Longer-term Safety and Efficacy of Selinexor Maintenance Therapy for Patients With *TP53*wt Advanced or Recurrent Endometrial Cancer: Follow-up Subgroup Analysis of the ENGOT-EN5/GOG-3055/SIENDO Study

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Disclosure

Alejandro Pérez-Fidalgo, MD, PhD

GEICO and Hospital Clínico Universitario de Valencia, Valencia, Spain

Company Name	Honoraria/ Expenses	Consulting/ Advisory Board	Funded Research	Royalties/ Patent	Stock Options	Ownership / Equity Position	Employee	Other (please specify)
AstraZeneca	X		X					
Merck Sharp & Dohme	X		X					
GlaxoSmithKline	X							Received equipment
Pharma&			X					
Amgen		X						
Clovis		X						

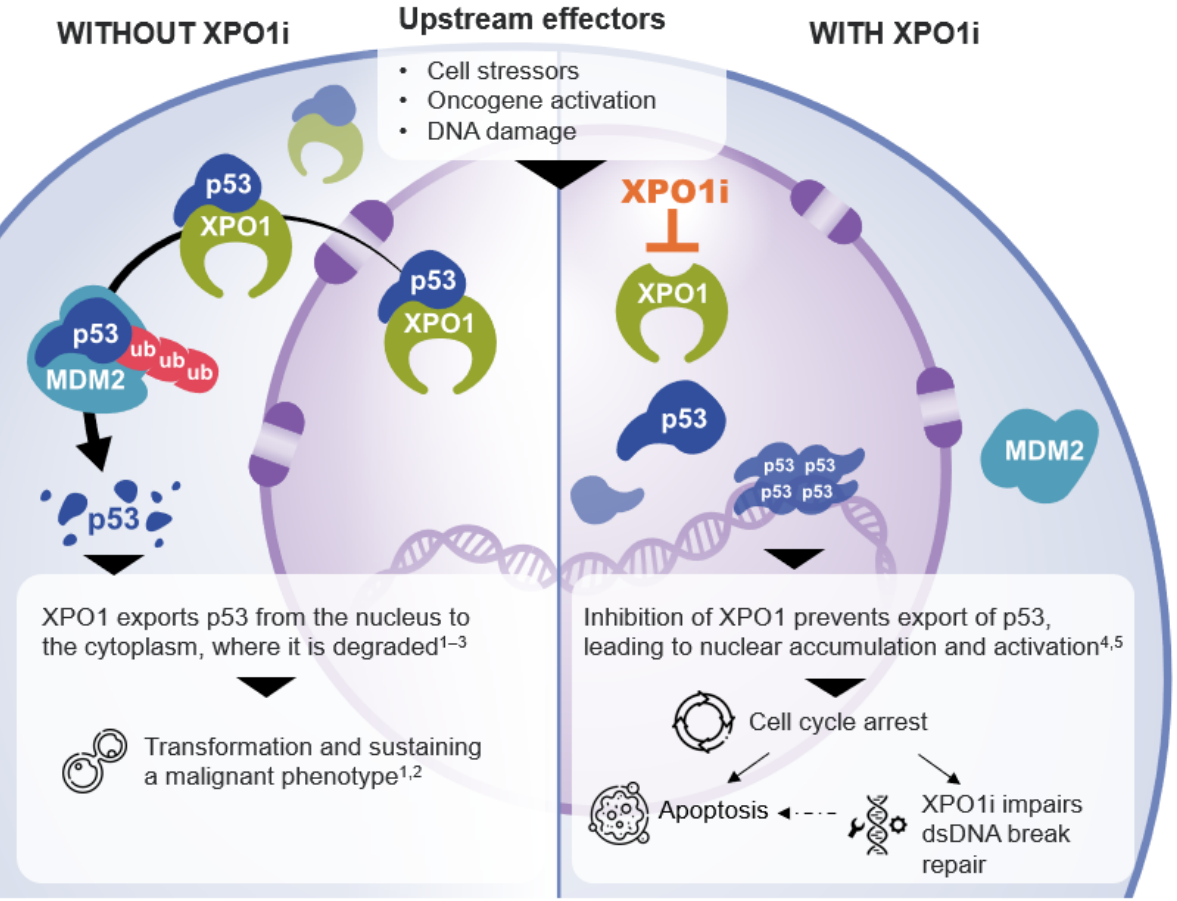
Selinexor is a Novel Oral Maintenance Therapy Targeting *TP53*wt Endometrial Cancer

- Immune checkpoint inhibitors showed clinically meaningful benefit in patients with dMMR EC, but benefit in those with pMMR tumors was more modest[1-6]
  - dMMR tumors (mPFS, 30-NR mo; mOS, NR)[1-5]
  - pMMR tumors (mPFS, 10-14 mo; mOS, 28-34 mo)[1-5]
  - Q-TWiST difference: pMMR tumors: 2.57 mo; dMMR tumors: 5.44 mo (RUBY-I)[6]
- *TP53* is a well-recognized prognostic marker for EC; >50% of advanced or recurrent EC tumors are *TP53*wt, and ~40-55% are both *TP53*wt and pMMR[7-9]
- Selinexor is a novel oral maintenance therapy targeting *TP53*wt EC[8,10]
  - At primary analysis of the phase 3 SIENDO study of selinexor maintenance therapy in patients with advanced or recurrent EC, the improvement in PFS for the ITT population was not clinically meaningful
  - A prespecified exploratory analysis of *TP53* wild-type status showed a promising efficacy signal in patients with *TP53*wt

dMMR, deficient mismatch repair; EC, endometrial cancer; ITT, intent-to-treat; mo, month; pMMR, proficient mismatch repair; PFS, progression-free survival; Q-TWiST, *TP53*, tumor protein 53 gene; wt, wild-type; XPO1, exportin 1; XPO1i, XPO1 inhibition.

1. Mirza MR, et al. *N Eng J Med.* 2023;388:2145-2158. **2.** Eskander RN, et al. *N Eng J Med.* 2023; 388:2159-2170. **3.** Powell MA, et al. Presentation at: SGO Annual Meeting on Women's Cancer; March 16-18, 2024. **4.** Mirza MR, et al. Presentation at: SGO Annual Meeting on Women's Cancer; March 16-18, 2024. **5.** Eskander RN, et al. Presentation at: SGO Annual Meeting on Women's Cancer; March 16-18, 2024. **6.** Chase DN, et al. Presentation at: ESGO; September 28-October 1, 2023. **7.** Leslie KK, et al. *Gynecol Oncol*. 2021;161(1):113-121. **8.** Vergote I, et al. *J Clin Oncol*. 2023;41(35):5400-5410. **9.** Mirza MR, et al. Presentation at: ESMO Congress; October 20-24, 2023. **10.** Vergote I, et al. Presentation at: European Society for Medical Oncology Virtual Plenary; March 17-18, 2022; Abstract VP2-2022.

Selinexor is a Novel Oral Maintenance Therapy Targeting *TP53*wt Endometrial Cancer



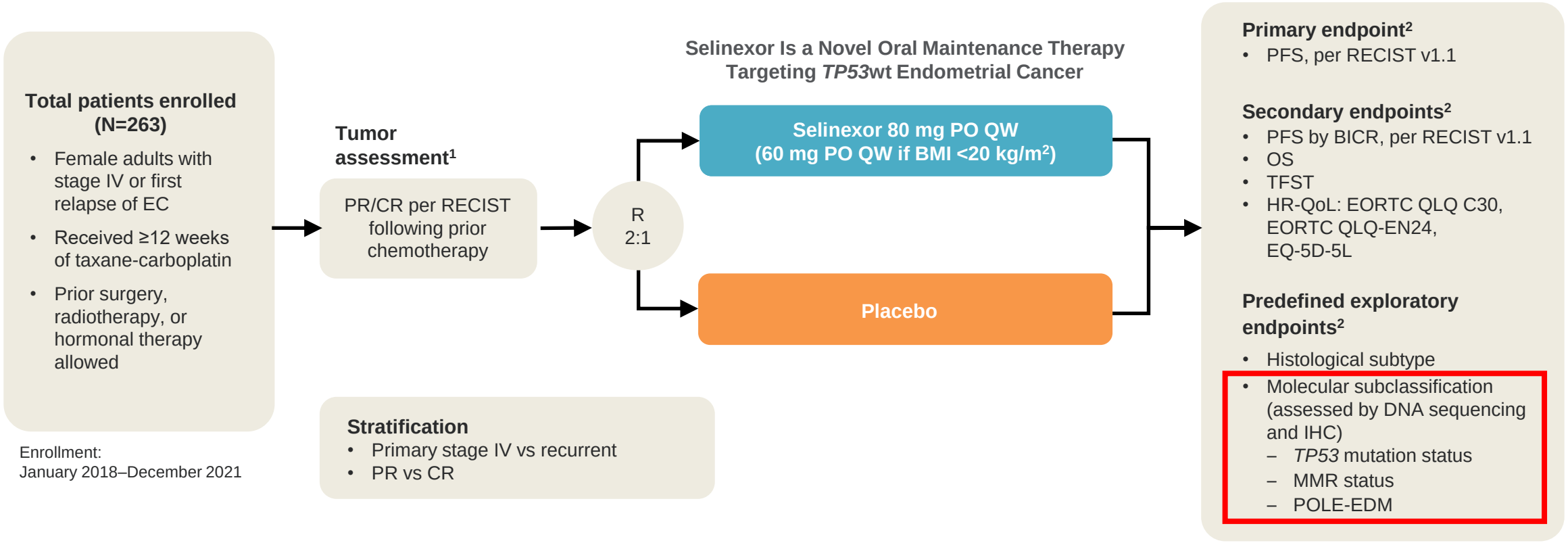
- XPO1 inhibition by selinexor results in nuclear retention and functional reactivation of tumor suppressor proteins (TSPs), which selectively kills cancer cells and largely spares normal cells[1,4,6]
- XPO1 inhibition (XPO1i) sequesters p53 in the nucleus, leading to cell cycle arrest with impaired DNA repair and apoptosis[4,5]

While there are multiple mechanisms by which selinexor induces cancer cell death, **in EC, the primary mechanism is believed to be through nuclear retention and reactivation of TSPs such as wild-type p53**

dMMR, deficient mismatch repair; dsDNA, double-stranded DNA; EC, endometrial cancer; ITT, intent-to-treat; p53, tumor protein 53; PFS, progression-free survival; pMMR, proficient mismatch repair; *TP53*, tumor protein 53 gene; TSP, tumor suppressor protein; wt, wild-type; XPO1, exportin 1; XPO1i, XPO1 inhibition.

1. Bogani G et al. *Curr Probl Cancer.* 2023;47(6):100963. **2.** Gandhi UH et al. *Clin Lymphoma Myeloma Leuk*. 2018;18(5):335-345. **3.** Marchenko ND et al. *Cell Death Differ.* 2010;17(2):255-267. 4. Kashyap T, et al. *Oncotarget*. 2018;9(56):30773-30786. **5.** Tai Y-T, et al. *Leukemia*. 2014;28(1):155-165. **6.** Kashyap T, et al. *Oncotarget*. 2016;7(48):78883-78895.

ENGOT-EN5/GOG-3055/SIENDO (NCT03555422): A Randomized Double-Blind, Phase 3 Trial of Maintenance With Selinexor/Placebo After Combination Chemotherapy for Patients With Advanced or Recurrent Endometrial Cancer



BICR, blinded independent central review; BMI, body mass index; CR, complete response; EC, endometrial cancer; EDM, exonuclease domain mutation; EORTC, European Organisation for Research and Treatment of Cancer; EQ-5D-5L, 5-level EuroQoL 5-dimensional questionnaire; HR-QoL, health-related quality of life; IHC, immunohistochemistry; IV, intravenous; MMR, mismatch repair; OS, overall survival; PFS, progression-free survival; PO, by mouth; *POLE*, polymerase epsilon; PR, partial response; QLQ, quality-of-life questionnaire; QW, once weekly; R, randomized; RECIST, Response Evaluation Criteria in Solid Tumors; TFST, time to first subsequent therapy; *TP53*, tumor protein 53 gene; wt, wild-type.

1. ClinicalTrials.gov. NCT03555422. https://www.clinicaltrials.gov/study/NCT03555422?term=NCT03555422. Accessed April 1, 2024. **2.** Vergote I, *et al.* Presentation at: European Society for Medical Oncology Virtual Plenary; March 17-18, 2022. Abstract VP2-2022.
Primary study results previously published in Vergote I, et al. *J Clin Oncol.* 2023;41(35):5400-5410.

Patient Demographics and Baseline Characteristics

Characteristics	*TP53*wt*	
	Selinexor n=77	Placebo n=36
Age, years, median (range)	64.0 (40-81)	61.5 (33-74)
≥70 years, n (%)	23 (29.9)	8 (22.2)
Race, n (%)		
White	75 (97.4)	34 (94.4)
Black	1 (1.3)	0
Other†	1 (1.3)	2 (5.6)
ECOG performance status, n (%)		
0	43 (55.8)	22 (61.1)
1	33 (42.9)	14 (38.9)
2	1 (1.3)	0
Histology, n (%)		
Endometrioid	65 (84.4)	29 (80.6)
Serous	3 (3.9)	3 (8.3)
Undifferentiated	0	1 (2.8)
Carcinosarcoma	1 (1.3)	0
Adenocarcinoma	8 (10.4)	3 (8.3)

Characteristic	*TP53*wt*	
	Selinexor n=77	Placebo n=36
Disease at time of taxane-platinum combination therapy, n (%)		
Primary stage IV disease	34 (44.2)	17 (47.2)
Recurrent disease	41 (53.2)	18 (50.0)
Missing	2 (2.6)	1 (2.8)
Response after the most recent chemotherapy, n (%)		
CR	31 (40.3)	17 (47.2)
PR	46 (59.7)	19 (52.8)
Molecular characterization of mismatch repair status, n (%)		
pMMR	47 (61.0)	23 (63.9)
dMMR	20 (26.0)	9 (25.0)
Unknown	10 (13.0)	4 (11.1)

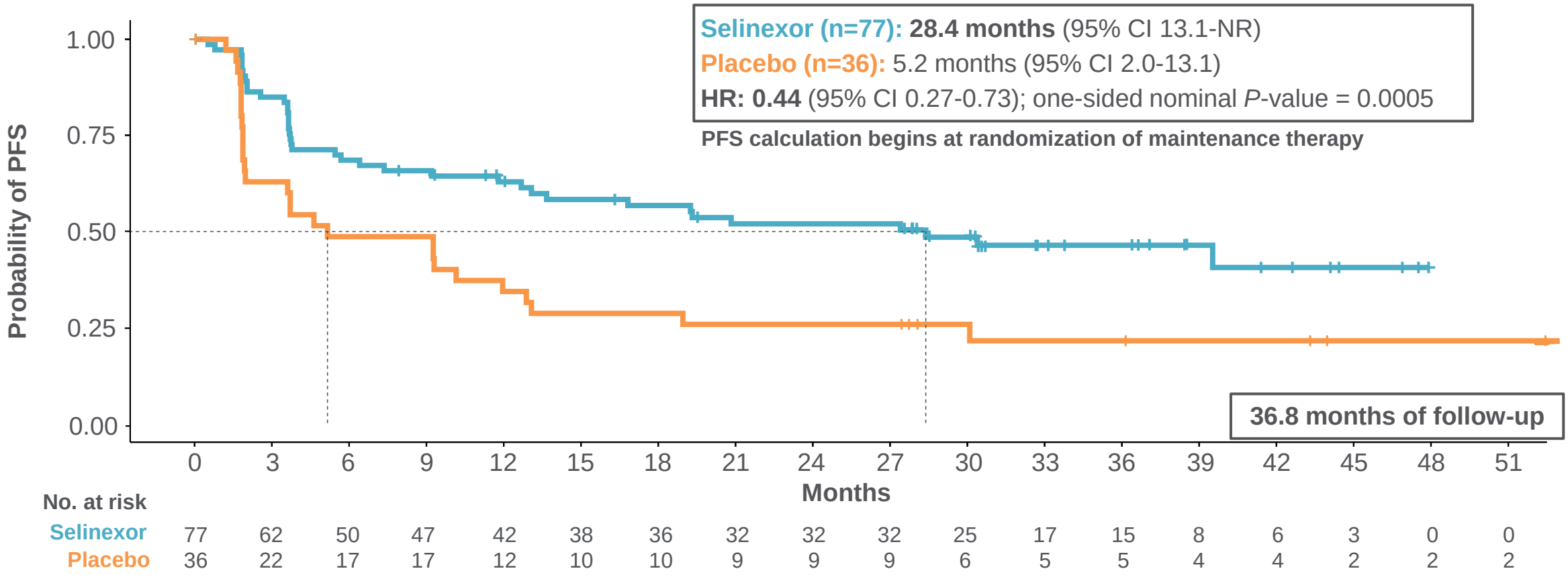
Data cutoff date: April 1, 2024.

CR, complete remission; dMMR, deficient mismatch repair; ECOG, Eastern Cooperative Oncology Group; NGS, next-generation sequencing; pMMR, proficient mismatch repair; PR, partial remission; *TP53*, tumor protein 53 gene; wt, wild-type.

*Molecular status determined by NGS (*TP53*wt, n=99; *TP53* mutant, n=97; unknown, n=43.

†Includes, Asian, Native Hawaiian or other Pacific Islander, unreported, and unknown.

Long-term mPFS of 28.4 Months in *TP53*wt Subgroup

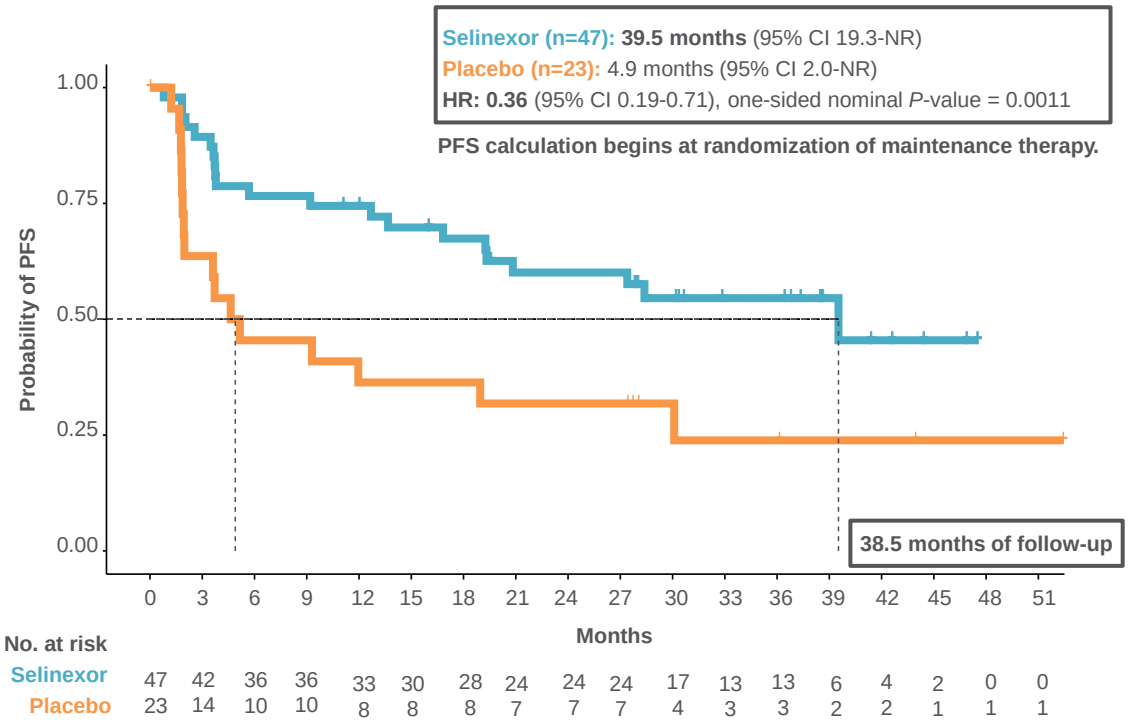


Data cutoff date: April 1, 2024.

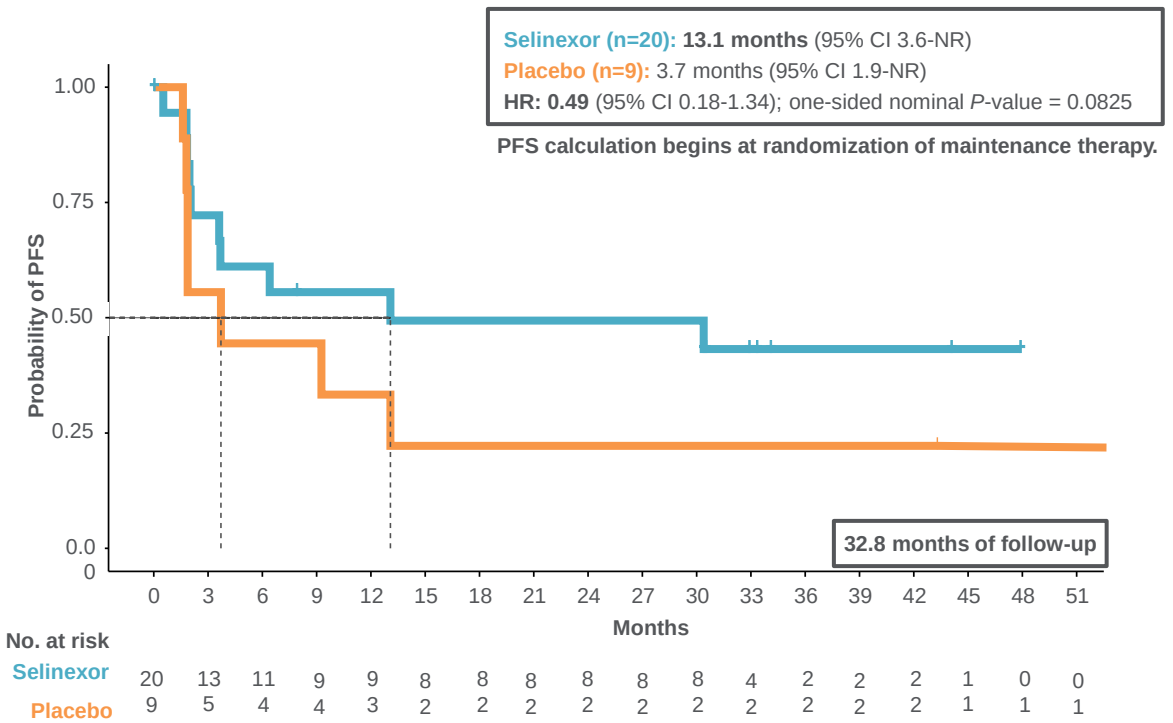
CI, confidence internal; dMMR, deficient mismatch repair; HR, hazard ratio; mPFS, median progression-free survival; NR, not reported; pMMR, proficient mismatch repair; *TP53*, tumor protein 53 gene; wt, wild-type.

Long-term mPFS of 39.5 Months 13.1 Months in *TP53*wt/pMMR and *TP53*wt/dMMR Subgroups, Respectively

*TP53*wt/pMMR



*TP53*wt/dMMR



Data cutoff date: April 1, 2024.

CI, confidence internal; dMMR, deficient mismatch repair; HR, hazard ratio; mPFS, median progression-free survival; NR, not reported; pMMR, proficient mismatch repair; *TP53*, tumor protein 53 gene; wt, wild-type.

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Preliminary Overall Survival

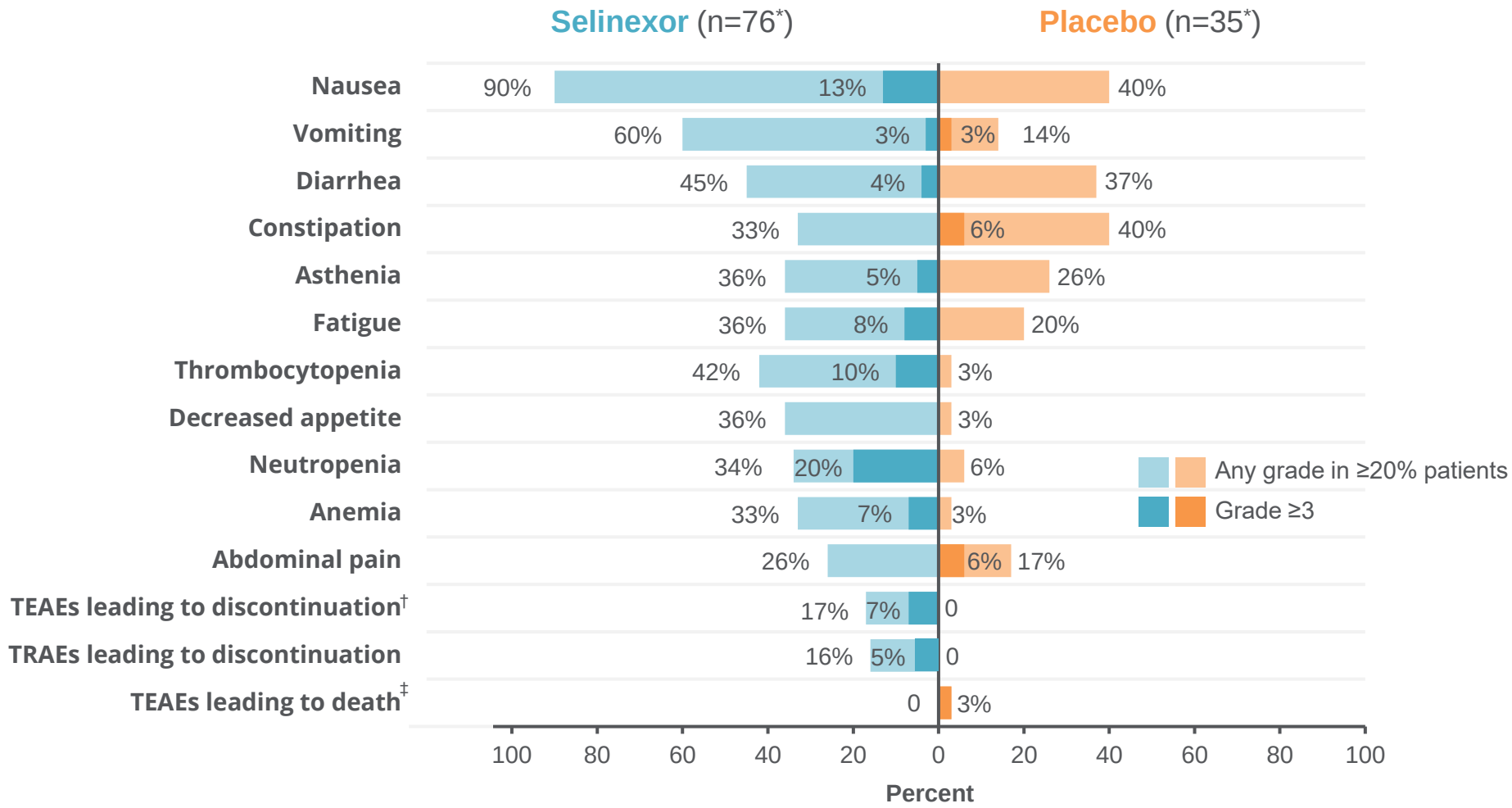
	No. with events	Median, months (95% CI)	Overall maturity	HR (95% CI)	Nominal one-sided *P*-value	Median follow-up (months)
***TP53*wt**						
Selinexor (n=77)	24.7%	NR (45.4-NR)	29.2%	**0.65** (0.32-1.29)	0.11	36.8
Placebo (n=36)	38.9%	NR (35.2-NR)				
***TP53*wt/pMMR**						
Selinexor (n=47)	25.5%	NR (45.4-NR)	34.3%	**0.48** (0.22-1.07)	0.03	38.5
Placebo (n=23)	52.2%	35.2 (26.9-NR)				
***TP53*wt/dMMR**						
Selinexor (n=20)	10.0%	NR (NR-NR)	10.3%	**0.62** (0.06-6.81)	0.35	32.8
Placebo (n=9)	11.1%	NR (NR-NR)				

OS calculation begins at randomization of maintenance therapy.

Data cutoff date: April 1, 2024.

CI, confidence interval; dMMR, deficient mismatch repair; HR, hazard ratio; No., number; NR, not reported; pMMR, proficient mismatch repair; OS, overall survival; *TP53*, tumor protein 53 gene; wt, wild-type.

Treatment-emergent Adverse Events



Data cutoff date: April 1, 2024.

TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

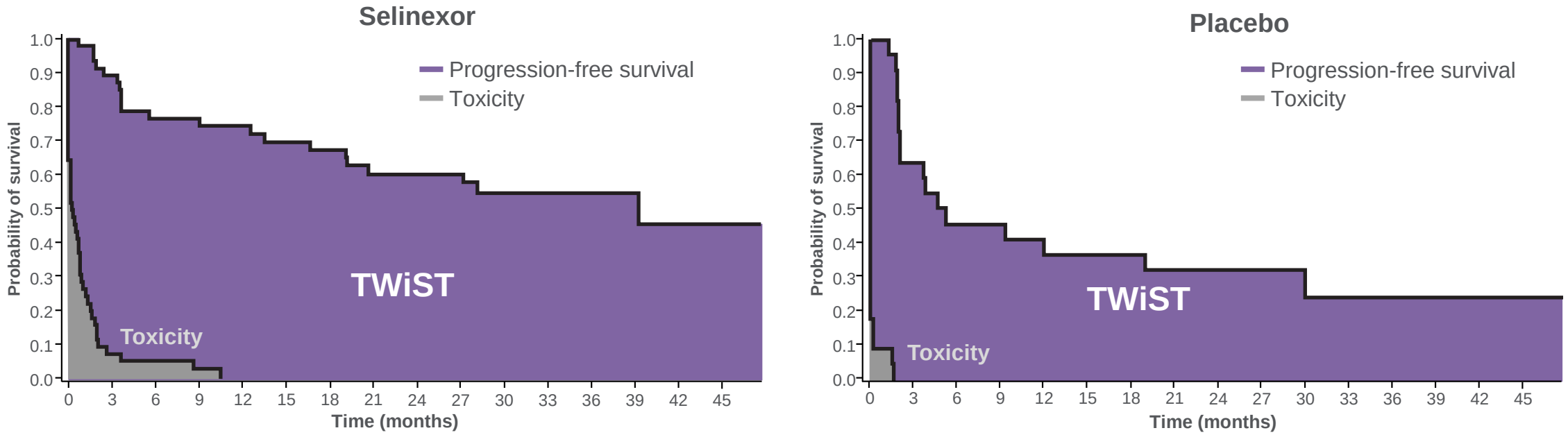
*Two patients total did not receive treatment (n=1, selinexor; n=1, placebo) and were excluded from this analysis.

†Reasons for discontinuation: nausea (n=5), fatigue (n=3), vomiting (n=3), asthenia, cataract, general physical health deterioration, ileus, neutropenia (all n=1).

‡Reason for death was unknown/missing.

Exploratory Q-TWiST Analysis of *TP53*wt/pMMR Subgroup

- **In the *TP53*wt group, the clinically meaningful improvement in PFS was maintained while adjusting for quality of life and toxicity, with a difference of 10.63 months**
- **Additionally, a clinically meaningful improvement in PFS was observed in the *TP53*wt/pMMR subgroup after adjusting for quality of life and toxicity, with a difference of 12.70 months**



Health state	Selinexor, mo (95% CI*)	Placebo, mo (95% CI*)	Difference, mo (95% CI*)
Q-TWiST†	29.60 (23.90-35.15)	16.90 (9.06-25.54)	12.70 (2.47-22.18)

Data cutoff date: April 1, 2024.

CI, confidence interval; mo, month; PFS, progression-free survival; pMMR, proficient mismatch repair; TOX, time with ≥3 grade adverse events; *TP53*, tumor protein 53 gene; TWiST, time without symptoms and toxicity; wt, wild-type.

*95% CI's are based on 10000 times of bootstrapping. †Q-TWIST = (Utility$_{TWiST}$ × TWiST) + (Utility$_{TOX}$ × TOX), where Utility$_{TWiST}$ = 1; Utility$_{TOX}$ = 0.5.

Note: The Q-TWiST analysis begins from the start of maintenance therapy and does not include overall survival due to data immaturity.

ENGOT-EN20/GOG-3083/XPORT-EC-042 (NCT05611931) Selinexor Maintenance Therapy After Systemic Therapy for Patients With Advanced or Recurrent P53wt Endometrial Carcinoma

Study is ongoing and actively enrolling

Planned enrollment (N=220)

Patients aged ≥18 years with
- Known *TP53*wt EC by central NGS
- Primary stage IV disease or first recurrent EC
- Received ≥12 weeks of platinum-based chemotherapy ± immunotherapy

PR/CR per RECIST v1.1 following prior chemotherapy

R 1:1

Selinexor 60 mg PO QW
Until PD, toxicity, or 3 years if in CR

Placebo PO QW
Until PD, toxicity, or 3 years if in CR

Stratification
- Primary stage IV vs recurrent
- PR vs CR

Primary endpoint
- PFS assessed by investigator

Key secondary endpoint
- OS

Other secondary endpoints
- Safety
- TFST
- TSST
- PFS2
- PFS assessed by BICR
- QoL (EQ-5D-5L)

Exploratory endpoints
- PFS per histology subtypes and per other molecular features
- CR rate
- Duration of CR
- Tumor biomarkers
- PK exposure parameters and efficacy/safety endpoints

BICR, blinded independent central review; CR, complete response; EC, endometrial cancer; EQ-5D-5L, 5-level EuroQoL 5-dimensional questionnaire; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; PR, partial response; QoL, quality of life; QW, once weekly; RECIST, Response Evaluation Criteria in Solid Tumors; TFST, time to first subsequent therapy; *TP53*, tumor protein 53 gene; TSST, time to second subsequent treatment; wt, wild-type.
ClinicalTrials.gov identifier: NCT05611931. Updated Sep 19, 2023. Accessed Sep 24, 2024. https://classic.clinicaltrials.gov/ct2/show/NCT05611931

Acknowledgments

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We thank participating patients and their families, all investigators, and academic study groups for participating in the SIENDO trial

BGOG	GOG	GEICO	CEEGOG	MITO	ISGO	NOGGO	USOC	HeCOG	China	Canada	USA
Vergote	Randall	Perez-Fidalgo	Cibula	Valabrega	Helpman	Sehouli	Tibayan	Fountzilas	Zhou	Oza	Cappuccini
Van Gorp	Pothuri	Fariñas-Madrid	Klat	Scambia	Safra	Wimberger	Cloven	Christopoulou	Wang	Gilbert	Amin
Cadron	Robison	Raposo	Melichar	Mangili	Levy	Bauerschlag	De la Garza	Papadimitriou	Yang Y.	Welch	Shum
Barbeaux	Boone	Romero	Zikan	Raspagliesi	Bruchim	Trillsch	Lee	Zagouri	Tu	Kolinsky	Gilmore
Cornez	Barlin	Iglesias	Reginacova	Pisano	Rosengarten	Tome	Matthews		Wang L.		Hamilton
Henry	Ghamande	Santaballa	Weinberger	Sartori	Zick	Schochter	Preibe		Lou		LyBarger
Kerger	Guirguis	Ancizar		De Giorgi		Battista	Teneriello		Yang		Spitz
Debaere	Sharma	Estévez				Aktas	Anderson		Lv		Tenney
Denys	Podzielinski	Maximiano				Luebbe	Monk		Yang J.		Buscema
	Landrum	Yubero				Deryal			Wang D.		Chon
	Nevadunsky	Oaknin									Berek
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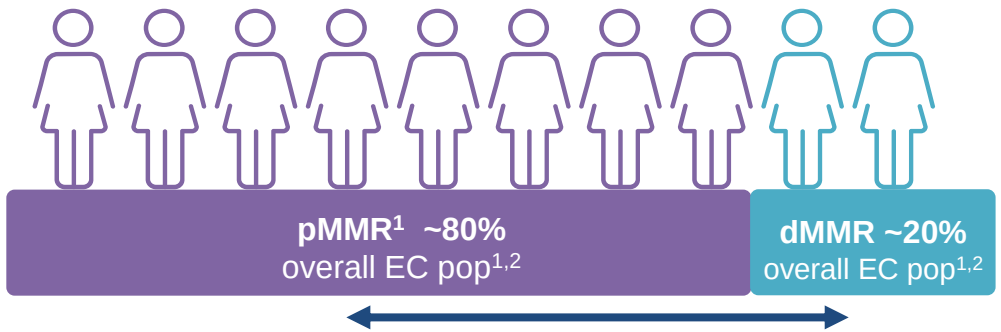
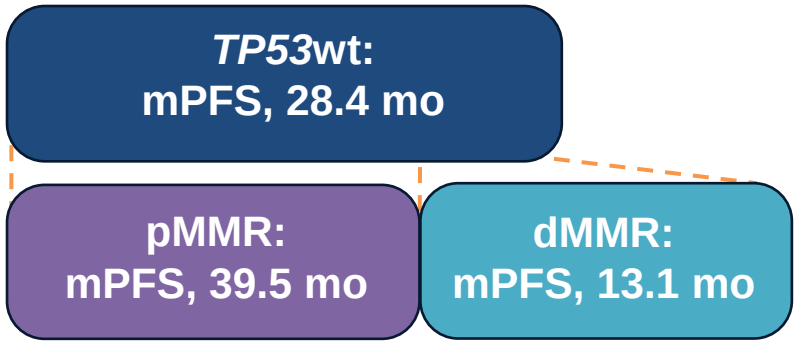
Study Sponsor: Karyopharm Therapeutics
Mansoor Raza Mirza
Pratheek Kalyanapu

These Results Further Support the Ongoing Phase 3 ENGOT-EN20/GOG-3083/XPORT-EC-042 Trial of Selinexor 60 mg QW as Maintenance Therapy in Patients With Advanced or Recurrent *TP53*wt EC



Selinexor maintenance therapy



- A marked PFS benefit was observed with selinexor maintenance therapy in the novel *TP53*wt/pMMR subgroup (mPFS 39.5 mo), a patient population with limited effective therapeutic options
- Encouraging signals in overall survival analyses were also observed across all subgroups
- No new safety signals were identified
- The substantial signal of PFS improvement with selinexor in *TP53*wt and *TP53*wt/pMMR EC is reinforced by the Q-TWiST analysis, which integrates both quality and quantity of life
- The data support the potential role of selinexor as a maintenance treatment option in advanced or recurrent *TP53*wt EC

dMMR, deficient mismatch repair; EC, endometrial cancer; MMR, mismatch repair; mo, month; mPFS, median progression-free survival; PFS, progression-free survival; pMMR, proficient mismatch repair; QW, once weekly; *TP53*, tumor protein 53 gene; TWiST, time without symptoms and toxicity; wt, wild-type.

1. Mirza M, et al. Presentation **at**: ESMO Congress Oct 20-24 2023, Abstract 740MO. **2.** Vergote I, et *al J Clin Oncol.* 2023;41(35):5400-5410. **3.** Leslie KK, et al. *Gynecol Oncol*. 2021; 161(1):113-121.