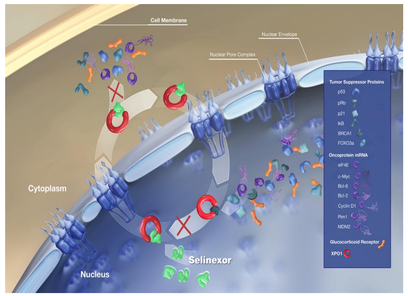
SIENDO/ENGOT-EN5: A randomized phase 3 trial of maintenance with selinexor/placebo after combination chemotherapy in patients with advanced or recurrent endometrial cancer.

TPS6105

Ignace Vergote[1], Erika Paige Hamilton[2], Ignacio Romero[3], Eva M. Guerra[4], Joseph Buscema[5], Annouschka Laenen[6], Tamar Perri[7], Purificación Estévez-García[8], Cesar Gomez Raposo[9], Tally Levy[10], Giorgio Valabrega[11], Jeronimo Martinez Garcia[12], Giorgia Mangili[13], Vicky Makker[14], Dayana Michel[15], Hongwei Wang[15], Mansoor Raza Mirza[16]

[1]BGOG and University Hospitals Leuven, Leuven Cancer Institute, Leuven, Belgium; [2]Sarah Cannon Research Institute and Tennessee Oncology, Nashville, TN; [3]Instituto Valenciano de Oncología, Valencia, Spain; [4]Hospital Universitario Ramon y Cajal, Madrid, Spain; [5]GBMC Physicians Pavilion, Towson, MD; [6]BGOG and Leuven Cancer Institute, Leuven, Belgium; [7]Sheba Medical Center, Ramat Gan, Israel; [8]Consorcio Hospital General Universitario de Valencia, Valencia, Spain; [9]Hospital Infanta Sofia, Madrid, Spain; [10]Wolfson Medical Center, Holon, Israel; [11]Department of Oncology, University of Torino, Italy. Candiolo Cancer Institute, FPO - IRCCS - Str. Prov.le 142, km. 3,95, 10060 Candiolo (TO), Italy, Torino, Italy; [12]Hospital Clinico Universitario Virgen de la Arrixaca, Murcia, Spain; [13]Department of Obstetrics and Gynecology, IRCCS San Raffaele Hospital, Milan, Italy; [14]Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY; [15]Karyopharm Therapeutics Inc., Newton, MA; [16]The Finsen Centre 5073, Copenhagen, Denmark

Selinexor: First-in-Class, Oral Selective Inhibitor of Nuclear Export (SINE)



Exportin 1 (XPO1) is the major nuclear export protein for:[1]

- Tumor suppressor proteins (TSPs, e.g., p53, IkB, and FOXO)
- eIF4E-bound oncoprotein mRNAs (e.g., c-Myc, Bcl-xL, cyclins)

Inhibition of XPO1 impacts tumor cells via 2 core mechanisms:[1]

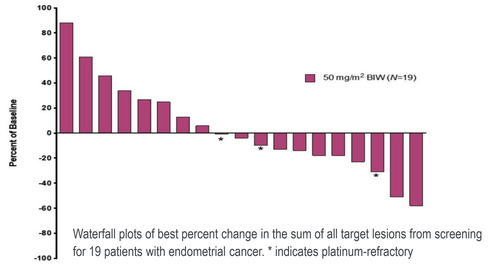
- Increases nuclear levels and activation of tumor suppressor proteins (p53, etc)
- Traps oncoprotein mRNA in the nucleus leading to reduced oncoprotein levels (c-Myc, etc.)

Selinexor is an oral selective **XPO1 inhibitor –** Preclinical data supports that selinexor:[2]

- Reactivates multiple TSPs by preventing nuclear export
- Inhibits oncoprotein translation

Background: Selinexor Activity in Gynecological Malignancies

- Nuclear XPO1 is overexpressed in ovarian cancers with aggressive behavior and is correlated with poor outcome and platinum resistance.[3]
- Selinexor showed anti-tumor activity in various ovarian cancer cell lines, increased nuclear localization of FOXO1 and facilitated the anti-tumor effect of cisplatin.[4]
- Selinexor, alone or in combination with platinum, reduced tumor growth in platinum-resistant PDX mice and in ovarian-cancer patients and was well tolerated .[3]
- Ovarian and endometrial cancer (EC) are similar in many aspects.[5] In a phase 2 study[6], selinexor 50 mg/m2(~80 mg) twice weekly (BIW) demonstrated a disease control rate of 35% (median duration 6.3 months) with 2 confirmed partial responses among 23 patients with heavily pretreated EC. Patients with disease control had markedly improved overall survival (OS) compared to patients without disease control. Thus median OS was 20.4 months for patients with disease control versus 3.9 months in patients without disease control. Nearly all patients had been previously treated with a platinum-based chemotherapy (52% refractory) and taxanes.
- We are conducting this study to evaluate the efficacy of selinexor compared with placebo as maintenance therapy in patients with advanced or recurrent EC as an effort to improve PFS after platinum-based chemotherapy.

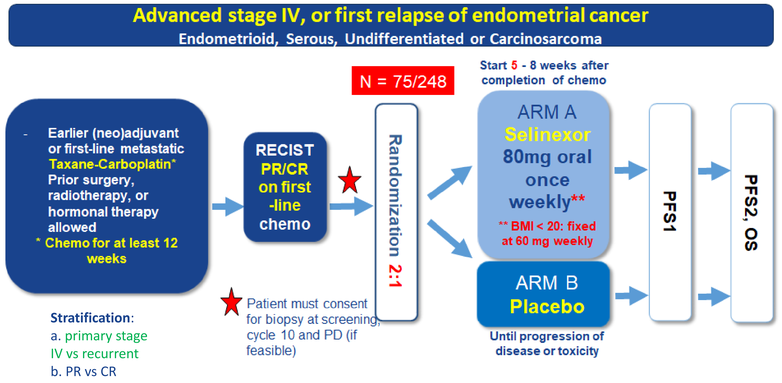


Waterfall plots of best percent change in the sum of all target lesions from screening for 19 patients with endometrial cancer. * indicates platinum-refractory

SIENDO/ENGOT-EN5 Study Design

This is a randomized, multi-center, double-blinded, placebo-controlled phase 3 study aimed at evaluating and comparing the efficacy of selinexor versus placebo, assessed by the investigator, as maintenance therapy for advanced or recurrent EC.

A total of 248 patients will be randomized in a 2:1 ratio (2 selinexor:1 placebo)



Hypothesis testing will be used for the primary efficacy endpoint and for selected secondary efficacy endpoints in order to evaluate the superiority of selinexor compared with placebo.

Key Inclusion/Exclusion Criteria

Key Inclusion Criteria

- Female patients ≥ 18 years with histologically confirmed EC of the endometroid, serous or undifferentiated type. Carcinosarcoma of the uterus is also allowed
- In PR or CR according to RECIST v1.1
- Completed a single line of at least 12 weeks of taxane-platinum combination therapy and achieved PR or CR according to RECIST V1.1:
  - For Primary Stage IV disease OR
  - At first relapse
- ECOG 0-1
- Adequate organ functions

Key Exclusion Criteria

- Has any sarcomas, small cell carcinoma with neuroendocrine differentiation, or clear cell carcinomas
- Previous treatment with an XPO1 inhibitor or with anti-PD-1 or anti-PD-L1 immunotherapy
- Known contraindications or uncontrolled hypersensitivity to selinexor
- Active brain metastases

SIENDO/ENGOT-EN5 Trial Endpoints

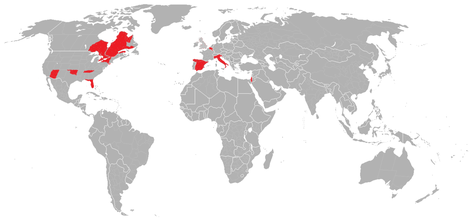
Primary

- **PFS as assessed by the investigator**

Secondary

- **PFS, as assessed by a blinded independent central review**
- **Disease-specific survival**
- **Overall survival**
- **Time to first subsequent therapy**
- **Quality of Life Questionnaire Secondary cont'd**
- **Disease-control rate among patients with PR as best response to prior chemotherapy (QLQ)-C30, EuroQol-5 Dimension 5 Level (EQ-5D-5L), and EORTC QLQ-EN24.**
- **The safety and tolerability of study drug**

Current Enrollment Sites



Target enrollment	N=248
Current enrollment	N=78
Locations	**USA:** New York, Oklahoma, Florida, Arizona, Tennessee **Canada:** Ontario, Quebec **Europe:** Belgium, Spain, Italy Israel

Results from phase II study (SIGN) showed that selinexor administered twice weekly (50 mg/m²= ~80 mg) to patients with heavily pretreated EC resulted in disease control rate of 35%. These data, as well as the unmet medical need to manage patients with advanced or recurrent EC support further development of selinexor treatment for EC.

The current clinical trial is enrolling patients with advanced or recurrent EC with a response (PR or CR) after at least 12 weeks of platinum-taxane combination therapy for primary stage IV or recurrent disease, for maintenance therapy with selinexor or placebo control.

References

1. Fung HY, Chook YM. Atomic basis of CRM1-cargo recognition, release and inhibition. Semin Cancer Biol. 2014;27:52–61.
2. Tai YT, Landesman Y, Acharya C, et al. CRM1 inhibition induces tumor cell cytotoxicity and impairs osteoclastogenesis in multiple myeloma: molecular mechanisms and therapeutic implications. Leukemia. 2014;28(1):155–165.
3. Chen Y, Camacho SC, Silvers TR, et al. Inhibition of the Nuclear Export Receptor XPO1 as a Therapeutic Target for Platinum-Resistant Ovarian Cancer. Clin Cancer Res. 2017;23(6):1552–1563.
4. Corno C, Stucchi S, De Cesare M, et al. FoxO-1 contributes to the efficacy of the combination of the XPO1 inhibitor selinexor and cisplatin in ovarian carcinoma preclinical models. Biochem Pharmacol. 2018;147:93–103.
5. Cramer DW, The epidemiology of endometrial and ovarian cancer. Hematol Oncol Clin North Am. 2012;26(1):1–12.
6. Vergote IB, Lund B, Peen U, et al. Phase 2 study of the Exportin 1 inhibitor selinexor in patients with recurrent gynecological malignancies. Gynecol Oncol. 2020;156(2):308–314

This study is supported by Karyopharm Therapeutics.