A Multicenter Phase II Randomized Trial of Durvalumab (D) Versus Physician's Choice Chemotherapy (PCC) in Patients (pts) with Recurrent Ovarian Clear Cell Carcinoma (MOCCA/ APGOT-OV2/ GCGS-OV3/GCIG)

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BACKGROUND

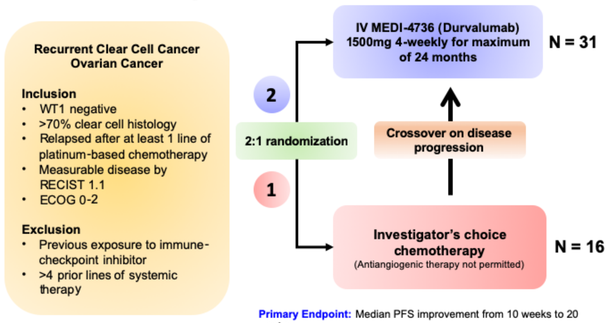
- The optimal treatment of recurrent ovarian clear cell carcinoma (rOCCC) remains unknown.
- Prior data suggested rOCCC is a chemoresistant disease that may respond to PD-1/ PD-L1 immune checkpoint inhibition.
- We aimed to determine the efficacy of D versus PCC in pts with rOCCC.

METHODS

Trial Design

- This is a multicentre, open-label, randomised phase 2 trial, 9 academic centers across Singapore, South Korea and Australia (**Figure 1**).
- Eligible patients were randomly assigned (2:1), using dynamic block randomization with block size of 6, and stratification by ECOG PS, to receive D (1500mg on day 1, in 28-day cycles) or PCC until disease progression, intolerable toxicity or withdrawal of consent.
- This trial is registered at Clinicaltrials.gov: NCT03405454

Figure 1: MOCCA Trial Schema



*Int J Gynecol Cancer. 2020 Aug;30(8):1239-1242. doi: 10.1136/**ijgc**-2020-001604.*

- **Primary Endpoint:** PFS following D or PCC. Radiological disease progression was evaluated by RECIST 1.1 criteria.
- **Secondary Endpoints:**
  - Objective response rate (ORR) of D or PCC in rOCCC.
  - Overall survival (OS) of D or PCC in rOCCC.
  - Adverse event profile of D in rOCCC.
  - Effect of D or PCC in health-related quality of life (QoL) using validated tools.

PATIENT CHARACTERISTICS

- Between 7 Nov 2017 and 17 Feb 2020, 57 pts were assessed for eligibility, of whom 47 were randomly assigned to treatment with D or PCC (**Table 1**).

Table 1: Baseline patient demographics and clinical characteristics

	PCC (n = 16)	D (n = 31)
Age (Years)		
Median [Range]	56 [36 – 81]	56 [35 – 70]
Ethnicity		
Caucasian	1 (6.2%)	6 (19.4%)
Chinese	8 (50.0%)	9 (29.0%)
Indian	1 (6.2%)	0 (0%)
Korean	5 (31.2%)	13 (41.9%)
Malay	0 (0%)	1 (3.2%)
Other	1 (6.2%)	2 (6.5%)
Country of trial		
Australia	2 (12.5%)	7 (22.6%)
Korea	5 (31.2%)	12 (38.7%)
Singapore	9 (56.2%)	12 (38.7%)
ECOG		
0	10 (62.5%)	17 (54.8%)
1	6 (37.5%)	14 (45.2%)
Number of prior treatment lines		
1	12 (75.0%)	22 (71.0%)
2	2 (12.5%)	7 (22.6%)
3	2 (12.5%)	1 (3.2%)
4	0 (0%)	1 (3.2%)

RESULTS

EFFICACY

- At the data-cut off date of 10 Jan 2022, the median duration of follow-up was 83.0 weeks (interquartile range (IQR) 54.1-97.0) for PCC and 107.0 weeks (IQR 82.7-116.4) for D.

Primary Endpoint Analysis

- No difference was observed in median PFS between D and PCC was observed (**Figure 3A**). Median PFS was 7.4 weeks (IQR: 6.0—16.0) in the D group and 14.0 (IQR: 7.0—28.6) in the PCC group (HR 1.5 [95% CI 0.8-2.8], one-sided log-rank p = 0.89).
- On unplanned subgroup analyses, median PFS was longest amongst patients receiving platinum-based combination PCC (**Figure 3B**), median PFS was 17.3 weeks (7.0-30.7) versus 10.7 weeks (7.0-26.6) for platinum-based combination versus single agent PCC.

Figure 3A: PFS of D versus PCC

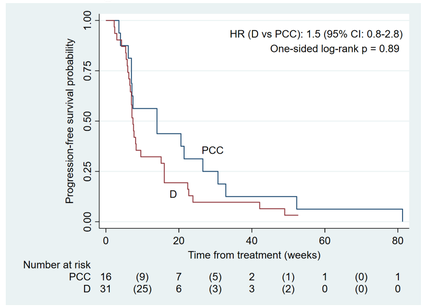
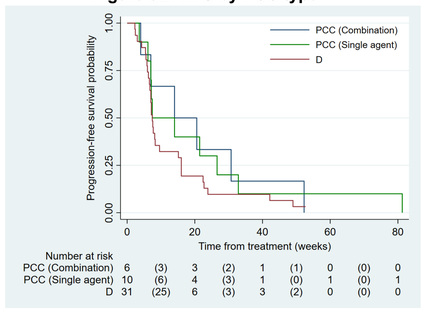


Figure 3B: PFS by PCC type



Secondary Endpoint Analysis

- No difference in median OS was observed between D and PCC (**Figure 4**).
- ORR was 10.7% in pts randomized to D and 18.8% in those randomized to PCC (p = 0.884) (**Figure 5, Table 2**).
- Clinical benefit rate (CR/PR/SD for ≥16weeks) was similar for PCC (37.5%) and D (32.1%) (p = 0.756) (**Figure 5, Table 2)**.
- 9 pts on PCC crossed over to receive D, with 2 of the 8 evaluable pts achieving partial response (PR). When crossover D pts were included, ORR to D was 13.9% (5/36) (**Table 2**).

Figure 4: OS of D versus PCC

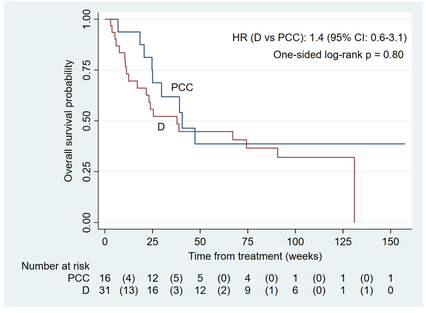
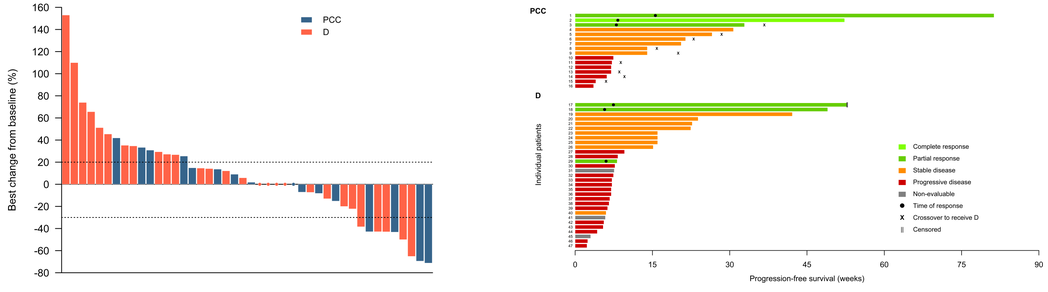


Table 2: Treatment response by RECIST1.1

	PCC (n = 16)	D (primary) (n = 31)	D (crossover) (n = 9)	D (all) (n = 40)	Difference (D primary - C) (95% CI)
CR	1 (6.2%)	0 (0%)	0 (0%)	0 (0%)	-
PR	2 (12.5%)	3 (9.7%)	2 (22.2%)	5 (12.5%)	-
SD	6 (37.5%)	9 (29.0%)	2 (22.2%)	11 (27.5%)	-
NE	0 (0%)	3 (9.7%)	1 (11.1%)	4 (10.0%)	-
ORR (CR + PR) NE excluded	3 (18.8%)	3 (10.7%)	2 (25.0%)	5 (13.9%)	-8.0% (-30.3%, 14.3%) (P = 0.884)
CBR (CR/ PR/ SD≥ 16 weeks) NE excluded	6 (37.5%)	9 (32.1%)	-	11 (30.6%)	-5.4% (-34.7%, 24.0%) (P = 0.756)

Figure 5A-B: Waterfall plot and swimmer's plot of best response to D or PCC



SAFETY

- Frequency of adverse events (AEs) across all grades was 68.8% for PCC and 38.7% for D.
- Grade 3/4 AEs were observed in 37.5% of PCC pts and 9.7% of D pts.
- No treatment-related grade 5 toxicities were observed.

	PCC (n = 16)		D (n = 31)	
	Grade 3/4	All grades	Grade 3/4	All grades
Anemia	2 (12.5%)	3 (18.8%)	0	0
Neutropenia	4 (25.0%)	5 (31.2%)	0	1 (3.2%)
Thrombocytopenia	1 (6.2%)	3 (18.8%)	0	1 (3.2%)
Hyperthyroidism	0	0	0	2 (6.5%)
Hypothyroidism	0	0	0	1 (3.2%)
Abdominal pain	0	2 (12.5%)	0	1 (3.2%)
Constipation	0	2 (12.5%)	0	0
Diarrhea	0	0	0	1 (3.2%)
Gastritis	0	1 (6.2%)	0	0
Mucositis oral	1 (6.2%)	2 (12.5%)	0	0
Nausea	0	3 (18.8%)	0	1 (3.2%)
Vomiting	0	1 (6.2%)	0	1 (3.2%)
Edema limbs	0	1 (6.2%)	0	1 (3.2%)
Fatigue	0	6 (37.5%)	0	7 (22.6%)
Fever	0	1 (6.2%)	0	0
Allergic reaction	0	1 (6.2%)	0	0
Alanine aminotransferase increased	0	0	0	1 (3.2%)
Anorexia	0	1 (6.2%)	0	1 (3.2%)
Aspartate aminotransferase increased	0	0	0	1 (3.2%)
Hypokalemia	0	0	1 (3.2%)	2 (6.5%)
Hypomagnesemia	0	0	1 (3.2%)	1 (3.2%)
Hyponatremia	0	0	1 (3.2%)	2 (6.5%)
Serum amylase increased	0	0	1 (3.2%)	1 (3.2%)
Arthralgia	0	0	0	1 (3.2%)
Back pain	0	1 (6.2%)	0	0
Lethargy	0	1 (6.2%)	0	0
Tremor	0	0	0	1 (3.2%)
Proteinuria	0	0	0	1 (3.2%)
Pneumothorax	1 (6.2%)	1 (6.2%)	0	0
Dry skin	0	1 (6.2%)	0	0
Nail pigmentation	0	2 (12.5%)	0	0
Pruritus	0	0	0	1 (3.2%)
Rash	0	1 (6.2%)	1 (3.2%)	2 (6.5%)
Seborrheic keratosis	0	1 (6.2%)	0	0
Skin pigmentation	0	1 (6.2%)	0	0

CONCLUSIONS

- No significant differences in PFS, ORR or CBR were observed between D and PCC treatment in rOCCC.
- Treatment with D was associated with less grade 3-4 adverse events.
- Correlative translational analyses to elucidate predictive biomarkers of response and resistance are ongoing.

ACKNOWLEDGEMENTS

- We are deeply grateful to the patients who participated in this study, their families and the trial coordinators that supported this study.
- We thank the members of the GCIG Rare Tumor Committee for their input on this study.
- This study is funded by the Ministry of Health National Medical Research Council Singapore (NMRC/MOHIAFCat1/0061/2016) and AstraZeneca.

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