



Phase 2 study of MKC-1 in patients with metastatic or resistant epithelial ovarian cancer or advanced endometrial cancer

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Abstract

Background: MKC-1 is a novel oral cell cycle inhibitor with preclinical activity in xenograft models of human ovarian and endometrial cancers. MKC-1 also reduces pAKT, an attractive target in endometrial cancer due to frequent PTEN mutations.

Patients and Methods: The objective of this Phase 2 study is to assess the efficacy of MKC-1 in 2 patient (pt) populations: metastatic or recurrent platinum-resistant ovarian cancer (EOC) and advanced endometrial cancer (EC). Three prior lines of treatment were allowed in both groups. A two arm, parallel group multi-center 2-stage design was used. The primary endpoint was tumor response by RECIST or CA-125. MKC-1 125 mg/m² was administered orally twice daily for 14 days in 28-day cycles.

Results: Accrual to stage one is complete with 21 pts in each arm. 19 pts with EOC (median age 56 yrs, range 31-71) and 9 patients with EC (median 63 range 50-74) were available for efficacy. A total of 66 cycles (EOC/EC: 39/27cycles) median 2 per patient (range 1-8) were delivered. 11/4 pts had prior adjuvant CT, 14/10 had prior systemic CT for advanced disease and 2/6 received prior radiation. In pts with EOC, 7 pts have stable disease (SD), 12 progressive disease (PD), 2 remain on study. Median time to progression is 1.8 months. In pts with EC 4 pts had SD, 5 PD, 6 remain on study. Toxicity data are available in 28 pts (17/11). Most common adverse events (AE) possibly related to MKC-1 were fatigue, nausea, elevated ALT or AST, urine discoloration, anemia, anorexia, elevated AP and gastrointestinal disorder in 55%, 39%, 36%, 24%, 23%, 21%, 21% and 21 % of cycles respectively. The only possibly related grade 3+ AEs were neutropenia, leucopenia and hyponatremia in 9%, 3%, and 2% of cycles.

Conclusions: MKC-1 was well-tolerated in both patient populations. Single agent MKC-1 has insufficient activity in platinum resistant EOC to warrant further investigation. Updated clinical data for both patient groups will be presented at the meeting.

Background

- MKC-1 is a novel cell cycle inhibitor
- At low concentrations, MKC-1 inhibits mitotic spindle formation, prevents chromosome segregation in the M-phase of the cell cycle and induces hyperploidy and apoptosis in multiple cell lines. Likely this is mediated by blockage of nuclear uptake of proteins essential to this process
- At high concentrations, MKC-1 inhibits progression into the S-phase
- In rodents, MKC-1 resulted in growth inhibition of several carcinomas including ovarian (TOV-21G) and endometrial (MES-Asa/DX5)
- Synergy has been observed with Paclitaxel, Carboplatin, Gemcitabine, and Capecitabine
- CYP 3A4 is the principal metabolizing enzyme, MKC-1 is metabolized into several inactive and two active metabolites

Patients and Methods

OBJECTIVES:

- To determine the antitumor activity of MKC-1 in patients with advanced ovarian cancer resistant to or relapsing after platinum- and taxane-based chemo or advanced endometrial cancer using response rate as primary endpoint
- To evaluate safety of MKC-1
- To evaluate response duration
- To evaluate Progression Free Survival

DESIGN AND STATISTICS:

- Two-arm, parallel group Phase 2 trial
- Open label, multicentre, 7 Canadian Centers participating
- Simon optimal 2-Stage design, H0 0.05, H1 0.20
- Go to Stage 2, if $\geq 2/21$ pts. respond in each arm
- Accept as active, if $\geq 5/41$ pts. respond in each arm

ELIGIBILITY:

- Inclusion:** Histologically confirmed ovarian-, primary peritoneal-, fallopian tube, endometrial cancer
- ECOG 0-2, age ≥ 18 years, sufficient baseline bloodwork
 - Measurable disease or Ca125 $\geq 2x$ ULN
 - No more than 3 prior lines of chemotherapy
- Exclusion:** Medical condition imposing excessive risk
- Significant bowel obstruction, active malabsorption, total gastrectomy
 - Pregnant, breastfeeding women
 - CNS Mets unless treated, stable and off steroids
 - Paracentesis >2 liters / week

TREATMENT:

- MKC-1 125 mg/m² po bid for 14 days in 28-day cycles

Results

TABLE 1:

Demographics	Ovarian	Endometrial
Total	21	23
Median Age (Range)	56 (31 – 71)	63 (50 – 74)
ECOG PS 0 / 1 / 2	12 / 9 / 0	6 / 14 / 3
# Prior Regimen 0/1/2/3/4	3 / 1 / 4 / 6 / 7	1 / 11 / 5 / 6 / 0
Prior Therapy		
•RT	2	10
•Adjuvant CT	13	8
•CT	8	18
Median # Cycles (Range)	2 (1 – 11)	2 (1 – 9)
Total # Cycles	63	74

TABLE 2: Efficacy

	Ovarian	Endometrial
Best Response (RECIST)		
•SD	8 (38%)	10 (43%)
•PD	13 (62%)	13 (57%)
•CR, PR	0	0
Best Response (Ca125)		
•Non-responder	16 (76%)	
•IE	5 (24%)	
Median SD duration, months (range)	3.7 (1.6 – 11.1)	3.8 (3.7 - 8.1)
TTP months (95% CI)	1.8 (1.6 – NR)	2 (1.6 – NR)
3 month progression free rate (95% CI)	29% (14 – 61)	45% (28 – 73)

TABLE 3: Toxicity *

(at least possibly related)	All Grades # of patients (%)	Grades 3+ # of patients (%)
Fatigue	30 (68%)	1 (2%)
Nausea	23 (52%)	0
Elevated AST	17 (39%)	1 (2%)
Anorexia	17 (39%)	1 (2%)
Urine Discoloration	17 (39%)	0
Elevated ALT	16 (36%)	1 (2%)
GI disorder	14 (32%)	1 (2%)
Vomiting	14 (32%)	0
Diarrhea	13 (30%)	0
Anemia	13 (30%)	1 (2%)
Neutropenia	12 (27%)	6 (14%)
Elevated AP	9 (20%)	0
Febrile neutropenia	1 (2%)	1 (2%)
Hyponatremia	2 (4%)	1 (2%)
Syncope	1 (2%)	1 (2%)

* CTC NCI version 3

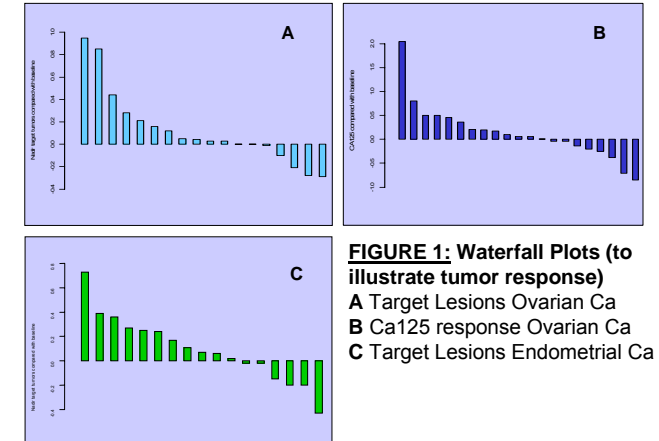
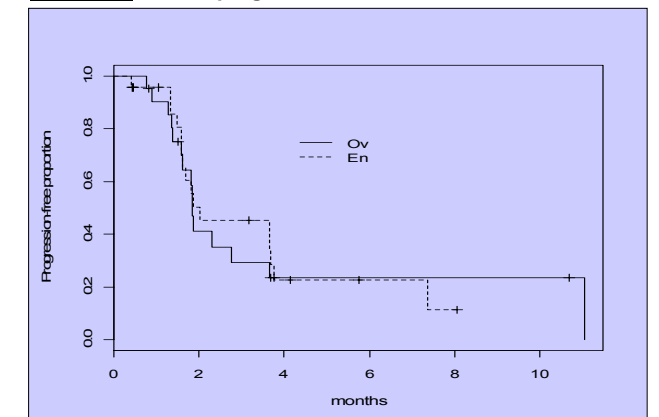
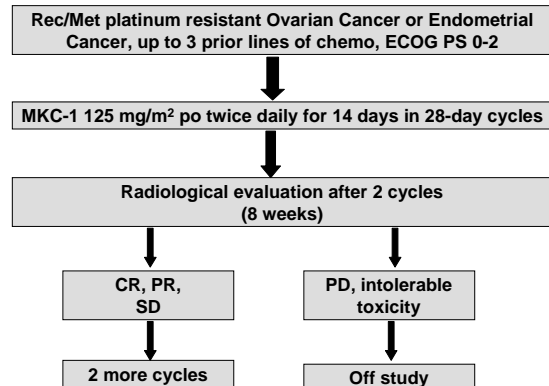


FIGURE 1: Waterfall Plots (to illustrate tumor response)
A Target Lesions Ovarian Ca
B Ca125 response Ovarian Ca
C Target Lesions Endometrial Ca

FIGURE 2: Time to progression



Study Schema



Conclusions

MKC-1 was well-tolerated in both patient populations. Single agent MKC-1 has insufficient activity in platinum resistant epithelial ovarian cancer and in endometrial cancer to warrant further investigation. Given good tolerance and preclinical synergy with other cytotoxic agents, further investigations as part of combination therapy might be warranted.