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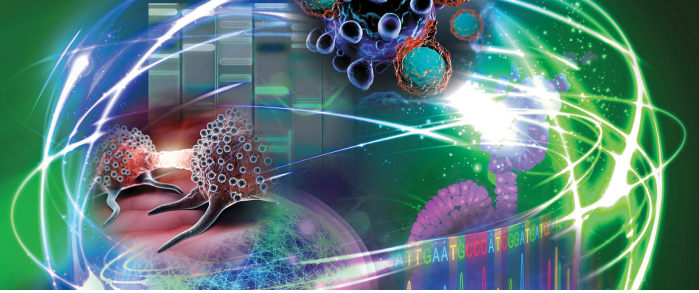

# FRAME: A phase I trial of the combination of the dual RAF-MEK inhibitor VS-6766 and the FAK inhibitor Defactinib; Evaluation of efficacy in KRAS mutated NSCLC.

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The University of Manchester and The Christie NHS Foundation Trust, Manchester, UK,
Drug Development Unit, Royal Marsden NHS Foundation and the Institute of Cancer Research, London UK

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

# Disclosure Information



**Dr Matthew Krebs**

I have the following financial relationships to disclose:
Consultant for: Achilles Therapeutics, Bayer, Janssen, OM Pharma, Roche, Seattle Genetics
Speaker's Bureau for: Janssen, Roche
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Travel expenses: BergenBio, Immutep
Stockholder in: nil to disclose

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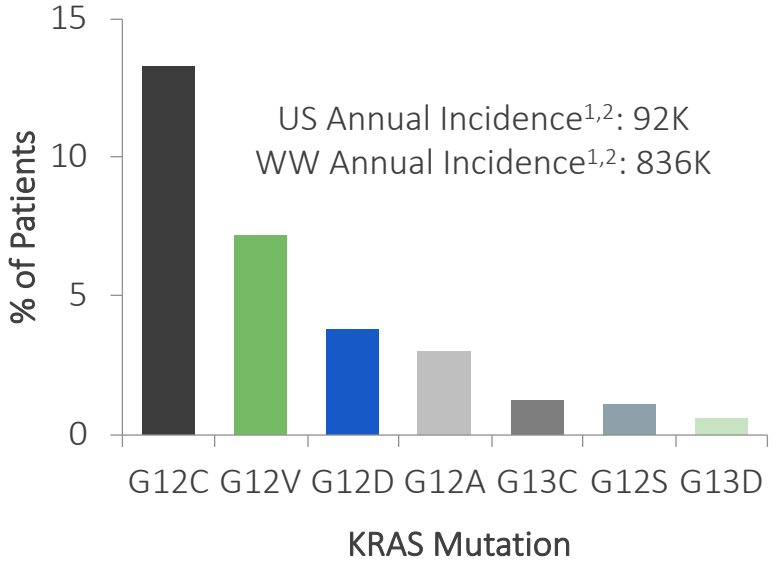
I will discuss the following off label use and/or investigational use in my presentation: VS-6766 and Defactinib

# High Unmet Need in Refractory *KRAS*$^{M}$ NSCLC Adenocarcinoma



KRAS mutations represent 25% of lung adenocarcinoma (EGFR 17%, ALK 7%)[4]

## NSCLC Adenocarcinoma[3]




[1] Globocan, 2018

[2] https://www.ncbi.nlm.nih.gov/books/NBK519578/

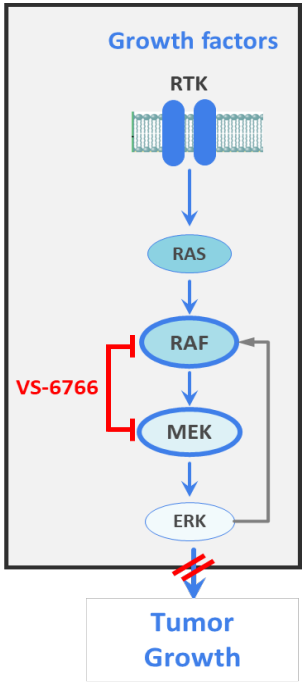
[3] TCGA PanCancer Atlas (cBioPortal analysis)

[4] www.thelancet.com Vol 389 January 21, 2017

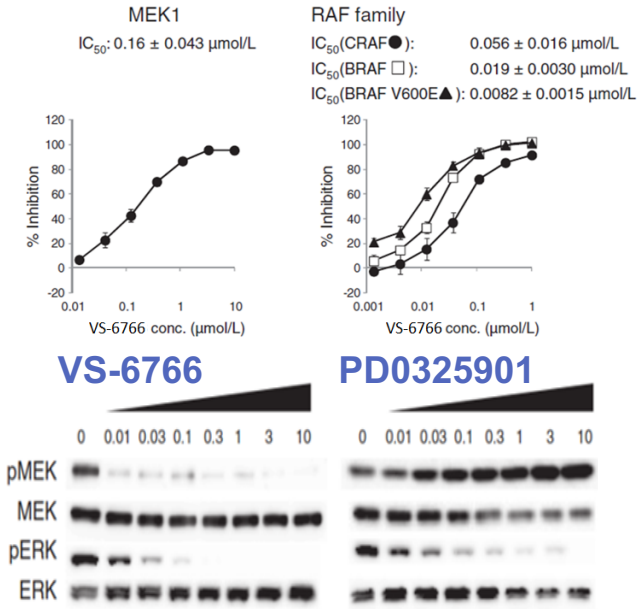
[5] Adapted from NCCN Non-small cell lung cancer guidelines Version 3.2020

# Mechanism of action of VS-6766





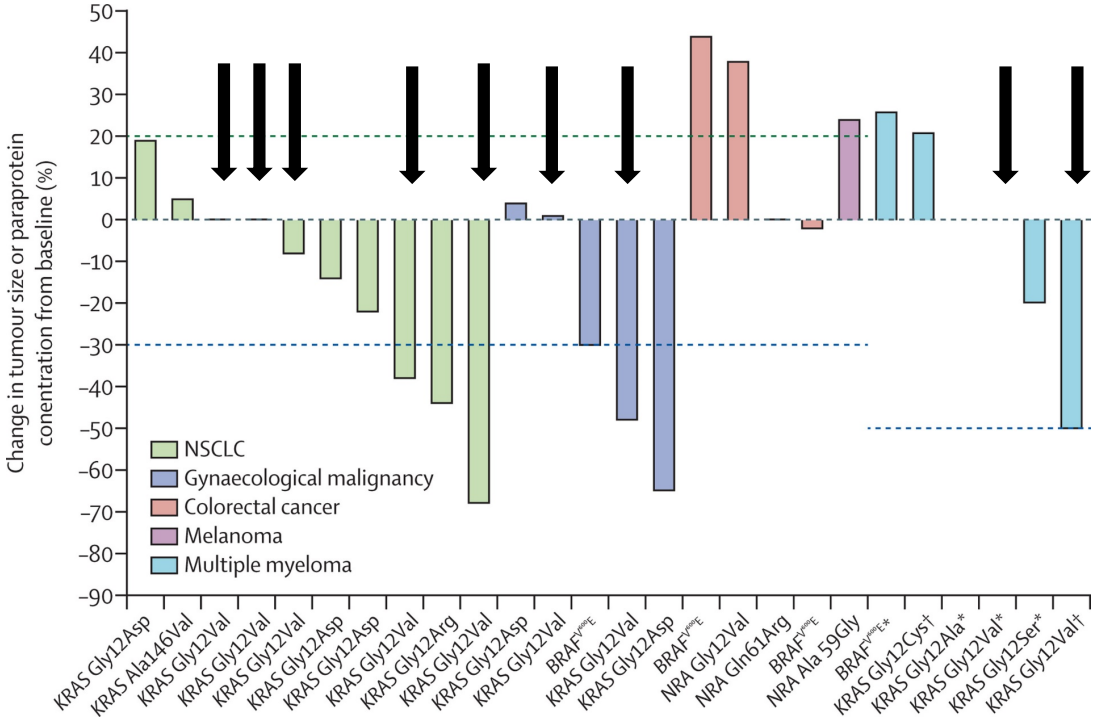

- VS-6766 inhibits both MEK & RAF kinase activities
- MEK inhibitors paradoxically induce MEK phosphorylation (pMEK) by relieving ERK-dependent feedback inhibition of RAF
- By inhibiting RAF phosphorylation of MEK,VS-6766 has advantage of not inducing pMEK
- VS-6766 inhibits ERK signaling more completely; may confer enhanced therapeutic activity




Reference: Ishii et al., *Cancer Res*, 2013; Lito et al., *Cancer Cell*, 2014; Blasco, R. B. et al. *Cancer Cell* (2011); Sanclemente, M. et al. *Cancer Cell* (2018))

# Single Agent Activity of VS-6766



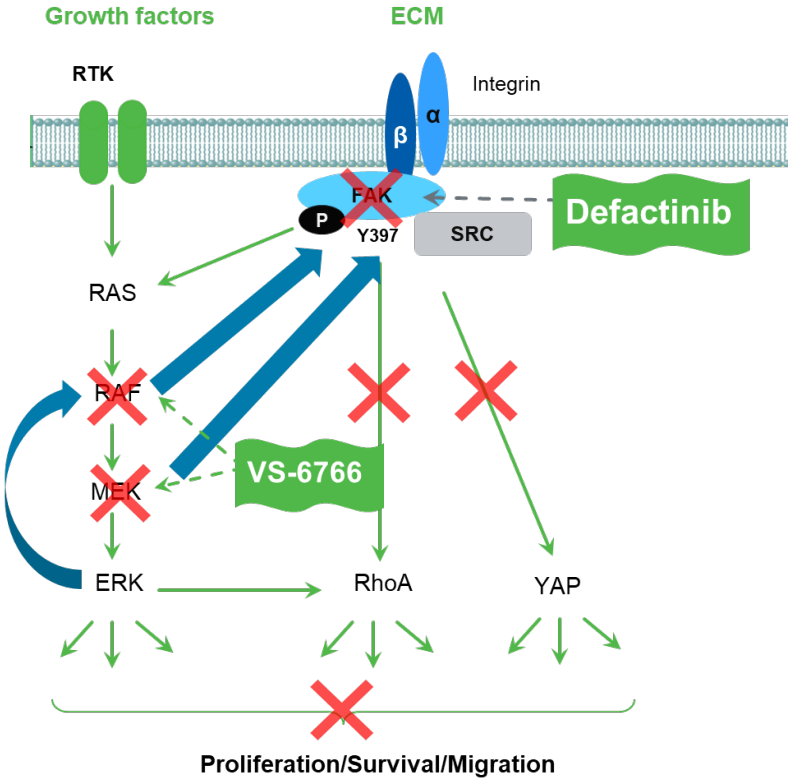



Single agent activity seen across a spectrum of *KRAS* mutant tumours including *KRAS* $^{G12V}$ NSCLC

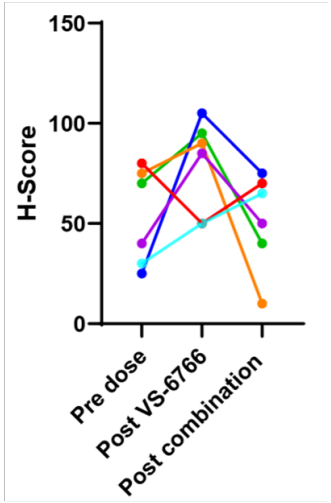
*Guo et al Lancet Oncology 2020, 21:1478-1488*

# Rationale for Combination of VS-6766 with a FAK Inhibitor



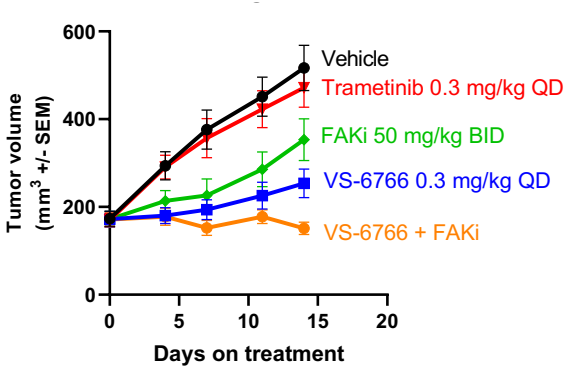



VS-6766 induces pFAK in Patient's Tumors




U. Banerji, AACR 2020

NSCLC cancer model
H358 KRAS (G12C) mutant




Pachter et al., RAS meeting 2020

# FRAME: Investigator-Sponsored Basket Trial of VS-6766 + Defactinib in *KRAS*$^{M}$ Cancers

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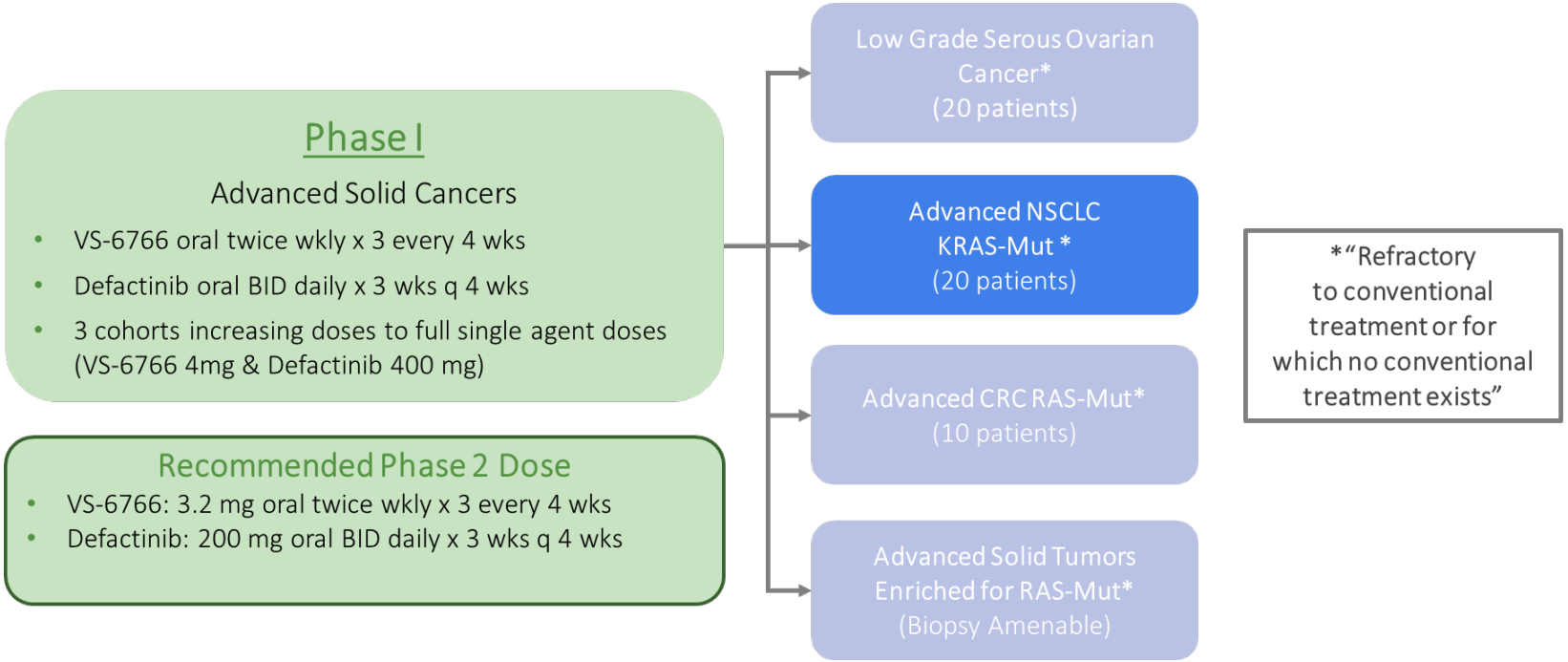



- 3+3 dose escalation trial design followed by tumour-specific or molecularly stratified dose expansion cohorts
- Primary endpoint: determine the dose at which no more than one patient out of up to six patients experience a highly probable or probable drug-related dose limiting toxicity

# Demographics and Toxicity seen in patients with *KRAS*$^{M}$ NSCLC



## Patient demographics

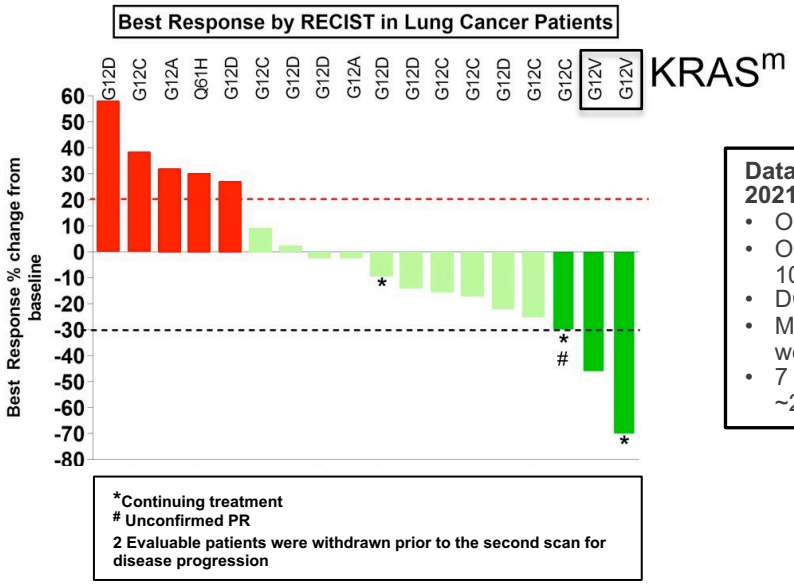
| All NSCLC Patients (n=20) | | |
|---|---|---|
| **Median Age (range)** | | **62 (22 - 73)** |
| **Gender** | Male<br>Female | **8**<br>**12** |
| **Tumor types** | NSCLC | **20** |
| **KRAS Mutation** | *G12D*<br>*G12C*<br>*G12A*<br>*G12V*<br>*Q61H* | **8**<br>**7**<br>**2**<br>**2**<br>**1** |
| **Prior treatments** | All lines: median (range) | **3 (1 - 5)** |
| **ECOG PS** | PS 0<br>PS 1 | **2**<br>**18** |

## Treatment related adverse events

| Adverse event details | NSCLC | | | | | | Total (n=20) |
|---|---|---|---|---|---|---|---|
| | Escalation | | Expansion | | | | |
| | RO 4mg VS 200mg (n=1) | | RO 4mg VS 200mg (n=10) | | RO 3.2mg VS 200mg (n=9) | | |
| | 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 | 1 | | 7 | 2 | 8 | 1 | 19 |
| CK elevation | | | 4 | 2 | 4 | | 10 |
| Glossitis/Mucositis/Mouth ulcers | | | 5 | 1 | 4 | | 10 |
| AST rise | | | 7 | | 2 | | 9 |
| Peripheral oedema | | | 5 | | 3 | | 8 |
| Visual distrubance | 1 | | 4 | | 3 | | 8 |
| Fatigue | | | 4 | | 2 | 1 | 7 |
| ALT rise | 1 | | 5 | | | | 6 |
| Diarrhoea | 1 | | 3 | | 2 | | 6 |
| Dry skin/scalp | | | 3 | | 2 | | 5 |
| Hyperbilirubinemia | | | 5 | | | | 5 |
| Nausea | 1 | | 2 | | 1 | | 4 |
| Pruritis | | | 1 | 1 | 2 | | 4 |
| Thrombocytopenia | | | 2 | | 2 | | 4 |
| Vomiting | | | 2 | | 2 | | 4 |
| Neutropenia | | | 1 | | 2 | | 3 |

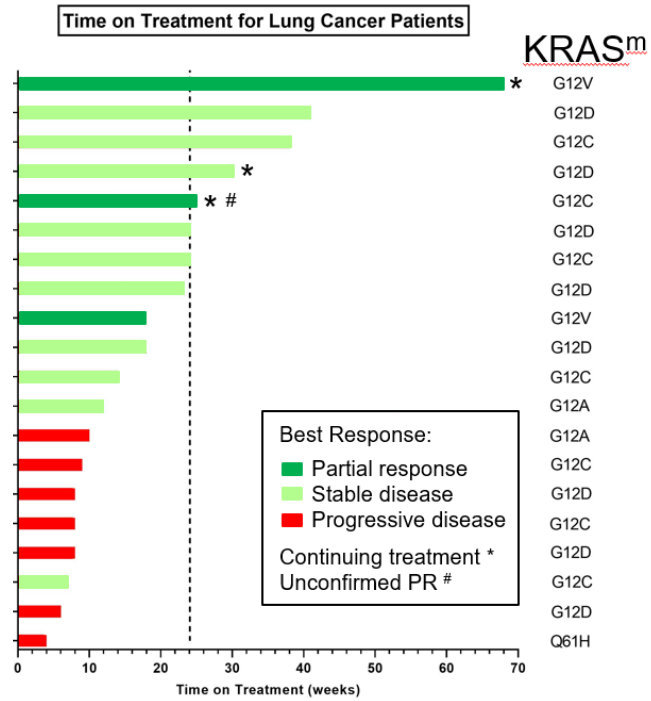
# Clinical activity in *KRAS*$^{M}$ NSCLC






**Data cut off March 5, 2021**

- ORR = 15% (3/20)
- ORR in G12V mt = 100% (2/2)
- DCR = 65% (13/20)
- Median PFS = 16 weeks
- 7 pts on treatment ≥ ~24 weeks



# Response in a patient with *KRAS*$^{G12V}$ NSCLC

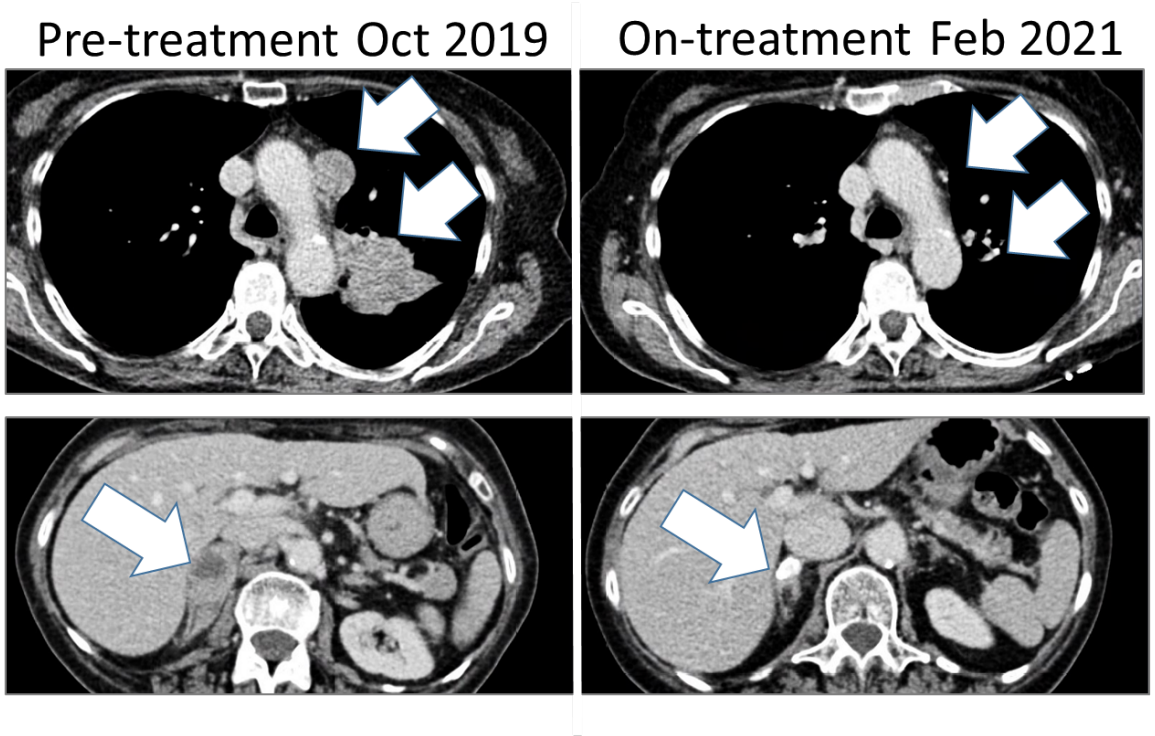


72F - Diagnosed with NSCLC May 2019

June 2019- Sept 2019 treated with first line Carboplatin + Pemetrexed + Pembrolizumab

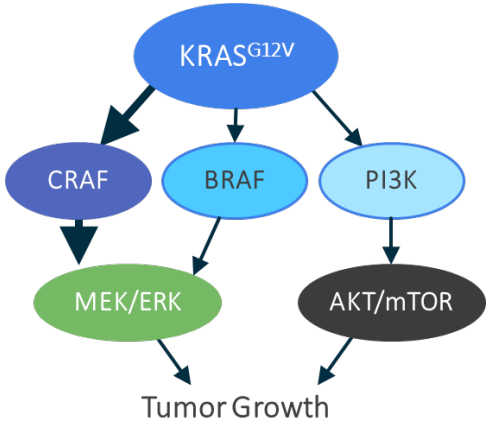
Oct 2019- Progression, palliative RT to right hip

Nov 2019- To present on treatment on FRAME study VS-6766 + Defactinib



# Importance of CRAF in KRAS signaling





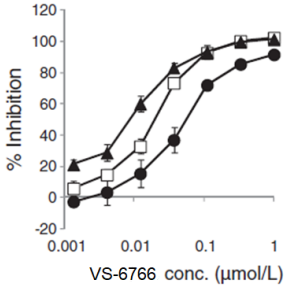

- KRAS G12V signals mainly through RAF/MEK in contrast to other variants, such as KRAS G12D, which signal more through PI3K/AKT
- KRAS G12V NSCLC models are especially dependent on CRAF, a target of VS-6766

RAF family

$IC_{50}$(CRAF●): 0.056 ± 0.016 µmol/L

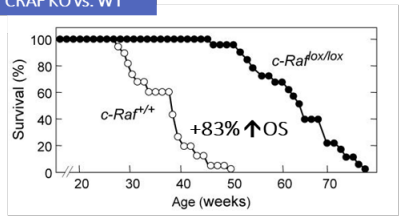
$IC_{50}$(BRAF □): 0.019 ± 0.0030 µmol/L

$IC_{50}$(BRAF V600E▲): 0.0082 ± 0.0015 µmol/L

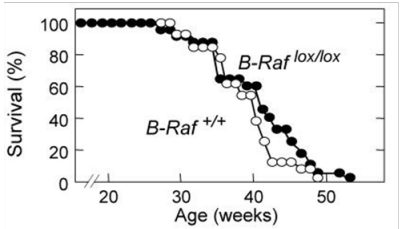



CRAF Drives KRAS$^{G12V}$ NSCLC[1,3]

CRAF KO vs. WT




BRAF KO vs. WT




CRAF, but not BRAF, ablation improves survival of mice with KRAS G12V induced lung cancer in vivo

Source: Ishii et al. *Cancer Res* (2013), Blasco, R. B. et al. *Cancer Cell* (2011), Lito, P. et al. *Cancer Cell* (2014), Sanclemente, M. et al. *Cancer Cell* (2018)

# Summary & Conclusions



- The combination of VS-6766 (RAF/MEKi) + defactinib (FAKi) with a novel, intermittent schedule exhibits a manageable safety profile, with no patients discontinuing for adverse events to date
- VS-6766 as monotherapy and in combination with defactinib shows confirmed partial responses in NSCLC especially in patients with *KRAS* G12V mutation
- Based on the premise of VS-6766 + defactinib in *KRAS* G12V NSCLC, a cohort (n=10) of patients with *KRAS* G12V NSCLC has been added to the FRAME study
- Additionally, a registration-directed clinical study in KRAS G12V NSCLC has been initiated (NCT04620330)

# Acknowledgements

Participating patients and their families.

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Drug Development Unit ICR/RMH.

Experimental Cancer Medicine Team, The Christie NHS Foundation Trust.

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