A Phase Ib/II study of Debio 1347 plus Fulvestrant in Patients with FGFR-Amplified Endocrine Receptor Positive Metastatic Breast Cancer

PROTOCOL FACE PAGE FOR
MSK THERAPEUTIC/DIAGNOSTIC PROTOCOL

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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

This is an open-label, single institution, phase Ib/phase II non-randomized trial that evaluates the safety, tolerability and anti-tumor activity of fulvestrant and Debio 1347 in patients with ER+/HER2- metastatic breast cancer (MBC) that are FGFR-amplified (as confirmed by a CLIA certified laboratory). The phase Ib portion will evaluate 2 dose cohorts (80mg (cohort/dose level 1), and one dose de-escalation cohort (60 mg dose level -1) in case dose level 1 is deemed to have intolerable toxicity. Only the dose of Debio 1347 will be de-escalated. Fulvestrant will be administered intramuscularly at standard doses. Total number of patients expected in the phase 1b portion: minimum 4 and maximum 12.

The phase 2 portion will be comprised of an optimal Simon two-stage design to determine the efficacy (defined as clinical benefit rate (CBR): overall response rate (ORR) + Stable disease (SD) ≥ 24 weeks) of Debio 1347 plus fulvestrant. Patients enrolled to the phase II portion will be treated at the recommended phase 2 doses (RP2D) identified from the phase Ib portion of the study. Total number of patients expected in the phase 2 portion: minimum 18, maximum 43.

Briefly, patient's eligibility criteria will include: pre/peri/post-menopausal women and men with metastatic ER+/HER2-/FGFR-amplified breast cancer, in first or second line of treatment in the metastatic setting (phase II portion) without prior use of a FGFR inhibitor; ECOG performance status ≤1, normal baseline blood counts and chemistry laboratory profile; and no intercurrent uncontrolled illness. Treatment will be given until disease progression or unacceptable toxicity. To assess the anti-tumor effect of therapy, we will estimate the overall tumor burden at baseline to which subsequent measurements (performed every 8 weeks for the first 6 months and then every 12 weeks thereafter using the Solid Tumor Response Criteria [RECIST] v1.1) will be compared.

Pharmacokinetic and pharmacodynamic data will be obtained throughout the phase Ib/Phase II portion of the study. A baseline biopsy of a metastatic site will be required for all the patients enrolled on the trial, with the acquisition of at least 3 fragments of a core biopsy and in addition archival tissue will also be obtained, whenever available. Tissue will be evaluated for FGFR amplifications by FISH and protein and mRNA expression in collaboration with Dr. Jorge Reis-Filho.

Plasma will also be serially obtained, for measurement of plasma cell-free tumor DNA (cfDNA) at baseline, Cycle 1 Day15, Cycle 3 D1 and at disease progression). This would allow us to determine biomarkers of response and/or resistance associated with FGFR inhibition.

2.1 OBJECTIVES AND SCIENTIFIC AIMS

Primary Objectives:

Phase 1:

- To determine the safety, tolerability, maximum tolerated dose (MTD)/recommended phase 2 dose (RP2D) of Debio 1347 Plus Fulvestrant in patients with ER+/HER2-/FGFR amplified metastatic breast cancer

Phase 2:

- To investigate the anti-tumor activity of Debio 1347 in combination with fulvestrant in patients with ER+/HER2-/FGFR-amplified metastatic breast cancer as defined as clinical benefit rate (CBR: Objective Response Rate plus Stable disease ≥ 24 weeks)

Secondary objectives:

Phase 1:

- To obtain a preliminary assessment of the anti-tumor activity (CBR and overall response rate (ORR)) of Debio 1347 in combination with fulvestrant in patients with ER+/HER2-/FGFR-amplified metastatic breast cancer

Phase 2:

- To further characterize the safety and tolerability of Debio 1347 in combination with fulvestrant in patients with ER+/HER2-/FGFR- amplified metastatic breast cancer
- To determine the overall response rate (ORR), time to progression (TTP), progression-free survival (PFS) and overall survival (OS) for the combination of Debio 1347 with fulvestrant in patients with ER+/HER2-/FGFR- amplified metastatic breast cancer

Exploratory Objectives:

Phase 1 and Phase 2:

- To measure the pharmacokinetic (PK) parameters of Debio 1347 in combination with fulvestrant
- To measure pharmacodynamic biomarkers of FGFR inhibition
- To make an assessment of biomarkers of response and/or resistance from archival tissue and fresh tumor biopsies (using next generation sequencing, FISH, protein and mRNA expression) and plasma (cell-free DNA) and correlate with clinical benefit

3.0 BACKGROUND AND RATIONALE

3.1 Estrogen Receptor positive Breast Cancer

Despite advances in early detection and therapeutic options, unresectable or metastatic breast cancer (MBC) remains incurable and is one of the leading causes of cancer-related mortality. Breast cancer is a molecularly heterogeneous disease with three distinct molecular subtypes [1]. The first group is characterized by estrogen receptor (ER) expression positivity and/or progesterone receptor (PgR) positivity with the absence of over-expression or amplification of HER2. The second group is characterized by over-expression or amplification of HER2, with more than half of these tumors being positive (+) for expression of ER/PgR. The third group lacks detectable ER and PgR, and overexpression of HER2, and is thus referred to as triple-negative breast cancer. Approximately 65% of newly diagnosed breast cancers are ER/PgR+ and HER2- negative (also referred to as luminal tumors), while an additional 20% of newly diagnosed cases are HER2+. ER-targeted drugs, specifically drugs that antagonize estrogen binding to the ER (tamoxifen), drugs that block estrogen biosynthesis (non-steroidal and steroidal aromatase inhibitors [AI] - only effective in postmenopausal patients), and drugs that antagonize and downregulate the ER (fulvestrant), have been the mainstay of systemic treatment for patients with both localized and metastatic ER/PgR+ breast cancers [2].

Fulvestrant is the most recent addition to the armamentarium of hormonal therapies available to treat these patients. However, acquired resistance (and occasionally primary resistance) to antiestrogen therapy universally develops in patients with ER+ MBC[3]. Interestingly, even after acquired resistance develops, breast cancer cells appear to still depend on low-level ER activity in addition to signaling through sometimes acquired oncogenic signaling pathways [4]. In addition, in patients initially diagnosed with ER/PgR+ localized breast cancer who later recur, tumors usually demonstrate some degree of resistance to antiestrogen therapy at the time of recurrence[5]. Therefore, improving the efficacy of endocrine therapy would be of great benefit to patients with breast cancer and represents a large unmet medical need.

3.1.1 Fulvestrant as first-line or second-line therapy for ER+ MBC

Fulvestrant (a selective estrogen receptor down-regulator or SERD) is currently a standard of care hormonal therapy option in patients with ER+ MBC[6]. Fulvestrant has an affinity for ER comparable to estradiol. It blocks the trophic actions of estrogens without any partial agonist (estrogen-like) activity and is currently indicated for the treatment of ER+ MBC in postmenopausal women with disease progression following primary antiestrogen therapy. Clinical trials in postmenopausal women with primary breast cancer have shown that fulvestrant significantly downregulates tumor ER protein levels compared with placebo. There was also a significant decrease in PgR expression consistent with inhibition of ERα transcription. Further, treatment with fulvestrant inhibits tumor cell proliferation as measured by Ki67 immunohistochemistry[7].

Two phase III clinical trials were completed in a total of 851 postmenopausal women with breast cancer who had disease recurrence on or after adjuvant endocrine therapy or progression following endocrine therapy for advanced disease[8]. These trials compared the safety and efficacy of monthly administration of fulvestrant 250 mg vs. the non-steroidal AI anastrozole at 1 mg/daily. Monthly 250 mg fulvestrant was at least as effective as anastrozole

in terms of PFS, OR, and time to death. The combined data showed an objective response rate for fulvestrant of 19.2% compared with 16.5% for anastrozole. The median time to death was 27.4 months for patients treated with fulvestrant and 27.6 months for patients treated with anastrozole. The hazard ratio of fulvestrant 250 mg to anastrozole for time to death was 1.01 (95% CI 0.86 to 1.19).

Doses of fulvestrant higher than 250 mg have greater pharmacodynamic activity against the ER pathway. Thus, a 500 mg monthly dose after an initial load is now the FDA-approved standard of care. A phase III clinical trial (CONFIRM)[9] was completed in 736 postmenopausal women with breast cancer who had disease recurrence on or after adjuvant endocrine therapy or progression following endocrine therapy for advanced disease. The study included 423 patients whose disease had recurred or progressed during antiestrogen therapy and 313 patients whose disease had recurred or progressed during AI therapy. This trial compared the efficacy and safety of fulvestrant 500 mg (n=362) vs. 250 mg (n=374). PFS for fulvestrant 500 mg was 6.5 months compared to 5.5 months for fulvestrant 250 mg. Overall survival data from the time of final analysis showed a median time to death of 26.4 months for fulvestrant 500 mg vs. 22.3 months for fulvestrant 250 mg [HR (95%CI) 0.81 (0.69, 0.96), p=0.016].

More recently results from the randomized, double-blind, multicenter phase III FALCON (***F***ulvestrant and ***A***nastrozo***L***e ***CO***mpared in hormonal therapy ***N***aïve advanced breast cancer) trial for the treatment of locally-advanced or metastatic breast cancer, in post-menopausal women who have not had prior hormonal treatment for hormone-receptor-positive (HR+) breast cancer was published in Lancet[10]. That trial enrolled a total of 462 patients, (n=230) were randomized to 500mg intramuscular injections of fulvestrant (Days 0, 14, 28, then every 28 days), and (n=232) to 1mg of anastrozole daily. Patients were also allowed one prior line of chemotherapy. After a median follow-up of 25 months, patients treated with fulvestrant had a statistically significant 21% improvement in progression-free survival compared to those treated with anastrozole (16.6 months vs. 13.8 months, p = 0.048). Further, subgroup analysis showed an even greater impact on progression-free survival in patients whose disease had not spread to the liver or lungs at baseline (22.3 vs. 13.8 months). These data therefore support the use of fulvestrant even in the first-line metastatic setting.

3.1.2 Resistance to Endocrine Therapies and CDK 4/6 Inhibitors

Despite the multiple effective treatment options for ER+ breast cancer, many patients progress after initial endocrine therapy. Resistance mechanisms are incompletely understood. One mechanism known to contribute to resistance is ligand independent ER signaling in the setting of acquired *ESR1* mutation (*ESR1* is the gene which codes for the estrogen receptor). Highly recurrent mutations in the *ESR1* ligand binding domain (LBD) (p.Tyr537Ser/Asn and p.Asp538Gly) are present in approximately 20% of metastatic ER+ breast cancer tumors after treatment with endocrine therapy but rarely prior to treatment with endocrine therapy[11,12]. Mutant forms of ER mediate clinical resistance to aromatase inhibitor therapy[13]. Mutant receptors also require higher doses of tamoxifen or fulvestrant to antagonize mutant ER signaling. Two other emerging mechanisms of endocrine resistance include a decoupling of

the cell cycle control from ER-signaling (e.g. genetic mechanisms such as CCND1 amplification) and alternate proliferation signals via receptor tyrosine kinases (RTK) and their intracellular signaling cascades via phosphatidylinositol 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR)[14-16]. These proposed mechanisms of endocrine therapy resistance result in tumor cells that have bypassed estrogen control of cell proliferation.

While preclinically, oral serum ER down-regulators are thought to be similar or better than fulvestrant against the mutant ESR1 and many agents are in various phases of clinical development, none are approved to date.

The introduction of CDK4/6 inhibitors into the treatment of ER+ breast cancer was supported by strong preclinical data and rationale[17]. Cyclin D proteins are critical in cancer cell division and complex with the CDK4 and CDK6 protein kinases to promote G1 progression by hyperphosphorylating and activating the retinoblastoma protein (pRb)[18]. Abnormalities that result in CDK activation are highly enriched in luminal A and B breast cancer subtypes, ~85% of which were ER+/HER2− (Cancer Genome Atlas Network 2012). The luminal subtypes also maintain expression of pRb[19], which is essential for benefit from treatment with a CDK4/6 inhibitor. ER+ breast cancer cell lines are among the cancer models most sensitive to single agent CDK4/6 inhibition as well as to the combination of endocrine therapy and CDK4/6 inhibition[20]. In contrast to the oral SERDs, clinically, CDK4/6 inhibitors have recently demonstrated efficacy in ER+ breast cancer and have led to the FDA approval of the first-in-class agent, palbociclib. The PALOMA-1 trial demonstrated that the combination of letrozole and palbociclib was more effective than letrozole alone (median PFS 20.2 months versus 10.2 months) in the front line setting[21]. The confirmatory phase III randomized PALOMA-2 study completed accrual and its results corroborate the benefit of CDK4/6 inhibitors in first line. In PALOMA 2 a total of 666 post-menopausal patients with no prior systemic therapy for ER+ MBC were randomized 2:1 to receive letrozole with palbociclib or letrozole with placebo. Median PFS (primary endpoint) was 24.8 months vs. 14.5 months in favor of the palbociclib arm (HR=0.58 [0.46–0.72], $p < 0.000001$). Response rate was also improved in the palbociclib arm (42.1% vs. 34.7%, p=0.031; 55.3% vs. 44.4% in patients with measurable disease [p=0.013]), and clinical benefit rate was 84.9% vs. 70.3% ($p < 0.0001$)[22]. Similarly, the combination of fulvestrant with palbociclib (median PFS = 9.2 months) in the PALOMA-3 trial was more effective than single agent fulvestrant (median PFS = 3.8 months) after progression on endocrine therapy[23].

3.2 Fibroblast Growth Factor Receptor Pathway in Cancer ER+ Breast Cancer

The family of fibroblast growth factors (FGFs) and FGF receptors (FGFRs) plays a critical role in cell behaviours, such as proliferation, differentiation, migration and survival, and are fundamental to embryonic development, regulation of angiogenesis, and skeletal development.

The FGFR family, which is phylogenetically closely related to the VEGFRs and PDGFRs, comprises of five members, of which four are receptor-type tyrosine kinases (FGFR1-4)[24]. By

alternative splicing, they form seven FGFR proteins (FGFR1b, FGFR1c, FGFR2b, FGFR2c, FGFR3b, FGFR3c, and FGFR4) which are expressed in a tissue specific manner and with differing ligand-binding specificities.

Each of the 4 FGF receptors have an extracellular domain that contains 3 IG like domain and an acidic box, a transmembrane domain and an intracellular TK domain. There are 22 FGF ligands that bind to the 2nd and 3rd IG domains of different FGFR receptors and splice variants creating ligand binding specificity. Ligand binding causes receptor dimerization, enabling transphosphorylation of intracellular kinases and phosphorylation of intracellular signaling proteins[25]. This downstream signaling occurs through two main pathways - the intracellular receptor substrates FGFR substrate 2 (FRS2) and phospholipase C γ (PLC γ), leading ultimately to upregulation of the Ras-dependent mitogen-activated protein kinase (MAPK) and Ras-independent phosphoinositide 3-kinase (PI3K)–Akt signaling pathways[26].

FGFR are susceptible to be hijacked by cancer cells and have been shown to have oncogenic roles in many cancers. These receptors are also known to be involved in cancer cell proliferation, angiogenesis, cell migration, invasion and metastasis. Activation of FGFRs as a result of amplification, mutation or translocation of FGFR genes or over-expression of FGFR proteins or overproduction of FGF ligands has been shown to be oncogenic. Genes encoding FGFRs have been identified as among the most commonly mutated kinase genes in human cancer, with mutations in FGFR2 and FGFR3 being most prevalent[27]. Gene amplification or aberrant transcriptional regulation can result in receptor overexpression, whilst a number of point mutations have been identified that produce receptors that are either constitutively active or exhibit a reduced dependence on ligand binding for activation. In addition translocations can result in expression of FGFR-fusion proteins with constitutive FGFR kinase activity[28]. Finally, isoform switching alters the ligand binding specificity of resulting receptors and hence sensitizes cells to FGFs that they would not normally be responsive to [29,30].

Activating oncogenic FGFR2 mutations confer sensitivity to FGFR inhibition. Aberrant expression, amplification and/or overexpression of FGF proteins, as well as altered gene-splicing of FGFRs represent other mechanisms through which FGF/FGFR signaling can become deregulated in cancer[29,31,32].

Inhibition of FGFR may have clinical utility in cancers that overexpress FGFRs, such as breast[33,34], esophageal, bladder[35], gastric, and lung cancers[34,36], or display a prevalence of FGFR mutations, such as bladder cancer[37,38]. FGF/FGFR signaling may also serve as an escape pathway in tumours that are being treated with inhibitors of other cellular signaling components, such as vascular endothelial growth factor receptor (VEGFR).

3.2.1 Fibroblast Growth Factor Receptor Pathway in ER+ MBC

FGFR1 amplification (Amplification of a region at chromosome 8p12) is present in up to 17% of all breast cancers and up to 27% of luminal B type breast cancer

[39,40]. Based on the TCGA FGFR2 amplifications have been reported in 2-3% and FGFR 3 and 4 amplifications in 1% of breast cancer.

Furthermore, ER+ luminal B tumors overexpressing FGFR1 exhibited increased proliferation and decreased distant metastasis-free survival. FGFR1 amplification was also shown to be an independent predictor of overall survival in patients with ER+ breast cancer treated with tamoxifen[40]. In fact, preclinical studies have demonstrated that FGFR1 amplification conferred resistance to endocrine-based therapies through activation of the MAPK and PI3K pathways.[40,41] About 30-40% of breast tumors with *FGFR1* amplification also exhibit amplification of *CCND1*, *FGF3/4/19* in chromosome 11q29. This co-amplification is also associated with a reduction of patients' survival[42].

Based on these data, several pharmaceutical companies have developed selective and non-selective FGFR inhibitors, focusing their clinical development on tumor subtypes with a high likelihood of dependence on FGFR pathway signaling, including in metastatic breast cancer.

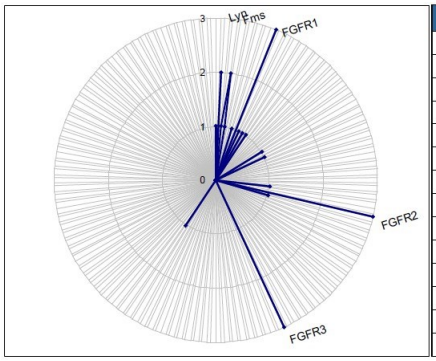
A phase 1/2a clinical trial of lucitanib, a pan VEGFR, PDGFR and FGFR inhibitor in women with *FGFR1-* or *11q (FGF3, FGF4, Cyclin D1, or FGF19)*-amplified MBC demonstrated a promising objective response rate [ORR] of 50%[43]. However, the larger, phase 2 trial of lucitanib in MBC was just recently reported at the 2016 San Antonio Breast Cancer Symposium and showed a modest ORR of 3.5% (6/178) and SD 29.5%. median PFS was 2.9 months (95% CI 2.7, 3.8). Toxicities reflected those of a potent anti-angiogenic agent and most frequent adverse effects were hypertension, fatigue, nausea, hypothyroidism, and headache. Both patients with FGFR1 amplification and/or 11q amplification were enrolled and the clinical activity could not be linked to a particular biomarker or selection factor.

3.3 Debio 1347

The orally-active small molecule Debio 1347 is an ATP competitive and highly selective inhibitor of FGFR1, FGFR2 and FGFR3 at the low nanomolar level in cell-free systems (IC50: 7.6 –22 nM). Preclinical studies have shown that Debio 1347 is effective in multiple tumour models of different origins with FGFR alterations.

3.3.1 Pharmacology – in vitro

F (IC50: 7.6–22 nM) with less potent inhibitory activity on FGFR4 (290 nM) in cell-free systems. The compound is highly selective and does not act on VEGF receptor kinase KDR as demonstrated in vascular endothelial cells.



Kinase	IC50 (nM)
FGFR1	4
FGFR2(N549H)	4
FGFR3	7
FGFR2	10
cKit(V560G)	16
Fms	36
Fms(Y969C)	76
Lyn	102
Ret	103
PDGFRα(D842V)	133
PDGFRα(V561D)	167
FGFR1(V561M)	228
KDR	300
PDGFRα	1940

Figure 1: Radar plot showing selectivity of Debio 1347 over 234 recombinant kinases (0: remaining activity ≥ 50% at 1μM, 1: remaining activity < 50% at 1μM, 2: remaining activity ≤ 10% at 1μM + ≤ 50% at 0.1 μM, 3: remaining activity ≤ 10% at 1M + < 20% at 0.1μM)

The activity of Debio 1347 was evaluated in vitro in a large panel of human cancer cell lines. In cancer cells, Debio 1347 demonstrated a similar potent inhibition of phosphorylation of FGFR2 and of its downstream signaling molecules AKT and ERK1/2. In addition, Debio 1347 selectively inhibits proliferation in cancer cell lines with FGFR alterations. The compound was specifically active in gastric cancer cell lines with FGFR2 amplification or high expression, endometrial cancer cell lines with FGFR2 mutations, bladder cancer lines with FGFR3 mutation multiple myeloma cell lines with FGFR3 translocation, breast and colon cancer cell lines with FGFR2 amplification, squamous NSCLC cell lines and a small-cell lung cancer cell line with FGFR1 amplification (IC50: 12 – 620 nM). Interestingly, Debio 1347 also showed in vitro antiproliferative activity in several bladder cancer cell lines with FGFR3 fusions (IC50: 18 – 350 nM).

3.3.2 Pharmacology – in vivo

Debio 1347 potently inhibits cell growth in a dose-dependent manner in tumour models with FGFR genetic alterations when administered orally once a day. When given orally in gastric tumours with FGFR2 amplification or high expression, Debio 1347 displayed tumour-shrinking effects at non-toxic doses, whereas no anti-tumour activity was observed in a non-amplified model. Strong anti-tumour activity was confirmed in endometrial tumour models with FGFR2 mutations, multiple myeloma models with FGFR3 translocation, SCLC tumour models with FGFR1 amplification and breast tumour model with FGFR1 amplification. Debio 1347 showed remarkable tumor growth inhibition in the CAL-120 breast cancer xenograft model harboring FGFR1 amplification, with an inhibitory value of 87% at 50 mg/kg/day. Potent anti-tumour activity was also observed in vivo in several bladder tumour models carrying FGFR3 fusions, or mutation.

These studies show that the small molecule FGFR inhibitor Debio 1347 is effective in multiple tumour models of different origins with FGFR alterations. The data provides guidance to the future clinical applications of Debio 1347 in the new segment that consists of cancers with FGFR genetic alterations (mutations, translocations, amplifications).

Additional preclinical studies using patient-derived xenograft (PDX) models have recently demonstrated that FGFR high mRNA expression levels were better correlated with sensitivity to Debio 1347 than amplification only. Debio 1347 induced tumour regressions in gastric PDX models with FGFR2 amplification or FGFR2 high expression levels, ESCC PDX models with FGFR1 high expression levels and urothelial cancer PDX models with FGFR3 high expression levels.

Please refer to the Investigator's Drug Brochure for more information.

3.3.3 Toxicology and Safety Pharmacology

The toxicology profile of Debio 1347 was assessed after single and repeated oral administration of up to four weeks duration in Wistar rats and Cynomolgus monkeys. In the 4-week studies, a recovery period of four weeks was included to evaluate the reversibility of any findings. The safety of Debio 1347 was also assessed in a battery of safety pharmacology in vitro and in vivo tests.

In the single dose studies in rats, a Debio 1347 dose of 100 mg/kg - the highest dose tested - was well tolerated, but slight reductions in body weight and food consumption were observed. In monkeys, except for loose stools observed in one animal on the day after dosing, there were no observations at 10 mg/kg.

In the GLP 4 week toxicity study in rats (0, 3, 10, 30 mg/kg/day), no deaths occurred at any Debio 1347 dose up to the highest dose, 30 mg/kg/day. At 30 mg/kg/day, thoracic deformity was seen in the general condition observations, and changes in cartilage and bone including the sternum were seen in the histopathological examinations. Also seen were mineralisation in multiple organs, changes in epithelial tissues, and changes in parameters of blood and urine related to renal function. At 10 mg/kg/day or less, the above-mentioned histopathological changes were not seen; at those doses, mainly changes in parameters of blood and urine that suggested effects on bone were observed. At the lowest dose of 3 mg/kg/day, high blood TRACP-5b (tartrate-resistant acid phosphatase 5b, a bone resorption marker) was seen, so the no observed adverse effect level (NOAEL) was judged to be less than 3 mg/kg/day. The NOAEL was considered to be lower than 3 mg/kg/day.

In the GLP 4-week repeated-dose toxicity study in monkeys (0, 0.4, 1.3, and 4 mg/kg/day), no deaths occurred at any Debio 1347 dose up to the highest dose, 4 mg/kg/day. At 4 mg/kg/day, very slight histopathological changes in bone and cartilage and related changes in parameters of blood and urine were seen, and in one female, very slight histopathological changes in kidneys were observed. At the middle dose of 1.3 mg/kg/day, only high urinary excretion of inorganic phosphorus in females was seen. No effects were observed at the lowest dose of 0.4 mg/kg/day, so that was judged to be the no observed adverse effect level in this study. On the basis of these results, the highest non-severely toxic dose for monkeys (HNSTD) was set at 4 mg/kg/day (NOAEL: 0.4 mg/kg/day). The principal target organs of Debio 1347 toxicity in rats and monkeys were bone/cartilage, epithelial tissues and the kidneys. In addition, effects on lymphohematopoietic tissues, liver and the gastrointestinal tract were observed. Mineralisation in multiple organs was also seen, with a broader range of organs and tissues

affected in rats than in monkeys. On the other hand, periosteal changes occurred only in monkeys but not in rats. Except for thoracic deformity and mineralisation in multiple organs in rats, the changes seen in rats and monkeys in the 4-week repeated-dose toxicity studies either reversed or tended to reverse over the 4-week recovery period.

The genotoxic potential of Debio 1347 was assessed in several in vitro and in vivo tests: no mutagenic potential was observed in the Ames test and no increases in structural chromosome aberrations or in polyploid cells were observed in a chromosomal aberration test using human peripheral blood lymphocytes. In an in vivo micronucleus test in rats, however, the numbers of micronucleated immature erythrocytes were slightly increased, suggesting a micronucleus-inducing potential. In vitro, the principal mechanism of micronucleus induction seems not to be due to abnormal chromosome segregation. Based on these results, Debio 1347 is thought to be genotoxic to mammalian cells. Debio 1347 may have an in vivo phototoxic risk based on 1) an in vitro phototoxicity test using a fibroblast cell line, where the compound was suggested as a phototoxic substance (absorbance wavelengths of 200 nm to 400 nm); 2) a whole-body autoradiography in rats after single oral dose of 1 mg/kg of [14C] Debio 1347 suggesting a slower elimination rate of Debio 1347 from skin compared with blood. Although any reproductive and developmental toxicity studies of Debio 1347 have not been conducted, some changes in reproductive organs, such as thinning of vaginal mucosal epithelium and atrophic changes in testes, epididymides, prostate gland, seminal vesicles and uterus were observed at lethal dose in preliminary dose-repeated toxicity in rats. From the above findings and those on bone and cartilage, it is inferred that Debio 1347 may affect reproduction and development.

In the safety pharmacology studies, no effects on the central nervous system or respiratory system were seen in rats at Debio 1347 doses up to 100 mg/kg. Debio 1347 was a potent hERG inhibitor in vitro (IC50: 677ng/mL). However, in the monkey telemetry study, Debio 1347 did not modify the blood pressure, heart rate, and ECG or body temperature at doses up to 10 mg/kg.

No carcinogenicity studies or local tolerance studies have been conducted to date.

Please refer to the Investigator's Drug Brochure for more information.

3.3.4. Clinical data

Based on these data a phase 1 first –in-human trial was undertaken, and it has now completed the patients' enrollment in the dose-escalation portion.

A total of 57 patients with genomically activated advanced solid tumours were included into the dose-escalation part up to 06 April 2017. All had received at least one dose of Debio 1347 and were assessable for safety. Of these, 54 were evaluable for efficacy. Eight dose levels had been tested at the time of cut-off (10, 20, 30, 40, 60,80, 110 and 150 mg daily).

The MTD is 80mg since 2 DLTs were observed at110 mg daily. Five patients experienced DLTs: NCI-CTCAE Grade 2 intolerable dry mouth and dry eyes at 60 mg, Grade 3 hypercalcaemia and Grade 3 hyperamylasaemia both at 80 mg, and Grade 3 bilirubin increase and Grade 3 hyperphosphatemia and Grade 3 stomatitis in two patients at 110 mg,

respectively. At cut-off, treatment emergent adverse events (TEAEs) had been reported by all patients. At data cut-off, the most common treatment-emergent adverse events (TEAE) were hyperphosphatemia (75%), fatigue (40%), diarrhea (39%), nausea (40%), and inappetence (32%). Eighteen patients (32%) experienced a grade ≥ 3 related TEAE. Twenty-eight patients (49%) required dose modification, primarily due to hyperphosphatemia and cutaneous toxicity.

Decreased left ventricular ejection fraction (LVEF) was reported in 1 patient (Grade 2) and 2 patients experienced respectively non-clinically significant Grade 1 and 2 ECG QTc prolongation.

Clinical activity started at the dose of 30 mg. Five patients had a partial response (PR): an endometrial cancer patient with FGFR1 amplification (30 mg), a cervical cancer patient with FGFR2 mutation (80 mg), an urothelial cancer harbouring a FGFR3-TACC3 translocation (80 mg), a cholangiocarcinoma patient with FGFR2 mutation (110 mg), and a colon cancer patient with FGFR2 fusion (110 mg) and an urothelial cancer with FGFR3 harbouring a FGFR3-TACC3 translocation (150 mg). An additional 10 patients had target regression < 30%. Two out of these patients had a breast cancer. A triple-negative breast cancer patient with FGFR1 amplification showed a reduction in the target lesions of 19% (40 mg), while a HR+ Her2- breast cancer patient with FGFR1 amplification showed a reduction in the target lesion of 12% (60 mg).

Preliminary PK data from 54 patients treated with 10-150 mg/day during the dose escalation part indicate that Debio 1347 was rapidly absorbed after oral administration with a median t_{max} occurring at 3 hours post-dose. Apparent oral clearance (CL/F) and volume of distribution (Vz/F) were on average 7 L/hour and 120 L, respectively. Inter-patient variability was moderate to high, but PK appeared overall linear. Debio 1347 mean plasma exposure increased with dose in an approximately proportional manner in the 10-150 mg range. Half-life was 14 hours on average, with a limited accumulation (1.7-fold on average) after 28-day repeated once daily dosing. The Debio 1347 PK profiles and plasma exposure of the capsule and tablet formulations used in the trial were comparable.

Please refer to the Investigator's Drug Brochure for other information.

3.4 Study Rationale

As discussed, even after acquired resistance develops, ER+ breast cancer cells appear to still depend on low-level ER activity in addition to signaling through sometimes acquired oncogenic signaling pathways[4]. FGFR amplification confers resistance to endocrine-based therapies.[40,41] Additionally, in ER+ breast cancers, most *FGFR1* amplifications can coexist with 11q amplification (*CCND1, FGF3/4/19*).

Ongoing clinical trials with FGFR inhibitors are being enriched for tumors harboring specific FGFR mutations and amplifications presumed to be highly addicted to this pathway. Preliminary clinical data demonstrated that FGFR and/or FGF3/4/19 ligand amplification is associated with clinical benefit from FGFR inhibitors[43,44], suggesting that these could be biomarkers of tumor dependence on the FGF/FGFR pathway. However, the recently presented

larger phase 2 trial of lucitanib did not reproduce the promising clinical activity reported in the phase 1/IIa study. Additionally, no specific biomarker could be identified that would benefit from lucitanib therapy. This could be related to the following:

1. Lucitanib is a non-selective FGFR inhibitor with toxicity profile similar to anti-angiogenic therapy

2. Patients were treated with monotherapy and not in combination with endocrine therapy

3. Additionally, the amplicon containing FGFR (8p) in lung cancer is more focal; in breast cancer this amplicon is rather broad and complex and therefore it remains to be seen if these differences influence the degree of addiction to FGFR1. The lucitanib trial allowed patients with 11q amplification without co-occurring FGFR amplifications to the study.

We plan to address these issues in our proposed clinical trial with Debio 1347 + Fulvestrant as follows:

1. In 2015, we sequenced tumors from approximately 500 patients with metastatic breast cancer using MSK-IMPACT. Specifically, we have a large pool of pre-identified FGFR amplified (**N=87**) and 11q amplified co-occurring with FGFR1 amplified tumors (**N=35)** using our in house, next generation sequencing assay- MSK-IMPACT. We will exclude patients with 11q amplification without co-occurring FGFR amplifications.

2. We also have a lot of experience with non-specific and specific FGFR inhibitors, including Debio 1347 (IRB # 13-131; PI: Martin Voss). Preliminary evidence with FGFR blockade using the selective FGFR inhibitor, Debio 1347 has a manageable tolerability profile with promising clinical activity including stable disease in metastatic breast cancer patients with FGFR amplifications at lower than the RP2D of Debio 1347. In this trial we will be combining Debio 1347 with Fulvestrant.

3. Lastly, In situ hybridization scoring techniques for characterizing FGFR1-2 amplification have varied in trials reported to date [45]. Although amplification of FGF3/4/19 ligands may also predict those patients more likely to benefit from FGFR blockade[44], the heterogeneity in published definitions makes it difficult to assess the true significance of these biomarkers given the lack of standardized measurement. In order to better understand if the FGFR pathway is truly activated, we will not only have the information from a CLIA certified laboratory, but we also plan to collaborate with Dr. Jorge Reis-Filho and plan to perform FISH, protein expression and mRNA expression from fresh tumor biopsies that we plan to obtain for all patients enrolled on to this study. Beyond this, we plan to leverage our state of the art molecular profiling program to help further clarify biomarkers of response and/or resistance in this subtype. For instance, we could use outlier analyses together with further genomic analyses to attempt to better define the subset of tumors for which FGFR amplification represents a driver event.

Hence, we hypothesize that combination therapies using selective FGFR inhibitors (in this case Debio 1347) along with standard endocrine therapy (such as fulvestrant) may lead to better responses in patients with ER+/ FGFR-amplified breast cancer. This study will also

afford us a better understanding of the role of FGFR pathway in endocrine resistant metastatic breast cancer.

3.4.1 Rationale for the dose of Debio 1347

Based on the preliminary analysis from the dose escalation portion of the phase 1 study, the recommended dose of Debio 1347 to be further explored in the expansion part of the study was chosen as 80mg once daily. 60 mg once daily is proposed as reduced dose in the case of intolerable toxicity. Due to non-overlapping toxicities with fulvestrant, we plan to start with dose level 1/cohort 1 also at 80mg in this study. A dose de-escalation cohort (dose level -1/60mg) is also built in if dose level 1 is deemed intolerable. Patients in the phase 2 portion will be treated at the MTD/RP2D of Debio 1347 from the phase 1b portion of the study *without* concomitant prophylaxis for hyperphosphatemia (see section 9.2.1).

4.1 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.2 Design

This is an open-label, single institution, phase Ib/phase II non-randomized trial that evaluates the safety, tolerability and anti-tumor activity of fulvestrant and Debio 1347 in patients with ER+/HER2- metastatic breast cancer (MBC) that are FGFR-amplified (as confirmed by a CLIA certified laboratory).

The phase I portion of this trial will have 2 dose levels: dose level 1 (80mg) and a de-escalation level (60mg) if the 80mg dose level has intolerable toxicities (N= minimum 4 and maximum 12). Fulvestrant will be administered intramuscularly at standard doses (500 mg loading dose on days 1, 14, and 28 of the first month, then maintenance dosing every 28 days, ±3 days) with no dose-escalation. Only the dose of Debio 1347 will be de-escalated as shown below. There will be no intra-patient dose escalation. 1 cycle = 28 days.

The Dose Limiting Toxicity (DLT) observation period includes Day 1 to Day 28 of Cycle 1, plus the assessments prior to drug administration on Cycle 2, Day1.

Cohort/Dose level	Debio 1347	Fulvestrant
-1	60mg	500mg IM
1 (Starting dose cohort)	80mg	500mg IM

If none *or* one of the initial 3 patients in dose level 1 has DLT, 3 additional patients will be treated at the same dose level. If 2 or more patients experience DLT at this dose level, then dose level -1 will be evaluated. Should 2 or more patients experience DLT at dose level -1, the study will stop accrual. If only 1 of the 3 initial patients experiences a DLT at dose level -1, 3

additional patients will be evaluated at this dose level. Patients who withdraw before completing a full cycle of treatment for reasons other than development of a DLT will be replaced.

The phase 2 portion will be comprised of an optimal Simon two-stage design to determine the efficacy (defined as clinical benefit rate (CBR): proportion of patients who have a best overall response of a complete response, a partial response, or stable disease (SD) for at least 24 weeks (SD ≥ 24 weeks) of Debio 1347 plus fulvestrant (N: 18 in the first stage with possibility of going on to 43 if 3 out of the first 18 have a CBR ≥ 24 weeks). The dosage in the phase 2 portion will be the RP2D determined in the phase 1b dose-escalation portion. The treatment schedule and duration in the phase 2 portion will be identical to the phase 1b part except that concomitant prophylaxis for hyperphosphatemia will not be required. Patients enrolled in the phase 1b portion will not be eligible for the phase 2 component.

4.3 Intervention

Fulvestrant will be administered according to its approved dose of 500 mg intramuscularly on days 1, 15, 28 and then every 28 days (+/-3 days) thereafter. Debio 1347 will be administered orally daily (1 cycle is 28 days) and the dose of Debio 1347 could be de-escalated as detailed in section 4.1. The dosage in the phase 2 portion will be the MTD/RP2D determined in the phase 1b portion.

Pharmacokinetic and pharmacodynamic data will be obtained throughout the phase Ib/Phase II portion of the study. A baseline biopsy of a metastatic site will be required, with the acquisition of at least 3 fragments on a core biopsy for all the patients enrolled on the trial and in addition archival tissue will also be obtained, whenever available. Tissue will be evaluated for FGFR amplifications by FISH and protein and mRNA expression in collaboration with Dr. Jorge Reis-Filho.

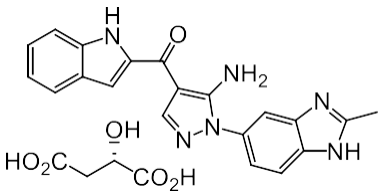
Plasma will also be serially obtained, for measurement of plasma cell-free tumor DNA (cfDNA) at baseline, at Cycle 1 Day 15, Cycle 3 Day 1 and at disease progression. This would allow us to determine biomarkers of response and/or resistance associated with FGFR inhibition.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

5.1. Debio 1347

5.1.1 Chemical Structure, Formula, and Molecular Weight

Structural formula:



Chemical name: 5-amino-1-(2-methyl-1H-benzo[d]imidazol-5-yl)-1*H*-pyrazol-4-yl 1*H*-indol-2-yl ketone mono[(*S*)-2-hydroxysuccinate]

Molecular weight: 490.47l

Molecular formula: C20H16N6O·C4H6O5

5.1.2 International Non-proprietary Name, Brand Name, and Code Name

INN (International Non-proprietary Name) Not applicable

Brand name: Not applicable

Company code name: Debio 1347 malate (malate salt)

Debio 1347 (free base)

Former code name: CH5183284

5.1.3 Finished product

Tablets: Debio 1347 20mg and 50mg coated tablets contain the following excipients: lactose hydrate, microcrystalline cellulose, croscarmellose sodium, hydroxypropyl cellulose, sodium lauryl sulfate, and magnesium stearate.

5.1.4 Stability

Expiry date: 36 months after the manufacturing date (the shelf life may be extended when new stability data are available).

Storage: mentioned on labels

A certificate of analysis (CoA) will be provided with the product.

5.1.5 Packaging

Fifty-six capsules or tablets in HDPE bottles.

5.1.6 Storage and handling

Debio 1347 capsules or tablets should be stored at 15-25°C.

5.1.7 Other

The in vitro, in vivo, toxicology and clinical data to date are detailed in section 3.3.1-3.3.4.

Debio 1347 will be provided by Debiopharm International SA. Please refer to the Investigator Brochure for any further details.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

5.2 Fulvestrant

Fulvestrant 500 mg should be administered intramuscularly into the buttocks slowly (1 - 2 minutes per injection) as two 5 mL injections, one in each buttock, on days 1, 15, 28 and once every 28 days as per standard of care.

6.1 CRITERIA FOR SUBJECT ELIGIBILITY

6.2 Subject Inclusion Criteria

- Males and Females, Age > 18 years
- Written informed consent and authorization obtained from the subject/HIPAA-appointed legal representative prior to performing any protocol-related procedures including screening evaluations.
- Patients with metastatic histologically or cytologically confirmed invasive breast cancer.
- Female patients of postmenopausal status
  Postmenopausal status will be defined as following:
  - Age ≥ 60 years
  - Age < 60 years and 12 months of amenorrhea plus follicle stimulating hormone and plasma estradiol levels within postmenopausal range by local laboratory assessment in the absence of oral contraceptive pills, hormone replacement therapy, or gonadotropin-releasing hormone (GnRH) agonist or antagonist
  - Prior bilateral oophorectomy

  Pre or perimenopausal women allowed with the addition of goserelin.
- ECOG performance status 0 -1
- Tumor must be estrogen receptor and/or progesterone receptor positive (i.e. Hormone receptor positive (HR+) and HER-2 negative as defined by the ASCO-CAP guidelines: HR+ is defined as expression of ER and/PR in ≥ 1% of cells, or HR+ by local laboratory or regional definition. HER2− is defined as a HER2 IHC score of 0 or 1+, or an IHC score of 2+ accompanied by a negative fluorescence, chromogenic, or silver in situ hybridization test indicating the absence of HER2 gene amplification, or a HER2/CEP17 ratio of < 2.0, or local clinical guidelines.

- Tumors must have FGFR amplifications as determined by a CLIA certified laboratory. Patients with FGFR amplifications co-occurring with 11q amplification (CCND1, FGF3,4, 19 amplifications) are also eligible.
- Measurable or evaluable disease per RECIST1.1 or pure lytic or mixed lytic-blastic bone lesions
- No more than 1 prior chemotherapy regimen in the metastatic setting for the phase 2 portion. Patients in the phase 1 portion could have received any number of prior lines of therapy.
- Willing to undergo a new core or excisional biopsy from a metastatic, not previously irradiated tumor lesion during screening
- Life expectancy of greater than 3 months
- Archival Tumor (up to 10 unstained slides) will be obtained, whenever available for additional biomarker analyses
- Hematologic parameters:
    - White blood cell (WBC) count of > 3000/ul
    - Absolute neutrophil count (ANC) > 1000/ul
    - Platelets > 100,000/ul, hemoglobin > 9.0 g/dl
- Non-hematologic parameters:
    - Corrected calcium value ≤1.1 x ULN
    - Total bilirubin ≤1.5 x ULN (upper limit of normal) except subject with documented Gilbert's syndrome (≤5 x ULN) or liver metastasis, who must have a baseline total bilirubin ≤3.0 mg/dL
    - AST and ALT ≤ 3 x ULN, unless associated with hepatobiliary metastases, in that case ≤5 x ULN
    - ALP ≤ 2.5 x ULN or ≤ 5.o x ULN for patients with bone metastases
    - Gamma-glutamyltransferase ≤ 2.5 x ULN
    - Albumin ≥ 2.5 g/dL
    - Phosphate ≤ 1.1 x ULN
    - Prothrombin time (PT) and/or prothrombin time international normalized ratio (PT-INR) and/or activated partial thromboplastin time (APTT) ≤ 1.3 x ULN
    - Serum creatinine ≤ 1.5 × ULN or creatinine clearance ≥ 50 mL/min on the basis of the
      Cockcroft−Gault glomerular filtration rate estimation:
      $\frac{(140 - \text{age}) \times (\text{weight in kg}) \times (0.85 \text{ if female, } 1.00 \text{ if male})}{72 \times (\text{serum creatinine in mg/dL})}$

- Patients with “treated and stable” brain lesions for a duration of > 4 weeks may be enrolled.
- Female subjects of childbearing potential should have a negative urine or serum pregnancy test within 72 hours prior to receiving the first dose of study medication and agree to use effective contraception. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.

6.3 Subject Exclusion Criteria

- Prior Fulvestrant for metastatic breast cancer will be allowed for phase 1 portion but not for the phase 2 portion
- History of hypersensitivity to any of the excipients in the Debio 1347 formulation (lactose hydrate, microcrystalline cellulose, croscarmellose sodium, hydroxypropyl cellulose, sodium lauryl sulfate, and magnesium stearate).
- Other malignancies requiring active treatment in the last 6 months.
- Brain tumors and/or brain metastases unless they are asymptomatic, stable on recent imaging (not dated more than 30 days from the inclusion date) and have not required active treatment in the last 6 months.
- History and/or current evidence of endocrine alteration of calcium-phosphate homeostasis.
- History of myocardial infarction or stroke within 6 months, congestive heart failure greater than NYHA class II, unstable angina pectoris, unexplained recurrent syncope, cardiac arrhythmia requiring treatment or family history of sudden death from cardiac-related causes.
- Baseline Frederica’s corrected QT (QTcF) interval greater than 470 msec (female) or greater than 450 msec (male), history of congenital long QT syndrome, the presence in the screening ECG of a conduction abnormality that in the opinion of the Investigator would preclude safe participation in this study.
- Concomitant use of a drug with a known risk of QTc prolongation
- Current anticoagulation therapy with therapeutic doses of warfarin (low-dose warfarin ≤ 1mg/day or low molecular-weight heparin are permitted).
- History and or current evidence of ectopic mineralisation/calcification including but not limited to the soft tissue, kidneys, intestine, myocardium and lung with the exception of calcified lymph nodes and asymptomatic coronary calcification.

- Concomitant use of high dose systemic steroids and other drugs such as calcitonin preparations, active Vitamin D3 preparations, estrogen preparations, selective estrogen receptor modulators, Vitamin K2 preparations, parathyroid hormones, phosphorus absorbers. Note, inhaled, topical steroids and low tapering doses of steroid especially in patients treated recently for brain metastases will be included.
- Corneal disease, such as bullous or band keratopathy, corneal desquamation, keratitis, corneal ulcer, or keratoconjunctivitis.
- Known infection requiring the systemic use of, for example, an antibiotic or antiviral agent.
- Known HIV, HBV or HCV infection.
- Known untreated or uncontrolled acute infection, including urinary tract infection, within 7 days of study entry.
- History of organ, bone marrow, or stem cell transplantation.
- Pregnant or lactating woman (any woman of childbearing potential who has menstruated within the year prior to enrolment will undergo pregnancy testing within 72 hours prior to receiving the first dose of study medication).
- Women of childbearing potential or men who are unwilling to use an appropriate method of contraception during the study period and for 6 months after completing treatment with Debio 1347. Oral or injectable contraceptive agents cannot be the sole method of contraception. Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.
- Poorly controlled diabetes mellitus or hypertension (e.g., systolic > 180 mmHg or diastolic > 100 mmHg).
- Inability or unwillingness to swallow oral medications.
- Clinically significant gastrointestinal abnormality that would affect the absorption of drug such as gastrointestinal dysfunction, malabsorption syndrome, major resection of the small bowel or total gastrectomy or inflammatory bowel disease.
- Uncontrolled hydropericardium.
- Chemotherapy or radiotherapy within 14 days prior to starting study treatment. In case of monoclonal antibodies/biologics, within 28 days prior to starting study treatment.
- Administration of investigational agents within 28 days prior to treatment initiation.
- Major surgery and surgery for brain metastases within 28 days prior to screening start. Of note, Intravenous port placement is not considered as a major surgery.

- Not recovered from AEs or toxicities due to previous treatments to a Grade 1 or less specified in NCI-CTCAE version 4.0 excepting, albumin (< 2.5 g/dL), AST and ALT in patients with liver metastases (> 5 × ULN) ALP in patients with bone metastases (> 5 × ULN) and alopecia.

- Prior use of a drug targeting FGF or FGFR. Patients previously treated with medications that affect FGFR signaling as a secondary target (e.g., multi-tyrosine kinase inhibitors that primarily inhibit VEGF, but to a lesser extent also affect FGFR signaling) can be considered after discussion with the Principal Investigator.

- Currently under alcohol or drug abuse rehabilitation or treatment program.

- Uncontrolled intercurrent illness or psychiatric illness/social situations that would limit compliance with study requirements.

Eligibility Note: Patients could have progressed on prior aromatase inhibitors

7.0 RECRUITMENT PLAN

The Evelyn H. Lauder Breast Center, in the Breast and Imaging Center at MSKCC provides a large referral base, with approximately 2000 patients with metastatic breast cancer consults each year. In 2015, we sequenced tumors from approximately 500 patients with metastatic breast cancer using MSK-IMPACT. Specifically, we have a large pool of pre-identified FGFR amplified (**N=87**) and 11q amplified co-occurring with FGFR1 amplified tumors (**N=35)** using our in house, next generation sequencing assay- MSK-IMPACT. This study will be available to all patients seen at Memorial Sloan Kettering Cancer Center (MSKCC, New York, NY), who meet the eligibility criteria outlined in section 6.0. Dr. Komal Jhaveri will facilitate accrual within Breast Medicine Service.

The investigators take due notice of the NIH policy concerning inclusion of women and minorities in clinical research populations. There will be no limitation to access with regard to race or gender. Patients will be required to read, agree to, and sign an IRB-approved informed consent form prior to registration on this trial. Participants will also be asked to sign a procedural consent form, detailing standard of care risks. Patients will then be registered by study research staff. The registration procedure will be conducted as described in section 15.0. Patients' clinical details will become part of an outcomes database for future analysis. Patients will not receive payment for their participation on this study.

7.1 LIMITED WAIVER OF AUTHORIZATION

Potential research subjects will be identified by a member of the patient's treatment team, the protocol investigator, or research team at Memorial Sloan-Kettering Cancer Center (MSKCC). If the investigator is a member of the treatment team, s/he will screen their patient's medical records for suitable research study participants and discuss the study and their potential for enrolling in the research study. Potential subjects contacted by their treating physician will be referred to the investigator/research staff of the study.

The principal investigator may also screen the medical records of patients with whom they do not have a treatment relationship for the limited purpose of identifying patients who would be eligible to enroll in the study and to record appropriate contact information in order to approach these patients regarding the possibility of enrolling in the study. For the majority of the potential research participants, most will have a treatment relationship with the investigators and consenting professionals listed on the front sheet of protocol. We plan to maintain a screening log for all patients considered for this study.

During the initial conversation between the investigator/research staff and the patient, the patient may be asked to provide certain health information that is necessary to the recruitment and enrollment process. The investigator/research staff may also review portions of their medical records at MSKCC in order to further assess eligibility. They will use the information provided by the patient and/or medical record to confirm that the patient is eligible and to contact the patient regarding study enrollment. If the patient turns out to be ineligible for the research study, the research staff will destroy all information collected on the patient during the initial conversation and medical records review, except for any information that must be maintained for screening log purposes.

In most cases, the initial contact with the prospective subject will be conducted either by the treatment team, investigator or the research staff working in consultation with the treatment team. The recruitment process outlined presents no more than minimal risk to the privacy of the patients who are screened and minimal PHI will be maintained as part of a screening log. For these reasons, we seek a (partial) limited waiver of authorization for the purposes of (1) reviewing medical records to identify potential research subjects and obtain information relevant to the enrollment process; (2) conversing with patients regarding possible enrollment; (3) handling of PHI contained within those records and provided by the potential subjects; and (4) maintaining information in a screening log of patients approached (if applicable).

8.1 PRETREATMENT EVALUATION

To be completed within 28 days of starting Cycle 1 Day1 (unless otherwise indicated):

- Signed informed consent for study participation
- History and physical examination including height, weight, vital signs (temperature, pulse rate, respiratory rate, blood pressure, pulse oximetry), performance status (ECOG), and review of pathology and concomitant medications: medications taken within 28 days of starting Debio 1347 and fulvestrant
- Urine or serum pregnancy test for all women of childbearing potential. If the test result is positive related to pregnancy, the patient will not be allowed to participate in this study
- CBC with differential and platelet count
- Complete metabolic panel (sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, total protein, albumin, bilirubin, alkaline phosphatase, AST, ALT, calcium)
- Magnesium

- Phosphorous
- γGTP
- CPK
- CRP
- Uric Acid
- LDH
- Calcium regulating hormones (whole-PTH, 1,25(OH)2D, PTHrP)
- PT/INR & aPTT
- Serology for HepBsAg, HepBcAb, HIV and hepatitis C antibody (negative test acceptable prior to screening period)
- Tumor markers: CEA and Ca 15-3
- Urinalysis including urinary protein, blood, glucose, urobilinogen, pH, sediment, creatinine, calcium (CA), phosphate
- 12-lead Electrocardiogram (EKG)
- ECHO
- Complete ophthalmologic examination. The examination will be interpreted by a qualified ophthalmologist, including visual acuity testing, slit-lamp ophthalmoscopy and indirect ophthalmoscopy.
- CT scan with contrast (chest, abdomen and pelvis). If patient is unable to receive CT contrast, or the abdominal/pelvic target lesion is indeterminate on CT scan, then MRI with contrast (abdomen and pelvis) plus CT chest without contrast may be performed.
- A baseline brain MRI or CT scan with contrast (the same method of imaging done at baseline should be done throughout the study at indicated time points) is required only for patients with a history of brain metastases
- Research blood samples: for PK and cfDNA as detailed in section 12.0
- Baseline tumor biopsies will be obtained during screening for all patients enrolled in the study

9.1 TREATMENT/INTERVENTION PLAN

This is an open-label, single institution, phase Ib/phase II non-randomized trial that evaluates the safety, tolerability and anti-tumor activity of fulvestrant and Debio 1347 in patients with ER+/HER2- metastatic breast cancer (MBC) that are FGFR-amplified (as confirmed by a CLIA certified laboratory).

The phase I portion of this trial will evaluate 2 dose cohorts (dose level 1 (starting dose level) 80mg Debio 1347, and dose level -1, 60mg Debio 1347). Fulvestrant will be administered at standard doses. Only the dose of Debio 1347 will be de-escalated as per section 4.1.

Phase 2 portion: The phase 2 portion will be comprised of an optimal Simon two-stage design to determine the efficacy of Debio 1347 plus fulvestrant (N: 18 in the first stage with possibility of going on to 43 if 3 out of the first 18 have a CBR ≥ 24 weeks). The dosage in the phase 2 portion will be the MTD/RP2D determined in the phase 1b portion (**80mg daily)**, except that concomitant prophylaxis for hyperphosphatemia will not be required.

1 cycle: 28 days. Patients will be on treatment until progression of disease or unacceptable toxicity.

9.1 Concomitant Medications

Administration of concomitant when administered between the date of informed consent signature and the last visit (including follow-up) will be recorded.

9.1.1 Permitted Concomitant Medication

Supportive therapies against pain, nausea, vomiting, constipation and diarrhea, and granulocyte colony-stimulating factors (G-CSF) are allowed as per the Investigator's decision. Since drugs that alter gastric pH (e.g., proton pump inhibitors, histamine receptors antagonists, antacids) may interfere with the absorption of Debio 1347, they should be administered at least 2 hours after Debio 1347 administration.

Treatment of pain should be done according to severity and recommended drugs. Study-specific guidelines will be provided separately.

Concomitant radiotherapy may only be given for the control of bone pain or as indicated to 30% of the bone marrow. Irradiated lesions will not be evaluable for response. Radiotherapy should start no sooner than 24 hours after the previous dose of Debio 1347, and study treatment may be resumed with the resolution of any radiation toxicity to ≤ grade 1.

Any other medication necessary for the well-being of the patient (with the exception of those mentioned as prohibited/excluded concomitant medications, see Section below) may be given at the Investigator's discretion. Particular attention should be paid to treatment that could influence the intended effects or mask side effects of treatment.

9.1.2 Excluded Concomitant Medications

Subjects must be instructed not to take any medications, including over-the-counter products, without first consulting with the investigator.

The following medications are considered exclusionary during the study. The Principal Investigator must be notified if a subject receives any of these during the study.

- Any investigational anticancer therapy.

- Any concurrent chemotherapy, immunotherapy, or biologic therapy. Note: concurrent use of bone-directed therapies (such as bisphosphonates or denosumab) is permitted.
- Other antineoplastic agents are prohibited except GnHR agonists and GnHR antagonists for premenopausal women.
- Concurrent use of hormones for non-cancer-related conditions (e.g., insulin for diabetes) is acceptable.
- Immunosuppressive medications including, but not limited to systemic corticosteroids (>10 mg/day prednisone or equivalent), methotrexate, azathioprine, and tumor necrosis factor alpha (TNF-α) blockers. \ In addition, use of inhaled and intranasal corticosteroids is permitted.
- Fibroblast growth factors injections, cosmetics containing FGF.
- High dose systemic steroids, calcitonin preparations, active Vitamin D3 preparations, estrogen preparations, selective estrogen receptor modulators, Vitamin K2 preparations, parathyroid hormones, phosphorus absorbers

In nonclinical studies, Debio 1347 has been seen to affect the cornea. Since corneal disorders may occur when contact lenses are being worn, and the use of Debio 1347 may exacerbate these symptoms, caution should be exercised when using Debio 1347 in a patient wearing contact lenses, and the patient should be monitored.

Although the possibility of Debio 1347 affecting cardiac function in nonclinical studies is low, caution should be exercised when using Debio 1347 with drugs with a known risk of QTc prolongation (see Arizona CERT database at website ttp://www.crediblemeds.org/).

The hepatic oxidative metabolism of Debio 1347 has been shown in vitro to be mainly mediated by CYP 4F3b, with no or only minor contribution of other metabolic enzymes. Furthermore, according to bi-directional permeability experiments in Caco-2 cells, Debio 1347 is not a substrate of P-glycoprotein (P-gp) or breast cancer resistance protein (BCRP) efflux transporters. Therefore, based on current knowledge, Debio 1347 appears to have a low risk of being victim of PK interaction from other drugs. In contrast, as per in vitro results available so far and Debio 1347 plasma exposure achieved in patients, Debio 1347 is considered at possible risk of perpetrating drug-drug interactions through CYP3A inhibition, CYP3A induction (some transporters such as P-gp might also be co-induced), CYP1A2 repression, or inhibition of several transporters (P-gp, BCRP, multidrug and toxin extrusion protein 1 [MATE1], organic cation transporter 2 [OCT2]; bile salt export pump [BSEP] is also
inhibited).

The clinical impact of these in vitro observations is not known. While patients are not precluded from receiving any drugs based upon the potential for a PK drug interaction, patients who are taking concurrent drugs that are known substrates of either CYP3A, CYP1A2, P-gp, BCRP, MATE1 or OCT2 should be carefully monitored.

Notably, due to the irreversible nature of CYP3A inhibition by Debio 1347 and also its in vitro potential for enzyme induction, it should be noticed that the potential for drug-drug

interactions with CYP3A substrates (and possibly also with P-gp substrates) is time-dependent; it may increase with time as patients continue to take Debio 1347, and it may persist for some days after Debio 1347 discontinuation.

A list of drugs that are sensitive or narrow-therapeutic-range substrates of CYP3A, CYP1A2, and substrates of P-gp, BCRP, MATE1 or OCT2 can be consulted in:

- Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University
  School of Medicine (2007): http://medicine.iupui.edu/clinpharm/ddis/table.aspx, and
- http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

If treatment with a prohibited medication is necessary, the patient will be withdrawn from the study.

9.2 Supportive Care

The following are the supportive care guidelines for the study:

9.2.1 Hyperphosphataemia prevention

- All treated patients should receive adequate instructions concerning dietary phosphate restriction. The main natural sources of phosphate are:
  - Dairy products (milk, cheese, ice-cream, yogurt)
  - Meat
  - Dried beans
  - Peas
  - Nuts and peanut butter
  - Wholegrains
  - Cola
- During the dose-escalation phase of the debio 1347 trial, only 50% of patients needed to be treated with phosphate chelators. In the expansion phase, three patients did recieve prophylactic sevelamer, and there was no clear difference with regard phosphate levels in these patients. In view of the side-effects associated with use of phosphate chelators, prophylaxis *will not be required* in phase 2 portion of the study. Phosphate levels will be measured on cycle 1 D4 (+/-1 day), and treated according to the guidelines provided in section 9.4.2. At the time of this amendment, all patients on the phase 1 cohort were off study.

9.2.2 Gastrointestinal disorders

For nausea, vomiting, diarrhea or constipation, treatment may include anti-emetics, anti-diarrheas or laxative bowel regimen consistent with standard of care. Since drugs that alter gastric pH (e.g., proton pump inhibitors, histamine receptors antagonists, antacids) may

interfere with the absorption of Debio 1347, they should be administered at least 2 hours after Debio 1347 administration.

9.2.3 Haematological support

- The use of red blood cell transfusions will be permitted as clinically indicated during the study.
- The use of bone marrow colony stimulating factors (such as granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor) is permitted as clinically indicated. Prophylactic use is prohibited.

9.2.4 Infections

- CR-BSI (Catheter-Related Bloodstream Infection) should be managed according current Clinical Practice Guidelines[46].
- Febrile neutropenia: Antibacterial and antifungal prophylaxis for fever and treatment of neutropenia should be managed according the current Clinical Practice Guidelines[47,48].
- MSRA (Methicillin-Resistant Staphylococcus Aureus) infection should be managed according the current Clinical Practice Guidelines[49].

9.2.5 Pain

- The management of pain should be done according to severity and recommended drugs.

9.2.6 Hypercalcaemia prophylaxis

Patients with asymptomatic hypercalcaemia do not require immediate treatment if calcium remains < 12 mg/dL (3 mmol/L). However, the patient should be advised to avoid factors that can aggravate hypercalcaemia (such as thiazide diuretics, volume depletion, prolonged bed rest or inactivity, and a high calcium diet [> 1000 mg/day]).

Adequate hydration (at least 6 to 6 glasses of water per day) is recommended to minimise the risk of nephrolithiasis.

9.2.7 Prophylaxis for skin toxicity and alopecia

Guidelines for prophylaxis are detailed in Appendix A.

9.3 Dose-limiting toxicity during Phase 1

The following AEs or laboratory abnormalities, graded according to NCI-CTCAE version 4, are considered to be DLTs when occurring during the DLT evaluation period (Day 1 to Day 28 of Cycle 1, plus the assessments prior to drug administration on Cycle 2, Day 1 and the Investigator feels are possibly, probably, or definitely related to Debio 1347 excluding those that are clearly and incontrovertibly due to disease progression or extraneous causes.:

- Febrile neutropenia (ANC < 1.0 X 10^9/L and fever ≥ 38.2°C [101° F])

- Grade 3 or higher neutropenia with infection.
- Grade 4 neutropenia persisting for more than 7 days.
- Grade 4 thrombocytopenia persisting for more than 7 days or Grade 3 thrombocytopenia requiring platelet transfusion.
- Grade 3 diarrhea, constipation, nausea, vomiting or skin toxicity that lasts longer than 72 hours despite optimal symptomatic therapy.
- Any Grade 4 diarrhea, constipation, nausea, vomiting or skin toxicity.
- Grade 3 or higher liver function tests (ALT, AST, ɣGPT) and ALP unless as clarified below
- Grade 3 or higher non-hematologic toxicity including Hy's law: AST and/or ALT > 3x ULN and bilirubin > 2x ULN, and without initial findings of cholestasis (serum alkaline phosphatase (ALP) activity < 2x ULN) and no other reason that could explain the combination of increased transaminases and serum total bilirubin, such as viral hepatitis A, B, or C, preexisting or acute liver disease (including preexisting liver metastases), or another drug capable of causing the observed injury.
- The following non-hematologic AEs are not considered DLTs:
  a. Grade 3 electrolyte abnormalities lasting <24 to 72 hours, is not clinically complicated, and resolves spontaneously or responds to conventional medical interventions; and ≥ Grade 3 amylase or lipase that is not associated with symptoms or clinical manifestations of pancreatitis.
  b. Grade 3 or higher of ALP clearly related to bone metastases evolution. The relationship should be discussed with the study Medical Monitor on a case by case basis.
- Hyperphosphataemia:
  a. Serum Pi > 7.0 mg/dL for > 7 consecutive days despite phosphorus lowering therapy for at least 14 days.
  b. Serum Pi > 9.0 mg/dL, despite phosphorus lowering therapy for at least 14 days.
  c. Serum Pi > 10.0 mg/dL.
- Any treatment delay more than 7 days because of treatment-related AEs or laboratory abnormalities occurring during the DLT period.
- Any other life-threatening toxicity.
- Other AEs considered intolerable by the Investigator.
- Death not clearly due to the underlying disease or extraneous causes

Patients experiencing a DLT during the DLT period may continue treatment after treatment adjustments if there is a potential benefit from treatment.

9. 4 Dose Modifications or Scheduling Delays

- This study will use the NCI Common Toxicity Criteria (CTC) AE version 4.0 for toxicity.
- Study treatment will be temporarily or permanently discontinued due to the occurrence of AEs as specified in Table 1 below, for both the phase 1 and 2 portions of this study.
- Additionally, non-treatment related or unexpected toxicities may require interruption of therapy at the discretion of the Investigator.

- Failure to recover to the specified levels following temporary discontinuation within 7 days in the phase 1b portion and 14 days in the phase 2 portion will result in permanent treatment discontinuation. The treating Investigator and the PI will discuss the case of any patient whose treatment has been delayed for more than 7 or 14 days, respectively, who they think may benefit from continued treatment, prior to resuming treatment.
- In addition, if Grade 2 or higher toxicity occurs, treatment may be temporarily discontinued at the discretion of the Investigator. The patients may resume at the same dose level when toxicity has resolved to Grade 1 or below or the baseline level if resolution is achieved within 7 days in the phase 1b part and 14 days in the phase 2 part.
- In the event the patient requires temporary treatment discontinuation, the Investigator may choose to increase the frequency of the assessments performed to weekly collections until resolution.
- Only in the phase 2 portion, one dose reduction can be undertaken except for dose level -1 (60mg). Patients resuming treatment following a temporary discontinuation can do so at their original dose level or at one lower dose level.
- Patients experiencing a DLT during the DLT period may continue treatment after dose adjustments if there is a potential benefit from treatment after discussion with the PI
- Patients will be permanently discontinued if reduction beyond <60mg/day is necessary in both phase 1 and phase 2 portions of the study
- Reduced doses may not be re-escalated.
- If a patient discontinues Debio 1347 purely due to toxicity, they can stay on study and continue to receive fulvestrant. The patient will be captured as coming off of Debio 1347 due to toxicity and report TTF.

Table 1: Dose Modifications and Delays during Phase 1 and Phase 2

Adverse Event	Grade	Action	
		Phase I part: DLT evaluation period only	**Phase I part**: non-DLT evaluation period **Phase 2 portion**
Febrile neutropenia, Neutropenia with infection	4	Permanent discontinuation Permanent discontinuation	Permanent discontinuation Permanent discontinuation
	3	Permanent discontinuation	Temporary discontinuation until recovery to Grade 0
Neutropenia	3, 4	Temporary discontinuation until recovery to Grade 2	Temporary discontinuation until recovery to Grade 2
Thrombocytopenia	4	Permanent discontinuation	Temporary discontinuation until recovery to Grade 1
	3	Temporary discontinuation until recovery to Grade 1 Permanent discontinuation if a platelet	If a platelet transfusion is required, temporary

Adverse Event	Grade	Action	
		transfusion is required	discontinuation until recovery to Grade 1
Diarrhea, constipation, nausea, vomiting	3,4	Permanent discontinuation, if not manageable by optimal symptomatic therapy	Temporary discontinuation until recovery to Grade 2, or baseline
Skin toxicity (See additional guidelines in 9.4.1)	3,4	Permanent discontinuation, if not manageable despite prophylaxis and optimal symptomatic therapy	Temporary discontinuation until recovery to Grade 2, or baseline
Hyperphosphataemia		Please use the treatment guidelines per 9.4.2	Please use the treatment guidelines per 9.4.3
Hypertension	4	Permanent discontinuation	Permanent discontinuation
	3	Permanent discontinuation	If uncontrolled, temporary discontinuation until control is achieved
Hepatotoxicity (AST, ALT, ALP, γGTP increased)	4	Permanent discontinuation	Permanent discontinuation
	3	Temporary discontinuation, until recovery to Grade 2	Temporary discontinuation, until recovery to Grade 2
Other non-haemotoxicity (except for transient electrolyte abnormalities)	4	Permanent discontinuation	Permanent discontinuation
	3	Permanent discontinuation	Temporary discontinuation until recovery to Grade 1 or baseline
Recovery from above AEs		Permanent discontinuation, if failure to recover within 7 days, Otherwise treatment at same dose level. Dose reduction during the DLT has to be discussed with the PI	Permanent discontinuation, if failure to recover within 14 days, otherwise retreatment at next lowest dose level

9.4.1 Skin Toxicity, nail toxicity and alopecia

Patients will be referred to Dr. Mario Lacouture (Dermatology) for management of alopecia, skin, nail toxicity and stomatitis as needed. Of note, patients will be allowed to receive prophylaxis for skin toxicity and alopecia per section 9.2.7 and Appendix A. Specific treatment guidelines are also detailed in Appendix A.

9.4.2 Hyperphosphatemia (Phase I)

1. Initial Modifications on Treatment:

Serum phosphorus level	
5.5 – 6.9 mg/dL	1. Continue Debio 1347 2. Continue (or increase) sevelamer powder 2400mg TID 3. Add Fosrenol 1g TID 4. Recheck within 7 days

≥ 7 mg/dL	1. Hold Debio 1347 2. Continue (or increase) sevelamer powder 2400mg TID 3. Add Fosrenol 1g TID 4. check within 7 days -> resume if Ph < 5.5 and recheck within 7 days of resumption

*If sevelamer is not available or tolerable, alternate phosphate reducing agents or preparations can be utilized.

2. Second Modification on Treatment

Serum phosphorus level	
5.5 – 6.5 mg/dL	1. Cont Debio 1347 2. Cont sevelamer powder to 2400mg TID increase Fosrenol to 1.5mg TID 3. recheck within 7 days
6.6-6.9mg/dL	1. Cont Debio 1347 2. Cont sevelamer powder to 2400mg TID 3. Cont Fosrenol 1g TID 4. add acetazolamide 250mg BID 5. recheck within 7 days
≥ 7 mg/dL	1. Hold Debio 1347 – consider dose reduction 2. Cont sevelamer powder to 2400mg TID 3. increase Fosrenol to 1.5g TID 4. add acetazolamide 250mg BID 5. check within 7 days -> resume if Ph < 5.5

*If sevelamer is not available or tolerable, alternate phosphate reducing agents or preparations can be utilized.

3. Subsequent Modifications:

Serum phosphorus level	
> 5.5 mg/dL-6.9mg/dL	1. <u>If not already</u>, maximize regimen to include: sevelamer powder to 2400mg TID fosrenol to 1.5g TID acetazolamide 250mg BID 2. <u>If already maximized</u>, consider dose reduction (without interrupting drug) 3. Recheck within 7 days
≥ 7 mg/dL	1. Hold Debio 1347 – dose reduction needed 2. Maximize regimen to include: sevelamer powder to 2400mg TID fosrenol to 1.5g TID acetazolamide 250mg BID

	3. check within 7days -> resume with dose reduction if Ph < 5.5

*If sevelamer is not available or tolerable, alternate phosphate reducing agents or preparations can be utilized.

4. For patients whose phosphorous control improves after Debio 1347 dose reductions, de-escalation of the phosphorus regimen can be considered at the discretion of the investigator. Subsequent to any such adjustment, phosphorous level should be rechecked within 7 days.
5. In case of patients with hepatic or renal impairment, it is recommended not to change hyperphosphatemia treatment even in the case of Debio 1347 dose reduction.

9.4.3 Hyperphosphatemia (Phase II)

INITIAL TREATMENT MODIFICATION	
Serum Phosphorous Level	Intervention/Modi fication
5.5 – 6.9 mg/dL	• Continue treatment with Debio 1347 at current dose AND • Start on sevelamer oral POWDER 1200mg three times a day (subjects may use tablets if preferred, but tends to have more gastrointestinal toxicity) • Escalate to sevelamer oral POWDER or tablets 2400mg three times a day if tolerated. • Reassess serum phosphorus within 7 days
≥ 7 mg/dL	• **Hold treatment with Debio1347** • Start sevelamer oral POWDER or tablets 2400mg three times a day • Add treatment with lanthanum carbonate (Fosrenol®) 1g three times a day • Reassess serum phosphorus level within 7 days: ○ If serum phosphorus level < 5.5 mg/dL, resume Debio 1347 at same dose and recheck within 7 days of resumption
Note:	• Sevelamer should be preferably taken in the middle of meals • Lanthanum carbonate should be taken just after meals • Sevelamer and lanthanum must be administered at least 2 hours after or 4 hours before Debio 1347

SECOND TREATMENT MODIFICATION	
Serum Phosphorous Level	Intervention/Modi fication
5.5 – 6.5 mg/dL	• Continue treatment with Debio 1347 at a current dose AND • Continue sevelamer oral POWDER or tablets 2400mg three times a day • Introduce treatment with lanthanum carbonate (Fosrenol®) to 1.0g three times a day or increase to 1.5g three times a day • Reassess serum phosphorus level within 7 days
6.6-6.9 mg/dL	• Continue treatment with Debio 1347 at current dose AND • Continue sevelamer oral POWDER or tablets 2400mg three times a day • Introduce treatment with lanthanum carbonate (Fosrenol®) to 1.0g three times a day or increase the dose to 1.5g three times a day • Add treatment with oral acetazolamide 250mg twice a day • Reassess serum phosphorus level within 7 days
≥ 7 mg/dL	• Hold treatment with Debio 1347 – consider dose reduction • Continue sevelamer oral POWDER or tablets 2400mg three times a day • Increase treatment with lanthanum carbonate (Fosrenol®) to 1.5g three times a day AND

	• Add treatment with oral acetazolamide 250mg twice a day • Reassess serum phosphorus level within 7 days: ○ If serum phosphorus level < 5.5 mg/dL, resume Debio 1347 with dose reduction
Note:	• Sevelamer should be preferably taken in the mid of meals • Lanthanum carbonate should be taken just after meals • Sevelamer and lanthanum must be administered at least 2 hours after or 4 hours before Debio 1347 • Acetazolamide should be preferably taken just after breakfast and dinner

SUBSEQUENT TREATMENT MODIFICATIONS	
Serum Phosphorous Level	Intervention/Modi fication

5.5 – 6.9 mg/dL	• If not already done, maximize regimen to include:
	  ○ Sevelamer oral POWDER or tablets to 2400mg three times a day
	  ○ Lanthanum carbonate (Fosrenol®) to 1.5g three times a day
	  ○ Oral acetazolamide 250mg twice a day
	• If regimen already maximized, consider dose reduction (without interrupting Debio 1347 assumption)
	• Reassess serum phosphorus level within 7 days

≥ 7 mg/dL	• **Hold treatment with Debio1347** – dose reduction needed
	• Maximize regimen to include:
	  ○ Sevelamer oral POWDER or tablets to 2400mg three times a day
	  ○ Lanthanum carbonate (Fosrenol®) to 1.5g three times a day
	  ○ Oral acetazolamide 250mg twice a day
	• Reassess serum phosphorus level within 7 days:
	  ○ If serum phosphorus level < 5.5 mg/dL, resume Debio 1347 with dose reduction

Note:	• Sevelamer should be preferably taken in the mid of meals • Lanthanum carbonate should be taken just after meals • Sevelamer and lanthanum must be administered at least 2 hours after or 4 hours before Debio 1347 • Acetazolamide should be preferably taken just after breakfast and dinner

GENERAL RECOMMENDATIONS
• In subjects whose serum phosphorus control improves after Debio 1347 dose reduction, de-escalation of the hyperphosphatemia treatment can be considered at the discretion of the Investigator. Subsequent to any such adjustment, serum phosphorus level should be reassessed within 7 days. • In case of subjects with hepatic or renal impairment, it is recommended not to change hyperphosphatemia treatment even in the case of Debio 1347 dose reduction.

9.4.4 Guidelines for significant QTc prolongation

Significant QTc prolongation is defined as an interval > 500 ms or an interval which increases by 60 ms over baseline.

If the prolongation is confirmed on 2 out of the 3 ECGs by either criteria (i.e., QTc interval > 500 ms or > 60 ms increase from baseline) treatment with Debio 1347 should be stopped and the following actions will be taken:

- The patient will be withdrawn from Debio 1347 treatment.
- The patient will be monitored, treated appropriately, and closely followed (ECGs at least three times per week) until the QT and QTc interval return to within 30 ms of baseline.

If an ECG shows significant QTc prolongation the patient should be referred to a cardiologist.

9.5 Subject replacement strategy

- Patients not eligible for the MTD/RP2D determination of the phase 1b portion will be replaced (see section 12.3.3)
- Patients not eligible for efficacy evaluation for the Phase II portion of the study will also be replaced

10.1 EVALUATION DURING TREATMENT/INTERVENTION

	Screening	Treatment								EOT	F/U[a]
Cycle		1					2		3+		Every 12 weeks
Day	-28 to -1	1	4	8	15	28	1	15	1		
		±2	±1	±2	±2	-4	±3	±3	±3	±7	±14
Written Informed Consent	X										
Review of Eligibility Criteria	X										
Demographic Information	X										
Vital Signs, ECOG PS[b]	X	X			X		X	X	X	X	
Height	X										
Physical Exam and Weight	X	X			X		X	X	X	X	
12-lead ECG[c]	X	X				X			X	X	
ECHO[c]	X								X	X	
Haematology and Chemistry blood work [d]	X	X		X	X		X	X	X	X	
Tumor markers (CEA and CA15-3)	X	X					X		X	X	
Other Bloodwork (CRP LDH, uric acid and γGTP)	X	X		X	X		X	X	X	X	
Phosphate (P)			X								
Blood coagulation (PT (INR), APTT)	X	X					X		X	X	
Urinalysis[e]	X	X		X	X		X	X	X	X	
Calcium regulating hormones bloodwork[f]	X	X					X		X	X	
Serum pregnancy test	X									X	
Ophthalmological testing[g]	X									X	
Adverse events		X		X	X	X	X	X	X	X	

Fulvestrant		X			X	X			X		
Tumour assessment[h]	X								X	X	
Plasma sample for CfDNA[i]		X			X				X	X	
Pharmacokinetics[j]		X[j]			X		X		X		
Tumor Biopsy[k]	X										
HepBsAg, HepBcAb, HIV and hepatitis C antibody[l]	X										

Abbreviations: DEXA, dual-energy X-ray absorptiometry; ECHO, echocardiogram; ECOG, Eastern Cooperative Oncology Group; EOS, end-of-study; EOT, end-of-treatment (any study treatment); IV, intravenous; PS, performance status.

a) Survival and disease status will be assessed every 12 weeks (+/- 14 days) until death, withdrawal of consent, or end of the study, whichever is first. Assessments can be collected through phone call or review of patient records.

b) Blood pressure and heart rate to be collected. BP and pulse rate to be taken after at least 5 minutes of supine rest.

c) ECG recorded every 3RD cycle *after* Cycle 3. If an ECG shows QTc prolongation (> 470 msec.), the ECG must be repeated twice additionally to obtain values in triplicate. ECHO will be done at baseline, every 3 cycles and at EOT during the phase 1 portion of the study.

d) Haematology: red blood cells, haemoglobin, hematocrit, platelet count, white blood cells, neutrophils, lymphocytes, monocytes, eosinophils, basophils.

Blood chemistry(Fasting): total protein, albumin, total bilirubin, AST, ALT, LDH, ALP, γGTP, CK, total cholesterol, sodium (Na), potassium (K), calcium (Ca), chloride (Cl), phosphate (P), magnesium (Mg), creatinine, BUN, CRP, uric acid, glucose.

e) Urinalysis: protein, blood, glucose, urobilinogen, pH, sediment, creatinine, calcium (Ca), phosphate (P).

f) Calcium regulating hormone assessments (whole-PTH, 1,25(OH) 2D, PTHrP) will be performed every cycle until Cycle 3 and every 3 cycles thereafter.

g) Ophthalmological tests to be repeated as clinically indicated during treatment. Complete ophthalmologic examinations will be performed at screening and, as soon as clinically indicated, if a patient reports any visual abnormality. Complete ophthalmologic examination will be performed and interpreted by a qualified ophthalmologist, including visual acuity testing, slit-lamp ophthalmoscopy and indirect ophthalmoscopy. At the final visit and 28 days after the last dose, slit-lamp ophthalmoscopy will be performed.

h) Tumor assessments (patients with a history of brain mets will be required to have brain CT scans with contrast or MRIs) to be performed every 8 weeks for 48 weeks (i.e. cycle 2, 4, 6 between days 22 and 28) and then every 12 weeks thereafter (i.e. cycle 9, 12, 15 again between days 22 and 28 etc.).

i) Plasma samples for cfDNA analysis will be collected prior to dosing on cycle 1, cycle 1 day 15, day 1 of C3 and then at EOT.

j) Plasma samples for PK will be collected both during phase 1 and 2. Phase 1 PK will be collected prior to dosing on day 1 and 15 of cycle 1 and then day 1 of each cycle thereafter. Phase 2 PK will be collected prior to dosing on day 15 of cycle 1 and day 1 of cycle 2.

k) Baseline tumor biopsies will be obtained during screening for all patients enrolled in the study, at least three fragments on a core biopsy

l) Documented negative tests prior to screening period is acceptable.

10.1 Follow up visits

The mandatory End of Treatment Visit should be conducted approximately 2-4 weeks after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the End of Treatment Visit should be recorded. Subjects with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first. SAEs that occur within 30 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded.

10.1.2 Survival Follow-up

Once a subject experiences confirmed disease progression or starts a new anti-cancer therapy, the subject moves into the survival follow-up phase and should be contacted by telephone or review of patient records every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

10.1.3 End-of-Treatment Criteria

Treatment with Debio 1347 will continue until any of the following occur:

- Patient withdraws consent.
- Disease progression documented by CT scan, physical exam or other objective method of measurement. An exception could be made for patients who progressed due to brain metastases; patients may continue treatment with Debio 1347 if, in the Investigator's opinion, there was reasonable evidence of ongoing clinical benefit.
- Unacceptable toxicity.
- Pregnancy.
- Patient's interests as judged by the Investigator.
- In the event of a Debiopharm International SA decision to no longer supply study drug, ample notification will be provided so that appropriate adjustments to subject treatment can be made.

Patients who are removed from study treatment due to AEs are to be treated and followed-up according to accepted medical practice. All pertinent information concerning the outcome of such treatment will be recorded.

10.1.4 End-of-Treatment Visit

Patients will undergo the EOT assessment and exit from the study, unless they are prematurely discontinued from the study for any of the following reasons:

1. Patient requests to leave the study.

2. Adverse event, e.g. intercurrent illness that would, in the judgment of the Investigator, affect assessments of clinical status to a significant degree; or intercurrent illness that, in the opinion of the Investigator compromises the patients safety.

3. Patient non-compliance.

4. Patient lost to follow-up.

5. If, in the Investigators opinion, continuation in the trial would be detrimental to the patient's wellbeing.

6. A major protocol violation occurs.

7. Prohibited medication as indicated in Section 9 is required/used during the course of the trial. In the event a patient is found to be taking a prohibited medication during the trial, the site should immediately contact the Medical Monitor. The decision to withdraw the patient will be made in conjunction with the Sponsor.

8. Non-drug related reason; e.g. patient relocates too far from study centre.

9. Study is terminated.

Should a patient be withdrawn, EOT assessments should be performed prior to any further therapeutic intervention whenever possible. Results of these assessments will be recorded together with a description of the reasons for study discontinuation.

10.1.5 Correlative analyses

Plasma samples for pharmacokinetics (PK) will be collected during both phase 1 and 2. Phase 1 PK will be collected prior to dosing on day 1 and 15 of cycle 1 and then day 1 of each cycle thereafter. Phase 2 PK will be collected prior to dosing on day 15 of cycle 1 and day 1 of cycle 2. These samples may be analyzed by LC-MS/MS to assess the PK (trough levels at steady-state) of both fulvestrant and Debio 1347 in combination. These data will be compared with historical PK data in monotherapy (Faslodex® prescribing information; PK results from Study Debio 1347-101), in order to investigate potential PK interactions and to support interpretation of safety and/or efficacy results in the trial, and tumor specimens will be studied.

Archival tissue will be obtained, whenever available as well.

Baseline tumor biopsies will be obtained. We will perform FISH, protein and mRNA expression analyses from formalin-fixed paraffin-embedded tissue samples in the laboratory of Dr. Jorge Reis-Filho along with the MSKCC Integrated Genomics Operation (IGO) and MSKCC Molecular Cytogenetics Core facilities.

1) ***FGFR1* FISH** will be performed as follows: *FGFR1* amplification will be assessed using the ZytoLight SPEC FGFR1/CEN 8 Dual Color Probe (ZytoVision, Bremerhaven, Germany). Tissue processing, hybridization, post-hybridization washing, and fluorescence detection will be performed according to standard lab procedures. Slides will be scanned using a Zeiss Axioplan 2i epifluorescence microscope equipped with a CCD camera (CV-M4+CL, JAI) controlled by Isis 5.5.9 (MetaSystems Group Inc.). Marked region(s) within a given tissue section will be scanned at 63X or 100X and at least five images per representative region captured, each image being a compressed stack of 12 z-section images taken at 0.5 µm intervals. Signal counts will be performed on the captured images and a minimum of 100 discrete nuclei scored. Amplification will be defined as >10 copies of discrete *MYB or NFIB* signals or small cluster of signals (>4 copies; representing tandem duplications/repeats). Tumors will be considered as *FGFR1*-amplified under one of the following conditions: a) The FGFR1/CEN8 ratio is ≥2.0; b) Average number of FGFR1 signals per tumor cell nucleus is ≥6; or c) Presence of large or small cluster of signals FGFR*1*/CEN8 ratio will be also reported as a continuous variable.

2) **Immunohistochemistry**: the expression of FGFR1 at the protein level will be assessed using immunohistochemistry, using the monoclonal D8E4 antibody (Cell Signaling, Boston, MA). Antibody dilution and antigen retrieval is currently being optimized. Stained slides will be analyzed in a semi quantitative manner using the H score method.

3) **mRNA expression**: We will quantify the mRNA expression levels of *FGFR1* along with other key targets using Nanostring. RNA will be extracted the RNAeasy Mini Kit (Qiagen) according to the manufacturers' instructions. One hundred ng of total RNA will be hybridized to a custom designed gene CodeSet (non-enzymatic RNA profiling using barcoded fluorescent probes) according to the manufacturers protocol (Nanostring Technologies). Barcodes will be counted (600 fields of view per sample) on an nCounter Digital Analyzer following the manufacturer's instructions (NanoString® Technologies) and normalized to housekeeping transcripts. Further analysis will follow previously published methods to identify the range of FGFR1 expression levels, which will be compared to IHC and FISH findings.

11.1 TOXICITIES/SIDE EFFECTS

11.1 Debio 1347

Expected side effects include:

- **Constitutional**: asthenia, fatigue, decreased appetite
- **Musculoskeletal**: myalgia, back pain
- **Neurologic**: dizziness
- **Cardiovascular**: hypertension, decline in LVEF, QTc prolongation
- **ENT**: blurry vision, diplopia, dry eyes
- **Respiratory**: dyspnea, cough
- **Dermatologic**: maculo papular rash, nail changes, alopecia, hand foot syndrome, dry skin

- **Gastrointestinal**: elevations in AST/ALT/Alk Phos/bilirubin/amylasemia, nausea/vomiting, constipation, diarrhea, abdominal pain, dry mouth, dysgeusia, stomatitis
- **Renal/Electrolyte abnormalities**: hyperphosphatemia, increased creatinine, hypomagnesemia, hypokalemia

Please refer to Section 3.3.4 and the Investigator's Drug Brochure for more information.

11.2 Fulvestrant

The most common adverse reactions occurring in ≥5% of patients receiving 500 mg fulvestrant were: injection site pain, nausea, bone pain, arthralgia, headache, back pain, fatigue, pain in extremity, hot flash, vomiting, anorexia, asthenia, musculoskeletal pain, cough, dyspnea, and constipation.

Increased hepatic enzymes (ALT, AST, ALP) occurred in >15% of FASLODEX users and were not dose-dependent.

Because Fulvestrant is administered intramuscularly, it should be given with caution in patients with bleeding diathesis, thrombocytopenia, or anticoagulant use. For further details regarding the safety profile of fulvestrant, refer to the fulvestrant package insert.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

Tumor response is based on the RECIST v.1.1. A copy of the full article is provided as Appendix B. Key elements of the criteria are summarized below.

12.1 Measurability of Tumor at Baseline

RECIST v.1.1 provides the following definitions for designating the tumor lesion/lymph node as measurable or non-measurable at baseline.

12.1.1 Measurable Lesions

12.1.1.1 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 as follows:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm; see Appendix II of Eisenhauer et al, 2009 for imaging guidance)
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with caliper should be recorded as non-measurable)
- 20 mm by chest X-ray

12.1.1.2 Malignant Lymph Nodes

To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm 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. For additional information on lymph node measurement, see notes in Eisenhauer et al, 2009 under the heading "Baseline documentation of target and non-target lesions," as well as a companion paper on lymph node assessment using RECIST [50].

12.1.2 Non-measurable Lesions

Non-measurable lesions are all other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions. Truly non-measurable lesions include leptomeningeal disease, ascites, pleural or pericardial effusions, inflammatory breast disease, lymphangitic involvement of skin or lung, and abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

12.1.3 Special Considerations Regarding Lesion Measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment.

12.1.3.1 Bone Lesions

Bone scan, PET scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

Lytic bone lesions or mixed lytic-blastic lesions, *with identifiable soft tissue components,* that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

Blastic bone lesions are non-measurable.

12.1.3.2 Cystic Lesions

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

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

12.1.3.3 Lesions with Prior Local Treatment

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

12.1.4 Methods of Tumor Measurement

Please refer to Eisenhauer et al, 2009, Section 3.2 for details concerning details of how measurements of lesions/lymph nodes should be done. For the current study, CT is the only acceptable measurement method.

12.2 Tumor Response Evaluation

12.2.1 Designation of Target and Non-Target Lesions

When more than one measurable lesion is present at baseline, all lesions, up to a maximum of 5 lesions (and a maximum of 2 lesions per involved organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. In the current study, the baseline measurement will be based on the scans and measurements taken at the end of the pre-study standard chemotherapy, as submitted by the investigator.

Target lesions should be selected on the basis of their size (lesions with longest diameter) and be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that on occasion, the largest lesion does not lend itself to reproducible measurement; in such cases, the next largest lesion that can be reproducibly measured should be selected.

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. The baseline sum diameters will be used as the reference to characterize any objective changes in the measurable dimension of disease.

All other lesions or sites of disease (i.e., non-measurable lesions), including pathological lymph nodes, should be identified as non-target lesions. Measurements of non-target lesions, even if measurable, are not required, as they are intended to be assessed qualitatively and should be designated as present or absent at baseline. It is also possible to record multiple non-target lesions in the same organ as a single item, e.g., “multiple enlarged pelvic lymph nodes.”

12.2.2 Definitions of Response

12.2.2.1 Target Lesions

Definitions of response for individual patients at each assessment time point for target lesions are shown in Table 2.

Table 2 Evaluation of Response in Target Lesions

Response Category	Definition
CR	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
PR	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
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). *For this study*, *PD should be confirmed at least 4 weeks later.*
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

Abbreviations: CR, complete response; PR, partial response; PD, progressive disease; SD, stable disease

12.2.2.1.1 Lymph Nodes as Target Lesions

Please refer to RECIST v.1.1 in Appendix B for special notes on the assessment of lymph nodes as target lesions, lesions that become too small to measure, and lesions that split or coalesce after treatment.

12.2.2.2 Non-target Lesions

Definitions of response for individual patients at each assessment time point for non-target lesions are shown in Table 18. Non-target lesions, even if measurable, are to be evaluated qualitatively, as noted above, and are to be designated as CR, non-CR/non-PD, or PD, as defined in Table 3.

Table 3 Evaluation **of Response at Each Time Point in Non-target Lesions**

Response Category	Definition
CR	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).
Non-CR/Non-PD	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
PD	Unequivocal progression (see comments below) of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).[a]

Abbreviations: CR, complete response; SD, stable disease; PD, progressive disease.

[a] Although a clear progression of "non-target" lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail.

12.2.2.2.1 Special Notes on Designation of Progression in Non-Target Disease

The concept of progression of non-target disease in the setting of concurrent measurable disease as in this study requires further explanation. In this setting, to assign unequivocal progression on the basis of the non-target disease (see determination of overall response in Section 0), there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in the target disease, the overall tumor burden has increased sufficiently to warrant discontinuation of therapy (see examples in the RECIST v.1.1 guidelines in Appendix B). A modest increase in the size of one or more non-target lesions is usually not sufficient to qualify for a designation as unequivocal progression. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

12.2.2.3 New Lesions

The appearance of new malignant lesions denotes disease progression. Refer to RECIST v.1.1 in Appendix B for notes concerning the detection of new lesions.

12.2.2.4 Missing Data

When no imaging/measurement is done at all at a particular time point, the subject is not evaluable (NE) at that time point. If only a subset of lesion measurements is made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesions would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a subject had a baseline sum of 50 mm with three measured lesions and at the assessment only two lesions were assessed, but those gave a sum of 80 mm, the subject will have achieved PD status regardless of the contribution of the missing lesion measurement.

12.2.2.4.1 Additional Notes Relevant to Designations of Disease Progression

Per RECIST v.1.1, patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression should be reported as

"symptomatic deterioration," and every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy. The objective response of such subjects is to be determined by evaluation of target and non-target disease as shown in Table 17 and Table 18. In the current study, scans are to be done every 3 cycles and at any time deemed appropriate by the investigator (i.e., when progression is suspected). PD at first response scan must be confirmed at least 4 weeks later.

12.2.2.5 Overall Response for Each Subject at Each Assessment Time Point

Overall response at each assessment time point is based on the totality of the responses for target and non-target lesions, as shown in Table 19.

Table 4 Rubric for Determination of Overall Response at Each Assessment Time Point for Each Patient

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease

12.2.2.6 Additional Information Concerning RECIST v1.1

Full details concerning the use of RECIST v.1.1 may be found in the full article by Eisenhauer et al. (2009), which is attached as Appendix B.

12.3 Evaluable patients

12.3.1 Safety Population

Patients who received any dose of the study drug.

12.3.2 MTD/RP2D Determination Population during Phase 1b portion

The population evaluable for MTD/RP2D determination will consist of all patients who received at least 75% of the planned Debio 1347 dose during the DLT period (Day 1 to Day 28 of Cycle 1 and assessments prior to drug administration on C2D1). Patients who experienced a DLT will be included in the MTD/RP2D determination population regardless of the dose of Debio 1347 received.

Patients who fulfill any of the following situations will be excluded from the MTD/RP2D determination population:

1. Administration during the DLT period of non-permitted concomitant treatments with impact on DLT evaluation.
2. Proper DLT/safety evaluation is judged to be difficult because of protocol violation(s).

12.3.3 Efficacy population

Patients who have measurable and/or non-measurable disease, according to RECIST version 1.1. criteria, undergo a baseline disease assessment, at least one on-treatment assessment, but excluding those who fulfill any of the following conditions:

1. Violation of clinically relevant inclusion/exclusion criteria.
2. Administration of non-permitted concomitant treatments.

13.1 CRITERIA FOR REMOVAL FROM STUDY

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons.

A subject must be discontinued from the trial for any of the following reasons:

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- Confirmed radiographic disease progression

Note: A subject may continue on treatment with confirmed radiographic progression if clinically stable or clinically improved.

- Unacceptable adverse experiences
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- Subject death
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up

After the end of treatment, each subject will be followed for 30 days for adverse event monitoring (serious adverse events will be collected for 90 days after the end of treatment).

Subjects who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up, for up to 2 years. After documented disease progression, each subject will be followed by telephone for overall survival until death, withdrawal of consent, the end of the study, or 2 years, whichever occurs first.

If consent is withdrawn, the subject will not receive any further investigational product or further study observation.

14.0 BIOSTATISTICS

Phase I: The phase I portion of this trial will evaluate 2 dose cohorts including 1 de-escalation cohort (N= minimum 4 and maximum 12) as shown in the table below. Only the dose of Debio 1347 will be de-escalated. There will be no intra-patient dose escalation. 1 cycle = 28 days.

The Dose Limiting Toxicity (DLT) observation period includes Day 1 to Day 28 of Cycle 1, plus the assessments prior to drug administration on Cycle 2, Day1.

Cohort/Dose level	Debio 1347	Fulvestrant
-1	60mg	500mg IM
1 (Starting dose cohort)	80mg	500mg IM

If none or one of the initial 3 patients in dose level 1 has DLT, 3 additional patients will be treated at the same dose level. If 2 or more patients experience DLT at this dose level, then dose level -1 will be evaluated. Should 2 or more patients experience DLT at dose level -1, the study will stop accrual. If only 1 of the 3 initial patients experiences a DLT at dose level -1, 3 additional patients will be evaluated at this dose level. Patients who withdraw before completing a full cycle of treatment for reasons other than development of a DLT will be replaced.

Selected non-hematologic and hematologic toxicities, as measured by the NCI CTCAE Version 4.0, will be described by frequency and grade, by cycle and over all cycles, with the maximum grade over all cycles used as the summary measure per patient. In a descriptive secondary analysis, clinical benefit rate will be estimated by dose.

We anticipate accruing 1-2 patients/month in the phase 1b portion of the study.

Phase II: The purpose of the phase II portion of the study is to evaluate the efficacy of this regimen, using the MTD/RP2D as determined in the Phase Ib part of the trial. Efficacy will be measured by the clinical benefit rate: proportion of patients who have a best overall response

of a complete response, a partial response, or stable disease (SD) for at least 24 weeks (SD ≥ 24 weeks) i.e. (CR+PR+SD >=24 weeks). In the PALOMA-3 trial where ER+ MBC patients were randomized to fulvestrant plus palbociclib versus fulvestrant, the CBR (ORR + SD > 24 weeks) was 34%(95% CI, 29.0 to 39.3) vs 19% (95% CI, 13.4 to 25.6). There is no historic data available for patients who have progressed on palbociclib. Since this trial will allow patients who have received prior palbociclib, it was decided that a target clinical benefit rate below 10% will not be worthy of further consideration and a response rate of 25% will be considered promising.

Simon's two-stage optimal design will be used to study the treatment efficacy since it permits early termination of the study. We will allow early termination only if the data at the first stage indicate that the treatment is highly inactive. 18 patients will initially enter the study. If there are 2 or fewer patients with clinical benefit (CR, PR or SD>=24) observed, the study will be terminated early and declared to have a negative result. If 3 or more patients have clinical benefit, enrollment will be extended to 43 patients. Note, we will halt the trial after the first stage while awaiting results from the first 18 patients.

If 8 or more patients with clinical benefit are observed among the 43 patients, the study will be considered to have a positive result and this regimen would be considered worthy of further testing in this disease. The probability of early termination is 0.73 if the true clinical benefit probability is ≤ 10%. This design would effectively discriminate between true clinical benefit rates of ≤ 10% and ≥ 25%. This design has 80% power and a type I error of 5%.

Upon completion of the study, the true clinical benefit rate will be estimated via the observed rate and an exact confidence interval will be constructed.

The maximum of 43 patients requires about 2 years of patient accrual with an anticipated enrollment of 1-2 patients per month.

In secondary analyses for the Phase Ib portion of the trial, the ORR will be summarized as a proportion with a 95% exact confidence interval. TTP, PFS and OS will be evaluated using Kaplan-Meier methods. All toxicities as measured by the NCI CTCAE Version 4.0, will be described by frequency and grade, by cycle and over all cycles, with the maximum grade over all cycles used as the summary measure per patient. All patients will be included in the safety analyses regardless of whether a patient is not evaluable for the efficacy endpoint.

All exploratory analyses will be conducted for each phase of the trial separately. PK/PD measures such as AUC, Cmax, and Cmin will be calculated and summarized. Exploratory endpoints that aim to investigate biomarkers of clinical benefit and/or resistance will be evaluated descriptively and graphically. If there are a sufficient number of clinical benefit events, nonparametric tests (Fisher's exact or Wilcoxon rank sum) will be used to test the exploratory hypotheses depending on the distribution of the biomarker.

Deaths will be censored for the TTP endpoint in secondary analyses. However, we will also evaluate PFS which treated deaths and progression as events. These are secondary

analyses, and if there are a sufficient number of events and types of events, we can consider other approaches, such as the calculation of cumulative incidence functions.

15.1 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.2 Research Participant Registration

Confirm eligibility as defined in the section entitled Inclusion/Exclusion Criteria. Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures. During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist. The individual signing the Eligibility Checklist is confirming whether or not the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

15.3 Randomization

If the research study requires randomization procedures, this section should be referenced by the Biostatistics section (14.0). Describe in detail the process of randomization, when it should occur, how it is being conducted and who is responsible for carrying it out.

16.1 DATA MANAGEMENT ISSUES

A MSKCC Research Study Assistant (RSA) and Research Project Coordinator (RPC) will assist the PI, Dr. Komal Jhaveri with the oversight and conduct of this study. The RSA will be responsible for protocol compliance, data collection, data reporting, AE tracking and reporting, SAE reporting, regulatory submissions, and for coordinating all study participant research activities. The RPC will be responsible for regulatory compliance, overall project compliance, data quality assurance, SAE review, and Medidata database management. Both the RSA and RPC will report to and regularly meet with the PI to review study, data and enrollment status; protocol aberrations, regulatory requirements and any participant toxicities on study.

16.2 Quality Assurance

Throughout the life of the study, the study team comprising of the PI, research fellows, research nurses, RSA, and RPC will meet regularly. During these meetings, they will address accrual rates, review adverse events, and discuss any challenges with using the device in this population. Regular registration reports will be generated to monitor patient accruals and completeness of data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and accuracy of evaluations and follow-up will be monitored periodically throughout the study and potential problems will be brought to the attention of the PI and CRM for discussion and action.

Random sample data quality audits will be performed by the RPC and evaluated at the study team meetings.

16.3 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials" which can be found at: http://cancertrials.nci.nih.gov/researchers/dsm/index.html. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: *http://mskweb2.mskcc.org/irb/index.htm*

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Center's Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

17.1 PROTECTION OF HUMAN SUBJECTS

Participants will be informed that information collected during their participation in this study is considered confidential. All data gathered will be kept in a secured location and available only to members of the research study team. Findings will be presented in aggregate form only - with no references made to the individual participant's data. Confidentiality of each participant's data will be protected with utmost care; data will be identified solely by a code number. A list matching participant's names and code numbers will be maintained on a secure and password protected database in MSKCC servers. Participation in this study is entirely voluntary. All participants will be required to sign a statement of informed consent that adheres to MSKCC guidelines. Should a patient decide not to participate in this study or to withdraw their consent to participate at any time during the study, their treatment at MSKCC or participating institutions will in no way be compromised.

17.2 Privacy

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

The consent indicates that individualized de identified information collected for the purposes of this study may be shared with other qualified researchers. Only researchers who have received approval from MSK will be allowed to access this information which will not include protected health information, such as the participant's name, except for dates. It is also stated in the Research Authorization that their research data may be shared with other qualified researchers.

17.3 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant starts investigational treatment/intervention. SAE reporting is required for 30-days after the participant's last investigational treatment/intervention. Any event that occur after the 30-day period that is unexpected and at least possibly related to protocol treatment must be reported.

Please note: Any SAE that occurs prior to the start of investigational treatment/intervention and is related to a screening test or procedure (i.e., a screening biopsy) must be reported.

All SAEs must be submitted in PIMS. If an SAE requires submission to the HRPP office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be submitted within 5 calendar days of the event. All other SAEs must be submitted within 30 calendar days of the event.

The report should contain the following information:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment(s)
- If the AE was expected
- Detailed text that includes the following

- An explanation of how the AE was handled
- A description of the participant's condition
- Indication if the participant remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

17.3.1 SAE Reporting to Debiopharm International S.A.

All SAEs, irrespective of their cause, that occur between signature of informed consent and 30 days after the last IMP administration, have to be reported by the Institution to Debiopharm International SA within 24 hours after being informed of their occurrence.

- Serious AEs will be reported to Debiopharm by FAX, e-mail, or phone.
- When reported by FAX, SAEs will be transmitted via the "Serious Adverse Event Report transmittal form" to:

Debiopharm International SA
Fax: + 41 21 321 06 97

- When reported by e-mail, SAEs will be transmitted to:
- Safety-Debio-1347-101@debiopharm.com
- When reported by phone, SAEs will be notified to the Pharmacovigilance Manager of Debiopharm International SA as specified in the site study file.
- All SAEs shall be promptly confirmed in writing at the latest within 3 days of being informed using the "Serious Adverse Event Report transmittal form" of Debiopharm International SA

17.2.1

18.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.

5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

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20.0 APPENDICES

Appendix A: Guidelines for prophylaxis and Treatment of Dermatologic Toxicity

Appendix B: Recist 1. 1 Guideline