A Phase 1 Study of Selinexor in Combination with Paclitaxel and Carboplatin in Patients with Advanced Ovarian or Endometrial Cancers

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BACKGROUND

- XPO1 is a major nuclear export protein for tumor suppressor proteins (TSPs), including p53, p73, FOXO, pRB, BRCA1 and PP2A.
- Selective Inhibitor of Nuclear Export (SINE) compounds inhibit XPO1, leading to nuclear retention of TSPs and selective tumor cell apoptosis.
- Selinexor (S) is a first-in-class oral, covalent SINE compound.
- In a Phase II clinical trial of pts with relapsed ovarian cancer (OC) and endometrial cancer (EC), treatment with single-agent selinexor demonstrated anti-cancer activity. (1)
- Preclinical studies have shown that SINE compounds behave synergistically to enhance cancer cell death when combined with different therapeutic agents.
- Paclitaxel and carboplatin (TC) chemotherapy is commonly utilized in the treatment of advanced GYN malignancies.
- Phase IB study (NCT02419495) to evaluate the safety of selinexor in combination with multiple standard chemotherapy agents including TC in advanced malignancies is ongoing.
- Clinical exploratory analysis has demonstrated selinexor target engagement and a relationship between baseline circulating tumor cells and duration of response.

Figure 1:
Mechanism of action of Selinexor

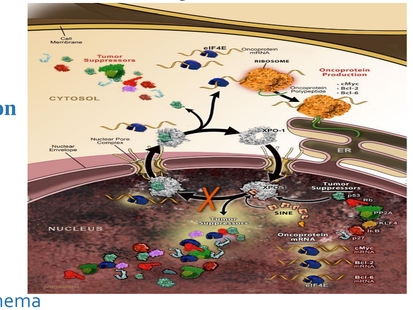

Table 1. Treatment Schema

Regimen #	Number of Patients	Regimen Details
1	4	Carboplatin AUC5 (day 1), Paclitaxel 175 mg/m^2 (day 1) and Selinexor 20 mg/m^2 (days 1, 4, 8, 11, 15, 18)
2	6	Carboplatin AUC5 (day 1), Paclitaxel 80 mg/m^2 (days 1, 8, 15) and Selinexor 20 mg/m^2 (days 1, 4, 8, 11, 15, 18)
3	3	Carboplatin AUC5 (day 1), Paclitaxel 80 mg/m^2 (days 1, 8, 15) and Selinexor 60 mg flat dose (days 1, 8, 15)
4	3	Carboplatin AUC5 (day 1), Paclitaxel 175 mg/m^2 (day 1) and Selinexor 60 mg flat dose (days 1, 8, 15)

METHODS

•This is a single-institution, open label, Phase I study. NCT02269293
•3+3 dose escalation design for each of 4 regimens.
•Patients with OC received 1 prior platinum therapy.
•Patients with EC and endometrial carcinosarcomas (ECS) could be chemotherapy naïve or have received 1 prior platinum-based therapy.
•Patients were enrolled to 1 of 4 regimens regardless of disease type as described in **Table 1**.
•Response was evaluated every 9 weeks via RECIST 1.1.

Key Inclusion Criteria
•Age: ≥ 18 years of age.
•Histologically confirmed OC, EC or ECS.
•Eastern Cooperative Oncology Group (ECOG) performance status of 0–1.
•Adequate bone marrow, renal, hepatic and neurologic function.
•Neuropathy (sensory and motor) ≤ to grade 1.
•Hormonal therapy must be discontinued >1 week prior to study initiation.
•Other tumor-directed therapy, including chemotherapy, biologic/targeted therapy and immunologic therapy, must be discontinued >3weeks prior
•Investigational agents must be discontinued >30 days prior to study initiation.
•Radiation therapy must be discontinued >4 weeks prior to study initiation.
•>4 weeks must have lapsed since major surgery prior to study initiation.

Key Exclusion Criteria
•Patients with CNS disease, uncontrolled, brain metastases and/or epidural disease, or history of cerebrovascular accident within 6 months prior
•Patients requiring drainage gastrostomy, parenteral hydration and/or nutrition.
•Patients with clinically significant cardiovascular disease

Primary Endpoints
• Evaluate safety, tolerability and determine the Recommended Phase 2 Dose (RP2D) of selinexor in combination with TC in advanced OC, EC or ECS.

Secondary Endpoints
•Explore clinical efficacy of S in combination with TC in advanced OC, EC, or ECS cancers by tumor response as defined by RECIST 1.1, duration of response (DOR) , progression-free survival (PFS), and overall survival (OS).
•Evaluate the pharmacokinetics of S when given in combination with TC.

Exploratory Endpoints
•Explore association of biomarkers of S effect focusing on XPO1 and TSPs transported by XPO1. Evaluate XPO1 inhibition in leukocytes utilizing whole blood RNA. For EC and ECS patients who have had their tumors molecularly profiled using the MSK-IMPACT platform, we will collect this information to evaluate if the expression profile correlates with response to this cancer subtype.

RESULTS

This ongoing study has enrolled 16 patients (data cutoff: August 25, 2017) with baseline characteristics shown in **Table 2** and tumor genomic testing results of EC/ECS pts in **Table 3.** All patients experienced an adverse event (AE). A summary of AEs is shown in **Tables 4 & 5**. Efficacy outcomes are summarized in **Table 6** with an objective response rate of 73.3%. The duration of treatment and overall time point assessments for patients in the full analysis set are shown in **Figure 2.** Duration of Response and Progression Free Survival are shown in **Figures 3 & 4**.

Table 2: Baseline Characteristics

Parameter	Total (N=16)
Median age, years (range)	64 (53–77)
Race, n (%)	
White	13 (81.0)
Black or African American	2 (13.0)
Other	1 (6.0)
ECOG performance status, n (%)	
0	14 (87.5)
1	2 (12.5)
Prior anticancer therapy regimens, n (%)	
0	8 (50.0)
1	6 (37.5)
2	2 (12.5)
Prior radiotherapy, n (%)	
Yes	4 (25.0)
No	12 (75.0)
Baseline Histology	
Grade 3 Serous Adenocarcinoma of Uterus	4 (25.0)
Grade 3 Endometrioid Adenocarcinoma of Uterus	3 (18.75)
Grade1 /2 Endometrioid Adenocarcinoma of Uterus	2 (13.0)
Grade 3 Uterine Carcinosarcoma	3 (18.75)
Grade 3 Serous Adenocarcinoma of the Ovary	4 (25.0)

Table 3: Alterations by MSK-IMPACT Assay

Patient	Alterations Detected in EC/ECS Pts
002	PIK3CA, TP53
003	AKT2, PIK3R1, ARID1B, TP53
005	No alterations detected
006	Not performed
007	FGFR1, FGFR3, ERBB3, TP53
008	PIK3CA, CTNNb1, PTEN
009	PIK3R1, ERBB3, TP53
010	PI3KR1, PTEN, ARID1A, CTNNB1, ERBB2, MTOR
012	PIK3CA, FGFR2, ARID1A, CTNNB1, PTEN
015	KRAS, NTRK1
016	KRAS, TP53
017	PI3KR1, ERBB2, FGFR1, TP53

Table 4. Adverse Events by Preferred Term and Grade Occurring in >10% of Patients [N=16]

TEAE, N(%)	Grade 2	Grade 3	Grade 4
Anemia	5 (31.3)	**10 (62.5)**	0 (0.0)
Leukopenia	**7 (43.8)**	**7 (43.8)**	1 (6.3)
Lymphocyte Count Decreased	0 (0.0)	**7 (43.8)**	0 (0.0)
Neutropenia	3 (18.8)	**6 (37.5)**	**5 (31.3)**
Hyperglycemia	**6 (37.5)**	4 (25.0)	0 (0.0)
Fatigue	**6 (37.5)**	1 (6.3)	0 (0.0)
Anorexia	4 (25.0)	0 (0.0)	0 (0.0)
Peripheral Sensory Neuropathy	4 (25.0)	0 (0.0)	0 (0.0)
Thrombocytopenia	3 (18.8)	3 (18.8)	2 (12.5)
Nausea	3 (18.8)	1 (6.3)	0 (0.0)
Constipation	3 (18.8)	0 (0.0)	0 (0.0)
Hypocalcemia	3 (18.8)	0 (0.0)	1 (6.3)
Hypomagnesemia	2 (12.5)	1 (6.3)	0 (0.0)
Hypoalbuminemia	2 (12.5)	0 (0.0)	0 (0.0)
Diarrhea	2 (12.5)	0 (0.0)	0 (0.0)
Hypophosphatemia	2 (12.5)	0 (0.0)	0 (0.0)
Hypokalemia	0 (0.0)	2 (12.5)	0 (0.0)
Syncope	0 (0.0)	2 (12.5)	0 (0.0)

Table 5: Overview of Adverse Events Analysis

Adverse Event (AE)	Total (N=16)
Any AE	16 (100%)
Treatment-related AE	16 (100%)
Any grade 3 or 4 AE	16 (100%)
Any serious AEs	6 (37.5%)
AEs leading to study-drug withdrawal/discontinuation	4 (25%)
AEs leading to study-drug dose reduction	8 (50%)
AEs leading to study-drug interruption	11 (68.7%)

Figure 2: Response

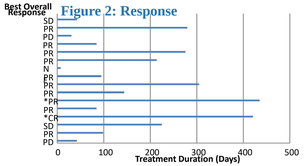

Table 6: Tumor Response by RECIST 1.1

Patient ID	Parameter	Number 15 (%)
014	Complete Response	1 (6.7)
002, 004, 005, 006, 008, 009, 010, 011, 012, 016	Partial Response	10 (66.7)
001, 015	Stable disease	2 (13.3)
003, 017	Progressive Disease	2 (13.3)

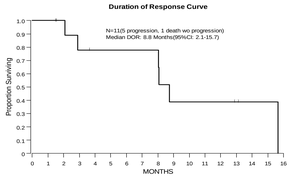

Figure 3 : Duration of Response curve

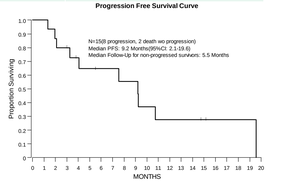

Figure 4 : Progression Free Survival curve

Conclusions

•Selinexor in combination with TC in advanced OC, EC, and ECS was tolerated.

•Bone Marrow toxicity appears to be greater in this study compared to that seen with TC in this patient population. (2-5)

•At this time, expansion of 3 additional patients for cohorts for regimens 3 and 4 are planned, and will be accrued by 1/2018.

•The RP2D of Selinexor in combination with TC has been established as 60mg flat dose weekly, and this formulation will developed further.

•Frequent molecular alterations seen in the endometrial carcinoma patients included: TP53, PIK3CA, PIK3R1 and KRAS.

•Evaluation of Selinexor target engagement and correlates of response is ongoing.

References and Acknowledgements

JCO 33, 2015; suppl; abstr 5565; Gynecol Oncol 2012;125:771-3; Br J Cancer 2012 Aug 7;107(4):588-91;Gynecol Oncol 2017 Jul 20.S0090-8258(17)31174-5;Lancet Oncol 2013 Sep;14(10):1020-6

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