Oral Selinexor as Maintenance Therapy After First-Line Chemotherapy for Advanced or Recurrent Endometrial Cancer

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ABSTRACT

PURPOSE Selinexor inhibits exportin-1 (XPO1) resulting in nuclear accumulation of tumor suppressor proteins including p53 and has clinical activity in endometrial cancer (EC). The primary end point was to assess progression-free survival (PFS) with once-weekly oral selinexor in patients with advanced or recurrent EC.

PATIENTS AND METHODS ENGOT-EN5/GOG-3055/SIENDO was a randomized, prospective, multicenter, double-blind, placebo-controlled, phase III study at 107 sites in 10 countries. Patients 18 years or older with histologically confirmed EC were enrolled. All had completed a single line of at least 12 weeks of taxane-platinum combination chemotherapy and achieved partial or complete response. Patients were assigned to receive 80 mg oral selinexor once weekly or placebo with 2:1 random assignment (ClinicalTrials.gov identifier: NCT03555422).

RESULTS Between January 2018 and December 2021, 263 patients were randomly assigned, with 174 allocated to selinexor and 89 to placebo. The median PFS was 5.7 months (95% CI, 3.81 to 9.20) with selinexor versus 3.8 months (95% CI, 3.68 to 7.39) with placebo (hazard ratio [HR], 0.76 [95% CI, 0.54 to 1.08]; two-sided $P = .126$), which did not meet the criteria for statistical significance in the intent-to-treat population. Incorrect chemotherapy response stratification data for 7 (2.7%) patients were identified. In a prespecified exploratory analysis of PFS in audited stratification data, PFS for selinexor met the threshold for statistical significance (HR, 0.71; 95% CI, 0.499 to 0.996; two-sided $P = .049$). Furthermore, patients with the *TP53* wild-type (wt) EC had a median PFS of 13.7 and 3.7 months with selinexor and placebo. The most common grade 3 treatment-related adverse events were nausea (9%), neutropenia (9%), and thrombocytopenia (7%).

CONCLUSION The significance level for PFS was only met in the audited analysis. However, a preliminary analysis of a prespecified exploratory subgroup of patients with *TP53*wt EC showed promising results with selinexor maintenance therapy.

ACCOMPANYING CONTENT

Appendix

Protocol

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INTRODUCTION

Patients with advanced or recurrent endometrial cancer (EC) have a poor prognosis and a median survival of 12-18 months.[1] Mortality varies depending on factors such as histologic subtype, tumor grade, disease stage, and molecular phenotype.[2,3] Although maintenance therapy can prolong response to chemotherapy and delay the need for typical parenteral therapies with associated toxicities, there are currently no approved maintenance-only strategies for advanced or first recurrent EC.[4]

The karyopherin protein exportin-1 (XPO1, also known as CRM1) is responsible for the export of >200 proteins[5] including tumor suppressor proteins such as p53, PTEN and FOXO1, along with growth/cell cycle regulatory proteins such as p21 and p27.[6-8] Overexpression of XPO1 occurs in a myriad

CONTEXT

Key Objective

Does prevention of exportin-1–mediated nuclear export by once-weekly selinexor act as a novel therapy in patients with advanced or first recurrent endometrial cancer (EC)?

Knowledge Generated

As the mechanism of selinexor primarily drives the nuclear retention and functional activation of tumor suppressor proteins like p53, a preliminary analysis of the prespecified exploratory subgroup of patients with *TP53*wt tumors (found at diagnosis in approximately 75% of ECs) showed longer progression-free survival compared with placebo.

Relevance *(G.F. Fleming)*

A randomized clinical trial using selinexor as maintenance therapy for participants with p53 wild-type advanced or recurrent endometrial is currently underway.*

*Relevance section written by *JCO* Associate Editor Gini F. Fleming, MD.

of cancers[9] and is correlated with advanced disease, resistance to therapy, and poor survival in humans.[6]

Selinexor is a selective inhibitor of nuclear export (SINE) compound that prevents XPO1-mediated nuclear export.[10] Inhibition of XPO1 by selinexor leads to nuclear accumulation and functional reactivation of tumor suppressor proteins such as p53 in both solid tumors and hematologic malignancies.[11] In addition, in vitro selinexor reduces mRNA levels of key DNA damage repair genes including *MSH6*, *MSH2*, *CHEK1*, *MLH1*, and *RAD51* and inhibits PMS2 steady-state protein levels in a dose-dependent manner.[12] This implies that selinexor on both transcriptional and translational levels can play a role in the downregulation of the expression of DNA damage repair gene products, which may contribute to enhancement of DNA-damaging agents.

Selinexor is US Food and Drug Administration–approved for relapsed/refractory multiple myeloma[13,14] and relapsed/refractory diffuse large B-cell lymphoma[15] and demonstrates a manageable safety profile. The phase II SIGN study included 114 patients with advanced, progressing gynecologic malignancies treated with oral selinexor monotherapy once or twice weekly. Among the 23 patients with recurrent EC, the disease control rate was 35% and the confirmed objective response rate was 9%.[16] Tolerability was improved with once-weekly compared with twice-weekly selinexor dosing in patients with heavily pretreated ovarian cancer, with low-grade and reversible side effects and no clinically significant long-term effects or major organ toxicities.[16] This supported the further investigation of selinexor in gynecologic cancers such as EC where patients have a paucity of treatment options.[16] On the basis of these results, we designed the current study to evaluate the efficacy and tolerability of oral, once-weekly selinexor versus placebo as a maintenance therapy after chemotherapy in patients with advanced or first recurrent EC.

PATIENTS AND METHODS

Patients and Study Design

The ENGOT-EN5/GOG-3055/SIENDO study was a randomized, prospective, multicenter, double-blind, placebo-controlled, phase III study performed in 107 sites in 10 countries in patients with advanced or recurrent EC in partial or complete remission to their previous chemotherapy.[17]

Eligible patients were 18 years or older with histologically confirmed EC of the endometrioid, serous or undifferentiated type, or uterine carcinosarcoma. All patients had completed at least 12 weeks of taxane-platinum combination chemotherapy for primary stage IV disease (FIGO 2009)[18] or at first relapse EC and achieved a partial response or complete response according to RECIST v1.1[17] and had an Eastern Cooperative Oncology Group performance status score[19] of 0 to 1. Patients were excluded if they had sarcomas, small cell carcinoma with neuroendocrine differentiation, or clear cell carcinomas; had previous treatment with an XPO1 inhibitor, anti–PD-1 or anti–PD-L1 immunotherapy; or had brain metastases. A full list of inclusion/exclusion criteria is provided in Appendix Table A1 (online only).

This study was approved and performed in accordance with the International Conference on Harmonization, the Guidelines for Good Clinical Practice, and appropriate regulatory requirements and with approval of institutional review boards at individual enrolling institutions. All patients provided written informed consent before study start. The study was performed according to ENGOT model C.[20]

Random Assignment

Patients were randomly assigned in a ratio of 2:1 to receive selinexor or placebo after at least 12 weeks of chemotherapy. Random assignment was stratified on the basis of primary

TABLE 1. Baseline Demographic and Clinical Characteristics

Characteristic	Selinexor (n = 174)	Placebo (n = 89)
Age, years, median (range)	65.5 (40-81)	64.0 (33-81)
<70	116 (66.7)	61 (68.5)
≥70	58 (33.3)	28 (31.5)
Race, No. (%)		
Asian	4 (2.3)	4 (4.5)
Black or African American	7 (4.0)	2 (2.2)
Native Hawaiian or other Pacific Islander	1 (0.6)	0
White	158 (90.8)	81 (91.0)
Others	4 (2.3)	2 (2.2)
Ethnicity, No. (%)		
Hispanic or Latino	9 (5.2)	5 (5.6)
Not Hispanic or Latino	160 (92.0)	83 (93.3)
Not reported	1 (0.6)	0
Unknown	4 (2.3)	1 (1.1)
ECOG performance status,[a] No. (%)		
0	99 (56.9)	54 (60.7)
1	71 (40.8)	35 (39.3)
2	1 (0.6)	0
Histology, No. (%)		
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[b]	15 (8.6)	6 (6.7)
No. of previous antineoplastic regimens, No. (%)		
1	172 (98.9)	85 (95.5)
2	2 (1.1)	3 (3.4)
3	0	1 (1.1)
Molecular characterization of *TP53* mutation status,[c] No. (%)		
Wild type	67 (38.5)	36 (40.4)
Mutant/aberrant	74 (42.5)	40 (44.9)
Unknown	33 (19)	13 (14.6)
Molecular characterization of microsatellite instability status,[c] No. (%)		
MSS/pMMR	113 (64.9)	59 (66.3)
MSI-H/dMMR	22 (12.6)	13 (14.6)
Unknown	39 (22.4)	17 (19.1)
Disease at the time of taxane-platinum combination therapy, No. (%)		
Unaudited stratification factors		
Primary stage IV disease	82 (47.1)	41 (46.1)
Recurrent disease	83 (47.7)	41 (46.1)
Missing[d]	9 (5.2)	7 (7.9)
Audited stratification factors[e]		
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, No. (%)		
Unaudited stratification factors		
Complete response	72 (41.4)	37 (41.6)
Partial response	102 (58.6)	52 (58.4)
Audited stratification factors[e]		
Complete response	70 (40.2)	40 (44.9)
Partial response	104 (59.8)	49 (55.1)

Abbreviations: CR, complete response; dMMR, deficient mismatch repair; ECOG, Eastern Cooperative Oncology Group; MSI-H, microsatellite instability high; MSS, microsatellite stable; NGS, next-generation sequencing; pMMR, mismatch repair–proficient; PR, partial response.

[a]ECOG performance status scores range from 0 to 5, with higher scores reflecting greater disability.

[b]Not otherwise specified.

[c]Molecular status was determined by sequencing (*TP53*wt n = 84; *TP53* mutant n = 89; MSS/pMMR n = 144) and, if NGS is not available, by immunohistochemistry (p53wt = 19; p53-mutant/p53-aberrant n = 25; MSS/pMMR n = 28).

[d]The stratification factor of disease at the time of taxane-platinum chemotherapy was added in protocol version 2.0. Missing therefore denotes that the patients were enrolled before protocol version 2.0.

[e]In seven patients (2.7% of 263), the stratification factor of CR/PR was incorrect and was corrected by the investigators before database lock and unblinding; placebo arm: PR to CR (n = 3); selinexor arm: CR to PR (n = 3) and PR to CR (n = 1). The term unaudited refers to analyses on the basis of stratification factors entered into the interactive response technology form at the time of random assignment, and audited refers to the analysis on the basis of corrected stratification data entered into the electronic case report form before database lock.

stage IV disease versus recurrent disease before platinum-based combination therapy and disease status after completion of chemotherapy (partial response *v* complete response). The random assignment schedule was allocated in blocks of size 6 and produced using computer software that incorporated a standard procedure for generating random numbers.

Study Treatments

Patients were administered 80 mg selinexor or placebo, orally, once weekly in a 28-day cycle until disease progression or discontinuation. Patients with a BMI of <20 kg/m² received 60 mg of selinexor or placebo once weekly in 28-day cycles. Before each dose of study drug, all patients were required to receive 8 mg of ondansetron or equivalent 2-3 times daily, for the first 1-3 days following each study drug dose, and 2.5-5.0 mg olanzapine once daily during the first 2 months of treatment and longer if needed. Other supportive care measures were provided at the discretion of the investigator, which might have included transfusions and hematopoietic growth factors.

Assessments

TP53 mutations and microsatellite instability (MSI) status assessments were performed centrally by Tempus Labs

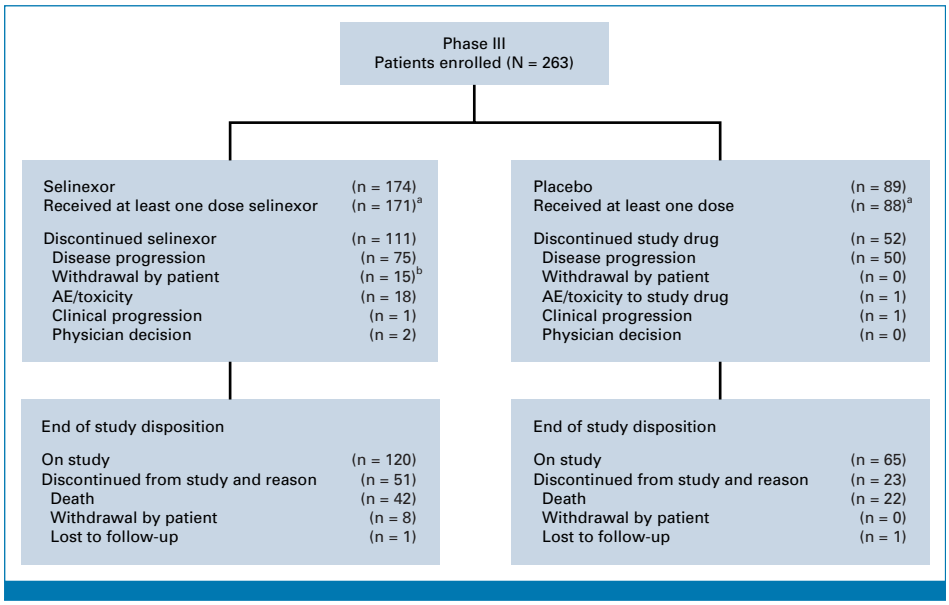

FIG 1. CONSORT diagram. [a]Reasons include patient withdrawal (n = 3); after random assignment and before dosing, laboratory values did not meet eligibility (n = 1). [b]Reasons for withdrawal by the patient: AE (n = 4), travel complications (n = 1), and unspecified (n = 10). AE, adverse event.

(Chicago, IL). Briefly, DNA isolated from paired tumor tissue slides (formalin-fixed and paraffin-embedded; n = 173) and blood samples (normal DNA source; n = 134) was sequenced using the Tempus xT platform with Tempus panel xT version 4, which covers a targeted panel of 648 genes in a Clinical Laboratory Improvement Amendments–certified laboratory. The detection limit of the analysis was 5% for single-nucleotide variants and 10% for insertions/deletions. Additional details are provided in Appendix 1 and Appendix Tables A2 and A3.

Outcomes

This is a double-blind study, where patients, investigators, study site staff, and sponsor were masked to treatment assignment.

The primary outcome was progression-free survival (PFS) defined as the time from random assignment until documented progressive disease or death because of any cause, whichever occurred first.

Secondary end points included overall survival (OS) defined as the time from random assignment until death because of any cause and disease control rate defined as the proportion of patients remaining in partial response or complete response by week 16 as assessed by the investigator, per RECIST v1.1. Health-related quality-of-life outcomes were measured by the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30 (version 3),[21] EORTC-QLQ-EN24, [22] and the EuroQol-5 Dimensions-5 Levels (EQ-5D-5L) questionnaires (see Appendix 1 for definitions).

Exploratory end points included PFS by a blinded independent central review, defined as time from random assignment until documented progressive disease or death because of any cause, whichever occurred first, and identification of predictive biomarkers including p53 tumor suppressor protein. Molecular profiling of tumor biomarkers was performed on archival tissue (at diagnosis or restaging).

Statistical Analysis

The sample size was designed to have 80% power to detect a hazard ratio (HR) of 0.60 with a two-sided alpha of .05. The HR of 0.60 corresponds to a 67% increase in median PFS, assuming a median PFS of 4.5 months for placebo and 7.5 months for selinexor. One interim analysis was planned once 56 PFS events were observed (40% of the total PFS events). The interim analysis allowed for early stoppage of futility (nonbinding). The futility boundary *P* value was calculated using the Lan DeMets spending function with the O'Brien-Fleming type of boundary. The intent-to-treat (ITT) population consisted of all patients randomly assigned to study drug, regardless of whether they received study drug. The safety population consisted of all patients who received at least one dose of study drug. The primary analysis of PFS was performed by treatment arm in the ITT population. A two-sided stratified log-rank test with random assignment strata as stratification factors was used to compare PFS of selinexor versus placebo. The HR and the corresponding two-sided 95% CI were estimated using a stratified Cox proportional hazards model adjusting for the stratification factors to control the family-wise type I error at 5%, and a multiple hierarchical testing procedure was using across the primary end point (PFS) and key secondary end point (OS). Statistical significance of the key secondary end point (OS) would not be claimed until the primary analysis of PFS had reached significance. Before database lock and unblinding, discrepancies

TABLE 2. Efficacy

Response Category[a]	Selinexor (n = 174), PFS Months, Median	Placebo (n = 89), PFS, Months, Median	Two-Sided *P*	HR (95% CI)
	5.7	3.8	.13	0.76 (0.54 to 1.08)
PFS at 3 months, % (95% CI)	72.4 (65.5 to 80.1)	66.4 (56.9 to 77.7)		
PFS at 6 months, % (95% CI)	48.2 (40.3 to 57.7)	40.9 (31.0 to 54.0)		
PFS at 12 months, % (95% CI)	35.3 (27.3 to 45.6)	25.8 (16.7 to 39.7)		
Subgroup				
TP53 wild-type[b] (selinexor n = 67, placebo n = 36)	13.7	3.7	.002	0.41 (0.23 to 0.72)
TP53-mutant/aberrant[b] (selinexor n = 74, placebo n = 40)	3.7	5.6	.24	1.34 (0.82 to 2.21)
TP53-unknown (selinexor n = 33, placebo n = 13)	3.8	3.8	.94	1.02 (0.40 to 2.60)
Histologic subtype				
Endometrioid (selinexor n = 96, placebo n = 48)	9.2	3.8	.09	0.66 (0.40 to 1.07)
Serous (selinexor n = 49, placebo n = 28)	3.8	3.7	.70	0.89 (0.50 to 1.58)
Others[c] (selinexor n = 29, placebo n = 13)	3.7	5.2		
MSS/pMMR[b] (selinexor n = 113, placebo n = 59)	6.9	5.4	.03	0.64 (0.42 to 0.97)
Partial response at entry (selinexor n = 102, placebo n = 52)	3.7	3.6	.03	0.64 (0.43 to 0.97)
Complete response at entry (selinexor n = 72, placebo n = 37)	11.8	9.3	.62	0.85 (0.44 to 1.62)
PFS 2, months, median	15.9	18.0	.75	1.08 (0.69 to 1.68)
Time to first subsequent treatment, months, median	10.0	8.2	.15	0.76 (0.52 to 1.01)
Time to second subsequent therapy, months, median	15.9	14.4	.76	0.93 (0.61 to 1.45)
Disease-specific survival, months, median	NR	NR	.10	1.00 (0.58 to 1.71)

Abbreviations: HR, hazard ratio; MSS, microsatellite stable; NGS, next-generation sequencing; NR, not reached; PFS, progression-free survival; PFS 2, progression-free survival on subsequent therapy; pMMR, mismatch repair–proficient.
[a]All data are unaudited, which refers to analyses on the basis of stratification factors entered into the interactive response technology form at the time of random assignment.
[b]Molecular status was determined by sequencing (*TP53*wt n = 84; *TP53* mutant n = 89; MSS/pMMR n = 144) and, if NGS is not available, by immunohistochemistry (p53wt n = 19; *p53*-mutant/*p53*-aberrant n = 25; MSS/pMMR n = 28).
[c]Undifferentiated carcinoma, carcinosarcoma, endometrial adenocarcinoma (not otherwise specified).

in response to chemotherapy entered in the interactive response technology were identified in seven patients (2.7% of 263); an exploratory analysis of PFS was performed on these audited data as well (Table 1: placebo arm: PR to CR [n = 3]; selinexor arm: CR to PR [n = 3] and PR to CR [n = 1]). The statistical analysis was validated by the independent ENGOT statistician and approved by the study Steering Committee and Independent Data Monitoring Committee. This trial is registered with ClinicalTrials.gov identifier: NCT03555422.

RESULTS

Patients and Treatment

From January 2018 through December 2021, a total of 263 patients underwent random assignment. A total of 171 of the 174 patients assigned to selinexor and 88 of the 89 patients assigned to placebo received trial intervention (Fig 1). The majority of patients were White in both treatment arms (selinexor 150 [90.8%] and placebo 81 [91.0%]), and the median age in the selinexor arm was 65.5 years (range, 40-81) and 64.0 years (range, 33-81) in the placebo arm. Patients predominately had endometrioid (selinexor 96 [55.2%] and placebo 48 [53.9%]) and serous adenocarcinomas (selinexor 49 [28.2%] and placebo 28 [31.5%]). Baseline patient characteristics were well balanced (Table 1).

Outcomes

In this study of oral, once-weekly selinexor as maintenance therapy in patients with advanced or recurrent EC after one line of taxane-platinum therapy with partial or complete remission, the median PFS was 5.7 months (95% CI, 3.81 to 9.20) with selinexor versus 3.8 months (95% CI, 3.68 to 7.39) with placebo, HR, 0.76 (95% CI, 0.54 to 1.08), two-sided $P = .13$, which did not meet the criteria for statistical significance in the ITT population (Fig 2). PFS at 3, 6, and 12 months is presented in Table 2. The median follow-up of the patients at data cutoff was 10.2 months (95% CI, 8.97 to 13.57).

On the basis of the mechanism of action of selinexor, we analyzed outcomes in a prespecified subgroup of patients with *TP53* wild-type (wt) tumors (n = 103). Baseline characteristics of patients with *TP53*wt tumors were similar to

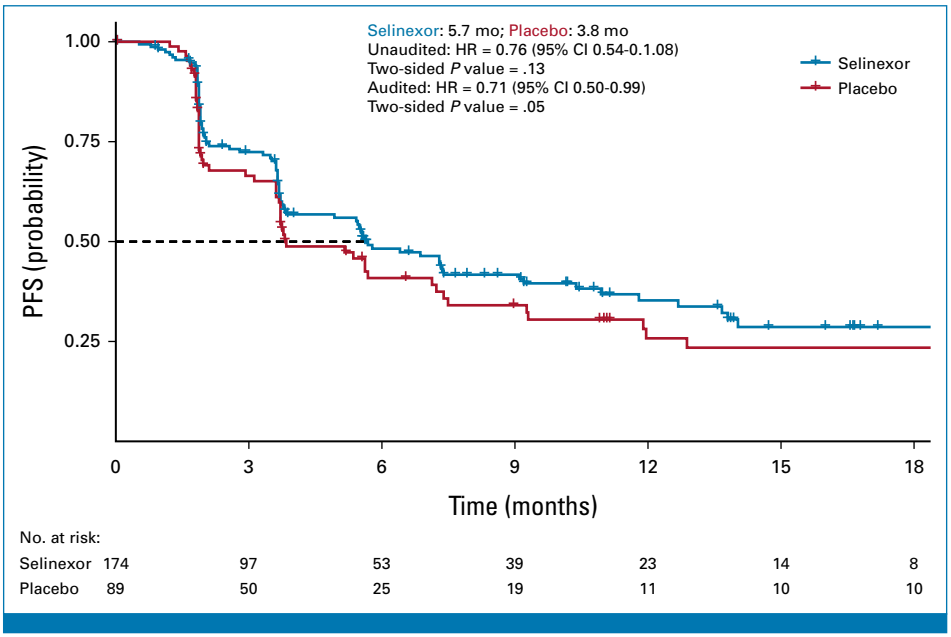

FIG 2. PFS of the ITT population. HR, hazard ratio; ITT, intent-to-treat; PFS, progression-free survival.

those of the overall population (Appendix Table A4). A comparison of *TP53* mutation frequency and of histologic subtype between the selinexor arm and the placebo arm showed no effective bias (Fisher's exact two-tailed test and chi square test, respectively; $P = 1.00$ and $P = .91$). In the exploratory analysis, the median PFS of patients with *TP53*wt tumors was 13.7 months with selinexor and 3.7 months with placebo (HR, 0.41; 95% CI, 0.23 to 0.72, nominal two-sided $P = .002$; Fig 3); the median PFS for patients with *TP53*-mutant/*TP53*-aberrant tumors (n = 114) was 3.7 and 5.6 months, respectively (HR, 1.34; 95% CI, 0.82 to 2.21; nominal two-sided $P = .24$), and for *TP53*-unknown tumors (n = 46), it was 3.8 and 3.8 months, respectively (HR, 1.02; 95% CI, 0.40 to 2.60; nominal two-sided $P = .94$; Table 2; Appendix Fig A1).

In addition, prespecified, exploratory analyses showed that patients with endometrioid carcinoma, microsatellite stable (MSS)/mismatch repair–proficient (pMMR) disease, and partial response at entry had a trend for prolonged median PFS with selinexor treatment compared with placebo (endometrioid: 9.2 *v* 3.8 months [HR, 0.66; 95% CI, 0.40 to 1.07; nominal two-sided $P = .09$]; MSS/pMMR: 6.9 *v* 5.4 months [HR, 0.64; 95% CI, 0.42 to 0.97; nominal two-sided $P = .03$]; and partial response at entry: 3.7 *v* 3.6 months [HR, 0.64; 95% CI, 0.43 to 0.97; nominal two-sided $P = .03$]; Table 2; Appendix Figs A2 and A3).

Preliminary exploratory analysis of outcomes was also determined for tumors stratified into each of the mutually exclusive TCGA molecular subgroups including MSI-H/deficient mismatch repair (dMMR) and *POLE* mutation status (Appendix Figs A1 and A4).

In the ITT population, the time to first subsequent therapy was 10.0 months with selinexor and 8.2 months with placebo (HR, 0.76; 95% CI, 0.52 to 1.10; two-sided $P = .15$). The time to second subsequent treatment was 15.9 months with selinexor and 14.4 months with placebo (HR, 0.93; 95% CI, 0.61 to 1.45; two-sided $P = .76$). Median disease-specific survival was not reached with either selinexor or placebo (Table 2). Among the subpopulations, these secondary end points generally trended with the PFS analyses. Analysis for OS is immature, with 64 OS events observed as of data cutoff.

In a prespecified exploratory analysis of PFS in audited stratification data, PFS for selinexor met the threshold for statistical significance (HR, 0.71; 95% CI, 0.499 to 0.996; two-sided $P = .049$; Fig 2). The audited HR for patients with *TP53*wt tumors was 0.38, 95% CI, 0.21 to 0.67 (nominal two-sided $P = .001$), for those with *TP53*-mutant/*TP53*-aberrant tumors, it was 1.31, 95% CI, 0.79 to 2.15 (nominal two-sided $P = .29$), and for those with *TP53*-unknown tumors, it was 0.69, 95% CI, 0.25 to 1.89 (nominal two-sided $P = .50$). In addition, the audited HR for patients with endometrioid carcinoma was 0.57, 95% CI, 0.35 to 0.94, nominal two-sided $P = .03$, for those with MSS/pMMR disease, it was 0.59, 95% CI, 0.39 to 0.91, nominal two-sided $P = .01$, and for those with PR at entry, it was 0.65, 95% CI, 0.43 to 0.97, nominal two-sided $P = .03$. Audited data for all outcomes are presented in Table 3.

Safety

The most common treatment-related adverse events of any grade were nausea (137 [80%] selinexor and 25 [28%] placebo), vomiting (86 [50%] and 8 [9%]), and

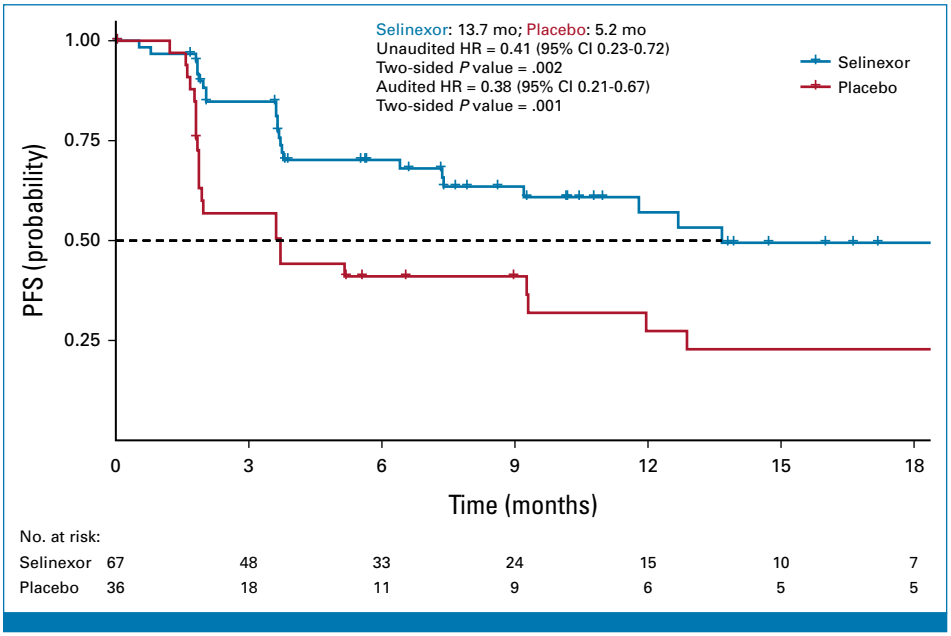

FIG 3. PFS of patients with *TP53* wild-type EC. EC, endometrial cancer; HR, hazard ratio; PFS, progression-free survival.

TABLE 3. Audited Efficacy

	PFS, Median, Months			
Response Category	Selinexor (n = 174)	Placebo (n = 89)	Two-Sided *P*	HR (95% CI)
	5.7	3.8	.049	0.71 (0.499 to 0.996)
PFS at 3 months, % (95% CI)	72.4 (65.5 to 80.1)	66.4 (56.9 to 77.7)		
PFS at 6 months, % (95% CI)	48.2 (40.3 to 57.7)	40.9 (31.0 to 54.0)		
PFS at 12 months, % (95% CI)	35.3 (27.3 to 45.6)	25.8 (16.7 to 39.7)		
Subgroup				
TP53 wild-type[a] (selinexor n = 67, placebo n = 36)	13.7	3.7	.001	0.38 (0.21 to 0.67)
TP53-mutant/*TP53*-aberrant[a] (selinexor n = 74, placebo n = 40)	3.7	5.6	.29	1.31 (0.79 to 2.15)
TP53-unknown (selinexor n = 33, placebo n = 13)	3.8	3.8	.50	0.69 (0.25 to 1.89)
Histologic subtype				
Endometrioid (selinexor n = 96, placebo n = 48)	9.2	3.8	.03	0.57 (0.35 to 0.94)
Serous (selinexor n = 49, placebo n = 28)	3.8	3.7	.62	0.86 (0.48 to 1.53)
Others[b] (selinexor n = 29, placebo n = 13)	3.7	5.2	.77	1.13 (0.47 to 2.72)
MSS/pMMR[a] (selinexor n = 113, placebo n = 59)	6.9	5.4	.01	0.59 (0.39 to 0.91)
Partial response at entry (selinexor n = 104, placebo n = 49)	3.7	3.6	.03	0.65 (0.43 to 0.97)
Complete response at entry (selinexor n = 70, placebo n = 40)	11.8	9.3	.68	0.87 (0.46 to 1.65)
PFS 2, months, median	15.9	18.0	.97	1.01 (0.65 to 1.57)
Time to first subsequent treatment, months, median	10.0	8.2	.06	0.70 (0.48 to 1.02)
Time to second subsequent therapy, months, median	15.9	14.4	.54	0.87 (0.57 to 1.35)
Disease-specific survival, months, median	NR	NR	.77	0.92 (0.54 to 1.59)

NOTE. In seven patients (2.7% of 263), the stratification factor of CR/PR was incorrect and was corrected by the investigators before database lock and unblinding; placebo arm: PR to CR (n = 3); selinexor arm: CR to PR (n = 3) and PR to CR (n = 1). Audited data refer to the analysis on the basis of corrected stratification data entered into the electronic case report form before database lock. Numbers do not change whether unaudited or audited.

Abbreviations: CR, complete response; HR, hazard ratio; MSS, microsatellite stable; NGS, next-generation sequencing; NR, not reached; PFS, progression-free survival; PFS 2, progression-free survival on subsequent therapy; pMMR, mismatch repair–proficient.

[a]Molecular status was determined by sequencing (*TP53*wt n = 84; *TP53* mutant n = 89; MSS/pMMR n = 144) and, if NGS is not available, by immunohistochemistry (p53wt n = 19; *p53*-mutant/*p53*-aberrant n = 25; MSS/pMMR n = 28).

[b]Undifferentiated carcinoma, carcinosarcoma, endometrial adenocarcinoma (not otherwise specified).

TABLE 4. Treatment-Related AEs

	Selinexor n = 171[a] (per patient), No. (%)		Placebo n = 88[a] (per patient), No. (%)	
Event	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Hematologic AEs				
Thrombocytopenia	61 (35.7)	12 (7.0)	0	0
Anemia	42 (24.6)	4 (2.3)	2 (2.3)	0
Neutropenia	41 (24.0)	15 (8.8)	5 (5.7)	0
Leukopenia	15 (8.8)	2 (1.2)	1 (1.1)	0
Nonhematologic AEs				
Nausea	137 (80.1)	16 (9.4)	25 (28.4)	0
Vomiting	86 (50.3)	2 (1.2)	8 (9.1)	0
Constipation	32 (18.7)	0	13 (14.8)	2 (2.3)
Diarrhea	46 (26.9)	1 (0.6)	12 (13.6)	0
Fatigue	53 (31.0)	10 (5.8)	10 (11.4)	1 (1.1)
Asthenia	48 (28.1)	10 (5.8)	15 (17.0)	1 (1.1)
Decreased appetite	52 (30.4)	2 (1.2)	4 (4.5)	0
Dysgeusia	28 (16.4)	0	7 (8.0)	0
Dizziness	20 (11.7)	2 (1.2)	6 (6.8)	0
Abdominal pain	15 (8.8)	2 (1.2)	7 (8.0)	0
Decreased weight	15 (8.8)	0	1 (1.1)	0
Headache	11 (6.4)	0	4 (4.5)	0
Dose reduction	84 (49.1)		3 (3.4)	
Dose interruption	78 (45.6)		5 (5.7)	
Discontinuation because of AE	17 (9.9)		1 (1.1)	

NOTE. No reported febrile neutropenia. Events that have occurred in ≥10% of total population and had a >5% difference between the arms. AEs were coded using MedDRA and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.
Abbreviation: AE, adverse event.
[a]Four patients did not receive treatment (n = 3 selinexor; n = 1 placebo).

thrombocytopenia (61 [36%] and 0 [0%]). The most common grade 3 treatment-related adverse events were nausea (16 [9%] with selinexor and 0 [0%] with placebo), neutropenia (15 [9%] and 0 [0%]), and thrombocytopenia (12 [7%] and 0 [0%]; Table 4). Treatment-emergent adverse events are reported in Appendix Table A5. There was one case of treatment-related grade 4 thrombocytopenia with no severe bleeding and no cases of febrile neutropenia. Serious treatment-related adverse events occurred in 4 (2.3%) patients treated with selinexor and 0 (0%) with placebo (Appendix Table A6). No deaths were deemed related to selinexor treatment. Duration and intensity of adverse events were generally manageable with dose modifications and/or standard supportive care.

Treatment-related adverse events leading to dose discontinuation occurred in 17 (9.9%) patients treated with selinexor and 1 (1.1%) treated with placebo. The most common treatment-related adverse events leading to dose discontinuation in patients who received selinexor were nausea (7 [4.1%]), fatigue (5 [2.9%]), and vomiting (3 [1.8%]). Treatment-related adverse events leading to dose modification occurred in 101 (59.1%) patients treated with selinexor and 6 (6.8%) treated with placebo.

No clinically substantial differences in Global Health Status (derived from the EORTC QLQ-C30) were observed between selinexor or placebo arms (Appendix Fig A5).

DISCUSSION

The promising initial responses from the phase II SIGN study provided preliminary data to initiate the phase III ENGOT-EN5/GOG-3055/SIENDO study, the aim of which was to develop a maintenance therapy for patients with advanced or recurrent EC after first-line platinum/taxane-based chemotherapy.[16] While PFS was not meaningfully improved in all patients, selinexor tended toward prolongation of time-to-first and time-to-second subsequent therapies.

The mechanism of action of selinexor is primarily to drive the nuclear retention and functional activation of wt (ie, biologically active) tumor suppressor proteins including p53. wt p53 is found at diagnosis in approximately 75% of EC cases, the majority with endometrioid subtype.[3,23,24] Treatments for patients with EC primarily target p53 mutations because of higher chemosensitivity and association with higher tumor grade.[25,26] Consistent with its mechanism of action, in patients with *TP53*wt EC, a clinically meaningful

reduction in the risk of disease progression or death was observed with selinexor. The median PFS with selinexor was 13.7 versus 3.7 months observed with placebo (HR, 0.41); patients with *TP53*-mutant/*TP53*-aberrant tumors showed no benefit of selinexor over placebo (HR, 1.34).

The observations in the *TP53*wt subgroup are further substantiated by the trend of benefit in the endometrioid and MSS/MMR subgroups, given that *TP53*wt is predominant in these two groups. Patients with endometrioid histologic subtype showed a median PFS benefit of 9.2 versus 3.8 months, which aligns with the fact that the majority of endometrioid cases are *TP53*wt.[24] Conversely, patients with serous endometrial carcinoma, the majority of whom present with a *TP53* mutation (pathogenic or likely pathogenic),[23] did not show a benefit from selinexor. In addition, analysis of the prespecified exploratory subset of patients with MSS/pMMR disease showed a trend for an improved HR for progression or death as compared with placebo (Appendix Fig A1), consistent with the finding that the majority of these cases are *TP53*wt.[3]

Further evidence of potential benefit is observed in selinexor prolonging the time-to-first and time-to-second subsequent therapies compared with placebo and allowing patients to delay intravenous chemotherapy or immunotherapy although no clinically relevant difference in global health status was observed. Improvements in these secondary end points generally followed the PFS end points and were most pronounced in patients with *TP53*wt and to a lesser degree in endometrioid tumors (predominantly *TP53*wt).

The most common treatment-emergent adverse events such as nausea, vomiting, and constipation were generally low grade and reversible. Oral maintenance selinexor at 80 mg once weekly resulted in mostly grade 1 and 2 AEs that were generally manageable with supportive care and dose modifications (in 47% of patients) with a discontinuation rate of 9.9% because of treatment-related adverse events. The majority of treatment-related adverse events associated with selinexor appeared early in the treatment course and then declined over time with appropriate dose modifications, supportive care, and/or dose modifications. Studies are underway to investigate dose optimization of selinexor. Clinically relevant cumulative toxicities were uncommon, and major organ dysfunction did not occur.

Overall, efficacy of immunotherapy for advanced/recurrent pMMR ECs has been limited until recently.[27-30] Single-agent immunotherapy has shown clinical benefit in MSI-H/dMMR ECs.[31] By contrast, in recurrent pMMR or MSS ECs, responses to checkpoint inhibitor monotherapy have been modest.[27,29,30,32] Recent studies[33,34] showed the capacity of checkpoint inhibitors to prolong PFS in first-line recurrent EC in addition to chemotherapy, especially in MSI-H/dMMR patients. While *TP53*wt tumors are most often pMMR, patients with *TP53*wt/MSI-H/dMMR or *TP53*wt/MSI-H/pMMR EC are a unique subset of patients for whom the outcomes with checkpoint inhibitors are not known.

In summary, despite not achieving statistical significance for PFS in the ITT population, in a prespecified exploratory analysis of PFS in audited stratification data, PFS for selinexor met the threshold for statistical significance in patients with advanced or recurrent EC. No substantial cumulative toxicity or unexpected adverse events occurred although dose optimization would benefit patients in the maintenance setting. Preliminary analysis of prespecified exploratory subgroups identified *TP53*wt as an important predictor of efficacy of selinexor. Further investigation is warranted for selinexor as a treatment for patients with *TP53*wt EC, and it is being investigated in the phase III, double-blind, randomized ENGOT-EN20/GOG-3083/XPORT-EC-042 trial in patients with advanced or recurrent EC (ClinicalTrials.gov identifier: NCT05611931).

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Karyopharm Therapeutics is committed to providing qualified scientific researchers access to anonymized data and clinical study reports from the company's clinical trials for the purpose of conducting legitimate scientific research, consistent with the EFPIA/PhRMA Principles for Responsible Clinical Trial Data Sharing. Karyopharm is also obligated to protect the rights and privacy of trial participants and, as such, has a procedure in place for evaluating and fulfilling requests for sharing company clinical trial data with qualified external scientific researchers. Interested researchers can send their requests to medinfo@karyopharm.com.

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Oral Selinexor as Maintenance Therapy After First-Line Chemotherapy for Advanced or Recurrent Endometrial Cancer

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No other potential conflicts of interest were reported.

APPENDIX 1. SUPPLEMENTARY METHODS

Definitions

Imaging was performed at screening, once every 8 weeks for 1 year, and then once every 12 weeks thereafter until disease progression was documented. Progressive disease was assessed by the investigator, per RECIST version 1.1.[17]

1. Time-to-first subsequent treatment defined as the time from random assignment until initiation of first subsequent systemic therapy for endometrial cancer (EC) or death because of any cause, whichever occurred first.
2. Time-to-second subsequent treatment defined as the time from random assignment until initiation of second subsequent systemic therapy for EC or death because of any cause, whichever occurred first.
3. End of study was defined as 12 months after the last enrolled patient, when the last patient in the study had withdrawn consent, had been withdrawn from the study by the investigator, had died, or had been lost to follow-up, whichever occurred first. As there were still 50 patients on study treatment at the end of this 12-month period, protocol version 7.0 extended the end of study period to 3 years after enrollment.

Health-Related Quality of Life

For health-related quality-of-life (HR-QoL) measures, raw scores for multi-item scales were calculated by averaging items within scales first. Raw scores were summarized by time point with descriptive statistics for each scale. Raw scores for multi-item scales and single-item measures were linearly transformed to obtain the score ranging from 0 to 100 according to European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30 (version 3) Scoring Manual[21] to EQ-5D-5L and according to EORTC-QLQ-EN24.[22] The global health status/QoL scale on the basis of Q29 and Q30 was used as the overall summary measure. The HR-QoL scores including the overall summary measure were summarized at baseline and by time point in evaluable patients. The changes from baseline over time were analyzed using mixed effects models. Missing items were imputed as the average of the items, which are present for a multi-item scale if at least half of the items from the scale have been answered. A missing single-item measure was not imputed. Missing forms were not imputed. Patients with missing baseline scores were excluded from the analysis for a scale when the change from baseline was analyzed or the baseline score was used as a covariate.

Central Laboratory Immunohistochemistry

Formalin-fixed and paraffin-embedded (FFPE) slides of pretreatment tumor specimens obtained from 24 patients were stained with hematoxylin and eosin and for the following proteins: p53, MLH1, PMS2, MSH2, and MSH6. Analyses were performed in a Clinical Laboratory Improvement Amendments–certified laboratory operated by Genuity, a division of Molecular Pathology Laboratory Network, Inc (Maryville, TN), where board-certified histopathologists interpreted the stains to infer histology, wild-type or aberrant p53, and deficient/proficient mismatch repair (MMR).

TP53 Mutations and Microsatellite Instability Status Assessments

Variant annotation was performed using a proprietary pipeline considering public databases (eg, gnomAD, dbSNP, etc) and the internal repository of previously sequenced normal DNAs. Copy number variants were reported only at copy numbers greater than five. Somatic small insertion/deletions or single-nucleotide variants changing the coding sequencing of *TP53* that are not annotated common polymorphisms were considered *TP53* mutations. Microsatellite instability (MSI) status was determined by Tempus informaticians using priority software on the basis of DNA sequencing of microsatellites. For patients whose tumor samples were unable to be sequenced at a central laboratory, site-reported p53 and MSI/MMR status was enabled using FFPE slides of pretreatment tumor specimens stained with hematoxylin and eosin, p53, and MMR genes (MLH1, PMS2, MSH2, and MSH6) and evaluated according to institutional standards. Normal or abnormal staining was used to infer *TP53* mutations and MMR status, respectively.

Statistical Analysis

For categorical variables, summary tabulations of the number and percentage of patients within each category (with a category for missing data) of the parameter were presented. For continuous variables, the number of patients, mean, median, standard deviation, and minimum and maximum values were presented. Time-to-event data were summarized using the Kaplan-Meier methodology using the 25th, 50th (median), and 75th percentiles with associated two-sided 95% CIs, as well as number and percentage of censored observations.

TABLE A1. Inclusion/Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
1. Female, at least age 18 years at the time of informed consent. 2. Histologically confirmed endometrial cancer of the endometrioid, serous, or undifferentiated type. Carcinosarcoma of the uterus is also allowed. 3. Completed a single line of at least 12 weeks of taxane-platinum combination therapy (not including adjuvant or neoadjuvant therapy) and achieved partial or complete remission (PR or CR) according to RECIST version 1.1 for a. Primary stage IV disease, defined as i. having a primary or later debulking surgery during first-line taxane-platinum therapy with *R0 resection* (R0 resection indicates a macroscopic complete resection of all visible tumors) and achieving *CR* after at least 12 weeks of taxane-platinum chemotherapy, or ii. having a primary or later debulking surgery during first-line taxane-platinum therapy with *R1 resection* (R1 resection indicates incomplete removal of all macroscopic disease) and achieving *PR or CR* after at least 12 weeks of taxane-platinum chemotherapy, or iii. having *no surgery* and achieving *PR or CR* after at least 12 weeks of taxane-platinum chemotherapy; or b. At first relapse (ie, relapse after primary therapy including surgery and/or chemotherapy therapy for stage I-IV disease), defined as i. having *stage I-III* disease at diagnosis and *receiving* at initial diagnosis adjuvant chemotherapy and *relapsing* later. Patients should have PR or CR after at least 12 weeks of taxane-platinum chemotherapy compared with the start of this chemotherapy at the time of relapse, or ii. having *stage I-III* disease at diagnosis and *not receiving* adjuvant chemotherapy at initial diagnosis and relapsing later. Patients should have PR or CR after at least 12 weeks of taxane-platinum chemotherapy compared with the start of this chemotherapy at the time of relapse, or c. having *stage IV* disease at diagnosis and receiving initially chemotherapy with or without surgery and relapsing later. At the time of relapse, patients should have PR or CR after at least 12 weeks of taxane-platinum chemotherapy compared with the start of this chemotherapy at the time of relapse. iii. Patients who required their chemotherapy dose held during the 12-week therapy may be considered if they meet the other criteria above and achieve PR or CR per RECIST V1.1. 4. Must be able to initiate study drug 5-8 weeks after completion of their final dose of chemotherapy. 5. ECOG performance status of 0-1. 6. Patients must have adequate bone marrow function and organ function within 2 weeks before starting study drug as defined by the following laboratory criteria: a. Hepatic function: total bilirubin up to 1.5 × ULN; ALT and AST ≤2.5 × ULN in patients without liver metastasis. For patients with known liver involvement of their tumor: AST and ALT ≤5 × ULN. b. Hematopoietic function: ANC ≥1.5 × 10^9/L; platelet count ≥100 × 10^9/L; Hb ≥9.0 g/dL. c. Renal function: estimated CrCl of ≥20 mL/min, calculated using the Cockcroft-Gault formula. 7. In the opinion of the investigator, the patient must a. Have a life expectancy of at least 12 weeks b. Be fit to receive experimental therapy 8. Premenopausal females of childbearing potential must have a negative pregnancy test (serum β-human chorionic gonadotropin test) before the first dose of study drug. Female patients of childbearing potential must agree to use highly effective methods of contraception throughout the study and for 1 week after the last dose of study drug. 9. Written informed consent in accordance with federal, local, and institutional guidelines. The patient must provide informed consent before the first screening procedure.	1. Has any sarcomas, small-cell carcinoma with neuroendocrine differentiation, or clear cell carcinomas. 2. Received a blood or platelet transfusion during 4 weeks before random assignment. 3. Being treated with a concurrent cancer therapy. 4. Previous treatment with an XPO1 inhibitor. 5. Previous treatment with anti-PD1 or anti–PD-L1 immunotherapy (eg, pembrolizumab). 6. Concurrent treatment with an investigational agent or participation in another clinical trial. 7. Patients who received any systemic anticancer therapy including investigational agents or radiation ≤3 weeks (or ≤5 half-lives of the drug [whichever is shorter]) before C1D1. 8. Palliative radiotherapy may be permitted for symptomatic control of pain from bone metastases in extremities, provided that the radiotherapy does not involve target lesions, and the reason for the radiotherapy does not reflect PD. 9. Major injuries or surgery within 14 days before C1D1 and/or planned surgery during the on-treatment study period. 10. Previous malignant disease, except patients with other malignant diseases, for which the patient has been disease-free for at least 3 years. Concurrent other malignant disease except for curatively treated carcinoma in situ of the cervix or basal cell carcinoma of the skin. 11. Any life-threatening illness, medical condition, or organ system dysfunction which, in the investigator's opinion, could compromise the patient's safety or compliance with the protocol. 12. Known contraindications to selinexor. 13. Known uncontrolled hypersensitivity to the investigational drug or to its excipients. 14. Radiotherapy to the target lesion within the past 3 months before baseline imaging. 15. Persistent grade 3 or 4 toxicity from previous chemotherapy and/or radiotherapy, with the exception of alopecia. 16. Active brain metastases (eg, stable for <8 weeks, no adequate previous treatment with radiotherapy and/or surgery, symptomatic, requiring treatment with anticonvulsants. Corticoid therapy is allowed if administered as stable dose for at least 1 month before random assignment). 17. Known unstable cardiovascular function: a. Symptomatic ischemia, or b. Uncontrolled clinically significant conduction abnormalities (ie, ventricular tachycardia on antiarrhythmia is excluded; first-degree atrioventricular block or asymptomatic left anterior fascicular block/right bundle branch block will not be excluded), or c. Congestive heart failure of New York Heart Association NYHA class ≥3, or d. Myocardial infarction within 3 months 18. Females who are pregnant or actively breastfeeding. 19. Uncontrolled (ie, clinically unstable) infection requiring parenteral antibiotics, antivirals, or antifungals within 1 week before first dose; however, prophylactic use of these agents is acceptable even if parenteral. 20. Active hepatitis C and/or B infection. 21. Patients unable to swallow tablets and patients with malabsorption syndrome, or any other GI disease or GI dysfunction that could interfere with absorption of study drug. A history of bowel obstruction requiring a nasogastric tube or intravenous infusion during the past 2 months is not allowed (except when this obstruction is caused by surgery or other nonmalignant causes). 22. Psychiatric illness or substance use that would prevent the patient from giving informed consent or being compliant with the study procedures. 23. Patients unwilling or unable to comply with the protocol. 24. Persons who have been committed to an institution by official or judicial order. 25. Patients with dependency on the sponsor, investigator, or study site.

Abbreviations: ALP, alkaline phosphatase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; CR, complete response; CrCl, creatine clearance, ECOG, Eastern Cooperative Oncology Group; Hb, hemoglobin; NYHA, New York Heart Association; PD, progressive disease; PR, partial response; ULN, upper limit of normal; XPO1, exportin-1.

TABLE A2. *TP53* Status by Histologic Subtype

Histologic Subtype	*TP53* Status		
	Wild-Type	Mutant	Unknown
Carcinosarcoma	1	12	3
Endometrial adenocarcinoma (not otherwise specified)	11	6	4
Endometrioid carcinoma	83	32	29
Serous carcinoma	7	61	9
Undifferentiated carcinoma	1	3	1

TABLE A3. *TP53* Status by Microsatellite Instability Status

Microsatellite Instability Status	*TP53* Status		
	Wild-Type	Mutant	Unknown
MSS/pMMR	69	96	7
MSI-H/dMMR	25	7	3
Unknown	9	11	36

Abbreviations: dMMR, deficient mismatch repair; MSI-H, microsatellite instable-high; MSS, microsatellite stable; pMMR, mismatch repair–proficient.

TABLE A4. Patient Characteristics of the p53 Wild-Type Subgroup

Characteristic	Selinexor (n = 67)	Placebo (n = 36)
Age, years, median (range)	64.0 (40-81)	61.0 (33-74)
<70, No. (%)	46 (68.7)	29 (80.6)
≥70, No. (%)	21 (31.3)	7 (19.4)
ECOG performance status, No. (%)		
0	36 (53.7)	23 (63.9)
1	30 (44.8)	13 (36.1)
2	1 (1.5)	0
Histology, No. (%)		
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[a]	8 (11.9)	3 (8.3)
No. of previous antineoplastic regimens, No. (%)		
1	67 (100.0)	35 (97.2)
2	0	1 (2.8)
Disease at the time of taxane-platinum combination therapy—eCRF, No. (%)		
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, No. (%)		
CR	29 (43.3)	16 (44.4)
PR	38 (56.7)	20 (55.6)

Abbreviations: CR, complete response; ECOG, Eastern Cooperative Oncology Group; eCRF, electronic case report form; PR, partial response.
[a]Not otherwise specified.

TABLE A5. Treatment-Emergent AEs

	Selinexor (n = 171),[a] No. (%)		Placebo (n = 88),[a] No. (%)	
Event[b]	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Hematologic AEs				
Thrombocytopenia	63 (37)	12 (7)	0	0
Anemia	48 (28)	9 (5)	4 (5)	0
Neutropenia	42 (25)	15 (9)	5 (6)	0
Nonhematologic AEs				
Nausea	143 (84)	17 (10)	30 (34)	1 (1)
Vomiting	88 (52)	3 (2)	15 (17)	1 (1)
Constipation	64 (37)	1 (1)	33 (38)	2 (2)
Diarrhea	58 (34)	3 (2)	20 (23)	0
Fatigue	60 (35)	10 (6)	13 (15)	1 (1)
Asthenia	53 (31)	11 (6)	18 (21)	1 (1)
Decreased appetite	60 (35)	2 (1)	6 (7)	0
Abdominal pain	31 (18)	4 (2)	15 (17)	0
Dysgeusia	30 (18)	3 (2)	9 (10)	1 (1)
Headache	21 (12)	0	13 (15)	0
Dizziness	24 (14)	3 (2)	8 (9)	0
Arthralgia	13 (8)	0	15 (17)	0
Abdominal pain	31 (18)	4 (2)	15 (17)	0
Dysgeusia	30 (18)	0	9 (10)	0
Dose reduction	85 (49.7)		3 (3.4)	
Dose interruption	88 (51.5)		16 (18.2)	
Discontinuation	18 (10.5)		1 (1.1)	

NOTE. No reported febrile neutropenia.
Abbreviation: AE, adverse event.
[a]Four patients did not receive treatment (n = 3 selinexor; n = 1 placebo).
[b]Events that have occurred in ≥5% of the total population and had a >5% difference between the arms. AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

TABLE A6. Serious Treatment-Related AEs

Event	Selinexor (n = 171),[a] No. (%)	Placebo (n = 88),[a] No. (%)	Total (n = 259), No. (%)
Patients with at least one serious treatment-emergent treatment-related adverse event	4 (2.3)	0	4 (1.5)
Anemia	1 (0.6)	0	1 (0.4)
Confusional state	1 (0.6)	0	1 (0.4)
Ileus	1 (0.6)	0	1 (0.4)
Vertigo—positional	1 (0.6)	0	1 (0.4)

Abbreviation: AE, adverse event.
[a]Four patients did not receive treatment (n = 3 selinexor; n = 1 placebo).

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Francesco Raspagliesi, MD	Istituto Nazionale dei Tumori IRCCS—Milano, Italy
Carmela Pisano, MD	Istituto Nazionale Tumori IRCCS "Fondazione G. Pascale", Napoli, Italy
Donata Sartori, MD	ULSS 3 Serenissima, UOC Oncologia Ed Ematologia Oncologica, Italy
Ugo de Giorgi, MD	IRCCS Istituto Romagnolo Per Lo Studio Del Tumori "Dino Amadori"—Irst S.R.L., Italy
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Cesar Gomez-Raposo, MD	Hospital Universitario Infanta Sofía, Spain
Ignacio Romero, MD	Instituto Valenciano de Oncología, Spain
Maria Iglesias, MD	Hospital Son Llàtzer, Spain
Ana Santaballa, MD	Hospital Universitario y Politécnico de La Fe, Spain
Nerea Ancizar, MD	Hospital Universitario Donostia, Spain
Purificación Estévez, MD	Hospital Universitario Virgen del Rocío, Spain
Constanza Maximiano, MD	Hospital Universitario Puerta de Hierro, Majadahonda, Spain
Alfonso Yubero, MD	Hospital Clínico Universitario Lozano Blesa, Spain
Ana Oaknin, MD	Hospital Universitari Vall d' Hebrón, Spain
Eva Guerra, MD	Hospital Universitario Ramón y Cajal, Spain
Lydia Gaba, MD	Hospital Universitari Clínic de Barcelona, Spain
Jeronimo Martinez, MD	Virgen de la Arrixaca University Clinical Hospital, Spain
Emma Dotor, MD	Terrassa Health Consortium, Spain
Vicky Makker, MD	Memorial Sloan Kettering Cancer Center
Debra Richardson, MD	University of Oklahoma Health Sciences Center—Stephenson Cancer Center
Jonathan Berek, MD	Stanford University
Hye Sook Chon, MD	Moffitt Cancer Center
Joseph Buscema, MD	Arizona Oncology—Tucson—Wilmot Road Location (US Oncology Network)
Meaghan Tenney, MD	Northside Hospital
David Miller, MD	University of Texas Southwestern Medical Center
Gregory Sutton, MD	Covenant HealthCare
Daniel Spitz, MD	Florida Cancer Specialists (Sarah Cannon Research Institute)
Kristopher LyBarger, MD	HCA Midwest Health—Kansas City (Sarah Cannon Research Institute)
Erika Hamilton, MD	Tennessee Oncology Nashville (Sarah Cannon Research Institute)
Gregory Gilmore, MD	The Oncology Institute of Hope and Innovation
Merrill Shum, MD	The Oncology Institute of Hope & Innovation
Harshad Amin, MD	BRCR Medical Center Inc
Leslie Randall, MD	VCU Massey Cancer Center
Bhavana Pothuri, MD	NYU Langone
Katina Robison, MD	Women & Infants Hospital of Rhode Island
Jonathan Boone, MD	University of Tennessee Medical Center
Joyce Barlin, MD	Women's Cancer Care Associates, LLC
Sharad Ghamande, MD	Augusta University
Alfred Guirguis, MD	Gynecological Cancer Institute of Chicago
Sudarshan Sharma, MD	Sudarshan K. Sharma, Ltd
Iwona Podzielinski, MD	Parkview Research Center
Lisa Landrum, MD	Indiana University Simon Cancer Center
Nicole Nevadunsky, MD	Albert Einstein College of Medicine, Montefiore
Amanda Jackson, MD	University of Cincinnati Medical Center
Eirwen Miller, MD	West Penn Hospital
Radhika Gogoi, MD	Karmanos Cancer Institute
Bradley Monk, MD	Arizona Oncology Associates, PC—HAL
Restituto Tibayan, MD	Comprehensive Cancer Centers of Nevada

(continued on following page)

TABLE A7. List of ENGOT-EN5/GOG-3055/SIENDO Investigators (continued)

Noelle Cloven, MD	Texas Oncology Fort Worth
Joseph de la Garza, MD	Texas Oncology, San Antonio
Christine Lee, MD	Texas Oncology, the Woodlands
Carolyn Mathews, MD	Texas Oncology, Dallas
Anna Priebe, MD	Texas Oncology, Tyler
Michael Teneriello, MD	Texas Oncology, Austin
Charles Anderson, MD	Oncology Associates of Oregon
Bhavana Pothuri, MD	NYU Long Island
Fabio Cappuccini, MD	MemorialCare Todd Cancer Institute at Long Beach Medical Center; UC Irvine School of Medicine
David Miller, MD	Parkland Health Services
Michael G. Kaufman, MD, PhD	Formerly of Karyopharm
Sharon Shacham, PhD	Formerly of Karyopharm
Yosef Landesman, PhD	Formerly of Karyopharm
Christopher J. Walker, PhD	Karyopharm
Xulong Wang, PhD	Karyopharm
Feng Wang, PhD	Formerly of Karyopharm
Changting Meng, MD	Formerly of Karyopharm
Dayana Michel, MD	Formerly of Karyopharm
Patricia Judson, MD	Formerly of Karyopharm
Reshma Rangwala, MD	Karyopharm

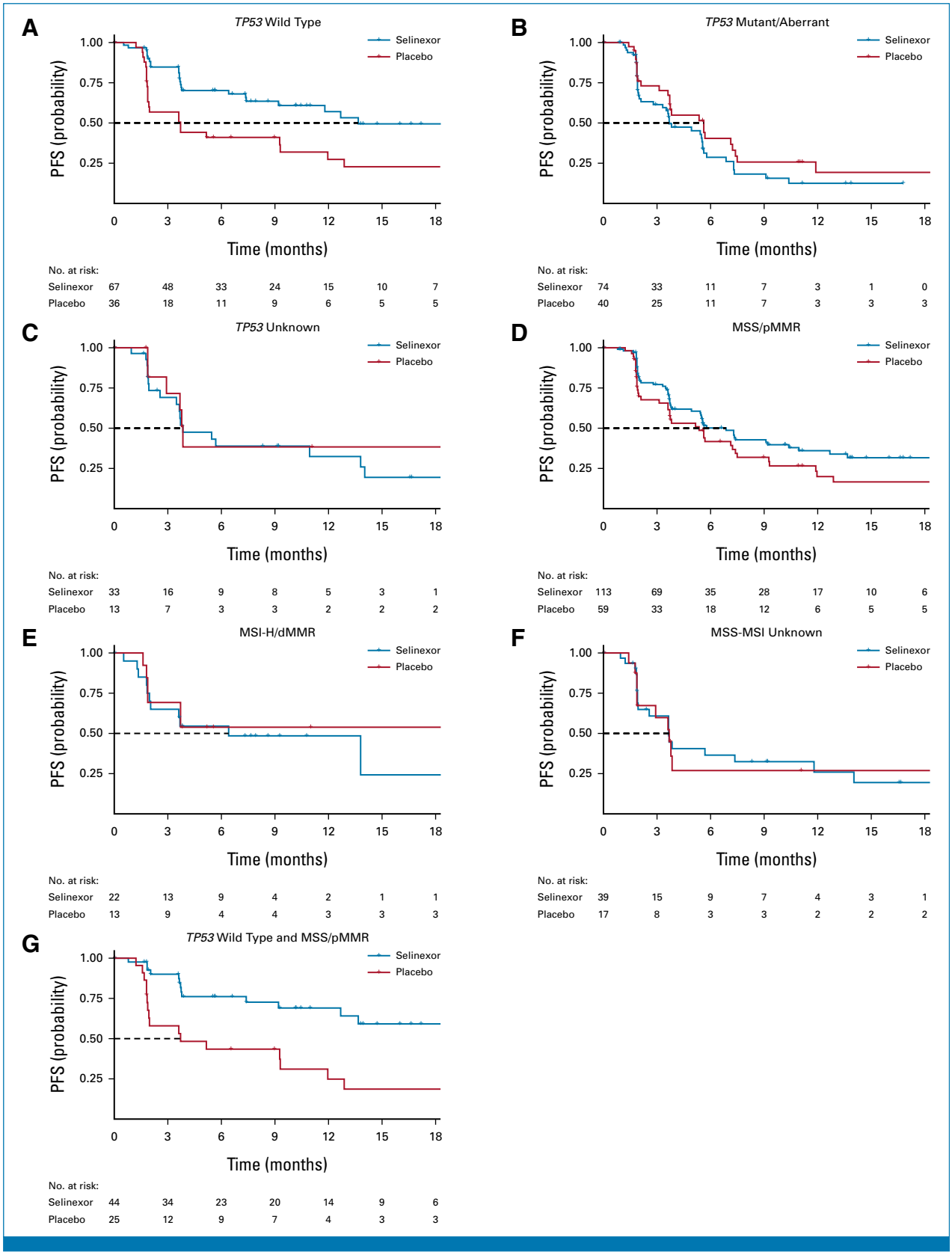

FIG A1. Kaplan-Meier progression-free survival stratified by patients with (A) *TP53* wild type, (B) *TP53* mutant/aberrant, (C) *TP53* unknown, (D) MSS/pMMR, (E) MSI-H/dMMR, (F) MSS/MSI unknown, and (G) both *TP53* wild type and MSS/pMMR (patients whose samples had unknown *TP53* and/or MSI status were not included). POLE-mutated groups not shown due to small patient numbers. abn, aberrant; dMMR, deficient mismatch repair; EDM, exonuclease domain; mismatch repair deficient; pMMR, mismatch repair proficient; MSI, microsatellite instable; MSS, microsatellite stable; PFS, progression-free survival.

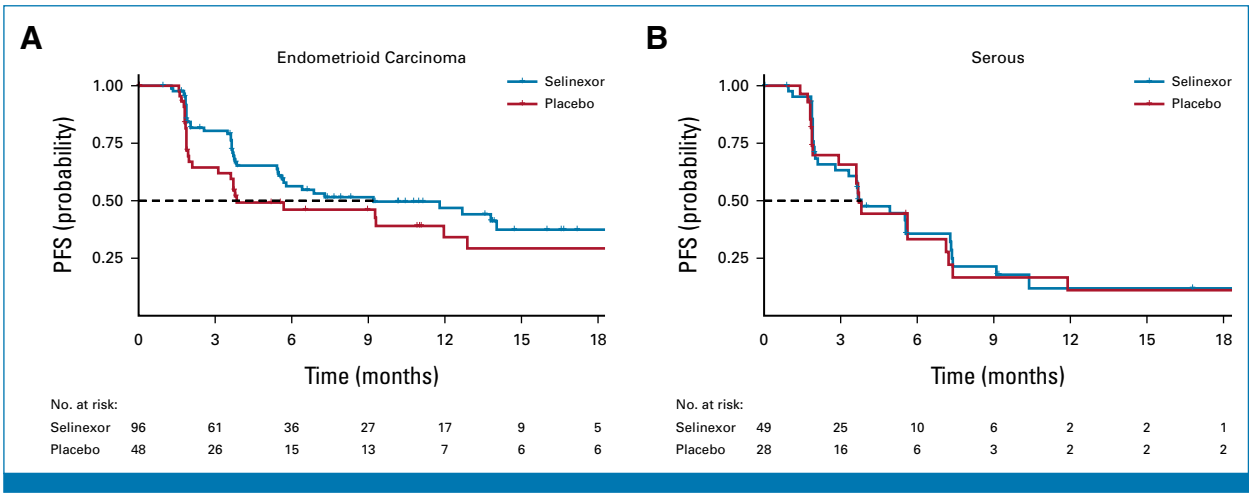

FIG A2. Kaplan-Meier progression-free survival stratified by patients with (A) endometrioid and (B) serous histological subtype endometrial cancer. Other histological subtype endometrial cancer not shown due to small patient numbers. PFS, progression-free survival.

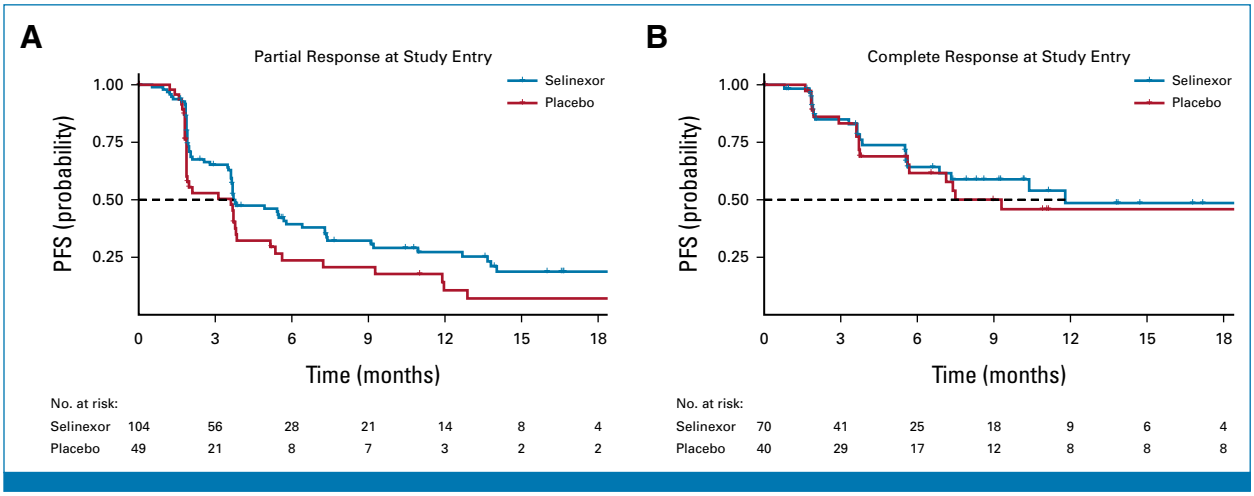

FIG A3. Kaplan-Meier progression-free survival stratified by prior chemotherapy response with (A) partial response at study entry, or (B) complete response at study entry. PFS, progression-free survival.

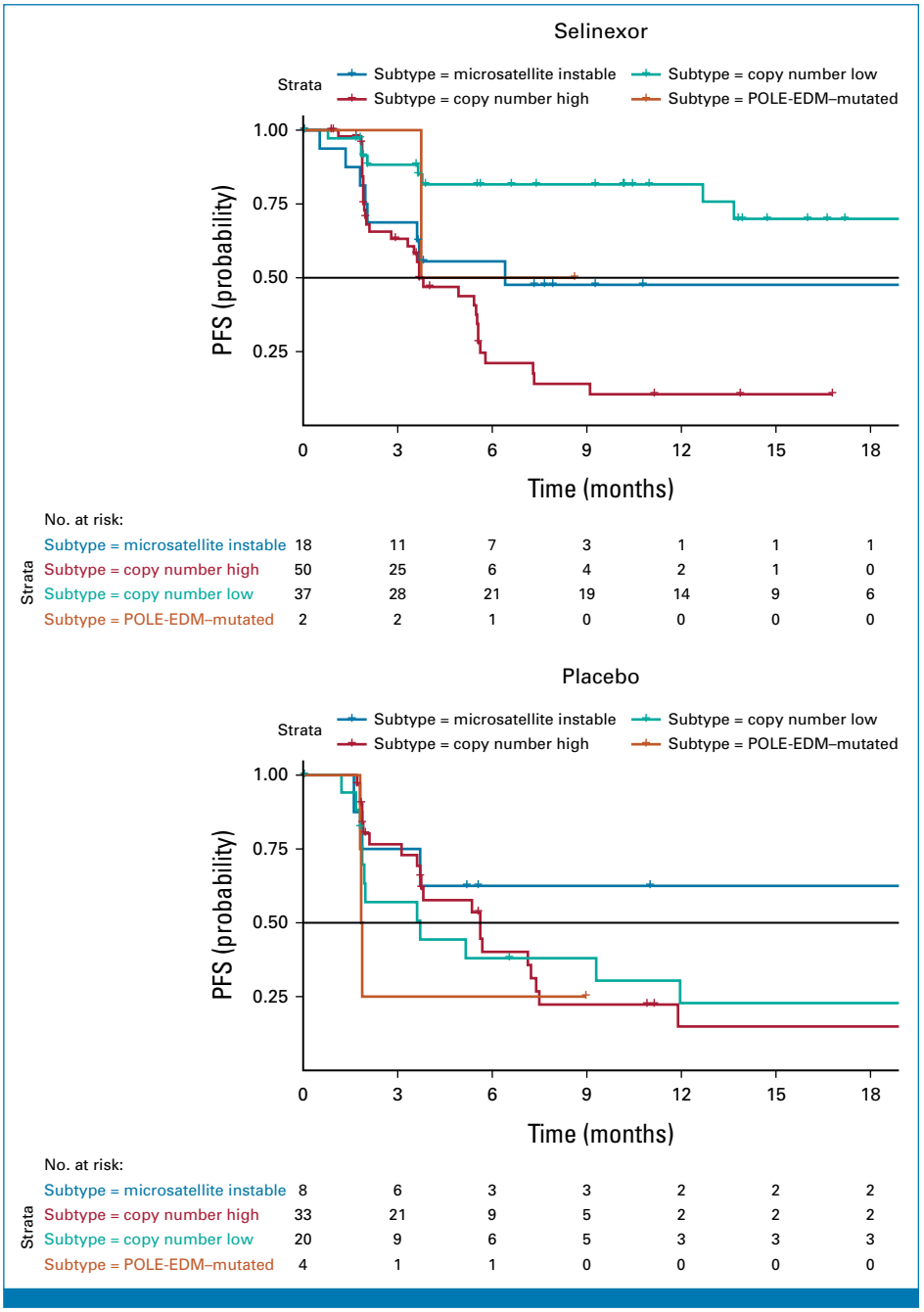

FIG A4. Kaplan-Meier progression-free survival stratified by mutually exclusive TCGA molecular subgroups for patients on the (A) selinexor arm or (B) placebo arm. Patients whose samples had unknown status for *TP53*, MSI, and/or *POLE* were not included. EDM, exonuclease domain; PFS, progression-free survival; *POLE*, exonuclease domain of the DNA polymerase epsilon; TCGA, The Cancer Genome Atlas.

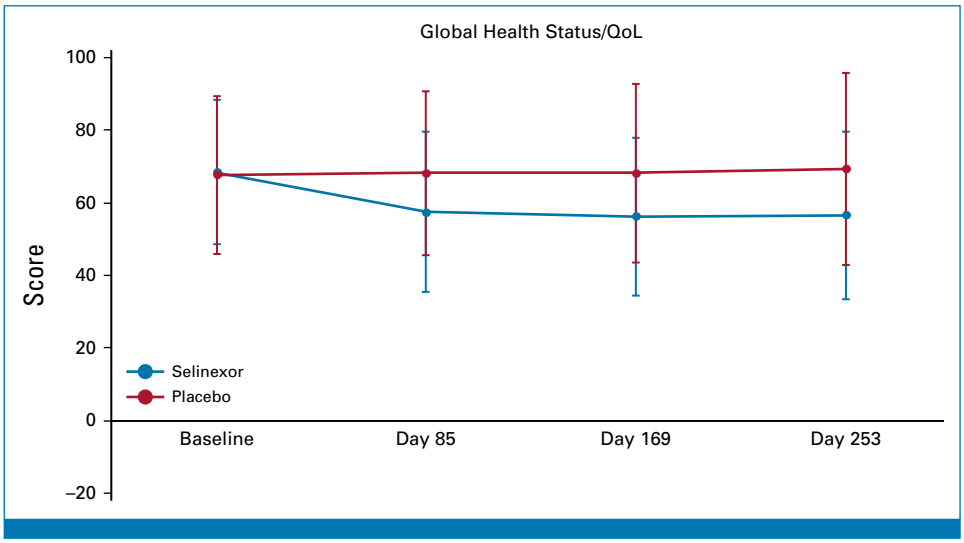

FIG A5. Patient-reported outcomes. Global health status/quality of life scores for patients in the selinexor arm or placebo arm.