Verastem Oncology

# FAK and RAF/MEK Program Targeting KRAS Mutant Cancers

Investor Presentation - January 8, 2020

# Safe Harbor Statement



This presentation includes forward-looking statements about, among other things, Verastem Oncology's products and product candidates, including the performance and potential benefits of Verastem Oncology products and product candidates, and the potential success and safety profile of certain product combinations, that are subject to substantial risks and uncertainties that could cause actual results to differ materially from those expressed or implied by such statements.

Additional information regarding these factors can be found in Verastem's Annual Report on Form 10-K for the fiscal year ended December 31, 2018 and in any subsequent filings with the SEC, including in the sections thereof captioned "Risk Factors" and "Forward-Looking Information and Factors that May Affect Future Results", as well as in our subsequent reports on Form 8-K, all of which are filed with the U.S. Securities and Exchange Commission (SEC) and available at www.sec.gov and www.verastem.com.

The forward-looking statements in this presentation speak only as of the original date of this presentation, and we undertake no obligation to update or revise any of these statements.

# Speakers



## Science

**Udai Banerji,**
**MBBS, MD, DNB, PhD, FRCP**
Lead Investigator

Professor Udai Banerji is the deputy head of the Drug Development Unit where he is involved in running the portfolio of more than 40 Phase I trials. He plays a key role bridging pre-clinical and clinical drug discovery designing and conducting phase I studies.

In addition to clinical trials, Professor Banerji leads the Clinical Pharmacodynamics Biomarker Group and the Clinical Pharmacology – Adaptive Therapy groups at The Institute of Cancer Research. His laboratory interests include anticancer drug resistance and pharmacological aspects of cancer evolution.

Professor Banerji holds a PhD from The Institute of Cancer Research, and completed his medical oncology training at The Royal Marsden Hospital.

## Corporate VSTM

**Brian Stuglik**
CEO

**Dan Paterson**
COO

**Rob Gagnon**
CFO

**Jon Pachter**
CSO

# Verastem Oncology

## Corporate Overview

Novel small molecule kinase inhibitors targeting malignant cells both directly and through modulation of the tumor microenvironment

- **NASDAQ:** VSTM
- **Headquarters:** Needham, MA
- **Incorporated:** 2010

## Products

Copiktra® (duvelisib) 15mg | 25mg capsules

- The first-approved oral inhibitor of PI3K-δ and PI3K-γ
- Exclusively marketed in the US by Verastem Oncology
- Partnered in Japan, China, Russia/CIS, Turkey, Middle East, & Africa

**Full prescribing information, including BOXED WARNING and Medication Guide, is available at www.COPIKTRA.com**

## Investigational Research & Pipeline

### Duvelisib Program

- Ongoing clinical expansion in PTCL (FDA Fast Track Designation)
- Ongoing clinical investigation as monotherapy and in combination in multiple hematologic malignancies
- I-O Combination in Solid Tumors

### Defactinib Program

- Investigational oral FAK inhibitor
- Phase 1/2 FAK + RAF/MEK Combination for KRAS Mutant Cancers
- Studying in I-O Combinations
- Orphan Designation: Ovarian & mesothelioma in the US & EU

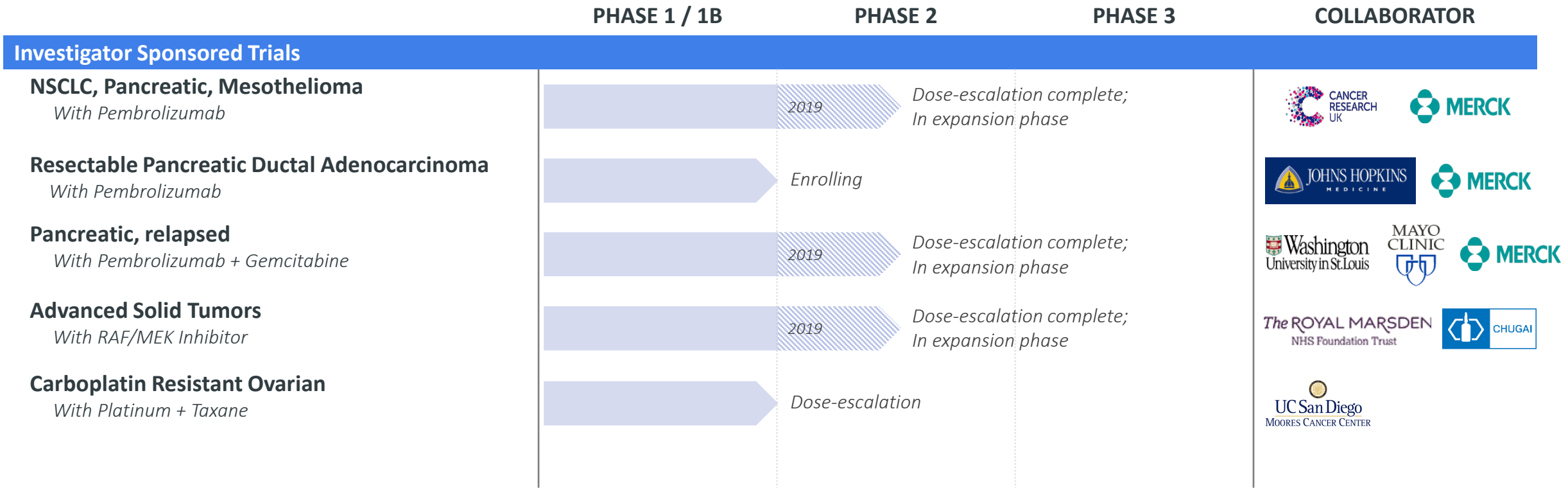
# Agenda



- Overview of Licensing Agreement with Chugai
- KRAS Overview
- FAK Overview
- RAF/MEK Overview
- FAK & RAF/MEK Combination
- Q&A

# Defactinib Pipeline – FAK Inhibitor






These studies are investigating treatments or outcomes that have not received approval from a Health Authority. The information presented is not intended to convey conclusions of safety or efficacy. There is no guarantee that the outcome of these studies will result in approval by a Health Authority.

# Overview of Licensing Agreement



Verastem Oncology  CHUGAI

- Verastem acquires worldwide development and commercialization rights to the RAF/MEK inhibitor CH5126766 (CKI27) from Chugai
- Verastem to make an upfront payment of $3.0M and pay royalties to Chugai

# High Unmet Need in RAS/RAF/MEK/ERK-Driven Cancers



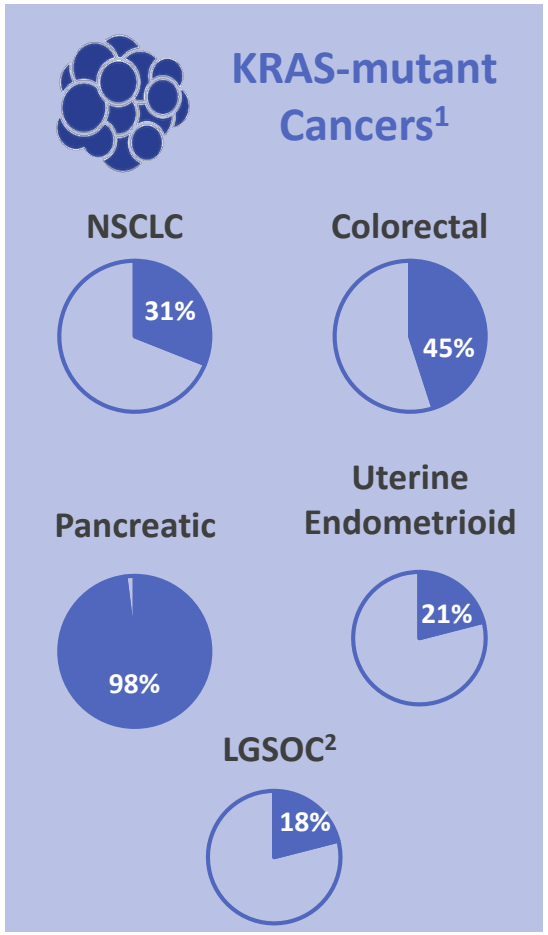
- 30 percent of all human cancers are driven by mutations of the RAS family of genes
- Patients with mutations of the RAS family have an overall worse prognosis
- Multiple approaches (direct targeting, blocking downstream signal processing, identify new targets that oncogenic RAS proteins depend on for their survival) have resulted in modest progress with a limited number of approved therapies
- Single agent therapies (e.g. MEK inhibitors) associated with the development of resistance
- Tolerable combination regimens with MEK inhibitors have been challenging

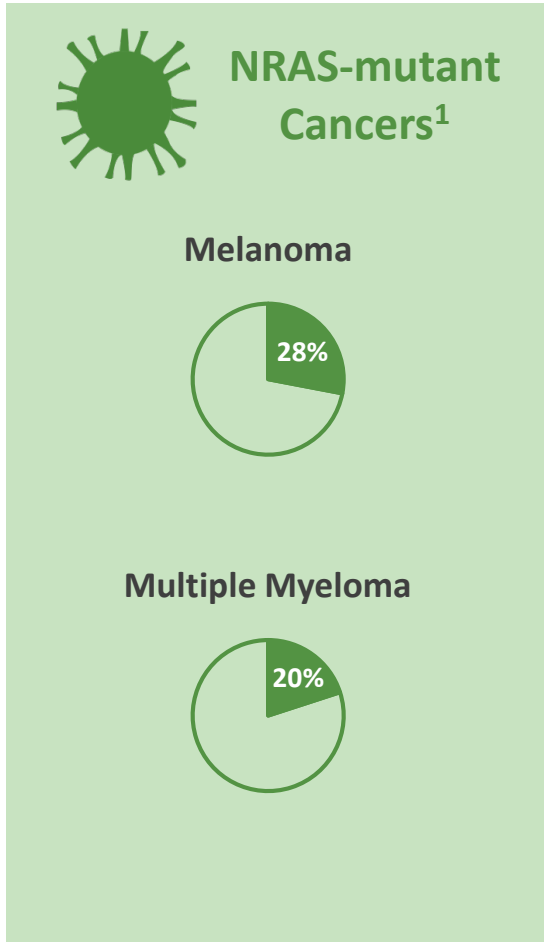
**References:**
McCormick F Clin Cancer Res 15April2015
Adderley H et al. EBioMedicine 01Mar2019
Papke B et al. Science 17Mar2017
Ryan M et al. Nature Reviews Clinical Oncology 01Oct2018
NIH cancer.gov/research/key-initiatives/ras

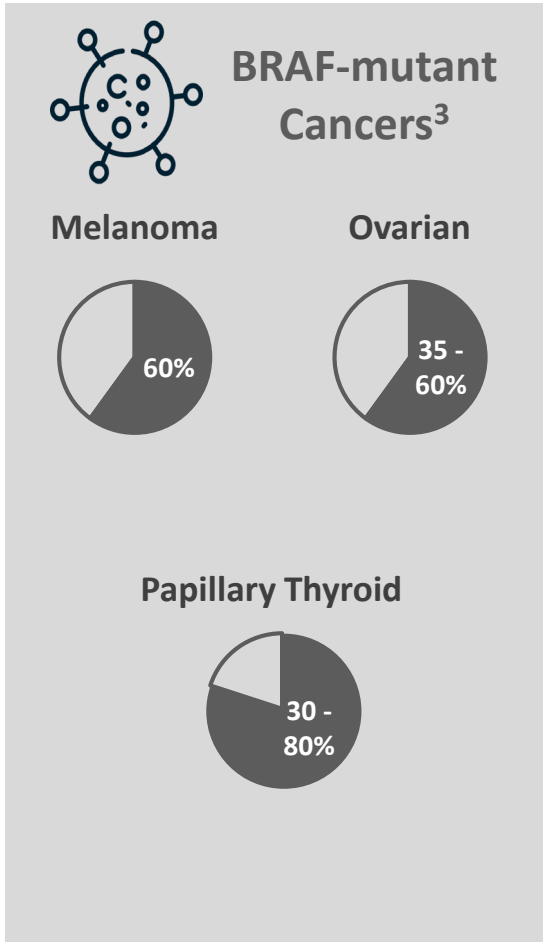
# The Importance of RAS Pathway in Human Cancers

## *Common Mutations in Many Large Cancer Types*






Other cancers driven by MEK-ERK pathway activation

**References:**

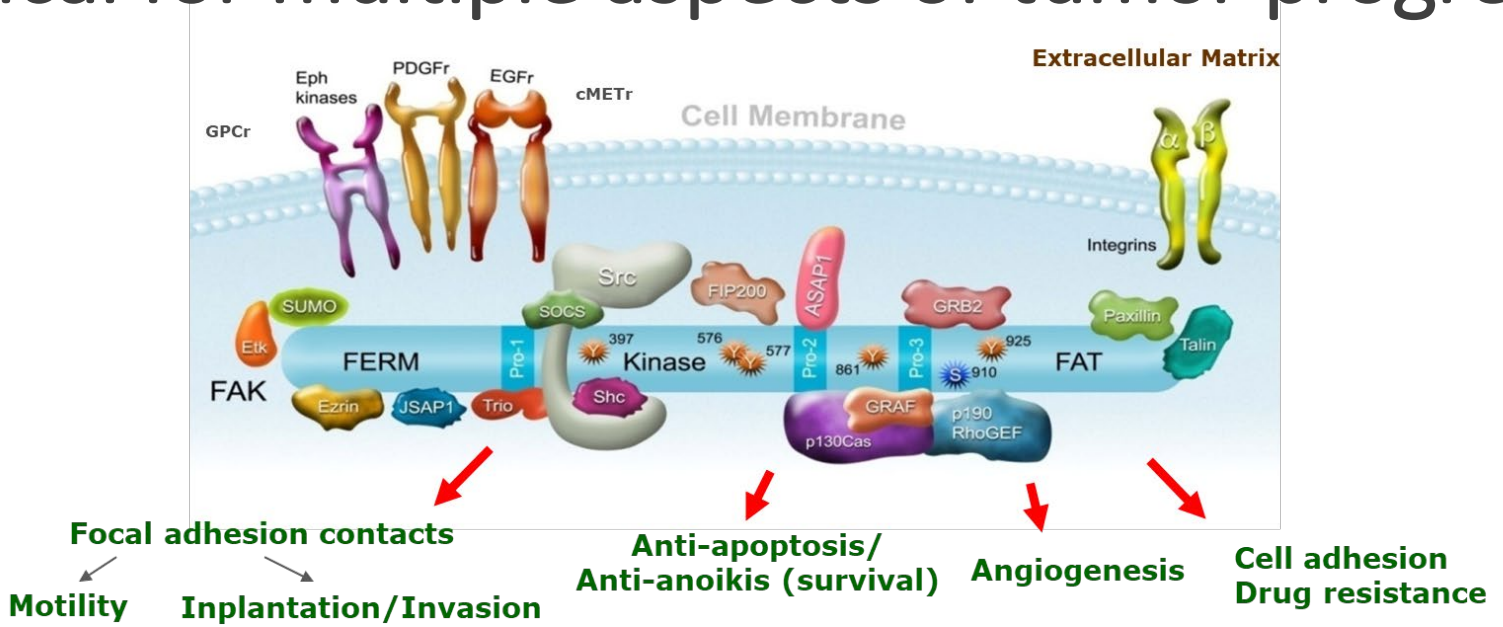
1. Reference for RAS mt frequencies – Cox et al. Nature Reviews 13: 828, 2014
2. Reference for KRAS mt in LGSOC – Grisham ASCO 2012
3. Reference for BRAF mt frequencies – Turski et al. Mol Cancer Ther 15: 533, 2016



Verastem Oncology

# FAK is critical for multiple aspects of tumor progression





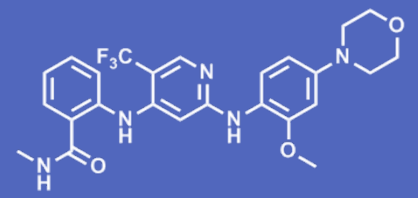

Brunton VG & Frame MC. *Curr Opin Pharmacol.* 2008;8:427
Schlaepfer DD et al. *Biochim Biophys Acta.* 2004;1692:77

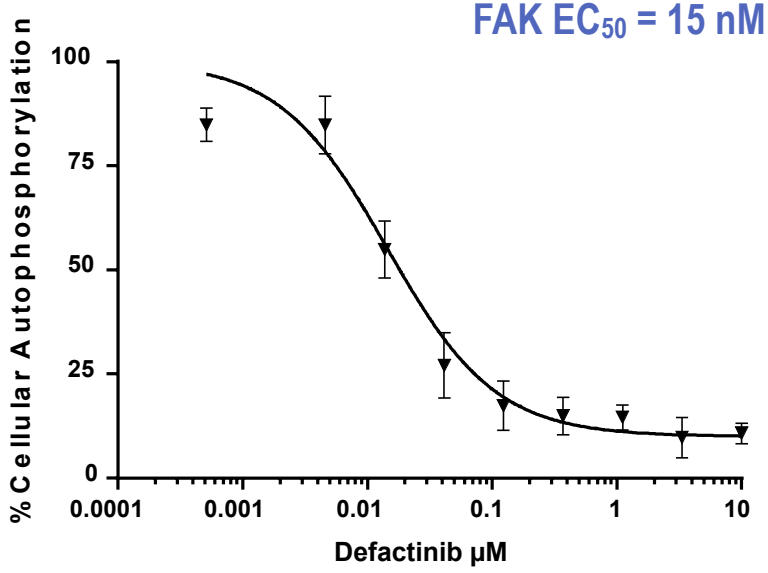
- Focal Adhesion Kinase (FAK) is a non-receptor tyrosine kinase that mediates signaling downstream of integrins & growth factor receptors
- Plays key roles in metastasis and drug resistance
- Immuno-Oncology/Tumor Microenvironment
  - FAK inhibition reduces immune suppressive cell populations in the tumor microenvironment: Tregs, M2 tumor-associated macrophages, MDSCs
  - FAK inhibition reduces stromal density: Facilitates entry of cytotoxic T cells into tumor

# Defactinib (VS-6063) – Selective FAK Inhibitor



## Defactinib

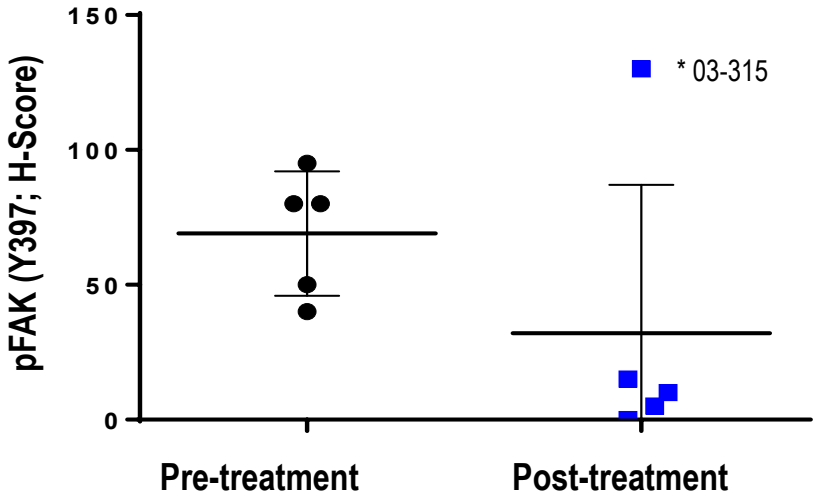




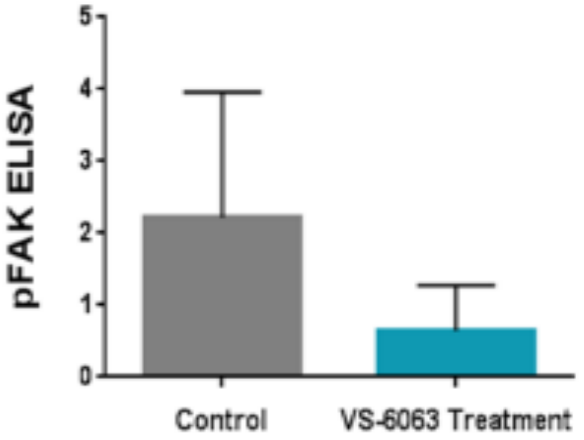

**Dosage**: Oral, 400mg BID

- **Studied in 300+ patients with good safety profile observed to date**
- DLT not reached
- Early signs of clinical efficacy
- Well established safety profile as a single agent and in combination:
  - MEK/RAF, PD-1, Chemotherapy

## OVARIAN CANCER: TUMOR BIOPSIES



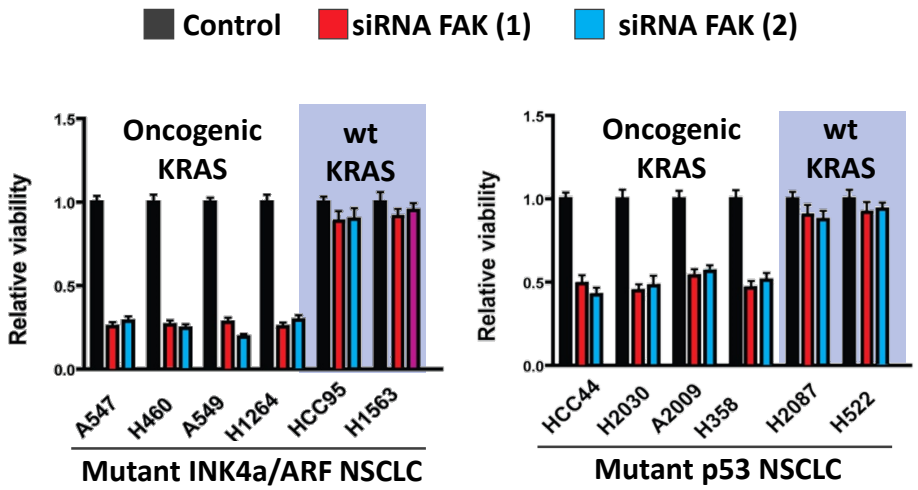

## MESOTHELIOMA: TUMOR BIOPSIES



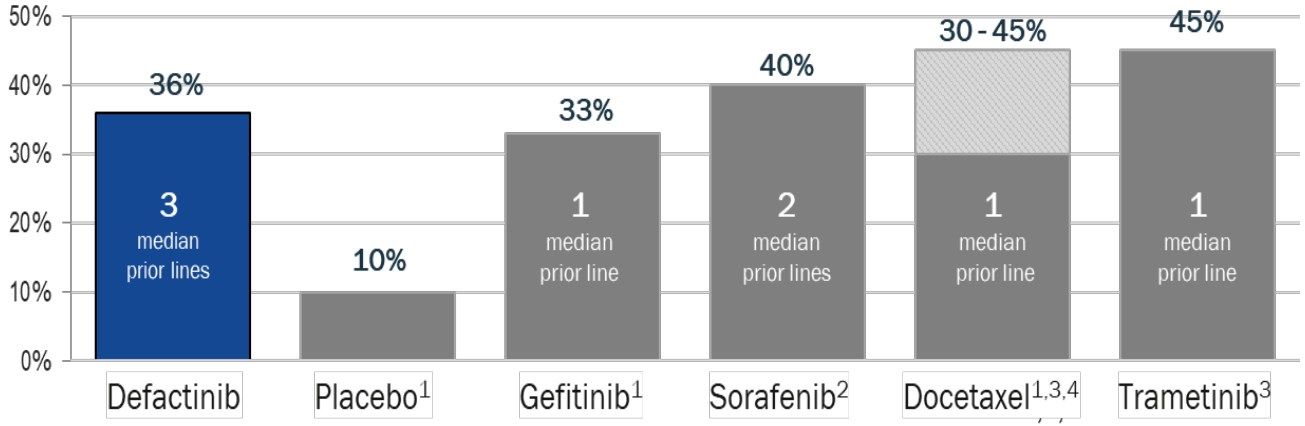
# Clinical Activity of Defactinib Monotherapy in KRAS mutant NSCLC



## KRAS mt is necessary for sensitivity to FAK inhibition in NSCLC cell lines




## 12-week PFS rate of experimental agents for KRAS mt NSCLC




*"VS-6063 was generally well tolerated and suitable for long-term dosing. In this cohort of heavily pretreated patients, there were signs of single-agent activity comparable to other targeted agents and docetaxel. **Future directions include possible combination studies with existing standard and emerging therapies, including checkpoint inhibitors.**"*
—Dr. David Gerber, IASLC 2015; Lung Cancer 2020

**Reference:**

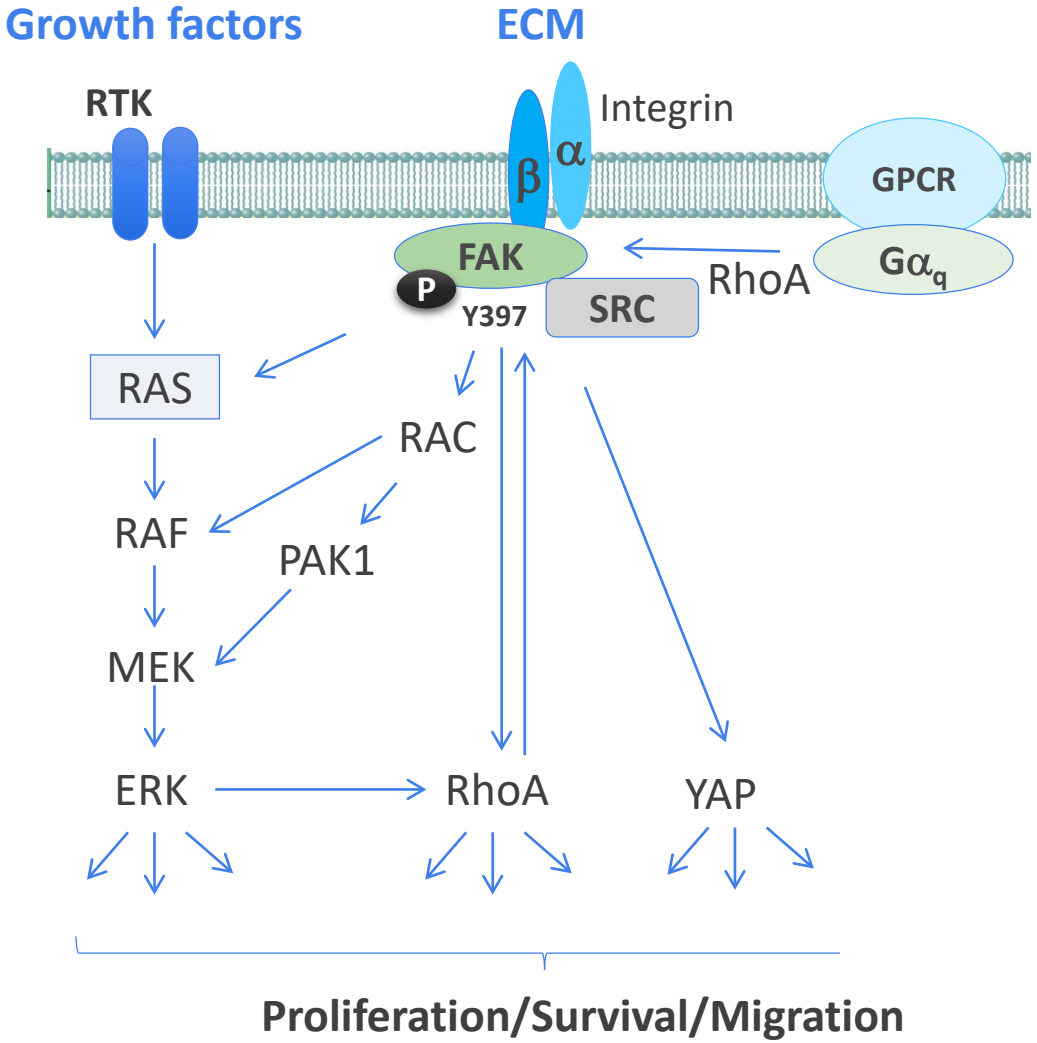
Konstantinidou G et al. Cancer Discovery 2013;3:444-57

**References:**

1. Phase 3 INTEREST, Douillard et al., JCO 2010
2. Phase 3 MISSION, Mok et al., ESMO 2012
3. Phase 2, Blumenschein et al., Ann Oncol 2015
4. Phase 2, Janne et al., Lancet 2013

# Targeting FAK Overcomes Key Resistance Mechanisms to BRAF & MEK Inhibitors



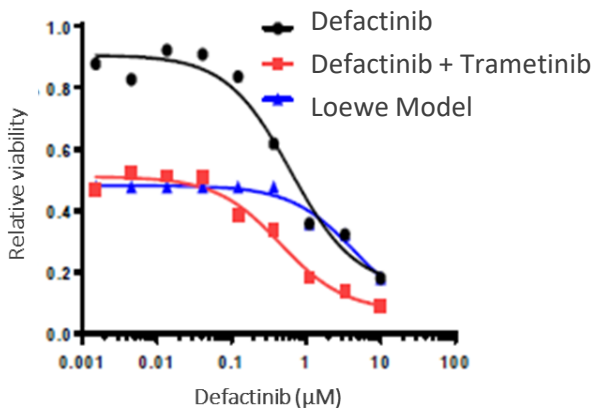



- MEK inhibition induces compensatory activation of pFAK preclinically and clinically (Banerji, BTOG 2019)
- BRAF & MEK inhibitors can block Growth Factor-stimulated ERK signaling, but Cell Attachment can also stimulate ERK signaling through a FAK-dependent pathway (Slack-Davis, JCB 162:281, 2003)
- GPCR-mediated activation of RhoA and YAP pathways through FAK (Feng, Cancer Cell, 2019) may also confer cancer cell proliferation and survival bypassing the ERK pathway
- Signaling through a RhoA-FAK axis is required for maintenance of KRAS-dependent lung adenocarcinomas (Konstantinou, Cancer Discovery 3:444, 2013)
- BRAF inhibition generates a drug-tolerant microenvironment for melanoma cells which can be abolished by FAK inhibition (Hirata, Cancer Cell 27:574, 2015)

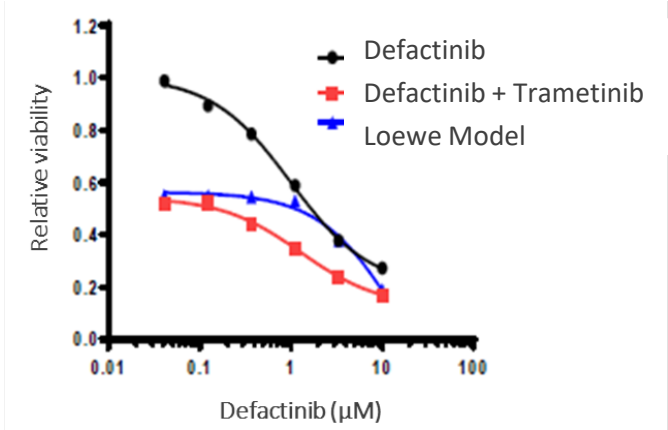
# Screen for Synergy with Defactinib Identified MEK Inhibitors (& CH5126766) as Top Hit



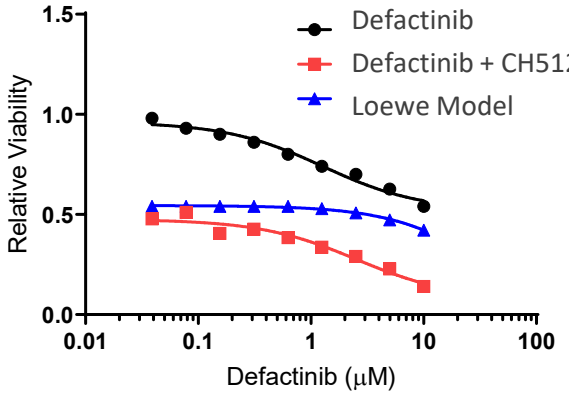
**TOV-21G CELLS KRAS-MUTANT OVARIAN CANCER**



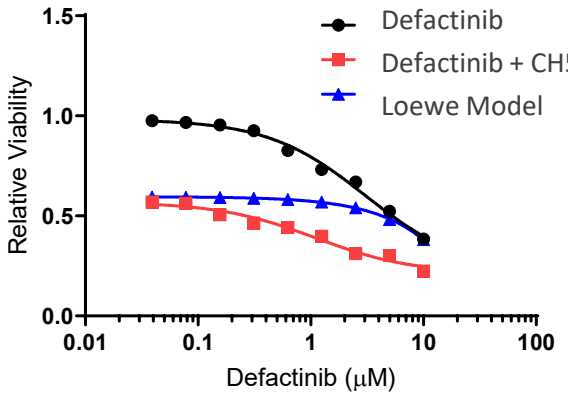

**H441 CELLS KRAS-MUTANT NON-SMALL-CELL LUNG CANCER**



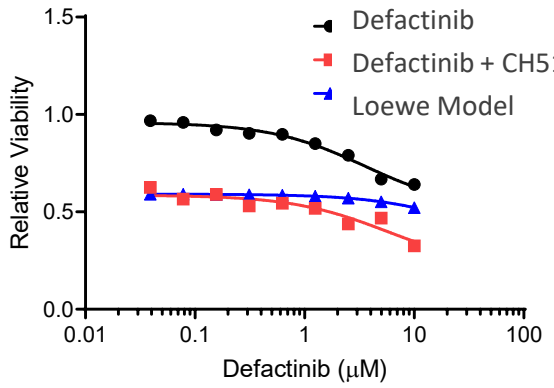

**SW982 CELLS SARCOMA BRAF:pV600E**




**MERO-14 CELLS MESOTHELIOMA**




**CAL-51 CELLS TRIPLE NEGATIVE BREAST CANCER**






***Verastem issued patent on FAK/MEK inhibitor combinations***

# CH5126766 is a Unique Small Molecule RAF/MEK Inhibitor



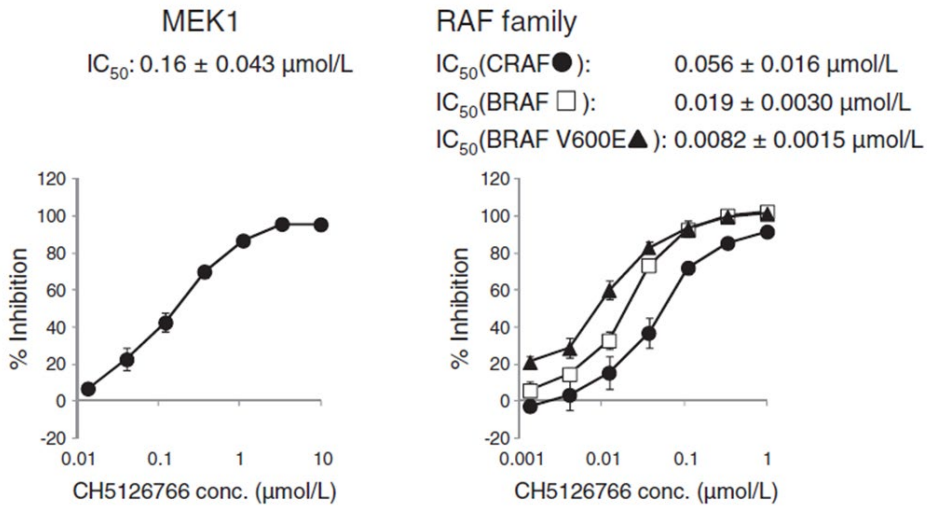
- CH5126766 uniquely inhibits both MEK kinase and RAF kinase activities

RAS → RAF → MEK → ERK → Proliferation & Survival

- Standard MEK inhibitors (e.g. PD0325901) paradoxically induce MEK phosphorylation (pMEK) by relieving ERK-dependent feedback inhibition of RAF which may limit their efficacy

- By inhibiting RAF phosphorylation of MEK, CH5126766 has the advantage of not inducing pMEK

- This unique mechanism of CH5126766 enables more effective inhibition of ERK signaling, and may confer enhanced therapeutic activity against ERK-dependent, RAS or BRAF mutant tumors



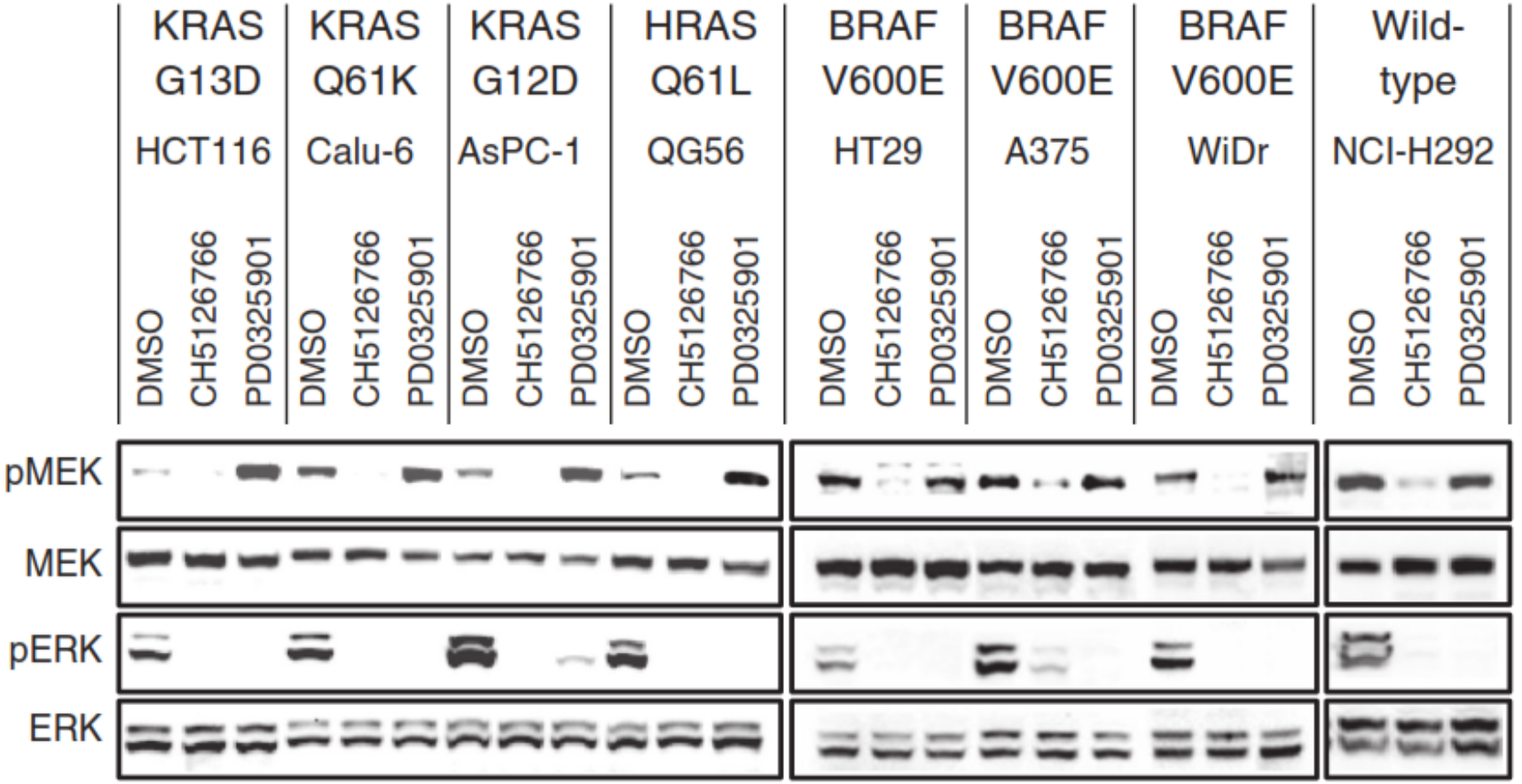


**Reference:**

Ishii et al., Cancer Research, 2013

# CH5126766 is effective against multiple RAS & RAF mutations:
## Potential to act more broadly or be combined with agents targeting specific mutations only

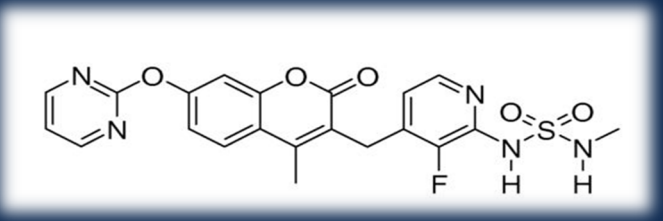




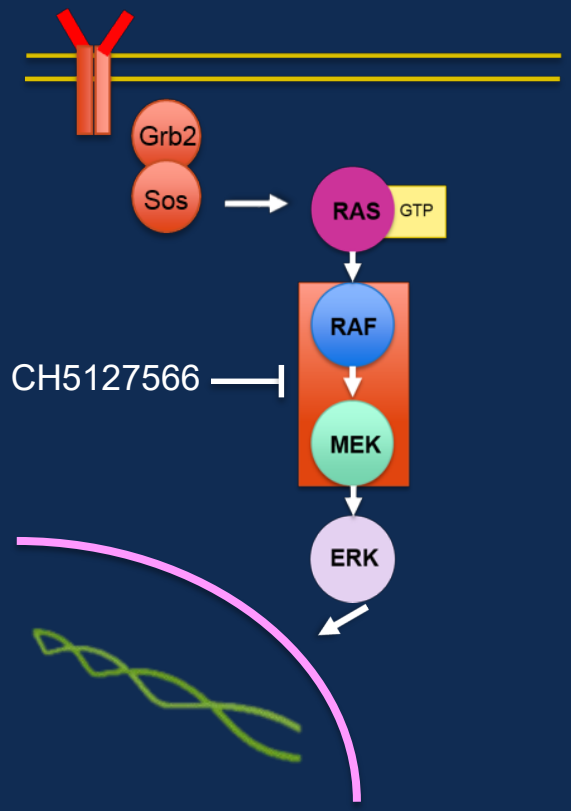

**Reference:**
Ishii et al., Cancer Research, 2013

*PD0325901 (mirdametinib) is a conventional MEK inhibitor*

# Background





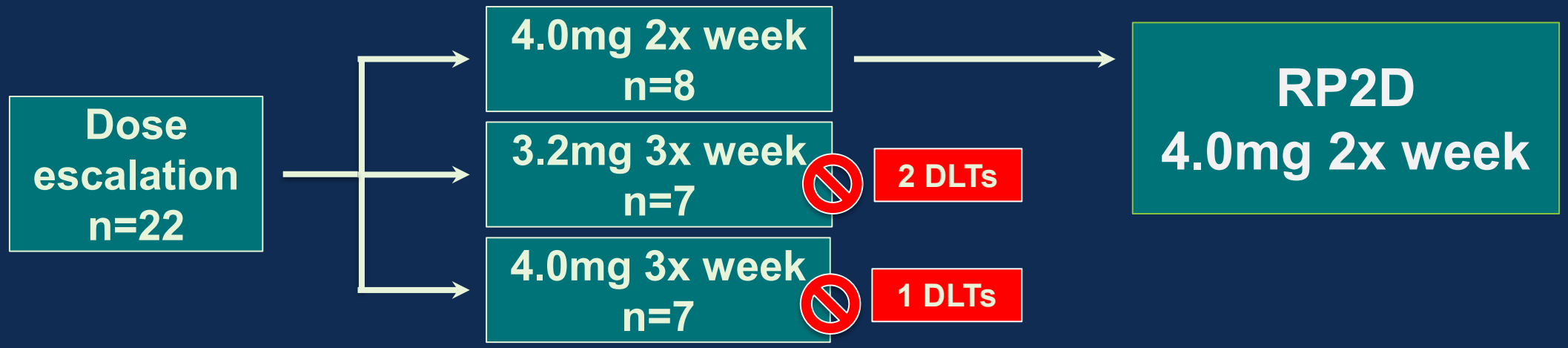



- CH5126766: MEK inhibitor with functional pan-RAF inhibition, first-in-class agent
- Dose escalation by Martinez-Garcia et al. 2012
  - MTD 2.25 mg, once daily
  - MTD 4.0 mg, 4 days on/3 days off
  - MTD 2.7 mg, 7 days on/7 days off
- Promising activity: tumor shrinkage in 40 % of pts
- Development of these schedules challenging

*Ishii et al. Cancer Res; 2013 Jul 1;73(13):4050-60*
*Martinez-Garcia et al. Clin Cancer Res. 2012 Sep 1;18(17):4806-19*

# Background

- In view of promising activity, a different trial design was investigated to mitigate toxicity
- Mean terminal $t_{1/2}$ of ≈ 60 hours
  - 2x-weekly and 3x-weekly scheduling, in 4 week cycles
- Led by the Drug Development Unit at RMH/ICR



# Adverse Events



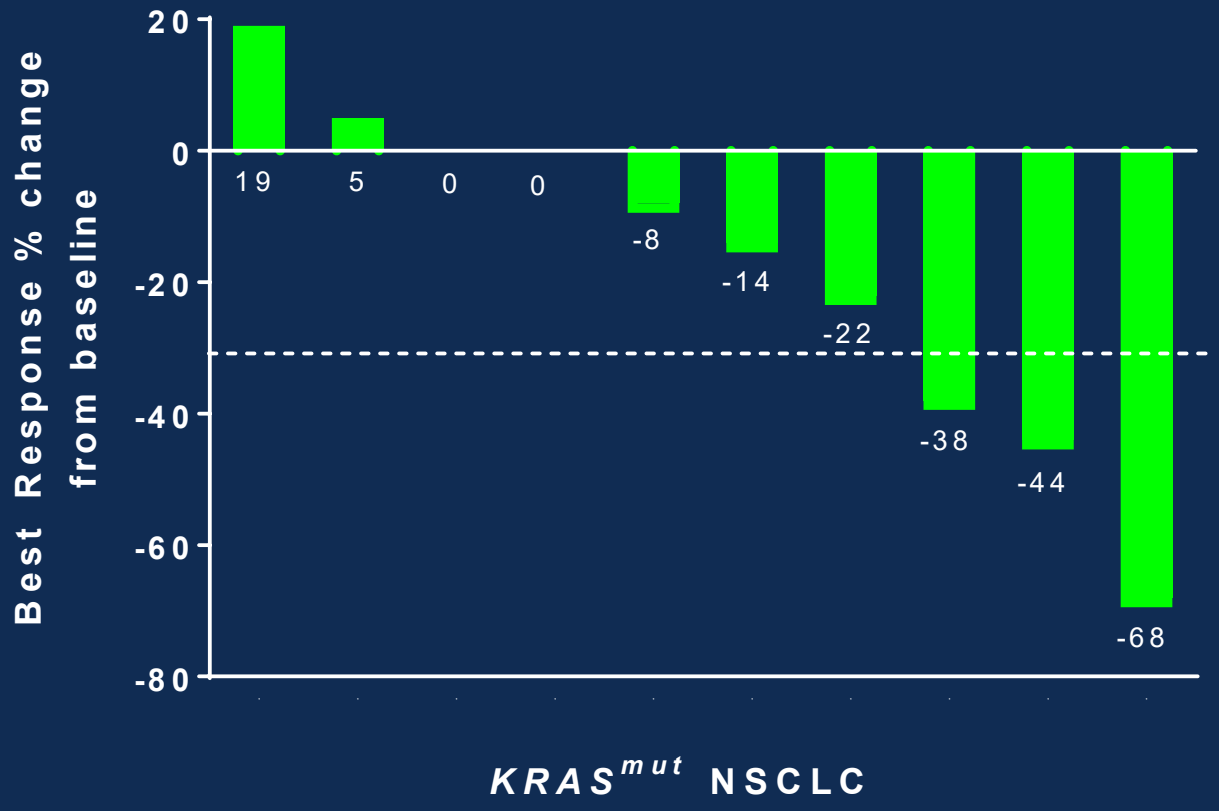
| Adverse event details | Expansion: 4mg 2x weekly n=26 | | Martinez-Garcia *et al.* CCR 2012 Patient treated at OD MTD n=6 |
|---|---|---|---|
| | All grades | ≥ Gr. 3 | ≥ Gr. 3 |
| Rash-related | 22 (84.6 %) | 5 (**19.2 %**) | 3 (**50.0 %**) |
| CK elevation | 15 (57.7 %) | 2 (**7.6%**) | 1 (**16.7 %**) |
| Blurred vision | 13 (50 %) | 0 | 0 |
| Peripheral oedema | 10 (38.5 %) | 0 | 0 |
| Diarrhoea | 9 (34.1 %) | 1 (3.8 %) | 0 |
| Mucositis/Mouth ulcer | 8 (30.8 %) | 1 (3.8 %) | 0 |
| Fatigue | 6 (23.1 %) | 1 (3.8 %) | 0 |
| Nausea | 5 (19.2 %) | 0 | 0 |

Martinez-Garcia et al. Clin Cancer Res. 2012 Sep 1;18(17):4806-19

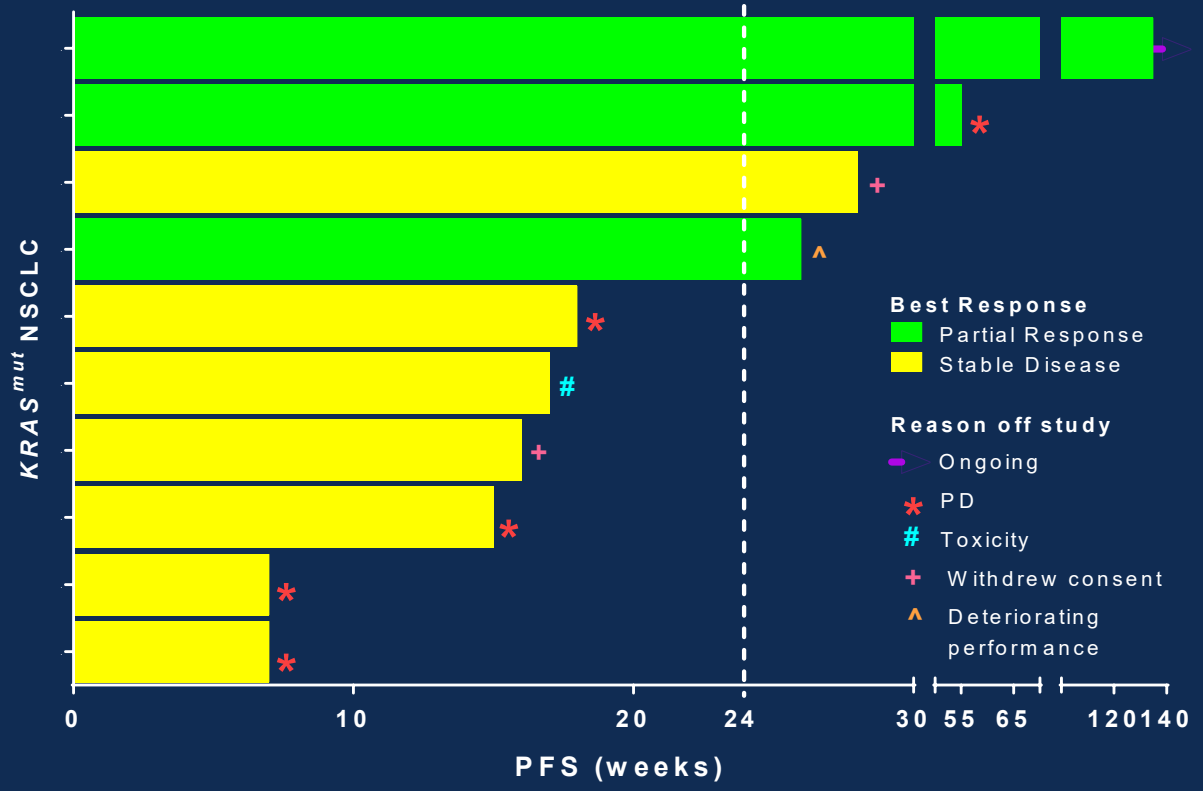
# Results: *KRAS*$^{mut}$ NSCLC - Adenocarcinoma



## Best response by RECIST v1.1



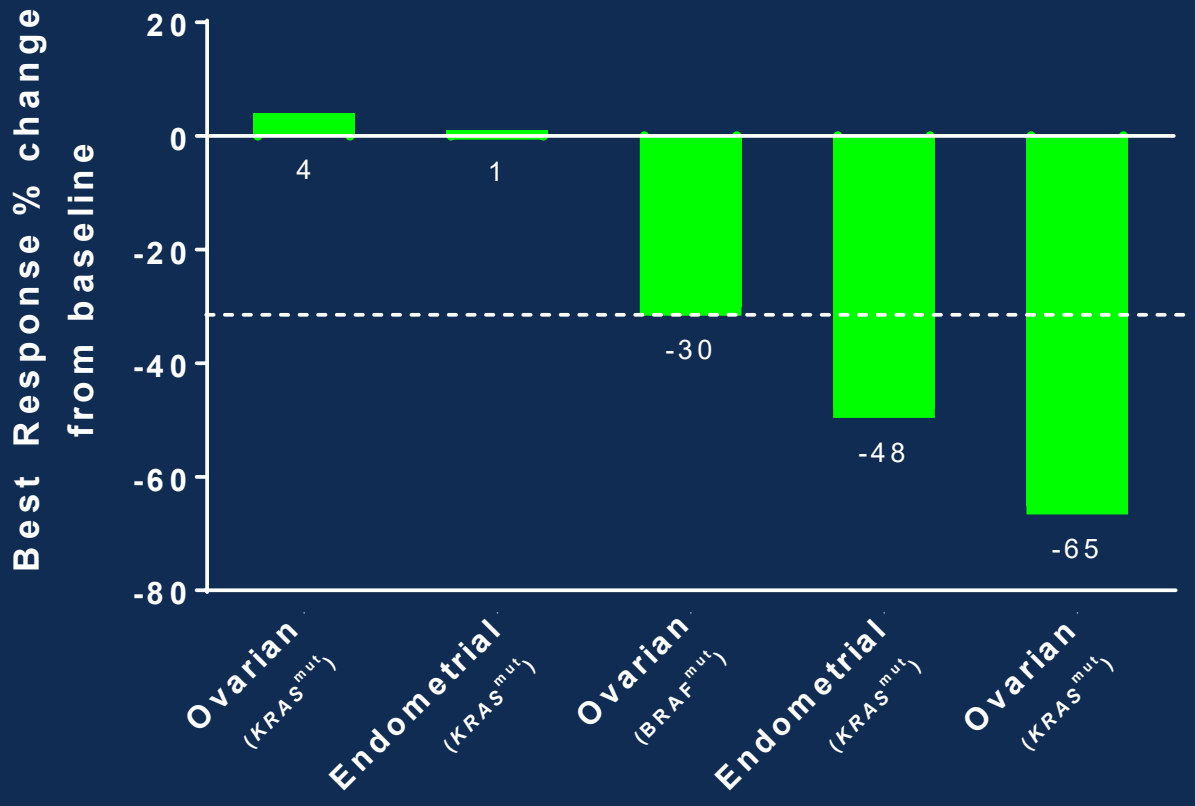

## Progression Free Survival



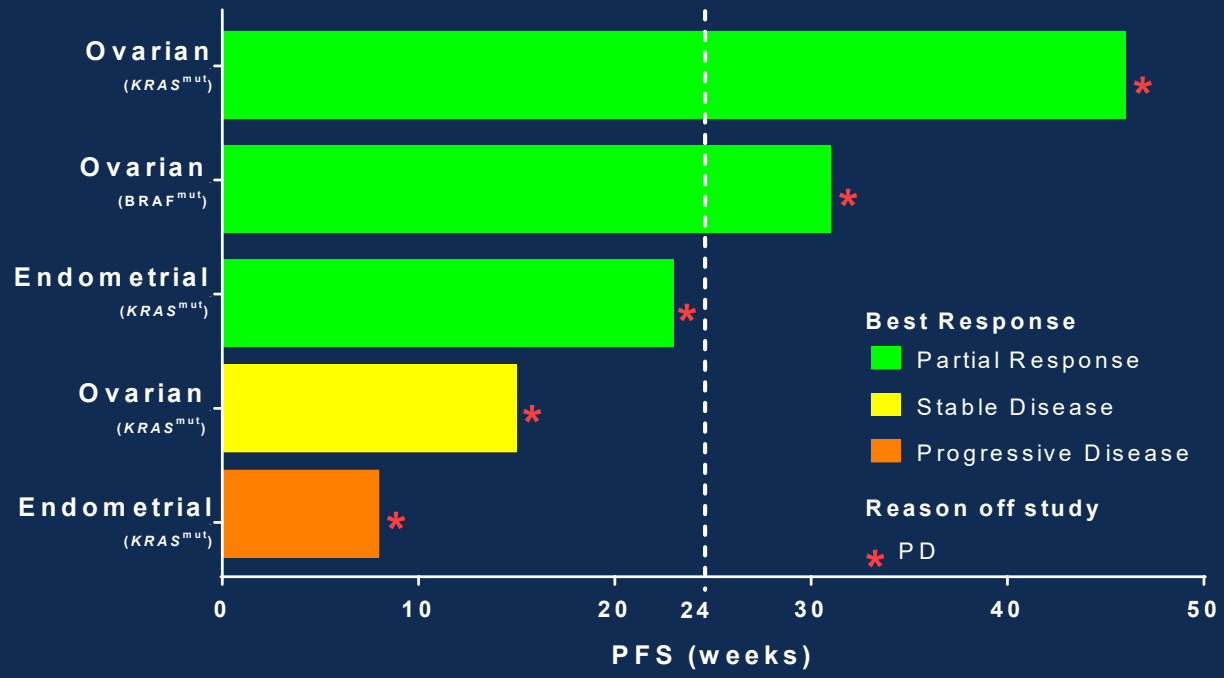
# Results: Gynaecological cancers



## Best response by RECIST v1.1




## Progression Free Survival



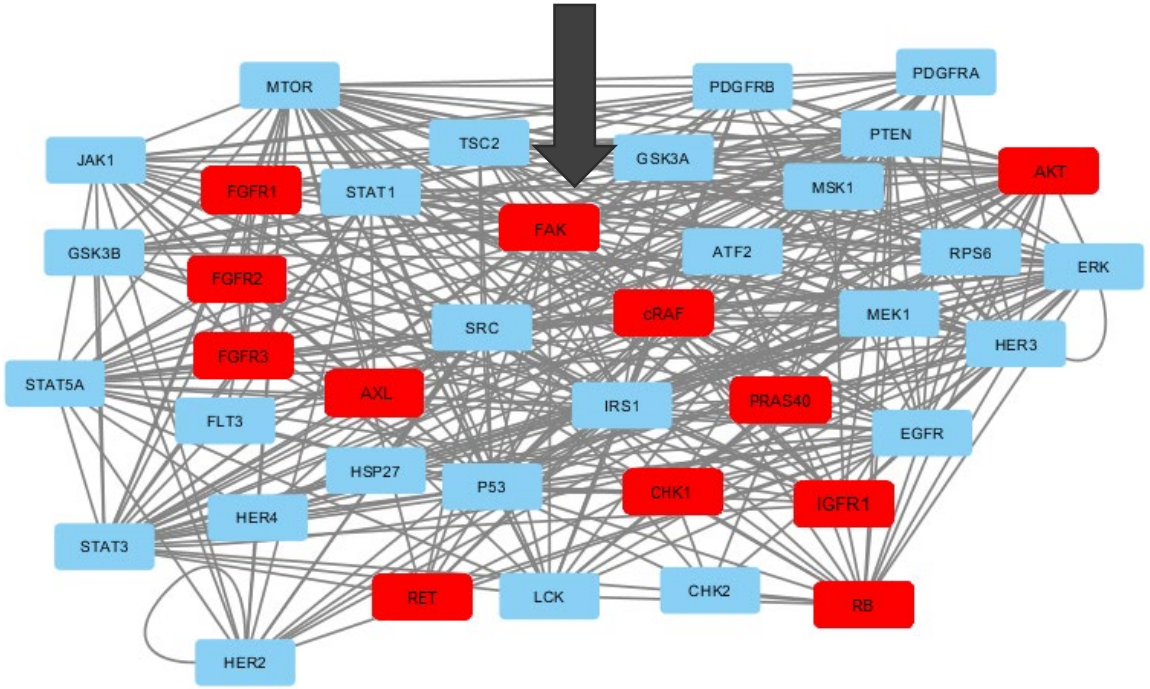
# Conclusion



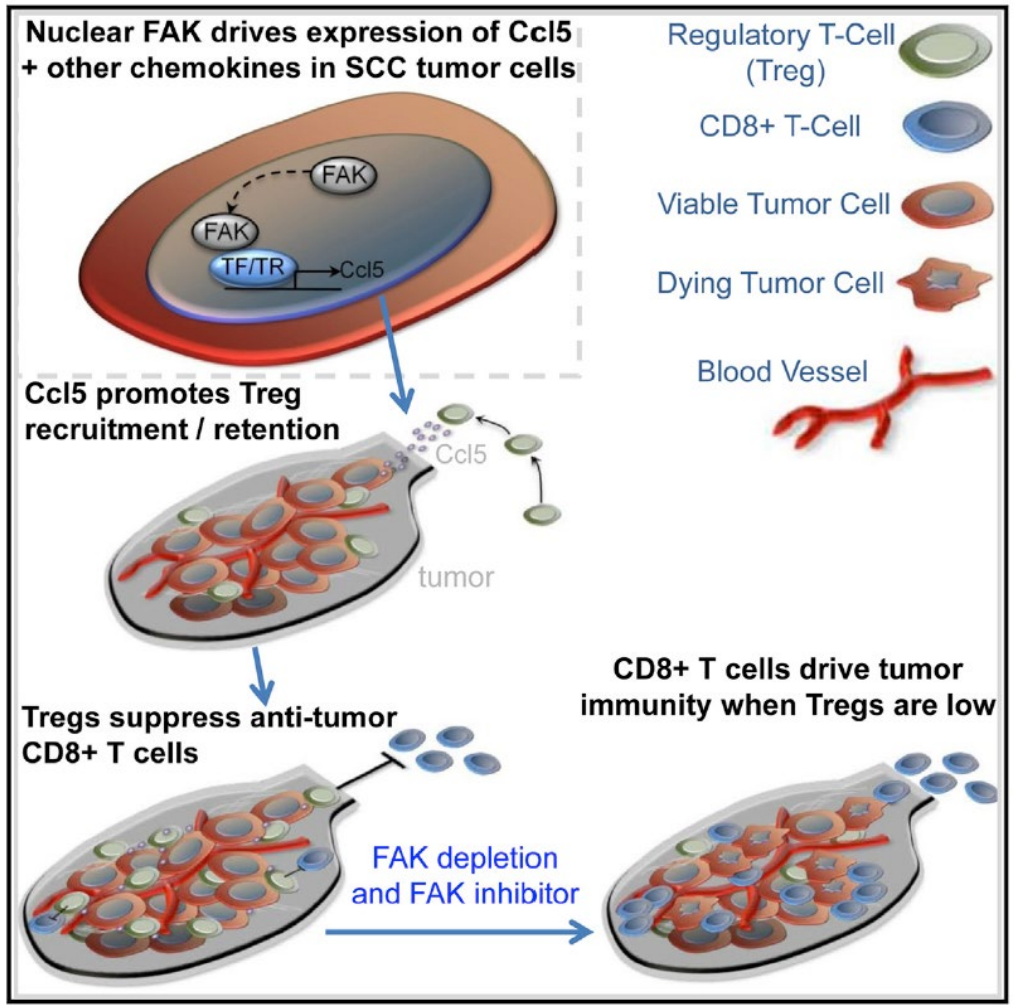
- CH5127566 (RO5126766) is a potent and well-tolerated RAF-MEK inhibitor
- Twice-weekly scheduling improved therapeutic index
- Multiples responses in *KRAS*- and *BRAF*-mutated malignancies, with impressive results in NSCLC and gynaecological cancers
- Preliminary results suggesting single-agent activity in relapsed/refractory multiple myeloma
  - Ongoing cohort

# *KRAS*$^{M}$ MEK + FAK inhibitor combinations






Phosphoproteomic signature of *KRAS*$^{M}$ A549 NSCLC cell line exposed to Trametinib for 1hr shows feedback loops involving FAK




*Serrels A Cell 2015, 163:160-173*



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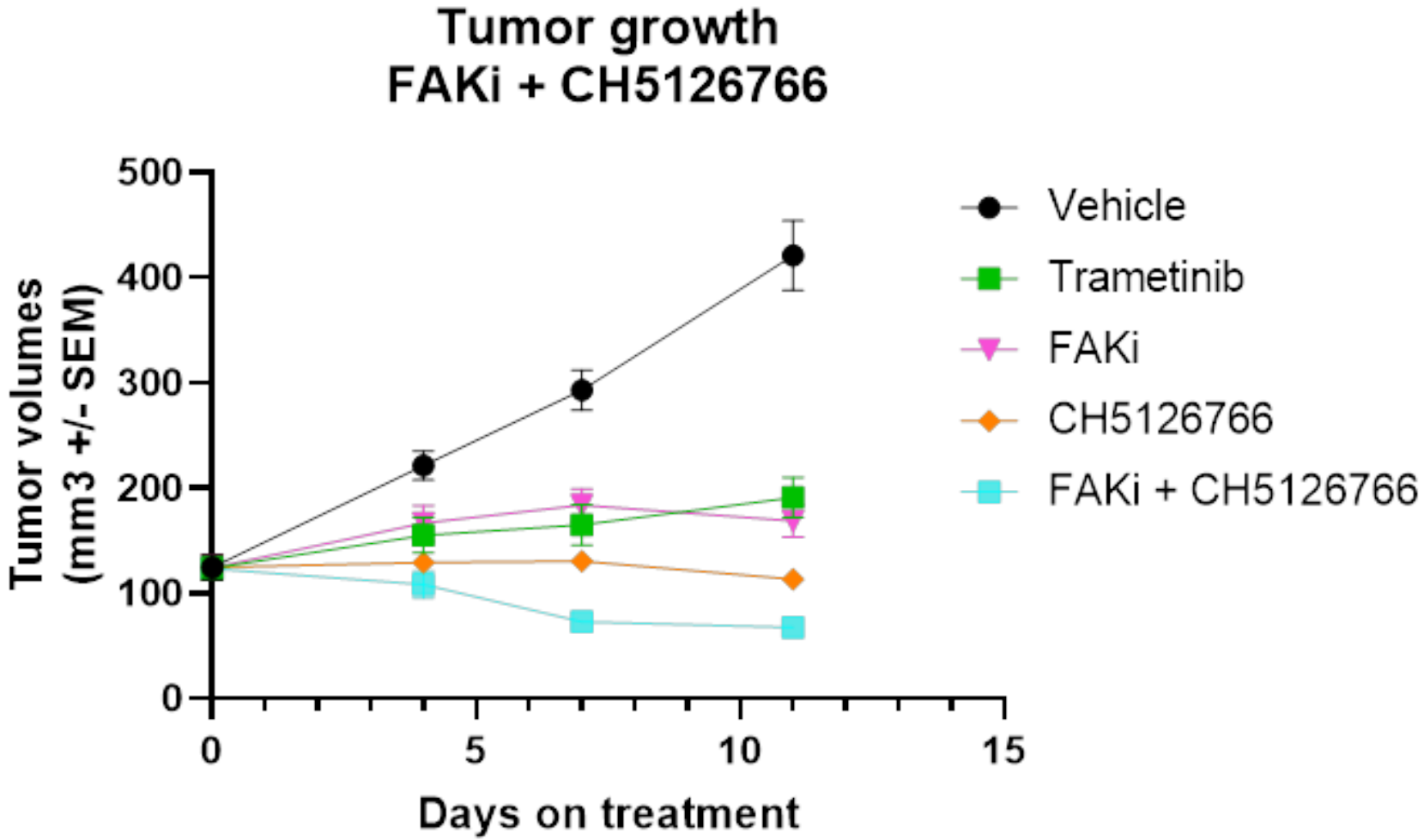
# Tumor regression achieved with FAK + RAF/MEK Combination in KRAS-mutant Ovarian Xenograft Model (TOV21G)








Verastem Oncology

# Ongoing Investigator-Sponsored Basket Study of CH5126766 + Defactinib in KRAS-mutant Cancers

**Dr. Udai Banerji**
Royal Marsden Hospital

## Phase I

Advanced Solid Cancers

- CH5126766 oral twice wkly x 3 every 4 wks
- Defactinib oral BID daily x 3 wks q 4 wks
- 3 cohorts increasing doses to full single agent doses (CH5126766 4mg & Defactinib 400 mg)

**Recommended Phase 2 Dose has been determined and expansion cohorts are underway**

- **Advanced NSCLC KRAS-Mut*** (20 patients)
- **LGSOC*** (20 patients)
- **Advanced CRC RAS-Mut*** (10 patients)
- **Advanced Solid Tumors Enriched for RAS-Mut*** (Biopsy Amenable)

***"Refractory to conventional treatment or for which no conventional treatment exists"**

*Results to be presented at a scientific conference in 1H-2020*



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# Defactinib + CH5126766: Potential Best-in-Class Combination for RAS/RAF-Mutant Cancers



- Defactinib and CH5126766 have each shown independent clinical activity in RAS mutant cancers
- MEK blockade activates pFAK as a potential escape mechanism
- Multiple preclinical studies provide rationale for why FAK and MEK inhibitors are synergistic
- Defactinib is generally well tolerated, and has a non-overlapping safety profile relative to CH5126766. A manageable all-oral combination regimen has been defined.
- Initial clinical data with the combination are promising including both objective response rate and durability
- We are exploring the breadth of this activity against KRAS mutant cancers and the clinical results will be presented at an upcoming scientific meeting (1H 2020)

# This licensing transaction and combination of defactinib + CH5126766 are potentially transformative for Verastem Oncology

- This transaction is aligned with and supports our 6-2-5 strategy to build a company with multiple products as we continue to make progress with our lead agent Copiktra®
- The RAS/RAF/MEK pathway represents a large market with high unmet need
- Given the potential of this opportunity, the company will be evaluating various partnering strategies
- Based on the promising objective response rate and manageable safety profile of this combination in patients with KRAS mutant tumors:
  - Verastem Oncology has in-licensed world-wide rights to CH5126766
  - Verastem Oncology to initiate regulatory discussions in 1H 2020 to further define the initial registration-directed study for the defactinib + CH5126766 combination


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Oncology
Thank You