Exome Sequencing of Recurrent Low Grade Serous Ovarian Carcinoma Patients Highlights a Lack of Common Mutations and Divergent Treatment Opportunities

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Background: Recurrent low grade serous ovarian cancer (LGSOC) presents significant clinical challenges, with limited therapeutic options. NGS may identify novel therapeutic targets. Here we present data on three patients with LGSOC who underwent whole exome sequencing (WES).

A total of 11 somatic samples - 8 in Case 1, 2 in Case 2 and 1 in Case 3 - had DNA extracted from FFPE blocks. Each case included a patient-matched germline sample from blood. All cases were TP53 wild-type.

Case 1:
- 20 SNVs were shared in at least 2 samples (Figure A).
- A class 3 (kinase-dead) BRAF D594G mutation is evident in all recurrence and metastasis.
- CNA evident covering NRAS (Figure B).
- Single-gene testing showed wildtype for KRAS, BRAF V600E and NRAS.
- TMB normal (<5 SNV/MB) for all samples.
- MSI normal for all samples.

Case 2:
- Very few shared SNVs between two recurrences.
- TMB elevated (>10 SNV/MB), PDL1 expression <1%.
- MSI normal.
- Screened for trial (NCT02484404) on anti-PDL1 in combination with olaparib and/or cediranib - deemed unsuitable.

Case 3:
- Declined initial adjuvant chemotherapy.
- Stop-gain SNV in NBS1 (R43*).
- TMB high (>20 SNV/MB), PD-L1 negative.
- NBS1 was wildtype in germline.
- A number of non-pathogenic mutations identified in the other members of DNA damage response pathway.
- Advised cytotoxic chemotherapy based on WES profile.

Discussion

Case 1: BRAF D594: Literature describes this mutation as activating the MAPK/ERK pathway, particularly in the presence of increased RAS expression. This indicated potential benefit for the patient from an EGFR or MEK inhibitor. This lady commenced a MEK inhibitor trimetanib on compassionate grounds, however showed minimal clinical response and succumbed after 10 weeks. The presumed dimerization of BRAF was not seen using proximity ligation assay, a possible reason that the treatment failed.

Case 2: Elevated TMB but low PDL1: No potentially mechanistic SNVs were found, despite an increased level of mutation. Coupled with low PDL1 expression no further treatment options are obvious from the exome data. This lady currently has stable disease on anti-endocrine therapy.

Case 3: NBS1 stop-gain: high TMB possibly owing to reduced ability to repair double-strand breaks based on NBS1 SNV. This fits with partial response to cytotoxic chemotherapy given tumour cells would have reduced capability to repair or maintain.

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