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COMPREHENSIVE CANCER CENTER

OASIS: Phase II trial of **O**r**A**l **S**M-88 in patients with metastatic hormone receptor-pos**I**tive HER2-negative (HR+/HER2-) brea**S**t cancer

Georgetown Protocol #:	**STUDY00003282**
Clinicaltrials.gov #:	**NCT # 04720664**
Protocol Version Date:	**Version 2.2, 11/18/2022** Version 2.1, 5/9/2022 Version 2.0, 3/15/2022 Version 1.6, 3/8/2022 Version 1.5, 1/4/2022 Version 1.4, 11/23/2021 Version 1.3, 8/23/2021 Version 1.2, 4/21/2021
Initial Protocol Version Date:	Version 1.1, 11/18/2020
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Funding Sources:	TYME, Inc
Study Drug:	SM-88 Methoxsalen Phenytoin Sirolimus
IND Number:	**153564**

Clinical Phase:	Phase II
Number of Patients:	50

The study will be conducted according to the protocol and in compliance with Good Clinical Practice (GCP), with the Declaration of Helsinki, and with other applicable regulatory requirements including but not limited to Institutional Review Board/Ethics Committee (IRB/EC) approval.

Confidentiality Statement

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SPONSOR SIGNATURE PAGE

Declaration of Sponsor or Responsible Medical Officer

Title: A Phase II trial of SM-88 in patients with metastatic hormone receptor-positive and HER2-negative (HR+/HER2-) breast cancer

This study protocol was subjected to critical review and has been approved by the Sponsor. The information it contains is consistent with the current risk/benefit evaluation of the investigational product as well as with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki and the guidelines on Good Clinical Practice.

_____ _____

Name: Date

Affiliation Tyme, Inc.

INVESTIGATOR SIGNATURE PAGE

Declaration of the Investigator

Title: A Phase II trial of SM-88 in patients with metastatic hormone receptor-positive and HER2-negative (HR+/HER2-) breast cancer

I have read this study protocol, including all appendices. By signing this protocol, I agree to conduct the clinical study, following approval by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), in accordance with the study protocol, the current International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP), and applicable regulatory requirements. I will ensure that all personnel involved in the study under my direction will be informed about the contents of this study protocol and will receive all necessary instructions for performing the study according to the study protocol.

_____ _____

Nadia Ashai, MD
Lombardi Comprehensive Cancer Center
Georgetown University Medical Center

Date

Document History

Document	Version Date	Summary of Changes and Rationale
Original Protocol (Version 1.0)	11 September 2020	Not applicable (N/A)
Version 1.1	18 November 2020	Revised the protocol to obtain CBC and CMP assessments every 2 weeks for the first two cycles and then every cycle thereafter per FDA.
Version 1.2	23 February 2021	Protocol Clarifications and corrects made: • Removed circulating tumor cells and replace with cell free DNA throughout protocol • Removed research blood sample collection for storage throughout the protocol • Added clarification to exploratory objectives “(pre-treatment on C1D1)” throughout protocol • 4.5 Study Activities Checklist: o Added “Lipid Panel” to screening checklist, to be consistent with Study Calendar. o Removed CT c/a/p and Tumor Measurements from C1D1 to be consistent with Study Calendar. o Added clarification to cfDNA tumor collection “(pre-treatment)” to C1D1 checklist, o Added cell free DNA (cfDNA) collection to visits according to Table 3. Study Calendar and section 9.1 o Changed title of “Off study/End of Treatment” checklist to “Disease Progression/End of Treatment” be consistent with the title in the Study Calendar • Study Calendar o Added column for Cycle 3-N o Added “End of Treatment” to heading “Disease Progression” to be consistent with the Study Activities Checklist o Moved the Blood sample for collection for future research and cfDNA collection from baseline to C1D1 to be consistent with the Study Activities Checklist and section 9.1 o Removed “Serum” from Blood sample collection for future research o Added footnote 10 to cfDNA collection o Footnote 4 updated to clarify the timing of the collection of CBC and Biochemical Profiles o Updated footnote 10 to include cfDNA and further clarify that the samples are collected “(pre-treatment)”

		• 9.1 cfDNA: added clarification on baseline timepoint "(pre-treatment)", added timepoints and updated how samples will be collected. Added reference to the lab manual for additional details. • Deleted section 9.2 • Appendix A: Study Eligibility checklist- added signature lines for the study coordinator and Investigator • Appendix D: Patient Drug Diary- revised diary inserted
Version 1.3	23 Aug 2021	**Corrected Table numbering throughout protocol** **Study Synopsis and Section 3.3:** Removed the following Exclusion Criteria: • Active hepatitis B (defined as having a positive hepatitis B surface antigen [HBsAg]), active hepatitis C (defined as positive test for hepatitis C viral load by polymerase chain reaction [PCR]) or other active, uncontrolled infection. • Clinically significant cataracts or aphakia. **Section 3.3 Exclusion Criteria:** Added the following Exclusion Criteria: • Known chronic hepatitis B virus infection (testing not required prior to enrollment). o Patients with chronic hepatitis C virus infection may be enrolled if there is no clinical/laboratory evidence of cirrhosis per investigator AND the patient's liver function tests fall within the parameters set in the inclusion criteria, Section 3.2. Clarified "at the discretion of investigator" for exclusion criteria #7 Clarified active viral "(including hepatitis B, hepatitis C, etc.)" **3.7.4 Conference Calls:** Added description of biweekly conference calls between Lombardi-Georgetown and other sites. **4.4.1.1 Patient Sample Labeling:** Revised labeling scheme to include OASIS instead of Tyme. **4.5 Study Activities Checklist:** updated to be consistent with Table 3 Study Calendar. **Table 3. Study Calendar:** • Removed Baseline visit column since everything is encompassed in Screening/C1D1. • Added "All subsequent cycles" column for added clarification • Removed "Disease Progression" from "End of treatment column" • Added Optional Bone Scan to End of Treatment visit • Removed requirement for HIV, Hepatitis B and C serology and/or viral load, as this is not a requirement for eligibility • Removed typo "CTC" from Study Calendar • Removed footnotes that were no longer applicable

		• Added clarifications to footnotes.
		• Added footnotes:
		  ○ Lipid profile must be done at baseline and within 8 days prior to C4D1 and then every 12 weeks within 8 days of day 1 of that cycle.
		  ○ End of Treatment visit should occur 30 days +/- 10 days from last dose. Imaging and tumor assessments do not need to be performed at this visit if performed within 30 days prior to the visit"
		  ○ Bone scan at investigator discretion
		  ○ Long term follow up assessment (+/- 4 weeks). Patients will be contacted by phone call or e-mail for vital status data collection, adverse events evaluation (if AEs from study have not yet been closed), subsequent anti-breast cancer therapy (systemic therapy, radiation, or surgery), and development of a secondary malignancy.
		
		Table 4 and Table 5. Dose Modifications for Toxicities Related to SM-88 and MPS: Corrected typos
		6.2 Study Monitoring: clarified SAEs will be reported to the IRB according to IRB reporting guidelines.
		6.3.2 Serious Adverse Events: clarified SAEs will be reported to DSMC per DSMC guidelines.
		6.4 Adverse Event Collection Period: clarified SAEs related to the study or study procedures will be collected from time of consent, All SAEs, regardless of relationship to the study will be reported from the time of first dose until the End of Treatment visit.
		6.5 Adverse event reporting:
		• Clarified SAEs will be reported to the PI, Dr. Collins, the Multicenter Project Managers, and IRB according to IRB reporting guidelines.
		• Added contact information for reporting SAEs to Tyme.
		• Clarified to report SAEs which occur after cessation of study drug to the Study PI, Multicenter project managers and IRB, per IRB policy.
		• Removed sentence referencing international reporting obligations.
		
		6.7 Pregnancy: removed CRO and added Multicenter Project Managers and other contact information for reporting of Pregnancy.
		8.3 Sample Size Considerations: corrected the # of patient with responses from "7 or more" to "8 or more"
		Appendix A:
		• removed fax number and project manager personal email addresses and added main Project Manager email address.

		• Updated Exclusion to be consistent with changes made to section 3.3 **Appendix C: deleted data sharing plan and re-letter the appendices** **Appendix C (Previously D):** Patient Drug Diary- revised to add "Take one hour before or two hours after a meal."
Version 1.4	23 Nov 2021	**Principal Investigator changed to Candace Mainor, MD**
Version 1.5	04 Jan 2022	• Clarified inclusion criteria for prior lines of therapy to include "or been intolerant of" • Clarified measurable disease definition in inclusion criteria • Updated Creatinine clearance to ≥ 55 mL/min • Clarified inclusion criteria for acute toxic effects of prior therapy must be grade ≤ 1 or patients baseline • Clarified in exclusion criteria and section 3.5 and 3.5.2.2 that GnRH agonists such as leuprolide or goserelin are allowed. • Added Table Dose Modifications for Toxicities related to SM-88 to the protocol (Synopsis and Section 5.6) • Clarified Conference Calls (3.7.4) which will be monthly • Relabeled table numbers. • Added clarifications to Section 5.6 on treatment/dose modifications, Table 5 Management of Toxicities related to SM-88 and MPS and section 6.8.1 so all sections are consistent. • Edited definitions of disease measurement and progression to reflect updated RECIST 1.1 criteria • Corrected typos in the protocol (3.5 and Appendix A) • Appendix A updated to be consistent with the clarifications and updates to inclusion and exclusion criteria.
Version 1.6	08Mar2022	• Principal Investigator changed to Nadia Ashai, MD throughout protocol • Section 4.5, updated End of Treatment visit to occur within 10 days from last dose to be consistent with Table 3 updates and section 4.3.12.1. • Table 3 Study Calendar, footnote 11 corrected to state: End of Treatment visit should occur as soon as possible at the time of progression or discontinuation of treatment, preferably before the subject starts the next therapy, + 10 days from last dose to be consistent with section 4.3.12.1.
Version 2.0	15Mar2022	• First Response Assessment has been changed from 12 weeks after treatment (C4D1) to 8 weeks after treatment (C3D1) throughout protocol • Schedule of restaging scans have been changed from every 12 weeks to every 8 weeks. If patient has achieved a complete response (CR), partial response (PR), or

		stable disease (SD) confirmed on two consecutive restaging scans by RECIST v1.1 criteria, restaging scans may then transition to every 12 weeks; throughout protocol. • Cycle 4 D1 removed from 4.5 Study Activities checklist and Table 3. Study Calendar, and was replaced with Cycle 3 Day 1, to correspond with the change to First Response Assessment, and resulted in updates to: o Footnote 4: Lipid panel will be done at each restaging scan (C3D1 and then every 8-12 weeks at each additional restaging scan), o Footnote 10: cfDNA will be obtain at each restaging scan (C3D1 and then every 8-12 weeks at each additional restaging scan).
Version 2.1	09May2022	• Updated Eligibility Criteria definition of Measurable disease to include the presence of one lytic bone lesion and/or mixed lytic-blastic bone lesion with an associated soft tissue component ≥ 10mm as noted on CT or MRI. Target lesions cannot have undergone radiation therapy prior to measurement. • Removed exclusion of bone only metastases.
Version 2.2	18Nov2022	• Adding clarification: “Disease progression is an efficacy criterion and is therefore not considered an AE or SAE (even if fatal). Disease progression should be documented. If AEs/SAEs occur in relation to disease progression that are not consistent with the natural progression of the patient’s disease, these AEs/SAEs must be reported per AE/SAE reporting requirements.” • Removed collection of Subsequent anti-breast cancer therapy (systemic therapy, radiation, or surgery) and Development of a Secondary Malignancy as follow up assessments

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Glossary of Abbreviations and Definition of Terms

AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
BID	Twice Daily
BUN	Blood urea nitrogen
CBC	Complete blood count
CBR	Clinical benefit rate
CLIA	Clinical laboratory improvement amendments
CNS	Central nervous system
CR	Complete response
CRF	Case Report Form
CRO	Clinical research organization
CT	Computed tomography
cfDNA	Cell Free-DNA
CYP	Cytochrome P450
DOR	Duration of response
DSMB	Data and safety monitoring review board
ECOG	Eastern Cooperative Oncology Group
ECG	Electrocardiogram
GI	Gastrointestinal
GCSF	Granulocyte colony-stimulating factor
HIV	Human immunodeficiency virus
ICH	International Conference on Harmonization
IEC	Independent ethics committees
IHC	Immunohistochemistry
IV	Intravenous
HER2-	Human epidermal growth factor receptor 2-negative
HR+	Hormone receptor-positive
LCCC	Lombardi Comprehensive Cancer Center
LD	Longest diameter
LFT	Liver function test
MPS	Methoxsalen, phenytoin, sirolimus
MRI	Magnetic resonance imaging
mTOR	Mammalian target of rapamycin
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Toxicity Criteria for Adverse Events
ORR	Objective response rate
OS	Overall survival
PET	Positron emission tomography
PD	Progressive disease
PFS	Progression-free survival
PGP	P-glycoprotein
PI	Principal Investigator
PK	Pharmacokinetics
PO	By mouth
POR	Proof of receipt
PR	Partial response
PS	Performance Status
Qd	Once Daily
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase II Dose
SAE	Significant adverse event

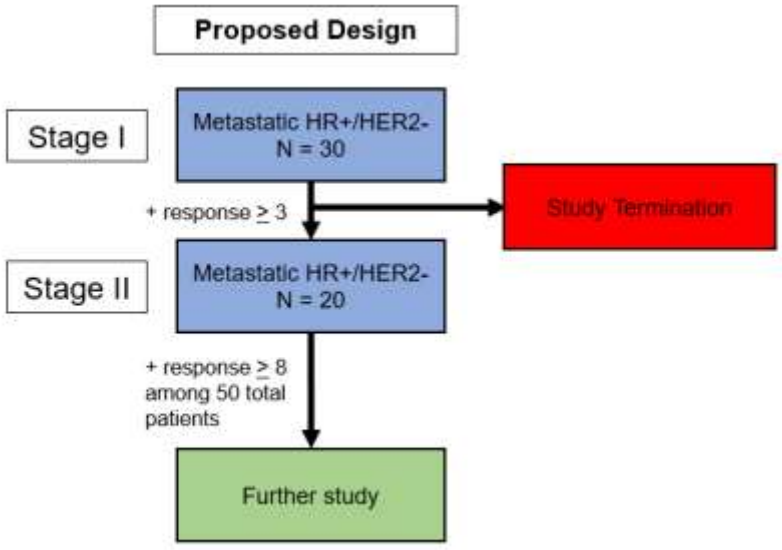
SD	Stable disease
TCBSR	Tissue Culture and Biobanking Shared Resource
TRAE	Treatment-related adverse event
ULN	Upper limit of normal

Study Synopsis

Title	OASIS: Phase II Trial of OrAl SM-88 in Patients With Metastatic Hormone Receptor-posItive HER2-negative (HR+/HER2-) breaSt Cancer
Short Title	SM-88 in metastatic HR+/HER2- breast cancer
Protocol Number	STUDY00003282
Clinicaltrials.gov number:	NCT # 04720664
Phase	Phase II
Investigational Agents	1. SM-88 (racemic D/L-alpha-metyrosine; racemetyrosine), an oral dysfunctional tyrosine derivative 2. Methoxsalen, an oral psoralen (subtherapeutic dose) 3. Phenytoin, an oral barbiturate relative with 5-membered ring (subtherapeutic dose) 4. Sirolimus, an oral mTOR inhibitor (subtherapeutic dose)
Indication	Metastatic HR+/HER2- breast cancer
Study Overview	This is an Investigator initiated multicenter phase II single arm trial designed to evaluate the efficacy of SM-88 plus three subtherapeutic conditioning agents (methoxsalen, phenytoin, and sirolimus [MPS]) in patients with metastatic hormone receptor-positive, HER2 negative (HR+/HER2-) breast cancer. The study rationale is based on important translational science regarding the LAT1 transporter conducted by Dr. Robert Clarke's laboratory at Lombardi. Patients will be enrolled at multiple MedStar sites. Patients with an adequate performance status (PS), hematologic, hepatic, and renal function as well as measurable disease will be eligible and screened for enrollment. Thirty patients will be enrolled in first stage of the study, and if 3 or more patients have an objective response (complete or partial response) then an additional 20 patients will be enrolled in the second stage of the study. Patients will receive the recommended phase 2 dose (RP2D) of SM-88 (460 mg by mouth [PO] twice a day [BID] D1 – 28) as well as three conditioning agents (MPS): methoxsalen (10 mg PO daily [Qd] D1 – 28), phenytoin (50 mg PO Qd D1 – 28), and sirolimus (0.5 mg PO Qd D1 – 28). Assessment of efficacy will be conducted every 2 cycles (approximately every 8 weeks) with CT chest/abdomen/pelvis using RECIST v1.1 criteria for imaging. For patients who achieve a complete response (CR), partial response (PR), or stable disease (SD) confirmed on two consecutive restaging scans by RECIST v1.1 criteria, restaging scans may transition to every 12 weeks. Safety including clinic visits, and exams will occur every 4 weeks on Day 1 of each cycle. Laboratory testing will be performed every 2 weeks for the first 2 cycles and then on Day 1 of each subsequent cycle. We hypothesize that SM-88 used with MPS will lead to significant anti-tumor responses with acceptable toxicities in patients with metastatic HR+/HER2- breast cancer.
Study Duration	24 months for accrual

Study Center(s)	➢ MedStar Georgetown University Hospital, Lombardi Comprehensive Cancer Center, Washington, DC ➢ MedStar Washington Hospital Center, Washington, DC ➢ MedStar Franklin Square Medical Center, Baltimore, MD ➢ MedStar Good Samaritan Hospital, Baltimore, MD ➢ Hackensack University Medical Center, Hackensack, NJ
Objectives	Primary Objectives: To determine the objective response rate (ORR) of SM-88 plus the conditioning agents methoxsalen, phenytoin, and sirolimus (MPS) in patients with advanced hormone receptor-positive (HR+)/HER2-negative breast cancer. Secondary Objectives: To assess: o Progression free survival (PFS), o Clinical benefit rate (CBR) at ≥ 24 weeks, o Duration of response (DOR), and o Safety/tolerability (adverse events, serious adverse events, incidence of dose delays or dose reductions, treatment discontinuations due to adverse events, and all deaths). Exploratory Objectives: o To evaluate cell free DNA (cfDNA) at baseline (pre-treatment on C1D1), during treatment, and at disease progression.
Number of Patients	The anticipated number of patients will be 50.

Diagnosis and Main Inclusion and Exclusion Criteria	Key Inclusion Criteria 1) Histologically or cytologically proven diagnosis of HR+/HER2- breast cancer with evidence of metastatic or locally advanced disease, not amenable to curative treatment by surgery or radiotherapy 2) Measurable disease by RECIST v1.1 criteria. This includes the presence of one lytic bone lesion with an associated soft tissue component and/or one mixed lytic-blastic bone lesion with an associated soft tissue component ≥ 10mm as noted on CT or MRI. Target lesions cannot have undergone radiation therapy prior to measurement. 3) Pre- or postmenopausal women and men age ≥ 18 years 4) Life expectancy of more than 3 months 5) Eastern Cooperative Oncology Group (ECOG) performance status 0 to 1 6) Signed informed consent form 7) Adequate hepatic, hematologic, and renal function as defined below in the body of the protocol 8) Must have progressed on (or been intolerant of) ≥ 2 lines of endocrine therapy in either the adjuvant or metastatic setting and progressed on (or been intolerant of) a CDK4/6 inhibitor but have received ≤ 4 lines of systemic therapy in the metastatic setting Key Exclusion Criteria 1) Diagnosis of other invasive cancer except for adequately treated cervix cancer, or more than 5 years since other diagnosis of invasive cancer (including invasive squamous cell cancers due to contraindication for methoxsalen use) without current evidence of disease. 2) Active uncontrolled or symptomatic brain metastases. Previously treated and clinically stable, as per Investigator's judgement, brain metastases are permitted. 3) Patients that have a variety of factors influencing oral drugs (such as unable to swallow, nausea, vomiting, chronic diarrhea, and intestinal obstruction, etc.). 4) Cardiovascular disease problems including unstable angina, therapy for life-threatening arrhythmia, or a diagnosis of congestive heart failure (New York Heart Association [NYHA] class ≥ II) 5) Women who are pregnant or breastfeeding 6) Patients receiving any other investigational agents 7) History of the light sensitive diseases for which methoxsalen would be contraindicated. Diseases associated with photosensitivity include lupus erythematosus, porphyria cutanea tarda, erythropoietic protoporphyria, variegate porphyria, xeroderma pigmentosum, and albinism. 8) Prior organ transplant or being treated, or anticipated to be treated, with cyclosporine (because long-term administration of the combination of cyclosporine and sirolimus is associated with deterioration of renal function). 9) Seizure disorder that is not well controlled or who have required a change in seizure medications within 60 days of enrollment to the trial. 10) Treatment or anticipated treatment with a calcineurin inhibitor (because concomitant use of sirolimus and a calcineurin inhibitor increases the

	risk of calcineurin inhibitor-induced hemolytic uremic syndrome/thrombotic thrombocytopenic purpura/thrombotic microangiopathy [HUS/TTP/TMA]). 11) Treatment or anticipated treatment with delavirdine (due to potential for loss of virologic response and possible resistance to delavirdine or to the class of non-nucleoside reverse transcriptase inhibitors caused by phenytoin).
Study Design	This is a phase II single arm, open-label study of SM-88 used with methoxsalen, phenytoin, and sirolimus (MPS) in metastatic HR+/HER2- breast cancer. It is designed to determine efficacy, defined as the objective response rate (ORR) of this investigational treatment in patients with metastatic HR+/HER2-breast cancer. All patients will take SM-88 460 mg PO twice a day and MPS PO once a day. Dose de-escalation of SM-88 will be permitted. No dose adjustments will be permitted for MPS. Thirty patients will be enrolled in stage 1. If there are 3 or more objective responses among these 30 patients then an additional 20 patients will be enrolled in stage 2; otherwise, the study will be terminated. If there are 8 or more objective responses among the 50 total patients, the null hypothesis will be rejected and SM-88 will be deemed a promising therapy for patients with metastatic HR+/HER2- breast cancer.  **Figure 1. Study Design**

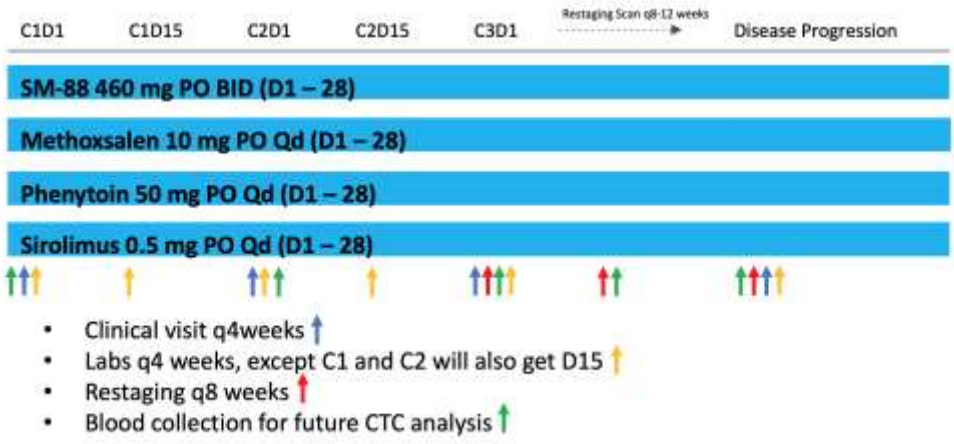


Figure 2. Study Schedule

Patients will be evaluated, including physical exam and laboratory testing, every 4 weeks on Day 1 of each cycle. Laboratory testing will be performed every 2 weeks for the first 2 cycles and then on Day 1 of each subsequent cycle. Restaging will occur every 8 weeks. For patients who achieve a complete response (CR), partial response (PR), or stable disease (SD) confirmed on two consecutive restaging scans by RECIST v1.1 criteria, restaging scans may transition to every 12 weeks. If there is no evidence of progressive disease (PD), as determined by RECIST v1.1, and the patient is tolerating therapy, then the patient will continue with study therapy. Patients will continue to remain on study as long as there is no evidence of PD (according to RECIST v1.1) and the therapy is adequately tolerated.

Two (2) 10.0 mL Streck cell-free DNA collection tubes (DNA BCT catalog #230470) will be collected for cell free DNA (cfDNA) analysis at baseline, C2D1, C3D1, at each additional restaging scan (every 8-12 weeks) and at the time of progression. These vials shall be processed as per the laboratory manual and banked at Georgetown University and stored at -70C.

All findings will be correlated with patient outcomes.

Table 1. Dose Modifications for Toxicities Related to SM-88

Dose Level	SM-88 Dose	Dose Adjustment for Next Treatment
1	460 mg BID (920 mg/day)	Decrease dose to 230 mg BID
-1	230 mg BID (460 mg/day)	Discontinue study treatment for up to 28 days and attempt mitigation; if this dose is not tolerated then patient should be removed from the study

	Initiation of Treatment, Patient Assessment, and Response Assessment Prior to treatment initiation, all patients will undergo baseline imaging and screening for enrollment within 28 days of initiating therapy. At the screening evaluation, the patient's performance status will be confirmed, and standard laboratory tests will be obtained. Patients must have measurable, metastatic disease or measurable locally advanced incurable disease, as per RECIST v1.1, including measurable bone only disease. Treatment will be initiated on Cycle 1 Day 1, and patients will be evaluated every 4 weeks on Day 1 of each cycle. Laboratory testing will be performed every 2 weeks for the first 2 cycles and then on Day 1 of each subsequent cycle. These "protocol defined visits" will include an interval history and physical, update of concomitant medications, assessment of treatment toxicities, laboratory evaluations, and may or may not coincide with the regular visits that a physician may wish to have with the patient – BUT these will be required visits used for data collection. Radiologic evaluations initially will occur every 8 weeks. For patients who achieve CR, PR or SD confirmed on two consecutive restaging scans by RECIST v1.1 criteria, restaging scans may transition to every 12 weeks.Following the first response assessment, any patient with stable or responding disease as per RECIST v1.1 may stay on therapy and will be evaluated every 8-12 weeks until disease progression, at which point he/she will be removed from the study. Longitudinal Outcomes Assessment Subsequent therapies will be administered at the discretion of the treating physician. Patients will be followed every 6 months for two years after stopping study treatment.
Multi-Institutional Trial Coordination	Personnel At each site, personnel dedicated to this protocol will be: - A study PI - A research coordinator - A data manager In addition, the clinical research organization (CRO), KPS will oversee the multi-institutional coordination. Patient Enrollment If a patient is being screened for enrollment, the local research coordinator must send an email within 24 hours containing the patient's name to the local principal Investigator (PI), and to the CRO. If a patient is successfully screened, the local research coordinator must send all supporting documentation to the Principal Investigator. Patients should not start therapy until the Principal Investigator or the local PI and the CRO have reviewed the patient's records and confirmed that the patient is indeed eligible for enrollment. Data Collection and Management Patient data will be entered into the on-line accessible database. This database is housed at Lombardi-Georgetown, but is accessible anywhere there is internet access. The data manager and research coordinator at each site will attend an on-line training session so that they may learn how to enroll data into the data base. All screening data should be entered prior to starting therapy, and all ongoing patient data should be entered within 10 business days of each patient visit. Conference Calls The Principal Investigator and the Co-Investigators will review the data including safety monitoring at frequent disease group meetings and network disease group

	teleconferences. The Investigators shall regularly review toxicities and follow up on results of patients enrolled on the study. Trial Auditing The company will arrange all primary source documents for the patients to be audited by a Tyme-appointed CRA. This will include collecting copies of the primary source data for any patients treated at other sites.
Duration of therapy	All drugs will be administered until disease progression or unacceptable toxicity is observed.
Statistical Design, Feasibility, and Trial Duration	This is a phase II trial with single arm, open-label study of SM-88 used with MPS in metastatic HR+/HER2- breast cancer. The primary endpoint of this phase II study is to determine the objective response rate (ORR) of SM-88 therapy in patients with metastatic HR+/HER2- breast cancer. The phase II portion of the trial will follow Simon's minimax two-stage design (Simon 1989). In Stage 1, 30 patients will be accrued. If there are 2 or fewer objective responses among these 30 patients with the SM-88 plus MPS therapy, the therapy will be rejected and the trial stopped. However, if 3 or more patients achieve an objective response in the Stage 1, then an additional 20 patients will be enrolled in Stage 2, for a total of 50 patients in this phase II study. If 8 or more patients exhibit an objective response among these 50 patients, then the treatment will be considered for further investigation. Any unplanned interim analysis, e.g., due to slow accrual, external information etc, will utilize the sequential conditional probability ratio test (TAN and XIONG 1996, Tan and Xiong 2011) which allows an early assessment of statistical evidence for both efficacy and futility while retaining the rigor of the trial and provides a discordance probability that early trend could be reversed should the trial continue to enroll all 50 patients. Response classification will follow the RECIST v1.1 criteria and will be defined as stable disease (SD), partial response (PR), or complete response (CR). The overall objective response rate (ORR, PR + CR) will be computed for all patients with at least one cycle of the study therapy. The proportion of response rate will be reported with 95% exact binomial confidence interval (CI). DOR will be estimated by Kaplan-Meier methodology, and the median of the DOR with 95% CI will be reported (calculated based on Kaplan-Meier). The PFS is defined as the time in days from study entry to the first documented disease progression per RECIST v1.1 as assessed by local site or death. Patients who are alive and free from progression on the date of closing follow-up will be censored on that date. PFS will be estimated by Kaplan-Meier methodology, and median PFS with 95% CI will be reported. Clinical benefit rate (CBR) at ≥ 24 weeks will be reported. The total number and percentage of patients who achieve complete response (CR), partial response (PR), or had stable disease (SD) at ≥ 24 weeks will be reported. Descriptive statistics will be used to characterize safety. Overall safety monitoring will be performed throughout the study. The safety of the SM-88 therapy will be assessed by evaluating study drug exposure, adverse events, serious adverse events, incidence of dose delays or dose reductions, treatment discontinuations due to adverse events, and all deaths. A summarization of the number of days and/or cycles patients were exposed to study drug will be provided. Adverse events (and serious adverse events) will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 5.0. Toxicities will be characterized in terms of seriousness,

	causality, toxicity grading, and action taken with regard to trial treatment. The percentage of patients experiencing an adverse event at a given severity, NCI CTCAE toxicity grade, and relationship to study drug will be provided. The number of patient deaths throughout the study will be summarized. Descriptive statistics of genomic changes will be used to characterize cell-free DNA (cfDNA) analysis during the therapy as well as scheduled collection time points. P-values less than 0.05 will be considered significant. All statistical analyses will be performed using RStudio (Version 0.99.902) and SAS (Version 9.4). <u>Number of Centers</u> In order to recruit 50 patients with advanced HR+/HER2- breast cancer in a timely manner it will be critical to have access to a large pool of potential patients. Thus, we propose a multicenter trial. Georgetown-Lombardi will act as the primary site, and a dedicated CRO will oversee patient enrollment and on study activities at other sites. Georgetown-Lombardi will also be responsible for generation of the case report forms, which can be accessed through an on-line data entry portal (training for this portal can be done on-line).

1. Background and Justification

In 2019, there were approximately 270,000 new breast cancer diagnoses and 42,000 breast cancer-related deaths in the United States (Siegel, Miller et al. 2019). Hormone receptor-positive (HR+) breast cancer accounts for approximately 70% of breast cancers. First-line systemic therapies for advanced or metastatic HR+ breast cancer are typically endocrine therapy alone or endocrine therapy plus a cyclin dependent kinase 4/6 inhibitor (CDK4/6i) and the next line of therapy is typically fulvestrant, an intramuscular selective estrogen receptor degrader (SERD) +/- a CDK4/6i depending on whether the patient received a CDK4/6i as first-line. Although many metastatic HR+/HER2- breast tumors initially respond to these therapies, most eventually become resistant leading to progressive disease and the need for intravenous (IV) chemotherapy or toxic targeted therapies such as the mammalian target of rapamycin (mTOR) inhibitor, everolimus, plus exemestane. There is a critical unmet need for oral and less toxic therapies for this very common disease.

1.1. SM-88 used with MPS Background

SM-88 (racemic D/L-alpha-metyrosine; racemetyrosine [USAN]) is a novel oral dysfunctional tyrosine derivative used in conjunction with subtherapeutic doses (lower than doses for approved indications) of three conditioning agents, methoxsalen, phenytoin, and sirolimus (MPS). Tyrosine is a non-essential or conditionally essential amino acid that is readily consumed by cancer cells but has shown minimal uptake by normal healthy cells. SM-88 is designed to be absorbed by the cancer cell as if it were a functional tyrosine, but after uptake, interrupt the processes of protein synthesis. It is hypothesized to be transported into cancer cells via the amino acid transporter, LAT-1. LAT-1 is overexpressed in a variety of cancers including breast (Hafliger and Charles 2019) but is not expressed in most healthy tissues, allowing increased uptake of SM-88 in cancer cells and reducing the likelihood of off-target effects. SM-88 is believed to disrupt protein synthesis within cancer cells increasing oxidative stress, inducing autophagy, and modulating the immune microenvironment (unpublished data). D-amino acids have been shown to cause translational arrest in breast cancer cells (Fleisher, Cornish et al. 2018) based on the ribosome discrimination of the chirality of amino acids and saturation of tRNAs covalently bound to D-amino acids (Zheng, Liu et al. 2008). D-amino acids are also recognized to lead to cellular oxidative stress via conversion of D-Amino Acid Oxidase (DAO) and subsequent production of H2O2 that can ultimately lead to apoptosis (Bardaweel, Abu-Dahab et al. 2013).

The L-isomer of SM-88 inhibits tyrosine hydroxylase, the rate limiting enzyme of catecholamine biosynthesis (Korner, Noain et al. 2015). Catecholamines have been shown to directly promote tumor growth (Partecke, Speerforck et al. 2016, Renz, Takahashi et al. 2018) and an immunosuppressive tumor microenvironment by driving macrophages towards the M2 phenotype (Hermano, Meirovitz et al. 2014).

SM-88 is administered along with the three low-dose conditioning agents, MPS, that each leverage physiologic properties that increase uptake of SM-88 in cancer cells and make them more susceptible to its effects. These conditioning agents are given at doses ranging from ¼ to 1/20 of their approved doses with the goal of remaining physiologically relevant but eliminating side effects. Methoxsalen and sirolimus work to target the PI3K/ALT/mTOR intracellular signaling pathway, which is known to play a vital role in tumor growth and proliferation (Paplomata and O'Regan 2014). Methoxsalen, a psoralen, induces apoptosis and inhibits the AKT signaling pathway, which is involved in tumor proliferation and leads to endocrine resistance in breast cancer (Panno and Giordano 2014, Bartnik, Slawinska-Brych et al. 2017). Sirolimus, an mTOR inhibitor, drives the upregulation of cellular channels including LAT-1 (Fuchs and Bode 2005, Wang and Holst 2015, Goberdhan, Wilson et al. 2016), thereby increasing uptake of SM-88 into cancer cells. Phenytoin increases the production of reactive lipid and oxygen species (Eghbal, Taziki et al. 2014) and has been shown to inhibit the in vivo migration, invasion, and metastasis in breast cancer models (Nelson, Yang et al. 2015, Djamgoz, Fraser et al. 2019).

The three conditioning agents, methoxsalen, phenytoin, and sirolimus, are intended to be used to modulate the tumor microenvironment to increase the effectiveness of SM-88, rather than for their indicated/approved uses. These three agents are administered at significantly lower doses than for their approved uses. The safety information for these three agents is taken from their respective Reference Listed Drug packaging inserts and prescribing information. Sirolimus is an approved immunomodulator used for prophylaxis of organ rejection in renal transplantation (Rapamune®; Package Insert, 2018). The recommended dose of sirolimus is 2 to 5 mg/day with a 6 to 15 mg loading dose, higher than the 0.5 mg/day dose to be studied in this trial. Methoxsalen is approved for the treatment of psoriasis, eczema, vitiligo, and some cutaneous lymphomas when simultaneously exposing the skin to ultraviolet A (UVA) light (PUVA therapy) (Oxsorlan Ultra® Package Insert, 2015). The recommended dose of methoxsalen for these indications is 20 to 80 mg/day, which is higher than the 10 mg/day dose to be studied in this trial. Phenytoin is approved as an anti-seizure medication (Dilantin® Package Insert, 2017). The recommended dose of phenytoin for the management of seizure disorders is 300 to 600 mg/day, which is much higher than the planned 50 mg/day dose to be used in this trial.

SM-88 (D/L-alpha-metyrosine; racemetyrosine) is the racemic mixture of alpha-metyrosine. A related drug, L-alpha-metyrosine (Demser®), is approved for the treatment of pheochromocytoma (Demser® Package Insert, 2015). The approved dose of L-metyrosine is 1000 to 4000 mg/day. SM-88 will given at a dose of 920 mg/day in two divided doses in this trial. Further discussion of the mechanism of action for SM-88 used with MPS is included in Appendix E.

1.2. LAT1 and Breast Cancer

The solute carrier family 7 member 5 (SLC7A5 or LAT1) is expressed across the cell membrane and is the primary transporter of large, neutral amino acids such as tyrosine, which support cell proliferation (Hafliger and Charles 2019). LAT1 expression is increased in malignant vs normal tissues and in late-stage vs early-stage breast cancer (Liang, Cho et al. 2011, Furuya, Horiguchi et al. 2012, Hafliger and Charles 2019). LAT1 has been implicated in the survival of cancer cells that have gone through epithelial-to-mesenchymal transition (Halldorsson, Rohatgi et al. 2017). Mesenchymal cells lose their polarity leading to aggressiveness, invasion, and metastasis. High expression of LAT1 in estrogen receptor-positive and tamoxifen-treated breast cancer patients is associated with a poor prognosis (Furuya, Horiguchi et al. 2012, Halldorsson, Rohatgi et al. 2017).

Dr. Robert Clarke's laboratory at Georgetown Lombardi Comprehensive Cancer Center has extensively studied LAT1 and its role in breast cancer (Sevigny, Sengupta et al. 2018, Sevigny, Sengupta et al. 2019). LAT1 expression is estrogen-regulated in endocrine sensitive cells but this regulation is lost in endocrine resistant cells. Preclinical studies from the Clarke laboratory have shown that LCC9 breast cancer cells (endocrine resistant breast cancer cell line) have a 2.75-fold higher upregulation of LAT1 protein and a 71-fold upregulation of LAT1 mRNA compared to MCF7 breast cancer cells (endocrine sensitive breast cancer cell line) without any estrogen regulation. They have shown that treatment with fulvestrant, a selective estrogen receptor degrader, does not significantly alter LAT1 expression in LCC9 cells whereas in MCF7 cells estrogen upregulates LAT1 expression and fulvestrant blocks this upregulation. These data indicate that higher levels of LAT1 in endocrine resistant breast cancer cells are involved in transporting key amino acids, such as tyrosine, from the microenvironment into cancer cells to support cell growth. SM-88 is a modified tyrosine and thus can exploit the high levels of LAT1 to be transported into endocrine resistant breast cancer cells where it can disrupt protein synthesis and lead to cell death, whereas typically overexpression of LAT1 leads to increased protein synthesis.

1.3. Safety of SM-88 used with MPS

Data obtained from in vitro studies (bacterial reverse mutation test, chromosomal aberration test, and rat micronucleus test) demonstrated that SM-88 was neither clastogenic nor mutagenic (TYME regulatory study reports, filed with FDA). Results from long-term toxicology studies in 2 species (a 6 month study in rats and a 9 month study in dogs) and a 10 week developmental study conducted in juvenile rats did not identify any new potential safety concerns (Sokol, Dickey et al. 2016). The No Observed Effect Level

(NOEL) of SM-88 was determined to be 150 mg/kg/day, significantly higher than the dose used in this study.

To date, 180 patients evaluable for safety have received treatment with SM-88 plus either MPS (see above for dosing) or M2PS (melanin, melanotan II, phenytoin, sirolimus), 77 patients have received SM-88 (doses ranging from 230-960 mg/day) plus MPS, and 23 patients have received SM-88 460 mg PO BID plus MPS, which is the treatment regimen and doses used in this study. There have been no specific risks associated with SM-88 used with MPS. SM-88 has not been associated with any dose-limiting toxicities (DLTs). There have been no deaths related to the study drug; all reported deaths have been due to progression of disease. Patients almost universally experienced hyperpigmentation with M2PS due to the inclusion of melanin. Since melanin is not included in MPS, hyperpigmentation is not seen with SM-88 used with MPS.

In an open-label, first in human (FIH) study (Hoffman, Bruckner et al. 2013, Hoffman 2013, Stega, Noel et al. 2019) a similar SM-88 based therapy (referred to as SM-88 used with M2PS) was administered to patients with progressive metastatic cancer. In this study, SM-88 used with M2PS was comprised of an oral regimen of 225 mg SM-88, 50 µg melanin, 15 mg phenytoin, and 0.2 mg sirolimus, and a subcutaneous regimen of 5 mg SM-88, 10 µg melanotan II, 2 mg phenytoin, and 0.05 mg sirolimus. Thirty patients were enrolled, 14 of whom had breast cancer. All treatment-related adverse events (TRAEs) were Grade 1 or 2 and there were no treatment-related severe adverse events (SAEs). TRAEs occurring in ≥10% of patients included hyperpigmentation (30 [100%]), fatigue (17 [56.7%]), and pain (3 [10.0%]). Fatigue was expected as it is a well-known side effect of the L-alpha-metyrosine isomer used in the treatment of pheochromocytoma (Wei, Tominaga et al. 2016), and was generally transient. Four SAEs occurred during the study (decreased weight, edema, hip pain, generalized pain), each in 1 patient, but none were deemed related to study drug. No DLTs were observed. No patient was withdrawn from the study or discontinued treatment due to an AE, and no patient had a dose reduction or interruption of study drug administration due to an AE. In addition, average Eastern Cooperative Oncology Group (ECOG) decreased from 1.6 at baseline to 0.6 after six weeks of treatment.

In a phase Ib/II clinical trial (Tyme 2016b), SM-88 used with MPS was studied in 23 patients with biochemical recurrent prostate cancer (Roach, Gostout et al. 2018, Gartrell, Del Priore et al. 2019). SM-88 dosing ranged from 230 mg PO Qd to 230 mg PO BID used with MPS and was administered daily over a six-month period. 10 mg/day of methoxsalen was substituted for the unavailable same class components in the pilot study (melanin and melanotan II), without a change in observed tolerability or therapeutic effect. All AEs were Grade 1 or 2 except for one Grade 3 AE (hyperkalemia) that was deemed unrelated to study drug. Preliminary results showed no reported serious adverse events over 85 months of cumulative patient experience as presented at American Society of Clinical Oncology (ASCO) GU in 2018 and elsewhere.

The Tyme-88-Panc phase II/III study (NCT03512756) is an ongoing clinical trial enrolling patients with metastatic pancreatic cancer who have progressed on at least two lines of systemic therapy (Noel, Wang-Gillam et al. 2019). In Part 1, 38 patients received either SM-88 230 mg BID or 460 mg BID plus MPS, and in Part 2, 125 patients will receive SM-88 460 mg BID plus MPS and 125 patients will be treated with physician's choice of chemotherapy. In Part 1, the regimen was well tolerated with no Grade 4 or 5 TRAEs; 52.6% of treated patients (20/38) had 94 AEs, with 18.0% (17/94) being at least possibly treatment related, of which three were Grade 3 (arthralgia, fatigue and asthenia). There have been two reported cases of possibly drug related/related serious adverse events (Grade ≥ 3), arthralgia and hypotension, both occurring in one patient.

There were no ocular toxicities reported in the Tyme 2016b prostate cancer trial and no ocular toxicities have been reported in the ongoing Tyme-88-Panc trial.

Previously completed and ongoing studies indicate that SM-88 used with MPS is safe and well-tolerated with most AEs attributed as at least possibly related to the investigational agent following typical

complications of the disease. The distribution of SAEs/AEs observed to date in this ongoing study does not suggest any trends in safety issues.

1.4. SM-88 Pharmacokinetic (PK) Data

1.4.1. Pharmacokinetics in Animal Models

PK data suggest that SM-88 is rapidly absorbed. When the toxicokinetic profile was evaluated in the rats and dogs, systemic exposure to the SM-88 generally increased dose dependently, but in a less than dose-proportional manner across the dose range (Sokol, Dickey et al. 2016). In general, Cmax was reached at 1-3 hours post-dose in rats and 2-8 hours post-dose in dogs. There were no sex-related differences. SM-88 tended to slightly accumulate over the treatment period in rats and demonstrated no accumulation over time in dogs.

SM-88 was metabolically stable in liver microsomes and plasma from three species (rat, dog, and human) (TYME regulatory study reports, filed with FDA). No partitioning into red blood cells was seen. The pKa values suggest that SM-88 is a polar molecule, with high aqueous solubility and potentially lower passive permeability.

1.4.2. Pharmacokinetics of SM-88 in healthy subjects and food effects

Study Y101 was an open-label, 2-part study of the pharmacokinetics of SM-88 in 16 healthy volunteers. Part 1 utilized a randomized 2-way crossover design to assess the effect of food on the PK profile of SM-88. In Part 1, subjects received a single 300 mg dose of SM-88 under fasting or fed (high-fat breakfast). The dosing in each period was separated by a washout of at least 7 days. In Part 2, subjects received multiple doses of SM-88 300 mg BID for 5 days for a total of 9 consecutive doses approximately every 12 hours. PK parameters reported below are based on data collected following the morning dose on Day 5.

The pharmacokinetic parameters of SM-88 under both fed and fasted condition are presented in table 2 below.

When administered in the presence of a high-fat, high-calorie meal, the Cmax and AUC of SM-88 increased by approximately 80%. Tmax was also prolonged by approximately 2 hours by administration in the presence of a high-fat, high-calorie meal.

Accumulation following five days of 300 mg BID administration was observed. The accumulation ratios of Cmax and AUC0-12 were 1.50 and 1.83 respectively.

SM-88 will be taken twice a day and MPS (methoxsalen, phenytoin, and sirolimus) will be taken daily. It is best to take doses one hour before or two hours after meals to ensure an empty stomach. They should be taken together consistently either in the morning or in the evening with a full glass of water. A second dose of SM-88 will be taken 8-16 hours after the SM-88 plus MPS dose -- for example, before bedtime and upon waking up in the morning.

Table 2: Pharmacokinetic parameters of SM-88 in healthy subjects under single dose fed and fasted conditions, and following 5 days of BID dosing.

Parameter	SM-88 300 mg single dose (fasted)	SM-88 300 mg single dose (fed)	SM-88 300 mg steady state (fasted)
n	16	16	15
C_{max} (ng/mL)	2,010 (238)	3,320 (154)	3,010 (216)
T_{max} (h) Mean (SD) Min, Max	2.75 (0.289) 1, 6	4.28 (0.281) 2.5, 6	2.43 (0.341) 1, 6
AUC_{0-12} (hr*ng/mL)	11,200 (1,210)	18,300 (643)	20,500 (1400)
AUC_{0-inf} (hr*ng/mL)	15,900 (1,550)	27,800 (1,220)	na
$t_{1/2}$ (h) mean (SD) Min, Max	14.3 (1.51) 7.87, 28.4	10.8 (0.513) 7.99, 16.5	12.4 7.97, 19.7
CL/F (L/h)	20.9 (1.54)	11.1 (0.475)	15.7 (1.22)
Vz/F (L)	449 (66.4)	172 (9.65)	na

All data presented as mean (+/- SD) unless otherwise stated.

1.4.3. Pharmacokinetics of SM-88 in Subjects with Pancreatic Cancer

In Part 1 of Tyme-88-Panc, pharmacokinetic samples were collected from all subjects for both dose levels for analysis of all four components of SM-88 during Cycles 1 and 2 at pre-dose (0), 0.5, 1, 2, 4, and 6 hours. Pharmacokinetic parameters for SM-88 by cycle and dose (230 mg BID and 460 mg BID) are presented below in Table 3.

Table 2: Pharmacokinetic Parameters for SM-88 in Tyme-88-Panc Part 1

	Cycle 1		Cycle 2	
	230 mg BID	**460 mg BID**	**230 mg BID**	**460 mg BID**
C_{max} (ng/mL) Mean (SD)	1911 (647) n = 19	3546 (2124) n = 19	3506 (2217) n = 10	5420 (2204) n = 8
T_{max} (h) Median (Range)	2 (1 - 64) n = 19	4 (2 – 6) n = 19	2 (2 – 6) n = 10	3 (1 – 4) n = 8
AUC_{0-6} (ng*h/mL) Mean (SD)	8071 (3228) n = 19	14672 (8374) n = 19	16808 (13191) n = 10	24805 (10880) n = 8
$t_{1/2}$ (h) Median (Range)	3.5 (2.2 - 8.1) n = 10	4.1 (2.7 – 7.5) n = 8	10.2 (1.8 – 15.8) n = 4	4.8 (3.1 – 16.7) n = 6

SM-88 appears to be rapidly absorbed. Following administration of the 230 mg dose, median Tmax occurs approximately 2 hours after dosing. Following administration of the 460 mg dose, median Tmax occurs approximately 3-4 hours after dosing.

Following administration of a single oral dose (C1D1), exposure to SM-88 increased in a dose-dependent manner but were less than dose proportional. A doubling of the dose from 230 mg to 460 mg,

resulted in Cmax and AUC increasing by approximately 85%. At steady state (C2D1), dose proportionality of SM-88 was reduced, with a doubling of dose resulting in Cmax and AUC increasing by approximately 50%.

Drug accumulation was observed between Cycle 1 and Cycle 2, with less drug accumulation observed in subjects receiving 460 mg BID compared to those receiving 230 mg BID.

For subjects receiving 230 mg BID, the accumulation ratios based on Cmax and AUC were 1.83 and 2.08, respectively. For subjects receiving 460 mg BID, the accumulation ratios based on Cmax and AUC were 1.53 and 1.69, respectively.

1.4.4. Pharmacokinetics of MPS Conditioning Agents

Mean methoxsalen Cmax at steady state (Cycle 2) was 384.2 ng/mL, and the single highest concentration observed in Part 1 of Tyme-88-Panc was 224 ng/mL. In methoxsalen and long wave UVA (PUVA) therapy, methoxsalen Cmax ranges from 50 - 250 ng/mL, based on a standard dose of 0.5-0.7 mg/kg. Mean methoxsalen Cmax in Part 1 of Tyme-88-Panc was below the lower bound of those concentrations typically associated with the treatment of vitiligo.

Mean phenytoin Cmax at steady state (Cycle 2) was 809 ng/mL, and the single highest concentration observed in Part 1 of Tyme-88-Panc was 1420 ng/mL. All phenytoin concentrations observed in Tyme-88-Panc were less than 10% the level of clinical concern, defined as 20 mg/L (20,000 ng/mL), when patients may begin to experience nystagmus. Additionally, all phenytoin concentrations observed in Part 1 of Tyme-88-Panc were well below the therapeutic range (defined by trough levels) for epilepsy of 10-20 mcg/mL (10,000 – 20,000 ng/mL).

Mean sirolimus Cmax at steady state (Cycle 2) was 2.9 ng/mL, and the single highest concentration observed in Part 1 of Tyme-88-Panc was 6.9 ng/mL. All sirolimus levels observed in Tyme-88-Panc were below concentrations associated with risk of adverse events, typically trough levels of >15-18 ng/mL. Additionally, most Part 1 of Tyme-88-Panc subjects had sirolimus Cmax values below the trough values associated with transplant rejection (4-20 ng/mL) and treatment of lymphangioleiomyomatosis (5-15 ng/mL).

1.5. SM-88 Clinical Data

Preliminary data suggest that SM-88 used with MPS/M2PS is efficacious in a variety of metastatic malignancies. Data from the FIH study of SM-88 (Stega, Noel et al. 2019) and a robust compassionate use program (Zhu, Noel et al. 2018, Zhu, Noel et al. 2018) demonstrate confirmed responses in patients with a variety of metastatic cancers including HR+/HER2- breast cancer. All patients in the FIH study and the compassionate use program had progressive metastatic cancer prior to receiving SM-88. Among 30 patients (14 breast, 5 lung, 3 pancreas, 2 prostate, and 1 each of colon, tongue, thyroid, liver, appendix, and biliary) in the FIH study, 10 (33%) experienced an objective response (OR), 4 patients had a complete response (CR), 3 of whom had HR+/HER2- breast cancer, and 6 patients had a partial response (PR), 3 of whom had breast cancer. Among patients who had an OR, time to best response ranged from 1.5-15.5 months with the majority occurring after 3 months of treatment, indicating that long term administration of SM-88 may be needed to achieve full therapeutic potential. An additional 17 patients had stable disease (SD) with a median duration of 11 months (range 1-31 months). Median progression-free survival (PFS) was 13 months and median overall survival (OS) was 29.8 months. Thirteen patients had responses lasting > 12 months and six patients had responses lasting > 24 months. Since there was no control group in this study, an exploratory analysis comparing each patient's penultimate PFS (PFS on standard treatment before enrollment in the study) to PFS on the investigational treatment. The median penultimate PFS was 4 months (95% CI: 3–8, KM estimate) while the median PFS on study was 11 months (95% CI: 6–26, KM estimate) ($p = 0.0021$, log-rank test), which suggests that SM-88 therapy may provide clinical benefit. The majority of patients (N = 25, 83%) had an improvement in ECOG performance status by the end of cycle 1. Following treatment in the FIH study, 13/30 (43%) patients went on to receive subsequent cancer therapy (chemotherapy, radiation, or surgery). The breast cancer patients had been treated with an average of 2.5 prior

lines of systemic therapy in the metastatic setting. The delay to achieve best clinical response and significant durable clinical benefit were not unexpected as SM-88 is not cytotoxic, but rather disrupts protein synthesis and various cellular mechanisms resulting in increased oxidative stress and apoptosis of cancer cells.

In a combined analysis of the FIH study and the compassionate use program, the overall objective response rate (ORR) was 41% and the clinical benefit rate (CBR) was 81% though data collection time points varied (Zhu, Noel et al. 2018)(unpublished data). Breast cancer comprised the largest proportion of tumor type in both cohorts. Among 25 metastatic breast cancer patients, mean age was 51 (range: 35 – 70), baseline ECOG was 1 (range: 0 – 4), and they had received a median of 3 prior systemic therapies (range: 1 – 8) (Zhu, Noel et al. 2018) (unpublished data). All patients had progressing metastatic breast cancer and were considered incurable. The ORR was 44% and CBR was 76% (varying time points of data collection) with a median OS of 15 months (mean OS of 29 months). CBR and OS were no different with bone metastases (N = 13) compared to without. Twelve patients had HR+/HER2- breast cancer and the ORR was 42% and CBR was 75% with a median PFS of 5 months (range: 0 – 68) and a median OS of 10 months (mean: 22 months; range: 2 – 68). Breast cancer patients who achieved stable disease experienced a median and mean OS of 19 and 27 months, respectively. Ten (40%) of the breast cancer patients survived > 3 years and six (24%) survived > 5 years despite many being heavily pretreated.

The phase Ib/II TYME 2016b trial assessed SM-88 plus MPS in 23 patients with biochemical recurrent prostate cancer who had detectable circulating tumor cells (CTCs) (Chen, Friedlander et al. 2018, Roach, Gostout et al. 2018, Gartrell, Del Priore et al. 2019). The median age was 70.6 years (range: 53 – 84) and all patients had received prior androgen deprivation therapy (ADT) plus either curative intent radiotherapy or surgery. No patients remained on ADT during the study. Prostate specific antigen (PSA) declined in 4% of patients and stabilized in 83%. Median PSA doubling time improved from 6.2 to 8.0 months for all patients completing 3 cycles of therapy. CTCs were evaluated prospectively in 13 patients using a cell adhesion matrix (CAM)-based platform, Vita-Assay™ plate (Chen, Friedlander et al. 2018). Eleven of 13 patients had a reduction in CTCs within the first cycle (28 days) (Chen, Friedlander et al. 2018) and after 12 weeks, there was a 65.3% (-100% to -8.8%) median CTC decrease from baseline, with all patients having CTC counts below baseline and CTCs became undetectable in two patients (Gartrell, Del Priore et al. 2019). Two patients experienced biochemical progressions (one also had radiographic progression), which were paralleled by increases in CTCs. In one patient, disease progression was predicted by an increase in CTCs 8 weeks earlier than PSA increase (Chen, Friedlander et al. 2018).

The Tyme-88-Panc phase II/III study (NCT03512756) of SM-88 used with MPS is a multicenter (> 10 sites) clinical trial currently evaluating efficacy in patients with metastatic or recurrent pancreatic cancer who have progressed on at least one (phase II) or two (phase III) line(s) of systemic therapy (Noel, Ocean et al. 2018, Noel, Wang-Gillam et al. 2019, Ocean, Noel et al. 2019, Pant, Chawla et al. 2020). The primary endpoints are ORR (phase II) and OS (phase III). Preliminary data is currently available for 49 patients (ITT) of which 38 were deemed to be evaluable per the protocol. Median age is 66 years (range: 45 – 85) and patients have received a median of 2 prior lines of therapy (range: 1 – 6). In the phase II portion, patients were randomized 1:1 to receive either SM-88 230 mg BID plus MPS or SM-88 460 mg BID plus MPS. In the phase III portion, all patients receive SM-88 460 mg BID plus MPS, which is the same regimen and dose in this metastatic HR+/HER2- breast cancer trial. As of April 2019, for Part 1, 11/25 evaluable patients (44%) had at least stable disease despite having progressive disease upon study entry. At baseline, CTCs were detected in 100% of patients (mean 138 cells/4 mL). Twenty-nine patients have been evaluable for a change in CTCs with investigational treatment; CTCs decreased in 23/29 (79%) patients from a median of 153 cells/4 mL to a nadir of 54 cells/4 mL (median reduction 63%). In addition, 4/33 (12%) evaluable patients had a decrease in CA19.9 levels (-8% to -97% decline within 3 months), three of whom also had a decline in CTCs, suggesting that CTCs may be prognostic. Overall, this trial demonstrates that SM-88 plus MPS is well tolerated with early signals of efficacy in a heavily pretreated metastatic cancer population.

Ongoing development of SM-88 is planned for multiple cancer types with future studies planned in pancreas, prostate, Ewing’s sarcoma, hematologic malignancies, and this HR+/HER2- breast cancer trial.

1.6. Rationale for Current Study

HR+/HER2- breast cancer represents 70% of all breast cancer but remains underrepresented in clinical trials. Although patients with metastatic HR+/HER2- breast cancer typically initially respond to anti-estrogen therapy and CDK4/6 inhibition, inevitably they at some point become resistant and their disease progresses. Generally, patients are then treated with toxic, often intravenous therapies that require frequent clinic and infusion center visits and carry serious potential side effects. An approach to the treatment of metastatic HR+/HER2- negative breast cancer that limits side effects and provides more freedom to patients beyond second or third-line therapies is urgently needed.

SM-88 is transported into cancer cells via the LAT1 transporter, which is upregulated in malignant vs normal tissue and in late-stage compared to early-stage breast cancer, making it an exciting potential targeted oral treatment for breast cancer. Data from the FIH study and compassionate use program of SM-88 indicate that this investigational therapy may be efficacious in the treatment of HR+/HER2- breast cancer and carry a favorable toxicity profile.

We therefore propose a therapeutic approach combining the RP2D of SM-88 used with the conditioning agents MPS in advanced breast cancer to further evaluate the efficacy and safety of this investigational combination.

2. Study Objectives

2.1. Primary Objectives

To determine the objective response rate (ORR) of SM-88 plus the conditioning agents methoxsalen, phenytoin, and sirolimus (MPS) in patients with advanced HR+/HER2 negative breast cancer.

2.2. Secondary Objectives

To assess:

- Progression free survival (PFS),
- Clinical benefit rate (CBR) at ≥ 24 weeks,
- Duration of response (DOR), and
- Safety/tolerability (adverse events, serious adverse events, incidence of dose delays or dose reductions, treatment discontinuations due to adverse events, and all deaths)

2.3. Exploratory Objective

To evaluate changes in cell-free DNA (cfDNA) at baseline (pre-treatment on C1D1), during treatment, and at disease progression.

2.4. Indication

Patients with advanced breast cancer. This pilot trial will enroll a pre-defined number of patients with HR+/HER2- advanced/metastatic breast cancer.

3. Patient Population

3.1. Patient Population, Number of Patients, and Feasibility

3.1.1. Patient Population

This trial will enroll up to 50 evaluable patients with advanced HR+/HER2- breast cancer. Patients will have measurable disease by RECIST v1.1 criteria. This may include at least one lytic bone lesion or mixed lytic - blastic lesion with an associated soft tissue component ≥ 10mm noted on CT or MRI. Patients will also have an adequate PS, hematologic, hepatic, and renal function.

3.1.2. Number of Patients

Fifty evaluable patients will be enrolled.

3.1.3. Feasibility

At the multiple centers participating in this study, we anticipate being able to enroll ~29 patients per year. The expected accrual duration will be approximately 24 months.

3.2. Inclusion Criteria

Patients must meet all the following inclusion criteria to be eligible for enrollment in the study:

1. Histologically or cytologically proven diagnosis of breast cancer with evidence of metastatic or locally advanced disease, not amenable to resection or radiation therapy with curative intent.
2. Documentation of ER-positive and/or PR-positive tumor (≥1% positive stained cells) based on most recent tumor biopsy (discuss with the Principle Investigator if results in different biopsies are discordant in terms of hormone receptor positivity) utilizing an assay consistent with local standards.
3. Documented HER2-negative tumor based on local testing on most recent tumor biopsy: HER2-negative tumor is determined as immunohistochemistry score 0/1+ or negative by in situ hybridization (FISH/CISH/SISH) defined by current ASCO/CAP (American Society of Clinical Oncology/College of American Pathologists) guidelines. Patients with equivocal HER2 in situ hybridization results according to current ASCO/CAP guidelines are eligible, as long as they have not received and are not scheduled to receive anti-HER2 treatment.
4. Must have progressed on (or been intolerant of) at least 2 lines of endocrine therapy in either the adjuvant or metastatic setting and progressed on (or been intolerant of) a CDK4/6 inhibitor.
5. Must have received no more than 4 lines of systemic therapy (for example, including but not limited to endocrine therapy, targeted therapy, biologic therapy, chemotherapy, or experimental therapy) for the treatment of breast cancer in the metastatic setting.
6. Premenopausal or postmenopausal female or male patients 18 years of age or older.
7. Measurable disease as defined by RECIST v1.1 criteria (tumor ≥ 1 cm in longest diameter on axial image on computed tomography (CT) or magnetic resonance imaging (MRI) or tumor ≥ 10 mm by caliper measurement on clinical exam and/or lymph node(s) ≥ 1.5 cm in short axis on CT or MRI) at baseline. Lytic bone lesions or mixed lytic-blastic lesions with an associated soft tissue component ≥ 10mm noted on CT or MRI are also included as per RECIST 1.1 criteria. Index lesions must not have undergone prior radiation therapy.
8. Asymptomatic brain metastases are allowed if the lesions are not considered to need local therapy. Previously treated brain metastases are allowed as long as they are > 4 weeks from local therapy, clinically asymptomatic, and not requiring high-dose corticosteroids. Patients may remain on steroids for CNS disease if they are taking a stable dose that is less than 10mg of prednisone per day, or the equivalent.

9. Must be capable of understanding and complying with parameters as outlined in the protocol and able to sign and date the informed consent, approved by the IRB, prior to the initiation of any screening or study-specific procedures.
10. Life expectancy of more than 3 months.
11. ECOG performance status 0-1 (Appendix A, Table 7).
12. Pregnancy must be ruled out in women of childbearing potential. Serum or urine pregnancy test must be negative within 14 days of treatment start in women of childbearing potential and must be willing to have pregnancy test approximately every 4 weeks. Pregnancy testing does not need to be pursued in patients who are judged to be postmenopausal before enrollment, or who have undergone bilateral oophorectomy, total hysterectomy, or bilateral tubal ligation.
    a. Patients may be considered postmenopausal in the case that one of the following criteria applies:
        i. Prior bilateral oophorectomy, OR
        ii. Age ≥ 60 years, OR
        iii. Age < 60 years with intact uterus and amenorrhoeic for ≥ 12 consecutive months **prior to** chemotherapy and/or endocrine therapy exposure
13. Willingness to utilize adequate contraception if of childbearing potential. Women of childbearing potential must use adequate contraception for the duration of protocol treatment and for at least 6 months after the last treatment with SM-88 used with MPS.
    a. Adequate contraception is defined as one highly effective form (i.e., abstinence, (fe)male sterilization) OR two effective forms (IUD [non-hormonal preferred], condom with spermicidal foam / gel / film / cream / suppository, occlusive cap with spermicidal foam / gel / film / cream / suppository).
14. Must be able and willing to swallow pills whole and retain oral medication.
15. Adequate hematologic parameters (Patients must be able to meet the following criteria without transfusion or receipt of colony stimulating factors within 2 weeks before obtaining sample):
    a. Absolute neutrophil count (ANC) ≥ 1,500/mm3; Patients must be able to meet the criteria without receipt of colony stimulating factors within 2 weeks before obtaining sample
    b. Platelets ≥ 100,000/mm3; Patients must be able to meet the criteria without receipt of transfusion within 2 weeks before obtaining sample
    c. Hemoglobin ≥ 9 g/dL; Patients must be able to meet the criteria without receipt of transfusion within 2 weeks before obtaining sample
16. Serum creatinine clearance ≥ 55 mL/min based on Cockcroft-Gault equation
17. Adequate hepatic parameters:
    a. Aspartate aminotransferase (AST) and/or Alanine aminotransferase (ALT) ≤ 3 x ULN
    b. Total serum bilirubin ≤ 1.5 x ULN, except for patients with a documented history of Gilbert's Syndrome who can be enrolled at PI discretion
    c. For patients with liver metastases, AST and ALT $\underline{\leq}$ 5x the institution's ULN and/or total bilirubin ≤ 3.0x the institution's ULN are acceptable as long as there is no persistent nausea, vomiting, right upper quadrant pain or tenderness, fever, or rash.
18. Alkaline phosphatase ≤2.5 x ULN (≤5.0 x ULN if bone metastases present)
19. Resolution of all acute toxic effects of prior therapy, including radiotherapy to grade ≤1 or patient's baseline (except toxicities not considered a safety risk for the patient) and recovery from surgical procedures.
20. Must have discontinued all previous therapies for cancer (including endocrine therapy, CDK4/6 inhibitor therapy, cytotoxic chemotherapy, targeted therapy [including, but not limited to, everolimus], radiotherapy, immunotherapy, and investigational therapy) for at least 14 days prior to receiving study drugs.

3.3. Exclusion Criteria

1. Concurrent therapy with other approved or investigational cancer treatment agents, except bisphosphonates, RANKL inhibitors, GnRH agonists such as leuprolide or goserelin.
2. Inability to comply with study requirements.

3. Diagnosis of other invasive cancer except for adequately treated cervix cancer, or more than 5 years since other diagnosis of invasive cancer (including invasive squamous cell cancers due to contraindication for methoxsalen use) without current evidence of disease.
4. Pregnant women or women of childbearing potential without a negative pregnancy test (serum or urine) within 14 days prior to starting study treatment.
5. Breastfeeding must be discontinued prior to study entry.
6. Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of the study drugs (e.g., ulcerative diseases, uncontrolled nausea/vomiting, chronic diarrhea, malabsorption syndrome, intestinal obstruction, or small bowel resection) at discretion of investigator.
7. Patients with clinically significant liver disease, including active viral (including hepatitis B, hepatitis C, etc) or other known active hepatitis, current alcohol abuse, or cirrhosis.
8. Known chronic hepatitis B virus infection (testing not required prior to enrollment).
    a. Patients with chronic hepatitis C virus infection may be enrolled if there is no clinical/laboratory evidence of cirrhosis per investigator AND the patient's liver function tests fall within the parameters set in the inclusion criteria, Section 3.2.
9. Uncontrolled HIV infection defined as any of the following 3 criteria: CD4 counts ≤ 350 cells/μL; serum HIV viral load ≥ 400 copies/mL; on a antiretroviral regimen for < 4 weeks prior to treatment with study drugs if anti-retroviral therapy is deemed necessary or appropriate by the investigator.
10. Previous enrollment in this study or any other study investigating SM-88.
11. History of any known drug allergies to any study medication.
12. Clinically significant and uncontrolled major medical condition(s) including, but not limited to uncontrolled nausea/vomiting/diarrhea; active, uncontrolled infection; symptomatic congestive heart failure (New York Heart Association [NYHA] class ≥ II); unstable angina pectoris; cardiac arrhythmia requiring hospitalization in the past 3 months; stroke or MI in the past 6 months.
13. Psychiatric illness or social situation that would limit compliance with study requirements.
14. Active uncontrolled or symptomatic brain metastases. Previously treated and clinically stable brain metastases, as per Investigator's judgement, are permitted.
15. Patients with a seizure disorder that is not well controlled or who have required a change in seizure medications within 60 days of enrollment to the trial.
16. Patients with a history of hypersensitivity to phenytoin, its inactive ingredients, or other hydantoins; or a history of prior acute hepatotoxicity attributable to phenytoin.
17. Patients treated, or anticipated to be treated, with delavirdine (due to potential for loss of virologic response and possible resistance to delavirdine or to the class of non-nucleoside reverse transcriptase inhibitors caused by phenytoin).
18. Patients exhibiting idiosyncratic reactions to psoralen compounds.
19. Patients with a history of the light sensitive diseases for which methoxsalen would be contraindicated. Diseases associated with photosensitivity include lupus erythematosus, porphyria cutanea tarda, erythropoietic protoporphyria, variegate porphyria, xeroderma pigmentosum, and albinism.
20. Patients with cutaneous melanoma or invasive squamous cell carcinomas or a history thereof, except for those with stage 1A melanoma or in complete remission for ≥5 years (due to contraindication for use of methoxsalen).
21. Patients with a hypersensitivity to sirolimus. Sirolimus does cause immune suppression at the prescribed doses and physicians should note the drugs black box warning to exclude any patient they believe the other exclusion criteria does not reflect.
22. Patients with prior allogenic bone marrow transplant or solid organ transplant organ transplant or being treated, or anticipated to be treated, with cyclosporine (because long-term administration of the combination of cyclosporine and sirolimus is associated with deterioration of renal function).
23. Patients treated, or anticipated to be treated, with a calcineurin inhibitor (because concomitant use of sirolimus and a calcineurin inhibitor increases the risk of calcineurin inhibitor-induced hemolytic uremic syndrome/thrombotic thrombocytopenic purpura/thrombotic microangiopathy [HUS/TTP/TMA]).
24. Current use of known strong inhibitors or inducers of CYP3A4, CYP2C9 or CYP2C19 within 14 days of initiation of study drug. When possible these medications and grapefruit juice should be avoided for the duration of the study treatment and alternate therapies are preferred. For a list, refer to Section 3.5 or Appendix D of the protocol.

3.4. Additional Study Restrictions

3.4.1. Granulocyte Colony-Stimulating Factor (GCSF)

GCSF administration should not be given within 2 weeks of study drug initiation or during the study treatment.

3.4.2. Other Anticancer Therapy

For purposes of this protocol, anti-tumor treatment may be defined as, but is not limited to, anti-cancer agents (anti-estrogen endocrine therapy, cytotoxic chemotherapy, immunotherapy, or biologic therapy), radiotherapy, and investigational agents. An investigational agent is any drug or therapy not currently approved for use in humans. No other anticancer therapy is permitted during the course of the study treatment for any patient (the patient can receive a stable dose of corticosteroids during the study as long as these were started at least 4 weeks prior to enrollment and the total daily dose does not exceed 10mg of prednisone, or the equivalent, per exclusion criteria above). If the patient discontinues study treatment, this restriction no longer applies; however, the patient will remain enrolled in the study for the purpose of collecting subsequent outcomes.

3.4.3. Birth Control

Birth control should be used from the signing of the patient consent form and for 3 months following the last dose of SM-88 and/or MPS. Acceptable methods of birth control include:

- Age ≥ 60 years
- At least one highly effective form of contraception (i.e., abstinence, (fe)male sterilization/tubal ligation)
- At least two effective forms (IUD [non-hormonal preferred], condom with spermicidal foam / gel / film / cream / suppository, occlusive cap with spermicidal foam / gel / film / cream / suppository).
- Permanent sterilization, defined as hysterectomy, bilateral salpingectomy, bilateral oophorectomy, or bilateral orchidectomy
- Postmenopausal, defined as a female patient < 60 years of age with intact uterus and amenorrhoeic for ≥ 12 consecutive months **prior to** chemotherapy and/or endocrine therapy exposure

In addition, men must not conceive a child or donate sperm during SM-88 and/or MPS therapy, and for 6 months after receiving the last dose of study therapy.

3.4.4. Breastfeeding

Patients must not breast-feed from the first dose of SM-88 and/or and for 1 month following the final dose of SM-88 and/or MPS.

3.4.5. Blood Donation

Patients must not donate blood during the study or for 90 days after the last dose of study treatment.

3.5. Other Prior and Concomitant Therapy

Patients will be instructed to consult the Investigator or other appropriate study personnel before taking any new medications, supplements, or vaccines during the study.

Concomitant medications taken within 30 days prior to baseline will be recorded. At each study visit, all concomitant medications taken since the previous visit, including prescription and non-prescription medications, vitamin and mineral supplements, herbal and naturopathic remedies, vaccines, and supportive therapies, will be recorded.

- Treatment with any other anticancer agents is not allowed except for bisphosphonates, RANK-L inhibitors, and GnRH agonists
- Medications that are clinically known to induce or inhibit metabolic enzymes or transporters, including CYP3A4, CYP2C9, CYP2C19, and p-glycoprotein (Pgp) must be used with caution or

avoided. Known strong inhibitors or inducers of CYP3A4, CYP2C9 or CYP2C19, such as those listed below, are not allowed within 14 days prior to the first dose of study medication and for the duration of study treatment. When possible these medications and grapefruit juice should be avoided for the duration of the study treatment and alternate therapies are preferred:

- CYP2C9:
  - Strong inhibitors: fluconazole
  - Strong inducers: none known
- CYP2C19:
  - Strong inhibitors: fluconazole, fluvoxamine, ticlopidine
  - Strong inducers: none known
- CYP3A4:
  - Strong inhibitors: atazanavir, boceprevir, ciclosporin, clarithromycin, conivaptan, danazol, erythromycin, gemfibrozil, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, osaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole,
  - Strong inducers: avasimibe, carbamazepine, phenobarbital, rifabutin, rifampin, St. John's Wort
  - Delavirdine
  - Cyclosporine
  - Calcineurin inhibitors

3.5.1. Prior Surgery

Patients must have fully recovered from all effects of surgery.

3.5.2. Supportive Care

Patients should receive best supportive care and treatment of symptoms during the study as appropriate, including transfusion of blood and blood products, oxygen therapy, nutritional support, intravenous fluids, and treatment with appropriate medications (antibiotics, antiemetics, antidiarrheals, and analgesics, etc.). Medications that are given for supportive care, such as appetite stimulation, may be given concurrently.

3.5.2.1. Bisphosphonates and denosumab

Bisphosphonates and denosumab are permitted for the treatment of osteoporosis and prevention of skeletal related events for patients with bone metastases.

3.5.2.2. GnRH agonists

GnRH agonists are permitted at the discretion of the treating physician.

3.5.2.3. Hematopoietic growth factors

Hematopoietic growth factors are not permitted during study treatment. The patient should be referred to a hematologist for further evaluation (1) if frequent transfusions are required or (2) if the treatment-related hematologic toxicities have not recovered to CTCAE Grade 1 or less after 4 weeks.

3.6. Removal/Replacement of Patients from Therapy or Assessment

3.6.1. Screen Failures

All patients must continue to meet the inclusion and exclusion criteria up to and including the first day of treatment. Reasons for patients who have enrolled, but become ineligible could include (but are not limited to):

- The patient is no longer eligible based on laboratory parameters
- The patient's performance status has declined

- The patient no longer has measurable disease

Patients who become ineligible prior to initiation of therapy per protocol will be considered screen failures. Screen failures must be replaced until 50 patients with advanced HR+/HER2- breast cancer are enrolled.

3.6.2. Evaluable Patients

3.6.2.1. Objective Response Evaluable

To be considered evaluable for the primary endpoint of ORR as determined by RECIST v1.1, the patient must meet all inclusion/exclusion criteria and remain on study treatment at least until the first re-staging after cycle 2 of SM-88 used with MPS unless they are taken off for disease progression, clinical progression, or death related to the underlying solid tumor malignancy (as determined by the treating oncologist) in which case they ***will be*** deemed evaluable. However, patients who have initiated therapy and who withdraw from the study for any reason other than clinical or radiographic progression, or death believed unrelated to their underlying solid tumor malignancy ***will not be*** considered evaluable for response. Reasons for patients who have initiated therapy, but are no longer evaluable for response could include (but are not limited to):

- The patient cannot tolerate therapy despite dose modifications, and there is no evidence of clinical/radiographic disease progression at the time of stopping therapy
- An unexpected and/or unrelated medical illness, such as a stroke or myocardial infarction that is considered unrelated to the underlying solid tumor malignancy
- An unexpected trauma or death that is considered unrelated to the underlying solid tumor malignancy

If a patient is deemed to be non-evaluable for the primary endpoint of ORR they will be replaced.

3.6.2.2. Safety/Tolerability Evaluable

Any patient who receives at least one dose of SM-88 and/or MPS will be evaluable for safety and tolerability as measured by NCI CTCAE v5.0.

3.7. Multicenter Trial Management

3.7.1. Personnel

At each site, personnel dedicated to this protocol will be:

- A study PI
- A research coordinator
- A data manager

In addition, Georgetown University's Multicenter Project Management Office will oversee the conduct of the trial at Lombardi-Georgetown and additional sites. Georgetown University's Multicenter Project Management Office will be the main point of contact for Dr. Ashai and the other site PIs for any study related concerns, including data management and regulatory.

3.7.2. Patient Enrollment

Enrollment at the sites will be competitive. If a patient is being screened for enrollment, the local research coordinator must send an email containing the patient's initials to the local PI, to Dr. Ashai, and to the Georgetown University's Multicenter Project Management Office. If a patient is successfully screened, the local research coordinator must send all supporting documentation to Georgetown University's Project Management Office by secure email to confirm eligibility. Patients should not start therapy until Dr. Ashai and Georgetown University's Project Management Office have reviewed the patient's records and confirmed that the patient is indeed eligible for enrollment.

3.7.3. Data Collection and Management

Patient data will be entered into the on-line accessible database. This database is housed at Lombardi-Georgetown, but is accessible anywhere there is internet access. The data manager and research coordinator at each site will attend an on-line training session (if not done previously) so that they may learn how to enroll data into the database. All screening data should be entered prior to starting therapy, and all ongoing patient data should be entered within 10 business days of each patient visit.

3.7.4. Conference Calls

A monthly conference call will be held between Lombardi-Georgetown and the other sites. Lombardi-Georgetown will conduct the conference call to review screening and enrollment metrics, participant milestone dates, troubleshoot study challenges, and answer site questions. Site PI, participating investigators, study coordinators and data managers may attend. At least one site representative should attend each call.

3.7.5. Trial Auditing

Georgetown University's Multicenter Project Management Office will arrange all primary source documents for the patients to be audited. This will include collecting copies of the primary source data for any patients treated at other sites.

4. Study Procedures

4.1. Study Procedures

The study-specific assessments are detailed in this section are outlined in Table 3.

Thirty patients will be enrolled in first stage of the study, and if 3 or more patients have an objective response (complete or partial response) then an additional 20 patients will be enrolled in the second stage of the study. Patients will receive the recommended phase 2 dose (RP2D) of SM-88 (460 mg by mouth [PO] twice a day [BID] D1 – 28) as well as three conditioning agents (MPS): methoxsalen (10 mg PO daily [Qd] D1 – 28), phenytoin (50 mg PO Qd D1 – 28), and sirolimus (0.5 mg PO Qd D1 – 28).

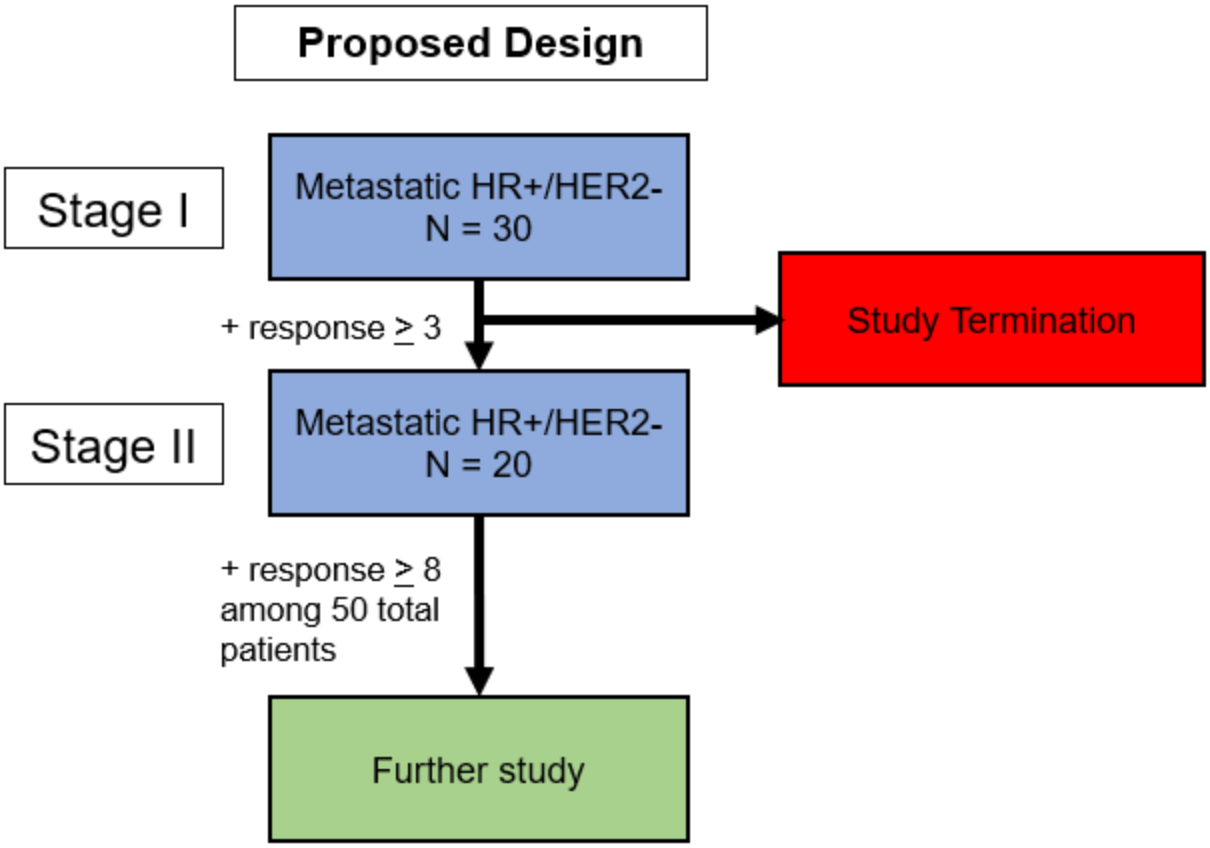


Figure 1. Study design

Patients will be evaluated, including physical exam and laboratory testing, every 4 weeks on Day 1 of each cycle. Laboratory testing will be performed every 2 weeks for the first 2 cycles and then on Day 1 of each subsequent cycle. Restaging scans will occur every 8 weeks (+/- 7 days) to evaluate for objective response. For patients who achieve a complete response (CR), partial response (PR), or stable disease (SD) confirmed on two consecutive restaging scans by RECIST v1.1 criteria, restaging scans may transition to every 12 weeks. Scans will occur as per this schedule determined by the calendar and not the cycle number. However, if there are any significant delays, restaging exams should not occur more than 12 weeks apart (+/- 7 days). Patients will continue to remain on study as long as there is no evidence of PD (according to RECIST v1.1 criteria) and the therapy is adequately tolerated. Interim analyses to assess secondary endpoints of CBR, PFS, and DOR will be scheduled to occur at 12 months and 24 months.

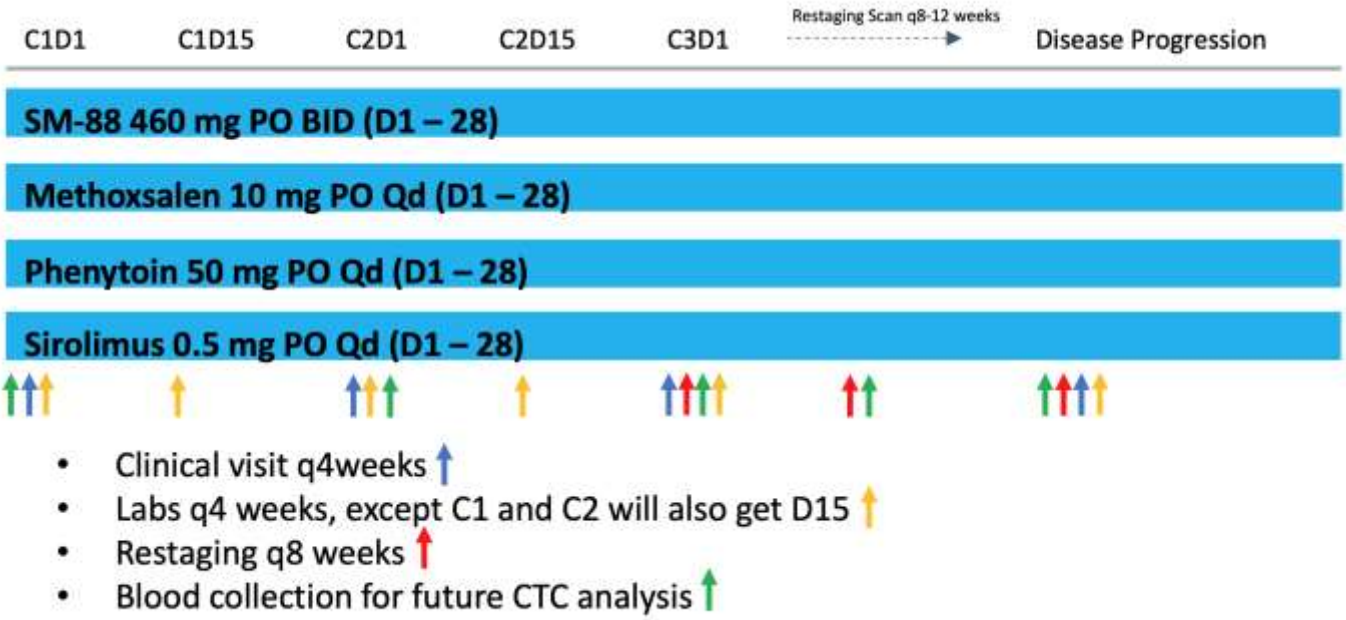


Figure 2: Study Schedule

4.2. Treatment Regimen

The trial is designed to assess the efficacy of SM-88 used with MPS in patients with advanced HR+/HER2- breast cancer.

Potential trial patients will be pre-identified at participating centers.

Patients who have an adequate performance status (PS), hematologic, hepatic, and renal function will be screened for enrollment. Patients who ultimately meet the inclusion and exclusion criteria as detailed in Section 3, and desire participation, will be enrolled.

4.3. Patient Screening, Enrollment, and Monitoring Assessments

Screening scans and laboratories must be completed within 28 days prior to the first dose of investigational product. Any results falling outside of the reference ranges may be repeated at the discretion of the Investigator. Assessments performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values even if the studies were done before informed consent was obtained. Treatment or visit delays for public holidays or weather conditions do not constitute a protocol violation.

Assessments performed exclusively to determine eligibility for this study will be done only after obtaining informed consent. Signed informed consent will be obtained from the patient or the patient's legally acceptable representative before any study-specific procedures are undertaken. For procedures performed at screening and repeated, the later procedure performed prior to dosing, will serve as a baseline for clinical assessment. A complete history and physical will be obtained at the screening visit. Additionally, labs will be reviewed/ordered during the screening visit, prior to the initiation of therapy.

Patients who pass screening will again undergo a full evaluation on Cycle 1 Day 1, including a physical examination, vital signs, performance status, chemistry, hematology, serum or urine pregnancy test, medication review, and adverse event evaluation. If any abnormality is identified at patient assessment on Cycle 1 Day 1, prior to initiating therapy, the patient will be deemed a screen failure and will not start treatment.

The screening and monitoring procedures include the following listed below. Details are provided in Table 3.

4.3.1. Informed Consent

Signed informed consent will be obtained from the patient or the patient's legally acceptable representative before any study-specific procedures are undertaken.

4.3.2. Medical History

The following information should be collected during the Screening Period:

1) Complete medical history, including documentation of any clinically significant medical conditions
2) Presence and severity of any symptoms/conditions associated with their advanced solid tumor malignancy
3) Detailed oncology history, including:
    a. Date of primary cancer diagnosis
    b. Pathology (histology or cytology) of primary tumor
    c. Metastasis information (including the location)
    d. Surgical history
    e. Anti-cancer and radiation treatments administered (including dates and type of modality, and if therapy was in the neoadjuvant, adjuvant, or metastatic setting)
4) At each visit, the patient's medical history will be reviewed and any changes from baseline will be recorded in the CRF. On Cycle 1 Day 1 any changes observed from the screening assessments, prior to dosing, will be recorded in the patient's medical history. All medications (prescription or over-the-counter, including vitamins and/or herbal supplements) will be recorded beginning with the Screening Visit and continuing up through the date of the off study visit
5) When available, also collect genomics,

4.3.3. Demographics

Age, gender, and self-reported race/ethnicity will be recorded.

4.3.4. Review patient eligibility criteria

See Section 3.2 (Inclusion criteria) and Section 3.3 (Exclusion criteria).

4.3.5. Review previous and concomitant medications

See Section 3.5.

4.3.6. Physical exam including vital signs, height, and weight

At screening, a physical examination, height, weight, blood pressure and pulse rate is required. Symptom-directed physical examinations, blood pressure, weight and pulse rate will be performed. All physical examinations and vital signs assessments should be performed by a physician or registered nurse or other qualified health care provider according to local regulations.

4.3.7. Performance Status (PS)

PS will be evaluated prior to study entry according to Table 7 in Appendix A.

4.3.8. Laboratory samples

Laboratory samples for this study will be assessed using the certified laboratory at the Investigators' institutions or at a clinical laboratory such as Quest or LabCorp and these data will be used for all data analysis. The Principal Investigator or sub-Investigator will review, initial and date all laboratory results. Any laboratory value outside the reference range that is considered clinically significant by the Investigator will be followed as appropriate. Clinically significant laboratory values will be recorded as adverse events if they meet the criteria as specified in Section 6.3.

4.3.8.1. Hematology

Hematology samples (complete blood count [CBC]) will be collected and assessed using a certified laboratory. The Investigator will review, initial, and date all laboratory results. Any laboratory value outside the reference range stated in the inclusion criteria will preclude the patient from study participation.

4.3.8.2. Serum chemistries

Comprehensive metabolic panel (CMP) to include: albumin, alkaline phosphatase, ALT, AST, blood urea nitrogen (BUN), creatinine, electrolytes (sodium, potassium, calcium, chloride, bicarbonate), glucose, and total bilirubin. Any laboratory value outside the reference range stated in the inclusion criteria will preclude the patient from study participation.

4.3.8.3. Lipid panel

Lipid panel to include: total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides. Laboratory values outside the reference ranges at an institution will not preclude the patient from participation in the study at the treating physician's discretion, but values will be followed throughout the study.

4.3.8.4. Pregnancy Test

For female patients of childbearing potential, a serum or urine pregnancy test will be performed at the Screening Visit and a serum or urine pregnancy test will be done at the Cycle 1 Day 1 visit prior to the first dose of study drug if > 14 days from screening pregnancy test. A female patient will not be eligible for enrollment if she has a positive serum or urine pregnancy test ≤ 3 days prior to study drug administration, is breast-feeding, or is planning to conceive children within the projected duration of the study treatment. The test results must be reviewed and determined to be negative prior to dosing. If a urine pregnancy test is positive at Cycle 1 Day 1, it should be confirmed by a serum pregnancy test. Urine/Serum pregnancy tests for women of childbearing potential must be performed within 8 days of each subsequent cycle (approximately every 4 weeks) during treatment with study drugs. The test may be repeated more frequently at the discretion of the Investigator at any time during the study. Should a female study patient become pregnant or suspect she is pregnant while participating in this study, she should inform the treating Investigator immediately. The study PI Dr. Ashai and TYME should be notified as well, as outlined in Section 6.7. If a patient becomes pregnant, or if a patient's spouse becomes pregnant while on trial, he or she will be removed from the study immediately.

Pregnancy testing does not need to be pursued in patients who are judged to be postmenopausal before enrollment, or who have undergone bilateral oophorectomy, total hysterectomy, or bilateral tubal ligation. Patients may be considered postmenopausal in the case that one of the following criteria applies:

- Prior bilateral oophorectomy, OR
- Age ≥ 60 years, OR
- Age < 60 years with intact uterus and amenorrhoeic for ≥ 12 consecutive months **prior to** chemotherapy and/or endocrine therapy exposure

4.3.9. Tumor assessment

Patients must have measurable disease, defined as at least 1 unidimensionally measurable lesion as defined by RECIST v1.1 (tumor ≥ 1 cm in longest diameter on axial image on CT or MRI, tumor ≥ 10 mm by caliper measurement on clinical exam and/or lymph node(s) ≥ 1.5 cm in short axis on CT or MRI). This includes lytic bone lesions or mixed lytic-blastic lesions with an associated soft tissue component ≥ 10mm noted on CT or MRI as per RECIST v1.1. I. Index lesions cannot have been previously treated with local therapy, such as radiation.

Baseline imaging must be performed within 28 days of initiating therapy. Ideally, this will include a CT scan of the chest, abdomen, and pelvis with IV contrast, or can consist of an MRI of the chest, abdomen, and pelvis or

positron emission tomography (PET) scan with diagnostic non-contrasted CT of the chest, abdomen, and pelvis for patients who cannot undergo a contrast-enhanced CT scan. Bone scan will be done at screening and repeated only if clinically indicated or at the treating physician's discretion. If a patient has an allergy to IV contrast, appropriate pre-medication can be given to prevent a contrast reaction. Patients may undergo other modalities such as an MRI instead of a CT scan at the treating physician's discretion if appropriate (such as severe allergy to CT contrast, extremity tumors, bone metastases requiring bone scans, etc.).

Patients will receive therapy until disease progression, as per RECIST v1.1 criteria, or therapy intolerance. Response assessment will occur every 8 weeks (+/- 7 days), attempting to occur close to the start of a new cycle. If there are any significant delays, restaging exams must not occur more than 12 weeks (+/- 7 days) apart. For patients who achieve a CR, PR, or SD (as demonstrated by RECIST v1.1) confirmed on two consecutive restaging scans, restaging scans may transition to every 12 weeks. Re-staging CT scan of the chest, abdomen, and pelvis with IV contrast, MRI of the chest, abdomen, and pelvis, or positron emission tomography (PET) scan with diagnostic non-contrasted CT of the chest, abdomen, and pelvis will be repeated every 8 weeks (+/-7 days), or 12 weeks (+/- 7 days) if the patient has achieved CR, PR or SD on two consecutive restaging scans. Bone scan is optional. Only patients with SD, PR, or CR, as demonstrated by RECIST v1.1 will continue on treatment per protocol.

4.3.10. Adverse Event Assessment

Baseline symptoms at Cycle 1 Day 1 (prior to initiating therapy) should be detailed and graded. Once treatment has started, adverse events will be assessed every 4 weeks on Day 1 (+/-7 days). The individual Investigator should record any adverse event in detail including the date of onset, event diagnosis (if known) or sign/symptom, severity, time course, duration and outcome, relationship of the adverse event to study drug, and any action(s) taken. For serious adverse events not considered "probably related" to study drug, the Investigator will provide an "Other" cause of the event. For adverse events to be considered intermittent, the events must be of similar nature and severity. See Section 6.5 for Adverse Event monitoring and reporting. The Principal Investigator or sub-Investigators will assess adverse events, laboratory data and vital signs throughout the study. Adverse events will be assessed by NCI CTCAE Version 5.0. Adverse events, whether in response to a query, observed by site personnel, or reported spontaneously by the patient will be recorded. All adverse events will be followed to a satisfactory conclusion.

4.3.11. Correlative Blood Samples

Correlative blood samples will be obtained at time frames detailed below in Section 9.

4.3.12. Removal of Patients from Study Treatment

Each patient has the right to withdraw from study treatment at any time. In addition, the Investigator may discontinue a patient from the study treatment at any time for any reason if the Investigator considers it necessary, including the occurrence of an adverse event or noncompliance with the protocol. Each patient will be withdrawn from study treatment if any of the following occur:

1) The patient experiences either clinical or radiographic progressive disease.
2) The patient requires radiotherapy or alternate antineoplastic agents during the study period.
3) The Investigator believes it is in the best interest of the patient.
4) Clinically significant deterioration of the patient's medical status as determined by the Investigator.
5) Patient becomes pregnant or begins breastfeeding or partner becomes pregnant during the treatment portion of the study.
6) Any other medical reason that the study Investigator deems appropriate.

Note: If a patient requires one of the MPS conditioning agents to be discontinued, treatment with the other study medications may be continued at the discretion of the Investigator in consultation with Sponsor. If a patient requires SM-88 to be discontinued, treatment with the other study agents (MPS) will also be discontinued.

4.3.12.1. Discontinuation of Individual Patients

When a patient discontinues from the study treatment (without reaching a protocol-defined endpoint), the Investigator will notify the principal Investigator as soon as possible (provided, in each case, patient care and safety are not compromised). When a patient discontinues the study treatment, a final visit will be conducted, preferably prior to the initiation of another anticancer therapy. However, these procedures should not interfere with the initiation of any new treatments or therapeutic modalities that the Investigator or patient's treating physician feel are necessary to treat the patient's condition. Following discontinuation of the study drug, the patient will be treated in accordance with the Investigator's/treating physician's best clinical judgment. At the final visit, the reason(s) for the discontinuation from the study will be recorded and a physical examination, body weight, vital signs measurement, laboratory analyses, performance status, tumor assessment, collection of unused study drug, and an assessment of adverse events will be performed as soon as possible after discontinuation from the study treatment. If a patient is discontinued from the study with an ongoing adverse event or an unresolved clinically significant laboratory result, the site will attempt to provide follow up until a satisfactory clinical resolution of the laboratory result or adverse event is achieved. In the event of a positive result on a pregnancy test for a patient during the study, the administration of study drug to that patient must be discontinued immediately.

4.3.12.2. Patient Replacement Criteria

To be considered evaluable for the primary endpoint of ORR as determined by RECIST v1.1, the patient must meet all inclusion/exclusion criteria and remain on study treatment at least until the first re-staging after cycle 3 of SM-88 used with MPS unless they are taken off for disease progression, clinical progression, or death related to the underlying solid tumor malignancy (as determined by the treating oncologist) in which case they ***will be*** deemed evaluable. However, patients who have initiated therapy and who withdraw from the study for any reason other than clinical or radiographic progression, or death believed unrelated to their underlying solid tumor malignancy ***will not be*** considered evaluable for response. Reasons for patients who have initiated therapy, but are no longer evaluable for response could include (but are not limited to):

- The patient cannot tolerate therapy despite dose modifications, and there is no evidence of clinical/radiographic disease progression at the time of stopping therapy
- An unexpected and/or unrelated medical illness, such as a stroke or myocardial infarction that is considered unrelated to the underlying solid tumor malignancy
- An unexpected trauma or death that is considered unrelated to the underlying solid tumor malignancy

If a patient is deemed to be non-evaluable for the primary endpoint of ORR they will be replaced.

4.3.12.3. Discontinuation of Entire Study

The Investigators may terminate this study provided that written notice is submitted at a reasonable time in advance of the intended termination. The following procedures for discontinuation will be followed:

1) If the Investigators have decided to prematurely discontinue the study, the Investigators will promptly notify in writing the IRB of the decision and give detailed reasons for the discontinuation.
2) The principal Investigator must promptly notify the enrolled patients of the premature discontinuation and administer appropriate treatments such as replacement of protocol therapy, if applicable, by other appropriate regimens.

4.3.13. Longitudinal Outcomes Assessment

Patients will be followed after progression until death (or up to 24 months) to assess overall survival, and to monitor for the development of secondary malignancies. Information pertaining to survival and post-treatment therapy will be collected approximately every 24 weeks (Month 6, 12, 18, and 24) beginning after the final visit, for a period up to 24 months.

4.3.14. Protocol Deviations

The Investigator should not implement any deviation from the protocol without prior review and agreement by the Sponsor and in accordance with the IRB and local regulations, except when necessary to eliminate an immediate hazard to study patients.

4.4. Treatment Assignment and Tumor Assessment

4.4.1. Patient Study Number Assignment and Sample Labeling

4.4.1.1. Patient Sample Labeling

Patients will be de-identified and labeled with a 8 character study label (OASIS-XXX-####-XX):

- Each ID will start with “OASIS”
- The first three letters will be the site name.
    - GUH = Georgetown
    - WHC = Washington Hospital Center
    - HAC = Hackensack
    - FRA = Franklin Square
    - GOO = Good Samaritan
- The four numbers will refer to the patient number preceded by the site number
    - 1 = Georgetown
    - 2 = Washington Hospital Center
    - 3 = Hackensack
    - 4 = Franklin Square
    - 5 = Good Samaritan
- This will be followed by 2 letters that will be the 2 patient initials (first name, last name)

4.5. Study Activities Checklist

Screening

Eligibility Criteria _____
Informed Consent _____
Demographics _____
Medical History _____
Concomitant Medications _____
Pregnancy Test _____
Vital Signs _____
Height _____
Weight _____
History and Physical _____
Performance Status _____
CBC with Differential _____
Serum Chemistries (sodium, potassium, calcium, chloride, bicarbonate), BUN, creatinine, AST, ALT, total bilirubin, albumin, alkaline phosphatase) _____
Lipid Panel (total cholesterol, LDL, HDL, and triglycerides) _____
CT c/a/p with IV contrast or MRI or PET/CT (diagnostic CT) _____
Bone scan (optional, at investigator discretion) _____
Brain MRI (if history of brain metastases or current suspicious neurologic symptoms) _____
Tumor Measurements _____

Cycle 1, Day 1

Concomitant Medications _____
Pregnancy Test (within 14 days of C1D1) _____
Weight _____
Vital Signs _____
Interval History and Physical _____
Performance Status _____
Adverse Event Evaluation _____
CBC with Differential (within 8 days) _____
Serum Chemistries (sodium, potassium, calcium, chloride, bicarbonate), BUN, creatinine, AST, ALT, total bilirubin, albumin, alkaline phosphatase) (within 8 days) _____
Dispense SM-88 and MPS _____
Cell free DNA (cfDNA) collection (pre-treatment) _____

Cycle 1, Day 15

CBC with Differential (+/- 3 days) _____
Serum Chemistries (sodium, potassium, calcium, chloride, bicarbonate), BUN, creatinine, AST, ALT, total bilirubin, albumin, alkaline phosphatase) (+/- 3 days) _____

Cycle 2, Day 1

Concomitant Medications _____
Pregnancy Test (within 8 days) _____
Weight _____
Vital Signs _____
Interval History and Physical _____
Performance Status _____
Adverse Event Evaluation _____
CBC with Differential (within 8 days) _____
Serum Chemistries (within 8 days) _____
Cell free DNA (cfDNA) collection _____
Study Drug Accountability _____
Dispense SM-88 and MPS _____

Cycle 2, Day 15

CBC with Differential (+/- 3 days) _____
Serum Chemistries (sodium, potassium, calcium, chloride, bicarbonate), BUN, creatinine, AST, ALT, total bilirubin, albumin, alkaline phosphatase) (+/- 3 days) _____

First Response Assessment (after 8 weeks on treatment, Cycle 3 Day 1)

Pregnancy test (within 8 days) _____
Weight _____
Vital Signs _____
Concomitant Medications _____
Interval History and Physical _____
Performance Status _____
Adverse Event Evaluation _____
CBC with Differential (within 8 days) _____
Serum Chemistries (within 8 days) _____
Lipid Panel (total cholesterol, LDL, HDL, and triglycerides) (within 8 days) _____
Study Drug Accountability _____
Dispense SM-88 and MPS _____
CT c/a/p with IV contrast or MRI or PET/CT (diagnostic CT) _____
Bone scan (optional, at investigator discretion) _____
Brain MRI (if history of brain metastases or current suspicious neurologic symptoms) _____
Tumor Measurements _____
Cell-free DNA (cfDNA) collection _____
Study Drug Accountability _____

Every 8 Weeks After First Response Assessment

(Until CR, PR, or SD confirmed on two consecutive restaging scans)

CT c/a/p with IV contrast or MRI or PET/CT (diagnostic CT) _____
Bone scan (optional, at investigator discretion) _____
Brain MRI (if history of brain metastases or current suspicious neurologic symptoms) _____

Tumor Measurements _____
Lipid Panel (total cholesterol, LDL, HDL, and triglycerides) (within 8 days) _____
Cell-free DNA (cfDNA) collection _____

Every 8-12 Weeks - After Disease Response Confirmed

(If patients achieve a CR, PR, or SD confirmed on two consecutive restaging scans, Response Assessment may transition to every 12 weeks)

CT c/a/p with IV contrast or MRI or PET/CT (diagnostic CT) _____
Bone scan (optional, at investigator discretion) _____
Brain MRI (if history of brain metastases or current suspicious neurologic symptoms) _____
Tumor Measurements _____
Lipid Panel (total cholesterol, LDL, HDL, and triglycerides) (within 8 days) _____
Cell-free DNA (cfDNA) collection _____

Day 1 of Subsequent Cycles

Concomitant Medications _____
Pregnancy Test (within 8 days) _____
Weight _____
Vital Signs _____
Interval History and Physical _____
Performance Status _____
Adverse Event Evaluation _____
CBC with Differential (within 8 days) _____
Serum Chemistries (within 8 days) _____
Study Drug Accountability _____
Dispense SM-88 and MPS _____

End of Treatment (+ 10 days from last dose)

Weight _____
Vital Signs _____
Concomitant Medications _____
Interval History and Physical _____
Performance Status _____
Adverse Events Evaluation _____
CBC with Differential (within 8 days) _____
Serum Chemistries (within 8 days) _____
Lipid Panel (total cholesterol, LDL, HDL, and triglycerides) (within 8 days) _____
Study Drug Accountability _____
CT c/a/p with IV contrast or MRI or PET/CT (diagnostic CT); if not done within 30 days prior to the visit _____
Bone scan (optional, at investigator discretion) _____
Brain MRI (if history of brain metastases or current suspicious neurologic symptoms); if indicated and not done within 30 days prior to the visit _____
Tumor Measurements _____
Cell free DNA (cfDNA) collection _____

Follow-up Assessments (every 6 months x 2 years)

Patient Assessment (may be done via phone or email)	_____
Adverse Events Evaluation (if AE(s) from study have not yet been closed)	_____
Vital Status Data Collection	_____

4.6. Study Calendar

Screening assessments are to be conducted within 28 days prior to initiating protocol therapy unless otherwise specified. Screening assessments occurring within 28 days prior to initiating study treatment do not need to be repeated on Cycle 1 Day 1 unless otherwise specified.

CBC with differential and biochemical profile (sodium, potassium, calcium, chloride, bicarbonate, BUN, creatinine, AST, ALT, total bilirubin, albumin, alkaline phosphatase) assessments must be done within 8 days prior to initiating protocol therapy and within 8 days of each subsequent cycle. For women of childbearing potential, as defined in the eligibility criteria, a pregnancy test must be completed within 14 days prior to initiating protocol therapy and within 8 days of each subsequent cycle. If a urine pregnancy test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

Assessments must be performed prior to administration of any study agent. Study assessments and agents should be administered within +/- 7 days of the protocol-specified date, unless otherwise noted.

Table 3. Study Calendar

	Screening <28 days prior to C1D1	Cycle 1[1]	C1D15	Cycle 2	C2D15	Cycle 3	All subsequent Cycles	Every 8-12 weeks	End of Treatment[11]	Long Term FU[13]
		D1	D15	D1	D15	D1	D1			
Sign informed consent	X									
Review of eligibility criteria	X									
Demographics	X									
Clinical visit	X	X		X		X	X		X	
Medical History	X									
Interval History		X		X		X	X		X	
Physical exam	X	X		X		X	X		X	
ECOG PS	X	X		X		X	X		X	
Height	X									
Weight	X	X		X		X	X		X	
Vital Signs (temperature, pulse, respiratory rate, blood pressure)	X	X		X		X	X		X	
CBC w/ differential[3]	X	X	X	X	X	X	X		X	
Biochemical profile[2,3]	X	X	X	X	X	X	X		X	
Lipid profile (total cholesterol, LDL, HDL, triglycerides)[4]	X					X		X	X	
Serum or urine pregnancy test[5]	X	X		X		X	X			
Adverse event evaluation		X		X		X	X		X	X
Review of concomitant meds	X	X		X		X	X		X	
CT c/a/p or MRI[6, 11]	X					X		X	X	
Bone scan[12]	X					X (optional)		X (optional)	X (optional)	
Brain MRI[7, 11]	X					X		X	X	
Dispense SM-88 + MPS[8]		X		X		X	X			
Study drug accountability				X		X	X		X	
Tumor measurements[9, 11]	X					X		X	X	
cfDNA collection[10]		X		X		X		X	X	
Telephone or email contact every 6 months x 2 years[13]										X

[1] Cycle length is 4 weeks (+/- 7 days). Evaluations performed at baseline do not need to be repeated on Day 1 of Cycle 1 if performed within prior 28 days, except CBC, biochemical profile, and pregnancy test.

[2] Biochemical Profile: sodium, potassium, calcium, chloride, bicarbonate, BUN, creatinine, AST, ALT, total bilirubin, albumin, alkaline phosphatase.

[3] CBC with differential and biochemical profile must be done within 8 days prior to C1D1, on C1D15 and C2D15 +/- 3 days, and then within 8 days of each subsequent cycle day 1 (C2D1, C3D1, C4D1, etc.).

[4] Lipid profile must be done at baseline and within 8 days prior to C3D1 and then every 8-12 weeks (at each additional restaging scan) within 8 days of day 1 of that cycle.

[5] Applies to females of childbearing potential as defined in the eligibility criteria. Serum or urine pregnancy test must be negative within 14 days of C1D1 and within 8 days of each subsequent cycle.

[6] CT scan of chest, abdomen and pelvis with IV contrast or MRI or PET scan with diagnostic CT (CT can be non-contrast if contraindication to contrast per investigator). Every 8 weeks (+/- 7 days) after start of study therapy. For patients who

achieve a CR, PR, or SD (as demonstrated by RECIST v1.1) confirmed on two consecutive restaging scans, restaging scans may transition to every 12 weeks.

[7] Brain MRI, preferably with and without IV contrast if history of brain metastases or current suspicious neurologic symptoms. Every 12 weeks (+/- 8 days) after the start of therapy, if patient has a history of brain metastases, whether or not brain metastases have been locally treated.

[8] SM-88 460 mg PO twice a day D1 – 28; Methoxsalen 10 mg PO daily D1 – 28; Phenytoin 50 mg PO daily D1 – 28; Sirolimus 0.5 mg PO daily D1 – 28.

[9] Tumor measurements will be conducted according to RECIST v1.1 criteria.

[10] cfDNA will be collected at baseline (pre-treatment), C2D1, C3D1, at each additional restaging scan (every 8-12 weeks) and at progression of disease. Samples will be banked and can be analyzed in the future. If a cycle is delayed then these samples will be collected prior to restarting the study agents. If cfDNA sample has already been collected at the time point and then it is decided that the cycle must be delayed then the cfDNA sample does not need to be re-collected.

[11] End of Treatment visit should occur as soon as possible at the time of progression or discontinuation of treatment, preferably before the subject starts the next therapy, + 10 days from last dose. Imaging and tumor assessments do not need to be performed at this visit if performed within 30 days prior to the visit.

[12] Bone scan at investigator discretion

[13] Long term follow up assessment (+/- 4 weeks). Patients will be contacted by phone call or e-mail for vital status data collection, adverse events evaluation (if AEs from study have not yet been closed), subsequent anti-breast cancer therapy (systemic therapy, radiation, or surgery), and development of a secondary malignancy.

4.7. Long-term follow up

After patients complete participation on study, patients will be followed for survival and AE evaluation (if AEs from study have not yet been closed) every 6 months (+/- 4 weeks) until death, lost to follow-up, patient withdrawal of consent, study discontinued by the Sponsor, or 2 years, whichever comes first. These visits may be conducted in-clinic or by remote contact (e.g., telephone or email).

5. Dosages and Dispensation of Drugs

5.1. Dispensation of Study Drug and Treatments Administered

The study drugs are defined as SM-88, methoxsalen, phenytoin, and sirolimus. Patients will self-administer all study drugs by mouth on an outpatient basis. Patients will receive sufficient quantities of each study for 1 cycle of administration on Day 1 of each cycle. Patients will receive bottles of the study drugs from the on-site study coordinator and will be provided with drug diaries (see Appendix C) to record the date and time they took the drugs. On days when patient is scheduled for a clinic visit, the patient should take scheduled SM-88 and MPS doses once all visit assessments have been performed and are within acceptable range, unless otherwise indicated.

It is best to take doses one hour before or two hours after meals, so as to ensure an empty stomach. SM-88 and MPS should be taken together consistently either in the morning or in the evening with a full glass of water. A second dose of SM-88 will be taken 8-16 hours after the SM-88 plus MPS dose -- for example, before bedtime and upon waking up in the morning.

If vomiting occurs, no re-dosing of the patient is allowed prior to the next scheduled dose. If doses of any of the four study drugs are not taken within 4 hours of the intended time, the dose should be skipped and not replaced or made up on a subsequent day. If the AM dose of SM-88 is missed, patients will continue with the PM dose as scheduled. If the PM dose of SM-88 is missed, patients will skip that dose and resume dosing with the AM dose the following day. If a dose of MPS is missed, patients will skip that dose and resume dosing the following day.

Patients should return bottles of the study drugs (empty, partially filled, or full) and their diaries (See Appendix C) to the study site prior to start of next cycle and at the final visit.

Investigational product will be labeled according to applicable regulatory requirements. All investigational products will be stored, inventoried, reconciled, and destroyed according to applicable regulations.

Tyme, Inc. designee ALMAC will provide:

- SM-88 (D,L-alpha-metyrosine) which will be provided in 230 mg capsules. Two 230 mg capsules taken orally twice daily (920 mg daily).
- Methoxsalen will be provided in 10 mg capsules. One 10 mg capsule taken orally once daily.
- Phenytoin will be provided in 50 mg tablets. One 50 mg tablet taken orally once daily.
- Sirolimus will be provided in 0.5 mg tablets. One 0.5 mg tablet taken orally once daily.

5.2. SM-88 Description

SM-88 capsules, 230 mg, contain the drug substance, D,L-alpha-metyrosine. The drug substance is manufactured by Patheon API Services Inc. The drug product is manufactured by QS Pharma.

SM-88 230 mg capsules contain the following excipients: hydroxypropyl cellulose, colloidal silicon dioxide, and magnesium stearate. The drug product is encapsulated in HPMC shells. The excipients are U.S. Pharmacopeia Convention/National Formulary (USP/NF) grade. The excipients meet IID limits for solid oral dosage form.

5.3. Storage and Disposition of SM-88 and MPS

All components of SM-88 used with MPS should be kept in a secure area and stored as follows:

- SM-88 should be stored at room temperature 15 to 25 degrees C (59° to 77°F) and protected from light and moisture (USP Controlled Room Temperature).
- Methoxsalen capsules should be stored at 25 degrees C (77°F) (excursions permitted); temperatures between 15 to 30 degrees C (59° to 86° F are acceptable) and protected from light and moisture (USP Controlled Room Temperature). Preserve in a tight, light-resistant container as defined in the USP.
- Phenytoin should be stored at room temperature 20 to 25 degrees C (68° to 77°F) and protected from light and moisture (USP Controlled Room Temperature), dispensed in tight (USP), child resistant containers
- Sirolimus should be stored at room temperature (20 to 25 degrees C (68° to 77° F) and protected from light and moisture (USP Controlled Room Temperature). Dispense in a tight, light-resistant container as defined in the USP.

Investigational products are for investigational use only, and are to be used only within the context of this study. The clinical supplies supplied for this study must be maintained under adequate security and stored under conditions specified on the label. Destruction of used and unused study drug will be performed at the site.

5.4. Treatment Compliance

Patients will be instructed to return all bottles of SM-88, methoxsalen, phenytoin, and sirolimus to the study site personnel prior to each cycle and at the final visit. The study site personnel will document the bottles of study drug returned and the number of capsules per bottle, according to institutional policy. If the number of capsules taken and the number of capsules returned do not add up to the number of capsules dispensed, an explanation will be provided. Unless otherwise directed by the principal Investigator, a patient will be considered compliant with study drug if 85% of the assigned dose is taken during a cycle.

5.5. Drug Accountability

The Investigator or designee will verify that SM-88 and MPS supplies are received intact and in the correct amounts. A signed and dated Proof of Receipt (POR) or similar document will support documentation of the receipt of supplies. An accurate running inventory of SM-88 and MPS will be maintained by the site, and will include the lot number, POR number(s), the bottle and vial numbers, and the date study drug was dispensed for

each patient. Upon completion or termination of the study, all original containers (empty or containing unused study drug) will be returned to the manufacturer or destruction of used and unused study drug will be performed at the site. Labels must remain attached to the containers. The Investigator or his/her designated representative agrees not to supply study medication to any persons not enrolled in the study or not named as a sub-Investigator. The site will record the lot number(s) and doses of SM-88 and MPS given to each patient.

5.6. Recommended Dose Modifications

Every effort should be made to administer each investigational product at the planned dose and schedule.

In the event of significant toxicity, dosing may be interrupted, delayed and/or reduced, only as described for each investigational product. In the event of multiple toxicities, treatment/dose modifications should be based on the worst toxicity observed. Patients are to be instructed to notify Investigators at the first occurrence of any adverse symptom.

Treatment/dose modifications may occur independently for each investigational product in the combination based on the observed toxicity and the general guidance, as follows:

a. SM-88: Dose modifications (dose interruptions, or dose reductions) may be implemented to manage toxicities.
    i. If SM-88 is held then MPS should be held concurrently.
b. Methoxsalen, phenytoin, and sirolimus (MPS): No dose reductions are permitted in this study, but if methoxsalen, phenytoin, or sirolimus are considered to be the component associated with a grade 3 or 4 toxicity, the individual components may be discontinued for up to 28 days while mitigating measures are attempted (e.g. changing the timing of phenytoin to address phenytoin related fatigue if experienced). This may be applied to any or all of the MPS components. If after 28 days the grade > 2 toxicity continues, the patient will be removed from the study. If the patient restarts the MPS medication(s) but the toxicity recurs then the 28 day hold clock restarts so that further mitigation efforts can be implemented; if multiple holds are required then it is at investigator discretion if the patient should continue or come off the study.
    i. If any or all components of MPS are held then SM-88 can be continued at investigator discretion.

The RP2D of SM-88 is 920 mg/day administered as two 230 mg capsules every 12 hours. For patients experiencing a grade 3 or 4 toxicity, dose modifications of SM-88 can be made as outlined in **Table 4 and Table 5**.

Table 4. Dose Modifications for Toxicities Related to SM-88

Dose Level	SM-88 Dose	Dose Adjustment for Next Treatment
1	460 mg BID (920 mg/day)	Decrease dose to 230 mg BID
-1	230 mg BID (460 mg/day)	Discontinue study treatment for up to 28 days and attempt mitigation; if this dose is not tolerated then patient should be removed from the study

Table 5. Management of Toxicities Related to SM-88 and MPS

	SM-88 + MPS
Hematologic Toxicities	
Grade 1 and 2	No requirement for dose interruption or dose reduction
Anemia Grade ≥ 3 (hemoglobin < 8 g/dL or transfusion indicated)	• 1st occurrence: Hold SM-88 and MPS; monitor at least weekly and if hemoglobin recovers to ≥ 8 g/dL within 28 days then resume drugs and decrease SM-88 to dose level -1. Transfusion of blood and blood products are permitted. • Recurrence: Hold SM-88 and MPS; monitor at least weekly and if hemoglobin recovers to ≥ 8 g/dL within 28 days resume drugs and patient can remain on study at investigator discretion. • Permanently discontinue SM-88 and MPS if these parameters have not been met after 28 days of dose interruption.
Neutropenia Grade ≥ 3 (ANC < 1000/mm^3) associated with a documented infection or fever ≥ 38.5°C	• 1st occurrence: Hold SM-88 and MPS; monitor at least weekly and if ANC recovers (ANC ≥ 1000/mm^3) within 28 days, then resume drugs and decrease SM-88 to dose level-1. Hematopoietic growth factors are not permitted. • Recurrence: Hold SM-88 and MPS; monitor at least weekly and if ANC recovers (ANC ≥ 1000/mm^3) within 28 days then resume drugs at same dose level. • Permanently discontinue SM-88 and MPS if these parameters have not been met after 28 days of dose interruption.
Grade 4 neutropenia (ANC < 500/mm3)	• 1st occurrence: Hold SM-88 and MPS. Monitor at least weekly and if ANC recovers to ≥ 1000/mm^3 in ≤ 7 days, then resume study drugs at same dose level. If ANC remains < 1000/mm^3 for > 7 days, hold SM-88 and MPS until ANC ≥ 1000/mm^3 and decrease SM-88 to dose level -1. • Recurrence: Hold SM-88 and MPS; monitor at least weekly and if ANC recovers (ANC ≥ 1000/mm^3) within 28 days then decrease SM-88 to dose level -1 or resume drugs at same dose level if already at dose level -1. • Permanently discontinue SM-88 and MPS if these parameters have not been met after 28 days of dose interruption.
Thrombocytopenia Grade ≥ 3 (platelets <50,000/mL)	• Hold SM-88 and MPS; monitor at least weekly and if platelets recover (≥ 50,000/mL) within 28 days, then resume drugs at same dose level. • If Grade 3 thrombocytopenia (platelets < 50,000/mL) with bleeding, hold SM-88 and MPS. Monitor at least weekly and if platelets recover (≥ 50,000/mL) and bleeding stops within 28 days, resume drugs and decrease SM-88 to dose level -1. • If Grade 4 thrombocytopenia (platelets < 25,000/mL), hold SM-88 and MPS. Monitor at least weekly and if platelets recover (≥ 50,000/mL) within 28 days, resume drugs and decrease SM-88 to dose level -1. • Permanently discontinue SM-88 and MPS if Grade ≥ 3 thrombocytopenia (platelets <50,000/mL) recurs or persists for > 28 days.
Non-hematologic Toxicities	
Grade 1 and 2	• No requirement for dose interruption or dose reduction.
Grade ≥ 3	• 1st occurrence: Hold SM-88 and MPS; monitor and if toxicity decreases to Grade 1 or to baseline within 28 days, then resume drugs and decrease by SM-88 to dose level -1.

	• Recurrence: Hold SM-88 and MPS; monitor and if toxicity decreases to Grade 1 or to baseline within 28 days then resume drugs at same dose level. • *Exceptions are: Nausea, vomiting, or diarrhea lasting ≤72 hours; fatigue lasting ≤ 7 days; hypertension controlled with medical therapy; increase in indirect bilirubin indicative of Gilbert's syndrome; serum lipase or amylase lasting ≤ 7 days without clinical signs or symptoms of pancreatitis; endocrinopathies controlled with hormonal therapy; laboratory values that do not have any clinical correlate.*

All dose modifications should be clearly documented in the patient's medical chart and in the CRF.

6. Safety Variables and toxicity assessment

The Principal Investigator or Sub-Investigators will assess adverse events, laboratory data, and vital signs throughout the study. Adverse events will be assessed by NCI CTCAE Version 5.0. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

6.1. Adverse Events Assessment

The Investigators will monitor each patient for clinical and laboratory evidence of adverse events on a routine basis throughout the study. The Investigator will assess and record any adverse event in detail including the date of onset, event diagnosis (if known) or sign/symptom, severity, time course, duration and outcome, relationship of the adverse event to study drug, and any action(s) taken. For serious adverse events not considered "probably related" to study drug, the Investigator will provide an "Other" cause of the event. For adverse events to be considered intermittent, the events must be of similar nature and severity. Adverse events, whether in response to a query, observed by site personnel, or reported spontaneously by the patient will be recorded. All adverse events will be followed to a satisfactory conclusion.

6.2. Study Monitoring

6.2.1. Data Safety Monitoring Committee at Georgetown

The Georgetown Lombardi Comprehensive Cancer Center (LCCC) will be responsible for the data and safety monitoring of this trial. As this study is an Investigator initiated Phase II study utilizing investigational agents and FDA-approved off label therapies, it is considered a high risk study which requires real-time monitoring by the PI and study team and quarterly reviews by the LCCC Data and Safety Monitoring Committee (DSMC).

The Principal Investigator, Dr. Ashai, and the Study Chairs will review the data including safety monitoring at their monthly teleconferences with participating sites.

SAEs are required to be reported to the local and to the Georgetown IRB according to the IRB reporting guidelines. Based on SAEs, the IRB retains the authority to suspend further accrual pending more detailed reporting and/or modifications to further reduce risk and maximize the safety of participating patients.

Progress on the trial and the toxicities experienced will be reviewed by the LCCC Data and Safety Monitoring Committee every 3 months from the time the first patient is enrolled on the study. Results of the DSMC meetings will be forwarded to the IRB with recommendations regarding need for study closure.

DSMC recommendations should be based not only on results for the trial being monitored as well as on data available to the DSMC from other studies. It is the responsibility of the PI to ensure that the DSMC is kept

apprised of non-confidential results from related studies that become available. It is the responsibility of the DSMC to determine the extent to which this information is relevant to its decisions related to the specific trial being monitored.

A written copy of the DSMC recommendations will be given to the trial PI and the IRB. If the DSMC recommends a study change for patient safety or efficacy reasons the trial PI must act to implement the change as expeditiously as possible. In the unlikely event that the trial PI does not concur with the DSMC recommendations, then the LCCC Associate Director of Clinical Research must be informed of the reason for the disagreement. The trial PI, DSMC Chair, and the LCCC Associate Director for Clinical Research will be responsible for reaching a mutually acceptable decision about the study and providing details of that decision to the IRB. Confidentiality must be preserved during these discussions. However, in some cases, relevant data may be shared with other selected trial Investigators and staff to seek advice to assist in reaching a mutually acceptable decision.

If a recommendation is made to change a trial for reasons other than patient safety or efficacy the DSMC will provide an adequate rationale for its decision. If the DSMC recommends that the trial be closed for any reason, the recommendation will be reviewed by the Associate Director for Clinical Research at LCCC. Authority to close a trial for safety reasons lies with the IRB, with the above described input from DSMC and the Associate Director for Clinical Research.

Of note, the DSMC will also review the safety data of the patients enrolled outside of Georgetown University. The Georgetown Multicenter Project Manager(s) will be tasked with requesting primary source documentation for patients enrolled outside of Georgetown University, as needed. In addition, the data managers at each site will be entering data into the Georgetown database, so that all data will be available for the DSMC at Georgetown to review. Records should be sent via email to the Georgetown Multicenter Project Manager(s) and Dr. Ashai.

6.3. Adverse Event and Toxicity Definitions

6.3.1. Adverse Events

An AE is defined as any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product. Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an adverse event. Laboratory abnormalities and changes in vital signs are considered to be adverse events only if they result in discontinuation from the study, necessitate therapeutic medical intervention, and/or if the Investigator considers them to be adverse events.

An elective surgery/procedure scheduled to occur during a study will not be considered an adverse event if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure has been pre-planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (*e.g.*, surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an adverse event.

All AEs experienced by a patient, irrespective of the suspected causality, will be monitored until the AE has resolved, any abnormal laboratory values have returned to baseline or stabilized at a level acceptable to the Investigator, until there is a satisfactory explanation for the changes observed, until the patient is lost to follow-up, or until the patient has died.

6.3.2. Serious Adverse Events

If an adverse event meets any of the following criteria, it is to be reported to the DSMC as a SAE per DSMC reporting guidelines.

1) **Death of Patient** An event that results in the death of a patient.
2) **Life-Threatening** An event that, in the opinion of the Investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
3) **Hospitalization** (unless planned for observation, protocol compliance, elective procedures, social reasons) **or**
4) **Prolongation of Hospitalization** An event that results in an admission to the hospital for any length of time or prolongs the patient's hospital stay. This does not include an emergency room visit or admission to an outpatient facility.
5) **Congenital Anomaly** An anomaly detected at or after birth, or any anomaly that results in fetal loss.
6) **Persistent or Significant Disability/Incapacity** An event that results in a condition that substantially interferes with the activities of daily living of a study patient. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).
7) **Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome** An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the patient and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of patient, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Examples of such 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.
8) **Spontaneous Abortion** Miscarriage experienced by study patient.

Disease progression is an efficacy criterion and is therefore not considered an AE or SAE (even if fatal). Disease progression should be documented. If AEs/SAEs occur in relation to disease progression that are not consistent with the natural progression of the patient's disease, these AEs/SAEs must be reported per AE/SAE reporting requirements.

6.3.3. Adverse Event Severity

The study Investigator will rate the severity of each adverse event according to the NCI CTCAE Version 5.0. For adverse events not captured by the NCI CTCAE Version 5.0, the following should be used:

1) **Grade 1 (Mild)** The adverse event is transient and easily tolerated by the patient.
2) **Grade 2 (Moderate)** The adverse event causes the patient discomfort and interrupts the patient's usual activities.
3) **Grade 3/4 (Severe or Life Threatening)** The adverse event causes considerable interference with the patient's usual activities and may be incapacitating or life-threatening.
4) **Grade 5 (Severe, Resulting in Death)** The adverse event resulted in death of the patient.

6.3.4. Relationship to Study Drug

6.3.4.1. Assessment of Toxicity Relatedness to Study Medications

The Investigator will use the following definitions to assess the relationship of the adverse event to the use of study drug(s).

1) **Definitely Related** An adverse event has a clear temporal relationship to study drug(s) and/or recurs on re-challenge and another cause of event is extremely unlikely.
2) **Probably Related** An adverse event has a strong temporal relationship to study drug(s) or recurs on re-challenge and another cause of event is unlikely or significantly less likely.
3) **Possibly Related** An adverse event has a strong temporal relationship to the study drug(s) and another cause of event is equally or less likely compared to the potential relationship to study drug.
4) **Probably Not Related** An adverse event has little or no temporal relationship to the study drug(s) and/or a more likely Other cause of event exists.

5) **Not Related** An adverse event is due to an underlying or concurrent illness or effect of another drug(s) and is not related to the study drug (e.g., has no temporal relationship to study drug or has a much more likely Other cause of event).

6.3.4.2. Binary Assessment of Toxicity Relatedness to Study Medications

For the purposes of study reporting, we will use a binary reporting system for documenting relation to study medications. Specifically, any adverse event that is **not related** or **probably not related** to the study medications WILL NOT be reported as treatment related toxicities. Conversely, any adverse event that is **possibly related**, **probably related**, or **definitely related** WILL be reported as treatment related toxicities.

6.3.4.3. Attribution of Relationship to Study Medications

For every adverse event, the Investigator must also attribute whether the adverse event was due to (A) SM-88, (B) methoxsalen, (C) phenytoin, (D) sirolimus, (E) a combination of study medications (specify which), or (F) other causes.

If an Investigator's opinion of probably not or not related to study drug(s) is given, another cause of event must be provided by the Investigator for the adverse event.

6.4. Adverse Event Collection Period

All adverse events reported from the time of the administration of study drug until discontinuation of therapy will be collected, whether elicited or spontaneously reported by the patient. Serious adverse events related to the study or study procedures will be collected from the time the patient signs the study-specific informed consent. All SAEs, regardless of relationship to the study, will be reported from the time of first dose until the End of Treatment visit.

6.5. Adverse Event Reporting

In the event of an SAE, whether related to study drugs, study procedures, or even if not directly related to any study intervention, the Investigator will notify the PI, Dr. Ashai, the Multicenter Project Managers, and IRB as required per local IRB policy after being made aware of the serious adverse event. Furthermore, the Investigator will forward all treatment emergent SAE reports regardless of causality, to TYME within 24 hours of completion of the initial report. The institution will forward both initial and follow-up versions of each SAE report.

TYME REPORTING:

[redacted]

The SAE report should comprise a full written summary, detailing relevant aspects of the adverse events in question. Where applicable, information from relevant hospital case records and autopsy reports should be included. Follow-up information should be forwarded to TYME within 24 hours. SAEs brought to the attention of the Investigator at any time after cessation of the study drugs and considered by the Investigator to be related or possibly related to the study drugs must be reported to the study PI, Dr. Ashai, Multicenter Project Manager(s) and to the IRB when they occur, if required by the local IRB policy.

For patients enrolled outside of Georgetown University, serious adverse events will also be reported, and all supporting documentation sent (emailed) to the Multicenter Project Manager(s) and to the study PI, Dr. Ashai, within 24 hours. Emailed records should be sent to the Multicenter Project Manager(s) [redacted] and to Dr. Ashai.

6.6. Reporting Product Quality Complaints for SM-88

Any written, electronic, or oral communication that alleges dissatisfaction related to manufactured clinical drug product with regards to its manufacturing, testing, labeling, packaging, or shipping, must be reported by the

sponsor-Investigator or qualified designee to TYME within 1 working day of first becoming aware of the possible defect. The product and packaging components in question, if available, must be stored in a secure area under specified storage conditions until it is determined whether the product is required to be returned for investigation of the defect. If the product complaint is associated with an SAE, the SAE must be reported separately in accordance with the protocol, and the SAE report should mention the product quality complaint.

6.7. Pregnancy

Pregnancies (and pregnancy outcomes) occurring in a female patient or a female partner of a male patient must be reported to the Institution within 24 hours. Elective abortions without complications should not be considered AEs unless they were therapeutic abortions. Hospitalization for normal delivery of a healthy newborn should not be considered an SAE. Spontaneous abortions should always be reported as SAEs. The Investigator should follow-up with the study patient or the female partner of the study patient until delivery or termination of pregnancy, even if the patient was withdrawn from the clinical study or the clinical study was completed. TYME will be informed of all pregnancy outcomes.

In the event of a positive pregnancy test result, study drugs will be immediately discontinued. The Investigator must report the positive pregnancy test within 24 hours of the site becoming aware of the pregnancy to the IRB and to TYME. For patients enrolled outside of Georgetown University, documentation should be emailed to the Multicenter Project manager(s) at [redacted] and to the study PI, Dr. Ashai, within 24 hours.

Patients should also notify the Investigator if it is determined after completion of the study that they become pregnant either during the treatment phase of the study or within 30 days after the treatment period. Information regarding a pregnancy occurrence in a study patient and the outcome of the pregnancy will be collected, and the status of the mother and child should be reported to the IRB and TYME after delivery. Pregnancy in a study patient is not considered an adverse event but does require discontinuation of the patient from the study. However, the medical outcome of a spontaneous abortion, stillbirth, or congenital anomaly is considered a serious adverse event and must be reported to the IRB and TYME within 24 hours of the site becoming aware of the event.

6.8. General Management of Significant Toxicities

6.8.1. Significant Toxicities Management

The following are general guidelines for dose delay and discontinuation of the study drugs if a patient experiences an adverse event; Refer to **Table 5** for specific guidance:

- Patients may delay treatment for up to 28 days to allow the toxicity to resolve. If the toxicity requiring dose interruption has not resolved completely or to CTCAE Grade 1 (or to baseline if Grade 2 at time of study entry) during the maximum 28-day dose interruption period, the patient must permanently discontinue treatment on study
- Patients may restart therapy if toxicity(ies) resolve to Grade 1 or lower (or to baseline if Grade 2 at time of study entry).
- If a dose interruption is required at any point on study because of hematologic toxicity, weekly blood draws for CBC will be monitored until the AE resolves or the patient comes off study.
- The patient must be referred to a hematologist for further evaluation (1) if frequent (at investigator discretion) transfusions are required or (2) if the treatment-related hematologic toxicities have not recovered to CTCAE Grade 1 or less after 28 days.
- For major surgery while on treatment, up to 28 days of study treatment interruption is allowed.
- All dose interruptions (including any missed doses), and the reasons for the reductions/interruptions, are to be recorded.

6.8.2. Rescue Medications and Supportive Care Guidelines During Treatment with SM-88 and MPS

Patients should receive appropriate supportive care measures as deemed necessary by the treating Investigator.

6.8.3. Detailed Descriptions of Potential Adverse Events associated with MPS

6.8.3.1. Related to Phenytoin

Withdrawal Precipitated Seizure, Status Epilepticus

Abrupt withdrawal of phenytoin in epileptic patients may precipitate status epilepticus. When, in the judgment of the clinician, the need for dosage reduction, discontinuation, or substitution of alternative anticonvulsant medication arises, this should be done gradually. However, in the event of an allergic or hypersensitivity reaction, more rapid substitution of alternative therapy may be necessary. In this case, alternative therapy should be an anticonvulsant not belonging to the hydantoin chemical class.

Suicidal Behavior and Ideation

Phenytoin can increase the risk of suicidal thoughts or behavior in patients. Patients should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior. The increased risk of suicidal thoughts or behavior can occur as early as one week after starting treatment and persist for the duration of treatment. Should suicidal thoughts and behavior emerge during treatment, Investigators need to consider whether the emergence of these symptoms in any given patient may be related to the disease being treated. Patients, their caregivers, and families should be informed that AEDs increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence of or worsening of the signs and symptoms of depression, any unusual changes in mood or behavior, the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

Serious Dermatologic Reactions

Serious and sometimes fatal dermatologic reactions, including TEN and SJS, have been reported with phenytoin treatment. The onset of symptoms is usually within 28 days but can occur later. Phenytoin should be discontinued at the first sign of a rash, unless the rash is clearly deemed not drug-related. If signs or symptoms suggest SJS/TEN, phenytoin should be discontinued and not re-administered. If a rash occurs, the patient should be evaluated for signs and symptoms of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) (see next paragraph).

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multiorgan hypersensitivity

DRESS, also known as Multiorgan hypersensitivity, has been reported in patients taking phenytoin. Some of these events have been fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, and/or lymphadenopathy, in association with other organ system involvement, such as hepatitis, nephritis, hematological abnormalities, myocarditis, or myositis sometimes resembling an acute viral infection. Eosinophilia is often present. Because this disorder varies in its expression, other organ systems not noted here may be involved, and it is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, the patient should be evaluated immediately. Phenytoin should be discontinued and not re-administered if an alternative etiology for the signs or symptoms cannot be established.

Hypersensitivity

Patients with a history of hypersensitivity to phenytoin, its inactive ingredients, or other hydantoins; or a history of prior acute hepatotoxicity attributable to phenytoin, are excluded from this trial (see Exclusion Criteria). If there is a history of hypersensitivity reactions to structurally similar drugs, such as carboxamides (e.g., carbamazepine), barbiturates, succinimides, and oxazolidinediones (e.g., trimethadione) in the patient or

immediate family members, care must be taken to avoid potential patients' hypersensitivity to phenytoin. Discontinue and do not re-administer phenytoin if patients exhibit hypersensitivity to phenytoin during the study.

Hepatic Injury

Cases of acute hepatotoxicity, including infrequent cases of acute hepatic failure, have been reported with phenytoin. These events may be part of the spectrum of DRESS or may occur in isolation. Other common manifestations include jaundice, hepatomegaly, elevated serum transaminase levels, leukocytosis, and eosinophilia. The clinical course of acute phenytoin hepatotoxicity ranges from prompt recovery to fatal outcomes. In these patients with acute hepatotoxicity, phenytoin should be immediately discontinued and not re-administered.

Hematopoietic Complications

Hematopoietic complications, some fatal, have occasionally been reported in association with phenytoin. These have included thrombocytopenia, leukopenia, granulocytopenia, agranulocytosis, and pancytopenia with or without bone marrow suppression. There have been a number of reports suggesting a relationship between phenytoin and the development of lymphadenopathy (local or generalized) including benign lymph node hyperplasia, pseudolymphoma, lymphoma, and Hodgkin's disease. Although a cause and effect relationship has not been established, the occurrence of lymphadenopathy indicates the need to differentiate such a condition from other types of lymph node pathology. Lymph node involvement may occur with or without symptoms and signs of DRESS. In all cases of lymphadenopathy, follow-up observation for an extended period is indicated.

Effects on Vitamin D and Bone

The chronic use of phenytoin in patients with epilepsy has been associated with decreased bone mineral density (osteopenia, osteoporosis, and osteomalacia) and bone fractures. Phenytoin induces hepatic metabolizing enzymes. This may enhance the metabolism of vitamin D and decrease vitamin D levels, which may lead to vitamin D deficiency, hypocalcemia, and hypophosphatemia. Consideration should be given to screening with bone-related laboratory and radiological tests as appropriate and initiating treatment plans according to established guidelines.

Renal or Hepatic Impairment or Hypoalbuminemia

Because the fraction of unbound phenytoin is increased in patients with renal or hepatic disease, or in those with hypoalbuminemia, the monitoring of phenytoin serum levels should be based on the unbound fraction in those patients.

Exacerbation of Porphyria

In view of isolated reports associating phenytoin with exacerbation of porphyria, caution should be exercised in using this medication in patients with porphyria.

Teratogenicity and Other Harm to the Newborn

In this study, female patients must either be of non-reproductive potential, not breast-feeding or must have a negative urine or serum pregnancy test within 28 days of study treatment, confirmed prior to treatment on Day 1 (see Inclusion Criteria). Patients who are found pregnant during the study must discontinue treatment immediately.

Phenytoin may cause fetal harm when administered to a pregnant woman. Prenatal exposure to phenytoin may increase the risks for congenital malformations and other adverse development outcomes.

Increased frequencies of major malformations (such as orofacial clefts and cardiac defects), and abnormalities characteristic of fetal hydantoin syndrome, including dysmorphic skull and facial features, nail and digit hypoplasia, growth abnormalities (including microcephaly), and cognitive deficits, have been reported among children born to epileptic women who took phenytoin alone or in combination with other antiepileptic drugs during pregnancy. There have been several reported cases of malignancies, including neuroblastoma.

The overall incidence of malformations for children of epileptic women treated with antiepileptic drugs, including phenytoin, during pregnancy is about 10%, or two-to threefold that in the general population.

A potentially life-threatening bleeding disorder related to decreased levels of vitamin K-dependent clotting factors may occur in newborns exposed to phenytoin in utero. This drug-induced condition can be prevented with vitamin K administration to the mother before delivery and to the neonate after birth.

Slow Metabolizers of Phenytoin

A small percentage of individuals who have been treated with phenytoin have been shown to metabolize the drug slowly. Slow metabolism may be caused by limited enzyme availability and lack of induction, and it appears to be genetically determined. If early signs of dose-related CNS toxicity develop, serum levels should be checked immediately.

Hyperglycemia

Hyperglycemia, resulting from the drug's inhibitory effects on insulin release, has been reported. Phenytoin may also raise the serum glucose level in diabetic patients.

Serum Phenytoin Levels above Therapeutic Range

Serum levels of phenytoin sustained above the therapeutic range may produce confusional states referred to as "delirium," "psychosis," or "encephalopathy," or rarely irreversible cerebellar dysfunction and/or cerebellar atrophy. Accordingly, at the first sign of acute toxicity, serum levels should be immediately checked. Since dose reduction of phenytoin is not applicable in this study due to the dose of phenytoin being one 50 mg tablet, dosing with phenytoin should be terminated.

Overdosage

The lethal dose in pediatric patients is not known. The lethal dose in adults is estimated to be 2 to 5 grams. The initial symptoms are nystagmus, ataxia, and dysarthria. Other signs are tremor, hyperreflexia, lethargy, slurred speech, blurred vision, nausea, and vomiting. The patient may become comatose and hypotensive. Death is caused by respiratory and circulatory depression.

There are marked variations among individuals with respect to phenytoin serum levels where toxicity may occur. Nystagmus, on lateral gaze, usually appears at 20 mcg/mL, ataxia at 30 mcg/mL; dysarthria and lethargy appear when the serum concentration is over 40 mcg/mL, but as high a concentration as 50 mcg/mL has been reported without evidence of toxicity. As much as 25 times the therapeutic dose has been taken to result in a serum concentration over 100 mcg/mL with complete recovery. Irreversible cerebellar dysfunction and atrophy have been reported.

Treatment is nonspecific since there is no known antidote. The adequacy of the respiratory and circulatory systems should be carefully observed, and appropriate supportive measures employed. Hemodialysis can be considered since phenytoin is not completely bound to plasma proteins. Total exchange transfusion has been used in the treatment of severe intoxication in pediatric patients. In acute overdosage, the possibility of other CNS depressants, including alcohol, should be borne in mind.

Information for Patients

Advise patients to read the FDA-approved patient labeling for phenytoin. The patient counseling information included in the FDA-approved prescribing information is described below.

Administration Information

Advise patients taking phenytoin of the importance of adhering strictly to the prescribed dosage regimen, and of informing the physician of any clinical condition in which it is not possible to take the drug orally as prescribed, e.g., surgery, etc.

Withdrawal of Phenytoin

Advise patients not to discontinue use of phenytoin without consulting with their healthcare provider. Phenytoin should normally be gradually withdrawn to reduce the potential for increased seizure frequency and status epilepticus.

Suicidal Ideation and Behavior

Counsel patients, their caregivers, and families that antiepileptic drugs, including phenytoin, may increase the risk of suicidal thoughts and behavior and advise them of the need to be alert for the emergence or worsening of symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

Potential Signs of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) and Other Systemic Reactions

Advise patients of the early toxic signs and symptoms of potential hematologic, dermatologic, hypersensitivity, or hepatic reactions. These symptoms may include, but are not limited to, fever, sore throat, rash, ulcers in the mouth, easy bruising, lymphadenopathy, facial swelling, and petechial or purpuric hemorrhage, and in the case of liver reactions, anorexia, nausea/vomiting, or jaundice. Advise the patient that, because these signs and symptoms may signal a serious reaction, that they must report any occurrence immediately to a physician. In addition, advise the patient that these signs and symptoms should be reported even if mild or when occurring after extended use.

Effects of Alcohol Use and Other Drugs and Over-the-Counter Drug Interactions

Caution patients against the use of other drugs or alcoholic beverages without first seeking their physician’s advice.

Inform patients that certain over-the-counter medications (e.g., antacids, cimetidine, and omeprazole), vitamins (e.g., folic acid), and herbal supplements (e.g., St. John’s wort) can alter their phenytoin levels.

Hyperglycemia

Advise patients that phenytoin may cause an increase in blood glucose levels.

Gingival Hyperplasia

Advise patients of the importance of good dental hygiene in order to minimize the development of gingival hyperplasia and its complications.

Neurologic Effects

Counsel patients that phenytoin may cause dizziness, gait disturbance, decreased coordination and somnolence. Advise patients taking DILANTIN not to drive, operate complex machinery, or engage in other hazardous activities until they have become accustomed to any such effects associated with phenytoin.

Use in Pregnancy

In this study, female patients must either be of non-reproductive potential, not breast-feeding or must have a negative urine or serum pregnancy test within 28 days of study treatment, confirmed prior to treatment on Day 1 (see Inclusion Criteria). Inform pregnant women and women of childbearing potential that use of phenytoin during pregnancy can cause fetal harm, including an increased risk for cleft lip and/or cleft palate (oral clefts), cardiac defects, dysmorphic skull and facial features, nail and digit hypoplasia, growth abnormalities (including microcephaly), and cognitive deficits.

Advise women of childbearing potential to use effective contraception during the study while using phenytoin, keeping in mind that there is a potential for decreased hormonal contraceptive efficacy.

Instruct patients to notify their physician if they become pregnant or intend to become pregnant during the study, and to notify their physician if they are breastfeeding or intend to breast feed during the study. Encourage patients to enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry if they become pregnant. This registry is collecting information about the safety of antiepileptic drugs during pregnancy.

6.8.3.2. Related to Methoxsalen

Protection from UVA on the Skin

Patients must avoid sun exposure, even through window glass or cloud cover, for at least 8 hours after methoxsalen ingestion. If sun exposure cannot be avoided, the patient should wear protective devices such as a hat and gloves, and/or apply sunscreens which contain ingredients that filter out UVA radiation (e.g., sunscreens containing benzophenone and/or p-aminobenzoic (PABA) esters which exhibit a sun protective factor equal to or greater than 15). These chemical sunscreens should be applied to all areas that might be exposed to the sun (including lips). Exposure to sunlight and/or ultraviolet radiation may result in “premature aging” of the skin.

Overdosage

In the event of methoxsalen overdosage, induce emesis and keep the patient in a darkened room for at least 24 hours. Emesis is most beneficial within the first 2 to 3 hours after ingestion of methoxsalen, since maximum blood levels are reached by this time.

6.8.3.3. Related to Sirolimus

Increased Susceptibility to Infection and Possible Development of Lymphoma

Increased susceptibility to infection and the possible development of lymphoma and other malignancies, particularly of the skin, may result from immunosuppression. Oversuppression of the immune system can also increase susceptibility to infection, including opportunistic infections such as tuberculosis, fatal infections, and sepsis. Patients receiving the drug should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources. The physician responsible for maintenance therapy should have complete information requisite for the follow-up of the patient.

Hypersensitivity Reactions

Hypersensitivity reactions, including anaphylactic/anaphylactoid reactions, angioedema, exfoliative dermatitis and hypersensitivity vasculitis, have been associated with the administration of sirolimus. Discontinue and do not re-administer sirolimus if patients exhibit hypersensitivity during the study.

Angioedema

Sirolimus has been associated with the development of angioedema. The concomitant use of sirolimus with other drugs known to cause angioedema, such as angiotensin-converting enzyme (ACE) inhibitors, may increase the risk of developing angioedema. Elevated sirolimus levels (with/without concomitant ACE inhibitors) may also potentiate angioedema. In some cases, the angioedema has resolved upon discontinuation or dose reduction of sirolimus. Since dose reduction of sirolimus is not applicable in this study due to the dose of sirolimus being one 0.5 mg tablet, dosing with sirolimus should be terminated when angioedema occurs.

Fluid Accumulation and Impairment of Wound Healing

There have been reports of impaired or delayed wound healing in patients receiving sirolimus, including lymphocele and wound dehiscence. mTOR inhibitors such as sirolimus have been shown in vitro to inhibit production of certain growth factors that may affect angiogenesis, fibroblast proliferation, and vascular permeability. Lymphocele, a known surgical complication of renal transplantation, occurred significantly more often in a dose-related fashion in patients treated with sirolimus. Appropriate measures should be considered to minimize such complications. Patients with a body mass index greater than 30 may be at increased risk of abnormal wound healing based on data from the medical literature.

There have also been reports of fluid accumulation, including peripheral edema, lymphedema, pleural effusion, ascites, and pericardial effusions (including hemodynamically significant effusions and tamponade requiring intervention in children and adults), in patients receiving sirolimus. Discontinue and do not re-administer sirolimus if patients exhibit fluid accumulation.

Hyperlipidemia

Increased serum cholesterol and triglycerides requiring treatment occurred more frequently in patients treated with sirolimus compared with azathioprine or placebo controls in clinical studies. There were increased incidences of hypercholesterolemia (43-46%) and/or hypertriglyceridemia (45-57%) in patients receiving sirolimus compared with placebo controls (each 23%). The risk/benefit should be carefully considered in patients with established hyperlipidemia before initiating an immunosuppressive regimen including sirolimus.

Any patient who is administered sirolimus should be monitored for hyperlipidemia. If detected, interventions such as diet, exercise, and lipid-lowering agents should be initiated as outlined by the National Cholesterol Education Program guidelines.

In clinical trials of patients receiving sirolimus plus cyclosporine or sirolimus after cyclosporine withdrawal, up to 90% of patients required treatment for hyperlipidemia and hypercholesterolemia with anti-lipid therapy (e.g., statins, fibrates). Despite anti-lipid management, up to 50% of patients had fasting serum cholesterol levels >240 mg/dL and triglycerides above recommended target levels. The concomitant administration of sirolimus and HMG-CoA reductase inhibitors resulted in adverse reactions such as CPK elevations (3%), myalgia (6.7%) and rhabdomyolysis (<1%). In these trials, the number of patients was too small and duration of follow-up too short to evaluate the long-term impact of sirolimus on cardiovascular mortality.

During sirolimus therapy with or without cyclosporine, patients should be monitored for elevated lipids, and patients administered an HMG-CoA reductase inhibitor and/or fibrate should be monitored for the possible development of rhabdomyolysis and other adverse effects, as described in the respective labeling for these agents.

Decline in Renal Function

In this study, patients treated, or anticipated to be treated, with cyclosporine are excluded (see Exclusion Criteria) because long-term administration of the combination of cyclosporine and sirolimus is associated with deterioration of renal function. Patients treated with cyclosporine and sirolimus were noted to have higher serum creatinine levels and lower glomerular filtration rates compared with patients treated with cyclosporine and placebo or azathioprine controls. The rate of decline in renal function in these studies was greater in patients receiving sirolimus and cyclosporine compared with control therapies.

Appropriate adjustment of the immunosuppressive regimen, including discontinuation of sirolimus and/or cyclosporine, should be considered in patients with elevated or increasing serum creatinine levels. In patients at low- to moderate-immunologic risk, continuation of combination therapy with cyclosporine beyond 4 months following transplantation should only patients. Caution should be exercised when using agents (e.g., aminoglycosides and amphotericin B) that are known to have a deleterious effect on renal function. In patients with delayed graft function, sirolimus may delay recovery of renal function.

Latent Viral Infections

Immunosuppressed patients are at increased risk for opportunistic infections, including activation of latent viral infections. These include BK virus-associated nephropathy, which has been observed in renal transplant patients receiving immunosuppressants, including sirolimus. This infection may be associated with serious outcomes, including deteriorating renal function and renal graft loss. Patient monitoring may help detect patients at risk for BK virus-associated nephropathy. Reduction in immunosuppression should be considered for patients who develop evidence of BK virus-associated nephropathy.

Cases of progressive multifocal leukoencephalopathy (PML), sometimes fatal have been reported in patients treated with immunosuppressants, including sirolimus. PML commonly presents with hemiparesis, apathy, confusion, cognitive deficiencies and ataxia. Risk factors for PML include treatment with immunosuppressant therapies and impairment of immune function. In immunosuppressed patients, physicians should consider PML in the differential diagnosis in patients reporting neurological symptoms and consultation with a neurologist should be considered as clinically indicated. Consideration should be given to reducing the amount of immunosuppression in patients who develop PML. In transplant patients, physicians should also consider the risk that reduced immunosuppression represents to the graft.

Interstitial Lung Disease/Non-Infectious Pneumonitis

Cases of ILD (including pneumonitis, BOOP, and pulmonary fibrosis), some fatal, with no identified infectious etiology have occurred in patients receiving immunosuppressive regimens including sirolimus. In some cases, the ILD was reported with pulmonary hypertension (including pulmonary arterial hypertension) as a secondary event. In some cases, the ILD has resolved upon discontinuation or dose reduction of sirolimus. The risk may be increased as the trough sirolimus concentration increases.

Increased Risk of Calcineurin Inhibitor-Induced Hemolytic Uremic Syndrome/Thrombotic Thrombocytopenic Purpura/Thrombotic Microangiopathy

In this study, patients treated, or anticipated to be treated, with a calcineurin inhibitor are excluded (see Exclusion Criteria). The concomitant use of sirolimus with a calcineurin inhibitor may increase the risk of calcineurin inhibitor-induced hemolytic uremic syndrome/thrombotic thrombocytopenic purpura/thrombotic microangiopathy (HUS/TTP/TMA).

Different Sirolimus Trough Concentration Reported between Chromatographic and Immunoassay Methodologies

Currently in clinical practice, sirolimus whole blood concentrations are being measured by various chromatographic and immunoassay methodologies. Patient sample concentration values from different assays may not be interchangeable.

Skin Cancer Events

Patients on immunosuppressive therapy are at increased risk for skin cancer. Exposure to sunlight and ultraviolet (UV) light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.

Overdosage

Reports of overdose with sirolimus have been received; however, experience has been limited. In general, the adverse effects of overdose are consistent with the adverse reactions section.

General supportive measures should be followed in all cases of overdose. Based on the low aqueous solubility and high erythrocyte and plasma protein binding of sirolimus, it is anticipated that sirolimus is not dialyzable to any significant extent. In mice and rats, the acute oral LD50 was greater than 800 mg/kg.

7. MEASUREMENT OF EFFECT

7.1. Definitions

Tumor response and/or disease progression will be assessed by either physical exam measurements or CT scan (or other appropriate imaging modalities such as MRI consistent with the modality used prior to treatment) utilizing RECIST v1.1 criteria. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions and in only the short axis of lymph node lesions are used in the RECIST v1.1 criteria. Assessments will be performed within 28 days of initiating study treatment, every 12 weeks thereafter.

7.1.1. Response Evaluable

A patient who initiates therapy per protocol, and is taken off study for disease progression or clinical progression, including death related to the underlying solid tumor malignancy (as determined by the treating oncologist) ***will be*** considered evaluable for response assessment. However, patients who have initiated therapy and who withdraw from the study for any reason other than clinical or radiographic progression, or death believed unrelated to their underlying solid tumor malignancy ***will not be*** considered evaluable for response. Reasons for patients who have initiated therapy, but are no longer evaluable for response could include (but are not limited to):

- The patient cannot tolerate therapy despite dose modifications, and there is no evidence of clinical/radiographic disease progression at the time of stopping therapy.
- An unexpected and/or unrelated medical illness, such as a stroke or myocardial infarction that is considered unrelated to the underlying solid tumor malignancy
- An unexpected trauma or death that is considered unrelated to the underlying solid tumor malignancy

7.1.2. Disease Parameters

7.1.2.1. Measurable Disease

The presence of at least one measurable lesion. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as:

- By chest x-ray: ≥ 20 mm;
- By CT scan or MRI: ≥ 10 mm

All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters). Previously irradiated lesions are non-measurable except in cases of documented progression of the lesion since the completion of radiation therapy. Previously irradiated brain lesions will not be eligible to be target lesions.

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

Bone lesions: Lytic bone lesions or mixed lytic-blastic lesions with identifiable associated soft tissue components that are 10 mm or larger in size and can be evaluated via cross-sectional imaging such as CT or MRI are considered measurable lesions per RECIST v1.1.

7.1.2.2. Non-measurable disease

All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, without associated soft tissue components, blastic 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.

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. Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is required.

7.2. Methods of Measurement

CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen and pelvis. For accurate objective response evaluation, ultrasound should not be used to measure tumor lesions. However, ultrasound is a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. Ultrasound might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

7.2.1. Baseline Documentation of "Target" and "Non-Target" Lesions

7.2.1.1. 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) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). 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 longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

- Previously irradiated brain lesions will not be eligible to be selected as target lesions.
- If a patient has measurable disease outside of the brain, the lesion(s) outside of the brain will be selected as the target lesion(s).

7.2.1.2. Non-Target Lesions

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

7.3. Assessment of Response by RECIST v1.1

RECIST v1.1 will be used by the Investigator as the primary measure for assessment of tumor response, date of disease progression, and as a basis for all protocol guidelines related to disease status.

7.4. RECIST v1.1 Response Criteria

7.4.1. Evaluation of Tumor Response-Measurable Disease

7.4.1.1. Complete Response (CR)

The disappearance of all known target lesions, determined by two observations not less than 4 weeks apart. There can be no appearance of new lesions.

7.4.1.2. Partial Response (PR)

A 30% or more decrease in the sum of the LD of target lesions that have been measured to determine the effect of therapy by two observations not less than 4 weeks apart. There can be no appearance of new lesions.

7.4.1.3. Progressive Disease (PD)

At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started, or the appearance of one or more new lesions, and/or an unequivocal progression of non-target lesions.

7.4.1.4. Stable Disease (SD)

Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

7.5. 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.

Table 6. Response Evaluation

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this Category Also Requires:
CR	CR	No	CR	>4 wks confirmation
CR	Non-CR/Non-PD	No	PR	>4 wks confirmation
PR	Non-PD	No	PR	
SD	Non-PD	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	

* 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.
Note: If patients respond to treatment and are able to have their disease resected, the patient’s response will be assessed prior to the surgery.

7.6. Definition of Disease Progression

Disease progression will be defined as:

- Progression of disease by RECIST v1.1 criteria.
- Clinical progression as determined by the Investigator, which may be characterized as, but is not limited to:
  - Increase of at least 2 points in ECOG performance status attributable to cancer progression.
  - Requirement for palliative chemotherapy or surgery.
- Death from any cause that is not unequivocally unrelated to disease progression (e.g. motor vehicle accident)

8. STATISTICAL CONSIDERATIONS

8.1. Objectives

8.1.1. Primary Objective:

To determine the objective response rate (ORR) of SM-88 plus the conditioning agents methoxsalen, phenytoin, and sirolimus (MPS) in patients with advanced HR+/HER2 negative breast cancer.

8.1.2. Secondary Objectives:

To assess:

- Progression free survival (PFS),
- Clinical benefit rate (CBR) at ≥ 24 weeks,
- Duration of response (DOR), and
- Safety/tolerability (adverse events, serious adverse events, incidence of dose delays or dose reductions, treatment discontinuations due to adverse events, and all deaths).

8.1.3. Exploratory Objectives:

To evaluate cell-free DNA (cfDNA) at baseline (pre-treatment on C1D1), during treatment, and at disease progression.

8.2. Study Design

This is a multicenter phase II trial with single arm, open-label study of SM-88 used with MPS in metastatic HR+/HER2- breast cancer. The primary endpoint of this phase II study is to determine the ORR of SM-88 therapy in patients with metastatic HR+/HER2- breast cancer. The phase II portion of the trial will follow Simon’s minimax two-stage design (Simon 1989).

In the Stage 1, 30 patients will be accrued. If there are 2 or fewer objective responses among these 30 patients with the SM-88 plus MPS therapy, the therapy will be rejected and the trial stopped. However, if 3 or more patients achieve an objective response in the Stage 1, then an additional 20 patients will be enrolled in Stage 2, for a total of 50 patients in this phase II study. If 8 or more patients exhibit an objective response among these 50 patients, then the treatment will be considered for further investigation. Any unplanned interim analysis, e.g., due to slow accrual, external information, etc, will utilize the sequential conditional probability ratio test (TAN and XIONG 1996, Tan and Xiong 2011), which allows an early assessment of statistical evidence for both efficacy and futility while retaining the rigor of the trial and provides a discordance probability that early trend could be reversed should the trial continue to enroll all 50 patients.

8.3. Sample Size Considerations

This proposed phase II study will utilize the Simon's minimax two-stage design (Simon 1989). The desirable ORR is 20% (based on the ORR of 19.7% seen with abemaciclib monotherapy in the MONARCH 1 Phase II clinical trial, which was conducted in ≥ 3rd line treatment of metastatic HR+/HER2- breast cancer)(Dickler, Tolaney et al. 2017) and the undesirable ORR of 9.5% (based on ORR of 9.5% seen in a trial of exemestane plus everolimus in the Phase III BOLERO-2 study in patients who had progressed on a non-steroidal aromatase inhibitor and had a median of 3 previous therapies) (Baselga, Campone et al. 2012).

The null hypothesis is that the true response rate is 0.095, and the alternative hypothesis is that the true response rate is 0.2. The trial is carried out in two stages. In Stage 1, a total number of 30 patients is accrued. If there are 2 or fewer responses among these 30 patients, the study will be stopped early. Otherwise, additional 20 patients will be accrued in Stage 2, resulting in a total number sample size of 50. If there are 8 or more responses among these 50 patients, we reject the null hypothesis and claim that the treatment is promising. The design controls the type I error rate at 0.1 with a power of 0.8.

8.4. Endpoints and Analysis Plans

P-value less than 0.05 will be considered significant. All statistical analyses will be performed using RStudio (Version 0.99.902) and SAS (Version 9.4).

8.4.1. Primary Endpoints

Response classification will follow the RECIST v1.1 criteria and will be defined as partial of stable disease (SD), response (PR), or complete response (CR). The overall objective response rate (ORR, PR + CR) will be computed for all patients with at least one cycle of the study combination therapy. The proportion of response rate will be reported with 95% exact binomial confidence interval (CI).

8.4.2. Secondary Endpoints:

8.4.2.1. Duration of Response (DoR)

The distribution of duration of response (DOR) will be estimated by Kaplan-Meier methodology, and the median of the DOR with 95% CI will be reported (calculated based on Kaplan-Meier).

8.4.2.2. Progression Free Survival (PFS)

The PFS is defined as the time in days from study entry to the first documented disease progression per RECIST v1.1 as assessed by local site or death. Patients who are alive and free from progression on the date of closing follow-up will be censored on that date. PFS will be estimated by Kaplan-Meier methodology, and median PFS with 95% CI will be reported.

8.4.2.3. Clinical Benefit rate at ≥ 24 weeks

Clinical benefit rate (CBR) at ≥ 24 weeks will be reported. The total number and percentage of patients who achieve complete response (CR), partial response (PR), or had stable disease (SD) at ≥ 24 weeks will be reported.

8.4.2.4. Safety Assessments

Overall safety monitoring will be performed throughout the study. The safety of the SM-88 therapy will be assessed by evaluating study drug exposure, adverse events, serious adverse events, and all deaths.

A summarization of the number of days and/or cycles patients were exposed to study drug will be provided. Adverse events (and serious adverse events) will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 5.0. Toxicities will be characterized in terms of seriousness, causality, toxicity grading, and action taken with regard to trial treatment. The percentage of patients experiencing an adverse event at a given severity, NCI CTCAE toxicity grade, and relationship to study drug will be provided. The number of patient deaths throughout the study will be summarized.

8.4.3. Exploratory Endpoints:

Descriptive statistics will be used to analyze any changes in cell-free DNA (cfDNA) measurement at baseline (pre-treatment on C1D1), during the SM-88 therapy, and at disease progression time points.

Baseline Characteristics

All baseline summary statistics and analyses will be based on characteristics prior to the initiation of study drug. Frequency and percentages for categorical variables, and mean (SD) or median (IQR, interquartile range) for the continuous variables based on the normalization of the data.

9. Correlative Research Management

9.1. cfDNA

Blood sample collection for analysis of cfDNA analysis will be collected at multiple time points: baseline (pre-treatment), C2D1, C3D1, at each additional restaging scan (every 8-12 weeks) and disease progression. cfDNA samples will be banked at Georgetown University, and eventually shipped to Foundation Medicine for analysis.

All specimens will be collected in two (2) 10 mL Streck cell-free DNA collection tubes (DNA BCT catalog # 230470). These vials shall be processed as per the laboratory instructions provided by Foundation Medicine, and categorized and banked at Georgetown as per protocol. Refer to the Lab Manual for more details on collection, processing, and storage instructions.

10. Ethical Considerations

10.1. Institutional Review Board (IRB)

GCP requires that the clinical protocol, any protocol amendments, the Investigator's Brochure, the informed consent and all other forms of patient information related to the study (e.g., advertisements used to recruit patients) and any other necessary documents be reviewed by an IRB. IRB approval of the protocol, informed consent and patient information and/or advertising, as relevant, will be obtained prior to the authorization of drug shipment to a study site. Any amendments to the protocol will require IRB approval prior to implementation of any changes made to the study design. Any serious adverse events that meet the reporting criteria, as dictated

by local regulations, will be reported to the IRB. During the conduct of the study, the Investigator should promptly provide written reports to the IRB of any changes that affect the conduct of the study and/or increase the risk to patients.

10.2.Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, ICH guidelines, applicable regulations and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki.

10.3.Patient Information and Consent

Prior to the initiation of any screening or study-specific procedures, the Investigator or his/her representative will explain the nature of the study to the patient and answer all questions regarding this study. Each informed consent will be reviewed, signed and dated by the patient and the person who administered the informed consent. A copy of each informed consent will be given to the patient and each original will be placed in the patient's medical record. An entry must also be made in the patient's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the patient received a signed copy.

10.4.Ethical Consideration for Enrollment

Only patients with advanced cancer, for whom no curative therapy exists, will be considered for enrollment. The only treatment options for these patients are conventional chemotherapy, radiation, or participation in a clinical trial. As described above, the combination of SM-88 used with MPS is a rational and promising combination for such patients.

10.5.Protection of Patient Confidentiality

All patient records, questionnaires, and tissue specimens will be de-identified using a letter and number assigned to their case at the time of enrollment on study. No record or specimen will contain information which could identify the patient. The key which connects patient identifiable information with this assigned number will be held by the Principal Investigator. For computer records, the key will be protected by a double password protection system. Any paper records will be contained in a locked cabinet within a locked office to ensure patient’s privacy is protected.

11.0 APPENDICES

APPENDIX A: STUDY ELIGIBILITY CHECKLIST

A Phase II trial of SM-88 in patients with metastatic hormone receptor-positive and HER2-negative (HR+/HER2-) breast cancer

Study ID: _____

Instructions: This form should be completed by the research staff before registering the patient into the trial.
Completed form can be emailed to Georgetown Project managers [redacted]

☐ MedStar Georgetown University Hospital

☐ MedStar Washington Hospital Center

☐ MedStar Franklin Square Medical Center

☐ MedStar Good Samaritan Hospital

☐ Hackensack University Medical Center

INCLUSION CRITERIA (ALL ITEMS MUST BE CHECKED YES)	
YES | NO	
☐ | ☐	Histologically or cytologically proven diagnosis of breast cancer with evidence of metastatic or locally advanced disease, not amenable to resection or radiation therapy with curative intent.
☐ | ☐	Documentation of ER-positive and/or PR-positive tumor (≥1% positive stained cells) based on most recent tumor biopsy (discuss with the Principle Investigator if results in different biopsies are discordant in terms of hormone receptor positivity) utilizing an assay consistent with local standards.
☐ | ☐	Documented HER2-negative tumor based on local testing on most recent tumor biopsy: HER2-negative tumor is determined as immunohistochemistry score 0/1+ or negative by in situ hybridization (FISH/CISH/SISH) defined by current ASCO/CAP (American Society of Clinical Oncology/College of American Pathologists) guidelines. Patients with equivocal HER2 in situ hybridization results according to current ASCO/CAP guidelines are eligible, as long as they have not received and are not scheduled to receive anti-HER2 treatment.
☐ | ☐	Must have progressed on (or been intolerant of) at least 2 lines of endocrine therapy in either the adjuvant or metastatic setting and progressed on (or been intolerant of) a CDK4/6 inhibitor.
☐ | ☐	Must have received no more than 4 lines of systemic therapy (for example, including but not limited to endocrine therapy, targeted therapy, biologic therapy, chemotherapy, or experimental therapy) for the treatment of breast cancer in the metastatic setting.
☐ | ☐	Life expectancy of more than 3 months.
☐ | ☐	Premenopausal or postmenopausal men or women.
☐ | ☐	Age ≥ 18 years
☐ | ☐	ECOG performance status (PS) of 0 to 1
☐ | ☐	Measurable disease by RECIST v1.1 criteria (tumor ≥ 1 cm in longest diameter on axial image on computed tomography (CT) or magnetic resonance imaging (MRI) or tumor ≥ 10 mm by caliper measurement on clinical exam and/or lymph node(s) ≥ 1.5 cm in short axis on CT or MRI) on baseline imaging. Lytic bone lesions or mixed lytic-blastic lesions with an associated soft tissue component ≥ 10mm noted on CT or MRI are also included as per RECIST 1.1 criteria. Index lesions must not have undergone prior radiation therapy.
☐ | ☐	Asymptomatic brain metastases are allowed if the lesions are not considered to need local therapy. Previously treated brain metastases are allowed as long as they are > 4 weeks from local therapy, clinically asymptomatic, and not requiring high-dose corticosteroids. Patients may remain on steroids for CNS disease if they are taking a stable dose that is less than 10mg of prednisone per day, or the equivalent.
☐ | ☐	Must be capable of understanding and complying with parameters as outlined in the protocol and able to sign and date the informed consent, approved by the IRB, prior to the initiation of any screening or study-specific procedures.

☐ | ☐	Pregnancy must be ruled out in women of childbearing potential. Serum or urine pregnancy test must be negative within 14 days of treatment start in women of childbearing potential and must be willing to have pregnancy test approximately every 4 weeks. Pregnancy testing does not need to be pursued in patients who are judged to be postmenopausal before enrollment, or who have undergone bilateral oophorectomy, total hysterectomy, or bilateral tubal ligation. o Patients may be considered postmenopausal in the case that one of the following criteria applies: ▪ Prior bilateral oophorectomy, OR ▪ Age ≥ 60 years, OR ▪ Age < 60 years with intact uterus and amenorrhoeic for ≥ 12 consecutive months **prior to** chemotherapy and/or endocrine therapy exposure, OR
☐ | ☐	Willingness to utilize adequate contraception if of childbearing potential. Women of childbearing potential must use adequate contraception for the duration of protocol treatment and for at least 6 months after the last treatment with SM-88 used with MPS. Men must not donate sperm or conceive a child for the duration of protocol treatment and for at least 6 months after the last treatment with SM-88 used with MPS. o Adequate contraception is defined as one highly effective form (i.e. abstinence, (fe)male sterilization) OR two effective forms (IUD [non-hormonal preferred], condom with spermicidal foam / gel / film / cream / suppository, occlusive cap with spermicidal foam / gel / film / cream / suppository).
☐ | ☐	Must be able and willing to swallow pills whole and retain oral medication.
☐ | ☐	Resolution of all acute toxic effects of prior therapy, including radiotherapy to grade ≤1 or patient's baseline (except toxicities not considered a safety risk for the patient) and recovery from surgical procedures.
☐ | ☐	Must have discontinued all previous therapies for cancer (including endocrine therapy, CDK4/6 inhibitor therapy, cytotoxic chemotherapy, targeted therapy [including, but not limited to, everolimus], radiotherapy, immunotherapy, and investigational therapy) for at least 14 days prior to receiving study drugs.

LAB VALUES (ALL MUST BE CHECKED YES)	
YES | NO	
☐ | ☐	ANC ≥ 1,500/mm^3; Patients must be able to meet the criteria without receipt of colony stimulating factors within 2 weeks before obtaining sample
☐ | ☐	Platelets ≥ 100,000/mm^3; Patients must be able to meet the criteria without transfusion within 2 weeks before obtaining sample
☐ | ☐	Hemoglobin ≥ 9.0 g/dL; Patients must be able to meet the criteria without transfusion within 2 weeks before obtaining sample
☐ | ☐	Creatinine clearance ≥ 55 mL/min based on Cockcroft-Gault equation
☐ | ☐	Hepatic function: AST and ALT ≤ 3 × the upper normal limit of institution's normal range. Total bilirubin ≤ 1.5 × the upper normal limit of institution's normal range (except for patients with a documented history of Gilbert's Syndrome who can be enrolled at PI discretion). For patients with liver metastases, AST and ALT ≤ 5 × the upper normal limit of institution's normal range, and total bilirubin < 3.0 x the upper normal limit of institution's normal range are acceptable as long as there is no persistent nausea, vomiting, right upper quadrant pain or tenderness, fever, or rash.
☐ | ☐	Alkaline phosphatase ≤2.5 x ULN (≤5.0 x ULN if bone metastases present)

EXCLUSION CRITERIA (ELIGIBLE PATIENTS MUST ALL BE CHECKED NO)	
YES | NO	
☐ | ☐	Concurrent therapy with other approved or investigational cancer treatment agents, except bisphosphonates, RANKL inhibitors, GnRH agonists such as leuprolide or goserelin.
☐ | ☐	Inability to comply with study requirements.
☐ | ☐	Diagnosis of other invasive cancer except for adequately treated cervix cancer, or more than 5 years since other diagnosis of invasive cancer (including invasive squamous cell cancers due to contraindication for methoxsalen use) without current evidence of disease.
☐ | ☐	Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of the study drugs (e.g., ulcerative diseases, uncontrolled nausea/vomiting, chronic diarrhea, malabsorption syndrome, intestinal obstruction, or small bowel resection) at discretion of investigator.
☐ | ☐	Patient with clinically significant liver disease, including active viral (including hepatitis B, hepatitis C, etc.) or other known hepatitis, current alcohol abuse, or cirrhosis.

☐ | ☐	Known chronic hepatitis B virus infection (testing not required prior to enrollment): • Patients with chronic Hepatitis C virus may be enrolled if there is no clinical/laboratory evidence of cirrhosis AND the patient's liver function tests fall within the parameters set in Section 3.2.
☐ | ☐	Uncontrolled HIV infection defined as any of the following 3 criteria: CD4 counts ≤ 350 cells/μL; serum HIV viral load ≥ 400 copies/mL; on a antiretroviral regimen for < 4 weeks prior to treatment with study drugs if anti-retroviral therapy is deemed necessary or appropriate by the Investigator.
☐ | ☐	Previous enrollment in this study or any other study investigating SM-88.
☐ | ☐	Clinically significant and uncontrolled major medical condition(s) including, but not limited to uncontrolled nausea/vomiting/diarrhea; active, uncontrolled infection; symptomatic congestive heart failure (New York Heart Association [NYHA] class ≥ II); unstable angina pectoris; cardiac arrhythmia requiring hospitalization in the past 3 months; stroke or MI in the past 6 months.
☐ | ☐	Psychiatric illness or social situation that would limit compliance with study requirements.
☐ | ☐	Active uncontrolled or symptomatic brain metastases. Previously treated and clinically stable brain metastases, as per Investigator's judgement, are permitted.
☐ | ☐	Patients with a seizure disorder that is not well controlled or who have required a change in seizure medications within 60 days of enrollment to the trial
☐ | ☐	History of any known drug allergies to any study medication.
☐ | ☐	Patients with a history of hypersensitivity to phenytoin, its inactive ingredients, or other hydantoins; or a history of prior acute hepatotoxicity attributable to phenytoin.
☐ | ☐	Patients treated, or anticipated to be treated, with delavirdine (due to potential for loss of virologic response and possible resistance to delavirdine or to the class of non-nucleoside reverse transcriptase inhibitors caused by phenytoin).
☐ | ☐	Patients exhibiting idiosyncratic reactions to psoralen compounds.
☐ | ☐	Patients with a history of the light sensitive diseases for which methoxsalen would be contraindicated. Diseases associated with photosensitivity include lupus erythematosus, porphyria cutanea tarda, erythropoietic protoporphyria, variegate porphyria, xeroderma pigmentosum, and albinism.
☐ | ☐	Patients with cutaneous melanoma or invasive squamous cell carcinomas or a history thereof, except for those in complete remission for ≥5 years (due to contraindication for use of methoxsalen).
☐ | ☐	Patients with a hypersensitivity to sirolimus.
☐ | ☐	Patients with prior allogenic bone marrow transplant or solid organ transplant or being treated, or anticipated to be treated, with cyclosporine (because long-term administration of the combination of cyclosporine and sirolimus is associated with deterioration of renal function).
☐ | ☐	Patients treated, or anticipated to be treated, with a calcineurin inhibitor (because concomitant use of sirolimus and a calcineurin inhibitor increases the risk of calcineurin inhibitor-induced hemolytic uremic syndrome/thrombotic thrombocytopenic purpura/thrombotic microangiopathy [HUS/TTP/TMA]).
☐ | ☐	Women who are pregnant or breastfeeding.
☐ | ☐	Current use of known strong inhibitors or inducers of CYP3A4, CYP2C9 or CYP2C19 within 14 days of initiation of study drug. When possible these medications and grapefruit juice should be avoided for the duration of the study treatment and alternate therapies are preferred. For a list, refer to Section 3.5 or Appendix D of the protocol.

Study Coordinator Signature:_____Date: _____

Investigator Signature:_____ Date: _____

Table 7: ECOG Performance Status Scale

Grade	ECOG
0	Fully Active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

APPENDIX B: PATIENT REGISTRATION FORM

A Phase II trial of SM-88 in patients with metastatic hormone receptor-positive and HER2-negative (HR+/HER2-) breast cancer

Study ID (IRB#): _____ Patient Initials: _____
Instructions: This form and all supporting documentation should be completed by the research staff and scanned/emailed to the Georgetown Project Managers ([redacted] and Study PI ([redacted]).

Patient may not start treatment until eligibility is verified and Patient Study ID is assigned by Georgetown PMs.

Enrolling Site:
☐ MedStar Georgetown University Hospital (Lombardi Comprehensive Cancer Center)
☐ MedStar Washington Hospital Center
☐ MedStar Franklin Square Medical Center
☐ MedStar Good Samaritan Hospital
☐ Hackensack University Medical Center

1. Site PI: _____
2. Enrolling MD: _____
3. Date Informed Consent signed: ___/___/_____
4. Date HIPAA Authorization signed: ___/___/_____
5. Proposed Start Date for Treatment: ___/____/_____
6. Treatment Location: _____
7. Date of Last Systemic anti-cancer therapy: ___/____/_____
8. Prior Therapies (Date Initiated/Type):

_____
_____
_____
_____

9. Please fax documentation supporting eligibility per protocol (check those included):
☐ Eligibility Checklist
☐ Pathology Report
☐ Physicians Note
☐ Baseline CT/RECIST
☐ Laboratory Results (per protocol)
☐ Past Medical History
☐ ECOG score
☐ Other _____

APPENDIX C – PATIENT DRUG DIARY

Study ID: _____ Initials: _____

Cycle: _____ Date/Time of Next Appointment:_____

Instructions:

- Take one hour before or two hours after a meal.
- Be sure to document the day and time of each dose and note any missed doses in the comments.
- If a component of MPS is not taken then please only write the drugs that are taken; for example, if you forget to take sirolimus then write "MP" under Tabs taken and in the comments write "sirolimus not taken" and the reason.

Treatment Day	Date	SM-88 (AM)		Methoxsalen = M Phenytoin = P Sirolimus = S		SM-88 (PM)		Comments
		Time	# tabs	Time	Tabs taken (M P S)		# tabs	
example	*1/1/2021*	*10:15 am*	*2*	*10:20 am*	*M P S*	*10:16 PM*	*2*	
1								
2								
3								
4								
5								
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APPENDIX D – STRONG INHIBITORS OR INDUCERS OF CYP3A4, CYP2C9, OR CYP2C19

Medications that are clinically known to induce or inhibit metabolic enzymes or transporters, including CYP3A4, CYP2C9, CYP2C19, and p-glycoprotein (Pgp) must be used with caution or avoided.

Known strong inhibitors or inducers of CYP3A4, CYP2C9 or CYP2C19, such as those listed below, are not allowed within 14 days prior to the first dose of study medication and for the duration of study treatment. When possible these medications and grapefruit juice should be avoided for the duration of the study treatment and alternate therapies are preferred:

- CYP2C9:
  - Strong inhibitors: fluconazole
  - Strong inducers: none known
- CYP2C19:
  - Strong inhibitors: fluconazole, fluvoxamine, ticlopidine
  - Strong inducers: none known
- CYP3A4:
  - Strong inhibitors: atazanavir, boceprevir, ciclosporin, clarithromycin, conivaptan, danazol, erythromycin, gemfibrozil, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole,
  - Strong inducers: avasimibe, carbamazepine, phenobarbital, rifabutin, rifampin, St. John's Wort
  - Delavirdine
  - Cyclosporine
  - Calcineurin inhibitors

APPENDIX E: SM-88 USED WITH MPS MECHANISM OF ACTION

The components of SM-88 used with MPS are thought to be effective in altering cancer cell metabolism and as anti-neoplastics (Liu, Li et al. 2004, Joka, Boeck et al. 2014, Enriquez-Navas, Kam et al. 2016). SM-88 used with MPS-related agents have been previously described to possess characteristics now proposed by several groups as anticancer agents (Gibbons 2002, Imaoka, Osada et al. 2004, Hu, Rosen et al. 2005, Engel and Evens 2006, Steffen, Wiswedel et al. 2006, Leonarduzzi, Poli et al. 2007, Lordan, Mackrill et al. 2008, Trachootham, Alexandre et al. 2009, Vejux and Lizard 2009, Ruggiero, Bruzzo et al. 2012, Kasichayanula, Boulton et al. 2014) and have been used clinically in the treatment of neoplastic conditions such as pheochromocytoma (Perry, Keiser et al. 1990). Similarly, CYP3A4 inducers, including phenytoin, have been "repurposed" for other novel off-label uses (Fillekes, Muro et al. 2013). In some cases, repurposed, off-label uses of nontraditional anti-neoplastic non-cytotoxic drugs have been associated with an OS significantly longer than the standard of care (Watkins, Thaker et al. 2015). When considering repurposing drugs approved for non-cancer indications for use with cancer therapies, the history of prior clinical use often provides support for safe use in cancer patients, especially when approved uses require higher doses than proposed for use in cancer treatment (Perry, Keiser et al. 1990, Bremner, Vythilingam et al. 2003).

Here we discuss possible mechanisms of action for the four components of SM-88 used with MPS.

SM-88:
Tyrosine isomers are employed in SM-88 to interfere with the cancer cell's ability to create peptides, especially high turnover ones (Ruggiero, Bruzzo et al. 2012, Hosios, Hecht et al. 2016). SM-88 is transported into cancer cells via the L-type amino acid transporter (LAT1) which is known to facilitate the intracellular delivery of amino acids including tyrosine (Ruggiero, Bruzzo et al. 2012, Stretton, Hoffmann et al. 2015, Yazawa, Shimizu et al. 2015). SM-88 used with MPS provides a mixture of non-nutritive tyrosine isomers to cancer cells which are unable to be used in cellular metabolism (Ruggiero, Bruzzo et al. 2012).

Biopsies and correlative data suggest SM-88 activity is associated with an increased inflammatory response (proprietary unpublished data) consistent with attenuation of the barrier between tumors and the host immune system. It is believed that SM-88 interferes with cancer cells' ability to synthesize critical proteins, including the protective transmembrane protein Mucin 1 (MUC1), which is thought to act as a barrier against the host immune system (Yin, Li et al. 2003). The loss of MUC1 reduces the activity of intracellular anti-apoptotic pathways and increases sensitivity to reactive oxygen species (ROS). Certain changes in dietary amino acid supplementation have also been shown to alter mucin production (Faure, Mettraux et al. 2006). In 2016 and 2017, the FDA approved amino acids for imaging of cancers, Axumin a fluorine, and as therapy for a hematologic disorder, L-glutamine, respectively:
https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm503920.htm ;
https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm566097.htm?platform=hootsuite .

Phenytoin:
Cytochrome P4503A4-inducing agents (e.g., phenytoin), stimulate the synthesis of reactive oxygen lipid species such as cholesterol, oxysterols, and related lipoproteins. These in turn are a source of high oxidizing potential molecules (Gibbons 2002, Imaoka, Osada et al. 2004, Pedruzzi, Guichard et al. 2004, Hu, Rosen et al. 2005, Engel and Evens 2006, Steffen, Wiswedel et al. 2006, Leonarduzzi, Poli et al. 2007, Lordan, Mackrill et al. 2008, Wang and Yi 2008, Lordan, Mackrill et al. 2009, Lordan, O'Brien et al. 2009, Trachootham, Alexandre et al. 2009, Vejux and Lizard 2009, Kasichayanula, Boulton et al. 2014). Elevated levels of cholesterol, and oxidized cholesterol (oxysterols) can have direct effects on the membrane to disaggregate portions and make them "leaky", or to affect cholesterol rafts, thus disrupting cell signaling (Janes, Ley et al. 1999, Simons and Toomre 2000, Gniadecki, Christoffersen et al. 2002). ROS, such as these lipids, also stimulate apoptosis (Gniadecki, Thorn et al. 2001, Kim, Kim et al. 2006).

Cancer cells that are deprived of glucose and amino acids actively take up lipids as fuel. This increased uptake of lipids and shift to lipid metabolism is routed to the mitochondria for oxidation (Gniadecki, Thorn et al. 2001, Kim, Kim et al. 2006). In mitochondria, high levels of cholesterol and oxysterols in the presence of melanin,

overwhelm the protective mechanisms that prevent free radical damage, inducing mitochondrial oxidation, depolarization, and apoptosis (Gray-Schopfer, Wellbrock et al. 2007, Mostert, Powell et al. 2012). The propensity for lipids to be spontaneously peroxidized and stimulate oxidative stress is another mechanism by which SM-88 causes targeted cancer cell damage and death (Akladios, Andrew et al. 2015).

Methoxsalen:
Melanin contributes to the lethal interaction of cells with deleterious ROS. Melanin functions as an intracellular catalyst similar to platinums, but with less toxicity (McGinness 1972, McGinness, Corry et al. 1974, MENTER, TOWNSEL et al. 1990). Melanin-inducing agents combined with oxidizing agents are utilized in clinical oncology to treat malignant skin conditions such as mycosis fungoides and T cell lymphoma (Edelson, Berger et al. 1987, Wozniak, Tracey et al. 2009).

Sirolimus:
Sirolimus like other mTOR inhibitors, is an essential regulator of cellular lipids, protein synthesis, and proliferation (Lin, Kong et al. 1995, Hara, Yonezawa et al. 1998, Shigemitsu, Tsujishita et al. 1999, Hay and Sonenberg 2004). This is at least partly mediated by effects of insulin, serine/threonine protein kinase B (AKT), and insulin-like growth factor (IGF) (Patti, Brambilla et al. 1998, Cheng, Meng et al. 2010, Xiao, Huang et al. 2011). Even at low doses, these mechanisms may reduce the availability of typical extracellular nutrients such as glucose, thereby increasing the tumor cells' already exaggerated metabolic demand to use alternative energy sources i.e., lipids and amino acids (Warburg effect) provided by the other components of SM-88 (Proud 2007, Joka, Boeck et al. 2014, Motzer, Porta et al. 2014, Vendelbo, Møller et al. 2014, Gillies and Gatenby 2015). FDG-PET, also demonstrates that mammalian target of rapamycin (mTOR) inhibitors are able to further reduce glucose uptake by cancer cells, which supports the hypothesis that SM-88 components increase alternative energy substrate utilization such as the substituted tyrosine and induced reactive oxygen lipid species (Chen, Appelbaum et al. 2013, Boers-Sonderen, de Geus-Oei et al. 2014).

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