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). Approximately 50% of CCOC are characterized by inactivating mutations in ARID1A and upregulation of PI3K/AKT/mTOR pathway. Loss of ARID1A expression is associated with poor prognosis in CCOC (2).
- ENMD-2076 is an oral multi-target kinase inhibitor with an antiangiogenic and antiproliferative profile; selective activity against the mitotic kinase Aurora A and VEGFRs.

Objectives
- To determine the duration of response.
- To correlate somatic mutations in PIK3CA and ARID1A with patient outcome.

Methods
- Mutli-center, open-label, Phase II study of single agent ENMD-2076 (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.

Exclusion criteria:
- Known CNS metastases.
- Known asymptomatic sarcoma.
- Pre-existing uncontrolled cardiovascular condition. QT 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

Conclusions
1. Eight patients (38 evaluable) achieved PFS ≥6 months, which did not meet the primary endpoint.
2. The median PFS was 3.7 (1.4–6.4) 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

References