

A Clinical and Molecular Phase II Trial of Oral ENMD-2076 in Ovarian Clear Cell Carcinoma (OCCC): A Study of the Princess Margaret Phase II Consortium



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Abstract

Purpose: Patients with recurrent ovarian clear cell carcinoma (OCCC) have limited effective options due to chemoresistance. A phase II study was designed to assess the activity of ENMD-2076, an oral multitarget kinase selective against Aurora A and VEGFR.

Patients and Methods: This multicenter phase II study included patients with recurrent OCCC who received prior platinum-based chemotherapy. Primary endpoints were objective response and 6-month progression-free survival (PFS) rates. Correlative analyses include ARID1A and PTEN expression by IHC and gene sequencing with a targeted custom capture next-generation sequencing panel.

Results: Forty patients were enrolled with a median age of 54, of which 38 patients were evaluable. ENMD-2076 was well tolerated with main related grade 3 toxicities being hypertension (28%), proteinuria (10%), and diarrhea (10%). Best

response was partial response for 3 patients (1 unconfirmed) and stable disease for 26 patients. The overall 6-month PFS rate was 22% and differed according to ARID1A expression (ARID1A⁻ vs. ARID1A⁺; 33% vs. 12%, $P = 0.023$). PTEN-positive expression was observed in 20 of 36 patients, and there was no correlation with outcome. Median PFS in patients with *PI3KCA* wild-type versus *PI3KCA*-mutated group was 5 versus 3.7 months ($P = 0.049$). Molecular profiling showed variants in *PI3KCA* (27%), *ARID1A* (26%), and *TP53* (7%). The patient with the longest treatment duration (22 months) was *PTEN* wild-type, diploid *PTEN* with putative biallelic inactivation of *ARID1A*.

Conclusions: Single-agent ENMD-2076 did not meet the preset bar for efficacy. Loss of ARID1A correlated with better PFS on ENMD-2076 and warrants further investigation as a potential predictive biomarker. *Clin Cancer Res*; 24(24); 6168–74. ©2018 AACR.

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Introduction

Ovarian clear cell carcinoma (OCCC) represents 6% of all epithelial ovarian carcinomas and, compared with other subtypes, is associated with a poorer prognosis and relative resistance to platinum-based chemotherapy (1–3). In the recurrent OCCC setting, response to second-line therapy is low and independent of the platinum-free interval (4, 5). Consequently, patients with OCCC require new therapeutic strategies based on the unique biology of this disease.

VEGF is strongly expressed in both early- and advanced-stage OCCC and seems an interesting pathway to target. Early-stage OCCC with high levels of VEGF has significantly shorter survival than early-stage OCCC with lower levels of VEGF expression (6). In addition, expression of VEGF *in vitro* is significantly higher in cisplatin-refractory human OCCC cells when compared with the cisplatin-sensitive parental cells (6). Anglesio and colleagues (7) demonstrated overexpression of the proangiogenic IL6–STAT3–HIF (interleukin 6-signal transducer and activator of transcription 3-hypoxia induced factor) pathway in OCCC tumors compared with high-grade serous cancers. In this study, sustained clinical and functional imaging responses were reported in 2 of 29 patients with chemotherapy-resistant OCCC

Translational Relevance

ENMD-2076 is an orally active, multitarget kinase inhibitor that has selective activity against Aurora A and potent anti-angiogenic activity. Ovarian clear cell carcinoma (OCCC) is associated with chemoresistance, and approximately 50% of cases are characterized by inactivating mutations in *ARID1A* and upregulation of the PIK3 pathway. Loss of *ARID1A* expression is associated with a poor prognosis. This is the first phase II study evaluating the efficacy of ENMD-2076 in recurrent OCCC patients. The median progression-free survival (PFS) was 3.7 months, and 22% of evaluable patients reached a 6-month PFS. Loss of *ARID1A* expression by IHC (*ARID1A*⁻) in patient tumors (*ARID1A*⁺) was associated with better PFS compared with those *ARID1A*⁺ (6 months PFS = 33% vs. 12%, *P* = 0.023). Further evaluation is needed to assess the role of *ARID1A* loss in response to therapy, as a potential predictive biomarker for selection of patients who may benefit from ENMD-2076 therapy.

treated with sunitinib, a multitargeted receptor tyrosine kinase inhibitor, which inhibits both platelet-derived growth factor receptor and the VEGF receptor. The whole gene-expression profiling of microdissected OCCC showed increased activity of pathways involved in angiogenesis and hypoxic cell growth, as well as marked inhibition of OCCC cell growth *in vitro* and *in vivo* following inhibition of HIF1- α and treatment with sunitinib (8).

In addition to angiogenesis, OCCC has a number of different molecular aberrations that drive pathogenesis and outcome (9). Somatic mutations in the AT-rich interactive domain 1A (SWI-like) gene (*ARID1A*) are the most common genetic changes in OCCC and are found in approximately 50% of OCCC cases (10). Loss of *ARID1A* expression has been correlated with shorter progression-free survival (PFS) and overall survival (OS) in women with OCCC following platinum-based chemotherapy (11, 12). *ARID1A* is a subunit of the SWI/SNF chromatin-remodeling complex, which alters chromatin structure by ATP-dependent disruption of histone-DNA interaction (13). The SWI/SNF complex is recognized as a tumor suppressor complex with mutations in a number of subunits identified in a variety of malignancies (13). The SWI/SNF chromatin-remodeling complex regulates the dynamic repositioning of nucleosomes; therefore, the loss of *ARID1A* could globally affect gene expression through deregulated transcription (14). The upregulation of the PIK3/AKT/mTOR pathway is also commonly seen in OCCC. Loss of PTEN protein expression by IHC has been described in one third of OCCC cases (15). PTEN is a key negative regulator of the PI3K pathway and is thought to be an early event in OCCC development (15). Activating mutations in phosphatidylinositol 3-kinase (*PIK3CA*) have been detected in up to 40% of patients with OCCC (16). PI3K regulates G₁ cell-cycle progression and cyclin expression through activation of the AKT/mTOR/p70S6K1 signaling pathway in ovarian cancer cells (17) and promotes cell survival through a variety of mechanisms (18).

The Aurora kinases are a family of serine-threonine kinases integral to mitotic cell division and have recently emerged as novel anticancer targets (19). Aurora Kinase A is overexpressed in

various malignant tumors including ovarian and breast cancer and its upregulation induces chromosomal instability, which leads to aneuploidy and cell transformation in many human cancers. This overexpression is also correlated with decreased survival in women with early-stage disease (20, 21). In advanced OCCC, increased Aurora A expression was associated with worse OS (22). A recent study had shown that overexpression of Aurora Kinase A was significantly associated with chemoresistance in OCCC and thus, targeting Aurora Kinase might be an interesting therapeutic option (23). The knockdown of Aurora A has been shown to impair cell growth, induce mitotic arrest, and increase cell death and caspase 3/7-mediated apoptosis in rhomboid tumor cells but not in normal cells, suggesting that Aurora A may be a viable therapeutic target for the cancer treatment (24). Multiple Aurora Kinase inhibitors are currently in clinical development (25).

Given the potential interest of combining different targets for therapeutic approach, the multitarget kinase inhibitor ENMD-2076, which has selective activity against Aurora A and potent activity toward a broad spectrum of targets linked to angiogenesis and lymphangiogenesis, including kinase domain receptor (KDR; VEGFR2), was assessed in early-phase trials with preliminary signal of activity, including OCCC (26). In the phase I study of ENMD-2076, from the 20 ovarian cancer patients enrolled at all dose levels, 12 (60%) experienced partial response or stable disease \geq 12 weeks. A subsequent open-label single-arm phase II study of single-agent ENMD-2076 in recurrent platinum-resistant ovarian cancer was designed and enrolled a total of 64 patients. The PFS rate at 6 months was 22% with a median time to progression of 3.6 months (27). Fifty-eight percent of patients had stable disease or partial response (PR) as their best response. Five patients (8%) had PR and the median duration of response was 7 months. Notably, 2 of 3 patients with OCCC who were enrolled in this study had a longer PFS than the median, suggesting that ENMD-2076 may be beneficial in this subset of patients (27). The purpose of this study was to examine the antitumor activity of ENMD-2076 administered as single agent in recurrent OCCC and identify potential biomarkers by analyzing the *ARID1A* expression and the PIK3/AKT/mTOR pathway.

Patients and Methods

Study design

This was a multicenter, phase II study in patients with recurrent OCCC. The primary objective was to determine the activity of ENMD-2076 as defined by objective response rate and the 6-month PFS rate. Objective tumor response was assessed at the end of cycle 2 using RECIST 1.1 criteria and every other cycle for the duration of study participation, including assessment at 6 months. The secondary objective was to determine the duration of response. Translational research objectives include the impact of known mutations and molecular aberrations (e.g., *ARID1A* loss, PTEN loss, *PIK3CA*, and *ARID1A* mutations) in OCCC on tumor response and patient outcome following treatment with ENMD 2076. The protocol was approved by the institutional review boards of participating institutions, and written informed consent was obtained from all patients prior to performing study-related procedures. The study was conducted in accordance with the declaration of Helsinki.

Eligibility criteria

Eligibility included patients with platinum-resistant or -sensitive recurrence who had documented diagnosis of OCCC with any number of prior chemotherapy regimens but must include at least one line of platinum-based chemotherapy. There is no limitation to the number of previous biologics or other targeted therapies but patients who have previously had Aurora A targeted therapies were excluded.

Other eligibility criteria included measurable disease by RECIST v1.1, at least 4 weeks from major surgical procedures or other therapies, acceptable organ function (ALT and AST \leq 2.5 times upper limit of normal, creatinine and bilirubin \leq 1.5 times the upper limit of normal, neutrophil count \geq 1,500/cells/mm³, platelets \geq 150,000/mm³, hemoglobin \geq 9 g/dL) with an Eastern Cooperative Oncology Group (ECOG) performance status of \leq 2. Patients had to consent to access archival material for correlative studies. Patients were excluded if they had active, acute, or chronic clinically significant infections or bleeding; uncontrolled hypertension, history of congestive heart failure (\geq grade 2), QTc interval corrected $>$ 470 ms, known central nervous system metastasis; any medical condition that would impair administration of an oral medication; or uncontrolled serious medical or psychiatric illness.

Dose administration

ENMD-2076 was supplied by CASI Pharmaceuticals. The starting dose was 275 mg (250 mg for patients with a BSA \leq 1.65 m²) taken daily orally without interruption for a 28-day cycle. Patients were treated until disease progression or unacceptable toxicity. Two dose reductions were allowed 225 and 150 mg (for patients with a BSA $<$ 1.65 m², dose -1 was 200 mg/d and dose -2, 150 mg). Dosing interruptions/delays of up to 2 weeks were allowed for recovery from toxicities or intercurrent illness. Longer interruptions were considered if the patient was benefiting from therapy with ENMD-2076.

Molecular profiling and variant analysis

Molecular testing was performed at CAP/CLIA-certified Advanced Molecular Diagnostics Laboratory at Princess Margaret Cancer Center (Toronto, Canada). After central pathology review, DNA samples were extracted from archival formalin-fixed paraffin-embedded (FFPE) tumor specimens. Tumor regions of FFPE specimens were acceptable if tumor cellularity was \geq 20%, and tumor regions were isolated by 1–2 \times 1 mm punch from FFPE blocks or by microdissection of unstained material from 15 to 20 slides (4–7 μ m sections). Next-generation sequencing (NGS) libraries were constructed from 250 ng of DNA sheared by sonication (Covaris), with end repair and ligation with barcoded sequencing adaptors, followed by hybrid capture with RNA baits (SureSelect; Agilent) and sequencing on the NextSeq (Illumina). The custom 555-gene panel (UHN Hi5) covers exons and minimum of 10 bp of flanking intronic region of 555 cancer-related genes (Supplementary Table S1). Variant analysis from NGS data used a custom bioinformatic pipeline that included alignment to the human genome reference (build GRCh37/hg19) using the Burrows-Wheeler Aligner (BWA-MEM), followed by marking duplicates using Picard Mark Duplicates and application of the Genome Analysis Toolkit (GATK) base quality score recalibration and indel realignment according to the GATK Best Practices recommendations. Somatic point mutation and insertions/deletions (InDels) discovery was performed using VarScan

(8, 9). Initial variant filtration was done using Cartagenia Bench Lab NGS v.4.2. (Agilent Technologies) (see Supplementary Materials for details).

Tissue pharmacodynamics analysis

FFPE archival tissue samples were obtained from patients for immunohistochemistry (IHC) analysis of ARID1A and PTEN. Paraffin sections at 4- μ m thickness were dried at 60°C for 1 to 2 hours before staining. The ARID1A IHC was completed using an automated slide stainer (BenchMark XT, Ventana Medical Systems Inc.) with standard antigen retrieval (CC1, Tris/Borate/EDTA pH8.0, #950-124). The ARID1A antibody (cat. #HPA5456, rabbit polyclonal, Millipore Sigma) dilution was 1:200 and incubated for 60 minutes, followed by Ultraview Universal DAB Detection Kit (#760-500, Ventana) processing for visualization. Tonsil was used as control. The slides were counterstained with Harris Hematoxylin and Bluing in PBS, dehydrated in graded alcohol, cleared in xylene and coverslipped in Permount.

PTEN IHC was performed manually at the Pathology Research Program Laboratory, University Health Network Toronto, and performed by incubating slides for 10 minutes at 100°C in 10 mmol/L sodium citrate, pH 6.0. Slides were blocked in 10% donkey serum in PBS for 1 hour and then incubated for 1 hour with primary antibody diluted in 2% donkey serum-PBS. PTEN antibody (Dako, mouse anti-human, clone 6H2.1, cat. #M3627) was used at dilution 1:100. Images were visualized and analyzed using ImageScope (Aperio).

ARID1A and PTEN IHC were scored by expert gynecologic pathologists (P.A. Shaw and B. Clarke). Loss of ARID1A expression was interpreted as negative (ARID1A⁻) if less than 5% of the tumor cells showed nuclear staining. Focal loss of ARID1A expression was determined if IHC staining was modest (between 5% and 50% of the tumor cells). Intact ARID1A was reported when more than 50% of the cells showed ARID1A expression. Both intact and focal loss of expression of ARID1A were grouped together as positive for ARID1A (ARID1A⁺).

PTEN expression was scored as positive, negative, and heterogeneous. Tumors considered positive showed diffuse positive cytoplasmic and nuclear staining in the majority ($>$ 90%) of cells. Tumors with no or only rare cells staining ($<$ 1%) were considered negative. Tumors with distinctive positive and negative staining foci were designated as having a heterogeneous staining pattern. PTEN protein loss included negative and heterogeneous scored cases.

Statistical methods

Any enrolled patient who received at least one dose of ENMD-2076 was included in the intent-to-treat population (ITT) and used for all analyses. The sample size for this single-arm trial was based on assumptions concerning PFS rate at 6 months in recurrent OCCC. The null hypothesis was a 6-month PFS rate of 20% and the alternative hypothesis of interest was a 6-month PFS rate of 40%. Based on the use of a single-stage design at the 10% significance level, a sample size of 36 provides 90% power of rejecting the null hypothesis if \geq 11 patients have a PFS of 6 months or more on treatment. PFS was also analyzed using Kaplan-Meier method. Duration of PFS was measured from the time of first ENMD-2076 dose to date of documented progression based on RECIST v1.1 criteria or death. All results from Kaplan-Meier analyses have included 40 patients. Response and duration of response were assessed by RECIST v1.1 from the time that the

Table 1. Patient characteristics

Number of patients	Total	40
	Evaluable	38
Median (range) age		54 (39, 78)
Performance status	0:1:2	4:30:6
Race (White/Asian/ Unknown)		28:11:1
Prior regimens, <i>n</i>	1:2:3	24:12:4
Prior therapy	Radiotherapy	13
	Adjuvant chemotherapy	26
	Systemic chemotherapy	19
Median (range) Cycles/patient		4 (1, 20)
Total cycles		208
Best response	PR confirmed	2 (5%)
	PR unconfirmed	1 (2.5%)
	Stable disease (SD)	26 (65%)
	Progressive disease (PD)	9 (22.5%)
	Not evaluable	2 (5%)
	PFS ≥ 6 months	8 (1 PR + 7 SD) 21%

Table 2. Treatment-related adverse events (AE) observed greater than 10% (*n* = 40)

AE terminology (>10%)	Grade 1-2, % (<i>n</i>)	Grade ≥ 3, % (<i>n</i>)
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)
Hypothyroidism	20 (8)	0
AST increased	18 (7)	0
Hypophosphatemia	15 (6)	8 (3)
ALT increased	15 (6)	0
Hyponatremia	10 (4)	13 (5)

measurement criteria were met for response until progression. Log-rank test was used to examine the association between PFS and biomarkers.

Results

Patient characteristics

Of the 40 patients who were enrolled between October 2013 and January 2017 at 6 cancer centers representing the ITT population, 38 were evaluable for activity (2 patients did not complete one cycle of therapy and were considered not evaluable for response). Table 1 lists demographics and patient characteristics. Most patients (25/40) had recurrent disease within 6 months of completing a platinum-containing chemotherapy regimen (i.e., platinum-resistant disease). Twelve and 4 patients had 2 or 3 prior regimens, respectively.

Efficacy

The estimated 6-month PFS was 0.22 (0.10–0.36) with a median time to progression of 3.7 months (95% CI, 3.5–4.4).

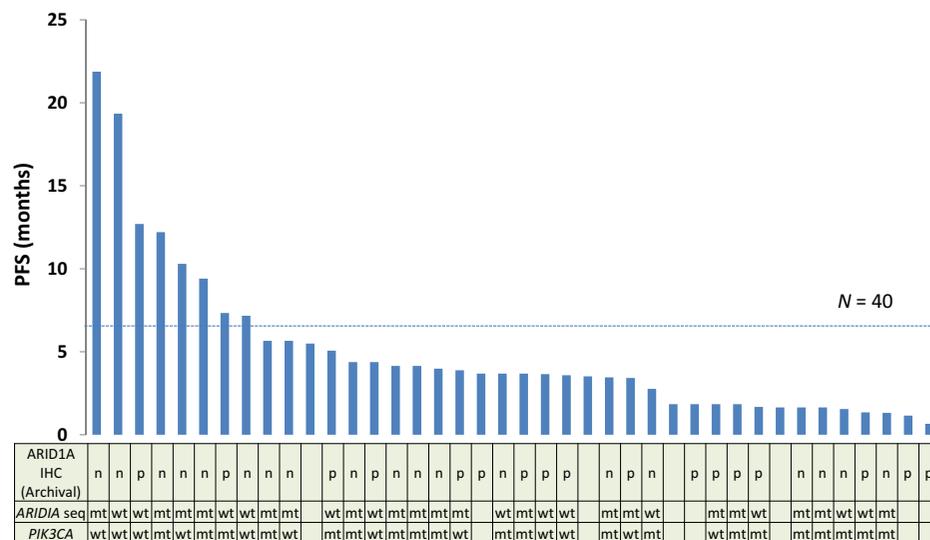
Eight patients (21% of the 38 patients evaluable) achieved PFS more than 6 months (Fig. 1), which did not meet the primary endpoint. Best response was PR for 3 patients (1 unconfirmed), stable disease for 26 and progressive disease for 9 patients. Two patients were taken off study prior to the first radiologic scan and are therefore not evaluable for response criteria.

Adverse events

The most common events were fatigue (70%), nausea (68%), constipation (58%), diarrhea (50%), and hypomagnesemia (48%; Table 2). The most common ≥ grade 3 treatment-related adverse events were hypertension (28%), hypoalbuminemia (13%), hyponatremia (13%), proteinuria (10%), and diarrhea

Figure 1.

PFS and mutational profile (ARID1A and PIK3CA) and ARID1A-IHC status. *n* = negative, *p* = positive, WT = wild-type, mt = mutation; seq = sequencing.



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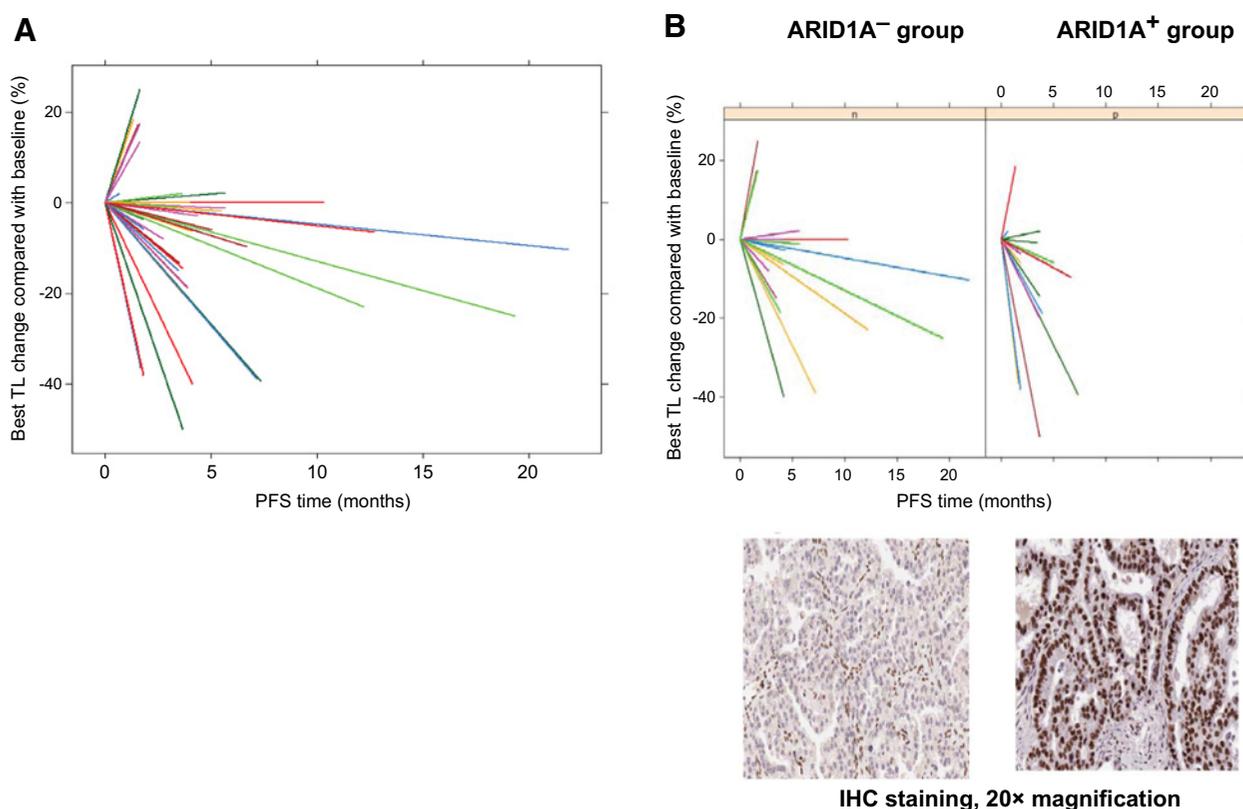


Figure 2. Spider plot of best target lesions change from baseline (%) with PFS. **A**, All patients. **B**, According to ARID1A IHC status (IHC staining, 20× magnification).

(10%). Adverse events resulted in dose reductions in 16 patients (41%) and led to treatment discontinuation in 4 patients (grade 3 skin rash, grade 3 hypertension, grade 2 generalized muscle weakness, grade 3 heart failure). No death drug-related was reported.

Correlative studies

Archival tumor tissue from 36 patients was obtained and examined for molecular mutations and associated with response to ENMD-2076. ARID1A and PTEN protein expression were detected by IHC in 36 patients. Of these, 19 patients were ARID1A⁻ (53%) with a median PFS (95% CI) of 4.4 months (3.5–10.3), and 17 patients were ARID1A⁺ (47%) with a median PFS (95% CI) of 3.6 months (1.7–3.9). The median PFS in these 2 subgroups was significantly different with an estimated 6-month PFS rate for the ARID1A⁻ group of 0.33 (0.11–0.55) and 0.12 (0.02–0.31) for the ARID1A⁺ group ($P = 0.023$). Changes of tumor target lesions over the treatment from baseline in all patients and according to ARID1A were also plotted as a spider plot (Fig. 2). In addition, 20 patients were PTEN-positive expression (56%) with a median PFS (95% CI) of 3.7 months (1.6–4.4), and 16 patients were PTEN negative (44%), with a median PFS (95% CI) of 4.3 months (1.8–7.4; $P = 0.184$).

Of the 36 patients with OCCC that underwent NGS (UHN Hi5), 4 patients had insufficient DNA, 20 (63%) and 19 patients (60%) were found to have *PIK3CA* and *ARID1A* mutation, respectively (Fig. 1). There were no *PTEN* mutations detected in 32 OCCC samples.

Median PFS in the *PIK3CA* wild-type population was 5 months (3.4–12.7) versus 3.7 months (1.6–4.4) in the mutated group ($P = 0.049$). The difference between the median PFS in the wild-type *ARID1A* (4.4 months; 1.7–12.7) and mutation group (4.0 months; 1.8–5.7) was not significant ($P = 0.776$). The patient with the longest treatment duration (22 months) was PTEN wild-type, diploid PTEN, putative biallelic inactivation of *ARID1A*.

Additional few other mutations were observed, particularly in the DNA repair pathway (Supplementary Fig. S1).

Discussion

This was the first study to evaluate the efficacy of the multitarget kinase inhibitor ENMD-2076, which has selective activity against Aurora A and potent antiangiogenic activity, in patients with recurrent OCCC. The expected side effects of hypertension, nausea, and diarrhea were observed and manageable in most patients. The median PFS was 3.7 months with a 6-month PFS rate at 22% for the 38 evaluable patients. Although the study did not meet the primary endpoint as the median PFS reported is similar to standard chemotherapy, 8 of 38 evaluable patients had a 6-month PFS benefit from the ENMD-2076 treatment.

Molecular analysis was planned as part of the trial to identify potential biomarkers for treatment response. There is a trend toward improved PFS associated with no *PIK3CA* mutation as there was a PFS of 5 months (3.4–12.7) in the wild-type group versus 3.7 months (1.6–4.4) in the mutated group ($P = 0.049$).

The activation of the AKT/mTOR/p70S6K1 signaling pathway promotes cell survival and resistance to therapy (17), which may explain the difference in terms of PFS between the 2 groups. Whereas the difference of median PFS by *ARID1A* sequencing status was not significant, the *ARID1A*⁻ tumor by IHC was associated with improved outcome to ENMD-2076, with an estimated 6-month PFS rate of 0.33 (0.11–0.55) for the *ARID1A*⁻ group and 0.12 (0.02–0.31) for the *ARID1A*⁺ group ($P = 0.023$). The difference between the two methods of assessment (IHC and NGS: 22 were concordant and 10 are discordant; concordance rate of 69%) may reflect other mechanisms than mutation involved in the suppression of *ARID1A* expression. This potential benefit in this subgroup is intriguing, given this biomarker has been associated with poor prognosis (12, 13) and loss of *ARID1A* has been identified as a driving mutation of OCCC and seems to work as a tumor suppressor (16). *ARID1A* may play a role in response to therapy and further investigation is required to establish the impact of *ARID1A* status for treatment. Recently, a study suggested that *ARID1A* deficiency contributes to impaired mismatch-repair and mutator phenotype in cancer and may cooperate with immune checkpoint blockade therapy (28).

There was no *PTEN* variant (SNVs and indels; refer to the Materials and Methods section) detected by NGS in our analyses, consistent with previous observations in a whole-exome study (29). In this study, the authors suggested epigenetic silencing and copy-number alterations as other possible mechanisms of *PTEN* loss. Another possible explanation for the loss of the dominant-negative *PTEN* mutation is the biological redundancy of the *PTEN*-inactivating and *PIK3CA*-activating mutations that both lead to an elevated signaling through the PI3K pathway (29). These results indicate that other mechanisms rather than sequence mutations are involved in activating the pathway for OCCC with wild-type *PIK3CA*.

OCCC is a rare subtype of ovarian cancer with limited therapeutic options. ENMD-2076 did not meet the efficacy bar set in this trial, but its potential benefit has been observed for patients with *ARID1A* loss tumor, which requires further evaluation. Several studies are ongoing targeting the angiogenesis pathway and the immune microenvironment, which will provide essential data to improve the management of this rare disease.

Disclosure of Potential Conflicts of Interest

A. Tinker reports receiving commercial research grants and speakers bureau honoraria from AstraZeneca. M.O. Butler is a consultant/advisory board member for Bristol-Myers Squibb, EMD Serono, GlaxoSmithKline, Immunocore, Merck, and Novartis. D.S.P. Tan reports receiving commercial research grants from Astra Zeneca, Bayer, and Karyopharm Therapeutics, and speakers bureau honoraria from Astra Zeneca, MSD, and Roche. A.M. Oza is a consultant/advisory board member for AstraZeneca, Clovis, and Intas. No potential conflicts of interest were disclosed by the other authors.

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