

# Phase II Single Agent Study of Selinexor (KPT-330) in Patients with Metastatic Castration-Resistant Prostate Cancer (mCRPC) and Prior Therapy with Abiraterone and/or Enzalutamide

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1. I agree to follow this protocol version as approved by the UCSF Protocol Review Committee (PRC), Institutional Review Board (IRB), and Data Safety Monitoring Committee (DSMC).
2. I will conduct the study in accordance with applicable IRB requirements, Federal regulations, and state and local laws to maintain the protection of the rights and welfare of study participants.
3. I certify that I, and the study staff, have received the requisite training to conduct this research protocol.
4. I have read and understand the information in the Investigators' Brochure (or Manufacturer's Brochure) regarding the risks and potential benefits. I agree to conduct the protocol in accordance with Good Clinical Practices (ICH-GCP), the applicable ethical principles, the Statement of Investigator (Form FDA 1572), and with local regulatory requirements. In accordance with the FDA Modernization Act, I will ensure the registration of the trial on the [www.clinicaltrials.gov](http://www.clinicaltrials.gov) website.
5. I agree to maintain adequate and accurate records in accordance with IRB policies, Federal, state and local laws and regulations.

**UCSF Principal Investigator / Study Chair**

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Printed Name

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Date

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**Abstract**

Title	Phase II Single Agent Study of Selinexor (KPT-330) in Patients with Metastatic Castration-Resistant Prostate Cancer (mCRPC) and Prior Therapy with Abiraterone and/or enzalutamide
Patient population	Patients with abiraterone- or enzalutamide-refractory mCRPC.
Rationale for Study	<p>Abiraterone acetate is now considered the standard of care for patients with metastatic castrate-resistant prostate cancer (mCRPC) in the pre-chemotherapy setting. Patients with primary or acquired abiraterone resistance typically have rapidly progressive, refractory disease for which limited treatment options are available. The development of new therapies in mCRPC requires a focus on patients with primary or acquired resistance to abiraterone. Patients with abiraterone-refractory mCRPC have a poor prognosis overall with median survival after progression of disease at approximately 19 months. While chemotherapy is a standard approach in this setting, it is refused by many patients and clinicians due to toxicity concerns.</p> <p>Selinexor is a first in class Selective Inhibitor of Nuclear Export (SINE) that specifically blocks the karyopherin protein Exportin 1 (XPO1/Exportin 1). XPO1 is a key regulatory protein responsible for the nuclear export leading to functional inactivation of tumor suppressor proteins (TSPs) and is up-regulated 2-4 fold in all cancers studied to date. Selinexor, given orally, has demonstrated potent anti-cancer activity in animal models of prostate cancer including inhibition of PC3 driven bone metastasis.</p> <p>The goal of this trial is to evaluate the potential for a progression free survival benefit associated with selinexor administration in patients with abiraterone-refractory mCRPC.</p>
Primary Objective	To describe radiographic progression free survival (rPFS) associated with selinexor in patients with abiraterone- and/or enzalutamide-refractory mCRPC
Secondary Objectives	<ul style="list-style-type: none"> <li>• To measure PSA changes at 12 weeks post-selinexor initiation</li> <li>• To measure time to PSA progression</li> <li>• To measure time to development of <math>\geq 2</math> new bone lesions</li> <li>• To compare the relationship of abiraterone-resistance status (primary vs acquired) and treatment outcome</li> <li>• To describe the safety profile of selinexor</li> <li>• To measure reduction in pain for symptomatic patients based on the brief pain inventory short form.</li> <li>• To determine the effect of selinexor on XPO-1 expression, leukocyte gene expression profile, and macrophage inhibitory cytokine-1 (MIC-1) mRNA expression</li> <li>• To assess serum levels of selinexor as a function of dose and time since last dose</li> </ul>

Study Design	Single agent phase II open label study of selinexor in patients with mCRPC with prior therapy with standard hormone ablation agents and abiraterone.
Number of patients	A maximum of 54 evaluable patients will be accrued for this study, provided the early stopping criteria are not met.
Duration of Therapy	In the absence of treatment delays due to adverse events, treatment may continue until: <ul style="list-style-type: none"> <li>• Disease progression</li> <li>• Inter-current illness that prevents further administration of treatment</li> <li>• Unacceptable adverse event(s), including any occurrence of grade 4 neurotoxicity</li> <li>• Patients decides to withdraw from the study</li> <li>• Significant patient non-compliance with protocol</li> <li>• General or specific changes in the patients' condition render the patient unacceptable for further treatment in the judgment of the investigator</li> </ul>
Duration of Follow up	Patients will be followed for 30 days after completion of treatment or removal from study, or until death, whichever occurs first. Patients removed from study for unacceptable treatment related adverse event(s) will be followed until resolution or stabilization of all treatment related adverse events to Grade 2 or lower.
Duration of study	The study will reach the final procedure for primary outcome 24 months from the time the study opens to accrual. Data collection will be completed 36 months after the study opens to accrual.
Study Drugs	The starting dose for all patients will be an oral dose of 60 mg, given twice per week at least 48 hours apart (Mon/Wed, Tue/Thurs or Wed/Fri) on Weeks 1, 2 and 3 of a 4-week cycle. Selinexor will not be taken during Week 4 (total six doses per cycle). Cycles are repeated every 28 days until disease progression. Tablets for selinexor oral administration will be supplied in two (2) strengths: 10 and 25 mg of active ingredient per tablet. Ondansetron 8 mg q8h and olanzapine 5 mg PO qbedtime will be administered on the day of dosing
Safety Assessments	Each patient receiving selinexor will be evaluable for safety. The safety parameters include all laboratory tests and hematological abnormalities, physical findings, and spontaneous reports of adverse events reported to the investigator by patients. We will monitor for anorexia, loss of appetite, fatigue, thrombocytopenia, neutrocytopenia, diarrhea, blurred vision, liver enzyme increase, and hyponatremia.
Efficacy Assessments	Response and progression will be evaluated in this study using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria. Changes in only the longest diameter (unidimensional measurement-LD) of the tumor lesions are used in the RECIST criteria.

Unique Aspects of this Study	This trial represents will assess a first-in-class SINE selinexor in treatment of metastatic castrate resistant prostate cancer. Not only does selinexor reflect a novel treatment modality in mCRPC, this may reflect a potential therapeutic option for patients with primary or acquired abiraterone resistance.
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**List of Abbreviations**

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical (Classification System)
AUC	area under the curve
BUN	blood urea nitrogen
CBC	complete blood cell (count)
CR	complete response
CRC	Clinical Research Coordinator
CRF	case report form
CRM1	Chromosome Region Maintenance 1
CT	computerized tomography
CTCEA	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
CTMS	Clinical Trial Management System
DLT	dose limiting toxicity
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HCT	Hematocrit
HDFCCC	Helen Diller Family Comprehensive Cancer Center
HGB	Hemoglobin
ICH	International Conference on Harmonization
IND	investigational new drug application
IRB	Institutional Review Board
LDH	lactate dehydrogenase
LMB	Leptomycin B
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI	National Cancer Institute

**List of Abbreviations**

ORR	overall response rate
PD	disease progression
PO	<i>Per os</i> (by mouth, orally)
PR	partial response
PRC	Protocol Review Committee (UCSF)
PRN	Pro re nata (as needed)
RBC	red blood cell (count)
SD	stable disease
SD	standard deviation
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SINE	Selective Inhibitor of Nuclear Export
SU2C	Stand-up 2 Cancer
ULN	upper limit of normal
XPO1	Exportin 1

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## 1 Introduction

### 1.1 Background on Indication

Prostate cancer is the second most common cancer in men representing approximately 30% of all cancers diagnosed in men. When confined to the prostate gland the disease is curable with local therapy. However approximately 50% of men fail local therapy and develop incurable metastatic disease.

Abiraterone acetate (Zytiga®) is now considered the standard of care for patients with metastatic castration resistant prostate cancer (mCRPC) who are asymptomatic or minimally symptomatic and have not been treated with docetaxel chemotherapy [1]. In its current clinical use, approximately 30% of such patients do not experience a significant reduction in tumor burden or decline in PSA level and thus have *primary resistance*. Of the remaining approximately 70% of patients, the vast majority will experience benefit but develop *acquired resistance* within a median period of time of approximately 16 months. Following the development of resistance, the disease is often virulent and can be rapidly fatal. The median survival after progression of disease is approximately 19 months. To date, no therapy has been shown to consistently improve outcomes in patients with abiraterone-refractory mCRPC.

Thus, the development of new therapies in mCRPC requires a focus on patients with primary or acquired resistance to abiraterone. Further, it is likely that subsequent therapies, to be active, will be required to be agents with a unique mechanism of action, and not be antagonists of the androgen receptor and its related pathways.

### 1.2 Background on the selinexor

Selinexor is an oral, first in class, slowly reversible covalent, potent, Selective Inhibitor of Nuclear Export (SINE) that specifically blocks the karyopherin protein Exportin 1 (XPO1/Exportin 1), also called chromosome region maintenance 1 (CRM1). XPO1 is overexpressed 2-4 fold in all cancers studied to date, including prostate cancer (Fesstucia, AACR). XPO1 is an exclusive nuclear transporter for shuttling the major Tumor Suppressor Proteins (TSPs) and other growth regulators out of the nucleus. Because TSPs require nuclear localization to mediate their deoxyribonucleic acid (DNA) damage assessment/tumor suppressing functions, nuclear export leads to their functional inactivation. In addition, many TSPs are degraded by the proteasome when they are transported to the cytoplasm. Blockade of XPO1 leads to marked accumulation of TSPs in the nucleus of all cells, leading to cell cycle arrest at the G1±G2 checkpoints. Cells with damaged genomes – *i.e.*, cancer cells – undergo apoptosis, whereas undamaged normal cells remain in cell cycle arrest until the XPO1 block is released. Consistent with its activation of multiple TSPs, selinexor has shown broad anti-cancer activity in nonclinical murine xenograft, orthotopic, primagraft, and leukemograft models including activity in xenograft of androgen independent prostate cancer cells and prostate cancer bone metastatic models and largely independent of the resistance profile of the cancer cell line being investigated.

Complete information is available in the Investigational Drug Brochure.

#### 1.2.1 SINE XPO1 inhibition

Blockade of XPO1 has been studied for over 10 years, mainly with the naturally occurring, non-drug-like bacterial toxin Leptomycin B (LMB) (Kau *et al.*, 2003; Kudo *et al.*, 1999).

LMB is a potent, selective, irreversible XPO1 inhibitor used as a tool to study nuclear export.

LMB and other natural product XPO1 inhibitors have potent antitumor activity *in vitro*, but are also toxic to normal cells, probably because they irreversibly block all XPO1 functions (Kudo *et al.*, 1999). Despite marked toxicities in animals, LMB was administered intravenously to patients with refractory solid tumors in the 1980's (Newlands *et al.*, 1996). It showed the expected GI toxicities (nausea, vomiting, watery diarrhea) along with marked fatigue/asthenia and malaise; as a result, its development was halted. Typical cytotoxic agent side effects such as neutropenia, mucositis, and alopecia were not observed. Transient tumor marker responses in ovarian adenocarcinoma and trophoblastic tumor, and stable disease in a refractory sarcoma were observed.

Kosan Biosciences Inc., prior to its acquisition by Bristol-Myers Squibb, created derivatives of LMB with improved pharmacologic properties, which showed a superior therapeutic window across multiple tumor xenografts, although transient anorexia remained (Mutka *et al.*, 2009). Consistent with observed minimal effects on normal cells, myelosuppression, mucositis or bloody diarrhea, and alopecia were not observed. Although the development of these semi-synthetic derivatives of LMB has not progressed into the clinic to date, these data suggest that XPO1 inhibitors with adequate therapeutic windows can be created. Drug-like, small-molecule SINE compounds exemplified by selinexor have shown markedly improved therapeutic windows and oral bioavailability in animal studies.

XPO1 inhibitors have been shown to block the nuclear export of key TSP and GRP, leading to accumulation of these proteins in the nucleus, as nuclear import appears to proceed unimpeded. Moreover, nuclear retention appears to prevent proteasome-mediated degradation (which is typically cytoplasmic). Forced nuclear retention of TSP/GRP can counteract a multitude of oncogenic (and inflammatory) pathways that perpetuate the neoplastic phenotype (Table 1.1). Moreover, certain proteins such as survivin (Stauber *et al.*, 2007) and p21<sup>CIP1</sup> (Gartel and Tyner, 2002) can be anti-apoptotic when in the cytoplasm; forcing their nuclear retention by XPO1 inhibition can prevent their anti-apoptotic functions and, for p21, expose its antitumor activities.

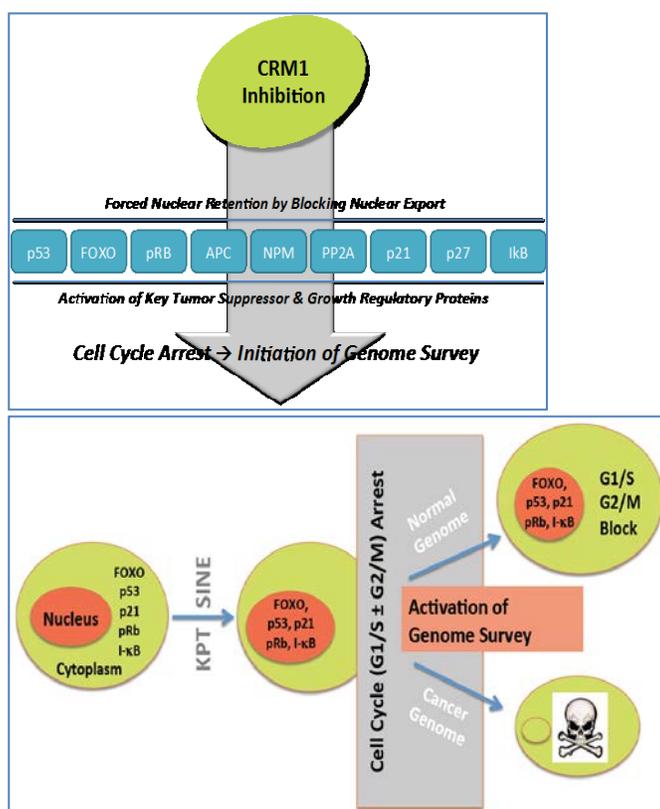
**Table 1.1 Oncogenic Pathways and TSP/GRP Functions Enhanced by XPO1 Inhibition**

Oncogenic Pathway	TSP/GRP Enhanced by XPO1 inhibition	Oncogenic Pathway	TSP/GRP Enhanced by XPO1 inhibition
AKT↑, PI3K↑, PTEN↓	FOXO, p27	CDK2-CyclinE-E2F1	pRb, p27 <sup>KIP</sup> , p21 <sup>CIP1</sup>
deletion p53, MDM2↑	p21 <sup>CIP1</sup> , p53, p14 <sup>ARF</sup>	Cyclin D-CDK4/6	INK4, pRb, p21, p27
HER2, EGF-R (HER1)	FOXO, pRB	NPM1c Mutation	p53, p14 <sup>ARF</sup> , NPM1
p16 <sup>INK4A</sup> ↓ or p14 <sup>ARF</sup> ↓	pRB, p53, E2F4	c-Myc ↑	PP2A, p21CIP1
mTOR↑	p53, p27, FOXO	Bcr-Abl	PP2A, Abl
Wnt / β-Catenin ↑	APC, HMGBP1	Bcl2 ↑, Bcl-xL ↑	p53, p16 <sup>INK4A</sup>
deletion pRb	p27	Notch ↑	FOXO

survivin - cytoplasmic	survivin – nuclear	NF-κB ↑	I-κB
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Transient XPO1 (CRM1) inhibition (~4 hours) appears to be sufficient for nuclear retention of TSP/GRP and activation of the genomic survey (Figure 1). As normal (undamaged) cells have an intact genome, they remain in cell cycle arrest following XPO1 inhibition. Malignant cells, in contrast “fail” their genomic survey, and a death pathway is initiated (Figure 1). Along these lines, small interfering ribonucleic acid (siRNA) knockdown of XPO1 specifically induces apoptosis in malignant cervical cells, but not in their normal cell counterparts (van der Watt *et al.*, 2009).

**Figure 1: XPO1 (CRM1) inhibition activates TSP/GRP and induces selective tumor cell death**



In summary, as the restoration of multiple tumor suppressor and growth regulatory pathways results in the death of cancer cells, this mechanism of action represents a unique approach to achieve an antitumor effect.

### 1.3 Rationale for the Proposed Study

The development of new therapies in mCRPC requires a focus on patients with primary or acquired resistance to abiraterone. Patients with abiraterone-refractory mCRPC have a poor prognosis overall with median survival after progression of disease at approximately 19 months. While chemotherapy is a standard approach in this setting, it is refused by many patients and clinicians due to toxicity concerns.

Selinexor, given orally, has demonstrated potent anti-cancer activity in animal models of prostate cancer including inhibition of PC3 driven bone metastasis. In a Phase 1 clinical study, selinexor showed acceptable tolerability with clear signs of anti-cancer activity in both hematological and solid tumors. Seven patients with mCRPC were enrolled in the expansion phase of the ongoing Phase 1 study in patients with advance solid tumors (NCT01607905), one patient with abiraterone and enzalutamide refractory prostate cancer showed stable disease (~20% reduction in PSA and stable disease according to RECIST, >180 days on study) with marked reduction in pain scale. A second patient with mCRPC and 7/10 pain on study initiation had ~50% reduction in PSA with stable disease according to RECIST; he is now pain free and continues >180 days on study. A third mCRPC has also achieved stable disease and is doing well (>150 days on study with stable PSA). One patients achieved >50% reduction in PSA and continues >20 days on study. One patient is still cycle 1 >20 days on study. Two mCRPC patients withdrew consent due to poor tolerability; however, there was no evidence of disease progression. All of these Phase 1 patients have received standard hormone ablation therapies, and most have also received docetaxel.

Further, it is likely that subsequent therapies, to be active, will be required to be agents with a unique mechanism of action, and not be antagonists of the androgen receptor and its related pathways. As a potent, oral, first in class, slowly reversible covalent Selective Inhibitor of Nuclear Export (SINE) that specifically blocks the karyopherin protein Exportin 1 (XPO1), also called chromosome region maintenance 1 (CRM1), the therapy targets a unique pathway not actively explored in prostate cancer research. XPO1 is overexpressed 2-4 fold in all cancers studied to date. XPO1 exclusively exports the major Tumor Suppressor Proteins (TSPs) and other growth regulators out of the nucleus. Blockade of XPO1 leads to marked accumulation and activation of TSPs in the nucleus resulting in selective apoptosis in cancer cells, while undamaged normal cells remain in cell cycle arrest until the XPO1 block is released.

#### 1.4 Rationale for Proposed Dose

More than 200 patients with advanced cancers have received KPT-330 orally in two Phase 1 studies of KPT-330. KCP-330-001 is a dose escalation study in patients with advanced hematologic malignancies. KCP-330-002 is a dose escalation study in patients with advanced solid tumors. The DLTs were anorexia/nausea and fatigue at 40 mg/m<sup>2</sup> (10 times per 4-week cycle) in KCP-330-002 and the maximum tolerated dose (MTD) was 30mg/m<sup>2</sup>. The recommended phase 2 dose (RP2D) for 10 times per cycle dosing is 30mg/m<sup>2</sup> in both solid and hematologic malignancies. However, pharmacodynamics analyses suggest that at doses > 6 mg/m<sup>2</sup>, selinexor inhibits XPO1 activity for >48 hrs. Therefore a reduced intensity dosing at twice weekly (8 times per cycle) was initiated and has shown improved tolerability. Doses of 65 mg/m<sup>2</sup> twice weekly have cleared DLT assessment and this is the MTD in advanced solid tumors, KCP-330-002 (IND 114044). It should also be noted that a dose of 70 mg/m<sup>2</sup> cleared DLT in the AML arm of the ongoing Phase1 study in patients with heavily pretreated hematological malignancies (KCP-330-001, IND 11404X). The most common AEs in KCP-330-002 are GI in nature, typically fatigue (73%), nausea (70%), anorexia (57%), and vomiting (49%). Most of these AEs, which are Grade 1-2 events, are generally responsive to standard supportive care including serotonin antagonists, dopamine D<sub>2</sub> blockers, low dose glucocorticoids, etc. Olanzapine, (or mirtazapine), megesterol acetate (Megace®), and glucocorticoids have been most useful in improving appetite in many patients treated with KPT-330. Aggressive prophylaxis with glucocorticoids, appetite stimulating agents, and anti-nausea

agents can greatly reduce or eliminate these AEs. In over >290 patients treated as of 1-April-2014, no specific organ toxicity was observed at doses  $\leq 70$  mg/m<sup>2</sup>. Several patients have continued on single agent selinexor for >12 months.

This Phase 2 study will begin dosing selinexor at 60 mg flat dose, twice per week at least 48 hours apart (Mon/Wed, Tue/Thurs or Wed/Fri) on Weeks 1, 2 and 3 of a 4-week cycle. Recent analysis of the existing PK data from Phase 1 trials KCP-330-001 and KCP-330-002 supports the use of fixed rather than BSA-based dosing. The 5<sup>th</sup> and 95<sup>th</sup> percentile for BSA values encountered to date in Phase 1 trials KCP-330-001 and KCP-330-002 are 1.5 and 2.3 m<sup>2</sup>, respectively (N=331). PK values ( $C_{max}$  and  $AUC^{(0-\infty)}$ ) for a given flat (fixed) dose of selinexor were similar across this typical BSA range, indicating that exposure is not strongly correlated with BSA. Selinexor will not be taken during Week 4 (total six doses per cycle). Cycles are repeated every 28 days until disease progression. For each patient, dose reductions of Selinexor is allowed until the dose has been reduced below 20 mg dose per week, at which time treatment will be discontinued.

### 1.5 Correlative Studies

Correlative studies seeking predictive biomarkers for selinexor treatment and associations between biomarkers and treatment outcomes will be performed on blood and biopsy tissue collected, when available. Blood (10 mL) will be collected at baseline, 8 and 16 weeks post initiation of treatment, and at time of progression. Histologic confirmation of adenocarcinoma will be required prior to initiating treatment. Pre-therapy tumor biopsy may be obtained under the auspices of a separate protocol active at UCSF exploring adaptive responses and mechanisms of resistance to abiraterone. Leftover tissue will be used for genetic and histology studies. Patients will be asked to participate in the companion Radiologically Guided Biopsy protocol of mCRPC; participation in the biopsy study is optional but will be strongly encouraged.

Circulating tumor cells (CTC) may be isolated and quantified from blood per a companion CTC study protocol. Quantitative circulating tumor cell (CTC) counting has demonstrated promise as a biomarker of response in men with CRPC treated with abiraterone and with chemotherapy and has been used as a prognostic indicator of survival in metastatic prostate cancer..

Biopsy of metastatic tissue offers a similar potential to describe the expression profile of metastatic tumors and explore genetic changes. Left-over pre-therapy biopsy tissue will be used for mRNA sequencing and histology studies. Tissue will be evaluated for the presence of proteins such as XPO-1, P27, P21, I $\kappa$ B, pRB. For those patients with a pre-treatment biopsy available through the Stand Up 2 Cancer Dream Team initiative (also mentioned above), an exploratory analysis comparing pre- and post-treatment XPO-1 expression will be performed. XPO1 is the exclusive mediator of nuclear export of p53, p73, pRb, FOXO, p21, p27, BRCA1, the endogenous inhibitor of Nuclear Factor  $\kappa$ B (NF- $\kappa$ B) known as I $\kappa$ B, and other tumor suppressor and growth regulatory proteins. Nuclear export of these key proteins leads to their functional inactivation. Blockade of XPO1 with SINEs forces the accumulation and activation of tumor suppressor and growth regulatory proteins in the nucleus, leading to potent and selective tumor cell apoptosis while sparing normal cells. Exploratory analysis of XPO1 expression either at the transcription level or protein, may inform the further development of selinexor.

Analyses of tissue biopsies, in combination with exploratory CTC analysis per our companion study protocol, therefore has the potential to generate a wealth of data about the expression profile of metastatic tumor. The relationship of XPO-1 expression to PSA

decline will also be evaluated along with the expression profile of metastatic tumor and clinical outcomes.

In the ongoing Phase 1 study in patients with advance solid tumors (NCT01607905), patients with mCRPC reported reduction in pain. The study will further determine which, if any, type of progression (e.g. pain, bone, etc.) is mitigated by selinexor therapy.

## **2 Objectives of the Study**

### **2.1 Primary**

- To describe radiographic progression free survival (rPFS) associated with selinexor in patients with abiraterone refractory mCRPC

### **2.2 Secondary**

- To measure PSA changes at 12 weeks post-selinexor initiation
- To assess time to PSA progression
- To measure time to development of  $\geq 2$  new bone lesions
- To compare the relationship of abiraterone-resistance status (primary vs acquired) and treatment outcome
- To determine the effect of selinexor on persistent pain associated with bone metastasis using the brief pain inventory (BPI) short form.
- To describe the safety profile of selinexor in patients with metastatic castration-resistant prostate cancer.
- To determine the effect of selinexor on circulating leukocyte XPO-1 expression, leukocyte gene expression profile and macrophage inhibitory cytokine-1 (MIC-1) mRNA expression
- To assess serum selinexor trough levels as a function of dose and time since last dose

### **2.3 Exploratory Objectives, Other Assessments**

- To describe the relationship of XPO-1 expression to PSA decline
- To describe the expression profile of metastatic tumor and outcome
- To describe the type of progression (e.g. Pain, bone etc)
- To define XPO-1 expression in patients for whom pre- and post-treatment biopsy is obtained

### **2.4 Endpoints**

#### **2.4.1 Primary Endpoints**

Radiographic progression free survival (rPFS). This is defined from study start until one of the following events occurs:

- $\geq 2$  new bone lesions on Technetium bone scan. If  $\geq 2$  new lesions are detected at or 12 weeks following initiation of treatment, progression must be confirmed by the presence of  $\geq 2$  or more additional lesions to rule out bone scan flare as a cause of the radiographic changes.

- RECIST-defined tumor progression.
- Clinical deterioration requiring a change in prostate cancer therapy, or at clinician discretion
- Surgery or Radiation to treat a prostate cancer related indication
- Death from any cause.

#### **2.4.2 Secondary Endpoints**

- PSA decline of  $\geq 50\%$  at 12 weeks post therapy initiation
- Time to PSA progression. Defined as a rise in PSA of 50% above nadir value or 25% above baseline if there is no decline.
- Relationship of abiraterone resistance status (primary vs acquired) and outcome
- Time to confirmed development of  $\geq 2$  new bone lesions that cannot be attributable to bone scan flare
- Reduction in pain for symptomatic patients
- Safety
- Serum selinexor levels as a function of dose and time
- Pharmacodynamic analysis of selinexor impact on XPO-1 expression, leukocyte gene expression profile, and macrophage inhibitory cytokine-1 (MIC-1) mRNA expression

#### **2.4.3 Exploratory Endpoints**

- Relationship of XPO-1 expression to PSA decline.
- Expression profile of metastatic tumor and outcome.
- Type of progression (e.g. Pain, bone etc)
- Comparison of pre- and post-treatment XPO-1 expression in patients for whom pre-treatment biopsy is available through the Stand Up 2 Cancer "Dream Team" program.

### **3 Study Design**

#### **3.1 Characteristics**

Single agent phase II open label study of selinexor in patients with mCRPC with prior therapy with standard hormone ablation agents and abiraterone. We anticipate the involvement of at least 3-5 centers participating in the SU2C West Coast Dream Team (SU2C WCDT - UCSF, UCLA, UC Davis, Oregon Health Sciences University, University of British Columbia), as well as participating sites of the Prostate Cancer Clinical Trials Consortium. Pre therapy and end of therapy biopsies will be offered to patients at the SU2C WCDT centers only.

#### **3.2 Number of Subjects**

A maximum of 54 evaluable patients will be accrued for this study, provided the early stopping criteria are not met. The early stopping rules are described in the statistical section.

### 3.3 Eligibility Criteria

Patients must have baseline evaluations performed prior to the first dose of study drug and must meet all inclusion and exclusion criteria. In addition, the patient must be thoroughly informed about all aspects of the study, including the study visit schedule and required evaluations and all regulatory requirements for informed consent. The written informed consent must be obtained from the patient prior to enrollment. The following criteria apply to all patients enrolled onto the study unless otherwise specified.

#### 3.3.1 Inclusion Criteria

1. Age  $\geq$  18 years.
2. Histologically confirmed adenocarcinoma of the prostate.
3. Patients must have castrate levels of testosterone ( $< 50$  ng/dL) on GnRH analogues or have had prior orchiectomy. GnRH analogues must be continued while on study.
4. Tumor tissue submitted for molecular and genetic analysis through the companion SU2C radiologically guided biopsy of abiraterone and/or enzalutamide refractory mCRPC protocol.
  - a. Patients who consent to participate in the companion biopsy protocol and are subsequently determined to be ineligible for biopsy are eligible to participate in the current protocol.
5. Progressive disease as demonstrated by a rising PSA (at least two determinations) prior to study entry, and/or radiographic evidence of tumor progression in soft tissue according to modified RECIST criteria or identification of new lesions by bone scan (i.e.,  $\geq 2$  new lesions).
6. Primary resistance or acquired resistance (i.e., acquired resistance will be defined as disease progression following a period of response defined as  $\geq 50\%$  decline in PSA within 12 weeks of starting therapy and not otherwise meeting criteria for primary resistance) to any of the following agents/combinations of therapy:
  - a. Abiraterone acetate. Primary resistance to abiraterone will be defined as:
    - No PSA decline
    - PSA decline less than 50% after 12 weeks of abiraterone therapy
    - PSA progression within 12 weeks of AA treatment (by PCWG2 criteria), after initial response to therapy
    - Objective progression, by RECIST criteria for soft tissue lesions and by modified PCWG2 criteria for bone lesions within 12 weeks of starting abiraterone treatment
    - Unequivocal clinical progression (per the treating provider's discretion) within 12 weeks of starting abiraterone treatment
  - b. Enzalutamide. Primary resistance to enzalutamide will be defined as:
    - No PSA decline
    - PSA decline less than 50% after 12 weeks of enzalutamide therapy

- PSA progression within 12 weeks of enzalutamide treatment (by PCWG2 criteria), after initial response to therapy
  - Objective progression, by RECIST criteria for soft tissue lesions and by modified PCWG2 criteria for bone lesions within 12 weeks of starting enzalutamide treatment
  - Unequivocal clinical progression (per the treating provider's discretion) within 12 weeks of starting enzalutamide treatment
- c. Other second-generation investigational anti-androgen/androgen-receptor targeted therapies, including ARN-509. Primary resistance will be defined as:
- i. No PSA decline
  - ii. PSA decline less than 50% after 12 weeks of enzalutamide therapy
  - iii. PSA progression within 12 weeks of enzalutamide treatment (by PCWG2 criteria), after initial response to therapy
  - iv. Objective progression, by RECIST criteria for soft tissue lesions and by modified PCWG2 criteria for bone lesions within 12 weeks of starting enzalutamide treatment
  - v. Unequivocal clinical progression (per the treating provider's discretion) within 12 weeks of starting enzalutamide treatment
- d. Combination therapy with abiraterone, enzalutamide and/or other second-generation investigational anti-androgen/androgen-receptor targeted therapies, including ARN-509. Primary resistance to combination therapy will be defined as:
- No PSA decline
  - PSA decline less than 50% after 12 weeks of abiraterone and enzalutamide therapy
  - PSA progression within 12 weeks of abiraterone and enzalutamide treatment (by PCWG2 criteria), after initial response to therapy
  - Objective progression, by RECIST criteria for soft tissue lesions and by modified PCWG2 criteria for bone lesions within 12 weeks of starting abiraterone and enzalutamide treatment
  - Unequivocal clinical progression (per the treating provider's discretion) within 12 weeks of starting abiraterone and enzalutamide treatment
- e. Sequenced therapy, including any of the following:
- i. Abiraterone acetate followed by enzalutamide
    - 1. Primary resistance will be defined per criteria for abiraterone monotherapy primary resistance, section 3.3.1, item 5a
  - ii. Enzalutamide followed by abiraterone acetate
    - 1. Primary resistance will be defined per criteria for enzalutamide monotherapy primary resistance, section 3.3.1, item 5b
  - iii. Other second-generation investigational anti-androgen/androgen-receptor targeted therapies, including ARN-509.

1. Primary resistance will be defined per criteria for other investigational anti-androgen monotherapy primary resistance, section 3.3.1, item 5c
7. Presence of 1 or more bone metastasis.
8. ECOG Performance status 0 or 1.
9. Prior and ongoing zoledronic acid or denosumab therapy is allowed.
10. Prior therapy with radium-223 is allowed.
11. Discontinuation of prior therapy for mCRPC: A Washout period of 28 days for the following therapies is required: Abiraterone, enzalutamide, fluconazole, itraconazole, flutamide, bicalutamide, nilutamide, and other experimental hormonal agents (ARN509, TAK-700, etc.), sipuleucel-T (Provenge), other experimental vaccines (PROSTVAC-V/F, etc.), Strontium-89, Samarium, and Radium-223 chloride.
12. Baseline laboratory parameters:
  - Adequate bone marrow function:

Leukocytes	> 3,000/mcL
absolute neutrophil count	> 1,500/mcL
Platelets	> 125,000/mcL
Hemoglobin	≥ 5.59 mmol/L or 9 g/dL

Up to 5% deviation is tolerated. Transfusions and growth factors are allowed.
  - Adequate hepatic function:

Total bilirubin	within normal institutional limits
AST(SGOT)	< 3 X institutional upper limit of normal
ALT(SGPT)	< 3 X institutional upper limit of normal
  - Adequate renal function:

Creatinine	within normal institutional limits
OR	> 60 mL/min/1.73 m <sup>2</sup> for patients with creatinine levels above institutional normal
creatinine clearance	
13. Ability to understand a written informed consent document, and the willingness to sign it
14. Life expectancy of at least 12 weeks
15. Able to swallow and retain oral medication

### 3.3.2 Exclusion Criteria

1. Untreated brain metastases. Brain metastases ≤1 cm and not associated with any focal neurologic deficits are allowed.

2. Prior docetaxel or other chemotherapy for mCRPC. Patients who have received docetaxel for metastatic hormone-sensitive prostate cancer are eligible.
3. Active or symptomatic viral hepatitis or chronic liver disease
4. Clinically significant heart disease as evidenced by myocardial infarction, or arterial thrombotic events in the past 6 months, severe or unstable angina, or New York Heart Association (NYHA) Class II-IV heart disease or known cardiac ejection fraction measurement of <50 % at baseline.
5. Patients with significantly diseased or obstructed gastrointestinal tract or uncontrolled vomiting or diarrhea or other gastrointestinal disorders (medical disorders or extensive surgery) that may interfere with the absorption of the study agents
6. Pure small cell carcinoma of the prostate or any mixed histology cancer of the prostate (eg: neuroendocrine) that contains <50% adenocarcinoma, as observed on biopsy obtained at the time of diagnosis or on any subsequent biopsies. Any "currently active" second malignancy, other than non-melanoma skin cancer. Patients are not considered to have a "currently active" malignancy, if they have completed therapy and are considered by their physician to be at least less than 30% risk of relapse over next year.
7. Any condition, which in the opinion of the investigator, would preclude participation in this trial.
8. Active psychiatric illnesses/social situations that would limit compliance with protocol requirements.
9. Patients in whom urgent treatment with docetaxel is indicated, per clinician discretion. This includes, but is not limited to patients with symptomatic visceral metastatic disease
10. Uncontrolled infection or concomitant medical illness that is not adequately controlled with current medical management, as determined per clinician discretion.
11. Active bleeding disorders or evidence of evidence of chronic or acute disseminated intravascular coagulation (DIC)
12. Severely compromised immunological state, including known human immunodeficiency virus (HIV)
13. Any acute toxicities due to prior anti-cancer treatments and/or radiotherapy that have not resolved to a NCI CTCAE Grade of  $\leq 1$  (except alopecia)
14. Prior radiation therapy completed <3 weeks or single fraction of palliative radiotherapy <14 days prior to first dose of KPT-330
15. Initiation of bisphosphonate therapy <4 weeks prior to first dose of KPT-330. Patients receiving bisphosphonate or denosumab therapy must be on stable doses for at least 4 weeks prior to first dose of KPT-330.
16. Men unable or unwilling to employ 2 forms of highly effective contraception throughout the study and for 8 weeks after the end of study treatment

### 3.4 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment may continue until:

- Disease progression
- Inter-current illness that prevents further administration of treatment
- Unacceptable adverse event(s), including any occurrence of grade 4 neurotoxicity
- Patients decides to withdraw from the study
- Significant patient non-compliance with protocol
- General or specific changes in the patients' condition render the patient unacceptable for further treatment in the judgment of the investigator.

### 3.5 Duration of Follow Up

Patients will be followed for 30 days after completion of treatment or removal from study, or until death, whichever occurs first. Patients removed from study for unacceptable treatment related adverse event(s) will be followed until resolution or stabilization of all treatment related adverse events to Grade 2 or lower.

### 3.6 Study Timeline

#### 3.6.1 Primary Completion

The study will reach the final procedure for primary outcome 24 months from the time the study opens to accrual.

#### 3.6.2 Study Completion

The study will reach primary completion of data collection 36 months from the time the study opens to accrual.

## 4 Study Drug

### 4.1 Description, Supply and Storage of Selinexor

Tablets for selinexor oral administration will be supplied in two (2) strengths: 10 and 25 mg of active ingredient per tablet. Bulk bottles of 50 tablets per bottle will be supplied for each of the two strengths. The tablets are clear coated with Opadry II clear and prepared from a common blend prepared from a wet granulation of active compound (selinexor), Kollidon® 30 (polyvinyl pyrrolidone), sodium lauryl sulfate, croscarmellose sodium, and Avicel PH-101 (Microcrystalline cellulose). The granulation is adjusted to final compression blend with Avicel PH-102 (Microcrystalline cellulose), Aerosil® (colloidal silicon dioxide), magnesium stearate, and additional croscarmellose sodium. All tablet excipients are GRAS and suitable for use in pharmaceuticals.)

Classification - Cell biological modifier: Apoptosis-inducing agent

Mechanism of Action - Selinexor is a small molecule, potent, oral Selective Inhibitor of Nuclear Export (SINE). Selinexor forms a slowly reversible ( $t_{1/2}$  ~24 hours) covalent bond with XPO1 (also called CRM1) at cysteine 528. Selinexor is a potent inhibitor ( $IC_{50}$  ~20nM) of XPO1-mediated nuclear export in intact cells and to have minimal activity (>10  $\mu$ M)

against 114 other proteins including enzymes, receptors, transporters, ion channels and other CysteinyI-active site kinases and proteases in binding assays.

Metabolism - preliminary analysis from a subset of patients (N=22) suggests that the primary metabolism of selinexor in plasma is through glucuronidation as well as hydroxylation and addition of cysteine/glycine groups (derived from GSH conjugation) to the parent compound. Relative proportions of the putative metabolites are low, typically less than 1% of parent at peak selinexor concentrations and these metabolites are not expected to be pharmacologically active.

Availability - Selinexor will be supplied by Karyopharm Therapeutics Inc.

Storage and handling - Selinexor tablets will be stored at ambient or refrigerated temperatures between (36 – 86 °F) or (2–30 °C) in a locked and secured area with restricted access to study staff. The tablets should not be stored at freezer temperatures or allowed to freeze. Tablets will be supplied in white high density polyethylene (HDPE) bottles.

Side Effects – >200 patients have been treated with selinexor to date. The most common adverse events (AEs) are gastrointestinal in nature: nausea, anorexia, vomiting. Fatigue is also observed, and, like the nausea, is sometimes associated with anorexia. Mucositis or stomatitis are not observed, consistent with nonclinical toxicological studies. Active administration of appetite stimulating agents, leads to markedly improved tolerability. In addition, anorexia appears to decline with longer treatment on selinexor. Idiosyncratic reductions in platelets have been observed; these were not seen in any of the nonclinical models. No cases of clinically significant bleeding have been reported to date. Neutropenia and anemia are minimal, consistent with a lack of myelosuppression observed in nonclinical studies. Ocular symptoms of various kinds (blurred vision is the most common one) have been reported by a number of patients. Other than changes in visual acuity, corrected with new prescriptions in a few cases, no objective findings on ophthalmological examination have been associated with these ocular symptoms, except for five patients that had experience worsening of pre-existing cataracts. No major organ toxicities or drug-related deaths have been observed to date. Patients with advanced cancers have remained on selinexor for >10-12 months. Complete and updated adverse event information is available in the Investigational Drug Brochure.

Based on the experience of >200 patients, each patient in this study will be assessed periodically for the development of any toxicity as outlined in Section 6 of this protocol. Toxicity will be assessed according to the NCI CTCAE v4.0. Dose adjustments will be made according to the system showing the greatest degree of toxicity, as described in Section 5.2.

## 4.2 Drug Accountability

The Investigational Pharmacist will manage drug accountability records.

## 4.3 Drug Ordering

UCSF will obtain selinexor directly from Karyopharm Therapeutics as study supply.

#### 4.4 Packaging and Labeling of Study Drug

Each bottle of selinexor tablets will be labeled in accordance with current ICH GCP, FDA and specific national requirements.

Drugs will be packaged and labeled per UCSF institutional standards, adhering to applicable local and federal laws.

### 5 Treatment Plan

#### 5.1 Dosage and Administration

Treatment will be administered on an outpatient basis. Patients will be provided with a study diary for documentation of selinexor administration. Study diaries will be collected every cycle.

**Table 5.2.1 Regimen Description**

Study Drug	Premedication; precautions	Dose	Route	Schedule	Cycle Length
Selinexor	Pre-medicate with ondansetron 8 mg PO q8h on D0-D3 and olanzapine (2.5-5.0 mg QHS) on D1 and D3*	60 mg	Oral	Ondansetron: four-times weekly (D0 – D3) of each 4-week cycle. Olanzapine: Twice weekly (D1 and D3 of each week 1 – 3 of each 4-week cycle. Drug holiday on week 4).	4 weeks (28 days)

\*Prophylaxis prior to initiation of therapy with selinexor is recommended.

Selinexor will be administered at a starting dose of 60 mg on D1 and D3 of weeks 1 – 3 of each 4 week cycle, with subsequent dose titration for dose limiting toxicity (Table 5.3).

- All adjustments of dose must be maintained either in the pharmacy records or subject’s medical records.

Number of Tablets per Total Mg Dose		
Mg Dose (from Rounded Dose Table)	Number of Tablets of Each Strength	
	10 mg tablets	25 mg tablets
20	2	0
40	4	0
60	1	2

Patients will receive prophylactic treatment to prevent anorexia and nausea, which will include the following:

- Ondansetron 8 mg PO q8h on day prior to and day of dosing (D0-D3)
- Olanzapine 5 mg PO qbedtime or 2.5 mg PO BID on day of dosing (D1, D3)

If nausea and/or anorexia persist despite administration of ondansetron and olanzapine on the days of dosing, additional prophylactic treatment may include the addition of any of the following:

- Dexamethasone 2-4 mg PO BID on days of dosing (D1, D3)  
AND/OR
- Olanzapine 5 mg PO qbedtime or 2.5 mg PO BID on days prior to dosing (D0, D2)  
AND/OR
- Megestrol acetate 160-400 mg daily, 0-3 days before the first dosing day of KPT-330  
AND/OR
- Mirtazapine 15 mg qd (qpm/qhs), 0-3 days before the first dosing day of KPT-330  
AND/OR
- Marinol 5 mg PO BID  
AND/OR
- NK1R antagonist: Aprepitant 120 mg PO x1 on D1, then 80 PO qAM on D2-D3 of each dosing week or equivalent should be considered and will be covered for selected patients who have severe nausea and vomiting.

If the patient is on steroids coming on the study, megestrol acetate should be added prophylactically to prevent anorexia. Other androgenic-anabolic steroids including exogenous testosterone or synthetic testosterone derivatives (e.g., oxandrolone) are contraindicated in patients with metastatic castration resistant prostate cancer, and therefore must not be administered at any point during trial participation.

If an increased risk of adverse effects due to olanzapine is anticipated, olanzapine can be omitted. However, it is recommended that mirtazapine or other appetite stimulating serotonergic agent be used. Additional standard supportive care agents may be used as needed (prn), and as per table 5.3.

Supportive care may be tapered or discontinued in Cycle 2 or later in patients who tolerate selinexor well in Cycle 1.

## 5.2 Dose Modifications and Dosing Delays

If a patient experiences an intolerable toxicity (CTCAE v4.0 Grade 3 or 4) selinexor should be held. Following resolution of the toxicity to Grade 1 or to the patient's baseline value the patient may resume treatment with study drug. In general, patients who resume therapy following toxicity should resume treatment at a lower dose level assessed to be safe. However, following recovery from toxicity that was not considered clinically important, and that could be managed if it were to recur (e.g., replacement of an electrolyte), the patient may resume therapy without dose reduction if the Investigator considers this to be in the best interest of the patient. Provisional dose levels for selinexor are listed in Table 5.2.

Management of severe or intolerable adverse reactions may require dose reduction and/or interruption of the study drug. Recommendation of dose reduction, interruption or discontinuation in the management of adverse reactions are summarized below. Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessments.

If a patient requires a dose delay > 21 days due to a study drug-related toxicity, then the patient must be discontinued from the study unless the patient has experienced evidence of clinical benefit. If the patient has experienced evidence of clinical benefit, and in the opinion of the Investigator it is in the best interest of the patient to remain on treatment, the patient may continue on study after discussion and with approval by Karyopharm.

**Table 5.2 Dose Modifications and Dosing Delays for patients demonstrating clinical response or stable disease**

Dose level	Dose of selinexor
Dose level 0	60 mg twice weekly (D1, D3 on weeks 1, 2, 3 of each 4 week cycle)
Dose level -1	40 mg twice weekly (D1, D3 on weeks 1, 2, 3 of each 4 week cycle)
Dose level -2	20 mg twice weekly (D1, D3 on weeks 1, 2, 3 of each 4 week cycle)
Dose level -3	20 mg once weekly (D1 on weeks 1, 2, 3 of each 4 week cycle)
Dose level -4	Discontinue dosing

Patients will continue to receive selinexor until they need to have their dose reduced below 20 mg once weekly dose, at which time treatment will be discontinued.

Treatment or visit delays for public holidays or weather conditions do not constitute a protocol violation.

### 5.3 Monitoring and Toxicity Management

Each patient receiving selinexor will be evaluable for safety. The safety parameters include all laboratory tests and hematological abnormalities, physical findings, and spontaneous reports of adverse events reported to the investigator by patients.

Each patient will be assessed periodically for the development of any toxicity as outlined in [Section 6 Study Procedures and Observations](#). Toxicity will be assessed according to the NCI [CTCAE v4.0](#). Dose adjustments will be made according to the system showing the greatest degree of toxicity.

We will monitor for anorexia, loss of appetite, fatigue, thrombocytopenia, neutrocytopenia, diarrhea, blurred vision, liver enzyme increase, and hyponatremia.

Acute toxicity will be managed by supportive care or delay of dose. Further management will depend upon the judgment of the clinician, and may include dose reduction.

Treatment will be started at a dose of 60 mg administered twice weekly. For those patients experiencing dose limiting toxicity (as defined below) yet thought to be benefiting from therapy (i.e., reduction in PSA, reduced pain, or reduction in size and/or number of bony metastases), the treatment dose will be reduced per Table 5.2. Subsequent reductions for persistent grade 3 toxicities will include dose reduction per Table 5.2.

**Table 5.3 Criteria for dose adjustments of Selinexor-related toxicities**

Toxicity and Intensity	Dose Modification
<b>Fatigue (common)</b>	
Grade 1	Insure adequate caloric intake and assess volume status. Adjust other medications. Consider addition/increased dose of corticosteroids (e.g., 2-4 mg BID dexamethasone the day of selinexor dosing). Rule out other causes of fatigue such as adrenal insufficiency or thyroid dysfunction.
Grade 2	Insure adequate caloric and fluid intake and assess volume status. May consider additional corticosteroid, per clinician discretion. If fatigue dose not resolve to Grade 1, reduce dose of selinexor by one level (Table 5.2).
Grade 3	Insure adequate caloric and fluid intake and assess volume status. Interrupt selinexor dosing until resolved to Grade $\leq$ 2, reduce dose of selinexor by 1 level (Table 5.2).
<b>Anorexia (common)</b>	
Grade 1	Assess dietary options (e.g. try a variety of other foods). Add high-calorie supplements (e.g., Ensure®). If fatigue or nausea also present, consider addition/increased dose of dexamethasone (e.g., 2-4 mg dexamethasone BID on the day of selinexor dosing), or consider addition of other anti-emetic per section 5.1

Toxicity and Intensity	Dose Modification
Grade 2	Add high-calorie supplements (e.g., Ensure®). Consider addition/increased dose of dexamethasone (e.g., 2-4mg dexamethasone BID on the day of selinexor dosing and/or on the day prior to dosing, or consider addition of other anti-emetic per section 5.1. Consider dronabinol (Marinol®). Skip intermittent doses of selinexor while supportive medications are instituted. If Grade 2 anorexia does not resolve after institution of supportive medications, reduce selinexor dose by 1 level (Table 5.2).
Grade 3	Interrupt dosing with selinexor. Add high calorie supplements. Use supportive medications alone or in combinations. Restart selinexor at 1 dose level reduction (Table 3) once anorexia resolves to Grade ≤2. If Grade 2 anorexia persists with supportive medications, reduce dose of selinexor another level (Table 5.2).
<b>Nausea/Emesis (common)</b>	
Grade 1	D2 antagonists, addition/increased dose of corticosteroids (e.g., 2-4mg dexamethasone with each dose of selinexor the day prior to dosing), NK1 antagonists, or dronabinol (Marinol) or combinations can prevent nausea in the majority of patients.
Grade 2	Implement one or more combinations of additional anti-nausea medications per section 5.1. If nausea does not resolve to Grade ≤1, reduce dose of selinexor by one dose level (Table 5.2).
Grade 3	Implement one or more combinations of anti-nausea medications per section 5.1 and interrupt dosing of selinexor. Selinexor may be restarted with one dose level reduction (Table 5.2) when nausea is Grade ≤2 and adequate caloric and fluid intake have been achieved.
<b>Hematologic</b>	
<b>Neutropenia (rare)</b>	
Grade 1 (ANC < LLN - 1500/mm <sup>3</sup> ) Grade 2 (ANC < 1500 - 1000/mm <sup>3</sup> ) Grade 3 (ANC < 1000 - 500/mm <sup>3</sup> )	Maintain dose level  The use of growth factors during selinexor treatment is permitted and in patients with poor marrow function, encouraged. If ANC drops to <1000/mm <sup>3</sup> , growth factors are encouraged to reduce dose interruptions.
Grade 4 (ANC < 500/mm <sup>3</sup> )	Delay study treatment until ANC returns to >800/mm <sup>3</sup> , then: If increased to >800/mm <sup>3</sup> by ≤ 7 days after suspending selinexor, maintain dose level If increased to >800/mm <sup>3</sup> by > 7 days after suspending selinexor, then reduce by 1 dose level (Table 5.2). The use of growth factors during selinexor treatment is encouraged.

Toxicity and Intensity	Dose Modification
Febrile neutropenia, or fever of unknown origin without clinically or microbiologically documented infection (ANC $<1.0 \times 10^9/L$ , fever $\geq 38.5^\circ C$ )	Delay study treatment until patient has stabilized, then reduce selinexor by 1 dose level (Table 5.2). Selinexor may be re-initiated at the reduce dose when patient's condition has stabilized following initiation of antibiotic therapy. Selinexor dose may be re-escalated up one level (Table 5.2) after $\geq 1$ cycle at the reduced dose provided ANC is adequate.
<b>Thrombocytopenia (Platelets) (uncommon)</b>	
Grade 1 (PLT $< LLN - 75,000/mm^3$ )	Maintain dose level.
Grade 2 (PLT $< 75,000 - 50,000/mm^3$ )	Delay selinexor treatment until resolved to $\leq$ grade 1
Grade $\geq 3$ (PLT $< 50,000 - 25,000/mm^3$ ) without bleeding	Delay selinexor treatment until resolved to $\leq$ grade 1 and restart at one dose level below (Table 5.2 ). All patients with Grade 4 thrombocytopenia should have a manual blood smear analysis to determine if clumping (e.g., "pseudo-thrombocytopenia") and/or giant platelets are present. Platelet transfusions may be given to support platelet levels in patients with clear clinical benefit from selinexor.
Grade 4 (PLT $< 25,000/mm^3$ ) without bleeding	Delay study treatment until resolved to $\leq$ grade 3, then follow guidelines above.
Platelet Stimulators	The use of platelet stimulators may be considered in patients with a history of thrombocytopenia or compromised marrow function, or in patients in whom selinexor is having demonstrable clinical benefit. IL-11 (oprelvekin, Neumega®), eltrombopag (Promacta®), or romiplostim (N-Plate®) should be considered.
<b>Hyponatremia (common)</b>	
Grade 1 (Lower Limit of Normal to 130nM)	Maintain dose level, assure adequate fluid, electrolyte and caloric intake, adjust other medications, consider salt supplementation, rule out other causes.
Grade 3 (120-130nM)	Discontinue selinexor until resolved to grade $\leq 1$ then reduce dose by 1 level. Check renal function, serum and urinary electrolytes, and rule out other causes.
<b>Renal (rare)</b>	
<b>Serum creatinine</b>	
Calculated or measured creatinine clearance $\geq 20$ cc/min	Maintain dose level
Calculated or measured creatinine clearance $< 20$ cc/min	Reduce selinexor by 1 dose level until resolved. Dose may also be re-escalated if lower dose is tolerated after 1 full cycle.
<b>Hepatic (rare)</b>	
<b>Bilirubin</b>	
Total bilirubin $< 1.5 \times ULN$	Maintain dose level

Toxicity and Intensity	Dose Modification
Total bilirubin 1.5 - 3 x ULN	Reduce selinexor to once weekly dosing until resolved to ≤ Grade 1, then restart twice weekly dosing
Grade 3 (> 3.0 - 10.0 x ULN) Grade 4 (> 10.0 x ULN)	Discontinue selinexor until resolved to Grade ≤2, then follow guidelines above. Note: If Grade 3 or Grade 4 hyperbilirubinemia is due to the indirect component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (e.g. review of peripheral blood smear and haptoglobin determination), then reduce selinexor dose by 1 level (Table 5.2) and continue treatment at the discretion of the investigator. Discontinuation of selinexor is required if concurrent elevations of total bilirubin > 2.0 X upper limit of normal (ULN) and ALT or AST > 3.0 X ULN are observed and other causes have been ruled out. In order to characterize hepatic toxicity more precisely, fractionation of bilirubin and alkaline phosphatases will be required for elevated values > 2.0 X ULN and ≥ CTCAE Grade 2, respectively.
AST or ALT (rare)	
Grade 1 (> ULN - 2.5 x ULN)	Maintain dose level
Grade 2 (> 2.5 - 5.0 x ULN)	Delay selinexor until resolved to Grade ≤1, then maintain dose level. Consider addition of S-adenosylmethionine (SAM) 400mg qd-bid.
Grade 3 (> 5.0 - 20.0 x ULN)	Delay selinexor until resolved to ≤ grade 2, then reduce by 1 dose level (Table 5.2 ). Consider addition of S-adenosylmethionine (SAM) 400mg qd-qid. If no further AST or ALT elevations occur during one cycle (4 weeks) at the reduced dose level, then dose may be continued at the reduced dose. Discontinuation of selinexor is required if concurrent elevations of direct bilirubin > 2.0 X upper limit of normal (ULN) and ALT or AST > 3.0 X ULN are observed. In order to characterize hepatic toxicity more precisely, fractionation of bilirubin and alkaline phosphatases will be required for elevated values > 2.0 X ULN and ≥CTCAE grade 2, respectively.
Grade 4 (> 20.0 x ULN)	Delay selinexor until resolved to ≤ Grade 2, then reduce by 2 dose levels
Cardiac (rare)	
Hypertension	Treatment-emergent hypertension should be treated as per standard cardiology practice. Recommended agents for the management of blood pressure elevations on selinexor include angiotensin-converting enzyme inhibitors and calcium channel blockers.
Grade 1	Maintain dose level

Toxicity and Intensity	Dose Modification
Grade 2 / 3	Delay selinexor and initiate/intensify antihypertensive therapy. Selinexor may be restarted in conjunction with standard anti-hypertensive medication if BP is controlled (i.e BP $\leq$ 150/100 mmHg). If BP is controlled $\leq$ 7 days after suspending selinexor, maintain dose level If BP is controlled $>$ 7 days after suspending selinexor, then reduce by 1 dose level
Grade 4	Delay the selinexor and initiate/intensify antihypertensive therapy, then reduce by 1 dose level. Selinexor may be restarted in conjunction with anti-hypertensive medication if BP is controlled (i.e BP $\leq$ 150/100 mmHg).
Cardiac – Other (rare)	
Grade 1 or 2	Maintain dose level
Grade 3	Delay selinexor until resolved to $\leq$ Grade 1, then reduce by 1 dose level (Table 5.2).
Grade 4	Discontinue study treatment
Diarrhea (uncommon)	
Grade 1 (despite maximal anti-diarrheal medication)	At the first sign of abdominal cramping, loose stools, or onset of diarrhea, it is recommended that the patient be treated according to institutional standard of care. Maintain dose level of selinexor.
Grade 2 (despite maximal anti-diarrheal medication)	Reduce to selinexor to one weekly until resolved to $\leq$ grade 1, then re-start twice weekly at the current dose level. If diarrhea returns as $\geq$ Grade 2, then reduce selinexor dose by one dose level and dose once weekly until resolved to $\leq$ grade 1, then re-start twice weekly at reduced dose level
Grade 3/4 (despite maximal anti-diarrheal medication)	Delay selinexor until resolved to $\leq$ grade 2, then re-start twice weekly at reduced dose level
Neurotoxicity (not observed to date)	
CTCAE grade 1 / 2	Grade 0 $\rightarrow$ Grade 1: maintain dose level Grade 0 or 1 $\rightarrow$ Grade 2 : delay study treatment until resolved to $\leq$ Grade 1, then reduce by 1 dose level (Table 5.2).
CTCAE grade 3	Discontinue study treatment until resolved to Grade $\leq$ 1 then reduce by 2 dose levels (Table 5.2 ).
CTCAE grade 4	Discontinue study treatment.
Amylase and/or lipase elevations (rare)	
Grade 1 or 2	Maintain dose level
Asymptomatic Grade 3 or 4	Delay selinexor until $\leq$ Grade 2, then restart at 1 dose level reduction (Table 3). Rule out other causes of amylase/lipase elevation. If levels have not returned to $\leq$ Grade 2 within 3 weeks then no further selinexor may be given and the patient should discontinue permanently from the study. A CT scan or other imaging study to assess the pancreas, liver and gallbladder must be performed within 1 week of the first occurrence of any grade 3 elevation of amylase and/or lipase.

Toxicity and Intensity	Dose Modification
Symptomatic Grade 3 or 4	Selinexor must be stopped immediately and proper supportive care provided. Evaluate enzyme levels at least twice weekly until resolution to $\leq$ Grade 1. Clinical manifestations should be monitored as needed until resolution or stabilization of the disease condition. Selinexor may be re-started at 2 dose levels below (Table 5.2) after resolution to $\leq$ Grade 1.
Pancreatitis (not observed to date)	
Grade 1	Maintain dose level
Grade 2, 3 or 4	Discontinue study treatment.
Other Selinexor-related adverse events	
Grade 1 or 2	Maintain dose level and initiate standard supportive care.
Grade 3	Delay dose until resolved to $\leq$ Grade 1, then reduce by 1 dose level
Grade 4	Discontinue selinexor and rule out other causes. If other causes of Grade 4 adverse event are uncovered, selinexor may be re-initiated at 1 dose level reduction (Table 5.2).
<p>Notes: All dose modifications should be based on the worst preceding toxicity.</p> <p>Isolated values of <math>\geq</math> grade 3 alkaline phosphatase values will NOT require dose interruption. Determination of liver vs. bone etiology should be made, and evaluation of GGT, 5'NT, or other liver enzymes should be performed.</p> <p><math>\geq</math> Grade 3 anemia judged to be a hemolytic process secondary to study drug will require interruption of study treatment until resolved to <math>\leq</math> Grade 1. Selinexor may then be re-instituted at 2 levels below original dose (Table 5.2 ).</p> <p><math>\geq</math> Grade 3 lymphopenia considered clinically significant will require dose interruption until resolved to <math>\leq</math> grade 2, then reduce by 1 dose level.</p> <p>Patients are allowed dose reductions to a minimum dose of 35 mg/m<sup>2</sup> as described in Table 5.2</p> <p>If a patient requires a dose interruption of &gt;21 days due to a study drug related toxicity, then the patient must be discontinued from the study. Patients who discontinue the study for a study related adverse event or abnormal laboratory value must be followed at least once a week for 28 days and subsequently at 28 day intervals until resolution or stabilization of the event, whichever comes first.</p>	

## 6 Study Procedures and Observations

### 6.1 Schedule of Procedures and Observations

The study-specific assessments are detailed in this section and outlined in Section 6. Screening assessments must be performed 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. All on-study visit procedures are allowed a **window of  $\pm$  3 days** unless otherwise noted. Treatment or visit delays for public holidays or weather conditions do not constitute a protocol violation.

A written, signed, informed consent form (ICF) and a Health Insurance Portability and Accountability Act (HIPAA) authorization must be obtained before any study-specific assessments are initiated. A copy of the signed ICF will be given to the subject and a

copy will be filed in the medical record. The original will be kept on file with the study records.

All patients who are consented will be registered in OnCore<sup>®</sup>, the UCSF Helen Diller Family Comprehensive Cancer Center Clinical Trial Management System (CTMS). The system is password protected and meets HIPAA requirements.

## 6.1.1 Pretreatment Period

### 6.1.1.1 Screening Assessments

With the exception of CT or MRI imaging for the purposes of tumor/lesion assessment, all screening procedures and assessments must be completed within 28 days of the Day 1 Visit. Any requisite imaging must be obtained within 42 days of day 1 of study participation.

- Physical examination
- Vital signs
- Complete medical history
- Baseline conditions assessment
- ECOG Performance status
- Ophthalmologic exam including slit lamp examination and visual acuity prior to dilation, and a dilated fundoscopic evaluation and slit lamp examination.
- Neurological evaluation
- Pulse oximetry
- History of prior treatments and any residual toxicity relating to prior treatment
- Baseline medications taken within 28 days of Day 1
- Brief Pain Inventory (BPI) short form
- Laboratory evaluations
  - Complete blood count (CBC) with differential and platelet count and coagulation tests
    - Coagulation indices including international normalized ratio (INR), prothrombin time (PT) and activated partial thromboplastin time (aPTT) do not need to be repeated at screening if patients have already completed a biopsy through the companion radiologically guided mCRPC protocol or they have been deemed ineligible for biopsy.
  - Blood chemistry assessment, including:
    - Alkaline phosphatase, aspartate aminotransferase/alanine aminotransferase (ALT/AST), total bilirubin, calcium, phosphorus, blood urea nitrogen (BUN), creatinine, total protein, albumin, fasting glucose, potassium, sodium, chloride, bicarbonate, uric acid, lactate dehydrogenase (LDH), fasting lipid panel (low-density lipoprotein [LDL], total cholesterol, triglycerides)
  - Prostate Specific Antigen (PSA)
  - Serum total testosterone

- Imaging (CT or MRI) of chest, abdomen and pelvis for tumor/lesion assessment, contrast is to be used unless clinically contraindicated.
- Electrocardiogram (ECG)
- Bone scan (Technetium)
- Prophylactic therapy (initiated 0-3 days prior to first selinexor dose)
- Tumor biopsy -- optional, per companion Radiologically Guided Biopsy protocol of mCRPC, offered to patients treated at UCSF, UCLA, UC Davis, Oregon Health Sciences University, University of British Columbia

## **6.1.2 Treatment Period**

### **6.1.2.1 Study Procedures, Cycle 1, Day 1**

- Physical examination
- Vital signs
- Performance status
- Evaluation of adverse events
- Concomitant medications
- Brief Pain Inventory (BPI) short form
- Laboratory evaluations
  - CBC with differential and platelet count
  - Blood chemistry assessment
  - PSA
  - Selinexor serum levels – obtained 10 minutes prior to first dose, then 2 hours after first dose, and 4 hours after first dose.
  - Treated leukocyte lysate collection– obtained 10 minutes prior to first dose
  - Serum macrophage inhibitory cytokine-1 (MIC-1) – obtained 10 minutes prior to first dose
  - Leukocyte collection for XPO1 inhibition analysis - obtained 10 minutes prior to first dose, then 4 hours after first dose

### **6.1.2.2 Study Procedures, Cycle 1, Day 3 – via telephone**

- Evaluation of adverse events

### **6.1.2.3 Study Procedures, Cycle 1, Day 15**

- Serum macrophage inhibitory cytokine-1 (MIC-1) – obtained 10 minutes prior to first dose
- Leukocyte collection for XPO1 inhibition analysis - obtained 10 minutes prior to first dose, then 4 hours after first dose

### **6.1.2.4 Study Procedures Cycle 2+, Day 1**

These procedures must be completed within 3 days of Day 1

- Physical examination
- Vital signs
- Performance status
- Evaluation of adverse events
- Concomitant medications
- Brief Pain Inventory (BPI) short form
- Imaging (CT or MRI) for tumor/lesion assessment - at completion of cycle 2, cycle 4, cycle 6, day 22-28, and then every 12 three cycles weeks thereafter
- Bone scan (Technetium) - at completion of cycle 2, cycle 4, cycle 6, day 22-28 and every 12 weeks thereafter
- Ophthalmologic exam to be performed every 3 months while on study if cataracts are identified at screening and/or as clinically indicated. This exam will include slit lamp examination and visual acuity prior to dilation, and a dilated fundoscopic evaluation and slit lamp examination. Ophthalmologic evaluations will be performed by the Department of Ophthalmology at the participating study institution.
- Laboratory evaluations
  - CBC with differential and platelet count
  - Blood chemistry assessment
  - PSA - monthly and at time of progression
  - Serum macrophage inhibitory cytokine-1 (MIC-1) – at cycles 2 and 3 – obtained 10 minutes prior to dose
  - Leukocyte collection for XPO1 inhibition analysis – at cycles 2 and 3 - obtained 10 minutes prior to dose, then 4 hours after dose

### 6.1.3 End-of-Treatment Study Procedures

- To be completed within 30 days of the last dose of study drug.
- Physical examination
- Vital signs
- Performance Status
- Evaluation of adverse events
- Concomitant medications
- Brief Pain Inventory (BPI) short form
- Tumor biopsy -- optional, per companion Radiologically Guided Biopsy protocol of mCRPC, offered to patients treated at UCSF, UCLA, UC Davis, Oregon Health Sciences University, University of British Columbia
- Ophthalmologic exam including slit lamp examination and visual acuity prior to dilation, and a dilated fundoscopic evaluation and slit lamp examination.
- Laboratory evaluations
  - CBC with differential and platelet count
  - Blood chemistry assessment
  - PSA

#### **6.1.4 End-of-treatment long-term follow-up**

- To be completed at 6 month intervals after the last dose of study drug.
- Telephone visit for assessment of adverse events, concomitant medications and subsequent antitumor therapy.

#### **6.1.5 Discontinuation of Therapy**

The Investigator will withdraw a patient whenever continued participation is no longer in the patient's best interests. Reasons for withdrawing a patient include, but are not limited to, disease progression, the occurrence of an adverse event or a concurrent illness, a patient's request to end participation, a patient's non-compliance or simply significant uncertainty on the part of the Investigator that continued participation is prudent. There may also be administrative reasons to terminate participation, such as concern about a patient's compliance with the prescribed treatment regimen.

**Table 6.1 Schedule of Study Procedures and Assessments**

Visits must occur ±7 days of planned visit unless otherwise noted.

Period/ Procedure	Screening	Cycle 1			Cycle 2 and future Cycles	End of Treatment visit	Follow- up visits
		1	3 <sup>9</sup>	15			
Study Day/Visit Day	-28 to 0	1	3 <sup>9</sup>	15	1	Within 30 days of last dose	By phone Every 6 months
Informed consent	X						
Baseline conditions	X						
AE assessment		X	X		X	X	X
Concomitant medications		X			X	X	X
<b>Treatment/Drug Administration</b>							
Selinexor		Oral, twice weekly (On Days 1 and 3 of each week 1-3 of each 4 week cycle)					
<b>Clinical procedures</b>							
Physical exam	X	X			X	X	
Vital signs	X	X			X	X	
Medical history	X						
Disease assessment	X				X		
Performance status	X	X			X	X	
Neurologic evaluation <sup>1</sup>	X						
Ophthalmic evaluation	X <sup>8</sup>				X <sup>8</sup>	X <sup>8</sup>	
Pulse oximetry <sup>1</sup>	X						
BPI Short Form	X	X			X	X	
Tumor biopsy(optional)	X <sup>2</sup>					X <sup>2</sup>	
<b>Laboratory procedures</b>							
CBC w/ Diff & platelets	X	X			X	X	
Coagulation <sup>1</sup>	X						
Blood chemistry <sup>3</sup>	X	X			X	X	
PSA	X				X <sup>4</sup>	X	
Leukocyte collection for XPO1 inhibition <sup>6</sup>		X		X	X		

**Table 6.1 Schedule of Study Procedures and Assessments**

Visits must occur ±7 days of planned visit unless otherwise noted.

Period/ Procedure	Screening				Cycle 1		Cycle 2 and future Cycles	End of Treatment visit	Follow- up visits
	-28 to 0	1	3 <sup>9</sup>	15	1	1	Within 30 days of last dose	By phone Every 6 months	
Treated leukocyte lysate <sup>6</sup>		X							
Serum MIC-1 mRNA <sup>6</sup>		X		X	X				
Selinexor PK <sup>6</sup>		X							
Testosterone	X								
<b>Imaging procedures</b>									
CT c/a/p with contrast or MRI	X					X <sup>7</sup>			
ECG/EKG	X								
Bone scan (Technetium)	X					X <sup>7</sup>			

<sup>1</sup> Required at screening and as clinically indicated while on study. Coagulation labs include PT, PTT/INR.

<sup>2</sup> Only offered to patients at UCSF, UCLA, UC Davis, Oregon Health Sciences University, University of British Columbia. If no intervening therapy is initiated, the tumor biopsy can be performed within a 2-month window (60 days) of day 1 of Selinexor.

<sup>3</sup> Including alkaline phosphatase, ALT/AST, total bilirubin, calcium, phosphorus, (BUN), creatinine, total protein, albumin, fasting glucose, potassium, sodium, chloride, bicarbonate, uric acid, LDH, fasting lipid panel (LDL, total cholesterol, triglycerides).

<sup>4</sup> Monthly and at time of progression

<sup>5</sup> Only Cycle 2 and Cycle 4, Day 22-28, and at time of progression

<sup>6</sup> PK samples will be collected on Cycle 1 Day 1 only. PD Samples will be collected on Cycle 1 Day 1 and 15, Cycle 2 Day 1, and cycle 3 Day 1. Refer to section 6.3 for PK and PD collection schedule.

<sup>7</sup> At the completion of Cycle 2, Cycle 4, Cycle 6, Day 22-28, and every 12 weeks thereafter

<sup>8</sup> Required at screening, every 3 months thereafter if cataracts identified at screening and if clinically indicated, and at the end of treatment study visit.

<sup>9</sup> C1D3 visit will be conducted via telephone call

## 6.2 PK and PD Calendar

TIME POINT	Total Volume of blood (ml)	PK	PDn		
		Plasma (1 tube x 1ml)	Cytokines (1 tube x 1ml)	Leukocytes (2 PAX gene tubes x 2.5ml)	Leukocytes (1 tube x 3ml)
<b>Cycle 1, Day 1</b>					
Pre-dose (within 10 min before administration)	13	X	X	X	X
2 hr (~10 min) post dose	2	X			
4 hr (~20 min) post dose	7	X		X	
<b>Cycle 1, Day 15</b>					
Pre-dose (within 10 min before administration)	7		X	X	
4 hr (~20 min) post dose	5			X	
<b>Cycle 2 and 3, Day 1</b>					
Pre-dose (within 10 min before administration)	7		X	X	
4 hr (~20 min) post dose	5			X	

## 6.3 Dietary Restrictions

Patients should be encouraged to always take selinexor within 30 minutes before or after a meal, so as to prevent variations in plasma KPT-330 exposure related to prandial state. There are no specific restrictions on meal size nor content.

Patients will be instructed to avoid alcohol consumption within 4 hours of selinexor administration, given concern for glutathione depletion and subsequent impaired clearance of selinexor (see section 6.3).

## 6.4 Prohibited Medications

The primary metabolism of selinexor *in vitro* and *in vivo* appears to be inactivation by glutathione (GSH) conjugation. This process can be mediated in the absence of proteins, indicating that it is thermodynamically favorable. *In vitro* studies using human liver microsomes confirm *in vivo* findings that selinexor undergoes minimal CYP450 metabolism. There was also no induction of CYP450 activity observed for CYP1A2 or CYP3A4.

Therefore, administration of selinexor with drugs which undergo substantial GSH conjugation should be minimized until further data are available. These drugs include acetaminophen (paracetamol) and alcohol (ethanol). Alcohol ingestion should be avoided 4 hours before and after selinexor administration in order to minimize GSH depletion. In the event that GSH depletion is believed to be contributing to patients' symptoms, signs or laboratory findings, replenishment with S-adenosylmethionine (SAM) oral (e.g., 400 mg PO BID-TID) or N-acetylcysteine (e.g., up to 140 mg/kg PO loading dose followed by 70 mg/kg PO Q4 hours thereafter) until symptoms resolve. It should be noted that no studies of selinexor in combination with acetaminophen have been performed to date and that these recommendations are empirical.

Androgenic-anabolic steroids including exogenous testosterone or synthetic testosterone derivatives (e.g., oxandrolone) are contraindicated in patients with metastatic castration resistant prostate cancer, and therefore must not be administered at any point during trial participation.

Complete and updated information is available in the Investigational Drug Brochure.

## 7 Reporting and Documentation of Results

### 7.1 Evaluation of Efficacy (or Activity)

Response and progression will be evaluated in this study using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria. Changes in only the longest diameter (unidimensional measurement- LD) of the tumor lesions are used in the RECIST criteria.

**Note:** lesions are either measurable or non-measurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used because it does not provide additional meaning or accuracy.

### 7.2 Definitions

#### **Evaluable for toxicity**

All patients will be evaluable for toxicity from the time of their first treatment with the study drug.

#### **Evaluable for objective response**

Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered

evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of Cycle 1 will also be considered evaluable.)

### 7.3 Disease Parameters

#### **Measurable disease**

Measurable disease is defined as lesions (or tumors) that can be accurately measured in at least one dimension (longest diameter to be recorded) with a minimum size of 10mm by CT scan (irrespective of scanner type) or bone scan. All tumor measurements will be recorded in millimeters or decimal fractions of centimeters. Previously irradiated lesions are considered non-measurable except in cases of documented progression of the lesion since the completion of radiation therapy.

#### **Target lesions**

All measurable lesions up to a maximum of 5 lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target lesions will 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). 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.

#### **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. It is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. "multiple enlarged pelvic lymph nodes" or "multiple liver metastases"). Bone lesions may be measurable if  $\geq 1$  cm on MRI. Measurements of these lesions are not required, but the presence or absence of each will be noted throughout follow-up.

#### **Non-measurable disease (PSA)**

All patients will be evaluated for PSA decline. Patients with disease that is not measurable will be eligible for this study and will be assessed for response based on changes in PSA and serial bone scans (if appropriate). Patients who show PSA increases will not be evaluated for PSA progression prior to 12 weeks of study therapy.

**50% PSA Decline:** PSA decline of at least 50% from baseline confirmed by a second measurement at least 3 weeks later. The reference for these declines should be a PSA measured within 2 weeks prior to starting therapy.

**PSA Progression:** Prostate Cancer Working Group 2 (PCWG2) Criteria will be reported. PSA progression occurs when the PSA has increased 25% or greater above nadir and an absolute increase of 2 ng/mL or more from the nadir is documented. Where no decline is observed, PSA progression similarly occurs when a 25% increase from baseline value along with an increase in absolute value of 2 ng/mL or more. Patients will receive a minimum of 12 weeks of therapy prior to being evaluable for this endpoint. PSA progression (without evidence of progression on scans) will not be a criterion for discontinuation of study therapy.

**PSA Response Duration:** The PSA response duration commences on the date of the first 50% decline in PSA. The response duration ends when the PSA value increases by 25% above the nadir, provided that the increase in the absolute-value PSA level is at least 5 ng/mL or back to baseline, whichever is lower.

**Progressive Disease by PSA** (as defined by PSA Progression, above)

**Time to PSA Progression:** The start of the time to PSA progression is the day treatment is initiated. The end date is the time of PSA progression as defined above.

### **Evaluation of non-measurable bone disease**

Bone scans obtained after the baseline evaluation will be used to evaluate post-treatment changes. Bone scans obtained will be evaluated as either “no new lesions” or “new lesions” on the tumor measurement forms. Progression is defined as the appearance of 2 or more new lesions.

**PSAWG2 Criteria for Bone Scan Evaluation:** For the first scheduled reassessment: New lesions at the first scheduled evaluation (8 weeks) will require a confirmatory bone scan 6 or more weeks later. If no new lesions are observed on the confirmatory bone scan, study therapy is continued. If additional new lesions (a minimum of 2 more additional new lesions) are observed, then the patient has experienced progression. Progression in this situation is dated as the time of the first reassessment scan.

For subsequent scheduled reassessments: If no new lesions are observed, study therapy will continue. If new lesions are observed, this is evidence of disease progression. Date of progression is the date at which the scan was obtained.

#### **7.3.1.1 Methods for Evaluation of Measurable Disease**

All measurements will be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations will be performed as closely as possible to the beginning of treatment and never more than 28 days before the beginning of the treatment, with the exception of imaging which may be performed up to 42 days before the beginning of the treatment.

The same method of assessment and the same technique will be used to characterize each identified and reported lesion at baseline and during follow-up.

#### **7.3.1.2 Methods for Evaluation of Non-Measurable Disease**

PSA levels will be monitored monthly.

Bone scans obtained after the baseline evaluation will be used to evaluate post-treatment changes. Outcome is listed as new lesions or no new lesions. Progression is defined as the appearance of 2 or more new lesions. This is based on the PCWG2 criteria in standard practice for trials in metastatic CRPC.

#### **7.3.1.3 Response Criteria**

##### **Evaluation of Target Lesions**

###### **Complete Response (CR)**

Disappearance of all target lesions, determined by two separate observations conducted not less than 4 weeks apart. Any pathological lymph nodes (whether target or non-target)

must have reduction in short axis to <10 mm (the sum may not be “0” if there are target nodes). There can be no appearance of new lesions.

**Partial Response (PR)**

At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD. There can be no appearance of new lesions.

**Progressive Disease (PD)**

At least a 20% increase in the sum of the SLD of target lesions, taking as reference the smallest sum SLD recorded since the treatment started and minimum 5 mm increase over the nadir, or the appearance of one or more new lesions.

**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.

**Evaluation of Non-Target Lesions**

**Complete Response (CR)**

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

**Incomplete Response/Stable Disease (SD)**

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

**Progressive Disease (PD)**

Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

**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.

<b>Target Lesions</b>	<b>Non-Target Lesions</b>	<b>New Lesions</b>	<b>Overall Response</b>	<b>Best Response for this Category Also Requires</b>
CR	CR	No	CR	> 4 weeks confirmation
CR	Non-CR/ Non-PD	No	PR	> 4 weeks confirmation
PR	Non-PD	No	PR	
SD	Non-PD	No	SD	documented at least once > 4 weeks from baseline
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD*	Yes or No	PD	
Any	Any	Yes	PD	

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

## **Duration of Response**

### **Duration of overall response**

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

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

### **Duration of stable disease**

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

### **Progression-Free Survival**

Progression-free survival (PFS) is defined as the duration of time from start of treatment to time of progression.

## **7.4 Evaluation of Safety**

Analyses will be performed for all patients having received at least one dose of study drug. The study will use the [CTCAE v4.0](#) for reporting of non-hematologic adverse events and modified criteria for hematologic adverse events.

For multicenter studies, the Principal Investigator at the UCSF Coordinating Center will hold the role of Study Chair. The Study Chair is responsible for the overall conduct of the study and for monitoring its safety and progress at all participating sites.

## **7.5 Definitions of Adverse Events**

### **7.5.1 Adverse Event**

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

### **7.5.2 Adverse reaction**

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

### 7.5.2.1 Suspected

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

### 7.5.2.2 Unexpected

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

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

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

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

### 7.5.2.3 Serious

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

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

Important medical events that may not result in death, are life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such

medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

#### 7.5.2.4 Life-threatening

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

### 7.6 Recording of an Adverse Event

All grade 3 and above adverse events will be entered into OnCore<sup>®</sup>, whether or not the event is believed to be associated with use of the study drug. Data about these events and their severity will be recorded using the NCI CTCAE v4.0.

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

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

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

Grade 0	No AE (or within normal limits)
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local, or noninvasive intervention (e.g., packing, cautery) indicated; limiting age-appropriate instrumental activities of daily living (ADL)
Grade 3:	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
Grade 4:	Life-threatening consequences; urgent intervention indicated
Grade 5:	Death related to AE

## 7.7 Follow-up of Adverse Events

All adverse events will be followed with appropriate medical management until resolved. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. For selected adverse events for which administration of the investigational drug was stopped, a re-challenge of the subject with the investigational drug may be conducted if considered both safe and ethical by the Investigator.

## 7.8 Adverse Events Monitoring

All adverse events, whether or not unexpected, and whether or not considered to be associated with the use of the study drug, will be entered into OnCore<sup>®</sup>, as noted above.

The Investigator will assess all adverse events and determine reportability requirements to the UCSF Data and Safety Monitoring Committee (DSMC) and UCSF's Institutional Review Board, the Institutional Review Board (IRB); and, when the study is conducted under an Investigational New Drug Application (IND), to the Food and Drug Administration (FDA) if it meets the FDA reporting criteria.

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

All grade(s) 3-5 adverse events entered into OnCore<sup>®</sup> will be reviewed on a monthly basis at the Site Committee meetings. The Site Committee will review and discuss the selected toxicity, the toxicity grade, and the attribution of relationship of the adverse event to the administration of the study drug(s).

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

For a detailed description of the Data and Safety Monitoring Plan, please refer Appendix 2 Multicenter Institutional Studies.

## 7.9 Expedited Reporting

### **Reporting to the Data and Safety Monitoring Committee**

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

### **Reporting to UCSF Committee on Human Research (Institutional Review Board)**

The Principal Investigator must report events meeting the UCSF IRB definition of "Unanticipated Problem" (UP) within 10 business days of his/her awareness of the event.

### **Expedited Reporting to the Food and Drug Administration**

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

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

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

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

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

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

### **Reporting to Pharmaceutical Company providing Study Drug**

Any clinical adverse event or abnormal laboratory test value that is serious occurring during the course of the study from the date of signing the informed consent, irrespective of the treatment received by the patient, must be reported to the study drug sponsor within one working day of knowledge (expedited reporting). For each patient, all serious adverse events must be reported up to 30 days after the last dose of investigational product. Serious adverse events occurring more than 30 days after a patient is discontinued from the study treatment may be reported at the discretion of the investigator.

In addition to reporting to the FDA, the Sponsor-Investigator will forward completed SAE and pregnancy forms to representatives of the pharmaceutical company providing Study Drug. All forms will be completed and emailed to [pvg@karyopharm.com](mailto:pvg@karyopharm.com)

The study drug sponsor will medically review all SAEs.

The following detailed information must be recorded for each serious adverse event in the SAE report form:

- A description of the AE in medical terms according to NCI-CTC Version 4.0, not as reported by the subject
- The severity grade as assessed by the investigator according to the definitions in NCI-CTC Version 4.0
- The date of becoming serious and the date of becoming known (if different)
- The reason for seriousness
- The outcome of the SAE at the time of the report
- Information on administration of the study drug and chemotherapy and any action taken
- Information on any treatment procedures necessary for the SAE, concomitant medications, relevant lab tests and relevant medical history

If in any one subject the same SAE occurs on several occasions, then the SAE in question must be documented and assessed anew each time.

The investigator is required to submit SAE Follow-up reports until the SAE has resolved or stabilized and all queries have been answered.

## **8 Statistical Considerations and Evaluation of Results**

### **8.1 Study Endpoints**

The primary endpoint is radiographic progression free survival (rPFS).

The secondary endpoints are to describe the following:

- PSA decline of  $\geq 50\%$  at 12 weeks post therapy initiation
- Time to PSA progression. Defined as a rise in PSA of 50% above nadir value or 25% above baseline if there is no decline.
- Relationship of abiraterone resistance status (primary vs acquired) and outcome
- Time to confirmed development of  $\geq 2$  new bone lesions that cannot be attributable to bone scan flare.
- Safety
- Exploratory endpoints are to describe the following:
  - Relationship of XPO-1 expression to PSA decline.
  - Expression profile of metastatic tumor and outcome.
  - Type of progression (e.g. Pain, bone etc)
  - Comparison of pre- and post-treatment XPO-1 expression in patients for whom pre-treatment biopsy is available through the Stand Up 2 Cancer "Dream Team" program.

## 8.1.1 Study Design

This is a single agent, phase II open label study of selinexor in patients with mCRPC with prior therapy with standard hormone ablation agents and abiraterone. Up to 54 patients could be enrolled in the study.

## 8.2 Determination of Sample Size and Accrual Rate

### 8.2.1 Sample Size and Power Estimate

In the first stage, 18 patients will be accrued. If there are 10 or fewer patients classified as progression-free at 16 weeks in these 18 patients, the study will be stopped. Otherwise, up to 36 additional patients will be accrued for a maximum total of 54. The null hypothesis is that 55% of patients are progression-free at 16 weeks. The alternative hypothesis is 75% are progression-free at 16 weeks. The null hypothesis will be rejected if 36 or more patients classified as progression-free at 16 weeks are observed in 54 patients. There is a 60.9% chance of stopping early for futility. This design yields a type I error rate of 0.048 and power of 90.0%.

### 8.2.2 Replacement Policy

Patients removed from study for unacceptable treatment related adverse event(s) will be followed until resolution or stabilization of all treatment related adverse events to Grade 2 or lower; however, they will not be replaced.

### 8.2.3 Accrual estimates

Five patients per month are estimated to be accrued.

## 8.3 Interim Analyses and Stopping Rules

Toxicity is continuously monitored for all patients. However, a full safety assessment will also be carried out after the first ten patients have completed Cycle 1 of therapy. If 3 or more of the initial 10 patients experience grade 3 or 4 toxicity within 4 weeks of starting therapy, then accrual will be suspended. This indicates that greater than 25% of the patients have experienced unacceptable toxicity. The study may continue to proceed while the safety analysis is performed.

Additionally, in the first stage, 18 patients will be accrued. If there are 10 or fewer patients classified as progression-free at 16 weeks in these 18 patients, the study will be suspended. Further, if >33% (i.e., >6 of 18 patients) have experienced unacceptable toxicity (i.e., defined as toxicity precluding the administration of selinexor at any dose level) at the time of interim analysis, the accrual will be suspended. Otherwise, 36 additional patients will be accrued for a total of 54. There is a 60.9% chance of stopping early for futility.

## 8.4 Analyses Plans

### 8.4.1 Analysis Population

All patients who receive at least 1 dose of selinexor will be evaluated for response.

Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. All analyses will be performed with respect to all patients treated

with selinexor, regardless of prior therapy, with a separate analysis performed according to prior treatment status with cohorts of patients as follows:

- (A) Prior abiraterone only
- (B) Prior enzalutamide only
- (C) Prior concomitant therapy with abiraterone and enzalutamide
- (D) Prior sequenced therapy with abiraterone and enzalutamide

#### **8.4.2 Primary Analysis (or Analysis of Primary Endpoints)**

The primary end point is proportion of patients without evidence of radiographic progression at 16 weeks. This is defined from study start until one of the following events occurs:

- $\geq 2$  new bone lesions on Technetium bone scan
- RECIST defined tumor progression
- Cancer related pain requiring opiate analgesics
- Surgery or Radiation to treat a prostate cancer related indication
- Death from any cause

Radiographic PFS will be defined as the time from treatment initiation to the occurrence of either tumor progression in soft tissue according to modified RECIST criteria, identification of new lesions by bone scan ( $\geq 2$  new lesions confirmed  $\geq 12$  weeks later). If no such event exists, then rPFS will be defined as time from start of study until clinical deterioration requiring a change in prostate cancer therapy or at clinician discretion, surgery and/or radiation therapy to treat a prostate-cancer related indication, or death from any cause. PFS will be censored at the last scheduled disease assessment on study. PFS of living patients with no assessment on-study, and PFS of patients with no baseline assessment will be censored at enrollment.

rPFS will be estimated using the Kaplan-Meier product limit method. The median times to event with two-sided 95% confidence intervals will be estimated, together with the estimate of event rates at 6 and 12 months. The score statistic from the cox proportional hazards model will be used in the estimation of the hazard ratio and the associated 95% confidence interval will also be provided.

#### **8.4.3 Secondary Analysis (or Analysis of Secondary Endpoints)**

##### PSA decline of $\geq 50\%$ at 12 weeks post therapy initiation

The proportion of patients experiencing a PSA decline from baseline of at least 50% in PSA at 12 weeks following the initiation of study therapy will be presented with a 95% confidence interval.

##### Time to PSA progression (TTPP).

Time to PSA progression, is defined as the time interval between the date of treatment initiation and the date of either first documented PSA progression, or death due to any cause, whichever comes first. PSA is measured monthly until PSA progression as defined by the PSAWG2 criteria.

Duration of PSA response defined as the time between the first evaluation at which the response criteria are met and the first documentation of PSA progression or death. Early increase in PSA within 12 weeks, when followed by subsequent decline, is ignored in determining this endpoint.

Kaplan-Meier methods will be used to estimate the median time to PSA progression with a 95% confidence interval.

#### Relationship of abiraterone resistance status (primary vs acquired) and outcome

Radiographic progression free survival will be compared for patients with primary abiraterone resistance and acquired abiraterone resistance using a Cox proportional hazards model, and will be presented with a 95% confidence interval.

#### Time to confirmed development of $\geq 2$ new bone lesions

Time to development of  $\geq 2$  new bone lesions, defined as the time interval between the date of treatment initiation and the date of documented new lesions. Bone scans will be performed at week 8, 16, 24, and every 12 weeks thereafter; evaluation criteria is defined by the PSAWG2 criteria for bone scan evaluation. The time will be 'backdated' to when the  $\geq 2$  new lesions were detected if a second scan is done to confirm progression.

Kaplan-Meier methods will be used to estimate the median time to development of  $\geq 2$  new bone scans with a 95% confidence interval.

#### Safety

Safety endpoints include incidence of worst grade adverse events; incidence of deaths and other serious and significant adverse events; and incidence of worst grade laboratory abnormalities. All recorded adverse events will be listed and tabulated by system organ class, preferred term, and by dose group and cohort and coded according to the Medical Dictionary for Regulatory Activities (MedDRA). Vital signs, physical examinations, clinical laboratory test, medical history, ECOG, and ECGs results will be listed and summarized by dose groups.

#### **8.4.4 Pharmacokinetic and pharmacodynamic analyses**

Serum selinexor concentrations, leukocyte collection, treated leukocyte lysate, and macrophage inhibitory cytokine-1 (MIC-1 mRNA) will be submitted to Karyopharm Therapeutics for analysis.

Summary statistics will be tabulated for the pharmacokinetic parameters of selinexor and study day. Geometric means and coefficients of variation will be presented for  $C_{\min}$ ,  $C_{\max}$ , AUC(TAU), and AUC(INF). Medians, minima, maxima will be presented for  $T_{\max}$ . Means and standard deviations will be provided for the remaining pharmacokinetic parameters. To describe the dependency on dose, scatter plots of  $C_{\min}$  and AUC(TAU) or AUC(INF) versus dose will be provided for each day measured. To assess the attainment of steady state, geometric mean  $C_{\min}$  values will be plotted by study day and dose.

Isolated leukocytes and serum samples will be studied for the temporal effects of KPT-330 on XPO1 inhibition and induction of macrophage-inhibitory cytokine 1 (MIC-1), a secreted biomarker reflecting the activation of p53 mediated apoptosis. Total RNA will be isolated from leukocytes of patients and the expression of XPO1 and MIC-1 will be measured by quantitative polymerase chain reaction analysis (qPCR). XPO1 mRNA induction will then

be assessed by comparing the fold increase of XPO-1 and MIC-1 expression from pre-dose levels as a function of selinexor dose and total time on treatment.

#### **8.4.5 Other Analyses/Assessments**

Additional correlative studies including pain scale changes measured by the brief pain inventory short form will be descriptively summarized.

### **8.5 Evaluation of Safety**

Analyses will be performed for all patients having received at least one dose of study drug. The study will use the NCI CTCAE v4.0.

## **9 Study Management**

### **9.1 Pre-study Documentation**

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

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

The clinical investigation will not begin until either FDA has determined that the study under the Investigational Drug Application (IND) is allowed to proceed or the Investigator has received a letter from FDA stating that the study is exempt from IND requirements.

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

### **9.2 Institutional Review Board Approval**

The protocol, the proposed informed consent form, and all forms of participant information related to the study (e.g. advertisements used to recruit participants) will be reviewed and approved by the UCSF IRB (Institutional Review Board). Prior to obtaining IRB approval, the protocol must be approved by the Helen Diller Family Comprehensive Cancer Center Site Committee and by the Protocol Review Committee (PRC). The initial protocol and all protocol amendments must be approved by the IRB prior to implementation.

### **9.3 Informed Consent**

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

## 9.4 Changes in the Protocol

Once the protocol has been approved by the UCSF IRB, any changes to the protocol must be documented in the form of an amendment. The amendment must be signed by the Investigator and approved by PRC and the IRB prior to implementation.

If it becomes necessary to alter the protocol to eliminate an immediate hazard to patients, an amendment may be implemented prior to IRB approval. In this circumstance, however, the Investigator must then notify the IRB in writing within five (5) working days after implementation. The Study Chair and the UCSF study team will be responsible for updating any participating sites.

## 9.5 Registration/Enrollment

Screening procedures will occur when a subject and investigator signs and dates an informed consent form and the subject provides authorization to use protected health information. The informed consent form will be completed prior to any study-specific procedures. Screening procedures that are standard of care and were performed prior to consent, do not need to be repeated if they were conducted within the eligible screening period, unless otherwise specified.

To initiate enrollment, the investigator will verify eligibility according to all inclusion and exclusion criteria. All eligible subjects must be centrally registered through the GU Clinical Research Office. To complete the registration process, the study site must fax or email the signed completed study-specific eligibility checklist, all source documents verifying eligibility, any supporting documents, and the signed informed consent to the GU Clinical Research Office. These data must also be entered into the OnCore database. Once the enrollment packet is received at UCSF, the Study Chair will review the packet and if eligibility is confirmed, assignment to treatment can occur. Subjects failing to meet all study eligibility requirements will not be registered.

## 9.6 Handling and Documentation of Clinical Supplies

The UCSF Principal Investigator and each participating site will maintain complete records showing the receipt, dispensation, return, or other disposition of all investigational drugs. The date, quantity and batch or code number of the drug, and the identification of patients to whom study drug has been dispensed by patient number and initials will be included. The sponsor-investigator will maintain written records of any disposition of the study drug.

The Principal Investigator shall not make the investigational drug available to any individuals other than to qualified study patients. Furthermore, the Principal Investigator will not allow the investigational drug to be used in any manner other than that specified in this protocol.

## 9.7 Case Report Forms (CRFs)

The Principal Investigator and/or his/her designee, will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Study specific Case Report Forms (CRFs) will document safety and treatment outcomes for safety monitoring and data analysis. All study data will be entered into OnCore® via standardized CRFs in accordance with the CTMS study calendar, using single data entry with a secure access account. The Clinical Research Coordinator (CRC) will complete the CRFs as soon as possible upon completion of the study visit; the Investigator will review and approve the completed CRFs.

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

In accordance with federal regulations, the Investigator is responsible for the accuracy and authenticity of all clinical and laboratory data entered onto CRFs. The PI will approve all completed CRFs to attest that the information contained on the CRFs is true and accurate.

All source documentation and CTMS data will be available for review/monitoring by the UCSF DSMC and regulatory agencies.

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

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

## **9.8 Oversight and Monitoring Plan**

The UCSF Helen Diller Family Comprehensive Cancer Center DSMC will be the monitoring entity for this study. The UCSF DSMC will monitor the study in accordance with the NCI-approved Data and Safety Monitoring Plan (DSMP). The DSMC will routinely review all adverse events and suspected adverse reactions considered "serious". The DSMC will audit study-related activities to ensure that the study is conducted in accordance with the protocol, local standard operating procedures, FDA regulations, and Good Clinical Practice (GCP). Significant results of the DSMC audit will be communicated to the IRB and the appropriate regulatory authorities at the time of continuing review, or in an expedited fashion, as applicable. See Appendix 2 Data and Safety Monitoring Plan for additional information.

## **9.9 Record Keeping and Record Retention**

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

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

The case history for each individual shall document that informed consent was obtained prior to participation in the study.

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

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

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

## **9.10 Coordinating Center Documentation of Distribution**

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

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

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

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

## **10 Protection of Human Subjects**

### **10.1 Protection from Unnecessary Harm**

Each clinical site is responsible for protecting all subjects involved in human experimentation. This is accomplished through the IRB mechanism and the process of informed consent. The IRB reviews all proposed studies involving human experimentation and ensures that the subject's rights and welfare are protected and that the potential benefits and/or the importance of the knowledge to be gained outweigh the risks to the individual. The IRB also reviews the informed consent document associated with each study in order to ensure that the consent document accurately and clearly communicates the nature of the research to be done and its associated risks and benefits.

### **10.2 Protection of Privacy**

Patients will be informed of the extent to which their confidential health information generated from this study may be used for research purposes. Following this discussion, they will be asked to sign the HIPAA form and informed consent documents. The original signed document will become part of the patient's medical records, and each patient will

receive a copy of the signed document. The use and disclosure of protected health information will be limited to the individuals described in the informed consent document.

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**Appendix 1 Performance Status Criteria**

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity Fully active, able to carry on all pre-disease performance without restriction	100	Normal, no complaints, no evidence of disease
		90	Able to carry on normal activity; minor signs or symptoms of disease
1	Symptoms, but ambulatory 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)	80	Normal activity with effort; some signs or symptoms of disease
		70	Cares for self, unable to carry on normal activity or to do active work
2	In bed < 50% of the time Ambulatory and capable of all self-care, but unable to carry out any work activities Up and about more than 50% of waking hours	60	Requires occasional assistance, but is able to care for most of his/her needs
		50	Requires considerable assistance and frequent medical care
3	In bed > 50% of the time Capable of only limited self-care, confined to bed or chair more than 50% of waking hours	40	Disabled, requires special care and assistance
		30	Severely disabled, hospitalization indicated Death not imminent
4	100% bedridden Completely disabled Cannot carry on any self-care Totally confined to bed or chair	20	Very sick, hospitalization indicated Death not imminent
		10	Moribund, fatal processes progressing rapidly
5	Dead	0	Dead

## Appendix 2 Data and Safety Monitoring Plan for Multicenter Institutional Study

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The UCSF Helen Diller Family Comprehensive Cancer Center (HDFCCC) Data and Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and subject safety for all HDFCCC institutional clinical studies. A summary of DSMC activities for this study includes:

- Review of subject data
- Review of suspected adverse reactions considered “serious”
- Monthly monitoring (depending on study accrual)
- Minimum of a yearly regulatory audit

### Monitoring and Reporting Guidelines

All institutional Phase 2 or 3 therapeutic studies are designated with a moderate risk assessment. The data is monitored every six months, with twenty percent of the subjects monitored (or at least three subjects if the calculated value is less than three).

The UCSF Coordinating Center provides administration, data management, and organizational support for the participating sites in the conduct of a multicenter clinical trial. The UCSF Coordinating Center will also coordinate quarterly conference calls with the participating sites to communicate the review of adverse events, safety data, and other study matters.

The Principal Investigator at the UCSF Coordinating Center will hold the role of Study Chair. The Study Chair is responsible for the overall conduct of the study and for monitoring its safety and progress at all participating sites. The Study Chair will conduct continuous review of data and subject safety and discuss each subject’s treatment at monthly UCSF Site Committee meetings. The discussions are documented in the UCSF Site Committee meeting minutes.

### Multicenter communication

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

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

Adverse events reporting to the DSMC will include reports from both the UCSF Coordinating Center, as well as the participating sites. The DSMC will be responsible for monitoring all data entered in OnCore® at the UCSF Coordinating Center and the participating sites. The data (i.e. copies of source documents) from the participating sites will be sent electronically or faxed over to the UCSF Coordinating Center prior to the

monitoring visits in order for the DSMC to monitor the participating site's compliance with the protocol, patient safety, and to verify data entry.

## Adverse Event Review and Monitoring

### Adverse Event Monitoring

All Grade 3-5 Adverse Events, whether or not unexpected, and whether or not considered to be associated with the use of study drug, will be entered into OnCore<sup>®</sup>, UCSF's Clinical Trial Management System.

All Grade 3-5 adverse events entered into OnCore<sup>®</sup> will be reviewed on a monthly basis at the UCSF Site Committee meetings. All clinically significant adverse events must be reported to the UCSF Coordinating Center by the participating sites within 10 business days of becoming aware of the event or during the next scheduled quarterly conference call, whichever is sooner. The UCSF Site Committee will review and discuss the selected toxicity, the toxicity grade, and the attribution of relationship of the adverse event to the administration of the study drug(s) from the UCSF Coordinating Center and the participating sites.

In addition, all suspected adverse reactions considered "serious" must be entered in OnCore<sup>®</sup> and reported to the UCSF Coordinating Center within 1 business day. The suspected adverse reactions considered "serious" will be reviewed and monitored by the Data and Safety Monitoring Committee on an ongoing basis and discussed at the DSMC meeting, which take place every six (6) weeks.

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

### Increase in Adverse Event Rates

If an increase in the frequency of Grade 3 or 4 adverse events (above the rate reported in the Investigator Brochure or package insert), the Study Chair at the UCSF Coordinating Center is responsible for notifying the DSMC at the time the increased rate is identified. The report will indicate if the incidence of adverse events observed in the study is above the range stated in the Investigator Brochure or package insert.

If at any time the Study Chair stops enrollment or stops the study due to safety issues, the DSMC Chair and DSMC Manager must be notified within 1 business day via e-mail. The DSMC must receive a formal letter within 10 business days and the IRB must be notified.

### Data and Safety Monitoring Committee Contacts:

DSMC Chair:	Thierry Jahan, MD	DSMC Monitors
Phone:	415-353-7065	Box 0128
Email:	<a href="mailto:Thierry.Jahan@ucsf.edu">Thierry.Jahan@ucsf.edu</a>	UCSF Helen Diller Family
Address:	Box 1674	Comprehensive Cancer Center
	UCSF	San Francisco, CA 94158
	San Francisco, CA 94115	

\* DSMP approved by NCI 09/February2012

## **Appendix 3 UCSF Policy/Procedure for Required Regulatory Documents for a UCSF Multicenter Investigator-Initiated Oncology Clinical Trials with an Investigator held Investigational New Drug (IND)**

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### **Purpose**

This policy defines the required Regulatory Documents for Single Site and Multicenter Investigator Initiated Oncology Clinical Trials at the Helen Diller Family Comprehensive Cancer Center (HDFCCC) where the Principal Investigator (PI) holds the IND.

### **Background**

The International Conference on Harmonization (ICH) Good Clinical Practices (GCP) Guidelines define Essential Regulatory Documents as those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of data produced. These documents serve to demonstrate compliance with standards of GCP and with all applicable regulatory requirements. Filing essential documents in a timely manner can greatly assist in the successful management of a clinical trial.

The Regulatory Documents will consist of electronic files in both iMedRIS and OnCore<sup>®</sup>, as well as paper files in the Regulatory Binders for both the Coordinating Site and the Participating Site(s) in the HDFCCC Investigator Initiated Oncology Clinical Trials.

### **Procedures**

#### **1. HDFCCC Essential Regulatory Documents**

##### **Documents Filed in iMedRIS:**

- IRB approvals for initial submission of application, all modifications, and continuing annual renewals
- Current and prior approved protocol versions with signed protocol signature page(s)
- Institutional Review Board (IRB) approval letters and Informed Consent Form(s) (ICF)
- Current and prior versions of the Investigator Brochure (IB).
- Serious Adverse Event Reporting
- Protocol Violations and Single Patient Exception (SPE) Reports to IRB with supporting fax documentation

##### **Documents Filed in OnCore<sup>®</sup>:**

- Package Insert (if the study drug is commercial) or Investigator Brochure
- Protocol Review Committee (PRC) approved protocols, protocol amendments and Summary of Changes (SOC)
- Patient handouts
- Screening/enrollment log
- Data and Safety Monitoring Committee (DSMC) monitoring reports
- OnCore<sup>®</sup> Case Report Form (CRF) completion manual

**Documents Filed in Regulatory Binder:**

- Completed Food and Drug Administration (FDA) 1572 document with Principal Investigator's signature
- For all Principal Investigators and Sub-Investigators listed on the FDA 1572, will need Financial Disclosure Forms, CVs, MD Licenses, Drug Enforcement Agency (DEA) Licenses, and Staff Training Documents (i.e. Collaborative Institute Training Initiative (CITI), etc.)
- Site Initiation Visit (SIV) minutes and correspondence with participating site(s).
- As applicable, approvals for Biosafety Committee, Radiation Committee, and Infusion Center
- Serious Adverse Event (SAE) reports to IRB and sponsor.
- MedWatch reporting to FDA and sponsor
- Delegation of Authority Form
- Drug Destruction Standard Operating Procedure (SOP)
- For all laboratories listed on the FDA 1572, will need CLIA certifications, CAP certifications, lab licenses, CVs of Lab Directors, and laboratory reference ranges

***2. Additional Essential Documents for Multicenter Trials for the Coordinating Center (filed in Regulatory Binder or OnCore)***

- Institutional Review Board (IRB) approval letters, IRB roster, Informed Consent Form (ICF), and Health Insurance Portability and Accountability Act (HIPAA) Consent Form for the Participating Site(s)
- For all Principal Investigators and Sub-Investigators listed on the 1572 at the Participating Site(s) – Financial Disclosure Forms, CVs, MD Licenses, and Staff Training documents (i.e. Collaborative Institute Training Initiative (CITI), etc.) (for Investigational New Drug Application
- Site Initiation Visit (SIV) minutes and correspondence with Participating Site(s).
- As applicable, approvals for Biosafety Committee, Radiation Committee, and Infusion Center for the Participating Site(s)
- Protocol Violations and Single Patient Exception (SPE) reports to IRB with supporting fax documentation for Participating Site(s)
- Drug Destruction Standard Operating Procedure (SOP) for the Participating Site(s)
- Data and Safety Monitoring Committee (DSMC) monitoring reports for the Participating Site(s)
- For all laboratories listed on FDA 1572, will need CLIA certifications, CAP certifications, lab licenses, CVs of Lab Directors, and laboratory reference ranges for the Participating Site(s)
- Copy of the Data and Safety Monitoring Plan (DSMP) Monitoring Plan for all participating site(s) in Multicenter studies or Contract Research Organization (CRO) Monitoring Plan (if an outside CRO is used for the study)
- Serious Adverse Event (SAE) forms submitted to both the IRB and the sponsor for the Participating Site(s)

27 April 2012

**3. Required Regulatory Documents for Sub-sites Participating in a UCSF Investigator Initiated Multicenter Trial (Checklist)**

Directions:

- 1) Scan the documents and email to the UCSF Coordinating center or
- 2) Scan the documents and upload to OnCore® and create a Note to File for the on-site Regulatory binder to indicate where these documents may be found

**1572**

PI and Sub investigators:

- CV and Medical license
- Financial disclosure form
- NIH or CITI human subject protection training certification
- Laboratories
- CLIA and CAP
- CV of Lab Director and Lab Licenses
- Laboratory reference ranges

**Local Institutional Review Board**

- IRB Approval letter
- Reviewed/Approved documents
  - Protocol version date: \_\_\_\_\_
  - Informed consent version date: \_\_\_\_\_
  - Investigator Brochure version date: \_\_\_\_\_
  - HIPAA
- Current IRB Roster

**Other**

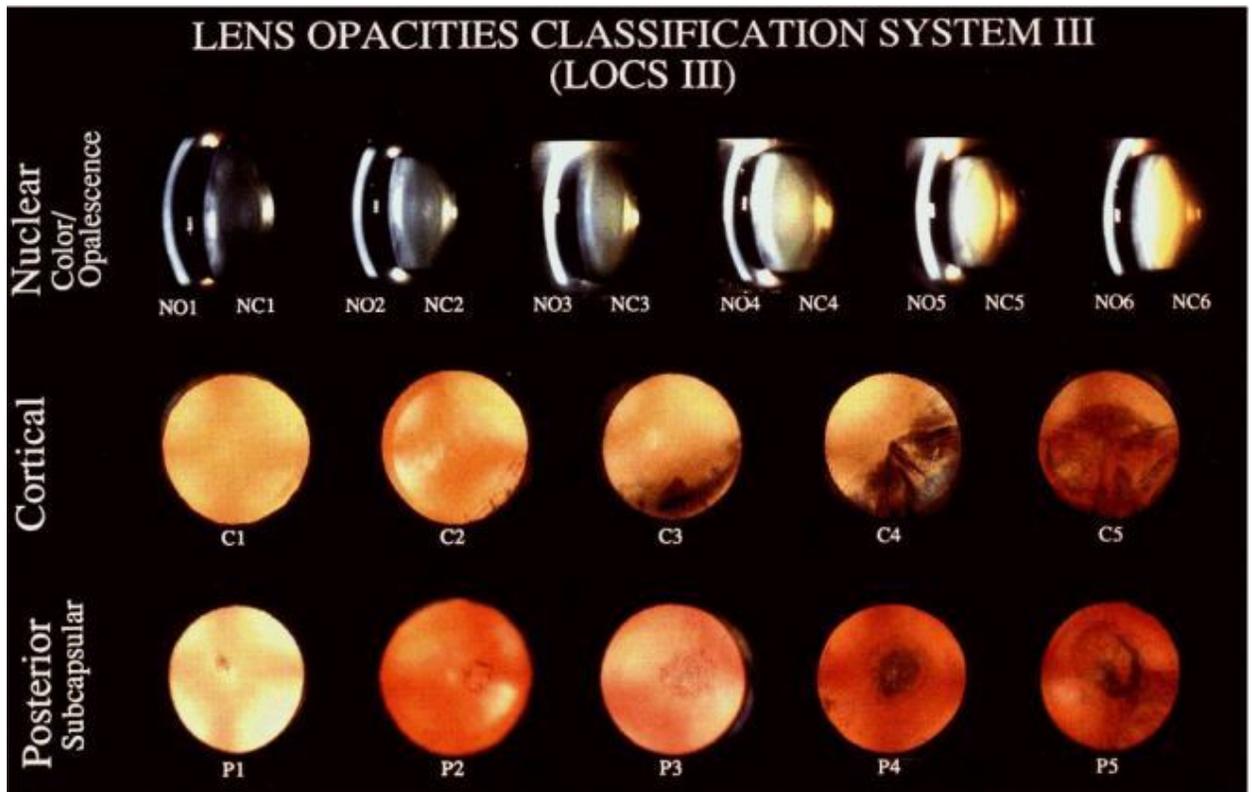
- Delegation of Authority Log
  - Include NIH or CITI human subject protection training certificates or GCP training certification
- Pharmacy
  - Drug destruction SOP and Policy
- Protocol signature page
- Executed sub contract

27.apr.2012

## Appendix 4 Full Ophthalmological Exam

**Full ophthalmological exam:** required of all patients in all selinexor studies at screening, every 3 months if cataracts present at screening and if clinically indicated during study.

1. Prior to dilation:
  - best corrected visual acuity
  - slit lamp examination including tonometry
2. Dilated:
  - fundoscopy
  - slit lamp examination
    - if a cataract is seen during the exam, cataract will be graded according to the Lens Opacities Classification System III (LOCS III)



**Ophthalmological Exam Assessments**

Best Corrected Visual Acuity (BCVA):

Adnexa	Normal	Abnormal	Description
lids			
lashes			
conjunctiva			
cornea			
ant. Chamber			
iris			
lens*(1)			
Intraocular pressure			
Fundus			
vitreous			
optic disc*(2)			
macula			
retina			

\*(1) Does lens show cataract change, follow grading system in description

\*(2) Cup/disc ratio and any abnormalities if seen

