Clinical Combinations: Dual RAF-MEK & FAK Inhibition for the Treatment of *KRAS* Mutant Cancers With a Focus on Low Grade Serous Ovarian Cancer

Udai Banerji

NIHR Professor of Molecular Cancer Pharmacology

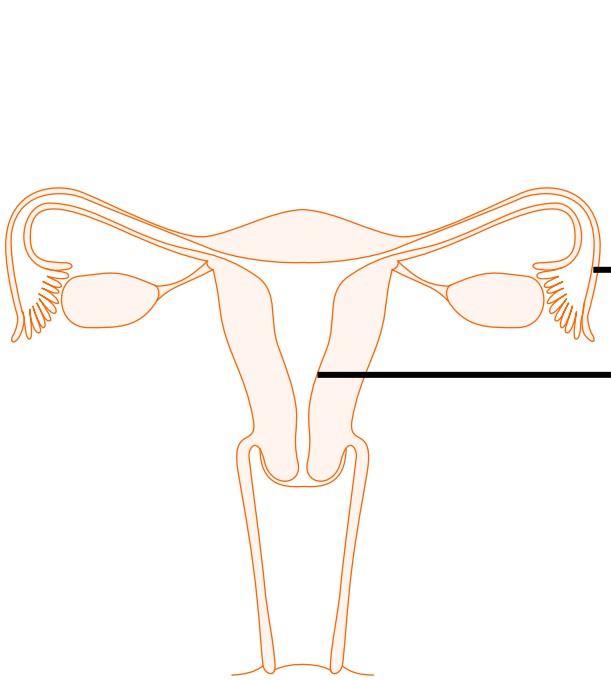
The Institute of Cancer Research/ The Royal Marsden Hospital NHS Foundation Trust

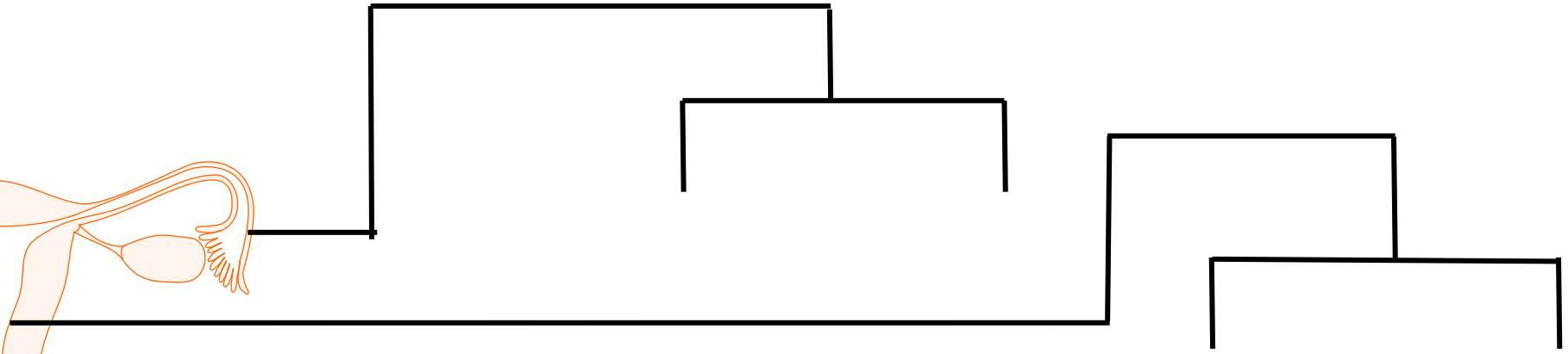
London, UK

Conflicts of Interest

- Udai Banerji has received grant funding for preclinical research from Verastem Oncology and the academically sponsored study presented is funded by Verastem Oncology

Types of Ovarian Cancer





	High Grade serous ovarian cancer	Low grade serous ovarian cancer	Clear Cell	Endometrioid	Mucinous
% of Ovarian cancers	70-80%	5-10%	10-15%	5-10%	5%
Mutations and genetic abnormalities	*TP53, BRCA, HRD*	*KRAS, BRAF*	*PIK3A, ARID1A*	PTEN, *ARID1 KRAS*, MMR	HER2

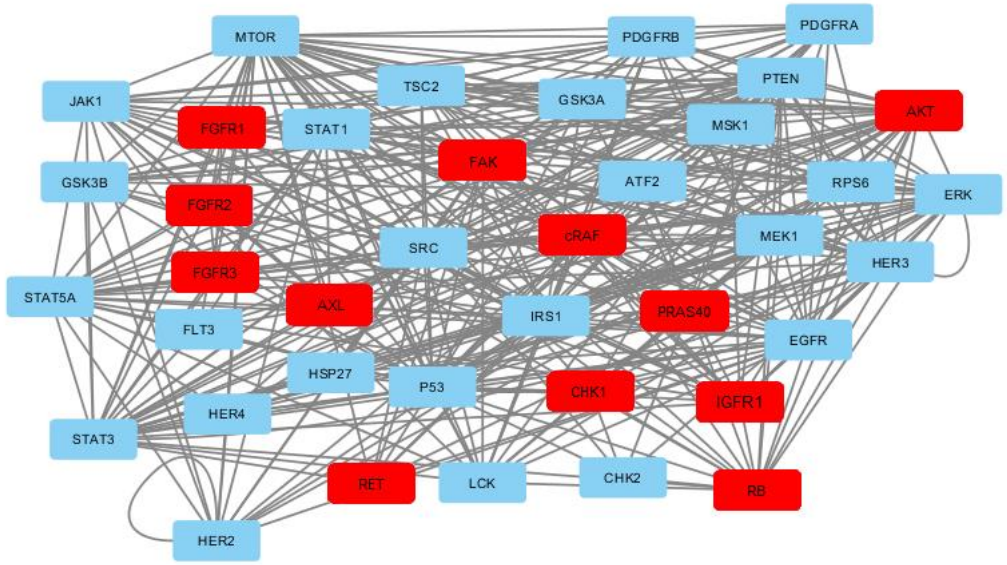
- Low grade serous ovarian cancer arises from the lining of the fallopian tube and occurs in younger women and when metastatic is incurable, patients survive longer than HGSOC

Treatment Options for Patients with LGSOC

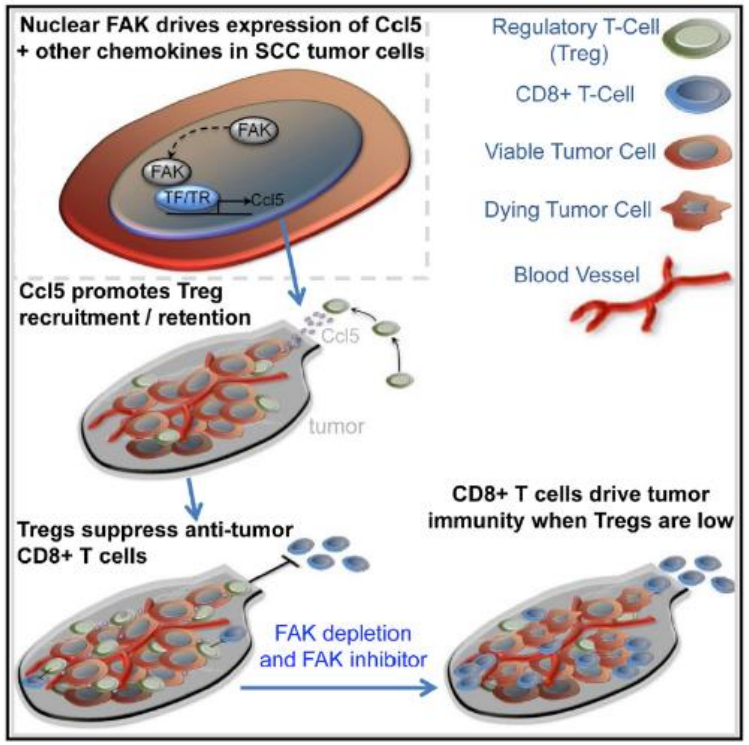
- Surgery
  - Patients with stage II-IV disease with optimal primary cytoreductive surgery (residual disease <1 cm) have a longer survival than those who don't (97 months vs 35 months).
  - Secondary de-bulking surgery also indicated if possible
- Chemotherapy
  - Chemotherapy has response rates of approximately 5-10%
  - Endocrine therapy response rates 14% with PFS 11 months
- Targeted Therapy
  - Will be discussed later

Gershenson DM M Gynaecol Oncol 2009, 114:48-52
Tang M Gynaecol Oncol 2019, 154:531-538

Rationale for using a combination of RAF-MEK and FAK inhibitors



Rewiring of signal transduction following MEK inhibition in *KRAS*^{M} cell line A549



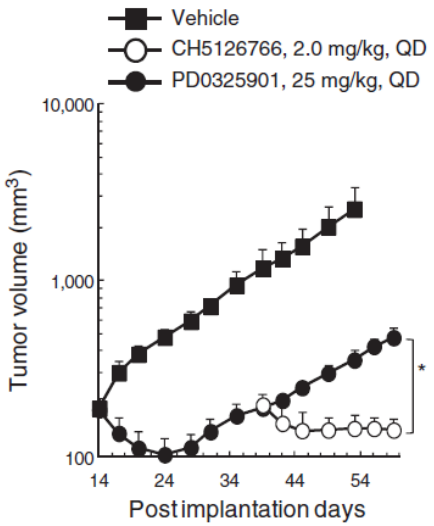
FAK inhibition reduces Treg populations

Serrels A Cell 2015, 163:160-173

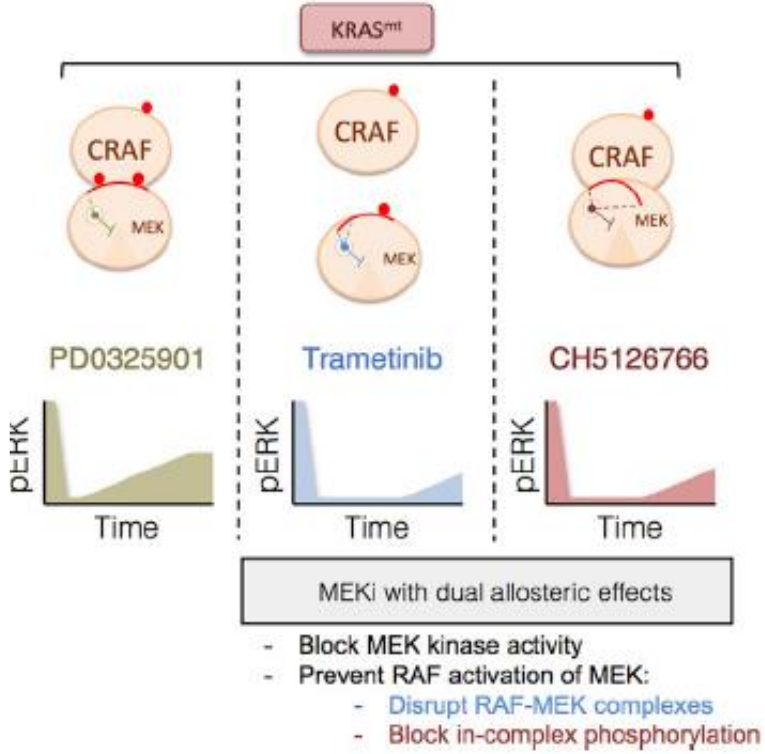
Adam Stewart, Anna Minchom CPAT group ICR, UK

Drugs used in the combination- VS6766/CH5126766 (RAF-MEK inhibitor)

Preclinical



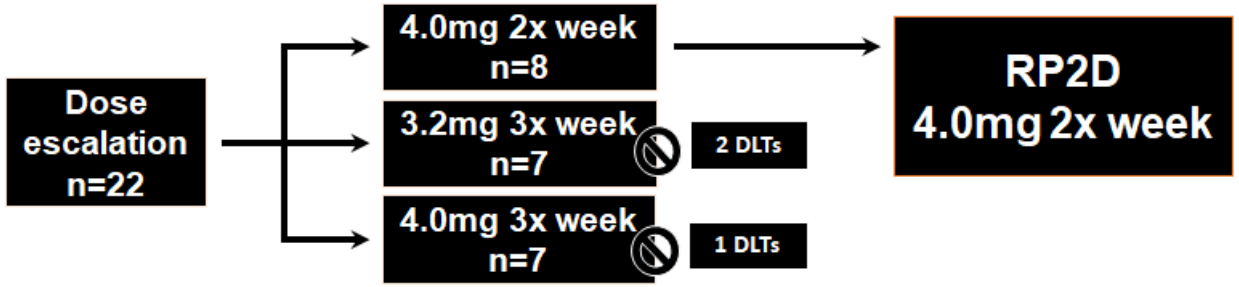
- Different MEK inhibitors have distinct mechanisms of action
- VS6766/CH5126766 blocks in complex phosphorylation of MEK and resulting in reduction in phosphorylation of MEK in addition to ERK

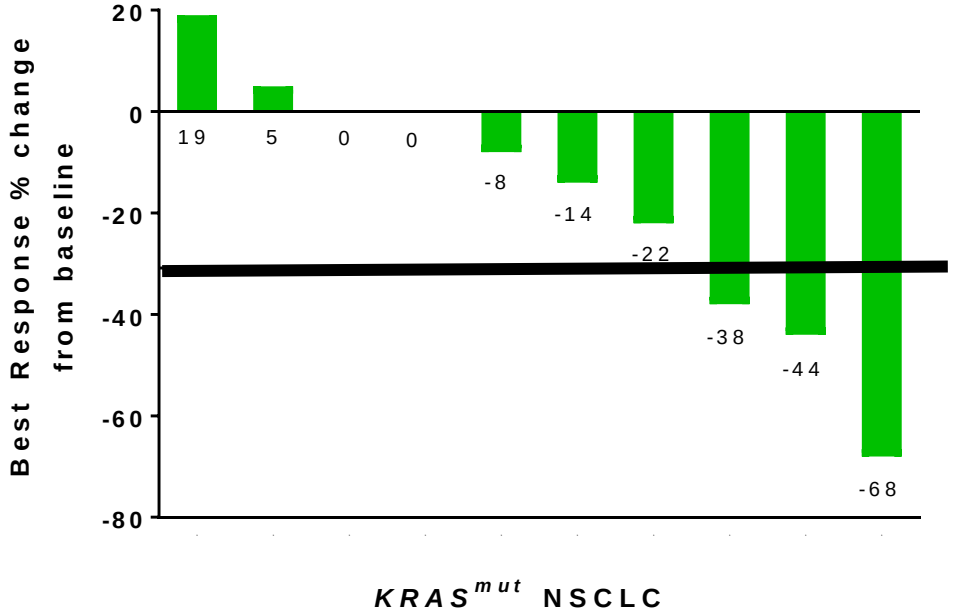


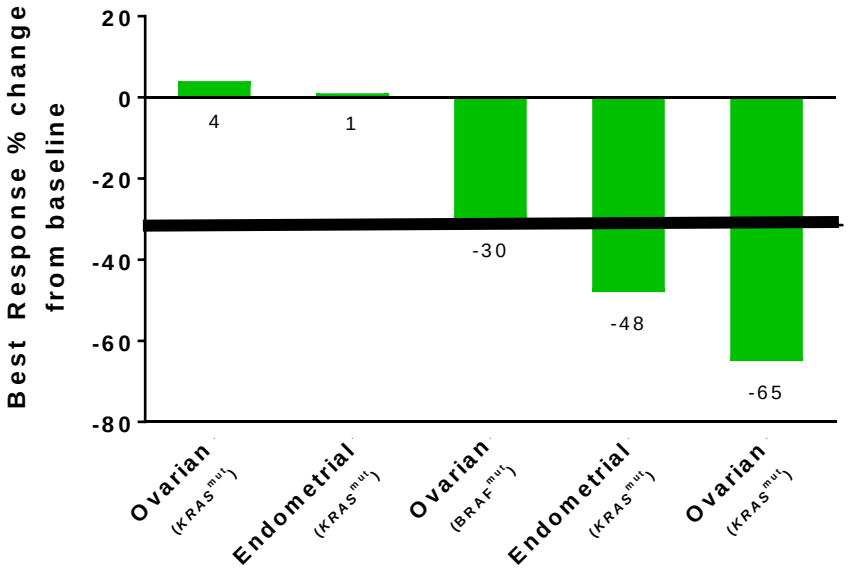
Ishii N Cancer Res 2013,73:4050-60
Lito P Cancer Cell 2014, 25:697-710

Drugs used in the combination- VS6766/CH5126766 (RAF-MEK inhibitor)

Clinical





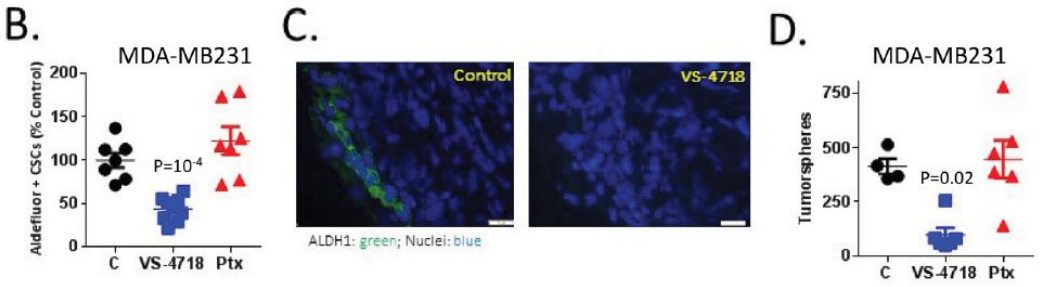


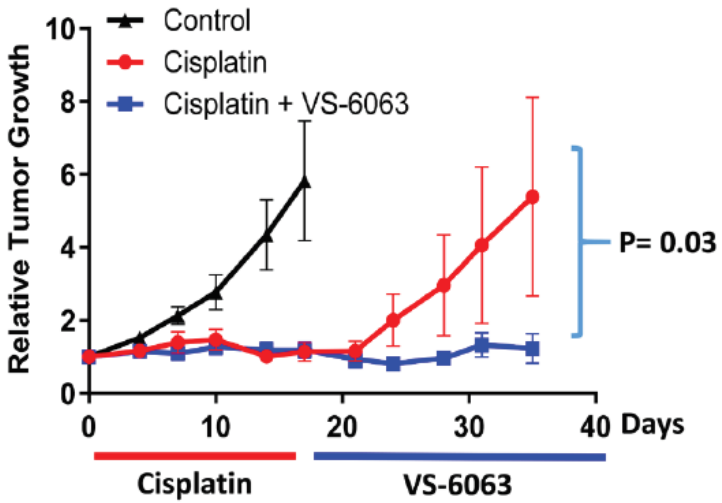
- Highly intermittent dosing based on PK modelling
- Interesting single agent activity in *KRAS/RAF* mutated cancers observed in biomarker enriched expansions

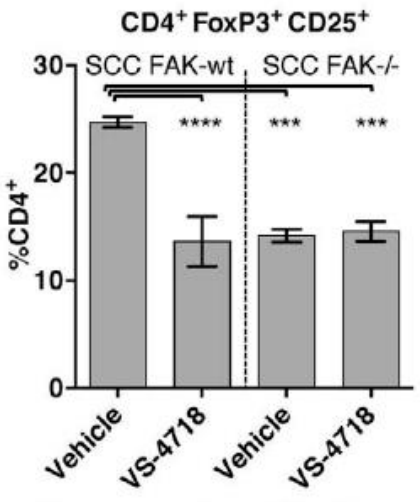
Banerji U Targeted anticancer Therapies (TAT) meeting 2019
In press Lancet Oncology 2020

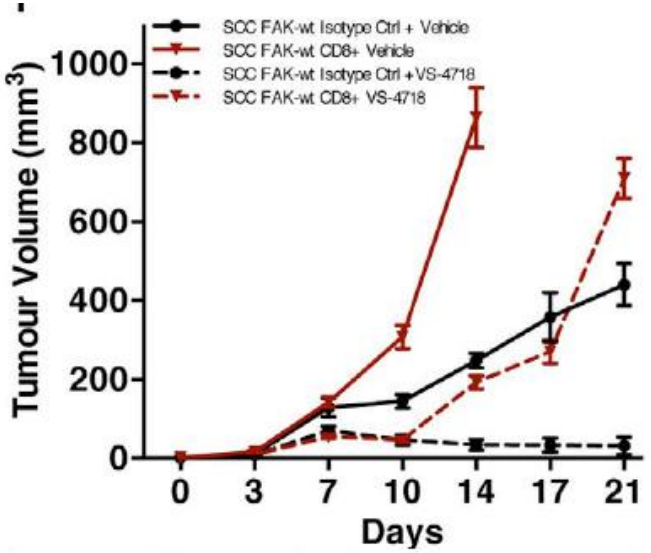
Drugs used in the combination – Defactinib/VS6063

Preclinical ..







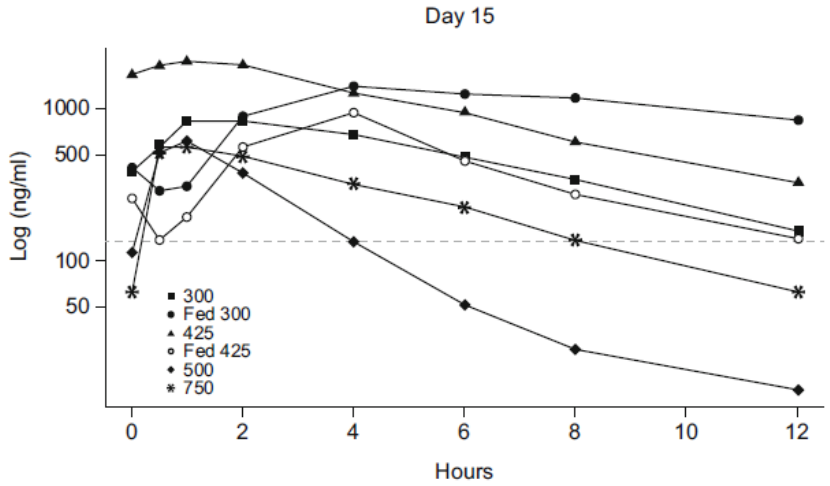


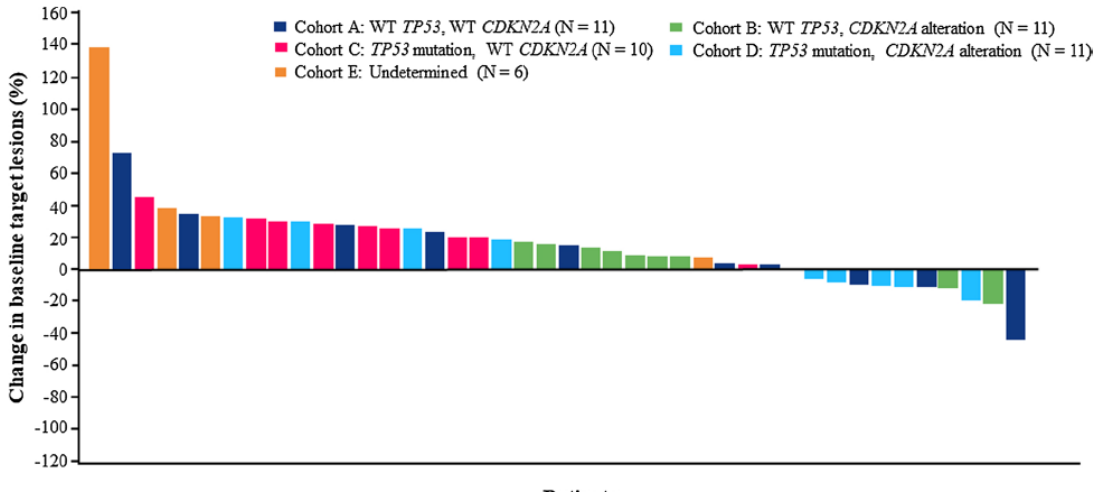
- Inhibition of FAK has effects across multiple cell types within the tumour including cancer cells, stromal cells and immune cells

Kholev VN Oncotarget 2017, 8:51733-51747
Serrels A Cell 2015,163:160-173

Drugs used in the combination – Defactinib/VS6063

Clinical

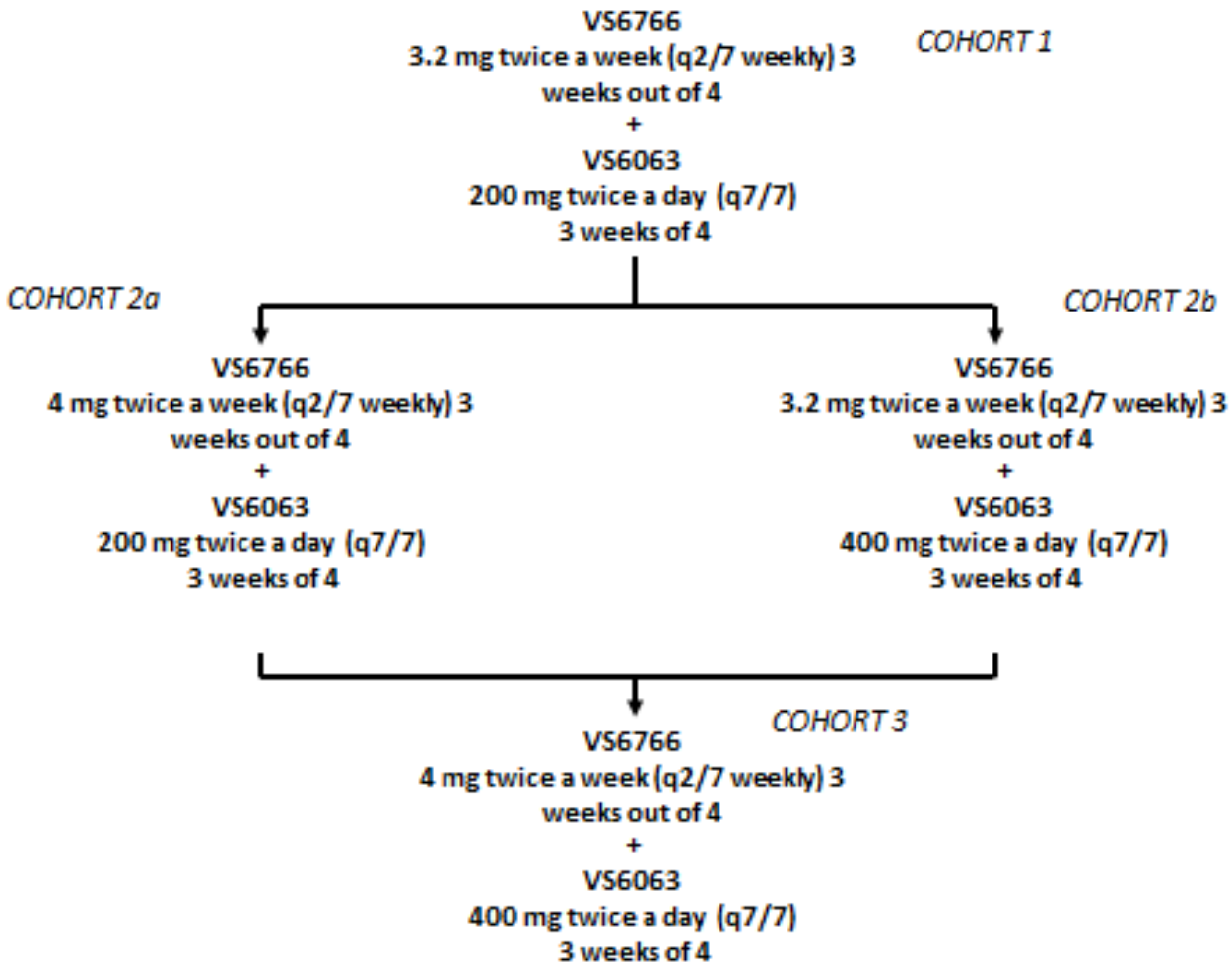




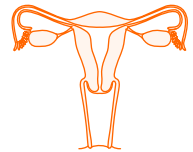
- Phase I clinical trial did not establish an MTD and drug levels were in the range that showed target engagement in preclinical models
- Well tolerated in BID dosing
- Trials as a single agent in *KRAS* mutated cancers and multiple combination studies are either complete or ongoing

Jones SF, Cancer Invest New Drugs 2015,33:1100-7
Gerber DE Lung Cancer 2020,19:60-67

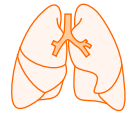
Design of Phase I Clinical Trial



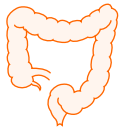
Current expansion cohorts



LGSOC (n= 20)

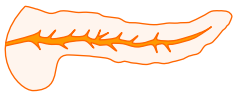


KRAS^{M} NSCLC (n=20)

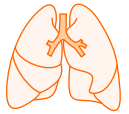


KRAS^{M} CRC (n=10)

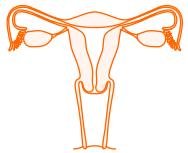
Planned expansion cohorts



PDAC (n= 10)



KRAS$^{M\ G12V}$ NSCLC (n=10)



RAS/RAF^{M} Endometrioid (n=10)

Toxicity Profile VS6766 + Defactinib

Adverse event details	Escalation						Total (n=12)
	RO 3.2mg VS 200mg (n=3)		RO 4mg VS 200mg (n=6)		RO 3.2mg VS 400mg (n=3)		
	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		6		3		11
CK elevation	2		2	1	1		6
Nausea	1		3		2		6
Hyperbilirubinemia	1	1	1	1	1		5
Diarrhoea	2		1		2		5
Visual disturbance			2		2		4
Vomiting	1		2				3
Paronychia	1		1		1		3
AST elevation			1		1		2
Fatigue			2				2
ALT elevation			1		1		2
Anaemia		1			1		2
Alopecia			2				2
Thrombocytopenia			2				2
Skin infection			1		1		2
Fever					1		1
Conjunctivitis	1						1
Mouth soreness			1				1
Face pain					1		1
Total:	11	2	28	2	18	0	61

- Recommended phase 2 dose is CH5126766 3.2 mg twice a week (Mon-Thu) + 200 mg of defactinib twice a day, both given 3 weeks out of 4 in 28 day cycles.
- No patients at the RP2D have had to discontinue treatment due to toxicity in the LGSOC arm

Pharmacokinetic Profile of the Combination of VS6766 + Defactinib

VS6766/ CH5126766 (RAF-MEK inhibitor)

Cohort	Dose (mg)	N	Subject	$AUC_{0\text{-}24h}$ (h*ng/mL)	C_{last} (ng/mL)	C_{max} (ng/mL)	T_{max} (h)
1	3.2 (with 200mg VS)	3	***Mean***	***6179***	***276***	***354***	***6.6***
			Range	3953	174	212	7.8
			CV%	32.1	31.6	30.4	68.0
2a	4 (with 200mg VS)	5	***Mean***	**5353**	**242**	**289**	**11.6**
			Range	2179	101	120	19.3
			CV%	15.8	18.6	16.0	62.6
2b	3.2 (with 400mg VS)	3	***FRA101-007***	***3302***	***229.0***	***229.0***	***24.3***

Defactinib (FAK inhibitor)

Cohort	Dose (mg)	Subject	N	AUClast (h*ng/mL)	Cmax (ng/mL)	Tmax (h)	Clast (ng/mL)	HL Lambda_z (h)	Cl_F obs (mL/h)
1	200 (with 3.2mg RO)	Median	3	1702	192	4.0	119	14	48372
		Range		4254	440	0.2	233	13	171050
		Geometric Mean		**2071**	**273**	**4.0**	**83**	**8**	**55450**
		CV% Geometric Mean		103	80	1.9	217	154	170
2a	200 (with 4mg RO)	Median	5	1871	295	3.9	132	8	69650
		Range		10768	1293	4.0	686	7	91030
		Geometric Mean		**2252**	**318**	**4.4**	**128**	**6**	**53465**
		CV% Geometric Mean		124	117	31.8	154	60	124
2b	400 (with 3.2mg RO)	Median	3	2695	365	4.2	112	4	127813
		Range		1723	225	7.4	40	4	49544
		Geometric Mean		**2807**	**360**	**2.5**	**107**	**4**	**114471**
		CV% Geometric Mean		31	32	273.6	20	63	25

- Pharmacokinetic parameters in the range of single agent studies at that dose
- Though not formally studied, no major drug-drug interaction as in previous MEK+FAK studies

Ruth Ruddle, Florence Raynaud DMPK group, ICR, UK

Mak, G BJC 2019, 120:978-981

Hypothesis testing of rationale of combining of VS6766 + Defactinib

Patient with LGSOC

Pre-treatment

Run-in dose VS6766 (RAF-MEKi)

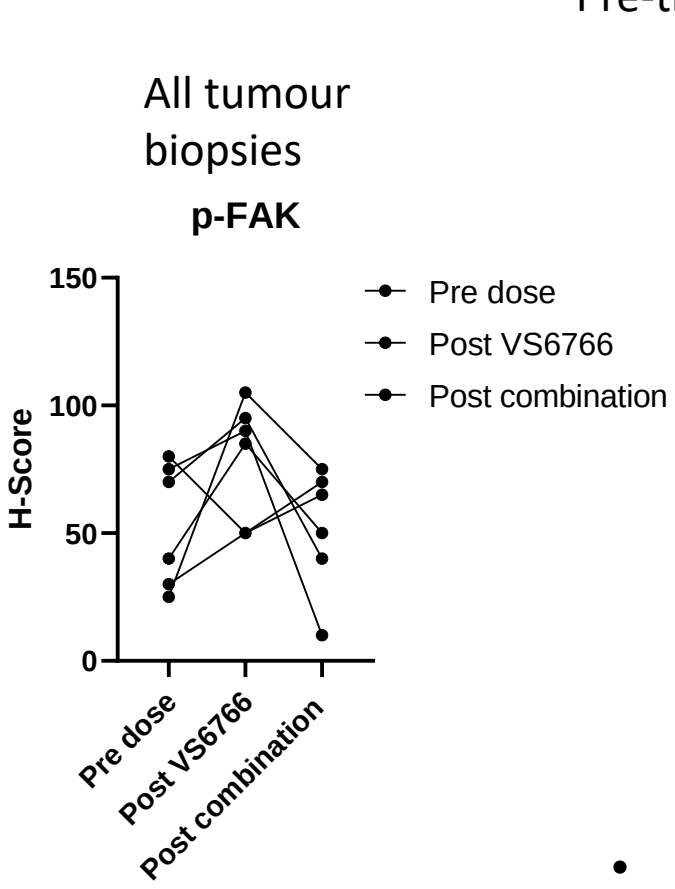
Post combination dose VS6766+Defactinib (RAF-MEKi+ FAKi)

Biopsy Day-28 to -7

Biopsy Day-7to -3

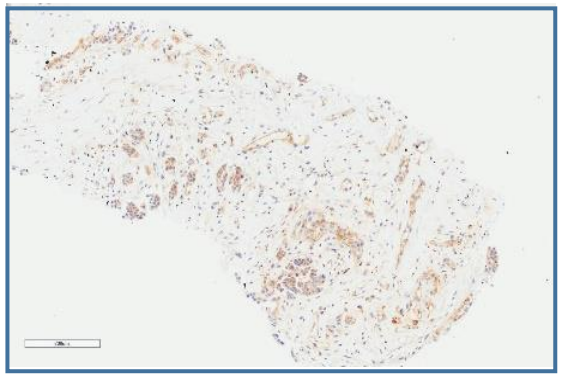
Biopsy Day 1-48 of combination

All tumour biopsies

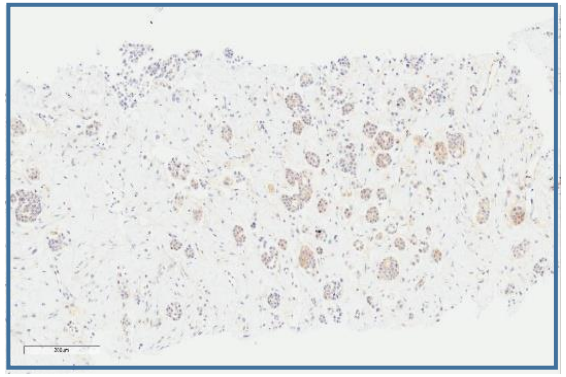


H score 40

H score 85



H score 50



- P-FAK levels increased in biopsies of multiple patients following dosing with VS6766 and it levels were lower once the combination was instituted

Ruth Riisnaes, Bora Gurel, Johann De Bono, Cancer Biomarker team ICR, UK

Hypothesis testing of rationale of combining of VS6766 + Defactinib

Patient with LGSOC

Pre-treatment

Run-in dose VS6766 (RAF-MEKi)

Post combination dose VS6766+Defactinib (RAF-MEKi+ FAKi)

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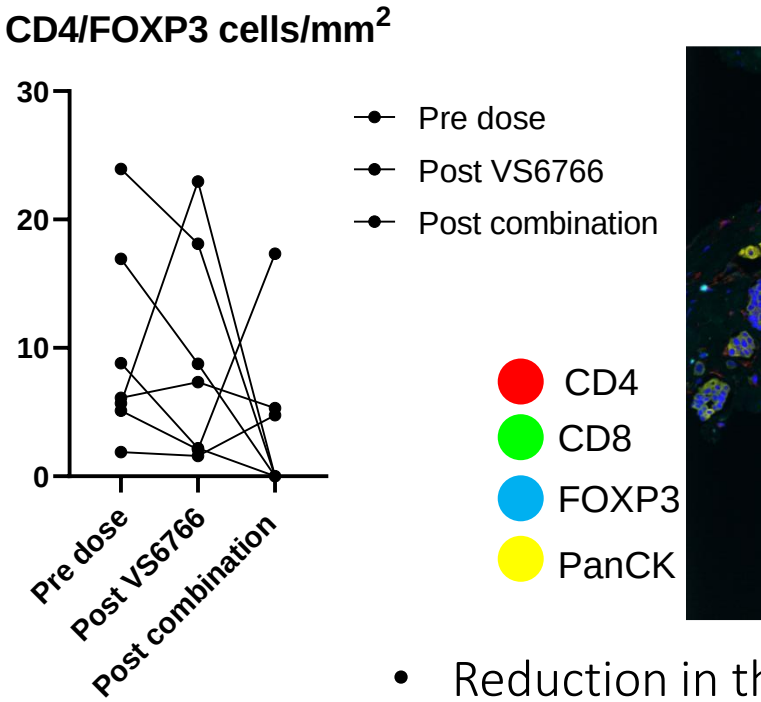
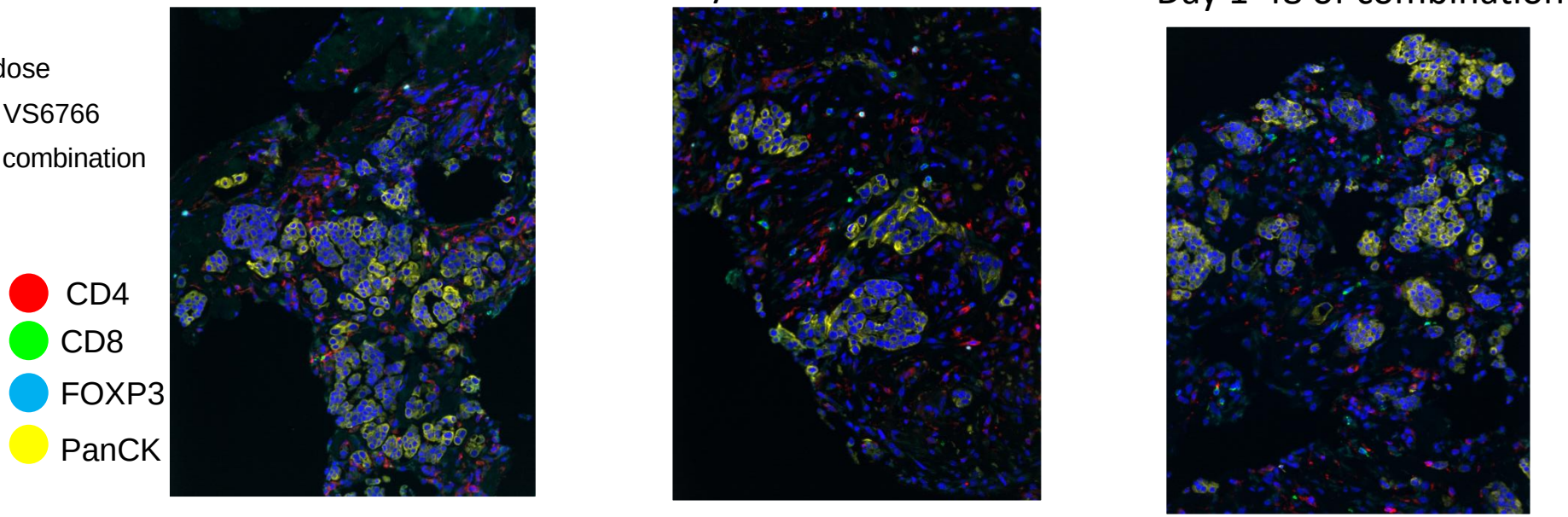
Biopsy Day-7to -3

Biopsy Day 1-48 of combination

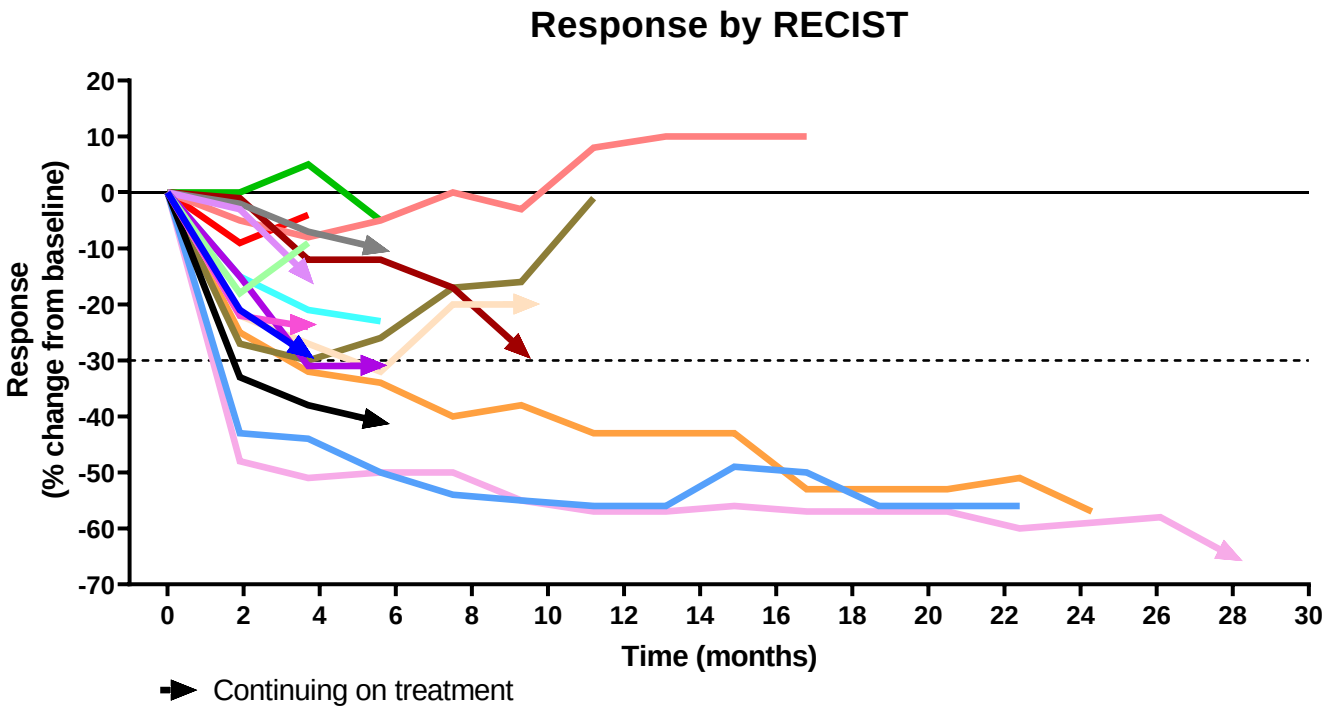


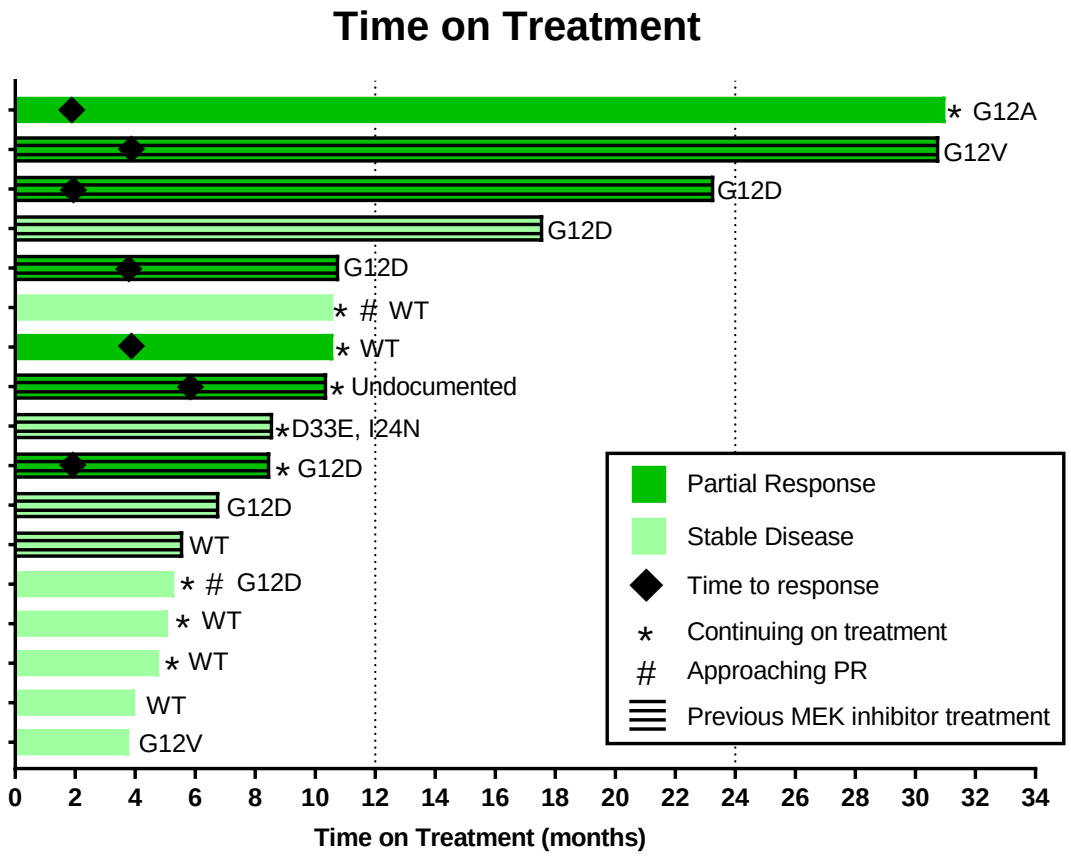


- Reduction in the number of CD4 $^{+}$FOXP3^{+} cells in the tumour seen on day 15, however numbers start decreasing even after a single dose of VS6766

Mateus Crespo, Bora Gurel, Johann De Bono, Cancer Biomarker team ICR, UK

Response and duration of response of patients with LGSOC on study

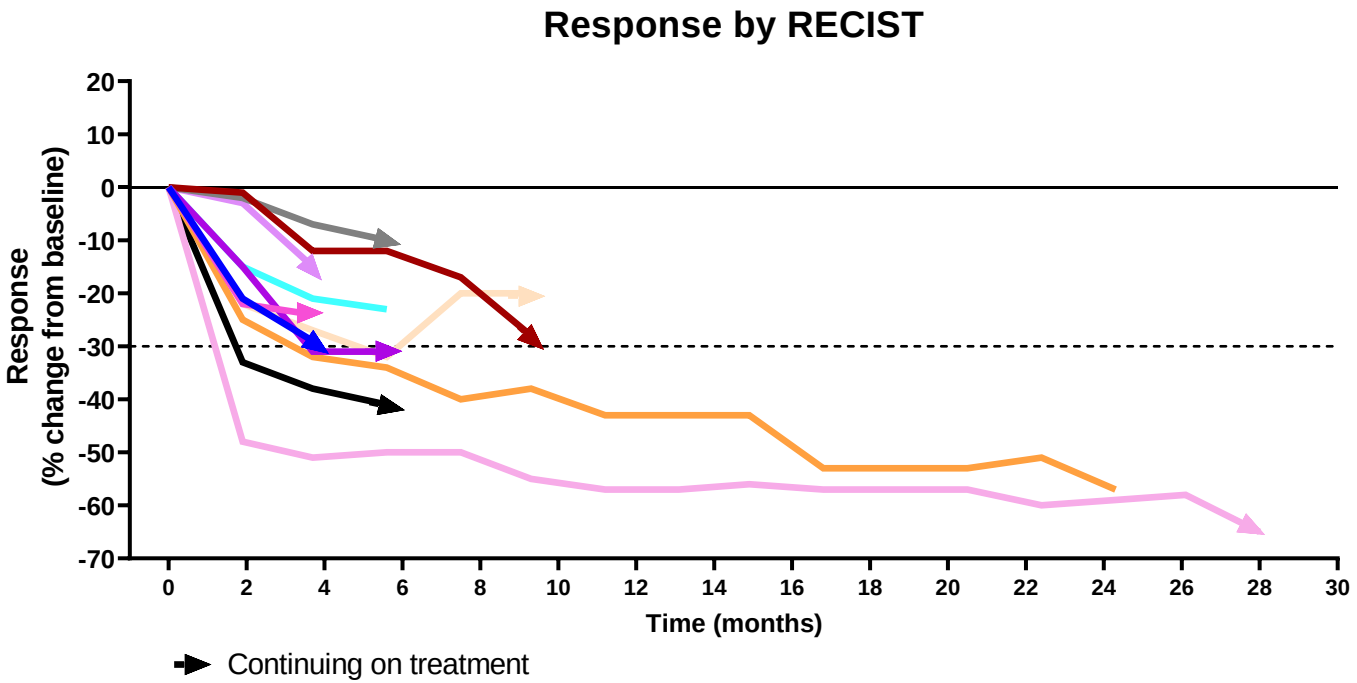


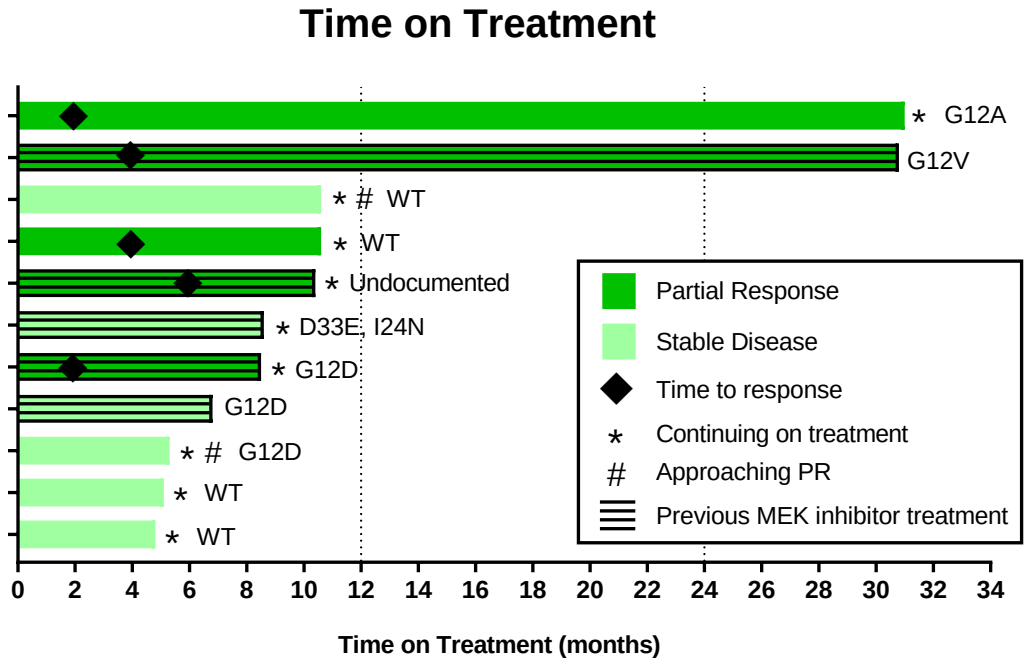


- Current ORR = 41% (7/17); data still maturing
- *KRAS*^{G12} mutations ORR = 56% (5/9); data still maturing
- 5/7 PRs in pts who had previous MEK inhibitors
- 2 pts on treatment for ≥ 2 years

Cut-off August 17, 2020

Response and duration of response of patients with LGSOC on study at RP2D



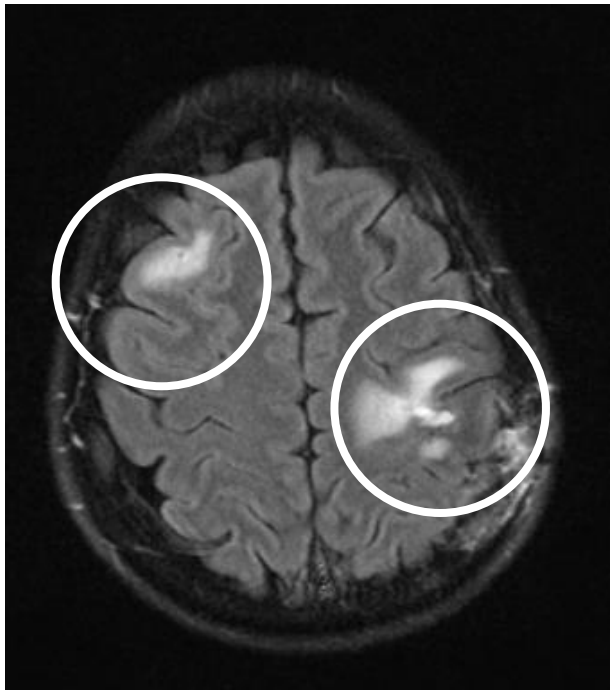


- Current overall ORR = 45% (5/11); data still maturing
- ORR in KRAS mt = 50% (3/6); data still maturing
- 9/11 (82%) still on study at RP2D
- 2 pts on treatment for 2 years

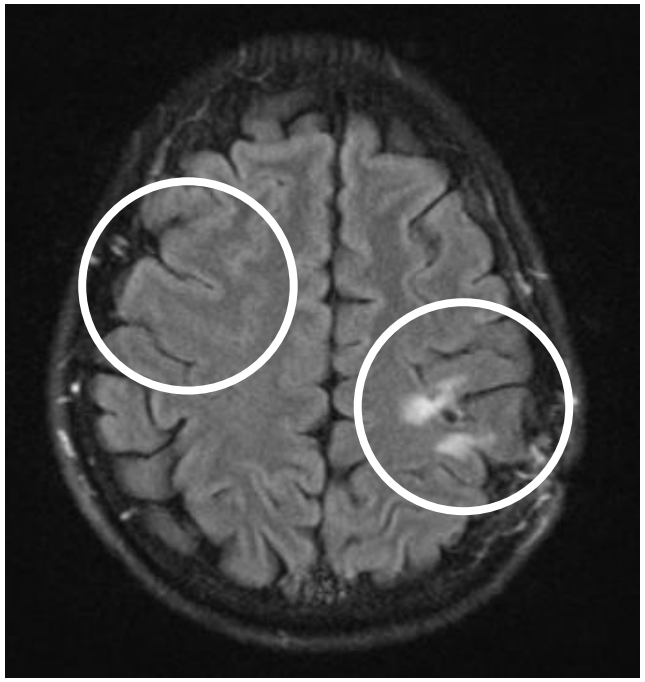
Cut-off August 17, 2020

Interesting response

Pre treatment



Post treatment



- 3 previous lines of chemotherapy
- 1 line of hormonal therapy
- 2 clinical trials of MEK+PI3K inhibitors
- Stereotactic radiotherapy and neurosurgery
- Responded to VS6766+Defactinib and had been on study for more than 2 years

Comparison of results from multiple trials of MEK inhibitors in LGSOC

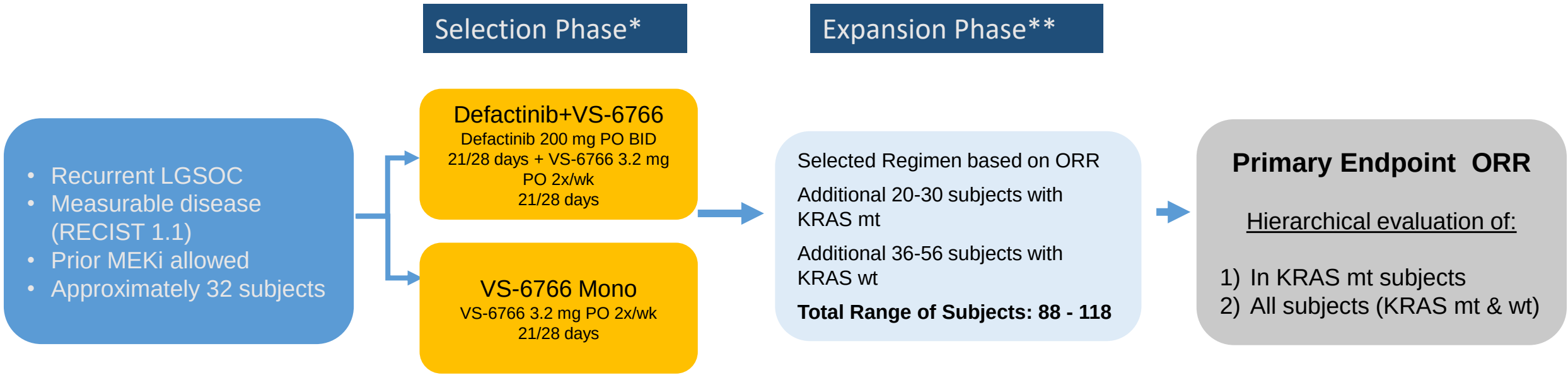
	Response Rate	Response Rate in *KRAS*^{M} tumours	Progression free survival	Overall survival	Randomised
Selumetinib[1]	15%	15%	11 months	2 year survival 55%, median OS not reached	No
Binimetinib[2]	**16%** Vs 13%	**44%** Vs 19%	**9.1** Vs 10.6 months	**34.6** Vs 34.2 months	Yes
Trametinib[3]	**26.2** Vs 6.2		**13** Vs 7.2 months	**37** Vs 29.2 months	Yes
VS6766 + Defactinib RP2D	45%	50%	Data immature 82% still on study	Not studied	No

1. Farley J Lancet Oncol 2013, 14:134-40
2. Monk BJ JCO 2020 E-pub
3. Gershenson DM ESMO 2019

Key questions for this this study

- Are combinations of targeted agents necessary?
  - May increase ORR and PFS/Survival
  - May be important in treating patients who have already been treated with MEK inhibitors
- Is the combination effective in only *KRAS* mutated LGSOC?
  - Will need larger studies that treat patient with both *KRAS*^{M} and *KRAS*^{WT} LGSOC
- Both questions being answered in an innovative adaptive trial design in patients with LGSOC run by Verastem Oncology

Planned study for VS6766+Defactinib in LGSOC



*Selection Phase – KRAS mt only

**Expansion Phase – final sample size to be adjusted based on adaptive design

Conclusions

- The combination of VS6766 and Defactinib is tolerable
- On preliminary analysis, no major PK interactions and proof of concept of target inhibition and immunological effects
- Durable responses seen in patients heavily pre-treated LGSOC including patients treated with MEK inhibitors
- The combination should be urgently tested in randomized registration studies in LGSOC as it an area of unmet need

Acknowledgements

Patients and families

- Investigator initiated trials team at The Institute of Cancer Research
- Drug Development Unit and Gynaecological Oncology Unit at The Institute of Cancer Research and The Royal Marsden Hospital , London UK
- The phase I unit Christie Hospital Manchester, UK
- Cancer Biomarkers team, The Institute of Cancer Research, London UK
- The Drug Metabolism PK group, The Institute of Cancer Research UK
- The Clinical Pharmacology-Adaptive Therapy Group, The Institute of Cancer Research UK

ICR The Institute of Cancer Research

The ROYAL MARSDEN NHS Foundation Trust

The Christie NHS NHS Foundation Trust

NHS National Institute for Health Research

ecmc

CANCER RESEARCH UK

Verastem Oncology