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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).

Clinical trial identification

NCT03875820.

Legal entity responsible for the study

The Institute of Cancer Research and The Royal Marsden Hospital NHS Foundation Trust.

Funding

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Disclosure

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