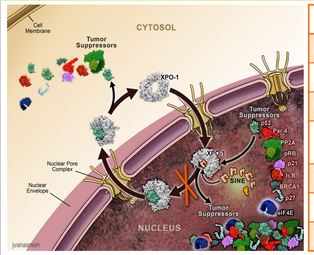
Clinical Activity of the Oral Selective Inhibitor of Nuclear Export (SINE™) Selinexor (KPT-330) in Patients with Head & Neck Squamous Cell Carcinoma (HN-SCC)

Abstract 6980

Amit Mahipal[1], Nashat Y Gabrail[2], Ammar Sukari[3], Hemchandra Mahaseth[3], Morten Mau-Sorensen[4], Sharon Friedlander[5], Yosef Landesman[5], Joel Ellis[5], Eran Shacham[5], Jean-Richard Saint-Martin[5], John McCartney[5], Tracey Marshall[5], Darcy Vincent[6], Tami Rashal[5], Robert Carlson[5], Sharon Shacham[5], Michael Kauffman[5], Mansoor R Mirza[5] and Albiruni R. Abdul Razak[7]

(1) Moffitt Cancer Center, Tampa, FL, USA; (2) Gabrail Cancer Center, Canton, OH, USA; (3) Karmanos Cancer Institue, Detroit, MI, USA; (4) Dept. of Oncology, Rigshospitalet, Copenhagen, Denmark; (5) Karyopharm Therapeutics Inc, Newton, MA, USA; (6) Ozmosis Research Inc., Toronto, Canada (7) Drug Development Program, Princess Margaret Cancer Center, Toronto, Canada

Selinexor Mechanism of Action



Pathway Affected	Effect of XPO1 Inhibition
p53 mutation	p73 activation, p21 activation
p53 and/or pRb destabilization	Nuclear p53 and pRB retention and stabilization
MDM2 activation	Nuclear p53 retention and activation
Decreased pRb signaling	Decreased pRB phosphorylation and increased nuclear pRB
NF-kB activation	IkB nuclear retention and activation
PIK3 or AKT activation	FOXO1, -3, -4 activation
Survivin - cytoplasmic	Survivin nuclear retention

Exportin 1 (XPO1) as a Target for Cancer

- XPO1 is the sole nuclear exporter of major tumor suppressor proteins (TSPs)
- XPO1 is overexpressed in esophageal SCC and many other solid tumors and its levels often correlate with poor outcomes

Selinexor Inhibits XPO1

- **Selinexor (KPT-330) is a covalent, slowly-reversible, selective inhibitor of nuclear export (SINE™) that inhibits XPO1**
- Selinexor forces nuclear restoration and reactivation of TSPs leading to selectively induce cancer cell apoptosis

Selinexor MOA Relates to HN-SCC Biology

- TP53, CDKN2A, NOTCH1, PIK3CA, EGFR, PTEN, HRAS and FBXW7 are some of the most commonly mutated or deleted genes in HNSCC
- Fbxw7 E3 ligase regulates Notch protein stability and SINE™ compounds related to selinexor induce nuclear retention of Fbxw7 and degradation of Notch
- HPV infection is associated with 14% of HN-SCC overall and 53% of oropharyngeal cancer
- HPV E6 protein traps p53 in the cytoplasm leading to its degradation and selinexor prevents p53 from leaving the nucleus

Study Design

Primary: Safety, tolerability and Recommended Phase 2 Dose (RP2D)

Secondary: Pharmacokinetics (PK), pharmacodynamics (PDn), anti-tumor response and confirmation of RP2D of selinexor

Selinexor Design:

- Phase 1, open label, dose escalation, Modified "3+3" design, study conducted at 6 sites in US, Canada and Denmark in patients with advanced, metastatic solid tumors
- Clinical Trials Number: **NCT01607905**
- 10 doses/cycle (2-3 doses/week) or 8 doses/cycle (twice weekly) or 4 doses/cycle (once weekly)

Major Eligibility Criteria:

- Solid tumor patients with no available standard treatments
- ECOG 0-1
- Documented progression at study entry
- Stable brain metastases permissible

Summary data are presented here from the ongoing first in human phase 1 study of oral selinexor and focused on patients with advanced head and neck solid tumors

Head & Neck Patient Characteristics

Characteristic N=19	
Median Age (Range)	58 (31 – 71)
Male to Female	16 Males : 3 Females
Median Prior Treatment Regimens (Range)	2.5 (1 – 7)
ECOG PS 0:1	4 : 15

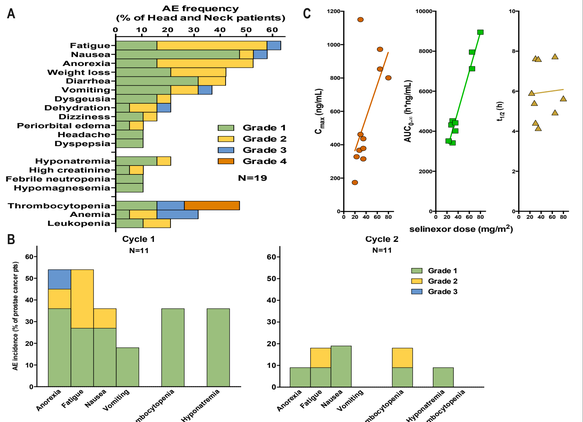
Head & Neck Patients Schedule & Dosing Arm

- 12 patients were treated in Dose Escalation cohorts; doses ranging from 20mg/m^2 – 80mg/m^2 dosing twice weekly or three times a week (8 or 10 doses per cycle)
- 7 patients were treated in Dose Expansion 1 at a dose of 35mg/m^2 dosing twice weekly (8 doses per cycle)

Dose Levels & Doses Per Cycle

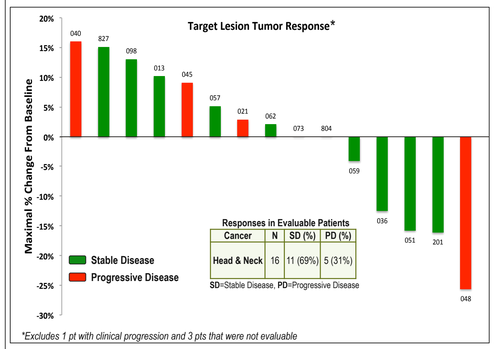
Dose Level	N	Cohort	Number of Doses per Cycle
20 mg/m^2 – 28 mg/m^2	3	Escalation	8 or 10
30 mg/m^2	3	Escalation	10
35 mg/m^2	10	Escalation & Expansion	8
65 mg/m^2 – 80 mg/m^2	3	Escalation	8

Safety & Pharmacokinetics

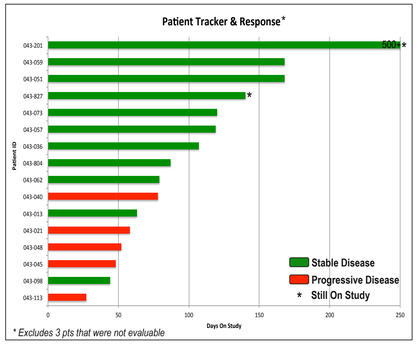


SAFETY SUMMARY: (A) The majority of adverse events (AEs) are reversible Grade 1 and 2, primarily nausea, anorexia and fatigue. Thrombocytopenia is the most common hematologic adverse event, rarely with bleeding. **(B)** These AEs (for patients that completed Cycle 1 & 2) are more common in Cycle 1 and decline in Cycles 2 and beyond due to supportive care and dose reductions. **PK SUMMARY: (C)** Selinexor C_{max} and AUC in plasma are proportional to dose and $t_{1/2}$ is independent of dose.

Clinical Activity



*Excludes 1 pt with clinical progression and 3 pts that were not evaluable

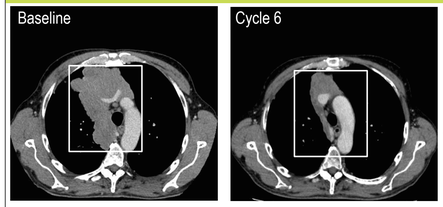


* Excludes 3 pts that were not evaluable

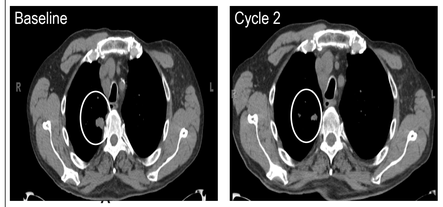
Prior Therapies for Patients on Selinexor > 3 Months

Patient No.	Dose (mg/m^2)	Days on Study	Best Response	Last Therapy Prior to Selinexor	Time to Progression (Days)
043-201	35	>500	SD	Gemcitabine, Capecitabine	99
043-059	20	168	SD	Gemcitabine	49
043-051	35	168	SD	mTor Inhibitor	56
043-827	65	>140	SD	Gemcitabine, Capecitabine	118
043-073	35	120	SD	Carboplatin, Taxol	153
043-057	35	119	SD	Cetuximab	unknown
043-036	35	107	SD	Cetuximab, Carboplatin, Cisplatin, 5FU	118

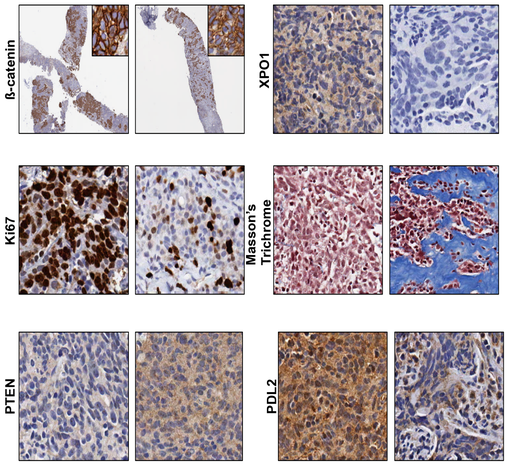
Patient Scans and Tissue Biopsy Staining



Pt 201: 63 y.o. man with type 2b thymic epithelial cancer, extensive mediastinal growth. Pt had 2 lines of treatment (Cyclo/Vinc/Cisp/Doxo and Capecit/Gem). Pt has stable disease (16% reduction) by RECIST, remains on study 500+ days. (Patient 827 also has type 2b thymic epithelial cancer and is on study 140+ days with ~20% tumor shrinkage.)



Pt 051: 64 y.o. man with type 2 hypopharyngeal cancer. Pt had 4 lines of treatment (Cisplatin, Carboplatin, mTor Inhibitor, and Taxol). Pt has stable disease (16% reduction) by RECIST, remained on study 168 days.



Pt 098: Tissue samples obtained prior & 3 weeks post selinexor treatment underwent immunohistochemical staining for ß-catenin (Wnt signaling), XPO1, Ki67 (proliferation marker), PTEN (tumor suppressor), Masson's Trichrome (fibrotic tissue) and PDL2 (programmed cell death ligand 2). Entire sections were imaged using Aperio ScanScope AT Turbo at 20x magnification.

Conclusions

- Selinexor (KPT-330), an XPO1 antagonist, is rational therapy for HN-SCC based upon an MOA that involves forced nuclear retention of the tumor suppressors p53 and Fbxw7, leading to disruption of HPV- and Notch1-dependent tumor cell survival
- Selinexor is tolerated with manageable side effects of fatigue, anorexia, nausea and weight loss
- Selinexor single agent can stabilize disease progression with tumor shrinkage in different types of head and neck squamous cell carcinomas
- Phase 2 single agent of selinexor in patients with squamous H&N (65 mg/m^2 PO BIW for 3 out of each 4- weeks cycle, **NCT02213133**) and combination studies have begun or are planned

Contact Information: Amit Mahipal <Amit.Mahipal@moffitt.org>