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

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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 0 or 1 and had adequate organ function (hematologic, hepatic, renal). 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. 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. On disease relapse, objective response rates to second-line chemotherapy have been reported to be strikingly low, ranging between 6%–9%. Efforts to improve response rates to chemotherapy in ovarian clear cell carcinoma over the past decade have been unsuccessful, underscoring the need for further drug discovery to treat this resistant disease.

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.
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Clinical trial

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-negative 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 kinase (MAPK) signaling axes. 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 PI3KCA 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-kB) signaling pathways, lead to increased interleukin-6 (IL6) and -8 expression, and further immune suppression. ARID1A is integral in the SWI/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. 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. 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, 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 histotype. In a phase II study of nivolumab in patients with platinum-resistant recurrent ovarian cancer, a response rate of 23% and disease control rate of 54% was noted, with three patients showing durable partial response. 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. 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-Onco Group (KGOG) and Australia New Zealand Gynecological Oncology Group (AZGOG) 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 to receive any systemic cytotoxic chemotherapy, and the study drug administration was 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.
The immune-suppressive milieu in ovarian clear cell carcinoma arises from genetic alterations as well as tumor microenvironmental changes which highlight the potential therapeutic role for immune checkpoint inhibitors in 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. 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 INO.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. 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.
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.\(^\text{15}\) 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.

### REFERENCES

1. Saito T, Takahashi F, Katabuchi H, et al. Annual report of the Committee on Gynecologic Oncology, Japan Society of Obstetrics and Gynecology. Jpn J Clin Oncol 2018;51:381–9.
2. Kim SL, Lim MC, Lim J, et al. Incidence of epithelial ovarian cancer according to histologic subtypes in Korea, 1999 to 2012. J Gynecol Oncol 2016;27:45; e5.
3. Fujiwara K, Shinomiya D, Nishikawa T. Clear-cell carcinoma of the ovary. Ann Oncol 2016;27 Suppl 1:S50–2.
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 personalized medicine in ovarian clear cell carcinoma. Mod Pathol 2012;25:282–8.
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 2015;28:1080–7.
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 G, 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. Pembrolizumab plus pembrolizumab in patients with advanced endometrial cancer. J Clin Oncol 2020;JC01902627.