J Gynecol Oncol. 2024 Sep;35(5):e69
https://doi.org/10.3802/jgo.2024.35.e69
pISSN 2005-0380·eISSN 2005-0399

JOURNAL OF GYNECOLOGIC ONCOLOGY

Original Article

Comprehensive characterization of genomic features and clinical outcomes following targeted therapy and secondary cytoreductive surgery in OCCC: a single center experience

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Received: May 7, 2023
Revised: Nov 3, 2023
Accepted: Feb 11, 2024
Published online: Mar 29, 2024

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ABSTRACT

Objective: Ovarian clear cell carcinoma (OCCC) is associated with chemoresistance. Limited data exists regarding the efficacy of targeted therapies such as immune checkpoint inhibitors (ICI) and bevacizumab, and the role of secondary cytoreductive surgery (SCS).
Methods: We retrospectively analyzed genomic features and treatment outcomes of 172 OCCC patients treated at our institution from January 2000 to May 2022. Next-generation sequencing (NGS) was performed where sufficient archival tissue was available.
Results: 64.0% of patients were diagnosed at an early stage, and 36.0% at an advanced stage. Patients with advanced/relapsed OCCC who received platinum-based chemotherapy plus bevacizumab followed by maintenance bevacizumab had a median first-line progression-free survival (PFS) of 12.2 months, compared with 9.3 months for chemotherapy alone (hazard ratio=0.69; 95% confidence interval [CI]=0.33, 1.45). In 27 patients who received an ICI, the overall response rate was 18.5% and median duration of response was 7.4 months (95% CI=6.5, 8.3). In 17 carefully selected patients with fewer than 3 sites of relapse, median PFS was 35 months (95% CI=0, 73.5) and median overall survival was 96.8 months (95% CI=44.6, 149.0) after SCS. NGS on 58 tumors revealed common mutations in *ARID1A* (48.3%), *PIK3CA* (46.6%), and *KRAS* (20.7%). Pathogenic alterations in *PIK3CA*, *FGFR2*, and *NBN* were associated with worse survival outcomes. Median tumor mutational burden was 3.78 (range, 0–16). All 26 patients with available loss of heterozygosity (LOH) scores had LOH <16%.
Conclusion: Our study demonstrates encouraging outcomes with bevacizumab and ICI, and SCS in select relapsed OCCC patients. Prospective trials are warranted.

Keywords: Immunotherapy; Bevacizumab; Ovarian Neoplasms; Adenocarcinoma, Clear Cell; Cytoreduction Surgical Procedures

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Funding

This research is funded by National Medical Research Council (NMRC) CSASI21jun-0003 and the Pangestu Family Foundation Gynaecological Cancer Research Fund. We thank Lena Kwok, Kah Wieng Tham, Shu Jun Chan, and Putri Elissa for their support with project administration and data curation for this study.

Presentation

This data was selected for poster presentation at the ESMO Congress 2020, Barcelona, Spain.

Conflict of Interest

Natalie YL Ngoi reports honorarium and travel from AstraZeneca, and honorarium from Pfizer and Merck.

David SP Tan reports personal fees for advisory board membership from AstraZeneca, Bayer, Boehringer Ingelheim, Eisai, Genmab, GSK, MSD, and Roche; personal fees as an invited speaker from AstraZeneca, Eisai, GSK, Merck Serono, MSD, Roche, and Takeda; ownership of stocks/shares of Asian Microbiome Library (AMiLi); institutional research grants from AstraZeneca, Bayer, Karyopharm Therapeutics, and Roche; institutional funding as coordinating PI from AstraZeneca and Bergen Bio; institutional funding as local PI from Bayer, Byondis B.V. and Zeria Pharmaceutical Co Ltd; a previous non-renumerated role as Chair of the Asia-Pacific Gynecologic Oncology Trials Group (APGOT); a previous non-renumerated role as the Society

Synopsis

Ovarian clear cell carcinoma (OCCC) is relatively chemoresistant, with poorer stage-adjusted outcomes. We evaluated genomic features and treatment outcomes in a multi-ethnic Asian population. Bevacizumab, immune-checkpoint inhibitors, and secondary cytoreductive surgery showed promising results, supporting trials of novel strategies in OCCC.

INTRODUCTION

Ovarian clear cell carcinoma (OCCC) is a distinct and rare histological subtype of epithelial ovarian cancer (EOC) with unique epidemiology and molecular profile. OCCC is of particular interest in East Asian populations where it has been described to comprise up to 25% of diagnosed EOC in Singapore, Japan and South Korea [1,2]. To date, the optimal treatment of OCCC both in the early and recurrent/advanced stages remains poorly defined. Consistently lower objective response rates to front- and subsequent-line chemotherapy as well as poorer stage-adjusted prognosis have been described for OCCC compared with high-grade serous ovarian cancer. Thus, the treatment of OCCC remains an area of unmet need and effective therapies to improve its prognosis are urgently required. Novel approaches such as targeting the vascular endothelial growth factor (VEGF) pathway or immune pathways have become of interest in OCCC [3]. Several gene expression profiling studies have described the upregulation of the interleukin 6-signal transducer and activator of transcription 3-hypoxia induced factor axis in approximately half of OCCC [4], as well as the activation of major pathways involved in hypoxia, angiogenesis and glucose metabolism, that is not observed in other EOC subtypes [5]. Preclinical studies have also demonstrated the elevation of VEGF expression in platinum-resistant OCCC models compared with parental cells, with subsequent marked response demonstrated to bevacizumab therapy *in vitro* and *in vivo* [6]. Furthermore, although EOC has been typically described as being immunologically 'cold', increasing rationale now supports the role of immune checkpoint inhibitors (ICI) targeting the programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) axis in OCCC. The distinct molecular profile of OCCC may contribute towards a unique immune microenvironment in this disease. For example, OCCC have been associated with increased lymphocyte activation gene 3, T-cell immunoglobulin mucin-3 and PD-1 expression [7]; while *ARID1A* deficiency, which is observed in ≤40% of OCCC, has been associated with increased PD-L1 expression, increased mutational burden and deficient mismatch repair (dMMR) [8]. To date, although bevacizumab and ICI therapy have been broadly investigated in advanced EOC, limited data exists regarding the role of these novel agents in the treatment of OCCC specifically. Additionally, it remains unclear whether treatment approaches that have been shown to improve progression-free survival (PFS) and overall survival (OS) in EOC, such as adjuvant chemotherapy for early stage disease, or secondary cytoreductive surgery (SCS) for relapsed disease, are indeed beneficial in this rare and under-studied disease entity.

Importantly, inter-ethnic differences in the molecular characteristics of OCCC are incompletely understood, although intriguing differences have been described in Asian OCCC patients in terms of DNA methylation[9] and transcriptomic profiles [10]. We previously described clinical and transcriptomic differences amongst OCCC patients from Asian and Caucasian populations [10]. OCCC patients from Singapore and Japan tended to be diagnosed at a younger age compared with those from the United Kingdom with slight differences in immune-related gene expression signatures. For example, a greater proportion

President of the Gynecologic Cancer Group Singapore; non-renumerated membership of the Board of Directors of the GCIG; and product samples from AstraZeneca, Eisai, and MSD (non-financial interest).

Author Contributions
Conceptualization: N.N.Y.L., T.D.S.P.; Data curation: W.S.T., N.N.Y.L., L.J.W.Z., L.A.; Formal analysis: W.S.T., N.N.Y.L., L.J.W.Z., T.T.Z.; Investigation: L.D., K.I.S., T.Y.L., A.B.W.L., T.P., N.J., L.J.J.H., I.A.; Methodology: N.N.Y.L., T.D.S.P.; Resources: N.N.Y.L., T.P., N.J., L.J.J.H., I.A., L.S.E., L.Y.W., T.D.S.P.; Supervision: N.N.Y.L., T.D.S.P.; Visualization: W.S.T., L.J.W.Z., T.T.Z.; Writing – original draft: W.S.T., N.N.Y.L., L.J.W.Z.; Writing – review & editing: W.S.T., N.N.Y.L., T.T.Z., L.D., K.I.S., T.Y.L., L.A., A.B.W.L., T.P., N.J., L.J.J.H., I.A., L.S.E., L.Y.W., T.D.S.P.

of Singaporean OCCC patients had a PD1-high subtype compared with the rest, which was associated with a worse prognosis [10]. Further attention should be paid to understanding the molecular characteristics of OCCC in Asia, where this disease is particularly prevalent, and the potential impact of molecular profile on clinical outcomes. In this retrospective analysis, we sought to address these questions with real-world experience of these approaches in a multi-ethnic Asian cohort of 172 OCCC patients treated at our institution, as well as to correlate our findings with potential genomic biomarkers.

MATERIALS AND METHODS

1. Study participants

We conducted a single-institution retrospective study between January 2000 to May 2022. This study was approved by the National Health Group Domain Specific Review Board (2013/00705) in accordance with the principles of the Declaration of Helsinki. Data was retrieved from medical record review. All tumor samples were reviewed by a specialist Gynecologic Pathologist who was blinded to the patient's clinical data (DL). Histological subtype was determined to be OCCC based on the following features: cells containing typical abundant clear cytoplasm or hobnail cells within papillary, solid or tubule cystic structures, that were negative for Wilm's tumor 1 and showed normal p53 staining by immunohistochemistry (IHC).

2. Clinical data, treatment response assessment, molecular profiling and follow-up

Medical records of patients with diagnosis of OCCC were reviewed retrospectively for the following information: date and age at diagnosis, Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) surgical stage, completeness of primary debulking surgery, tumor and germline next-generation sequencing (NGS) data, tumor IHC performed as part of routine care (including mismatch repair [MMR] protein proficiency and PD-L1 combined positive score), types and dates of systemic therapy received, as well as treatment outcomes from surgeries and systemic treatments. Treatment response was assessed by the Response Evaluation Criteria in Solid Tumours guidelines version 1.1. Where sufficient archival tissue was available, NGS using FoundationOne CDx (Foundation Medicine, Cambridge, MA, USA) was performed on archival formalin-fixed paraffin embedded tumor samples. FoundationOne CDx is a qualitative NGS based *in vitro* diagnostic test that uses targeted high throughput hybridization-based capture technology for detection of substitutions, insertion and deletion alterations, and copy number alterations in 324 genes and select gene rearrangements, as well as genomic signatures including microsatellite instability (MSI), tumor mutational burden (TMB), and positive homologous recombination deficiency (HRD) status (tumor BRCA-mutant and/or genomic loss of heterozygosity [LOH] high) in ovarian cancer (detailed information available at https://www.foundationmedicine.com/test/foundationone-cdx). Gene alterations identified by the FoundationOne CDx panel are categorized as known or likely pathogenic variants in the Foundation Medicine database, which includes entries in the COSMIC database, or variants of unknown significance; these are addressed in the FoundationOne CDx report.

3. Statistical analysis

Comparisons between groups were analyzed using X^2 or Fisher's exact test for categorical variables, as appropriate. PFS was defined as the date of treatment initiation to date of last

visit, disease progression or death from any cause. OS was defined as the date of diagnosis to the date of last visit or death from any cause. Relapse-free survival (RFS) was analyzed in patients who were rendered disease-free by complete debulking surgery, and was defined as the date of surgery to date of first confirmed radiological relapse. Univariate Cox regression analyses were performed to identify predictors of survival. Kaplan-Meier curves were used to calculate median survival for each index and to compare survival times between patient populations, while the log-rank test was used to assess the equality of survival between patient populations. Mutation in any of the genes included in a pathway gene list was counted as mutation in the pathway [11,12]. Statistical significance was determined with a p-value <0.05. All statistical analyses were performed using SPSS 26.0 (IBM Corp., Armonk, NY, USA).

RESULTS

1. Patient characteristics

A total of 172 patients with confirmed OCCC were identified during the study period. The baseline characteristics of the patients are presented in **Table 1**. The median age of diagnosis was 53.0 (range, 24.2–82.6) years in the entire cohort. Patients were of Chinese (70.9%), Malay (11.6%), Indian (7.6%) and other (9.9%) ethnicities, respectively. 64.0% (stage I 53.5%, stage II 10.5%) of patients had early FIGO stage at the time of first diagnosis, while 36.0% (stage III 26.2%, stage IV 9.9%) of patients were diagnosed at advanced FIGO stage. 94.7% of patients underwent radical primary debulking surgery and 79.6% of patients had no residual disease after primary debulking surgery. Overall, 82.6% of patients received neoadjuvant/adjuvant chemotherapy across the entire cohort. Venous thrombotic events occurred at the time of presentation for 27 (15.7%) of patients overall and 66 (38.4%) patients were noted to have either a personal history of endometriosis or had evidence of endometriosis at the time of surgery. Full details including patient characteristics, treatments received (up to fifth line), response to treatment, survival, and results of genomic profiling for each patient can be found in **Table S1**.

2. Treatment of early stage OCCC

Amongst 110 patients diagnosed with early stage (stage I–II) OCCC, the median age at diagnosis was 53.0 (range, 24.2–82.7) years. Following primary debulking surgery, 105 (95.5%) had no residual disease at time of surgical closure, while 4 (3.6%) were noted to have residual disease; data was missing for the remaining 1 (0.9%) patient. 89 (80.9%) of patients received adjuvant chemotherapy, all of whom received carboplatin plus paclitaxel as the adjuvant regimen. At the time of follow up, 37 (33.6%) early stage patients had relapsed, while 73 (66.4%) remained in remission (**Table 1**). Rates of disease relapse according to stage are summarized in **Table S2**. No significant difference in relapse was observed for early stage OCCC patients treated with adjuvant carboplatin plus paclitaxel chemotherapy compared to no adjuvant chemotherapy (odds ratio [OR]=1.02; 95% confidence interval [CI]=0.37, 2.79). Median RFS was numerically improved with adjuvant chemotherapy, although this did not reach statistical significance (162.9 months with adjuvant chemotherapy vs. 109.2 months without adjuvant chemotherapy (hazard ratio [HR]=0.57; 95% CI=0.25, 1.32; log-rank p=0.19) (**Fig. 1**).

3. Treatment of relapsed/advanced OCCC

Amongst 99 patients with relapsed or advanced OCCC, 37 (37.4%) patients had relapsed disease while 62 (62.6%) patients had de novo advanced disease at presentation (**Table 1**). The treatments received by advanced and relapsed patients from the first to fifth lines

Table 1. Clinical and molecular characteristics of OCCC patients

Patient characteristics	Early stage I–II (n=110)	Advanced stage III–IV (n=62)	p-value
Median age at diagnosis in years	53.0 (24.2–82.7)	53.1 (33.3–74.3)	0.869
Ethnicity			0.216
Chinese	79 (71.8)	43 (69.4)	
Malay	9 (8.2)	11 (17.7)	
Indian	9 (8.2)	4 (6.5)	
Others	13 (11.8)	4 (6.5)	
FIGO stage at diagnosis			
I	92 (83.6)		
IA	25 (22.7)		
IB	3 (2.7)		
IC1	32 (29.1)		
IC2	12 (10.9)		
IC3	10 (9.1)		
IC (subgroup unknown)	6 (5.5)		
I (subgroup unknown)	4 (3.6)		
II	18 (16.4)		
IIA	3 (2.7)		
IIB	8 (7.3)		
IIC	5 (4.5)		
II (subgroup unknown)	2 (1.8)		
III		46 (74.2)	
IIIA		12 (19.3)	
IIIB		5 (8.1)	
IIIC		24 (38.7)	
III (subgroup unknown)		5 (8.1)	
IV		16 (25.8)	
IVA		0 (0)	
IVB		16 (25.8)	
Primary surgery			<0.001
No residual disease	105 (95.5)	32 (51.6)	
Residual disease	4 (3.6)	22 (35.5)	
No surgery	0 (0)	7 (11.3)	
Missing data	1 (0.9)	1 (1.6)	
Adjuvant chemotherapy			0.448
Platinum/paclitaxel	89 (80.9)	42 (67.7)	
Platinum/paclitaxel/Bev	0 (0)	8 (12.9)	
Platinum/PLD	0 (0)	1 (1.6)	
Platinum/paclitaxel/anti-PD(L)1	0 (0)	1 (1.6)	
Platinum/paclitaxel/PARPi	0 (0)	1 (1.6)	
None	21 (19.1)	9 (14.5)	
Relapsed			<0.01
Yes	37 (33.6)	41 (66.1)	
No	73 (66.4)	21 (33.9)	
Clinical features			
Thrombotic presentation	11 (10)	16 (25.8)	0.005
Concurrent endometriosis	49 (44.5)	17 (27.4)	0.027
Molecular features			
Tumor NGS performed	32 (29.1)	26 (41.9)	0.087
LOH performed	12 (10.9)	14 (66.7)	
LOH <16% (% of pts with available LOH scores)	12 (100)	14 (100)	
Median TMB	3.89 (0–16)	3 (1–9)	0.397
MSI/MMR performed	27 (24.5)	23 (37.1)	
MSI-H/dMMR (% of pts with available MSI/MMR)	2 (7.4)	2 (8.7)	0.867

Values are presented as median (interquartile range) or number (%).
Anti-PD(L)1, anti-programmed cell death protein 1/anti-programmed death-ligand 1; Bev, bevacizumab; dMMR, deficient mismatch repair; FIGO, Fédération Internationale de Gynécologie et d'Obstétrique; LOH, loss of heterozygosity; MMR, mismatch repair; MSI-H, microsatellite instability-high; NGS, next-generation sequencing; OCCC, ovarian clear cell carcinoma; PARPi, poly(ADP)-ribose polymerase inhibitor; PLD, pegylated liposomal doxorubicin; pts, patients; TMB, tumor mutational burden.

https://doi.org/10.3802/jgo.2024.35.e69

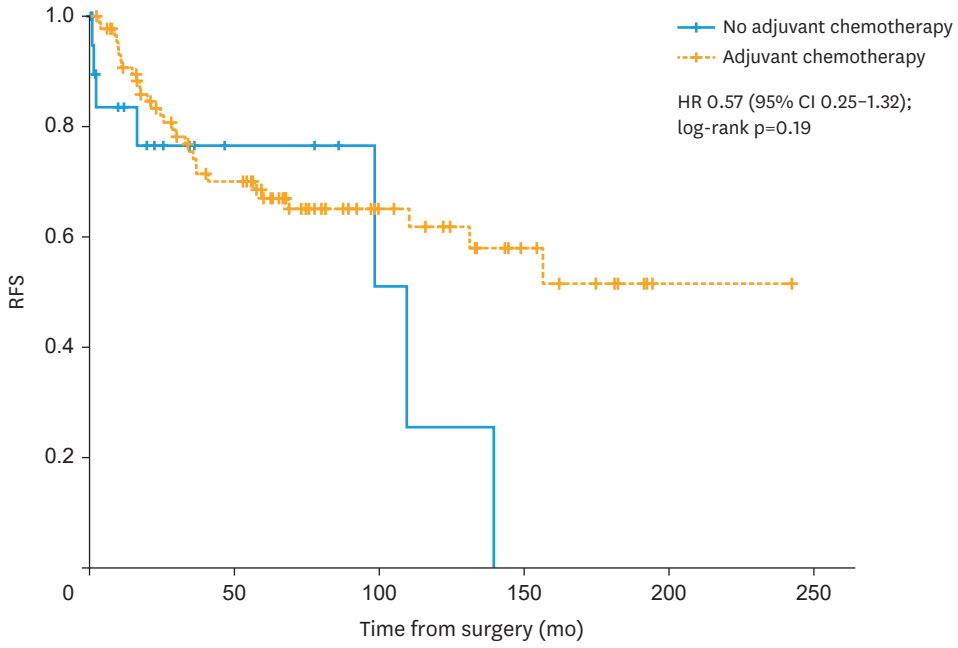

Fig. 1. RFS for early stage OCCC patients treated with adjuvant chemotherapy vs. no adjuvant chemotherapy. CI, confidence interval; HR, hazard ratio; OCCC, ovarian clear cell carcinoma; RFS, relapse-free survival.

of therapy (**Table S3**) and the response rates to platinum-based and non-platinum chemotherapy at first and subsequent lines (**Table S4**) are summarized.

Amongst 62 patients with advanced (stage III/IV) disease at presentation, 53 (85.5%) underwent systemic therapy and received platinum-based chemotherapy as their first-line therapy. Of these, 1 patient received carboplatin and pegylated liposomal doxorubicin, while the remaining 52 patients received carboplatin and paclitaxel. Forty-three patients (81.1%) received conventional 3-weekly carboplatin and paclitaxel, 7 (13.2%) received 3-weekly carboplatin with weekly dose-dense paclitaxel, and 2 (3.8%) received weekly carboplatin and paclitaxel per MITO-7 [13]. Nine patients (17%) received bevacizumab concurrent with chemotherapy and as maintenance therapy. First-line overall response rate (ORR) was 56.9% and median PFS was 8.2 months (95% CI=5.5, 10.8). Median OS of advanced stage patients was 26.5 months (95% CI=21.0, 32.1).

Amongst 37 patients with relapsed disease, 34 underwent systemic therapy and were given platinum-based chemotherapy as their first-line treatment in the relapsed setting. Four (11.8%) of these patients also received bevacizumab concurrently and as maintenance therapy. Twenty-nine patients (78.4%) had received prior adjuvant chemotherapy following initial primary debulking surgery. 75.9% (22/29) had a platinum-free interval (PFI) of at least 6 months, while 24.1% (7/29) had a PFI of less than 6 months. First-line ORR in the relapsed setting for patients with PFI ≥6 months was 70%, compared with 42.9% for patients with PFI <6 months (OR=3.1; 95% CI=0.53, 18.4). The first-line median PFS was 16 months for patients with PFI ≥6 months, compared with 7.9 months for patients with PFI <6 months (HR=0.13; 95% CI=0.04, 0.47; p=0.002) (**Fig. S1**).

SCS for selected relapsed OCCC patients

Amongst patients who suffered disease relapse after initial complete debulking surgery, 17 patients (29.2%) underwent SCS at first relapse (**Table 2**). Majority of these patients had

https://doi.org/10.3802/jgo.2024.35.e69

Table 2. Patients who underwent secondary cytoreductive surgery at first disease relapse

Patient No.	Stage at diagnosis	Completeness of primary surgery	RFI from primary surgery (mo)	Site of relapse	Completeness of second surgery	Further 'adjuvant' chemotherapy post-operatively	Relapsed since second surgery (yes/no)	PFS since second surgery (mo)	Status at last follow up	OS since second surgery (mo)
1	IC1	R0	110.1	Pelvis	R0	No	Yes	6.6	Dead	69.7
2	IIC	R0	36.6	Pelvis and peritoneum	R1	Yes	No	129	Dead	129
3	IC	R0	68.4	Pelvis	R0	Yes	Yes	35	Dead	96.8
4	IIB	R0	19.7	Pelvis	R0	Yes	No	111.7	Alive	111.7
5	IIIC	R0	14.2	Peritoneum	R0	Yes	Yes	146.2	Alive	146.2
6	IC1	R0	98.2	Pelvis	R0	No	No	57.2	Alive	57.2
7	IIC	R0	25.3	Pelvis	Missing data	Yes	Yes	14.7	Dead	31.5
8	IA	R0	32.8	Pelvis and inguinal nodes	R0	Yes	Yes	13.2	Dead	20.7
9	IC	R0	9.8	Peritoneum	R0	No	No	49.7	Alive	49.7
10	IA	R0	16.1	Para-aortic lymph node and psoas muscle	R0	Yes	No	69.1	Alive	69.1
11	IIB	R0	24.2	Peritoneum	R0	No	Yes	8.2	Alive	15.9
12	I	Missing data	156.3	Pelvis and para-aortic lymph nodes	R0	Yes	Yes	7.7	Alive	37.7
13	IIC	R0	59.1	Para-aortic lymph node and psoas muscle	R0	Yes	No	72.1	Alive	72.1
14	IIIC	R0	11.2	Para-aortic lymph nodes	R1	Yes	Yes	6.6	Dead	9.2
15	IA	R0	40.7	Spleen	R0	Yes	Yes	29.4	Alive	57.2
16	IC1	R1	109.3	Pelvis	R0	Yes	Yes	5.6	Dead	23.6
17	IC3	R1	0.7	Pelvis	R0	Yes	No	8.3	Alive	8.3

OS, overall survival; PFS, progression-free survival; RFI, relapse-free interval; R0, no residual disease; R1, residual disease.

early stage disease, complete debulking with no residual disease at the primary surgery, and less than 3 sites of disease at the time of relapse. The median relapse-free interval from primary debulking surgery amongst these patients was 32.8 months (95% CI=16.1, 68.4). Post-SCS, 13 (76.5%) patients received further adjuvant chemotherapy with platinum-based doublets (12 patients) and liposomal doxorubicin (1 patient). Amongst the 17 patients who underwent SCS, the median progression-free survival from the time of SCS to data cut off was 35 months (95% CI=0.0, 73.5) (**Fig. S2A**). The median OS from the time of SCS to data cut off was 96.8 months (95% CI=44.6, 149.0) (**Fig. S2B**).

Bevacizumab in relapsed/advanced OCCC

Amongst relapsed/advanced OCCC patients, 72 patients received platinum-based chemotherapy only as first-line treatment, while 13 patients received platinum-based chemotherapy plus bevacizumab followed by maintenance bevacizumab (**Table S3**); the addition of bevacizumab was associated with longer first-line median PFS compared with platinum-based chemotherapy alone (12.2 vs. 9.3 months; HR=0.69; 95% CI=0.33, 1.45; p=0.33) (**Fig. 2**).

Anti-PD(L)1 ICI in relapsed/advanced OCCC

Twenty-seven (27.3%) advanced/relapsed patients received anti-PD(L)1 ICI in second or later line. The median PFS amongst patients receiving ICI was 2.9 months (standard error=0.8 months; 95% CI=1.3, 4.4). ORR for ICI in any line was 18.5% (5/26). The median duration of response with ICI was 7.4 months (95% CI=6.5, 8.3). The treatment course of patients that received ICI therapy is illustrated in **Fig. S3**. None of the patients treated with ICI were known to be MSI high or dMMR. None of the patients treated with ICI were known to have a high TMB of 10 or higher. There was no statistically significant difference in median TMB between ICI-responders and non-responders (median TMB 3 vs. 4 Mut/Mb respectively, p=1.00). Two exceptional responders were noted, who demonstrated durable response to off-label pembrolizumab, receiving 29 and 36 cycles of pembrolizumab respectively (**Figs. S4** and **S5**).

https://doi.org/10.3802/jgo.2024.35.e69

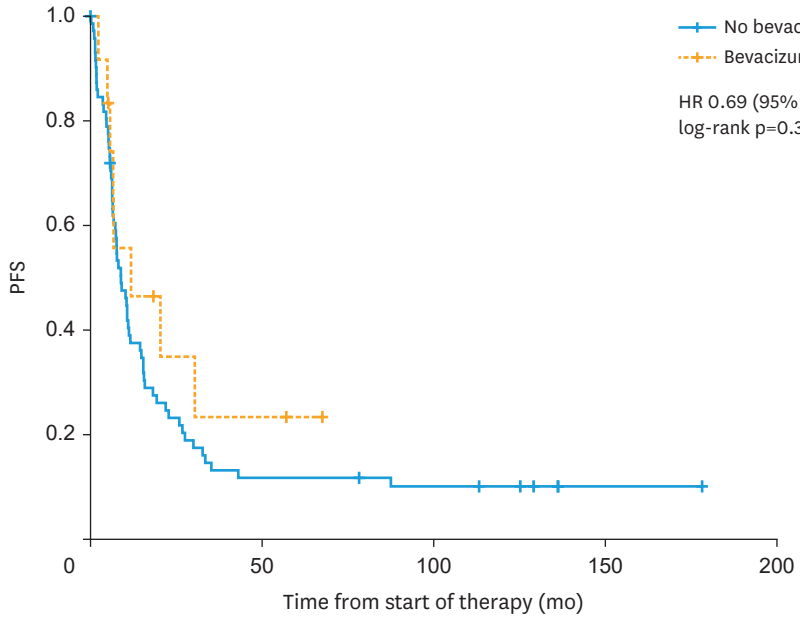

Fig. 2. PFS for advanced or relapsed OCCC patients who received first-line platinum-based chemotherapy with concurrent and maintenance bevacizumab vs. platinum-based chemotherapy only.
CI, confidence interval; HR, hazard ratio; OCCC, ovarian clear cell carcinoma; PFS, progression-free survival.

One of these durable responders was re-challenged with pembrolizumab and bevacizumab after disease progression on pembrolizumab monotherapy, and responded for an additional 8 months. Another patient who demonstrated primary resistance to ICI monotherapy was re-challenged with off-label combination pembrolizumab and lenvatinib therapy and achieved a partial response (**Fig. S6**).

Genomic analyses

Overall, 58 (33.7%) patients had successful tumor NGS profiling. Common (>20%) mutations were detected in *ARID1A* (48.3%), *PIK3CA* (46.6%) and *KRAS* (20.7%) (**Fig. 3**; see **Fig. S7** for complete list). Three (5%) patients had *ERBB2* amplification, none had *BRCA1/2* mutations, and homologous recombination repair pathway gene mutations were rare (1.7% had a *BRIP1* mutation). *TP53* mutations were found in 10 (17.2%) tumors, a frequency similar to that previously reported [9]. The mean TMB was 3.8 Mut/Mb (range, 0–16). There was no statistically significant difference in mean TMB between tumors with and without *ARID1A* mutations (mean TMB 4.10 vs. 3.24 Mut/Mb, mean difference −.86, 95% CI=−2.77, 1.05). MSI/MMR status was available for 50 patients, and 4 (8%) of patients were found to be MSI-high/deficient in MMR protein expression (**Table 1**). LOH scores using the FoundationOne CDX assay were reported in 26 patients, all of whom had LOH% <16% (**Table 1**). Pathological alterations in several genes including *PIK3CA*, *FGFR2*, *NBN*, *PTEN*, *MET*, *RET* and *TERT* were associated with worse survival outcomes (**Table 3**; see **Table S5** for complete list). *PIK3CA* mutations were associated with worse RFS (HR=2.14; 95% CI=1.10, 4.18; p=0.03). *FGFR2* mutations were associated with worse OS (HR=4.98; 95% CI=1.06, 23.5; p=0.04). Mutations in *NBN* were associated with worse OS in all patients (HR=8.28; 95% CI=2.27, 30.3; p=0.001) and worse OS (HR=9.18; 95% CI=1.77, 47.67; p=0.01) and first-line PFS (HR=7.08; 95% CI=1.46, 34.45; p=0.02) in advanced stage OCCC. *RET* mutations were associated with worse RFS (HR=37.50; 95% CI=2.35, 599.55; p=0.01) and OS among all patients (HR=6.09; 95% CI=1.33, 27.97; p=0.02). Mutations in *PTEN*, *MET*, and *TERT* were significantly associated with

https://doi.org/10.3802/jgo.2024.35.e69

Fig. 3. Oncoplot of most common genomic alterations detected amongst OCCC patients using next-generation sequencing (see **Fig. S7** for complete list).
OCCC, ovarian clear cell carcinoma.

worse OS among patients with advanced stage OCCC (**Table 3**). Co-mutation with *ARID1A* and *PIK3CA* was found in 20 (34.5%) tumors and was associated with a trend towards worse RFS (HR=1.79; 95% CI=0.89, 3.62; p=0.10) (**Table S5**).

DISCUSSION

The role of adjuvant chemotherapy in early stage OCCC remains controversial, with many retrospective studies presenting conflicting results [14-16]. A systematic review and meta-analysis conducted by Bogani et al. [17] evaluating adjuvant chemotherapy vs. observation in stage I OCCC found that adjuvant chemotherapy improves OS in stage IC OCCC (OR=0.70; 95% CI=0.52, 0.93; p=0.01) but not in stage IA and IB OCCC.

Current European Society for Medical Oncology-European Society of Gynaecological Oncology consensus conference recommendations and US National Comprehensive Cancer

https://doi.org/10.3802/jgo.2024.35.e69

Table 3. Genomic alterations and pathways significantly associated with clinical outcomes (see **Table S2** for complete list)

Gene/pathway	Prevalence (total n=58)	RFS			OS (all patients)			OS (advanced stage)			1st line PFS		
		HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
CCNE1	2	1.90	0.45, 8.13	0.386	3.62	0.46, 28.81	0.224	6.74	0.76, 60.45	0.088	1.50	0.36, 6.3	0.582
CDK4	2	3.37	0.75, 15.13	0.113	10.37	2.07, 51.96	0.004	5.16	1.04, 25.83	0.046	2.21	0.52, 9.48	0.286
CREBBP	2	4.23	0.53, 33.83	0.174	11.09	2.35, 52.46	0.002	6.30	1.31, 30.49	0.022	2.65	0.35, 20.18	0.347
ERBB2	3	1.66	0.5, 5.59	0.416	2.10	0.27, 16.58	0.483	6.74	0.76, 60.45	0.088	1.22	0.38, 4.03	0.742
FBXW7	3	2.27	0.68, 7.67	0.185	1.01	0.14, 7.62	0.994	NE	NE	NE	5.74	1.56, 21.17	0.009
FGFR2	4	4.14	0.91, 19.04	0.068	4.98	1.06, 23.5	0.043	2.54	0.54, 12.16	0.242	2.03	0.47, 8.89	0.346
MDM2	2	3.37	0.75, 15.13	0.113	10.37	2.07, 51.96	0.004	5.16	1.04, 25.83	0.046	2.21	0.52, 9.48	0.286
MET	3	1.83	0.25, 13.8	0.559	2.98	0.68, 13.15	0.149	5.42	1.05, 28.16	0.044	2.26	0.54, 9.6	0.270
NBN	3	1.07	0.15, 7.97	0.946	8.28	2.27, 30.3	0.001	9.18	1.77, 47.67	0.008	7.08	1.46, 34.45	0.015
PIK3CA	27	2.14	1.1, 4.18	0.025	1.82	0.75, 4.41	0.187	1.67	0.55, 5.13	0.374	1.09	0.59, 2.05	0.788
PTEN	6	2.46	0.84, 7.27	0.103	2.99	0.64, 13.97	0.164	27.48	2.34, 323.63	0.008	2.27	0.87, 5.95	0.094
RET	2	37.50	2.35, 599.55	0.010	6.09	1.33, 27.97	0.020	5.25	0.62, 44.99	0.131	2.90	0.38, 22.22	0.305
TERT	7	1.01	0.39, 2.61	0.991	1.54	0.5, 4.87	0.458	6.00	1.16, 31.26	0.033	1.53	0.64, 3.69	0.348
PI3K events in ERBB2 signalling	35	2.03	1.03, 4.06	0.043	2.26	0.86, 5.97	0.100	2.45	0.55, 11.11	0.245	0.89	0.48, 1.66	0.703
PI3K/AKT/mTOR signalling	12	2.64	1.12, 6.26	0.028	1.91	0.62, 5.97	0.266	2.03	0.61, 6.8	0.249	0.89	0.41, 1.94	0.763
IL2/STAT5 signalling	3	1.38	0.42, 4.59	0.602	3.46	0.78, 15.54	0.105	6.74	0.76, 60.45	0.088	1.36	0.42, 4.51	0.610

Only genes with number ≥1 alterations were included.
CI, confidence interval; HR, hazard ratio; NE, not evaluable; OS, overall survival; PFS, progression-free survival; RFS, relapse-free survival.

Network guidelines suggest that adjuvant chemotherapy should be given in stage IC2–IIA OCCC, but is optional in stage IA–IC1 OCCC with complete surgical staging given the uncertain benefit [18,19]. An ongoing randomized phase III trial by the Japanese Gynecologic Oncology Group (JGOG) aims to provide further clarity by evaluating whether adjuvant chemotherapy improves oncologic outcomes in stage I EOC (stage IA/IB clear cell carcinoma or grade 2/3 other histological type and stage IC1 with all grades and histological types) after comprehensive staging surgery (JGOG3020, UMIN000008481). In our cohort, we found a trend towards improved RFS with the use of adjuvant chemotherapy in stage I to II OCCC which did not reach statistical significance.

SCS can be considered in select cases of relapsed OCCC [18] on the basis of two randomized phase III trials (DESKTOP-III and SOC-1) showing improved oncologic outcomes with SCS followed by chemotherapy vs second-line chemotherapy alone in patients with relapsed platinum-sensitive EOC [20,21]. However, relapsed ovarian cancers of clear cell histology were under-represented in these trials and there is a paucity of data to support SCS specifically in this subtype. A retrospective study by Kajiyama et al of 169 patients with relapsed OCCC observed no significant difference in disease-free and OS between the 25 patients who underwent SCS compared with the 144 patients treated with chemotherapy alone. It was observed, however, that patients who underwent complete resection had a significantly longer median post-recurrence survival of 30.1 months compared with 10.4 months in those who had incomplete resection (p=0.002), emphasizing the importance of achieving no gross residual disease [22]. In our cohort, a subset of well-selected patients—characterized by optimal debulking at initial surgery, prolonged relapse-free interval, and two or fewer sites of relapse—who underwent SCS had excellent survival outcomes, suggesting that SCS should be explored in selected relapsed OCCC patients.

While early stage OCCC has a favorable prognosis, recurrent or advanced OCCC has been shown to have remarkably poorer oncologic outcomes compared to their high-grade serous counterparts [23]. This has been attributed to the proclivity for OCCC to recur at multiple sites [24] and its intrinsic resistance to chemotherapy. Bevacizumab, an anti-VEGF

https://doi.org/10.3802/jgo.2024.35.e69

monoclonal antibody, is the first targeted therapy to receive approval, in combination with chemotherapy, for the treatment of EOC in the first-line and relapsed settings. ICON7, a phase III randomized trial, demonstrated a significant PFS benefit in high-risk, early stage (stage I or IIA and clear cell or grade 3) or advanced stage IIB to IV tumors when bevacizumab was added to front-line carboplatin/paclitaxel. Although it did not show an OS benefit in the intention-to-treat analysis, a post-hoc subgroup analysis indicated a statistically significant OS benefit in patients at high risk of progression (FIGO stage III with >1 cm residual disease or stage IV) [25]. It is worth noting that the subgroup analysis of clear cell carcinoma patients in this study demonstrated no benefit with bevacizumab. However, this analysis was underpowered, and the clear cell tumor group included some patients with mixed histology. Gene expression profiling studies have shown remarkable similarities between OCCC and clear cell renal cell carcinoma [26], for which multiple anti-angiogenic therapies have been approved. A few phase II studies have since investigated anti-angiogenics such as sunitinib, cabozantinib and ENMD-2076 in OCCC, but have unfortunately shown limited efficacy [27-29]. To date, no randomized trial has examined the role of bevacizumab specifically in OCCC. However, a recent multicenter retrospective analysis has found that incorporating bevacizumab in front-line chemotherapy significantly improved PFS and OS in patients with advanced OCCC [30]. Concordant with this finding, in our population we observed a longer median PFS with the addition of bevacizumab to chemotherapy in patients with relapsed or advanced OCCC, although this was not statistically significant. Furthermore, our analysis has limitations which must be acknowledged. First, it should be noted that a relatively small percentage of patients (13.1%) were administered bevacizumab in addition to chemotherapy as first line treatment for relapsed/advanced ovarian cancer. This can be attributed to two factors: firstly, a subset of these patients underwent treatment prior to the routine use of bevacizumab in the management of advanced ovarian cancer; and secondly, financial limitations hindered the use of bevacizumab as the generic version was not available at the time of this study. Second, the retrospective comparison between patients who received bevacizumab and those who did not would inherently involve selection bias. Patients with venous thromboembolism are not precluded from receiving bevacizumab at our institution, provided that they have received appropriate anticoagulation treatment. Patients with significant intestinal serosal involvement would however have been excluded from the use of bevacizumab; nonetheless, serosal involvement in itself has not been demonstrated to portend a worse prognosis. Molecular markers to predict response to bevacizumab in OCCC have yet to be validated. Tan et al identified two gene expression subtypes in OCCC patients: EpiCC—epithelial-like, associated with early-stage disease and a higher rate of gene mutations in the SWI/SNF complex; and MesCC—mesenchymal-like, associated with late-stage, poorer PFS, and higher enrichment of immune-related pathway activity [31]. Interestingly, applying this EpiCC/MesCC classification to the TCGA renal cell carcinoma cohort revealed interoperability, and MesCC-like renal clear cell carcinoma patients had improved clinical outcomes following bevacizumab treatment, although this was not statistically significant (p=0.19) [31]. Further study and prospective validation is needed to determine whether the MesCC-subtype might help predict response to bevacizumab in OCCC.

Several molecular and gene expression studies suggest that OCCC tumors have a unique microenvironment, making immunotherapy an attractive strategy for their treatment [7]. The recent MOCCA phase II randomized trial however only showed modest efficacy with durvalumab in previously treated recurrent OCCC, with an ORR of 10.7% and a median PFS of 7.4 weeks, both of which were not significantly different from the control arm of physicians' choice chemotherapy [32]. PEACOCC was a multicenter phase II single arm trial

that investigated the use of pembrolizumab in pre-treated clear cell gynecological cancers, 85.4% of which were ovarian in origin. The results were promising, with an ORR of 25% and a 12-week PFS rate of 43.8% [33]. This suggests perhaps that PD-1 inhibitors may be more efficacious than PD-L1 inhibitors in OCCC; however, further translational analyses are awaited. Our OCCC cohort similarly showed encouraging results with anti-PD-1 therapy. There are currently no prospectively validated predictive biomarkers of response to ICIs specific to ovarian cancer. Despite preclinical evidence that *ARID1A* deficiency was associated with MMR deficiency, increased tumor infiltrating lymphocytes, and sensitization to immunotherapy [8], our study found no difference in TMB based on *ARID1A* mutation status, and no correlation between *ARID1A* mutation status and response to ICIs (**Table S6**).

Recent advances in our understanding of the molecular characteristics and pathogenesis of OCCC are paving the way for more personalized treatment strategies. Similar to our findings, multiple studies have reported that OCCC are enriched for *ARID1A* (40%–57%) [34-36] and *PIK3CA* (29%–40%) mutations, which frequently co-occur [37,38]. We found an *ARID1A*/*PIK3CA* co-mutation rate of 34.5%, while Cunningham et al. [9] have previously reported a rate of 24.4%. As such, novel approaches targeting these alterations are attractive and the objective of several current and upcoming trials [39].

It is noteworthy that the LOH score was found to be less than 16%, suggesting homologous recombination proficiency, in all patients evaluated. This finding is consistent with previous studies that have reported a very low prevalence of HRD of approximately 2% in OCCC [40,41], which stands in stark contrast to the HRD frequency approximating 50% observed in high grade serous ovarian carcinoma (HGSOC). This finding further reinforces that OCCC is a distinct entity from HGSOC, and suggests that HRD may have a limited role in the pathogenesis and clinical implications for therapy in OCCC.

Our study provides real-world evidence of encouraging responses to antiangiogenic therapy and ICI in a multi-ethnic Asian cohort of OCCCs, however limitations include a small sample size as well as those inherent to retrospective studies, such as selection bias and treatment heterogeneity. Our findings also demonstrate excellent survival outcomes with SCS, supporting its consideration in carefully selected patients with relapsed OCCC. Further clinical trials are warranted, and considering the rarity of OCCC, collaborative international clinical trials based on its clinical and molecular characteristics are urgently needed to develop individualized treatment approaches and improve clinical outcomes.

SUPPLEMENTARY MATERIALS

Table S1
Patient characteristics, treatment lines, response, survival and genomic data of all 172 OCCC patients

Table S2
Frequency of disease relapse by stage at diagnosis

Table S3
Systemic therapies received by relapsed (stage I/II at diagnosis with subsequent relapse) and advanced (stage III/IV at diagnosis) OCCC patients

https://doi.org/10.3802/jgo.2024.35.e69

Table S4
Response rates to chemotherapy (platinum-based and non-platinum) in relapsed/ advanced OCCC patients

Table S5
All genomic alterations/pathways and their associations with survival outcomes

Table S6
Genomic alterations and their associations with response and clinical benefit with bevacizumab and immune checkpoint inhibitors

Fig. S1
First-line PFS of patients with relapsed disease (PFI ≥6 months versus <6 months).

Fig. S2
Survival outcomes of 17 patients who underwent secondary cytoreductive surgery at first disease relapse. (A) PFS of patients following secondary cytoreductive surgery. (B) OS of patients following secondary cytoreductive surgery.

Fig. S3
Swimmer plot depicting the treatment course of 26 patients who received ICI therapy.

Fig. S4
This patient received 29 cycles of off-label pembrolizumab at fifth line with partial response. (A) Right para-cardiac mediastinal node (white arrow) is smaller and less enhancing. (B) Left iliacus intramuscular deposit (asterisk) is smaller and less enhancing.

Fig. S5
This patient received 36 cycles of off-label pembrolizumab at third line with partial response. (A) Baseline scan showing multiple right perihepatic and subdiaphragmatic peritoneal deposits (arrowheads) scalloping the liver. Large cystic lesion in the pelvis (asterisk). (B) Complete resolution of perihepatic and subdiaphragmatic peritoneal disease and pelvic cystic lesion. (C) Baseline scan showing enlarged aortocaval node (white arrow) posterior to the horizontal segment of the duodenum. (D) Resolution of the aortocaval node, with residual small unenlarged 4 mm node.

Fig. S6
This patient demonstrated primary resistance to anti-PDL1 therapy and was re-challenged with fourth line off-label combination pembrolizumab and lenvatinib, achieving partial response. (A) Smaller right paratracheal node (asterisk). (B) Smaller left supraclavicular node (white arrow).

Fig. S7
Oncoplot of all genomic alterations detected amongst OCCC patients using next-generation sequencing.

https://doi.org/10.3802/jgo.2024.35.e69

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