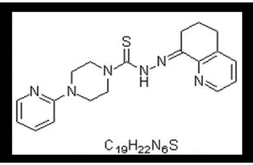

Safety of COTI-2, an orally available small molecule targeting p53, in a phase 1 study in recurrent gynecological cancer

#CT033

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Background

- Mutated p53 tumor suppressor protein is involved in >50% of all cancers.
- COTI-2, an orally available 3rd-gen thiosemicarbazone, has been shown to restore the structure and function of mutated p53 proteins in vitro.
- In xenograft studies, COTI-2 inhibited tumor growth of a number of p53 mutated cell lines.

Objective

Assess safety and tolerability of COTI-2 in gynecological malignancies and establish RP2D (Recommended Phase 2 Dose) for ovarian cancer.

Explore PK and PD measures.

Methods

Key Inclusion Criteria

1. Recurrent ovarian, peritoneal, fallopian tube, endometrial, or cervical cancer.
2. Unlimited prior therapy
3. Normal end organ function
4. Life expectancy > 3 months
5. Any p53 status

Methods

- Multicenter open label 3+3 dose escalation
- COTI-2 PO 5x/week, cycle length 28 days
- Responses evaluated every 2 cycles using RECIST 1.1.
- Baseline p53 profile obtained when possible

Table 1. Demographics (n=24 enrolled)

Characteristic	
Primary Site, n (%)	
Ovarian/Peritoneal/Fallopian tube	19 (79)
Endometrial	2 (8)
Cervical	3 (13)
Race, n (%)	
Caucasian	16 (67)
Black	2 (8)
Asian	2 (8)
Unknown/Not reported	4 (17)
p53 mutation status, n (%)	
Mutated	15 (63)
Wild-type	3 (13)
not available	6 (25)
Age, median years (range)	60 (45-73)

Previous Therapy (n=15 efficacy set)

- Patients had a median of 5 (0-8 range) previous chemotherapy regimens, and 2 patients had had radiotherapy.
- 5 patients had received bevacizumab (Avastin) as mono or combination therapy.
- 1 patient had received immune checkpoint inhibitor therapy.

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NCT02433626

Results

Table 2. Dose Escalation (n=24 enrolled)

Dose (mpk)	N	# DLTs
0.25	3	0
0.50	4	0
1.00	9	1
1.70	8	2

Cohort 3 DLT:
abd pain, p neuropathy

Cohort 4 DLTs:
neuralgia; myalgia

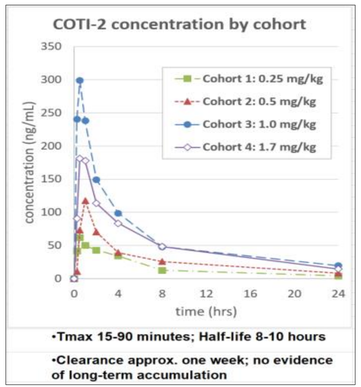

Table 3. Adverse Events, > 10% (n=24 enrolled)

Toxicity	Any grade, n (%)	G3/4, n (%)
Nausea	16 (67)	2 (8)
Vomiting	16 (67)	3 (13)
Fatigue	13 (54)	1 (4)
Abdominal pain	11 (46)	10 (42)
Constipation	7 (29)	0 (0)
Anemia	7 (29)	1 (4)
Dyspnea	7 (29)	3 (13)
Decreased appetite	6 (25)	0 (0)
Urinary tract infection	5 (21)	1 (4)
Hypokalemia	5 (21)	1 (4)
Myalgia	4 (17)	1 (4)
Diarrhea	4 (17)	0 (0)
Pyrexia	4 (17)	0 (0)
Peripheral neuropathy	4 (17)	3 (13)
Small intestine obstruction	4 (17)	4 (17)
Increased creatinine	3 (13)	0 (0)
Weight loss	3 (13)	0 (0)

2 patients (8%) required dose reduction.

Table 4. Responses Observed (n=15 efficacy set)

Cancer	Dose (mpk)	Cycles	p53	Response - Stable?
Ovarian	0.25	1	wild type	Nontarget lesion
Ovarian	0.25	2	mutated	Nontarget lesion
Ovarian	0.25	2	mutated	
Fallopian tube	0.5	4	mutated	Target Lesion
Cervical	0.5	2	wild type	Nontarget lesion
Endometrial	0.5	2	mutated	Inevaluable
Ovarian	1	2	mutated	Stable Disease
Ovarian	1	1	mutated	Target Lesion
Ovarian	1	1	mutated	
Fallopian tube	1	1	n/a	
Ovarian	1	2	n/a	
Ovarian	1	2	mutated	Target Lesion
Ovarian	1.7	1	n/a	Target Lesion
Ovarian	1.7	1	wild type	Nontarget lesion
Ovarian	1.7	1	mutated	Nontarget lesion

No significant decreases in CA-125 were observed.

Conclusions

- COTI-2 was deemed generally safe and well tolerated
- RP2D was established at 1.0 mg/kg
- Further exploration of the agent is ongoing in head and neck cancers
- Assessment of combination therapy is planned

Acknowledgements
NIH SPORE in Ovarian Cancer
Andrew Sabin Family Fellowship