ANNUAL MEETING ON WOMENS' CANCER®

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SGO // PHOENIX, ARIZONA // MARCH 18 – 21, 2022

Prospective double-blind, randomized phase III ENGOT-EN5/GOG-3055/SIENDO study of oral selinexor/placebo as maintenance therapy after first-line chemotherapy for advanced or recurrent endometrial cancer

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This abstract was accepted and previously presented by

Ignace Vergote et al. at
ESMO Virtual Plenary, March 17, 2022, #350.

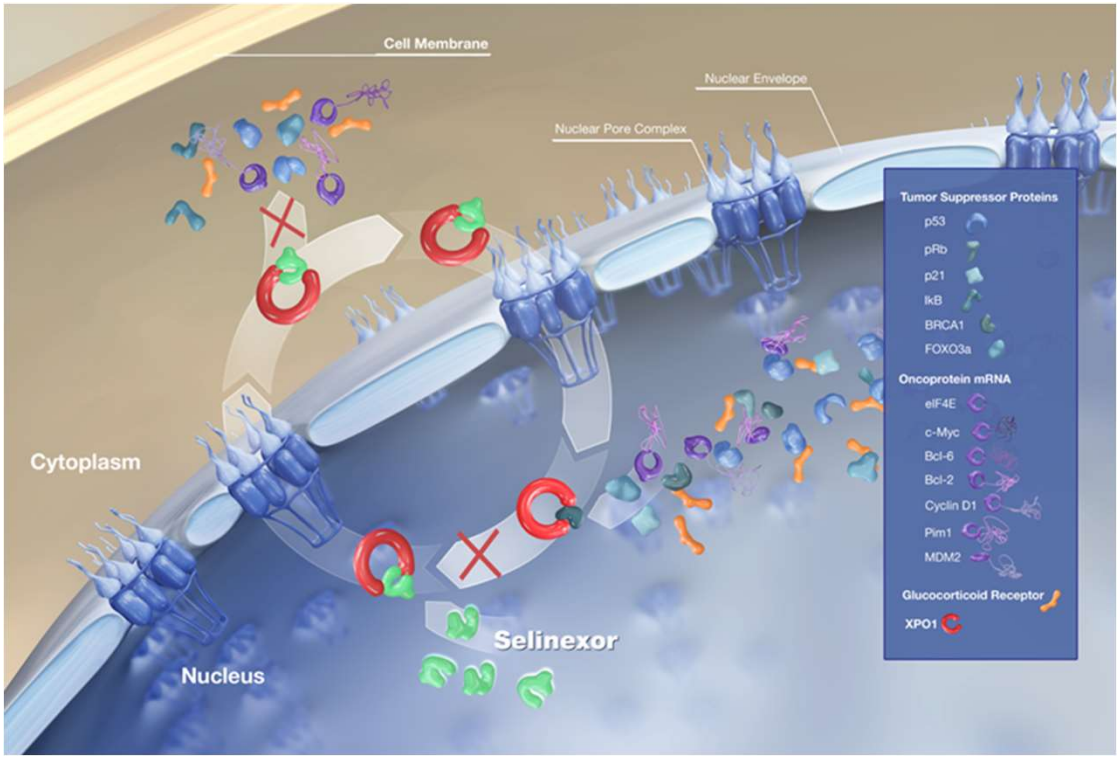
Financial Disclosures

- I have the following financial relationships with ACCME defined ineligible companies to report over the past 24 months:
  - Consulting for: Agenus, Aksebio, AstraZeneca, Bristol Myers Squibb (2021), Deciphera Pharmaceuticals, Eisai, Elevar Therapeutics, F. Hoffmann-La Roche Ltd, Genmab, GSK, Immunogen Inc., Jazzpharma, Karyopharm, Mersana, MSD, Novocure, Novartis, Oncoinvent AS, Seagen, Sotio a.s., Verastem Oncology, Zentalis
  - Contracted Research (via KULeuven): Oncoinvent AS (2019-2020)
  - Grant/Corporate Sponsored Research: Amgen, F. Hoffmann-La Roche
  - Accommodations, travel expenses: Amgen, MSD, Tesaro, AstraZeneca, Karyopharm, F. Hoffmann-La Roche

Unlabeled/Investigational Uses

- I will be discussing unlabeled or investigational uses of pharmaceutical products or medical devices.

Selinexor: XPO1 inhibition



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

- Tumor suppressor proteins (TSPs, e.g., p53, IkB, PTEN, and FOXO1)

Inhibition of XPO1 results in:[1]

- The increase in nuclear levels and activation of TSPs
- Reduction of oncoprotein levels

Selinexor is an oral selective XPO1 inhibitor

Preclinical data for selinexor:[2]

- Reactivates multiple TSPs, including p53 wild type, by preventing nuclear export

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.

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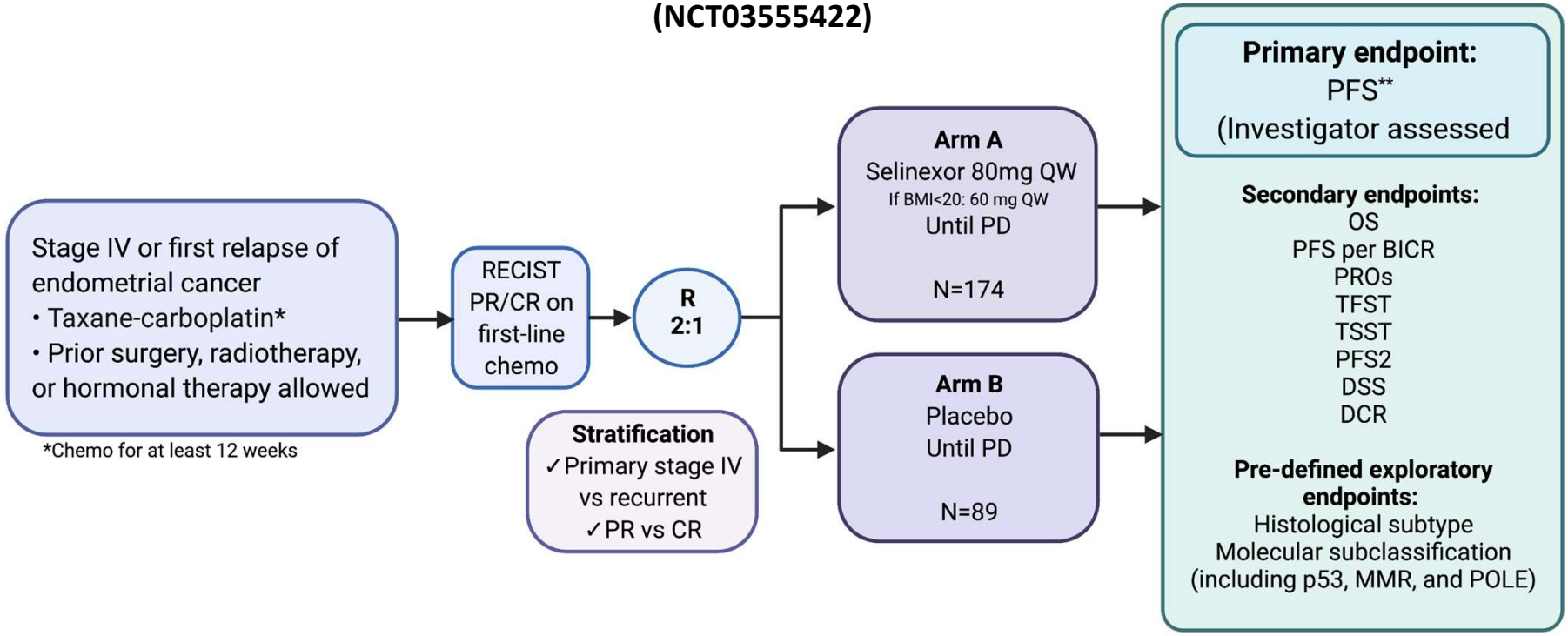
Trial Design

Stage IV or first relapse of endometrial cancer endometrioid, serous, undifferentiated, or carcinosarcoma (NCT03555422)



**140 PFS events needed to provide 80% power to detect a hazard ratio of 0.6 (median PFS 4.5 months for placebo and 7.5 months for selinexor) with a one-sided alpha of 0.025 and 2:1 randomization ratio favoring selinexor.

BMI, body mass index; DCR, disease control rate; DSS, disease-specific survival; QW, once weekly; CR, complete response; OS, overall survival; PFS, progression-free survival; PFS2, progression-free survival on subsequent therapy; PR, partial response; PROs, patient-reported outcomes ; R, randomized; TFST, time to first subsequent therapy; TSST, time to second subsequent treatment

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ENGOT-EN5/GOG-3055/SIENDO Patient Characteristics

CHARACTERISTIC	Selinexor N = 174	Placebo N = 89
Age, years median (range), n (%)	65.5 (40-81)	64.0 (33-81)
<70 years, n (%)	116 (66.7)	61 (68.5)
≥70 years, n (%)	58 (33.3)	28 (31.5)
ECOG performance status, n (%)		
0	99 (56.9)	54 (60.7)
1	71 (40.8)	35 (39.3)
2	1 (0.6)	0
Histology, n (%)		
Endometrioid	96 (55.2)	48 (53.9)
Serous	49 (28.2)	28 (31.5)
Undifferentiated	4 (2.3)	1 (1.1)
Carcinosarcoma	10 (5.7)	6 (6.7)
Endometrial Adenocarcinoma*	15 (8.6)	6 (6.7)
Number of Prior Antineoplastic Regimens, n (%)		
1	172 (98.9)	85 (95.5)
2/3	2 (1.1)	3 (3.4)/1 (1.1)
Disease at Time of Taxane-Platinum Combination Therapy -eCRF, n (%)		
Primary Stage IV Disease	78 (44.8)	43 (48.3)
Recurrent Disease	96 (55.2)	46 (51.7)
Disease Status After the Most Recent Chemotherapy -eCRF, n (%)		
CR	70 (40.2)	40 (44.9)
PR	104 (59.8)	49 (55.1)

*Not otherwise specified

CR, complete response; ECOG, Eastern Cooperative Oncology Group; eCRF, electronic case report form; PR, partial response

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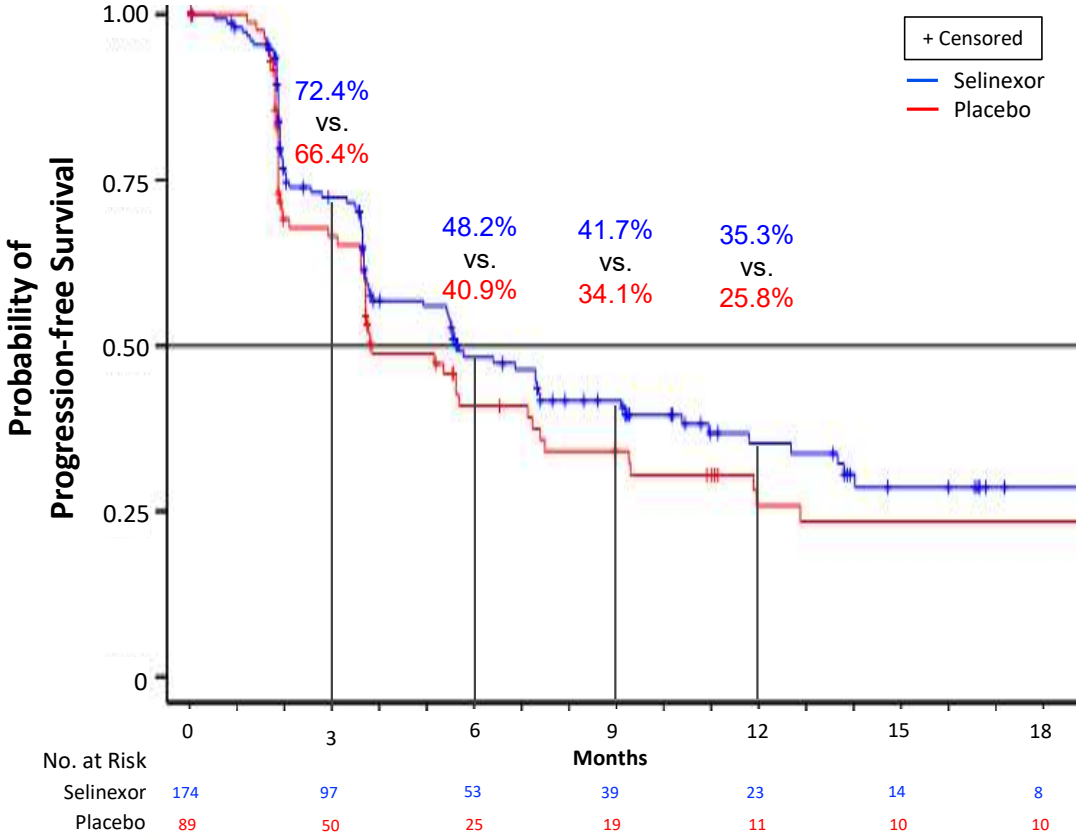
Primary Endpoint: PFS in ITT population

(based on audited stratification factors)*



Median PFS (Investigator assessed)

Selinexor (n=174): 5.7 mo (95% CI 3.81-9.20)

Placebo (n=89): 3.8 mo (95% CI 3.68-7.39)

HR* = 0.705 (95% CI 0.499-0.996)

One-sided P value = 0.024

* In 7 patients (2.7% of 263), the stratification factor of CR/PR was incorrect and was corrected by the Investigators prior to database lock and unblinding.

The statistical analysis was validated by the independent ENGOT statistician and approved by the IDMC.

HR for ITT without correction of the stratification factors was 0.76 (95% CI: 0.543, 1.076).

median follow-up: 10.2 months (95% CI 8.97, 13.57)

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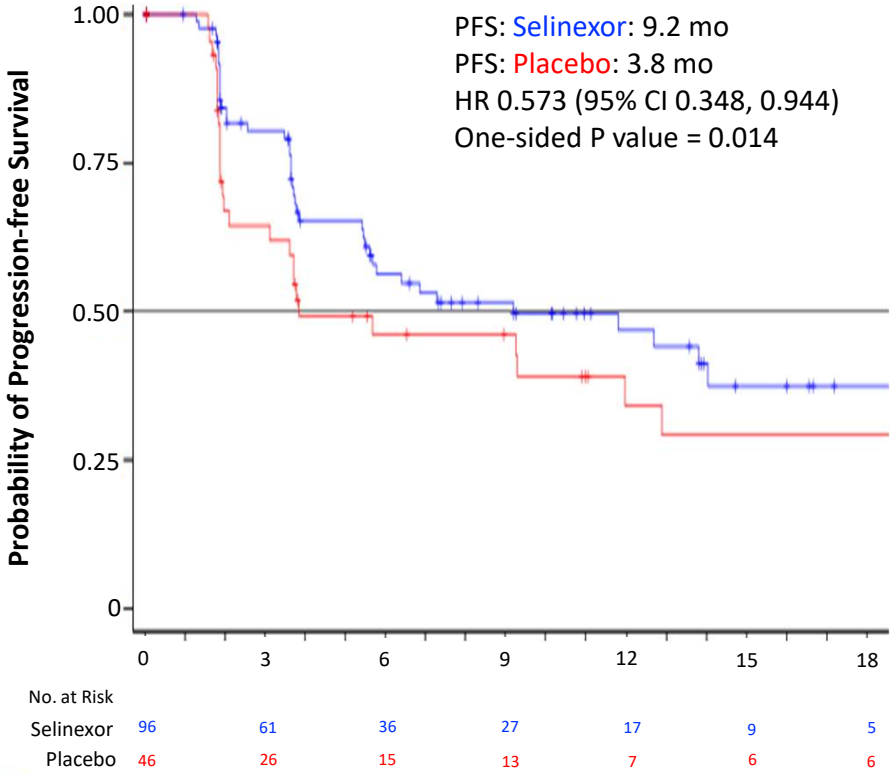
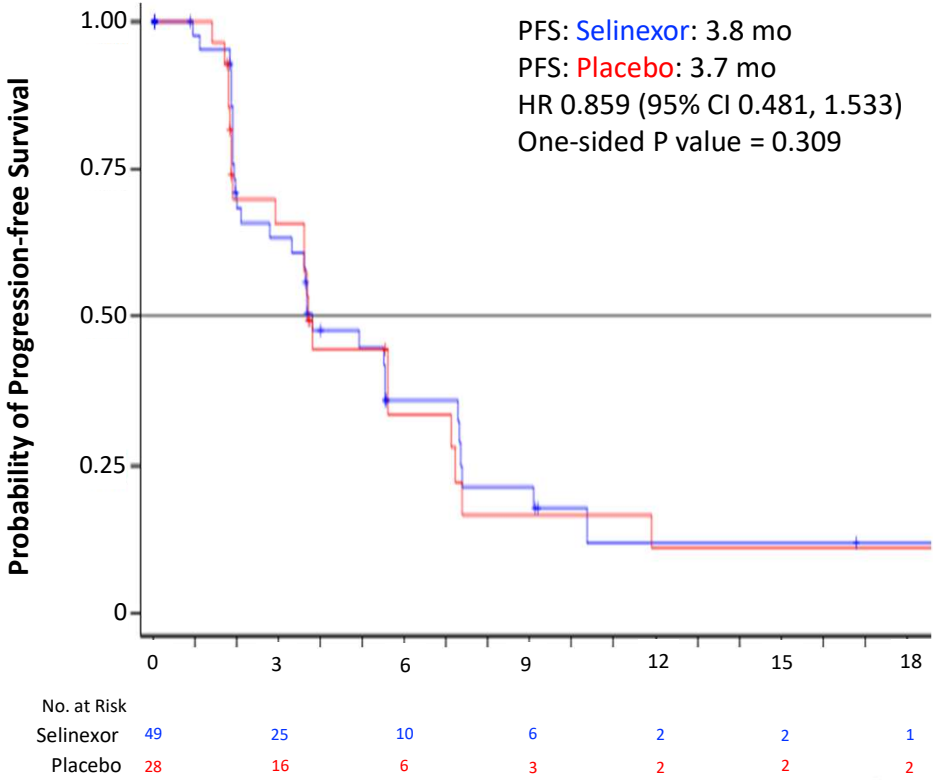
Subgroup PFS: by Histological Subtype

(based on audited stratification factors)

Endometrioid Carcinoma



Serous Carcinoma



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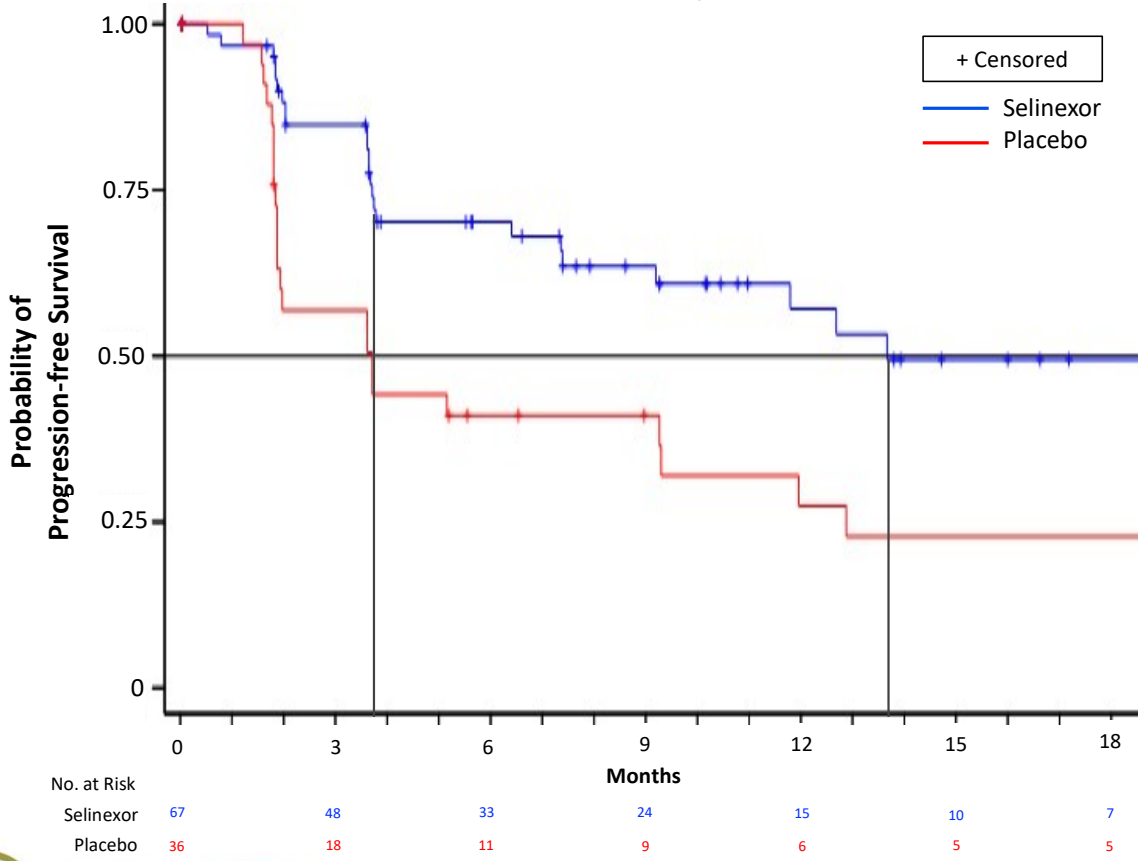
Subgroup PFS: Patients with wild type p53 EC

(based on audited stratification factors)



Median PFS

Selinexor (n=67): 13.7 mo (95% CI 9.20-NR)

Placebo (n=36): 3.7 mo (95% CI 1.87-12.88)

HR = 0.375 (95% CI 0.210-0.670)

One-sided P value = 0.0003

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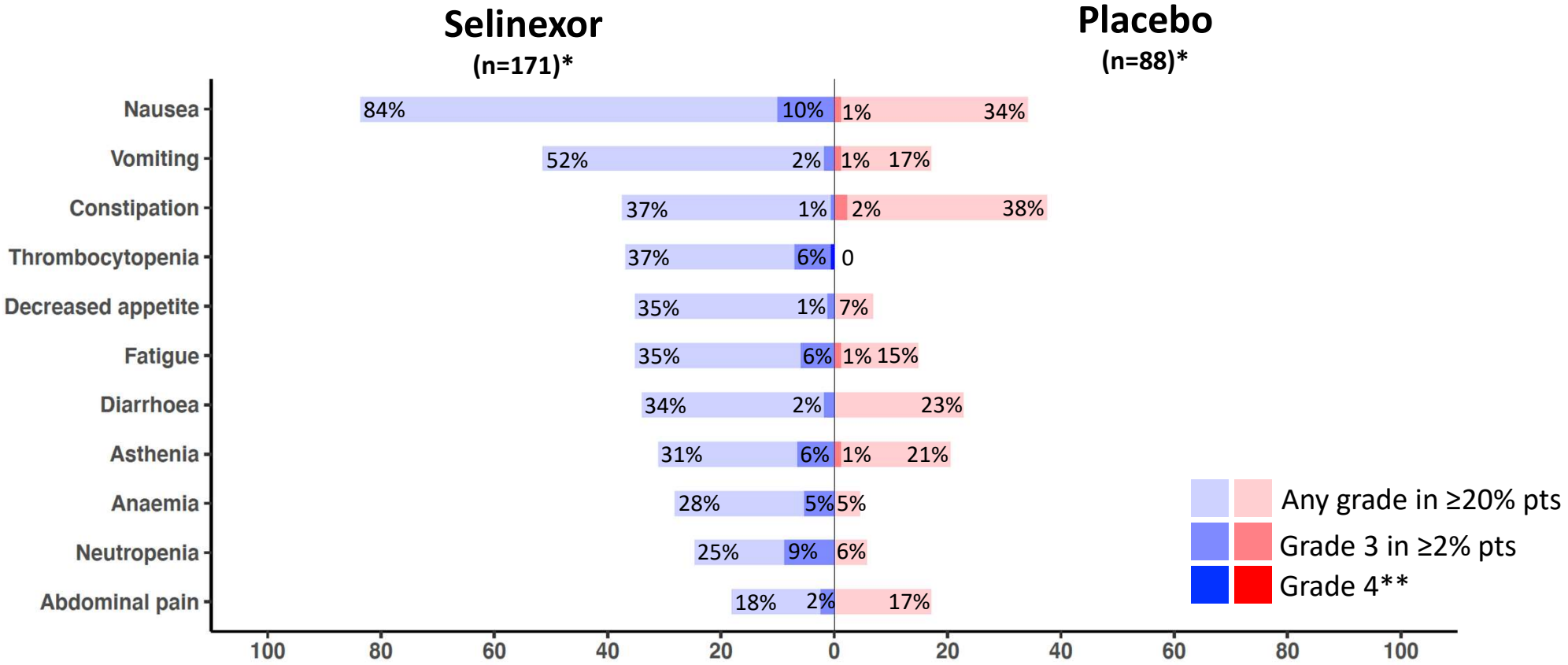
Safety: Treatment-Emergent Adverse Events



*Four patients did not receive treatment (n=3 selinexor; n=1 placebo)
**n=1 Grade 4 thrombocytopenia; No cases of severe bleeding in patients with thrombocytopenia; No cases of febrile neutropenia

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Safety

Event	Selinexor n=171* n (%) (per patient)	Placebo n=88* n (%) (per patient)
TEAE leading to:		
Dose reduction	85 (49.7)	3 (3.4)
Dose interruption	88 (51.5)	16 (18.2)
Discontinuation	18 (10.5)	1 (1.1)
Death	0	0

*Four patients did not receive treatment (n=3 selinexor; n=1 placebo)

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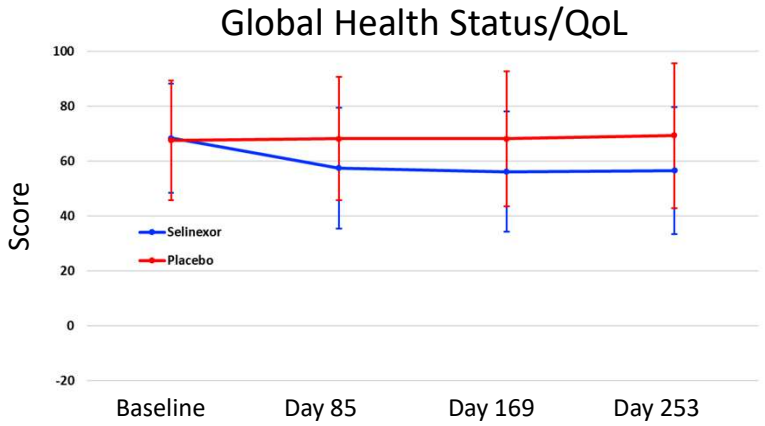
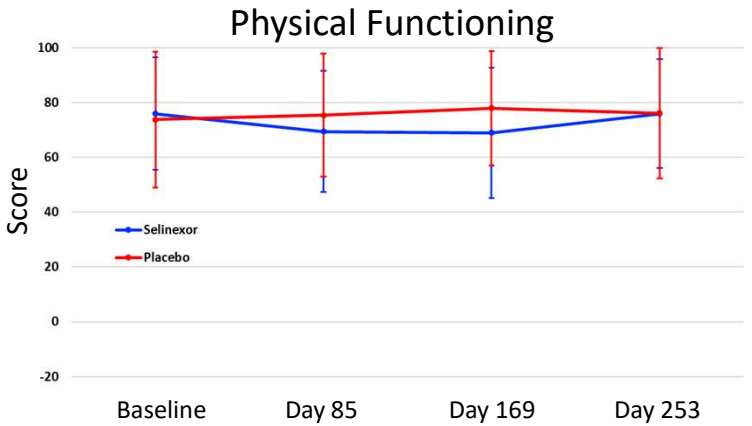
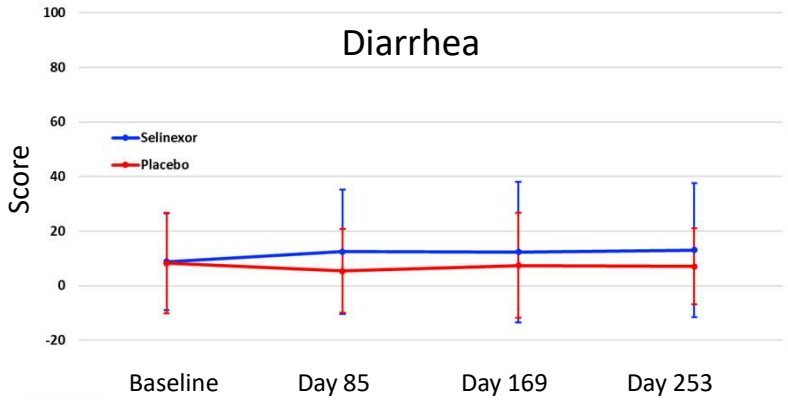
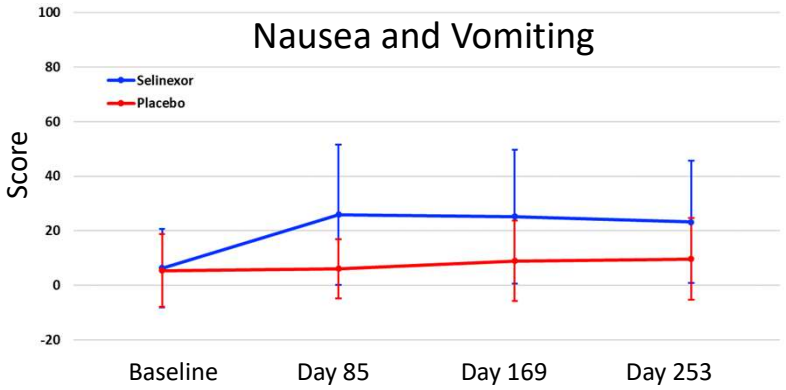
QoL -Patient-Reported Outcomes (EORTC QLQ-C30)

No significant differences in global health, physical functioning or symptoms









EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core Module

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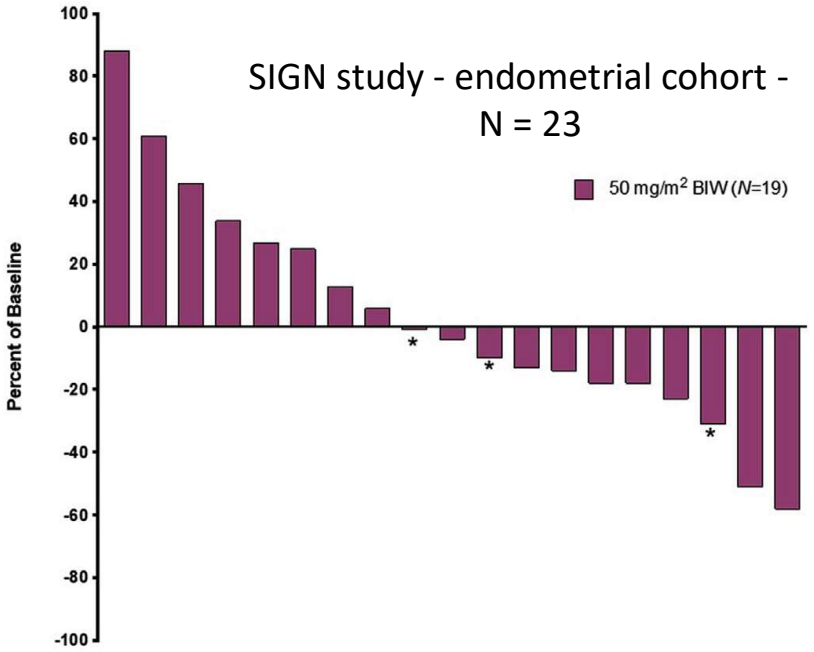
Summary and Conclusions

- Selinexor demonstrated in the audited ITT population, a **30% decrease of risk for progression and/or death compared to placebo** (HR: 0.705; CI: 0.499-0.996; median PFS 5.7 vs 3.8 months, respectively) which was statistically significant (one-sided p=0.024); In the non-audited ITT population (HR 0.76 (95% CI: 0.543, 1.076; one-sided p=0.063)
- Patients with **endometrioid** histology have a marked decrease in risk for progression and/or death in a pre-specified exploratory analysis (HR 0.57; 95% CI 0.348, 0.944; one-sided p=0.014)
- Patients in the pre-specified exploratory **p53 wild-type** subgroup (based on the mode of action of selinexor) achieved a **62% decrease of risk for progression and/or death to placebo** (HR: 0.38; 95% CI 0.210-0.670; one-sided p=0.0003)
- **QOL** data were similar in both groups
- **OS** data are immature (final OS analysis expected Q1 2023)
- AEs were generally manageable with supportive care and dose modifications. No new safety signals were identified

Selinexor Activity in Gynecological Malignancies



Maximal percent change in tumor size from screening for 19 patients with endometrial cancer. * indicates platinum-refractory[2]

- Selinexor, alone or in combination with platinum, reduced tumor growth in platinum-resistant PDX mice as well as ovarian-cancer patients.[1,2]
- SIGN phase 2 study[2], selinexor monotherapy in gynecological malignancies (endometrial cancer, n=23)
  - DCR (SD ≥ 12 weeks or a PR)=35%
  (median duration 6.3 months) with 2 (9%) PR
  - OS = 7.0 months
  - PFS = 2.8 months
  - No new safety signals

[1]Chen Y, et al. Clin Cancer Res. 2017
[2]Vergote IB, et al. Gynecol Oncol. 2020

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Eligibility

Key Inclusion Criteria

- **Female patients ≥ 18 years**
- **Histology: Endometrioid, serous, carcinosarcoma, or undifferentiated**
- **CR or PR after platinum-taxane combination therapy:**
  - **Primary Stage IV disease OR**
  - **At first relapse**
- **ECOG 0-1**

Key Exclusion Criteria

- **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**
- **Active brain metastases**

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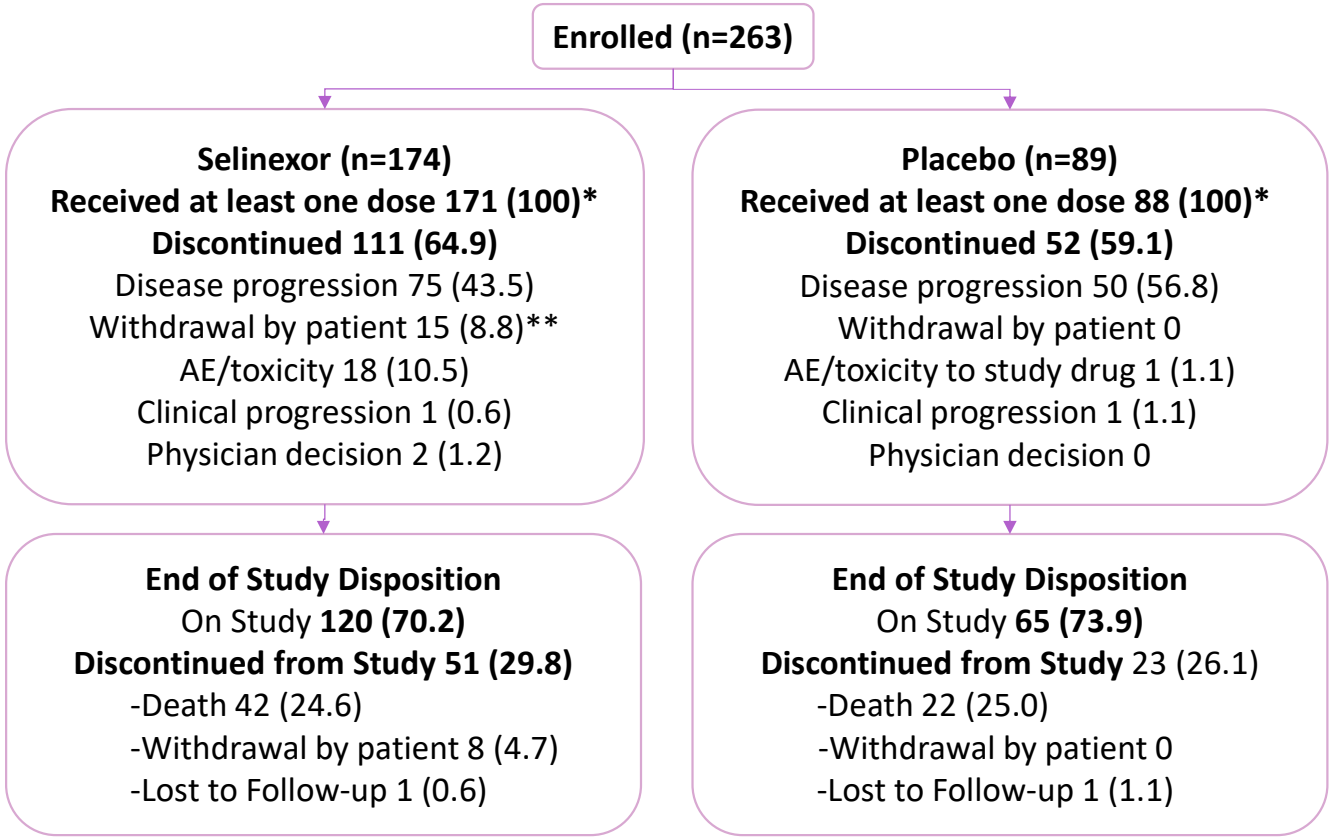
Disposition



*Reasons include patient withdrawal (n=3); after randomization and before dosing, lab values did not meet eligibility (n=1)
**Reasons for withdrawal by patient: AE (n=4), travel complications (n=1), unspecified (n=10)
Data reported as n (%)

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Subgroup Patient Characteristics: p53 wild type

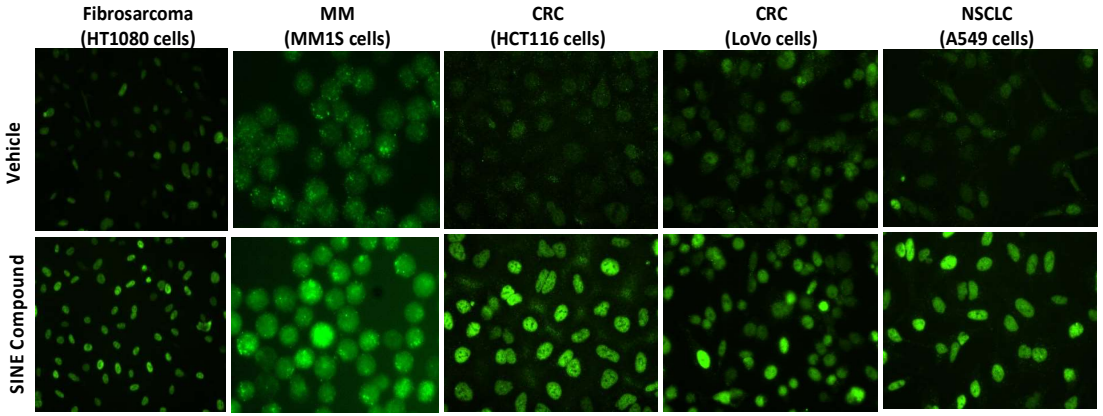
CHARACTERISTIC	Selinexor N = 67	Placebo N = 36
Age, years median (range), n (%)	64.0 (40-81)	61.0 (33-74)
<70 years, n (%)	46 (68.7)	29 (80.6)
≥70 years, n (%)	21 (31.3)	7 (19.4)
ECOG performance status, n (%)		
0	36 (53.7)	23 (63.9)
1	30 (44.8)	13 (36.1)
2	1 (1.5)	0
Histology, n (%)		
Endometrioid	55 (82.1)	28 (77.8)
Serous	3 (4.5)	4 (11.1)
Undifferentiated	0	1 (2.8)
Carcinosarcoma	1 (1.5)	0
Endometrial Adenocarcinoma*	8 (11.9)	3 (8.3)
Number of Prior Antineoplastic Regimens, n (%)		
1	67 (100.0)	35 (97.2)
2	0	1 (2.8)
Disease at Time of Taxane-Platinum Combination Therapy -eCRF, n (%)		
Primary Stage IV Disease	25 (37.3)	18 (50.0)
Recurrent Disease	42 (62.7)	18 (50.0)
Disease Status After the Most Recent Chemotherapy -eCRF, n (%)		
CR	29 (43.3)	16 (44.4)
PR	38 (56.7)	20 (55.6)

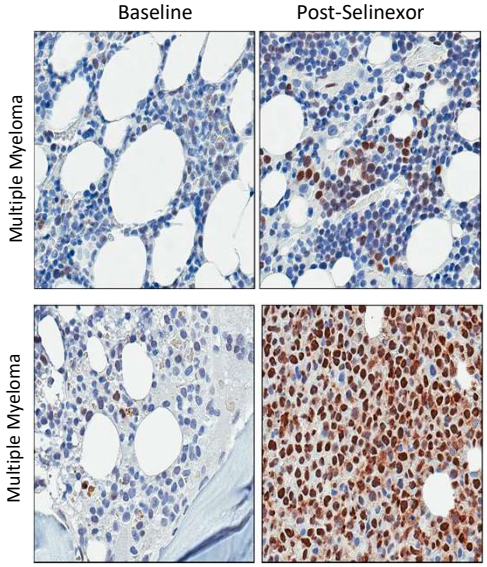
*Not otherwise specified

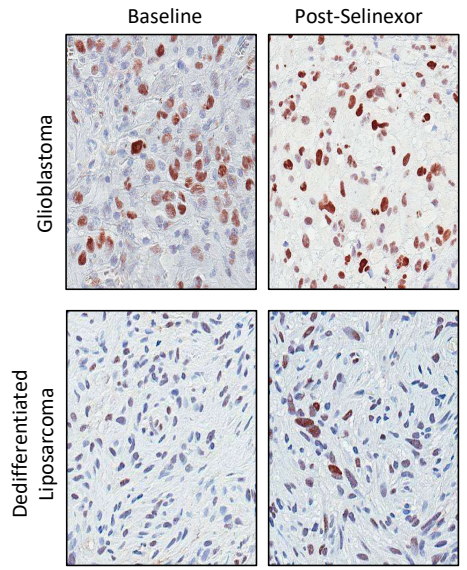
CR, complete response; ECOG, Eastern Cooperative Oncology Group; eCRF, electronic case report form; PR, partial response

Selinexor induces nuclear accumulation of p53

- p53 wild type tumors account for 45-65% of all endometrial cancers
  - Generally endometrioid in histology and occurs in younger patients
- Inhibition of XPO1 leads to nuclear accumulation of tumor suppressor proteins such as p53
- Selinexor induces nuclear localization of p53 in patients treated with selinexor







Oncogenic signaling pathways in The Cancer Genome Atlas. Cell. 2018; 173: 321-37
Pan-cancer analysis of whole genomes. Nature. 2020; 578: 82-93
Soumerai et al. Clin Cancer Res. 2018; 24: 5939-47

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Subgroup Patient Characteristics: by histological subtype

CHARACTERISTIC	Endometrioid Carcinoma		Serous Carcinoma		Others	
	Selinexor N = 96	Placebo N = 48	Selinexor N = 49	Placebo N = 28	Selinexor N = 29	Placebo N = 13
Age, years median (range), n (%)	64.0 (40-81)	60.5 (40-74)	66.0 (41-79)	68.5 (58-80)	67.0 (46-81)	66.0 (33-81)
<70 years, n (%)	66 (68.8)	38 (79.2)	32 (65.3)	15 (53.6)	18 (62.1)	8 (61.6)
≥70 years, n (%)	30 (31.3)	10 (20.8)	17 (34.7)	13 (46.4)	11 (37.9)	5 (38.5)
ECOG performance status, n (%)						
0	57 (59.4)	27 (56.3)	27 (55.1)	18 (64.3)	15 (51.7)	9 (69.2)
1	37 (38.5)	21 (43.8)	21 (42.9)	10 (35.7)	13 (44.8)	4 (30.8)
Histology, n (%)						
Endometrioid	96 (100.0)	48 (100.0)	0	0	0	0
Serous	0	0	49 (100.0)	28 (100.0)	0	0
Undifferentiated	0	0	0	0	4 (13.8)	1 (7.7)
Carcinosarcoma	0	0	0	0	10 (34.5)	6 (46.2)
Endometrial Adenocarcinoma*	0	0	0	0	15 (51.7)	6 (46.2)
Number of Prior Antineoplastic Regimens, n (%)						
1	96 (100.0)	46 (95.8)	48 (98.0)	27 (96.4)	28 (96.6)	12 (92.3)
2	0	1 (2.1)	1 (2.0)	1 (3.6)	1 (3.4)	1 (7.7)
Disease at Time of Taxane-Platinum Combination Therapy -eCRF, n (%)						
Primary Stage IV Disease	41 (42.7)	19 (39.6)	23 (46.9)	17 (60.7)	14 (48.3)	7 (53.8)
Recurrent Disease	55 (57.3)	29 (60.4)	26 (53.1)	11 (39.3)	15 (51.7)	6 (46.2)
Disease Status After the Most Recent Chemotherapy -eCRF, n (%)						
CR	40 (41.7)	23 (47.9)	20 (40.8)	13 (46.4)	10 (34.5)	4 (30.8)
PR	56 (58.3)	25 (52.1)	29 (59.2)	15 (53.6)	19 (65.5)	9 (69.2)

*Not otherwise specified

CR, complete response; ECOG, Eastern Cooperative Oncology Group; eCRF, electronic case report form; PR, partial response

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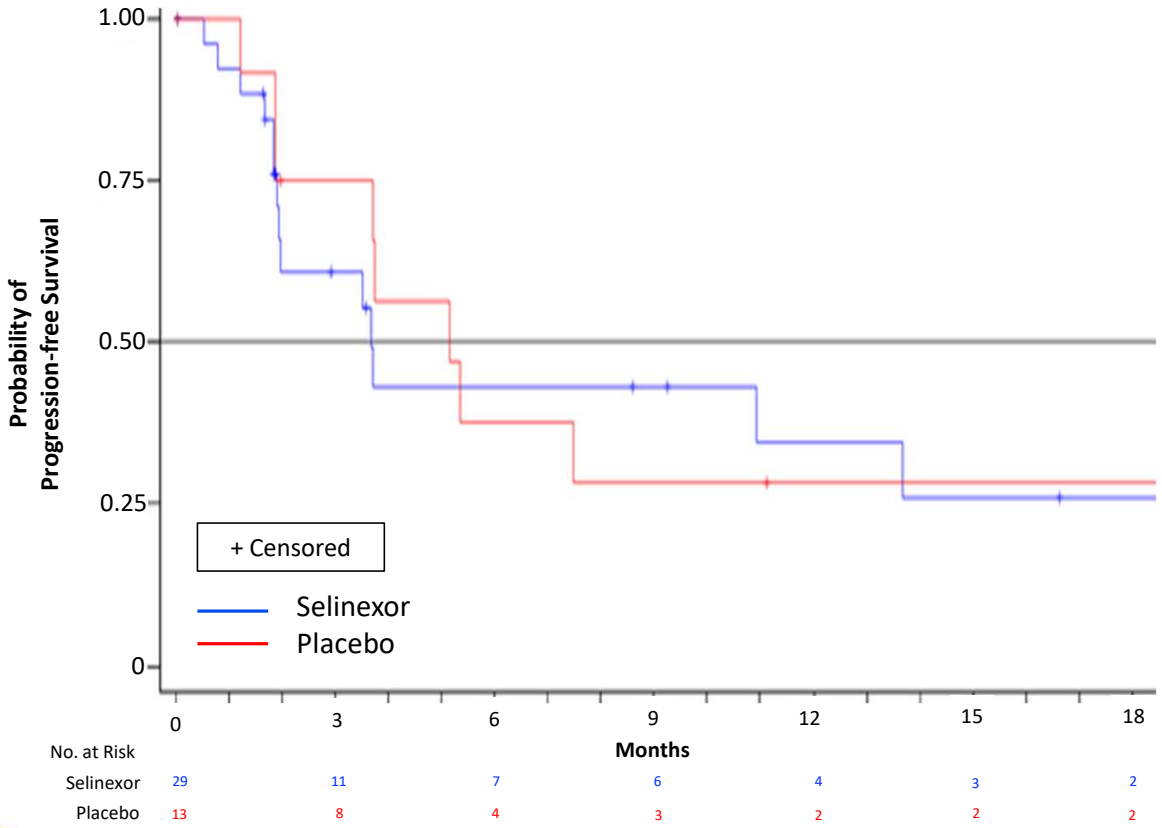
Subgroup PFS: by Histological Subtype - Other*



Median PFS

Selinexor: 3.7 mo (95% CI 1.94, not reached)

Placebo: 5.2 mo (95% CI 3.71, not reached)

HR 1.103 (95% CI 0.459, 2.652)

One-sided P value = 0.592

*Undifferentiated Carcinoma, Carcinosarcoma, Endometrial Adenocarcinoma (Not otherwise specified)

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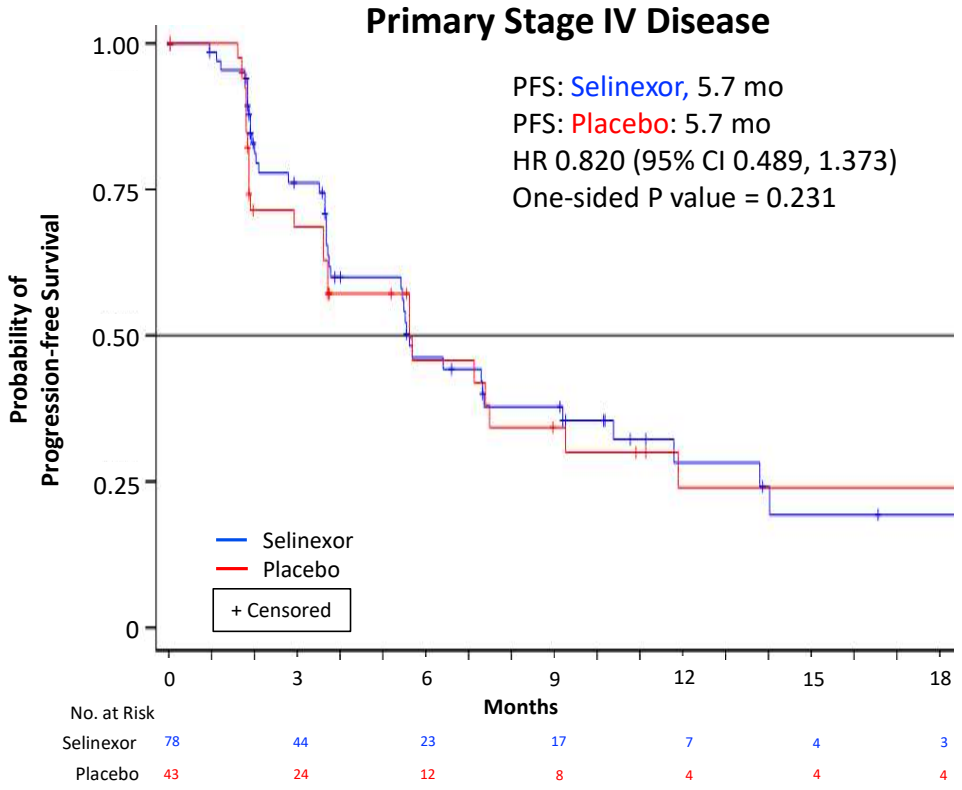
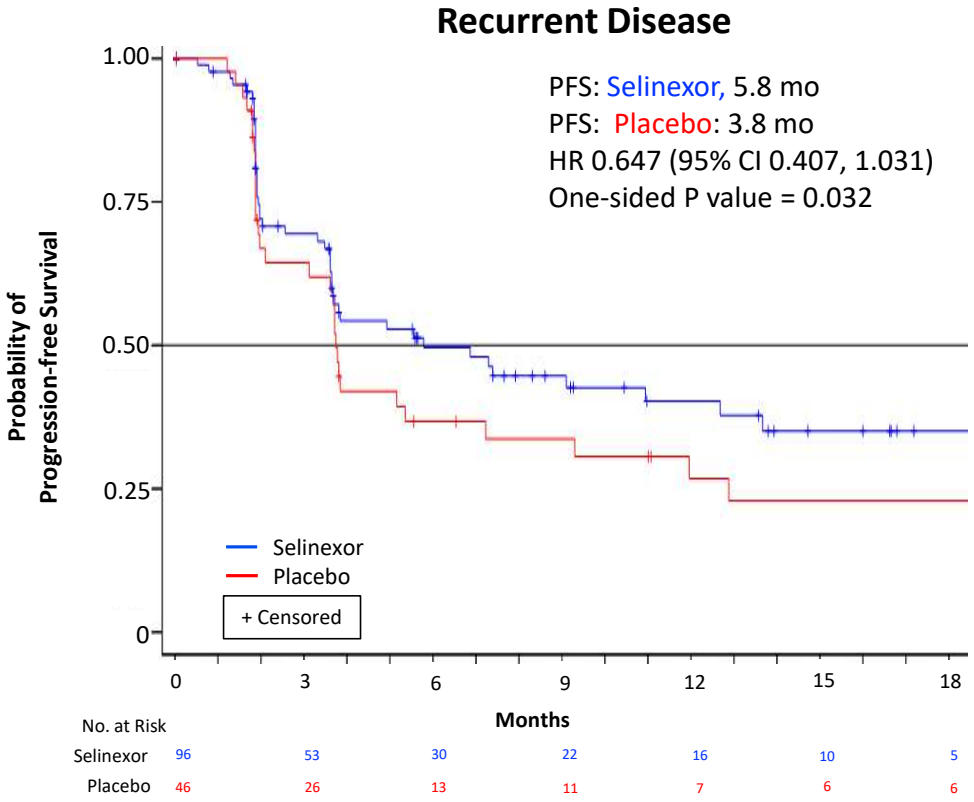
Subgroup PFS: by Disease at Time of Taxane-Platinum Combination Therapy





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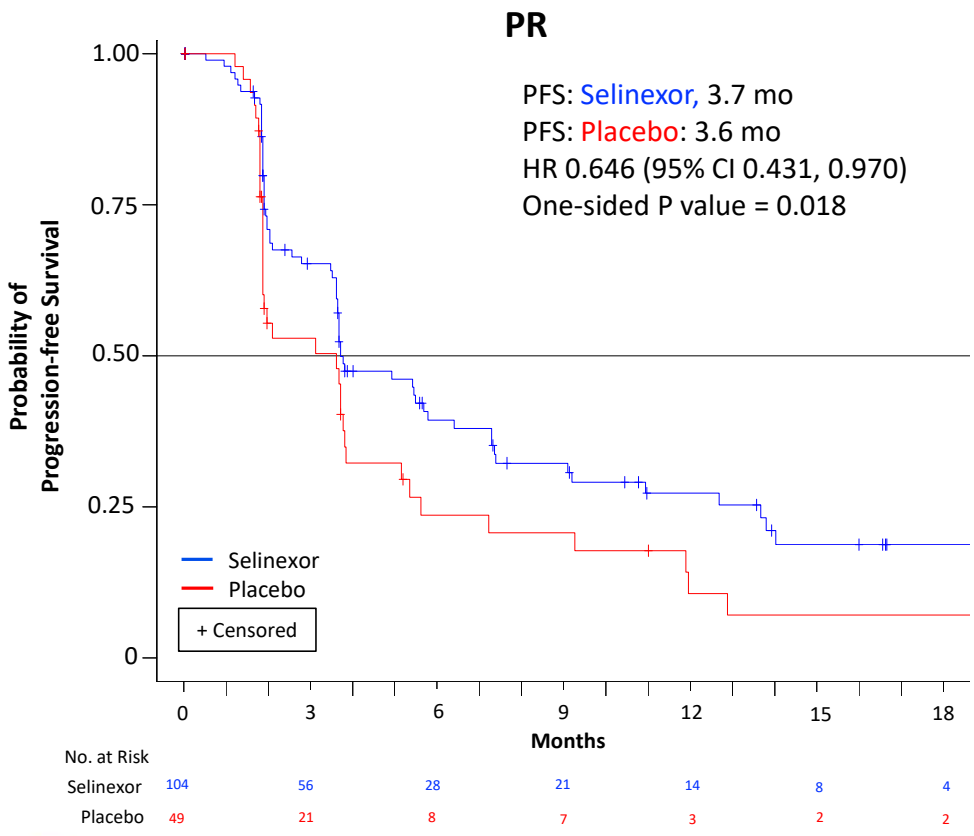
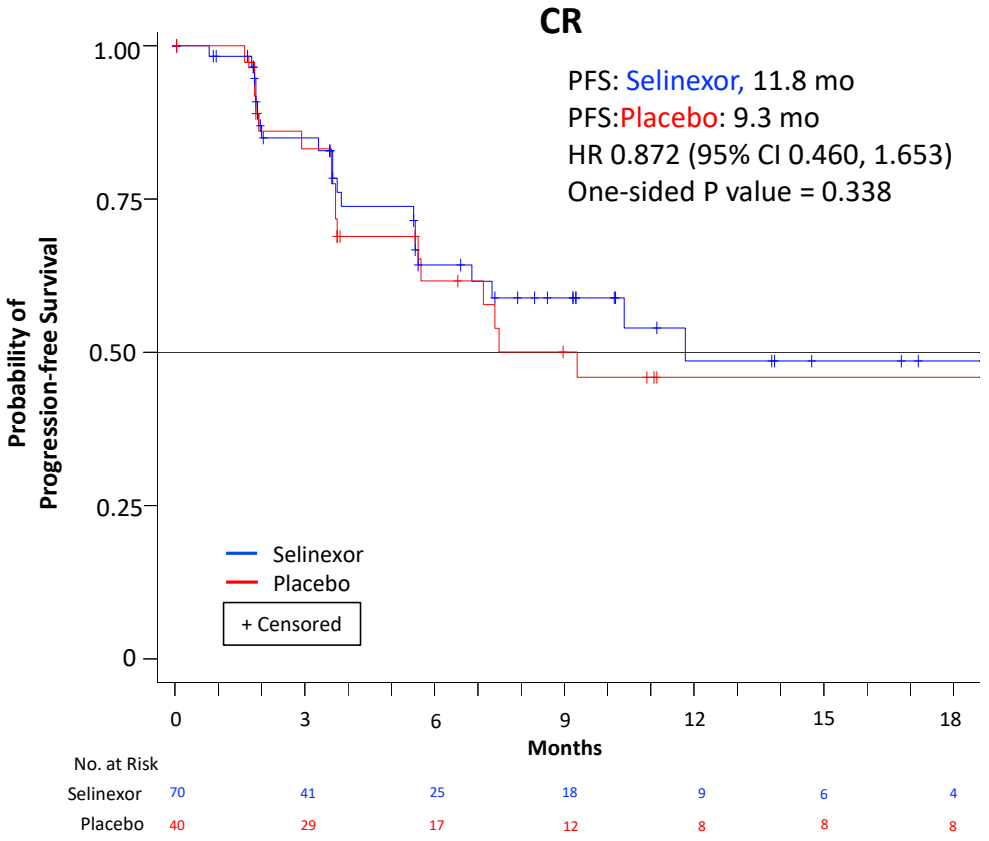
Subgroup PFS: by PR vs CR stratification





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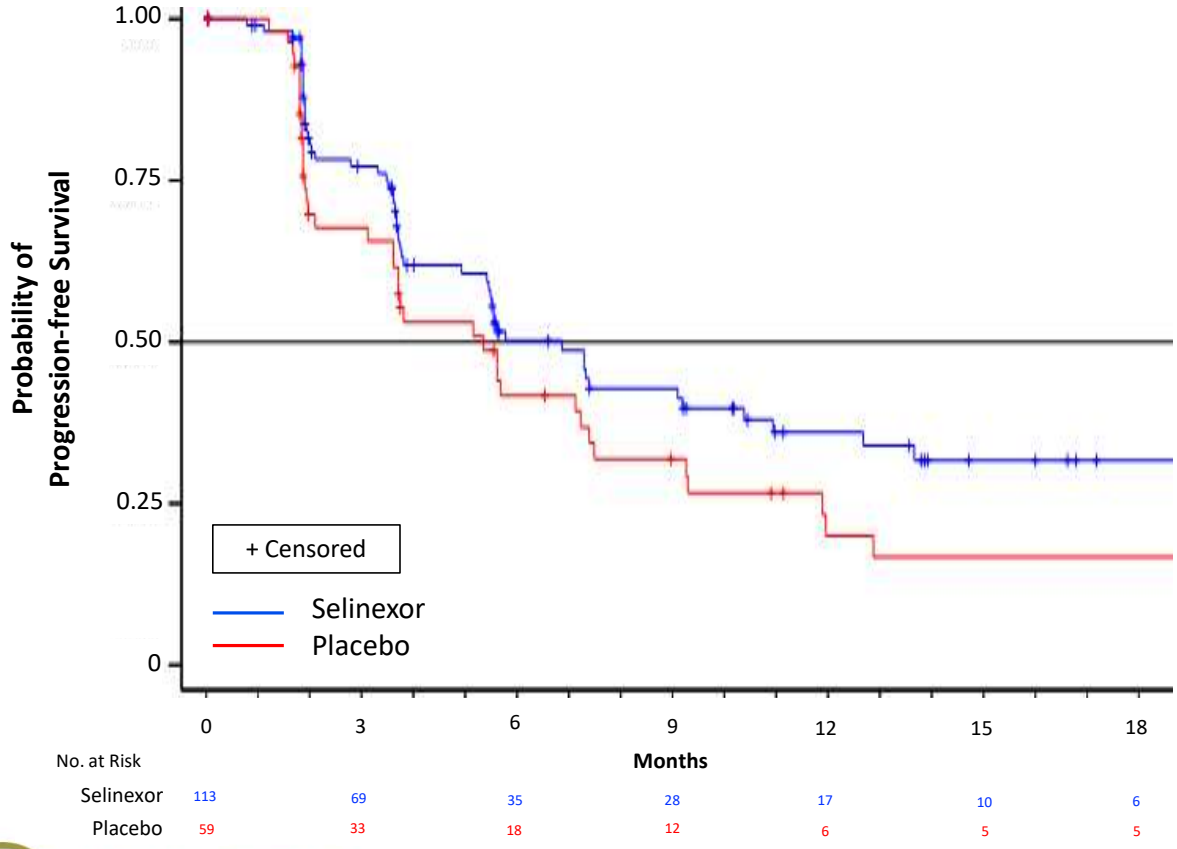
ENGOT-EN5/GOG-3055/SIENDO

Subgroup PFS: Patients with endometrial cancer with MSS/pMMR



Median PFS

Selinexor: 6.9 mo (95% CI 5.42-10.94)

Placebo: 5.4 mo (95% CI 3.61-7.49)

HR=0.593 (95% CI 0.388-0.905)

One-sided P value = 0.007

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Use of IRT vs eCRF

- SIENDO primary analysis used IRT, but a misclassification of data made resulting analysis erroneous
- Errors corrected by Investigators before database lock and unblinding
- eCRF is correct and appropriate to use in primary endpoint analysis of PFS
- Data discrepancy due to mistake in classifying stratification factor of CR/PR by clinical sites for 7 patients in IRT

Number of Patients	Arm	Incorrect Assignment in IRT	Correct Data eCRF
3	Selinexor	CR	PR
3	Placebo	PR	CR
1	Selinexor	PR	CR

- Disease burden at baseline is prognostic
  - These errors had substantial effect on endpoint of study
- All other demographic parameters remained balanced when using eCRF ITT

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Incorrect stratification at randomization

- Per SAP (v3.0), the stratified analysis (based on IRT value of the disease status after chemotherapy, CR vs. PR) is the primary analysis for PFS, which was determined to be erroneous for the SIENDO study
  - The baseline disease status has a marked effect on primary endpoint PFS (expected median PFS <4 months for PR patients (pts) and >7 months for CR pts from literature, in SIENDO Placebo arm, mPFS 3.6 months for PR pts and 9.3 months for CR pts)
  - Seven (7) patients had this stratification factor incorrectly recorded in the IRT system, and the error is imbalanced between the 2 treatment arms (6 out of 7 against selinexor arm)
  - The stratified (IRT) analysis did not minimize bias, instead, it introduced bias due to the imbalance in errors and this imbalance in stratification factor error was unknown to the Sponsor until the study was unblinded for primary objective analysis
- The stratified (eCRF) analysis uses correct disease status derived based on corrected information study sites entered to pts' eCRF prior to database lock

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Reasons for reduction, interruptions, discontinuations

Treatment-Emergent Event Leading to	Dose Reduction		Dose Interruption		Discontinuation	
	Selinexor	Placebo	Selinexor	Placebo	Selinexor	Placebo
Thrombocytopenia	28 (16.4)	0	24 (14.0)	0	1 (0.6)	0
Nausea	23 (13.5)	1 (1.1)	19 (11.1)	1 (1.1)	7 (4.1)	0
Fatigue	19 (11.1)	1 (1.1)	17 (9.9)	1 (1.1)	5 (2.9)	0
Asthenia	15 (8.8)	1 (1.1)	14 (8.2)	2 (2.3)	2 (1.2)	1 (1.1)
Vomiting	11 (6.4)	0	13 (7.6)	0	3 (1.8)	0
Neutropenia	6 (3.5)	0	13 (7.6)	0	--	--

COVID-19 Cases
- Selinexor: 6 (3.5%)
- Placebo: 3 (3.4%)