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Transforming Gynecologic Cancer Care

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ANNUAL MEETING
ON WOMEN'S CANCER

San Diego, CA • 2024

Preclinical efficacy of RAF/MEK clamp avutometinib in combination with FAK inhibition in low grade serous ovarian cancer

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Financial Disclosure for:
Blair McNamara

I have the following financial relationships with ACCME defined ineligible companies to report over the past 24 months:

Avutometinib, defactinib and VS-4718 were provided by Verastem, Inc. via a material transfer agreement.

I have no financial relationships with ACCME defined ineligible companies to report

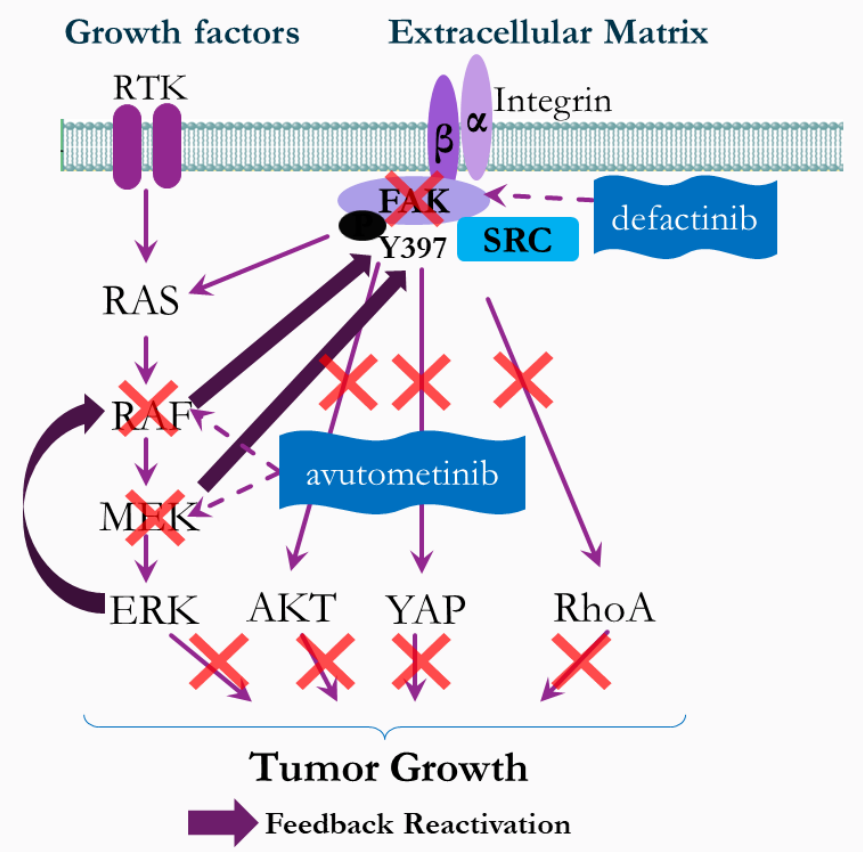
Unlabeled/Investigational Uses

I will not be discussing any unlabeled or investigational uses of any pharmaceutical products or medical devices.

Background

- Low grade serous ovarian carcinoma (LGSOC) is distinct from other epithelial ovarian cancers
- Compared to high grade serous ovarian carcinoma:
  - Younger age at diagnosis
  - Resistance to standard chemotherapies
  - Longer overall survival

Background



- Up to 60% of LGSOC harbor somatic alterations in the mitogen-activated protein kinase (MAPK) pathway
- Inhibition of MAPK signaling has shown therapeutic promise in LGSOC

- **Avutometinib** is a dual RAF/MEK clamp that induces an anti-tumor response through RAS/MAPK pathway inhibition
- **Defactinib** inhibits the avutometinib-induced reactivation of the FAK pathway

Objectives

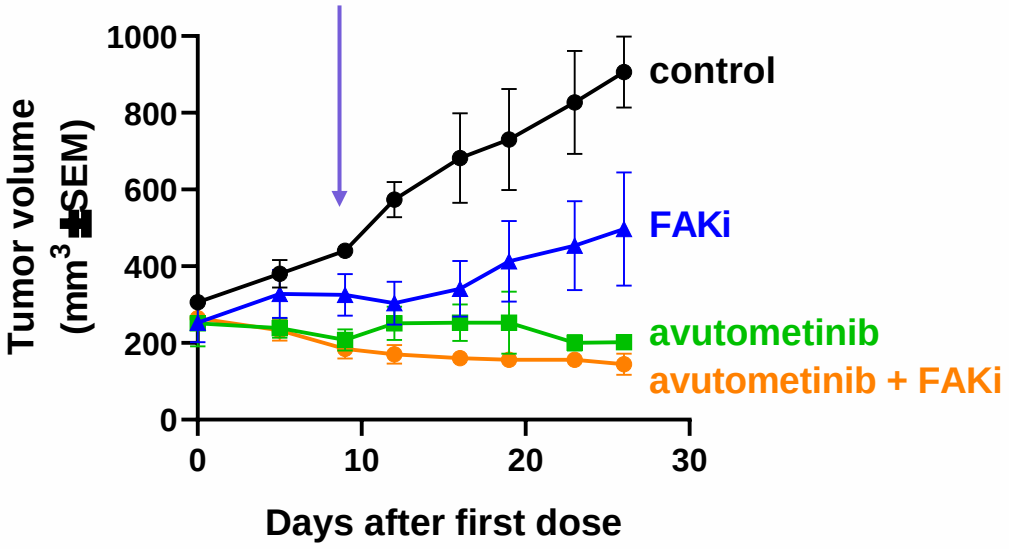
- Whole exome sequencing (WES) was used to characterize the genetic landscape of LGSOC patient-derived cell lines
- Patient derived xenografts (PDX) were used to establish the preclinical efficacy of the RAF/MEK clamp avutometinib alone and in combination with a FAK inhibitor
- The effect of avutometinib and defactinib on ERK and FAK pathways was evaluated by western blot

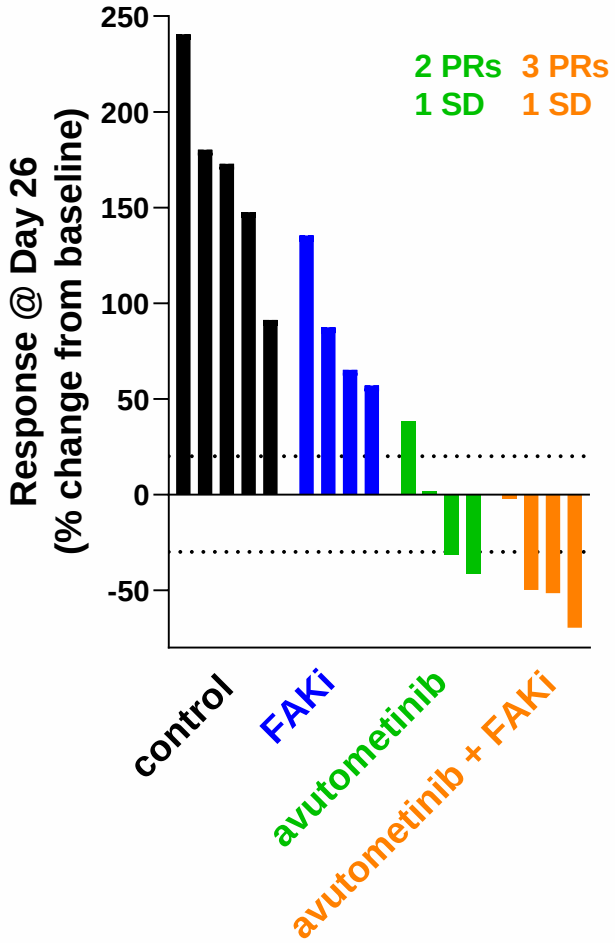
Results

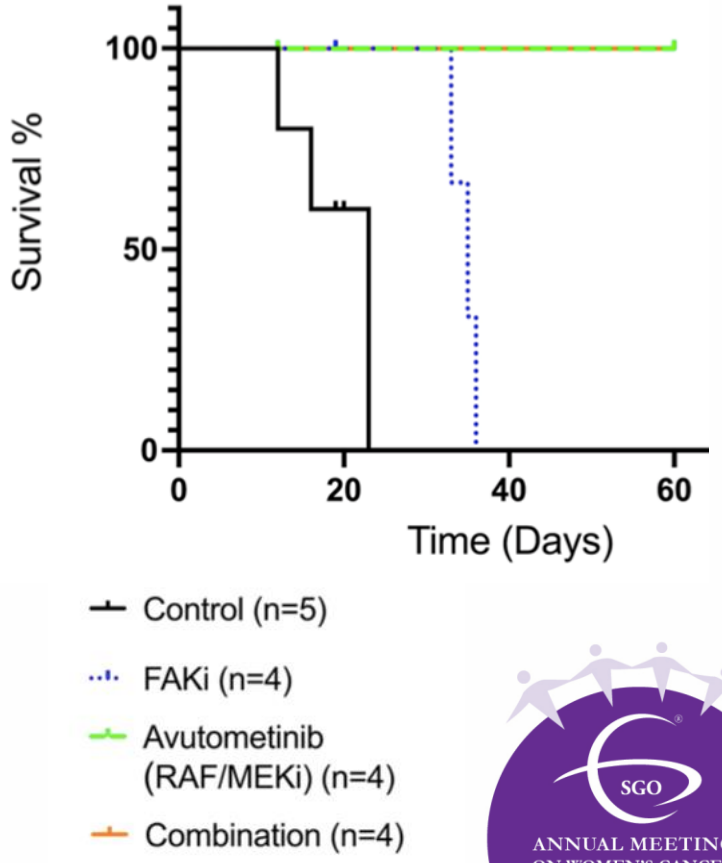
- WES of 3 patient-derived LGSOC detected wild type KRAS, NRAS, and BRAF
- The established PDX model demonstrated copy number variations in PTK2 (FAK) and PTK2B genes potentially sensitizing to FAK and RAF/MEK inhibitors

Results

In vivo avutometinib + FAKi led to a higher percentage of tumor regression compared to either agent as monotherapy

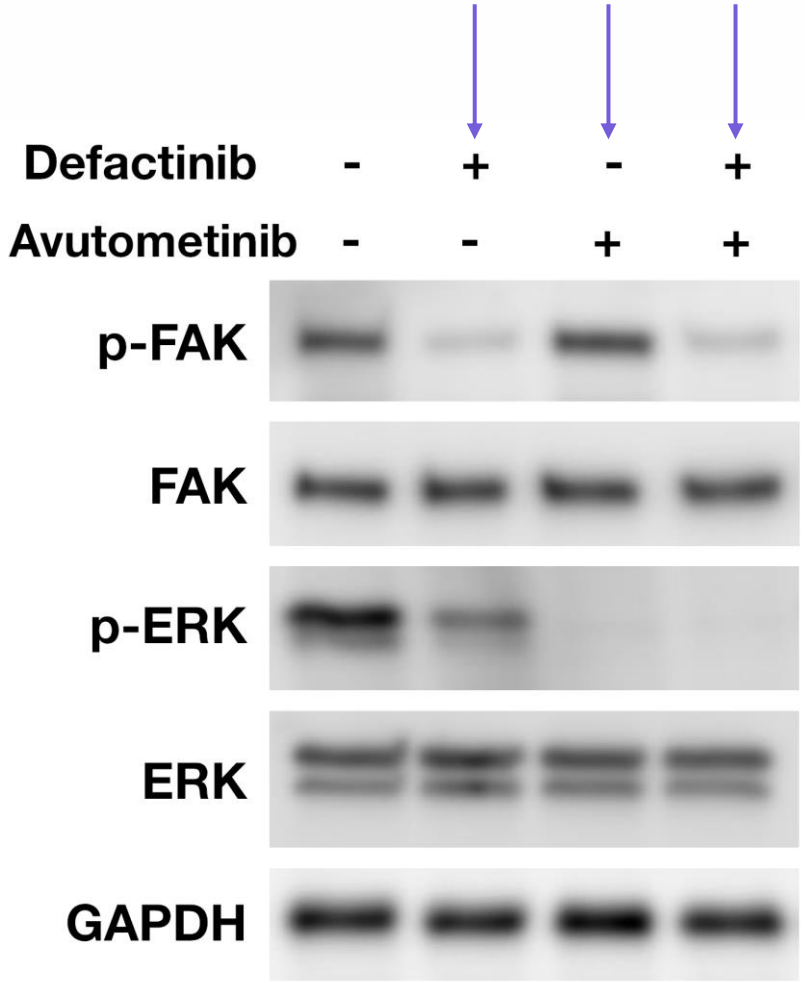






Results

- Defactinib and combined avutometinib and defactinib led to downregulated levels of p-FAK
- Defactinib reduced levels of p-ERK, combined avutometinib and defactinib led to greater reductions in p-ERK



Conclusions

- In a LGSOC PDX model, our study shows deeper tumor regression with the combination of avutometinib and FAKi relative to avutometinib alone
- In LGSOC patient-derived cells ex vivo, the combination of avutometinib + FAKi maximally blocked both pERK and pFAK
- These results support use of avutometinib in combination with defactinib for use in LGSOC regardless of KRAS mutation status
- Ongoing phase II (NCT04625270, RAMP 201) and phase III (NCT06072781, RAMP 301) clinical trials are investigating use of avutometinib with defactinib for patients with recurrent LGSOC

Thank you!

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