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Long-term follow-up of efficacy and safety of selinexor maintenance treatment in patients with *TP53*wt advanced or recurrent endometrial cancer: A subgroup analysis of the ENGOT-EN5/GOG-3055/SIENDO study

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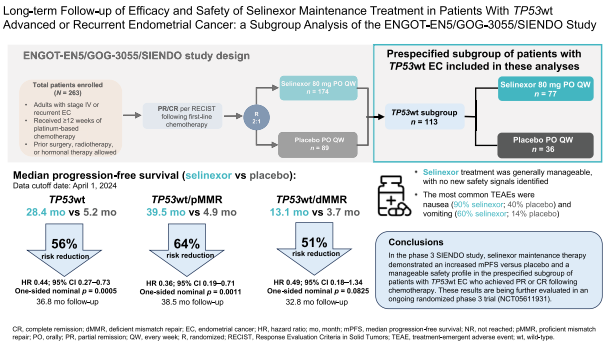
HIGHLIGHTS

- Patients with *TP53* wild-type (wt) advanced or recurrent endometrial cancer have limited effective treatment options.
- Selinexor is an oral exportin 1 (XPO1) inhibitor activating p53 through nuclear retention of key tumor suppressor proteins.
- Meaningful increase in median progression-free survival (mPFS) of *TP53*wt were seen with selinexor maintenance therapy.
- Increase in mPFS with selinexor in *TP53*wt subgroup was observed regardless of mismatch repair status.
- Selinexor was generally manageable, with no new safety signals observed.

GRAPHICAL ABSTRACT



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ABSTRACT

Objective. To report long-term efficacy and safety of selinexor maintenance therapy in adults with *TP53* wild-type (*TP53*wt) stage IV or recurrent endometrial cancer (EC) who achieved partial remission (PR) or complete remission (CR) following chemotherapy.

Methods. Analysis of the prespecified, exploratory subgroup of patients with *TP53*wt EC from the phase 3 SIENDO study was performed. Progression-free survival (PFS) benefit in patients with *TP53*wt EC and across other patient subgroups were exploratory endpoints. Safety and tolerability were also assessed.

Results. Of the 263 patients enrolled in the SIENDO trial, 113 patients had *TP53*wt EC; 70/113 (61.9%) had *TP53*wt/proficient mismatch repair (pMMR) EC, and 29/113 (25.7%) had *TP53*wt/deficient mismatch repair (dMMR) EC. As of April 1, 2024, the median PFS (mPFS) for *TP53*wt patients who received selinexor compared with placebo was 28.4 versus 5.2 months (36.8-month follow-up, HR 0.44; 95% CI 0.27–0.73). A benefit in mPFS was seen with selinexor versus placebo regardless of MMR status (patients with *TP53*wt/pMMR EC: 39.5 vs 4.9 months, HR 0.36; 95% CI 0.19–0.71; patients with *TP53*wt/dMMR EC: 13.1 vs 3.7 months, HR 0.49; 95% CI 0.18–1.34). Selinexor treatment was generally manageable, with no new safety signals identified.

Conclusion. In the phase 3 SIENDO study, selinexor maintenance therapy showed a promising efficacy signal and a manageable safety profile in the prespecified subgroup of patients with *TP53*wt EC who achieved a PR or CR following chemotherapy. These results are being further evaluated in an ongoing randomized phase 3 trial (NCT05611931).

1. Introduction

Molecular characterization has become integral to informed treatment of patients with endometrial cancer (EC) given its prognostic and, in some cases, predictive value [1,2]. Biomarker-driven treatments can lead to improved patient management and clinical outcomes [1,2]. The 4 molecular subtypes of EC identified using the Proactive Molecular risk classifier (ProMisE) are: 1) DNA polymerase epsilon mutated (*POLE*mut), 2) deficient mismatch repair (dMMR), 3) no specific molecular profile (NSMP), and 4) p53abnormal (p53abn) [3–6]. While patients with *TP53*wt EC are mostly diagnosed at early stages (stage I or II and grade 1 or 2) [7], ≥50% of all patients with advanced or recurrent EC are identified as *TP53*wt [7–9] and 60%–78% of these are also categorized as being proficient in mismatch repair (pMMR) [8,10–12].

TP53 mutation status is a well-recognized prognostic biomarker for patients with EC, with poor outcomes noted for *TP53* mutant (*TP53*mut) tumors [2,13]. HER2 expression ranges from 6% to 14% across serous, high-grade EC, carcinosarcoma, and clear cell carcinomas but is rare in endometrioid carcinomas. Approximately 94% of patients with HER2-positive EC also have a *TP53* mutation [13,14]. In the United States, one of the recommended systemic regimens for advanced or recurrent HER2-positive uterine serous carcinomas and carcinosarcomas is carboplatin/paclitaxel/trastuzumab [15]. However, an unmet need for therapy for patients with *TP53*wt EC following first-line chemotherapy and immunotherapy remains. Recent clinical trials of immunotherapy for first-line treatment of advanced or recurrent EC have shown a significant PFS benefit for patients with dMMR EC, and the current recommendation for maintenance therapy is to continue immunotherapy following first-line combined chemotherapy and immunotherapy treatment [16]. However, the reported PFS benefit of immunotherapy in patients with pMMR EC, many of which are also *TP53*wt, is more modest [11,17–19]. Moreover, patients with advanced or recurrent EC who progress after first-line treatment commonly develop chemoresistance [20], have poor response to second-line treatment [20,21], and tolerability to some treatment options may be of concern [22]. These findings suggest that identification of a maintenance therapy after response to chemotherapy in advanced or first-line recurrent EC is an important treatment option for patients with*TP53*wt EC.

Selinexor is an oral exportin 1 (XPO1) inhibitor that prevents the XPO1-mediated export of several tumor suppressor proteins (TSPs), including p53, which is encoded by the *TP53* gene [8]. The primary mechanism in which selinexor induces cancer cell death in EC [23] is

presumed to be through the nuclear retention and reactivation of p53 [8,24,25]. Due to its fundamental mechanism of action, selinexor has been shown to have a pan-tumor effect and is currently approved for use in relapsed or refractory multiple myeloma and has received accelerated approval for use in relapsed or refractory diffuse large B cell lymphoma [26–28].

Promising single-agent activity of selinexor was observed in advanced gynaecological malignancies in the phase 2 SIGN study prompted the evaluation of selinexor as a maintenance therapy in the Phase 3 SIENDO study [8,29]. The disease control rate for the 23 patients with heavily pretreated EC received selinexor treatment in the study was 35% (median duration of 6.3 months). At primary PFS analysis of the phase 3 SIENDO study of selinexor maintenance in patients with advanced or recurrent EC, the PFS observed in the intent-to-treat (ITT) population was not clinically meaningful; however, an exploratory analysis of a prespecified subgroup of patients with *TP53*wt EC showed a promising efficacy signal [8]. The objective of this prespecified subgroup analysis from the phase 3 SIENDO study is to report the long-term follow-up efficacy and safety data of selinexor maintenance treatment for patients with *TP53*wt advanced or recurrent EC.

2. Methods

2.1. Study design

The study design was previously described by Vergote et al. [8]. In short, the ENGOT-EN5/GOG-3055/SIENDO (NCT03555422) study is a phase 3, randomized, double-blind, clinical trial evaluating selinexor as a maintenance treatment versus placebo in patients with stage IV or first relapse of EC [8]. Study participants were randomized 2:1 to receive selinexor 80 mg (or 60 mg for patients with a body mass index of <20 kg/m^2) or placebo orally every week. Randomization was stratified based on advanced versus recurrent disease at the time of taxane-platinum combination therapy and disease status after chemotherapy (partial remission [PR] versus complete remission [CR]). All patients received 5-HT3 antagonists (ondansetron 8 mg or equivalent), if not contraindicated, 30–60 min prior to administration of each dosing of study drug and continued 2–3 times daily for the following few days, as needed. In addition, olanzapine 2.5–5.0 mg once daily (or equivalent) was given starting on Day 1 and continued for at least the first 2 months of the study; the treating physician could adjust the dose and/or continue dosing for longer than 2 months if deemed necessary. Study protocols were approved by institutional review boards or ethics committees at each site. The study adhered to the Declaration of Helsinki. All patients provided written informed consent before the study start and adhered to the Declaration of Helsinki.

2.2. Patients

The key study inclusion criteria specified female patients aged ≥18 years who had received ≥12 weeks of taxane-platinum-based chemotherapy for advanced or first-line recurrent EC and achieved PR or CR according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 [30]. Patients who had prior surgery, radiotherapy, or hormonal therapy were allowed in the study. Patients who had sarcomas, small cell carcinoma with neuroendocrine differentiation, or clear cell carcinomas; had previous treatment with an XPO1 inhibitor, anti–programmed death-1 (PD-1), or anti–programmed cell death-1 ligand (PD-L1) immunotherapy; or had active brain metastases were excluded. The analyses described herein were conducted in patients with *TP53*wt or p53wt EC (hereafter both types are referred to as *TP53*wt) as determined by next-generation sequencing (NGS; Tempus, Chicago, IL), or if not available, by immunohistochemistry (IHC). MMR status was determined either by NGS (Tempus, Chicago, IL) or local IHC.

2.3. Endpoints

Exploratory endpoints in this analysis included investigator-assessed PFS in the prespecified subgroup of patients with *TP53*wt EC from the SIENDO study and across the following subgroups within this population: MMR status, response after most recent chemotherapy, CR/PR, advanced or recurrent disease at the time of start of taxane-platinum combination therapy, and geographic location. Clinically relevant post hoc exploratory subgroup analyses within the *TP53*wt subgroup included age, Eastern Cooperative Oncology Group (ECOG) performance status, and duration of last systemic therapy. Safety and tolerability were also assessed.

2.4. Statistical analysis

Efficacy analyses for this prespecified subgroup were performed on all patients with *TP53*wt EC who were randomly assigned to study drug, regardless of whether they received study drug [8]. The cutoff date for data analysis was April 1, 2024. A 2-sided stratified log-rank test with random assignment strata, defined by using derived randomization factors of PR versus CR and primary stage IV versus recurrent disease, was used to compare PFS in the selinexor versus placebo arms [8]. The hazard ratio (HR) and the corresponding 2-sided 95% confidence interval (CI) were estimated using a stratified Cox proportional hazards model adjusting for the stratification factors [8]. Efficacy analyses were performed using stratified methods in prespecified subgroups according to response after most recent chemotherapy, advanced or recurrent disease at the time of the start of taxane-platinum–based chemotherapy, age, geographic location, ECOG performance status, and duration of last systemic therapy. All *P* values reported are nominal. Safety analysis was performed on the safety population, which included all patients who received at least 1 dose of study drug [8].

3. Results

3.1. Study population

Of the 263 patients enrolled in the SIENDO trial, 113 were identified for the *TP53*wt subgroup analysis. Of the 113 patients with *TP53*wt, 77 were randomized to receive selinexor and 36 were randomized to receive placebo (Fig. 1). Baseline characteristics of patients in the *TP53*wt subgroup were similar to those in the overall patient population [8]. Within the *TP53*wt subgroup, patients randomized to selinexor were slightly older compared with patients randomized to placebo (64.0 vs 61.5; Table 1). More than 80% of patients in both the treatment and placebo arms presented with endometrioid carcinoma and over 50% had recurrent disease. Patients with a CR to their most recent chemotherapy treatment accounted for >40% of patients in both treatment arms. The median duration of the most recent systemic chemotherapy was 19.9 weeks (approximately 5.0 months). Of the 99 patients with known MMR status, 70 (70.7%) were in the *TP53*wt/pMMR subgroup and 29 (29.3%) were in the T*P53*wt/dMMR subgroup.

3.2. Primary efficacy endpoint

The mPFS for patients with *TP53*wt EC was 28.4 months with selinexor versus 5.2 months with placebo at 36.8 months of follow-up (HR 0.44; 95% CI 0.27–0.73, 1-sided nominal $p = 0.0005$; Fig. 2A). The mPFS of patients in the *TP53*wt/pMMR subgroup was 39.5 months with selinexor versus 4.9 months with placebo at a median of 38.5 months of follow-up (HR 0.36; 95% CI 0.19–0.71; 1-sided nominal $p = 0.0011$; Fig. 2B). The mPFS of patients in the *TP53*wt/dMMR subgroup was 13.1 months with selinexor versus 3.7 months with placebo at a

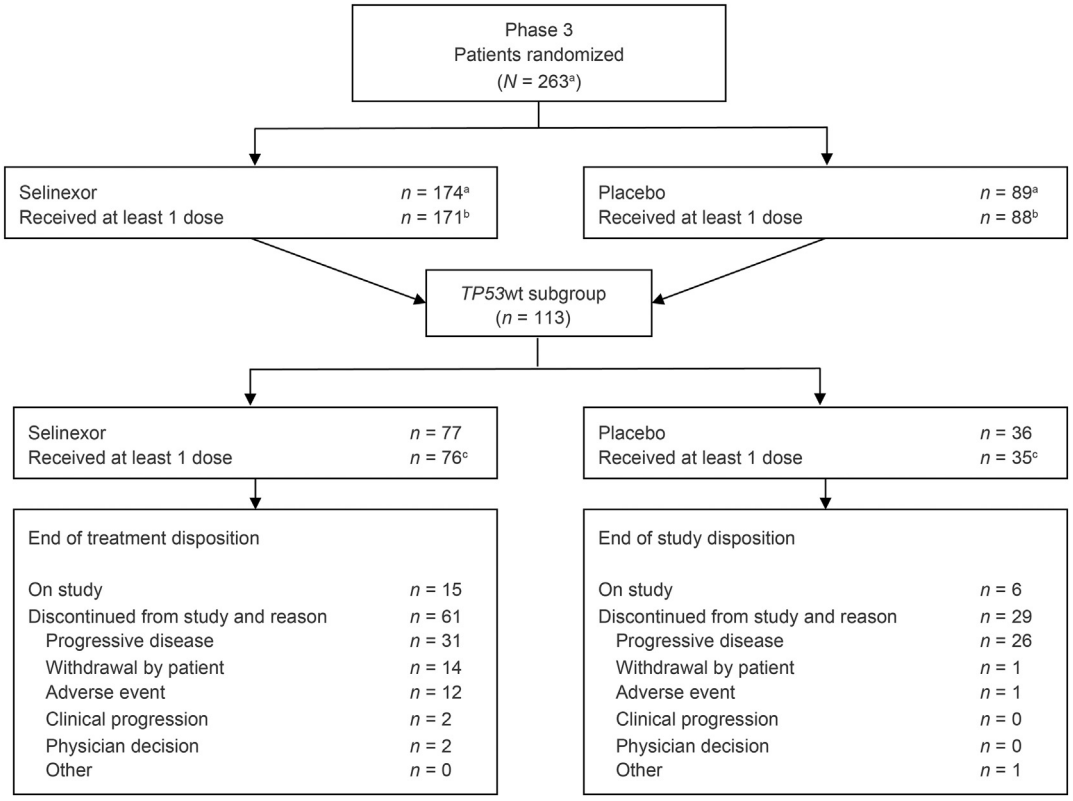

Fig. 1. Patient disposition. [a]From primary study [8]. [b]Reasons include patient withdrawal ($n = 3$); after random assignment and before dosing, laboratory values did not meet eligibility ($n = 1$) [8]. [c]Reasons include: $n = 1$ lab is not met after randomized in selinexor arm, $n = 1$ voluntarily withdrawal before dosing in placebo arm.

Table 1
Baseline patient demographics and disease history.

Characteristic	*TP53*wt	
	Selinexor ($n = 77$)	Placebo ($n = 36$)
Age, years, median, *n* (range)	64.0 (40–81)	61.5 (33–74)
≥70 years, *n* (%)	23 (29.9)	8 (22.2)
Race		
White	75 (97.4)	34 (94.4)
Black	1 (1.3)	2 (5.6)
Other[a]	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 carcinoma	65 (84.4)	29 (80.6)
Serous carcinoma	3 (3.9)	3 (8.3)
Undifferentiated carcinoma	0	1 (2.8)
Carcinosarcoma	1 (1.3)	0
Endometrial adenocarcinoma	8 (10.4)	3 (8.3)
Disease at time of platinum combination therapy, *n* (%)		
Primary stage IV disease	34 (44.2)	17 (47.2)
Recurrent disease	41 (53.2)	18 (50.0)
Response after the most recent chemotherapy,[b] *n* (%)		
CR	31 (40.3)	16 (44.4)
PR	46 (59.7)	20 (55.6)
Molecular characterization of microsatellite instability status,[c] *n* (%)	$n = 67$	$n = 32$
pMMR	47 (70.1)	23 (71.9)
dMMR	20 (29.9)	9 (28.1)

Abbreviations: CR, complete remission; dMMR, deficient mismatch repair ECOG, Eastern Cooperative Oncology Group; IRT, interactive response technology; NA, not applicable; NGS, next-generation sequencing; pMMR, proficient mismatch repair; PR, partial remission.
[a] Includes Asian, Native Hawaiian, and other Pacific Islander.
[b] *n* (%) determined by IRT.
[c] Molecular status was unknown for 14 patients.

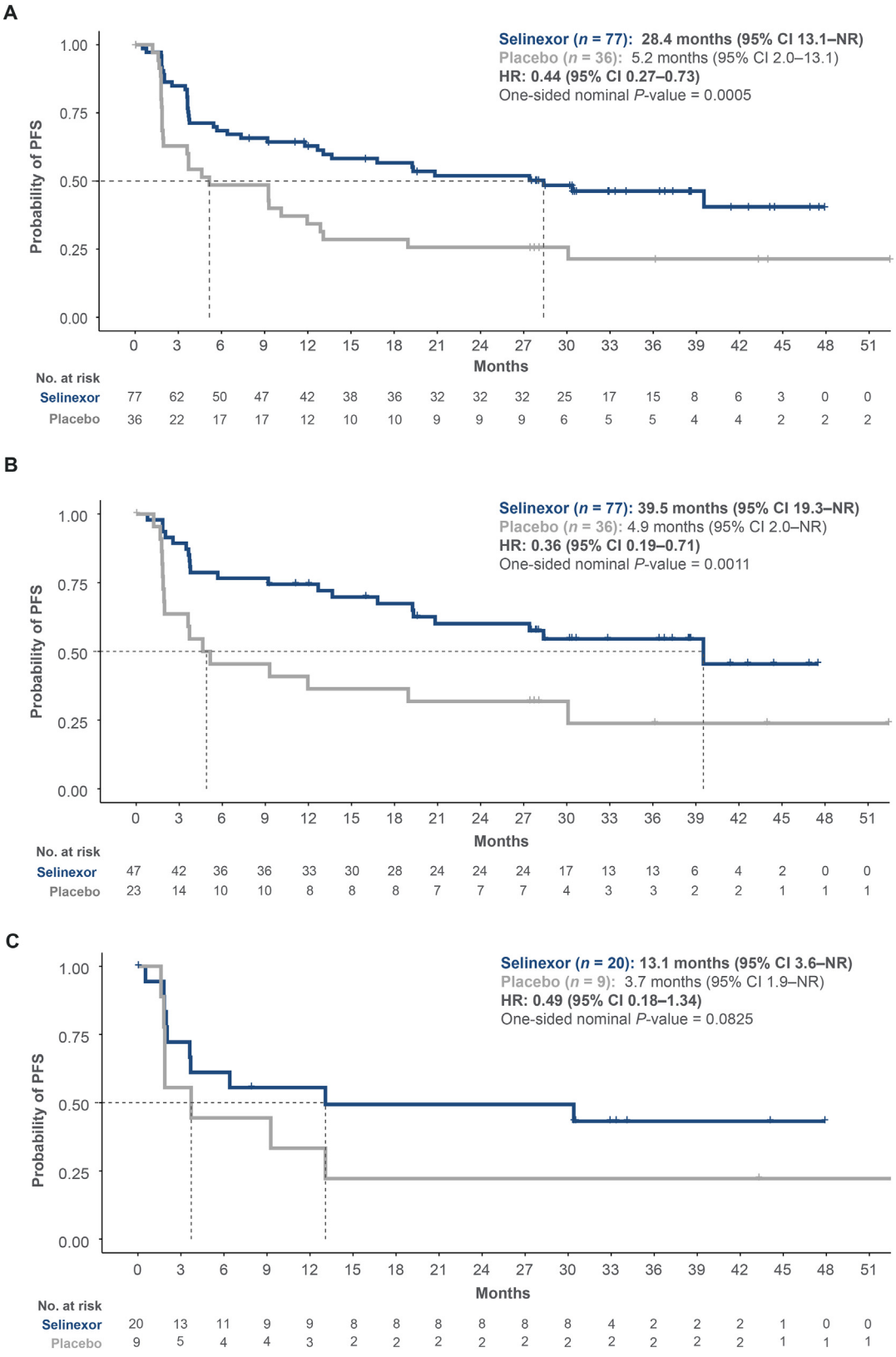

Fig. 2. Progression-free survival in the (A) all *TP53*wt patients,[a] (B) *TP53*wt/pMMR,[b] subgroup and (C) *TP53*wt/dMMR[c] subgroup. Abbreviations: CI, confidence interval; dMMR, deficient mismatch repair; HR, hazard ratio; NR, not reached; pMMR, proficient mismatch repair; wt, wild-type. [a]36.8 months of follow-up. [b]38.5 months of follow-up. [c]32.8 months of follow-up.

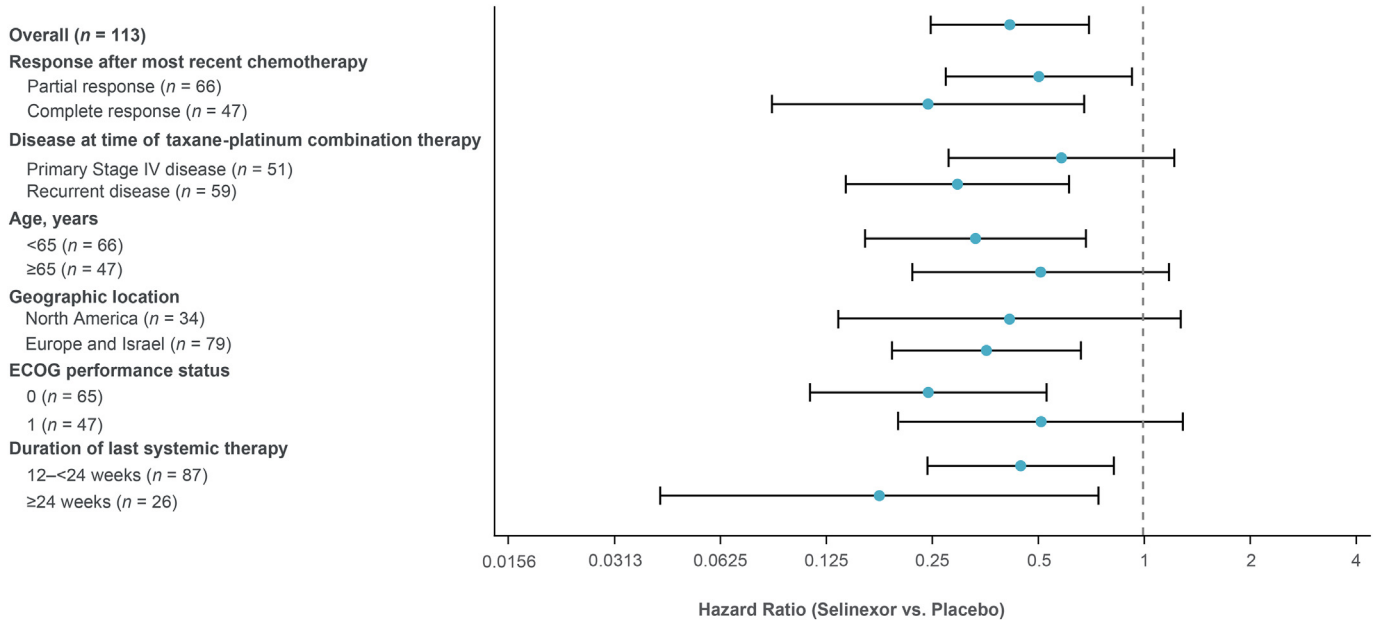

Fig. 3. Progression-free survival by subgroup. Abbreviation: ECOG, Eastern Cooperative Oncology Group.

median of 32.8 months of follow-up (HR 0.49; 95% CI 0.18–1.34; 1-sided nominal $p = 0.0825$; Fig. 2C). A benefit in mPFS was observed across all subgroups and regardless of whether the patient achieved PR or CR (Fig. 3).

3.3. Safety

The most common treatment-emergent adverse events (TEAEs) in the selinexor arm were nausea (68 [90%] selinexor; 14 [40%] placebo) and vomiting (46 [60%] selinexor; 5 [14%] placebo; Fig. 4). Diarrhea (34 [45%] selinexor; 13 [37%] placebo) and constipation (25 [33%] selinexor; 14 [40%] placebo) occurred at similar frequencies between the treatment and placebo arms. The most common grade ≥ 3 TEAEs in the selinexor arm were neutropenia (15 [20%] selinexor; 0 placebo), nausea (10 [13%] selinexor; 0 placebo), and thrombocytopenia (8 [10%] selinexor; 0 placebo). A total of 13 patients (17%) in the selinexor arm experienced TEAEs leading to treatment discontinuation compared with no patients

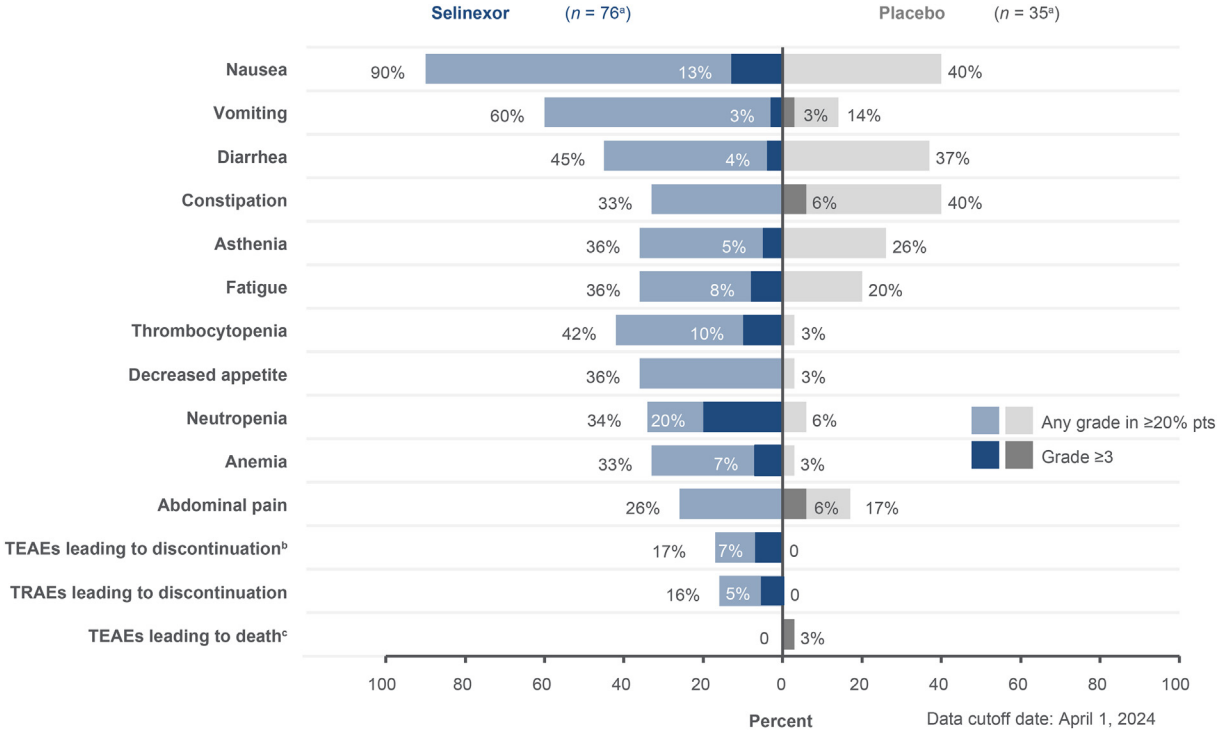

Fig. 4. Summary of treatment-emergent adverse events in the *TP53*wt group. Abbreviation: TEAE, treatment-emergent adverse event. [a]Two patients total did not receive treatment; $n = 1$ lab is not met after randomized to selinexor arm; $n = 1$ voluntarily withdrawal before dosing in placebo arm. [b]Reasons for discontinuation: nausea ($n = 5$), fatigue ($n = 3$), vomiting ($n = 3$), asthenia, cataract, general physical health deterioration, and ileus (all $n = 1$). [c]Reason for death unknown/missing.

in the placebo arm; some patients reported more than one TEAE. TEAEs leading to treatment discontinuation in patients who received selinexor were nausea (5 [7%]), fatigue (3 [4%]), vomiting (3 [4%]), asthenia (1 [1%]), cataract (1 [1%]), general physical health deterioration (1 [1%]), ileus (1 [1%]), and neutropenia (1 [1%]). TEAEs leading to dose modification occurred in 60 (79%) patients treated with selinexor and 10 (29%) patients treated with placebo. No deaths were deemed related to selinexor treatment.

4. Discussion

The initial report of long-term follow-up of the prespecified group of patients with *TP53*wt EC from the phase 3 SIENDO study showed promising efficacy signals for patients receiving selinexor maintenance therapy after attaining PR or CR following at least 12 weeks of chemotherapy compared with placebo (28.4 months vs 5.2 months at 36.8 months; HR 0.44, 1-sided nominal $p = 0.0005$). This trend was observed regardless of MMR status. The clinical benefit was potentially stronger in the *TP53*wt/pMMR subgroup compared with placebo (39.5 vs 4.9 months at 38.4 months; HR 0.36, 1-sided nominal $p = 0.0011$). Additional analyses showed mPFS benefit across the *TP53*wt population, regardless of previous systemic therapy response or response duration.

The safety profile for selinexor was generally manageable, and no new safety signals were identified in the *TP53*wt group. The most common adverse events (AEs) with selinexor were nausea (90%) and vomiting (60%). Grade ≥ 3 AEs were neutropenia (20%), nausea (13%), and thrombocytopenia (10%) and were manageable with supportive care [8]. In the ongoing ENGOT-EN20/GOG-3083/XPORT-EC-042 trial (NCT05611931) of selinexor as a maintenance therapy for patients with *TP53*wt EC, prophylactic dual antiemetics in the first 2 cycles are protocol required, and a 60 mg dose of selinexor (supported by an exposure/response analysis, unpublished) will be used to optimize the efficacy and safety (NCT05611931) [8].

Immunotherapy has recently become the preferred first-line treatment for advanced or recurrent EC, particularly for dMMR tumors, given its demonstrated clinical benefit in improving PFS rates [11,15,16,18,19,31]. Patients with *TP53*wt and pMMR EC remain a population where the benefits of immunotherapy are much more modest [11,18,19,32]. Furthermore, maintenance therapy in advanced or recurrent EC is still evolving. Currently, only 1 immune checkpoint inhibitor, dostarlimab, is approved for single-agent maintenance therapy for patients with dMMR EC following chemotherapy plus dostarlimab [11,18,19,33,34]. There are currently no approved treatments for EC that targets *TP53*wt tumors. In addition to the important prognostic role of *TP53* mutation status in EC, *TP53*wt status may represent a robust predictive biomarker for efficacy of selinexor maintenance therapy in advanced or recurrent EC [2]. *TP53* biomarker-driven maintenance therapy may prolong PFS as demonstrated with selinexor as maintenance therapy in this prespecified subgroup analysis of pretreated patients with *TP53*wt EC. The positive results of this subgroup analysis highlight the potential opportunity to further personalize therapies and provide a strong rationale to further evaluate selinexor as maintenance therapy in patients with *TP53*wt advanced or recurrent EC, which is currently being assessed in the ongoing phase 3 ENGOT-EN20/GOG-3083/XPORT-EC-042 trial.

4.1. Limitations

Limitations of this study include the small sample size of the prespecified *TP53*wt subgroup analyzed and the number of patients that discontinued treatment in both the selinexor and placebo arms.

5. Conclusion

The results of this prespecified subgroup analysis from the phase 3 SIENDO study of patients with advanced or recurrent *TP53*wt EC who achieved PR or CR on prior chemotherapy reported a promising efficacy signal of a PFS benefit compared with placebo and a manageable safety profile with selinexor as maintenance therapy.

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Data sharing statement

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 medicalinformation@karyopharm.com.

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