

**725MO Phase I study of the combination of the dual RAF/MEK inhibitor VS-6766 and the FAK inhibitor defactinib: Results of efficacy in low grade serous ovarian cancer**

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**Background:** Patients with low grade serous ovarian cancer (LGSOC) have limited response to conventional chemotherapy and hormonal therapy. Recently, MEK inhibitors have shown an overall response rate (ORR) 15-26%. Activation of p-FAK is a possible mechanism of resistance to MEK inhibitors and we hypothesised combination of a RAF/MEK inhibitor with a FAK inhibitor would overcome this.

**Methods:** We explored the safety, pharmacokinetics and pharmacodynamics in the dose escalation study and recommended a phase two dose of the combination of RAF/MEK inhibitor VS-6766 3.2 mg twice a week and the FAK inhibitor defactinib 200 mg twice daily, both administered 3 out of 4 weeks in 28 day cycles in a highly intermittent dosing schedule. We evaluated confirmed responses using RECIST 1.1. We present the efficacy of the combination in patients with LGSOC in this trial so far.

**Results:** Currently, 25 patients with LGSOC have been treated with 24 evaluated for response, median age 57 (range 31 to 75 years) and median previous lines of therapy 4 (range 1 to 9). Of the 24 evaluable patients, 11 (46%) had *KRAS* mutations and 10 (42%) received prior MEK inhibitor treatment. The most common adverse events were rash and CK elevation which were predominantly grade 1/2. The overall response rate in all patients was 46% (11/24, 95% CI: 28% to 65%), with ORR of 64% (7/11, 95% CI: 35% to 85%) in patients with *KRAS* mutations, and 44% (4/9, 95% CI: 19% to 73%) in patients with *KRAS* wildtype tumours. Four patients had undocumented *KRAS* status. Responses were observed in patients with and without prior MEK inhibitor treatment. The median progression free survival was 23 months for the whole cohort, 13/24 patients are still on study and updated results will be presented.

**Conclusions:** An intermittent dosing schedule of the combination of VS-6766 and defactinib has shown encouraging clinical activity in patients with recurrent LGSOC. These data support an ongoing registration-directed study of VS-6766 ± defactinib in patients with recurrent LGSOC (ENGOT-ov60/NCRI/GOG-3052; NCT04625270).

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