Preliminary Phase II Results of Selinexor (KPT-330), an Oral Selective Inhibitor of Nuclear Export, in Patients with Heavily Pretreated Gynecological Cancers

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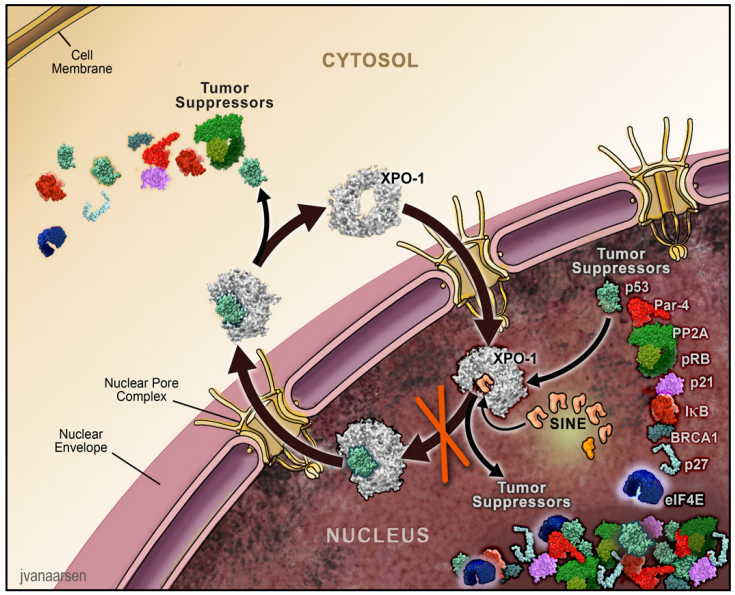
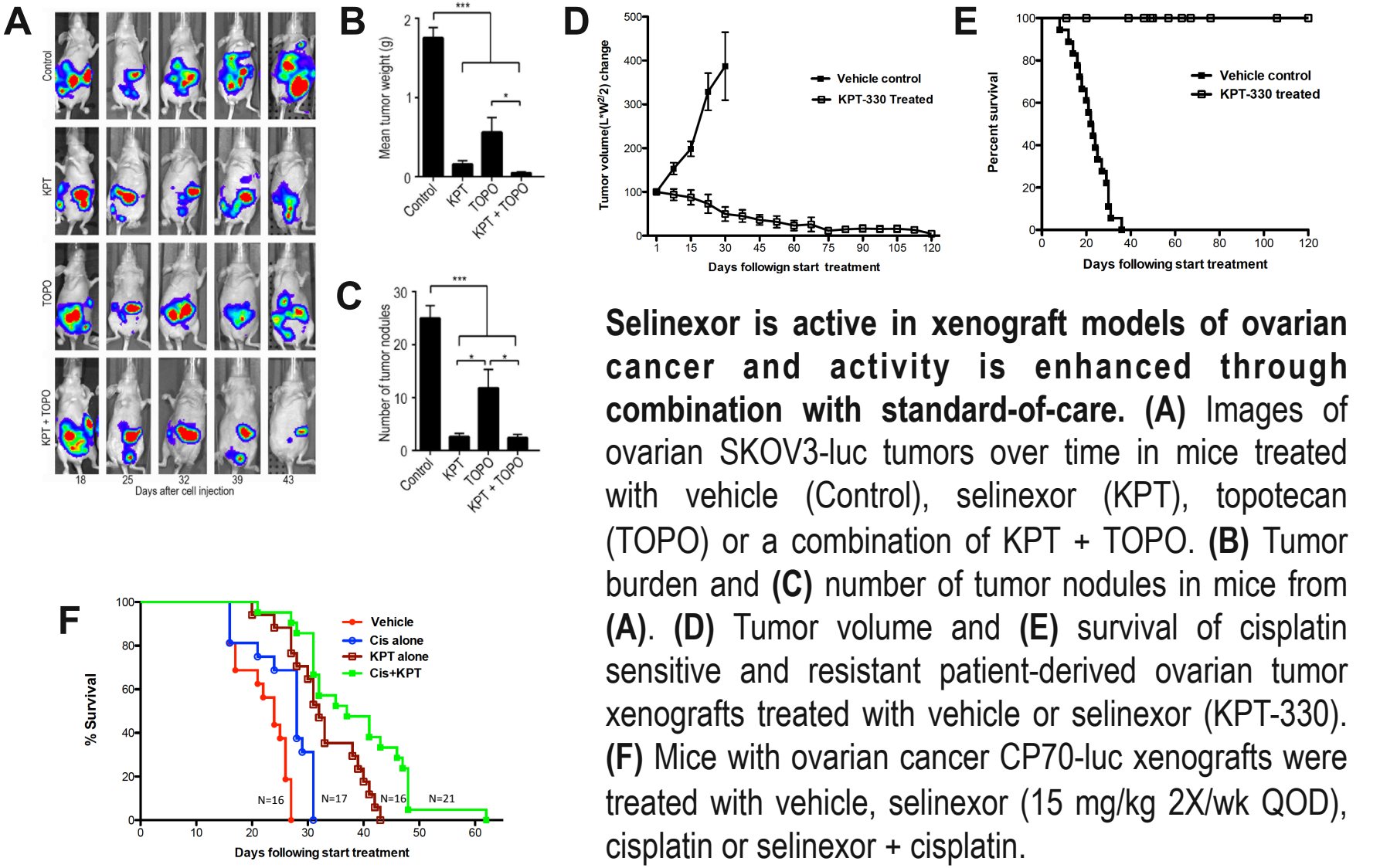
Selinexor – Mechanism of Action



- Exportin 1 (XPO1) is the major nuclear export protein for tumor suppressor proteins (TSPs)
- SINE compounds inhibit XPO1, leading to nuclear retention and reactivation of TSPs, inducing selective tumor cell apoptosis
- Selinexor is a novel oral SINE compound currently being evaluated in solid and hematological cancers

Gynecological malignancies are a rational indication for selinexor

- Elevated XPO1 expression is associated with invasive ovarian cancers (OVCA)
- XPO1 is the sole transporter for the TSPs p53, BRCA1 and pRB
- p53 and BRCA1 are very frequently mutated in OVCA
- p53 and pRB degradation are induced by the E7 protein of HPV, for which infection is associated with 90% of cervical cancers

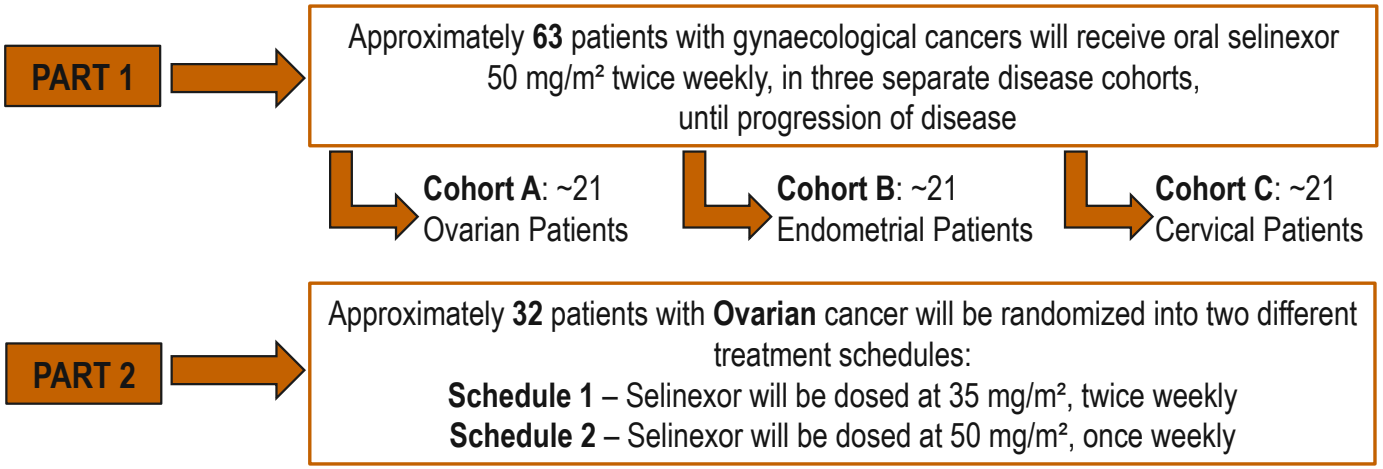


Selinexor is active in xenograft models of ovarian cancer and activity is enhanced through combination with standard-of-care. (A) Images of ovarian SKOV3-luc tumors over time in mice treated with vehicle (Control), selinexor (KPT), topotecan (TOPO) or a combination of KPT + TOPO. **(B)** Tumor burden and **(C)** number of tumor nodules in mice from **(A)**. **(D)** Tumor volume and **(E)** survival of cisplatin sensitive and resistant patient-derived ovarian tumor xenografts treated with vehicle or selinexor (KPT-330). **(F)** Mice with ovarian cancer CP70-luc xenografts were treated with vehicle, selinexor (15 mg/kg 2X/wk QOD), cisplatin or selinexor + cisplatin.

(A)-(C) from Martignetti et al. ESMO 2014
(D)-(F) from Miyake et al. Clin Cancer Res. Apr 15, 2015

Phase II Study Design – NCT02025985

- **S**elinexor **I**n **gynecological N**eoplasms (**SIGN**), is an open label two stage Phase II study in 3 separate gynecological disease cohorts
  - **Cohort A**: Ovarian (Part 1 & Part 2); **Cohort B:** Endometrial (Part 1)**; Cohort C:** Cervical (Part 1)
- **Primary Objective**: Determine efficacy of selinexor in patients with advanced or metastatic gynecological cancers by assessing disease control rate
- **Primary Efficacy Point**: Analysis of the disease control rate for patients with complete response, partial response or stable disease for at least 12 weeks
- **Treatment Scheme**: Patients are dosed twice weekly (8 doses) or once weekly (4 doses) per 28 day cycle
- **Main Inclusion Criteria**:
  - Patients ≥18 years old, ECOG performance status 0-1, Life expectancy ≥12 weeks
  - Ovarian patients – Platinum refractory/resistant patients, who have received ≥1 prior chemotherapy line
  - Endometrial/Cervical patients – Must have received ≥1 line of chemotherapy for relapsed or advanced disease



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SIGN – Patient Characteristics

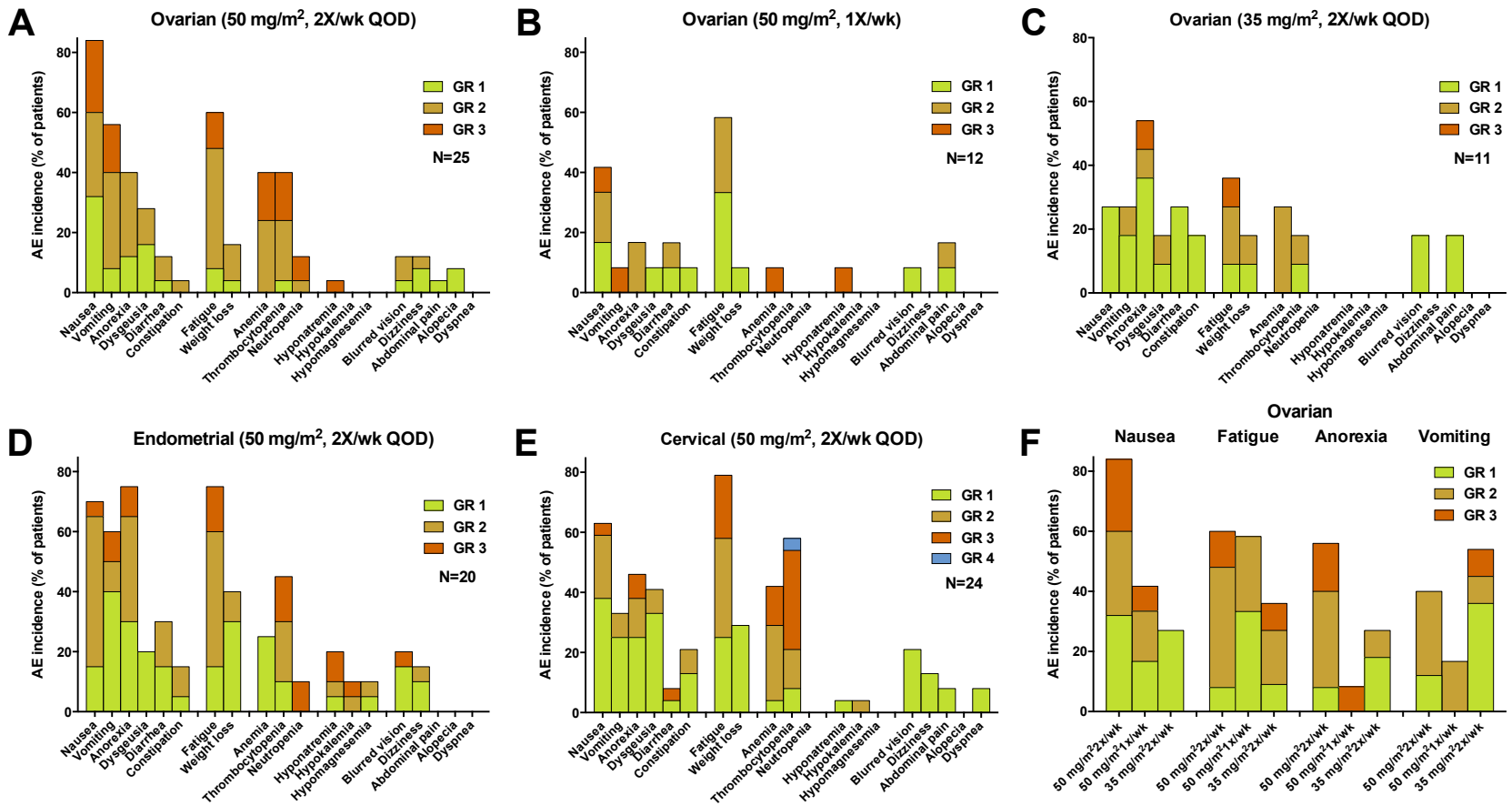
Ovarian	N
Patients Enrolled (Evaluable* for Efficacy)	48 (34)
Median Age (Range)	61 (31 – 78)
ECOG Status (0 : 1)	22 : 26
Median Prior Regimens (Range)	5 (1 – 11)

Endometrial	N
Patients Enrolled (Evaluable* for Efficacy)	20 (15)
Median Age (Range)	68 (53 – 75)
ECOG Status (0 : 1)	9 : 11
Median Prior Regimens (Range)	2 (1 – 5)

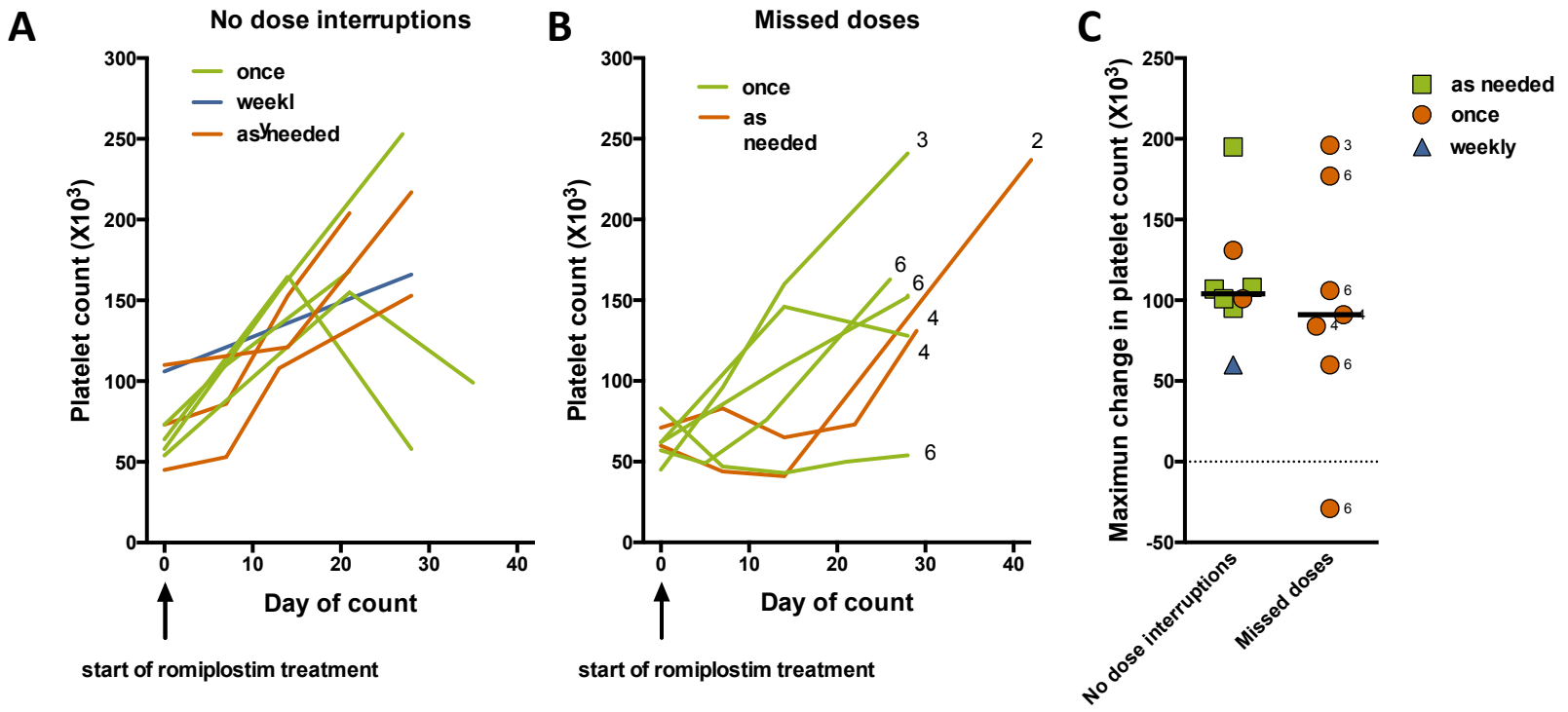
Cervical	N
Squamous Subtype (Evaluable* for Efficacy)	24 (21)
Median Age (Range)	54 (32 –75)
ECOG Status (0 : 1)	15 : 9
Median Prior Regimens (Range)	3 (1 – 8)

* All patients enrolled on or before 15-February-2015 (12 weeks) are evaluable for efficacy

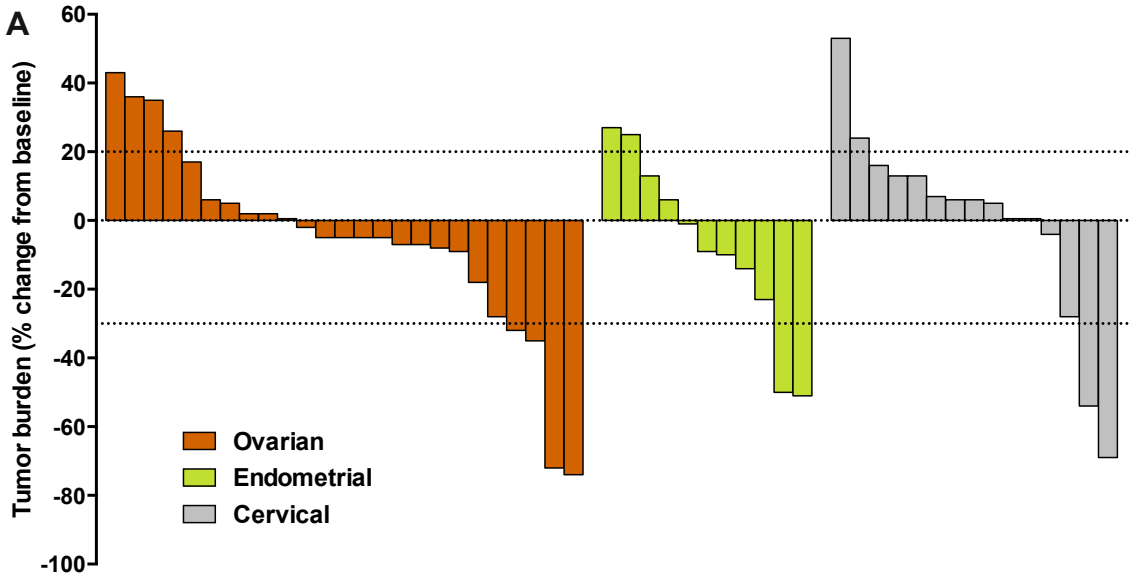
Selinexor – Related Adverse Events



Selinexor-related adverse event (AE) profiles by gynecological cancer type. Stack plots of % incidence are shown for AEs observed in at least 5% of patients. Across all cancer types, the majority of related AEs were grade 1/2 and reversible, with nausea, vomiting, fatigue, anorexia and thrombocytopenia being the most common. **(A)** Ovarian - 50 mg/m^2 selinexor twice weekly. **(B)** Ovarian - 50 mg/m^2 selinexor once weekly. **(C)** Ovarian - 35 mg/m^2 selinexor twice weekly. **(D)** Endometrial - 50 mg/m^2 selinexor twice weekly. **(E)** Cervical - 50 mg/m^2 selinexor twice weekly. **(F)** Comparison of major AE incidence for ovarian dosing schedules. 50 mg/m^2 selinexor twice weekly had similar AE profiles across gynecological cancer types and as compared to solid tumor patient AE profiles observed in Phase 1 (NCT01607905). Selinexor at 35 mg/m^2 twice weekly or 50 mg/m^2 once weekly had substantially reduced AE incidence, which may be due to a combination of lower dose or frequency and improved supportive care.

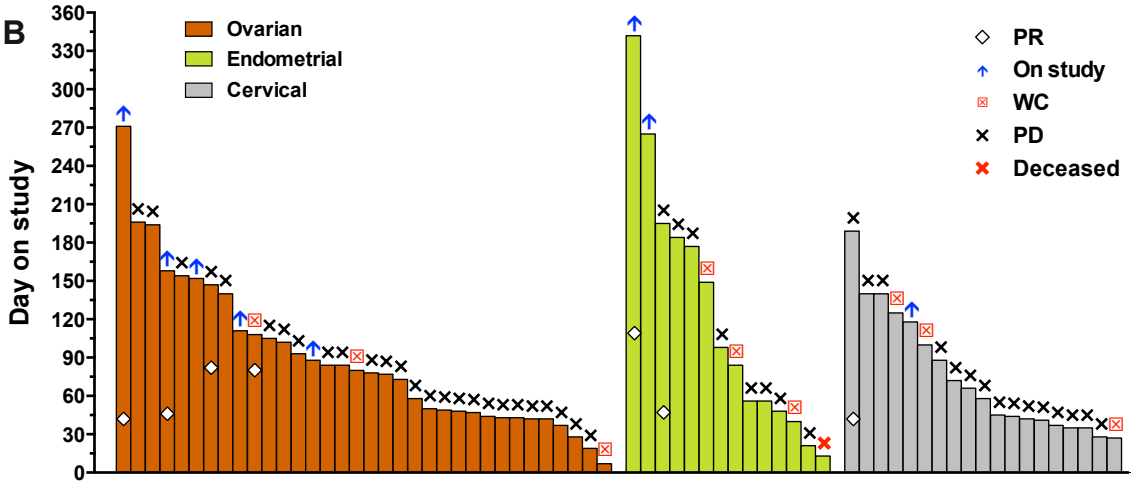


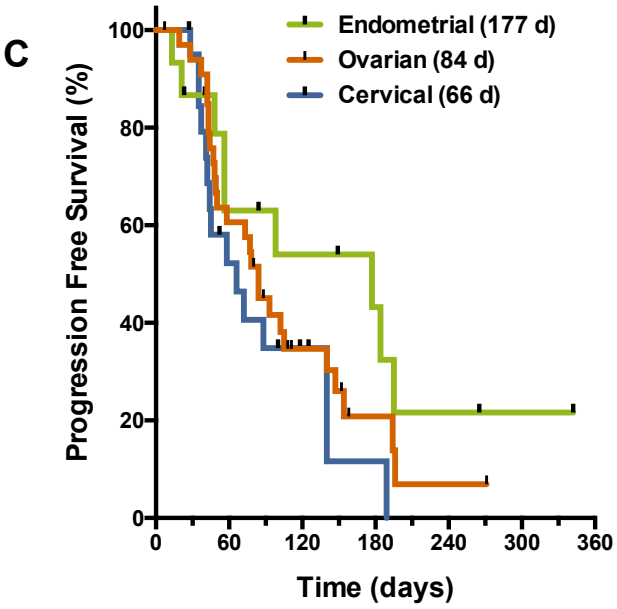
Romiplostim is effective for treatment of selinexor-induced thrombocytopenia. Eight ovarian and seven cervical cancer patients that developed thrombocytopenia were treated with the TPO agonist romiplostim once, weekly or as needed, with or without selinexor dose interruptions. **(A)** No selinexor dose interruptions (8 doses administered over one month). **(B)** Dose interruptions (2-6 missed doses out of 8). **(C)** Maximal change in platelet count within ~one month of of starting romiplostim treatment. Romiplostim was effective at stimulating increased platelet count. A single dose of romiplostim (250 µg) with uninterrupted selinexor dosing appeared as effective as repeated romiplostim treatment with or without dose interruptions.



Selinexor efficacy (RECIST v1.1) by gynecological cancer type as of 10-May-2015.

(A) Target Lesion Waterfall Plot: Patients with baseline and post treatment scans are shown with the greatest reduction in target lesion size from baseline. The upper and lower dotted lines at +20% and -30% mark the start boundary of progressive disease and partial response
(B) Duration on Study: Enrolled patients are shown with time on study (in days), and reasons for going off study. **(C)** Median PFS were 84 days for ovarian, 177 days for endometrial cancers, and 66 days for cervical cancer.





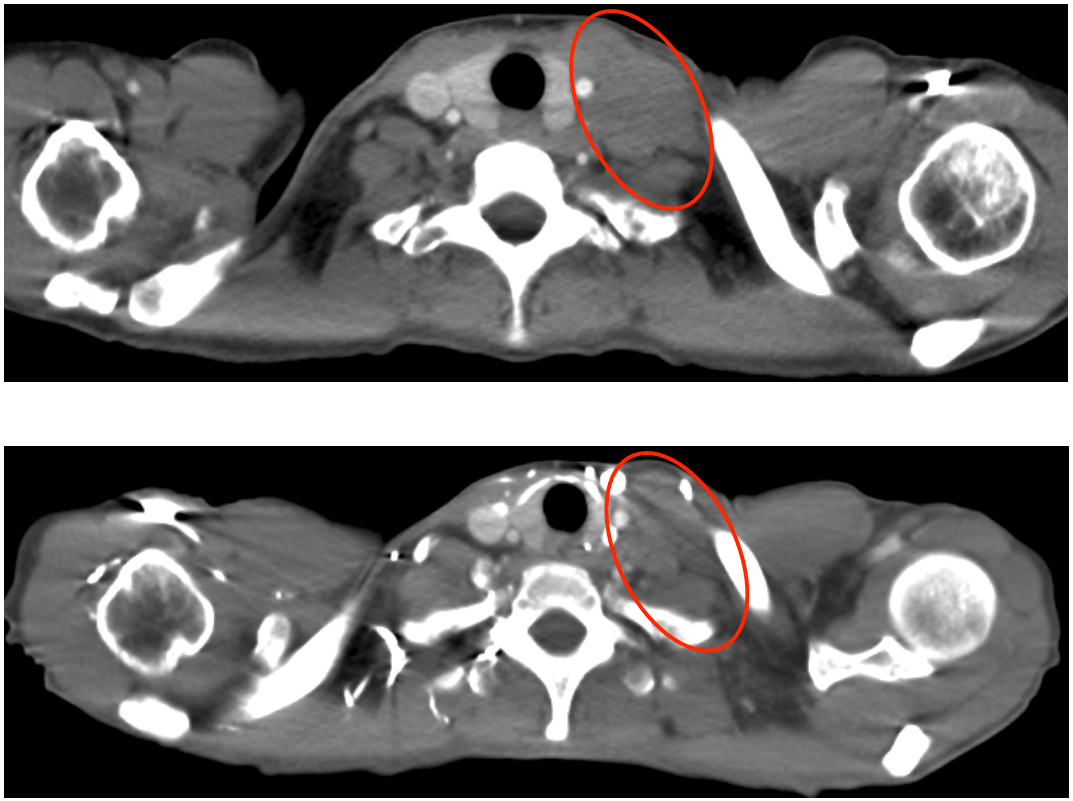
Overall Response Rates and Circulating Tumor Cells (CTC)

Cancer type	Dose	N	DCR	PR	SD ≥12 Weeks	PD
Ovarian	**All**	**33**	**18 (55%)**	**4 (12%)**	**14 (42%)**	**15 (46%)**
	50 mg/m^2 BIW	24	12 (50%)	3 (13%)	9 (37%)	12 (50%)
	50 mg/m^2 QW	5	3 (60%)	1 (20%)	2 (40%)	2 (40%)
	35 mg/m^2 BIW	4	3 (75%)	--	3 (75%)	1 (25%)
Endometrial	50 mg/m^2 BIW	**12**	**8 (67%)**	**2 (17%)**	**6 (50%)**	**4 (33%)**
Cervical	50 mg/m^2 BIW	**18**	**7 (39%)**	**1 (6%)**	**6 (33%)**	**11 (61%)**

Responses were adjudicated according to the *Response Evaluation Criteria in Solid Tumors (RECIST v1.1)* based on interim unaudited data
DCR=Disease Control Rate (PR+SD≥12), PR=Partial Response, SD≥12=Stable Disease for at least 12 weeks, PD=Progressive Disease

Circulating Tumor Cells (CTCs) as a predictive marker for tumor response. CTCs were isolated from patient whole blood using the Janssen CellSearch® method. Patient CTC counts were determined at baseline on Cycle 1 Day 1 and again post selinexor treatment. Patients with no CTCs appear to respond better to selinexor treatment, with only 8% progressive disease and median days on study of 118, as compared to patients with detectable CTCs with 70% progressive disease with median days on study of 47 (+ indicates patient still on selinexor treatment)

Patient ID	Disease Type	Cycles CTCs Collected	CTC Counts	Best Response	Days on Study
301-014	Endometrial	C1/C2	0/0	PR	342+
401-009	Ovarian	C1/C2	0/0	PR	147
303-020	Ovarian	C1	0	PR	108
401-005	Ovarian	C1/C2	0/0	SD	196
401-001	Ovarian	C1/C2	0/0	SD	194
303-021	Endometrial	C1	0	SD	177
401-017	Ovarian	C1	0	SD	140
401-065	Cervical	C2	0	SD	118+
401-066	Ovarian	C2	0	SD	111
401-006	Ovarian	C1/C3	0/0	SD	105
401-016	Ovarian	C1/C2	NA/0	SD	93
401-007	Ovarian	C1/C2	0/0	SD	80
401-018	Ovarian	C1/C2	NA/0	PD	42
401-071	Ovarian	C1/C3	0/2	SD	102+
401-067	Ovarian	C1/C2	11/17	SD	102
401-002	Ovarian	C1/C2	12/119	SD	78
401-008	Ovarian	C1	4	PD	50
303-015	Endometrial	C1/C2	NA/2	PD	48
401-013	Ovarian	C1/C2	3/0	PD	47
401-003	Ovarian	C1/C3	31/87	PD	44
401-012	Ovarian	C1	3	PD	43
401-069	Cervical	C1/C2	2/2	PD	42
401-013	Ovarian	C1/C2	3/0	PD	40



CT scans of patient 401-044. 37 year old female diagnosed with stage Ib cervical squamous cancer in March 2012. Selinexor was preceded by separate regimens of taxol-carboplatin+ISA vaccination, radiation, and surgery. Selinexor monotherapy (50 mg/m^2) began in September 2014, leading to a partial response in Cycle 4 with a 69% reduction in tumor burden. This patient remained on study 189 days before progressing.

Conclusions

- Selinexor showed broad anti-tumor activity across all three heavily pretreated gynecological cancer populations.
- Selinexor induced meaningful anti-cancer activity in patients with ovarian and endometrial cancers with disease control rates of 55% and 62% respectively and several patients remaining on study for 6-11 months.
- Side effects of selinexor were predominantly nausea, anorexia, fatigue and thrombocytopenia, typically Grade 1/2.
- Most attenuate over time and/or are responsive to supportive care (including romiplostim for low platelets).
- Patients with platin-resistant/refractory ovarian cancer had increased nausea and other gastrointestinal AEs.
- Reduction of dose or frequency of dosing substantially reduced these side effects, with preliminary evidence of consistent anti-tumor activity in ovarian, endometrial, & cervical cancers.
- These data support the ongoing and further development of selinexor for the treatment of gynecological neoplasms, both alone and in combination with other anti-cancer therapies.