follow-up will be followed for progression thereafter (patients who withdrew consent might not be followed with regular tumor assessments at the study site, but should ideally be followed until progression outside the study site). Ideally, all patients who discontinued study drug for progression without documented progression will still be followed with regular tumor assessments (e.g. in case of central radiology review). During that evaluation period, usually only tumor measurements (and/or response status) and survival data are collected. In some protocols, the subsequent anti-cancer therapies may also be recorded.

At the end of the study evaluation period, the **study evaluation completion page** is filled out with the following options:

- Subject withdrew consent
- Lost to follow-up

[redacted]

- Administrative problems (when follow-up for progression has met protocol required events, e.g. follow-up stopped at certain number of events or certain time)
- Death
- New cancer therapy (optional, to be used when follow-up for progression is stopped in this case)
- Disease progression

Thereafter, patients will be followed for survival using the survival follow-up pages. If information on death becomes available for patients who were lost to follow-up or withdrew consent, this may also be entered in the database. The reason for death must be documented (and will be coded using MedDRA); it must be also stated if death was due to 'Study indication' or 'Other' reason.

In comparative studies with long follow-up period and therefore extended visit schedule, it may be useful to collect the survival status at a pre-specified cut-off within a limited timeframe for all patients with no documented death. In this case, this requires a contact to be made with the patient or with any reliable source of information on the patient's status, but not requiring a specific visit to be scheduled

Until the specified cut-off point has been reached, the goal is to collect tumor assessments until disease progression for all patients regardless of whether the patients are still receiving study drug. If patients are not followed for progression, e.g. in a Phase I or II study mainly evaluating safety, the evaluation is completed when study drug is completed (in this case only the first completion page is used).

### 14.2.22 Medical validation of programmed overall lesion response

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

If Novartis elect to invalidate an evaluation of overall lesion response 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.

### 14.2.23 Programming rules

The following should be used for programming of efficacy results:

### 14.2.24 Calculation of 'time to event' variables

Time to event = enddate - startdate + 1 (in days)

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

### 14.2.25 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 14.2.17). 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.

### 14.2.26 Incomplete dates for last contact or death

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

### 14.2.27 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)'.

### 14.2.28 Study/project specific programming

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

### 14.2.29 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 (treatment / study evaluation / survival)
- Lost to follow-up (during treatment* / study evaluation* / survival)

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

[redacted]

- Ongoing without event (treatment / study evaluation)
- Lost to follow-up (during treatment / study evaluation)
- Withdrew consent (during treatment* / study evaluation)
- Study evaluation stopped (when follow-up for progression is stopped after certain number of events or at certain time, i.e. reason='Administrative problems' on study evaluation completion page, or when patients are not followed for progression after treatment completion)
- Death due to reason other than underlying cancer (only used for TTP)
- New cancer therapy added (optional; only if the protocol specified that PFS/TTP will be censored at that date)

*Note = this category is to be used if no further information is available (as information on death may be available in patients who were originally lost to follow-up, and information on progression may be received in patients who withdrew consent to continue study drug).

### 14.2.30 References (available upon request)

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

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.