OPEN ACCESS

A multicenter phase II randomized trial of durvalumab (MEDI-4736) versus physician's choice chemotherapy in recurrent ovarian clear cell adenocarcinoma (MOCCA)

Natalie YL Ngoi ,[1] Valerie Heong,[2] Samuel Ow,[1] Wen Yee Chay,[3] Hee Seung Kim,[4] Chel Hun Choi,[5] Geraldine Goss,[6] Jeffrey C Goh,[7,8] Bee Choo Tai,[9,10] Diana GZ Lim,[11] Nivashini Kaliaperumal,[12] Veonice B Au,[12] John E Connolly,[12,13] Jae-Weon Kim,[4] Michael Friedlander,[14,15] Kidong Kim ,[16] David SP Tan[1,10,17]

For numbered affiliations see end of article.

Correspondence to
Dr David SP Tan, Cancer Science Institute, National University of Singapore and National University Cancer Institute, SIngapore, National University Health System, Singapore 119074, Singapore; david_sp_tan@nuhs.edu.sg

Accepted 3 June 2020
Published Online First 25 June 2020

To cite: Ngoi NYL, Heong V, Ow S, *et al. Int J Gynecol Cancer* 2020;**30**:1239–1242.

ABSTRACT

Background The optimal treatment of recurrent ovarian clear cell carcinoma remains unknown. There is increasing rationale to support the role of immune checkpoint inhibitors targeting the programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) axis in ovarian clear cell carcinoma.

Primary objective To evaluate the efficacy of durvalumab (MEDI-4736) compared with standard chemotherapy in patients with recurrent ovarian clear cell carcinoma.

Study hypothesis Patients with recurrent ovarian clear cell carcinoma treated with durvalumab will have improved progression-free survival compared with those treated with chemotherapy of physician's choice.

Trial design The MOCCA study is a multicenter, open-label, randomized phase II trial in patients with recurrent ovarian clear cell carcinoma, which recruited from eight sites across Gynecologic Cancer Group Singapore (GCGS), Korean Gynecologic-Oncology Group (KGOG), and Australia New Zealand Gynecological Oncology Group (ANZGOG). Enrolled patients were randomized in a 2:1 ratio to receive durvalumab or physician's choice of chemotherapy until disease progression, intolerable toxicity, or withdrawal of patient consent.

Major inclusion/exclusion criteria Eligible patients required histologically documented diagnosis of recurrent ovarian clear cell carcinoma, as evidenced by WT1 negativity. All patients must have been of Eastern Cooperative Oncology Group (ECOG) performance status 2 or better, and have had previous treatment with, and progressed or recurred after prior platinum-based chemotherapy. No more than four prior lines of treatment were allowed and prior immune checkpoint inhibitor treatment was not permitted.

Primary endpoints The primary endpoint was the median progression-free survival following treatment with durvalumab, compared with physician's choice of chemotherapy. Progression-free survival was defined as the time from the first day of treatment to the first observation of disease progression, or death due to any cause, or last follow-up.

Sample size The target sample size was 46 patients.

Estimated dates for completing accrual and presenting results Accrual has been completed and results are expected to be presented by mid-2021.

Trial registration Clinicaltrials.gov: NCT03405454.

INTRODUCTION

Ovarian clear cell carcinoma is distinct from other epithelial ovarian cancers in terms of epidemiology, clinicopathological features, gene expression profile, and immune microenvironment. In the Western world, this is an uncommon disease and accounts for only 6% of epithelial ovarian cancer in the United States, but is far more prevalent in Singapore, the Republic of Korea, Taiwan, and Japan, where clear cell cancers constitute up to 25% of diagnosed ovarian cancer.[1 2] Histologically, ovarian clear cell carcinoma is characterized by cells containing abundant clear glycogen-containing cytoplasm and may be associated with surrounding features of endometriosis. Immunohistochemistry typically demonstrates negativity for Wilm's tumor 1 (WT1) and p53, but is often positive for hepatocyte nuclear factor 1-beta (HNF1-β).[3]

The treatment of women with advanced and recurrent ovarian clear cell carcinoma remains an area of significant unmet need. Clear cell ovarian cancers tend to occur in younger women and are associated with thromboembolic complications and paraneoplastic hypercalcemia.[4] Furthermore, advanced ovarian clear cell carcinoma is a chemotherapy-resistant disease, with lower objective response rates to first-line platinum-based chemotherapy compared with high-grade serous ovarian cancers (11% vs 73%), and worse 5-year stage-adjusted disease specific survival.[5] On disease relapse, objective response rates to second-line chemotherapy have been reported to be strikingly low, ranging between 6%–9%.[6] Efforts to improve response rates to chemotherapy in ovarian clear cell carcinoma over the past decade have been unsuccessful,[7] underscoring the need for further drug discovery to treat this resistant disease.

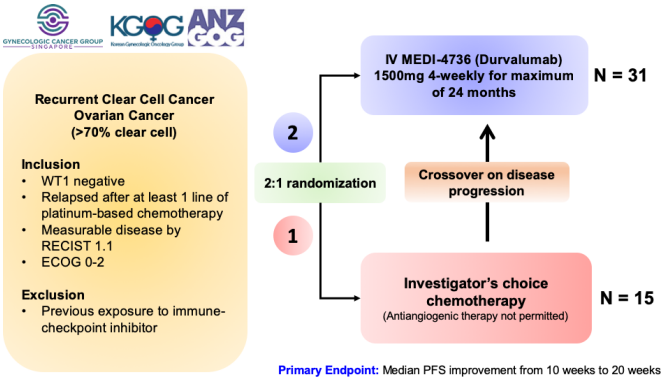

Figure 1 MOCCA trial schema. Patients with recurrent ovarian clear cell carcinoma who have progressed after at least one prior line of platinum-based chemotherapy, and who have histologically-proven clear cell carcinoma evidenced by WT1-negativity were enrolled and randomized 2:1 to receive durvalumab or physician's choice chemotherapy. The primary endpoint of the study is the progression-free survival of patients receiving durvalumab compared with chemotherapy. A total of 46 patients have been recruited across sites from Singapore, Australia, and the Republic of Korea. WT1: wilm's tumor 1; RECIST: Response Evaluation Criteria in Solid Tumors; ECOG: Eastern Cooperative Oncology Group; PFS: progression-free survival; GCGS: Gynecologic Cancer Group Singapore; KGOG: Korean Gynecologic Oncology Group; AZGOG: Australia New Zealand Gynecological Oncology Group.

There is increasing rationale to support the role of immune checkpoint inhibitors targeting the programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) axis in clear cell ovarian cancer. Interestingly, clear cell ovarian cancer shares more similarity in gene expression profiles with clear cell renal cell carcinoma rather than to other subtypes of epithelial ovarian cancer, and is characterized by frequent somatic mutations in *ARID1A*, overexpression of *MDM2*, and upregulation of the phosphoinositide 3-kinase (PI3K)- protein kinase B (Akt)- mammalian target of rapamycin (mTOR) and mitogen-activated protein kiase (MAPK) signaling axes.[8] The high level of somatic mutations and up to 15% of mismatch repair deficiency (dMMR) found in ovarian clear cell carcinoma provides a further rationale supporting the likelihood of response to immune checkpoint inhibitors. Increased expression of lymphocyte activation gene 3 (LAG3), T-cell immunoglobulin mucin-3 (TIM-3), and PD-1 in ovarian clear cell carcinoma has been linked to increased immune suppression, while *PIK3CA* mutations and *ARID1A* loss of function, together with upregulation of HNF1-β and activation of signal transducer and activator of transcription 3 (STAT3) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling pathways, lead to increased interleukin-6 (IL6) and −8 expression, and further immune suppression.[8] ARID1A is integral in the SWItch/Sucrose Non-Fermentable (SWI-SNF) chromatin remodeling complex and is seen in about 40% of clear cell cancers. The loss of *ARID1A* expression has been shown to correlate with chemo-resistance in this disease.[9] Though the prognostic and predictive effects of *ARID1A* loss in ovarian clear cell carcinoma remain poorly defined, *ARID1A*-deficiency has been associated with compromised MMR, increased mutational load, and PD-L1 expression.[10] In orthotopic and intraperitoneal mouse models of *ARID1A*-mutant ovarian cancer, compared with control tumors, increased and durable responses to anti-PD-L1 therapy was noted, leading to improved survival,[10] providing rationale for the inhibition of PD-1/PD-L1 in this context.

Furthermore, early phase clinical trials of anti-PD-1/PD-L1 immune checkpoint inhibitors in epithelial ovarian cancer suggest a possible signal of efficacy for this approach in the clear cell histiotype. In a phase II study of nivolumab in patients with platinum-resistant recurrent ovarian cancer,[11] a response rate of 23% and disease control rate of 54% was noted, with three patients showing durable partial response.[11] Notably, one of these three long-term responders was a patient with ovarian clear cell carcinoma. Supporting this finding, in the KEYNOTE-100 study, the response rate in patients with clear cell histology to pembrolizumab was 15.8%, compared with only 8% in the overall recurrent ovarian cancer population.[12] Therefore, the use of immune checkpoint inhibitors inhibiting the PD-1/PD-L1 axis is intriguing for further investigation in ovarian clear cell carcinoma and forms the basis for the current trial. This represents the first randomized trial to evaluate the efficacy of the anti-PD-L1 immune checkpoint inhibitor, durvalumab, compared with chemotherapy, in patients with recurrent ovarian clear cell carcinoma.

METHODS

Trial design

The "Multicenter Phase II Randomized Trial of Durvalumab (MEDI-4736) vs Physician's Choice Chemotherapy in Recurrent Ovarian Clear Cell Adenocarcinoma (MOCCA)" trial is an open-label study which recruited from eight sites across the Gynecologic Cancer Group Singapore (GCGS), Korean Gynecologic-Oncology Group (KGOG) and Australia New Zealand Gynecological Oncology Group (ANZGOG) groups, with institutional review board approval obtained from each site. Enrolled patients were randomized in a 2:1 ratio to receive durvalumab or physician's choice of chemotherapy until disease progression, intolerable toxicity, or withdrawal of patient consent, for up to 24 months (Figure 1). Patients randomized to physician's choice of chemotherapy were allowed to receive any systemic cytotoxic chemotherapy, however the addition of biologics including bevacizumab, or oral tyrosine kinase inhibitors, was prohibited. On discontinuation of chemotherapy due to disease progression or intolerable toxicity, patients randomized to physician's choice of chemotherapy were allowed crossover to receive durvalumab after completing a wash-out period of 4 weeks from the last anti-cancer therapy. Patients who discontinued treatment due to disease progression were followed up for a duration of 90 days from the end of study drug administration. Patients who discontinued treatment due to unacceptable adverse events were followed up monthly until the adverse event resolved, became stabilized or was no longer related.

During the study, a cycle was 4 weeks for both arms. Allowances were made for dose reductions due to treatment-related toxicities. Efficacy assessment using tumor measurements and serum CA-125 was performed every 8 weeks. Tumor response was determined using Response Evaluation Criteria in Solid Tumors (RECIST 1.1) for patients on both arms, and modified RECIST was also evaluated for patients randomized to durvalumab.

Participants

Eligible patients required histologically documented diagnosis of recurrent ovarian clear cell carcinoma, as evidenced by WT1 negativity. If tumors were of mixed histology,>70% of the tumor must consist of clear cell carcinoma. All patients must provide informed consent to participate in the study, have been of Eastern Cooperative Oncology Group (ECOG) performance status 2 or better, and have had previous treatment with, and progressed or recurred after prior platinum-based chemotherapy. No more than four prior lines of systemic treatment were allowed. Prior immune checkpoint inhibitor treatment was not permitted. Patients must have had one or more measurable lesions by RECIST 1.1 criteria within 28 days of treatment commencement. Patients with active or prior documented autoimmune disease within the previous 2 years, or who received recent systemic immunosuppressive treatments, were excluded. Finally, all patients were required to provide archival tissue of sufficient quantity for translational analysis.

Primary endpoint

The primary endpoint of the MOCCA trial is progression-free survival following treatment with durvalumab or physician's choice chemotherapy. Progression-free survival was defined as the time from the first day of treatment to the first observation of disease progression, or death due to any cause, or censored at the date of last follow-up. Radiological disease progression was evaluated by RECIST 1.1 criteria for patients on the chemotherapy arm, and by RECIST 1.1 and modified RECIST for patients on the durvalumab arm.

Secondary endpoints

The secondary endpoints of this study include the following – to determine the objective response rate of durvalumab or physician's choice chemotherapy in patients with recurrent ovarian clear cell carcinoma, to determine the overall survival of patients with recurrent ovarian clear cell carcinoma treated with durvalumab compared with physician's choice chemotherapy, and to determine the adverse event profile of durvalumab and to evaluate the effect of durvalumab or physician's choice chemotherapy on health-related quality of life, as measured using the European Organization for Research and Treatment of Cancer (EORTC) Core questionnaire QLQ-C30 and OV28.

Exploratory endpoint

The exploratory endpoint of this study is to identify predictive novel biomarkers of response and resistance to durvalumab in recurrent ovarian clear cell carcinoma. Potential biomarkers of response and resistance that will be studied include: PTEN loss, PIK3CA, ARID1A mutations, MMR status, PD-1/PD-L1 overexpression, cytokines, lymphocyte activation markers, human leukocyte antigen class I/II, and immune regulator status and expression.

Sample size

The sample size was estimated based on the primary endpoint of progression-free survival. A retrospective analysis of median progression-free survival in patients with ovarian clear cell carcinoma was 11 weeks.[13] Hence, a HR of 0.50 was postulated assuming a median progression-free survival of 10 weeks in the chemotherapy arm and 20 or more weeks in the durvalumab arm. Based on a 6-month progression-free survival probability of 15% in the chemotherapy arm,[13] a 2:1 treatment allocation, a one-sided 10% significance level, and a power of 80%, a sample size of 31 patients in the durvalumab arm and 15 patients in the chemotherapy arm was required, giving a total sample size of 46 patients.

Randomization and blinding

The Cenduit Interactive Web Response System was used to generate the dynamic block randomization allocation sequence (block size of six), with stratification by ECOG performance status.

Statistical methods

All enrolled patients receiving at least one dose of study medication will be included in the description of all demographic, baseline characteristic analysis as well as safety analysis. All patients completing one cycle of therapy were considered evaluable. Patients who discontinued treatment before completing one cycle for reasons other than progression were replaced.

The primary and secondary endpoints of progression-free survival and overall survival will be summarized using the Kaplan–Meier method with comparison of survival distributions made via the log-rank test. The secondary endpoint of objective response rate will be compared using Fisher's exact test, with the exact binomial 95% confidence intervals estimated for quantifying the difference in proportion. The secondary endpoint of health-related quality of life will be assessed by comparing the mean difference in domain scores using the Student's *t*-test. Statistical analyses for the primary and secondary outcomes will be conducted based on the principle of intention to treat, assuming a one-sided test at the 10% level of significance.

DISCUSSION

The immune-suppressive milieu in ovarian clear cell carcinoma arising from genetic alterations as well as tumor microenvironmental changes highlight the potential therapeutic role for immune checkpoint inhibitors in this chemotherapy-refractory disease. A recent study has suggested molecular heterogeneity within clear cell ovarian cancer, with two distinct and consistent immune-related gene expression subgroups denoted Epithelial-like (EpiCC) and Mesenchymal-like (MesCC), being defined.[14] MesCC subtype clear cell cancers were associated with the expression of immune-related genes, higher enrichment of immune-related pathway activity, and tumor infiltrating lymphocytes compared with EpiCC subtype, but the impact of gene expression subtype on immunotherapy response remains unknown. Currently, several studies are evaluating the role of immune checkpoint inhibitors in ovarian clear cell carcinoma. The MOCCA trial has completed recruitment and represents the first study to evaluate the efficacy of anti-PD-L1 therapy compared with chemotherapy in advanced or recurrent clear cell ovarian cancer. Importantly, flow cytometry, RNA sequencing, and cytokine analysis performed on tumor and paired blood samples obtained during the trial, will aim to determine the immune profiles of patients which correlate with durvalumab response or resistance, and may help to shed light on potential biomarkers for patient selection. Other ongoing studies of immune checkpoint inhibitor therapy in this disease are the IND.228 study, which is a single-arm phase II study examining the efficacy of durvalumab + tremelimumab in advanced rare tumors, including

ovarian clear cell carcinoma (NCT02879162), as well as the BrUOG 354 study which is a randomized phase II study comparing nivolumab ± ipilimumab in persistent or recurrent ovarian clear cell carcinoma (NCT03355976). Their results are eagerly awaited and may be able to finally advance treatment paradigms for this fatal disease. Recent data showing efficacy for lenvatinib plus pembrolizumab in patients with advanced recurrent clear cell endometrial cancer also suggests that the combination of vascular endothelial growth factor and PD-1 pathway inhibition should also be studied in ovarian clear cell carcinoma in the future.[15] Crucially, it is hoped that translational studies from the aforementioned trials will also help to determine the relevant biomarkers of sensitivity and resistance to immune checkpoint inhibitors in ovarian clear cell carcinomas and help transform the treatment for patients affected by this challenging disease.

Author affiliations
[1]Department of Haematology-Oncology, National University Cancer Institute, Singapore
[2]Department of Medical Oncology, Tan Tock Seng Hospital, Singapore
[3]Division of Medical Oncology, National Cancer Centre Singapore, Singapore
[4]Department of Obstetrics and Gynecology, Seoul National University, Seoul, Republic of Korea
[5]Department of Obstetrics and Gynecology, Samsung Medical Center, Seoul, Republic of Korea
[6]Box Hill Hospital, Box Hill, Victoria, Australia
[7]Royal Brisbane and Women's Hospital, Herston, Queensland, Australia
[8]The University of Queensland, Saint Lucia, Queensland, Australia
[9]Saw Swee Hock School of Public Health, National University of Singapore, Singapore
[10]Yong Loo Lin School of Medicine, National University of Singapore, Singapore
[11]Department of Pathology, National University Hospital, Singapore
[12]Institute of Molecular and Cell Biology, Agency for Science, Technology and Research, Singapore
[13]Institute of Biomedical Studies, Baylor University, Waco, Texas, USA
[14]The Prince of Wales Hospital, Randwick, New South Wales, Australia
[15]Prince of Wales Clinical School University of New South Wales, Randwick, New South Wales, Australia
[16]Seoul National University Bundang Hospital, Seoul, Republic of Korea
[17]Cancer Science Institute Singapore, Singapore

Twitter Kidong Kim @KIDONG_KIM_MD

Acknowledgements This study was supported by a research grant from AstraZeneca.

Contributors Conceptualization: all authors data curation: NYLN writing–original draft preparation: NYLN writing–review and editing: all authors visualization: all authors supervision: DT project administration: Vilianty.

Funding This study is funded by the Ministry of Health National Medical Research Council Singapore (NMRC/MOHIAFCat1/0061/2016) and AstraZeneca. DT is supported by the National Medical Research Council Singapore CSAINV16may008.

Competing interests VH has received honoraria from AstraZeneca. SO has received honoraria from AstraZeneca. JCG has received honoraria and sponsorship to attend a conference from AstraZeneca. DT has received honoraria and research funding from AstraZeneca. MF has received honoraria and research funding from Astra Zeneca.

Patient consent for publication Not required.

Provenance and peer review Commissioned; internally peer reviewed.

Data availability statement No data are available.

ORCID iDs
Natalie YL Ngoi http://orcid.org/0000-0003-2071-0715
Kidong Kim http://orcid.org/0000-0001-9254-6024

REFERENCES

1 Saito T, Takahashi F, Katabuchi H, *et al*. Annual report of the Committee on Gynecologic Oncology, Japan Society of Obstetrics and Gynecology: patient annual report for 2014 and treatment annual report for 2009. *J Obstet Gynaecol Res* 2017;43:1667–77.
2 Kim SI, Lim MC, Lim J, *et al*. Incidence of epithelial ovarian cancer according to histologic subtypes in Korea, 1999 to 2012. *J Gynecol Oncol* 2016;27:e5.
3 Fujiwara K, Shintani D, Nishikawa T. Clear-cell carcinoma of the ovary. *Ann Oncol* 2016;27 Suppl 1:i50–2.
4 Devlin M-J, Chandrasekaran D, Singh N, *et al*. Clear cell ovarian cancer (CCOC): 115 patient (pt) series showing access to experimental therapy may improve response rates in recurrent disease. *J Clin Oncol* 2018;36:5581.
5 Chan JK, Teoh D, Hu JM, *et al*. Do clear cell ovarian carcinomas have poorer prognosis compared to other epithelial cell types? A study of 1411 clear cell ovarian cancers. *Gynecol Oncol* 2008;109:370–6.
6 Takano M, Sugiyama T, Yaegashi N, *et al*. Low response rate of second-line chemotherapy for recurrent or refractory clear cell carcinoma of the ovary: a retrospective Japan clear cell carcinoma study. *Int J Gynecol Cancer* 2008;18:937–42.
7 Takahashi K, Takenaka M, Kawabata A, *et al*. Rethinking of treatment strategies and clinical management in ovarian clear cell carcinoma. *Int J Clin Oncol* 2020;25:425–31.
8 Oda K, Hamanishi J, Matsuo K, *et al*. Genomics to immunotherapy of ovarian clear cell carcinoma: unique opportunities for management. *Gynecol Oncol* 2018;151:381–9.
9 Katagiri A, Nakayama K, Rahman MT, *et al*. Loss of ARID1A expression is related to shorter progression-free survival and chemoresistance in ovarian clear cell carcinoma. *Mod Pathol* 2012;25:282–8.
10 Shen J, Ju Z, Zhao W, *et al*. ARID1A deficiency promotes mutability and potentiates therapeutic antitumor immunity unleashed by immune checkpoint blockade. *Nat Med* 2018;24:556–62.
11 Hamanishi J, Mandai M, Ikeda T, *et al*. Safety and antitumor activity of anti-PD-1 antibody, nivolumab, in patients with platinum-resistant ovarian cancer. *J Clin Oncol* 2015;33:4015–22.
12 Matulonis UA, Shapira-Frommer R, Santin AD, *et al*. Antitumor activity and safety of pembrolizumab in patients with advanced recurrent ovarian cancer: results from the phase II KEYNOTE-100 study. *Ann Oncol* 2019;30:5511:1080–7.
13 DSP T, Rye T, Barrie C, *et al*. Analysis of outcomes in patients (pts) with recurrent ovarian clear cell carcinoma (ROCCC): time to rethink our approach to treatment. *J Clin Oncol* 2014;32.
14 Tan TZ, Ye J, Yee CV, *et al*. Analysis of gene expression signatures identifies prognostic and functionally distinct ovarian clear cell carcinoma subtypes. *EBioMedicine* 2019;50:203–10.
15 Makker V, Taylor MH, Aghajanian C, *et al*. Lenvatinib plus pembrolizumab in patients with advanced endometrial cancer. *J Clin Oncol* 2020:JCO1902627.