PROTOCOL

STUDY TITLE:	Phase II study of everolimus beyond progression in postmenopausal women with advanced, hormone receptor positive breast cancer.
STUDY DRUG:	Everolimus
Provided by:	Novartis
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1. INTRODUCTION

1.1 Disease Background

Breast cancer is the most common malignancy among women in the United States and approximately 70% of these cancers are hormone receptor positive. Endocrine therapy is the cornerstone of treatment for hormone receptor positive breast cancer, either in the adjuvant or in the metastatic setting (1).

Hormone receptor-positive breast cancer tends to have a more favorable prognosis than hormone receptor-negative disease and the use of endocrine therapy has dramatically decreased breast cancer mortality. However, a subset of hormone receptor-positive breast cancers demonstrate primary (intrinsic) resistance to endocrine therapy, and eventually all hormone receptor-positive metastatic breast cancers develop resistance to hormonal therapies (acquired resistance) (2). Aromatase inhibitors (AIs) are the standard fist-line regimen in post-menopausal women with estrogen/progesterone receptor positive breast cancer. Anastrozole was the first AI approved in hormone receptor positive breast cancer in post-menopausal patients, followed by letrozole and exemestane (3-5)(6).

At disease progression or in the presence of side effects, treatment options include different classes of AIs or switching to tamoxifen or fulvestrant, since there is evidence that patients can respond to different agents (7). Most patients who have failed several hormonal agents in the metastatic setting have been traditionally treated with chemotherapy, which is associated with increased toxicity.

However, on July 20, 2012, the Food and Drug Administration (FDA) approved the combination of everolimus with exemestane for the treatment of postmenopausal women with advanced hormone receptor-positive, HER2-negative breast cancer. The combination was used upon recurrence or relapse after treatment with a non-steroidal aromatase inhibitor (anastrozole, letrozole). The combination of everolimus and exemestane has become the new standard of care in patients who fail an aromatase inhibitor and there is evidence that everolimus reverses hormone resistance.

1.2 Mechanisms of hormone-resistance

Much of our current understanding of the molecular mechanisms responsible for hormone-resistance comes from clinical and pre-clinical models. Clinical and

preclinical data indicate that hormone receptors interact with growth factor receptors, including Her2/neu, EGFR and IGFIR, which possibly play a role in hormone resistance.

Transfection of HER2 into estrogen receptor (ER)-positive breast cancer cells renders them resistant to tamoxifen (8). Breast cancers that have high levels of HER2 expression are felt to be somewhat intrinsically resistant to hormonal therapies, including tamoxifen and aromatase inhibitors (9, 10). Aberrant signaling through the AKT-PI3K pathway has been also suggested as a mechanism of resistance to endocrine therapy. The AKT pathway activates various downstream regulators which when phosphorylated, lead to inhibition of apoptosis, cell survival and proliferation, Figure 1 (2).

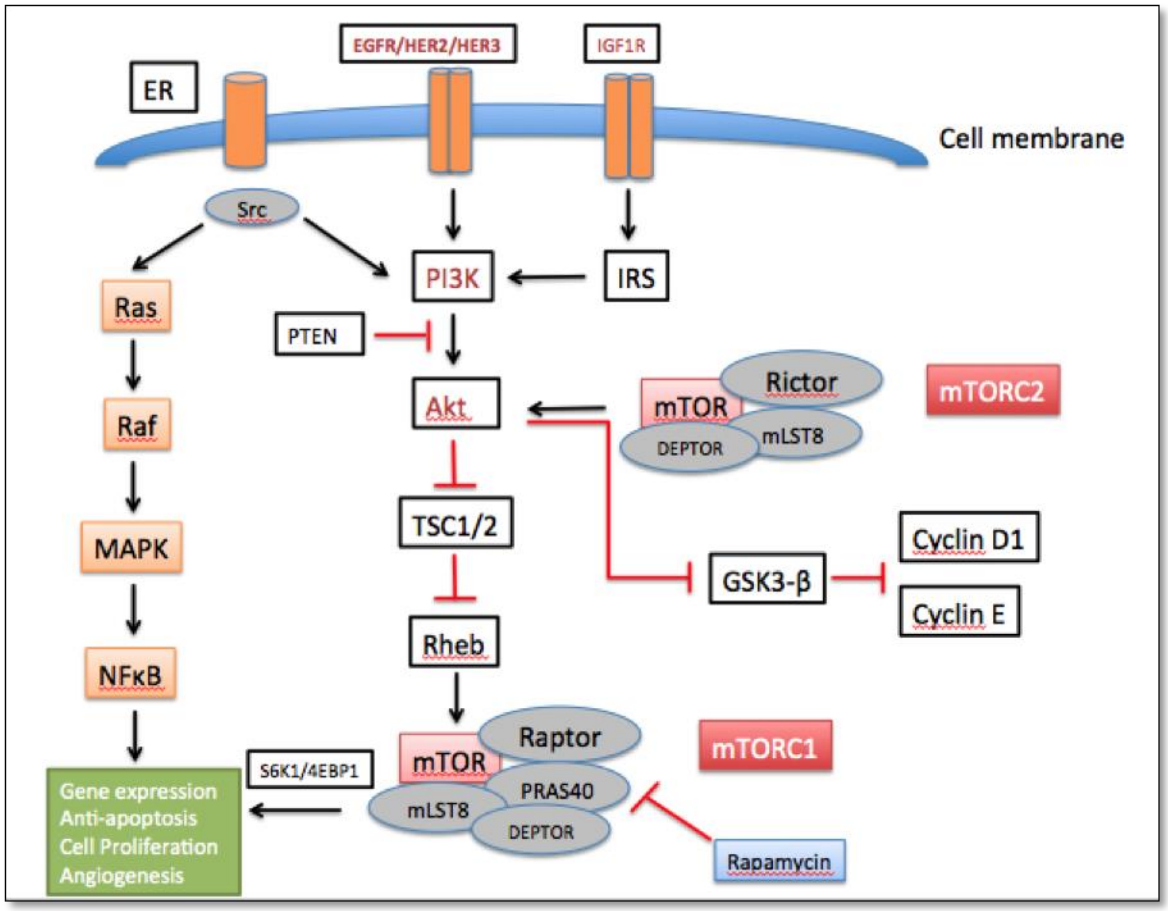

Figure 1. Crosstalk between the estrogen receptor and EGFR/HER2/IGF1R pathway can lead to cell growth independent of hormonal activation. The PI3K/Akt/mTOR pathway is a major downstream cellular circuit, which also leads to gene expression and cell proliferation.
The estrogen receptor can also be regulated by these membrane receptors, which act as coactivators and lead to phosphorylation of estrogen receptors in the absence of estrogen (ligand-independent receptor activation).
Abbreviations: EGFR, epidermal growth factor receptor; IGF1R, insulin-like growth factor-1 receptor; mTOR, mammalian target of rapamycin; HER2, human epidermal growth factor receptor-2; ER, estrogen receptor; TSC1/2, tuberous sclerosis complex proteins 1/2; PI3K,

phosphatidylinositol 3-kinase; MAPK, mitogen-activated protein kinase; Src, steroid receptor coactivator.

1.3 Rationale for mTOR inhibition in hormone receptor-positive disease

The PI3K/Akt/mTOR pathway is a major cellular circuit, which plays a significant role in nutrient uptake, cell proliferation and gene expression (11). Downstream of PI3K and Akt, mTOR is a serine/threonine protein kinase, which is activated by the inhibition of the tuberous sclerosis complex proteins (TSC1/2). mTOR exerts its effects via two protein complexes. mTORC1 is a complex consisting of mTOR (Raptor), mLST8, and proline-rich Akt substrate. It is the main target of rapamycin and rapamycin analogs, and it exerts its action by activating S6K1 (40S ribosomal protein S6 kinase 1) and eukaryotic initiation factor 4E-binding protein, thus leading to protein production, lipid production, glycolysis, and inhibition of apoptosis. mTORC2 has been less well studied but there is evidence that prolonged exposure to rapamycin can also induce inhibition of mTORC2. mTORC2 is believed to modulate cell lipid metabolism and cell growth via the activation of Akt (12, 13).

Via the inhibition of TSC1/2, the transmembrane receptors EGFR/HER2/IGFIR can lead to the activation of mTORC1 (Figure 1). This way, they create a pathway of hormone resistance, where mTOR leads to tumor growth independent of estrogen receptor activation in hormone receptor –positive tumors.

mTOR has been documented to play a role in tamoxifen-resistant preclinical models. MCF-7, hormone receptor-positive breast cancer cell lines, that express constitutively active Akt were found to be able to proliferate under reduced estrogen conditions and were resistant to tamoxifen, both *in vitro* as well as *in vivo* in xenograft models. However, co-treatment with rapamycin inhibited mTOR activity and restored sensitivity to tamoxifen, suggesting that tamoxifen resistance is mediated by the mTOR pathway (14).

mTOR inhibition has also been demonstrated to be more effective preclinically in cell lines with increased Akt signaling, PTEN loss and/or increased upstream signaling (15, 16). Additionally, mTOR inhibitors, such as rapamycin and everolimus, have been demonstrated to increase Akt activity, while decreasing downstream effectors of cell signaling. This increase in Akt activity is felt to be due to a feedback mechanism (17, 18). Sirolimus (formerly known as rapamycin) inhibits the mTOR pathway by blocking mTORC1 functions. Sirolimus also inhibits the negative feedback to the PI3K signaling and AKT (16).

Everolimus (RAD001), is an orally bioavailable mTOR inhibitor, which has been shown to inhibit tumor growth and exert antitumor activity in vivo and in animal models (19, 20). Everolimus appears to act synergistically with hormone receptor inhibitors and in preclinical models it causes apoptotic cell death and produces tumor regression, Figure 2 (19-21).

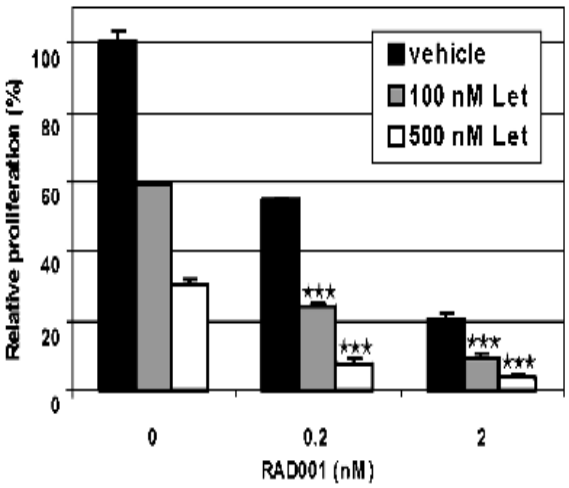

Figure 2: Combinations of RAD001 (everolimus) and letrozole result in enhanced antiproliferative activity in androstenedione driven MCF7 cells. The use of increasing doses of both drugs results in synergistic activity, inhibiting growth of estrogen receptor-positive MCF-7 cells.

Figure 2, taken from Boulay A, Rudloff J, Ye J et al. Dual inhibition of mTOR and estrogen receptor signaling in vitro induces cell death in models of breast cancer. *Clin Cancer Res* 2005; 11: 5319–5328.

Beeram et al (19) reported that mTOR kinase inhibitor can reverse endocrine resistance in breast cancer tumors in vivo. The authors generated an MCF-7 cell line with constitutively activated Akt. That model demonstrated resistance to the aromatase inhibitors letrozole and fulvestrant. The authors showed that co-treatment with everolimus restored sensitivity of the breast cancer cell lines to both endocrine agents.

In summary, these preclinical data strongly support that mTOR inhibition could play a significant role in the treatment of hormone receptor-positive breast cancer, especially in resistant tumors.

1.4 Everolimus clinical studies

In a phase II randomized trial comparing neoadjuvant letrozole with or without everolimus, in patients with estrogen receptor positive breast cancer, everolimus was found to significantly increase the efficacy of letrozole (22). The clinical response rate was higher in the everolimus arm and also marked reduction in the progesterone receptor, cyclin D1 expression and Ki67 expression was found in patients treated with the combination treatment.

The BOLERO-2 trial compared everolimus and exemestane versus exemestane alone in patients with hormone-receptor positive advanced breast cancers who had experienced recurrence or progression while on a non-steroidal aromatase inhibitor (anastrozole or letrozole) (23). A total of 724 women in 24 countries

were randomly assigned to exemestane and everolimus or exemestane and placebo in this phase III study. The BOLERO-2 study showed that the addition of everolimus to exemestane improved the progression-free survival (6.9 vs 2.8 months by local assessment, HR 0.43; 95% confidence interval [CI], 0.35 to 0.54; P<0.001). The PFS by central assessment was 10.6 versus 4.1 months respectively (Figure 3). The most common grade 3 or 4 adverse events in the everolimus group were stomatitis, anemia, dyspnea, hyperglycemia, fatigue, and pneumonitis.

The TAMRAD (tamoxifen and everolimus) trial compared tamoxifen and everolimus to tamoxifen alone in postmenopausal women with estrogen-receptor positive metastatic breast cancer who had failed aromatase inhibitor therapy (24). The clinical benefit rate (complete response + partial response + stable disease) at 6 months in the intent to treat population was 61% (95% CI, 47 to 74) in the combination arm versus 42% (95% CI, 29 to 56) in the tamoxifen alone arm (exploratory *P* = .045). The results were similar in the per protocol population (59%; 95% CI, 44 to 73 v 41%; 95% CI, 27 to 56).

The median TTP in the ITT population increased to 8.6 months (95% CI, 5.9 to 13.9) with tamoxifen plus everolimus from 4.5 months (95% CI, 3.6 to 8.7) with tamoxifen alone (exploratory P=_.002). This difference in TTP corresponded to a 46% reduction in the risk of progression associated with tamoxifen plus everolimus (HR, 0.54; 95% CI, 0.36 to 0.81). In an exploratory subgroup analysis, the everolimus benefit was mostly for patients with secondary hormone resistance, with a reduction in the risk of progression associated with everolimus of 54% in this subgroup (HR, 0.46; 95% CI, 0.26 to 0.83).

In contrast, patients with primary resistance benefited to a lesser degree (HR, 0.70; 95% CI, 0.40 to 1.21 (Figure 4). There was also a survival benefit in the patients treated with everolimus. 35% of patients discontinued OR had DOSE REDUCTIONS of everolimus due to side effects, stomatitis being the most common toxicity (Figure 5).

Based on the above, everolimus has been shown to exert antitumor activity and it appears to act synergistically with hormonal therapy in patients with estrogen/progesterone-receptor positive breast cancer, potentially reversing hormone resistance. This data mainly suggests that initially sensitive tumors undergo an adaptive upregulation of the PI3K/AKT/mTOR pathway, with subsequent cross-talk with ER signaling. This results in constitutive activation of cell growth pathways, rendering the patient resistant to hormone treatment. This hypothesis predicts the effectiveness of a PI3K/AKT/mTOR pathway inhibitor in combination with hormone therapy in patients with secondary hormone resistance.

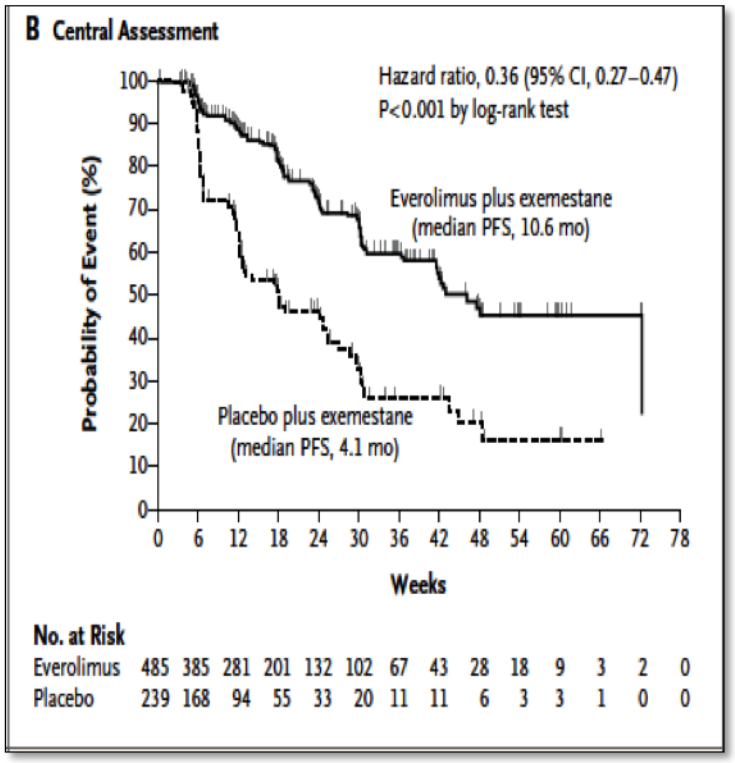

Figure 3: BOLERO-2. Everolimus and exemestane significantly improved PFS compared to exemestane alone.

Baselga J, Campone M, Piccart M et al (2012) Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. The New England journal of medicine 366 (6):520-529. doi:10.1056/NEJMoa1109653

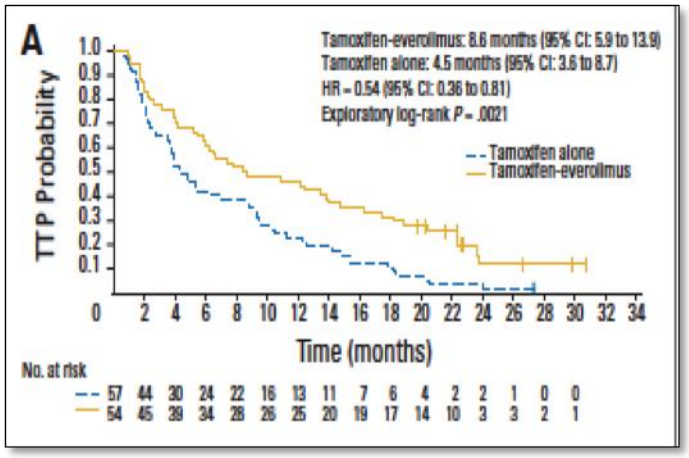

Figure 4:
TAMRAD.
Time to progression (TTP) in the ITT population.

Bachelot T, Bourgier C, Cropet C, et al. (2012) Randomized phase II trial of everolimus in combination with tamoxifen in patients with hormone receptor-positive, human epidermal growth factor receptor 2-negative metastatic breast cancer with prior exposure to aromatase inhibitors: a GINECO study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 30 (22):2718-2724. doi:10.1200/JCO.2011.39.0708

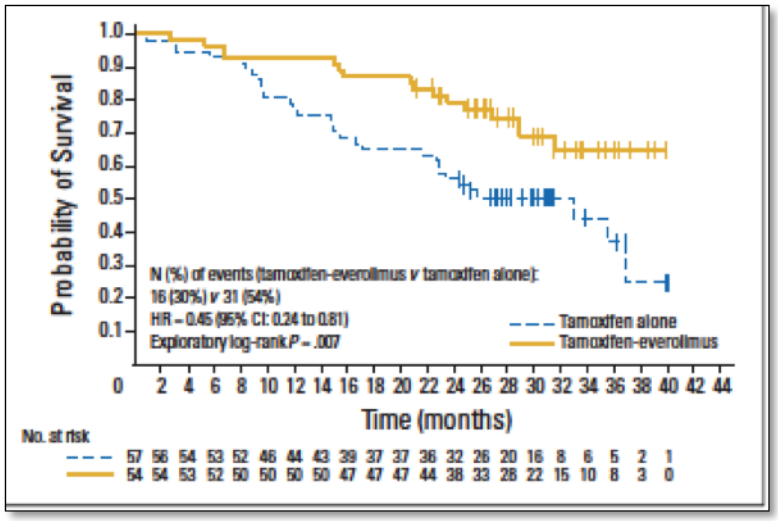

Figure 5:
Median OS was 32.9 months for the tamoxifen arm while it was not reached with tamoxifen plus everolimus; this translates to a 55% reduction in the risk of death

Bachelot T, Bourgier C, Cropet C, et al. (2012) Randomized phase II trial of everolimus in combination with tamoxifen in patients with hormone receptor-positive, human epidermal growth factor receptor 2-negative metastatic breast cancer with prior exposure to aromatase inhibitors: a GINECO study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 30 (22):2718-2724. doi:10.1200/JCO.2011.39.0708

1.5 Overview of everolimus

On July 20, 2012, the Food and Drug Administration (FDA) approved everolimus tablets (Afinitor®, made by Novartis Pharmaceuticals Corporation) for the treatment of postmenopausal women with advanced hormone receptor-positive, HER2-negative breast cancer in combination with exemestane, after failure of treatment with letrozole or anastrozole. The approval was based on the BOLERO-2 trial and approved dosing is 10 mg/day.

EVEROLIMUS (everolimus) is a synthetic derivative of rapamycin with improved pharmacodynamics and pharmacokinetic properties. EVEROLIMUS has been in clinical development since 1996 as an immunosuppressant in solid organ transplantation.

EVEROLIMUS has been 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 VEGF production and VEGF-induced proliferation of endothelial cells)

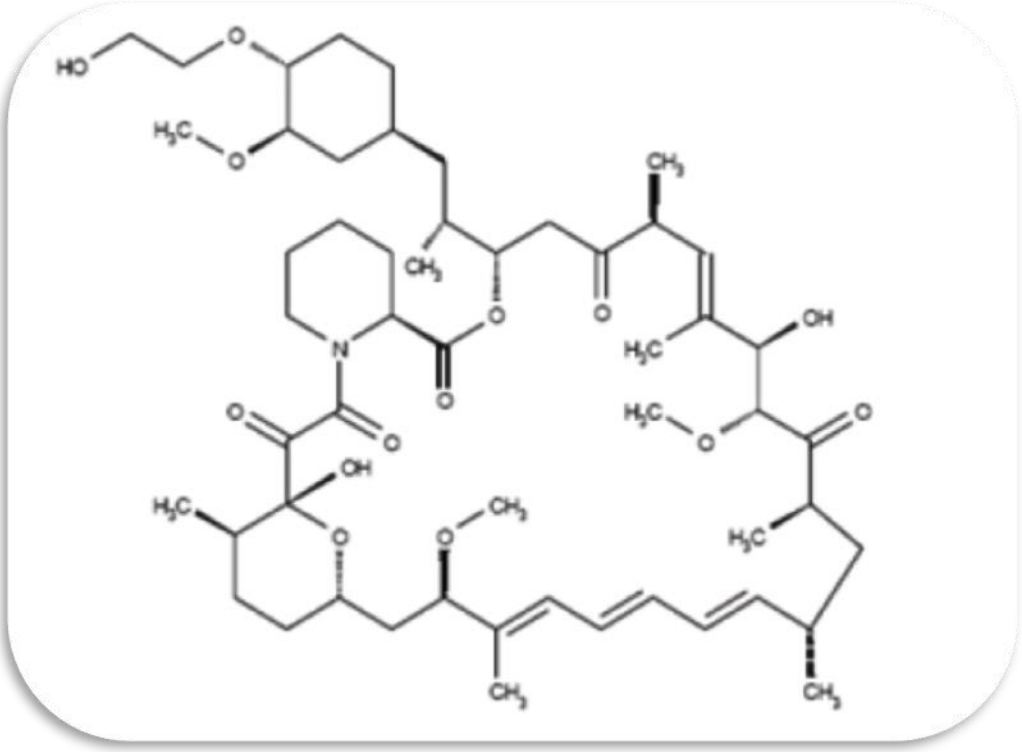

Figure 6: The structural formula of everolimus (taken from Afinitor brochure, www.afinitor.com)

Everolimus binds and forms a complex with the intracellular FK506–binding protein 12 (FKBP-12), thus inhibiting the mTORC1 complex and phosphorylating P70 S6 ribosomal protein kinase. Everolimus also reduces elongation factor 4E–binding protein (4E-BP1), which is involved in protein synthesis. In addition, everolimus inhibits the expression of hypoxia-inducible factor 1 (HIF-1) and reduces the expression of vascular endothelial growth factor (VEGF). S6K1 and 4EBP1 are downstream effectors of mTOR, which contribute to hormone resistance (Figure 7).

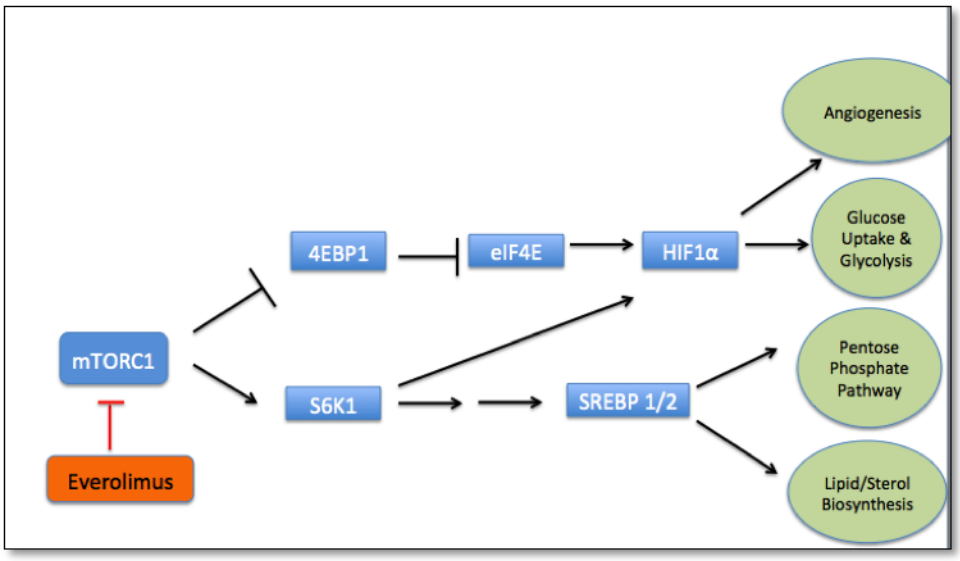

Figure 7: Everolimus by inhibiting the mTORC1 complex and phosphorylating P70 S6 ribosomal protein kinase, reduces elongation factor 4E–binding protein (4E-BP1), which is involved in protein synthesis. In addition, everolimus inhibits the expression of hypoxia-inducible factor 1 (HIF-1) and reduces the expression of vascular endothelial growth factor (VEGF).

1.5.1 Everolimus Pharmacokinetics

Everolimus reaches peak concentrations within 1 to 2 hours after a single oral dose, and following oral daily administration, steady state is achieved within one week. Age, sex or weight do not appear to affect the pharmacokinetic properties of everolimus; plasma protein binding is about 74%. Everolimus is extensively metabolized in the gastrointestinal tract and is a substrate for CYP3A4, CYP3A5, CYP2C8 and P-glycoprotein, which can lead to potentially significant drug interactions. The elimination half-life is from 18 to 35 hours but is prolonged by about 53% in patients with cirrhosis

Effect of food: in healthy subjects, high fat meals reduce systemic exposure to doses of 10 mg/day by 22% and the peak blood concentration Cmax by 54%. Light fat meals reduce AUC by 32% and Cmax by 42%.

Distribution: The apparent distribution volume (Vz/F) after a single dose is

4.7 L/kg.

Metabolism: EVEROLIMUS is mainly metabolized by CYP3A4 in the liver and to some extent in the intestinal wall. EVEROLIMUS is also a substrate of P-glycoprotein (P-gP). Therefore, absorption and subsequent elimination of systematically absorbed EVEROLIMUS may be influenced by medicinal products that interact with CYP3A4 and/or P-glycoprotein. *In vitro* studies showed that EVEROLIMUS is a competitive inhibitor of CYP3A4 and of CYP2D6 substrates, potentially increasing the concentrations of medicinal products eliminated by these enzymes. In two phase III clinical trials in patients following kidney transplantation, strong inhibitors of CYP3A4 (azoles, antifungals, cyclosporine, erythromycin) have been shown to reduce the clearance of EVEROLIMUS therapy thereby increasing EVEROLIMUS blood levels. Similarly, Rifampin, a strong inducer of CYP3A4, increases the clearance of EVEROLIMUS thereby reducing EVEROLIMUS blood levels. Caution should be exercised when co-administering EVEROLIMUS with CYP3A4 inhibitors or inducers.

Pharmacokinetic drug-to-drug interactions with cancer agents are being evaluated. Gemcitabine and paclitaxel did not alter EVEROLIMUS pharmacokinetics to a clinically relevant extent whereas imatinib notably increased EVEROLIMUS exposure with a mean increase in AUC by a multiple of 3.7 for EVEROLIMUS administered weekly and two-fold for EVEROLIMUS administered daily. Exposure to EVEROLIMUS in the presence of letrozole did not exceed that in monotherapy (study 2108). Co-administration of EVEROLIMUS did not influence pharmacokinetics of gemcitabine, imatinib or letrozole. Exposure to paclitaxel in the presence of EVEROLIMUS was slightly decreased (average by 23%).

EVEROLIMUS pharmacokinetics in transplant patients was investigated in special populations such as subjects with hepatic or renal impairment, various ethnic groups and pediatric renal transplant patients. In subjects with mild–moderate hepatic impairment, mean AUC to EVEROLIMUS is increased by 3-fold whilst renal impairment does not affect the pharmacokinetics of EVEROLIMUS. Age, weight (both over the adult range) and gender do not affect the pharmacokinetics of EVEROLIMUS to a clinically relevant extent. Also, pharmacokinetics does not alter in Japanese or Asian patients whereas black patients have 21% higher clearance compared to non-blacks. In children, the apparent clearance of EVEROLIMUS increases linearly with body surface. The clearance per square meter of body surface area is 12-fold higher compared with adult patients.

1.5.2 Pharmacodynamic studies

Pharmacokinetic/pharmacodynamic modeling based on inhibition in a peripheral biomarker (S6 kinase inhibition in peripheral blood mononuclear cells) suggests that 5-10 mg daily should be an adequate dose to produce a high-degree of sustained target inhibition. Furthermore, molecular pharmacodynamic (MPD) studies using IHC in biopsied tumor tissue assessed the degree of inhibition and

its duration (for p-S6, p-4E-BP1 and p-Akt expression) with the daily and weekly dosing. There was almost complete inhibition of p-S6 at all doses and schedules studied (p=0.001).

Data are available from phase I clinical studies of EVEROLIMUS given as a single agent to 147 patients with advanced solid tumors. Such studies included various doses and schedules (weekly dosing, range 5-70 mg and daily dosing 5-10 mg). Approximately, 46% of patients reported rash or erythema and 40% of the patients presented with stomatitis/mucositis.

The most frequent adverse events suspected to be drug-related observed in three studies using EVEROLIMUS as a single agent are listed in Table 1. The most frequent side effects (>10% of patients) seen in breast cancer studies compared to placebo are shown in Table 2 (25).

Table 1.Adverse events suspected to be drug-related in ≥10% of patients with advanced cancers reported in Phase I EVEROLIMUS monotherapy studies

	Weekly			Daily		Total
	5-30 mg n=30	50 mg n=18	70 mg n=38	5mg n=16	10 mg n=45	n=147
No. Pts with AEs						
Any event	23 (1)	17 (2)	38 (10)	14 (1)	43 (14)	135 (28)
By event						
- Rash	5	8	18	10	27 (1)	68 (1)
- Stomatitis/mucositis	6	8 (2)	16 (2)	6 (1)	23 (3)	59 (8)
- Fatigue	8	7 (1)	14 (1)	1	17 (1)	47 (3)
- Nausea	5	4	8	2	18 (1)	37 (1)
- Anorexia	1	6	10	3	15	35
- Diarrhea	1	7	7	-	9	24
- Vomiting	4	5	5	-	10	24
- Headache	7	4	6	6	4	20
- Pruritus	2	1	6	3	4	16
- Infections[1]	1	3	3 (1)	1	6 (2)	14 (3)
- Constipation	-	1	2	2	9	14

The numbers of patients (by dose level and dose schedule) who have reported grade ≥3[1] toxicities is given in brackets.

[1]. events included in brackets reached no more than grade 3 severity

[2] Infections noted as drug-related included:

Herpes simplex: 5 pts (1 at 50 mg/wk; 1 at 5mg/d; 3 at 10 mg/d)
Oral candidiasis: 5 pts (1 at 50 mg/wk; 3 at 70 mg/wk, 1 at 10 mg/d)
Pneumonia (gr3) 1 pt (10 mg/d)
Pustular rash 1 pt (20 mg/wk)
Rhinitis 2 pts (50 mg/wk)
URT Infection 1 pt (50 mg/wk
Urinary Tract Infection 1 pt (50 mg/wk)

Table 2: Adverse events (%) reported in >10% of patients in phase II/III studies of everolimus in breast cancer. The grade 3-4 AEs are highlighted.

Adverse events	Overall	Grade 3-4	Overall	Grade 3-4
Baselga et al, 2009 [22]	**Everolimus + Letrozole**		**Placebo + Letrozole**	
Stomatitis	36.5	2.2	6.1	-
Rash	20.4	0.7	7.6	-
Asthenia	17.5	-	9.8	0.8
Hot flush	10.9	-	16.7	-
Hypercholesterolemia	16.1	0.7	6.1	-
Thrombocytopenia	18.2	1.5	0.8	-
Fatigue	12.4	1.5	4.5	-
Anorexia	12.4	-	3.8	-
Hyperglycemia	13.1	5.1	3	-
Headache	10.9	-	5.3	-
Increased ALT	11.7	1.5	3.8	-
Pruritus	13.1	-	-	-
Anemia	11.7	-	0.8	-
Baselga et al, 2012 [23]	**Everolimus + Exemestane**		**Placebo + Exemestane**	
Stomatitis	56	8	11	1
Rash	36	1	6	-
Fatigue	33	3	26	1
Diarrhea	30	2	16	1
Decreased appetite	29	1	10	-
Nausea	27	<1	27	1
Cough	22	1	11	-
Dysgeusia	21	<1	5	-
Headache	19	<1	13	-
Decreased weight	19	1	5	-
Dyspnea	18	4	9	1
Arthralgia	16	1	16	-
Anemia	16	6	4	<1
Epistaxis	15	-	1	-
Vomiting	14	<1	11	<1
Peripheral edema	14	1	6	<1
Pyrexia	14	<1	6	<1
Increased AST	13	3	6	1
Constipation	13	<1	11	<1
Hyperglycemia	13	4	2	<1
Pneumonitis	12	3	-	-
Thrombocytopenia	12	3	<1	<1
Asthenia	12	2	3	0
Increased ALT	11	3	3	2
Pruritus	11	<1	3	-
Insomnia	11	<1	8	-
Back pain	11	-	8	1
Bachelot et al, 2009 [24]	**Everolimus + Tamoxifen**		**Tamoxifen alone**	
Pain	82	9	86	18
Fatigue	72	6	53	11
Nausea	35	4	35	-
Stomatitis	56	11	7	-

Anorexia	43	7	18	4
Hot flushes	22	-	33	-
Infection	35	7	19	5
Rash	44	4	7	-
Diarrhea	39	2	11	-
Constipation	17	-	23	-
Vomiting	17	-	12	4
Pneumonitis	17	2	4	4
Anemia	69	2	35	4
Leukopenia	54	2	18	-
Lymphopenia	48	2	21	4
Neutropenia	48	2	19	5

Non-infectious pneumonitis is a class effect of mTOR inhibitors. It has been reported in up to 19% of patients treated with everolimus in clinical trials. The incidence of grade 3 and 4 toxicity was up to 4% and 0.2% respectively.

Reduced blood cell counts at the initiation of treatment are frequent but remain mostly within the normal range or limited to grade 1 although grade 3 neutropenia was a DLT in one patient as was grade 3 thrombocytopenia in a patient receiving EVEROLIMUS with letrozole, where pharmacodynamic interaction is unlikely. This suggest that some patients may be particularly sensitive to the myelosuppressive effect of EVEROLIMUS making it necessary to monitor carefully blood cell counts at initiation of treatment.

Metabolic changes (hyperlipidemia and hyperglycemia) may be observed during treatment with EVEROLIMUS. Hyperlipidemia has been reported as an ADR in 10% of patients although review of the laboratory values suggests that as many as a quarter of patients develop grade 1-2 hyperlipidemia on treatment, mostly hypercholesterolemia. Hyperglycemia has been reported as an adverse event in 7% of patients. Grade 3 hyperglycemia has been observed, especially in diabetics receiving EVEROLIMUS treatment.

1.6 Rationale of continuing targeted therapies beyond progression

The concept of continuing a targeted therapy in order to offer a complementary mode of action and overcome resistance to chemotherapy is not new in oncology.

Bennouna et al (26) conducted a phase 3 study of continuation of bevacizumab (Avastin) after first progression in patients with metastatic colon cancer. It had been previously shown that bevacizumab had clinical activity in combination with chemotherapy in patients with metastatic colon cancer. However, at time of progression, it was unknown if the continuation of bevacizumab with a second-line chemotherapy regimen would have continued benefit. They found that continuing bevacizumab beyond progression improved median overall survival and median PFS.

Treatment with trastuzumab (Herceptin) beyond disease progression was also shown to improve TTP (time to progression) in HER2 overexpressing breast cancer. The German Breast Group presented a phase 3 trial, where patient who had previously received trastuzumab were randomized either to capecitabine alone or capecitabine with trastuzumab. The trial met its primary end point and showed that continuation of trastuzumab beyond disease progression offered clinical benefit (27). A post hoc analysis of this study showed that patients who received third line HER2-directed therapy also experienced significantly longer overall survival than those who did not, indicating than targeted therapy may add additional benefit even across further lines of treatment (28).

Thus, both of these studies indicate that targeted therapies act synergistically with cancer therapy and this synergy can be exploited beyond progression in pretreated patients. It is possible that even though resistance to chemotherapy occurs from changes to tumor cell biology, resistance to targeted agents is unlikely to occur through the same mechanisms, and thus a targeted therapy will continue to offer clinical benefit with acceptable toxicities.

Using the same rationale, we believe that one mechanism of resistance to hormonal agents occurs through the activation of the PI3K/Akt/mTOR pathway. When patients progress on the combination of everolimus and exemestane, it is unknown if the treatment failure is due to resistance to either agent or both. We hypothesize that when the mTOR pathway remains activated, it acts as an escape mechanism and leads to hormone resistance; thus, continued inhibition of the mTOR pathway is required.

2. OBJECTIVES

Evaluate the progression free survival in patients with breast cancer who receive everolimus beyond progression.

2.1 Primary Objectives

Progression free survival in patients with advanced or metastatic breast cancer receiving everolimus plus hormonal therapy beyond first progression.

2.2 Secondary Objectives

1. Clinical benefit rate (sum of stable disease, partial response, complete response)
2. Response rate (partial response and complete response)
3. Overall survival
4. Safety, side effects and tolerability profile of everolimus

3. STUDY DESIGN

3.1 Rationale of study design

- As stated above, EVEROLIMUS has been FDA approved in combination with EXEMESTANE in post-menopausal patients with advanced/metastatic hormone receptor-positive breast cancer who have progressed/recurred after treatment with a non-steroidal aromatase inhibitor (anastrozole or letrozole). The BOLERO-2 study found that patients receiving the combination of everolimus and exemestane had a median PFS of 10.6 months vs 4.1 months with exemestane alone (by central assessment).
- Thus, based on the current FDA approval, patients who have been started on everolimus with exemestane, have already progressed on a non-steroidal aromatase inhibitor, such as letrozole or anastrozole. At the time of disease progression on exemestane and everolimus, patients may be candidates for subsequent lines of hormonal therapy with tamoxifen or fulvestrant prior to beginning cytotoxic chemotherapy.
  - We hypothesize that progression of disease in the patients receiving everolimus plus exemestane may not represent failure of everolimus to control disease but rather hormone resistance to exemestane.
  - Since different hormonal agents have different modes of action and everolimus has been show25
  - n in preclinical studies to help overcome resistance to various hormonal agents, we hypothesize that by switching hormonal therapy and continuing inhibition of the mTOR pathway with everolimus, these patients will benefit by continuing everolimus.
  - As stated above (1.5.2), everolimus will inhibit the PI3K/Akt/mTOR pathway, which is an "escape mechanism" for hormone resistant cells, which is an effect that will continue beyond progression.
  - We thus hypothesize that even by re-instituting a hormone therapy that has been failed before, we will overcome resistance to that treatment with the use of everolimus. Alternatively, if we combine everolimus with a hormonal therapy which was not used before, everolimus is likely to help overcome resistance to this agent and prolong PFS.

3.2 Study Design

- This study will enroll patients who experience disease progression while on EVEROLIMUS and EXEMESTANE (FDA approved indication).
- After enrollment, patients will continue EVEROLIMUS but hormone therapy will be switched to any hormonal agent other than exemestane.
- Please see study schema (Figure 8)

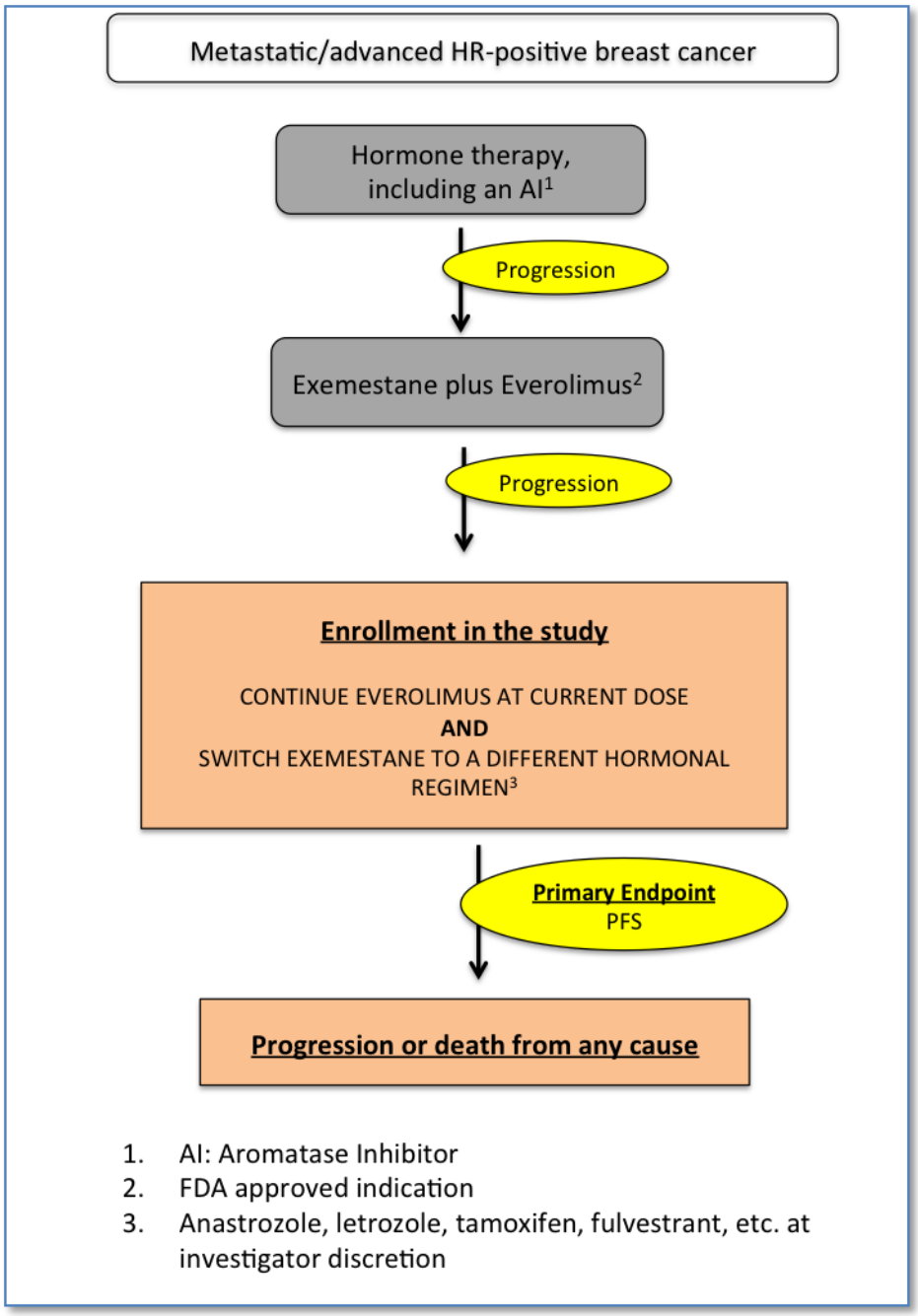

Figure 8: Study Schema
All patients enrolled will be most recently on exemestane plus everolimus, however all hormonal treatments prior to exemestane are allowed. Based on the current FDA approval of everolimus, all patients who receive everolimus with exemestane will already have received a non-steroidal aromatase inhibitor.

3.3 Drugs used in this study

- **Everolimus (study drug).** Patients enrolled will already be on everolimus. The patients will continue to receive everolimus 10 mg daily PO OR THEIR MOST RECENT DOSE IF THERE WERE PREVIOUS DOSE REDUCTIONS.
- **Hormonal therapy.** Since the patients most recently progressed on Exemestane, hormone therapy will need to be switched to another hormone agent, the choice of which will be left to investigator discretion.
- We expect that the eligible patients will have received 1-5 prior lines of hormonal therapy, (e.g. Tamoxifen, Fulvestrant, Anastrozole, Letrozole). **However, the most recent therapy will be EVEROLIMUS plus EXEMESTANE.**
- When a patient is switched from Exemestane to another type of hormone therapy, priority will be given to one of the agents not previously used (i.e. prior to being treated with Everolimus plus Exemestane).
- It is allowed to use a hormonal therapy that the patient has taken in the past, as long as the reason for discontinuation was not significant toxicity. If the patient has discontinued a prior hormonal treatment due to significant side effects (grade III or IV or life threatening side effects), it is recommended to avoid using a drug belonging to that class.

- **The dosing recommendations for most commonly used hormonal agents are listed below:**

a. Anastrozole (Arimidex): Anastrozole is a non-steroidal aromatase inhibitor (AI). Recommended dose is 1 mg oral daily.

b. Letrozole (Femara): Letrozole is a non-steroidal aromatase inhibitor (AI). Recommended dose is 2.5 mg oral daily.

c. Tamoxifen: Tamoxifen is a SERM (Selective Estrogen Receptor Modulator). Recommended dose is 20 mg oral daily.

d. Fulvestrant (Faslodex): Fulvestrant is an Estrogen Receptor Antanonist. It is given I.M. (intramuscularly) and recommended dosing is 500 mg on days 1, 15, and 29; maintenance with 500 mg monthly.

e. Megestrol acetate (Megace): Megestrol acetate is a progestin, which is usually dosed at 40 mg orally 4 times a day.

3.4 Description of the study

This is an open label, single arm, phase II study in patients with advanced hormone refractory breast cancer. Patients will be followed for progression free survival, response rate, clinical benefit rate, overall survival and safety.

At the time of disease progression the patient will be removed from the study but will still be followed for overall survival analysis.

38 (thirty eight) patients will be recruited.

3.5 Outcomes Measures

PFS (Progression Free Survival) will be measured as time to progression or death from any cause from the initiation of alternate hormonal treatment in combination with everolimus.

Clinical benefit rate (response rate plus stable disease) will also be assessed after 8, 16 and 24 weeks of treatment and then every 3 months (12 weeks).

Response rate will be measured after 8, 16 and 24 weeks of therapy and then every 3 months (12 weeks) using RECIST criteria. Response rate will be measured as the sum of partial and complete response.

OS (Overall Survival) will be measured as time to death from any cause from the initiation of alternate hormonal treatment in combination with everolimus.

See Appendix A, Study Flowchart

3.6 Safety Plan

The **safety** of everolimus in combination with hormonal therapy will be monitored continuously over the study period. Patients will be evaluated at each study visit for the duration of their participation in the study for side effects (clinical or laboratory). See Appendix A, Study Flowchart

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

Refer to text and tables 3 and 4 for the management of toxicities and dose adjustments of everolimus. DOSE REDUCTIONS WILL BE DONE BY ONE

LEVEL, which is defined as 2.5 mg daily, i.e. a patient receiving 10 mg will be subsequently treated with 7.5 mg and a patient taking 7.5 mg will be reduced to 5 mg. Please see table 5 for management of dose modifications (page 35).

3.6.1 Management of stomatitis/oral mucositis/mouth ulcers

Stomatitis is one of the most common side effects encountered in patients treated with mTOR inhibitors and was seen in up to 81% of patients in phase I studies with everolimus in breast cancer; in phase II and III studies, the overall incidence of stomatitis was ~50%. Most of the patients had mild symptoms, while only 10% had grade 3 or 4 toxicity.

The oral lesions are similar to aphthous or herpetic ulcers and are well demarcated, oval, and superficial. They contain a white necrotic center and they are surrounded by an erythematous ring. They can cause mouth pain, dysphagia and loss of taste (dysgeusia). Stomatitis should be distinguished from chemotherapy-induced mucositis, which usually affects the entire gastrointestinal tract and can be associated with diarrhea. The toxicity appears to be dose dependent and it most often appears during the first cycle (25).

Stomatitis/oral mucositis/mouth ulcers due to EVEROLIMUS should be treated using local supportive care, in combination with appropriate dose interruptions and reductions when indicated. If 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 and please refer to TABLE 3 for dose modification recommendations (non hematological toxicity):

a) For mild toxicity (grade 1), use conservative measures such as non-alcoholic mouthwash or salt water (0.9%) mouthwash several times a day until resolution. No dose changes for everolimus are recommended.
b) For more severe toxicity (grade 2 in which case patients have pain but are able to maintain adequate oral alimentation, or grade 3 in which case patients cannot maintain adequate oral alimentation), the suggested treatments are topical analgesic mouth treatments (i.e., local anesthetics such as, benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol, or phenol) with or without topical corticosteroids, such as triamcinolone oral paste 0.1% (Kenalog in Orabase®). Please see table 3 for dose interruption recommendations.
c) Agents containing hydrogen peroxide, iodine, and thyme derivatives may tend to worsen mouth ulcers. It is preferable to avoid these agents.
d) Antifungal agents must be avoided unless a fungal infection is diagnosed. In particular, systemic imidazole antifungal agents (ketoconazole, fluconazole, itraconazole, etc.) should be avoided in all patients due to their strong inhibition of everolimus metabolism, therefore leading to higher everolimus exposures. Therefore, topical antifungal agents are preferred if an infection is

diagnosed. Similarly, antiviral agents such as acyclovir should be avoided unless a viral infection is diagnosed.

e) For grade 4 toxicity (life threatening symptoms), everolimus will be discontinued.

3.6.2 Management of hyperlipidemia and hyperglycemia

mTOR inhibitors interfere with lipid and glucose metabolism and can lead to hyperlipidemia and hyperglycemia. Severe hypertriglyceridemia can lead to pancreatitis and elevated cholesterol can increase the risk of cardiovascular disease.

3.6.2.1 Management of hyperlipidemia

a) Treatment of hyperlipidemia should take into account the pre-treatment status and dietary habits. Blood tests to monitor hyperlipidemia must be taken in the fasting state.

b) For all grades of hyperlipidemia it is recommended to initiate diet modification and exercise per American Heart Association guidelines.

c) Grade 2 or higher hypercholesterolemia (>300 mg/dL) or grade 2 or higher hypertriglyceridemia (>300 mg/dL) should be treated with a statin or appropriate lipid-lowering medication, in addition to lifestyle modifications.

d) Patients should be monitored clinically and through serum biochemistry for the development of rhabdomyolysis and other adverse events as required in the product label/data sheets for HMG-CoA reductase inhibitors. 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 kinase (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.

e) For grade 2 hyperlipidemia, no dose adjustment is required for everolimus.

f) For grade 3 toxicity, temporary interruption of everolimus with following dose reduction by one level (2.5 mg) is recommended.

g) For grade 4 toxicity (cholesterol >500 mg/dl or triglycerides >1,000 mg/dl), everolimus should be discontinued

3.6.2.2 Management of hyperglycemia

mTOR inhibitors can cause hyperglycemia by affecting insulin metabolism. Hyperglycemia can be seen in diabetic or non-diabetic patients. Studies of everolimus in breast cancer report an incidence of up to 17 % (25).

We suggest that optimal glucose control should be achieved before starting a

patient on everolimus and thereafter glucose levels should be monitored during treatment according to the study schema.

Management recommendations are based on fasting glucose (FBG) measurements.

a) No intervention is required for grade 1 hyperglycemia (>upper limit of normal-160 mg/dl). We recommend monitoring as per study schema.
b) Grade 2 or higher hyperglycemia (fasting glucose >160 mg/dl) should be treated according to American Diabetes Association guidelines.
c) Grade 2 hyperglycemia (fasting glucose >160-250 mg/dl) does not require interruption or dose reductions for everolimus.
d) For grade 3 hyperglycemia (fasting glucose >250-500 mg/dl), everolimus should be temporarily interrupted and re-initiated at a lower dose (reduced by one level of 2.5 mg).
e) If grade 4 toxicity (fasting glucose >500 mg/dl) occurs, everolimus should be discontinued.

Table 3 Criteria for dose-modification in case of suspected EVEROLIMUS toxicity and re-initiation of EVEROLIMUS treatment

Toxicity	Actions
Non-hematological toxicity Grade 1	Symptomatic management, no dose modification required.
Grade 2 (except metabolic adverse events* and pneumonitis – refer to Table 4)	Interrupt EVEROLIMUS until recovery to grade ≤1. Then reintroduce EVEROLIMUS at current dose. If grade 2 toxicity recurs, interrupt until recovery to grade ≤1, then restart everolimus with one level reduction (by 2.5 mg daily, refer to table 6).
Grade 3 (except metabolic adverse events* and pneumonitis- see Table 4)	Interrupt EVEROLIMUS until recovery to grade ≤1. Then reintroduce EVEROLIMUS with one level reduction (by 2.5 mg daily, refer to table 6).

Grade 4	Discontinue EVEROLIMUS.
Hematological toxicity	
Grade 2 Thrombocytopenia (platelets <75, ≥ 50x10^9/L)	Interrupt EVEROLIMUS until recovery to grade ≤1 (>75 x10^9/L). Then reintroduce EVEROLIMUS by one level reduction (2.5 mg daily, refer to table 6). If thrombocytopenia again returns to grade 2, interrupt EVEROLIMUS until recovery to grade ≤1. Then reintroduce EVEROLIMUS at current dosing but every other day.
Grade 3 Thrombocytopenia (platelets <50, ≥ 25 x10^9/L)	Interrupt EVEROLIMUS until recovery to grade ≤1 (platelets ≥ 75 x10^9/L). Then resume EVEROLIMUS reduced by one level (2.5 mg/day, refer to table 6) and given every other day. If grade 3 thrombocytopenia recurs, discontinue EVEROLIMUS.
Grade 4 Thrombocytopenia (platelets < 25 x10^9/L)	Discontinue EVEROLIMUS.
Grade 3 Neutropenia (neutrophils <1, ≥0.5 x10^9/L)	Interrupt EVEROLIMUS until recovery to grade ≤1 (neutrophils ≥ 1.5 x 10^9/L). Then resume EVEROLIMUS by one level reduction (2.5 mg/day, refer to table 6). If ANC again returns to Grade 3, hold EVEROLIMUS until the ANC ≥ 1.5 x 10^9/L. Then resume EVEROLIMUS dosing at one level reduction every other day. Discontinue patient from study therapy for a third episode of grade 3 neutropenia.
Grade 4 Neutropenia (neutrophils < 0.5 x10^9/L)	Interrupt EVEROLIMUS until recovery to grade ≤ 1 (neutrophils ≥ 1.5 x 10^9/L). Then resume EVEROLIMUS at reduced by one level (2.5 mg/day, refer to table 6) every other day. If grade 3 or grade 4 neutropenia occurs despite this dose reduction, discontinue EVEROLIMUS.
Grade 3 febrile neutropenia (not life-threatening)	Interrupt EVEROLIMUS until resolution of fever and neutropenia to grade ≤ 1. Hold further EVEROLIMUS until the ANC ≥

	1,500/mm^3 and fever has resolved. Then resume EVEROLIMUS at reduced by one level (2.5 mg/day, refer to table 6) every other day. If febrile neutropenia recurs, discontinue EVEROLIMUS.
Grade 4 febrile neutropenia (life-threatening)	Discontinue EVEROLIMUS.
Any hematological or non-hematological toxicity requiring interruption for ≥ 3 weeks	Discontinue EVEROLIMUS
*** For metabolic adverse events (hyperlipidemia and hyperglycemia) see text (section 3.6.2)**	

3.6.3 Management of non-infectious pneumonitis

Both asymptomatic radiological changes (grade 1) and symptomatic non-infectious pneumonitis (grade 2 = not interfering with activities of daily living or grade 3 = interfering with activities of daily living and oxygen indicated) have been noted in patients receiving everolimus therapy. Non-infectious pneumonitis has been associated with everolimus and other mTOR inhibitors. In order to monitor for asymptomatic (grade 1) pulmonary infiltrates, a chest X-ray every 3 months is required if a CT scan of chest is not used for disease evaluations. Additional chest X-rays/CT scans may be done, when clinically necessary. If non-infectious pneumonitis develops, consultation with a pulmonologist should be considered. Management of non-infectious pneumonitis suspected to be associated with everolimus and dose modifications instructions are provided in TABLE 4.

The usual dose of steroids for the management of non-infectious pneumonitis is prednisone, 1 mg/kg. The steroids can be tapered slowly after clinical improvement and improvement of pulmonary function tests.

Non-infectious pneumonitis may be difficult to distinguish from lymphangitic tumor spread. If there is doubt about the cause of the clinical or radiologic abnormalities, bronchoscopic biopsies or repeat imaging after interruption of everolimus may be helpful.

Table 4 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	Administer 100% of EVEROLIMUS dose.
Grade 2	CT scan with lung windows. Consider pulmonary function testing includes: spirometry, DLCO, and room air O_2 saturation at rest. Repeat each subsequent Cycle until return to within normal limits. Consider a bronchoscopy.	Symptomatic only. Rule out infection. Prescribe corticosteroids if cough is troublesome.	Reduce EVEROLIMUS dose by one level (2.5 mg, refer to table 6) until recovery to $\leq$ grade 1. EVEROLIMUS may also be interrupted if symptoms are troublesome. Patients will be withdrawn from the study if they fail to recover to $\leq$ grade 1 within 3 weeks.
Grade 3	CT scan with lung windows and pulmonary function testing includes: spirometry, DLCO, and room air O_2 saturation at rest. Repeat each subsequent Cycle until return to within normal limits. Bronchoscopy is recommended.	Prescribe corticosteroids if infective origin is ruled out. Taper as medically indicated.	Hold treatment until recovery to $\leq$ grade 1. May restart protocol treatment within 3 weeks at a reduced dose (by one level=2.5 mg, refer to table 6) if evidence of clinical benefit. Patients will be withdrawn from the study if they fail to recover to $\leq$ grade 1 within 3 weeks.
Grade 4	CT scan with lung windows and required pulmonary function testing includes: spirometry, DLCO, and room air O_2 saturation at rest. Repeat each subsequent Cycle until return to within normal limits. Bronchoscopy is recommended.	Prescribe corticosteroids if infective origin is ruled out. Taper as medically indicated.	Discontinue treatment.

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

4. MATERIALS AND METHODS

4.1 Inclusion Criteria

Patients will be included in the study based on the following criteria:

- ER and/or PR-positive at primary diagnosis and at metastatic diagnosis where tissue is available (defined as > or = 1% of staining nuclei).
- Progressive or recurrent breast cancer defined as disease progression or recurrence while on a combination of exemestane with everolimus.
- HER2/neu-negative breast cancer by standard criteria (IHC < 3+ or FISH-negative if IHC 2+) at primary diagnosis.
- Histologically confirmed, measurable or evaluable disease. Patients should have at least one measurable lesion. If applicable, RECIST criteria should be used.
- Life expectancy> 6 months.
- Age >18 years.
- ECOG performance status ≤ 2.
- Adequate bone marrow function as indicated by the following:

  ANC >1,500/μL

  Platelets ≥100,000/μL

  Hemoglobin >10 g/dL
- Adequate renal function, as indicated by creatinine≤1.5× upper limit of normal (ULN).
- Adequate liver function, as indicated by bilirubin ≤1.5× ULN.
- INR ≤ 1.3 (or ≤ 3 on anticoagulants).
- AST or ALT <2× ULN unless related to primary disease.
- Signed informed consent.
- Adequate birth control.
- 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.

4.2 Exclusion Criteria

Patients will be excluded from the study based on the following criteria:

- Prior treatment with everolimus other than in combination with hormonal therapy for treatment of breast cancer or prior treatment with another mTOR inhibitor (sirolimus, temsirolimus) for any indication.
- HER2 positive disease as defined by 3+ IHC or positive FISH (both in primary and metastatic sites).

- Active infection: temperature >100F, fever of unknown origin, active symptoms or signs of infection as defined by the investigator.
- Uncontrolled central nervous system metastases.
- Life-threatening, visceral metastases.
- Pregnant or lactating women.
- Prior chemotherapy within the last 4 weeks.
- Prior radiation therapy within the last 4 weeks; prior radiation therapy to indicator lesion (unless objective disease recurrence or progression within the radiation portal has been documented since completion of radiation).
- Concomitant malignancies or previous malignancies within the last 5 years, with the exception of adequately treated basal or squamous cell carcinoma of the skin or carcinoma *in situ* of the cervix.
- History of significant cardiac disease, cardiac risk factors or uncontrolled arrhythmias
- Hypersensitivity to trial medications (everolimus).
- Emotional limitations, which the investigator judges could limit the patient's ability to follow up and comply with study procedures.
- Patients receiving chronic, systemic treatment with corticosteroids or another immunosuppressive agent
- Uncontrolled diabetes as defined by fasting serum glucose >1.5 x ULN
- Liver disease such as cirrhosis, chronic active hepatitis or chronic persistent hepatitis
- A known history of HIV seropositivity.
- 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).
- Patients with an active, bleeding diathesis.
- Female patients who are pregnant or breast feeding, or adults of reproductive potential who are not using effective birth control methods. If barrier contraceptives are being used, these must be continued throughout the trial by both sexes. Hormonal contraceptives are not acceptable as a sole method of contraception. (Women of childbearing potential must have a negative urine or serum pregnancy test within 7 days prior to administration of EVEROLIMUS).
- Symptomatic intrinsic lung disease or extensive tumor involvement of the lungs, resulting in dyspnea at rest.
- Taking any of the following agents:

- Chronic treatment with systemic steroids or another immunosuppressive agent (use of steroids as part of management of everolimus toxicities will be allowed).
- Live vaccines.
- Patients who have received live attenuated vaccines within 1 week of start of Everolimus and during the study. Patient should also avoid close contact with others who have received live attenuated vaccines. Examples of live attenuated vaccines include intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella and TY21a typhoid vaccines;
- Drugs or substances known to be inhibitors or inducers of the isoenzyme CYP3A.
- Please see section 4.4 for excluded therapies during the entirety of the study.

4.2.1 Screening for hepatitis

Screening for hepatitis B

(Depending on the indication please consider hepatitis B and C screening criteria below.)

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

- All patients who currently live in (or 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**

- Patients who test positive for active hepatitis should be excluded based on section 4.2, exclusion criteria.

Screening for hepatitis C

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

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

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

- Patients who test positive for active hepatitis should be excluded based on section 4.2, exclusion criteria.

4.3 Study medication (Everolimus)

Novartis will provide the study drug.

The Sponsor Investigator of the study will ensure maintenance of complete and accurate records of the receipt, dispensation, and disposal or return of all study drug in accordance with 21 Code of Federal Regulations

Dosage: Everolimus will be provided as an oral formulation as 2.5, 5 or 10 mg tablets and will be taken at the dose of 10mg daily or patient's dose at enrollment.

Upon receipt, everolimus should be stored according to the instructions specified on the drug labels. Everolimus should be opened only at the time of administration, as the drug is both hygroscopic and light sensitive.

These instructions should also be made clear to the patient for storage and self-administration of everolimus at home.

4.3.1 Dosing modifications

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

study treatment schedule adjustments and dose levels are provided in Table 5. Indications for dose modifications are provided in table 3 and table 4.

Table 5 Study treatment schedule adjustments and dose levels

Dose level	Dose and schedule
0 (starting dose)	**10 mg daily**
-1	**7.5 mg daily**
-2	**5 mg daily**
-3	**2.5 mg daily**
-4	**2.5 mg every other day**

4.4 Concomitant and excluded therapies

All medications and non-drug therapies taken within 30 days prior to starting study treatment should be reported to the Principal Investigator.

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

Concomitant treatments are discussed in section 3.3.

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

- No other investigational therapy should be given to patients.
- No chemotherapy agents other than the study medication should be given to patients. If such agents are required for a patient then the patient must first be withdrawn from the study.
- Concurrent administration of EVEROLIMUS and strong CYP3A4 inhibitors (such as ketoconazole, itraconazole, ritonavir) and inducers (such as rifampin,,rifabutin) should be avoided. Provided there is no alternative treatment available, patients should be closely monitored for potential toxicities.
- Concurrent administration of EVEROLIMUS and moderate CYP3A4 inhibitors (such as erythromycin, fluconazole, calcium channel blockers, benzodiazepines) and moderate CYP3A4 inducers (e.g. carbamazepine, phenobarbital, phenytoin) should also be avoided if possible, or used subject to caution (e.g. increased frequency of safety monitoring, temporary interruption of EVEROLIMUS).

- Competitive inhibition could occur when EVEROLIMUS is combined with drugs that are also CYP3A4 substrates. Therefore caution should be exercised in such cases.
- Co-administration with substrates, inducers, or inhibitors of P-glycoprotein should be avoided, if possible, or used subject to caution (e.g. increased frequency of safety monitoring, temporary interruption of EVEROLIMUS).
- Grapefruit and grapefruit juice affect cytochrome P450 and P-glycoprotein activity and should therefore be avoided.
- In addition, patients should avoid Seville oranges and star fruit, as well as the juice of these fruits, which are potent CYP3A4-inhibitors.
- EVEROLIMUS may affect the response to vaccinations making the response to the vaccination less effective. Live vaccines should be avoided while a patient is treated with EVEROLIMUS.
- 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 coadministration of EVEROLIMUS and oral anticoagulants is possible but should be subject to verification of coagulation (INR) once steady state

4.4.1 Antineoplastic therapy

The administration of anticancer agents other than study medication, including chemotherapy, investigational agents, and biologic agents is NOT permitted while patients are enrolled in this study. The need for other anti-cancer therapy will be attributed to disease progression and will require the patient to be withdrawn from study treatment.

Palliative radiotherapy for local peripheral metastases not being used as target lesions is permitted, but the need for such therapy may be an indication of disease progression and should be discussed prior to administration. Radiotherapy for central metastases (e.g., vertebral, mediastinal) is not permitted. Patients requiring such therapy prior to completion of the study should be considered to have progression of disease and study treatment should be discontinued.

4.4.2 Bisphosphonates

Patients who enter the study on bisphosphonates may continue this therapy. The need to start bisphosphonate therapy on study will be considered as an indication of disease progression and the patient will be discontinued from protocol therapy.

4.4.3 Hematopoietic growth factors and antibiotics

Hematopoietic growth factors and antibiotics should not be administered prophylactically. Antibiotics can be administered as required for treatment of infections, however drug interactions should be considered and antibiotics that can interact with everolimus should be avoided (please refer to table 6). Recombinant erythropoietin-like product (such as Procrit®) may be received throughout the study.

4.4.4 Anti-emetics

Approximately 25% of patients experience nausea when treated with EVEROLIMUS alone and 16% experience vomiting. The majority of nausea and vomiting events is of Grade 1 or 2. EVEROLIMUS is best classified as having moderate emetogenic potential, therefore prophylactic treatment with appropriate anti-emetic agents as per local institutional guidelines is recommended.

4.4.5 Analgesics

Baseline analgesics for tumor-related pain should be maintained during the study.

However, an increase in analgesic use or a step up on the WHO analgesic ladder for control of tumor-related pain may indicate disease progression. If an increase in analgesic medication from baseline is required during the study, the patient should be evaluated for progression of disease.

4.4.6 Systemic corticosteroids

Prolonged (greater than 2 weeks in duration) treatment with systemic corticosteroid treatment is not allowed during the study except for the treatment of non-infectious pneumonitis or everolimus toxicities as described in section 3.6. Prolonged treatment with topical steroids should be discussed with the Principal Investigator.

4.4.7 P-glycoprotein (P-gp) inhibitors

Patients receiving any concomitant medications known to inhibit P-gp function (e.g., verapamil, diltiazem, nicardipine, cyclosporine, quinine) will not be excluded from the study but these medications should be avoided.

4.4.8 Cytochrome p450 enzymes

EVEROLIMUS is mainly metabolized by CYP3A4 in the liver and to some extent in the intestinal wall. Therefore the following advice should be followed:

- Patients being treated with drugs recognized as being strong inhibitors or inducers of the isoenzyme CYP3A (Rifabutin, Rifampicin, Clarithromycin, Ketoconazole, Itroconazole, Voriconazole, Ritinavir, Telithromycin) within the last 5 days prior to enrollment should not be enrolled into the study
- Wherever possible, drugs or substances known to be inhibitors or inducers of the isoenzyme CYP3A should be avoided as systemic therapy in association with EVEROLIMUS as these can alter its metabolism (see Table 5).
- Patients should also refrain from herbal/alternative remedies and grapefruit juice.

Table 6 Clinically relevant drug interaction: substrates, inducers and inhibitors of isoenzyme CYP3A

<table>
<tr><th colspan="3">Substrates</th></tr>
<tr><td colspan="2">Antibiotics[1]:
clarithromycin*
erythromycin

telithromycin*

Anti-arrhythmics:
quinidine

Benzodiazepines:
alprazolam
diazepam
midazolam
triazolam

Immune Modulators:
cyclosporine
tacrolimus (FK506)

HIV Protease Inhibitors:
indinavir*
ritonavir*
saquinavir*

Prokinetic:
cisapride

Antihistamines:
astemizole
chlorpheniramine</td><td>Calcium Channel Blockers:
amlodipine
diltiazem
felodipine
nifedipine
nisoldipine
nitrendipine
verapamil

HMG CoA Reductase Inhibitors[2]:

cerivastatin
lovastatin

simvastatin

Miscellaneous:

buspirone

haloperidol
methadone
pimozide
quinine

sildenafil
tamoxifen
trazodone
vincristine
aprepitant</td></tr>
<tr><th colspan="3">Inducers</th></tr>
<tr><td>Carbamazepine
Phenobarbital
Phenytoin</td><td>Rifabutin*
Rifampin*</td><td>St John’s wort
Troglitazone</td></tr>
<tr><th colspan="3">Inhibitors</th></tr>
</table>

Amiodarone Cimetidine Clarithromycin Diltiazem Erythromycin	Fluvoxamine* Grapefruit juice Seville orange juice or product Indinavir Itraconazole* Ketoconazole* Voriconazole* Posaconazole*	Mibefradil Nefazodone* Nelfinavir* Troleandomycin Verapamil

Based on: Ingelman-Sundberg M, Human drug metabolising cytochrome P450 enzymes: properties and polymorphisms, NaunynSchmiedebergs Arch Pharmacol. 2004 Jan;369(1):89-104 and [http://www.medicine.iupui.edu/flockhart/clinlist.htm]

* asterisk denotes strong inhibition/ induction

Please note:

Strong inhibitor implies that it can cause ≥5-fold increase in AUC or ≥80% decrease in clearance of sensitive CYP substrates

Moderate inhibitor implies that it can cause 2 to 5-fold increase in AUC values or 50-80% decrease in clearance of sensitive CYP substrates.

(Distinction is not always categorical as interaction can vary according to conditions).

1. Macrolide antibiotics: Azithromycin is not a CYP3A substrate. It may therefore be employed where antibiotic therapy with a macrolide is desirable in a patient being treated with EVEROLIMUS

2. Statins: Atorvastatin and pravastatin may be administered concomitantly with EVEROLIMUS, since a PK interaction study has shown that there is no relevant PK interaction

4.5 Study Assessments- please refer to appendix A, Study Flowchart

- Monitor CBC, chemistries every visit. Monitor TSH and lipid profile every 4 weeks and then every 12 weeks (after 24 weeks in the study).

4.5.1 Assessments during Treatment

- Monitor CBC, chemistries, TSH, lipid profile per study flowchart.

4.5.2 Follow-Up Assessments

Patients will have repeat staging performed every 8, 16, 24 weeks and then every 3 months with CT scans ± bone scans. Repeat staging may be performed earlier if there is clinical evidence to suggest disease progression.

4.6 Discontinuation of Protocol-Specified Therapy

Protocol-specified therapy may be discontinued for any of the following reasons:

- Progressive disease
- Unacceptable toxicity
- Patient election to discontinue therapy (for any reason)
- Physician's judgment

4.7 Subject Discontinuation

Any patient, who suffers from a serious adverse event or intolerable side effect thought to be caused by, or associated with the study treatment, will be withdrawn from the study and receive alternative treatment recommendations from the principle investigator. Any participant who encounters an unexpected life emergency situation that is noncompliant or conflicts with the study protocol will be withdrawn. Any patient who revokes his/her consent to participation or voluntarily withdraw from the study will also be discontinued from the clinical trial. In addition, subjects will be withdrawn if the principal investigator determines that discontinuation from the study is in the best interests of the patients. All patients discontinued from the study will receive a final safety evaluation and all unused proportion of study medications will be recalled and collected from them. And the reasons for premature discontinuation will be captured separately in the corresponding Drug Administration CRF. And all study treatment discontinuations will be recorded in the Study Completion CRF.

4.8 Study Discontinuation

The principal investigator or the study sponsors have the rights to terminate this study in its entirety at any time. Reasons for premature discontinuation of the clinical trial may include but not limited to the following:

- The incidence or severity of adverse events, progressive disease, unacceptable toxicity in this or other studies indicates a potential health hazard to subjects

- Subject enrollment is unsatisfactory or patients elect to discontinue therapy
- Data recording is inaccurate or incomplete
- Compliance with the study protocol or FDA regulations is violated

Detailed rationale for this action and consequences of the termination will be documented. Also, all participants will be formally notified in writing of study discontinuation and advised of any potential risks to their health.

4.9 Statistical Methods

4.9.1 Data Cleaning

Prior to performing any analysis, standard data screening and cleaning procedures will be performed, which consist of (1) screening the data for implausible values and possible data-entry errors, (2) identifying potential outliers, (3) assessing the extent and pattern of missing data, and (4) checking whether appropriate statistical assumptions such as normality are satisfied when necessary.

4.9.2 Efficacy Analysis

Endpoints

The primary objective of this phase II clinical trial is to evaluate the progression free survival in patients who receive everolimus in combination with a hormonal agent in study subjects.

Response rate (partial response plus complete response) will be measured after 8, 16 and 24 weeks of therapy and then every 3 months (12 weeks) using RECIST criteria.

Clinical benefit rate (response rate plus stable disease) will be assessed after 8, 16 and 24 weeks of treatment and then every 3 months (12 weeks).

OS (overall survival) will be measured as time to death from any cause from the initiation of alternate hormonal treatment in combination with everolimus.

Safety, tolerability and side effect profile of everolimus will be continuously monitored by the **WCI DSMB.**

Moreover, we will investigate overall survival among patients switching to different hormonal agents but all combined with everolimus.

4.9.3 Sample Size Estimation:

Based on the work of Baselga et al (2012), we expect the median PFS to be approximately 4 months in the population studied treated with Everolimus, while it is approximately 2.5 months without everolimus. Single arm design was used, and we

estimate about about 48 months accrual time period, and each patients will be followed for about 24 months. Assuming an exponentially distributed progression free survival time, we will need to enroll 34 patients to secure 85% statistical power under a type I error of 0.05 by a one-sided test (https://stattools.crab.org/Calculators/oneArmSurvivalColored.html). After considering about 10% of drop-off rate, 38 patients will be enrolled in this study.

4.9.4 Statistical Methods

The median PFS/OS and survival rate at different time points for this study will be estimated by Kaplan-Meier method along with 95% confidence interval. For other clinical outcome, such as response rate, will be measured at different time points, e.g. 8, 16, and 24 weeks, and be summarized as percentage of stable disease, complete remission or partial remission along with 95% confidence interval.

4.9.5 Missing Data

All missing measurements will be excluded from the analysis.

4.10 Data Quality Assurance

Accurate, consistent, and reliable data will be ensured through the use of standard practices and procedures.

4.11 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in accordance with current U.S. Food and Drug Administration (FDA) Good Clinical Practices (GCPs), and local ethical and legal requirements.

5. REPORTING OF ADVERSE EVENTS

5.1 Adverse Event and Reporting Definitions

With the occurrence of an adverse event, the first concern will be for the safety of the subject. Investigators are required to report to Novartis Drug Safety any **serious adverse event**, whether **expected** or **unexpected**, and which is assessed by the investigator to be **reasonably or possibly related** to or caused by the study medication.

An **adverse event(AE)** is any untoward medical occurrence in a subject participating in an investigational study or protocol regardless of causality assessment. An adverse event can be an unfavorable and unintended sign (including an abnormal laboratory finding), symptom, syndrome or disease

associated with or occurring during the use of an investigational product whether or not considered related to the investigational product.

Serious adverse events (SAE) are adverse events occurring at any dose which meet one or more of the following **serious criteria**:

Results in **death** (i.e. the AE caused or led to death)

Is **life-threatening** (i.e. the AE placed the subject at immediate risk of death; it does not apply to an AE which hypothetically might have caused the death if it were more severe)

Requires or prolongs inpatient **hospitalization** (i.e. the AE required at least a 24-hour inpatient hospitalization or prolonged a hospitalization beyond the expected length of stay; hospitalizations for elective medical/surgical procedures, scheduled treatments, or routine check-ups are not SAEs by this criterion)

Is **disabling** (i.e. the AE resulted in a substantial disruption of the subject's ability to carry out normal life functions)

Is a **congenital anomaly/birth defect** (i.e., an adverse outcome in a child or fetus of a subject exposed to the study drug prior to conception or during pregnancy)

Does not meet any of the above serious criteria but **may jeopardize the subject** and **may require medical or surgical intervention** to prevent one of the outcomes listed above

Expected adverse events are those adverse events that are **listed** or characterized in the Package Insert or current Investigator Brochure.

Unexpected adverse events are those **not listed** in the Package Insert (P.I.) or current Investigator Brochure (I.B.). This includes adverse events for which the specificity or severity is not consistent with the description in the P.I. or I.B. For example, under this definition, hepatic necrosis would be unexpected if the P.I. or I.B. only referred to elevated hepatic enzymes or hepatitis.

5.2 Reporting of Serious Adverse Events

All SAEs that are serious and reasonably or probably related to the use of everolimus (this applies to both expected and unexpected events) should be recorded on a MedWatch 3500 Form:

Novartis Pharmaceuticals CS&E

FAX (888-299-4565)

The principal investigator has the obligation to report all serious adverse events to the FDA, IRB, and Novartis Pharmaceuticals Clinical Safety and Epidemiology Department (CS&E).

All events reported to the FDA by the investigator are to be filed utilizing the Form FDA 3500A (MedWatch Form).

All events must be reported, by FAX (888-299-4565), to Novartis Pharmaceuticals CS&E Department within 24 hours of learning of its occurrence. This includes serious, related, labeled (expected) and serious, related, unlabeled (unexpected) adverse experiences. All deaths during treatment or within 30 days following completion of active protocol therapy must be reported within 5 working days.

Any serious adverse event occurring after the patient has provided informed consent and until 4 weeks after the patient has stopped study participation must be reported. This includes the period in which the study protocol interferes with the standard medical treatment given to a patient (e.g. treatment withdrawal during washout period, change in treatment to a fixed dose of concomitant medication).

Serious adverse events occurring more than 4 weeks after study discontinuation need only be reported if causation to the Novartis study drug (or therapy) is suspected.

For Comparator Drugs/Secondary Suspects (Concomitant Medications), all serious adverse experiences will be forwarded to the product manufacturer by the investigator.

AND Emory IRB

1599-001-1AV

Institutional Review Board

Emory University, 1599 Clifton Road,

Atlanta, GA 30322

Tel: 404-712-0720

Fax: 404-727-1358

Email: IRB@emory.edu

Webpage: http://emory.edu/IRB/

5.2.1 MedWatch 3500 Reporting Guidelines:

In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description (section 5) of the MedWatch 3500 form:

- Protocol description (and number)
- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

Follow-up information:

Additional information may be added to a previously submitted report by any of the following methods:

- Adding to the original MedWatch 3500 report and submitting as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500 form
- Summarizing new information and faxing it with a cover letter including subject identifiers (i.e. D.O.B. initial, subject number), protocol description and number, if assigned, brief adverse event description, and notation that additional or follow-up information is being submitted). The patient identifiers are important so that the new information is added to the correct initial report)

Occasionally Novartis may contact the reporter for additional information, clarification, or current status of the subject for whom and adverse event was reported. For questions regarding SAE reporting, you may contact the Novartis Drug Safety representative.

Study Drug Relationship:

The investigator will determine which events are associated with the use of study drug. For reporting purposes, an AE should be regarded as possibly related to the use of everolimus if the investigator believes:

- There is a clinically plausible time sequence between onset of the AE and the study drug administration; and/or
- There is a biologically plausible mechanism for the study drug to cause or contribute to the AE; and
- The AE cannot be attributed solely to concurrent/underlying illness, other drugs, or procedures.

5.2.2 Data and Safety Monitoring Plan:

The data safety monitoring plan will be implemented by Dr. Elisavet Paplomata, the Principal Investigator (P.I.) of this study. The plan is based on self-monitoring, internal CTO real time monitoring using the quality assurance committee, and monitoring via Winship Cancer Institute ("WCI") Data Safety Monitoring Committee (DSMC) as per WCI CTO standard operating procedure. Dr. Paplomata and the investigators, the clinical research coordinator and the regulatory affairs coordinator will meet at least on a monthly basis to review and discuss study data to ensure subject safety. The research coordinators will maintain one spread sheet which will summarize all the patient data for patients actively being treated on the trial as well as a roadmap detailing pending tests/treatments for each individual patient. During the weekly meeting the group will review the eligibility criteria for each new patient. In addition, during these meeting the group will review all the toxicity (AE/SAE) logs, case report form completion and roadmap for each patient on the trial. Documentation of the discussions during these meetings are completed, filed and forwarded to the Winship Cancer Institute ("WCI") Data Safety Monitoring Committee (DSMC) at WCI.

The WCI has two internal monitoring committees. The first is the quality assurance and quality monitoring committee, which will perform a review of the first and then on a regular ongoing basis for selected patient enrolled on the trial to confirm that the trial is being conducted appropriately. The second monitoring process involves DSMC. The WCI DSMC is responsible for providing data safety-monitoring oversight for this protocol. Any comments that are generated by the WCI DSMC are forwarded to the IRB. The P.I. and the study investigators will discuss any required modifications to this study at the weekly meetings. No modifications to this study are implemented until they are submitted for review and approved by the Emory University IRB. The comments from the WCI DSMC are forwarded to the IRB at the time of the annual renewal of this study or sooner if warranted and requested by the WCI DSMC.

The Data and Safety Monitoring Committee (DSMC) of the Winship Cancer Institute will oversee the conduct of this study. This committee will review all pertinent aspects of study conduct including patient safety, compliance with protocol, data collection and efficacy. The committee will review the charts of 10% of patients enrolled to the study and two of the first 5 patients entered to the study. Reviews will occur annually for studies that are low risk or moderate risk. High-risk studies will be reviewed every 6 months. The committee reserves the right to conduct additional audits if necessary at any time-point. The Principal Investigator is responsible for notifying the DSMC about the accrual of patients when the first 5 have been entered to the study. The PI will also notify the DSMC of the study status within 2 months before the next annual review is due. The charter for the Winship DSMC is available upon request to the investigator or other study-related personnel.

The WCI DMSC does not tolerate protocol deviations, but does recognize that they occur unintentionally. Any protocol violations are reviewed and reported to the WCI DSMC, IRB, and all other designated regulatory agencies as required by the study protocol.

All study data reviewed and discussed during these meetings with the PI and the investigators and the WCI DSMC is kept confidential. Any breach in confidentiality during the conduct of the study is reported to the PI, WCI DSMC, sponsor, and the IRB.

6. INVESTIGATOR REQUIREMENTS

6.1 Study Initiation

Before the start of this study, the following documents must be on file with Novartis:

- Original U.S. FDA Form 1572 (for all studies conducted under U.S. Investigational New Drug [IND] regulations), signed by the Principal Investigator

  The names of any sub-investigators must appear on this form. Investigators must also complete all regulatory documentation as required by local and national regulations.

- Current *curriculum vitae* of the Principal Investigator
- Written documentation of IRB approval of protocol and informed consent document
- A copy of the IRB-approved informed consent document
- A signed Clinical Research Agreement

6.2 Study Completion

The following materials are requested by Novartis when a study is considered complete or terminated:

- A summary, prepared by the Principal Investigator, of the study, and/or a study manuscript, and/or a study abstract submitted to scientific conferences.

6.3 Informed Consent

An informed consent template will be provided, and the final IRB-approved document must be provided to Genentech and Novartis for regulatory purposes.

The informed consent document must be signed by the subject, or the subject's legally authorized representative, before his or her participation in the study. The case history for each subject shall document that informed consent was obtained prior to participation in the study. A copy of the informed consent document must be provided to the subject or the subject's legally authorized representative. If applicable, it will be provided in a certified translation of the local language.

Signed consent forms must remain in each subject's study file and must be available for verification by study monitors at any time.

6.4 Institutional Review Board or Ethics Committee Approval

This protocol, the informed consent document, and relevant supporting information must be submitted to the IRB for review and must be approved before the study is initiated. The study will be conducted in accordance with U.S. FDA, applicable national and local health authorities, and IRB requirements.

The principal investigator is responsible for keeping the IRB apprised of the progress of the study and of any changes made to the protocol as deemed appropriate, but in any case the IRB must be updated at least once a year. The principal investigator must also keep the IRB informed of any significant adverse events.

Investigators are required to promptly notify their respective IRB of all adverse drug reactions that are both serious and unexpected. This generally refers to serious adverse events that are not already identified in the Investigator Brochure and that are considered possibly or probably related to the molecule or study drug by the investigator. Some IRBs may have other specific adverse event requirements that investigators are expected to adhere. Investigators must immediately forward to their IRB any written safety report or update provided by Novartis (e.g., IND safety report, Investigator Brochure, safety amendments and updates, etc.).

6.5 Study Monitoring Requirements

Site visits may be conducted by an authorized Novartis representative to inspect study data, subjects' medical records, and CRFs in accordance with current U.S. GCPs and the respective local and national government regulations and guidelines (if applicable).

The Principal Investigator will permit authorized representatives of Novartis, the U.S. FDA, and the respective national or local health authorities to inspect facilities and records relevant to this study.

6.6 Study Medication Accountability (If Applicable)

Accurate records of all study drug dispensed from and returned to the study site should be recorded by using the institution's drug inventory log or the NCI drug accountability log.

All partially used or empty containers should be disposed of at the study site according to institutional standard operating procedure. Return unopened, expired, or unused study drug with the Inventory of Returned Clinical Material form as directed by Novartis for everolimus.

6.7 Disclosure of Data

Subject medical information obtained by this study is confidential, and disclosure to third parties other than those noted below is prohibited.

Upon the subject's permission, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare.

Data generated by this study must be available for inspection upon request by representatives of the U.S. FDA, national and local health authorities, Novartis and the IRB for the study site.

6.8 Retention of Records

U.S. FDA regulations (21 CFR §312.62[c]) require that records and documents pertaining to the conduct of this study and the distribution of investigational drug, including CRFs, consent forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 2 years after marketing application approval. If no application is filed, these records must be kept 2 years after the investigation is discontinued and the U.S. FDA and the applicable national and local health authorities are notified. Novartis will notify the Principal Investigator of these events.

For studies conducted outside the United States under a U.S. IND, the Principal Investigator must comply with U.S. FDA IND regulations and with the record retention policies of the relevant national and local health authorities.

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APPENDIX A- STUDY FLOWCHART

	Days –14 to -2	Day 1	Daily	First 24 weeks: Every 4 Weeks	First 24 weeks: Every 8 Weeks	After 24 weeks: Every 12 Weeks	Study Termination
Everolimus (EVEROLIMUS)	X	X	X				
Hormonal therapy[1]	X	X	X				
Complete medical history	X	X		X		X	
Complete physical exam	X	X		X		X	
Clinical assessment	X	X		X		X	
Weight, height	X	X		X		X	
ECOG performance status	X	X		X		X	
Toxicity evaluation	X	X		X		X	
Vital signs	X	X		X		X	
ECG (12-lead)	X						
Serum pregnancy test	X						
Tumor assessment[2]	X				X	X	X
Hematology (CBC, diff., platelets)[3]	X[5]			X		X	
Coagulation (PT/INR)[4]	X						
Chemistry panel (including TSH and lipid panel)[5]	X			X		X	

APPENDIX A STUDY FLOWCHART

(1) Any hormonal therapy is allowed (for example: tamoxifen, anastrozole, letrozole, fulvestrant, estrogen, megestrol acetate, androgens).
(2) Staging will be performed using CT scans: chest, abdomen and pelvis and bone scan. First staging assessment will be done at baseline, every 8 weeks for 24 weeks, then every 12 weeks until progression.
(3) Hematology should include CBC with differential.
(4) The coagulation profile should include a prothrombin time (PT/INR).
(5) Chemistry Panel should include: potassium, magnesium (optional), calcium, chloride, bicarbonate, creatinine, blood urea nitrogen, fasting glucose, albumin, total protein, AST, ALT, total bilirubin, alkaline phosphatase, fasting lipid profile (triglycerides, total cholesterol, HDL, and LDL), TSH. These assessments should be performed at screening and every 4 weeks.

APPENDIX B

Response Evaluation Criteria in Solid Tumors (RECIST Criteria, version 1.1)
[E.A. Eisenhauer, P. Therasse, J. Bogaerts, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). *EUROPEAN JOURNAL OF CANCER* 45 (2009) 228–247]

The RECIST criteria version 1.1 should be used to assess response to treatment. Only subjects with measurable disease should be entered in the study.

Definitions
At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

Measurable

Tumor lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:
• 10mm by CT scan (CT scan slice thickness no greater than 5 mm).

• 10mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
- 20 mm by chest x-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15mm in short axis 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
All other lesions, including small lesions (longest diameter <10mm or pathological lymph nodes with ≥10 to <15mm short axis), as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal,organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Evaluable lesions should be followed for the assessment of response.

When more than one measurable lesion is present at baseline, all lesions **up to a maximum of five lesions total (and a maximum of two lesions per organ)** representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved a maximum of two and four lesions respectively will be recorded).
A 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 as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Response Criteria- Evaluation of target lesions

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 diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of 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. (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.

- Clinical progressive disease

Subjects, who in the opinion of the treating physician investigator have had a substantial decline in their performance status and have clinical evidence of progressive disease, may be classified as having progressive disease.

APPENDIX C

Common Terminology Criteria for Adverse Events (CTCAE)
Version 4.0
Please refer to:
http://www.acrin.org/Portals/0/Administration/Regulatory/CTCAE_4.02_2009-09-15_QuickReference_5x7.pdf

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