PrECOG PROTOCOL NUMBER: PrE0102

Randomized, Double-Blind, Placebo-Controlled Phase II Trial of Fulvestrant (Faslodex) plus Everolimus in Post-Menopausal Patients with Hormone-Receptor Positive Metastatic Breast Cancer Resistant to Aromatase Inhibitor Therapy

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Version 1.0: December 19, 2012	Released to sites
Version 2.0: January 22, 2014	Released to sites

Revision History		
Version 1.0	12/19/2012	**Released to sites**
THE FOLLOWING AMENDMENT WAS MADE TO VERSION 1.0 OF THE PROTOCOL		
Version 2.0	1/22/2014	**Released to sites**

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Brief Protocol Synopsis- Patient Population

Was:

- Patients must be Aromatase Inhibitor (AI) resistant, defined as:
  - relapsed while receiving adjuvant therapy with an aromatase inhibitor (anastrozole, letrozole, or exemestane) or,
  - progressive disease while receiving an aromatase inhibitor for metastatic disease.

Is:

- Patients must be Aromatase Inhibitor (AI) resistant, defined as:
  - relapsed while receiving adjuvant therapy with an aromatase inhibitor (anastrozole, letrozole, or exemestane) or,
  - progressive disease while receiving an aromatase inhibitor for metastatic disease.

  Note: Patients may have received an endocrine agent (e.g., Tamoxifen) between the time of progression on an AI and registration.

3.1 Eligibility Criteria- Inclusion

Was:

7. Patients must be Aromatase Inhibitor (AI) resistant, defined as:
   - relapsed while receiving adjuvant therapy with an aromatase inhibitor (anastrozole, letrozole, or exemestane) or,
   - progressive disease while receiving an aromatase inhibitor for metastatic disease.

Is:

7. Patients must be Aromatase Inhibitor (AI) resistant, defined as:
   - relapsed while receiving adjuvant therapy with an aromatase inhibitor (anastrozole, letrozole, or exemestane) or,
   - progressive disease while receiving an aromatase inhibitor for metastatic disease.

   Note: Patients may have received an endocrine agent (e.g., Tamoxifen) between the time of progression on an AI and registration.

3.1 Eligibility Criteria- Inclusion

Was:

8. Patients who have received one prior dose of fulvestrant within 28 days of randomization are eligible so long as they meet other eligibility criteria.
   - patients previously treated with two or more prior **doses** of fulvestrant are not eligible.

Is:

8. Patients who have received one prior **cycle (**dose **on day 1 and day 15)** of fulvestrant within 28 days of randomization are eligible so long as they meet other eligibility criteria.
   - patients previously treated with two or more prior **cycles** of fulvestrant are not eligible

3.1 Eligibility Criteria- Exclusion

Was:

3. Patients must not be receiving any concomitant anticancer treatment or have received anticancer treatment within 4 weeks of randomization (including chemotherapy, radiation therapy, antibody based therapy, etc.), with the following exceptions:
   - Bisphosphonates **or** Zometa for bone metastases
   - a GnRH analog is permitted if the patient had progressive disease on a GnRH analog plus a SERM or an AI; the GnRH analog may continue but the SERM or AI must be discontinued.

Is:

3. Patients must not be receiving any concomitant anticancer treatment or have received anticancer treatment within 4 weeks of randomization (including chemotherapy, radiation therapy, antibody based therapy, etc.), with the following exceptions:
   - Bisphosphonates, Zometa **or Xgeva** for bone metastases
   - **Hormonal therapy (e.g., AI, Tamoxifen)**
   - a GnRH analog is permitted if the patient had progressive disease on a GnRH analog plus a SERM or an AI; the GnRH analog may continue but the SERM or AI must be discontinued.

5.2.1 Fulvestrant (Arm A and Arm B)- Induction Phase

Was:

Cycle 1 (28 day cycle)

Patients will receive fulvestrant 500 mg IM (two-250 mg injections each dose) on day 1 and 15.

Note: Cycle 1 is the only time fulvestrant is given on day 15.

Is:

Cycle 1 (28 day cycle)

Patients will receive fulvestrant 500 mg IM (two-250 mg injections each dose) on day 1 and 15.

Note: Cycle 1 is the only time fulvestrant is given on day 15. ***If patient previously received one cycle of fulvestrant (day 1 and day 15) prior to study entry as permitted in Inclusion Criteria #8, patient should receive fulvestrant 500 mg on day 1 only.***

5.2.2 Everolimus or Placebo (Arm A and Arm B)

Was:

- PrECOG, or their designee, will be responsible for blinding, drug randomization, and management of the electronic interactive web registration (IWR) system. Both tablets will be blinded and identified by **pack** number only. The IWR system will assign the proper **pack** to the patient based on the patient randomization. Conditions for study drug will be described on the medication label.

Is:

- PrECOG, or their designee, will be responsible for blinding, drug randomization, and management of the electronic interactive web registration (IWR) system. Both tablets will be blinded and identified by **kit** number only. The IWR system will assign the proper **kit** to the patient based on the patient randomization. Conditions for study drug will be described on the medication label.

5.3.1 Dose Modifications General Guidelines for Everolimus/Placebo

Table 5-1 Non-Hematological Criteria for Dose-Modification in Case of Suspected Everolimus or Placebo Related Adverse Events and Re-Initiation of Everolimus or Placebo Treatment

Was:

AST or ALT elevation Grade 4 (>20x ULN)* **Recurrence of grade 4 after dose reduction or toxicity requiring everolimus interruption for >28 days**	Interrupt everolimus administration until resolution to ≤ grade 1 (or ≤ grade 2 if baseline values were within the range of grade 2). If resolution occurs ≤ 7 days, everolimus should be re-started at one dose level lower. If resolution takes >7 days, discontinue everolimus. **Discontinue everolimus.**

Is:

AST or ALT elevation Grade 4 (>20x ULN)*	Interrupt everolimus administration until resolution to ≤ grade 1 (or ≤ grade 2 if baseline values were within the range of grade 2). If resolution occurs ≤ 7 days, everolimus should be re-started at one dose level lower. If resolution takes >7 days, discontinue everolimus.

5.3.1 Dose Modifications General Guidelines for Everolimus/Placebo

Table 5-1 Non-Hematological Criteria for Dose-Modification in Case of Suspected Everolimus or Placebo Related Adverse Events and Re-Initiation of Everolimus or Placebo Treatment

Was:

Intolerable Grade 2 mucositis (see Section 5.3.2.**6**) **OR** **Grade 3 AE, except hyperglycemia or hypertriglyceridemia or hypercholesterolemia** **(see Section 5.3.2.8)**	Interrupt everolimus administration until resolution to ≤ grade 1 or baseline grade/value. If resolution occurs within ≤ 7 days, everolimus should be re-started at the dose level prior to interruption. If resolution takes >7 days, or if event recurs within 28 days, hold everolimus until recovery to ≤ grade 1 or baseline grade/value and reintroduce everolimus at one dose level lower, if available. Patients will be withdrawn from the study if they fail to recover to ≤ grade 1 or baseline grade/value within **28** days.

Is:

Intolerable Grade 2 mucositis (see Section 5.3.2.**5**)	Interrupt everolimus administration until resolution to ≤ grade 1 or baseline grade/value. If resolution occurs within ≤ 7 days, everolimus should be re-started at the dose level prior to interruption. If resolution takes >7 days, or if event recurs within 28 days, hold everolimus until recovery to ≤ grade 1 or baseline grade/ value and reintroduce everolimus at one dose level lower, if available. Patients will be withdrawn from the study if they fail to recover to ≤ grade 1 or baseline grade/value within **21** days.
Grade 3 AE, except: **hyperglycemia or hypertriglyceridemia or hypercholesterolemia** **(see Section 5.3.2.7)**	**Interrupt everolimus administration until resolution to ≤ grade 1 or baseline grade/value.** **Reintroduce everolimus at one dose level lower, if available.** **Patients will be withdrawn from the study if they fail to recover to ≤ grade 1 or baseline grade/value within 21 days.**

5.3.1 Dose Modifications General Guidelines for Everolimus/Placebo

Table 5-1 Non-Hematological Criteria for Dose-Modification in Case of Suspected Everolimus or Placebo Related Adverse Events and Re-Initiation of Everolimus or Placebo Treatment

Was:

Recurrence of intolerable Grade 2 mucositis or Grade 3 event after dose reduction	Reduce dose to the next lower dose level, if available. The lowest possible dose level of everolimus is **2.5 mg daily**. Below this level, everolimus must be discontinued.
Any non-hematologic toxicity requiring everolimus interruption for >**28** days	Discontinue everolimus.

5.3.1 Dose Modifications General Guidelines for Everolimus/Placebo

Table 5-1 Non-Hematological Criteria for Dose-Modification in Case of Suspected Everolimus or Placebo Related Adverse Events and Re-Initiation of Everolimus or Placebo Treatment

Is:

Recurrence of intolerable Grade 2 mucositis or Grade 3 event after dose reduction	Reduce dose to the next lower dose level, if available. The lowest possible dose level of everolimus is **5 mg every other day**. Below this level, everolimus must be discontinued.
Any non-hematologic toxicity requiring everolimus interruption for >**21** days	Discontinue everolimus.

5.3.1 Dose Modifications General Guidelines for Everolimus/Placebo

Table 5-2 Hematological Criteria for Dose-Modification in Case of Suspected Everolimus or Placebo Related Adverse Events and Re-Initiation of Everolimus or Placebo Treatment

Was:

Recurrence of Grade 3 toxicity after dose reduction	Reduce dose to the next lower dose level, if available. The lowest possible dose level of everolimus is 5 mg every other day **(2.5 mg daily)**. Below this level, everolimus must be discontinued.
Any hematologic toxicity requiring everolimus interruption for >**28** days	Discontinue everolimus.

Is:

Recurrence of Grade 3 toxicity after dose reduction	Reduce dose to the next lower dose level, if available. The lowest possible dose level of everolimus is 5 mg every other day. Below this level, everolimus must be discontinued.
Any hematologic toxicity requiring everolimus interruption for >**21** days	Discontinue everolimus.

Removed:

5.3.2.1 Hepatic Impairment Dose Modifications

- **Mild hepatic impairment (Child-Pugh A) – the recommended dose is 7.5 mg daily.**
- **Moderate hepatic impairment (Child-Pugh B) – the recommended dose is 2.5 mg daily.**
- **Severe hepatic impairment (Child-Pugh C) – not recommended. If the desired benefit outweighs the risk, a dose of 2.5 mg daily must not be exceeded.**
- **Dose adjustments should be made if a patient's hepatic (Child-Pugh) status changes during treatment.**

Everolimus is not recommended for patients with hepatic impairment who require doses below 2.5 every other day.

5.3.2.**2** Monitoring and Prophylactic Treatment for Hepatitis B Reactivation

Table 5-4 Guidelines for Management for Hepatitis B

Was:

For patients with baseline results: Positive HBV-DNA OR Positive HBsAg ---------- Reactivation is defined as: Increase of 1 log in HBV-DNA relative to baseline HBV-DNA value OR new appearance of measurable HBV-DNA	Treat: Start a second antiviral AND Interrupt study drug administration until resolution: ≤ baseline HBV-DNA levels If resolution occurs within ≤ **28** days, study drug should be re-started at one dose lower, if available. If the patient is already receiving the lowest dose of study drug according to the protocol, the patient should restart at the same dose after resolution. Both antiviral therapies should continue at least 4 weeks after last dose of study drug. If resolution occurs >**28** days, patients should discontinue study drug but continue both antiviral therapies at least 4 weeks after last dose of study drug.

Is:

For patients with baseline results: Positive HBV-DNA OR Positive HBsAg ---------- Reactivation is defined as: Increase of 1 log in HBV-DNA relative to baseline HBV-DNA value OR new appearance of measurable HBV-DNA	Treat: Start a second antiviral AND Interrupt study drug administration until resolution: ≤ baseline HBV-DNA levels If resolution occurs within ≤ **21** days, study drug should be re-started at one dose lower, if available. If the patient is already receiving the lowest dose of study drug according to the protocol, the patient should restart at the same dose after resolution. Both antiviral therapies should continue at least 4 weeks after last dose of study drug. If resolution occurs >**21** days, patients should discontinue study drug but continue both antiviral therapies at least 4 weeks after last dose of study drug.

5.3.2.**2** Monitoring and Prophylactic Treatment for Hepatitis B Reactivation

Table 5-4 Guidelines for Management for Hepatitis B

Was:

For patients with baseline results: Negative HBV-DNA and HBsAg AND Positive HBsAb (with no prior history of vaccination against HBV), OR positive HBcAb --- Reactivation is defined as: New appearance of measurable HBV-DNA	Treat: Start first antiviral medication AND Interrupt study drug administration until resolution: ≤ baseline HBV-DNA levels If resolution occurs within ≤ **28** days, study drug should be re-started at one dose lower, if available. If the patient is already receiving the lowest dose of study drug according to the protocol, the patient should restart at the same dose after resolution. Antiviral therapy should continue at least 4 weeks after last dose of study drug. If resolution occurs >**28** days, patients should discontinue study drug but continue antiviral therapy at least 4 weeks after last dose of study drug.

Is:

For patients with baseline results: Negative HBV-DNA and HBsAg AND Positive HBsAb (with no prior history of vaccination against HBV), OR positive HBcAb --- Reactivation is defined as: New appearance of measurable HBV-DNA	Treat: Start first antiviral medication AND Interrupt study drug administration until resolution: ≤ baseline HBV-DNA levels If resolution occurs within ≤ **21** days, study drug should be re-started at one dose lower, if available. If the patient is already receiving the lowest dose of study drug according to the protocol, the patient should restart at the same dose after resolution. Antiviral therapy should continue at least 4 weeks after last dose of study drug. If resolution occurs >**21** days, patients should discontinue study drug but continue antiviral therapy at least 4 weeks after last dose of study drug.

5.3.2.**5** Management of Stomatitis/Oral Mucositis/Mouth Ulcers

Added:

Suggested prophylactic treatment for prevention of stomatitis/mucositis is listed below:

a) **Use 15 mL baking soda/salt mouth rinse QID (swish and spit). Mix 1/3 teaspoon baking soda and 1/3 teaspoon of salt in 1 quart of water (refrigeration is not needed); do not eat or drink anything for 10 minutes after rinsing.**

b) **Use 10 mL prescribed "miracle mouth wash" QID (swish and spit). For 16-ounce recipe: 320 mL Benadryl solution, 2 g tetracycline powder, 80 mg hydrocortisone, and 40 mL nystatin suspension, quantity sufficient with water. Wait 10-15 minutes after the baking soda/salt rinse before using "miracle mouthwash".[55]**

5.3.2.**5** Management of Stomatitis/Oral Mucositis/Mouth Ulcers

Was:

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 (e.g., 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 hydrogen peroxide, iodine, and thyme derivatives may tend to worsen mouth ulcers. It is preferable to avoid these agents.

Is:

1. For mild toxicity (Grade 1), use conservative measures **as noted above, baking soda/salt mouth rinse and "miracle mouth wash"**.
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:

   In addition to baking soda/salt mouth rinse and "miracle mouth wash" above, topical analgesic mouth treatments (e.g., 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®) **or Periogard® oral rinse.**
3. Agents containing hydrogen peroxide, iodine, and thyme derivatives may tend to worsen mouth ulcers. It is preferable to avoid these agents. **Alcohol–containing rinses and tooth paste with sodium lauryl sulfate should also be avoided. Avoid acidic, spicy, hard, or crunchy foods, and consume foods that are tepid rather than hot.** [55]

5.3.2.**8** Management of Non-Infectious Pneumonitis

Table 5-6 Management of Non-Infectious Pneumonitis

Was:

Worst Grade Pneumonitis	Everolimus Dose Adjustment
Grade 2	Rule out infection and consider interruption of everolimus until symptoms improve to Grade ≤ 1. Re-initiate everolimus at one dose level lower. Discontinue everolimus if failure to recover within ≤ **28** days.
Grade 3	Rule out infection and interrupt everolimus until symptoms improve to Grade ≤ 1. Consider re-initiating everolimus at one dose level lower. Discontinue everolimus if failure to recover within ≤ **28** days.

5.3.2.**8** Management of Non-Infectious Pneumonitis

Table 5-6 Management of Non-Infectious Pneumonitis

Is:

Worst Grade Pneumonitis	Everolimus Dose Adjustment
Grade 2	Rule out infection and consider interruption of everolimus until symptoms improve to Grade ≤ 1. Re-initiate everolimus at one dose level lower. Discontinue everolimus if failure to recover within ≤ **21** days.
Grade 3	Rule out infection and interrupt everolimus until symptoms improve to Grade ≤ 1. Consider re-initiating everolimus at one dose level lower. Discontinue everolimus if failure to recover within ≤ **21** days.

5.3.4 Prohibited Therapies and Restrictions

Was:

- No anticancer agents other than the study medication should be given to patients, with the following exceptions:
  - Bisphosphonates **or** Zometa for bone metastases
  - a GnRH analog is permitted if the patient had progressive disease on a GnRH analog plus a SERM or an AI; the GnRH analog may continue but the SERM or AI must be discontinued.

Is:

- No anticancer agents other than the study medication should be given to patients, with the following exceptions:
  - Bisphosphonates, Zometa **or Xgeva** for bone metastases
  - a GnRH analog is permitted if the patient had progressive disease on a GnRH analog plus a SERM or an AI; the GnRH analog may continue but the SERM or AI must be discontinued.

5.3.4 Prohibited Therapies and Restrictions

Added:

- **Concurrent radiation therapy is prohibited, however palliative radiotherapy may be considered on a case by case basis after discussion with the Study Chair.**

5.3.5.1 Inhibitors of CYPA34 and/or PgP

Was:

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 **2.5 mg daily**. Additional dose reductions to every other day may be required to manage toxicities. If the inhibitor is discontinued, the everolimus dose should be returned to the dose used prior to initiation of the moderate CYP3A4/PgP inhibitor after a washout period of 2-3 days.

5.3.5.1 Inhibitors of CYPA34 and/or PgP

Is:

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 **5 mg every other day**. Additional dose reductions to every other day may be required to manage toxicities. If the inhibitor is discontinued, the everolimus dose should be returned to the dose used prior to initiation of the moderate CYP3A4/PgP inhibitor after a washout period of 2-3 days.

5.3.5.2 Inducers of CYPA34 and/or PgP

Was:

Avoid the use of strong CYP3A4 inducers (e.g., phenytoin, carbamazepine, rifampin, rifabutin, phenobarbital, St. John's Wort). If a patient requires co-administration of strong CYP3A4 inducers, an increase in the dose of everolimus up to twice the currently used daily dose should be considered, 5 mg increments. Enzyme induction usually occurs within 7-10 days; therefore everolimus dose should be increased by one increment 7 days after the start of the inducer therapy. If no safety concerns are seen within the next 7 days, the dose can be increased again one additional increment up to a maximum of twice the daily dose used prior to initiation of the strong CYP3A4 inducer.

Is:

Avoid the use of strong CYP3A4 inducers (e.g., phenytoin, carbamazepine, rifampin, rifabutin, phenobarbital, St. John's Wort). If a patient requires co-administration of strong CYP3A4 inducers, an increase in the dose of everolimus up to twice the currently used daily dose should be considered, 5 mg increments. Enzyme induction usually occurs within 7-10 days; therefore everolimus dose should be increased by one increment 7 days after the start of the inducer therapy. If no safety concerns are seen within the next 7 days, the dose can be increased again one additional increment up to a maximum of twice the daily dose used prior to initiation of the strong CYP3A4 inducer. **The choice to adjust the dose of everolimus in a patient requiring co-administration of strong CYP3A4 inducers will be done at the discretion of the treating investigator.**

7.0 Study Parameters- Study Table

Was:

Serum Creatinine, Electrolytes (K, Na, Cl, CO2), Ca, BUN, **Bicarbonate,** Albumin, Total Protein, Phosphorus, AST (SGOT), ALT (SGPT), Alkaline Phosphatase, Total Bilirubin, Magnesium, Uric Acid.

Is:

Serum Creatinine, Electrolytes (K, Na, Cl, CO2), Ca, BUN, Albumin, Total Protein, Phosphorus, AST (SGOT), ALT (SGPT), Alkaline Phosphatase, Total Bilirubin, Magnesium, Uric Acid.

7.0 Study Parameters- Study Table

Was:

HBV DNA, **HCV RNA-PCR**

Is:

HBV DNA
HCV RNA-PCR

7.0 Study Parameters- Footnotes

Was:

c: **≤** 72 hour window allowed prior to D1 of each subsequent cycle after the first cycle for scheduled therapy/tests/visits. Delay due to holidays, weekends, bad weather or other unforeseen circumstances will be permitted.

e: **≤** 72 hours prior to Cycle 2 Day 1 then approximately every 12 weeks during treatment (and more frequently as clinically indicated), and at end of treatment.

Is:

c: **+/-** 72 hour window allowed prior to D1 of each subsequent cycle after the first cycle for scheduled therapy/tests/visits. Delay due to holidays, weekends, bad weather or other unforeseen circumstances will be permitted.

e: **+/-** 72 hours prior to Cycle 2 Day 1 then approximately every 12 weeks during treatment (and more frequently as clinically indicated), and at end of treatment.

7.0 Study Parameters- Footnotes

Was:

f: All patients should be screened for hepatitis risk factors and any past illnesses of hepatitis B and hepatitis C infection. It is highly recommended that patients positive HBV-DNA or HBsAg are treated prophylactically with an antiviral (e.g., Lamivudine) for 1-2 weeks prior to receiving study drug (see Table 5-3). The antiviral treatment should continue throughout the entire study period and for at least 4 weeks after the last dose of everolimus. **Patients with viral hepatitis C risk factors should be screened for HCV RNA-PCR. Patients on antiviral prophylaxis treatment or positive HBV antibodies should be tested for HBV-DNA ≤ 7 days prior to the start of C1D1 and ≤ 72 hrs prior to D1 of each subsequent cycle to monitor for reactivation. See Table 5-4 for reactivation instructions. Patients with positive HCV RNA-PCR results at screening and/or a history of past infection (even if treated and considered 'cured') should have HCV RNA-PCR testing performed on ≤ 7 days prior to the start of C1D1 and ≤ 72 hrs prior to D1 of each subsequent cycle to monitor for flare. Everolimus must be discontinued if HCV flare is confirmed according to the guidance in Table 5-5.**

Is:

f: All patients should be screened for hepatitis risk factors and any past illnesses of hepatitis B and hepatitis C infection **(see Section 7.1.1)**. **All patients with a positive medical history per Section 7.1.1 need hepatitis testing as noted on above table.** It is highly recommended that patients positive for HBV-DNA or HBsAg or HBsAb are treated prophylactically with an antiviral (e.g., Lamivudine) for 1-2 weeks prior to receiving study drug (see Table 5-3). The antiviral treatment should continue throughout the entire study period and for at least 4 weeks after the last dose of everolimus.

g: Patients on antiviral prophylaxis treatment or positive HBV antibodies should be tested for HBV-DNA ≤ 7 days prior to the start of C1D1 and +/- 72 hrs prior to D1 of each subsequent cycle to monitor for reactivation. See Table 5-4 for reactivation instructions.

h: Patients with positive HCV RNA-PCR results at screening and/or a history of past infection (even if treated and considered 'cured') should have HCV RNA-PCR testing performed on ≤ 7 days prior to the start of C1D1 and +/- 72 hrs prior to D1 of each subsequent cycle to monitor for flare. Everolimus must be discontinued if HCV flare is confirmed according to the guidance in Table 5-5.

7.0 Study Parameters- Footnote

Was:

g: Tumor measurements may be made using physical examination, CT Scans or MRI. Tumor assessments will be performed every 12 weeks, +/- week (every 3 months) **with first assessment within 2 weeks prior to Cycle 4 treatment**. Imaging will include chest and abdomen. Bone Scans and Brain CT/MRI may be performed as clinically indicated. Scans do not have to be repeated once disease progression is documented.

Is:

i: Tumor measurements may be made using physical examination, CT Scans or MRI. Tumor assessments will be performed every 12 weeks, +/- **1** week (every 3 months). Imaging will include chest and abdomen. Bone Scans and Brain CT/MRI may be performed as clinically indicated. Scans do not have to be repeated once disease progression is documented.

7.0 Study Parameters- Footnote

Was:

***** Day 1 of each cycle is defined as the day in which fulvestrant is given**, including the first fulvestrant dose, third fulvestrant dose, and every dose thereafter** (the second fulvestrant dose is given on day 15 of the first cycle only).

Is:

*** Cycle 1, Day 1 is defined as the first day on which fulvestrant is given in combination with placebo/everolimus** (the second fulvestrant dose is given on day 15 of the first cycle only). Day 1 of each **additional** cycle is defined as the day in which fulvestrant **is given in combination with everolimus/placebo.**

7.1.1 Pre-Study

Was:

- Serum Creatinine, Electrolytes (K, Na, Cl, CO2), Ca, BUN, **Bicarbonate**, Albumin, Total Protein, Phosphorus, AST (SGOT), ALT (SGPT), Alkaline Phosphatase, Total Bilirubin, Magnesium and Uric Acid

Is:

- Serum Creatinine, Electrolytes (K, Na, Cl, CO2), Ca, BUN, Albumin, Total Protein, Phosphorus, AST (SGOT), ALT (SGPT), Alkaline Phosphatase, Total Bilirubin, Magnesium and Uric Acid

7.1.2 Induction Phase (fulvestrant + everolimus/placebo)

Was:

Day 1 of each cycle is defined as the day in which fulvestrant is given, including the first fulvestrant dose, third fulvestrant dose, and every dose thereafter (the second fulvestrant doses is given on day 15 of the first cycle only).

Is:

Day 1 of each cycle is defined as the day in which fulvestrant is given, including the first fulvestrant dose, third fulvestrant dose, and every dose thereafter (the second fulvestrant doses is given on day 15 of the first cycle only). **Note: If patient previously received one cycle of fulvestrant (day 1 and day 15) prior to study entry as permitted in Inclusion Criteria #8, patient should receive fulvestrant 500 mg on day 1 only.**

7.1.2.1 Within 7 Days of Cycle 1 Day 1 and 7.1.2.2 Cycle 1 Day 15

Was:

- Serum Creatinine, Electrolytes (K, Na, Cl, CO2), Ca, BUN, **Bicarbonate**, Albumin, Total Protein, Phosphorus, AST (SGOT), ALT (SGPT), Alkaline Phosphatase, Total Bilirubin, Magnesium and Uric Acid

Is:

- Serum Creatinine, Electrolytes (K, Na, Cl, CO2), Ca, BUN, Albumin, Total Protein, Phosphorus, AST (SGOT), ALT (SGPT), Alkaline Phosphatase, Total Bilirubin, Magnesium and Uric Acid

Was:

7.1.2.3 **Within 72 Hours of** Cycle 2 (and each subsequent cycle) Day 1

- Serum Creatinine, Electrolytes (K, Na, Cl, CO2), Ca, BUN, **Bicarbonate**, Albumin, Total Protein, Phosphorus, AST (SGOT), ALT (SGPT), Alkaline Phosphatase, Total Bilirubin, Magnesium and Uric Acid
- Fasting Glucose (**≤ 72 hours of** Cycle 2 Day 1, then every 12 weeks during treatment, and more frequently as clinically indicated)
- Fasting Serum Lipid Profile (triglycerides, total cholesterol, HDL and LDL) (**≤ 72 hours of** Cycle 2 Day 1, then every 12 weeks during treatment, and more frequently as clinically indicated)

Is:

7.1.2.3 Cycle 2 (and each subsequent cycle) Day 1

- Serum Creatinine, Electrolytes (K, Na, Cl, CO2), Ca, BUN, Albumin, Total Protein, Phosphorus, AST (SGOT), ALT (SGPT), Alkaline Phosphatase, Total Bilirubin, Magnesium and Uric Acid
- Fasting Glucose (Cycle 2 Day 1, then every 12 weeks during treatment, and more frequently as clinically indicated)
- Fasting Serum Lipid Profile (triglycerides, total cholesterol, HDL and LDL) (Cycle 2 Day 1, then every 12 weeks during treatment, and more frequently as clinically indicated)

7.1.3 End of Induction Phase <OR> End of Treatment

Was:

- Serum Creatinine, Electrolytes (K, Na, Cl, CO2), Ca, BUN, **Bicarbonate**, Albumin, Total Protein, Phosphorus, AST (SGOT), ALT (SGPT), Alkaline Phosphatase, Total Bilirubin, Magnesium and Uric Acid

Is:

Serum Creatinine, Electrolytes (K, Na, Cl, CO2), Ca, BUN, Albumin, Total Protein, Phosphorus, AST (SGOT), ALT (SGPT), Alkaline Phosphatase, Total Bilirubin, Magnesium and Uric Acid

8.1.2 Storage Requirements/Stability

Was:

Everolimus should **not** be stored at temperatures **above 25°C**.

Is:

Everolimus should be stored at **room** temperature **between 20°C to 25°C (68°F to 77°F).**

8.1.3 4 Special Instructions for Unblinding

Was:

If a participant is in a life-threatening situation in which knowledge of the treatment is crucial to care AND the Medical Monitor cannot be reached immediately, the **investigator may unblind the participant without prior approval and must then immediately notify the Medical Monitor and submit a detailed report detailing the unblinding event**. Report information will include but is not limited to:

Is:

If a participant is in a life-threatening situation in which knowledge of the treatment is crucial to care AND the Medical Monitor cannot be reached immediately, **the PM should be contacted to facilitate the unblinding process. A report including the unblinding details will be generated after the patient has been unblinded and will be sent to the site for documentation (refer to Study Reference Manual for Unblinding Process).** Report information will include but is not limited to:

9.1 Primary Efficacy Endpoint

Was:

The primary efficacy endpoint is progression-free survival (PFS). PFS is defined as the time from randomization to documented disease progression or death. Based on results from the CONFIRM trial, median PFS among patients with AI-resistant disease on fulvestrant alone is 5.4 months. AI resistant disease is defined as: patients who have either relapsed while receiving adjuvant therapy with an aromatase inhibitor (anastrozole, letrozole, or exemestane) or have progressive disease while receiving an aromatase inhibitor for metastatic disease. (Patients previously treated with two or more prior **doses** of fulvestrant are not eligible. Patients who have received one prior **dose** of fulvestrant within 28 days of randomization are eligible so long as they meet other eligibility criteria). Randomization will be 1:1, stratified for balancing purposes using ECOG performance status (0 vs. 1), presence of measurable disease (yes vs. no), and prior chemotherapy (yes vs. no).

Is:

The primary efficacy endpoint is progression-free survival (PFS). PFS is defined as the time from randomization to documented disease progression or death. Based on results from the CONFIRM trial, median PFS among patients with AI-resistant disease on fulvestrant alone is 5.4 months. AI resistant disease is defined as: patients who have either relapsed while receiving adjuvant therapy with an aromatase inhibitor (anastrozole, letrozole, or exemestane) or have progressive disease while receiving an aromatase inhibitor for metastatic disease. (Patients previously treated with two or more prior **cycles** of fulvestrant are not eligible. Patients who have received one prior **cycle (day 1 and day 15)** of fulvestrant within 28 days of randomization are eligible so long as they meet other eligibility criteria). Randomization will be 1:1, stratified for balancing purposes using ECOG performance status (0 vs. 1), presence of measurable disease (yes vs. no), and prior chemotherapy (yes vs. no).

9.1 Primary Efficacy Endpoint

Removed:

If median PFS among patients treated with fulvestrant alone is 20 weeks (4.6 months), there will be acceptable power (86%) to detect a hazard ratio of 0.62, corresponding to a median PFS of 7.4 months if distributions are exponential. Full information of 104 events would be required for this analysis.

13.0 Appendix A: Eligibility Checklist

Inclusion Criteria

Was:

Patients must have had relapse while receiving adjuvant therapy with an aromatase inhibitor (anastrozole, letrozole, or exemestane), OR progressive disease while receiving an aromatase inhibitor for metastatic disease. Patients previously treated with two or more prior **doses** of fulvestrant are not eligible. Patients who have received one prior **dose** of fulvestrant within 28 days of randomization are eligible as long as they meet other eligibility criteria.

Is:

Patients must have had relapse while receiving adjuvant therapy with an aromatase inhibitor (anastrozole, letrozole, or exemestane), OR progressive disease while receiving an aromatase inhibitor for metastatic disease. **Note: Patients may have received an endocrine agent (e.g., Tamoxifen) between the time of progression on an AI and registration.**

Patients previously treated with two or more prior **cycles** of fulvestrant are not eligible. Patients who have received one prior **cycle (dose on day 1 and day 15)** of fulvestrant within 28 days of randomization are eligible as long as they meet other eligibility criteria.

13.0 Appendix A: Eligibility Checklist

Exclusion Criteria

Was:

Patients must not be receiving any concomitant anticancer treatment or have received anticancer treatment within 4 weeks of randomization (including chemotherapy, radiation therapy, antibody based therapy, e.g.), with the following exceptions:

- Bisphosphonates **or** Zometa for bone metastases
- a GnRH analog is permitted if the patient had progressive disease on a GnRH analog plus a SERM or an AI; the GnRH analog may continue but the SERM or AI must be discontinued.

Is:

Patients must not be receiving any concomitant anticancer treatment or have received anticancer treatment within 4 weeks of randomization (including chemotherapy, radiation therapy, antibody based therapy, e.g.), with the following exceptions:

- Bisphosphonates, Zometa **or Xgeva** for bone metastases
- **Hormonal therapy (e.g., AI, Tamoxifen)**
- a GnRH analog is permitted if the patient had progressive disease on a GnRH analog plus a SERM or an AI; the GnRH analog may continue but the SERM or AI must be discontinued.

Section 19. References

Added:

55. Divers J, RN BSN, Texas Oncology. Management of Stomatitis Associated with mTOR Inhibitors in Hormone Receptor-Positive HER2-Negative Advanced Breast Cancer: Clinical Experiences from a Single Center. Presented at the 38th Annual Oncology Nurses' Society Congress, April 25-28, 2013. Novartis Internal Communication.

Section 20 Investigator's Statement
Was:
Version **1.0** dated **12/19**/201**2**
Is:
Version **2.0** dated **1/22/**201**4**

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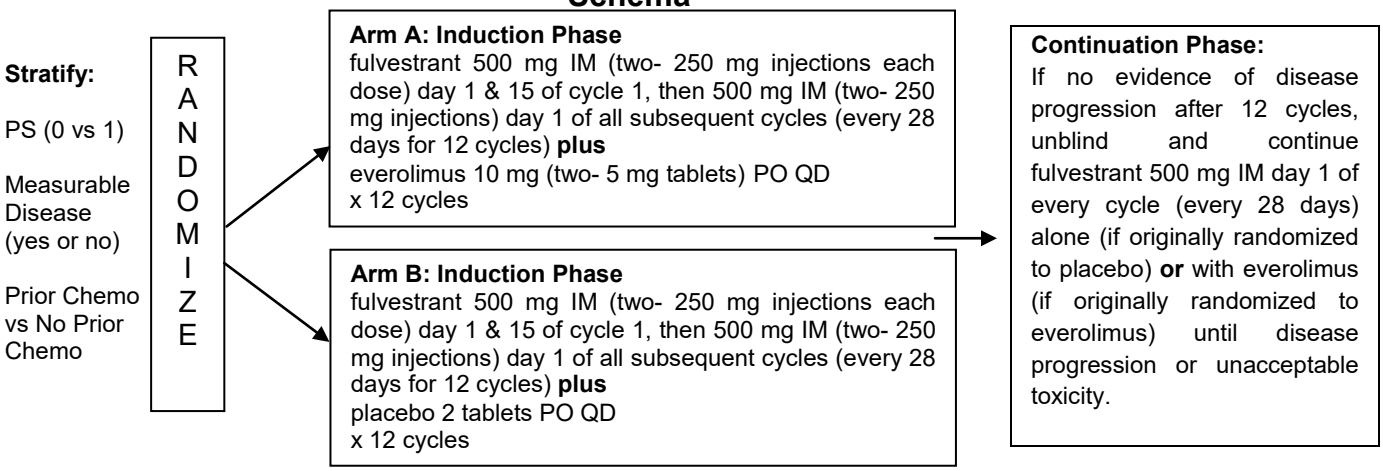
BRIEF PROTOCOL SYNOPSIS

(This section is provided as a brief summary and is not a substitution for referring to the full protocol details. See protocol document sections for complete details.)

Schema



This is a Phase II study. 25 sites will be activated. 130 patients will be enrolled. There will be a balanced 1:1 randomization of everolimus:placebo (e.g., for every patient randomized to receive everolimus, one patient will be randomized to receive placebo).

Patients will be treated for a maximum of 12 cycles with fulvestrant plus everolimus/placebo during the Induction Phase. Induction treatment continues until there is evidence of progressive disease or unacceptable toxicity for a maximum of 12 cycles (see Section 5.6). Patients with no evidence of progressive disease who remain on study **after completing** 12 cycles of the Induction Phase are unblinded and proceed to the Continuation Phase. Patients in the Continuation Phase should continue to receive fulvestrant alone (if originally randomized to placebo) **or** in combination with everolimus (if originally randomized to everolimus) until disease progression or unacceptable toxicity. Patients in both the Induction and Continuation Phases should have tumor measurements performed every 12 weeks (+/- 1 week).

Patient Population

- Patients must be postmenopausal and have stage IV disease or inoperable locally advanced disease.
- Patients must have ER and/or PR-positive disease as determined by their local pathology or reference laboratory by ASCO-CAP criteria. Tumors must be HER-2/neu negative or equivocal by standard ICH/FISH or ICH/CISH methodologies by ASCO-CAP criteria.
- Patients must be Aromatase Inhibitor (AI) resistant, defined as:
  - relapsed while receiving adjuvant therapy with an aromatase inhibitor (anastrozole, letrozole, or exemestane) or,
  - progressive disease while receiving an aromatase inhibitor for metastatic disease.

  Note: Patients may have received an endocrine agent (e.g., Tamoxifen) between the time of progression on an AI and registration.

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Table of Contents

1 Introduction

1.1 Background and Rationale

Endocrine therapy represents the foundation of treatment for hormone-receptor positive metastatic and locally advanced breast cancer. Multiple compounds in varying classes exist, and those most widely used include the selective estrogen receptor modulators (SERMs), aromatase inhibitors (AIs), and the selective estrogen receptor down-regulators (SERDs). Although the utility of these drugs is well established, as many as 50% of women with hormone-receptor positive breast cancer will fail to respond to endocrine treatment (*de novo resistance)*. Moreover, those who do respond will inevitably develop acquired resistance.[1] Resistance to endocrine therapy remains a serious clinical challenge.

Basic scientific research into the mechanisms surrounding endocrine therapy resistance has been particularly intense in recent years. Advances in this area of investigation are driving the development of novel treatments and therapeutic strategies. For example, various signal transduction pathways, when activated, have been demonstrated to allow breast cancer cells to escape the effect of endocrine therapy. The Protein Kinase B (Akt/PKB), a downstream target in the PI3 kinase signaling pathway appears to play a vital role in drug resistance.[2] Several studies identify a close association between aberrant Akt signaling and tamoxifen resistance.[3] High levels of Akt activity confer resistance to the aromatase inhibitor letrozole and the selective estrogen receptor down-regulator fulvestrant.[4] This Akt-induced resistance does not appear to be secondary to failure of these agents to inhibit the estrogen receptor α activity, but instead may lead to altered cell cycle and apoptotic response.[5] Clinically, Akt/PKB activation in breast cancer appears to predict an inferior outcome among patients treated with endocrine therapy.[6]

mTOR, mammalian target of rapamycin, is a cytoplasmic protein kinase that acts as a central regulator of many biological processes involved in cellular proliferation, angiogenesis and metabolism. mTOR is a key protein involved in control and regulation of the cell's translational machinery through multiple mechanisms including by directly activating or inhibiting ribosomal activity.[7] mTOR is a key intracellular point of convergence for a number of cellular signaling pathways, including Akt/PKB.[8] mTOR lies downstream to Akt/PKB, and targeted inhibition of this protein has emerged as an important therapeutic strategy in clinical oncology. Inhibition of mTOR activity has been shown to restore tamoxifen response in breast cancer cells with aberrant Akt activity.[9]

Everolimus is an orally bioavailable inhibitor of the mTOR pathway. Combination treatment with everolimus and either letrozole or fulvestrant has been shown to reverse Akt-mediated endocrine therapy resistance and restore responsiveness to anti-estrogens in preclinical studies.[5] These observations formed the rationale leading to the Phase I clinical trial evaluating the combination of everolimus and letrozole in women previously treated with letrozole ≥ 4 months without objective response (e.g., stable or progressive disease). Eighteen postmenopausal female patients with advanced HR^+ breast cancer were treated with letrozole 2.5 mg/day and everolimus at 5 mg/day (cohort 1) or 10 mg/day (cohort 2).[10] Overall the combination was well tolerated and toxicities were manageable and consistent with that expected for

everolimus monotherapy. The results suggest antitumor activity for this combination without Pharmacokinetic (PK) interactions.

This study will examine the efficacy and tolerability of the combination of fulvestrant and everolimus for the treatment of postmenopausal metastatic breast cancer resistant to an aromatase inhibitor.

1.2 Breast Cancer

Breast cancer is the most commonly diagnosed malignancy in women worldwide. In the United States, an estimated 230,480 new cases of invasive breast cancer were diagnosed in 2011, with 39,520 breast cancer deaths.[11] Despite the recent advances in breast cancer therapy, 40-80% of women with node-positive disease and up to 30% of women with node-negative disease at diagnosis will relapse. When distant metastases occur, the prognosis remains poor with a median survival of 18 to 36 months from time of recurrence. Among the 60-70% of women with hormone-receptor positive breast cancer, 40-60% of them will benefit from endocrine therapy. Endocrine therapy has shown to yield similar survival rates in hormone-sensitive disease as compared to chemotherapy; although response rates are lower and responses develop more slowly. Endocrine therapy is considerably less toxic than chemotherapy, and is therefore the preferred treatment option for patients with hormone-receptor (HR)-positive disease.[12,13] Chemotherapy is generally indicated in HR-negative disease, in cases unresponsive to endocrine therapy, or when extensive metastases require rapid tumor response.[14]

1.3 Endocrine Therapy for Breast Cancer

Several endocrine therapies are available for the treatment of metastatic breast cancer in postmenopausal women, including selective estrogen-receptor modulators (SERMs), aromatase inhibitors (AIs), progestins, androgens, and most recently the selective estrogen receptor downregulators (SERDs- e.g., fulvestrant). Tamoxifen was generally regarded as a standard option in HR-positive disease for adjuvant therapy, and for first-line therapy of metastatic disease in postmenopausal women. Within the past decade, however, the AIs (letrozole, anastrozole, exemestane) have supplanted tamoxifen as the preferred choice for adjuvant therapy and metastatic disease in postmenopausal women.[15,16] There is therefore a need to develop more effective endocrine therapies for patients with AI-resistant disease, and to enhance the effectiveness of existing endocrine therapies that have demonstrated efficacy in AI-resistant disease.

1.3.1 Fulvestrant for Post Menopausal Women with Breast Cancer

Fulvestrant (Faslodex®, AstraZeneca Pharmaceuticals LP, Wilmington, DE) has several unique characteristics. It is the first drug which acts as a pure estrogen receptor (ER) antagonist without known agonist effects. It competitively binds to the ERs with an approximately 100 times greater affinity than that of tamoxifen. Fulvestrant promotes the degradation of ERs and subsequently prevents ER-mediated gene transcription. Two studies that led to the approval of fulvestrant were performed in postmenopausal women with HR-positive metastatic breast cancer who had progressive disease after tamoxifen therapy. These trials compared fulvestrant

(250 mg IM injection monthly) with anastrozole (1 mg PO daily) (Table 1-0).[17,18] The primary endpoint for both studies was time to disease progression (TTP), which was similar between the two treatment arms (5.4 versus 3.4 months in the North American trial, and 5.5 versus 5.1 months in the European trial). Secondary endpoints were also comparable. The response rate for fulvestrant was 17-20% (versus 15.7-17.5% for anastrozole), Clinical Benefit Rate (CBR) was 42-45% (versus 36-45% for anastrozole), median duration of response was 15-19 months (versus 11-15 months for anastrozole), and median time to disease progression (TTP) was 5.5 months (versus 3.4-5.1 months for anastrozole). Further subgroups analyses confirm the clinical activity of fulvestrant in both visceral and non-visceral metastatic disease as compared with anastrozole.[19] These trials led to the approval of Faslodex® (fulvestrant) Injection for "…the treatment of hormone-receptor positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy".

Table 1-0

Phase III Studies Comparing Fulvestrant and Anastrozole after Tamoxifen-Failure in Postmenopausal Women with HR-Positive Metastatic Breast Cancer

	North American Trial[18]		European Trial[19]	
Treatment Group:	Fulvestrant	Anastrozole	Fulvestrant	Anastrozole
No. of Patients:	206	194	222	229
Overall RR (%):	17.5	17.5	20.7	15.7
CR (%):	4.9	3.6	4.5	1.7
PR (%):	12.6	13.9	16.2	14.0
Clinical Benefit Rate (%):	42.2	36.1	44.6	45.0
SD for more than 24 weeks (%):	24.8	18.6	23.9	29.3
Median TTP (months):	5.4	3.4	5.5	5.1
Median Duration of Response (months):	19.0	10.8	15.0	14.5
Withdrawal Rate (%):	2.5	2.6	3.2	1.3

Fulvestrant has also been compared with tamoxifen as first line therapy in a Phase III trial that included 587 postmenopausal women with HR-positive metastatic breast cancer**,** but proved to be no more effective than tamoxifen in this setting.[20] When comparing fulvestrant with tamoxifen, the objective response rate (34% versus 32%) and clinical benefit rate (57% versus 62%) were similar.

1.3.2 Fulvestrant for Aromatase Inhibitor (AI) Resistant Disease

Several trials have evaluated the role of fulvestrant in AI-resistant disease, as summarized in Table 1-1**.**

Table 1-1

Phase II or III Trial of Fulvestrant in AI-Resistant Disease

Reference	Treatment	No.	RR	CBR	Median TTP
Ingle, 2006[21]	Fulvestrant	77	14%	25%	3.0 mo.
Perey, 2007[22]	Fulvestrant	20	5%	37%	3.5 mo.
Chia, 2008[23]	Fulvestrant Exemestane	270 270	7% 7%	23% 19%	3.7 mo. 3.7 mo.

The Clinical Benefit Rate (CBR) for patients with AI-resistant disease is approximately 20-30%, and median TTP is approximately 3.5 months. In the EFECT trial reported by Chia et al, patients who had progressive disease after treatment with a non-steroidal AI (anastrozole, letrozole) were randomized to fulvestrant or the steroidal aromatase inhibitor exemestane. In contrast to most other trials that utilized a single 250 mg monthly dose based upon the original pharmacokinetic studies,[23] patients in the EFECT trial received a 500 mg loading dose on day 1, then 250 mg on day 15 and 28 (then every 4 weeks thereafter) based upon recent evidence that this dose/schedule may more rapidly achieve therapeutic blood levels. There was no significant difference in CBR between the two treatment arms. Nevertheless, the EFECT trial confirmed the effectiveness of fulvestrant previously reported in other smaller trials of fulvestrant in AI-resistant disease.

Previous trials had demonstrated that a dose of 125 mg was less effective than the 250 mg monthly dose.[16,20] Based upon evidence that dosing schedules higher than the 250 mg monthly dose may produce greater clinical benefit, several trials evaluated alternative dosing schedules (similar to that used in the EFECT trial), including FINDER I (NCT00305448), FINDER II (NCT00313170), and CONFIRM (NCT00099437).

1.3.3 Rationale for Fulvestrant for this Trial

Fulvestrant has demonstrated activity when used as first, second, or third line endocrine therapy, making it an attractive therapy for combination with other agents. In addition, it is commonly reserved for use following disease progression on AI therapy. The loading dose schedule employed in the EFECT trial will be used in this study taking advantage of the known dose-response effect observed for fulvestrant, the more rapid achievement of therapeutic blood levels, the extensive efficacy and safety experience with this schedule, and because it appears to be emerging as the preferred schedule for fulvestrant based upon the results of ongoing and recently completed clinical trials.

The recently reported CONFIRM trial compared fulvestrant dosing of 250 mg every 28 days (the previously FDA-approved dose) with 500 mg on days 1, 14, 28 and every 28 days thereafter (the current FDA-approved dose).[24] The study demonstrated that the higher dose was more effective. Median time to progression (TTP) was 6.5 months with the higher dose compared with 5.5 months with the lower dose (HR 0.8, p=0.006). The CBR was 45%, with the high dose as compared to 39.6% with the low dose arm (odds ratio 1.28, p=0.10). In the subgroup of patients who had

relapsed/progressed on an aromatase inhibitor (the population targeted in this study), median TTP was 5.4 months with the high-dose arm, and 4.1 months on the standard arm (with CBRs of 36% and 32% respectively). We will therefore use the high-dose regimen as utilized in the CONFIRM trial.[24]

1.4 Everolimus (RAD001)

Everolimus (RAD001) is a novel oral derivative of rapamycin that is an m-TOR inhibitor.

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

Everolimus was developed in oncology as Afinitor® and was approved for advanced renal cell carcinoma (RCC) in 2009. In 2010, Afinitor® received United States (US) approval for patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis (TS). Everolimus is also available as Votubia® in the European Union (EU) for patients with SEGA associated with TS. Afinitor® was approved for "progressive pancreatic neuroendocrine tumor (PNET) in patients with unresectable, locally advanced, or metastatic disease" in 2011 in various countries, including the US and Europe.

In 2012 Afinitor® received approval for the treatment of postmenopausal women with advanced hormone receptor-positive, HER2-negative breast cancer (advanced HR+ BC) in combination with exemestane, after failure of treatment with letrozole or anastrozole. Furthermore in 2012, Afinitor® received approval for the treatment of patients with Tuberous Sclerosis Complex (TSC) who have renal angiomyolipoma not requiring immediate surgery.

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

- Directly on the tumor cells by inhibiting tumor cell growth and proliferation.
- Indirectly by inhibiting angiogenesis leading to reduced tumor vascularity (via potent inhibition of tumor cell HIF-1 activity, VEGF production and VEGF-induced proliferation of endothelial cells). The role of angiogenesis in the maintenance of solid tumor growth is well established, and the mTOR pathway has been implicated in the regulation of tumor production of proangiogenic factors as well as modulation of VEGFR signaling in endothelial cells.

At weekly and daily schedules and at various doses explored, everolimus is generally well tolerated. The most frequent adverse events (rash, mucositis, fatigue and headache) associated with everolimus therapy are manageable. Non-infectious pneumonitis has been reported with mTOR inhibitors but is commonly low-grade and reversible.

1.4.1 mTOR Pathway and Mechanism of Action

At cellular and molecular levels, everolimus acts as a signal transduction inhibitor. Everolimus selectively inhibits mTOR (mammalian target of rapamycin), specifically

targeting the mTOR-raptor signal transduction complex. mTOR is a key and highly conserved serine-threonine kinase which is present in all cells and is a central regulator of protein synthesis and ultimately cell growth, cell proliferation, angiogenesis and cell survival. mTOR is the only currently known target of everolimus.[25]

mTOR is downstream of PI3K/AKT pathway, a pathway known to be dysregulated in a wide spectrum of human cancers (e.g. through loss/mutation of the PTEN negative regulator; through PI3K mutation/amplification; through AKT/PKB overexpression/ overactivation; through modulation of TSC1/TSC2 tumor suppressors). In addition, activation of the PI3K/AKT/mTOR pathway is associated with worsening prognosis through increased aggressiveness, resistance to treatment and progression.

The main known functions of mTOR include the following:[7,25]

- mTOR functions as a sensor of mitogens, growth factors and energy, and nutrient levels, facilitating cell-cycle progression from G1 to S phase in appropriate growth conditions.
- The PI3K-mTOR pathway itself is frequently activated in many human cancers, and oncogenic transformation may sensitize tumor cells to mTOR inhibitors.
- Through inactivating eukaryotic initiation factor 4E binding proteins (4E-BP1) and activating the 40S ribosomal S6 kinases (e.g., p70S6K1), mTOR regulates protein translation, including the HIF-1 proteins. Inhibition of mTOR is expected to lead to decreased expression of HIF-1.
- The activation of mTOR pathway is involved in the production of pro-angiogenic factors (i.e., VEGF) and inhibition of endothelial cell growth and proliferation.
- The regulation of mTOR signaling is complex and involves positive regulators, such as AKT that phosphorylate and inactivate negative regulators such as the Tuberous Sclerosis Complex (TSC1/TSC2).

mTOR is represented by two structurally and functionally distinct multiprotein signaling complexes, mTORC1 (mTOR complex 1, rapamycin sensitive) and mTORC2 (mTOR complex 2, rapamycin insensitive).[26]

mTORC1 is mainly activated via the PI3 kinase pathway through AKT (also known as PKB, protein kinase B) and the tuberous sclerosis complex (TSC1/TSC2).[7] Activated AKT phosphorylates TSC2, which leads to the dissociation of TSC1/TSC2 complex, thus inhibiting the ability of TSC2 to act as a GTPase activating protein. This allows Rheb, a small G-protein, to remain in a GTP bound state and to activate mTORC1. AKT can also activate mTORC1 by PRAS40 phosphorylation, thereby relieving the PRAS40-mediated inhibition of mTORC1.[27,28]

mTORC2 (mTOR complex 2) is activated through a currently unknown mechanism, possibly by receptor tyrosine kinase (RTK) signaling.[27] It has been suggested that mTORC2 phosphorylates and activates a different pool of AKT that is not upstream of mTORC1. PHLPP phosphatase plays a role of a negative regulator. mTORC2 is rapamycin insensitive and is required for the organization of the actin cytoskeleton.[26]

mTORC1-mediated signaling is subject to modulation by the macrocyclic lactone rapamycin and its derivatives, such as everolimus. Once these agents bind to the 12 kDa cytosolic FK506-binding protein immunophilin FKBP12, the resulting rapamycin-FKBP12 complexes bind to a specific site near the catalytic domain of mTORC1 and

inhibit phosphorylation of mTOR substrates. As a consequence, downstream signaling events involved in regulation of the G1 to S-phase transition are inhibited. This mechanism is thought to be responsible for the immunosuppressive effects of rapamycin as well as its putative antineoplastic activity.[29] As many cancers are characterized by dysregulation of G1 transit (for example, overexpression of cyclin or cyclin-dependent kinases), inhibition of mTOR becomes an intriguing target for inducing cytostasis.[7]

1.4.1.1 Preclinical Studies

Everolimus acts as an inhibitor of cytokine and growth-factor-dependent proliferation of cells. The only currently known target of everolimus is mTOR, a key regulatory protein affecting cell growth.[25] Everolimus exerts its activity through high affinity interaction with an intracellular receptor protein, the immunophilin FKBP12. The FKBP12/everolimus complex subsequently interacts with the mTOR protein kinase, inhibiting downstream signaling events involved in regulation of the G1 to S-phase transition.

The main known functions of mTOR include:

- Function as a sensor of mitogens, growth factors, energy and nutrient levels, facilitating cell-cycle progression from G1 - S phase in appropriate growth conditions.
- Regulation of protein synthesis important for tumor cell proliferation and angiogenesis through inactivating eukaryotic initiation factor 4E binding proteins and activating the 40S ribosomal S6 kinases (e.g. p70S6K1). For example, activation of the mTOR pathway leads to a) increased production of pro-angiogenic factors (e.g. VEGF) in tumors b) tumor, endothelial and smooth muscle cell growth and proliferation.

The PI3K-mTOR pathway itself is frequently activated in many human cancers, and oncogenic transformation may sensitize tumor cells to mTOR inhibitors. The regulation of mTOR signaling is complex and involves positive regulators such as AKT that phosphorylate and inactivate negative regulators such as the Tuberous Sclerosis Complex (TSC1/TSC2). In summary, mTOR has pleiotropic functions; hence, the activities of everolimus may vary depending upon cell type.

The mTOR inhibitory activities presumably contribute to the anti-proliferative activity of everolimus against tumor cell lines. However, everolimus may also exert an antitumor effect through the inhibition of angiogenesis. Indeed, both rapamycin and everolimus potently inhibit proliferation of endothelial cells and have antiangiogenic activity in vivo.[30,31] Exactly which molecular determinants predict responsiveness of tumor cells to everolimus is still unclear. Currently, the activation status of the PI3K/AKT/mTOR/p70 S6K pathway may be indicative of responsiveness to rapamycins. For example, pre-clinically, loss of PTEN or constitutive/hyper-activation of AKT has been suggested to sensitize tumors to the effects of inhibition of mTOR.[25,31] Also, clinically, it has been suggested that high p70S6K activation in baseline Glioblastoma Multiforme (GBM) tumor samples may predict a patient population more likely to derive benefit from mTOR inhibition.[32]

Everolimus is a highly specific inhibitor of mTOR, which is afforded by high-affinity binding to the protein FKBP-12 (IC_{50} of 5.3 nM) similar to that of rapamycin. Similar potency of rapamycin and everolimus was also demonstrated at forming the mTOR/ FKBP-12 tertiary complex in vitro. Specificity was demonstrated by a lack of inhibitory activity against 10 other protein kinases at concentrations up to 10 μM.

The anti-proliferative effects of everolimus were investigated in a mixed panel of 48 different tumor cell lines (including breast, colon, epidermoid, glioblastoma, lung, melanoma, prostate and renal). The majority of tumor cell lines were highly sensitive to the anti-proliferative effects of everolimus while a few others appeared intrinsically insensitive, or 'resistant' (IC_{50} range 0.2 to 4125 nM).[33] The median IC_{50} value of the 48 cell lines was 0.5 nM. Similar findings have been observed for rapamycin.[34] Everolimus was also shown to have activity in human pancreatic neuroendocrine cells, where induction of apoptosis was reported,[35] as well as in acute myeloid leukemia cells,[36] mantle cell lymphoma cells[37], adult T-cell leukemia cells[38], diffuse large B cell lymphoma cells,[39] pancreatic tumor cells,[40] ovarian cancer cells,[31,41] and hepatocellular carcinoma cells.[42]

Everolimus was also evaluated in a clonogenic assay using cells derived from 81 patient derived tumor xenografts never cultured in vitro (11 human tumor types with 3 to 24 tumors each: bladder, colon, gastric, Non-Small Cell Lung Cancer (NSCLC), Small Cell Lung Cancer (SCLC), breast, ovary, pancreatic, renal, melanoma, and pleuramesothelioma). Everolimus inhibited colony formation in a concentration-dependent manner (mean IC_{50}: 175 nM). In addition, normal hematopoetic stem cells were found to be relatively insensitive to everolimus, with an IC_{50} about 15 fold higher than the tumor lines.

Everolimus was effective and well tolerated against subcutaneous (s.c.) tumors established from a variety of tumor cell lines of diverse histotypes (NSCLC, pancreatic, colon, melanoma, epidermoid), including a PgP170-overexpressing, multi-drug resistant tumor line. Typically, the antitumor activity of everolimus was that of reduction of tumor growth rates rather than producing regressions or stable disease although, in the case of A549 and NCI-H596 lung and ARJ42 pancreatic tumors, regressions could be obtained. These effects occurred within the dose range of 2.5 to 10 mg/kg, P.O., once per day. The change in tumor volume of the treated mice divided by the change in tumor volume of control mice (T/C) typically ranged from approximately 15 to 50% at optimal doses. A marked loss of antitumor activity occurred when tumor-bearing mice were treated with everolimus once per week, but improved moderately with twice per week dosing. Antitumor activity of everolimus has also been demonstrated in mouse models of ovarian,[31] breast,[43,44] and gastrointestinal stromal tumors.[45]

1.4.2 Pre-Clinical Safety

In safety pharmacology studies, everolimus was devoid of relevant effects on vital organ functions including the cardiovascular, respiratory and nervous systems. Everolimus had no effects on QT interval. Furthermore, everolimus showed no antigenic potential. Although everolimus passes the blood-brain barrier, there was no indication of relevant changes in the behavior of rodents, even after single oral doses up to 2000 mg/kg or after repeated administration at up to 40 mg/kg/day.

The preclinical safety profile of everolimus was assessed in mice, rats, minipigs, monkeys, and rabbits. The major target organs were male and female reproductive systems (testicular tubular degeneration, reduced sperm content in epididymides and uterine atrophy) in several species; lungs (increased alveolar macrophages) in rats and mice; and eyes (lenticular anterior suture line opacities) in rats only. Minor kidney changes were seen in the rat (exacerbation of age-related lipofuscin in tubular epithelium, increases in hydronephrosis) and mouse (exacerbation of background lesions). There was no indication of kidney toxicity in monkeys or minipigs.

Genotoxicity studies covering relevant genotoxicity endpoints showed no evidence of clastogenic or mutagenic activity. Administration of everolimus for up to 2 years did not indicate any oncogenic potential in mice and rats up to the highest doses, corresponding respectively to 4.2 and 0.2 times the estimated clinical exposure. In reproduction studies, everolimus was toxic to the conceptus in rats and rabbits, and was considered potentially teratogenic in rats. It is therefore recommended that women of childbearing potential should use effective contraceptive measures during the entire treatment period and for 8 weeks thereafter.

More pre-clinical information is provided in the Investigator's Brochure.

1.4.3 Clinical Experience

1.4.3.1 Everolimus Pharmacokinetics

Everolimus is rapidly absorbed with a median t_{max} of 1-2 hours. The steady-state $AUC_{0-\tau}$ is dose-proportional over the dose range between 5 to 70 mg in the weekly regimen and 5 and 10 mg in the daily regimen. Steady-state was achieved within two weeks with the daily dosing regimen. C_{max} is dose-proportional between 5 and 10 mg for both the weekly and daily regimens. At doses of 20 mg/week and higher, the increase in C_{max} is less than dose proportional. In healthy subjects, high fat meals reduced systemic exposure to everolimus 10 mg (as measured by Area Under the Concentration Time-Curve (AUC)) by 22% and the peak plasma concentration C_{max} by 54%. Light fat meals reduced AUC by 32% and C_{max} by 42%. Food, however, had no apparent effect on the post absorption phase concentration-time profile.

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

Everolimus is a substrate of CYP3A4 and a substrate and moderate inhibitor of PgP. Following oral administration, everolimus is the main circulating component in human blood and is considered to contribute the majority of the overall pharmacologic activity. No specific excretion studies have been undertaken in cancer patients; however, data available from the transplantation setting found the drug to be mainly eliminated through the feces. There was a significant correlation between $AUC_{0-\tau}$ and pre-dose trough concentration at steady-state on the daily regimen. The mean elimination half-life of everolimus is approximately 30 hours.

Appendix C lists examples of clinically relevant CYP3A4 inhibitors and inducers.

Please refer to Section 5.3.5 for more information on the concomitant use of CYP3A4 inhibitors/inducers and other medications.

More information on everolimus pharmacokinetics is provided in the Investigator's Brochure.

1.4.3.2 Everolimus Pharmacodynamic Studies

Pharmacokinetic/pharmacodynamic modeling based on inhibition of the biomarker p70S6 kinase 1 [S6K1] in peripheral blood mononuclear cells [PBMC]) suggests that 5-10 mg daily should be an adequate dose to produce a high-degree of sustained target inhibition ([Study C2101]/[Study 2102]).[46] Molecular changes in tumor were evaluated through serial biopsy before and during treatment. Biopsy on treatment took place in week 4 (pharmacokinetic steady-state). All patients underwent a 24-hour post-dose biopsy. Patients following the weekly regimen had a further biopsy on Day 4 or 5 of the same week. Molecular activity was measured by immunohistochemistry. In the absence of a reliable technique for measuring mTOR phosphorylation, the phosphorylation status of downstream markers S6 and eIF4G, for which reliable antibodies exist, was selected as reflecting the immediate pharmacodynamic effect of everolimus. Also measured were changes in the phosphorylation status of upstream AKT and the proliferation index Ki67. Fifty-five patients were treated and the results revealed a dose and schedule dependent inhibition of the mTOR pathway with a near complete inhibition of pS6 and peIF-4G at the 10 mg/day and 50 mg/wk schedules. In addition, pAKT was upregulated in 50% of the treated tumors. In the daily schedule, there was a correlation between everolimus plasma trough concentrations and inhibition of peIF4G and p4E-BP1. There was good concordance of mTOR pathway inhibition between skin and tumor. [Study C2107].[47]

More information on everolimus pharmacodynamics is provided in the Investigator's Brochure (IB).

1.4.3.3 Clinical Experience with Everolimus

Everolimus has been in clinical development since 1996 as an immunosuppressant in solid organ transplantation and was approved in Europe in 2003 under the trade name Certican®, for the prevention of organ rejection in patients with renal and cardiac transplantation. It is also approved in the United States (trade name: Zortress®) for the prevention of organ rejection of kidney transplantation. Additional non-oncologic indications currently being explored are wet age-related macular degeneration (AMD) and autosomal dominant polycystic kidney disease (ADPKD). Clinical experience of everolimus in the transplant indication is summarized in a separate Investigator's Brochure.

In oncology, everolimus has been in clinical development since 2002 for patients with various hematologic and non-hematologic malignancies as a single agent or in combination with antitumor agents. Please note that safety pharmacology and toxicology studies as well as some human pharmacology studies which have been conducted in support of the transplant indication, are described in the oncology IB due to the relevance of these data for the oncology indication. Malignancies that are currently being evaluated in Novartis sponsored studies include the following:

metastatic renal cell carcinoma (mRCC), breast cancer, gastroenteropancreatic neuroendocrine tumors (GEP-NET), mantle cell lymphoma and diffuse large B cell lymphoma (DLBCL), hepatocellular cancer (HCC), gastric cancer, and lung cancer. In addition, treatment of patients with Tuberous Sclerosis Complex (TSC) associated subependymal giant cell astrocytoma (SEGA) and Angiomyolypoma is also being evaluated. Colorectal cancer (CRC) is no longer being evaluated.

Everolimus 2.5 mg, 5 mg and 10 mg tablets were approved under the trade name Afinitor® for patients with advanced renal cell carcinoma in the US, EU and several other countries and is undergoing registration in other regions worldwide. Recent approval was granted in the US for the treatment of patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis (TS) who require therapeutic intervention but are not candidates for curative surgical resection.

Phase I dose escalating studies, exploratory Phase I/II studies with everolimus as single agent or in combination with other anti-cancer agents, Phase II/III studies of everolimus in indications, and Phase III double-blind studies are contributing to the extensive database.

Approximately 18,730 cancer patients have been treated with everolimus as of 30-Sep-2011:

- 9,528 patients in Novartis-sponsored clinical trials
- 2,559 patients in the individual patient supply program
- 6,638 in investigator-sponsored studies.
- In addition, healthy volunteer subjects have participated in the clinical pharmacology studies as described in Section 1.4.3.1.

As of 30-Sep-2011, there are a total of 11 Phase III trials ongoing in the indications mRCC (1), advanced NET (2), breast cancer (3), TSC (2), DLBCL (1), gastric cancer (1) and HCC (1).

Recent approvals of everolimus (Afinitor®) were based upon a Phase III, international, multicenter randomized, double-blind, placebo-controlled study [C2240] in patients with metastatic renal cell carcinoma (mRCC) whose disease had progressed despite prior treatment with VEGFR-TKI (vascular endothelial growth factor receptor tyrosine kinase inhibitor) therapy. Progression-free survival (PFS) assessed *via* a blinded, independent central review, was the primary endpoint. Secondary endpoints included safety and objective tumor response.

In the pivotal, Phase III study [C2240], which included patients with advanced renal cell carcinoma, the most common adverse reactions (incidence ≥ 10%) were stomatitis, rash, fatigue, asthenia, diarrhea, anorexia, nausea, mucosal inflammation, vomiting, pneumonitis, cough, peripheral edema, infections, dry skin, epistaxis, pruritus, and dyspnea. The most common grade 3-4 adverse reactions (incidence ≥ 2%) were infections, stomatitis, fatigue, and pneumonitis. Non-infectious pneumonitis is a class effect of rapamycin derivatives, including everolimus and some of these cases have been severe and on rare occasions, fatal outcomes have been observed. 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 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.

The most common laboratory abnormalities (incidence ≥ 50%) were anemia, hypercholesterolemia, hypertriglyceridemia, hyperglycemia, lymphopenia, and increased creatinine. The most common grade 3/4 laboratory abnormalities (incidence ≥ 3%) were lymphopenia, hyperglycemia, anemia, hypophosphatemia, and hypercholesterolemia. Deaths due to acute respiratory failure (0.7%), infection (0.7%), and acute renal failure (0.4%) were observed on the everolimus arm. The rates of treatment-emergent adverse reactions resulting in permanent discontinuation were 7% and 0% for the everolimus and placebo treatment groups, respectively. Safety data from study [C2240] are described in detail in Section 1.4.3.3.

Overall, safety data available from completed, controlled and uncontrolled studies are consistent with the aforementioned findings of the Phase III trial. Everolimus is generally well tolerated at weekly and daily dose schedules. The safety profile is characterized by manageable adverse events (AEs). These AEs are generally reversible and non-cumulative.

Further detailed information regarding everolimus clinical development, safety and efficacy is provided in the Investigator's Brochure.

1.4.3.4 Clinical Experience with Everolimus in Metastatic Breast Cancer Resistant to Non-Steroidal Aromatase Inhibitors

Based on data indicating that resistance to endocrine therapy in breast cancer is associated with activation of the mammalian target of rapamycin (mTOR) intracellular signaling pathway, a Phase 3, randomized trial (BOLERO2) compared the steroidal aromatase inhibitor exemestane (25 mg PO daily) plus either everolimus (10 mg PO daily) or a placebo (randomly assigned in a 2:1 ratio) in 724 patients with HR-positive advanced breast cancer who had recurrence or progression while receiving previous therapy with a nonsteroidal aromatase inhibitor in the adjuvant setting or to treat advanced disease (or both). The primary end point was progression-free survival. Secondary end points included survival, response rate, and safety. A preplanned interim analysis was performed by an independent data and safety monitoring committee after 359 progression-free survival events were observed. Baseline characteristics were well balanced between the two study groups. The median age was 62 years, 56% had visceral involvement, and 84% had hormone-sensitive disease. Previous therapy included letrozole or anastrozole (100%), tamoxifen (48%), fulvestrant (16%), and chemotherapy (68%). 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%). At the interim analysis, median progression-free survival was 6.9 months with everolimus plus exemestane and 2.8 months with placebo plus exemestane, according to assessments by local investigators (hazard ratio for progression or death, 0.43; 95% confidence interval [CI], 0.35 to 0.54; P<0.001). Median progression-free survival was 10.6 months and 4.1 months, respectively, according to central assessment (hazard ratio, 0.36; 95% CI, 0.27 to 0.47; P<0.001). The study met its pre-specified endpoint, which led to FDA approval of everolimus in

combination with exemestane for this indication in the U.S. on July 20, 2012.[48]

Overall survival results were immature at the time of the interim analysis, with a total of 83 deaths: 10.7% of patients in the combination-therapy group and 13.0% of those in the exemestane-alone group died. Patients and investigators continue to be unaware of study assignments and will remain so until survival results are mature for analysis.[49]

1.5 Rationale and Study Design

We hypothesize more complete blockade of the ER-signaling pathway may be achieved with selective estrogen receptor downregulator fulvestrant (given at a high dose) than may be achieved with the steroidal AI exemestane, and that this will result in either comparable or greater effectiveness for the fulvestrant-everolimus combination than the exemestane-everolimus combination. This is supported by preclinical data demonstrating that fulvestrant is particularly effective when combined with agents targeting the PI3K-AKT-m-TOR pathway in tumors that have undergone long-term estrogen deprivation, as is the case for patients who have acquired resistance to AI therapy.[50]

We therefore propose to study the efficacy of fulvestrant in combination with everolimus for the treatment of post-menopausal HR-positive metastatic breast cancer in women who have progressed after treatment with an aromatase inhibitor. The combination of a novel class of agents (mTOR inhibitors) and an established standard treatment for metastatic HR-positive breast cancer may potentially increase the clinical benefit by targeting multiple different biological pathways.

This is a randomized, double-blind, placebo controlled Phase II study. It is expected that 130 patients will be accrued at 25 centers within the US. Patients will be randomized (1:1) to receive everolimus or placebo after consideration of stratification factors of performance status (0 vs.1), measurable disease (with or without non-measurable) vs. non-measurable disease, and prior chemotherapy for metastatic disease vs. no prior chemotherapy.

Induction Phase:

Treatment during the Induction Phase includes:

Fulvestrant 500 mg IM (two-250 mg injections per dose) on day 1 & 15 of Cycle 1, then 500 mg IM (two-250 mg injections) on day 1 of all subsequent cycles (every 28 days) plus everolimus 10 mg (two- 5 mg tablets) PO daily

OR

Fulvestrant 500 mg IM (two-250 mg injections per dose) on day 1 & 15 of Cycle 1, then 500 mg IM (two-250 mg injections) on day 1 of all subsequent cycles (every 28 days) plus placebo two tablets PO daily

Patients will be evaluated for disease response every 12 weeks (every 3 treatment cycles), +/- 1 week, and treated until disease progression, unacceptable toxicity or for a total of up to 12 cycles.

Continuation Phase:

Patients with no evidence of progressive disease who remain on study after completing Cycle 12 will be unblinded and proceed to the Continuation Phase. Patients in the Continuation Phase should continue to receive fulvestrant alone (if originally randomized to placebo) **or** in combination with everolimus (if originally randomized to everolimus) at the same dose and schedule. Patients will continue to be evaluated for disease response every 12 weeks (every 3 treatment cycles), +/- 1 week, and may continue treatment until disease progression or unacceptable toxicity.

All patients will be followed for 30 days for toxicity after the last dose of study therapy (fulvestrant and/or everolimus/placebo) or until recovery from all toxicity (to ≤ grade 1) attributed to study therapy, whichever is longer (or if >grade 1, event must be permanent and stable).

2 Objectives

2.1 Primary Objective

To assess progression-free survival in post-menopausal patients with hormone-receptor positive metastatic breast cancer that is resistant to aromatase inhibitor therapy treated with fulvestrant and everolimus compared to fulvestrant alone.

2.2 Secondary Objectives

To describe the safety profile, objective response rate, time to progression and overall survival in this patient population.

3 Selection of Patients

3.1 Eligibility Criteria

Each of the criteria in the following section must be met in order for a patient to be considered eligible for this study.

PrECOG will not grant any exceptions or waivers to protocol eligibility criteria.

In calculating pre-treatment days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday four weeks later would be considered Day 28.

Note: All questions regarding eligibility should be directed to the PrECOG Study Contact in study materials. Questions will be further discussed with the medical leads for the trial as deemed appropriate (e.g., medical monitor, study chair).

Investigator sites may use the eligibility checklist (see Appendix A: Eligibility Checklist) which will be provided as a separate study document, as documentation that eligibility criteria were verified. If used, it should be reviewed, signed, and dated prior to patient randomization by the treating physician, and all required elements of source documentation must be found in the patient record (e.g. scans, consent, pathology).

Inclusion Criteria:

1. Must be willing to sign a protocol-specific informed consent.
2. Patients must be 18 years of age or older.
3. Patients must have an ECOG Performance Status 0 or 1 (see Appendix B: ECOG Performance Status Scale).
4. Patients must have histologically or cytologically confirmed adenocarcinoma of the breast.
5. Patients must have stage IV disease or inoperable locally advanced disease.
6. Patients must have ER and/or PR-positive disease as determined by their local pathology or reference laboratory by ASCO-CAP criteria.[51] Tumors must be HER-2/neu negative or equivocal by standard ICH/FISH or ICH/CISH methodologies by ASCO-CAP criteria.[52]
7. Patients must be Aromatase Inhibitor (AI) resistant, defined as:
   - relapsed while receiving adjuvant therapy with an aromatase inhibitor (anastrozole, letrozole, or exemestane) or,
   - progressive disease while receiving an aromatase inhibitor for metastatic disease.

   Note: Patients may have received an endocrine agent (e.g., Tamoxifen) between the time of progression on an AI and registration.

8. Patients who have received one prior cycle (dose on day 1 and day 15) of fulvestrant within 28 days of randomization are eligible so long as they meet other eligibility criteria.
    - patients previously treated with two or more prior cycles of fulvestrant are not eligible.
9. Patients must be female and postmenopausal, defined as:
    - a history of at least 12 months without spontaneous menstrual bleeding or,
    - prior bilateral salpingo-oophorectomy, with or without hysterectomy or,
    - age ≥ 55 years with a prior hysterectomy with or without oophorectomy or,
    - age <55 years with a prior hysterectomy without oophorectomy or unknown status, with a documented FSH level in postmenopausal range within 4 weeks of randomization or,
    - receiving a gonadotropin releasing hormone analog (GnRH) to suppress ovarian function (e.g., goserelin 3.6 mg q 4 weeks).
10. Patients may have received up to one prior systemic chemotherapy regimen for metastatic disease.
11. Adequate organ function, as evidenced by ALL the following obtained within 4 weeks of randomization*:
    - total white blood cell count (leukocytes, WBC) ≥ 3.0 x 10^9/L, absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L and platelet count ≥ 100 x 10^9/L
    - hemoglobin ≥ 9 g/dL
    - serum bilirubin ≤ 1.5 x ULN
    - AST or ALT ≤ 2.5 x ULN (≤ 5 x ULN in patients with liver metastases)
    - serum creatinine ≤ 1.5 x ULN
    - serum albumin ≥ 3 g/dL
    - fasting serum cholesterol ≤ 300 mg/dL OR ≤ 7.75 mmol/L **AND** fasting triglycerides ≤ 2.5 x ULN. **Note:** In case one or both of these thresholds are exceeded, the patient can only be included after initiation of appropriate lipid lowering medication.
    - PT with INR ≤ 1.5 (Anticoagulation is allowed if target INR ≤ 1.5 on a stable dose of warfarin or on a stable dose of LMW heparin for >2 weeks at time of randomization.)

    *Please see study table in Section 7.0 for labs that may need to be repeated within ≤ 7 days of Cycle 1 Day 1 (C1D1).
12. Patients may have measurable disease, non-measurable disease (e.g., bone only metastases), or both per RECIST Version 1.1 Criteria. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm by chest x-ray, as ≥ 10 mm with CT scan, or ≥ 10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters). **Note:** Tumor lesions that are situated in a previously irradiated area are not considered measurable.

13. Patients with basal cell or squamous cell carcinoma of the skin or carcinoma *in situ* of the cervix within the past five years must have been treated with curative intent. Patients with a history of prior malignancy are eligible provided they were treated with curative intent and have been free of disease for >3 years.

Exclusion Criteria:

1. Patients who have had any major surgery or significant traumatic injury within 4 weeks of randomization, or have not recovered from the side effects of any major surgery (defined as requiring general anesthesia) or patients that may require major surgery during the course of the study are not eligible. (Placement of vascular access device will not be considered major surgery.)
2. Patients may not be receiving any other investigational agents or have received any investigational agent within 4 weeks of randomization.
3. Patients must not be receiving any concomitant anticancer treatment or have received anticancer treatment within 4 weeks of randomization (including chemotherapy, radiation therapy, antibody based therapy, etc.), with the following exceptions:
    - Bisphosphonates, Zometa or Xgeva for bone metastases
    - Hormonal therapy (e.g., AI, Tamoxifen)
    - a GnRH analog is permitted if the patient had progressive disease on a GnRH analog plus a SERM or an AI; the GnRH analog may continue but the SERM or AI must be discontinued.
4. Patients must not have received prior treatment with an mTOR inhibitor (sirolimus, temsirolimus, everolimus).
5. Patients must not be receiving chronic, systemic treatment with corticosteroids or another immunosuppressive agent greater than or equal to 5 mg prednisone or its equivalent daily. Topical or inhaled corticosteroids are allowed.
6. Patients must not receive immunization with attenuated live vaccines within one week of randomization or during the study period. Close contact with those who have received attenuated live vaccines should be avoided during treatment with everolimus. Examples of live vaccines include intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella and TY21a typhoid vaccines.
7. Patients must not have current or a prior history of brain metastases or leptomeningeal disease. Patients must not have rapidly progressive, life-threatening metastases. This includes patients with extensive hepatic involvement (>50% of the liver involved) and symptomatic lymphangitic metastases.
8. Patients must not have a known hypersensitivity/history of allergic reactions attributed to compounds of similar chemical or biologic composition to everolimus (or other rapamycins such as sirolimus, temsirolimus) or fulvestrant.

9. Since everolimus may cause bone marrow suppression, patients with congenital or acquired immune deficiency at increased risk of infection are not eligible. This includes patients being treated with chronic immunosuppressive agents (including greater than or equal to 5 mg prednisone or its equivalent daily), and patients with known HIV seropositivity.
10. Patients must not have any impairment of gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of everolimus (e.g., ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome or small bowel resection).
11. Patients must not have an active, bleeding diathesis.
12. Patients must not have a history of any condition or uncontrolled intercurrent illness including, but not limited to, ongoing or active infection or psychiatric illness/social situations that in the opinion of the local investigator might interfere with or limit the patient's ability to comply with the protocol or pose additional or unacceptable risk to the patient.
13. Patients must not have any severe and/or uncontrolled medical conditions or other conditions that could affect their participation in the study such as:

    - Symptomatic congestive heart failure of New York Heart Association Class III or IV (see Appendix D)
    - Unstable angina pectoris, myocardial infarction within 6 months of randomization, serious uncontrolled cardiac arrhythmia or any other clinically significant cardiac disease
    - History of symptomatic pulmonary disease or non-malignant pulmonary disease (e.g. COPD) requiring treatment. Such patients would be eligible if PFTs performed within 8 weeks of treatment noted a DLCO greater than 50%.
    - Uncontrolled diabetes as defined by fasting serum glucose >1.5 x ULN (**Note:** Optimal glycemic control should be achieved before starting trial therapy.)
    - Active (acute or chronic) or uncontrolled severe infections
    - Liver disease such as cirrhosis or severe hepatic impairment (Child-Pugh Class C).

    Note: A detailed assessment of Hepatitis B/C medical history and risk factors must be done at screening for all patients. HBV DNA and HCV RNA PCR testing are required at screening for all patients with a positive medical history based on risk factors and/or confirmation of prior HBV/HCV infection. (see Section 7.1.1 for additional details).

4 Randomization Procedures

4.1 Ethics

This study will be conducted in accordance with the ethical principles that have their origin in the current Declaration of Helsinki and will be consistent with applicable US regulatory requirements and International Conference on Harmonization Good Clinical Practice (ICH GCP).

The study will be conducted in compliance with the protocol. The protocol and any amendments and the patient informed consent will receive Institutional Review Board (IRB) approval prior to initiation of the study.

Freely given written informed consent must be obtained from every patient or their legally acceptable representative prior to clinical trial participation, including informed consent for any screening procedures conducted to establish patient eligibility for the trial.

Study personnel involved in conducting this trial will be qualified by education, training, and experience to perform their respective task(s). This trial will not use the services of investigators or study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g., loss of medical licensure, debarment). Investigators are responsible for the conduct of the study at their study site.

4.2 Regulatory Requirements

Before a site may enter patients, protocol-specific regulatory and other documents must be submitted to PrECOG as noted in study materials. Detailed information regarding document submission and control is provided to each site in separate study materials.

Once all required documents are received, reviewed and approved by PrECOG or their representative, a Study Reference Manual (SRM) will be forwarded to the site. Any changes to site regulatory documents must be submitted by the investigator to the responsible party in a timely manner. Initial study drug shipment will not occur until the regulatory packet is complete. No patients will begin protocol therapy without formal randomization as per the process below.

4.3 Patient Randomization

Patients must meet all of the eligibility requirements listed in Section 3 prior to randomization. Treatment must begin ≤ 7 working days from randomization.

An eligibility checklist has been appended *as an example* to the protocol and a usable version is available in separate study materials provided to the site. A confirmation of eligibility assessment by the investigator/site will be performed during the randomization process.

Information regarding stratification factors (performance status, measurable disease and prior chemotherapy) must be available at the time of randomization.

Once it is determined that a patient meets all eligibility requirements, the patient will be randomized to the study by site personnel using an electronic interactive web registration (IWR) system. Full information regarding registration and randomization procedures and guidelines can be found in the SRM provided to your site. All correspondence regarding patient randomization must be kept in the study records.

5 Treatment Plan

5.1 Administration Schedule

Note: 1 cycle = 28 days.

Patients must begin treatment within 7 working days of randomization.

Disease evaluations will occur after every 12 weeks, +/- 1 week (which corresponds to every 3 treatment cycles) and patients will be treated until disease progression, unacceptable toxicity or for a total duration of 12 cycles (Induction Phase). Patients with no evidence of progressive disease who remain on study after completing 12 cycles will be unblinded and proceed to the Continuation Phase. Patients in the Continuation Phase should continue to receive fulvestrant alone (if originally randomized to placebo) **or** in combination with everolimus (if originally randomized to everolimus) at the same dose and schedule. Disease evaluations will continue to occur after every 12 weeks (every 3 treatment cycles), +/- 1 week, and patients may continue treatment until disease progression is documented or unacceptable toxicity.

All patients will be followed for 30 days for toxicity after the last dose of study therapy (fulvestrant and/or everolimus/placebo) or until recovery from all toxicity (to ≤ grade 1) attributed to study therapy, whichever is longer (or if >grade 1, event must be permanent and stable).

See Sections 8.1 and 8.2 for information on study drug procurement, storage, preparation, handling and destruction information.

5.2 Dosing and Administration

5.2.1 Fulvestrant (Arm A and Arm B)

Induction Phase:

Cycle 1 (28 day cycle)

Patients will receive fulvestrant 500 mg IM (two-250 mg injections each dose) on day 1 and 15.

Note: *Cycle 1 is the only time fulvestrant is given on day 15. If patient previously received one cycle of fulvestrant (day 1 and day 15) prior to study entry as permitted in Inclusion Criteria #8, patient should receive fulvestrant 500 mg on day 1 only.*

Cycle 2, and thereafter (28 day cycles)

Patients will receive fulvestrant 500 mg IM (two-250 mg injections) on day 1 of all subsequent cycles for a maximum of 12 cycles.

Continuation Phase:

Patients with no evidence of disease progression after completing 12 cycles are unblinded and continue fulvestrant alone (if originally randomized to placebo) **or** in combination with everolimus (if originally randomized to everolimus) at the same dose and schedule until progression of disease or unacceptable toxicity.

Fulvestrant will be obtained from commercial pharmacy stock.

5.2.2 Everolimus or Placebo (Arm A and Arm B)

- The study drug everolimus/placebo will be self-administered (by the patients themselves). The local investigator will instruct the patient to take the study drug exactly as specified in the protocol. Everolimus/placebo should be administered orally once daily, preferably in the morning, at the same time every day with or without food. Everolimus/placebo tablets should be swallowed whole with a glass of water. The tablets must not be chewed or crushed. In cases where tablets cannot be swallowed, the tablets should be disintegrated in water just prior to being taken. Approximately 30 mL (2 tablespoons) of water should be put into a glass. The tablets should then be added and the contents stirred gently (for a maximum of 7 minutes) until the tablets are disintegrated. The contents should then be drunk. If the patient vomits after taking the study drug, they should not take another tablet that day. If the patient forgets to take the medication and remembers by 10 PM, they may take the dose. Otherwise, skip that dose and begin as usual the next day.
- Everolimus/placebo will be administered orally as once daily dose of 10 mg (two-5 mg tablets) continuously from study day 1 until progression of disease or unacceptable toxicity for 12 cycles. See Section 5.5 regarding duration of therapy (including guidelines for treatment beyond Cycle 12).
- If vomiting occurs, no attempt should be made to replace the vomited dose.
- All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded.
- PrECOG, or their designee, will be responsible for blinding, drug randomization, and management of the electronic interactive web registration (IWR) system. Both tablets will be blinded and identified by kit number only. The IWR system will assign the proper kit to the patient based on the patient randomization. Conditions for study drug will be described on the medication label.
- Both everolimus and placebo will be provided by Novartis. Everolimus is formulated as tablets for oral administration of 5 mg strength. Both placebo and everolimus tablets are blister-packed under aluminum foil in units of 10 tablets per blister card, which should be opened only at the time of administration as drug is both hygroscopic and light-sensitive.
- Dose modifications should be made prior to dose calculation at the beginning of each cycle and reasons recorded in source documents and on appropriate case report forms.

5.3 Dose Modifications and Toxicity Management

5.3.1 Dose Modifications General Guidelines for Everolimus/ Placebo

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE Version 4.0. A copy of the CTCAE Version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

All appropriate treatment areas should have access to a copy of the CTEP CTCAE Version 4.0. (see Appendix E).

Dose modifications for all drugs will be made using the general guidelines below.

- All dose reductions are permanent. Fulvestrant will not be dose reduced.
- Regardless of the reason for holding any study drug treatment, the maximum allowable length of treatment interruption is ≤ 3 weeks. If the delivery of any study drug due to toxicity is delayed for more than 3 weeks, that drug should be permanently discontinued.
- No more than 2 dose reductions for everolimus/placebo will be allowed. Further need for dose reduction will result in discontinuation of that drug.
- If dose is delayed due to toxicity, labs/toxicity should be reevaluated at least weekly until recovery to treatment levels, or as indicated in the dose modification tables.
- Patients who discontinue everolimus/placebo because of suspected everolimus-associated toxicity should continue treatment with fulvestrant alone until disease progression.
- In unusual circumstances where fulvestrant must be discontinued prior to disease progression due to intolerable fulvestrant-associated toxicity, the Medical Monitor should be contacted.

Table 5-0

Everolimus or Placebo Dose Level Modification Guidelines

	Everolimus/Placebo	Fulvestrant
Starting dose	10 mg daily (two- 5 mg tablets)	500 mg
Dose Level -1	5 mg daily	No reduction
Dose Level -2	5 mg every other day	No reduction

Table 5-1

Non-Hematological Criteria for Dose-Modification in Case of Suspected Everolimus or Placebo Related Adverse Events and Re-Initiation of Everolimus or Placebo Treatment

Adverse Event	Action
Non Hematological	
Reactivation of HBV or HCV flare	Please refer to Table 5-4 and Table 5-5.
Non-Infectious Pneumonitis	Please refer to Table 5-6.
AST or ALT elevation Grade 1 (>ULN - 3.0x ULN) Grade 2 (>3.0 - 5.0x ULN)	Maintain current dose level.
AST or ALT elevation Grade 3 (>5.0 - 20.0 ULN)*	Interrupt everolimus administration until resolution to ≤ grade 1 (or ≤ grade 2 if baseline values were within the range of grade 2). If resolution occurs ≤ 7 days, everolimus should be re-started at the dose level prior to interruption. If resolution takes >7 days, or if event recurs within 28 days, hold everolimus until recovery to ≤ grade 1 or baseline grade/ value and reintroduce everolimus at one dose level lower, if available.
AST or ALT elevation Grade 4 (>20x ULN)*	Interrupt everolimus administration until resolution to ≤ grade 1 (or ≤ grade 2 if baseline values were within the range of grade 2). If resolution occurs ≤ 7 days, everolimus should be re-started at one dose level lower. If resolution takes >7 days, discontinue everolimus.
Intolerable Grade 2 mucositis (see Section 5.3.2.5)	Interrupt everolimus administration until resolution to ≤ grade 1 or baseline grade/value. If resolution occurs within ≤ 7 days, everolimus should be re-started at the dose level prior to interruption. If resolution takes >7 days, or if event recurs within 28 days, hold everolimus until recovery to ≤ grade 1 or baseline grade/ value and reintroduce everolimus at one dose level lower, if available. Patients will be withdrawn from the study if they fail to recover to ≤ grade 1 or baseline grade/value within 21 days.
Grade 3 AE, except: hyperglycemia or hypertriglyceridemia or hypercholesterolemia (see Section 5.3.2.7)	Interrupt everolimus administration until resolution to ≤ grade 1 or baseline grade/value. Reintroduce everolimus at one dose level lower, if available. Patients will be withdrawn from the study if they fail to recover to ≤ grade 1 or baseline grade/value within 21 days.

Any other Grade 4	Hold everolimus until recovery to grade ≤ 1 or baseline value. Reintroduce everolimus at one dose level lower, if available.
Grade 3 or 4 clinical liver failure (asterixis or encephalopathy/ coma)	**Discontinue everolimus.**
Recurrence of intolerable Grade 2 mucositis or Grade 3 event after dose reduction	Reduce dose to the next lower dose level, if available. The lowest possible dose level of everolimus is 5 mg every other day. Below this level, everolimus must be discontinued.
Recurrence of Grade 4 after dose reduction	**Discontinue everolimus.**
Any non-hematologic toxicity requiring interruption of everolimus for >21 days	**Discontinue everolimus.**
* Should HCV flare be confirmed, the guidelines for flare must take precedence (Table 5-5).	

Table 5-2

Hematological Criteria for Dose-Modification in Case of Suspected Everolimus or Placebo Related Adverse Events and Re-Initiation of Everolimus or Placebo

Adverse Event	Action
Hematological	
Grade 2 thrombocytopenia (platelets <75, ≥ 50 x 10^9/L)	No action.
Grade 3 thrombocytopenia (platelets <50, ≥ 25 x 10^9/L)	Interrupt everolimus until resolution to grade ≤1 If resolution occurs ≤ 7 days, reintroduce everolimus at the dose level prior to interruption. If resolution occurs >7 days, or event occurs within 28 days, reintroduce everolimus at one dose level lower, if available.
Grade 4 thrombocytopenia (platelets <25 x 10^9/L)	Interrupt everolimus until recovery to grade ≤ 1. Then reintroduce everolimus at one dose level lower, if available.
Grade 3 neutropenia or anemia (neutrophil <1, ≥ 0.5 x 10^9/L)	Interrupt everolimus until resolution to grade ≤1 or baseline value If AE resolution occurs ≤ 7 days, reintroduce everolimus at the same dose level. If AE resolution occurs >7 days, or event occurs within 28 days, reintroduce everolimus at one dose level lower, if available.

Grade 4 neutropenia or anemia	Interrupt everolimus until recovery to grade ≤ 1 or baseline value. Reintroduce everolimus at one dose level lower, if available.*
Febrile neutropenia	Interrupt everolimus until resolution to grade ≤ 1 (or baseline value) and no fever. Reintroduce everolimus at one dose level lower, if available.*
Recurrence of Grade 3 toxicity after dose reduction	Reduce dose to the next lower dose level, if available. The lowest possible dose level of everolimus is 5 mg every other day. Below this level, everolimus must be discontinued.
***Recurrence of Grade 4 toxicity (including febrile neutropenia) after dose reduction**	**Discontinue everolimus.**
***Any hematologic toxicity requiring everolimus interruption for >21 days**	**Discontinue everolimus.**

5.3.2 Common Adverse Events Associated with Everolimus

The data described below reflect exposure to everolimus (n=274) and placebo (n=137) in a randomized Phase III study for the treatment of metastatic renal cell carcinoma. In total, 165 patients were exposed to everolimus 10 mg/day for ≥ 4 months. The median age of patients was 61 years (range 27 to 85). The most common adverse reactions (incidence ≥ 10%) were stomatitis, rash, fatigue, asthenia, diarrhea, anorexia, nausea, mucosal inflammation, vomiting, cough, peripheral edema, infections, dry skin, epistaxis, pruritus, and dyspnea. The most common grade 3-4 adverse reactions (incidence ≥ 2%) were infections, stomatitis, fatigue, and pneumonitis.

The median duration of blinded study treatment was 141 days (range 19 to 451) for patients receiving everolimus and 60 days (range 21 to 295) for those receiving placebo. The rates of treatment-emergent adverse reactions resulting in permanent discontinuation were 7% and 0% for the everolimus and placebo treatment groups, respectively. Most treatment-emergent adverse reactions were grade 1 or 2 in severity. Grade 3 or 4 treatment-emergent adverse reactions were reported in 39% versus 7% of patients receiving everolimus and placebo, respectively. Deaths due to acute respiratory failure (0.7%), infection (0.7%), and acute renal failure (0.4%) were observed on the everolimus arm.

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 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.

Reactivation of Hepatitis B (HBV) has been observed in patients with cancer receiving chemotherapy.[53] Sporadic cases of Hepatitis B reactivation have also been seen in this setting with everolimus. Use of antivirals during anti-cancer therapy has been shown to reduce the risk of Hepatitis B virus reactivation and associated morbidity and mortality.[54] A detailed assessment of Hepatitis B/C medical history and risk factors must be done for all patients at screening, with testing performed prior to the first dose of everolimus.

Hypersensitivity reactions manifested by symptoms including, but not limited to, anaphylaxis, dyspnea, flushing, chest pain or angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) have been observed with everolimus.

Elevations of serum creatinine, usually mild, have been reported in clinical trials. Monitoring of renal function, including measurement of blood urea nitrogen (BUN) or serum creatinine, is recommended prior to the start of everolimus therapy and periodically thereafter.

Decreased hemoglobin, lymphocytes, platelets and neutrophils have been reported in clinical trials. Monitoring of complete blood count is recommended prior to the start of everolimus therapy and periodically thereafter.

The use of live vaccines and close contact with those who have received live vaccines should be avoided during treatment with everolimus.

Hypophosphatemia, hypomagnesaemia, hyponatremia and hypocalcaemia have been reported as serious adverse reactions. Electrolytes should be monitored in patients treated with everolimus.

Table 5-1 and Table 5-2 provide general recommendations for the management of patients, with suspected drug toxicities while on treatment with everolimus as single-agent therapy.

More detailed information regarding everolimus reported suspected toxicities and individual cases are provided in the Investigator's Brochure.

5.3.2.1 Management of Hepatitis Reactivation/Flare

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.[54]

5.3.2.2 Monitoring and Prophylactic Treatment for Hepatitis B Reactivation

Table 5-3 provides details of monitoring and prophylactic therapy according to the baseline results of viral load and serologic markers testing.

Table 5-3
Action to be Taken for Positive Baseline Hepatitis B Results

Test	Result	Result	Result	Result	Result
HBV-DNA	+	+ or -	-	-	-
HBsAg	+ or -	+	-	-	-
HBsAb	+ or -	+ or -	+ and no prior HBV vaccination	+ or -	- or + with prior HBV vaccination
HBcAb	+ or -	+ or -	+ or -	+	-
Recommendation	Prophylaxis treatment should be started 1-2 weeks prior to first dose of study drug Monitor HBV-DNA approximately every 4-8 weeks		No prophylaxis 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 drug.

For hepatitis B reactivation, definition and management guidelines see Table 5-4 Guidelines for Management of Hepatitis B.

Table 5-4

Guidelines for Management of Hepatitis B

HBV Reactivation (with or without clinical signs and symptoms)*	
For patients with baseline results: Positive HBV-DNA **OR** Positive HBsAg ---------- **Reactivation is defined as:** Increase of 1 log in HBV-DNA relative to baseline HBV-DNA value OR new appearance of measurable HBV-DNA	**Treat:** Start a second antiviral AND Interrupt study drug administration until resolution: ≤ baseline HBV-DNA levels **If resolution occurs within ≤ 21 days,** study drug should be re-started at one dose lower, if available. If the patient is already receiving the lowest dose of study drug according to the protocol, the patient should restart at the same dose after resolution. Both antiviral therapies should continue at least 4 weeks after last dose of study drug. **If resolution occurs >21 days,** patients should discontinue study drug but continue both antiviral therapies at least 4 weeks after last dose of study drug.
For patients with baseline results: Negative HBV-DNA and HBsAg **AND** Positive HBsAb (with no prior history of vaccination against HBV), **OR** positive HBcAb ---------- **Reactivation is defined as:** New appearance of measurable HBV-DNA	**Treat:** Start first antiviral medication AND **Interrupt** study drug administration until resolution: ≤ baseline HBV-DNA levels **If resolution occurs within ≤ 21 days,** study drug should be re-started at one dose lower, if available. If the patient is already receiving the lowest dose of study drug according to the protocol, the patient should restart at the same dose after resolution. Antiviral therapy should continue at least 4 weeks after last dose of study drug. **If resolution occurs >21 days,** patients should discontinue study drug but continue antiviral therapy at least 4 weeks after last dose of study drug.

* All reactivations of hepatitis B are to be recorded as grade 3 (CTEP CTCAE Version 4.0 Metabolic Laboratory/Other: Viral Reactivation), unless considered life threatening by the investigator; in which case they should be recorded as grade 4 (CTEP CTCAE Version 4.0 Metabolic Laboratory/Other: Viral Reactivation).

5.3.2.3 Monitoring for Hepatitis C Flare

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 flare and the management guidelines, see Table 5-5 Guidelines for Management of Hepatitis C.

Table 5-5

Guidelines for Management of Hepatitis C

HCV Flare*	
For patients with baseline results: **Detectable HCV-RNA:** HCV Flare is defined as: >2 $\log_{10}$ IU/mL increase in HCV-RNA **AND** ALT elevation >5x ULN or 3x baseline level, whichever is higher	Discontinue study drug.
For patients with baseline results: **Knowledge of past hepatitis C infection with no detectable HCV-RNA:** HCV Flare is defined as: New appearance of detectable HCV-RNA **AND** ALT elevation >5x ULN or 3x baseline level, whichever is higher	Discontinue study drug.

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

5.3.2.4 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, diphenhydramine, oral prednisolone (short course), topical corticosteroids, or pimecrolimus.

5.3.2.5 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.

Suggested prophylactic treatment for prevention of stomatitis/mucositis:

a) Use 15 mL baking soda/salt mouth rinse QID (swish and spit). Mix 1/3 teaspoon baking soda and 1/3 teaspoon of salt in 1 quart of water (refrigeration is not needed); do not eat or drink anything for 10 minutes after rinsing.
b) Use 10 mL prescribed "miracle mouth wash'' QID (swish and spit). For 16-ounce recipe: 320 mL Benadryl solution, 2 g tetracycline powder, 80 mg hydrocortisone, and 40 mL nystatin suspension, quantity sufficient with water. Wait 10-15 minutes after the baking soda/salt rinse before using "miracle mouthwash''.[55]

Stomatitis/oral mucositis/mouth ulcers due to everolimus 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 your examination reveals mouth ulcers rather than a more general inflammation of the mouth, please classify the adverse event as such. Please follow the paradigm below for treatment of stomatitis/oral mucositis/mouth ulcers:

1. For mild toxicity (Grade 1), use conservative measures as noted above, baking soda/salt mouth rinse and "miracle mouth wash".
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:

   In addition to baking soda/salt mouth rinse and "miracle mouth wash" above, topical analgesic mouth treatments (e.g., 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®) or Periogard® oral rinse.
3. Agents containing hydrogen peroxide, iodine, and thyme derivatives may tend to worsen mouth ulcers. It is preferable to avoid these agents. Alcohol–containing rinses and tooth paste with sodium lauryl sulfate should also be avoided. Avoid acidic, spicy, hard, or crunchy foods, and consume foods that are tepid rather than hot.[55]
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, thereby 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.

Note: Stomatitis/oral mucositis should be appropriately graded using the functional grading given on the CTEP CTCAE Version 4.0.

5.3.2.6 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 (for example 4 mg orally followed by 2 mg orally every 2 hours until resolution of diarrhea).

5.3.2.7 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-hydroxy-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 creatine 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 clinical trials. Monitoring of fasting serum glucose is recommended prior to the start of everolimus therapy and periodically thereafter. Optimal glycemic control should be achieved before starting trial therapy.

5.3.2.8 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. Patients should be advised to report promptly any new or worsening respiratory symptoms.

Patients who develop radiological changes suggestive of non-infectious pneumonitis and have few or no symptoms may continue everolimus therapy without dose alteration. If symptoms are moderate (Grade 2), consideration should be given to interruption of therapy until symptoms improve. The use of corticosteroids may be indicated. Everolimus may be reintroduced at a reduced dose until recovery to Grade 1 or better.

For cases where symptoms of non-infectious pneumonitis are severe (Grade 3), everolimus therapy should be discontinued and the use of corticosteroids may be indicated until clinical symptoms resolve. Therapy with everolimus may be re-initiated at a reduced dose depending on the individual clinical circumstances.

For non-infectious pneumonitis definition and management guidelines, see Table 5-6 Management of Non-Infectious Pneumonitis.

Table 5-6

Management of Non-Infectious Pneumonitis

Worst Grade Pneumonitis	Required Investigations	Management of Pneumonitis	Everolimus Dose Adjustment
Grade 1	CT scans with lung windows.	No specific therapy is required	No dose adjustment required. Initiate appropriate monitoring.
Grade 2	CT scan with lung windows. Consider pulmonary function testing includes: spirometry, DLCO, and room air O_2 saturation at rest. Consider a bronchoscopy with biopsy and/or BAL. Monitoring at each visit until return to ≤ grade 1. Return to initial monitoring frequency if no recurrence.	Symptomatic only. Consider corticosteroids and/or other supportive therapy if symptoms are troublesome.	Rule out infection and consider interruption of everolimus until symptoms improve to Grade ≤ 1. Re-initiate everolimus at one dose level lower. Discontinue everolimus if failure to recover within ≤ 21 days.
Grade 3	CT scan with lung windows and pulmonary function testing includes: spirometry, DLCO, and room air O2 saturation at rest. Monitoring at each visit until return to ≤ grade 1. Return to initial monitoring frequency if no recurrence. Bronchoscopy with biopsy and/or BAL is recommended.	Consider corticosteroids if infective origin is ruled out. Taper as medically indicated.	Rule out infection and interrupt everolimus until symptoms improve to Grade ≤ 1. Consider re-initiating evero-limus at one dose level lower. Discontinue everolimus if failure to recover within ≤ 21 days.
Grade 4	CT scan with lung windows and required pulmonary function testing, if possible, includes: spirometry, DLCO, and room air O2 saturation at rest. Monitoring at each visit until return to ≤ grade 1. Return to initial monitoring frequency if no recurrence. Bronchoscopy with biopsy and/or BAL is recommended if possible.	Consider corticosteroids if infective origin is ruled out. Taper as medically indicated.	Rule out infection and discontinue everolimus.

All interruptions or changes to study drug administration must be recorded.

It will be documented whether or not each patient completed the clinical study. If for any patient either study treatment or observations were discontinued the reason will be recorded.

5.3.3 Concomitant Therapies

Patients will be instructed not to take any additional medications (including over-the-counter products) during the course of the study without prior consultation with the local investigator. At each visit, the investigator will ask the patient about any new medications he/she is or has taken after the start of the study drug.

Concomitant medications/significant non-drug therapies taken ≤ 28 days prior to start and after start of study drug, including physical therapy and blood transfusions, should be reviewed.

5.3.4 Prohibited Therapies and Restrictions

The following restrictions apply during the entire duration of the study:

- No other investigational therapy should be given to patients.
- No anticancer agents other than the study medication should be given to patients, with the following exceptions:
    - Bisphosphonates, Zometa, or Xgeva for bone metastases
    - a GnRH analog is permitted if the patient had progressive disease on a GnRH analog plus a SERM or an AI; the GnRH analog may continue but the SERM or AI must be discontinued.
- If any other anticancer agents are required for a patient then the patient must first be withdrawn from the study.
- Concurrent radiation therapy is prohibited, however palliative radiotherapy may be considered on a case by case basis after discussion with the Study Chair.
- Patients must not be receiving chronic, systemic treatment with corticosteroids or another immunosuppressive agent greater than or equal to 5 mg prednisone or its equivalent daily. Topical or inhaled corticosteroids are allowed.
- The use of live vaccines and close contact with those who have received live vaccines should be avoided during treatment with everolimus. Examples of live vaccines include intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella and TY21a typhoid vaccines.
- It is highly recommended that patients with positive HBV-DNA or HBsAg are treated prophylactically with an antiviral for 1-2 weeks prior to receiving study drug (see Table 5-3).
- The antiviral treatment should continue throughout the entire study period and for at least 4 weeks after the last dose of study drug.
- Patients on antiviral prophylaxis treatment or positive HBV antibodies should be tested for HBV-DNA according to study visit schedule.
- Oral contraceptives in preclinical and clinical data have shown everolimus to have CYP3A4 inhibitory activity rather than induction activity, induction of metabolism of contraceptive hormones by everolimus is unlikely. Consequently, administration of everolimus should not reduce the efficacy of oral contraceptives.
- Grapefruit and other citrus juices affect P450 and PgP activity. Concomitant use should be avoided.

5.3.5 Administration of Everolimus and CYP3A4 Inhibitors/ Inducers

5.3.5.1 Inhibitors of CYP3A4 and/or PgP

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.

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 5 mg every other day. Additional dose reductions to every other day may be required to manage toxicities. If the inhibitor is discontinued, the everolimus dose should be returned to the dose used prior to initiation of the moderate CYP3A4/PgP inhibitor after a washout period of 2-3 days.

Grapefruit and other citrus juices affect P450 and PgP activity. Concomitant use should be avoided.

Refer to Appendix C Table 15-0 for list of medications known to induce/inhibit CYP3A4 and Table 15-1 for a list of medications known to inhibit PgP.

5.3.5.2 Inducers of CYP3A4 and/or PgP

Avoid the use of strong CYP3A4 inducers (e.g., phenytoin, carbamazepine, rifampin, rifabutin, phenobarbital, St. John's Wort). If a patient requires co-administration of strong CYP3A4 inducers, an increase in the dose of everolimus up to twice the currently used daily dose should be considered, 5 mg increments. Enzyme induction usually occurs within 7-10 days; therefore everolimus dose should be increased by one increment 7 days after the start of the inducer therapy. If no safety concerns are seen within the next 7 days, the dose can be increased again one additional increment up to a maximum of twice the daily dose used prior to initiation of the strong CYP3A4 inducer. The choice to adjust the dose of everolimus in a patient requiring co-administration of strong CYP3A4 inducers will be done at the discretion of the treating investigator.

This dose adjustment of everolimus is intended 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 the everolimus dose should be returned to the dose used prior to initiation of the strong CYP3A4/PgP inducer. Refer to Appendix C Table 15-0 for list of medications known to induce CYP3A4 and Table 15-1 for a list of medications known to induce PgP.

Oral anticoagulants such as warfarin are CYP2C9 substrates and, as such, no interaction with everolimus is expected. However, drug-drug interaction studies between macrolide antibiotics and warfarin have produced mixed outcomes and the disparity in these findings has led to the conclusion that multiple factors may alter the

clearance of warfarin. The co-administration of everolimus and oral anticoagulants is possible but should be subject to verification of coagulation (INR) once steady state is reached (after one week's treatment).

A comprehensive list of cytochrome P450 isoenzymes and CYP3A4 inhibitors, inducers, and substrates can be found at:

http://medicine.iupui.edu/clinpharm/ddis/table.aspx. This website is continually revised and should be checked frequently for updates.

5.4 Supportive Care

All supportive measures consistent with optimal patient care will be given throughout the study.

The clinical tolerance of the patient, the overall tumor response, and the medical judgment of the investigator will determine if it is in the patient's best interest to continue or discontinue treatment. If treatment is discontinued due to any toxicity, the patient must be followed to monitor duration of toxicity, response and time to progression or survival and initiation of any new systemic therapy.

5.5 Duration of Therapy

CR, PR, or SD patients will continue therapy per their induction arm randomized assignments until evidence of progressive disease, unacceptable toxicity occurs, or for a total of 12 cycles (Induction Phase). Patients with no evidence of progressive disease who remain on study after completing 12 cycles will be unblinded and proceed to the Continuation Phase. Patients in the Continuation Phase should continue to receive fulvestrant alone (if originally randomized to placebo) or in combination with everolimus (if originally randomized to everolimus) at the same dose and schedule until disease progression or unacceptable toxicity.

Protocol therapy will be discontinued for progressive disease at any time. Patients are free to halt therapy at their request. Treatment may be discontinued if intercurrent co-morbidities occur, which, in the opinion of the treating physician, would preclude safe administration of study drugs.

Patients who discontinue everolimus/placebo because of suspected everolimus-associated toxicity should continue treatment with fulvestrant alone until disease progression. In unusual circumstances where fulvestrant must be discontinued prior to disease progression due to intolerable fulvestrant-associated toxicity, the medical monitor should be contacted. All patients who have discontinued protocol therapy will be followed for survival and for progression if protocol therapy was discontinued because of toxicity or for other reasons. All surviving patients who have discontinued induction protocol therapy (fulvestrant and everolimus/placebo) for any reason will be followed for 30 days for study drug related (fulvestrant and/or everolimus/placebo) toxicities to ≤ grade 1 (or if >grade 1, event must be permanent and stable).

5.6 Withdrawal of Patients from Study

Patients MUST be discontinued from study therapy AND be withdrawn from the study for the following reasons:

- Withdrawal of the patient's consent (patient's decision to withdraw for any reason)
- Termination of the study by PrECOG
- Any clinical adverse event, laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Inability to comply with protocol
- Discretion of the investigator
- Disease progression (patient will continued to be followed for survival)

All subjects who discontinue treatment should comply with protocol specified follow-up procedures as outlined in Section 7.1.5.

If a subject is withdrawn before completing the study, the reason for withdrawal must be entered on the appropriate case report form.

6 Measurement of Effect

6.1 Antitumor Effect- Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every 12 weeks, +/- 1 week. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than four weeks before randomization.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (Version 1.1).[56] Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

6.1.1 Definitions

Evaluable for toxicity: All patients will be evaluable for toxicity from the time of their first treatment with fulvestrant and everolimus/placebo. All patients will be followed for 30 days for toxicity after the last dose of study therapy (fulvestrant and/or everolimus/placebo) or until recovery from all toxicity (to ≤ grade 1) attributed to study therapy, whichever is longer (or if >grade 1, event must be permanent and stable).

Evaluable for objective response: Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (**Note:** Patients who exhibit objective disease progression prior to the end of Cycle 1 will also be considered evaluable.)

Evaluable non-target disease response: Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

6.1.2 Disease Parameters

Measurable lesions: are defined as those that can be accurately measured in at least one dimension (longest diameter in the plane of measurement) is to be recorded with a minimum size of:

- ≥ 20 mm by chest x-ray (if clearly defined and surrounded by aerated lung)
- ≥ 10 mm with CT scan (irrespective of scanner type) and MRI (no less than double the slice thickness and a minimum of 10 mm)
- ≥ 10 mm with calipers by clinical exam when superficial

All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

Malignant lymph nodes: to be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis (perpendicular to longest diameter) when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable lesions: all other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses/organomegaly (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lytic bone lesions, with an identifiable soft tissue component, evaluated by CT or MRI, can be considered as measurable lesions if the soft tissue component otherwise meets the definition of measurability noted above. Blastic bone lesions are non-measurable.

6.1.3 Methods for Evaluation of Measurable Disease

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 randomization.

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 unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥ 10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

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.

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

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. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published.[57-59] In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer.[60]

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
- No FDG-PET at baseline and a positive FDG-PET at follow-up:
  - If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.
  - If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan).
  - If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
- FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

6.1.4 Response Criteria

6.1.4.1 Evaluation of Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ and five 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 (those with the longest diameters), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

The sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum of the diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm over the nadir. (**Note:** the appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study. (**Note:** a change of 20% or more that does not increase the sum of the diameters by 5 mm or more is coded as stable disease).

6.1.4.2 Evaluation of Non-Target Lesions

All other lesions or sites of disease including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of unequivocal progression of each should be noted throughout follow-up.

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

When the patient also has measurable disease, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest “increase” in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The

designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient only has non-measurable disease, the increase in overall disease burden should be comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e., an increase in tumor burden from “trace” to “large”, an increase in nodal disease from “localized” to “widespread”, or an increase sufficient to require a change in therapy.

Although a clear progression of “non-target” lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

6.1.4.3 Evaluation of New Lesions

The appearance of new lesions constitutes Progressive Disease (PD).

6.1.4.4 Evaluation of Patient’s 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 progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Table 6-0

Patients with Measurable Disease (e.g., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	Confirmation not required
CR	Non-CR/Non-PD	No	PR	Confirmation not required
CR	Not Evaluated	No	PR	
PR	Non-CR/Non-PD/Not Evaluated	No	PR	
SD	Non-CR/Non-PD/Not Evaluated	No	SD	Confirmation not required
PD	Any	Yes or No	PD	No prior SD, PR or CR
Any	PD**	Yes or No	PD	
Any	Any	Yes	PD	

*See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

**In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration".* Every effort should be made to document the objective progression even after discontinuation of treatment.

Table 6-1

Patients with Non-Measurable Disease (e.g., Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD*
Not all evaluated	No	Not Evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

*'Non-CR/Non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

6.1.5 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for PD the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

6.1.6 Progression-Free Survival

PFS is defined as the duration of time from time of randomization to time of progression or death, whichever occurs first. A subject who has neither progressed nor died will be censored on the date of last tumor assessment.

7 Study Parameters

TREATMENT MUST BEGIN ≤ 7 WORKING DAYS FROM RANDOMIZATION

	Induction Phase (fulvestrant + everolimus or placebo for a maximum of 12 cycles)					**End of Induction Phase <OR> End of Treatment Section 5.6^**	**Continuation Phase[£] (until progression or unacceptable toxicity)**	**Follow-Up Off Therapy[o] (every 3 months for total of 3 yrs from date of randomization)**
Procedure	**Pre-Study**	**Cycle 1 Day 1***	**Cycle 1 Day 15**	**Day 1 Each Subsequent Cycle***	**Every 12 weeks**			
Eligibility Assessment	X[a]							
Informed Consent	X							
Medical History & Assessment of Baseline Signs and Symptoms	X[a]							
Physical Exam	X[a]	X[b]	X	X[c]		X		
Concomitant Meds (see Appendix C)	X[a]	X[b]	X	X[c]		X		
Vital Signs (Blood Pressure, Heart Rate, Temperature) and Weight	X[a] (includes Ht)	X[b]	X	X[c]		X		
ECOG Performance Status	X[a]	X[b]	X	X[c]		X		
Adverse Events Assessments		X[b]	X	X[c]		X[j]	X[j]	X[j]
Imaging Scans	X[a,i]				X[i]	X[i]	X[i]	X[i,m,o]
PT with INR	X[a]							
Urinalysis	X[a]							
CBC with differentials, Platelets	X[a]	X[b]	X[d]	X[c,d]		X[d]	X[k]	
Serum Creatinine, Electrolytes (K, Na, Cl, CO2), Ca, BUN, Albumin, Total Protein, Phosphorus, AST (SGOT), ALT (SGPT), Alkaline Phosphatase, Total Bilirubin, Magnesium, Uric Acid.	X[a]	X[b]	X	X[c]		X	X[k]	
Fasting Glucose	X[a]	X[b]		X[e]	X[e]	X[e]	X[k]	
Fasting serum Lipid Profile (triglycerides, total cholesterol, HDL and LDL)	X[a]	X[b]		X[e]	X[e]	X[e]	X[k]	

Procedure	Induction Phase (fulvestrant + everolimus or placebo for a maximum of 12 cycles)					End of Induction Phase <OR> End of Treatment Section 5.6^	Continuation Phase£ (until progression or unacceptable toxicity)	Follow-Up Off Therapy° (every 3 months for total of 3 yrs from date of randomization)
	Pre-Study	Cycle 1 Day 1*	Cycle 1 Day 15	Day 1 Each Subsequent Cycle*	Every 12 weeks			
HBV-DNA, HbsAg, HBsAb, HBcAb, HCV-RNA-PCR	X[a,f]							
HBV DNA		X[f,g]		X[f,g]			X[k]	
HCV RNA-PCR		X[f,h]		X[f,h]			X[k]	
Study Drug Compliance (Pill Diary)			X	X		X	X[l]	
PFTs with DLCO as medically indicated[n]								

a: ≤ 4 weeks of randomization; if assessments required ≤ 7 days of Cycle 1 Day 1 (C1D1), they do not need to be repeated (includes labs).

b: ≤ 7 days prior to the start of C1D1.

c: +/- 72 hour window allowed prior to D1 of each subsequent cycle after the first cycle for scheduled therapy/tests/visits. Delay due to holidays, weekends, bad weather or other unforeseen circumstances will be permitted.

d: In the event of grade 3 or 4 hematologic toxicity, CBC with differential and platelet count will be obtained every 1-3 days until there is evidence of hematologic recovery.

e: +/- 72 hours prior to Cycle 2 Day 1 then approximately every 12 weeks during treatment (and more frequently as clinically indicated), and at end of treatment.

f: All patients should be screened for hepatitis risk factors and any past illnesses of hepatitis B and hepatitis C infection (see Section 7.1.1). All patients with a positive medical history per Section 7.1.1 need hepatitis testing as noted on above table. It is highly recommended that patients positive for HBV-DNA or HBsAg are treated prophylactically with an antiviral (e.g., Lamivudine) for 1-2 weeks prior to receiving study drug (see Table 5-3). The antiviral treatment should continue throughout the entire study period and for at least 4 weeks after the last dose of everolimus.

g: Patients on antiviral prophylaxis treatment or positive HBV antibodies should be tested for HBV-DNA ≤ 7 days prior to the start of C1D1 and +/- 72 hrs prior to D1 of each subsequent cycle to monitor for reactivation. See Table 5-4 for reactivation instructions.

h: Patients with positive HCV RNA-PCR results at screening and/or a history of past infection (even if treated and considered 'cured') should have HCV RNA-PCR testing performed on ≤ 7 days prior to the start of C1D1 and +/- 72 hrs prior to D1 of each subsequent cycle to monitor for flare. Everolimus must be discontinued if HCV flare is confirmed according to the guidance in Table 5-5.

i: Tumor measurements may be made using physical examination, CT Scans or MRI. Tumor assessments will be performed every 12 weeks, +/- 1 week (every 3 months). Imaging will include chest and abdomen. Bone Scans and Brain CT/MRI may be performed as clinically indicated. Scans do not have to be repeated once disease progression is documented.

j: Adverse events related to fulvestrant and/or everolimus/placebo will be followed for 30 days after the last dose of study therapy (fulvestrant and/or everolimus/placebo) or until ≤ grade 1 or if the grade is >1, the event must be permanent and stable. Please note- Serious adverse events >30 days after last dose of fulvestrant and/or everolimus/placebo are not reported unless the event may be related to everolimus/placebo.

k: CBC and chemistry may be used to assess ongoing toxicity but are not required in the Continuation Phase for patients who receive fulvestrant alone. Patients who continue fulvestrant with everolimus should periodically have CBC, chemistries, fasting glucose, fasting lipids, HBV DNA, HCV RNA-PCR per labeling guidelines.

l: Study Drug Compliance (Pill Diary) for those patients who receive everolimus in the Continuation Phase.

m: All patients including those that discontinue protocol therapy will be followed for 3 years from the time of randomization. Patients that have not progressed during the Induction or Continuation Phase will continue to have imaging scans completed every 12 weeks, +/- 1 week (every 3 months) until documented progression.

n: PFTs with DLCO as medically indicated only, (PFTs are not otherwise required during course of study).

o: Follow every 3 months for disease progression and survival. Initiation of any new systemic therapy will also be documented.

***** Cycle 1, Day 1 is defined as the first day on which fulvestrant is given in combination with placebo/everolimus (the second fulvestrant dose is given on day 15 of the first cycle only). Day 1 of each additional cycle is defined as the day in which fulvestrant is given in combination with everolimus/placebo.

^ End of Induction/End of Treatment should be performed within 30 days of last dose of fulvestrant.

£ Continuation Phase: Patients in the Continuation Phase should continue to receive fulvestrant alone (if originally randomized to placebo) or in combination with everolimus (if originally randomized to everolimus) at the same dose and schedule (+/- 1 week window for scheduled therapy/tests/visits; delays due to holidays, weekends, bad weather or other unforeseen circumstances will be permitted) until disease progression or unacceptable toxicity.

7.1 Procedures by Visit

Written informed consent must be obtained prior to any study required procedures that would not have been performed as part of normal patient care at the site.

7.1.1 Pre-Study

Prior to randomization, patients will complete the informed consent process and have all required protocol assessments completed in order to assess eligibility requirements. All procedures and an assessment of eligibility should be documented in the patient record.

Within ≤ 4 weeks of randomization to protocol therapy:

- Medical history
- Assessment of baseline signs and symptoms
- Physical examination
- Concomitant medication assessment (see Appendix C for list of excluded or medications requiring monitoring on study)
- Vital signs, including blood pressure, heart rate and temperature, height and weight
- Assessment of ECOG performance status
- Imaging scans for complete disease assessment. Care should be taken to continue to use the same evaluation method during the study as used for initial evaluation. See Section 6 for additional details.
- PT with INR
- Urinalysis
- CBC with differential and platelets
- Serum Creatinine, Electrolytes (K, Na, Cl, CO2), Ca, BUN, Albumin, Total Protein, Phosphorus, AST (SGOT), ALT (SGPT), Alkaline Phosphatase, Total Bilirubin, Magnesium and Uric Acid
- Fasting Glucose
- Fasting Serum Lipid Profile (triglycerides, total cholesterol, HDL and LDL)

A detailed assessment of hepatitis B/C medical history and risk factors must be done for all patients. Patients with positive hepatitis B and/or hepatitis C test results must begin a course of antivirals within 1-2 weeks prior to the first dose of everolimus (as outlined in Section 5.3.2.2 and 5.3.2.3).

Testing for hepatitis B viral load and serologic markers: HBV-DNA, HBsAg, HBsAb, HBcAb and HCV RNA-PCR are required at screening for all patients in the following risk categories:

- All patients who have lived in Asia, Africa, Central and South America, Eastern Europe, Spain, Portugal, and Greece.
  [http://wwwnc.cdc.gov/travel/yellowbook/2012/chapter-3-infectious-diseases-related-to-travel/hepatitis-b.htm]

- 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.
- Additional patients at the discretion of the investigator

Testing for hepatitis C should be performed using quantitative RNA-PCR at screening for all patients in the following risk categories:

- known or suspected past hepatitis C infection (including patients with past interferon 'curative' treatment)
- blood transfusions prior to 1990
- current or prior IV drug users
- current or prior dialysis
- household contact of hepatitis C infected patient(s)
- current or prior high-risk sexual activity
- body piercing or tattoos
- At the discretion of the investigator, additional patients may also be tested for hepatitis C.

Final determination of eligibility and randomization to therapy should be done only after all assessments are completed.

7.1.2 Induction Phase (fulvestrant + everolimus/placebo)

Day 1 of each cycle is defined as the day in which fulvestrant is given, including the first fulvestrant dose, third fulvestrant dose, and every dose thereafter (the second fulvestrant doses is given on day 15 of the first cycle only). **Note:** If patient previously received one cycle of fulvestrant (day 1 and day 15) prior to study entry as permitted in Inclusion Criteria #8, patient should receive fulvestrant 500 mg on day 1 only.

Patients will be assessed continually for toxicity and study continuation. Protocol therapy doses should be calculated and modified as per Section 5. Assessment of disease for response should be performed as per Section 6.

One cycle in the Induction Phase is equal to 28 days. Patients are treated for a maximum of 12 cycles in the Induction Phase.

7.1.2.1 Within 7 Days of Cycle 1 Day 1

Note: The following assessments do not have to be repeated if the pre-study assessments were performed within ≤ 7 days of Cycle 1 Day 1.

- Physical examination
- Concomitant medication assessment (see Appendix C for list of excluded or medications requiring monitoring on study)
- Vital signs, including blood pressure, heart rate, temperature and weight
- Assessment of ECOG performance status
- Adverse event assessment and dose modifications as necessary (AEs should be monitored continuously). AE assessment should begin after the first dose of study medication has been administered.
- CBC with differential and platelets
- Serum Creatinine, Electrolytes (K, Na, Cl, CO2), Ca, BUN, Albumin, Total Protein, Phosphorus, AST (SGOT), ALT (SGPT), Alkaline Phosphatase, Total Bilirubin, Magnesium and Uric Acid
- Fasting Glucose
- Fasting Serum Lipid Profile (triglycerides, total cholesterol, HDL and LDL)
- Patients on antiviral prophylaxis treatment or positive HBV antibodies should be tested for HBV-DNA on Cycle 1 Day 1 and Day 1 of all subsequent cycles (every 28 days) to monitor for re-activation. If re-activation is confirmed, everolimus must be interrupted or discontinued according to the guidance in Table 5-4. Patients with positive HCV RNA-PCR results at screening and/or a history of past infection (even if treated and considered 'cured') should have HCV RNA-PCR testing performed on Cycle 1 Day 1 and Day 1 of all subsequent cycles (every 28 days) to monitor for flare. Everolimus must be discontinued if HCV reactivation is confirmed according to the guidance in Table 5-5.

7.1.2.2 Cycle 1 Day 15

- Physical examination
- Concomitant medication assessment (see Appendix C for list of excluded or medications requiring monitoring on study)
- Vital signs, including blood pressure, heart rate, temperature, and weight
- Assessment of ECOG performance status
- Adverse event assessment and dose modifications as necessary (AEs should be monitored continuously). (see Section 5.3 for dose modification guidelines)
- CBC with differential and platelets. In the event of grade 3 or 4 hematologic toxicity, CBC with differentia and platelet count will be obtained every 1-3 days until there is evidence of hematologic recovery.
- Serum Creatinine, Electrolytes (K, Na, Cl, CO2), Ca, BUN, Albumin, Total Protein, Phosphorus, AST (SGOT), ALT (SGPT), Alkaline Phosphatase, Total Bilirubin, Magnesium and Uric Acid
- Study Drug Compliance (Pill Diary) for everolimus/placebo

7.1.2.3 Cycle 2 (and each subsequent cycle) Day 1

- Physical examination
- Concomitant medication assessment (see Appendix C for list of excluded or medications requiring monitoring on study)
- Vital signs, including blood pressure, heart rate, temperature and weight
- Assessment of ECOG performance status
- Adverse event assessment and dose modifications as necessary (AEs should be monitored continuously, see Section 5.3 for dose modification guidelines).
- CBC with differential and platelets. In the event of grade 3 or 4 hematologic toxicity, CBC with differential and platelet count will be obtained every 1-3 days until there is evidence of hematologic recovery.
- Serum Creatinine, Electrolytes (K, Na, Cl, CO2), Ca, BUN, Albumin, Total Protein, Phosphorus, AST (SGOT), ALT (SGPT), Alkaline Phosphatase, Total Bilirubin, Magnesium and Uric Acid
- Fasting Glucose (Cycle 2 Day 1, then every 12 weeks during treatment, and more frequently as clinically indicated)
- Fasting Serum Lipid Profile (triglycerides, total cholesterol, HDL and LDL) (Cycle 2 Day 1, then every 12 weeks during treatment, and more frequently as clinically indicated)
- Patients on antiviral prophylaxis treatment or positive HBV antibodies should be tested for HBV-DNA on Cycle 1 Day 1 and Day 1 of all subsequent cycles (every 28 days) to monitor for re-activation. If re-activation is confirmed, everolimus must be interrupted or discontinued according to the guidance in Table 5-4. Patients with positive HCV RNA-PCR results at screening and/or a history of past infection (even if treated and considered 'cured') should have HCV RNA-PCR testing performed on Cycle 1 Day 1 and Day 1 of all subsequent cycles (every 28 days) to monitor for flare. Everolimus must be discontinued if HCV reactivation is confirmed according to the guidance in Table 5-5.
- Study Drug Compliance (Pill Diary) for everolimus/placebo

7.1.2.4 Every 12 Weeks

- Tumor evaluation every 12 weeks, +/- 1 week (every 3 months) during the Induction Phase. Scans should be repeated at the assigned intervals regardless of cycle or treatment delays.
- Fasting Glucose and Fasting Serum Lipid Profile (triglycerides, total cholesterol, HDL and LDL) to be done every 12 weeks during Induction Phase (and more frequently as clinically indicated)

7.1.3 End of Induction Phase <OR> End of Treatment

All patients will have the following assessments completed whether they are moving into the Continuation Phase or no longer will be receiving treatment and are moving into Follow-Up Off-Therapy due to reasons noted in Sections 5.5 or 5.6. The assessments should be completed within 30 days of last dose of fulvestrant and before moving from the Induction Phase into the Continuation Phase or before moving directly into the Follow-Up Phase. (**Note:** Day 1 of the Continuation Phase should start on D29 of cycle 12 if the assessments below are completed in order to maintain the 28 day fulvestrant dosing schedule).

- Physical examination
- Concomitant medication assessment (see Appendix C for list of excluded or medications requiring monitoring on study)
- Vital signs, including blood pressure, heart rate, temperature and weight
- Assessment of ECOG performance status
- Adverse event assessment. All patients will be followed for toxicity assessment for 30 days after the last dose of study therapy (fulvestrant and/or everolimus/placebo) or until resolution to ≤ grade 1 attributed to study therapy (or if >grade 1, event must be permanent and stable). Serious adverse events >30 days after last dose of fulvestrant and/or everolimus/placebo are not reported unless the event may be related to everolimus/placebo.
- Tumor evaluation if due per every 12 weeks +/- 1 week (every 3 months) evaluation schedule.
- CBC with differential and platelets
- Serum Creatinine, Electrolytes (K, Na, Cl, CO2), Ca, BUN, Albumin, Total Protein, Phosphorus, AST (SGOT), ALT (SGPT), Alkaline Phosphatase, Total Bilirubin, Magnesium and Uric Acid
- Fasting Glucose
- Fasting Serum Lipid Profile (triglycerides, total cholesterol, HDL and LDL)
- Study Drug Compliance (Pill Diary) for everolimus/placebo

Patients in the Continuation Phase should continue to receive fulvestrant alone (if originally randomized to placebo) or in combination with everolimus (if originally randomized to everolimus) at the same dose and schedule until disease progression or unacceptable toxicity.

Patients that are moving from the Induction Phase into Follow-Up Off Therapy should not receive further investigational therapies for at least 30 days after the last dose of study drug, if possible, in order to eliminate overlapping toxicity.

7.1.4 Continuation Phase (fulvestrant +/- everolimus)

Patients with no evidence of disease progression after 12 cycles of treatment (Induction Phase) will be unblinded and proceed to the Continuation Phase. Patients in the Continuation Phase should continue to receive fulvestrant alone (if originally randomized to placebo) **or** in combination with everolimus (if originally randomized to everolimus) at the same dose and schedule until disease progression is documented or unacceptable toxicity. Once progression is documented, patients will move into Follow-Up Off Therapy.

One cycle in the Continuation Phase is equal to 28 days. Day 1 of the Continuation Phase should start 28 days (D29) after the last dose of fulvestrant was given during Cycle 12 in the Induction Phase.

All adverse events that are related to fulvestrant and/or everolimus will be followed for 30 days after the last dose of study therapy (fulvestrant and/or everolimus) until ≤ grade 1 or if the grade is >1, the event must be permanent and stable.

- CBC and chemistry may be used to monitor any ongoing toxicities, but are not required for patients that receive fulvestrant alone.
- Patients who continue fulvestrant in combination with everolimus should periodically have CBC, chemistries, fasting glucose, fasting serum lipids, HBV DNA, and HCV RNA-PCR per labeling guidelines.
- Study Drug Compliance (Pill Diary) for those patients who receive everolimus in the Continuation Phase.

After the Continuation Phase, serious adverse events >30 days after last dose of fulvestrant and/or everolimus are not reported unless the event may be related to everolimus.

7.1.4.1 Every 12 Weeks

- Tumor evaluation every 12 weeks, +/- 1 week (every 3 months) during the Continuation Phase until disease progression is documented.

7.1.5 Follow-Up Off-Therapy

All patients, including those who discontinue protocol therapy, will be followed for 3 years from the time of randomization. Patients that did not progress during the Induction or Continuation Phase will continue to have imaging scans completed every 3 months until documented progression. Patients will then be followed for survival. Initiation of any new systemic therapy will also be documented. Patients that have adverse events related to fulvestrant and/or everolimus/placebo will be followed for 30 days after the last dose of study therapy (fulvestrant and/or everolimus/placebo) until ≤ grade 1 or if the grade is >1, the event must be permanent and stable. Serious adverse events >30 days after last dose of fulvestrant and/or everolimus/placebo are not reported unless the event may be related to everolimus/placebo.

8 Drug Formulation and Procurement

8.1 Everolimus

8.1.1 Packaging and Labeling

Full instructions for investigator sites and investigational pharmacies will be available in separate protocol-specific documents. The supply of everolimus or placebo will be shipped directly to the local investigator. Drug ordering procedures will be provided in supplemental study materials.

8.1.1.1 How Supplied

Everolimus and an identically appearing placebo will be provided by Novartis. Everolimus is formulated as tablets for oral administration of 5 mg strength. Tablets are blister-packed under aluminum foil in units of 10 tablets per blister card, which should be opened only at the time of administration as drug is both hygroscopic and light-sensitive. Each tablet contains as inactive ingredients: butylhyroxytoluene/butylated hydroxytoluene (BHT), magnesium stearate, lactose monohydrate, hypromellose, crospovidone and lactose anhydrous.

Medication labels will comply with US legal requirements and be printed in English. They will supply no information about the patient. The storage conditions for study drug will be described on the medication label.

8.1.2 Storage Requirements/Stability

Everolimus should be stored at room temperature between 20°C to 25°C (68°F to 77°F).

All investigational products must be kept in a secure place under appropriate storage conditions. A description of the appropriate storage and shipment conditions is specified on the investigational product label and investigator brochure. The stored study drug supplies must be accessible to authorized staff only. The storage area must also have adequate control of temperature in order to maintain stability and potency of study drug supplies. The tablets should be stored in the original pack until use. For further information, investigators should refer to the current Investigators Brochure (IB).

8.1.3 Handling, Dispensing and Administration

8.1.3.1 Handling

No special precautions are necessary when handling intact tablets. Avoid contact with skin and eyes. Wash hands after use. The risk to health in normal handling of tablets is very low. Exposure to dust from crushed tablets may cause adverse health effects.

8.1.3.2 Dispensing

Drug should be dispensed in original packaging. If other packaging is required by institutional policy, this procedure will need to be approved by PrECOG, or their designee, prior to proceeding. The PrECOG Site Contact should be contacted for further

instruction. Investigational product records should be kept as per Section 8.1.5 and institutional policies.

8.1.3.3 Administration

Patients should be instructed to take their assigned, once-a-day oral dose of everolimus/placebo at the same time each morning.

- Everolimus/placebo dose may be taken with or without food.
- Patients should be instructed to swallow the capsules whole and not chew them.
- Vomited doses should not be replaced.
- If the patient forgets to take the medication and remembers by 10 PM, they may take the dose. Otherwise, skip that dose and begin as usual the next day.

In cases where tablets cannot be swallowed, the tablets should be disintegrated in water just prior to being taken. Approximately 30 mL (2 tablespoons) of water should be put into a glass. The tablets should then be added and the contents stirred gently (for a maximum of 7 minutes) until the tablets are disintegrated. The contents should then be drunk.

Patients should be given instructions on correct dosing based on study requirements and toxicity management (dose modifications). All changes to recommended dosing regimen/schedule should be documented in the patient record. Documentation of patient instructions for dosing changes should also be in source records.

Patients should be instructed to record the reason for any missed doses and report to the investigator at the next visit. If a dose is vomited, that dose should not be replaced, (and recorded as a vomited dose).

Compliance with therapy will be assessed at the beginning of each cycle. Patients will be given a diary (see Appendix F for an Example Patient Pill Diary) for recording of doses of study drug as provided by each study site. A copy of the patient diary will be provided to sites in study materials.

8.1.3.4 Special Instructions for Unblinding

Patients on study therapy and all site study staff will remain blinded as to the assignment of everolimus or placebo. Patients who have not had progressive disease and remain on study after 12 cycles are unblinded and continue fulvestrant alone (if originally randomized to placebo) **or** in combination with everolimus (if originally randomized to everolimus) at the same dose and schedule in the Continuation Phase. If an emergency situation arises and the patient must be unblinded during the Induction Phase (Cycles 1-12), the Medical Monitor for the study must be consulted.

<u>Emergency Unblinding for Patients during the Induction Phase (within Cycles 1-12):</u>

Unblinding is a serious action that should be restricted in order to limit potential study bias. The breaking of the blinding code in all cases will render the patient off-protocol.

The Medical Monitor for the study must be involved in the decision to unblind and must grant approval for unblinding any individual. Requests for unblinding will only be considered in the event of an emergency or severe adverse reaction where identification

of the medication is considered important for the welfare of the patient, and the rationale for unblinding is applicable to the situation. All patients should be provided emergency medical care by the treating physician and appropriate therapies for the medical emergency should be initiated prior to the request for unblinding.

For example, a Serious Adverse Event (SAE) possibly, probably or definitely related to the study drug occurs during the trial and the treatment of the SAE would be influenced by whether he/she received everolimus or placebo. Unblinding is typically not necessary if the medical management of the patient would not be materially altered by knowledge of the treatment assignment. In the event that *accidental* unblinding occurs, the Principal Investigator should report the occurrence promptly to the Medical Monitor and document the incident in the patient records. All unblinding will be recorded as a protocol deviation.

If a participant is in a life-threatening situation in which knowledge of the treatment is crucial to care AND the Medical Monitor cannot be reached immediately, the PM should be contacted to facilitate the unblinding process. A report including the unblinding details will be generated after the patient has been unblinded and will be sent to the site for documentation (refer to Study Reference Manual for Unblinding Process). Report information will include but is not limited to:

- ID number of the participant whose treatment assignment was unblinded
- Date of unblinding and reconciliation of study drug in site and patient records
- Reason for unblinding, including initial SAE report
- Person responsible for unblinding
- List of persons who are unblinded (e.g. study staff)

8.1.4 Side Effects

The most common adverse reactions (incidence ≥ 10%) reported for everolimus include stomatitis, rash, fatigue, asthenia, diarrhea, anorexia, nausea, mucosal inflammation, vomiting, cough, peripheral edema, infections, dry skin, epistaxis, pruritus, and dyspnea. The most commonly reported grade 3-4 adverse reactions (incidence ≥ 2%) reported for everolimus include infections, stomatitis, fatigue, and pneumonitis.

8.1.5 Investigational Product Records at Investigational Site(s)

Investigational product dispensing record/inventory logs and copies of signed packing lists must be maintained at the investigational site for everolimus. It is the responsibility of the Investigator to ensure that a current record of investigational product disposition is maintained at each study site where investigational product is stored and/or dispensed. Records must comply with applicable regulations and guidelines, and should include:

- Amount received and placed in storage area.
- Amount currently in storage area.
- Label ID number or batch number.
- Dates and initials of person responsible for each investigational product inventory entry/movement.

- Amount dispensed to and returned by each patient, including unique patient identifiers.
- Amount transferred to another area for dispensing or storage.
- Non-study disposition (e.g., wasted, broken).
- Amount returned to manufacturer, if applicable
- Amount destroyed at study site, if applicable

8.1.6 Return and Destruction of Investigational Product

Investigational product should be maintained at the site for accountability purposes. Sites will be referred to the study pharmacy manual for instructions regarding the return or destruction of everolimus study drug supply (site's drug destruction policy must be reviewed and approved by PrECOG before any study drug can be destroyed at a site).

Patients will be instructed to return all blister packs (empty or partially used) to the study center.

8.2 Fulvestrant (Faslodex®)

8.2.1 Packaging and Labeling

Fulvestrant is commercially available and approved and is indicated for the treatment of HR-positive metastatic breast cancer in postmenopausal women whose disease has returned or progressed following antiestrogen therapy.

Investigators should review the approved Package Insert (PI) (http://www.faslodex.com/faslodex-prescribing-info/index.aspx) for full information on storage, handling, preparation and stability.

Fulvestrant is supplied as:

One clear neutral glass (Type 1) barrel containing 250 mg/5 mL (50 mg/mL) Injection for intramuscular injection and fitted with a tamper-evident closure. NDC 0310-0720-50. (**Note:** Patients will be receiving 500 mg doses IM therefore 2 injections of 250 mg will be required for one dose.)

The syringes are presented in a tray with polystyrene plunger rod and safety needles (SafetyGlide™) for connection to the barrel.

Each injection contains as inactive ingredients: Alcohol, USP, Benzyl Alcohol, NF, and Benzyl Benzoate, USP as co-solvents, and Castor Oil, USP as a co-solvent and release rate modifier.

8.2.2 Handling and Dispensing

8.2.2.1 Storage Requirements/Stability

Refrigerate 2°-8°C (36°-46°F). To protect from light, store in the original carton until time of use.

8.2.2.2 Preparation and Administration

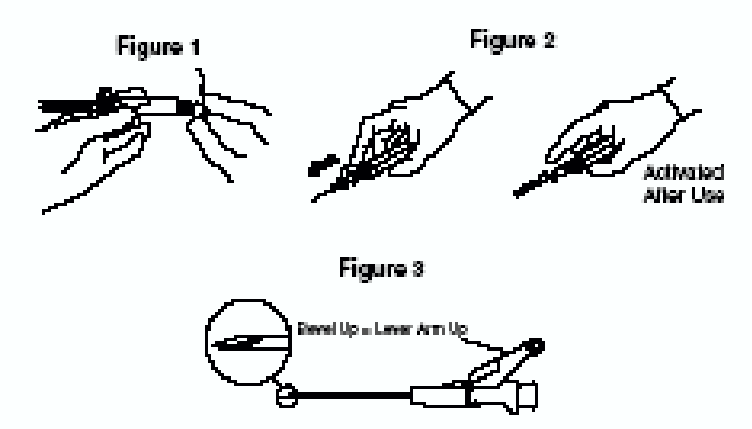
Fulvestrant should be disposed of or destroyed as per written institutional policies and per recommendations in the current approved Package Insert. To help avoid infectious diseases due to accidental needle sticks, contaminated needles should not be recapped or removed, unless there is no alternative or that such action is required by a specific medical procedure.

WARNING: - Do not autoclave safety needle before use. Hands must remain behind the needle at all times during use and disposal.

Directions:

(Source: Faslodex® Package Insert 1621903 Rev 12/11)

- Remove the glass syringe barrel from tray and check that it is not damaged
- Remove perforated patient record label from syringe
- Peel open the safety needle outer packaging.
- Break the seal of the white plastic cover on the syringe luer connector to remove the cover with the attached rubber tip cap (Figure 1).
- Twist to lock the needle to the luer container.
- Remove the needle sheath. Pull shield straight off needle to avoid damaging needle point.
- Remove excess gas from the syringe.
- Administer intramuscularly slowly in the buttock. Administer injection following package instruction. For user convenience, the needle 'bevel up' position is orientated to the lever arm (Figure 3).
- Immediately activate needle protection device upon withdrawal from patient by pushing lever arm completely forward until the tip is fully covered (Figure 2).
- Visually confirm that the lever arm has fully advanced and the needle tip is covered. If unable to activate, discard immediately into an approved sharps collector. Activation of the protective mechanism may cause minimal splatter of fluid that may remain on the needle after injection. *For greatest safety, use a one-handed technique and activate away from self and others.*
- If the 250 mg/5 mL formulation is used, repeat the above steps for the second syringe. After single use, discard in an approved sharps collector in accordance with applicable regulations and institutional policy.
- Review the official package insert for more information regarding the use of the SafetyGlide Needle.



8.2.3 Side Effects

The most commonly reported adverse experiences in the Faslodex® treatment groups, regardless of the investigator's assessment of causality, were gastrointestinal symptoms (including nausea, vomiting, constipation, diarrhea and abdominal pain), headache, back pain, vasodilatation (hot flushes), and pharyngitis.

Injection site reactions with mild transient pain and inflammation were seen with Faslodex® and occurred in 7% of patients (1% of treatments) given the single 5 mL injection (predominately European Trial) and in 27% of patients (4.6% of treatments) given the 2 x 2.5 mL injections (North American Trial).

Other adverse events reported as drug-related and seen infrequently (<1%) include thromboembolic phenomena, myalgia, vertigo, leukopenia and hypersensitivity reactions including angioedema and urticaria. Vaginal bleeding has been reported infrequently (<1%), mainly in patients during the first 6 weeks after changing from existing hormonal therapy to treatment with Faslodex® If bleeding persists, further evaluation should be considered.

9 Statistical Considerations

The efficacy endpoints will be assessed among all eligible patients who receive protocol therapy. Safety endpoints will be assessed among all treated patients, regardless of eligibility.

9.1 Primary Efficacy Endpoint

The primary efficacy endpoint is progression-free survival (PFS). PFS is defined as the time from randomization to documented disease progression or death. Based on results from the CONFIRM trial, median PFS among patients with AI-resistant disease on fulvestrant alone is 5.4 months. AI resistant disease is defined as: patients who have either relapsed while receiving adjuvant therapy with an aromatase inhibitor (anastrozole, letrozole, or exemestane) or have progressive disease while receiving an aromatase inhibitor for metastatic disease. (Patients previously treated with two or more prior cycles of fulvestrant are not eligible. Patients who have received one prior cycle (day 1 and day 15) of fulvestrant within 28 days of randomization are eligible so long as they meet other eligibility criteria). Randomization will be 1:1, stratified for balancing purposes using ECOG performance status (0 vs. 1), presence of measurable disease (yes vs. no), and prior chemotherapy (yes vs. no).

We hypothesize that the addition of everolimus to fulvestrant will result in an improvement in median PFS to 9.2 months. A one-sided stratified logrank test with a type I error rate of 10% will be used to evaluate whether the addition of everolimus shows promising improvement in PFS relative to fulvestrant alone. To have 90% power to detect the hypothesized improvement, enrollment of approximately 120 eligible patients (60 per arm) and full information of 98 events (deaths or progressions) are required. Allowing up to 10 patients to be ineligible or to not start study treatment, approximately 130 patients will need to be enrolled. With accrual of approximately 130 patients in 12 months, the required 98 events are expected to occur approximately 12 months after accrual is completed. Other endpoints that will be evaluated include clinical benefit rate (proportion stable or responding for at least 6 months), objective response rate (CR+PR), time to progression (TTP; defined as the time from randomization until progression of the disease), and overall survival (OS; defined as the time from randomization until death or censored at the date of last follow-up).

PFS will be evaluated using the stratified log-rank test described above, as will TTP and OS. Kaplan-Meier plots will be used to graphically portray these time-to-event endpoints. Clinical benefit rate and objective response rates will be compared between arms using Fisher's exact tests. 90% exact binomial confidence intervals on the rates will be provided.

9.2 Safety Analyses

A descriptive comparison of overall toxicity and of grade 3-4 toxicity in the combination arm and the fulvestrant arm will be provided. Assuming 65 patients are treated on each arm, the exact binomial 90% confidence interval on the rate of severe toxicities will be no wider than 22% (+/- 11%). The probabilities of observing a rare toxicity (true rate of 5%) will be 96% on each arm.

9.3 Analyses of Other Secondary Endpoints

Other endpoints that will be evaluated include overall survival, time to progression, and objective response rate. Overall survival will be characterized using Kaplan-Meier plots and other descriptive metrics. The objective response rate will be provided for each arm, with 90% exact binomial confidence intervals. Median time to progression will be estimated for each arm.

10 Adverse Event Reporting

10.1 Collection of Safety Information

Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a patient administered a medicinal product in a clinical investigation and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a product (investigational or marketed), whether or not considered related to the product (investigational or marketed). Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs and symptoms, are considered clinically significant, or require therapy.

Following written consent to participate in the study, all serious AEs should be collected on a patient. The collection of non-serious AE information should begin at initiation of therapy.

All identified AEs must be recorded and described on the appropriate page of the Case Report Form (CRF). If known, the diagnosis of the underlying illness or disorder should be recorded, rather than individual symptoms. The following information should be documented for all AEs: date of onset and resolution, severity of the event; the investigator's opinion of the relationship to investigational product (see definitions below); treatment required for the AE; cause of the event (if known); and information regarding resolution/outcome.

Severity

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 will be utilized for AE reporting. A copy of the CTCAE Version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

All appropriate treatment areas should have access to a copy of the CTEP CTCAE Version 4.0 (see Appendix E).

Attribution

The following categories and definitions of causal relationship or attribution to study drug should be used to assess Adverse Events:

- Definite: There is a reasonable causal relationship between the study drug and the event. The event responds to withdrawal of study drug (dechallenge) and recurs with rechallenge, if clinically feasible.
- Probable: There is a reasonable causal relationship between the study drug and the event. The event responds to dechallenge. Rechallenge is not required.
- Possible: There is a reasonable causal relationship between the study drug and the event. Dechallenge information is lacking or unclear.
- Unlikely: There is doubtful causal relationship between the study drug and the event.

- Unrelated: There is clearly not a causal relationship between the study drug and the event or there is a causal relationship between another drug, concurrent disease, or circumstances and the event.

Categories 'Definite', 'probable' and 'possible' are considered study drug related. Categories 'not likely' and 'not related' are considered not study drug-related.

The development of a new cancer should be regarded as an AE. New cancers are those that are not the primary reason for administration of study treatment and have been identified after inclusion of the patient into the clinical study.

AEs related to fulvestrant and/or everolimus/placebo will be followed for 30 days after the last dose of study therapy (fulvestrant and/or everolimus/placebo) until ≤ grade 1 or stabilization, and reported as SAEs if they become serious. Serious adverse events >30 days after last dose of fulvestrant and/or everolimus/placebo are not reported unless the event may be related to everolimus/placebo.

10.2 Handling of Serious Adverse Events (SAEs)

10.2.1 SAE Definitions

A ***serious AE*** is any untoward medical occurrence occurring after informed consent is granted or that at any dose:

- results in death,
- is life-threatening (defined as an event in which the study patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe),
- requires inpatient hospitalization or causes prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity,
- is a congenital anomaly/birth defect,
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the patient or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed in the definition above.)

  Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.

10.2.2 SAE Reporting Requirements

All serious adverse events require expeditious handling and reporting to comply with regulatory requirements. The Principal Investigator has the obligation to report all serious adverse events to PrECOG, or their designee. A study specific SAE form to be utilized for SAE reporting will be provided with supplemental study materials.

All serious adverse events that occur either during the study period (Induction and/or Continuation) or within 30 days of discontinuation of dosing regardless of event relationship to the study medications (fulvestrant and/or everolimus/placebo) should be reported to PrECOG, or their designee within 24 hours of the investigator's knowledge of the event or, when the event occurs on a weekend or national holiday, at the latest on the following working day. All deaths during treatment or within 30 days following completion of active protocol therapy must be reported. Serious adverse events that occur >30 days from last dose of fulvestrant and/or everolimus/placebo and are judged related to the everolimus/placebo (definitely, probably or possibly) must be reported to PrECOG, or their designee using the 24 hour timeline noted above. If only limited information is initially available, follow-up reports are required. Serious adverse events that occur >30 days from last dose of fulvestrant and are judged to be related to fulvestrant will follow normal reporting mechanisms for commercial drugs.

SAE Hotline Phone Number:

610-354-0404 during normal business hours (8:30 AM – 5 PM EST)

484-574-2367 after normal business hours (after 5 PM EST)

SAE Fax Number:

888-801-8795

PrECOG will notify Novartis Pharmaceuticals Drug Safety and Epidemiology Department (DS&E) of all SAE's within 24 hours of the Awareness Date. Relevant follow-up information will be provided to Novartis DS&E as soon as it becomes available.

In addition, Investigators should also report event(s) to their IRB as required.

Collection of complete information concerning SAEs is extremely important. Full descriptions of each event will be followed. Thus, follow-up information which becomes available as the SAE evolves, as well as supporting documentation (e.g., hospital discharge summaries and autopsy reports), should be collected subsequently, if not available at the time of the initial report, and immediately sent using the same procedure as the initial SAE report. The original and all follow-up SAEs form must be kept on file at the study site.

For Comparator Drugs/Secondary Suspects (Concomitant Medications), all serious adverse experiences will be forwarded to the product manufacturer by PrECOG (or their designee), if applicable.

10.3 Reporting of Second Primary Cancers

New cancers are those that are not the primary reason for administration of study treatment and have been identified after inclusion of the patient into the clinical study.

All cases of new primary cancers that occur during or after protocol treatment must be reported to PrECOG within 30 days of diagnosis, regardless of relationship to protocol treatment. Secondary primary malignancies should also be reported as a SAE. This form is not for use for reporting recurrence or development of metastatic disease. A copy of the pathology report, if applicable, should be sent, if available.

Note: Once data regarding survival and remission status are no longer required by the protocol, no follow-up data should be submitted, including the PrECOG Second Primary Form.

11 Administrative

11.1 Protocol Compliance

The study shall be conducted as described in this protocol. All revisions to the protocol must be discussed with, and be prepared by PrECOG and/or representatives. The Investigator should not implement any deviation or change to the protocol or consent without prior review and documented approval from PrECOG and/or representatives and the IRB of an amendment, except where necessary to eliminate an immediate hazard(s) to study patients.

If a deviation or change to the approved protocol is implemented to eliminate an immediate hazard(s) prior to obtaining IRB approval, notification will be submitted to the IRB for review and approval as soon as possible afterward. Documentation of approval signed by the chairperson or designee of the IRB(s) should be in the study records. If PrECOG and/or representatives provides an amendment that substantially alters the study design or increases the potential risk to the patient; the consent form must be revised and submitted to the IRB(s) for review and approval; the revised form must be used to obtain consent from patients currently enrolled in the study if they are affected by the amendment; and the new form must be used to obtain consent from new patients prior to study entry. Information as to who investigators should send correspondence will be provided in additional study documents.

11.2 Institutional Review Board

Before study initiation, the Investigator must have written and dated approval from their respective IRB for the protocol, consent form, patient recruitment materials/process and any other written information to be provided to patients. The Investigator should also provide the IRB with a copy of the Investigator Brochure or product labeling, and any updates.

The Investigator should provide the IRB with reports, updates, and other information (e.g., Safety Updates, amendments, and administrative letters) according to regulatory requirements, IRB or study site procedures.

11.3 Informed Consent Procedures

Investigators must ensure that patients who volunteer for clinical trials or their legally acceptable representative are clearly and fully informed about the purpose, potential risks and other information.

A protocol specific informed consent form (ICF) template will be provided to sites. Preparation of the site-specific consent form is the responsibility of the site Investigator and must include all applicable regulatory and IRB requirements, and must adhere to Good Clinical Practice (GCP) and to the ethical principles that have their origin in the Declaration of Helsinki. All changes to the ICF template will be approved by PrECOG and/or their representatives prior to implementation.

In accordance with the Health Information Portability and Accountability Act (HIPAA), the consent process will also include written authorization by patients to release medical information to allow PrECOG and/or its agents, regulatory authorities, and the IRB of

record at the study site for access to patient records and medical information relevant to the study, including the medical history. This will be documented in the informed consent form or other approved form obtained at the time of informed consent per institutional policies. This form should also be submitted to PrECOG and/or its agents for review prior to its implementation.

The Investigator must provide the patient or legally acceptable representative with a copy of the consent form and written information about the study in the language in which the patient is most proficient. The language must be non-technical and easily understood. The Investigator should allow time necessary for patient or patient's legally acceptable representative to inquire about the details of the study, then informed consent must be signed and personally dated by the patient or the patient's legally acceptable representative and by the person who conducted the informed consent discussion. The patient or legally acceptable representative should receive a copy of the signed informed consent and any other written information provided to study patients prior to patient's participation in the trial. The investigator is responsible for assuring adequate documentation of this process and for storage and maintenance of the original signed consent form for each patient/subject.

The informed consent and any other information provided to patients or the patient's legally acceptable representative, should be revised whenever important new information becomes available that is relevant to the patient's consent, and should receive IRB approval prior to use. The Investigator, or a person designated by the Investigator should inform the patient or the patient's legally acceptable representative of all pertinent aspects of the study and of any new information relevant to the patient's willingness to continue participation in the study. This communication should be documented in the patient record. During a patient's participation in the trial, any updates to the consent form and any updates to the written information will be provided to the patient.

11.4 Safety Communication

Investigators will be notified of all AEs that are serious, unexpected, and definitely, probably, or possibly related to the investigational product. Upon receiving such notices, the Investigator must review and retain the notice with the Investigator Brochure and submit a copy of this information to the Institutional Review Board (IRB) according to local regulations. The Investigator and IRB will determine if the informed consent requires revision. The Investigator should also comply with the IRB procedures for reporting any other safety information. All revisions should be submitted to PrECOG and/or agents for review.

11.5 Monitoring

Representatives and agents of PrECOG and, as applicable to the study, the manufacturer of Investigational Product must be allowed to visit all study site locations periodically to assess the data, quality and study integrity. The purpose of this visit is to review study records and directly compare them with source documents and discuss the conduct of the study with the Investigator, and verify that the facilities remain acceptable.

The study may be evaluated by other auditors and government inspectors who must be allowed access to electronic Case Report Forms (eCRFs), source documents and other

study files. The investigator must notify PrECOG of any scheduled visits by regulatory authorities, and submit copies of all reports. Information as to who investigators should notify of an audit or where to address questions will be provided in additional study materials. Monitoring of drug accountability will also occur.

11.6 Study Records

An Investigator is required to maintain adequate regulatory files with corresponding communication and approvals, accurate histories, observations and other data on each individual treated. Full details of required regulatory documents will be provided in additional study materials. Data reported on the eCRF must be consistent with the source documents as part of the patient record.

The confidentiality of records that could identify patients must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

A study specific signature record will be maintained to document signatures and initials of all persons at a study site who are authorized to make entries and/or corrections on eCRFs as well as document other study-specific roles.

11.7 Electronic Case Report Form (eCRF) Information

Additional information regarding eCRF instructions, timelines for data entry/submission and query completion can be found in supplemental materials provided to the site. Sites will be expected to complete eCRFs as per the schedule provided and submit all relevant data as per the specified timelines. All items recorded on eCRFs must be found in source documents.

The completed eCRF must be promptly reviewed, electronically signed, and dated by a qualified physician who is an Investigator or Sub-Investigator.

Instructions for management of patients who do not receive any protocol therapy:

If a patient is randomized and does not receive any assigned protocol treatment, baseline, Serious Adverse Event and follow-up data will still be entered and must be submitted according to the eCRF instructions. Document the reason for not starting protocol treatment on the appropriate electronic off-treatment form.

11.8 Records Retention

FDA Regulations (21CFR 312.62) require clinical investigators to retain all trial-related documentation, including source documents for the periods described below for studies performed under a US IND:

- two years after the FDA approves the marketing application, or
- two years after the FDA disapproves the application for the indication being studied, or
- two years after the FDA is notified by the sponsor of the discontinuation of trials and that an application will not be submitted.

The Investigator must retain investigational product disposition records, copies of eCRFs (or electronic files), and source documents for the maximum period required by

applicable regulations and guidelines, or Institution procedures, whichever is longer but not less than 5 years from the completion of the study. The Investigator must contact PrECOG and/or representatives prior to destroying any records associated with the study.

Information as to who investigators should contact for questions will be provided in additional study documents. PrECOG and/or representatives will notify the Investigator when the trial records for this study are no longer needed.

12 Glossary of Terms and List of Abbreviations

Term	Definition
4E-BP1	4E-Binding Protein
Ab	Antibodies
ADPKD	Autosomal Dominant Polycystic Kidney Disease
ADR	Adverse Drug Reaction
AE(s)	Adverse Events(s)
Akt/PKB	Protein Kinase B
AI	Aromatase Inhibitor
Alk Phos	Alkaline Phosphatase
ALT/SGPT	Alanine Aminotransferase/Glutamic Pyruvic Transaminase/Serum Glutamic-Pyruvic Transaminase
AMD	Age-Related Macular Degeneration
ANC	Absolute Neutrophil Count
ASCO-CAP	American Society of Clinical Oncology-College of American Pathologist
AST/SGOT	Aspartate Aminotransferase/Glutamic Oxaloacetic Transaminase/Serum Glutamic-Oxaloacetic Transaminase
AUC	Area Under the Concentration-Time Curve
°C	degrees Celsius
Ca	Calcium
CBC	Complete Blood Count
CBR	Clinical Benefit Rate
CI	Confidence Interval
CISH	Chromogenic In Situ Hybridization
Cl	Chloride
cm	centimeter
Cmax	Maximum plasma concentration
CO2	Carbon Dioxide
CoA	Coenzyme A
COPD	Chronic Obstructive Pulmonary Disease
CPK	Creatine Phosphokinase
CR	Complete Response
CRC	Colorectal Cancer
Creat	Creatinine
CRF	Case Report Form
CRO	Contract Research Organization
CT	Computer Tomography
CTC	Common Toxicity Criteria

Term	Definition
CTCAE	The CTEP Common Terminology Criteria for Adverse Events (CTCAE)
CTEP	Cancer Therapy Evaluation Program
CYP3A4	CytochromeP450 3A4 Isoenzyme
DLBCL	Diffuse Large B Cell Lymphoma
DLCO	Diffusing Capacity of the Lung for Carbon Monoxide
DLT	Dose Limiting Toxicity
DNA	Deoxyribonucleic Acid
DS&E	Drug Safety and Epidemiology
eCRF	Electronic Case Report Form
e.g.	exempli gratia (for example)
ER	Estrogen Receptor
FSH	Follicle Stimulating Hormone
EU	European Union
FDA	Food and Drug Administration
FDG-PET	Fluorine-18-2-fluoro-Deoxy-D-Glucose Positron Emission Tomography
FISH	Fluorescence In Situ Hybridization
FKBP-12	FK506-Binding Protein 12
FSH	Follicle Stimulating Hormone
GBM	Glioblastoma Multiforme
GCP	Good Clinical Practice
GEP-NET	Gastroenteropancreatic Neuroendocrine Tumor
GERD	Gastroesophageal Reflux Disease
GF	Growth Factor
GI	Gastrointestinal
GnRH	Gonadotropin-Releasing Hormone
HBV	Hepatitis B Virus
HBcAb	Hepatitis B core Antibodies
HBsAb	Hpatitis B surface Antibodies
HbsAg	Hepatitis B surface Antigen
HCC	Hepatocellular Cancer
HCV	Hepatitis C Virus
HER-2	Human Epidermal Growth Factor Receptor 2
HIF-1	Hypoxia-Inducible Factor-1
HIPAA	Health Information Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HMG	3-hydroxy-3-methyl-glutaryl
HR	Hormone-Receptor
HUVECS	Human Umbilical Endothelial Cells
IB	Investigator Brochure (also called Investigator Drug Brochure, IDB)

Term	Definition
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IND	Investigational New Drug
INN	International Non-Proprietary Name
INR	International Normal Ratio
IRB	Institutional Review Board
IU	International Unit
IV	Intravenous
IWR	Interactive Web Randomization
K	Potassium
kg	Kilogram
L	Liter
LDH	Lactate Dehydrogenase
LDL	Low-Density Lypoproteins
LFTs	Liver Function Tests
LLN	Lower Limit Normal
LMW	Low Molecular Weight
Log_{10}	Decadic logarithm (common logarithm)
M	Meter
mg	Milligram
Mg	Magnesium
min	minute
mL	Milliliter
mRCC	Metastatic Renal Cell Carcinoma
MRI	Magnetic Resonance Imaging
mTOR	mammalian Target of Rapamycin
N	Number of patients or observations
Na	Sodium
N/A	Not Applicable
NCI	National Cancer Institute
NSCLC	Non-Small Cell Lung Cancer
Ng	Nanogram
μM	Micromolar
Nm	Nanometer
nM	Nanomolar
OS	Overall Survival
PD	Progressive Disease
P13K	Phosphoinositide 3-kinase

Term	Definition
PI	Package Insert
PBMC	Peripheral Blood Mononuclear Cells
PCR	Polymerase Chain Reaction
PET	Proton Emission Tomography
PFS	Progression Free Survival
PgP	P-glycoprotein
PK	Pharmacokinetic
Plt	Platelet
PNET	Pancreatic Neuroendocrine Tumor
PO	Per Oral (by mouth route of administration)
PR	Partial Response
PR-positive	Progesterone Receptor
PSA	Prostate-Specific Antigen
PTEN	Phosphatase and Tensin Homolog Deleted on Chromosome 10
PT/PTT	Prothrombin Time/Partial Thromboplastin Time
QC	Quality Control
QD	Once Daily
QT	the interval between the beginning of the Q-wave and the end of the T-wave on an electrocardiogram
QTc	corrected Q to T wave interval on electrocardiogram
RCC	Renal Cell Carcinoma
RECIST	Response Evaluation Criterion Solid Tumors
RNA	Ribonucleic Acid
RR	Response Rate
RTK	Receptor Tyrosine Kinase
S6K1	S6 Kinase 1
SAE	Serious Adverse Event
SC	Subcutaneous
SCLC	Small Cell Lung Cancer
SD	Stable Disease
SEGA	Subependymal Giant Cell Astrocytoma
SERD	Selective Estrogen Receptor Down-Regulators
SERM	Selective Estrogen Receptor Modulator
T Bili	Total Bilirubin
TKI	Tyrosine Kinase Inhibitor
TS	Tuberous Sclerosis
TSC	Tuberous Sclerosis Complex
TTP	Time to Progression

Term	Definition
TUNNEL	Terminal Deoxynucleotidyl Transferase (TdT)-Mediated dUTP-Biotin Nick End Labeling
μg	microgram
ULN	Upper Limit Normal
US	United States
USP	United States Pharmacopeia
VEGF	Vascular Endothelial Growth Factor
WBC	White Blood Cell Count
WHO	World Health Organization

13 Appendix A: Eligibility Checklist

✓	Pt Initials: ___ ___ ___ Study Personnel: _____ F M L Date of Evaluation: ___/___/____
	INCLUSION CRITERIA
	Must be willing to sign a protocol-specific informed consent. Consent Date: _____/_____/_____ ☐ Consent in patient record
	Age ≥ 18 and female. Birth Date: _____/_____/_____ ☐ Documentation in patient record
	ECOG Performance Status 0 or 1. PS ☐ 0 ☐ 1 (must document in patient record)
	Patient must have histologically or cytologically confirmed adenocarcinoma of the breast. Pathology Date: _____/_____/_____ ☐ Pathology must be in patient record
	Must have stage IV disease or inoperable locally advanced disease. ☐ Documentation in patient record *(via imaging scans as per RECIST Section 6.0)*
	Patients must have ER and/or PR-positive disease as determined by their local pathology or reference laboratory by ASCO-CAP criteria.[51] Tumors must be HER-2/neu negative or equivocal by standard ICH/FISH or ICH/CISH methodologies by ASCO-CAP criteria.[52] ☐ ER+ ☐ PR+ ☐ ER+ and PR+ ☐ Tumor is HER-2/neu negative by standard ICH/FISH or ICH/CISH methodologies Pathology Date: _____/_____/_____ ☐ Pathology must be in patient record
	Patients must have had relapse while receiving adjuvant therapy with an aromatase inhibitor (anastrozole, letrozole, or exemestane), OR progressive disease while receiving an aromatase inhibitor for metastatic disease. **Note:** Patients may have received an endocrine agent (e.g., Tamoxifen) between the time of progression on an AI and registration. ☐ Documentation in patient record
	Patients previously treated with two or more prior cycles of fulvestrant are not eligible. Patients who have received one prior cycle (dose on day 1 and day 15) of fulvestrant within 28 days of randomization are eligible as long as they meet other eligibility criteria. ☐ Documentation in patient record
	Patients must be post menopausal. *(see Section 3.1)* ☐ Documentation in patient record

✓	Pt Initials: ___ ___ ___ Study Personnel: _____ F M L Date of Evaluation: ___/___/____
	Patient may have received up to one prior systemic chemotherapy regimen for metastatic disease. ☐ no prior systemic chemotherapy ☐ one prior systemic chemotherapy regimen ☐ documentation in patient record
	Adequate end organ function, as evidenced by the following obtained within 4 weeks of randomization: all must be present *(see Section 7.0 for labs that may need to be repeated within ≤ 7 days of Cycle 1, Day 1)* ☐ Total White Blood Cell Count (leucocytes, WBC) ≥ 3.0 x 10^9/L, absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L and platelet count ≥ 100 x 10^9/L (Total WBC value:_____unit_____) (ANC value:_____unit_____) (Platelet Count value:_____unit_____) ☐ Hemoglobin ≥ 9 g/dL (value:_____unit_____) ☐ Serum Bilirubin ≤ 1.5 x ULN (value:_____unit_____ULN_____) ☐ AST or ALT ≤ 2.5 x ULN (≤ 5 x ULN in patients with liver metastases) (AST value:_____unit_____ULN_____) (ALT value:_____unit_____ULN_____) ☐ Serum Creatinine ≤ 1.5 x ULN (value:_____unit_____ULN_____) ☐ Serum Albumin ≥ 3 g/dL (value:_____unit_____) ☐ Fasting Serum Cholesterol ≤ 300 mg/dL OR ≤ 7.75 mmol/L **AND** Fasting Triglycerides ≤ 2.5 x ULN **Note:** In case one or both of these thresholds are exceeded, the patient can only be included after initiation of appropriate lipid lowering medication. (Fasting Serum Cholesterol value:_____unit_____) (Fasting Triglycerides value:_____unit_____ULN_____) ☐ PT with INR ≤ 1.5. (Anticoagulation is allowed if target INR ≤ 1.5 on a stable dose of warfarin or on a stable dose of low molecular weight heparin for >2 weeks at time of randomization. (INR value:_____unit_____) (PT value:_____unit_____) ☐ Documentation in patient record

✓	Pt Initials: ___ ___ ___ Study Personnel: _____ F M L Date of Evaluation: ___/___/____
	Patients may have measurable disease, non-measurable disease (e.g., bone only metastases), or both. Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (Version 1.1) [*Eur J Ca* 45:228-247, 2009]. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm by chest x-ray, as ≥ 10 mm with CT scan, or ≥ 10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters). ☐ Measurable disease only ☐ Non-measurable disease only ☐ Both measurable and non-measurable disease ☐ Documentation in patient record **Note:** Tumor lesions in a previously irradiated field are not considered measurable.
	Patients with basal cell or squamous cell carcinoma of the skin or carcinoma *in situ* of the cervix within the past five years must have been treated with curative intent. Patients with a history of prior malignancy are eligible provided they were treated with curative intent and have been free of disease for >3 years. ☐ N/A ☐ Date of treatment: _____/_____/_____ ☐ Documentation in patient record
	EXCLUSION CRITERIA
	Patients who have had any major surgery or significant traumatic injury within 4 weeks of randomization, or have not recovered from the side effects of any major surgery (defined as requiring general anesthesia) or patients that may require major surgery during the course of the study are not eligible. (Placement of vascular access device will not be considered major surgery.) Date of surgery: _____/_____/_____ ☐ N/A ☐ Documentation in patient record
	Patients may not be receiving any other investigational agents or have received any investigational agent within 4 weeks of randomization. Date of last treatment: _____/_____/_____ ☐ N/A ☐ Documentation in patient record
	Patients must not be receiving any concomitant anticancer treatment or have received anticancer treatment within 4 weeks of randomization (including chemotherapy, radiation therapy, antibody based therapy, e.g.), with the following exceptions: • Bisphosphonates, Zometa or Xgeva for bone metastases • Hormonal therapy (e.g., AI, Tamoxifen) • a GnRH analog is permitted if the patient had progressive disease on a GnRH analog plus a SERM or an AI; the GnRH analog may continue but the SERM or AI must be discontinued. Date of last treatment: _____/_____/_____ ☐ N/A ☐ Documentation in patient record

✓	Pt Initials: ___ ___ ___ Study Personnel: _____ F M L Date of Evaluation: ___/___/____
	Patients must not have received prior treatment with an mTOR inhibitor (sirolimus, temsirolimus, everolimus). ☐ N/A ☐ Documentation in patient record
	Patients must not be receiving chronic, systemic treatment with corticosteroids or another immunosuppressive agent greater than or equal to 5 mg prednisone or its equivalent daily. Topical or inhaled corticosteroids are allowed. ☐ N/A ☐ Documentation in patient record
	Patients must not receive immunization with attenuated live vaccines within one week of randomization or during the study period. Close contact with those who have received attenuated live vaccines should be avoided during treatment with everolimus. Examples of live vaccines include intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella and TY21a typhoid vaccines. ☐ N/A ☐ Documentation in patient record
	Patients must not have current or a prior history of brain metastases or leptomeningeal disease. Patients must not have rapidly progressive, life-threatening metastases. This includes patients with extensive hepatic involvement (>50% of the liver involved) and symptomatic lymphangitic metastases. ☐ N/A ☐ Documentation in patient record
	Patients must not have a known hypersensitivity/history of allergic reactions attributed to compounds of similar chemical or biologic composition to everolimus (or other rapamycins such as sirolimus, temsirolimus) or fulvestrant. ☐ N/A ☐ Documentation in patient record
	Since everolimus may cause bone marrow suppression, patients with congenital or acquired immune deficiency at increased risk of infection are not eligible. This includes patients being treated with chronic immunosuppressive agents (including greater than or equal to 5 mg prednisone or its equivalent daily), and patients with known HIV seropositivity. ☐ N/A ☐ Documentation in patient record
	Patients must not have any impairment of gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of everolimus (e.g., ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome or small bowel resection). ☐ N/A ☐ Documentation in patient record
	Patients must not have an active, bleeding diathesis. ☐ N/A ☐ Documentation in patient record

✓	Pt Initials: ___ ___ ___ Study Personnel: _____ F M L Date of Evaluation: ___/___/____
	Patients must not have a history of any condition or uncontrolled intercurrent illness including, but not limited to, ongoing or active infection or psychiatric illness/social situations that in the opinion of the investigator might intefere with or limit the patient's ability to comply with the protocol or pose additional or unacceptable risk to the patient. ☐ N/A ☐ Documentation in patient record
	Patients must not have any severe and/or uncontrolled medical conditions or other conditions that could affect their participation in the study such as: • Symptomatic congestive heart failure of New York Heart Association Class III or IV (see Appendix D) • Unstable angina pectoris, myocardial infarction within 6 months of randomization, serious uncontrolled cardiac arrhythmia or any other clinically significant cardiac disease • History of symptomatic pulmonary disease or non-malignant pulmonary disease (e.g. COPD) requiring treatment. Such patients would be eligible if PFTs performed within 8 weeks of treatment noted a DLCO greater than 50%. • Uncontrolled diabetes as defined by fasting serum glucose >1.5 x ULN (**Note:** Optimal glycemic control should be achieved before starting trial therapy.) • Active (acute or chronic) or uncontrolled severe infections • Liver disease such as cirrhosis or severe hepatic impairment (Child-Pugh Class C). **Note:** A detailed assessment of Hepatitis B/C medical history and risk factors must be done at screening for all patients. HBV DNA and HCV RNA PCR testing are required at screening for all patients with a positive medical history based on risk factors and/or confirmation of prior HBV/HCV infection. ☐ N/A ☐ Documentation in patient record

14 Appendix B: ECOG Performance Status Scale

Grade	ECOG
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 house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

[61] *Source: Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair*

15 Appendix C: Medications that can Inhibit/Induce CYP3A4 and PgP

See Section 5.3.5.1 for guidelines on use of inhibitors and Section 5.3.5.2 for guidelines on use of inducers. Table 15-0 shows clinically relevant drug interactions for inhibitors and inducers of isoenzyme CYP3A. Table 15-1 shows clinically relevant drug interactions for substrates, inducers, and inhibitors of PgP and PgP/CYP3A.

Table 15-0

Clinically Relevant Drug Interactions: Inhibitors and Inducers of Isoenzyme CYP3A

INHIBITORS
Strong Inhibitors: clarithromycin, conivaptan, elvitegravir, indinavir, itraconazole, ketoconazole, lopinavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telithromycin, tipranavir, troleandamycin, voriconazole (Krishna et al, 2009) **Moderate Inhibitors:** aprepitant, amprenavir, atazanavir, casopitant, cimetidine, ciprofloxacin, darunavir, diltiazem, dronedarone, erythromycin, fluconazole, fosamprenavir, grapefruit juice (citrus parasidi fruit juice), imatinib, tofisopam, verapamil
INDUCERS
amprenavir, aprepitant, armodafinil (R-modafinil), avasimibe, bosentan, carbamazepine, dexamethasone, efavirenz, etravirine, glucocorticoids, modafinil, nafcillin, nevirapine, oxcarbazepine, phenobarbital, phenytoin, pioglitazone, prednisone, rifabutin, rifampin, ritonavir, rufinamide, St. John's wort, talviraline, tipranavir, topiramate, troglitazone

Table 15-1

Clinically Relevant Drug Interactions: Substrates, Inducers, and Inhibitors of PgP and PgP/CYP3A

SUBSTRATES
Colchicines, digoxin, fexofenadine, indinavir, paclitaxel, topotecan, vincristine
INDUCERS
Rifampin, St. John's wort
PgP INHIBITORS and PgP/CYP3A DUAL INHIBITORS
Amiodarone, captopril, carvedilol, clarithromycin, conivaptan, diltiazem, dronedarone, elacridar, erythromycin, felodipine, fexofenadine, ginkgo (ginkgo biloba), indinavir, itraconazole, lopinavir, mibefradil, milk thistle (silybum marianum), nifedipine, nitrendipine, quercetin, quinidine, ranolazine, ritonavir, saquinavir, Schisandra chinensis, St John's wort (hypericum perforatum), talinolol, telmisartan, tipranavir, valspodar, verapamil

Reference: Internal Clinical Pharmacology Drug-drug interaction (DDI) memo, updated Oct. 2, 2011, which summarizes DDI data from three sources including the FDA's "Guidance for Industry, Drug Interaction Studies", the University of Washington's Drug Interaction Database, and Indiana University School of Medicine's Drug Interaction Table.

16 Appendix D: New York Heart Association (NYHA) Cardiac Classification of Functional Capacity and Objective Assessment

In 1928 the New York Heart Association published a classification of patients with cardiac disease based on clinical severity and prognosis. This classification has been updated in seven subsequent editions of Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels (Little, Brown & Co.). The ninth edition, revised by the Criteria Committee of the American Heart Association, New York City Affiliate, was released March 4, 1994*. The new classifications are summarized below.

The NYHA classification system relates symptoms to everyday activities and the patient's quality of life.

Class	Symptoms
Class I	Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath), or anginal pain.
Class II	Patients with cardiac disease resulting in slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, dyspnea or anginal pain.
Class III	Patients with cardiac disease resulting in marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, dyspnea or anginal pain.
Class IV	Patients with cardiac disease resulting in inability to carry out any physical activity without discomfort. Symptoms of heart failure or anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort increases.

Objective Assessment

I: No objective evidence of cardiovascular disease

II: Objective evidence of minimal cardiovascular disease

III: Objective evidence of moderately severe cardiovascular disease

IV: Objective evidence of severe cardiovascular disease

Accessed October 2009* http://www.americanheart.org/presenter.jhtml?identifier=1712

The Criteria Committee of the New York Heart Association. *Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels*. 9th ed. Boston, Mass: Little, Brown & Co; 1994:253-256.

17 Appendix E: CTEP Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0

Common Terminology Criteria for Adverse Events (CTCAE)

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE Version 4.0. A copy of the CTCAE Version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

All appropriate treatment areas should have access to a copy of the CTEP CTCAE Version 4.0.

18 Appendix F: Patient Pill Diary

Copies of this form will be made available to study staff in study materials. This form is appended as an example only, and may be modified during the study.

Site Instructions:

1. If this or a similar diary is used this may be considered source documentation, if the diary has been reviewed and signed by a member of the study staff. Patient compliance with protocol therapy can be assessed using a pill record or by other documentation in the patient record.
2. Patients should be instructed to begin Day 1 with the beginning of each cycle, with each cycle being 28 days.
3. If a dose modification occurs, patients should be given instructions for dosing, and the form can be modified as appropriate. Any dose changes should be recorded in the patient chart with appropriate rationale as per protocol.
4. A new form can be used at any time during a cycle; as long as the patient is made aware of changes (e.g. study staff fills in dates and mark lines/dates not to be used).
5. It is the responsibility of the investigator to appropriately dispense and monitor study medications and to comply with the protocol.

Patient Name: _____	**Patient Study ID (filled in by Site Staff): _____**

Patient Instructions:

1. Complete each form as instructed by your physician or study nurse.
2. You will take 2 pill(s) each day. You should take the pill(s) the same time each day, and in the morning, if possible. If you forget to take a pill and remember by 10 PM, you may take the dose. Otherwise just skip that dose and begin as usual the next day. Please mark dates of any missed pills on your record.
3. .Each dose should be swallowed whole with a glass of water and may be taken with or without food. The tablets must not be chewed or crushed. In cases where tablets cannot be swallowed, the tablets should be disintegrated in water just prior to being taken. Approximately 30 mL (2 tablespoons) of water should be put into a glass. The tablets should then be added and the contents stirred gently (for a maximum of 7 minutes) until the tablets are disintegrated. The contents should then be drunk. If you vomit after taking the study drug, you should NOT take another tablet that day. If you forget to take the medication and remembers by 10 PM, you may take the dose. Otherwise, skip that dose and begin as usual the next day.
4. If you have any side effects or comments, please note in the comment section or on the back of the page. For questions or if you have any side effects that should be immediately reported to your study doctor, please call _____at: (_____) _____ - _____.
5. Please bring your pill(s) and this form to your study doctor when you go for each appointment. If your dose changes, the study nurse or doctor will let you know. You should note this on the form.

Date	Day	# Pills	Comments	Date	Day	# Pills	Comments
	1				**15**		
	2				**16**		
	3				**17**		
	4				**18**		
	5				**19**		
	6				**20**		
	7				**21**		
	8				**22**		
	9				**23**		
	10				**24**		
	11				**25**		
	12				**26**		
	13				**27**		
	14				**28**		

Patient Signature: _____ Date: _____

Physician Office to complete this section:

Study Personnel Signature: _____ Date: _____

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20 Investigator's Statement

1. I have carefully read this protocol entitled "**Randomized, Double-Blind, Placebo-Controlled Phase II Trial of Fulvestrant (Faslodex) plus Everolimus in Post Menopausal Patients with Hormone-Receptor Positive Metastatic Breast Center Resistant to Aromatase Inhibitor Therapy, Version 2.0 dated 1/22/2014" (Protocol number PrE0102)** and agree that it contains all the necessary information required to conduct the study. I agree to conduct the study as outlined in the protocol.
2. I agree to conduct this study according to the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, the principles of GCP as described in 21 CFR and any applicable local requirements.
3. I understand that this trial and any subsequent changes to this trial will not be initiated without approval of the appropriate Institutional Review Board, and that all administrative requirements of the governing body of the institution will be complied with fully.
4. Informed written consent will be obtained from all participating patients in accordance with institutional and FDA requirements as specified in Title 21, Code of Federal Regulations, Part 50.
5. I understand that my signature on the Case Report Form indicates that I have carefully reviewed each page and accept full responsibility for the contents thereof.
6. I understand that the information presented in this study protocol is confidential, and I hereby assure that no information based on the conduct of the study will be released without prior consent from PrECOG, LLC unless this requirement is superseded by the Food and Drug Administration.

Principal Investigator:

PI Name: _____

Site Name: _____

Signature of PI: _____

Date of Signature: _______________

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