753P Unlocking the circulating immune landscape of advanced clear-cell ovarian cancer: Insights from the MOCCA trial

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Background: Clear-cell ovarian cancer (CCOC) is an aggressive ovarian cancer subtype known for its chemoresistance and poor prognosis. While PD-(L)1 inhibitors represent a promising therapeutic strategy in CCOC, the MOCCA trial, a randomized phase 2 study comparing durvalumab (D) to physician's choice chemotherapy (PCC) in recurrent CCOC, failed to demonstrate a survival benefit with immunotherapy. This report aims to correlate the peripheral immune profile with outcomes to identify potential predictive biomarkers of immunotherapy benefit.

Methods: 47 patients (pts) were enrolled in the MOCCA trial, 31 received D and 16 PCC. Blood specimens were prospectively collected before D/PCC for immune profiling of leukocyte subsets and soluble factors. Flow cytometry analysis with 25 markers was performed on Day 7 blood stabilized in Cyto-Chex® BCT and acquired in BD FACSymphony A5 cell analyzer. Cell phenotypes were assessed with lineage markers post debris and antibody non-specificity removal. Plasma cytokine and chemokine concentrations were measured by bead-based multiplex assay (Milliplex) with Luminex Flexmap3D system.

Results: 35 blood samples were collected at baseline, 23 in the D arm and 12 in the PCC arm. Pts with a longer progression-free survival (PFS) (>12 weeks) exhibited significantly higher levels of circulating $CD3^+$ T-cells (p=0.01), $CD4^+$ T-cells (p=0.02), $CD19^+$ B-cells (p=0.048) and NK-cells (p=0.02), along with lower levels of neutrophils (p=0.009), compared to pts with <12w PFS. Additionally, pts with longer PFS to D showed significantly elevated baseline levels of CCL11 (p<0.001), CCL15 (p=0.009) and CCL2 (p=0.011) compared to those with shorter PFS. Conversely, no differences in the circulating immune profile were observed between pts treated with PCC who had >16w PFS vs <16w PFS, although circulating VEGF levels were significantly higher in pts with longer PFS (p=0.012).

Conclusions: In the MOCCA trial, patients with a favorable response to immunotherapy exhibited increased levels of circulating T-cells, B-cells, NK-cells, and specific cytokines along with decreased neutrophil levels. These circulating immune markers may serve as predictive tools for optimizing the use of immune-checkpoint inhibitors in CCOC.

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754P Initial results from a first-in-human study of AZD5335, a folate receptor α (FRα)-targeted antibody-drug conjugate, in patients (pts) with platinum-resistant recurrent ovarian cancer (PRROC)

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Background: FRα is a highly expressed cell-surface target in many cancers including ovarian cancer, and internalises folate, a co-factor required for DNA and RNA synthesis. AZD5335 is an FRα-targeted antibody-drug conjugate that binds to FRα with high affinity and delivers a topoisomerase 1 inhibitor payload. FONTANA (NCT05797168) is a Phase 1/2a, first-in-human, modular open-label study of AZD5335 in pts with advanced solid tumours. We report results from module M1A, the ongoing dose escalation.

Methods: Pts aged ≥18 years with PRROC were recruited irrespective of tumour FRα expression and without a limit on the number of prior lines of therapy. AZD5335 was administered intravenously Q3W until disease progression, unacceptable toxicity, or other reason for discontinuation. The primary objective was to determine safety and tolerability. Key secondary objectives included assessing pharmacokinetics (PK) and preliminary efficacy per RECIST v1.1, assessed Q6W.

Results: As of 30 March 2024, 28 pts (median age 62.0 [range 46–76] years; median 4 [range 1–15] lines of prior therapies) were treated across four dose levels. The most common (reported in ≥15% of pts) possibly treatment-related adverse events per investigator opinion (any Grade [G], G3–4) were nausea (61%, 0), anaemia (25%, 18%), neutrophil count decreased (21%, 7%), and pyrexia (21%, 0). No dose-limiting toxicities or deaths due to treatment were reported; maximum tolerated dose has not been reached. The PK of both AZD5335 and its payload were linear over the dose range. AZD5335 was stable in circulation with minimal accumulation prior to the second dose. Confirmed responses were observed at all doses. Among evaluable pts with high FRα expression (≥75% of tumour cells staining at ≥2+ intensity; n=8), 5 had an objective radiological response (1 pending confirmation); among those with high FRα expression receiving the top 3 dose levels (n=5), 4 had an objective radiological response (1 pending confirmation). Further updates will be provided at presentation.

Conclusions: AZD5335 demonstrated a manageable safety profile and preliminary signs of efficacy. Dose optimisation is underway in module M1B. Ronnie Shapiro-Frommer and Kazuki Sudo have contributed equally to the study.

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755P Beyond HRD status: Unraveling genetic variants impacting PARP inhibitor sensitivity in advanced ovarian cancer

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Background: The management of advanced ovarian cancer (AOC) has evolved with the advent of molecular diagnostics, particularly in predicting responses to poly (ADP-ribose) polymerase inhibitors (PARPi) based on homologous recombination deficiency (HRD) status. Despite this, a comprehension of PARPi sensitivity in HRD negative (HRDneg) tumors and resistance in HRD positive (HRDpos) tumors has not yet been fully achieved.

Methods: We conducted *post hoc* translational analysis of formalin-fixed paraffin-embedded tumor samples from the ENGOT-ov24/NSGO-AVANOVA part 1 and 2 trial (AVANOVA1&2; NCT02354131), focusing on alterations with regards to progression-free survival (PFS) and radiological response. DNA sequencing was performed using the TruSight Oncology 500 HT gene panel, and variants were classified according to recent guidelines. HRD status had been assessed by Myriad MyChoice® CDx.

Results: Among samples collected from 92 patients included in the AVANOVA1&2 trial, 151 oncogenic or likely oncogenic variants were identified across 81 samples. In terms of PFS, PARPi sensitizing variants were identified in two out of ten HRDneg samples from patients with clinical benefit (PFS $\geq$ 12 months), and with PARPi resistance in three out of ten HRDpos samples from patients having no benefit (PFS $\leq$ 6 months). Moreover, studying the location of pathogenic variants in *BRCA1* revealed, that truncating variants in exon 11 were associated with clinical benefit, only when niraparib was combined with bevacizumab in this study.

Conclusions: Our findings highlight the complexity of PARPi response in AOC and underscore the importance of exploring somatic variants beyond HRD status. Further investigation into exon 11 variants of *BRCA1* and the potential role of combination treatment is warranted.

Clinical trial identification: ENGOT-ov24/NSGO-AVANOVA1&2; NCT02354131.

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756P Final analysis of KGOG3046/TRU-D: A phase II study of durvalumab and tremelimumab with front-line neoadjuvant chemotherapy in patients with advanced-stage ovarian cancer

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Background: In the original cohort (O) of KGOG 3046 study (NCT03899610) on newly diagnosed advanced-stage epithelial ovarian cancer (aEOC), patients receiving neo-adjuvant chemotherapy (NAC) with durvalumab [D] and multiple low dose of tremelimumab [T] exhibited promising long-term survival outcomes. After completing enrollment of the original cohort, an expansion cohort (E) was initiated with a regimen of NAC with D and the single high dose of T. Here, we reported final long-term survival results from the KGOG 3046 study.

Methods: This open-label, investigator-initiated study enrolled patients with FIGO stage IIIC-IV EOC. Enrolled patients received the following neoadjuvant therapy (paclitaxel + carboplatin [3 cycles] + D 1,500 mg q3w + T (75mg q3w for O; 300 mg [1 cycle] for E). After NAC, all patients underwent interval debulking surgery (IDS), and three cycles of D (1,120 mg) and adjuvant chemotherapy followed by D maintenance (1,120 mg [total 12 cycles]). The primary endpoint was the 12-month PFS rate, and secondary endpoints were the pathologic complete response (pCR), overall survival, and safety.

Results: Between June 2019 and July 2021, 45 patients were enrolled (O, n=23; E, n=22); the median follow-up was 30.9 (95% CI: 9.7–42.2) months. The majority of the patients presented high-grade serous carcinoma (91.1%) and stage IV (77.8%) disease. After NAC, 5 (11.1%) had a pCR (17.4 in O *vs*. 4.6% in E). The 12-month, 24-month, and 30-month PFS rates were 65.9% (63.6% in O and 68.2% in E), 40.5% (45.0% in O and 36.4% in E), and 38.1% (40.0% in O and 36.4% in E), respectively. The 30-month OS rate was 87.7% (89.1 *vs*. 85.9%). Adverse events were manageable, with grade $\geq$ 3 skin rash (17.8%). In exploratory analysis, patients with high TIL and PD-L1 expression showed better survival outcomes.