Abstract 9018: Phase I trial of the RAF/MEK clamp VS-6766 in combination with everolimus using intermittent dosing schedule with expansion in NSCLC across multiple *KRAS* variants.

Authors: Minchom AR[1], Sanchez Perez V[1], Morton C[2], Manickavasagar T[1], Nintos G[3], Lai-Kwon JE[1], Guo C[1], Tunariu N[1], Parker T[4], Prout T[4], Parmar M[4], Turner AJ[4], Finneran L[4], Hall E[4], Pachter JA[5], Denis LJ[5], Spicer JF[3], Banerji U[1]

1. Drug Development Unit, The Institute of Cancer Research/The Royal Marsden Hospital NHS Foundation Trust, UK; 2. Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom; 3. King's College London, London, UK ; 4. The Institute of Cancer Research, Sutton, UK; 5. Verastem Oncology, Needham, MA

Background

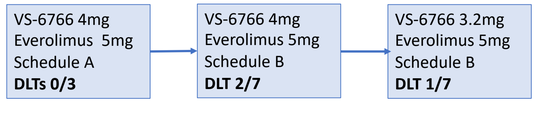
- VS-6766 is a small molecule RAF/MEK clamp that reduces p-MEK and p-ERK (1).
- There is cross talk between the RAS-RAF-MEK-ERK and PI3K-AKT-mTOR pathways and combination of VS-6766 + everolimus (mTOR inhibitor) induces synergistic inhibition of viability in *KRAS* mutated NSCLC in preclinical models (2).
- *KRAS* mutations are present in a number of solid tumours including approximately a third of NSCLC adenocarcinoma.
- There is a targeted therapeutic options approved for patients with *KRAS G12C* NSCLC but not for patients with other *KRAS* variants.
- The dosing schedule for VS-6766 monotherapy has been established and has shown clinical activity for patients with KRAS mt NSCLC or gynecologic cancers (3).
- This clinical trial evaluated the safety and efficacy of a novel intermittent regimen of VS-6766 and everolimus with an expansion in *KRAS* mutant (mt) NSCLC (NCT02407509).

Methods

The trial used a 3+3 dose escalation design (Figure 1):

- Schedule A: Once a week, 3 weeks on/1 week off, 28 day cycle, both drugs
- Schedule B: Twice a week (Mon-Thu or Tue-Fri), 3 weeks on/1 week off, 28 day cycle, both drugs
- The primary objective was to recommend a phase II dose and dosing schedule for VS-6766 in combination with everolimus.
- Patients with *RAS* or *RAF* mt cancers were eligible for the dose escalation cohort.
- 20 patients with *KRAS* mt NSCLC will be treated in the dose expansion cohort.
- Other inclusion criteria were ECOG performance status 0-1 and measurable or evaluable disease.
- Toxicity was evaluated by NCI CTC V4 and efficacy using RECIST 1.1.

Figure 1. Dose escalation



Results

- As of April 29th 2022, thirty patients have been treated; median age 61 years (range 36-78), median lines of previous treatment 2 (range 0-7).
- Seventeen patients have been treated in the dose escalation (3 in schedule A and 14 in the schedule B (2 of which are not evaluable for response) and thirteen patients have been treated in the dose expansion (1 of which is not evaluable for response).
- At 4 mg VS-6766 and 5 mg everolimus twice weekly (n=7 DLT evaluable patients) two DLT's was observed of grade 4 CPK elevation. One patient received less than 80% of the IMP dosing so was also assigned, per protocol, as having a DLT. At 3.2 mg VS-6766 and 5 mg everolimus twice weekly (n=7 evaluable patients), one DLT was observed of grade 3 rash.
- Twice weekly 3.2 mg VS-6766 and 5 mg everolimus was declared as the recommended phase 2 dose (RP2D).

TRAE	VS-6766 4mg Everolimus 5mg Schedule A [n=3]		VS-6766 4mg Everolimus 5mg Schedule B [n=7]		VS-6766 3.2mg Everolimus 5mg Schedule B [n=20]		Total G1-4 n (%) [n=30]	Total G3-4 n (%) [n=30]
	G1 - G2	G3 - G4	G1 - G2	G3 - G4	G1 - G2	G3 - G4		
Rash	3		5	1	13	4	26 (87%)	5 (17%)
CK elevation	1		3	2	11	1	18 (60%)	3 (10%)
Mouth ulcers/Mucositis	1		5		11		17 (57%)	0 (0%)
Diarrhoea			5		8		13 (43%)	0 (0%)
Visual disturbance			6		7		13 (43%)	0 (0%)
Pruritis	1		1		6	2	10 (33%)	2 (7%)
AST elevation			2		7		9 (30%)	0 (0%)
Fatigue			3		5		8 (27%)	0 (0%)
Thrombocytopenia			2		6		8 (27%)	0 (0%)
Anaemia			3		3	1	7 (23%)	1 (3%)
Nausea			2		4		6 (20%)	0 (0%)
Peripheral oedema					6		6 (20%)	0 (0%)

Table 1. Treatment Related Adverse Events occurring in 6 or more patients.
ALT: alanine aminotransferase
AST: aspartate aminotransferase
ALP: alkaline phosphatase
CK: creatinine kinase
G: grade
TRAE: Treatment Related Adverse Events

- At the RP2D (n=20), the grade 3-4 drug related AEs in 2 or more patients were rash (20%, 4/20) and pruritus (10%, 2/20).
- No patients discontinued trial due to toxicity.

- In the dose escalation cohorts, 3 partial responses (PRs) were reported (2 *KRAS G12D* low grade serous ovarian cancer [LGSOC] and 1 *NRAS Q61K* mut thyroid cancer).
- For the 2 patients with *KRAS G12D* mt LGSOC, PFS was 35.8 and 41.8 months with treatment ongoing.

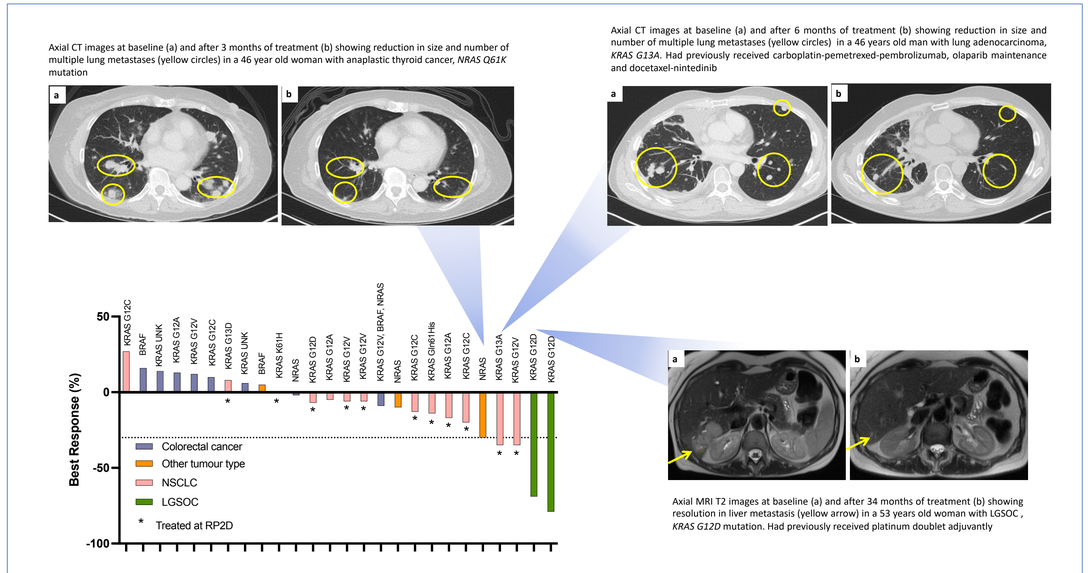
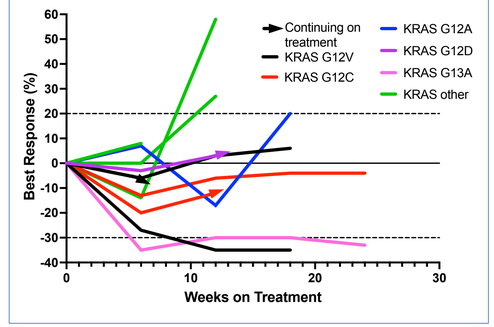


Figure 2. Waterfall plot of best response according to RECIST 1.1 including unconfirmed responses *NSCLC: Non-small cell lung cancer. UNK: unknown, LGSOC: low grade serous ovarian cancer*

- In the *KRAS* mt NSCLC expansion cohort 11 patients were evaluable for efficacy; 2 confirmed responses with an objective response rate (ORR) 18% (95%CI - 2.5 - 55.6).
- The median PFS for the *KRAS* mt NSCLC expansion cohort was 6.25 months (95%CI: 3.39 – 7.40).

Figure 3. Spider plot of NSCLC patients in Expansion Cohort



Conclusions

- A tolerable intermittent dosing schedule targeting both the MAPK and PI3K pathways has been established
- The combination of VS-6766 with everolimus has shown objective responses in patients with a variety of *RAS* mutation variants in NSCLC, LGSOC and thyroid cancers.
- Median progression free interval of 6.25 months in a heavily pre-treated population of *KRAS* mutated NSCLC may provide a possible non-chemotherapy alternative for the treatment of such patients
- Future clinical trials of VS-6766 with everolimus are warranted in *KRAS* mt NSCLC and other RAS/MAPK driven cancers

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Corresponding Author: Udai Banerji, PhD, MD, FCRP, DNB. Drug Development Unit, The Institute of Cancer Research, London, United Kingdom
udai.banerji@icr.ac.uk

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