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APRIL 25–30
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Abstract 6368

Correlative preclinical studies to elucidate mechanisms of synergy of the combination of the RAF/MEK clamp avutometinib and the FAK inhibitor defactinib in low grade serous ovarian cancer

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Disclosure Information

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Udai Banerji

I have the following relevant financial relationships to disclose:

Employee of: The Institute of Cancer Research that has commercial interests in CYP17, AKT, MPS-1 and FLT3/Aurora kinase inhibitors, molecular glues and folate receptor targeted therapies

Consultant for: None

Speaker's Bureau for: None

Grant/Research support: Verastem Oncology, Chugai, Avacta

Stockholder in: None

Honoraria from: Carrick Therapeutics, Pharmenable, Ellipsis Pharmaceuticals, Amalus Therapeutics, Dania Therapeutics, Pegascy

- and -

My additional financial relationship disclosures are: None

I am going to be discussing use of currently unlicensed anticancer drugs

Background – Low grade serous ovarian cancer (LGSOC)

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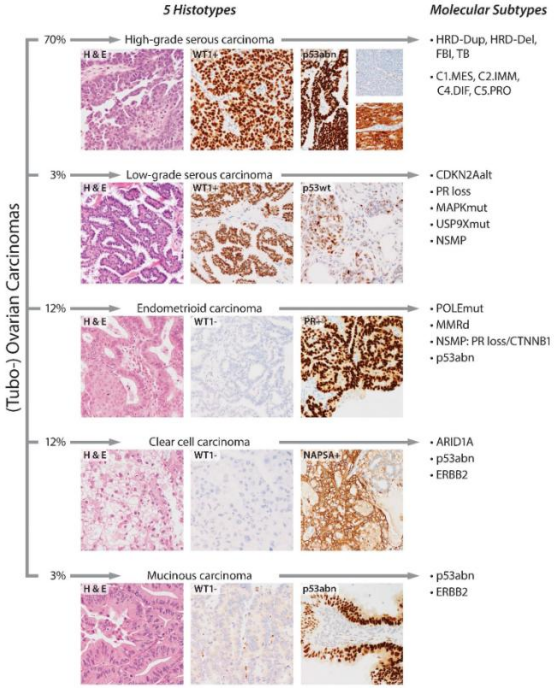


Pathway	Nasioudis et al, 2023[55]	Gershenson et al, 202218	Manning-Geist et al, 2022[14]	Musacchio et al, 2022[21]	Cheasley et al, 2021[19]	Etemadmoghadam et al, 2017[20]
Cohort	n=324	n=215	n=119	n=56	n=71	n=23*
Method	NGS database analysis (panel sequencing, MAPK/ERK pathway gene)	NGS (multiple academic and commercial panels)	NGS using the MSK-IMPACT (panel sequencing)	NGS platform FoundationOne CDX, targeted panels (HRR, MAPK, and endocrine-resistance pathways)	NGS (panel sequencing)	WES (n=22), WGS (n=1)
RAS/RAF/MAPK main pathway	*KRAS* 29.3% *BRAF* 8% *NRAS* 8.3% *HRAS* 0.3%	*KRAS* 33% *BRAF* 8.4% *NRAS* 11.2% *MAP2K1* 1.4% *RAF1* 0.5%	*KRAS* 32.8% *BRAF* 10.9% *NRAS* 10.9% *HRAS* 0.8% *MAP3K1* 1.7%	*KRAS* 21.4% *BRAF* 10.7% *NRAS* 14.3%	*KRAS* 26.7% *BRAF* 12.6% *NRAS* 8.5%	*KRAS* 21.7% *BRAF* 13% *NRAS* 21.7%
MAPK pathway-related genes	*NF1* 3.4% (n=10/288)	*NF1* 4.2% *NF2* 3.7% *ERBB2* 2.3% *EGFR* 0.5%	*EIF1AX* 10% *NF1* 1.7% *NF2* 1.7% *ERBB2* 4.2%	*NF1* 12.5% (3/7 VUS) *NF2* 3.6% (1/2 VUS) *ERBB2* 5.5% (2/3 VUS)	*EIF1AX* 5.6% *NF1* 4.2% *NF2* 4.2% *ERBB2* 2.8%	*EIF1AX* 13% *NF1* 8.7%
Cell cycle regulation	NA	*CDKN2A* 3.3% *CDKN2A/B* 2.8%	*CDKN2A* 8%	*CDKN2A/B* 19.6%	*CDKN2A* 15.5% (loss 9.9%, OE 5.6%; IHC)	NA
Ubiquitinylation	NA	NA	NA	NA	*USP9X* 26.7%	*USP9X* 13%
Rare genes with interesting biology	NA	*PIK3CA* 1.9% *CREBBP* 1.9% *ARID1A* 0.5%	*ARID1B* 2.5% *ARID1A* 1.7% *DOTIL* 1.7%	*PIK3CA* 5.4% (1/3 VUS) *AKT1* 1.8%	*PIK3CA* 5.6% *ARID1A* 8.5% *MACF1* 11.2% *DOT1L* 5.6% *ASH1L* 4.2%	*FFAR1* 8.7%

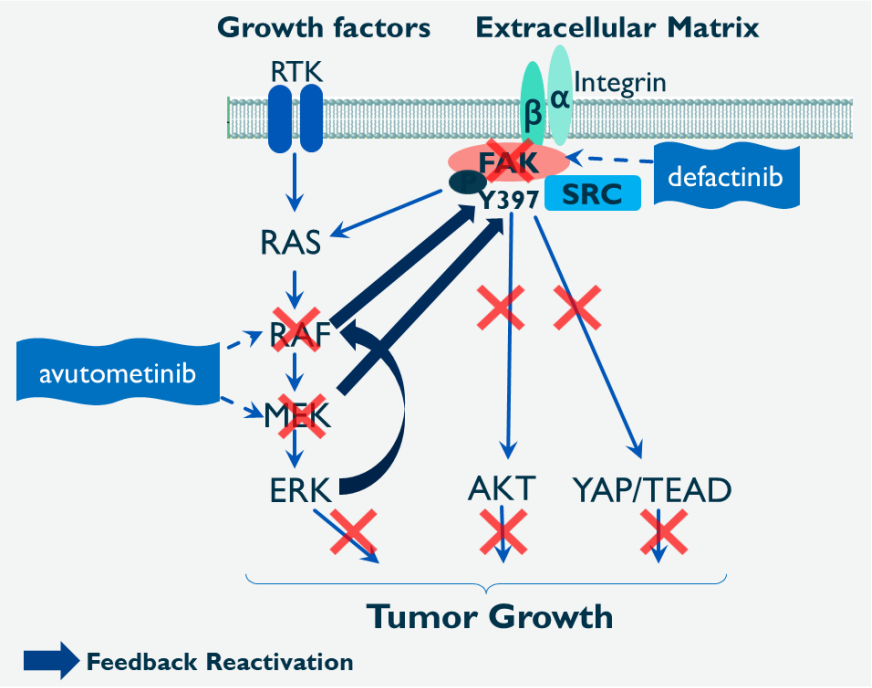
Subtype of ovarian cancer characterized by aberrations in the MAPK pathway and lack of response to chemotherapy

Kobel M et al.; Cancers 2022,14(2):416

Kelliher L et al., Int J Gynecol Cancer 2024,34(10):1630-1638

Aims

To understand mechanisms of synergy of the combination of MAPK and FAK inhibition in-vitro and in-vivo in the setting of LGSOC



Mechanism of action of drugs in combination being studied

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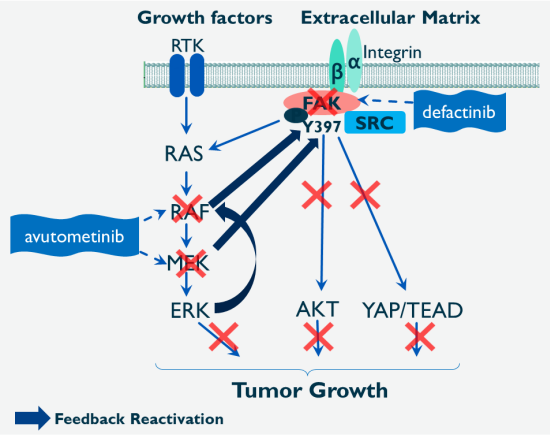

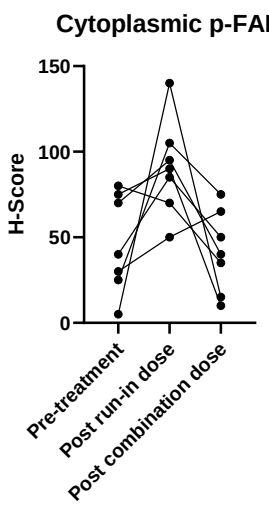

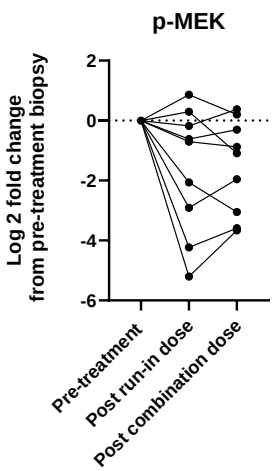

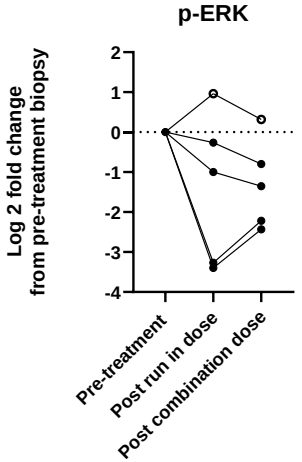

- Avutometinib is a RAF/MEK clamp that causes reduction in phosphorylation of MEK and ERK and possible increase in phosphorylation of FAK
- Defactinib is a FAK inhibitor that causes reduction on phosphorylation of FAK
- Clinical Trial FRAME (NCT03875820) has confirmed mechanism of action of both drugs in biopsy tissue

AACR abstract CT143 2020

Growth inhibition caused by combination of avutometinib and defactinib in 2D and 3D LGSOC models

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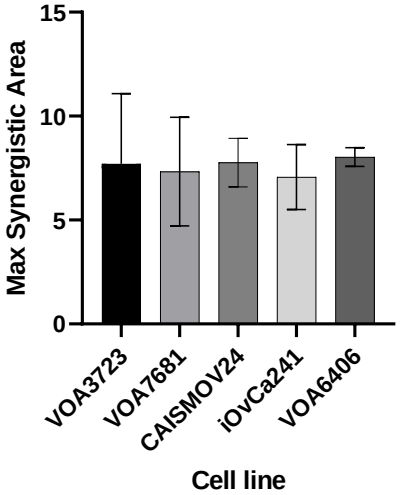
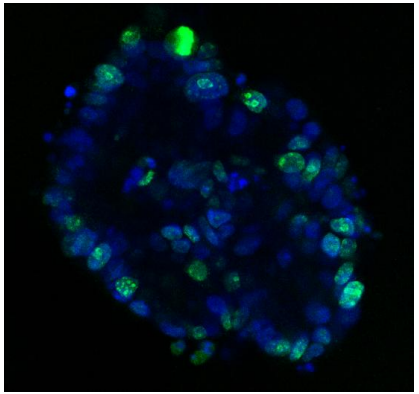
Avutometinib + Defactinib
(2D proliferation assay in cell lines)

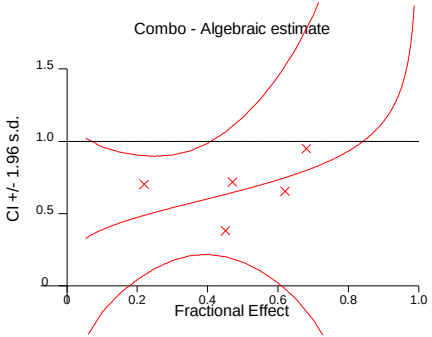


LGSOC organoid
***KRAS*^{G12V}**



Ki67 staining

Avutometinib + Defactinib
(3D proliferation assay in organoid)



Combination index
0.53 (SD 0.4)

- Synergy evident in a 3D organoid model and not in 2D LGSOC cell line models
- Synergy in 3D may be due to mechanism of action of defactinib related to integrin and YAP signaling

Evaluation of combination of avutometinib and FAK inhibitor VS4718 in PDX model

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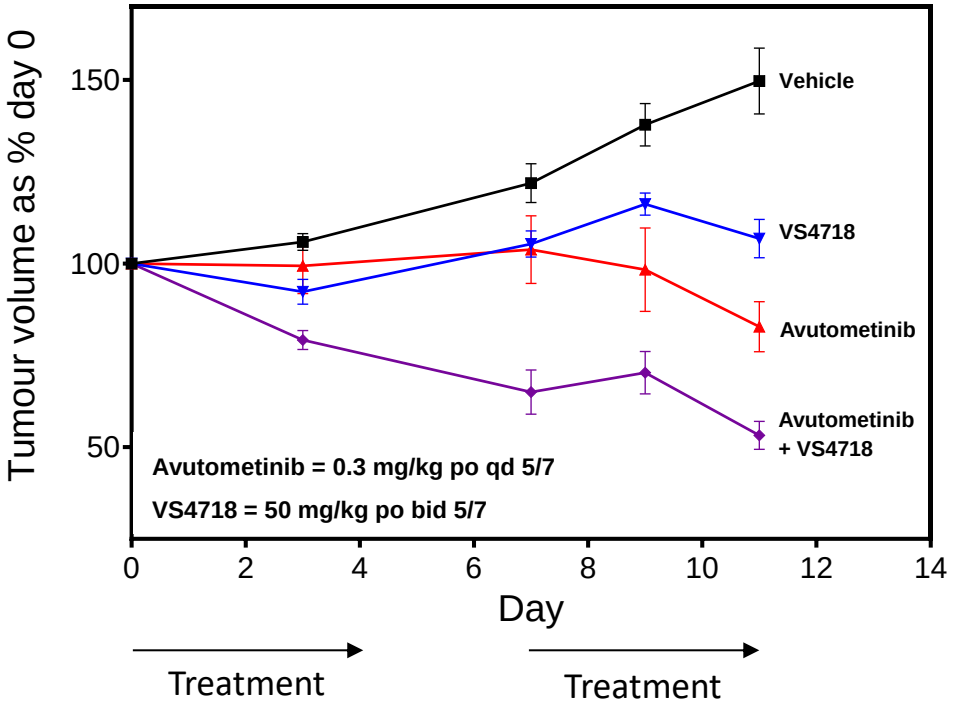

- Organoid isolated from a patient with LGSOC, characterized to have *KRAS*^{G12V} mutation
- Avutometinib (0.3 mg/kg oral qd) and FAK inhibitor (VS-4718; 50 mg/kg oral bid) administered 5 days on 2 days off for 2 cycles
- Samples taken 2 hours after the last dose of both drugs
- N=6 , tumors analyzed for pharmacodynamic changes by IHC, RNA seq and mass spectroscopy

Pharmacodynamic effects of combination

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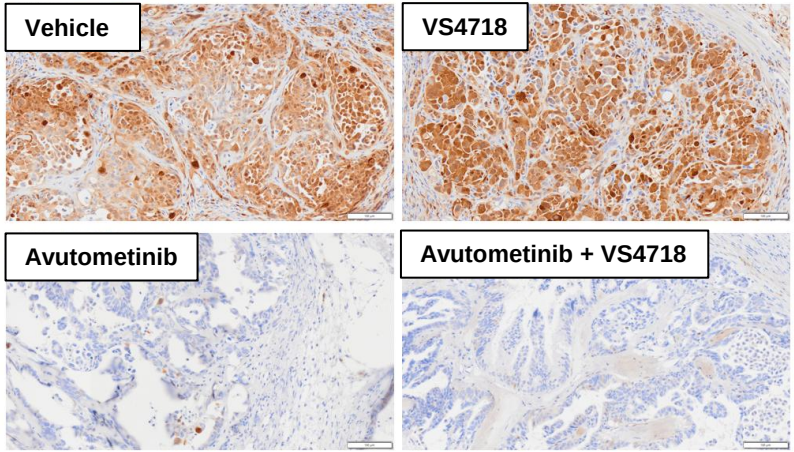
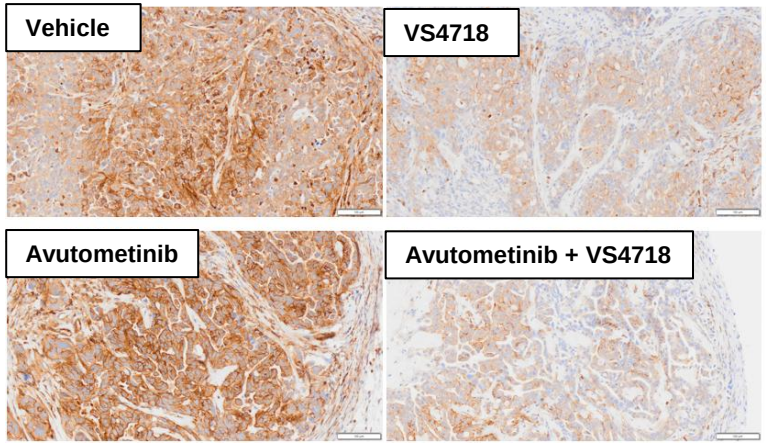
pERK



pFAK

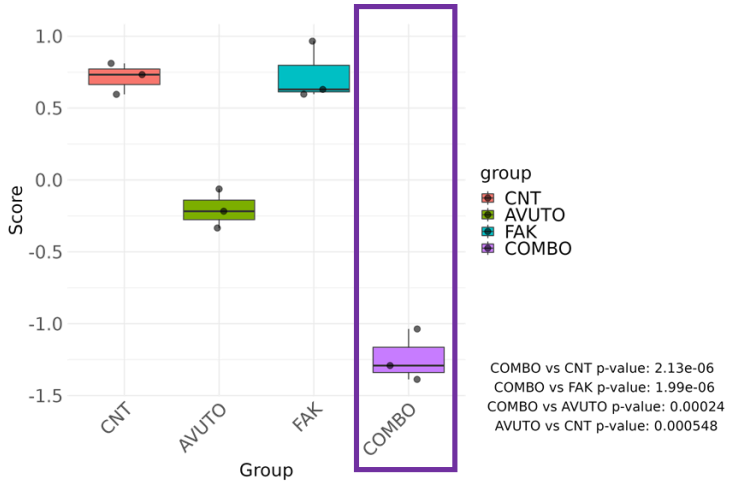


- Avutometinib shows reduction in levels of phosphorylated ERK and FAK inhibitor (VS-4718) shows reduction of phosphorylated FAK consistent with their mechanism of action

RNA seq RAS/MAPK signatures

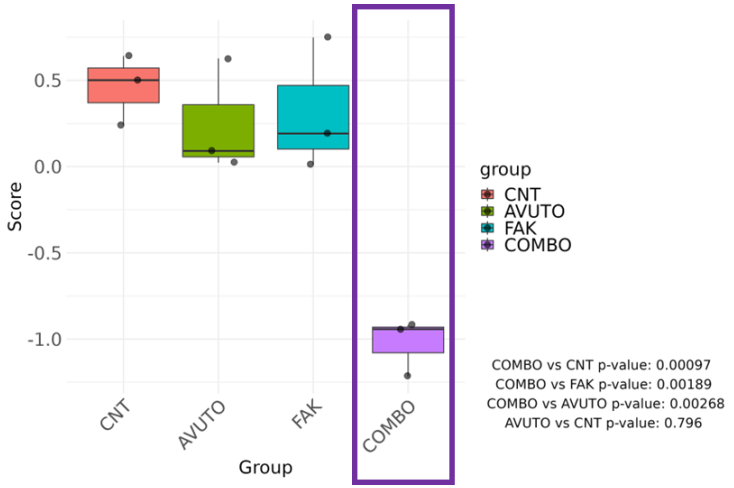
MAPK signaling

*MAPK public signature (*Wagle et al. 2018*)*



RAS signaling

RAS down signature (*Channing Der lab;* Klomp et al. 2024)



- Avutometinib + FAK inhibitor gives deeper inhibition of RAS/MAPK signaling

Similar reductions in MAPK effectors by RNA seq and Mass Spectroscopy

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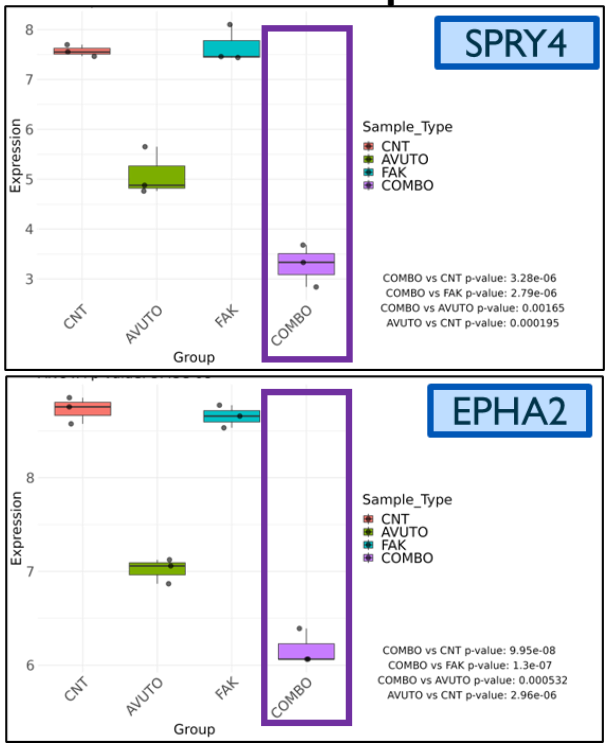
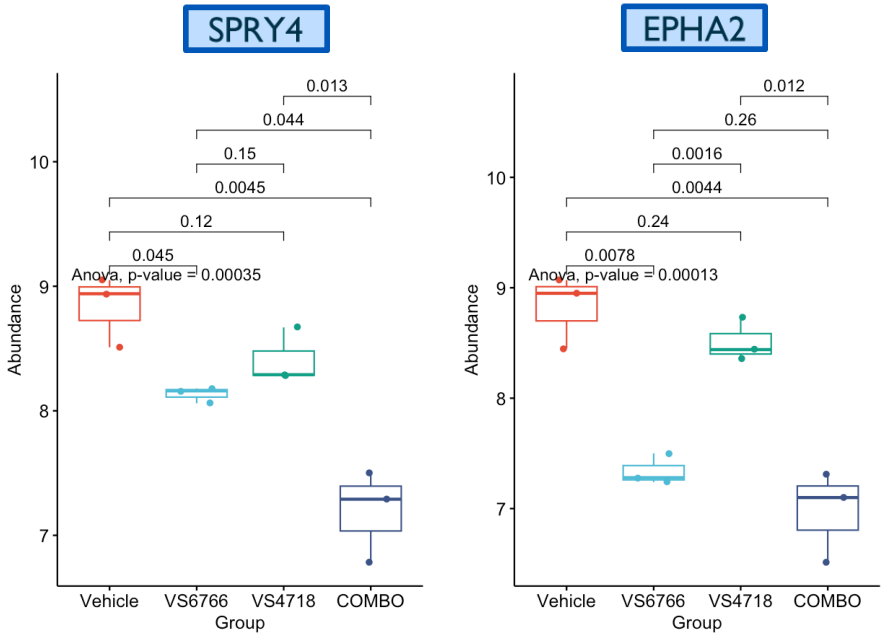
RNA seq



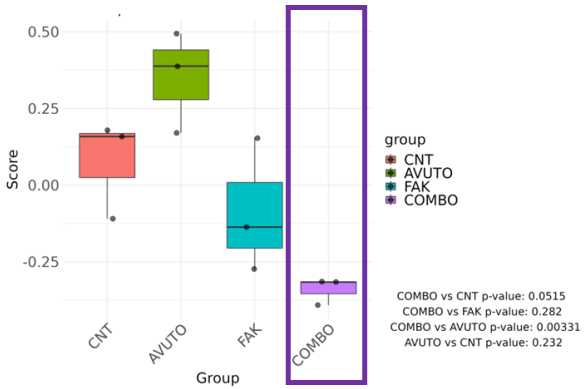
Mass Spec



RNA seq PI3K/MYC/TEAD signatures

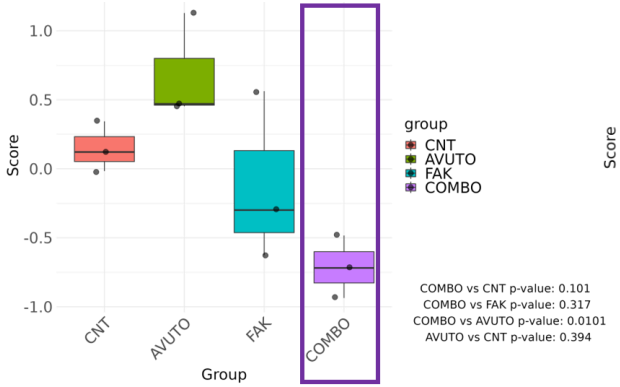
PI3K signaling

PI3K down signature (Zhang et al., 2018)



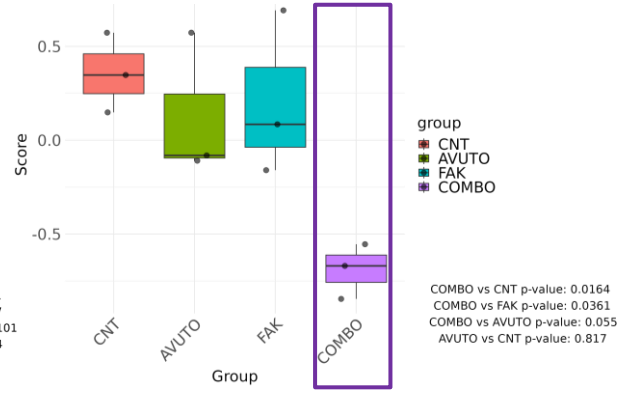
MYC signaling

MYC Hallmark V1 signature (MSigDB)



YAP/TEAD signaling

TEAD up signature (Channing Der lab; unpublished)



- Avutometinib activates PI3K and MYC signaling as potential adaptive resistance mechanisms and combination with VS4718 reverses this
- Combination of avutometinib and VS4718 causes synergistic downregulation of YAP/TEAD signaling

Combination Vs single agent efficacy in clinical trials

- RAMP 201 (NCT04625270) randomized phase 2 study randomized patients with LGSOC between single agent avutometinib and the combination of avutometinib and defactinib

Avutometinib (3.2 mg BIW) + Defactinib (200 mg BID)	Avutometinib monotherapy (4 mg BIW)
ORR: 31% overall • 44% in *KRAS*^{MT} • 17% in *KRAS*^{WT}	ORR: 17% overall • 23% in *KRAS*^{MT} • 13% in *KRAS*^{WT}

- Preliminary efficacy suggests superior objective response rates of the combination over avutometinib monotherapy

Banerjee SN et al., IGCS Annual meeting 2024

Conclusions

- Combination of avutometinib and defactinib causes synergistic growth delay in a 3D in-vitro model and patient derived LGSOC xenograft model
- Addition of FAK inhibition with avutometinib abrogates PI3K, MYC and TEAD signaling, reversing putative mechanisms of resistance
- Randomized clinical trial data suggest superior response rates for the combination of avutometinib and defactinib compared to avutometinib alone (RAMP 201; NCT04625270)
- The combination of avutometinib and defactinib is currently being evaluated in a randomized clinical trial against physician’s choice chemotherapy or hormonal therapy (RAMP 301; NCT06072781)

References for RNAseq Signatures

- MAPK public signature
  - Wagle MC et al. NPJ Precis Oncol 2018, Mar 7;2(1):7
- RAS down signature
  - Klomp JA et al. Science 2024 Jun 7;384(6700)
- PI3K down signature
  - Zhang et al., Cancer Cell 2018 Jun 12;31(6):820-832
- MYC Hallmark V1 signature
  - The Molecular Signatures Database (MSigDB)

Acknowledgements

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Patients and families of FRAME and RAMP201 studies

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- Clinical PD Biomarker Lab
  - Karen Swales
- Investigator Initiated Trials Team
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Monoceros
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RAMP201 Investigators

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Verastem Oncology

NHS National Institute for Health Research

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