PHASE 1B STUDY TO EVALUATE THE SAFETY OF SELINEXOR IN COMBINATION WITH MULTIPLE STANDARD CHEMOTHERAPY AGENTS IN PATIENTS WITH ADVANCED MALIGNANCIES

A. Naing, S. Fu, A. M. Tsimberidou, S. Pant, S. A.Piha-Paul, F. Janku, D. S. Hong, R.R. Colen, B.W. Carter, E. B. Evans, N. Paez-Arango, H. A. Tawbi, D. D. Karp, V. Subbiah, R. Dev, K. R. Hess, N. T. Ueno, G. R. Simon, M. J. Overman, R. L. Coleman, F. Meric-Bernstam

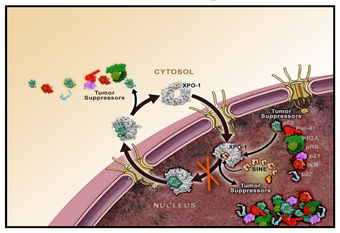
Department of Investigational Cancer Therapeutics (Phase I Program), Sheikh Khalifa Bin Zayed Al Nahyan Institute for Personalized Cancer Therapy, Department of Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

Introduction

Exportin 1 (XPO1), is a major nuclear export protein in the cell which is overexpressed in many types of cancer [1]. Selinexor (KPT-330) is a first-in-class, slowly reversible, Selective Inhibitor of Nuclear Export (SINE) compound that specifically blocks XPO1 (Figure 1). Inhibition of XPO1 results in nuclear localization, accumulation, and reactivation of tumor suppressor proteins (Table 1), therefore selectively inducing apoptosis in cancer cells, while largely sparing normal cells (Figure 2). This unique property of XPO1 inhibition has been deployed as a novel therapeutic strategy with success in several solid tumors and hematologic malignancy clinical trials. Preclinical studies have shown that SINE compounds behave synergistically when combined with different therapeutic agents to enhance cancer cell death. The primary objective of the study is to examine the safety and tolerability of selinexor when given in combination with thirteen standard chemotherapy regimens. The secondary objectives are to determine disease control and progression-free survival of patients receiving selinexor administered with standard chemotherapy and immunotherapy treatments in specific tumor subsets.

Figure 1. XPO1 Nuclear Export Cycle



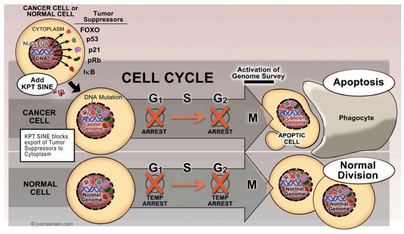
XPO1 is the sole exportin responsible for the transport of most of the tumor suppressor (TSP) and growth regulator proteins (GRP) out of the nucleus into the cell [2]. XPO1 forms trimeric transport complexes with RanGTP and a cargo molecule, a process promoted by the Ran-binding protein RanBP2. TSP and GRP mediate the majority of their control functions in the nucleus. Therefore the nuclear export of these molecules via XPO1 is an efficient mechanism of inactivating TSP and GRP.

Table 1. XPO1 Inhibition Enhances Multiple TSPs/GRPs

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, $p21^{CIP1}$
deletion p53, MDM2↑	$p21^{CIP1}$, p53, $p14^{ARF}$	NPM1 Mutation	p53, $p14^{ARF}$
HER2, EGF-R	FOXO, pRB	c-Myc ↑	PP2A, $p21^{CIP1}$
$p16^{INK4A}$↓ or $p14^{ARF}$↓	pRB, p53	Bcr-Abl	PP2A, Abl
mTOR↑	p53, p27, FOXO	Bcl2 ↑, Bcl-xL ↑	p53, $p16^{INK4A}$
Wnt / ß-Catenin ↑	APC, HMGBP1	Notch ↑	FOXO
deletion pRb	p27	NF-κB ↑	I-κB

Emerging data suggest that tumor cells have increased XPO1 levels [3,4]. XPO1 can be inhibited by selinexor. Thereby, the nuclear retention of key TSP/GRP is forced and multiple TSPs/GRPs are enhanced. For each of the major growth and tumor stimulating pathways found across the various cancers, XPO1 appears to stimulate at least one counteracting pathway.

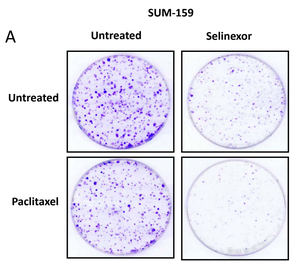
Figure 2. XPO1 Inhibitors Induce Distinct Outcomes in Normal and Malignant Cells



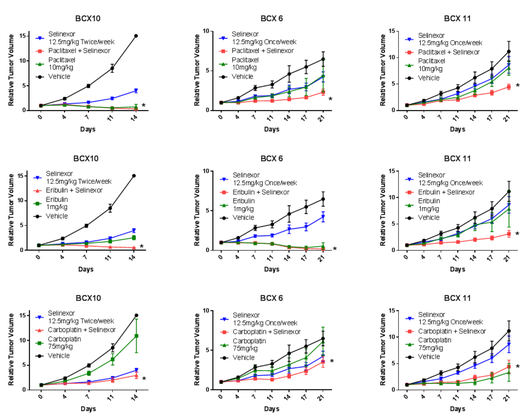
KPT-SINE compounds can induce distinct outcomes in normal and malignant cells. By activating a genome survey, TSP/GRP can "distinguish" between cancerous and normal cells, inducing apoptosis in the cancer cells, and maintain cell cycle arrest in the normal cells until the XPO1 export block is released.

Aim: To examine the safety and tolerability of selinexor when given in combination with standard chemotherapy and immunotherapy regimens

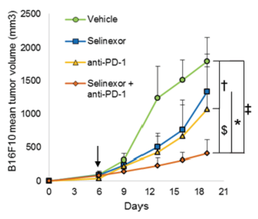
Effects of Selinexor *in vitro* and *in vivo*



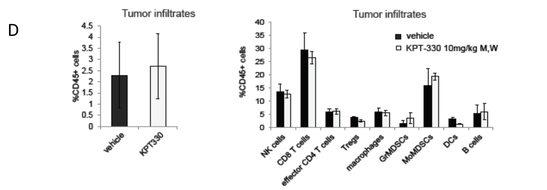
A. Selinexor in combination with paclitaxel has greater efficacy than compared to either agent alone. SUM-159 cells were plated at a density of 2 ×10^3 cells/60 mm plates in triplicate for each treatment group. Cells were treated for 2 weeks with vehicle, selinexor(50nM), paclitaxel(0.5nM) or in combination, colonies were then fixed and stained with crystal violet [7].



B. Selinexor has greater antitumor efficacy *in vivo* in combination with standard chemotherapy. Mice bearing three different TNBC PDXs were treated with vehicle, selinexor 12.5mg/kg twice a week for BCX10 and once weekly for BCX 6 and 11, paclitaxel 10mg/kg and eribulin 1mg/kg on day 1 and 8, carboplatin 75mg/kg day 1 and in combination of selinexor with each chemotherapy agent. Data is presented as mean ±SEM. The tumor volumes at the conclusion of experiment were compared to vehicle and the data was analyzed by two-way ANOVA to determine statistical significance (* P<0.001 vs. vehicle) [7].



C. Selinexor in combination with PD-1 blockade has greater efficacy compared to sing agent alone. C57BL/6 mice were inoculated with B16F10 melanoma cells on day 0. Mice were treated with Selinexor (15 mg/kg), anti-PD-1 antibody (200 µg) or combination of both twice a week [8].



D. Tumor Infiltrating Leukocytes (TIL) were not affected in vivo by Selinexor treatment. C57BL/6 mice were inoculated with B16 cells on day 0 and dosed with vehicle or 10 mg/kg Selinexor on days 7, 9, 14, 16. Tumors were harvested on day 21 and infiltrates analyzed by FACS [9].

Key Inclusion Criteria

- **Patients must have histologically or cytologically confirmed malignant neoplasms (not including hematological malignancies and brain tumors) untreated or previously treated requiring further treatment. Patients must be refractory to, intolerant of, established therapy known to provide clinical benefit for their condition. Patients in Arm L (pembrolizumab) and Arm M (nivolumab) that have FDA-approved indications for nivolumab and pembrolizumab do not have to fail first line nivolumab or pembrolizumab, and these patients may be treatment naïve if they have disease where pembrolizumab or nivolumab are FDA approved for the first-line setting**
- **ECOG performance status of 0-1**
- **Patients must have failed prior standard curative chemotherapy for their disease. Subjects must have failed, be intolerant to, or be ineligible for any potentially curative approved treatment, irrespective of line of therapy**
- **Patients must have either measurable disease (RECIST 1.1) or evaluable disease (non-measurable lesions) outside irradiated field on CT/MRI**
- **Adequate hematologic, liver and renal functions**
- **Able to swallow and retain oral medication**
- **Negative serum pregnancy test in women of childbearing potential within 7 days of first dose of treatment and patients of child-bearing potential must agree to use effective contraception during/after 3 months post dose**

Objectives and Endpoints

Objective

- **To determine disease control rate and progression free survival of selinexor administered with standard chemotherapy treatments**

Exploratory Objectives

- **To determine the correlation of translational biomarkers**
- **To compare serial assessment of mutation status in biopsies obtained at baseline and progression after clinical response to combination therapy**

Endpoints

- **Safety according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03**
- **Disease control rate (complete response, partial response + stable disease for at least 6 months, assessed according to RECIST 1.1 criteria)**
- **The objective tumor response rate (complete response + partial response), assessed according to RECIST 1.1 criteria**
- **Progression-free survival (PFS) defined as the time between the cycle 1 start date and the date of disease progression, death, or withdrawal of consent, whichever is reported first**

Exploratory Endpoints

- **Evaluation of biomarkers in a translational study**
- **Serial mutation assessment of biopsies**

Key Exclusion Criteria

- **Evidence of complete or partial bowel obstruction**
- **Patients with primary CNS tumor or CNS tumor involvement. However, patients with stable metastatic CNS tumors may participate in this study**
- **Need of Total Parenteral Nutrition**
- **Prior treatment with an agent targeting the exportin**
- **Allergic to Selinexor or any of the chemotherapy intended to receive**
- **Radiation, chemotherapy, or immunotherapy or any other systemic anticancer therapy ≤ 3 weeks prior to study drug administration date**
- **Diagnosis or recurrence of invasive cancer other than the present cancer within 3 years (except basal or squamous cell carcinoma of the skin that has been definitively treated)**
- **Unstable cardiovascular function**
- **Uncontrolled active infection requiring parenteral antibiotics, antivirals, or antifungals within one week prior to the first dose. Active infection with concurrent treatment is acceptable only if the patient is clinically stable**
- **Significantly diseased (as determined by the PI or treating physician) or obstructed gastrointestinal tract or uncontrolled vomiting or diarrhea**
- **Men whose partner is a woman of child-bearing potential, (i.e. biologically able to conceive), and who is not employing two forms of highly effective contraception**

References

1. Sharpless and DePinho. Gone but not forgotten. Nature. 8 February 2007. 445(7128):606-7.
2. Turner, et al. Nuclear export of proteins and drug resistance in cancer. Biochemical Pharmacology. 2012.
3. Turner and Sullivann. CRM1-Mediated Nuclear Export of Proteins and Drug Resistance in Cancer. Current Medicinal Chemistry,2008. 15(26):2648-2655.
4. Kau, et al. Nuclear Transport and Cancer: From Mechanism to Intervention. Nature Reviews Cancer. 4, 106-117 (February 2004).
5. Van der Watt, et al. The nuclear exporter, Crm1, is regulated by NFY and Sp1 in cancer cells and repressed by p53 in response to DNA damage. Biochimica et Biophysica Acta. 2011. 1809(7):316–326.
6. Golomb, et al. Importin 7 and Exportin 1 Link c-Myc and p53 to Regulation of Ribosomal Biogenesis. Mol Cell. 2012. Jan 27;45(2):222-32.
7. Paez Arango N, et al. Selinexor, a selective inhibitor of nuclear export, demonstrates efficacy in preclinical models of triple negative breast cancer. Poster presentation. San Antonio Breast Cancer Symposium, San Antonio, TX. December 2016.
8. Farren, et al. The exportin-1 inhibitor Selinexor exerts superior antitumor activity when combined with T-cell checkpoint inhibitors. Mol. Cancer Ther. 2017 Mar;16(3):417-427.
9. Tyler, et al. Clinical dosing regimen of Selinexor maintains normal immune homeostasis and T-cell effector function in mice: Implications for combination with immunotherapy. Mol. Cancer Ther. 2017 Mar;16(3):428-439.
10. Clinical trial number: NCT02419495

Study Design

Part 1 Dose Escalation: 3+3 Design

Arm A: Selinexor + Carboplatin
(Selinexor- 40- 80 mg PO once weekly; Carboplatin- AUC-6 IV Q3W)

Arm B: Selinexor + Paclitaxel
(Selinexor- 40- 80 mg PO days 1, 3, 8, and 10 of 21 day cycle; Paclitaxel- 80 mg/m^2 IV days 1 and 8 of 21 day cycle)

Arm C; Selinexor + Eribulin
(Selinexor- 60- 80 mg PO once weekly; Eribulin- 1.0 mg/m^2 IV days 1 and 8 of 21 day cycle)

Arm D: Selinexor + Doxorubicin + Cyclophosphamide
(Selinexor- 20- 80 mg PO once weekly; Doxorubicin- 60 mg/m^2; Cyclophosphamide- 600 mg/m^2 IV Q3W)

Arm E: Selinexor + Carboplatin + Paclitaxel
(Selinexor- 20- 80 mg PO once weekly; Carboplatin- AUC-4; Paclitaxel- 175 mg/m^2 IV Q3W)

Arm F: Selinexor + Carboplatin + Pemetrexed
(Selinexor- 20- 80 mg PO once weekly; Carboplatin- AUC-3; Pemetrexed- 500 mg/m^2 IV Q3W)

Arm G: Selinexor + Topotecan
(Selinexor- 40- 80 mg PO once weekly; Topotecan- 0.5 mg/m^2 days 1-5 of a 21 day cycle)

Arm H: Selinexor + FOLFIRI
(Selinexor- 40- 80 mg PO once weekly; Irinotecan- 180 mg/m^2;5- FU- 2400 mg/m^2 continuous; 5-FU- 400 mg/m^2 bolus; Leucovorin- 400 mg/m^2 IV Q2W)

Arm I: Selinexor + Irinotecan
(Selinexor- 40- 80 mg PO once weekly; Irinotecan- 125 mg/m^2 days 1 and 8 of a 21 day cycle)

Arm J: Selinexor + XELOX
(Selinexor- 20- 80 mg PO once weekly; Capecitabine- 900 mg/m^2 PO twice daily; Oxaliplatin- 100 mg/m^2 IV Q3W)

Arm K: Selinexor + Olaparib
(Selinexor- 20- 60 mg PO once weekly; Olaparib- 400 mg daily)

Arm L: Selinexor + Pembrolizumab
(Selinexor- 40- 80 mg PO twice weekly; Pembrolizumab- 2 mg/m^2 IV Q3W)

Arm M: Selinexor + Nivolumab
(Selinexor- 40- 80 mg PO twice weekly; Nivolumab- 240 mg IV Q2W)

→ **Dose Selection for each arm**
Maximum Tolerated Dose Determined →

Part 2 Expansion: Simon 2 Stage

- 15 tumor-specific expansion cohorts of up to 25 patients (Arms B, E, G, H,I, J, K, L, and M)
- 4 histology-independent expansion cohorts (Arms A, C, D, and F)

Trial Progress

Treatment Arm	Dose Escalation	Dose Expansion (N)	Additional Information
Selinexor + Carboplatin	completed	Any Histology (9)	
Selinexor + Paclitaxel	completed	Ovarian (25) Breast (25)	Dose expansion ongoing
Selinexor + Eribulin	ongoing	Any Histology (9)	MTD identified; Dose expansion to begin in July 2017
Selinexor + Doxorubicin/ Cyclophosphamide	completed	Any Histology (9)	
Selinexor + Carboplatin / Paclitaxel	ongoing	Ovarian (25) NSCLC (25)	Anticipated date of expansion opening: July 2017
Selinexor + Carboplatin / Pemetrexed	completed	Any Histology (9)	
Selinexor + Topotecan	ongoing	Ovarian (25)	Anticipated date of expansion opening: July 2017
Selinexor + FOLFIRI	completed	CRC (25)	
Selinexor + Irinotecan	completed	CRC (25)	
Selinexor + XELOX	completed	CRC (25)	
Selinexor + Olaparib	ongoing	Ovarian (25)	
Selinexor + Pembrolizumab	ongoing	Melanoma (25) NSCLC (25)	Anticipated date of expansion opening: July 2017
Selinexor + Nivolumab	ongoing	Melanoma (25) NSCLC (25) RCC (25)	