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Abstract 799

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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ICR The Institute of Cancer Research | The ROYAL MARSDEN NHS Foundation Trust | The Christie NHS Foundation Trust

NIHR | Biomedical Research Centre at The Royal Marsden and the ICR

DECLARATION OF INTERESTS

Susana Banerjee

Institutional Research Funding: Astrazeneca, Tesaro, GSK, Lady Garden Foundation Charity, Wellbeing of Women Charity

Personal Fees (Advisory Boards): Amgen, Astrazeneca, Epsilogen, Genmab, Immunogen, Mersana, MSD, Merck Serono, Oncxerna, Pfizer, Roche

Personal Fees (lectures, CME): Amgen, Pfizer, Astrazeneca, Tesaro, GSK, Clovis, Takeda, Medscape, Research to Practice, Peerview

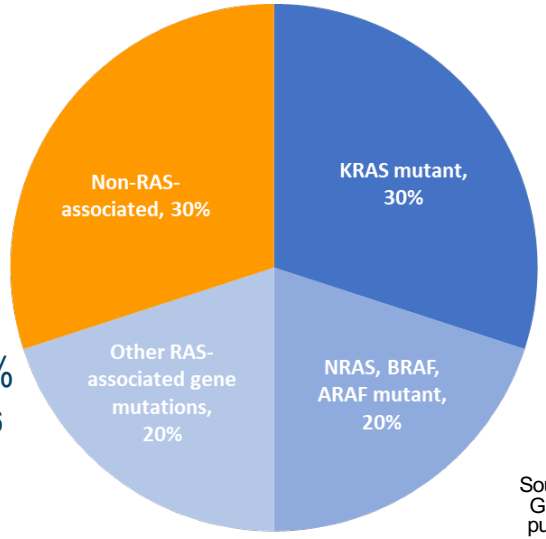
ESMO Director of Membership

Global PI ENGOTov60/GOG3052/RAMP201 trial: Verastem sponsored

Background-Low Grade Serous Ovarian Cancer (LGSOC)

- Rare subtype (up to 5-10% of serous)[1,2]
- Recurrent: Response to chemotherapy 0-13%[1,2,4,5]
  hormonal therapy 0-14%[1,4]
- Single agent MEK inhibitors
  - Response rate 15-26%[3-5]
  - Trametinib PFS improvement vs SOC[4]
    - Median PFS 13.0 vs 7.2 months
    - Discontinuation due to AE/complication 35.4% vs 12.3%
  - KRAS mutation associated with longer PFS with binimetinib[5,6]

Low-grade serous -
a RAS-driven subtype of ovarian cancer



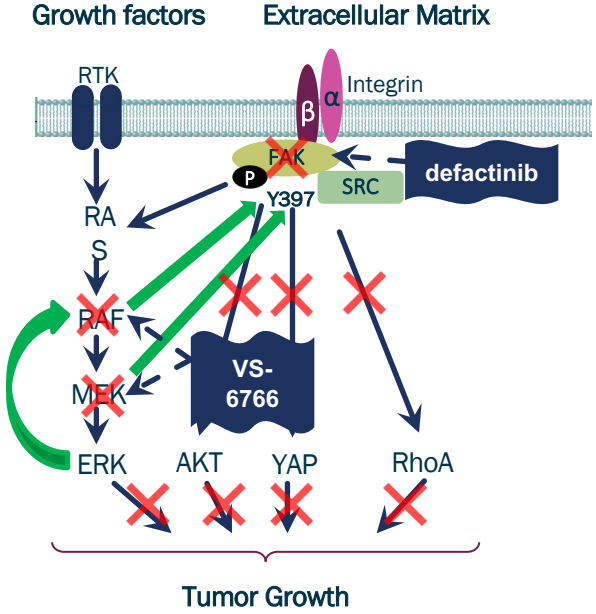
Source: AACR Project GENIE Cohort v9.0-public and Verastem unpublished analysis

~30% have a KRAS mutation
~70% have RAS Pathway-Associated mutations

1.McLachlan, Gore and Banerjee. Pharmacogenomics. 2016 Aug;17(12):1353-63; 2. Slomovitz, Gourley, Carey et al Gynecol Oncol. 2020 Mar;156(3):715-725. 3.Farley, Brady, Vathipadiekal et al. Lancet Oncol. 2013;14:134–140; 4.Gershenson, Miller, Brady et al Annals of Oncology (2019) 30 (suppl_5): v851-v934; 5. Grisham, Monk, Banerjee et al Journal Clin Oncol 38:3753-3762 2020; 6. Grisham, Vergote, Banerjee et al Journal Clin Oncol 39, no. 15_suppl (May 20, 2021) 5519-5519.

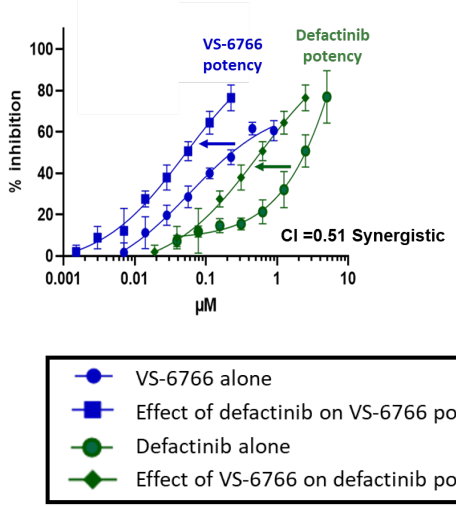
Preclinical Rationale: MEK and FAK inhibition in LGSOC

More Complete Shutdown of Tumor Growth Requires Addressing Multiple Resistance Mechanisms

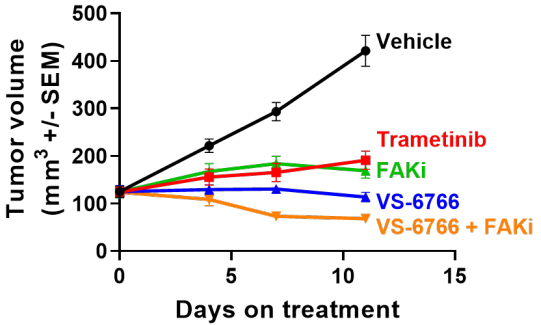


VS-6766 (RAF/MEK inhibitor) and FAK inhibitor combination leads to more robust anti-tumor efficacy in KRAS mutant ovarian cancer models

Patient-derived organoid *in vitro KRAS* G12V mutant LGSOC



Ovarian cancer model TOV-21G *KRAS* mutant xenograft



FRAME: Clinical trial design and results in LGSOC

NCT03875820

Escalation
12 patients
6 LGSOC

Expansions

- Low Grade Serous Ovarian Cancer * (20 patients)
- Advanced NSCLC KRAS-Mut * (20 patients)
- Advanced CRC RAS-Mut * (10 patients)
- Advanced solid Tumours Enriched for RAS-Mut * (Biopsy-amenable, 7 patients)
- Endometrioid RAS/RAF-Mut (10 patients)
- NSCLC KRAS G12V (10 patients)
- Pancreatic Cancer (10 patients)

Optimization of Novel Intermittent Dosing Regimen for Improved Safety While Maintaining Clinical Efficacy*

Adverse event details	LGSOC								Total G.3/4 (n=25)	Percentage of patients with G.3/4 AE (%)
	Escalation				Expansion					
	VS-6766 4mg D 200mg (n=2)		VS-6766 3.2mg D 200mg (n=3)		VS-6766 4mg D 200mg (n=3)		VS-6766 3.2mg D 200mg (n=17)			
	G.1 - G.2	G.3 - G.4	G.1 - G.2	G.3 - G.4	G.1 - G.2	G.3 - G.4	G.1 - G.2	G.3 - G.4		
Rash	2		2		3		15	2	**2**	**8%**
CK elevation	1	1	2		2	1	12	1	**3**	**12%**
Diarrhoea			2		2		10	1	**1**	**4%**
AST elevation	1				2		8		**0**	**0%**
Mouth ulcer/Mucositis/ Glossitis					2	1	8		**1**	**4%**
Hyperbilirubinemia		1	1				8		**1**	**4%**
ALT elevation	1				2		5		**0**	**0%**
Nausea	1		2		3		3		**0**	**0%**
Peripheral oedema							8		**0**	**0%**
Visual disturbance					1		7		**0**	**0%**
Total:	**6**	**2**	**9**	**0**	**17**	**2**	**84**	**4**	**8**	**32%**

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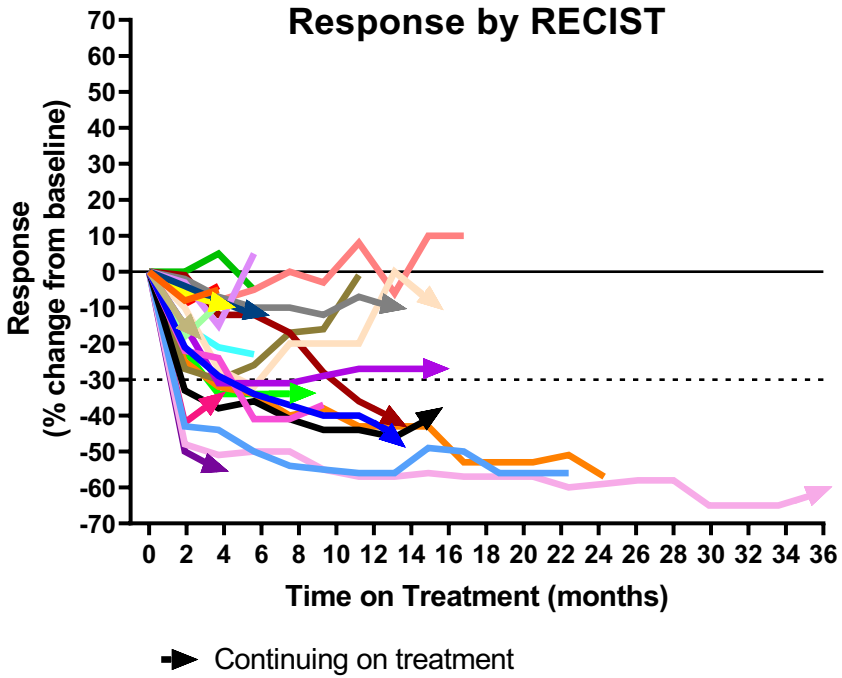
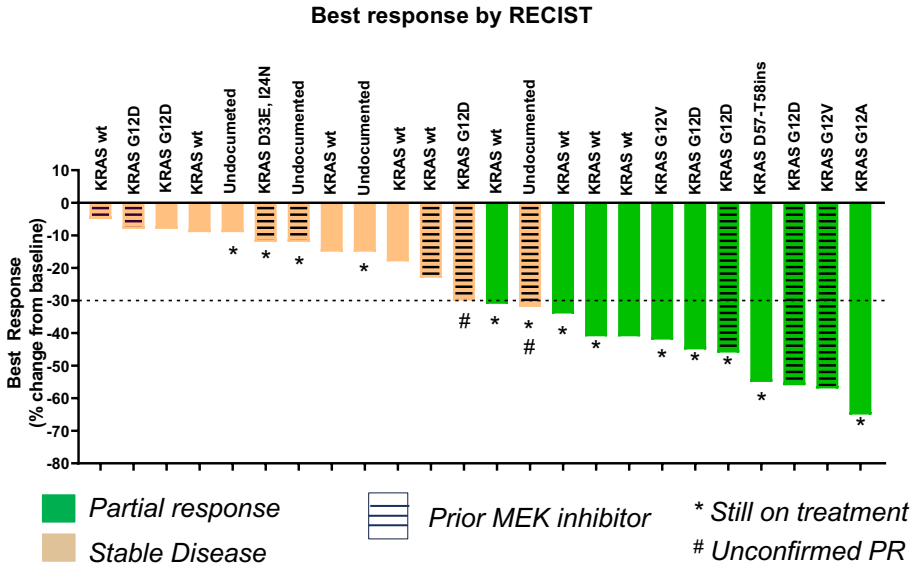
RP2D dose: VS-6766 3.2mg twice/week 21/28 days and Defactinib 200mg bid 21/28 days

FRAME: Efficacy of VS-6766 + Defactinib in LGSOC





- Overall response rate (ORR) = 46% (11/24)
- KRAS mutant ORR = 64% (7/11)
  - *KRAS* wild-type ORR = 44% (4/9)
  - *KRAS* status undetermined (3 SD; 1 unconfirmed PR)
- Responses in patients previously treated with MEKi
- Median PFS 23 months (95% CI 10.6-NR) across all LGSOC

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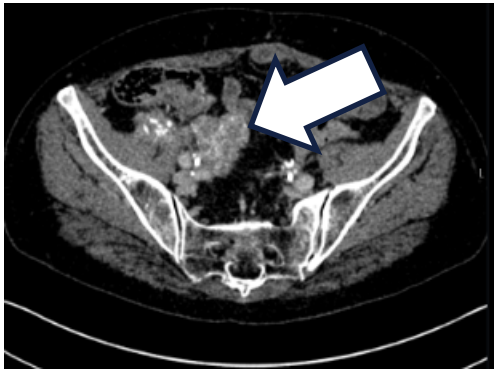
Data cut off April 2021

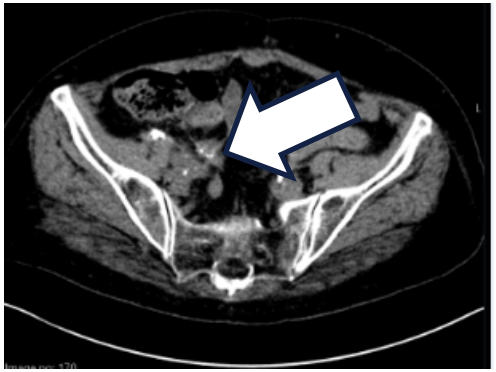
NR: Not reached

FRAME: Case Study VS-6766 + Defactinib in LGSOC

Jan 2018



Jul 2021



- 77 year-old female
- Diagnosis: Low grade serous ovarian cancer
- Nov 2010: Surgery
- Dec-2010-Feb 2011: Carboplatin + paclitaxel
- April 2011-Aug 2011: Liposomal doxorubicin
- Sept 2011:palliative surgery
- Sept 2011-Aug 2016: Letrozole
- Oct 2016- Aug 2017:Tamoxifen
- Jan 2018-Present: on VS6766 + Defactinib in FRAME study, ongoing Partial Response

Summary and Conclusions

- The combination of VS-6766 (RAF/MEKi) + defactinib (FAKi) with a novel, intermittent schedule exhibits a manageable safety profile, with only 1 patient discontinuing for adverse events to date
- VS-6766 in combination with defactinib shows encouraging response with durability across all LGSOC patients
    - All LGSOC ORR 46%; median PFS 23 months
        - KRAS mutated LGSOC ORR 64%; median PFS 23 months
- In May 2021, FDA granted Breakthrough Therapy Designation for VS-6766 + defactinib for treatment of patients with recurrent LGSOC after one or more prior lines of therapy, including platinum-based chemotherapy
- A registration-directed clinical study in LGSOC, ENGOT-ov60/GOG3052/RAMP201, is currently enrolling patients in Europe and US (NCT04625270)[1]

1. Banerjee S et al, J Clin Oncol 2021 39:15_suppl, TPS5603-TPS5603

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Patients and families
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ICR The Institute of Cancer Research

CANCER RESEARCH UK

NIHR | Biomedical Research Centre at The Royal Marsden and the ICR

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