Abstract #5594

Phase 3 Dose Selection for Selinexor in *TP53*wt Endometrial Cancer Based on Exposure-Response Analysis

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Introduction

- Molecular characterization informs treatment decisions in patients (pts) with EC[1-3]
- TP53 is a well-recognized prognostic marker for EC, >50% of advanced/recurrent EC tumors are *TP53* wild-type (*TP53*wt), of which ~60-78% are also *TP53*wt/pMMR[4-9]
  - Currently, there are no proven targeted therapies for pts with *TP53*wt EC
- Selinexor (SEL), an XPO1 inhibitor, prevents the XPO1-mediated export of several tumor suppressor proteins (TSPs), including TP53[10]
- An exploratory analysis of a prespecified subgroup of pts with *TP53*wt advanced/recurrent EC in the Phase 3 ENGOT-EN5/GOG-3055/SIENDO (NCT03555422) study showed a promising efficacy signal with SEL maintenance therapy following platinum-based therapy versus placebo (progression-free survival [PFS] hazard ratio = 0.41); full safety data were previously reported[6,11]
- Population pharmacokinetic (PopPK) and exposure-response (E-R) analyses were conducted to evaluate the relationship between SEL systemic exposure and clinical endpoints to select an optimal dose that enhances the benefit:risk profile of SEL maintenance therapy

Methods

- A previously developed SEL PopPK model,[12] using data from eight clinical trials of solid tumors and hematologic malignancies, was updated to include data from SIGN (SEL 50 mg/m^2 twice a week) and SIENDO (SEL 80 mg QW for pts with body mass index [BMI] ≥ 20 kg/m^2; SEL 60 mg QW for pts with BMI < 20 kg/m^2)[3,5]
- Simulations were performed to estimate the systemic exposure of SEL and for safety endpoints for different SEL QW dosing; maximum concentration (C_{max}) and area under the curve (AUC) at steady state were derived using Empirical Bayes estimates
- PFS results from the 23 pts treated with SEL in the SIENDO trial, who had available PK results, were used for the E-R efficacy analysis
- E-R analysis for safety included 43 pts from SIGN (as of Jan 9, 2018) and 111 pts from SIENDO (SEL, n = 23; placebo, n = 88; as of Jan 18, 2022)
- E-R safety analysis was performed to determine the relationship between SEL exposure and treatment-emergent adverse events (TEAEs) and to determine the probability of a decrease in safety endpoints by < 10% with reduction in SEL from 80 mg QW to 60 mg QW

Results

PopPK

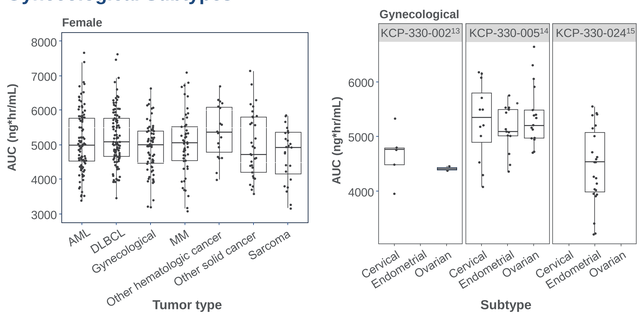
- A PopPK model for SEL was developed using the combined PK dataset comprising of 919 pts, including 74 (8.1%) with gynecological cancers, 36 (3.9%) of which were EC
- Of the 919 pts included in the PopPK model, 279 (34%) pts enrolled in clinical trials with extensive PK sampling
- Significant covariates were time-varying weight on apparent clearance (CL/F) and apparent peripheral volume of distribution (Vc/F) and sex on CL/F (**Table 1**)
- The PK of SEL in pts with advanced gynecologic malignancies from SIGN and SIENDO was similar to other tumor types in female pts (**Figure 1**)

Table 1. Final Model Parameter Estimates for SEL PK

Parameters	Symbol	Estimate	RSE (%)
CL/F (L/hr)	Θ_1	18.7	1.84
Vc/F (L)	Θ_2	112.0	1.72
Q/F (L/hr)	Θ_3	3.80	14.4
Vp/F (L)	Θ_4	18.9	9.18
Ka (1/hr)	Θ_5	2.28	7.59
D1 (hr)	Θ_6	1.15	3.30
Body weight–CL/F	Θ_9	0.598	9.91
Sex-CL-F	Θ_{10}	−0.108	23.8
Body weight–Vc/F	Θ_{11}	0.964	4.91
Random effects			
CL/F	$\omega^2_{1,1}$	0.0524	7.25
Vc/F × CL/F	$\omega^2_{1,2}$	0.0166	21.7
Vc/F	$\omega^2_{2,2}$	0.0285	15.4
Ka	$\omega^2_{3,3}$	1.96	8.60
Ka × D1	$\omega^2_{3,4}$	−0.426	12.8
D1	$\omega^2_{4,4}$	0.360	10.5
Interoccasion variability			
Ka	$\omega^2_{5,5}$	4.01	2.53
Residual error			
Proportional	Θ_7	0.438	1.10
Additive (ng/mL)	Θ_8	0.768	0.132

CL/F, apparent clearance; D1, zero-order drug release duration; F, bioavailability; Ka, absorption rate constant; PK, pharmacokinetics; Q/F, apparent inter-compartmental clearance; RSE, relative standard error; Vc/F, apparent central volume of distribution; Vp/F, apparent peripheral volume of distribution.

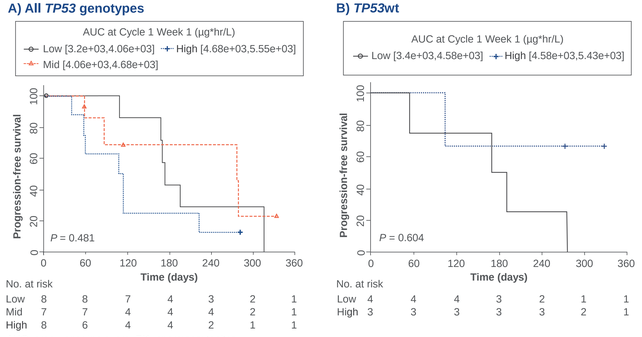
Figure 1. Similar SEL Exposure Across Tumor Types and Gynecological Subtypes



AML, acute myeloid leukemia; AUC, area under the curve; DLCBL, diffuse large B cell lymphoma; MM, multiple myeloma; QW, every week; PK, pharmacokinetics.

Efficacy

Figure 2. Progression-free Survival by AUC Levels in Patients With Endometrial Cancer



AUC, area under the curve; PK, pharmacokinetics.

- No E-R trend for efficacy (PFS) was observed with Week 1 PK parameters of AUC in the overall EC population despite the various doses of SEL that pts received in the included trials (**Figure 2A**)
  - Similarly, no E-R trend was observed for C_{max}
- No apparent increase in efficacy with increasing exposure was observed for the small subpopulation of pts with *TP53*wt EC (n = 7) (**Figure 2B**)

Safety

Table 2. Summary of Safety and AEs

Adverse event	SIGN16 Selinexor (n = 43) 50 mg/m² twice weekly		SIENDO[5] Placebo (n = 88)		SIENDO[5] Selinexor (n = 23) 80 mg QW	
	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)	All grades n (%)	Grade ≥ 3 n (%)
Anemia	23 (53.5)	10 (23.3)	4 (4.5%)	0	5 (21.7)	0
Neutropenia	5 (11.6)	3 (7.0)	5 (5.7)	0	8 (34.8)	4 (17.4)
Thrombocytopenia	23 (53.5)	13 (30.2)	0	0	10 (43.5)	4 (17.4)
Decreased appetite	26 (60.5)	3 (7.0)	6 (6.8)	0	10 (43.5)	0
Blurred vision	16 (37.2)	1 (2.3)	4 (4.5)	0	4 (17.4)	0
Constipation	14 (32.6)	1 (2.3)	33 (37.5)	2 (2.3)	12 (52.2)	0
Diarrhea	12 (27.9)	0	20 (22.7)	0	9 (39.1)	0
Fatigue	30 (69.8)	8 (18.6)	31 (35.2)	2 (2.3)	16 (69.6)	0
Hyponatremia	6 (14.0)	4 (9.3)	1 (1.1)	0	1 (4.3)	0
Nausea or vomiting	36 (83.7)	6 (14.0)	33 (37.5)	1 (1.1)	19 (82.6)	1 (4.3)
Weight decreased	25 (58.1)	1 (2.3)	1 (1.1)	0	2 (8.7)	0
AE leading to dose modification	36 (83.7)		17 (19.3)		12 (52.2)	
Grade ≥ 3 TEAE	37 (86.0)		13 (14.8)		9 (39.1)	

AE, adverse event; QW, every week; TEAE, treatment-emergent adverse event.

Table 3. Projected Rates of Safety Endpoints at 60 mg QW and 80 mg QW Regimen

Adverse event	Category	Exposure metric[a]	60 mg QW regimen, mean (90% CI)	80 mg QW regimen, mean (90% CI)	Change in rate between 80 and 60 mg
Anemia	≥ 2	AUCW1	12.7 (7.1, 19.2)	17.2 (10.3, 24.9)	4.5
Decreased appetite	≥ 2	AUCW1	8.9 (4.9, 13.8)	13.7 (7.7, 21.6)	4.8
Blurred vision[b]	≥ 1	CavgTOE	12.5 (6.8, 18.9)	16.8 (9.6, 25.2)	4.3
Constipation	≥ 2	AUCW1	—	—	—
Diarrhea	≥ 2	AUCW1	—	—	—
Fatigue	≥ 2	AUCW1	21.6 (14.8, 28.7)	25.6 (17.7, 33.6)	4.0
Hypertension	≥ 1	AUCW1	3.6 (0.0, 7.9)	4.7 (0.1, 9.2)	1.1
Nausea or vomiting	≥ 2	AUCW1	20.7 (14.8, 26.4)	24.9 (18.3, 31.5)	4.3
Neutropenia	≥ 3	AUCW1	9.2 (4.5, 18.2)	14.7 (6.7, 30.8)	5.5
Thrombocytopenia	≥ 3	AUCW1	6.8 (2.8, 15.1)	14.9 (6.8, 27.5)	8.0
Weight decreased	≥ 2	AUCW1	1.8 (0.5, 3.1)	2.9 (1.0, 4.6)	1.0
AE leading to dose modification	Yes/No	AUCW1	40.9 (31.9, 50.5)	48.1 (38.5, 57.7)	7.1
Grade ≥ 3 TEAE	Yes/No	AUCW1	33.4 (24.8, 41.2)	41.8 (33.0, 50.4)	8.4

AE, adverse event; AUCW1, area under the time-concentration curve calculated using total dose of the first week at Cycle 1; CavgTOE, time-to-event average selinexor concentration; CI, confidence interval; QW, every week; TEAE, treatment-emergent adverse event. [a]AUCw1 was used for selected exposure safety analysis, as it was the consistent predictor of safety endpoints. [b]CavgTOE was used for exposure safety analysis of blurred vision analysis, as it was found to be a better predictor for this analysis.

- Multivariate E-R relationships were observed for adverse events (AEs) leading to dose modifications, anemia, decreased appetite, blurred vision, fatigue, hyponatremia, thrombocytopenia, neutropenia, nausea/vomiting, decreased weight, and Grade ≥ 3 TEAEs (**Table 2**)
- Projected rate of AEs simulated using the multivariate E-R model at 60 mg SEL QW was compared with 80 mg SEL QW and predicted an 8.4% and 4.3% reduction in Grade ≥ 3 TEAEs and Grade ≥ 2 nausea/vomiting TEAEs, respectively (**Table 3**)

Limitations

- PK data were available from only 23 pts with EC in the SIENDO trial for E-R analysis of PFS

Conclusions

- This integrated E-R analysis demonstrated the potential for SEL 60 mg QW to improve safety while maintaining efficacy
- The Phase 3 ENGOT-EN20/GOG-3083/XPORT-EC-042 trial (NCT05611931) evaluating 60 mg SEL QW as maintenance therapy for pts with *TP53*wt advanced/recurrent EC is currently ongoing[17]
  - PK samples will be collected from all patients in this Phase 3 study to enable confirmatory integrated safety and efficacy E-R analysis

https://clinicaltrials.gov/ct2/show/NCT05611931

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