Enhancing Efficacy of Chemotherapy in Triple Negative/Basal-Like Breast Cancer by Targeting Macrophages: A Multicenter Phase Ib/II study of PLX 3397 and Eribulin in Patients with Metastatic Breast Cancer

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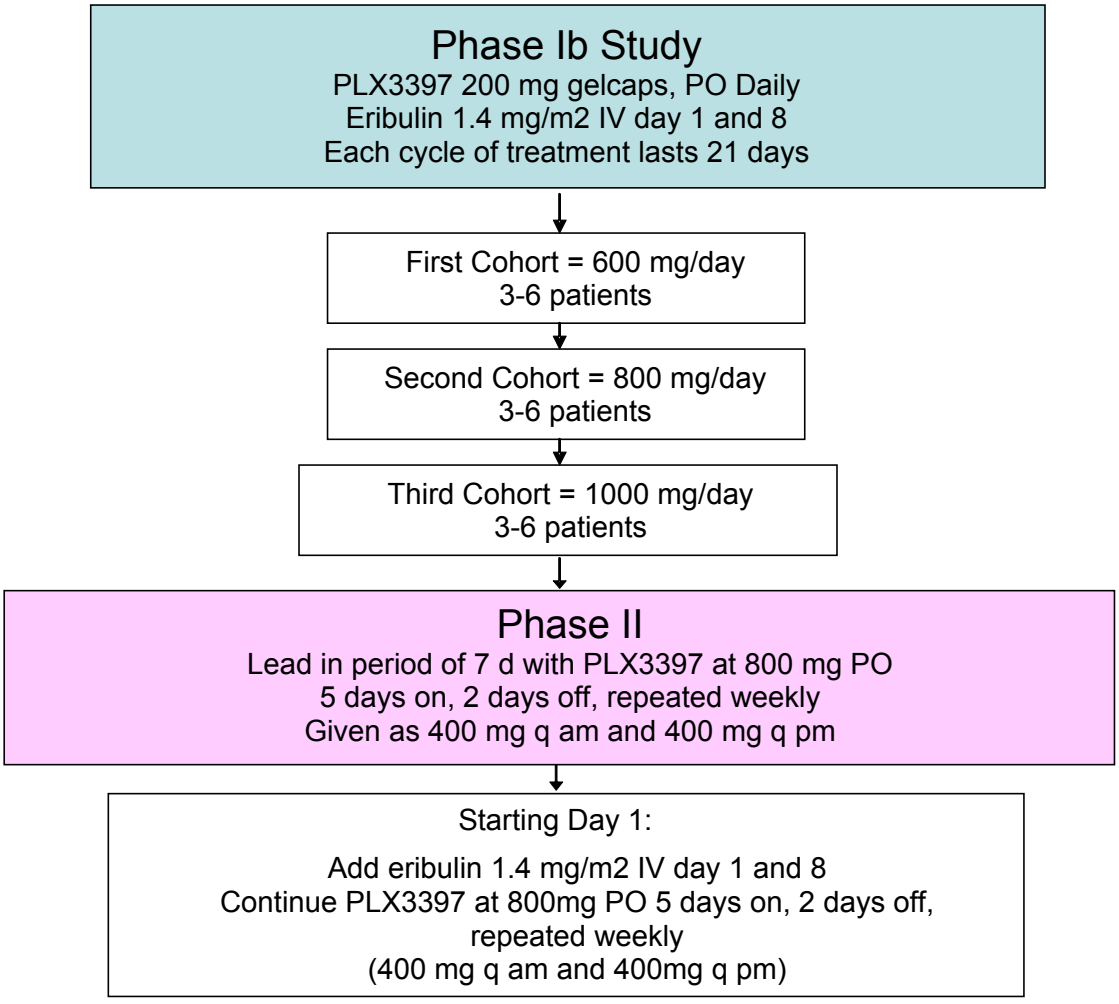

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LIST OF ABBREVIATIONS

AE	Adverse event
ALT	Alanine transaminase
ANC	Absolute neutrophil count
AST	Aspartate transaminase
BUN	Blood urea nitrogen
CCC	Comprehensive Cancer Center (UCSF)
CEC	Circulating endothelial cell
CHR	Committee on Human Research (UCSF IRB)
CR	Complete response
CSF	Colony-stimulating factor
CT	Computerized tomography
CTX	Chemotherapy
CTC	Circulating tumor cell
CTMS	Clinical Trials Management System
DLT	Dose limiting toxicity
DSMB	Data safety monitoring board
DSMC	Data safety monitoring committee (UCSF)
ECOG	Eastern Cooperative Oncology Group
EF	Ejection Fraction
FDA	Food and Drug Administration
FISH	Fluorescent in-situ hybridization
HER2	Human Epidermal Growth Factor Receptor 2
IHC	Immunohistochemistry
MCB	Metastatic breast cancer
MRI	Magnetic Resonance Imaging
MTD	Maximum tolerated dose
NCI	National Cancer Institute
OS	Overall survival
PET	Positron emission tomography
PK	Pharmacokinetics
PFS	Progression-free survival
PR	Partial response
RFS	Relapse-free survival
RR	Response rate
SAE	Serious adverse event
TAM	Tumor associated macrophage
TN	Triple negative
TNBC	Triple negative breast cancer
TTP	Time to progression
UCSF	University of California San Francisco
ULN	Upper limit of normal

1.0 Background and Rationale

1.1 Background

TRIPLE NEGATIVE BREAST CANCER

The marked difference in breast cancer (BC) outcome between black women and white women in the United States has long been recognized as an important health care concern[1]. Although BC incidence is lower overall among black women, the mortality rate is consistently higher[2-4]. Recent data has demonstrated a cross-over in age adjusted incidence of BC, with a higher rate in black women under age 40 than white women (number of BCs per 100,000 woman-years 15.5 versus 13.1), than with subsequent cross over with higher rates in white women than black women aged 40 or older (281.3 versus 239.5)[5]. Many of the determinants resulting in racial differences in BC outcome have been attributed to disparities in screening, diagnosis and treatment. However, studies of racial differences in BC treatment now indicate that factors apart from health care access contribute to disparities in BC outcome.

A significant finding to emerge has been the discovery that African American women have biologically more aggressive disease, independent of social factors[1]. In a SEER-based cancer registry of over 100,000 women, 57% of African American women had high-grade disease, compared to 41% in white women[6]. In both SEER and multi-center studies, estrogen receptor (ER)-negative, progesterone receptor (PR)-negative disease has been found to be more prevalent among African Americans. Carey et al evaluated 496 BCs in the Carolina Breast Cancer study, and found a significantly higher incidence of basal-like BCs in premenopausal compared to postmenopausal African American women (39 versus 14%) and non-African American women of any age (16%)[7]. In contrast, luminal A or low-grade, hormone receptor-positive BC, were found less commonly in younger black women. In the California Cancer Registry, women with ER, PR and HER2 negative BC (triple negative, TNBC) were more likely to be under age 40 and non-Hispanic black or Hispanic[8]. Non-Hispanic black women had the poorest survival, with a 5-year survival for late-stage tumors of only 14%.

There is now evidence that biological features of BC affect response to specific therapies. Analysis of gene expression patterns has led to classification of BCs into a number of subsets correlated with biologic behavior, outcome, and therapeutic response[9]. Perou et al used specific gene expression patterns to classify BC into four groups: luminal type, which are often ER positive, basal-like type, which are often ER negative, a type which over-expresses HER-2, and the *normal* breast type[10]. These groupings have been extensively validated, including one series of over 1000 BCs[11]. Further sub-classifications have been defined.

TNBC refers to a heterogeneous group of tumors defined on the basis of negative ER, PR, and lack of HER-2 gene amplification associated with a poor prognosis, some of which exhibit abnormalities in the *BRCA* genes. Many of these tumors are highly proliferative with short duration of response to therapy with either primary or rapid development of resistance to standard therapy[12]. The basal-like classification is based on gene expression data, and most, but not all TNBC are categorized as basal-like[13, 14]. Basal-like or TNBC account for ~15% of BC diagnoses. Compared to other BCs, TNBC is commonly of higher grade, occurs more frequently in younger women and those of African American descent, and is associated with

increased visceral and central nervous system metastasis as well as inferior survival[15, 16]. Despite initial high responses to combination neoadjuvant chemotherapy (CTX), relapses are seen early following diagnosis among women with TNBC[17].

CHEMOTHERAPY FOR ADVANCED STAGE BREAST CANCER

Approximately 30% of women diagnosed with early stage BC will develop systemic recurrence and 5% will present with de novo metastatic disease, with only a few patients achieving long-term survival with standard CTX. A disproportionate percent of patients with metastatic BC (MBC) will have TNBC. CTX is a critical component of treatment for metastatic BC (MBC), particularly for hormone resistant disease, resulting in improved cancer related symptoms and prolonged survival. Many combination CTX regimens have been studied in an effort to improve outcome. Although these have demonstrated improved response rates compared to single agents, this has been at the expense of increased toxicity without improved survival[18]. International guidelines recommend use of sequential single agent CTX except in the case of visceral crisis or rapidly progressing disease[19]. Microtubule inhibitors are one of the most effective classes of agents available for treating early and late stage BC, and are considered a standard of care for MBC treatment. Microtubule function is vital to cell survival and plays an important role in proliferation and motility, maintenance of cell shape and protein trafficking. Several agents affecting microtubule dynamics are active anti-tumor agents and induce polymerization, or cause non-functional tubulin aggregates blocking cell division by interfering with mitotic spindle function, consequently resulting in cell cycle arrest and cell death[20].

Paclitaxel (PTX) is one of the most widely used agents in this class, although its Cremaphor solvent causes bone marrow and peripheral nerve toxicity, and requires steroid premedication to prevent anaphylaxis. In advanced disease, weekly dosing is superior to an every 3 wk schedule[21]. Nab-paclitaxel (nab-PTX) is albumin-bound PTX delivered without premedication, and is associated with less toxicity than Cremaphor-based PTX. Weekly therapy is effective in PTX- and docetaxel-resistant disease[22]. Treatment with the novel halichondrin analogue, eribulin, improved survival (OS) compared to treatment of physician's choice (TPC) in patients with heavily pre-treated and taxane plus anthracycline-resistant MBC (eribulin:13.1 mo vs. TPC: 10.7 mos, HR 0.81, p=0.041)[23], and has been recently approved by the FDA for treatment of advanced breast cancer (see specific data below). Response rates were higher in the eribulin arm (12.2 vs. 4.7%, p=0.002), and although PFS was longer by investigator assessment, by central review PFS was not significantly different (3.7 versus 2.2 months, HR 0.87, p=0.14). Subset analysis suggested benefit from eribulin across risk groups. In the overall study, grade 3-4 toxicities included higher rates of neutropenia (21% versus 14%) and febrile neutropenia (3% versus 0.8%); anemia, asthenia/fatigue, nausea, mucositis and hand-foot syndrome were more prevalent in the TPC arm. Within patients with TNBC, current data indicates no difference in response to therapy based on race, although this remains controversial[24, 25]. Nonetheless, median time to progression (TTP) remains short for patients with this aggressive subtype of BC[12]; in the recent phase III eribulin trial, 144 patients were identified with TNBC, and in this group the PFS for eribulin was 2.23 mos, compared to 1.9 mos for TPC. Clearly, additional treatment approaches for patients with chemotherapy-resistant TNBC are critical.

MYELOID CELLS, MAMMARY GLAND DEVELOPMENT AND BREAST CANCER

Leukocytes are normal cellular components of all tissues, are critical for regulating normal tissue homeostasis, and are significant paracrine regulators of all physiologic and pathologic tissue

repair processes. In mammary glands, every stage of development is accompanied by changes in the surrounding stroma that is populated by immune cells particularly those of the innate lineage. Mechanisms whereby innate immune cells are recruited to developing mammary epithelial structures have not been fully elucidated, although the process is clearly triggered by estrogen[26]. Studies of mice in which CSF-1 is absent owing to a *Csf1* homozygous null mutation (*Csf1*$^{op/op}$) have shown that many tissues, including mammary glands, are severely depleted of macrophages (M∅s), indicating an essential requirement for CSF-1for M∅ maturation and function[27, 28]. *Csf1*$^{op/op}$ mice have inhibited mammary development characterized by fewer numbers of terminal end buds, reduced branching and diminished ductal length compared to wild type mice[26]. Thus, in M∅-deficient glands, although a ductal tree eventually develops that fills the fat pad, the resulting gland is atrophic[28]. A similar defect was reported in CSF-1 receptor (CSF1R)-null mutant mice[29].

While BC has not historically been linked to underlying inflammation or infection, it exhibits tumor-associated inflammation characterized by infiltration of leukocytes into developing tumors where increases in T cells and myeloid cells in neoplastic stroma parallels progression[30-32]. In BCs, M∅s are the most abundant innate immune cell type present where they regulate angiogenic processes via production of pro-angiogenic factors including vascular endothelial growth factor (VEGF) and proteases[33]. In a transgenic mouse model of mammary adenocarcinoma development, e.g., MMTV-PyMT mice[34], increased M∅ infiltration in premalignant tissue occurs immediately before activation of angiogenesis and onset of malignancy[35, 36]. CSF-1 is broadly expressed by mammary tumor cells, and its expression correlates with extent of M∅ infiltration[37]. MMTV-PyMT mice carrying the *Csf1*$^{op/op}$ mutation exhibit 95% decreased infiltration of M∅s in tumors, inhibited angiogenesis, significantly delayed tumor progression and diminished pulmonary metastasis[35].

Another myeloid population implicated in BC development are the so-called immature myeloid suppressor cells (IMCs)[38, 39] that express low to undetectable levels of major histocompatibility complex (MHC)-II and costimulatory molecules, thus they cannot induce anti-tumor responses similar to M∅s activated by type 1 cytokines (M1-M∅s). Rather, IMCs promote tumor development by exerting inhibitory activity on both tumor-specific and non-specific T cells and by providing factors for tumor growth and neovascularization[40, 41].

In BC, like in mammary gland development, M∅s are reregulated in part by CSF1, mediated by the CSF1R[42]. A second CSF1R ligand, interleukin (IL)-34, possesses similar binding affinities and also regulates M∅ recruitment to tissues, but exhibits distinct tissue distribution[43-45]. Paracrine interactions between M∅s and MECs form positive feed-forward loops involving M∅-expressed EGF, and CSF1 expressed by neoplastic cells, that together regulate carcinoma cell chemotaxis along collagen fibers towards blood vessels directed by perivascular M∅s[46, 47]. Based on these findings, it seems reasonable to postulate that blockade of cellular and/or molecular programs enhancing M∅ recruitment in BC may represent tractable targets for anti-cancer therapy. Indeed, blockade of CSF1 or CSF1R results in decreased M∅ presence in tissues and in experimental tumors, correlates with diminished angiogenesis, reduced tumor growth and metastasis in some models[35, 48-52].

T CELLS REGULATE PROTUMOR MACROPHAGE/MONOCYTE ACTIVITY

Experimental studies have revealed that B and T cells exert pro-tumor activity indirectly by regulating myeloid cell bioactivity, including MØs, IMCs and mast cells, resulting in resistance to endocrine therapies and enhanced development of metastasis[32, 53-55]. We reported that interleukin (IL)-4-expressing T_H2 $CD4^+$ T cells promote invasion and metastasis of mammary adenocarcinomas by regulating protumor MØ and IMC activity, i.e., increased expression of EGF, transforming growth factor (TGF)β, reactive oxygen species (ROS), inducible nitrogen oxygen synthase (iNOS)[32, 56], and repression of cytotoxic $CD8^+$ T lymphocytes (CTL)[32]. Using the MMTV-PyMT mouse model of mammary carcinogenesis[34], we revealed that PyMT/$CD4^+$ T cell-deficient mice (*CD4*$^{-/-}$) exhibited a significantly attenuated metastatic phenotype[32] similar to that of *CSF1*$^{op/op}$/PyMT mice[35]. IMCs and MØs in tumors of CD4-deficient/PyMT mice expressed elevated levels of type 1 cytokines, e.g., tumor necrosis factor (TNF)α, IL-6, IL-12p40, IL-1β, and *Nos2* mRNA, indicative of a prevalent T_H1 immune microenvironment and M1-MØ phenotype[32], whereas IMCs and MØs from CD4-proficient/PyMT mice were instead indicative of alternatively activated M2-MØs that expressed higher levels of *arginase-1* (Arg-1) and *Tgfβ,* thus characterizing a protumor T_H2 microenvironment[32]. PyMT/IL4Rα-deficient and PyMT mice treated with neutralizing antibodies to IL-4, phenocopied PyMT/$CD4^{-/-}$ mice with diminished metastasis and presence of M1-IMCs and M1-MØs in carcinomas[32]. Together this data indicates that T_H2-$CD4^+$ T cells promote metastasis by enhancing pro-tumor bioactivities of MØs and IMCs, and that depletion of MØs and/or IMCs, or blockade of their IL-4-regulated pathways, may provide a survival advantage by limiting progression and metastasis.

RATIONALE FOR MACROPHAGE TARGETING IN TNBC

Patients with metastatic TNBC represent a significant challenge as many have CTX-resistant disease at relapse, and others develop resistance quickly after initial response. Despite promising advances with agents inhibiting DNA repair, (PARP inhibitors), all patients with advanced TN disease will eventually die from their disease[57, 58]. Recently, Martin and colleagues reported that BCs in African Americans displayed different expression profiles correlating with the TN phenotype[59]. Importantly however, differences in the tumor microenvironment were also identified. Specifically, tumor-associated MØs were independently increased in tumors of African American women. Supporting this finding, a response signature for colony stimulating factor (CSF)1, a primary regulator of tissue MØ maturation and infiltration, was identified in 17-25% of BCs associated with decreased expression of ER and PR[60]. Campbell and colleagues studied tissue MØ infiltration in two independent cohorts and found a significant correlation between intratumoral MØs and specific tumor features, including high grade, hormone receptor-negativity, basal-like subtype, and the number of MØs was associated with increased risk of death from cancer[61]. Studies in transgenic mouse models of mammary carcinogenesis have revealed that MØs promote carcinogenesis and enhance metastasis by high-level expression of epidermal growth factor (EGF) and activation of EGF-regulated signaling cascades in mammary epithelial cells (MECs)[62]. These data, along with others, indicate that MØ infiltration may be a prognostic indicator, and could serve as a potential target for novel therapies. Since high-grade, TN tumors characterized by increased MØ infiltration are disproportionately represented among women of African American ancestry, identifying an alternate treatment approach to this biologic group of tumors has potential to close the outcome disparity observed among African

Americans diagnosed with breast cancer.[33, 63]

PRELIMINARY STUDIES

LEUKOCYTE PROFILING IN BC

Based on our previous studies demonstrating that $CD4^+$ T cells and M2-M∅s enhance development of pulmonary metastasis in MMTV-PyMT mice[32, 56], we postulated that the density of CD4, CD8 and CD68-positive immune cells in human BC would provide prognostic information. To evaluate this, we established a classification and regression tree algorithm to define a "signature" in a screening cohort of BC tissues (n=179, cohort I). High and low thresholds for each marker were established through a decision tree analysis with 10-fold cross-validation of each tree model. All BC samples were categorized as having either a $CD68^{high}/CD4^{high}/CD8^{low}$ or a $CD68^{low}/CD4^{low}/CD8^{high}$ *immune signature,* and the same thresholds were then applied to a validation BC cohort (cohort II, n=498). Kaplan Meyer analysis in the two cohorts (677 pts) demonstrated significantly reduced relapse-free survival (RFS) for pts bearing the $CD68^{high}/CD4^{high}/CD8^{low}$ signature (**Fig 1A-B**). Multivariate Cox regression analysis revealed that the $CD68^{high}/CD4^{high}/CD8^{low}$ signature was an independent predictor of decreased OS and RFS after controlling for grade, nodal status, tumor size, ER, PR and HER2 status in both cohorts ($p<0.05$ and $p=0.001$, respectively). Kaplan-Meier analysis of Cohort II also demonstrated significantly reduced RFS in node-positive pts (**Fig 1C**). Analysis of the prognostic value of the immune signature within individual tumor subtypes revealed that the $CD68^{high}/CD4^{high}/CD8^{low}$ phenotype was associated with reduced OS and RFS in TNBCs (**Fig 1D**). This correlation in TN disease is particularly important given the aggressive nature of TNBCs that often becomes refractory to CTX. These results indicate that infiltration by M∅s and T cells may influence BC recurrence in lymph node-positive pts.

NEOADJUVANT CTX CORRELATES WITH MYELOID INFILTRATION

To identify biomarkers or parameters of immune cell presence in BCs in a prospective manner, and to identify pts most likely to benefit from M∅-targeted therapy, we have started to evaluate freshly isolated, unfixed human BC tissue, resected from women undergoing surgery at UCSF, to reveal leukocyte complexity by fluorescent-activated cell sorting (FACS). Thus far, we have evaluated 4 invasive ductal carcinomas (IDC) and one ductal carcinoma in situ (DCIS), with adjacent normal breast tissue also available from 3 of the IDCs (**Fig 1D**). With regards to variances in immune complexity in these tumors, the most obvious variance identified thus far is that the samples from women who had received neoadjuvant CTX contained ~6-fold higher % of M∅s ($CD14^+CD11b^+$), as compared to BC tissue from women who had not received neoadjuvant CTX (**Fig 1E-F**). Since immunosuppressive monocytes (IMCs) regulate cancer development in murine models, and since these would not be efficiently depleted by therapeutic strategies targeting CSF1 or CSF1R, we evaluated samples for lineage markers that would identify accumulation of this population and thus far, have not found evidence of their accumulation within BC or adjacent normal tissue (**Fig 1E,G**).

CYTOTOXICS INDUCE EXPRESSION OF M∅/MONOCYTE CHEMOATTRACTANTS

To reveal the molecular mediators involved in CTX-associated M∅ recruitment, we evaluated MECs from murine mammary and human breast tumors *in vitro* for mRNA expression of monocyte/M∅ cytokines/chemokines following exposure to PTX, cisplatin or radiation therapy, and found increased expression of important M∅/IMC chemoattractant mRNAs, including

CSF1, *CCL8/MCP2* and *IL34* (**Fig 2A** shows analysis of PyMT-derived carcinoma cells treated with PTX *in vitro*). Analysis of *CSF1* mRNA expression *in vivo* revealed that mammary tumors of MMTV-PyMT mice had a 2-fold higher expression of *CSF1* mRNA following PTX exposure (**Fig 2B**) that correlated with increased density of MØs in tumor stroma (**Fig 2C**).

PLX3397: A POTENT ANTAGONIST OF THE CSF1R TYROSINE KINASE

PLX3397 is a competitive ATP inhibitor with potent (nM) specificity for CSF1 and cKIT receptor tyrosine kinases, with 10-100 fold selectivity for these target kinases as opposed to other related kinases (e.g. KDR)[64]. Specifically PLX3397 is a selective inhibitor of Fms (CSF1R, the receptor for colony stimulating factor [CSF-1, also known as macrophage-colony stimulating factor, M-CSF], as well as the ligand interleukin 34 [IL-34]), Kit (the receptor for stem cell factor, SCF), and oncogenic Flt3 (the receptor for Flt3 ligand) activity intended

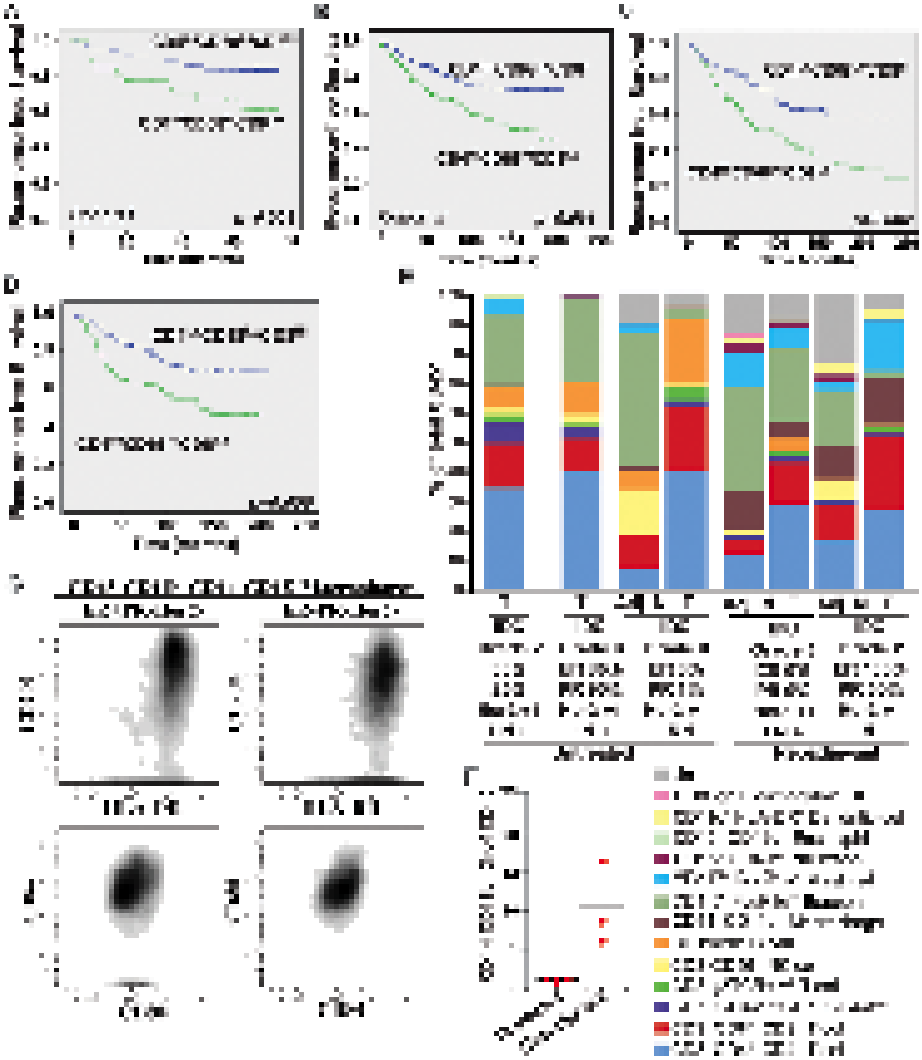


Fig 1: Immune signature in human BC predicts RFS in Cohorts I and II (**A, B;** log rank (Mantel-Cox) p-values are denoted) and (**C**) Kaplan-Meier estimates of RFS for lymph node-positive patients extracted from Cohort II with log-rank (Mantel-Cox) p value denoted. (**D**) Kaplan-Meier estimates of RFS in TNBC wit.h log-rank (Mantel-Cox) p value denoted (**E**) FACS evaluation of 5 human breast tumors (T, tumor; IDC, invasive ductal carcinoma), 3 of which were evaluated along with adjacent normal breast tissue (Adj N) from the same patient. Details on tumor grade, ER, PR, HER2 status and lymph node involvement are shown. (**F**) Increased percentage of MØs ($CD14^+CD11b^+$) revealed by FACS in BC tissue from women treated with neoadjuvant CTX, versus untreated women (n=3 each). (**G**) FACS analysis of macrophages in ER+PR-HER2- BC (left) vs ER-PR-HER2- TNBC (right) evaluated for CD206, HLA-DR and CD80 expression showing no segregation of subpopulations. ER, estrogen receptor; PR progesterone receptor; LN, lymph node positivity,

for oral administration. When screened against a broad panel of kinases, IC_{50} values were > 1.0 μM for all, with the majority > 10 μM. Ligand-dependent proliferation of M-NFS-60 and BAC1.2F5 cells is inhibited by PLX3397 with IC_{50}s of 0.33, 0.23 and 0.31 μM, respectively. In THP-1 cells, CSF1R autophos-phorylation induced by M-CSF is inhibited by 7.0 nM PLX3397. Human osteoclast precursor cells were induced to differentiate into mature osteoclasts by RANK-L and M-CSF, and inhibited by PLX3397 with an IC_{50} of 33 nM. By contrast, in RS4:11 cells, Flt3 auto-phosphorylation was induced by Flt3 ligand with autophosphorylation requiring high levels of PLX3397 (1500 nM) for inhibition. PLX3397 is currently in a phase 1 trial (ClinicalTrials.gov Identifier: NCT01004861) under Protocol PLX108-01 entitled, "A Phase 1 Study to Assess Safety, Pharmacokinetics, and Pharmacodynamics of PLX3397 in Pts with Advanced, Incurable, Solid Tumors in which the Target Kinases Are Linked to Disease Pathophysiology." The PLX3397 clinical formulation has demonstrated appreciable bioavailability and dose-dependent exposures to date, and is supplied as gel caps of 100 mg each. The plasma half-life of PLX3397 appears to be greater than 10 hours, and the trial has achieved exposures that are within the efficacious range predicted by preclinical studies. Nineteen pts have been enrolled to date, and the current dose level is 600 mg by mouth given once daily on an empty stomach. A maximum tolerated dose (MTD) has not yet been defined, and dose escalation is ongoing without consistent clinically significant toxicity. One younger pts experienced a reversible change in hair color to white, attributed to inhibition of KIT. The majority of the biomarker studies are ongoing; flow studies have demonstrated a reduction in monocytes that appear sensitive to CSF1 stimulation in pts treated with PLX3397.

MACROPHAGE-DEPLETION IMPROVES CHEMOSENSITIVITY

The combined implication of our preclinical data is that high levels of MØs such as observed in high grade TNBC, may limit response to CTX. Thus, we treated late-stage MMTV-PyMT mice with PTX, and agents blocking MØ and/or IMC infiltration. MMTV-PyMT mice were treated with PLX3397 starting at d80 followed with one cycle of PTX (10 mg/kg, Q5Dx3, i.v.) and monitored to endpoint (2.0 cm primary tumors or day 100). While PTX increased the MØs ($CD45^+CD11b^+Ly6C^-Ly6G^-F4/80^+$) in tumor stroma, combined treatment with PLX3397 significantly reduced PTX-induced MØ infiltration (**Fig 3A**) accompanied by reduced primary tumor growth (**Fig 3B**) and pulmonary metastasis (**Fig 3C**). Using a histopathological staging criteria[35, 65], PLX3397/PTX-treated mice developed fewer late-stage carcinomas containing large areas of necrosis and extensive cell death ($p<0.05$, cleaved caspase 3^+ cells), decreased density of $CD31^+$ vessels ($p<0.05$), with no accompanying change in epithelial proliferation (data not shown). PLX33897 treatment had no effect on infiltration of tumors by IMCs ($CD45^+CD11b^+Ly6C^{Hi}$) or DCs ($CD45^+CD11b^{lo/-}Ly6C^-CD22^-Ly6G^-CD11c^{Hi}MHCII^{Hi}$) (data not shown).

Since PLX3397 inhibits both CSF1R and cKIT kinases, we treated mice bearing orthotopic mammary tumors (derived from carcinoma cells of MMTV-PyMT mice) with neutralizing monoclonal antibody (mAB) to CSF1 as monotherapy, and in combination with PTX. PLX3397/PTX and αCSF1 mAB/PTX similarly depleted ~ 80% of MØs with no diminution in the presence of IMCs (data not shown), and significantly reduced primary tumor growth (**Fig 4A**), thus indicating that the cKIT inhibitory effects of PLX3397 were insignificant. Neither PLX3397 nor αCSF1 mAB depletes IMCs within PyMT tumors; thus, we evaluated αCD11b mAB/PTX to eradicate IMCs. CD11b is an integrin cell adhesion molecule expressed on granulocytes, MØs, IMCs, DCs, and NK cells that in part, regulates transendothelial migration of

cells into tissue and tumor parenchyma. αCD11b mAB treatment efficiently depletes both the MØ and IMC population in tumors[66]. PyMT tumor-bearing mice treated with either αCD11b mAB/PTX exhibited significant reduction in primary tumor growth similar to αCSF1mAB/PTX or PLX3397/PTX (**Fig 4B**). Similar results were observed when tumor-bearing mice were treated with PLX3397/carboplatin and PLX3397/cisplatin (data not shown).

ANTI-TUMOR RESPONSE IN PLX3397/PTX-TREATED MICE

Tumors from PLX3397/PTX-treated MMTV-PyMT mice revealed increased % of $CD4^+$, $CD8^+$ T cells (**Fig 5A**) and DCs (data not shown) correlating with significantly ($p<0.05$) increased expression of cytotoxic effector molecules (interferon (IFN)γ, granzyme A (GRZA), granzyme B (GRZB), perforin-1 (PRF1), and "Type-1" DC effectors molecules IL12p35 and interferon (IFN)α)[67], and decreased expression of immunosuppressive *ARG1* (**Fig 5B**), thus indicating an overall reprogramming of the immune microenvironment where anti-tumor immune pathways had been bolstered. To evaluate the significance of this, we depleted MMTV-PyMT/PLX3397/PTX-treated mice of $CD8^+$ T cells with a neutralizing mAB to CD8a, and found that the improved outcome following PLX3397/PTX therapy was lost (**Fig 5C**) indicating enhanced chemosensitivity accompanying M-depletion also involved bolstering productive $CD8^+$ T cell-dependent CTL responses.

CD68 AND CD8 MRNA EXPRESSION PREDICTED RESPONSE TO CTX

To determine if stratification of BCs by *CD68* and *CD8* mRNA expression predicted response to CTX, we analyzed *CD68* and *CD8a* mRNA expression in a cohort of 311 pts constructed from 2 independent data sets[68, 69]. All pts provided fine needle aspirates (FNA) taken prior to neoadjuvant CTX and pathological response was assessed at the time of surgery. Using median expression as a threshold, examination of *CD8* and *CD68* mRNA in FNA samples demonstrated 3 specific groups CD68>CD8, CD68<CD8 and CD68=CD8 (denoted $CD68^{high}/CD8^{low}$, $CD68/CD8^{equal}$ and $CD68^{low}/CD8^{high}$ respectively). Analysis of the rate of pathological complete response (pCR) in these groups revealed that the $CD68^{high}/CD8^{low}$ group had a significantly lower rate of pCR (7%) as compared to the other two groups, with the $CD68^{low}/CD8^{high}$ exhibiting the highest rate of pCR at 27%, thus indicating that the balance between M and CD8 infiltration can be used as a biomarker to predict response to neoadjuvant CTX.

NONCLINICAL PHARMACOLOGY

PLX3397 is a selective inhibitor of Fms (CSF1R, the receptor for colony stimulating factor [CSF-1, also known as macrophage-colony stimulating factor, M-CSF], as well as the ligand interleukin 34 [IL-34]), Kit (the receptor for stem cell factor, SCF), and oncogenic Flt3 (the receptor for Flt3 ligand) activity intended for oral administration. The effects of PLX3397 on multiple aspects of tumorigenesis have been characterized in cellular and in vivo assays. The proliferation of cell lines that depend on CSF-1, SCF, or endogenous Flt3-ITD (internal tandem duplications) is inhibited at inhibitory concentration of 50% (IC_{50}) values below 1 µM. Furthermore, CSF-1-induced autophosphorylation of Fms and SCF-induced autophosphorylation of Kit are potently inhibited by PLX3397. Finally, the RANK-L- and CSF-1-dependent differentiation of osteoclast precursors is also potently inhibited by PLX3397. These in vitro results translate to PLX3397 effects in a variety of in vivo models for Fms-dependent proliferation, Fms-dependent osteoclast differentiation, Flt3-ITD dependent tumor growth, and Kit-dependent mast cell proliferation. While pharmacologic effects due to the inhibition of Fms and Kit are expected, the relative selectivity of PLX3397 against other kinases suggests that off-target effects against other kinases should be reduced. The safety pharmacology of PLX3397 has been evaluated in 5 Good Laboratory Practice (GLP) studies (2 in vitro and 3 in vivo). Three of these studies addressed the potential adverse cardiovascular or cardiac electrophysiological effects of PLX3397.

An inhibitory concentration of 50% (IC50) of 0.7 µM was obtained in the human ether-a-go-go (hERG) channel assay. However, no PLX3397-related prolongation of action duration was observed in an isolated rabbit Purkinje fiber study. In an in vivo dog telemetry study, electrocardiographic parameters were unchanged by PLX3397 treatment, but left ventricular contractility (LV dP/dtmax) and arterial pulse pressure were significantly lower compared to controls in dogs that received 300 and 1000 mg/kg. Because PLX3397 binds to the hERG channel yet no QT prolongation has been identified nonclinically, an investigative safety pharmacology study was conducted in order to examine potential binding to hCav1.2 whose inhibition has

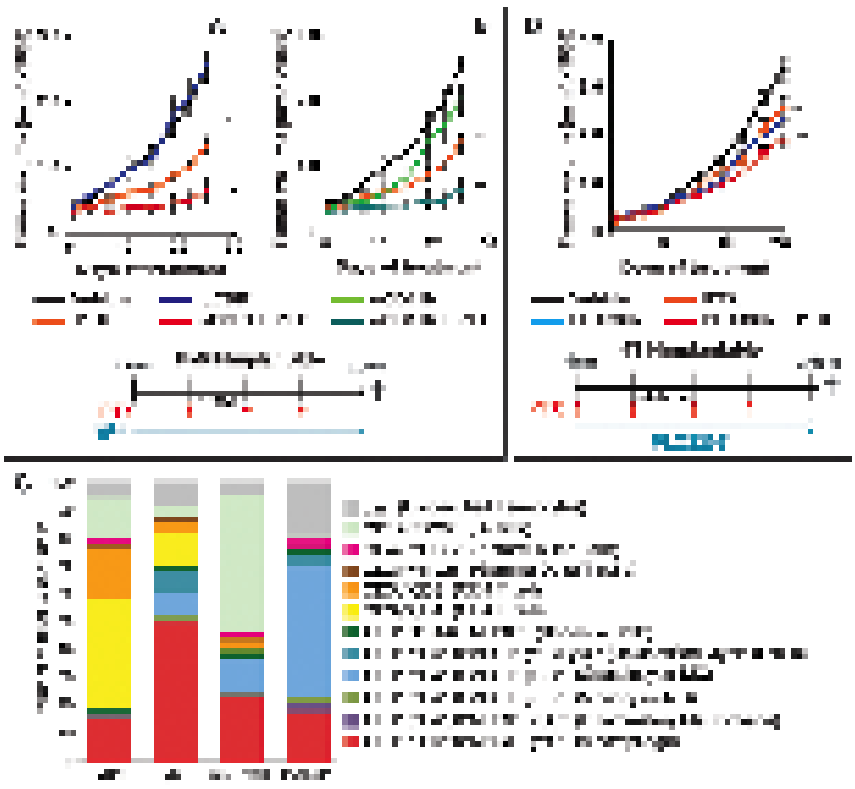
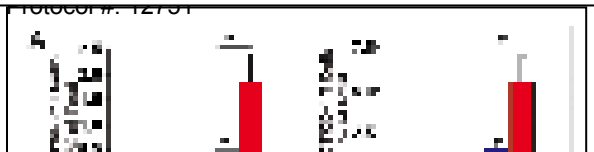


Fig 4: Combined treatment with αCSF1 mAB or αCD11b mAB and PTX reduces primary orthotopic PyMT-tumor growth (**A,B**). Higher percentage of IMCs in 4T1 tumors compared to PyMT tumors(**C**). PLX3397 plus PTX reduces 4T1 tumor growth (**D**). (*) p<0.05, (**) p <0.01. FVB/n: mammary



been negatively correlated with risk for QT prolongation. IC50 for the inhibitory effect of PLX3397 on hCav1.2 calcium current was determined to be 0.2 μM. Central nervous system (CNS) and respiratory function were not affected in rats.

NONCLINICAL PHARMACOKINETICS

PLX3397 binds extensively to albumin in 4 species (mouse, rat, dog and human). After intravenous (IV) administration in nonclinical studies, elimination terminal half-life (t1/2) values were 3.5 hours in mice, 5.1 hours in rats, 1.9 hours in dogs, and 3.7 hours in monkeys. PLX3397 is metabolically stable and not susceptible to rapid metabolic degradation. CYP3A4 is the main CYP enzyme that metabolizes PLX3397. The results also suggest that CYP1A2 and 2C9 might also play a minor role in its metabolism. PLX3397 had no inhibitory effect on CYP1A2 and 3A4 with an IC50 > 30uM. It had modest effects on the other major CYPs, (2C9, 2C19, and 2D6) with an IC50 ranging from 11.1 to 22.2 μMPLX3397, at 10 μM, did not significantly inhibit BCRP, BSEP, SMVT, OCT1, OCT2, OAT1,OAT3-mediated transport of probe substrate. Compared to vehicle control, PLX3397 inhibited the transport of probe substrates of uptake transporters OATP1B1, OATP1B3 and OATP2B1 with respective inhibition of 27.7%, 21.4% and 37.1%. PLX3397 also inhibited P-gp mediated transport of probe substrates with a small but statistically significant inhibition of 9.35% at 10 μM.

PLX3397 appears to penetrate into the CNS in rats.

NONCLINICAL TOXICOLOGY

Two high-dose GLP 4-week general toxicology studies were conducted with daily oral gavage administration of PLX3397 (once daily [QD] in rats and twice daily [BID] in dogs) at doses of 20, 60, and 200 mg/kg/day in rats and 50, 100, and 300 mg/kg/day in dogs, with 16-day (rat) or 14-day (dog) recoveries. Neither a noeffect-level (NOEL) nor a no-adverse-effect-level (NOAEL) of PLX3397 could be determined in either species due to toxicity. Significant adverse test article-related observations appear to be related to PLX3397-mediated inhibition of Fms and Kit kinases. PLX3397-related histopathologic observations included testicular spermatagonia reduction, bone marrow hypocellularity, thymic lymphoid reduction, bone hyperostosis and hypertrophy, ovarian follicular degeneration, and liver hepatocellular hypertrophy. All findings were partially or fully reversible. Two additional GLP toxicology studies at lower dose levels involved daily oral gavage administration of PLX3397 HCl for 4 weeks (QD in rats and dogs) at doses of 0.5, 2, and 10 mg/kg/day in rats and 1, 6, and 30 mg/kg/day in dogs, with 8-week recoveries. The NOAELs of PLX3397 were determined to be 10 mg/kg/day in rats and 6 mg/kg/day in dogs in these additional studies. All adverse findings were fully reversible, including testicular spermatagonia reduction in dogs.

Two 13-week GLP toxicology studies involved daily oral gavage administration of PLX3397 HCl for 13 weeks (QD in rats and dogs), with 8-week recoveries at doses of 0.5, 4 and 20 mg/kg/day in rats and 1, 6, and 30 mg/kg/day in dogs. NOAELs were determined to be 4 mg/kg/day in rats and 6 mg/kg/day in dogs. No new target organ toxicities were seen in either study In rats, anemia, and bone marrow depletion, and hepatocellular vacuolation associated with increased liver enzymes were seen. In dogs, findings of reproductive toxicity (spermatogonial reduction) and increased incidence of emesis were seen at the t 30 mg/kg dose level, which were reversible.

Potential effects of PLX3397 on embryofetal development in rats were assessed at 4, 10, and 40 mg/kg/day. Based on changes in hematology parameters at 40 mg/kg/day in the dams, and fetal external and visceral malformations and skeletal developmental variations (findings primarily related to decreases in ossification) in the fetuses at 40 mg/kg/day, a dose level of 10 mg/kg/day was considered to be the NOAEL. PLX3397 was not mutagenic or clastogenic in the Ames,chromosomal aberration and micronucleus) tests, andshowed no potential to cause phototoxicity in vitro in the NIH 3T3 fibroblast assay.

CONCLUSIONS FROM PRECLINICAL DATA

Results from these studies support a fundamental and functional interplay between M∅ presence/bioactivity and CTX response and demonstrate that mouse modeling can guide development of clinical studies, aid in clinical trial design, and identify pts most likely to benefit from M∅-targeted therapy. PLX3397 is a novel oral highly selective kinase inhibitor that inhibits M∅, osteoclasts and mast cells, and mice treated with PLX3397 phenocopy mice similarly treated with neutralizing mABs against CSF1 or CD11b and CTX. Interestingly, a number of studies suggest that TNBC may be relatively resistant to taxanes, particularly following prior exposure in the early stage setting. These preclinical data imply that leveraging either inhibition of the bioactivity of M∅s or eradicating their presence in tumor tissue will provide a survival advantage to women receiving CTX in a neoadjuvant setting, and may benefit women in an adjuvant setting when treated in combination with CTX. The combination of PLX3397 with CTX, therefore, is an entirely novel treatment strategy that has the potential to improve outcome not just for pts with advanced TNBC, which is the main goal for this clinical trial, but also as initial, potentially curable therapy in high risk TNBC, which is our long-term goal.

1.2 Clinical Studies

CLINICAL PHARMACOKINETICS PLX3397

PLX3397 human exposure has been evaluated in 8 clinical studies. PLX3397 HCl was administered as single agent in 5 studies and in combination with paclitaxel, temozolomide and vemurafenib in the other 3 studies. The PK of PLX3397 at dose levels between 200 mg/day and 1200 mg/day has been evaluated in the dose-escalation and extension study, PLX108-01, using QD or BID dosing in the fasting state. The Tmax is approximately 2 hours, and the mean accumulation ratio compared to Day 1 values is approximately 2-fold. In general, there is doseproportional exposure. In the PLX108-05 acute myeloid leukemia (AML) doseescalation study at dose levels between 800 mg/day and 5000 mg/day, saturation of exposure was observed at 2000 mg/day. The steady state exposure of 900 mg QD cohort in PLX108-03 Hodgkin's lymphoma study and of 1000 mg BID cohortsin all the other single agent studies (PLX108-04 glioblastoma , PLX108-05 AML, PLX108-06 prostate cancer) were similar to, exposure of the respective dose groups in PLX108-01 solid tumors study.

The mean PLX3397 plasma concentrations for the 800 mg BID cohorts at 2, 4 and 6 hours in the combination studies with paclitaxel (PLX108-07), temozolomide (PLX108-08), and vemurafanib (PLX108-09) were comparable to those seen in PLX3397 single agent studies. Subjects administered 600 mg of PLX3397 HCl with a high-fat, high-calorie meal displayed an approximately 2-fold increase in C_{max} and AUC compared to subjects administered PLX3397

HCl in the fasted state (PLX108-11). When PLX3397 HCl was administered in the presence of esomeprazole, overall exposure was reduced approximately 30%.

PLX3397 is currently in a Phase 1 trial (ClinicalTrials.gov Identifier: NCT01004861) under Protocol PLX108-01 entitled, "A Phase 1 Study to Assess Safety, Pharmacokinetics, and Pharmacodynamics of PLX3397 in Patients with Advanced, Incurable, Solid Tumors in which the Target Kinases Are Linked to Disease Pathophysiology." The PLX3397 clinical formulation has demonstrated appreciable bioavailability and dose-dependent exposures to date, and is supplied as gel caps of 100 mg each. The plasma half-life of PLX3397 appears to be greater than 10 hours, and the trial has achieved exposures that are within the efficacious range predicted by preclinical studies. Nineteen patients have been enrolled to date, and the current dose level is 600 mg by mouth given once daily on an empty stomach. A maximum tolerated dose has not yet been defined, and dose escalation is ongoing without consistent clinically significant toxicity. One younger patient experienced a reversible change in hair color to white, attributed to inhibition of KIT. The majority of the biomarker studies are ongoing; flow studies have demonstrated a reduction in monocytes that appear sensitive to CSF1 stimulation in patients treated with PLX3397.

No clinical studies on drug-drug interactions have been performed. However, preclinical biochemical and cellular studies predict that the drug-drug interaction potential is low. The plasma PK of paclitaxel (measured at multiple time points after 10 mg/kg injection) was determined to have a half-life of 1 hour in mice receiving vehicle chow, and was unchanged by 7 previous days consumption of the PLX3397 drug chow (measured 15 and 45 minutes after paclitaxel injection. It is assumed that eribulin will have a similar profile, however pharmacokinetics will be performed in the phase I portion of this trial.

Fig 6: **A**) Increased CD4 and CD8 T cells in tumors of PLX3397/PTX treated MMTV-PyMT mice. **B**) Mean fold change in cytokine mRNA expression of PyMT tumors from mice treated with PTX alone or in combination with PLX3397. **C**) 85-day-old MMTV-PyMT mice were treated with PTX and/or PLX3397 and anti-CD8 IgG. Total tumor burden/animal was assessed every 5 days. (*) $p<0.05$, (**) $p<0.01$.

The ongoing Phase 1 dose escalation study PLX108-01 in patients with solid tumors is designed to evaluate the safety and PK of PLX3397 administered orally in order to establish a maximum tolerated dose (MTD). As of June 2011, a total of 41 patients have been treated with PLX3397 PO. The dose levels have been 200 mg/day (n=3), 300 mg/day (n=6), 400 mg/day (n=6), 600 mg/day (n=6), 900 mg/day (n=7), 1000 mg/day (n=7) and 1200 mg/day (n=6). In summary, the T_{max} is approximately 2 hr, the mean elimination half-life is approximately 20 hr, and the mean accumulation ratio compared to Day 1 values is approximately 1.6. In general, there is increasing exposure with increasing dose. On Day 15, the $AUC_{0\text{-}24hr}$ was 62 uM•hr for the 200

mg/day dose group, 122 uM•hr for the 300 mg/day dose group, 98 uM•hr for the 400 mg/day dose group, 258 uM•hr for the 600 mg/day dose group, 254 uM•hr for the 900 mg/day dose group and 329 uM•hr for the 1200 mg/day dose group (pharmacokinetic data for the 1000 mg/day cohort is not currently available). Dose-limiting toxicities (DLTs) of Grade 3 AST elevation and Grade 4 neutropenia occurred at 1200 mg/day. A 1000 mg/day cohort was opened and 1 out of 7 patients experienced a DLT (Grade 3 AST), **establishing 1000 mg/day as the MTD**.

There have been no safety signals in vital signs, physical examinations, or ECGs (including careful evaluation of potential QT prolongation). A reduction in hemoglobin (usually G1) has been observed in several patients, but this has not resulted in treatment discontinuation in any patients. There have been a total of 6 patients with DLTs, as follows: G3 increased INR (300 mg/day) in a patient on warfarin; G3 lymphopenia (600 mg/day), subsequently exempted as a DLT; G3 lymphopenia and G4 hyponatremia (600 mg/day); G3 AST (1000 mg/day); G3 AST (1200 mg/day) which recovered after study drug discontinuation; and G4 neutropenia (1200 mg/day) which recovered after holding study drug and management with G-CSF. As this is a population of patients with metastatic solid tumors that have been heavily pretreated with cytotoxic therapies, adverse events are anticipated due to either the disease or previous treatments. The most common AEs have been nausea and fatigue. Please see the Investigator's Brochure for more details on adverse events and tolerability.

Response biomarkers are being assayed in order to profile the inhibitory activity of PLX3397 on Fms and Kit activity as a function of dose and exposure. These biomarkers include circulating tumor cells (CTCs) and CD14+/CD16+ proinflammatory monocyte cell numbers, IL-6, IL-1β, MMP3, and markers of osteoclast activity. Most of the soluble markers are not elevated at Baseline in the patients treated to date, so no decrease with treatment can be anticipated. However, in 4 patients with elevated CTCs at Baseline, 3 patients have shown a clinically relevant reduction during treatment with PLX3397. Marked reductions in the CD14+/CD16+ cell populations have also been observed in the majority of patients, with no change in the remainder.

CLINICAL PHARMACOKINETICS PLX3397

As of June 30, 2014, data are available on 345 patients who have been enrolled in the PLX3397 clinical program across 8 clinical studies PLX108-01, PLX108-03, PLX108-04, PLX108-05, PLX108-06, PLX108-07, PLX108-08, and PLX108-09. Of the 345 patients, 181 patients with solid tumors received as studies are a single agent (which included advanced, incurable, solid tumors; relapsed or refractory Hodgkin's lymphoma; recurrent glioblastoma multiforme; or progressive castration-resistant prostate cancer with high circulating tumor cell counts). Ninety patients received PLX3397 as a single agent for relapsed or refractory AML. Seventy-four patients received PLX3397 in combination with other therapies. Most of these studies are ongoing. The most frequent TEAEs (>20%) among all treated patients included fatigue, nausea, , decreased appetite, diarrhea, anemia, vomiting, and increases in aspartate aminotransferase (AST). Hair color changes (depigmentation) and constipation also commonly occurred in solid tumor patients receiving single agent PLX3397. With the exception of febrile neutropenia (which occurred at a high rate in the AML study), less than 10% of these common AEs were considered as Grade 3 or higher Treatment related SAEs) reported more than once included, neutropenia

(including febrile neutropenia), anemia, pneumonia, increased AST or ALT, increased INR, dehydration, hyponatremia, and maculo-papular rash.

ERIBULIN

Eribulin mesylate (E7389) is a nontaxane, microtubule dynamics inhibitor with a novel mechanism of action. Eribulin suppresses polymerization, has no effect on microtubule depoly merization, and sequesters tubulin into nonfunctional aggregates[70, 71]. Preclinical studies have demonstrated antitumor activity in cell lines that are taxane resistant as a result of β-tubulin mutations[72]. In addition, eribulin appears to have less neurotoxicity than other microtubule antagonists. A murine model compared the effect on nerve conduction of paclitaxel and ixabepilone to eribulin. This data, presented by Wozniak and colleagues at the annual European Society for Medical Oncology found that treatment with paclitaxel and ixabepilone resulted in a reduction in caudal nerve conduction velocity as well as caudal and digital amplitude, but eribulin had no deleterious effect on these endpoints. Eribulin also caused less severe morphological changes in dorsal root ganglion and sciatic nerves on pathological assessment. Nine Phase 1 clinical studies have been completed. The National Institutes of Health (NIH) sponsored two Phase 1 studies of E7389 (National Cancer Institute [NCI] Study 5730 and Study 7444), and Eisai has sponsored seven additional studies: E7389-A001-101 and E7389-A001-102 in the United States (US); E7389-E044-103, E7389-E044-108, E7389-E044-109, and E7389 E044-110 in Europe; and E7389-J081-105 in Japan. In general, the PK of E7389 is characterized by a rapid distribution phase, with a prolonged elimination phase after intravenous infusion. The disposition of E7389 follows linear kinetics over the dose range studied, as shown by consistent dose-independent pharmacokinetic parameters (terminal half-life [t½], clearance [CL], steady-state volume of distribution [Vss]) and similar dose-normalized parameters (Cmax/Dose, AUC0-t/Dose and AUC0-∞/Dose) between E7389 doses ranging from 0.25 to 1.4 mg/m2 (E7389-A001-101) and from 0.25 to 4.0 mg/m2 (E7389-A001-102). NCI Phase 1 Study 5730 included subjects with advanced solid tumors and was designed to evaluate the toxicity and PK of E7389 and to determine the maximum tolerated dose (MTD) using a bolus injection on Days 1, 8 and 15 of a 28-day cycle. Dose limiting toxicities (DLTs) were observed in approximately one third of subjects that received 1.4 mg/m2 and in four out of five subjects at 2 mg/m2. The principal investigators considered 1.4 mg/m2 as the MTD.

This schedule was selected as the initial schedule for the Phase 2 program. Two Phase 1 dose-finding studies were conducted by Eisai, administering E7389 as a 1-hour infusion. Study E7389-A001-101 determined the safety, toxicity, PK, and MTD of E7389 administered on Days 1, 8, and 15 of a 28-day cycle. The MTD was determined to be 1.0 mg/m2. Dose limiting toxicities were primarily Grade 3 and 4 neutropenia, but also included Grade 3 fatigue and Grade 3 anorexia. Study E7389-A001-102 determined the safety, PK, MTD and tumor response of E7389 administered on Day 1 of a 21-day cycle in subjects with advanced solid tumors. The MTD was determined to be 2.0 mg/m2 and Grade 4 febrile neutropenia was observed as the DLT. The DLT was observed in all three subjects who received 4.0 mg/m2 (Cycle 1, Days 7, 8 or 11); in two out of three subjects who received 2.8 mg/m2 (Cycle 1, Day 9 or 10); and in two out of seven subjects who received 2.0 mg/m2 (Cycle 1, Day 7 or 8). Although the study was not designed or powered to establish efficacy, of 21 subjects, one had an unconfirmed partial response (PR) at 12 weeks, and 12 subjects had stable disease (SD).

Study E7389-J081-105 was conducted at National Cancer Center Hospital East in Japan to evaluate the safety, toxicity, PK, and MTD of E7389 administered as a 2 to 5 minute bolus infusion on Days 1 and 8 of a 21-day cycle. DLTs were observed in five subjects at 1.4 mg/m2 and 2.0 mg/m2, and the MTD was determined to be 1.4 mg/m2. Studies E7389-E044-103, E7389-E044-108, E7389-E044-109 and E7389-E044-110 were also performed with E7389 administered as a 2 to 5 minute bolus infusion on Days 1 and 8 of a 21-day cycle. These studies investigated the excretion balance and metabolic pathway of E7389, the influence of hepatic impairment on exposure to E7389, the PK and tolerance of E7389 when co-administered with oral multiple doses of ketoconazole (a potent CYP3A4 inhibitor) and the impact of E7389 on ECG. NCI Phase 1 Study 7444, included subjects with refractory or advanced solid tumors and was designed to evaluate safety, tolerability, toxicity, and anti-tumor activity of E7389 and gemcitabine administered in combination as a 2 to 5 minute intravenous bolus on Days 1, 8, and 15 of a 28-day cycle or Days 1 and 8 of a 21-day cycle. The 21-day cycle was better tolerated. DLTs with E7389 at 1.4 mg/m2 and gemcitabine at 1000 mg/m2 included Grade 3 diarrhea, Grade 3 dizziness and fatigue. The recommended Phase 2 dose was E7389 at 1.0 mg/m2 and gemcitabine at 1000 mg/m2.

In the clinical setting, eribulin has demonstrated efficacy in patients with heavily pre-treated metastatic breast cancer, and is given in a 21 day cycle of an intravenous infusion weekly for two weeks followed by one week off. The first phase II trial treated 103 patients with a median of 4 prior chemotherapy regimens for advanced disease[73]. 70 subjects received 1.4 mg/m^2 eribulin administered as an IV bolus on days 1, 8, and 15 of a 28-day cycle; another 33 subjects received eribulin administered as an IV bolus on days 1 and 8 of a 21-day cycle). The 21-day cycle cohort was added because 63% of subjects in the 28-day cycle cohort experienced dose delays, reductions, or omissions due to neutropenia; in most cases the day 15 dose was being omitted. The response rate (RR) was 11.5% (all PR), the clinical benefit rate (CBR) was 17.2%, and progression free survival (PFS) was 2.6 months. The second trial enrolled 299 patients with prior therapy or resistance to anthracyclines, taxanes and capecitabine and the same median prior number of treatment regimens[74]; all patients received treatment on the day 1 and 8 schedule every 21 days. Results were similar by independent review, with an RR of 9.3%, a CBR of 17.1% and PFS of 2.6 months. Between the two trials, overall survival (OS) ranged from 9 to 10.4 months. The most common drug-related grades 3 to 4 toxicities were neutropenia (54-64%), fatigue (5-10%), peripheral neuropathy (5-6.9%), and febrile neutropenia (4-5.5%).

The results of a phase III trial comparing eribulin to treatment of physician's choice (TPC) in patients with anthracyline and taxane pre-treated MBC and at least two prior chemotherapy regimens for advanced disease has recently led to FDA approval of this novel chemotherapy agent [75]. The Embrace trial randomized 508 women to eribulin, and 254 women to TPC; the primary endpoint was OS, which was prolonged with eribulin to 13.12 months versus 10.65 months in the TPC arm (HR 0.81, p=0.041). The RR was also longer in the eribulin arm (12.2 versus 4.7%, p=0.002), and although PFS was significantly longer by investigator assessment, by central review PFS was not significantly different, likely due to the inclusion of patients with evaluable rather than solely measurable disease (3.7 versus 2.2 months, HR 0.87, p=0.14). Subset analysis suggested benefit from eribulin across identified risk groups. 144 patients were identified with ER/PR and HER2 negative disease, determined locally, and in this group the PFS for eribulin was 2.23 months, compared to 1.9 months for TPC. In the overall study, grade 3-4 toxicities included higher rates of neutropenia (21% versus 14%) and leukopenia (11.7% versus

5%) as well as febrile neutropenia (3% versus 0.8%). However, anemia, asthenia/fatigue, nausea, mucositis and hand-foot syndrome were more prevalent in the TPC arm.

1.3 Rationale

TNBC is a highly proliferative BC subtype associated with poor outcome, and acquisition of CTX resistance. This subtype of BC is found more frequently in young African American women, and the presence of M∅s correlates with more aggressive tumor biology and worse survival. Concordant with this data, the M∅-associated T_H1 signature ($CD4^{lo}/CD68^{lo}/CD8^{hi}$) predicted worse RFS in patients with TNBC (**Fig 1**). Preclinical data indicate that inhibition of CSF1R with PLX3397 enhances responsiveness to standard CTX, including PTX (**Fig 3-5**). However, in humans, therapy with PTX requires premedication with immune-suppressing steroids that may negate effects of macrophage-depletion. In addition, the majority of patients with TNBC presenting in the pre-treated metastatic setting will have already been exposed to taxanes as well as other CTX/targeted agent combinations. Eribulin is a well-tolerated, novel halichondrin analogue recently approved by the FDA for treatment of MBC not requiring steroid premedication and is therefore an ideal CTX choice to partner with PLX3397 in this population of patients. The phase Ib portion of the trial will include all BC subtypes in order to efficiently complete accrual and proceed to a phase II trial specifically designed for patients with TNBC. Both trials will be conducted at three Comprehensive Cancer Centers, with breast cancer investigators who have expertise in all phases of clinical trials, as well as acquisition of tumor biopsies. Breast cancer advocates from each center will be actively involved in the study design and clinical trial execution, as well as all patient education and recruitment.

<u>Phase I trial results (preliminary)</u>

Twenty-eight patients were enrolled in the Phase Ib trial, with a final MTD of 1000 mg of PLX3397 in two divided doses given each day combined with eribulin at 1.4 mg/m^2 day 1 and 8 every 21 days. The primary toxicities included rash, bone marrow suppression and transaminitis which were overall manageable with dose reduction, dose delays, growth factor support, and antihistamines and steroids for rash.

2.0 Objectives

2.1 Primary Objective

2.1.1 Phase Ib:

- To determine the maximum tolerated dose of PLX3397 given in combination with standard dose eribulin in patients with metastatic breast cancer.

2.1.2 Phase II

- To determine the percentage of patients with chemotherapy pre-treated triple negative metastatic breast cancer treated with PLX3397 in combination with eribulin who are progression free at 12 weeks.

2.2 Secondary Objectives

2.2.1 Phase Ib

- To determine the safety and tolerability of PLX3397 in combination with eribulin in patients with metastatic breast cancer.
- Correlative studies:
  - To determine the pharmacokinetics of the combination of PLX3397 and eribulin.
  - To correlate change in CSF1 levels during treatment with specific dose levels of PLX3397.
  - Make a preliminary assessment of the relationship between immune profile, tumor subtype, and tumor associated macrophages with response to therapy.
  - Correlate immune profile and tumor associated macrophages from primary tumor blocks with metastatic tumor tissue.

2.2.2 Phase II

- To determine the response rate of PLX3397 in combination with eribulin in patients with chemotherapy pre-treated triple negative metastatic breast cancer.
- To determine the duration of response from the above therapy in this patient population.
- To determine the safety and tolerability of PLX3397 in combination with eribulin in this patient population.
- Correlative studies:
  - Correlation of CSF1 levels and response/duration of response to treatment.
  - Correlation of immune profiling in blood with PLX3397 treatment.
  - Correlate tumor immune profile before and after therapy with tumor subtype and response to therapy.

3.0 Study Design and Eligibility Criteria

3.1 Study Design

This is a nonrandomized, open label phase Ib/II study evaluating the safety and efficacy of eribulin in combination with PLX3397, a novel CSF1 inhibitor, in patients with metastatic breast cancer. The phase II portion of this trial will be limited to patients with triple negative disease.

3.1.1 Phase Ib

The phase I portion of this trial is a dose escalation of PLX3397 to determine the maximum tolerated dose (MTD) of PLX3397 when given in combination with standard dose eribulin. Patients will be enrolled in cohorts of three, using the dose levels and plan outlined in the statistical section, with 6 patients enrolled at the MTD. All patients with accessible tumor will be required to have a tumor biopsy at study start before starting therapy. Pharmacokinetics of PLX3397 and eribulin, and blood levels of CSF1 will be obtained as outlined in section 14. To allow rapid accrual to phase Ib, and an earlier start to the phase II trial, patients will be enrolled in phase I with both hormone receptor positive and negative disease, and at any line of therapy assuming eligibility criteria are otherwise met.

Dose limiting toxicity (DLT) will be defined as any treatment-related toxicity meeting the criteria below and occurring within the first 21 days of combination therapy. Patients must receive at least 14 days of PLX3397 and 2 doses of eribulin during the first cycle in order to be considered evaluable for DLT (unless the missed doses are due to a DLT).

Patients discontinuing study therapy in Cycle 1 for reasons other than treatment-related or a DLT may be replaced.

Hematologic DLTs

- CTCAEv4 Grade 4 neutropenia lasting for ≥5 days in duration
- CTCAEv4 Grade 4 neutropenia with fever >38.5°C and/or infection requiring antibiotic or anti-fungal treatment
- CTCAEv4 Grade 4 thrombocytopenia (platelets ≤25.0/μL)
- CTCAEv4 Grade 3 thrombocytopenia associated with significant bleeding

Non-hematologic DLTs

- Any CTCAEv4 Grade ≥3 non-hematologic toxicity (except alopecia), **unless the event is clearly unrelated** to treatment with PLX3397 in combination with eribulin
- Grade ≥3 nausea, vomiting, or diarrhea that resolves to Grade ≤2 within 48 hours, with or without medical intervention or prophylaxis, will not be considered a DLT
- Grade 3 fatigue that resolves within 14 days, with or without medical intervention or prophylaxis, will not be considered a DLT
- Grade ≥3 hyperglycemia will not be considered a DLT

A treatment delay of greater than 7 days for PLX3397 or inability to get two doses of eribulin, even if a dose reduction is required on day 8 in the first cycle due to toxicity that is not related to cancer worsening or intercurrent illness will be considered a DLT.

A dose reduction required on Day 8 is not considered a DLT.

Patients in each cohort will be followed for at least 3 weeks (one full cycle) before opening accrual to the next dose level. If one patient in any cohort develops a DLT, an additional 3 patients will be enrolled at that level. A minimum of 12 patients will be enrolled in the phase I study. The phase II trial will not open until the last patient in the phase I study has been followed for at least 3 weeks.

3.1.2 Phase II

The phase II portion of this trial will evaluate PFS in patients with TNBC treated with PLX3397 and eribulin, using the dose of PLX3397 determined in the phase Ib study in a two-step design. Please see the statistical section for details regarding enrollment and statistical design. Treatment is preceded by a 6 to 7 day lead-in phase, in which patients will take PLX3397 800mg (400 mg in the morning and 400 mg at night) for 5 days, followed by 1 to 2 days off before starting eribulin combined with PLX3397. PLX3397 will continue to be given on a 5 days on, 2 days off schedule, repeated weekly, throughout the course of treatment. Patients with accessible

tumor will undergo a core biopsy of tumor before the start of PLX3397 treatment, and then a fine needle aspiration or core biopsy will be performed on the day of or the day before the start of eribulin (day -2 to day 0).

3.2 Inclusion Criteria

- Pathologically confirmed diagnosis of breast cancer with documented progressive disease.
- Patients with stable brain metastases are eligible for this trial. Stable brain metastases defined as stable disease for one month and not on active treatment including steroids.
- Concomitant therapy with bisphosphonates is allowed.
- Stable dose coumadin anticoagulation is allowed, providing that anticoagulation can be safely held to an INR within normal range for the purpose of tumor biopsy. LMWH is the preferred method of anticoagulation.
- PT/INR and PTT ≤ Grade 1 within two weeks before initial biopsy of visceral organs.
- Measurable disease, as defined by RECIST v1.1 guidelines or evaluable disease. Bone metastases must be evaluable.
- Disease amenable to core biopsy. Patients with pulmonary metastases as their only site of disease may enroll on this trial and will not undergo biopsy.
- For Phase Ib: patients with HER2 overexpressing disease must have been previously treated with trastuzumab (patients with HER2 overexpressing disease are not eligible for the Phase II trial).
- Age eighteen years or older.
- ECOG performance status ≤2.
- Life expectancy of ≥ 12 weeks.
- Patients with ≤ Grade 1 peripheral neuropathy are eligible for this trial using the CTCAE v4.0, regardless of use of therapy for neuropathy including gabapentin.
- Adequate bone marrow reserve: ANC ≥ 1000, platelets ≥ 100,000.
- Adequate renal function: serum creatinine ≤ 1.5x upper limit of normal OR calculated creatinine clearance ≥ 50 ml/min.
- Sodium and potassium levels ≤ Grade 1.
- Adequate hepatic function: AST and ALT ≤2.5 x ULN, and total bilirubin ≤ 1.5x upper limit of normal. In patients with liver dysfunction due to hepatic metastases, AST and ALT are permitted to be ≤ 5 times the ULN.No clinical evidence of heart failure or history of untreated ejection fraction below the lower limit of normal per institutional standards, or significant QT prolongation (> Grade 1, 480 msec) no history of congenital long QT syndrome, and no use of drugs known to increase the risk of Torsades de Point - patients may be eligible for study if the drug can be changed to another agent with less risk.
- Able to take oral medications and maintain hydration.

- Ability to give written informed consent and willingness to comply with the requirements of the protocol.
- Women of child-bearing potential must agree to use an effective method of birth control during treatment and for six months after receiving their last dose of study drug.

Specific inclusion criteria for Phase II

- Patients enrolling on the phase II portion of this trial must have ER, PR and HER2 negative disease defined as less than 10% staining for ER and PR, and HER2 0-1+ by IHC, or 2+ by IHC and no evidence of amplification by FISH using local laboratory testing.

3.3 Exclusion Criteria

- Treatment with another chemotherapy or hormonal therapy within the past 2 weeks.
- Treatment with trastuzumab, bevacizumab or other targeted therapies within the past 2 weeks.
- Concurrent radiation therapy is not allowed with the exception of brain metastases developing on study treatment (see section 5.2 for details).
- Ongoing treatment with any other investigational therapy.
- Prior treatment with eribulin.
- Severe, concurrent illness including congestive heart failure, significant cardiac disease and uncontrolled hypertension, that would likely prevent the patient from being able to comply with the study protocol.
- Inadequate bone marrow, renal, or hepatic function as defined above, or an active coagulopathy that precludes tissue biopsy.
- Pregnant or lactating women and women of child-bearing potential who are not using an effective method of birth control. Women of childbearing potential must undergo a pregnancy test within seven days of starting the study drug.

4.0 Patient Registration

4.1 Stratification

No stratification will be performed in this study.

4.2 Randomization and Blinding

No randomization or blinding will be performed in this study.

4.3 Registration

4.3.1 UCSF Helen Diller Family Comprehensive Cancer Center

Patients who have consented and are eligible for the study will be registered in the UCSF Comprehensive Cancer Center Clinical Trials Management System (CTMS). The CTMS is password protected and complies with HIPAA standards. The assigned CRC at UCSF will issue the patient a unique study number.

A log of patients who are screened but ineligible for the study will also be kept at each site.

4.3.2 Participating sites

To register patients on study, the site CRC will complete an eligibility form and fax it to the designated UCSF CRC (contact information to be provided by the start of study). Written confirmation of enrollment will be faxed to the enrolling site within 24 hours, along with assigned study number. Study numbers for each patient will be assigned serially. Pertinent information will be entered from the patient medical record.

5.0 Investigational Treatment Plan

5.1 Dose and Schedule

Phase Ib: In the phase Ib study, patients will start both PLX3397 and eribulin on day 1. Patients will take PLX3397 in two divided doses (twice daily), the first dose immediately followed by the IV administration of eribulin. A tumor biopsy will be obtained before treatment start. Pharmacokinetics will be obtained as outlined in section 14.4. The study will use a single-arm, open-label, phase I trial design with expanded cohort for response assessment. Eligible patients must have confirmed metastatic carcinoma of the breast and have received at least one prior cytotoxic chemotherapy regimen for advanced disease.

The study will follow a standard dose-escalation schema with 3 to 6 patients per cohort (3+3 design). The starting dose level will consist of PLX3397 at 600 mg by mouth daily. Enrollment to successive cohorts up to dose level 2 will be performed according to the table shown below, to establish the MTD. If 2 or more dose-limiting toxicities (DLTs) are observed at level 0, one dose reduction (to level -1) is built in to the study design. All patients at a given dose level will be followed on treatment for at least 3 weeks before accrual to the next cohort can commence. There will be no intra-patient dose escalation allowed. For any dose cohort, if a patient is removed from study for reasons that are clearly not treatment-related, then an additional patient will be accrued to that dose level. For the purposes of Phase Ib dose escalation, DLTs will be defined as any treatment-related toxicity occurring within the first 21 days of combination therapy as noted in section 3.1.1.

Dose Escalation Schedule		
	Dose	
Dose Level	**PLX3397**	**Eribulin**
Level -2	400 mg (200 mg BID)	0.7 mg/m2, 2-5 min IV Day 1, 8 q21 days
Level -1	400 mg (200 mg BID)	1.1 mg/m2, 2-5 min IV Day 1, 8 q21 days
Level 0 (starting dose)	600 mg (400 mg AM; 200 mg PM)	1.4 mg/m2, 2-5 min IV Day 1, 8 q21 days
Level 1	800 mg (400 mg BID)	1.4 mg/m2, 2-5 min IV Day 1, 8 q21 days

Level 2 (MTD)	**1000 mg (600 mg AM; 400 mg PM)**	**1.4 mg/m2, 2-5 min IV Day 1, 8 q21 days**

Due to the bone marrow suppression known to occur with eribulin, patients may receive myeloid growth factors at any time, at physician discretion (for guidelines regarding use of neupogen, see section 6.1). An eribulin premedication regimen of intravenous dexamethasone (6 mg, or physician-selected dose), or other equivalent steroid, <60 minutes prior to eribulin. This may be tapered with subsequent doses per investigator discretion.

Note: Patients enrolled on to the trial under protocol version 6.0 which allowed for Eribulin dosing schedule of Day 1 and Day 15 every 28 days will remain on that treatment and assessment schedule.

Phase II: The phase II portion will begin after the MTD for PLX3397 is determined and we will enroll a total of 56 patients with triple (ER/PR/HER2) negative metastatic breast cancer to evaluate the safety and efficacy of the proposed treatment. In the phase II study, treatment is preceded by a 6 to7 day lead-in phase, in which patients will take PLX3397 800mg (400 mg in the morning and 400 mg at night) alone for 5 days, followed by 1 to 2 days off before starting eribulin combined with PLX3397. PLX3397 will continue to be given on a 5 days on, 2 days off schedule, repeated weekly, throughout the course of treatment. Concomitant antihistamines are recommended to reduce the incidence of rash. A tumor core biopsy will be obtained before treatment start, and then again before the start of eribulin. Patients will be treated until clinical or radiographic disease progression or cumulative toxicity and will be evaluated regularly in clinic. Evaluation of disease response or progression will be accomplished with CT scans, and bone scans as indicated, every 6 weeks. Visits will take place before each dose of eribulin (Day 1 and Day 8) during cycle 1, and then on Day 1 before cycle 2 and beyond.

5.2 Duration of Therapy

Treatment with the combination of PLX3397 and eribulin will continue until patients experience disease progression based on RECIST v1.1 criteria, toxicity that prevents continued treatment, or in the case of patient decision.

Patients who have evidence of systemic response or disease control after at least one full cycle of eribulin and PLX3397 and who develop brain metastases may stay on study with a break in study therapy of up to one month in order to complete brain directed therapy. Brain directed therapy may include whole brain radiation or stereotactic radiosurgery. Eribulin should be held during whole brain radiation but need not be adjusted for stereotactic radiation. Stereotactic radiation should be scheduled for the week off of eribulin if at all possible. Patients may resume treatment, if deemed safe per the PI.

6.0 General Concomitant Medication and Supportive Care Guidelines

Concomitant treatment is permitted if the medication is not expected to interfere with the evaluation of safety or efficacy of the study drug. During the study, if the use of any concomitant treatment becomes necessary (e.g., for treatment of an adverse event), the treatment must be

recorded on the CRF, including the reason for treatment, generic name of the drug, dosage, route, and start and stop dates of administration. Antihistamines (i.e. loratadine or cetirizine) are recommended as pre-meds for all pts to prevent rash, and growth factor use is strongly recommended as prophylaxis for patients who have a history of bone marrow suppression on past chemotherapy and is allowed at the treating physicians discretion.

Although PLX3397 does not appear to inhibit CYP drug-metabolizing enzymes to an important extent, caution is warranted when administering PLX3397 to subjects taking drugs that are highly dependent on CYP3A4 for metabolism and have a narrow therapeutic index.

Of the five major CYP isoforms, 3A4 (BFC) may be involved in phase I metabolism (first pass) of PLX3397, with possibly CYP1A2 playing a minor role. Until information regarding exposure-toxicity and exposure-response relationships are available with PLX3397, concomitant CYP3A4 inhibitors and inducers should be administered with caution, in the event they alter the systemic exposure to PLX3397 (see Appendix I for a list of common CYP3A4 inhibitors and inducers). In general, strong inhibitors or inducers of CYP3A4 should be avoided unless absolutely clinically necessary without effective alternatives. These include anticonvulsants, mycin antimicrobials, and antiretrovirals. Some common examples include inhibitors such as erythromycin, fluoxetine, gemfibrozil, and inducers such as rifampicin, carbamazepine, phenytoin, efavirenz, and nevirapine.

6.1 Use of Myeloid Growth Factors

The primary toxicity of eribulin is bone marrow suppression, specifically neutropenia. Patients enrolling on this study will have had prior exposure to chemotherapy so will be at risk for bone marrow suppression. Myeloid growth factors will be allowed at physician discretion at any time, including during the DLT period. It is recommended that NCCN guidelines are followed. Myeloid growth factors will be allowed at any time following NCCN guidelines.

In particular, prophylactic neupogen should be considered for patients requiring growth factor support with prior systemic chemotherapy.

7.0 Toxicity Management & Dose Modifications

The following dose modification rules will be used with respect to potential toxicity. Toxicity will be assessed continuously according to the NCI Common Terminology Criteria for Adverse Events Version 4.0 (CTCAE v4.0)

The AE may be due to PLX3397 or eribulin alone in which case the respective agent should be reduced. If overlapping toxicity is suspected both drugs may be reduced with the potential to re-escalate the non-offending agent. Given the different nature of PLX3397 and eribulin toxicities, separate tables are shown for individual agents.

7.1 PLX3397

Phase I

PLX3397 dose reductions and interruptions will be permitted during the first 21 days of Cycle 1 **only if a patient experiences a protocol-defined DLT.** If a patient experiences a DLT during Cycle 1, PLX3397 treatment continuation at a lower dose may be permitted at the discretion of the Investigator including following Cycle Day 1 chemotherapy. In particular, prophylactic neupogen should be considered for patients requiring growth factor support with prior systemic chemotherapy. After Cycle 1 Day 21, dose reductions or interruptions for adverse events may take place at any time.

Phase II

Guidelines for dosage modification for PLX3397–related toxicities as well as guidelines for their management are noted in Table 7-1. Please notify the Principal Investigator or UCSF study coordinator about all dose modifications. Dose reductions should occur in increments of 200 mg. These parameters are only suggestions and are not intended to supersede the clinical judgment of the treating physician. All adjustments should be made in consultation with the site specific Principal Investigator.

Table 7-1. Dose Modifications Guidelines for PLX3397

Toxicity Grade (CTCAE v4)	PLX3397 dose changes during current treatment period	Dose adjustments for resumption of treatment
Non-Hematologic Toxicity		
Drug Related Grade 3 (start symptomatic treatment when possible)		
1st Appearance	Continue treatment and provide supportive care	Reduce by one dose level if symptoms persist for ≥5 days despite supportive management.
2nd Appearance	Interrupt until resolved (grade 0 -1 or baseline)	Reduce by an additional dose level.
3rd Appearance	Discontinue permanently	N/A
Drug Related Grade 4 (start symptomatic treatment when possible)		
1st Appearance	Interrupt until resolved (grade 0 -1 or baseline)	Reduce by one dose level.
2nd Appearance	Discontinue permanently	N/A
Hematologic Toxicity		
Grade 4 neutropenia		
1st Appearance	Interrupt until ANC recovers; provide growth factor support	Once recovered to ANC ≥500X10^6/L, resume at same dose. If ANC does not recover to ≥ 1X10^9/L after 7 days, reduce dose by one dose level
2nd Appearance	Interrupt until ANC recovers; provide growth factor support	Once resolved to ANC ≥500X10^6/L, reduce dose by one dose level. If ANC does not recover to ≥1X10^9/L after 7 days, reduce dose by an additional dose level .
3rd Appearance	Interrupt until ANC recovers; provide growth factor support	If ANC does not recover to ≥500X10^6/L after 14 days, discontinue permanently.
Grade 2 and > 2x Baseline elevation of liver enzymes (ALT, AST, AlkPhos)		
1st Appearance	Interrupt until recovers to less than	No Change

Table 7-1. Dose Modifications Guidelines for PLX3397

Toxicity Grade (CTCAE v4)	PLX3397 dose changes during current treatment period	Dose adjustments for resumption of treatment
	Grade 2	
2nd Appearance	Interrupt until recovers to less than Grade 2	Reduce byone dose level
3rd Appearance	Interrupt until recovers to less than Grade 2	Reduce by an additional dose level
4th Appearance	Discontinue permanently	
Grade 3 or Grade 4 febrile neutropenia		
1st Appearance	Interrupt until ANC and fever recovery; provide growth factor support	Once resolved to ANC $\geq 500X10^6$/L and T $\leq$ 38˚C, reduce dose by one dose level
2nd Appearance	Interrupt until ANC and fever recover; provide growth factor support	Once resolved to ANC $\geq 500X10^6$/L and T $\leq$38˚C, reduce dose by an additional dose level
3rd Appearance	Discontinue permanently	N/A
Grade 4 thrombocytopenia		
1st Appearance	Interrupt until PLT $\geq 25X10^9$/L	Reintroduce at same dose
2nd Appearance	Interrupt until PLT $\geq 25X10^9$/L	Reduce dose by one dose level
3rd Appearance	Interrupt until PLT $\geq 25X10^9$/L	Reduce dose by one dose level
4th Appearance	Discontinue permanently	N/A

Dose interruptions for Grade 2 non-hematologic toxicity for up to 1 week can be implemented at the discretion of the treating physician to manage intolerable or clinically significant toxicity. No dose reduction is required when resuming treatment.

A dose delay of greater than 21 days from the intended date of eribulin administration or a 21 day hold in administration of PLX3397 requires removal from study therapy.

Every effort should be made to adhere to the intended schedule whenever possible.

7.2 Eribulin

Phase I

Eribulin dose reductions will be permitted during the first 21 days of Cycle 1 **only if a patient experiences a protocol-defined DLT.** Patients starting at 1.4 mg/m2, eribulin dose reductions will be permitted at physician discretion on Cycle 1, Day 8 – this will not be considered a DLT.

If a patient experiences a protocol-defined DLT during Cycle 1, eribulin dose reduction will be permitted at physician discretion. After Cycle 1 Day 21, dose reductions or interruptions for adverse events may take place at any time.

Phase II

Guidelines for dosage modification for eribulin–related toxicities as well as guidelines for their management are noted in Table 7-2.

Table 7-2. Guidelines for dosage modification for eribulin–related toxicities

Toxicity	NCI-CTC grade, unless otherwise specified	Management of eribulin	Dose upon resumption
Neutropenia (ANC <1000) +/- fever (T>38)	1st episode	Hold until afebrile and ANC >1000	No change and add filgrastim
	2nd episode	Hold until afebrile and ANC >1000	No change If ANC does not recover to ≥ $1X10^9$/L after 7 days despite growth factor use, reduce by one dose level
	3rd episode	Hold until afebrile and ANC >1000	• Reduce by one dose level
	4th episode	Remove from study	Remove from study
Thrombocytopenia	Grade 2 or greater (<75K)	Hold until >75K	No change
	Recurrent grade 2 or greater	Hold until >75K	• Reduce by one dose level
	3rd occurrence grade 2 or greater	Hold until >75K	No change
	4th occurrence grade 2 or greater	Remove from study	Remove from study
Rash	Grade 1 or 2	Continue treatment; supportive care	No change**
	Grade 3	Hold until grade1 or less; supportive care	No change**
	Second episode grade 3	Hold until grade1 or less; supportive care	• Reduce by one dose level
	3rd occurrence grade 3	Remove from study; supportive care	Remove from study
GI toxicity: diarrhea, nausea, vomiting	Grade 1, 2	Continue treatment	No change; maximize supportive treatment
	Grade 3	Hold until grade 1 or less	No change; maximize supportive treatment
	Recurrent grade 3	Hold until grade 1 or less	No change
	3rd occurrence	Hold until grade 1 or less	• Reduce by one dose level
	4th occurrence grade 3 or 4	Remove from study	Remove from study
Liver function abnormalities (ALT, AST, Alk Phos only)	Grade 1, 2	Continue treatment	No change
	Grade 3 and >2x baseline	Hold until less than grade 3	No change
	recurrent 3 and >2x baseline	Hold until less than grade 3	• Reduce by one dose level
Neuropathy (motor and	Grade 1, 2	Continue treatment	No change

Table 7-2. Guidelines for dosage modification for eribulin–related toxicities

Toxicity	NCI-CTC grade, unless otherwise specified	Management of eribulin	Dose upon resumption
sensory)			
	Grade 3	Hold until less than grade 3	No change
	Recurrent grade 3	Hold until less than grade 3	• Reduce by one dose level
	3rd occurrence grade 3	Remove from study	Remove from study

Dose interruptions for Grade 2 non-hematologic toxicity for up to 1 week can be implemented at the discretion of the treating physician to manage intolerable or clinically significant toxicity. No dose reduction is required when resuming treatment.

A dose delay of greater than 21 days from the intended date of eribulin administration or a 21 day hold in administration of PLX3397 requires removal from study therapy.

Every effort should be made to adhere to the intended schedule whenever possible.

Dose Reduction Levels for PLX3397 and Eribulin		
	Dose	
Dose Level	**PLX3397**	**Eribulin**
Starting Dose	800 mg x 5 days/week (400 mg BID x 5days, followed by 2 days off, repeated weekly)	1.4 mg/m2, 2-5 min IV Day 1, 8 q21 days
1st dose reduction	600 mg x 5 days/week (400mg AM and 200mg PM x 5days, followed by 2 days off, repeated weekly)	1.1 mg/m2, 2-5 min IV Day 1, 8 q21 days
2nd dose reduction	400 mg x 5 days/week (200mg BID x 5days, followed by 2 days off, repeated weekly)	0.7 mg/m2, 2-5 min IV Day 1, 8 q21 days

8.0 Schedule of Assessments

Table 8-1 Study Calendar: Phase Ib

Cycle (1 cycle = 21 days)	**Comment**	**Screening**		**Cycle 1**				**Cycle 2**			**Cycle 3 & Beyond**			**EOT**
Real life time clock		**≤4 wks**	**≤2 wks**	**D 1[1]**	**D 2**	**D 8**	**D 15**	**D 1[1]**	**D 8**	**D15**	**D 1[1]**	**D 8**	**D15**	**≤ 30 days**
Informed Consent		X												
Registration			X											
History & Exam			X	X		X		X			X			X
ECOG			X	X		X		X			X			
ConMed Review			X	X		X		X	X		X	X		X
Peripheral Neuropathy		X		X				X			X			
CBC w/ 5 part diff.			X	X		X		X	X		X	X		X
Chemistry Panel	BUN, CO2, Cl, K, Na, Creatinine, Glucose (non-fasting), & Magnesium		X	X				X			X			X
Liver Function Tests	ALT, AST, AlkPhos, Total Bilirubin, & Albumin						X[10]			X[10]			X[10]	
PT/PTT	Completed prior to tumor biopsy		X											
Urine Pregnancy Test [2]	Within 7 days of beginning treatment		X								X			
EKG [3]		X						X						
Eribulin Therapy, IV[4]	Day 1 & 8, q 21 days			X		X[5]		X	X		X	X		
PLX3397 Therapy	Oral					Beginning Cycle 1, Day 1: Daily (self-administered)								
Bone Scan & other imaging	Baseline, then as indicated	X												
CT (C/A/P)	Every 6 weeks	X									X			X
PK Draws				X[6]	X[7]			X[8]						
Blood for CSF1[9]				X	X			X						
Blood for Leukocyte Subtyping[9]				X										
Tumor biopsy	Required for patients w/ accessible tumor		X											
Archived Tumor Tissue	Requested of all participants		X											

1. *Allowed a window of ± 3 days for Day 1 procedures*
2. *In women of child bearing potential*
3. *EKGs performed at the start of every other cycle (even numbered), at 6 week intervals*
4. *The following eribulin treatment delays are allowed for **patient coordination:** C1 D8 (up to 3 days), C2+ D1 (up to 14 days), and C2+ D8 (up to 3 days)*
5. *A delay in C1 D8 of up to 7 days is allowed for resolution of toxicity*
6. *Plasma samples for PK on C1 D1 will occur pre-PLX3397 administration and at 1, 2, and 5 hours post treatments (± 15 minutes)*
7. *Plasma samples for PK on C1D2 will occur 24 hours post eribulin treatment, but pre-PLX3397 administration (± 30 minutes)*
8. *Plasma samples for PK on C2D1 will occur pre-PLX3397 and at 2 hours post treatment (± 15 minutes)*
9. *All blood should be drawn before administration of IV eribulin*
10. *Liver function tests will be completed on D15 of the firsts three cycles only (C1D15, C2D15, and C3D15).*

Table 8-2 Study Calendar: Phase II

Cycle (1 cycle = 21 days)	Comment	Screening		Lead-In Phase	Cycle 1			Cycle 2			Cycle 3 & Beyond			EOT
Real life time clock		**≤4 wks**	**≤2 wks**	**Day -7 to -6**	**D 1[1]**	**D 8**	**D15**	**D 1[1]**	**D 8**	**D15**	**D 1[1]**	**D 8**	**D15**	**≤ 30 days [7]**
Informed Consent		X												
Registration			X											
History & Exam			X		X	X		X			X			X
ECOG			X		X	X		X			X			
ConMed Review			X		X	X		X	X		X	X		X
Peripheral Neuropathy		X			X			X			X			
CBC w/ 5 part diff.			X		X	X		X	X		X	X		X
Chemistry Panel	BUN, CO2, Cl, K, Na, Creatinine, Glucose (non-fasting), & Magnesium		X		X			X			X			X
Liver Function Tests	ALT, AST, AlkPhos, Total Bilirubin, & Albumin		X		X	X	X[10]	X	X	X[10]	X	X	X[10]	X
PT/PTT[11]	Completed prior to tumor biopsy		X											
Pregnancy Test [2]	Within 7 days of beginning treatment		X								X			
EKG [3]		X						X						
Eribulin Therapy, IV[4]	Day 1 & 8, q 21 days				X	X[5]		X	X		X	X		
PLX3397 Therapy	Oral				Beginning With Lead-In Phase (Day -7 to -6): Daily (self-administered)									
Bone Scan & other imaging	Baseline, then as indicated	X												
CT (C/A/P)	Every 6 weeks[9]	X									X			X
Blood for CSF1[6]				X	X			X			X[8]			
Blood for Leukocyte Subtyping[6]				X	X			X			X[8]			
Tumor biopsy	Required for patients w/ accessible tumor		X		X (Day 0/ -1)									
Archived Tumor Tissue	Requested of all participants		X											

1. *Allowed a window of ± 3 days for Day 1 procedures*
2. *In women of child bearing potential. Urine or Serum test allowed.*
3. *EKGs performed at the start of every other cycle (even numbered), at 6 week intervals*
4. *The following eribulin treatment delays are allowed for **patient coordiantion:** C1 D8 (up to 3 days), C2+ D1 (up to 14 days), and C2+ D8 (up to 3 days)*
5. *A delay in C1 D8 of up to 7 days is allowed for resolution of toxicity*

6. *Blood should be drawn before the first dose of PLX3397 during the lead-in phase, and before each administration of eribulin.*
7. *EOT procedures should occur within 30 days of last dose, after which the patient will be Off-Study.*
8. *Cycle 4 Day 1 only*
9. *Patients with either CR or PR and who have received at least 6 cycles of therapy may reduce the frequency of scans to every 9 weeks.*
10. *Liver function tests will be completed on D15 of the first three cycles only (C1D15, C2D15, and C3D15).*
11. *PT/PTT is only required for patients getting visceral organ biopsies*

8.1 Screening Assessments (same for both the Phase Ib and Phase II study)

The following screening procedures must be performed within 2 weeks (or 4 weeks where noted) of entering the clinical trial:

- Patients must have reviewed and signed the consent form (within 4 weeks)
- Complete medical history and physical to determine if patient meets the study entry criteria
- Review of concomitant medications
- Baseline laboratories, including: complete blood count with 5 part differential, chemistry panel, liver functions tests, PT/INR, and PTT
- Pregnancy test if patient has childbearing potential (within 7 days)
- Tumor imaging, including a CT scan of the chest, abdomen, and pelvis and bone scan, or a whole body PET CT for patients with measurable disease. PET CT scans must include a diagnostic CT to be study eligible (cannot use CT scans for attenuation only purposes).
- 12-lead EKG
- Request archived tumor tissue
- Tumor biopsy for patients with accessible tumor
- Blood for correlative studies

8.2 Assessments During Treatment

Once the patient is confirmed to be eligible based on screening assessments, the following study assessments will be performed. See Table 8-1 and 8-2 for summary. One cycle is defined as 21 days. Day 1 visit procedures for any cycle of therapy are allowed a window of ± 3 days unless otherwise noted. Following the first cycle of therapy, patients may delay the start of a new cycle of therapy up to 2 weeks as necessary for personal activities, such as travel or vacation although every attempt should be made to keep patients on schedule. Treatment or visit delays due to public holidays, weather conditions, or natural disasters, do not constitute protocol violations.

The following treatment delays are allowable for patient coordination:

- Cycle 1, Day 8 – delay eribulin administration up to 3 days
- Cycle 2+, Day 1 – delay eribulin administration up to 14 days
- Cycle 2+, Day 8 – delay eribulin administration up to 3 days

8.2.1 Lead in Phase - Phase II only, Day -7/-6

- Blood for CSF1 and leukocyte phenotyping
  - For CSF1: 5 cc of blood will be drawn into a serum separator tube (gold top)
  - For leukocyte phenotyping: 10 cc of blood will be drawn into an EDTA tube (purple top)

- Tumor Biopsy Day 0/-1

8.2.2 During Cycle 1 (same for Phase Ib and Phase II except where noted below)

The following assessments will be performed prior to receiving treatment on Day 1:

- Medical history and physical examination
- Review of concomitant medications
- Laboratories, including complete blood count, chemistry panel and liver function tests.
- Blood for CSF1 and leukocyte phenotyping
- Blood for pharmacokinetics (Phase I only)

The following assessments will be performed after receiving treatment on Day 1 (Phase Ib only):

- Blood for pharmacokinetics will be drawn at 1 hour, 2 hours and 5 hours post treatment

The following assessment will take place on Day 2 (Phase Ib only):

- Blood for pharmacokinetics and CSF1 will be drawn 24 hours post Day 1 treatment

The following assessment will take place on Day 8:

- Medical history and symptom-driven physical examination
- Laboratories, including complete blood count with differential
- Review of concomitant medications

The following assessment will take place on Day 15:

- Liver function tests

8.2.3 During Subsequent Cycles (Cycle 2 and beyond)

The following assessments will be performed prior to receiving treatment on Day 1:

- Medical history and physical examination
- Review of concomitant medications
- Laboratories, including complete blood count, chemistry panel
- and liver function tests. Urine Pregnancy test will only be done for women of childbearing potential (Cycle 3+)
- Blood for CSF1 and leukocyte phenotyping (Cycle 2 and 4 Day 1only)
- Blood for pharmacokinetics (Cycle 2, Phase Ib only)

The following assessments will be performed after receiving treatment on Day 1:

- Blood for pharmacokinetics will be drawn at 2 hours post treatment (C2, Phase Ib only)

The following assessments will take place on Day 8:

- Laboratories, including complete blood count with differential
- Review of concomitant medications

The following assessment will take place on Day 15:

- Liver function tests (Cycles 2 and 3 only)

Scans including all measurable and/or evaluable disease will be obtained every 6 weeks and at End of Treatment. Patients with either CR or PR and who have received at least 6 cycles of therapy may reduce the frequency of scans to every 9 weeks.

8.3 Follow-Up Assessments

Patients will be permitted to stay on treatment until they have disease progression.

Patients who develop progressive disease or Grade 3/4 toxicity that does not resolve after discontinuation of all study medications for 14 days will be removed from the study. All patients who leave the study must have a follow up visit within 30 days after their last dose of study medication. At this time, patients will have the following:

- Full medical history and physical exam for assessment of residual toxicities
- Blood draw for complete blood count with differential, chemistry panel, and liver function tests

If patients continue to have evidence of persistent toxicities at the first follow up visit, they will have continued monitoring at the discretion of the principal investigator until these symptoms are resolved or considered stable.

9.0 Criteria for Evaluation

9.1 Response Definitions

Evaluable for toxicity: All patients will be evaluable for toxicity from the time of their first treatment with PLX3397

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

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

Disease Parameters

Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm (≥2 cm) by chest x-ray or as ≥10 mm (≥1 cm) with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph

node must be ≥15 mm (≥1.5 cm) in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm [0.5 cm]). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter <10 mm [<1 cm] or pathological lymph nodes with ≥10 to <15 mm [≥1 to <1.5 cm] short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

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

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

Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as ***target lesions*** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

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

Methods for Evaluation of Measurable Disease

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

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial

(*e.g.*, skin nodules and palpable lymph nodes) and ≥10 mm (≥1 cm) diameter as assessed using calipers (*e.g.*, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm (0.5 cm) or less. If CT scans have slice thickness greater than 5 mm (0.5 cm), the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans).

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

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

Tumor markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

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

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens

during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

Response Criteria

Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (<1 cm).

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

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm (0.5 cm). (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm [<1 cm] short axis).

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

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

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

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

Evaluation of Best Overall Response

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

For Patients with Measurable Disease (*i.e.*, Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

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

For Patients with Non-Measurable Disease (*i.e.*, Non-Target Disease)

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

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

Duration of Response

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

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

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

9.2 Toxicity Definitions

All study toxicities will be graded by the NCI Common Terminology Criteria for Adverse Events Version 4.0.

10.0 Criteria for Termination

10.1 Conditions for Terminating the Study

The Principal Investigator may terminate the study for any of the following reasons:

- Significant toxicities: Patients with any grade 3/4 toxicity that persists and does not improve 21 days after discontinuation of all study medications, despite pharmacologic management, will be removed from the study. Any patient who experiences any grade 4 toxicity can be removed from the study at the discretion of the study investigator.
- If it becomes clear that the study treatment is less effective than standard treatment. The phase II study has a two-stage design (see section 3 for more details). If fewer than 8 out of the first 20 pts are progression-free at 12 weeks, this would be considered an unacceptably low PFS rate (<39%), the study will not continue and accrual will cease. Study accrual will continue while efficacy is being determined. Conversely, if at least 7 patients in the first stage of the phase II study are free of progressive disease at 12 weeks, then enrollment will continue to the second stage of the study. .
- Once all data collection has been completed.

10.2 Conditions for Individual Patient Termination

The Principal Investigator may terminate the participation of an individual patient for any of the following reasons:

- Disease progression
- Need for exclusionary concurrent treatment
- Withdrawn consent
- Protocol non-compliance
- Lost to follow-up

11.0 Drug Information

Eribulin is supplied in single-use vials containing 1 mg of the drug at a concentration of 0.5 mg/mL. The single-vial cartons should be stored at 25 °C.

The recommended dosage of eribulin is 1.4 mg/m^2 administered intravenously over two to five minutes on days 1 and 8 of a 21-day cycle. Eribulin may be administered undiluted or diluted in 100 mL of 0.9% Sodium Chloride Injection, USP. The drug should not be administered through an IV line that is delivering a dextrose-containing solution.

Syringes containing undiluted eribulin and containers of diluted eribulin may be stored up to 4 hours at room temperature or up to 24 hours refrigerated at 25 °C.

The labeling includes recommendations for dosage reductions in patients with liver or kidney impairment.

Also included in the labeling are recommendations for reducing and delaying scheduled doses in response to blood-count abnormalities that develop during treatment.

The labeling states that febrile or afebrile neutropenia occurred in 82% of eribulin recipients in the company's pivotal Phase III clinical trial, compared with 53% of patients in the control group. Other adverse events that affected at least 25% of eribulin recipients were anemia, weakness or tiredness, alopecia, peripheral neuropathy, nausea, and constipation.

According to the labeling, blood-cell counts should be monitored during eribulin therapy and dosages reduced or delayed in patients with low red- or white-blood-cell counts. Patients should also be periodically assessed for peripheral neuropathy.

QT-interval assessments are recommended during eribulin therapy for patients who have heart failure, bradyarrhythmia, or electrolyte abnormalities or are receiving concomitant treatment with drugs that prolong the QT interval.

PLX3397 is supplied in 200 mg gelcaps.

11.1 Eribulin mesylate (E7389)

11.1.2 Classification

Eribulin mesylate (E7389) is a synthetic analog of Halichondrin B (HalB), a natural product isolated from the marine sponge Halichondria okadai.1 HalB is a large polyether macrolide that exerts potent anticancer effects in cell-based and animal models of cancer. The structurally simplified synthetic analog eribulin mesylate (E7389) encompasses the biologically active macrocyclic portion of HalB, and shows similar or identical anticancer properties in preclinical models.

11.1.3 Mode of Action

E7389 exerts its antiproliferative effects via a tubulin-based antimitotic mechanism. Currently-available data indicate that its mechanism of action is similar or identical to that of HalB.4,5 Like HalB, E7389 was shown to be a potent inhibitor of tubulin polymerization into microtubules as well as microtubule dynamics in vitro and in whole cells.4,6 Nonclinical data show that sub- to low-nmol/L levels of E7389 inhibit cancer cell proliferation via induction of irreversible cell cycle blocks at G2/M, disruption ofmitotic spindles, and initiation of apoptosis.

Eribulin inhibits the growth phase of microtubules without affecting the shortening phase and sequesters tubulin into nonproductive aggregates. Eribulin exerts its effects via a tubulin-based

antimitotic mechanism leading to G2/M cell-cycle block, disruption of mitotic spindles, and, ultimately, apoptotic cell death after prolonged mitotic blockage.

11.1.4 Storage and Stability

The long-term storage condition for E7389 drug product is to store at 2°C to 8°C (do not freeze). Clinical supplies labeled for storage at temperatures up to 25°C have been reassigned to refrigerated storage (2°C to 8°C) to provide an extended provisional shelf life.

The drug product may be administered without dilution or diluted with 0.9% Sodium Chloride Injection to concentrations between 0.005 mg/mL and 0.2 mg/mL, and administered per Eisai's directions.

Photostability studies have demonstrated that protection from light is not necessary for the E7389 drug product.

11.1.5 Metabolism

Cytochrome 3A4 (CYP3A4) appears to be the major enzyme responsible for the human hepatic metabolism of E7389, and forms mainly isomeric monohydroxylates in vitro.

11.1.6 Preparation & Administration

Aseptically withdraw the required amount of HALAVEN from the single-use vial and administer undiluted or diluted in 100 mL of 0.9% Sodium Chloride Injection, USP. **Do not dilute in or administer through an intravenous line containing solutions with dextrose.** Do not administer in the same intravenous line concurrent with the other medicinal products. Store undiluted HALAVEN in the syringe for up to 4 hours at room temperature or for up to 24 hours under refrigeration (40°F or/ 4°C). Store diluted solutions of HALAVEN for up to 4 hours at room temperature or up to 24 hours under refrigeration. Discard unused portions of the vial.

11.1.7 Side Effects

The most common adverse reactions (≥25%) reported in patients receiving eribulin were neutropenia, anemia, asthenia/fatigue, alopecia, peripheral neuropathy, nausea, and constipation. The most common serious adverse reactions reported in patients receiving eribulin were febrile neutropenia (4%) and neutropenia (2%). The most common adverse reaction resulting in discontinuation of eribulin was peripheral neuropathy (5%). Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in other clinical trials and may not reflect the rates observed in clinical practice. In clinical trials, eribulin has been administered to 1,222 patients with multiple tumor types, including 240 patients exposed to eribulin for 6 months or longer. The majority of the 1,222 patients were women (82%) with a median age of 58 years (range: 26 to 91 years). The racial and ethnic distribution was Caucasian (83%), Black (5%), Asian (2%), and other (5%). The adverse reactions were identified in 750 patients treated in Study 1 [*see Clinical Studies (14)*]. In Study 1, patients were randomized (2:1) to receive either eribulin (1.4 mg/m2 on Days 1 and 8 of a 21-day cycle) or single agent treatment chosen by their physician(control group). A total of 503 patients received eribulin, and 247 patients in the control group received therapy consisting of chemotherapy [total 97% (anthracyclines 10%, capecitabine 18%, gemcitabine 19%, taxanes 15%, vinorelbine 25%, and other chemotherapies 10%)] or hormonal

therapy (3%). The median duration of exposure was 118 days for patients receiving eribulin and 63 days for patients receiving control therapy. Table 2 reports the most common adverse reactions occurring in at least 10% of patients in either group.

11.1.8 Nursing Implications

There are no premedications required for eribulin infusion and eribulin is not a significant vesicant.

11.2 PLX3397

11.2.1 PLX3397 Administration

PLX3397 will be administered orally using a capsule formulation (200 mg per capsule). PLX3397 will be administered only to patients who have signed and dated an informed consent form. PLX3397 will be administered on a 5 day on, 2 day off schedule, repeated weekly, , beginning C1D1 (baseline) for Phase Ib, or Day -7/-6 for Phase II. PLX3397 should be taken orally with 240 mL (8 oz) of room-temperature water in the fasting state. **The patient should fast at least 1 hour before administration and 1 hour after administration of PLX3397.** Patients will be permitted to eat a low-fat, bland snack (e.g., crackers, toast, tea) during the fasting period if needed.
PLX3397 should be taken by the patient at approximately the same time of day.

Instructions for BID Dosing:
The time between BID doses should be approximately 12 hrs. Dosing may occur once daily (QD) under certain circumstances (e.g. dose reductions) and at the discretion of the Investigator in consultation with the Principal Investigator.

On C1D1, C1D2 and C2D1, the patients should take the morning dose of PLX3397 at the clinical site after the pre-dose PK blood sample is obtained– patients should be instructed not to take the study drug at home prior to these clinic visits. The time of dosing will be recorded in the clinic. The evening dose of PLX3397 should be taken by the patient at home. On all other visit days, patients may administer the study drug at home and record dosing information in the PLX3397 administration diary.

Missed doses of greater than 2 hrs before or after the appropriate dosing time should be skipped and not taken as a double dose at the next dosing timepoint. For example, a patient who takes their PLX3397 at 8 a.m. and 8 p.m. each day should not take their dose if they are outside of the ±2 hr window period.

Patients who vomit their dose should be instructed to NOT make up that dose.

11.2.2 PLX3397 Packaging and Labeling

PLX3397-HCl capsules (200 mg strength of the active free base of PLX3397) are manufactured, packaged, and labeled according to GMP and GCP at the following address:

[redacted]

11.2.3 PLX3397 Storage and Stability

PLX3397-HCl capsules will be stored at the clinical site, as indicated on the study drug label, i.e., room temperature (between 15-30ºC, or 59-86ºF).

Patients will be requested to store PLX3397 at the recommended storage conditions noted on the label, out of the reach of children or other cohabitants.

11.2.4 PLX3397 Accountability, Reconciliation, and Return

The investigator is accountable for all test article supplied by the Sponsor. Copies of the completed source dispensing and inventory record(s) will be returned to the Sponsor (or designee) after the Sponsor (or designee) has performed accountability procedures. PLX3397 accountability will also be captured in the EDC throughout the course of the trial.

All PLX3397 capsules must be returned to the contract distribution center with the appropriate form if there is evidence that the product has been tampered within transit. Returned and unused PLX3397 capsules may also be destroyed and documented at the investigative site in accordance with GCP.

11.2.5 PLX3397 Compliance

At each clinic visit, patients will be questioned about their PLX3397 compliance. PLX3397 compliance will also be tracked through a patient diary.

11.2.6 PLX3397 Toxicity

PLX3397 treatment-emergent Adverse Events occurring in ≥10% of patients with solid tumors are listed in the table on the following page (combined data from 5 studies, including Phase I, Phase I/II, and Phase II studies).

Preferred Term	Overall AEs (any Grade) (N=92)	Related AEs (any Grade) (N=92)
ANY EVENT	87 (94.6%)	69 (75.0%)
FATIGUE	36 (39.1%)	23 (25.0%)
DECREASED APPETITE	35 (38.0%)	21 (22.8%)
NAUSEA	30 (32.6%)	19 (20.7%)
VOMITING	22 (23.9%)	9 (9.8%)
ANAEMIA	21 (22.8%)	11 (12.0%)
HAIR COLOR CHANGES	17 (18.5%)	17 (18.5%)
DIARRHOEA	16 (17.4%)	7 (7.6%)
AST INCREASED	13 (14.1%)	12 (13.0%)
PYREXIA	13 (14.1%)	3 (3.3%)
CONSTIPATION	11 (12.0%)	4 (4.3%)
DIZZINESS	11 (12.0%)	4 (4.3%)
DYSPNOEA	10 (10.9%)	1 (1.1%)
RASH	10 (10.9%)	6 (6.5%)

8 serious adverse events (SAEs) possibly or probably related to study drug have been reported in 5 patients in the pooled solid tumor studies (listed in table below). No SAE has been reported more than once.

System Organ Class	Preferred Term	(N=92)
ANY EVENT		5 (5%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	ANAEMIA	1 (1%)
	NEUTROPENIA	1 (1%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	PYREXIA	1 (1%)
HEPATOBILIARY DISORDERS	HEPATIC HAEMORRHAGE	1 (1%)
INFECTIONS AND INFESTATIONS	LUNG INFECTION	1 (1%)
INVESTIGATIONS	INR INCREASED	1 (1%)
NERVOUS SYSTEM DISORDERS	SYNCOPE	1 (1%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	HYPOXIA	1 (1%)

Please refer to the PLX3397 Investigator's Brochure (version 6 dated October 27, 2014) for more detailed information.

One patient experienced constrictive pericarditis. The finding was seen on one echocardiogram and resolved on the first follow-up echocardiogram 2 weeks later. This patient had cancer cells in the fluid around the heart, which may have contributed to the inflammation. The study doctor could not rule out the possibility of this event being related to study drug.

12.0 Statistical Considerations

12.1 Endpoint Definitions

Phase I

The study will follow a standard dose-escalation schema (Phase Ib portion) with 3 to 6 patients per cohort (3+3 design). The starting dose level will consist of PLX3397 600 mg. Enrollment to successive cohorts up to dose Level 2 will be performed according to the table shown below, to establish the MTD. If 2 or more dose-limiting toxicities (DLTs) are observed at level 0, one dose reduction (to Level -1) is built in to the study design. All patients at a given dose level will be followed on treatment for at least 3 weeks before accrual to the next cohort can commence. There will be no intra-patient dose escalation allowed. For any dose cohort, if a patient is removed from study for reasons that are clearly not treatment-related, then an additional patient will be accrued to that dose level.

Dose Escalation Schedule		
	Dose	
Dose Level	PLX3397	Eribulin

Dose Escalation Schedule		
Level -2	400 mg (200 mg BID)	0.7 mg/m2, 2-5 min IV Day 1, 8 q21 days
Level -1	400 mg (200 mg BID)	1.1 mg/m2, 2-5 min IV Day 1, 8 q21 days
Level 0 (starting dose)	600 mg (400 mg AM; 200 mg PM)	1.4 mg/m2, 2-5 min IV Day 1, 8 q21 days
Level 1	800 mg (400 mg BID)	1.4 mg/m2, 2-5 min IV Day 1, 8 q21 days
Level 2	1000 mg (600 mg AM; 400 mg PM)	1.4 mg/m2, 2-5 min IV Day 1, 8 q21 days

Phase II

The Phase II portion will begin after MTD is determined and we will enroll a total of 56 patients with TNBC to evaluate the safety and efficacy of the proposed treatment. Patients will be treated until clinical or radiographic disease progression or cumulative toxicity. Patients will be evaluated regularly in clinic with history, physical examination, and CT scans every 6 weeks. Visits will take place weekly during the first cycle (one cycle = 21 days) of study treatment, and then on day 1 and 8 of every 3 week cycle during the second cycle and beyond.

For Phase II, sample size is based under the Simon's 2-stage optimal design for progression-free survival at 3 months as a single proportion. The study is designed to determine the following hypothesis with >80% power and 2-sided type I error of 5% using binomial approximation: H0: PFS% <39% versus Ha: PFS% > 57% (with PLX3397), where PFS% is the proportion of progression-free (PFS) at 3 months. The PFS% of >57% would represent a clinically relevant improvement with the treatment in triple-negative patients with locally recurrent or metastatic breast cancer. Based on these considerations, a sample size of 51 evaluable patients is required for the study. We plan for a targeted enrollment of 56 patients with 10% dropout rate.

Interim assessment and stopping rules for Safety and efficacy

Safety and SAE data will be routinely monitored. Because of the possibility of unacceptable or excessive defined serious adverse events during treatment or the study enrollment period, stopping rules for safety/tolerability are also developed. We have set the maximum rate of treatment-related SAE at 15% in patient enrollment. Thus, we may consider terminating the study if the number of patients with SAE is greater than the number expected under the binomial distribution. The following table shows the early stopping guideline based on the number of SAE observed under the rate of unacceptable SAE in the group sequential enrolment for the study. For example, assuming the unacceptable rate of SAE is greater than 15%, if the study observes 3 or more SAE in the first 17 treated patients, then we may consider if the study should be stopped early.

Safety Stopping Rules:
Number of enrolled patients with excessive SAE to consider early study termination.

Number patients in study	1-17	18-29	30-41
Unacceptable SAE – 15%	3	4	6

Efficacy Stopping Rules
Failure to obtain early responses at the scheduled tumor assessments will be taken as evidence that the regimen in question is ineffective. If fewer than 8 out of the first 20 pts are progression-free at 12 weeks, this would be considered an unacceptably low PFS rate (<39%), the study will not continue and accrual will cease. Accrual will contiue while efficacy data is being determined. If 25 or fewer pts are progression free at 12 weeks at full accrual, then the treatment would be deemed ineffective. If the true PFS rate at 12 weeks is 39% for TNBC pts, the probability of terminating the study during the interim evaluation is 0.63; if the true PFS rate is 57% for TNBC pts, the probability that the trial will be stopped in the first stage is 0.10.

12.2 Analysis Plan

Primary Efficacy Endpoint

Demographics and Baseline Characteristics
Demographic data (age, sex, race, ethnicity, body weight) and baseline disease characteristics will be tabulated and summarized and presented in data listings.

Progression Free Survival
Progression-free survival at 3 months (PFS) is defined as the proportion of patients alive and progression-free 90 days after Study Day 1. Duration of PFS is defined as the time from Study Day 1 to the earlier of disease progression or death due to any cause.

Progression free survival will be calculated from the first administration of PLX3397 with eribulin. The analyses of PFS will be performed using the Per Protocol population. These analyses are designed to include only objective progression events per the RECIST v1.1 criteria. Patients who do not have any post-baseline tumor assessments will be right censored on the date of Study Day 1. Patients who receive subsequent anti-cancer therapy before experiencing an event will be right censored at the date of the last tumor assessment prior to the date of initiation of subsequent therapy. Patients who have not experienced an event (and are not otherwise censored) at the time of data cutoff will be right censored on the date of their last tumor assessment

PFS will be estimated as a simple proportion based upon the results of the 12-week tumor assessment. Patients for whom this assessment is not performed will be included as failures, even if known to be alive at this timepoint. Confidence intervals will be provided. PFS and duration of PFS will also be estimated using Kaplan-Meier methods with associated confidence intervals.

Secondary and Supportive Efficacy Endpoints

Objective Response Rate
The objective response rate (ORR) is defined as the proportion of patients for whom the best overall response at the time of data cutoff is confirmed CR or confirmed PR as assessed per RECIST v 1.1criteria. A table defining the derivation of best overall response to be applied will be provided in the SAP.

The analysis of ORR will employ the Per Protocol population. Patients who do not have any post-baseline tumor assessments will be counted as non-responders.

Point estimates of ORR and confidence intervals will be provided. As a basic measure of dose-response, ORR in the escalation phase will also be presented by dose cohort. Objective response will be assessed using the RECIST v 1.1 response criteria. The response will be collected on CRFs. The number and percent of subjects with each type of response will be summarized and presented in data listings. A 95% confidence interval will also be calculated using exact bionomial method. The 95% confidence interval for the difference in objective response rates will be calculated using exact binomial method. Time to onset of the response and duration of response will be also summarized using descriptive statistics.

Duration of Response
Duration of response is defined as the time from first documentation of objective response that is subsequently confirmed to PD by the criteria or death due to any cause. Responders who have not been documented to have progressed or died at time of data cutoff will be right censored at the last available adequate tumor assessment. Median duration of response for each treatment arm and its associated confidence interval will be estimated using the Kaplan-Meier method.

Time to Progression
Time to progression will be estimated using the Kaplan-Meier method. Efficacy responses, disease progression and relapse classified based on RECIST v1.1 criteria will be used to determine progression. Time to progression will be calculated from the first administration of PLX3397 with eribulin. Patients who do not have disease progression will be censored at the date of the last evaluation for study disease or at the time of initiation of the new therapy, whichever is earlier. Patients lacking any response assessment after randomization will be censored at Day 1.

12.3 Accrual Objectives

Phase I
A minimum of 12 patients will enroll in the Phase I trial, following a 3+3 design for 3 cohorts. We estimate that 10 patients will enroll at UCSF, and 7 patients each at Duke and Vanderbilt.
Phase I completed at UCSF with 28 patients enrolled as 03/10/2015

Phase II
This study will enroll 56 patients (n=22 in the first stage and n=34 in the second stage) in the Phase II portion with the assumed 10% dropouts. We estimate that 26 patients will enroll at UCSF and 15 each at Vanderbilt and Duke.

12.4 Estimated Duration of Study

The Phase I study is expected to complete accrual within 1.25 years, and the Phase II study is expected to complete accrual over a time course of 2.5 years.

12.5 Data Safety Monitoring

See Section 16.0.

12.6 Replacement Policy

Phase I
For any dose cohort, if a patient is removed from study for reasons that are clearly not treatment-related, then an additional patient will be accrued to that dose level.

Phase II
Patients who have no evaluation measures after starting therapy, and stop therapy for reasons other than progression or toxicity will be replaced. Patients who receive only one dose of eribulin or less than 14 days of PLX3397 for reasons other than progression or toxicity will be replaced.

12.7 Pharmacokinetic studies

Pharmacokinetic studies will be performed as outlined in section 14.4. Serum concentrations of PLX3397 with eribulin will be assessed by ELISA at Plexxikon Inc. and will be used to calculate the values of PK parameters, including maximum serum drug concentration (Cmax), area under the concentration-time curve from time zero to infinity (AUC 0-inf), systemic clearance (CL), volume of distribution (V), and elimination half-life (t1/2). Descriptive statistics (including number, mean and/or median, standard deviation, and coefficient of variation) will be used to describe the concentration time data. Where appropriate, these data may be combined with data from other studies as part of a metaanalysis. The influence of exposure on clinical safety parameters (e.g., selected AEs) will be explored. Results of the PK analysis will be evaluated in conjunction with available safety and pharmacodynamic data.

12.7 Correlative studies

Due to the small sample sizes expected from the proposed study design, the correlative studies will be hypothesis generating, but will also help provide pilot data to inform eligibility and follow up of future trials using an MO□targeting strategy. CSF1 levels will be analyzed as a continuous variable and categorical variable based on median CSF change with treatment. Mean and 95% confidence intervals of CSF1 levels will be estimated and compared for differences between dose cohorts. As a continuous measure, ANOVA and Pearson correlation will compare CSF1 levels between PLX3389 dose cohorts and response groups. As a categorical measure, Chi-square tests will determine the associations between tumor subtype (molecular profile) and immune profile (dichotomous variable) and between tumor molecular profile and CSF1 groups. FACS analysis of leukocyte populations as a percent of total CD45+ cells will be evaluated among the outcome groups, PFS and ORR. The relationship between mean and median immune infiltrate and continuous quantitative measurements of tumor classification will be reported using either parametric (Pearson) and Fisher's exact tests or nonparametric (Spearman) correlation coefficients and Rank tests and 95% confidence intervals for each statistic.

13.0 Data Collection and Management

The Study Chair and/or her designee, will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Study specific Case Report Forms (CRFs) will document safety and treatment outcomes for safety monitoring and data analysis. All study data will be entered into OnCore® via standardized CRFs in accordance with the CTMS study calendar, using single data entry with a secure access account. The

Clinical Research Coordinator (CRC) will complete the CRFs as soon as possible upon completion of the study visit; the Investigator will review and approve the completed CRFs.

Each participating site will complete study specific CRFs for safety monitoring and data analysis. Each site will enter the study data into OnCore® via standardized CRFs in accordance with the CTMS study calendar, using single data entry with a secure access account. The participating site's Clinical Research Coordinator (CRC) will complete the CRFs; the Investigator will review and approve the completed CRFs – this process must be completed within 3 business days of the visit. Study data from the participating site will be reported and reviewed in aggregate with data from patients enrolled at the coordinating center, UCSF. All source documentation and CTMS data will be available for review/monitoring as needed.

The information collected on CRFs shall be identical to that appearing in original source documents. Source documents will be found in the patient's medical records maintained by UCSF personnel. All source documentation should be kept in separate research folders for each patient.

In accordance with federal regulations, the Investigator is responsible for the accuracy and authenticity of all clinical and laboratory data entered onto CRFs. The Study Chair will approve all completed CRFs to attest that the information contained on the CRFs is true and accurate.
All source documentation and CTMS data will be available for review/monitoring by Plexxikon or the designated CRO and regulatory agencies.

The Study Chair will be responsible for ensuring the accurate capture of study data. At study completion, when the CRFs have been declared to be complete and accurate, the database will be locked. Any changes to the data entered into the CRFs after that time can only be made by joint written agreement among the Study Chair, the Trial Statistician, and the Protocol Project Manager.

14.0 Correlative studies

14.1 Tumor biopsies

Tumor biopsies will be obtained from accessible tumor tissue following the guidelines provided below before treatment start in all eligible patients. Patients enrolled on the Phase II trial will be asked to have a second core biopsy or FNA, depending on ease and site of biopsy. Patients who refuse the second biopsy will be allowed to stay on study treatment. Every attempt will be made to obtain tumor tissue at the time of a clinical procedure, if possible. Patients with lung only metastases will not be required to have biopsies, but will be allowed to enroll on this trial.

Core biopsies of the breast will be performed by a qualified radiologist or surgeon, according to institutional guidelines for a diagnostic biopsy. Biopsies of other sites may be done by radiology, pathology or qualified surgeons. When required, radiographic coordination will be arranged. Tissue specimens will be collected from recurrent or metastatic lesions using standard institutional procedures. The goal is to obtain 2 to 4 core needle biopsies using an 18 gauge needle. If a fine needle aspiration is performed, 3-6 passes should be obtained. Less than the goal amount of tissue is acceptable, and should be based upon the clinical judgment of the

Investigator and the clinician performing the procedure. The study coordinator will be present at the time of the biopsy to collect and process the tissue samples. Samples will be delivered to the laboratory of [redacted]. Specific processing and delivery instructions will be provided to all sites in the Laboratory Manual, which contains all details for specimen processing and handling.

14.2 CSF1 levels

Patients on both trials will have CSF1 levels drawn to assess the impact of PLX3397. 5 cc of blood will be obtained in a serum separator tube. For patients on the phase I trial, CSF1 levels will be drawn at Cycle 1, days 1 and 2, and Cycle 2, day 1. For patients on the phase II trial, CSF1 levels will be drawn at the start of the PLX3397 lead-in, at day 5 to 7 before the start of eribulin, at Cycle 1, day 1, and Cycle 2, day 1.

14.3 Blood for leukocyte subtyping

Blood will be drawn for flow cytometric analysis at baseline for patients in phase I, and at day -7/5 and day 0/1 for patients on the phase II trial. 10 cc of blood will be drawn into an EDTA tube and evaluated by flow cytometry. Processing will take place at each site. See Lab Manual for more details.

14.4 Pharmacokinetic sampling

Limited pharmacokinetic sampling will be performed in the phase I portion of this trial. PK sampling will occur on C1D1 (pre-PLX3397 administration and at 1, 2, 5, and 24 hours post treatment and on C2D1 (pre-PLX3397 administration and at 2 hours post treatment). Serum concentrations of PLX3397 with eribulin will be assessed by ELISA at Plexxikon Inc. and will be used to calculate the values of PK parameters, including maximum serum drug concentration (Cmax), area under the concentration-time curve from time zero to infinity (AUC 0-inf), systemic clearance (CL), volume of distribution (V), and elimination half-life (t1/2). Descriptive statistics (including number, mean and/or median, standard deviation, and coefficient of variation) will be used to describe the concentration time data. Where appropriate, these data may be combined with data from other studies as part of a metaanalysis. The influence of exposure on clinical safety parameters (e.g., selected AEs) will be explored. Results of the PK analysis will be evaluated in conjunction with available safety and pharmacodynamic data.

Blood Collection

Approximately 5 mL of blood will be collected via peripheral venipuncture into a lithium heparin tube. This blood sample will be used to measure concentrations of PLX3397 for each PK blood collection, as noted in the Study Calendar. Samples will be collected, processed and stored according to the study-specific laboratory manual.

Blood samples for PK analysis should be collected at the requested time but within a ±15 minute window (or ± 30 minute window where specified) of the requested time. The exact actual time of collection should be noted in the source documents and eCRFs.

Bioanalytical Methodology
The plasma samples will be analyzed for PLX3397 by using a validated method (high performance liquid chromatography (HPLC) with tandem quadruple mass spectrometric detection) of appropriate specificity and sensitivity.

14.5. Archival tumor samples

All patients will be asked to provide a sample of their original tumor pathology, if it is available.

14.6 Details of the correlative studies

The main goal of the correlative studies accompanying this trial will be to identify tissue and serum biomarkers capable of 1) predicting likelihood of response to macrophage-targeted therapy, or 2) providing an early indication of response to PLX3397 treatment likely to be seen at 12 wks of therapy. Both predictive and response biomarker assessment of tissue (core biopsy or FNA) and blood will be conducted as previously described[76, 77]. Phase I studies will be performed on all tumor subtypes, while Phase II studies will be performed on pts with TNBC. The lead-in period in Phase II will allow evaluation of the effect of PLX3397 alone on serum CSF1 levels and leukocyte subsets in blood and tissue prior to administration of eribulin.

14.6.1 Evaluation of baseline biomarkers most likely to predict response to MØ-targeted therapy

We will establish baseline values and variability of immune, and CSF1 measures in pts enrolled in phase I and phase II trials, and correlate these measures to magnitude of change in serum CSF1 levels and clinical response. Pts will be categorized as "good" or "poor" responders based on median change in serum CSF1, clinical response based in RECIST v1.1 imaging criteria at 12 wks and TTP. We will determine whether the tumor phenotype (ER, PR, HER2, and ki67), immune signature (CD68lo/CD4lo/CD8hi vs. CD68hi/CD4hi/CD8lo) and CSF1 signature at initial diagnosis (obtained from archived tumor blocks) correlates with response. In addition, we propose to explore whether the baseline immune and CSF1 signature differ between the early stage setting (derived from ongoing studies) and pts with MBC enrolled on this trial.

14.6.2 Evaluation of dynamic tissue and blood biomarkers most likely to show early biologic changes that predict clinical response

Identify whether leukocyte subpopulations are altered with PLX3397 treatment alone in a cohort of pts with metastatic TNBC. The lead-in design of the trial will allow evaluation of systemic response to PLX3397 alone in the absence of systemic chemotherapy (CTX). We will determine whether this single-agent therapy modulates leukocyte complexity in blood, with serum CSF1 measured between day -7/-5 and day 0/1. In addition, if ongoing studies demonstrates that core biopsy or FNA can reliably recapitulate the immune signature obtained from surgical samples, repeat biopsies will be used to determine whether immune infiltrate in tissue is modulated with PLX3397 treatment. This will provide confirmation that PLX3397 results in the expected macrophage, DC and T cell modulation at the tissue level.

14.6.3 Determine magnitude of change in serum CSF1

Determine whether magnitude of change in serum CSF1 is associated with: 1) dose levels of PLX3397 and 2) response to therapy. For patients on the phase I trial, CSF1 levels will be

drawn at Cycle 1, days 1 and 2, and Cycle 2, day 1. For patients on the phase II trial, CSF1 levels will be drawn at the start of the PLX3397 lead-in, at day 5 to 7 before the start of eribulin, at Cycle 1, day 1, and Cycle 2, day 1.. Baseline CSF1 and magnitude of change in CSF1 will be correlated to dose of PLX3397 and treatment response group.

15.0 Reporting Adverse Drug Reactions

15.1 Adverse Event Definitions

Adverse Event

An adverse event (also known as an adverse experience) is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. More specifically, an adverse event (can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. An adverse event can arise from any use of the drug (e.g., off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose.

Adverse reaction

An adverse reaction is defined as any adverse event caused by the use of a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event.

Suspected

A suspected adverse reaction is defined as any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, "reasonable possibility" indicates that there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.

Unexpected

An adverse event or suspected adverse reaction is considered *unexpected* if it is not listed in the investigator brochure or package insert(s), or is not listed at the specificity or severity that has been observed, or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application.

"Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

Adverse events that would be anticipated to occur as part of the disease process are considered *unexpected* for the purposes of reporting because they would not be listed in the investigator brochure. For example, a certain number of non-acute deaths in a cancer trial would be anticipated as an outcome of the underlying disease, but such deaths would generally not be listed as a suspected adverse reaction in the investigator brochure.

Some adverse events are listed in the Investigator Brochure as occurring with the same class of drugs, or as anticipated from the pharmacological properties of the drug, even though they have not been observed with the drug under investigation. Such events would be considered *unexpected* until they have been observed with the drug under investigation. For example, although angioedema is anticipated to occur in some patients exposed to drugs in the ACE inhibitor class and angioedema would be described in the investigator brochure as a class effect, the first case of angioedema observed with the drug under investigation should be considered *unexpected* for reporting purposes.

Serious

An adverse event or suspected adverse reaction is considered *serious* if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- Life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life function
- Congenital anomaly/birth defect

Important medical events that may not result in death, are life-threatening, or require hospitalization may be considered serious when, based upon appropriate 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. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Life-threatening

An adverse event or suspected adverse reaction is considered *life-threatening* if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

15.2 Recording of an Adverse Event

During Phase Ib, all adverse events will be entered into OnCore®, whether or not the event is believed to be associated with use of the study drug. During Phase II, all grade 3 and above adverse events will be entered into OnCore®, whether or not the event is believed to be associated with use of the study drug. Data about these events and their severity will be recorded using the NCI CTCAE v4.0.

The Investigator will assign attribution of the possible association of the event with use of the investigational drug, and this information will be entered into OnCore® using the classification system listed below:

Relationship	Attribution	Description
Unrelated to investigational drug/intervention	Unrelated	The AE *is clearly NOT related* to the intervention
	Unlikely	The AE *is doubtfully related* to the intervention
Related to investigational drug/intervention	Possible	The AE *may be related* to the intervention
	Probable	The AE *is likely related* to the intervention
	Definite	The AE *is clearly related* to the intervention

Signs or symptoms reported as adverse events will be graded and recorded by the Investigator according to the CTCAE. When specific adverse events are not listed in the CTCAE they will be graded by the Investigator as *none*, *mild*, *moderate* or *severe* according to the following grades and definitions:

Grade 0 No AE (or within normal limits)

Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated

Grade 2 Moderate; minimal, local, or noninvasive intervention (e.g., packing, cautery) indicated; limiting age-appropriate instrumental activities of daily living (ADL)

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL

Grade 4: Life-threatening consequences; urgent intervention indicated

Grade 5: Death related to AE

15.3 Follow-up of Adverse Events

Reportable SAEs are those that occur after the first dose of PLX3397 and until 21 days after the last dose of combined therapy. All adverse events will be followed with appropriate medical management until resolved. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. For selected adverse events for which administration of the investigational drug was stopped, a re-challenge of the subject with the investigational drug may be conducted if considered both safe and ethical by the Investigator.

15.4 Adverse Events Monitoring

The Investigator will assess all adverse events and determine reportability requirements to the UCSF Data and Safety Monitoring Committee (DSMC); UCSF's Institutional Review Board, the Committee on Human Research (CHR); and to the Food and Drug Administration (FDA) if it meets the FDA reporting criteria.

Adverse events entered into OnCore® will be reviewed by the Helen Diller Family Comprehensive Cancer Center Site Committee on a weekly basis during Phase Ib and on a monthly basis during Phase II. The Site Committee will review and discuss at each meeting the selected toxicity, the toxicity grade, and the attribution of relationship of the adverse event to the administration of the study drug(s).

In addition, all adverse events and suspected adverse reactions considered "serious," entered into OnCore® will be reviewed and monitored by the Plexxikon or the designated CRO every six (6) weeks, and prior to dose escalation. At the time of dose escalation, a written report will be submitted to the DSMC Chair (or qualified alternate) describing the cohorts, dose levels, adverse events, safety reports, and any Dose Limiting Toxicities observed, in accordance with the protocol. The report will be reviewed by the DSMC Chair (or qualified alternate). Approval for the dose escalation by the DSMC must be obtained prior to implementation. For a detailed description of the Data and Safety Monitoring Plan please see section 16.

15.5 Expedited Reporting

Participating Sites Reporting to Sponsor-Investigator (UCSF)

In addition to complying with all applicable regulatory reporting laws and regulations, each site will report the following information in writing to the Sponsor-Investigator within one business day of the Investigator's awareness of occurrence:

- All SAEs
- Reports of pregnancy exposure (pregnancy encompasses the entire course of pregnancy and delivery, perinatal and neonatal outcomes, even if there were no abnormal findings; both maternal and paternal exposure is collected);
- Reports of lactation exposure;
- Overdose (with or without an SAE);
- Abuse (use for non-clinical reasons with or without an SAE);
- Inadvertent or accidental exposure; and
- Follow-up information regarding any of the above.
- The participating investigator should include his or her assessment of the causal relationship between each SAE and the Grantor product.

Reports will include the cover page provided, and reference the Protocol Number.

A copy of the report should be sent to the coordinating center CRC at UCSF. Information will be provided.

Sponsor-Investigator Reporting to the Data and Safety Monitoring Committee

If a death occurs during the treatment phase of the study or within 30 days after the last administration of the study drug(s) and it is determined to be related either to the study drug(s) or to a study procedure, the Investigator or his/her designee must notify the DSMC Chair (or qualified alternate) within 1 business day of knowledge of the event. The contact may be by phone or e-mail.

Sponsor-Investigator Reporting to UCSF Committee on Human Research (Institutional Review Board)

The Sponsor-Investigator must report events meeting the UCSF CHR definition of "Unanticipated Problem" (UP) within 5 business days of his/her awareness of the event.

Sponsor-Investigator Expedited Reporting to the Food and Drug Administration

The Sponsor-Investigator is responsible for determining whether or not the suspected adverse reaction meets the criteria for expedited reporting in accordance with Federal Regulations (21 CFR §312.32).

The Sponsor-Investigator must report in an IND safety report any suspected adverse reaction that is both serious and unexpected. The Sponsor-Investigator needs to ensure that the event meets all three definitions:

- Suspected adverse reaction (as defined in 6.1.30)
- Unexpected (as defined in 0)
- Serious (as defined in 6.1.5)

If the adverse event does not meet all three of the definitions, it should not be submitted as an expedited IND safety report.

The timeline for submitting an IND safety report to FDA is no later than **15 calendar days** after the Investigator determines that the suspected adverse reaction qualifies for reporting (21 CFR 312.32(c)(1)).

Any unexpected fatal or life-threatening suspected adverse reaction will be reported to FDA no later than **7 calendar days** after the Investigator's initial receipt of the information (21 CFR 312.32(c)(2)).

Any relevant additional information that pertains to a previously submitted IND safety report will be submitted to FDA as a Follow-up IND Safety Report without delay, as soon as the information is available (21 CFR 312.32(d)(2)).

Sponsor-Investigator Reporting to Pharmaceutical Companies Providing Study Drug

The Sponsor-Investigator will report all Serious Adverse Events (SAEs) that occur during the SAE reporting period to the investigational drug manufacturer (Plexxikon) within 24 hours after first becoming aware of the event (immediately if the event is fatal or life-threatening). The Coordinating Center will report the SAE using an FDA MEDWATCH form and the *Serious Adverse Event Fax Cover Sheet* provided by the pharmaceutical partners for this trial. Events should be reported as soon as they are determined to meet the definition of an SAE, even if complete information is not yet available.

The medical monitor contact information for Plexxikon is listed below:

Follow-Up Information. Coordinating center and participating sites will assist the pharmaceutical partners in investigating any SAE and will provide any reasonable follow-up information requested.

15.6 Reporting DLTs

The investigator at the originating site must report suspected DLTs to the Study Chair or designee immediately, not more than 24 hours after awareness of the event. The Study Chair will determine whether the event meets the protocol criteria for DLT and may consult with the monitoring CRO, DSMC, UCSF Phase I Site Committee, and/or co-investigators to do so. All investigators and the CRC at both sites will be notified immediately if a DLT determination is made. Dose level assignments for any patients scheduled to begin treatment and cohort expansion must be determined as per protocol criteria by the Study Chair or designee based upon the new DLT results. See Section 5.0 for dose escalation rules and decision process.

The coordinating center CRC will utilize the CTMS to track enrollment of subject(s) at each dose level, as well as dose limiting toxicities (DLTs).

16.0 Data Safety Monitoring Plan

16.1 Oversight and Monitoring Plan

Under the IND Transfer of Obligations executed between UCSF and Plexxikon, Plexxikon will monitor all clinical investigations. The UCSF-CCC Data Safety Monitoring Committee (DSMC) will review the monitoring SOPs and subsequent monitoring reports from Plexxikon or the designated CRO. The DSMC will not be involved in the direct monitoring or auditing of this trial. DSMC activities for this study includes:

- Review of subject data in each cohort
- Review of suspected adverse reactions considered "serious"

16.2 Monitoring and Reporting Guidelines

All institutional Phase Ib therapeutic studies are designated with a high risk assessment. All subject data will be monitored at 6 week intervals data by the designated CRO. At the time of dose escalation, a written report will be submitted to the DSMC Chair outlining the cohort dose, all adverse events and suspected adverse reactions considered "serious," and any Dose Limiting Toxicity as described in the protocol. The report will be reviewed by the DSMC Chair or qualified alternate. Written authorization to proceed will be granted by the DSMC.

The Principal Investigator at the UCSF Coordinating Center will hold the role of Study Chair. The Study Chair is responsible for the overall conduct of the study and for monitoring its safety and progress at all participating sites. During Phase 1, the Study Chair will conduct continuous review of data and subject safety and discuss each subject's treatment at weekly UCSF Site Committee meetings. During Phase 2, the Study Chair will conduct continuous review of data and subject safety and discuss each subject's treatment at monthly UCSF Site Committee meetings. The discussions are documented in the UCSF Site Committee meeting minutes. For each dose level, the discussion will include the number of patients, significant toxicities in accordance with the protocol, doses adjustments, and observed responses.

Dose Level Considerations

The PI/Study Chair, participating investigators, and research coordinators from each site will review enrollment for each dose level cohort during the regularly scheduled conference calls. The dose level for ongoing enrollment will be confirmed for each subject scheduled to be enrolled at a site. Dose level assignments for any subject scheduled to begin treatment must be confirmed by the UCSF Coordinating Center via fax or e-mail.

If a Dose Limiting Toxicity (DLT) arises in a subject treated at a study site, all sites must be notified immediately by the UCSF Coordinating Center. The Study Chair has 1 business day (after first becoming aware of the event at either the UCSF Coordinating Center or the participating site) in which to report the information to all participating sites. If the DLT occurs at a participating site, the local investigator must report it to the UCSF Coordinating Center within **1 business day**, after which the UCSF Coordinating Center will notify the other participating sites.

16.3 Review and Oversight Requirements

Adverse Event Monitoring

During Phase 1, all clinically significant adverse events (AEs), whether or not unexpected, and whether or not considered to be associated with the use of study drug, will be entered into OnCore®, UCSF's Clinical Trial Management System. During Phase 2, all clinically significant grade 3 and above adverse events (AEs), whether or not unexpected, and whether or not considered to be associated with the use of study drug, will be entered into OnCore®, UCSF's Clinical Trial Management System.

During Phase 1, all clinically significant adverse events entered into OnCore® will be reviewed on a weekly basis at the UCSF Coordinating Center's Site Committee. During Phase 2, all clinically significant grade 3 and above adverse events entered into OnCore® will be reviewed on a monthly basis at the UCSF Coordinating Center's Site Committee, All clinically significant adverse events must be reported to the UCSF Coordinating Center by the participating sites within **10 business days** of becoming aware of the event. The Site Committee will review and discuss the selected toxicity, the toxicity grade, and the attribution of relationship of the adverse event to the administration of the study drug(s).

For Phase I patients, toxicity data must be entered into OnCore® by noon (Pacific Standard Time) on Wednesday of each week for review by Site Committee at UCSF.

For Phase II patients, toxicity data must be entered into OnCore® by noon (Pacific Standard Time) of the second Monday of each month for review by Site Committee at UCSF.

In addition, all suspected adverse reactions considered "serious" are entered into OnCore® and will be reviewed and monitored by the Data and Safety Monitoring Committee on an ongoing basis and discussed at the DSMC meetings, which take place every six (6) weeks.

All suspected adverse reactions considered "serious" should be reported to the UCSF Coordinating Center within **1 business day** of becoming aware of the event or during the next scheduled conference call, whichever is sooner.

If a death occurs during the treatment phase of the study or within 30 days after the last administration of the study drug(s) and is determined to be related either to the investigational drug or any research related procedure, the Study Chair at the UCSF Coordinating Center or the assigned designee must be notified within **1 business day** from the participating site(s) and the Study Chair must then notify the DSMC Chair or qualified alternate within **1 business day** of this notification. The contact may be by phone or e-mail.
UCSF Data and Safety Monitoring Committee Contacts:

DSMC Chair: [redacted]

[redacted] Study Management

17.1 Pre-study Documentation

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki as stated in 21 CFR §312.120(c)(4); consistent with GCP and all applicable regulatory requirements.

Before initiating this trial, the Investigator will have written and dated approval from the Institutional Review Board for the protocol, written informed consent form, subject recruitment materials, and any other written information to be provided to subjects before any protocol related procedures are performed on any subjects.

The clinical investigation will not begin until either FDA has determined that the study under the Investigational Drug Application (IND) is allowed to proceed.

The Investigator must comply with the applicable regulations in Title 21 of the Code of Federal Regulations (21 CFR §50, §54, and §312), GCP/ICH guidelines, and all applicable regulatory requirements. The IRB must comply with the regulations in 21 CFR §56 and applicable regulatory requirements.

17.2 Independent Ethics Committees/Institutional Review Board

This protocol and the informed consent will be approved by the Committee on Human Research (the UCSF IRB). The Principal Investigator is responsible for keeping the IRB advised of the progress of the study and of any changes made in the protocol. The Principal Investigator will also keep the IRB informed of any significant adverse reactions, and any protocol exceptions or deviations. Records of all study review and approval documents must be kept on file by the

Principal Investigator and are subject to FDA inspection during or after completion of the study. The IRB will receive notification of the termination of the study.

17.3 Informed Consent

All participants must be provided a consent form describing the study with sufficient information for each participant to make an informed decision regarding their participation. Participants must sign the CHR-approved informed consent form prior to participation in any study specific procedure. The participant must receive a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

17.4 Oversight and Monitoring Plan

This study is a multi-institution, investigator-initiated trial which will be coordinated by UCSF and conducted at both the UCSF Helen Diller Family Comprehensive Cancer Center (HDFCCC) and the participating site. The Principal Investigator at the coordinating center (UCSF) holds the role of Study Chair. The responsibilities of the Study Chair are described in the Code of Federal Regulations (Title 21, Subpart D, 312.50 through 312.69).

The UCSF Coordinating Center provides administration, data management, and organizational support for the participating sites in the conduct of a multicenter clinical trial. The UCSF Coordinating Center will also coordinate, at minimum, biweekly (during Phase 1) or monthly (during Phase 2) conference calls with the participating sites at the completion of each cohort or more frequently as needed to discuss risk assessment. The following issues will be discussed as appropriate:

- Enrollment information
- Cohort updates (i.e. DLTs)
- Adverse events (i.e. new adverse events and updates on unresolved adverse events and new safety information)
- Protocol violations
- Other issues affecting the conduct of the study

The coordinating center CRC will insure that participating sites are notified of safety events.

Questions regarding the study or reporting of adverse events may be directed to the designated coordinating center (UCSF) CRC (contact information to be provided by the start of study). [redacted]

[redacted] the IND Transfer of Obligations executed between UCSF and Plexxikon, Plexxikon or a designated CRO will monitor all clinical investigations. The DSMC will not be involved in the monitoring and auditing of this trial. Please refer to Section 16.0 for additional details.

17.5 Coordinating Center Processing and Documenting FDA Correspondence

This study will be conducted under an IND #114838 held by the Sponsor-Investigator. A copy of all files pertaining to this IND will also be maintained by the centralized regulatory staff of the HDFCCC. It is the responsibility of the Study Chair to relay to HDFCCC centralized regulatory staff any correspondence to or from the FDA regarding the IND.

17.6 Record Keeping and Record Retention

The Principal Investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects, as well as written records of the disposition of the drug when the study ends.

The Principal Investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

Study documentation includes all CRFs, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, CHR correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

In accordance with FDA regulations, the investigator shall retain records for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.

17.7 Regulatory Documentation

Prior to implementing this protocol at UCSF HDFCCC, the protocol, informed consent form, HIPAA authorization and any other information pertaining to participants must be approved by the UCSF Committee on Human Research (CHR). Prior to implementing this protocol at the participating sites, approval for the UCSF CHR approved protocol must be obtained from the participating site's IRB.

The following documents must be provided to UCSF HDFCCC before the participating site can be initiated and begin enrolling participants:

- Participating Site IRB approval(s) for the protocol, appendices, informed consent form and HIPAA authorization
- Participating Site IRB approved consent form
- Participating Site IRB membership list
- Participating Site IRB's Federal Wide Assurance number and OHRP Registration number

- Curriculum vitae and medical license for each investigator and consenting professional
- Documentation of Human Subject Research Certification training for investigators and key staff members at the Participating Site
- Participating site laboratory certifications and normals

Upon receipt of the required documents, UCSF HDFCCC will formally contact the site and grant permission to proceed with enrollment.

17.8 Patient Enrollment

Patients can be registered only after the pretreatment evaluation is complete and all eligibility criteria have been met. Patients must meet all inclusion criteria and no exclusion criteria should apply. The patient must have signed and dated an approved, current version of all applicable consent forms.

The participating site should fax a completed eligibility checklist and all supporting source documentation to the designated coordinating center CRC at UCSF (contact information to be provided by the start of study). The CRC will check the forms for completeness and contact the participating site with any discrepancies. Eligibility must be confirmed by the Study Chair, or designee before patient ID number is assigned.

The coordinating center will provide a study-specific patient ID number to the participating site. All future study documentation related to that patient should include the assigned patient ID number.

17.9 Study Drug Supply and Accountability

Study drug will be shipped directly to the participating site from Plexxikon for direct distribution of the drugs to the study patients in accordance with the IND Transfer of Obligations executed between UCSF and Plexxikon. The participating site will be responsible for drug accountability at their site. Plexxikon CRAs will monitor the participating sites to ensure that appropriate records are kept regarding drug accountability. All documentation will be provided by Plexxikon CRA to the coordinating center. See Section 11 for specific instructions regarding study drug availability. Eribulin is FDA approved and should be available through the infusion center at each institution.

17.10 Coordinating Center Documentation of Distribution

It is the responsibility of the Study Chair to maintain adequate files documenting the distribution of study documents as well as their receipt (when possible). The HDFCCC recommends that the Study Chair maintain a correspondence file and log for each segment of distribution (e.g., FDA, drug manufacturer, participating sites, etc.).

Correspondence file: should contain copies (paper or electronic) of all protocol versions, cover letters, amendment outlines (summary of changes), etc., along with distribution documentation and (when available) documentation of receipt.

Correspondence log: should be a brief list of all documents distributed including the date sent, recipient(s), and (if available) a tracking number and date received.

At a minimum, the Study Chair must keep documentation of when and to whom the protocol, its updates and safety information are distributed.

17.10.1 Approval of Protocol and Amendments

All protocol amendments must be approved by the participating sites' IRBs within 90 days of receipt. Failure to do so can result in the suspension of study activities at that site.

Upon approval of the protocol or amendment by a participating site's IRB, a copy of the approval documentation must be submitted (electronically or in hard form) to the office of the Study Chair. Documentation of participating sites' protocol approvals will be maintained in the correspondence files by the Study Chair or his/her designee.

18.0 References

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Appendix 1: Strong CYP3A4 Inhibitors and Inducers

Strong Inhibitors	Strong Inducers
Protease inhibitors • Ritonavir • Indinavir • Nelfinavir Macrolide antibiotics • Erythromycin • Telithromycin • Clarithromycin Azole antifungals • Fluconazole • Ketoconazole • Itraconazole Chloramphenicol (antibiotic) Nefazodone (antidepressant) Bergamottin (constituent of grapefruit juice) Aprepitant (antiemetic) Verapamil (calcium channel blocker)	Anticonvulsants, mood stabilizers • Phenytoin • Carbamazepine • Oxcarbazepine Non-nucleoside reverse transcriptase inhibitors • Efavirenz • Nevirapine • Etravirine Phenobarbital (barbiturate) Rifampicin (bactericidal) Modafinil (stimulant) Hyperforin (constituent of St Johns Wort) Cyproterone (antiandrogen, progestin)

Appendix 2: Drugs With A Risk Of Torsades De Pointes

Generic Name	Brand Name	Class/Clinical Use	Comments
Amiodarone	Cordarone®	Anti-arrhythmic / abnormal heart rhythm	Females>Males,TdP risk regarded as low
Amiodarone	Pacerone®	Anti-arrhythmic / abnormal heart rhythm	Females>Males,TdP risk regarded as low
Arsenic trioxide	Trisenox®	Anti-cancer / Leukemia	
Bepridil	Vascor®	Anti-anginal / heart pain	Females>Males
Chloroquine	Aralen®	Anti-malarial / malaria infection	
Chlorpromazine	Thorazine®	Anti-psychotic/ Anti-emetic / schizophrenia/ nausea	
Cisapride	Propulsid®	GI stimulant / heartburn	No longer available in the U.S.; available in Mexico
Citalopram	Celexa®	Anti-depressant / depression	
Clarithromycin	Biaxin®	Antibiotic / bacterial infection	
Disopyramide	Norpace®	Anti-arrhythmic / abnormal heart rhythm	Females>Males
Dofetilide	Tikosyn®	Anti-arrhythmic / abnormal heart rhythm	
Droperidol	Inapsine®	Sedative;Anti-nausea / anesthesia adjunct, nausea	
Erythromycin	Erythrocin®	Antibiotic;GI stimulant / bacterial infection; increase GI motility	Females>Males
Erythromycin	E.E.S.®	Antibiotic;GI stimulant / bacterial infection; increase GI motility	Females>Males
Flecainide	Tambocor®	Anti-arrhythmic / abnormal heart rhythm	
Halofantrine	Halfan®	Anti-malarial / malaria infection	Females>Males
Haloperidol	Haldol®	Anti-psychotic / schizophrenia, agitation	When given intravenously or at higher-than- recommended doses, risk of sudden death, QT prolongation and torsades increases.
Ibutilide	Corvert®	Anti-arrhythmic / abnormal heart rhythm	Females>Males
Mesoridazine	Serentil®	Anti-psychotic / schizophrenia	
Methadone	Methadose®	Opiate agonist / pain control, narcotic dependence	Females>Males
Methadone	Dolophine®	Opiate agonist / pain control, narcotic dependence	Females>Males
Moxifloxacin	Avelox®	Antibiotic / bacterial infection	
Pentamidine	Pentam®	Anti-infective / pneumocystis pneumonia	Females>Males
Pentamidine	NebuPent®	Anti-infective / pneumocystis pneumonia	Females>Males
Pimozide	Orap®	Anti-psychotic / Tourette's tics	Females>Males
Procainamide	Pronestyl®	Anti-arrhythmic / abnormal heart rhythm	
Procainamide	Procan®	Anti-arrhythmic / abnormal heart	

Appendix 2: Drugs With A Risk Of Torsades De Pointes

Generic Name	Brand Name	Class/Clinical Use	Comments
		rhythm	
Quinidine	Cardioquin®	Anti-arrhythmic / abnormal heart rhythm	Females>Males
Quinidine	Quinaglute®	Anti-arrhythmic / abnormal heart rhythm	Females>Males
Sotalol	Betapace®	Anti-arrhythmic / abnormal heart rhythm	Females>Males
Sparfloxacin	Zagam®	Antibiotic / bacterial infection	
Thioridazine	Mellaril®	Anti-psychotic / schizophrenia	
Vandetanib	Caprelsa®	Anti-cancer / Thyroid cancer	
Fluconazole	Diflucan®	Anti-arrhythmic / abnormal heart rhythm	
Ciprofloxacin	Ciloxan, Cipro, Neofloxin	Anti-arrhythmic / abnormal heart rhythm	

Appendix 3: Drug Diaries

PLX3397 QD - Patient Drug Diary – Phase Ib, Cycle #____

CC#12751: Enhancing Efficacy of Chemotherapy in Triple Negative/Basal-Like Breast Cancer by Targeting Macrophages: A Phase Ib/II study of PLX 3397 and Eribulin in Patients with Metastatic Breast Cancer

Study Subject ID #:_____Patient Name: _____

Current Assigned dose: _____ **Start Date:**_____

Reminders:

- Study medication should be stored at room temperature (Temperature storage range 15-30 °C or 59-86 °F).
- Take your dose of study medication every24 hours (± 2 hours) If it is after 2 hours from when your dose was due, skip that dose and continue with the subsequent dose.Fast for at least 1 hour prior to taking the study medication and 1 hour after you take the study medication. You are allowed to have a low-fat, bland snack (crackers, toast, tea, etc.) if needed (if you are feeling nauseous or weak) during this 2 hour period.
- Medication should be taken with at least 8 ounces (1 cup) of room temperature water.
- Missed doses should be skipped and not taken as a double dose at the next dosing timepoint. If you vomit your dose, you should not make-up that dose or take extra study drug at the next dosing timepoint.
- Write down the time each dose is taken.
- Bring your study medication and study diary with you every time you visit the clinic.
- Contact your study doctor if you have any questions/concerns.

Patient Signature: _____

Cycle #	Day	Date mm/dd/yyyy	Time of Dose	Were you fasting before and after to your dose?(circle one)		# of capsules taken	Reason for missed dose
Cycle __	Day 1*	/ /		Before: Yes/No	After: Yes/No		
Cycle __	Day 2**	/ /		Before: Yes/No	After: Yes/No		
Cycle __	Day 3	/ /		Before: Yes/No	After: Yes/No		
Cycle __	Day 4	/ /		Before: Yes/No	After: Yes/No		
Cycle __	Day 5	/ /		Before: Yes/No	After: Yes/No		
Cycle __	Day 6	/ /		Before: Yes/No	After: Yes/No		
Cycle __	Day 7	/ /		Before: Yes/No	After: Yes/No		
Cycle __	Day 8	/ /		Before: Yes/No	After: Yes/No		
Cycle __	Day 9	/ /		Before: Yes/No	After: Yes/No		
Cycle __	Day 10	/ /		Before: Yes/No	After: Yes/No		
Cycle __	Day 11	/ /		Before: Yes/No	After: Yes/No		
Cycle __	Day 12	/ /		Before: Yes/No	After: Yes/No		

PLX3397 QD - Patient Drug Diary – Phase Ib, Cycle #____

CC#12751: Enhancing Efficacy of Chemotherapy in Triple Negative/Basal-Like Breast Cancer by Targeting Macrophages: A Phase Ib/II study of PLX 3397 and Eribulin in Patients with Metastatic Breast Cancer

Study Subject ID #:_____Patient Name: _____

Current Assigned dose: _____ **Start Date:**_____

Reminders:

- Study medication should be stored at room temperature (Temperature storage range 15-30 °C or 59-86 °F).
- Take your dose of study medication every24 hours (± 2 hours) If it is after 2 hours from when your dose was due, skip that dose and continue with the subsequent dose.Fast for at least 1 hour prior to taking the study medication and 1 hour after you take the study medication. You are allowed to have a low-fat, bland snack (crackers, toast, tea, etc.) if needed (if you are feeling nauseous or weak) during this 2 hour period.
- Medication should be taken with at least 8 ounces (1 cup) of room temperature water.
- Missed doses should be skipped and not taken as a double dose at the next dosing timepoint. If you vomit your dose, you should not make-up that dose or take extra study drug at the next dosing timepoint.
- Write down the time each dose is taken.
- Bring your study medication and study diary with you every time you visit the clinic.
- Contact your study doctor if you have any questions/concerns.

Patient Signature: _____

Cycle #	Day	Date mm/dd/yyyy	Time of Dose	Were you fasting before and after to your dose?(circle one)		# of capsules taken	Reason for missed dose
Cycle __	Day 13	/ /		Before: Yes/No	After: Yes/No		
Cycle __	Day 14	/ /		Before: Yes/No	After: Yes/No		
Cycle __	Day 15	/ /		Before: Yes/No	After: Yes/No		
Cycle __	Day 16	/ /		Before: Yes/No	After: Yes/No		
Cycle __	Day 17	/ /		Before: Yes/No	After: Yes/No		
Cycle __	Day 18	/ /		Before: Yes/No	After: Yes/No		
Cycle __	Day 19	/ /		Before: Yes/No	After: Yes/No		
Cycle __	Day 20	/ /		Before: Yes/No	After: Yes/No		
Cycle __	Day 21	/ /		Before: Yes/No	After: Yes/No		

* For Cycle 1 and Cycle 2, Day 1, do not take your morning dose of PLX3397 until you are instructed to do so during your clinic visit.

** For Day 2 of Cycle 1 ONLY, do not take your morning dose of PLX3397 until you are instructed to so during your clinic visit.

PLX3397 BID - Patient Drug Diary – Phase Ib, Cycle #____

CC#12751: Enhancing Efficacy of Chemotherapy in Triple Negative/Basal-Like Breast Cancer by Targeting Macrophages: A Phase Ib/II study of PLX 3397 and Eribulin in Patients with Metastatic Breast Cancer

Study Subject ID #:_____Patient Name: _____

Current Assigned dose: _____ **Start Date:**_____

Reminders:

- Study medication should be stored at room temperature (Temperature storage range 15-30 °C or 59-86 °F).
- Take your dose of study medication every 12 hours (± 2 hours). If it is after 2 hours from when your dose was due, skip that dose and continue with your next scheduled dose.
- Fast for at least 1 hour prior to taking the study medication and 1 hour after you take the study medication. You are allowed to have a low-fat, bland snack (crackers, toast, tea, etc.) if needed (if you are feeling nauseous or weak) during this 2 hour period.
- Medication should be taken with at least 8 ounces (1 cup) of room temperature water.
- Missed doses should be skipped and not taken as a double dose at the next dosing timepoint. If you vomit your dose, you should not make-up that dose or take extra study drug at the next dosing timepoint.
- Write down the time each dose is taken.
- Bring your study medication and study diary with you every time you visit the clinic.
- Contact your study doctor if you have any questions/concerns.

Patient Signature: _____

Cycle #	Day	Date mm/dd/yyyy	Time of Dose**	Were you fasting before and after to your dose?(circle one)		# of capsules taken	Reason for missed dose
Cycle __	Day 1*		: AM	Before: Yes/No	After: Yes/No		
Cycle __	Day 1	/ /	: PM	Before: Yes/No	After: Yes/No		
Cycle __	Day 2**	/ /	: AM	Before: Yes/No	After: Yes/No		
Cycle __	Day 2	/ /	: PM	Before: Yes/No	After: Yes/No		
Cycle __	Day 3	/ /	: AM	Before: Yes/No	After: Yes/No		
Cycle __	Day 3	/ /	: PM	Before: Yes/No	After: Yes/No		
Cycle __	Day 4	/ /	: AM	Before: Yes/No	After: Yes/No		
Cycle __	Day 4	/ /	: PM	Before: Yes/No	After: Yes/No		
Cycle __	Day 5	/ /	: AM	Before: Yes/No	After: Yes/No		
Cycle __	Day 5	/ /	: PM	Before: Yes/No	After: Yes/No		
Cycle __	Day 6	/ /	: AM	Before: Yes/No	After: Yes/No		
Cycle __	Day 6	/ /	: PM	Before: Yes/No	After: Yes/No		
Cycle __	Day 7	/ /	: AM	Before: Yes/No	After: Yes/No		
Cycle __	Day 7	/ /	: PM	Before: Yes/No	After: Yes/No		

Study Subject ID #:_____Patient Name: _____

Current Assigned dose: _____ **Start Date:**_____

Reminders:

- Study medication should be stored at room temperature (Temperature storage range 15-30 °C or 59-86 °F).
- Take your dose of study medication every 12 hours (± 2 hours). If it is after 2 hours from when your dose was due, skip that dose and continue with your next scheduled dose.
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- Medication should be taken with at least 8 ounces (1 cup) of room temperature water.
- Missed doses should be skipped and not taken as a double dose at the next dosing timepoint. If you vomit your dose, you should not make-up that dose or take extra study drug at the next dosing timepoint.
- Write down the time each dose is taken.
- Bring your study medication and study diary with you every time you visit the clinic.
- Contact your study doctor if you have any questions/concerns.

Patient Signature: _____

Cycle #	Day	Date mm/dd/yyyy	Time of Dose**	Were you fasting before and after to your dose?(circle one)		# of capsules taken	Reason for missed dose
Cycle __	Day 8	/ /	: AM	Before: Yes/No	After: Yes/No		
Cycle __	Day 8	/ /	: PM	Before: Yes/No	After: Yes/No		
Cycle __	Day 9	/ /	: AM	Before: Yes/No	After: Yes/No		
Cycle __	Day 9	/ /	: PM	Before: Yes/No	After: Yes/No		
Cycle __	Day 10	/ /	: AM	Before: Yes/No	After: Yes/No		
Cycle __	Day 10	/ /	: PM	Before: Yes/No	After: Yes/No		
Cycle __	Day 11	/ /	: AM	Before: Yes/No	After: Yes/No		
Cycle __	Day 11	/ /	: PM	Before: Yes/No	After: Yes/No		
Cycle __	Day 12	/ /	: AM	Before: Yes/No	After: Yes/No		
Cycle __	Day 12	/ /	: PM	Before: Yes/No	After: Yes/No		
Cycle __	Day 13	/ /	: AM	Before: Yes/No	After: Yes/No		
Cycle __	Day 13	/ /	: PM	Before: Yes/No	After: Yes/No		
Cycle __	Day 14	/ /	: AM	Before: Yes/No	After: Yes/No		
Cycle __	Day 14	/ /	: PM	Before: Yes/No	After: Yes/No		
Cycle __	Day 15	/ /	: AM	Before: Yes/No	After: Yes/No		
Cycle __	Day 15	/ /	: PM	Before: Yes/No	After: Yes/No		

Study Subject ID #:_____Patient Name: _____

Current Assigned dose: _____ **Start Date:**_____

Reminders:

- Study medication should be stored at room temperature (Temperature storage range 15-30 °C or 59-86 °F).
- Take your dose of study medication every 12 hours (± 2 hours). If it is after 2 hours from when your dose was due, skip that dose and continue with your next scheduled dose.
- Fast for at least 1 hour prior to taking the study medication and 1 hour after you take the study medication. You are allowed to have a low-fat, bland snack (crackers, toast, tea, etc.) if needed (if you are feeling nauseous or weak) during this 2 hour period.
- Medication should be taken with at least 8 ounces (1 cup) of room temperature water.
- Missed doses should be skipped and not taken as a double dose at the next dosing timepoint. If you vomit your dose, you should not make-up that dose or take extra study drug at the next dosing timepoint.
- Write down the time each dose is taken.
- Bring your study medication and study diary with you every time you visit the clinic.
- Contact your study doctor if you have any questions/concerns.

Patient Signature: _____

Cycle #	Day	Date mm/dd/yyyy	Time of Dose**	Were you fasting before and after to your dose?(circle one)		# of capsules taken	Reason for missed dose
Cycle __	Day 16	/ /	: AM	Before: Yes/No	After: Yes/No		
Cycle __	Day 16	/ /	: PM	Before: Yes/No	After: Yes/No		
Cycle __	Day 17	/ /	: AM	Before: Yes/No	After: Yes/No		
Cycle __	Day 17	/ /	: PM	Before: Yes/No	After: Yes/No		
Cycle __	Day 18	/ /	: AM	Before: Yes/No	After: Yes/No		
Cycle __	Day 18	/ /	: PM	Before: Yes/No	After: Yes/No		
Cycle __	Day 19	/ /	: AM	Before: Yes/No	After: Yes/No		
Cycle __	Day 19	/ /	: PM	Before: Yes/No	After: Yes/No		
Cycle __	Day 20	/ /	: AM	Before: Yes/No	After: Yes/No		
Cycle __	Day 20	/ /	: PM	Before: Yes/No	After: Yes/No		
Cycle __	Day 21	/ /	: AM	Before: Yes/No	After: Yes/No		
Cycle __	Day 21	/ /	: PM	Before: Yes/No	After: Yes/No		

*For Cycle 1 and Cycle 2, Day 1, do not take your morning dose of PLX3397 until you are instructed to do so during your clinic visit.

**For Day 2 of Cycle 1 ONLY, do not take your morning dose of PLX3397 until you are instructed to so during your clinic visit.

PLX3397 BID - Patient Drug Diary – Phase II, Cycle #____

CC#12751: Enhancing Efficacy of Chemotherapy in Triple Negative/Basal-Like Breast Cancer by Targeting Macrophages: A Phase Ib/II study of PLX 3397 and Eribulin in Patients with Metastatic Breast Cancer

Study Subject ID #:_____Patient Name: _____

Current Assigned dose: _____ Start Date:_____

Reminders:

- Study medication should be stored at room temperature (Temperature storage range 15-30 °C or 59-86 °F).
- Take your dose of study medication every 12 hours (± 2 hours). If it is after 2 hours from when your dose was due, skip that dose and continue with your next scheduled dose.
- Take your study medication daily for 5 days, followed by 2 days off, then restart each week with the same schedule
- Fast for at least 1 hour prior to taking the study medication and 1 hour after you take the study medication. You are allowed to have a low-fat, bland snack (crackers, toast, tea, etc.) if needed (if you are feeling nauseous or weak) during this 2 hour period.
- Medication should be taken with at least 8 ounces (1 cup) of room temperature water.
- Missed doses should be skipped and not taken as a double dose at the next dosing timepoint. If you vomit your dose, you should not make-up that dose or take extra study drug at the next dosing timepoint. If you miss or hold a dose, maintain the 5 days on/2 days off schedule marked on the study calendar.
- Write down the time each dose is taken.
- Bring your study medication and study diary with you every time you visit the clinic.
- Contact your study doctor if you have any questions/concerns.

Patient Signature: _____

Cycle #	Day	Date mm/dd/yyyy	Time of Dose	Were you fasting before and after to your dose? (circle one)		# of capsules taken	Reason for missed dose
In Cycle 1, you will start taking PLX3397 six to seven days before starting eribulin.							
Cycle 1	Day -7		: AM	Before: Yes/No	After: Yes/No		
Cycle 1	Day-7	/ /	: PM	Before: Yes/No	After: Yes/No		
Cycle 1	Day-6	/ /	: AM	Before: Yes/No	After: Yes/No		
Cycle 1	Day-6	/ /	: PM	Before: Yes/No	After: Yes/No		
Cycle 1	Day-5	/ /	: AM	Before: Yes/No	After: Yes/No		
Cycle 1	Day-5	/ /	: PM	Before: Yes/No	After: Yes/No		
Cycle 1	Day-4	/ /	: AM	Before: Yes/No	After: Yes/No		
Cycle 1	Day-4	/ /	: PM	Before: Yes/No	After: Yes/No		
Cycle 1	Day-3	/ /	: AM	Before: Yes/No	After: Yes/No		
Cycle 1	Day-3	/ /	: PM	Before: Yes/No	After: Yes/No		
Cycle 1	Day-2	/ /	DO NOT TAKE STUDY DRUG				
Cycle 1	Day-2	/ /	DO NOT TAKE STUDY DRUG				

Study Subject ID #:_____Patient Name: _____

Current Assigned dose: _____ Start Date:_____

Reminders:

- Study medication should be stored at room temperature (Temperature storage range 15-30 °C or 59-86 °F).
- Take your dose of study medication every 12 hours (± 2 hours). If it is after 2 hours from when your dose was due, skip that dose and continue with your next scheduled dose.
- Take your study medication daily for 5 days, followed by 2 days off, then restart each week with the same schedule
- Fast for at least 1 hour prior to taking the study medication and 1 hour after you take the study medication. You are allowed to have a low-fat, bland snack (crackers, toast, tea, etc.) if needed (if you are feeling nauseous or weak) during this 2 hour period.
- Medication should be taken with at least 8 ounces (1 cup) of room temperature water.
- Missed doses should be skipped and not taken as a double dose at the next dosing timepoint. If you vomit your dose, you should not make-up that dose or take extra study drug at the next dosing timepoint. If you miss or hold a dose, maintain the 5 days on/2 days off schedule marked on the study calendar.
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- Bring your study medication and study diary with you every time you visit the clinic.
- Contact your study doctor if you have any questions/concerns.

Patient Signature: _____

Cycle #	Day	Date mm/dd/yyyy	Time of Dose	Were you fasting before and after to your dose? (circle one)		# of capsules taken	Reason for missed dose
Cycle 1	Day-1	/ /	DO NOT TAKE STUDY DRUG				
Cycle 1	Day-1	/ /	DO NOT TAKE STUDY DRUG				
Cycle __	Day 1	/ /	: AM	Before: Yes/No	After: Yes/No		
Cycle __	Day 1	/ /	: PM	Before: Yes/No	After: Yes/No		
Cycle __	Day 2	/ /	: AM	Before: Yes/No	After: Yes/No		
Cycle __	Day 2	/ /	: PM	Before: Yes/No	After: Yes/No		
Cycle __	Day 3	/ /	: AM	Before: Yes/No	After: Yes/No		
Cycle __	Day 3	/ /	: PM	Before: Yes/No	After: Yes/No		
Cycle __	Day 4	/ /	: AM	Before: Yes/No	After: Yes/No		
Cycle __	Day 4	/ /	: PM	Before: Yes/No	After: Yes/No		
Cycle __	Day 5	/ /	: AM	Before: Yes/No	After: Yes/No		
Cycle __	Day 5	/ /	: PM	Before: Yes/No	After: Yes/No		
Cycle __	Day 6	/ /	DO NOT TAKE STUDY DRUG				
Cycle __	Day 6	/ /	DO NOT TAKE STUDY DRUG				
Cycle __	Day 7	/ /	DO NOT TAKE STUDY DRUG				

Study Subject ID #:_____Patient Name: _____

Current Assigned dose: _____ Start Date:_____

Reminders:

- Study medication should be stored at room temperature (Temperature storage range 15-30 °C or 59-86 °F).
- Take your dose of study medication every 12 hours (± 2 hours). If it is after 2 hours from when your dose was due, skip that dose and continue with your next scheduled dose.
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Patient Signature: _____

Cycle #	Day	Date mm/dd/yyyy	Time of Dose	Were you fasting before and after to your dose? (circle one)		# of capsules taken	Reason for missed dose
Cycle __	Day 7	/ /	DO NOT TAKE STUDY DRUG				
Cycle __	Day 8	/ /	: AM	Before: Yes/No	After: Yes/No		
Cycle __	Day 8	/ /	: PM	Before: Yes/No	After: Yes/No		
Cycle __	Day 9	/ /	: AM	Before: Yes/No	After: Yes/No		
Cycle __	Day 9	/ /	: PM	Before: Yes/No	After: Yes/No		
Cycle __	Day 10	/ /	: AM	Before: Yes/No	After: Yes/No		
Cycle __	Day 10	/ /	: PM	Before: Yes/No	After: Yes/No		
Cycle __	Day 11	/ /	: AM	Before: Yes/No	After: Yes/No		
Cycle __	Day 11	/ /	: PM	Before: Yes/No	After: Yes/No		
Cycle __	Day 12	/ /	: AM	Before: Yes/No	After: Yes/No		
Cycle __	Day 12	/ /	: PM	Before: Yes/No	After: Yes/No		
Cycle __	Day 13	/ /	DO NOT TAKE STUDY DRUG				
Cycle __	Day 13	/ /	DO NOT TAKE STUDY DRUG				
Cycle __	Day 14	/ /	DO NOT TAKE STUDY DRUG				
Cycle __	Day 14	/ /	DO NOT TAKE STUDY DRUG				

Study Subject ID #:_____Patient Name: _____

Current Assigned dose: _____ Start Date:_____

Reminders:

- Study medication should be stored at room temperature (Temperature storage range 15-30 °C or 59-86 °F).
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Patient Signature: _____

Cycle #	Day	Date mm/dd/yyyy	Time of Dose	Were you fasting before and after to your dose? (circle one)		# of capsules taken	Reason for missed dose
Cycle __	Day 15	/ /	: AM	Before: Yes/No	After: Yes/No		
Cycle __	Day 15	/ /	: PM	Before: Yes/No	After: Yes/No		
Cycle __	Day 16	/ /	: AM	Before: Yes/No	After: Yes/No		
Cycle __	Day 16	/ /	: PM	Before: Yes/No	After: Yes/No		
Cycle __	Day 17	/ /	: AM	Before: Yes/No	After: Yes/No		
Cycle __	Day 17	/ /	: PM	Before: Yes/No	After: Yes/No		
Cycle __	Day 18	/ /	: AM	Before: Yes/No	After: Yes/No		
Cycle __	Day 18	/ /	: PM	Before: Yes/No	After: Yes/No		
Cycle __	Day 19	/ /	: AM	Before: Yes/No	After: Yes/No		
Cycle __	Day 19	/ /	: PM	Before: Yes/No	After: Yes/No		
Cycle __	Day 20	/ /	DO NOT TAKE STUDY DRUG				
Cycle __	Day 20	/ /	DO NOT TAKE STUDY DRUG				
Cycle __	Day 21	/ /	DO NOT TAKE STUDY DRUG				
Cycle __	Day 21	/ /	DO NOT TAKE STUDY DRUG				