Results of a Phase II Trial of Selinexor, in Patients with Gynaecological Cancers

Ignace Vergote[1], Bente Lund[2], Hanne Havsteen[3], Zaza Ujmajuridze[4], Els Van Nieuwenhuysen[1], Charlotte Haslund[2], Trine Juhler-Nøttrup[4], Patrick Neven[1], Morten Mau-Sørensen[4], Patrick Berteloot[1], Anne Kranich[6], Tami Rashal[5], Julie Meade[5], Yosef Landesman[5], Greg Wright[5], Marsha Crochiere[5], Jean-Richard Saint-Martin[5], Sharon Shacham[5], Michael Kauffman[5], Mansoor Raza Mirza[5]

(1) Katholieke Universiteit Leuven, Leuven, Belgium, European Union (2) Aalborg University Hospital, Aalborg, Denmark
(3) Herlev University Hospital, Herlev, Denmark (4) Rigshospitalet, University of Copenhagen, Copenhagen, Denmark
(5) Karyopharm Therapeutics Newton, MA, USA (6) GSO Hamburg; Germany

Presenter Disclosures

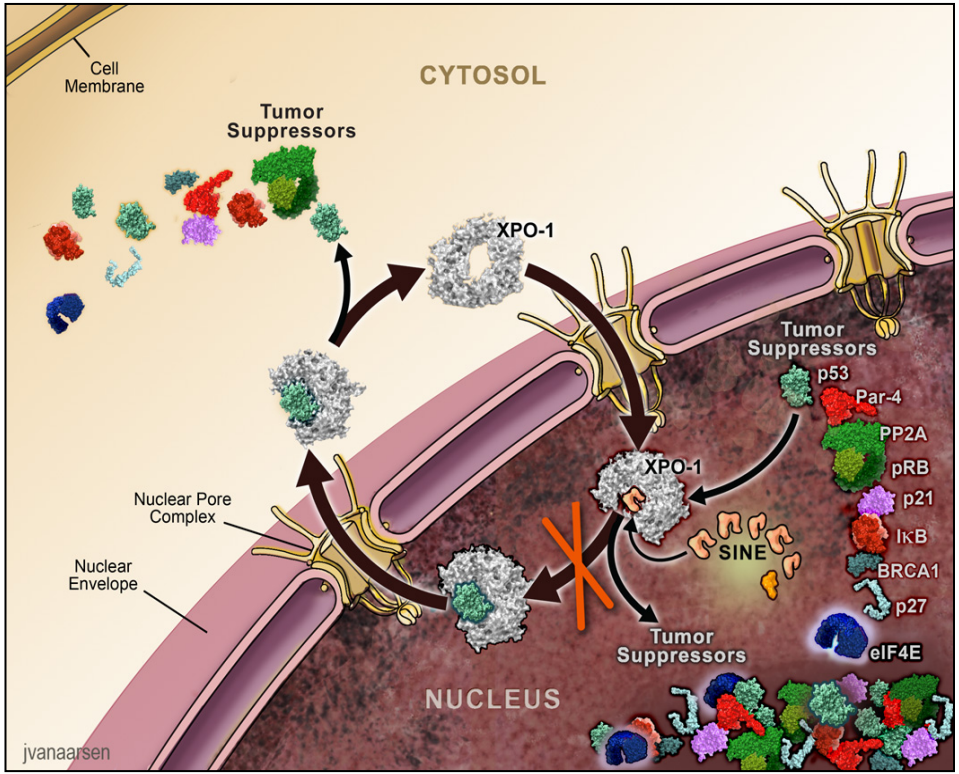
- Employment or Leadership Position: No
- Consultant/Advisory Role: No
- Stock Ownership: No
- Honoraria: No
- Research Funding: No
- Expert Testimony: No
- Other Remuneration: No

Acknowledgments

- We would like to thank:
  - Patients and their families
  - Investigators, co-investigators and the study teams at each participating center:
    - Katholieke Universiteit Leuven, Leuven, Belgium, European Union
    - Aalborg University Hospital, Aalborg, Denmark
    - Herlev University Hospital, Herlev, Denmark
    - Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

This study was sponsored by Karyopharm Therapeutics

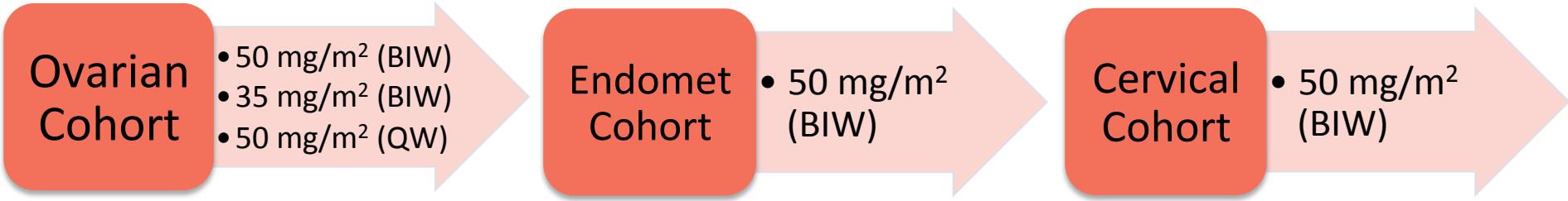
Selinexor – Mechanism of Action



- Exportin 1 (XPO1) is the only nuclear exporter for the major tumor suppressor proteins (TSPs) including p53, p73, BRCA1 and pRB
- Selinexor, a first-in-class inhibitor of XPO1, induces nuclear retention, accumulation and activation of TSPs
- Reactivation of TSPs leads to tumor apoptosis
- Selinexor has shown preclinical activity in-vivo as well as clinical activity in a Phase I study in ovarian patients *(Razak et. al, JCO 2016)*

Selinexor **I**n **G**ynecological **N**eoplasms (**SIGN**) – Phase II Study Design

- **Primary Endpoint**:
  - Disease control rate (DCR) *complete or partial response, or stable disease for at least 12 weeks (SD≥12)*
    - Looking for ≥ 8 patients in the first 21 patients enrolled per cohort to reach DCR, which will warrant Phase III exploration
- **Main Inclusion Criteria**:
  - Patients ≥18 years old, ECOG performance status 0-1, Life expectancy ≥12 weeks
  - Ovarian patients – Platinum refractory/resistant patients, ≥1 prior chemotherapy line
  - Endometrial/Cervical patients – ≥1 line of chemotherapy for relapsed or advanced disease
- **Treatment Scheme**: Twice Weekly (BIW) or Once Weekly Dosing (QW) / 28 day cycle



SIGN – Patient Characteristics

Characteristic	Ovarian (N=66)	Endometrial (N=23)	Cervical (N=25)
Patients Enrolled	66	23	25
Median Age (Range)	62 years (31 – 80)	67 years (53 – 75)	53 years (32 – 75)
Median Prior Treatment Regimens (Range)	6 (1 – 11)	2 (1 – 5)	3 (1 – 8)
Prior Treatments N (%)			
Platinums	66 (100%)	22 (96%)	25 (100%)
Taxanes	66 (100%)	23 (100%)	23 (92%)
Anthracyclines	55 (83%)	19 (83%)	2 (8%)

SIGN – Treatment Related Adverse Events ≥10 %

AE Term	Ovarian/Endometrial/Cervical 50 mg/m^2 Twice Weekly			Ovarian – 35 mg/m^2 Twice Weekly			Ovarian – 50 mg/m^2 Once Weekly		
	N=73			N=21			N=20		
Gastrointestinal	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 2**	**Grade 3**	**Grade 4**
Nausea	25 (34%)	9 (12%)	--	8 (38%)	--	--	10 (50%)	1 (5%)	--
Vomiting	16 (22%)	6 (8%)	--	3 (14%)	1 (5%)	--	6 (30%)	1 (5%)	--
Anorexia	19 (26%)	4 (6%)	--	6 (29%)	1 (5%)	--	6 (30%)	--	--
Dysgeusia	8 (11%)	--	--	--	--	--	1 (5%)	--	--
Diarrhea	7 (10%)	1 (1%)	--	2 (10%)	--	--	2 (10%)	--	--
Dehydration	--	2 (3%)	--	3 (14%)	--	--	--	--	--
Constitutional									
Fatigue	31 (43%)	11 (15%)	--	7 (33%)	5 (24%)	--	6 (30%)	1 (5%)	--
Weight Loss	15 (21%)	--	--	5 (24%)	1 (5%)	--	--	1 (5%)	--
Blood									
Thrombocytopenia	13 (18%)	17 (23%)	1 (1%)	2 (10%)	1 (5%)	--	1 (5%)	--	--
Anemia	21 (29%)	8 (11%)	--	6 (29%)	2 (10%)	--	3 (15%)	1 (5%)	--
Other									
Hyponatremia	--	6 (8%)	1 (1%)	--	1 (5%)	--	--	2 (10%)	--

- Grade 3-4 toxicities were reduced in the once weekly dosing (50 mg/m^2) regimen as compared to twice weekly dosing

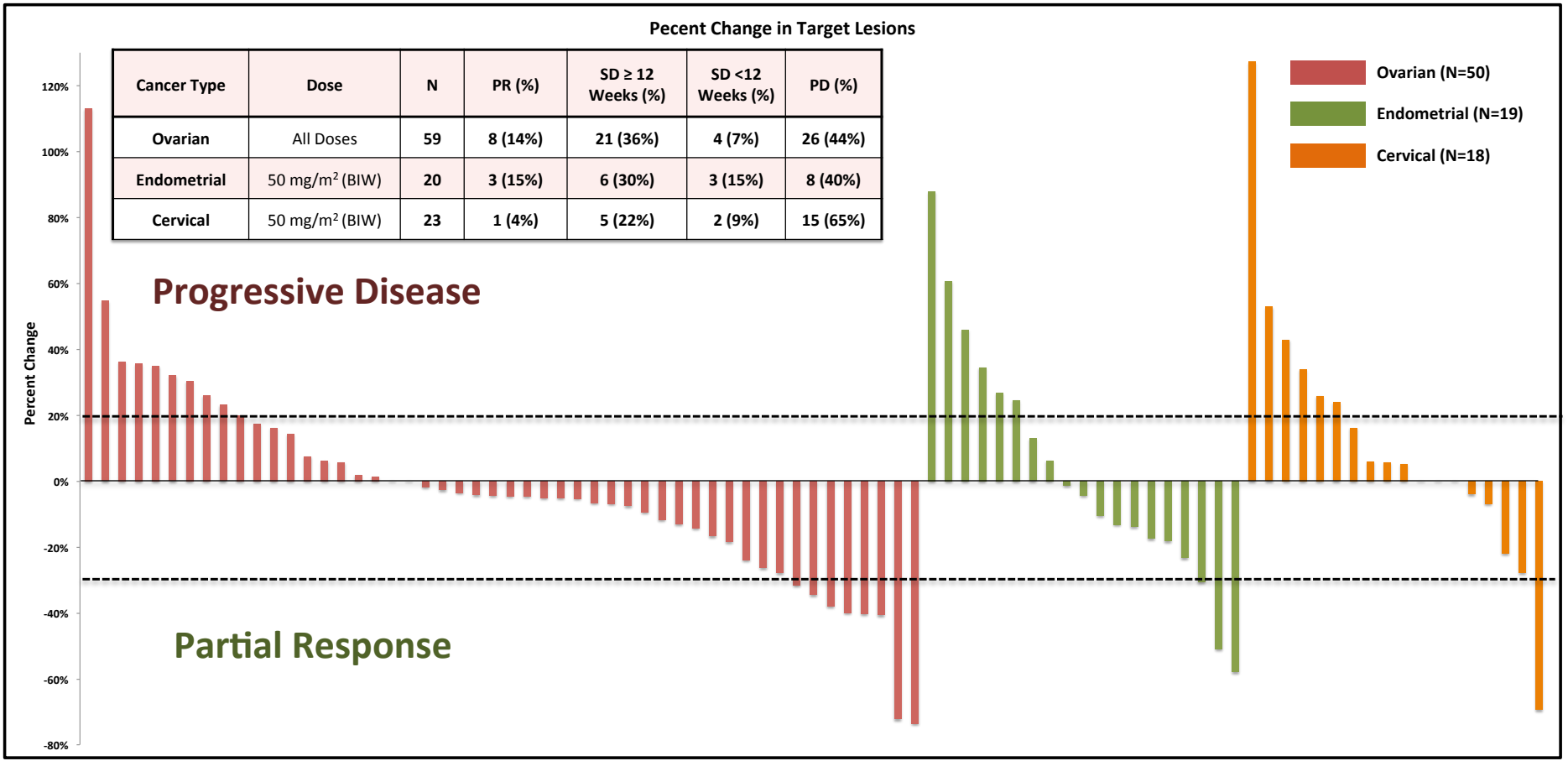
Primary Endpoint – Disease Control Rate *(CR + PR + SD≥12 Weeks)*

Cancer Type	Dose	N	DCR (%)	PR (%)
Ovarian	35 mg/m^2 (BIW)	18	11 (61%)	2 (11%)
	50 mg/m^2 (BIW)	22	10 (45%)	3 (14%)
	50 mg/m^2 (QW)	19	8 (42%)	3 (16%)
	All Doses	**59**	**29 (49%)**	**8 (14%)**
Endometrial	50 mg/m^2 (BIW)	**20**	**9 (45%)**	**3 (15%)**
Cervical	50 mg/m^2 (BIW)	**23**	**6 (26%)**	**1 (4%)**

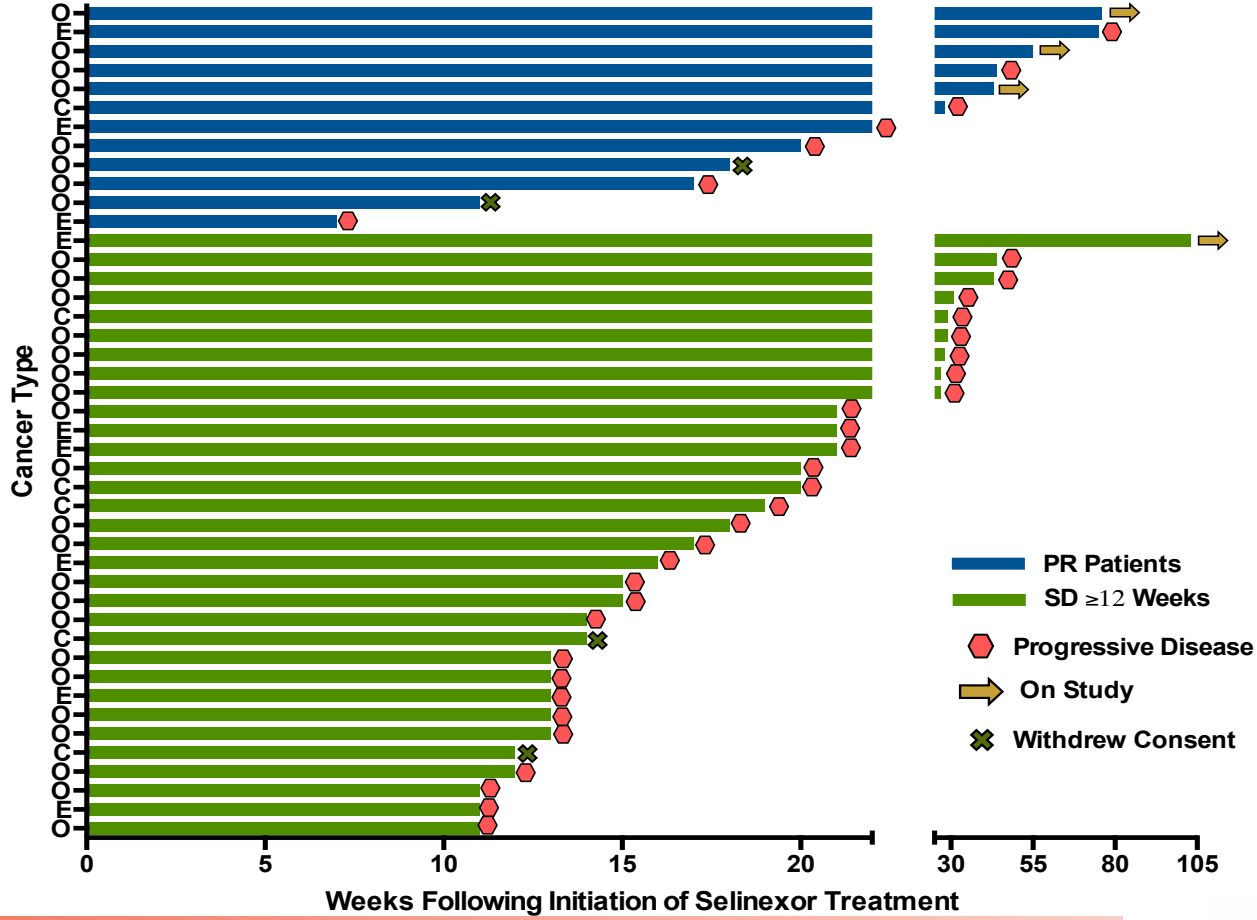
Responses were adjudicated according to the *Response Evaluation Criteria in Solid Tumors (RECIST v1.1)* based on interim unaudited data – DCR=Disease Control Rate (CR+PR+SD≥12)

SIGN – Tumor Response

Cancer Type	Dose	N	PR (%)	SD ≥ 12 Weeks (%)	SD <12 Weeks (%)	PD (%)
Ovarian	All Doses	59	8 (14%)	21 (36%)	4 (7%)	26 (44%)
Endometrial	50 mg/m^2 (BIW)	20	3 (15%)	6 (30%)	3 (15%)	8 (40%)
Cervical	50 mg/m^2 (BIW)	23	1 (4%)	5 (22%)	2 (9%)	15 (65%)



DCR Patients Response & Time on Study

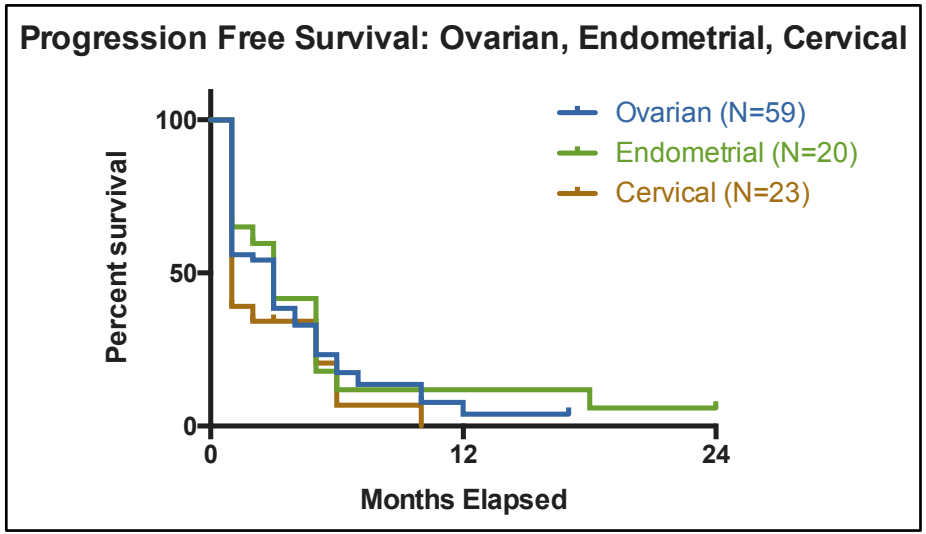


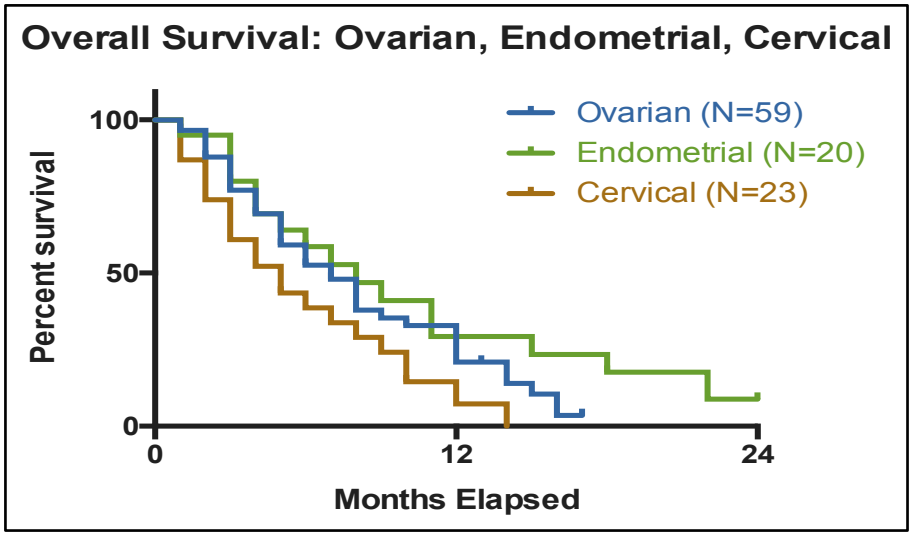
Disease Control Rate Patients – Time on Study

- For patients who met DCR (N=44), the median time on study was 20 weeks
- Four patients continue on treatment >40 weeks

PR=partial response, SD≥12 Weeks=stable disease ≥12 weeks, PD=progressive disease, WC=withdrew consent

SIGN – Progression Free Survival (PFS), Overall Survival (OS)





Median Progression Free Survival and Median Overall Survival

- Median PFS overall for the ovarian patients was **3** months, endometrial **3** months, and cervical **1** month
- Median OS overall for the ovarian patients was **7** months, endometrial **8** months, and cervical **5** months

SIGN – Conclusions

- Single agent selinexor has interesting anti-tumor activity in heavily-pretreated ovarian and endometrial cancer patients, with disease control for more than 12 weeks of 49% and 45% in the OC and EC cohort, respectively

- The main toxicities of Selinexor are nausea, anorexia, fatigue, and vomiting. These side effects are manageable with supportive care, especially in once weekly dosing (50 mg/m^2)
  - Major organ toxicities are rarely observed
  - Clinically significant cumulative toxicities are uncommon

- Fifteen patients (13%) remained on single agent selinexor > 6 months, including 4 patients > 12 months

- Combination studies are ongoing & Phase III trials in OC & EC are being planned