Phase II clinical and molecular trial of oral ENMD-2076 in clear cell ovarian cancer (CCOC)
A Study of the Princess Margaret Phase II Consortium

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Background

- Clear cell ovarian carcinoma (CCOC) represents 6% of all epithelial ovarian carcinomas and is associated with chemotherapy resistance and poor prognosis with advanced disease[1-2].
- Approximately 50% of CCOC are characterized by inactivating mutations in *ARID1A* and upregulation of PIK3/AKT/mTOR pathway[3]. Loss of ARID1A expression is associated with poor prognosis in CCOC[4].
- ENMD-2076 is an oral multi-target kinase inhibitor with antiangiogenic and antiproliferative profile; selective activity against the mitotic kinase Aurora A and VEGFRs, FGFRs [5].
- Single agent ENMD-2076 has shown activity in platinum-resistant ovarian cancer patients, with a 6-month progression free survival (PFS) rate of 22%[6].

Objectives

- **Primary Objectives:**

To assess the activity of ENMD-2076 defined by the 6-month PFS rate
To assess the objective response rate (ORR) using RECIST 1.1 criteria

- **Secondary Objectives:**

To determine the duration of response

- **Exploratory Objectives:**

To correlate somatic mutations in *PI3KCA* and *ARID1A* with patient outcome
To correlate the expression of ARID1A by immunohistochemistry in archival samples and pretreatment tumor biopsies with patient outcome

Methods

Multi-center, open-label, Phase II study of single agent ENMD-2706 (275 mg daily, 28 day cycle) in patients (pts) with recurrent CCOC.

Inclusion criteria:
- Histologically documented diagnosis of CCOC
- Any number of prior chemotherapy regimens were allowed, but must include one line of platinum-based chemotherapy. Prior Aurora A targeted therapies are excluded.
-Measurable disease defined by RECIST 1.1 criteria
-ECOG performance status ≤2
-Consent to access archival material for correlative studies and baseline fresh biopsy

Exclusion criteria:
-Known CNS metastases
-Uncontrolled hypertension (>150/100) or history of congestive heart failure (≥ grade 2). Pre-existing uncontrolled cardiovascular condition. QTc interval corrected >470 msec

Correlative Methodology:
-Immunostaining for ARID1A and PTEN on archival tumor tissue and baseline biopsy
-Next-generation sequencing using a 550-gene panel (exonic) to assess mutations in archival tumor tissue

Statistical Analysis:
-Sample size for primary endpoint: 6-month PFS rate : ≥11 patients (out of 36) *OR* Objective Response Rate ≥7/36.

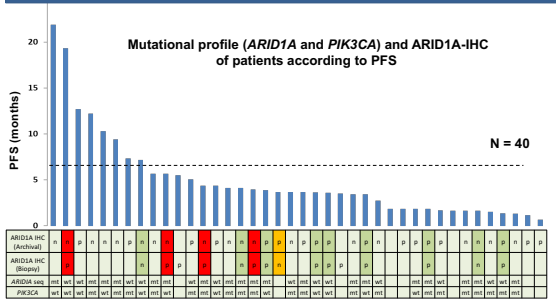
Patient Characteristics

Number of Patients (n)	40 (38 evaluable)
Median Age, Years (Range)	54 (39-78)
ECOG PS (0/1/2)	3/31/6
Race (White/Asian/Unknown)	28/11/1
Prior Regimens for Recurrent Disease (0/1/2)	27/9/4

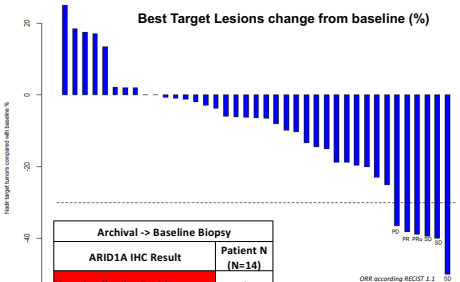
Adverse Events (n=40)

AE Terminology (>10%)	% Grade 1-2 (n)	% Grade ≥ 3 (n)
Fatigue	70 (28)	3 (1)
Nausea	68 (27)	5 (2)
Constipation	58 (23)	0
Diarrhea	50 (20)	10 (4)
Hypomagnesemia	48 (19)	3 (1)
Headache	45 (18)	0
Vomiting	40 (16)	5 (2)
Weight Loss	38 (15)	3 (1)
Hypoalbuminemia	38 (15)	13 (5)
Proteinuria	35 (14)	10 (4)
Anemia	33 (13)	8 (3)
Hypertension	33 (13)	28 (11)
Alkaline Phosphatase increased	28 (11)	0
Palmar-Plantar Erythrodysesthesia	25 (10)	0
Dysgeusia	25 (10)	0
Anorexia	25 (10)	0
White Blood Cell Decreased	23 (9)	5 (2)
Dizziness	23 (9)	0
Hypocalcemia	23 (9)	0
Elevated TSH	23 (9)	0
Mucositis	20 (8)	3 (1)
Hypothyrodism	20 (8)	0
AST increased	18 (7)	0
Hypophosphatemia	15 (6)	8 (3)
ALT increased	15 (6)	0
Hyponatremia	10 (4)	13 (5)

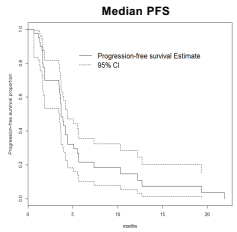
Clinical Efficacy

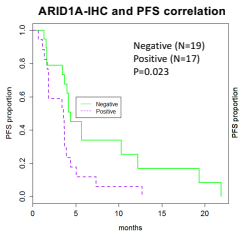


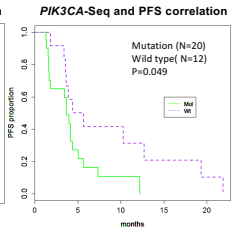
No correlation between *ARID1A*-Sequencing and PFS

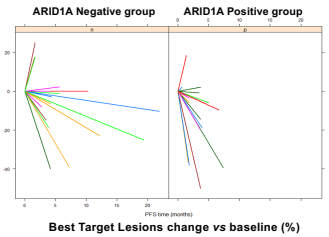


Archival -> Baseline Biopsy	
ARID1A IHC Result	**Patient N (N=14)**
Negative (loss)-> Positive	4
Positive (wild-type) -> Negative	1
No change	9









Best Target Lesions change *vs* baseline (%)

Conclusions

1. Eight patients (38 evaluable) achieved PFS>6 months, which did not meet the primary endpoint.
2. The median PFS was 3.7 (3.5-4.4) months. PFS at 6 months was 22% (0.10-0.36) for the evaluable pts, 33% (0.11-0.55) in ARID1A loss and 12% (0.02-0.31) in ARID1A positive pts (p =0.023). Loss of ARID1A on archival tissue appears to be associated with better PFS on ENMD-2076 that warrants further investigation.
3. Median PFS in wild-type *PIK3CA* was 5 months (3.4-12.7) *vs* 3.7 months (1.6-4.4) in mutated group (p=0.049).
4. Additional molecular profiling of baseline biopsy material is underway including the variation of expression between archival and baseline samples.

Acknowledgements

Patients and their families. Participating centres and clinical trials teams. Funding and drug supply from CASI Pharmaceuticals – Correlative analyses supported by OICR (Ontario Institute for Cancer Research)

References

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