2022 ASCO® ANNUAL MEETING

Randomized Phase III Study of Maintenance Selinexor vs Placebo in Endometrial Cancer (ENGOT-EN5/GOG-3055/SIENDO): Impact of Subgroup Analysis and Molecular Classification

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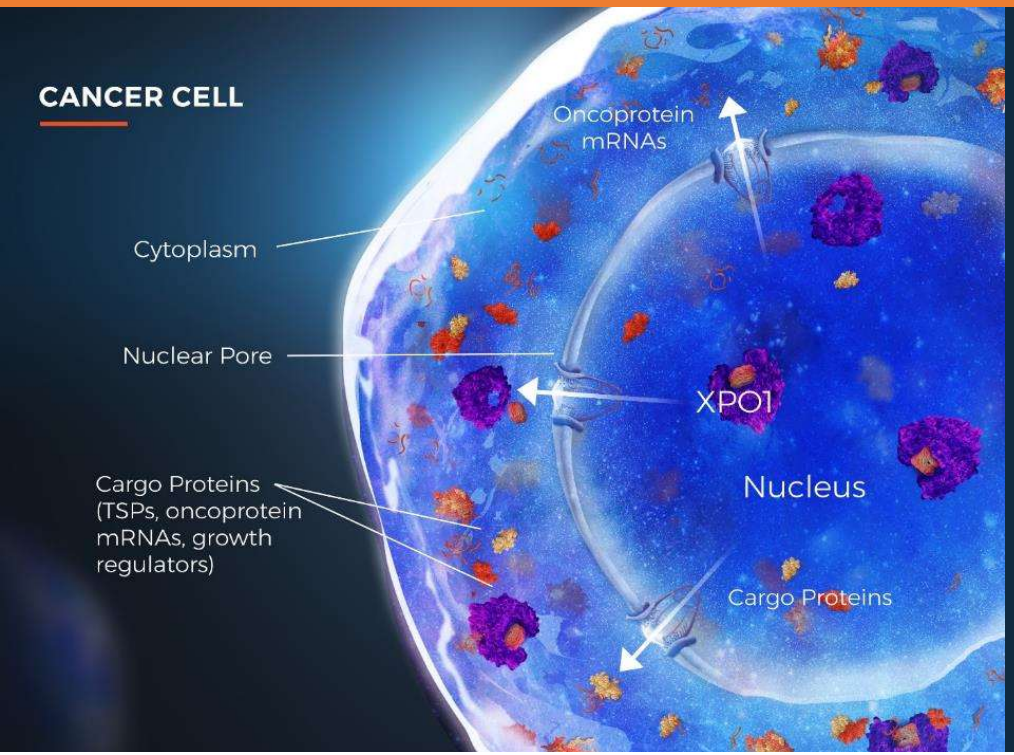
Selinexor: Oral XPO1 Inhibitor



Selinexor is an oral selective inhibitor of XPO1-mediated nuclear export (SINE) compound

- XPO1 exports the major tumor suppressor proteins (TSPs) including p53 away from the nucleus, where TSPs carry out their function
- Tumor cells overexpress XPO1
- Tumor cells inactivate cytoplasmic *p53* through protein degradation
- Selinexor inhibits XPO1 nuclear export, leads to retention / reactivation of TSPs in the nucleus and stabilization of p53
- Retention of wild-type *p53* (p53wt) and other TSPs in the cell nucleus leads to selective killing of cancer cells, while largely sparing normal cells

[1]Fung HY, Chook YM. Semin Cancer Biol. 2014;27:52–61. [2]Tai YT, Landesman Y, Acharya C, et al. Leukemia. 2014;28(1):155–165.

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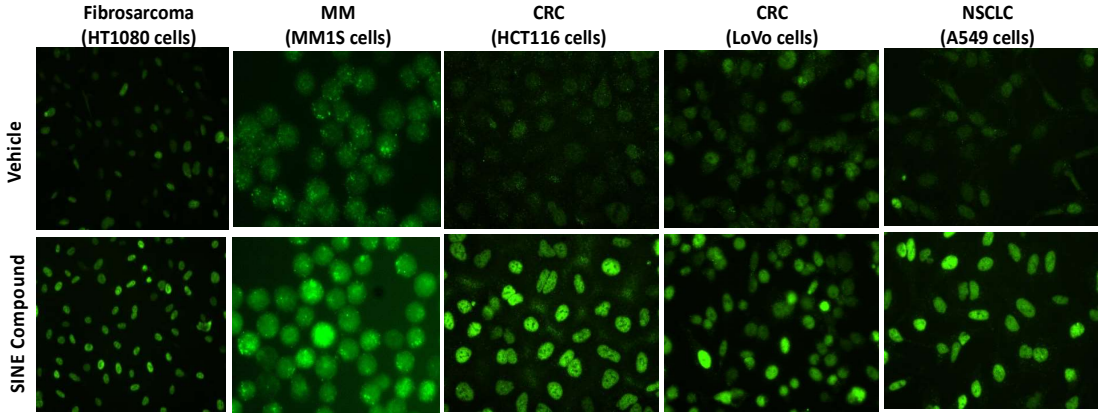
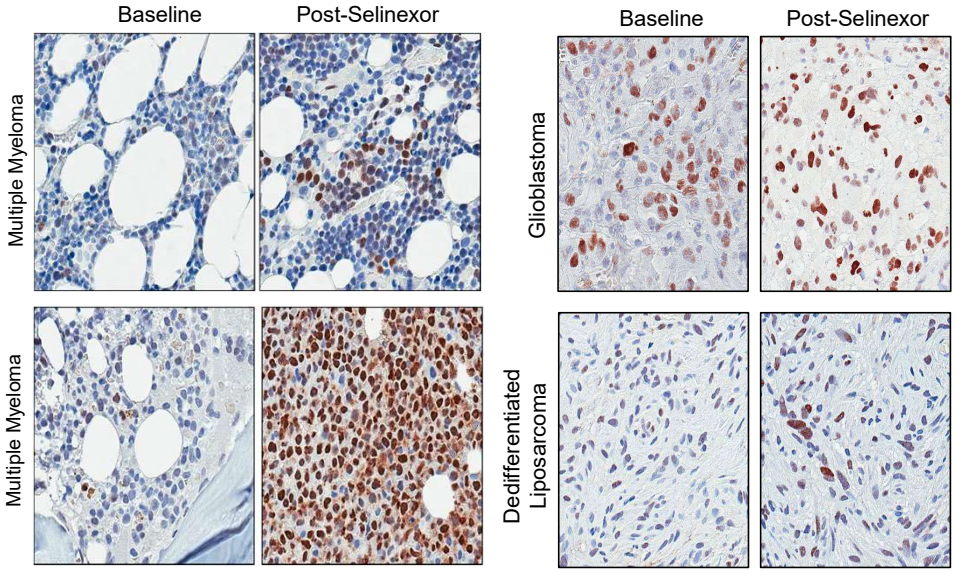
Selinexor Induces Nuclear Accumulation of p53

- Aberrant XPO1 mediated nuclear export of p53 is a mechanism by which cancer cells can inhibit p53
- Inhibition of XPO1 leads to nuclear accumulation of p53 across cancer types, as demonstrated in cell lines and patient samples
- p53 wild-type tumors account for 45-65% of all endometrial cancers
  - Generally, endometrioid in histology and occurs in younger patients

p53 IF in cell lines



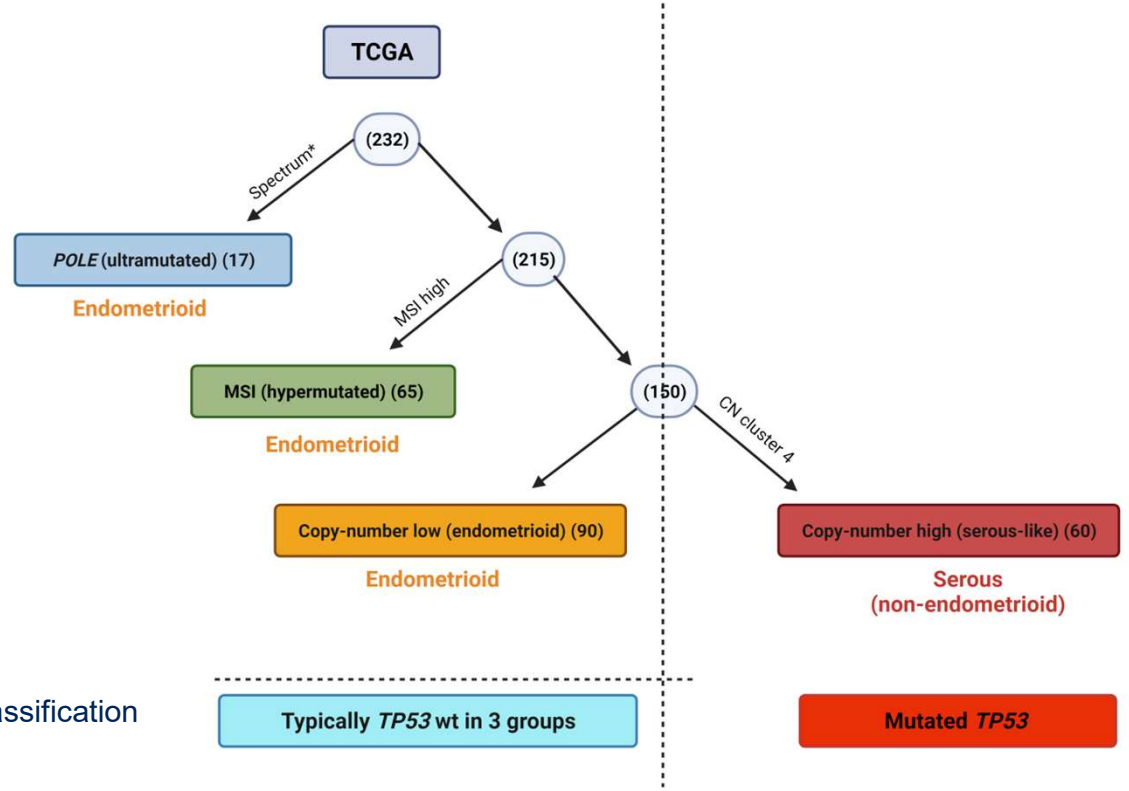
p53 IHC in human patient samples



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

Molecular Subclassification of Endometrial Cancer by the TCGA System of Four Independent Subtypes

- TCGA and others identified and validated 4 distinct molecular subtypes in endometrial cancer with each having its own prognostic significance:[1,2]
  - *POLE*-exonuclease domain mutant (ultramutated)
  - MSI-H (hypermutated)
  - Serous-like (copy-number high)
  - No specific molecular profile (copy-number low)

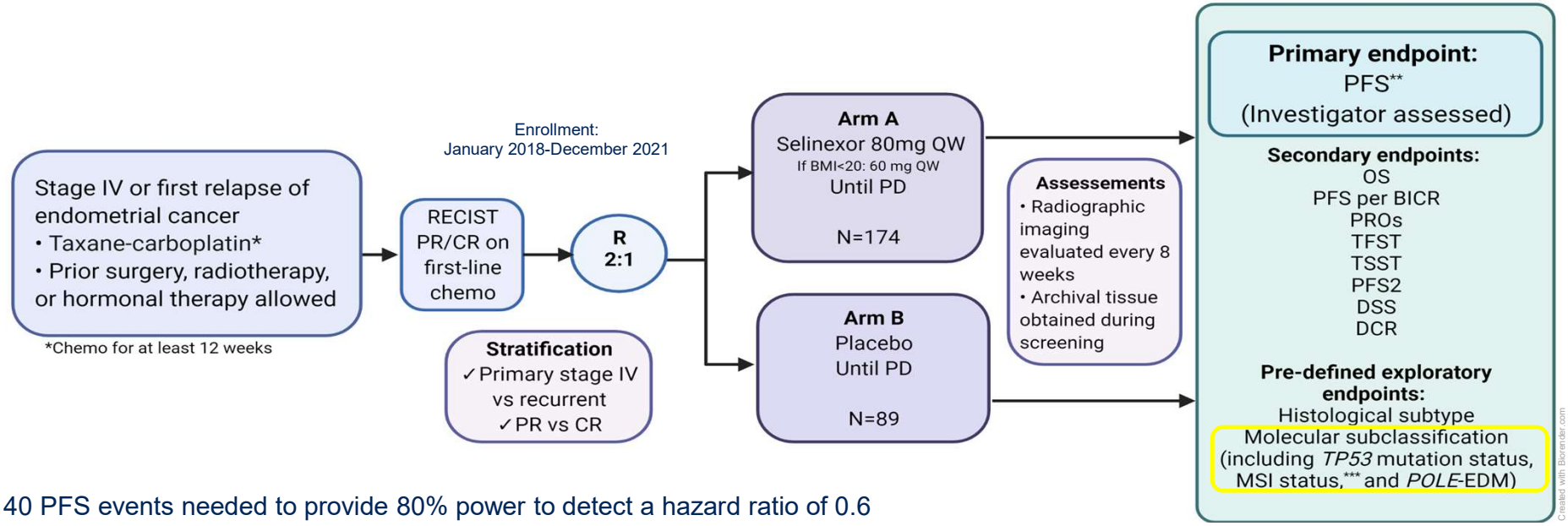


Four mutually exclusive groups assigned according to this classification system, ordered from top to bottom

[1]Abu-Rustum NR, Yashar CM, Bradley K, et al. NCCN Guidelines® Insights: Uterine Neoplasms, Version 3.2021: Featured Updates to the NCCN Guidelines. J Natl Compr Cancer Netw [Internet] 2021;19(8):888–95
[2]Getz G, Gabriel SB, Cibulskis K, et al. Integrated genomic characterization of endometrial carcinoma. Nature 2013;497(7447):67

Trial Design ENGOT-EN5/GOG-3055/SIENDO

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.

***Assessed by DNA sequencing and IHC

Data cutoff: January 18, 2022

BICR; blinded independent central review; BMI, body mass index; CR, complete response; DCR, disease control rate; DSS, disease-specific survival; EDM, exonuclease domain mutation; IHC, immunohistochemistry; MSI, microsatellite instability; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PFS2, progression-free survival on subsequent therapy; PR, partial response; PROs, patient-reported outcomes; QW, once weekly; R, randomized; RECIST, response evaluation criteria in solid tumors; TFST, time to first subsequent therapy; TSST, time to second subsequent treatment;

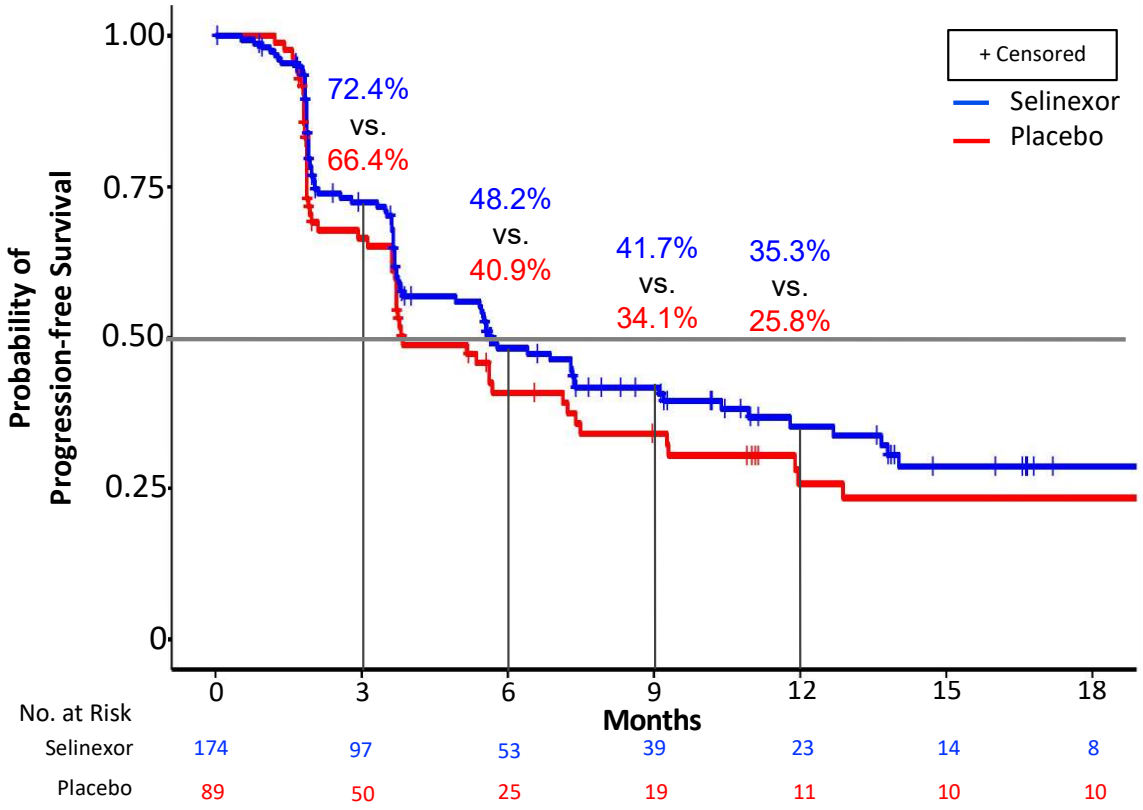
Previously presented at ESMO Virtual Plenary 2022 and SGO 2022

Patient Characteristics: ITT Population

CHARACTERISTICS	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 Not Otherwise Specified	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 -audited, 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 -audited, n (%)		
CR	70 (40.2)	40 (44.9)
PR	104 (59.8)	49 (55.1)

CR, complete response; ECOG, Eastern Cooperative Oncology Group; PR, partial response

Primary Endpoint: PFS in ITT Population



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

Median PFS

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

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

Audited* (by electronic case report form)

HR = 0.705 (95% CI 0.499-0.996)

One-sided P value = 0.024

Unaudited* (by interactive response technology)

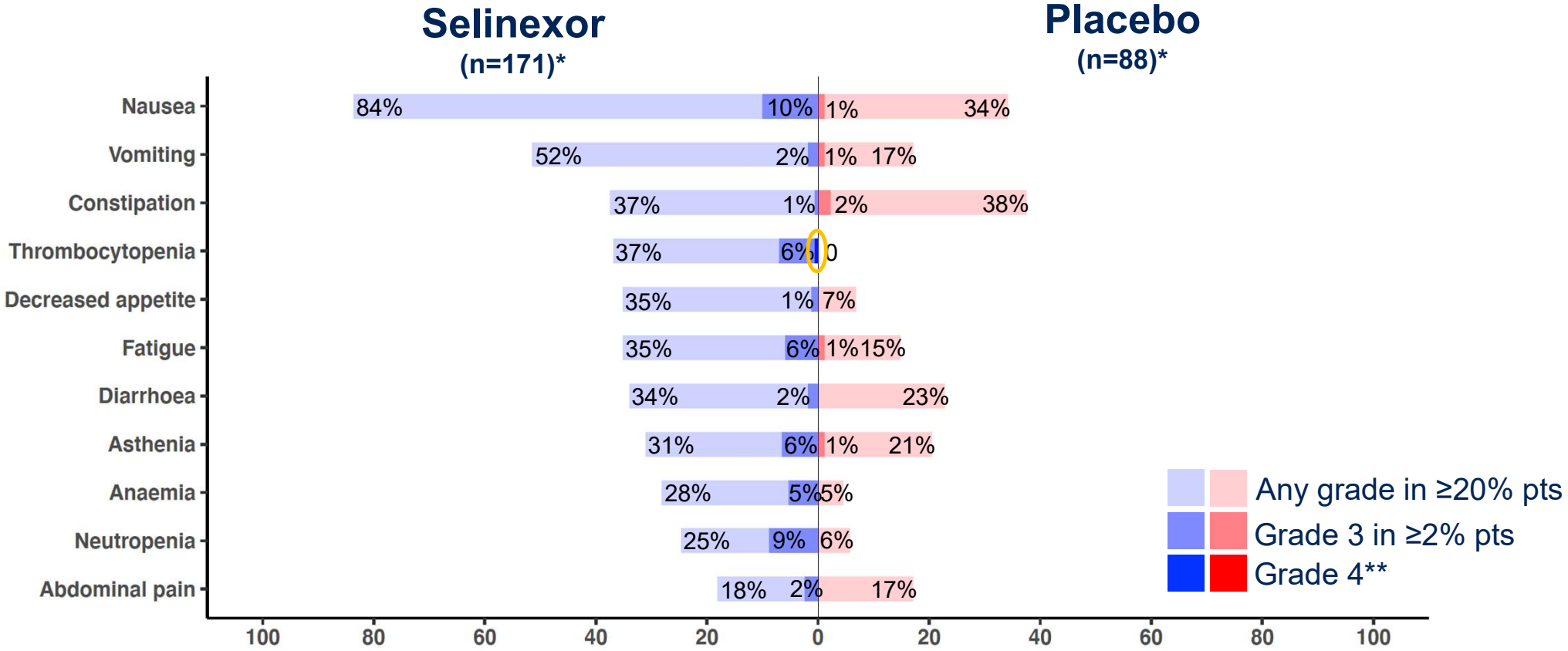
HR = 0.76 (95% CI 0.543-1.076)

One-sided P value = 0.063

*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.

CI, confidence interval; HR, hazard ratio; mo, months; PFS, progression-free survival

Treatment-Emergent Adverse Events in ITT Population



*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

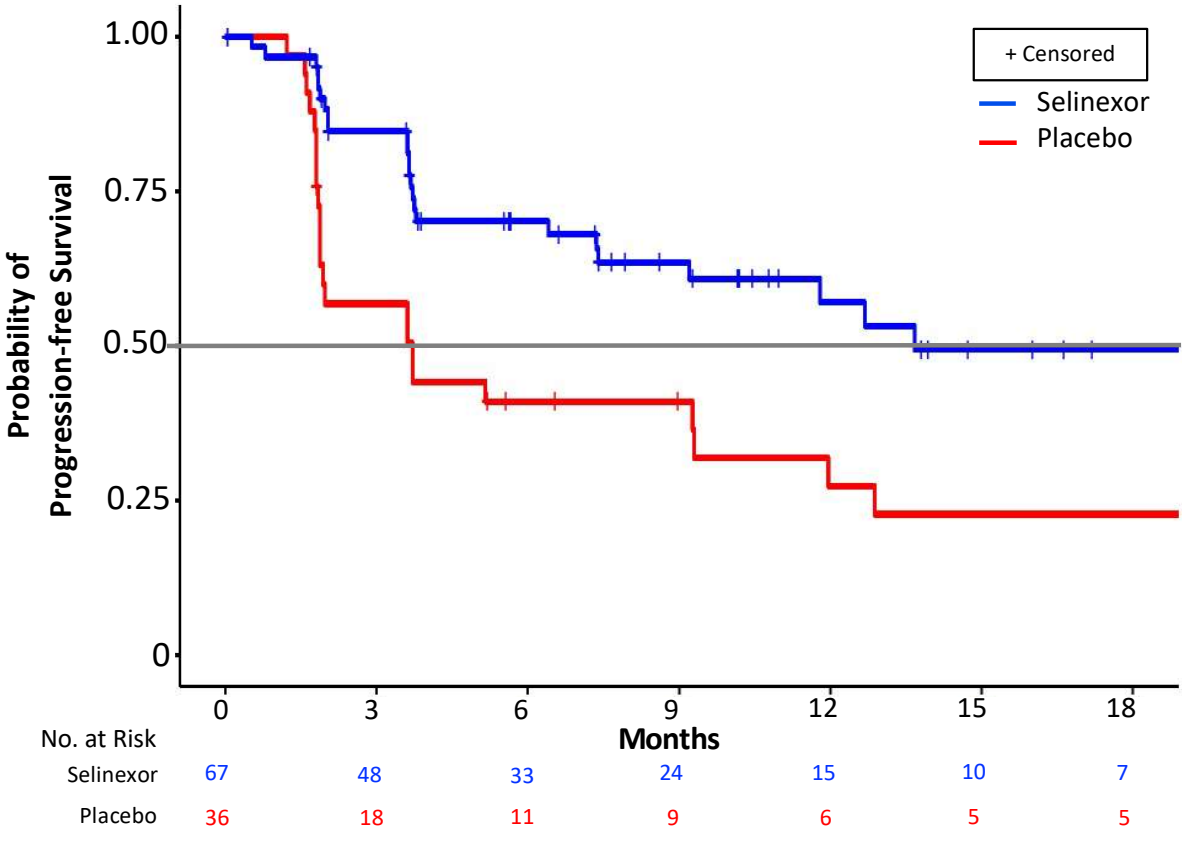
Subgroup Patient Characteristics: p53 Status

CHARACTERISTIC	p53 wild-type		p53 mutant/aberrant		Unknown	
	Selinexor N = 67	Placebo N = 36	Selinexor N = 74	Placebo N = 40	Selinexor N = 33	Placebo N = 13
Age, years median (range), n (%)	64.0 (40-81)	61.0 (33-74)	67.0 (41-79)	66.5 (46-81)	65.0 (40-74)	65.5 (40-81)
<70 years, n (%)	46 (68.7)	29 (80.6)	47 (63.5)	25 (62.5)	23 (69.7)	7 (53.8)
≥70 years, n (%)	21 (31.3)	7 (19.4)	27 (36.5)	15 (37.5)	10 (30.3)	6 (46.2)
ECOG performance status, n (%)						
0	36 (53.7)	23 (63.9)	44 (59.5)	25 (62.5)	19 (57.6)	6 (46.2)
1	30 (44.8)	13 (36.1)	29 (39.2)	15 (37.5)	12 (36.4)	7 (53.8)
2	1 (1.5)	0	0	0	0	0
Histology, n (%)						
Endometrioid	55 (82.1)	28 (77.8)	21 (28.4)	11 (27.5)	20 (60.6)	9 (69.2)
Serous	3 (4.5)	4 (11.1)	41 (55.4)	20 (50.0)	5 (15.2)	4 (30.8)
Undifferentiated	0	1 (2.8)	3 (4.1)	0	1 (3.0)	0
Carcinosarcoma	1 (1.5)	0	6 (8.1)	6 (15.0)	3 (9.1)	0
Endometrial Adenocarcinoma*	8 (11.9)	3 (8.3)	3 (4.1)	3 (7.5)	4 12.1)	0
Number of Prior Antineoplastic Regimens, n (%)						
1	67 (100.0)	35 (97.2)	73 (98.6)	39 (97.5)	32 (97.0)	11 (84.6)
2	0	1 (2.8)	1 (1.4)	1 (2.5)	1 (3.0)	1 (7.7)
Disease at Time of Taxane-Platinum Combination Therapy -audited, n (%)						
Primary Stage IV Disease	25 (37.3)	18 (50.0)	39 (52.7)	23 (57.5)	14 (42.4)	2 (15.4)
Recurrent Disease	42 (62.7)	18 (50.0)	35 (47.3)	17 (42.5)	19 (57.6)	11 (84.6)
Disease Status After the Most Recent Chemotherapy -audited, n (%)						
CR	29 (43.3)	16 (44.4)	33 (44.6)	18 (45.0)	8 (24.2)	6 (46.2)
PR	38 (56.7)	20 (55.6)	41 (55.4)	22 (55.0)	25 (75.8)	7 (53.8)

*Not otherwise specified

CR, complete response; ECOG, Eastern Cooperative Oncology Group; PR, partial response

Preliminary Analysis of a Prespecified Exploratory Subgroup PFS: Patients with p53 wild-type EC



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)

Audited

HR = 0.375 (95% CI 0.210-0.670)

Nominal one-sided P value = 0.0003

Unaudited

HR = 0.407 (95% CI 0.229-0.724)

Nominal one-sided P value = 0.0008

CI, confidence interval; HR, hazard ratio; mo, months; PFS, progression-free survival

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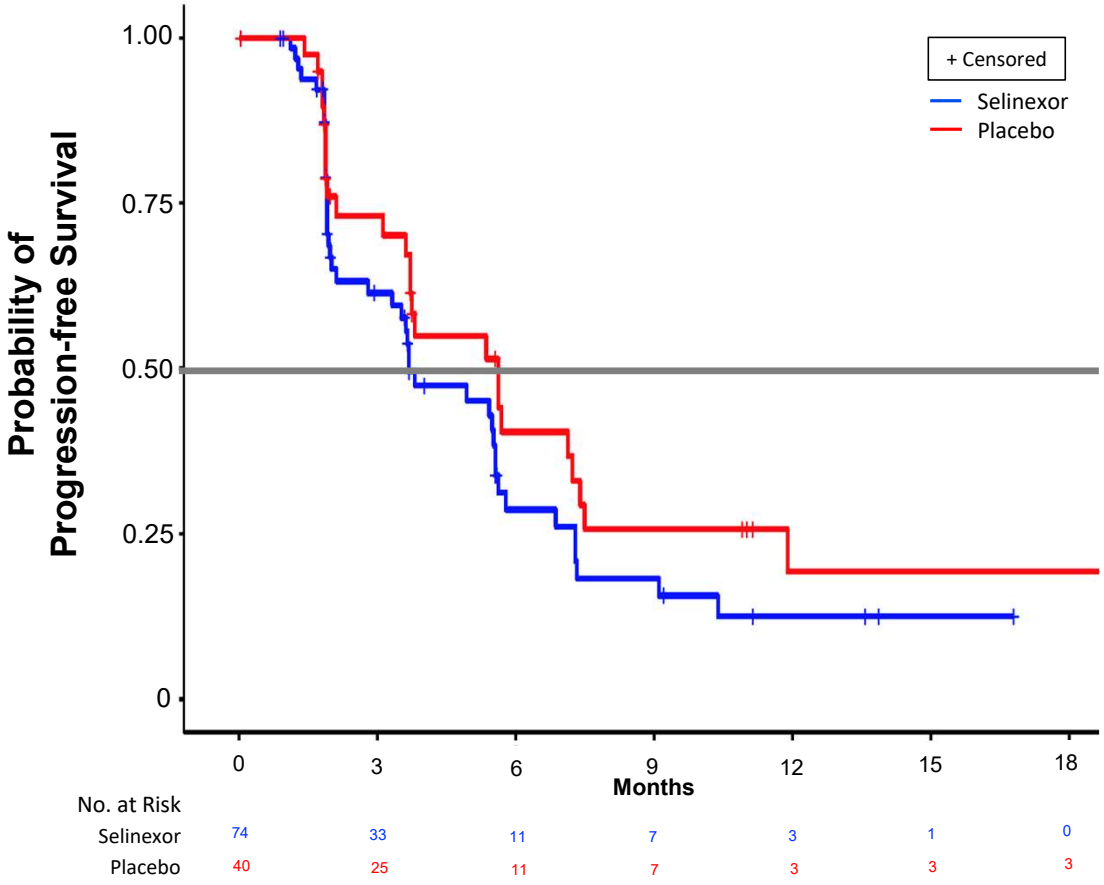
Preliminary Analysis of a Prespecified Exploratory Subgroup PFS: Patients with p53 Mutant/Aberrant EC



Median PFS

Selinexor (n=74): 3.7 mo (95% CI 3.32-5.55)

Placebo (n=40): 5.6 mo (95% CI 3.71-7.49)

Audited

HR = 1.306 (95% CI 0.795-2.145)

Nominal one-sided P value = 0.8530

Unaudited

HR = 1.345 (95% CI 0.819-2.208)

Nominal one-sided P value = 0.8785

CI, confidence interval; HR, hazard ratio; mo, months; PFS, progression-free survival

Preliminary Exploratory Analysis of Mutually-Exclusive TCGA Subgroups

	Selinexor	Placebo	*One-sided p-value* (nominal)	HR (95% CI)
	Progression-free survival — median, (months)			
POLE mutated (selinexor n=2, placebo n=4)				
Stratification-adjusted, audited	3.8	1.9	0.404	0.71 (0.04-11.79)
Stratification-adjusted, unaudited			0.404	0.71 (0.04-11.79)
MSI-H (selinexor n=18, placebo n=8)				
Stratification-adjusted, audited	6.4	NR	0.685	1.41 (0.35-5.67)
Stratification-adjusted, unaudited			0.685	1.41 (0.35-5.67)
Copy number low (selinexor n=37, placebo n=20)				
Stratification-adjusted, audited	NR	3.7	<0.0001	0.16 (0.06-0.44)
Stratification-adjusted, unaudited			0.0004	0.22 (0.09-0.58)
Copy number high (selinexor n=50, placebo n=33)				
Stratification-adjusted, audited	3.7	5.6	0.820	1.31 (0.74-2.31)
Stratification-adjusted, unaudited			0.860	1.37 (0.77-2.41)

CI, confidence interval; HR, hazard ratio; mo, months; NR, not reached; PFS, progression-free survival

Summary and Conclusions

- Once-weekly oral selinexor may prolong progression-free survival compared to placebo in patients with advanced or recurrent endometrial cancer; the audited ITT population had a 30% decrease of risk for progression and/or death compared to placebo

- Pre-specified exploratory subgroup analyses identified p53 wild-type as a potential predictor of efficacy of selinexor, with 10-month PFS improvement over placebo; no benefit for selinexor was seen in patients with p53 mutant/aberrant tumors

- In this small, exploratory subgroup analysis, potential benefit may be observed for selinexor over placebo in the patients with p53 wild-type including MSS and Copy-Number Low endometrial cancer

- Further investigation is warranted for selinexor as a maintenance treatment for patients with p53 wt endometrial cancer

Acknowledgments

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