RAF/MEK Clamp Avutometinib: Rational Combinations with FAK Inhibitor and Other Targeted Therapies

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5th Annual RAS-Targeted Drug Development Summit
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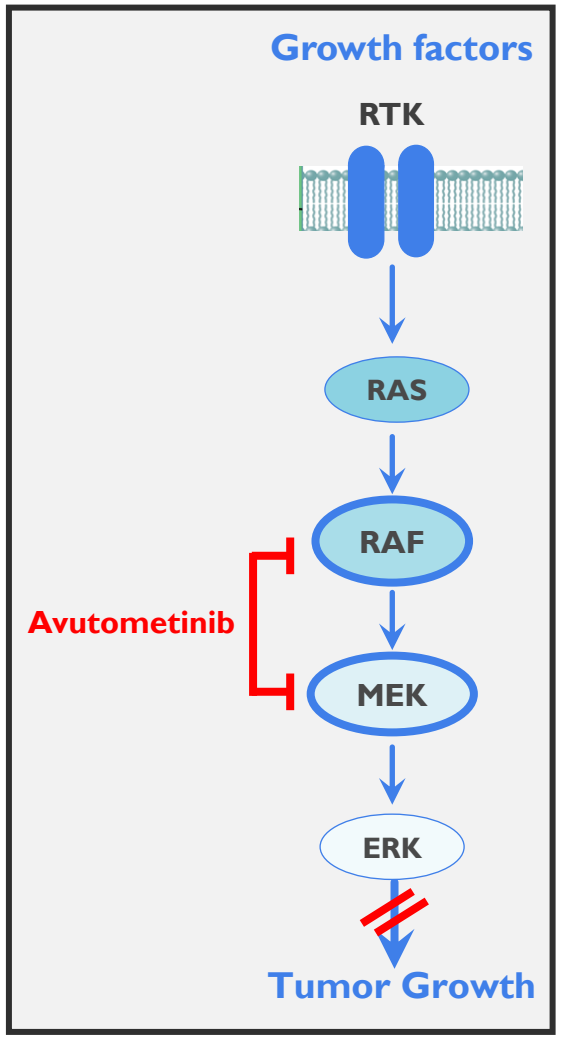
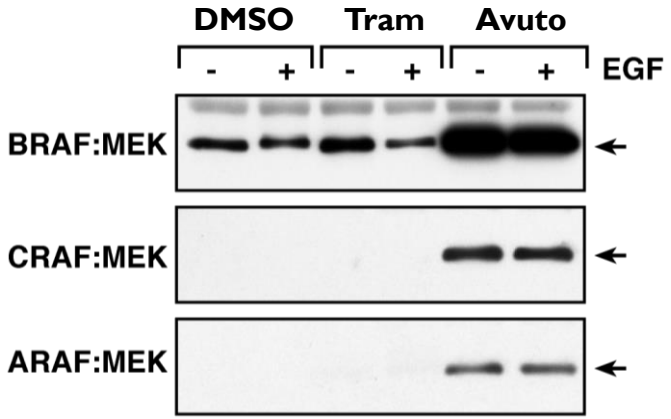
Avutometinib is a Unique Small Molecule RAF/MEK Clamp

Contrasting Mechanism of Action vs. MEK-Only Inhibitors



Avutometinib induces dominant negative RAF/MEK complexes



Collaboration with Deborah Morrison, NCI

Avutometinib inhibits both RAF and MEK activities

MEK1

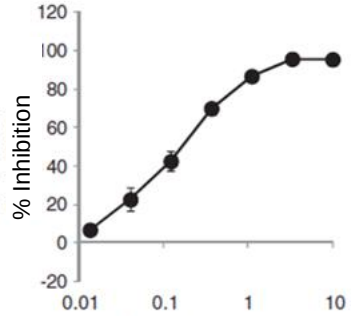
IC_{50}: 0.16 ± 0.043 µmol/L

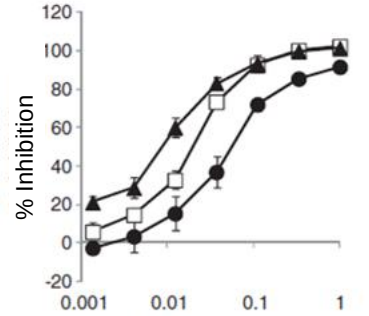
RAF family

IC_{50}(CRAF●): 0.056 ± 0.016 µmol/L

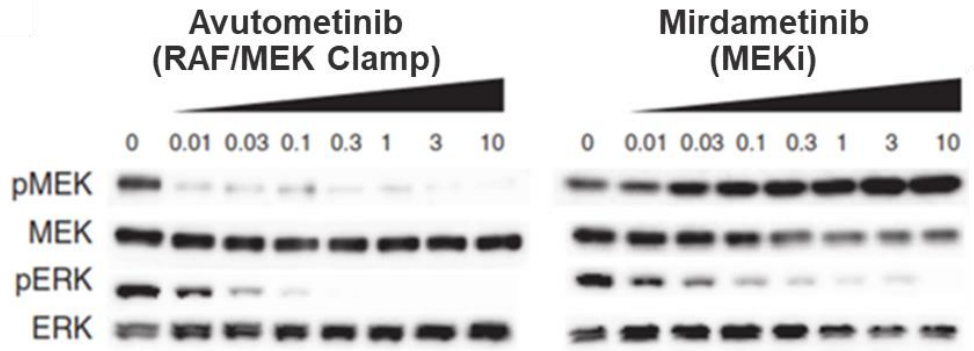
IC_{50}(BRAF □): 0.019 ± 0.0030 µmol/L

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





The RAF/MEK clamp mechanism avoids the compensatory activation of pMEK enabling more complete pERK inhibition



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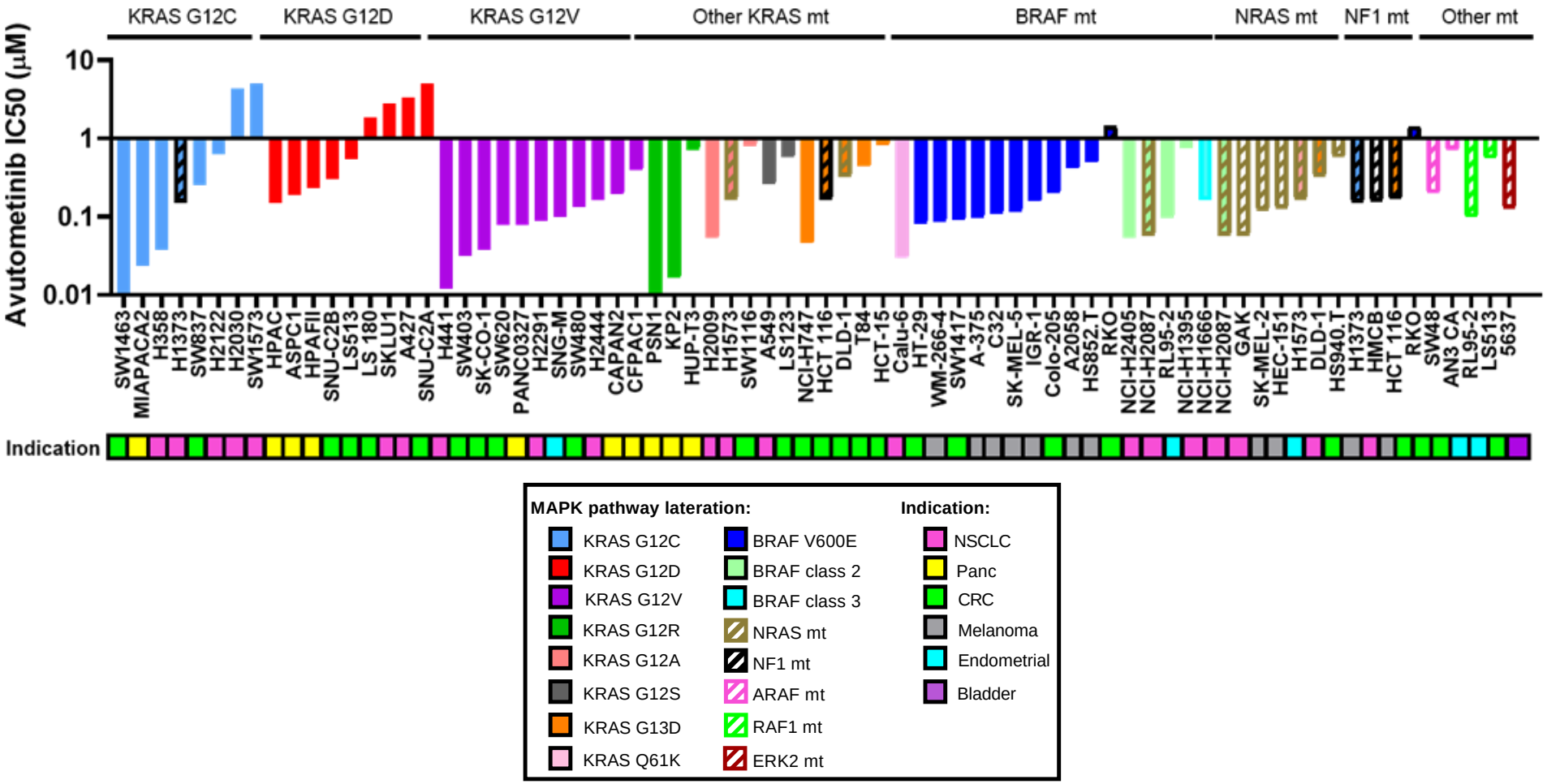
References: Coma et al., AACR 2022; Ishii et al., *Cancer Res*, 2013; Lito et al., *Cancer Cell*, 2014

Avutometinib Inhibits Cell Proliferation Across Multiple RAS/MAPK Pathway Alterations and Multiple Solid Tumor Histologies

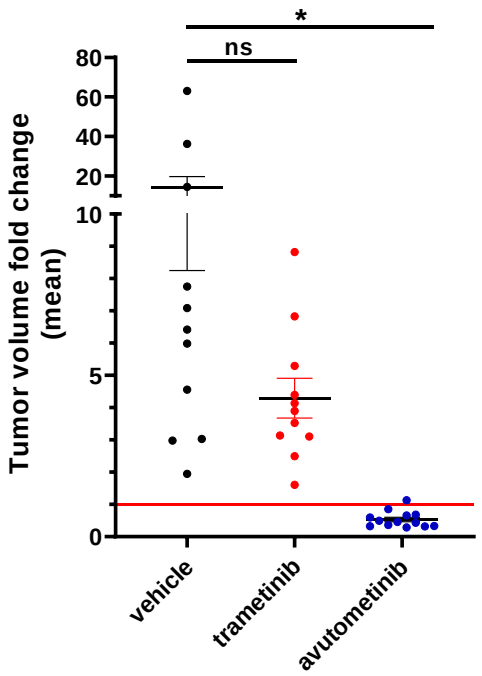


Verastem, unpublished data

Avutometinib Anti-Tumor Activity in KRAS Mutant Models

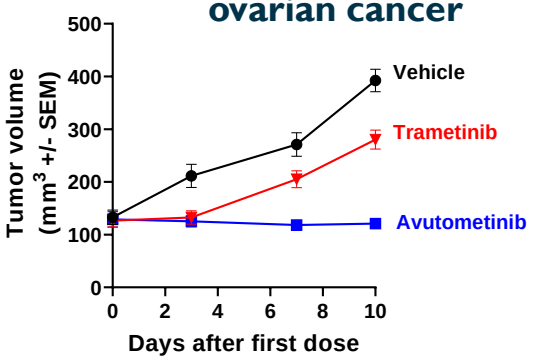
Superiority vs. Trametinib

KRAS G12V mt/Trp53 KO NSCLC GEMM



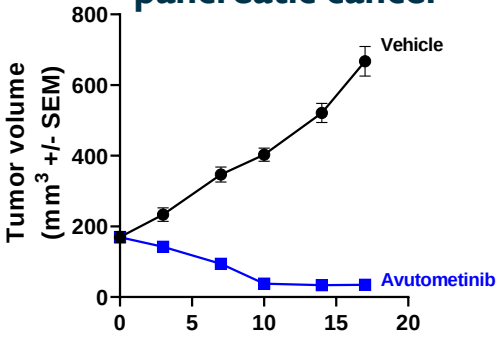
Avutometinib 0.1 mg/kg QD
Trametinib 0.1 mg/kg QD

TOV21G KRAS G13D ovarian cancer



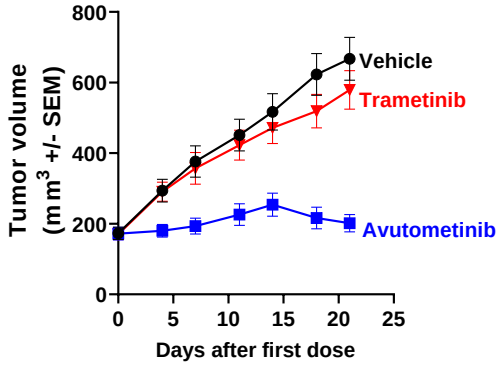
Avutometinib 0.5 mg/kg QD
Trametinib 0.5 mg/kg QD

MiaPaca2 KRAS G12C pancreatic cancer



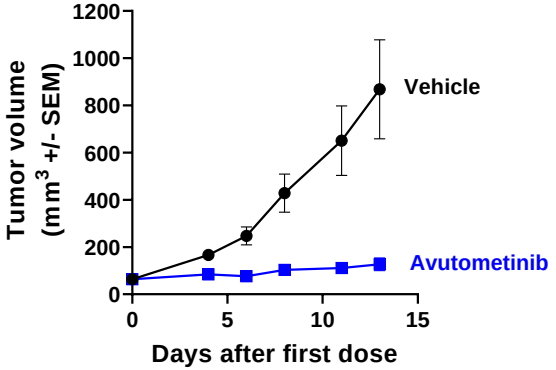
Avutometinib 0.3 mg/kg QD

H358 KRAS G12C NSCLC



Avutometinib 0.3 mg/kg QD
Trametinib 0.3 mg/kg QD

CT26 KRAS G12D colorectal cancer



Avutometinib 0.3 mg/kg QD

Collaboration with Mariano Barbacid, CNIO (Spain)

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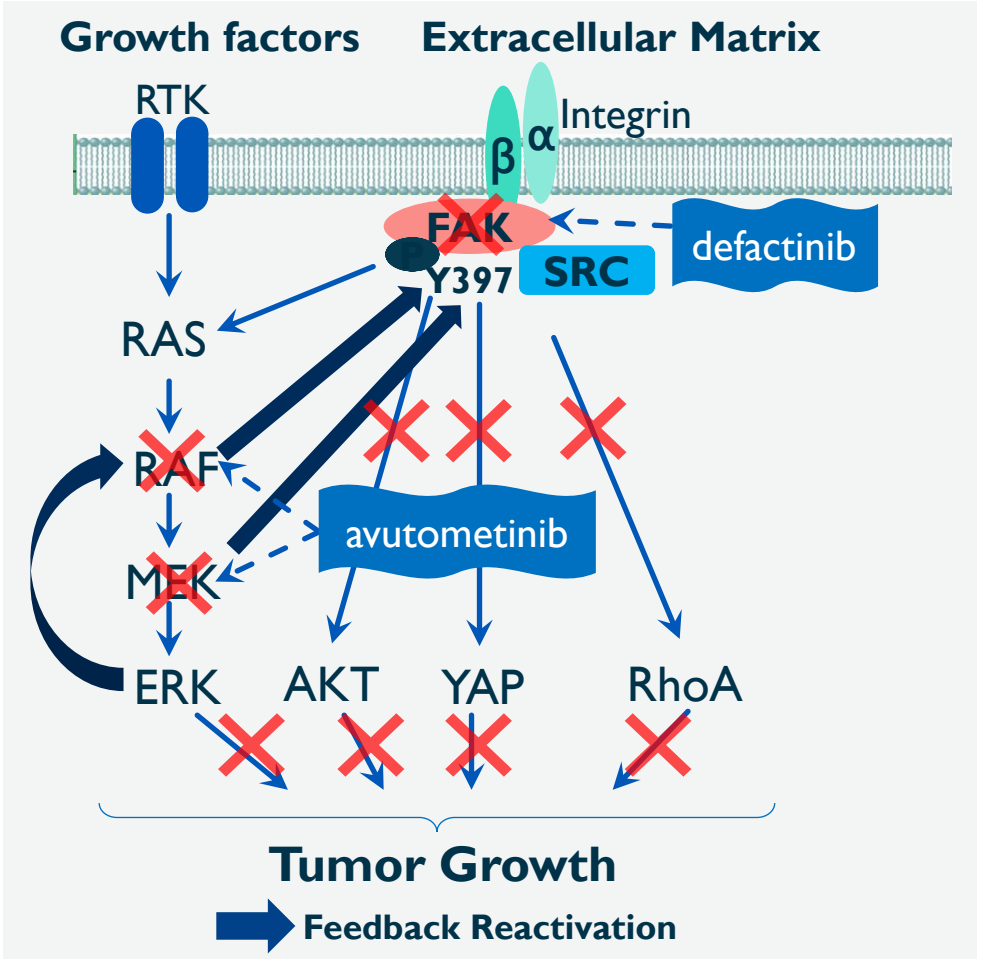
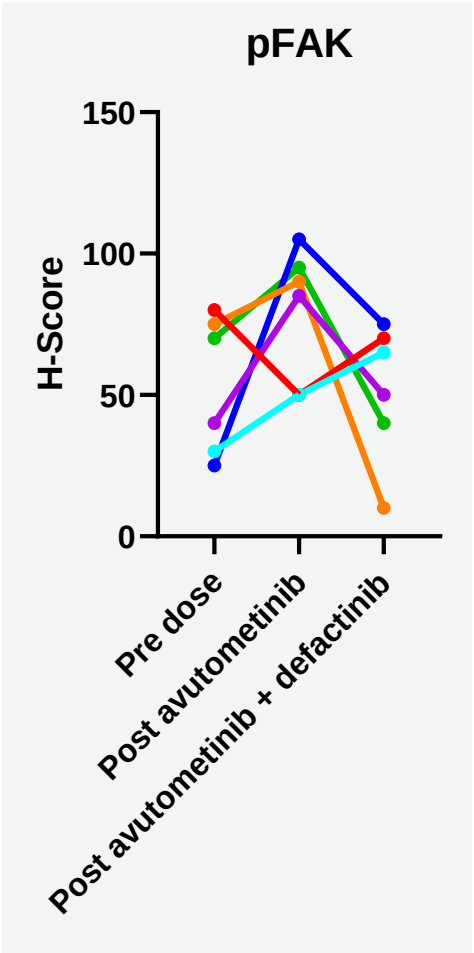
Verastem, unpublished data

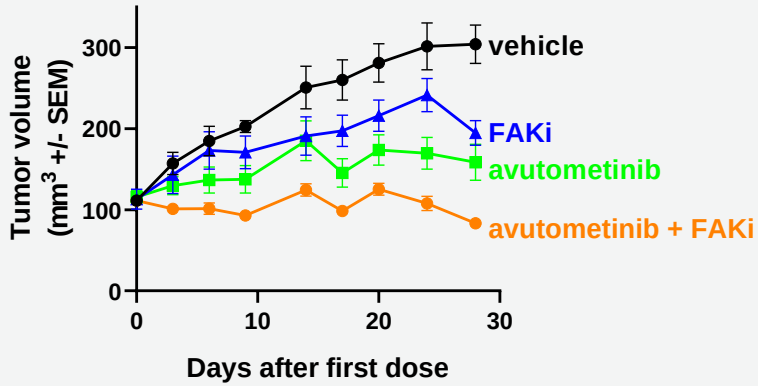
Strong Scientific Rationale for Avutometinib and FAK Inhibitor Combination

Anti-Tumor Efficacy in KRAS Mutant and Wild-Type LGSOC models



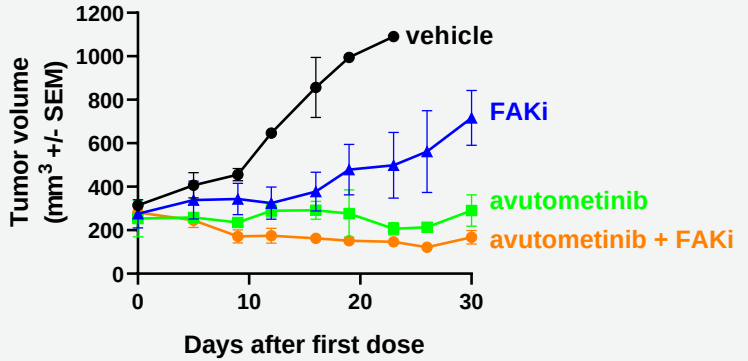


KRAS mutant LGSOC PDX model



Collaboration with Udai Banerji, ICR (UK)

KRAS wild-type LGSOC PDX model



Collaboration with Alessandro Santin, Yale

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References: Banerji, BTOG Dublin, Jan 23, 2019; Banerji, AACR VM 1, April 27, 2020, CT143; Banerji, unpublished; Santin, unpublished

LGSOC: Low-grade serous ovarian cancer

Optimized Dosing Schedule Defined: Favorable Tolerability Profile with Novel Intermittent Dosing Regimen

Summary of Adverse Events Grade ≥3 Occurring in ≥5% of Patients

	Avutometinib monotherapy Daily at MTD N=6 28-day cycle	**RP2D Avutometinib monotherapy 4mg twice weekly N=26 28-day cycle**	**RP2D (Avutometinib 3.2mg twice weekly + defactinib 200mg twice daily) N=38 21 days of 28-day cycle**
Treatment Related Adverse Event	**Grade ≥3**	**Grade ≥3**	**Grade ≥3**
Rash	3 (50%)	5 (19%)	2 (5%)
CK elevation (Creatine phosphokinase)	1 (17%)	2 (8%)	2 (5%)

References: Chenard-Poirier, *et al.* ASCO 2017; Banerji, Q4 2020 report; Data on file
RP2D: recommended phase 2 dosing

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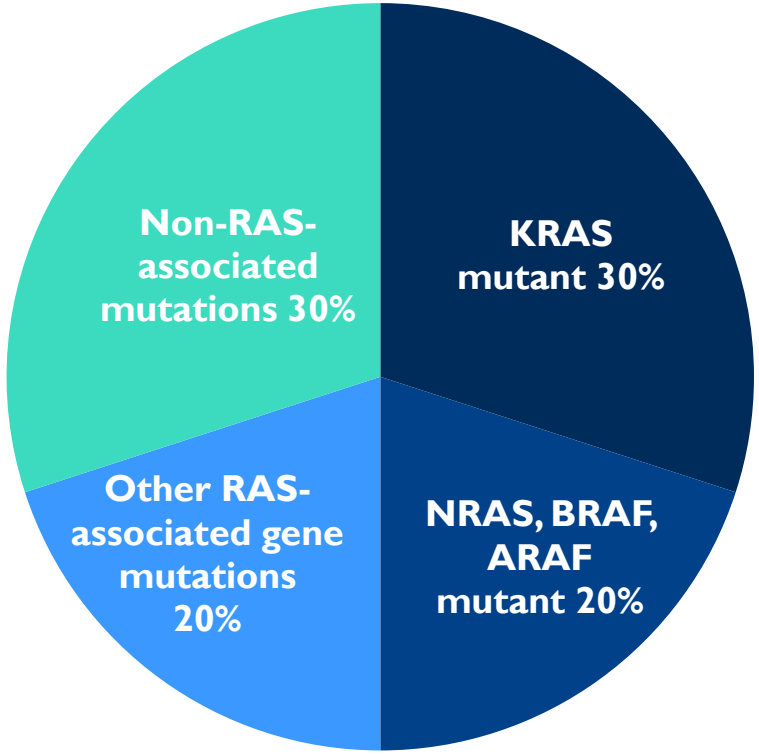
Low-Grade Serous Ovarian Cancer (LGSOC) is a MAPK Pathway-Driven Cancer with Limited Treatment Options

~30% of LGSOC Patients Have KRAS mt
~70% of LGSOC Shows MAPK Pathway-Associated mts



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

Therapy	Response Rate ORR	Median PFS Months (95% CI)	Discontinuation Rate due to AEs
Standard of Care[1]	6%	7.2 (5.6-9.9)	12 %
Trametinib[1]	26%	13.0 (9.9-15.0)	35%
Standard of Care[2]	13%	10.6 (9.2 to 14.5)	17%
Binimetinib[2]	16%	9.1 (7.3-11.3)	31%

[1] Gershenson et al., Lancet 2022
[2] Monk et al., J Clin Oncol 2020.

Standard of Care = letrozole, tamoxifen, chemotherapy
CI = confidence interval
PFS = progression-free survival

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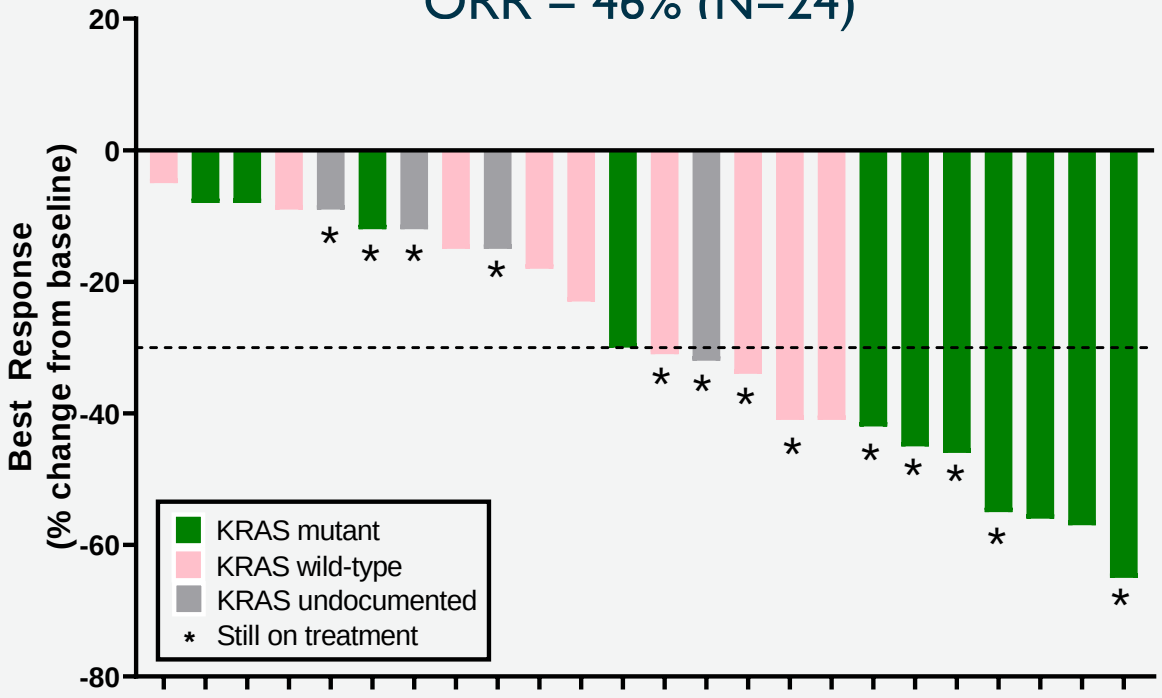
Combination of Avutometinib and Defactinib (FAKi) Yields Consistent High Response Rate in Recurrent Low-Grade Serous Ovarian Cancer

Initial Data from RAMP 201 (international phase 2) Trial Reinforce Findings from FRAME (UK phase 1/2) Trial

FRAME

Investigator Assessment

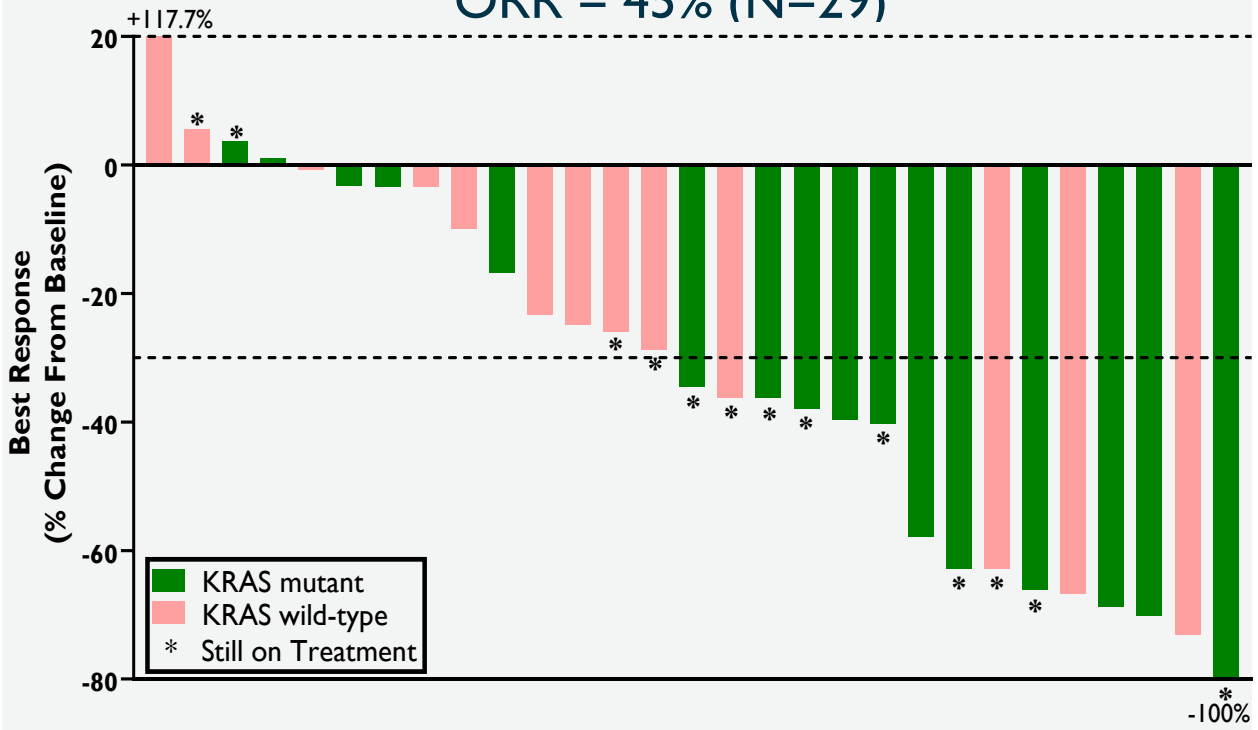
ORR = 46% (N=24)



RAMP 201 (Part A)

Interim Analysis - Blinded ICR

ORR = 45% (N=29)



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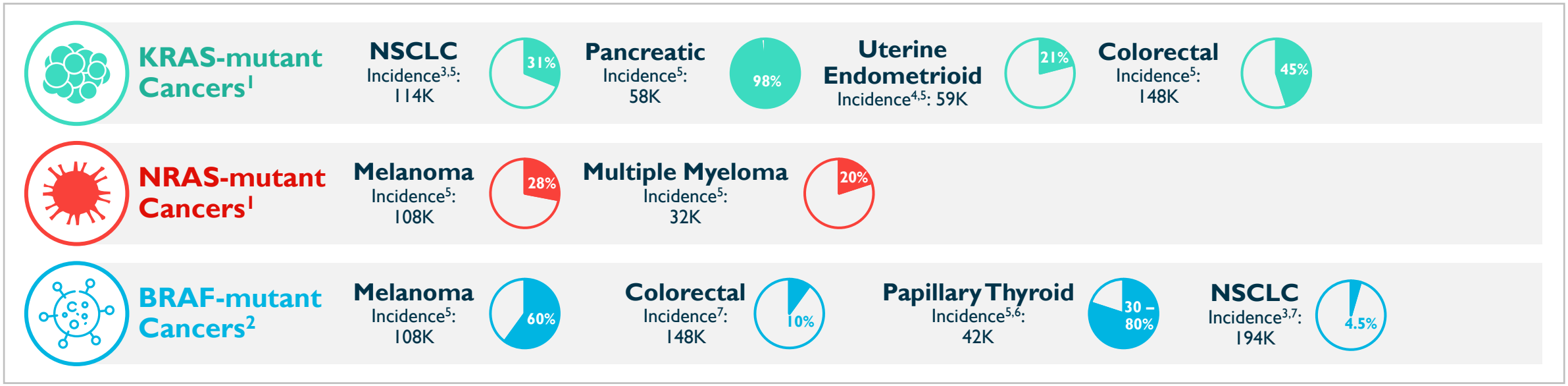
References: Banerjee, ASCO 2023; Banerjee, ESMO 2021

High Unmet Needs in Additional RAS/MAPK Pathway-Driven Cancers



Breadth of potential opportunity

- 30% of all human cancers are driven by mutations of the RAS family of genes[6]

Established prognostic significance

- Patients with mutations of the RAS family have an overall worse prognosis

Challenges with conventional approaches

- Modest progress; limited number of approved therapies
- Single agent therapies (e.g., MEK inhibitors) associated with resistance
- Tolerable combination regimens with MEK inhibitors have been challenging
- Approved RAS inhibitors address only a minority of all RAS mutated cancers (KRAS G12C)

Incidence References:
[1]Reference for RAS mt frequencies – Cox et al. *Nature Reviews* 13: 828, 2014; [2]Reference for BRAF mt frequencies – Turski et al. *Mol Cancer Ther* 15: 533, 2016
[3]50% of NSCLC is adenocarcinoma (Pakkala and Ramalingam JCI Insight 2018); [4]90% of all uterine cancers are of the endometrial type (ACS); [5]Cancer Statistics 2020, Siegel et. al. *CA Cancer J Clin* 2020;70:7-30; [6]8 out of 10 thyroid cancers are of the papillary type (ACS)[7]CbioPortal

References:
McCormick F Clin Cancer Res 15April2015; [6]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

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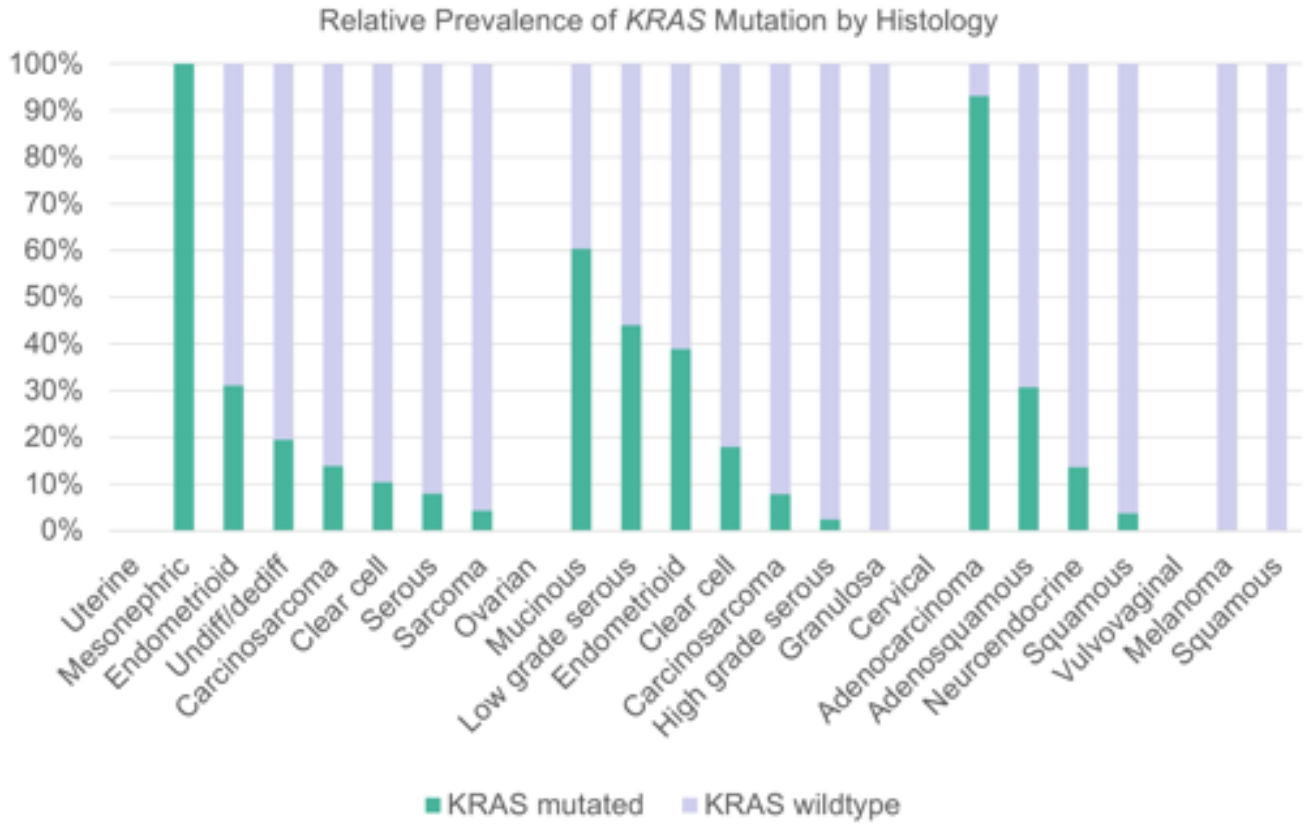
Combination of Avutometinib and Defactinib Being Explored in Additional MAPK-Driven Gynecological Cancers



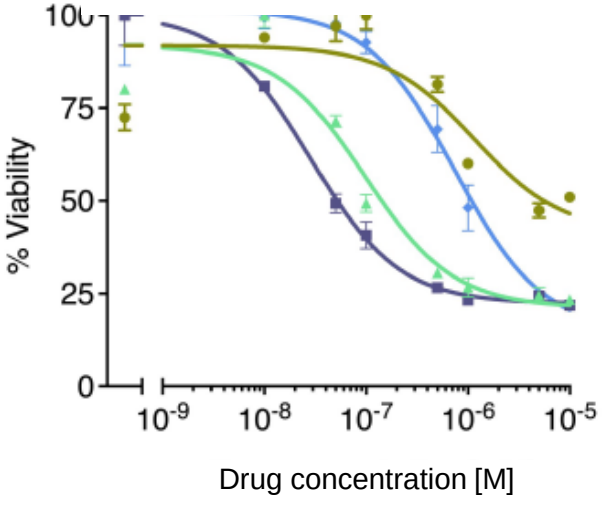
- High prevalence of KRAS mt in additional gynecological cancers including mesonephric, cervical cancer, mucinous ovarian cancer, etc.
- **These data support the ongoing clinical evaluation of avutometinib + defactinib for treatment of MAPK-driven gynecological cancers (NCT05512208, NCT05787561)**

Reference: Son, ASCO 2023

Avutometinib + FAK Inhibitor is Effective in BRAF V600E Melanoma Resistant to BRAFi + MEKi

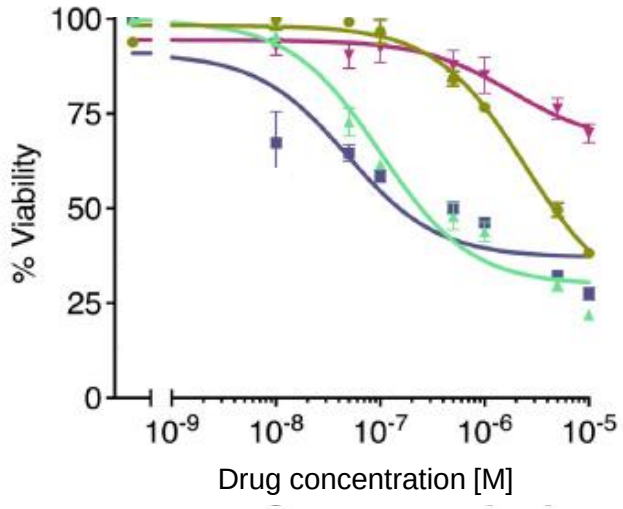
Avutometinib + FAKi combination inhibits proliferation of patient-derived melanoma cells resistant to BRAFi or MEKi

YUZEST (BRAF V600E)
- BRAFi resistant -



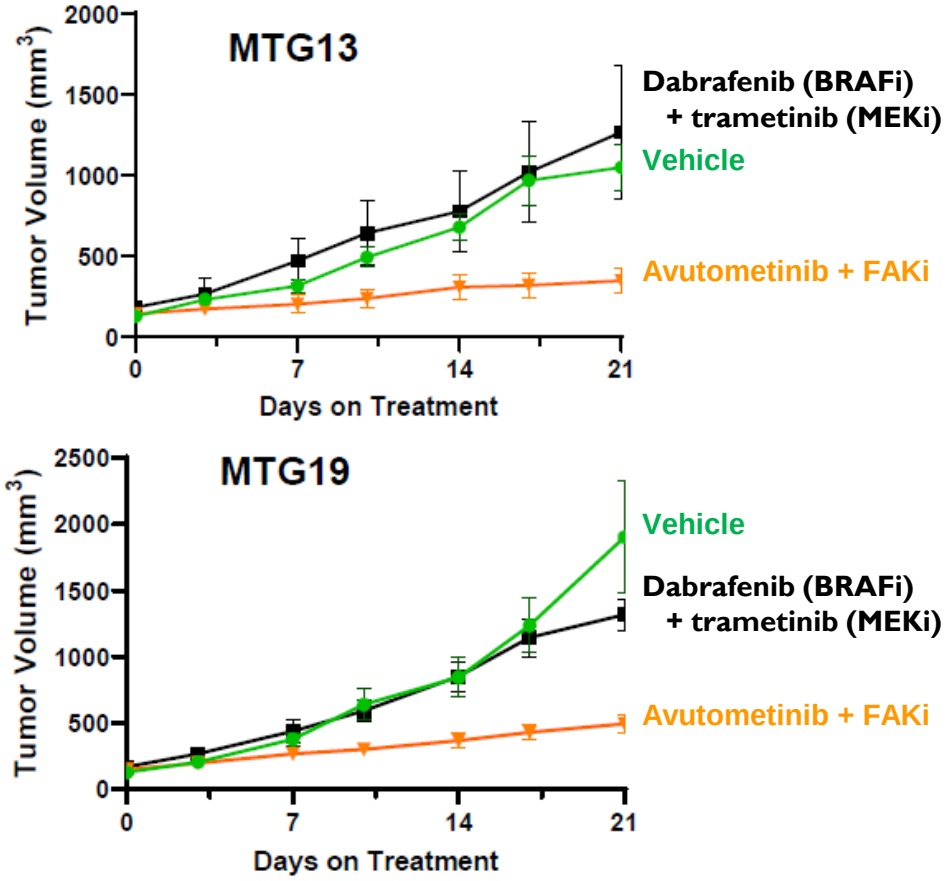
- Defactinib
- Vemurafenib (BRAFi)
- Avutometinib
- Avutometinib + defactinib

YUGASP (NRAS Q61L)
- MEKi resistant -



- Defactinib
- Trametinib (MEKi)
- Avutometinib
- Avutometinib + defactinib

Avutometinib + FAKi combination inhibits tumor growth in BRAFi+MEKi-resistant BRAF V600E patient-derived melanoma models



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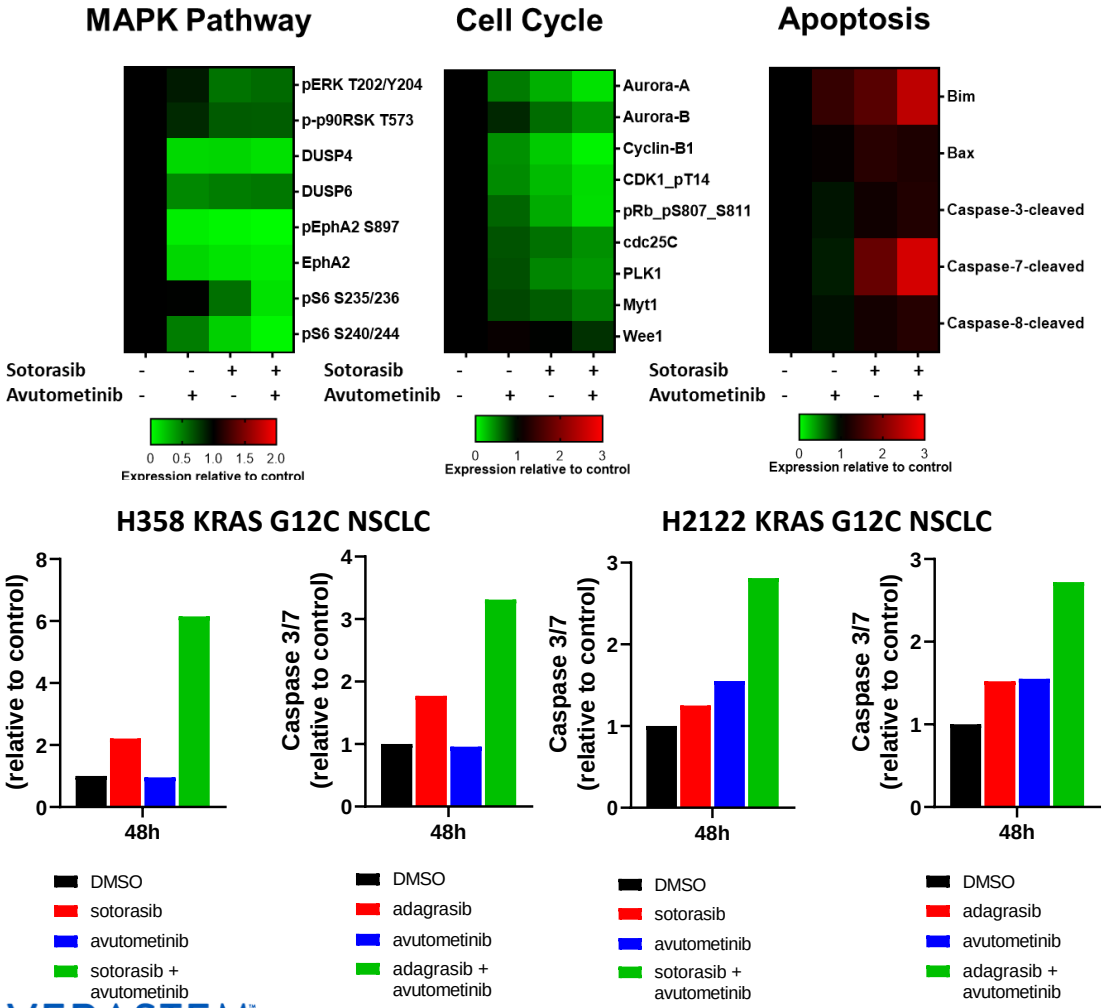
Collaboration with Silvio Gutkind, UCSD & Ruth Halaban, Yale

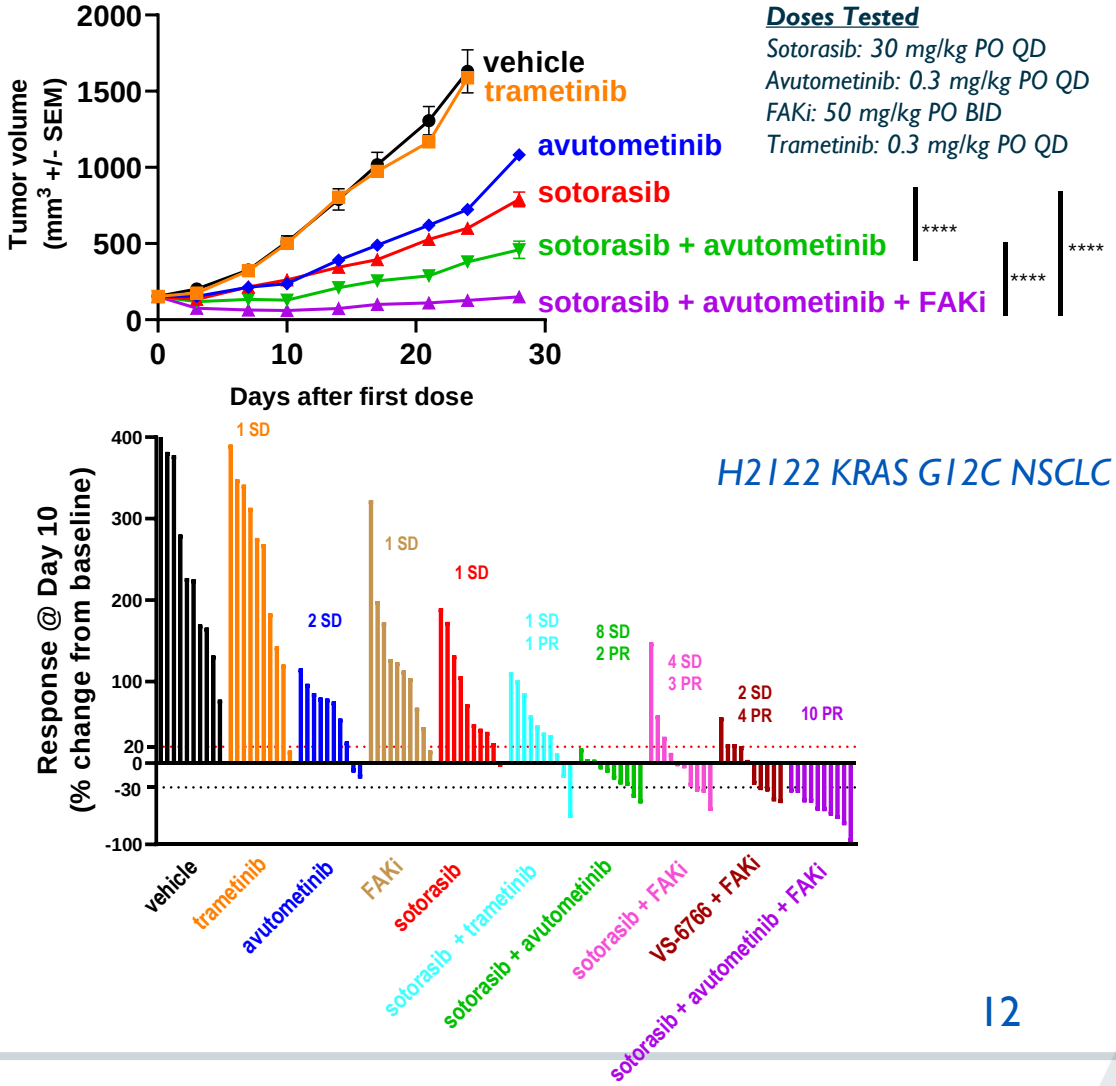
Collaboration with Sheri Holmen, U Utah

Avutometinib ± FAKi Potentiates Anti-Tumor Efficacy of G12Ci in G12Ci-Naïve KRAS G12C NSCLC Models

RAS, RAF & MEK blockade with avutometinib + G12C inhibitor confers anti-proliferative & pro-apoptotic signaling



Avutometinib & FAKi potentiate sotorasib-induced anti-tumor efficacy in KRAS G12C NSCLC models



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Reference: Coma et al., AACR 2021

Avutometinib ± FAKi Restores Anti-Tumor Efficacy of Sotorasib in G12Ci-Resistant KRAS G12C Models

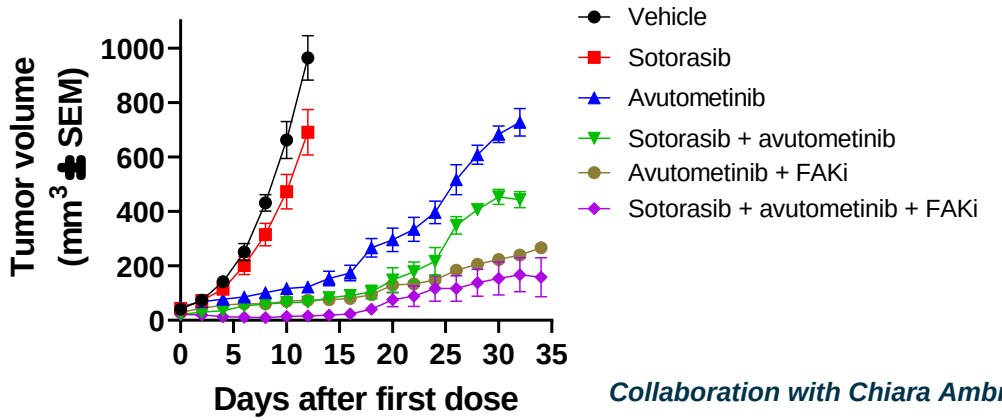
Avutometinib is effective against acquired KRAS mutations that occur clinically upon progression on G12C inhibitors

	IC50 (nM)		
Cell Line	Sotorasib	Adagrasib	Avutometinib
G12C	29	3	14
G12D	435	382	7
G12C/R68S	157	85	13
G12C/H95D	11	235	10
G12C/Y96C	438	216	4
G12C/Y96D	>5000	578	17

<30 nM	30 - 150 nM	>150 nM

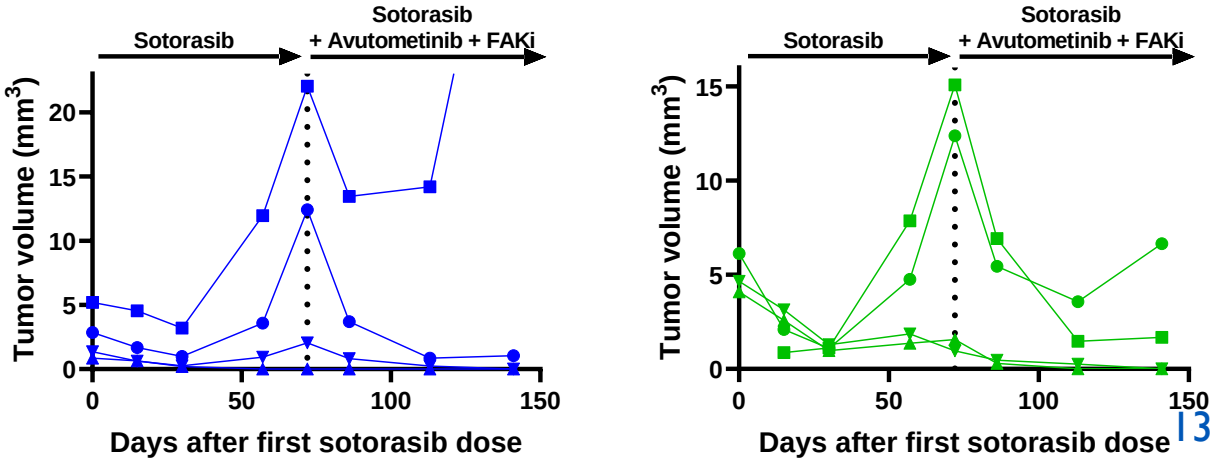
Collaboration with Andy Aguirre, DFCI

Addition of avutometinib + FAK inhibitor to sotorasib increases tumor growth inhibition in a sotorasib-resistant KRAS G12C/Y96D model



Collaboration with Chiara Ambrogio, U Turin (Italy)

Addition of avutometinib + FAKi restores anti-tumor activity after progression on sotorasib monotherapy in a KRAS G12C NSCLC GEMM model



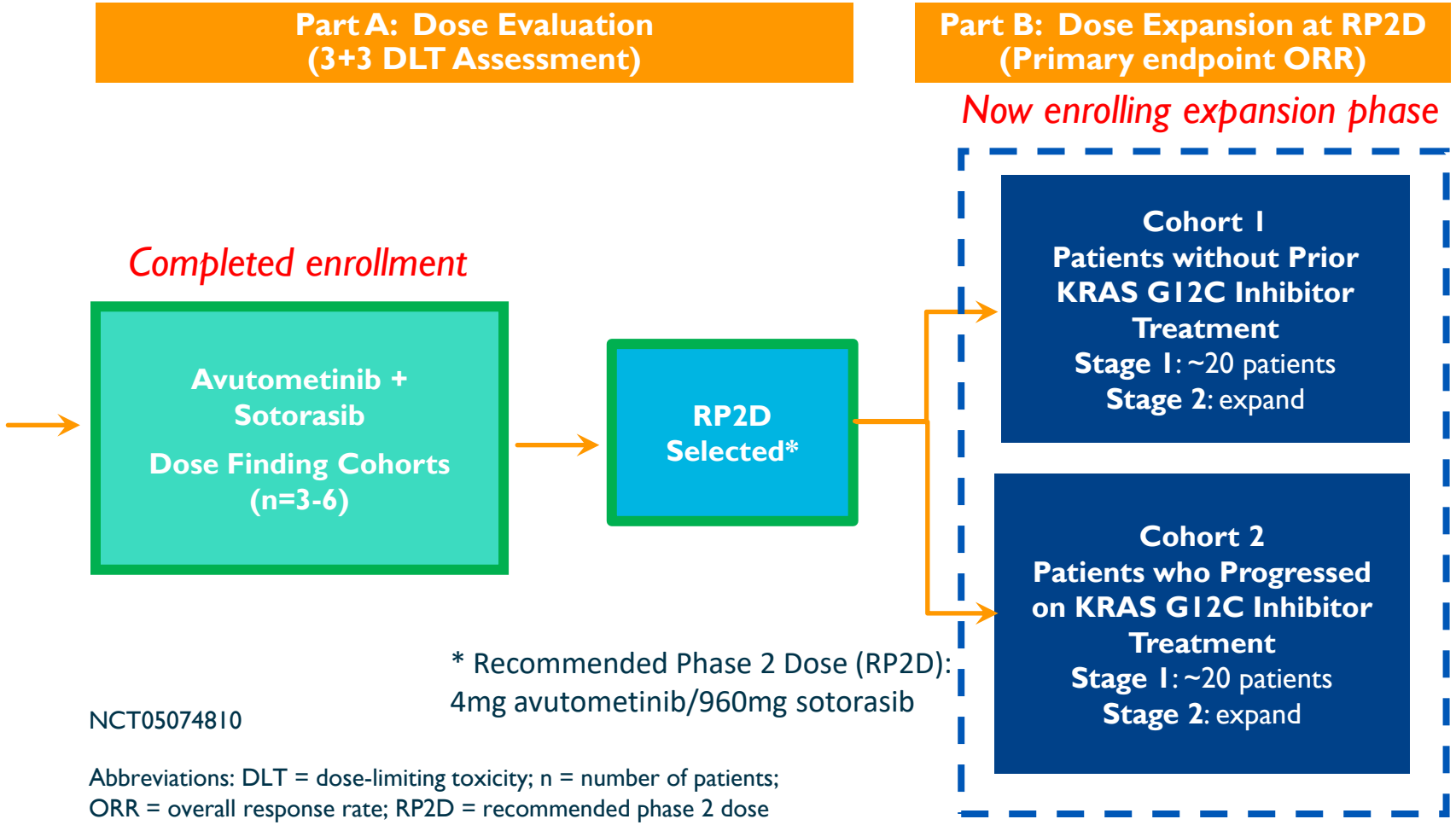
Reference: Coma et al., AACR RAS meeting 2023

Collaboration with Mariano Barbacid, CNIO (Spain)

RAMP 203: Phase 1/2 Trial of Avutometinib + Sotorasib in G12Ci-naïve and G12Ci-progressing KRAS G12C NSCLC

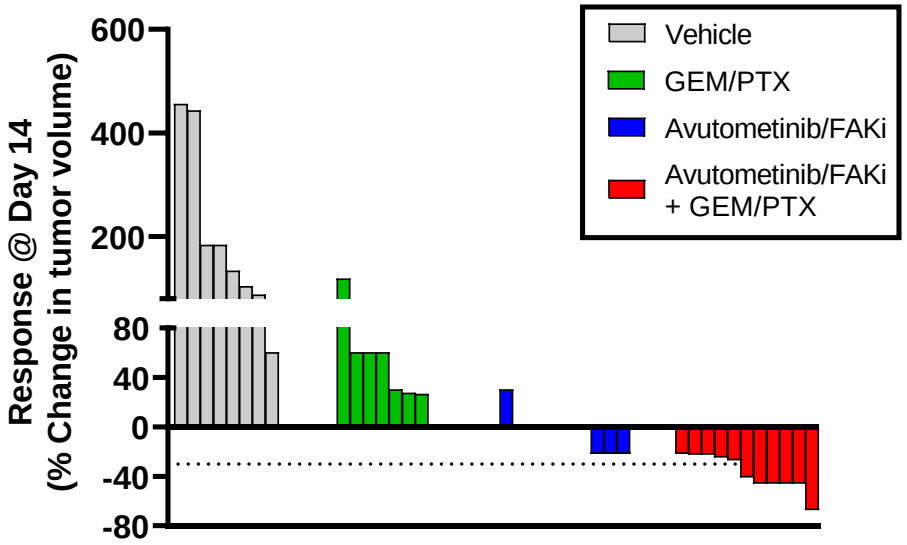
- Patients must have a KRAS G12C mutation determined using validated test
- Treatment with at least 1 but no more than 3 prior systemic regimens, for Stage 3B-C or 4 NSCLC*
- Patient may have previously received adjuvant chemotherapy for earlier-stage disease
- Measurable disease according to RECIST 1.1
- ECOG performance status ≤ 1

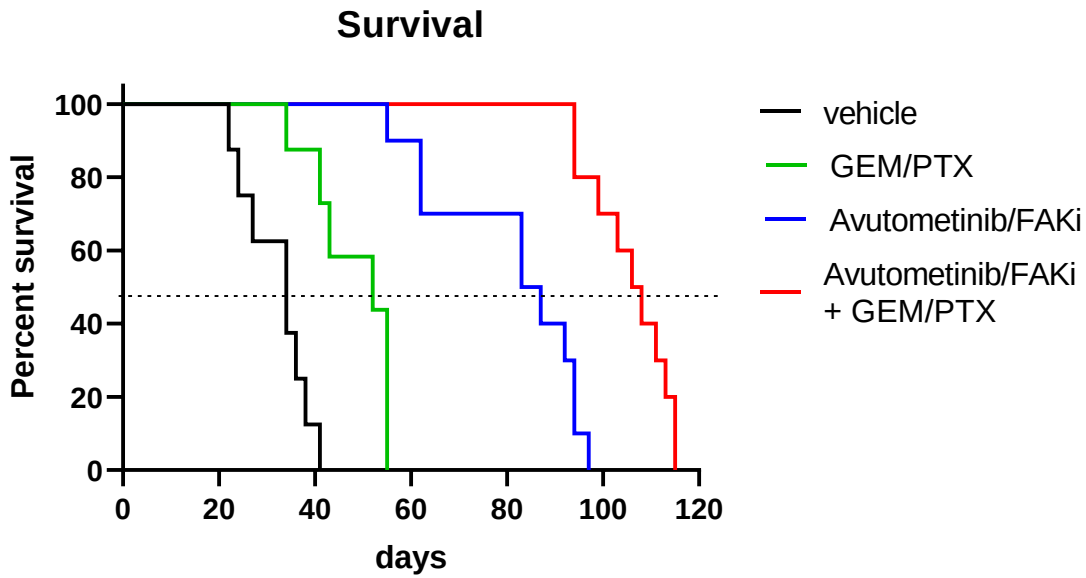
*may include patients with or without prior G12C therapy



Clinical trial also ongoing with avutometinib + adagrasib in KRAS G12C NSCLC (RAMP 204; NCT05375994)

Addition of Avutometinib + FAKi to Chemotherapy Induces Tumor Regression and Increases Survival in a KRAS/p53 Pancreatic Cancer Mouse Model





- The combination of avutometinib + FAKi induces tumor growth inhibition and increases survival but induces tumor regression only in some mice
- Addition of chemo (gemcitabine + paclitaxel) to avutometinib/FAKi induces tumor regression in all mice and further increases survival

RAMP 205: Phase 1/2 Trial of Avutometinib/Defactinib + Gemcitabine/Nab-paclitaxel in Front Line Metastatic Pancreatic Cancer

- Patients with confirmed metastatic pancreatic ductal adenocarcinoma
- Eligible for treatment in the first-line setting with standard gemcitabine and nab-paclitaxel
- Prior adjuvant or neoadjuvant chemotherapy, radiotherapy or surgery is permitted if the last intervention/ dose was ≥ 12 months prior to the diagnosis of metastatic disease
- Measurable disease according to RECIST 1.1
- ECOG performance status ≤ 1

Part A: Dose Evaluation (3+3 DLT Assessment)

Enrollment ongoing

Avutometinib + Defactinib + Gemcitabine + Nab-paclitaxel

Dose Finding Cohorts (n=3-6)

→ RP2D Selection →

Part B: Dose Expansion at RP2D (Primary endpoint ORR)

Patients with PDAC
KRAS G12D
KRAS G12V
KRAS G12R
Others

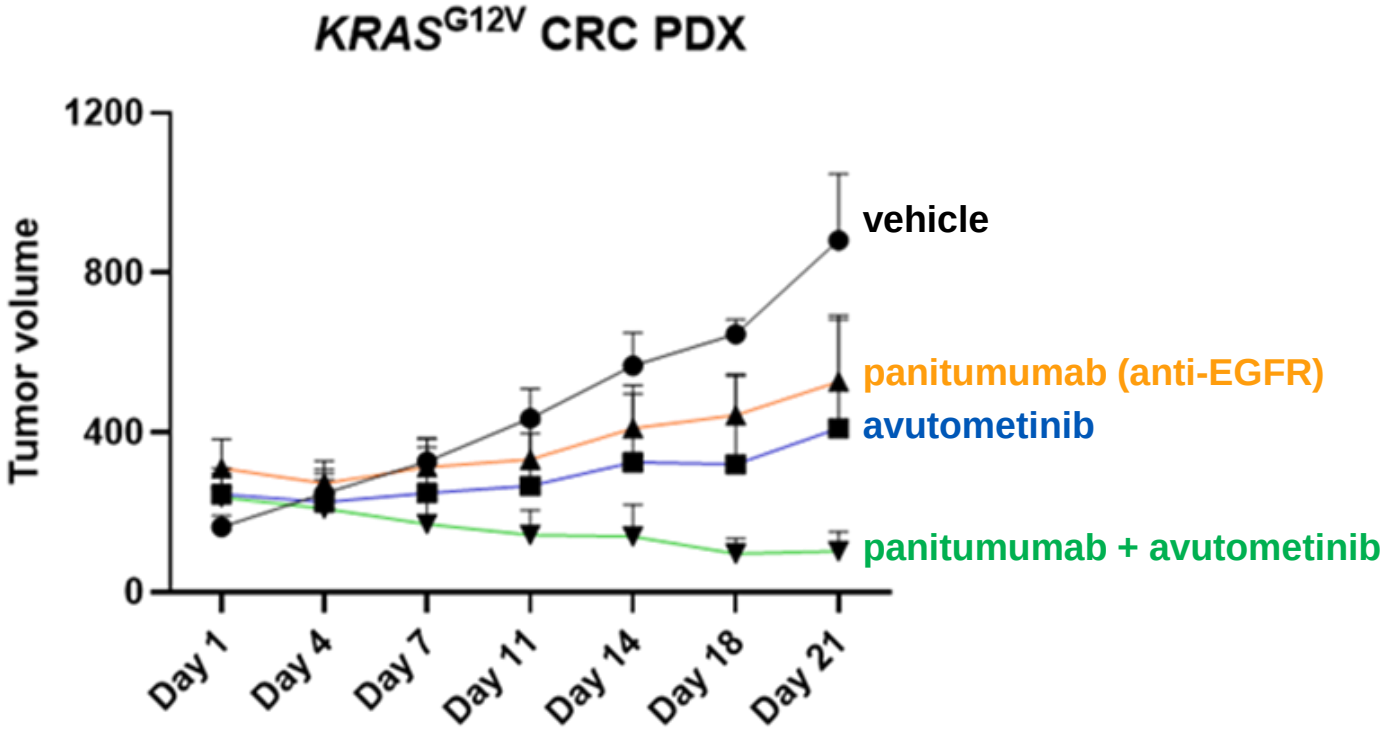
Treated with RP2D

Simon 2-stage design

NCT05669482

Abbreviations: DLT = dose-limiting toxicity; n = number of patients; ORR = overall response rate; RP2D = recommended phase 2 dose

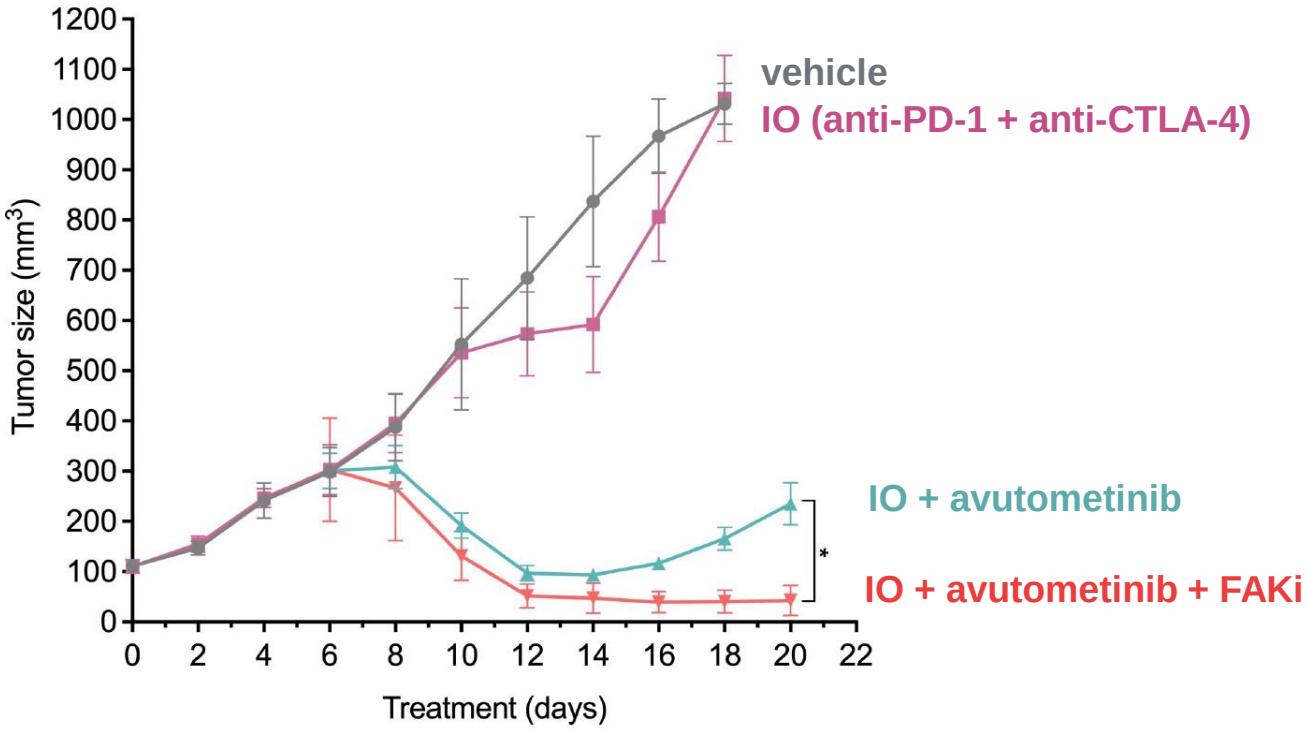
Combination of Avutometinib with Anti-EGFR mAb Induces Tumor Regression in a KRAS mt Patient-Derived Colorectal Cancer Model



Collaboration with Marwan Fakih, City of Hope

- Avutometinib + anti-EGFR (panitumumab) induces tumor regression in a KRAS mutant CRC patient-derived xenograft model
- G12Ci + anti-EGFR (sotorasib + panitumumab and adagrasib + cetuximab) have shown partial responses in KRAS G12C CRC (Fakih et al. ESMO 2021; Weiss et al. ESMO 2021)
- **These data support the ongoing clinical evaluation of avutometinib + cetuximab (anti-EGFR) for treatment of KRAS mt CRC (NCT05200442)**

Combination of Avutometinib + FAKi with Checkpoint Inhibitors Induces Tumor Regression in an IO-resistant BRAF V600E melanoma model



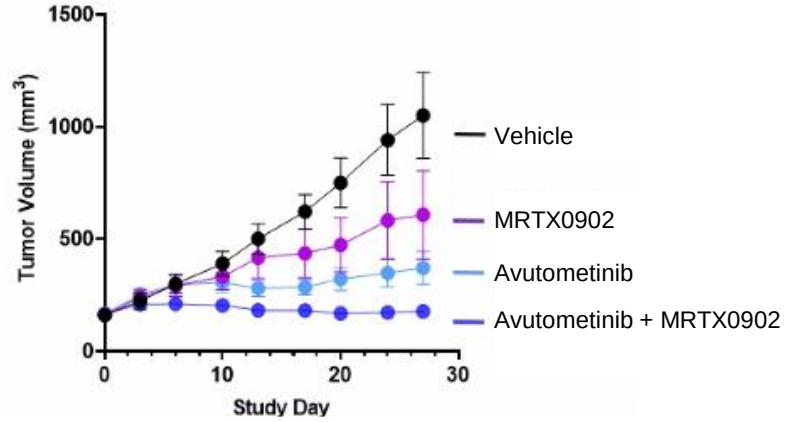
Collaboration with Silvio Gutkind, UCSD

- Avutometinib + IO (anti-PD-1 + anti-CTLA-4) induces tumor regression in an IO-resistant syngeneic BRAF V600E melanoma model (YUMM 1.7)
- FAK inhibition deepens and sustains avutometinib-induced tumor regression
- **These data support the imminent clinical evaluation of avutometinib + pembrolizumab (anti-PD-1) for treatment of BRAF V600E melanoma**

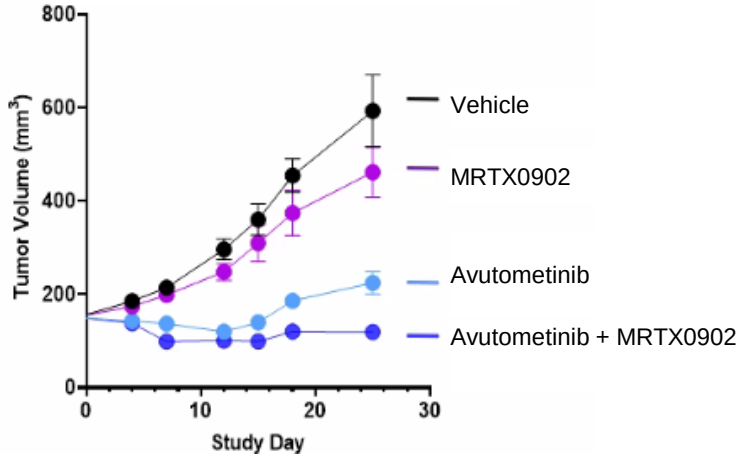
Additional Promising Combinations of Avutometinib with Upstream Blockers of the MAPK Pathway

Avutometinib + SOS1 inhibitor

NCI-H1435 (NF1^{K651N}) NSCLC

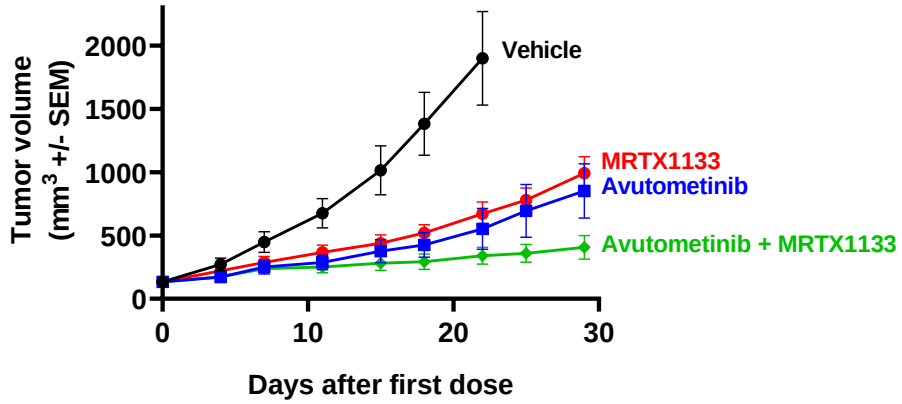


LN-229 (PTPN11^{A72S}) GBM

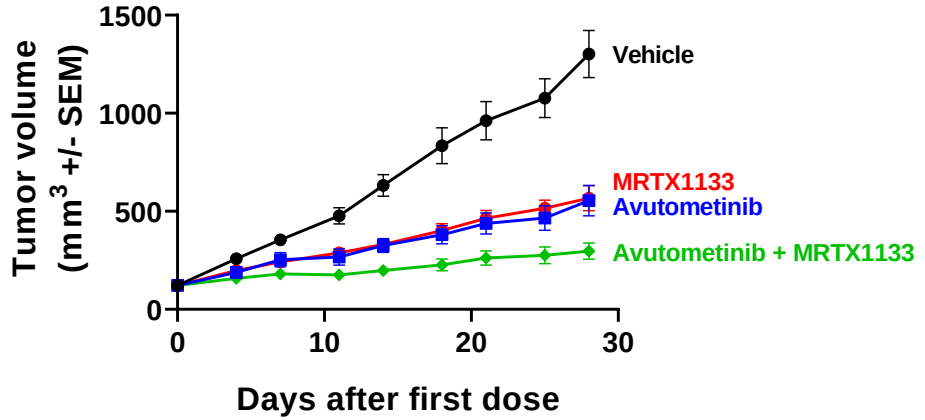


Avutometinib + KRAS G12D inhibitor

CR3300 KRAS G12D CRC PDX



PA1252 KRAS G12D pancreatic cancer PDX

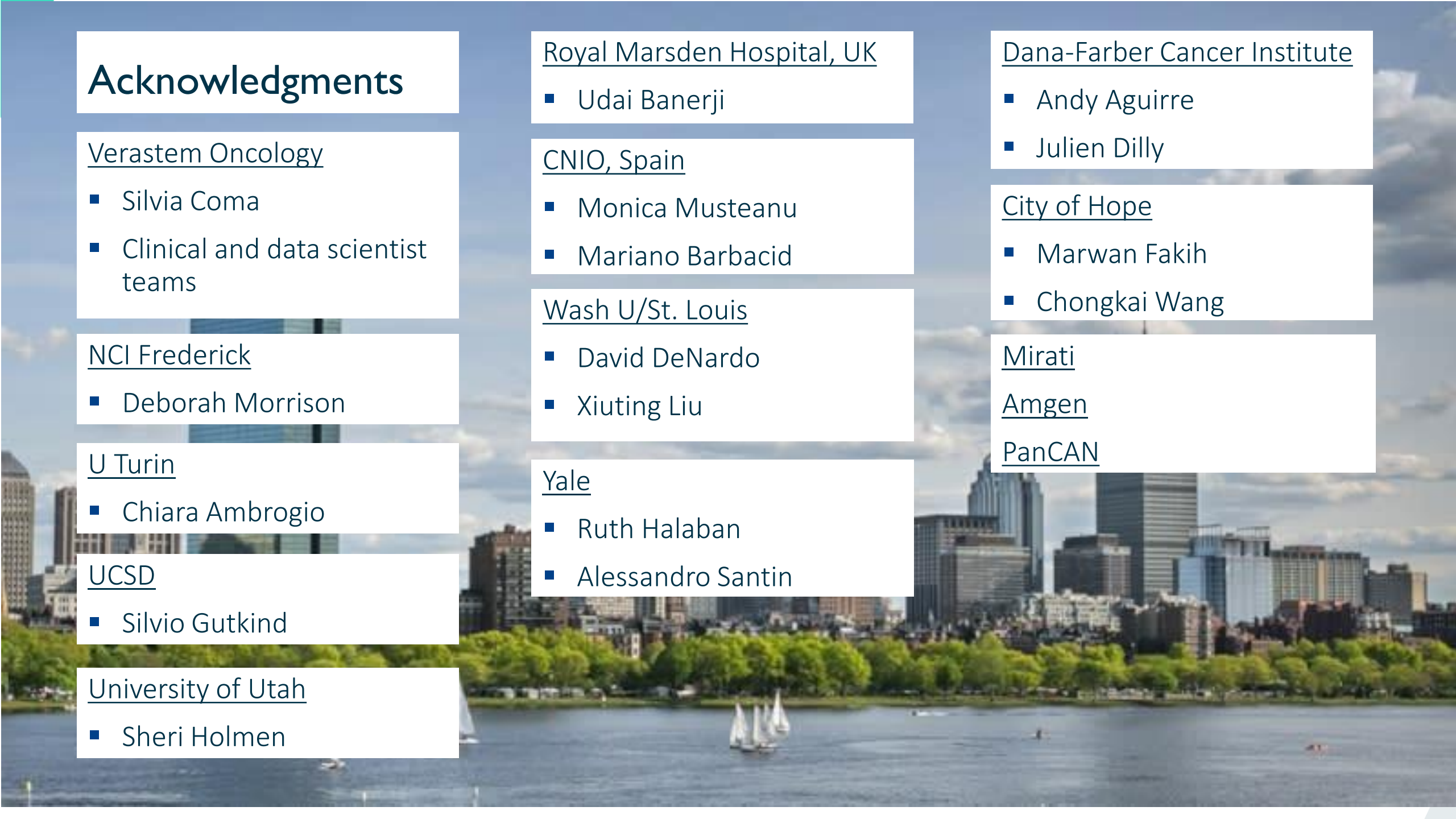


VERASTEM ONCOLOGY

Collaboration with Mirati Therapeutics

Conclusions: Avutometinib as Potential Backbone of Therapy for MAPK Pathway-Driven Cancers

- **Avutometinib** is a RAF/MEK clamp with activity across multiple MAPK pathway alterations and multiple cancer indications
  - Intermittent oral dosing schedule confers manageable clinical safety profile with potential for combinability with multiple target classes
- Combination of avutometinib with **defactinib** (FAKi) has shown consistent clinical efficacy with tolerability and has received Breakthrough Therapy Designation in low-grade serous ovarian cancer
  - Combination with **defactinib** also being evaluated in other gynecological cancers
- Combinations with **sotorasib** or **adagrasib** (G12Ci) being evaluated in KRAS G12C NSCLC based on strong preclinical data in both G12Ci-naïve and G12Ci-resistant models
- Additional combinations under clinical evaluation based on preclinical rationale:
  - Combination with **chemotherapy (gemcitabine/Nab-paclitaxel) and defactinib** being evaluated in 1st line pancreatic cancer
  - Combination with **cetuximab** (anti-EGFR) in KRAS mt CRC
- Vertical combinations of avutometinib with **SOS1i** or **KRAS G12Di** also appear promising based on preclinical data



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