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PRIMARY ANALYSIS: PHASE II STUDY OF AVUTOMETINIB AND DEFACTINIB IN WOMEN WITH ADVANCED OR RECURRENT GYNECOLOGIC MESONEPHRIC CANCER

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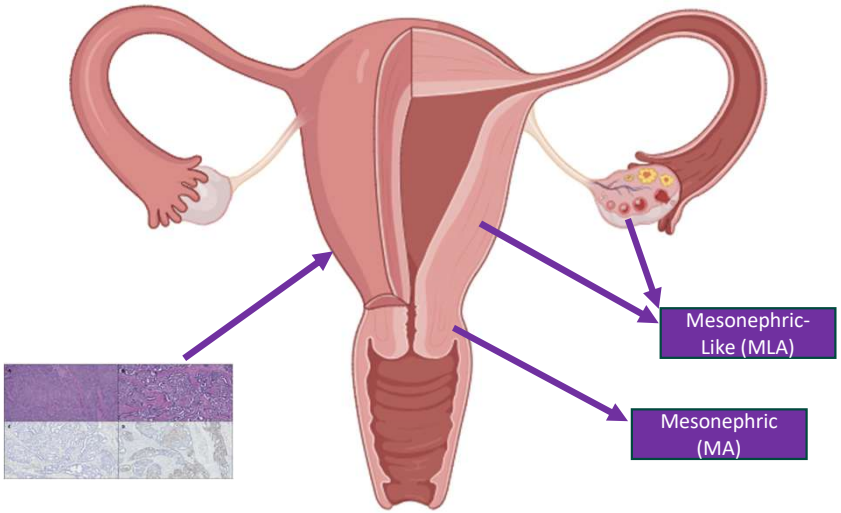
Disclosure

	No, nothing to disclose
x	Yes, please specify:

Company Name	*Honoraria/ Expenses*	*Consulting/ Advisory Board*	*Funded Research*	*Royalties/ Patent*	*Stock Options*	*Ownership/ Equity Position*	*Employee*	*Other (please specify)*
AZ		X						
Genmab		X						
Merck		X						
GSK		X						
Verastem			X					Travel expenses
Incyte		X						
Springworks		X						
Incyclix		X						

Mesonephric Adenocarcinoma (MA) and Mesonephric-Like Adenocarcinoma (MLA) Commonly Harbor KRAS Mutations



- Majority of cases recur
- Lung is most Common Site of Metastasis
- Often GAT3+, TTF1+, ER-, PR-

96% of Patients Harbor MAP Kinase Pathway Alterations

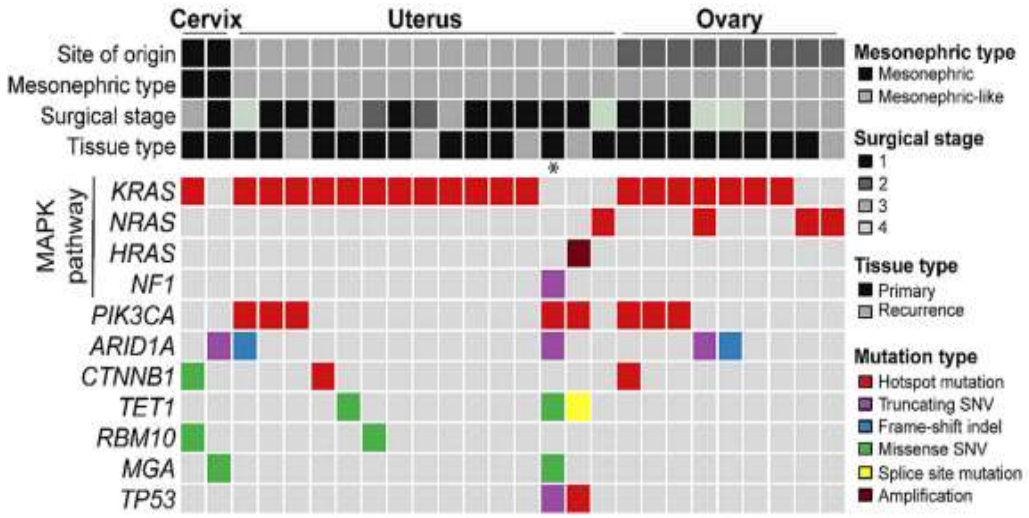
KRAS * (n = 20, 77%)

NRAS * (n = 3, 11%)

HRAS amplification (n = 1, 4%)

NF1 truncating mutation (n = 1, 4%)

*Hotspot missense mutation



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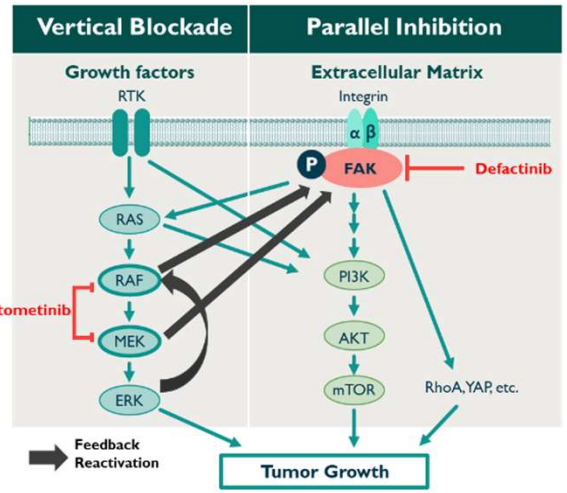
Praiss, White, Iasonos, Selenica, Zivanovic, Chi, Abu-Rustum, Weigelt, Aghajanian, Girshman, Park, Grisham, Gynecologic Oncology, December 2023.

Avutometinib With Defactinib Has Shown Prior Activity In KRAS Mutated Gyn Cancer



- **Avutometinib** is a first-in-class oral **RAF/MEK clamp** and **Defactinib** is an oral selective **inhibitor of FAK**, a key adaptive resistance mechanism to the RAS/MAPK pathway
- In the **ENGOT-ov60/GOG-3052/RAMP201** Phase II Study the combination of avutometinib and defactinib resulted in a **31% confirmed ORR in women with recurrent low grade serous ovarian cancer** (**44% in patients with KRAS mutation**; 17% in those without a KRAS mutation)
- On May 8, 2025 the combination of avutometinib and defactinib received accelerated **FDA approval** for treatment of women with recurrent low grade serous ovarian cancer with a KRAS mutation
- **Here we examined the activity of avutometinib and defactinib in women with advanced or recurrent MA/MLA**

Key Inclusion Criteria:

Advanced or Recurrent MA/MLA with RECIST measurable disease

No prior MEK, RAF or FAK inhibitor

Primary Endpoint:

Confirmed Response Rate via RECIST criteria

Key Secondary Endpoints:

Safety, PFS, OS

Stage I

Accrue 13 patients

If ≥ 1 response by RECIST criteria then advance to Stage II

Stage II

Accrue an additional 7 patients

If ≥ 3 responses seen in initial 20 patients, then the treatment is considered active

Expansion Cohort

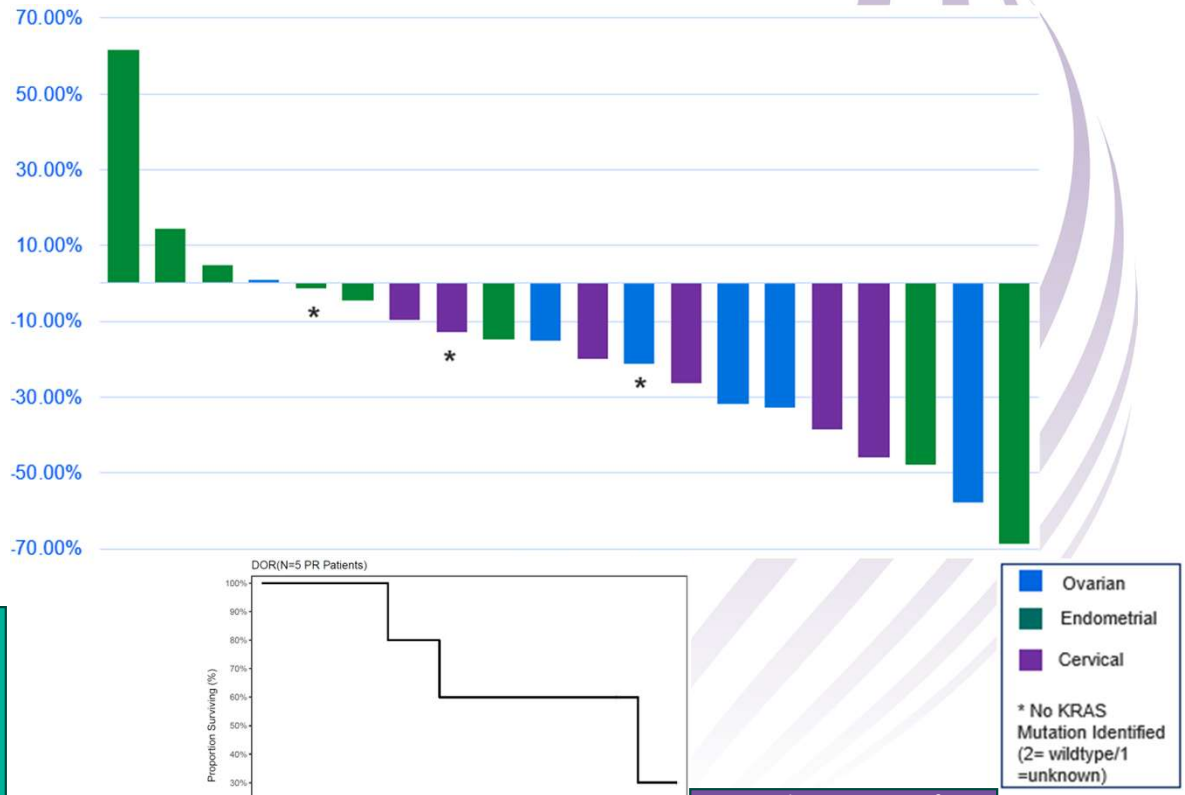
If criteria met for a positive study, then 20 additional patients enrolled in expansion cohort

Banerjee et al, Journal of Clinical Oncology, July 11, 2025

Avutometinib with Defactinib Is Active In Women With Advanced MA/MLA

	All Patients (n=20)	Cervix (n=6)	Endometrium (n=8)	Ovary (n=6)
Age *	64 (32-85)	69 (53-82)	61 (32-85)	66 (54-66)
Prior Therapies *	2 (0-7)	3 (0-3)	2 (1-2)	3 (1-7)
Prior Radiation*	14 [70%]	6 [100%]	4 [50%]	4 [67%]
Confirmed Response Rate†	5 [25%]	2 [33.3%]	2 [25%]	1 [16.7%]
Median PFS in months ‡	6.8 (3.9-9.4)	6 (3.5-NE)	6.3 (1.7-NE)	9.2 (5.7-NE)
PFS at 6 months	60% (35.7-77.6%)	50% (11.1-80.4%)	50% (15.2-77.5%)	83.3% (27.3-97.5%)

*median (range) ; †: all responses were partial response; ‡: (2-sided 95% CI)



Grade 3 Related Adverse Events Were Rare: Rash (n=3), Elevated CPK (n=2); Edema (n=1), Fatigue (n=1), Diarrhea (n=1), RPED (n=1), Elevated Bilirubin (n=1) , Elevated Alkaline Phosphatase (n=1)
1 Patient discontinued treatment due to toxicity

Median Duration of Response 11.8 months (3.9-NE)

9/2025 data cut ; 2 patients remain on treatment

Conclusions

- Mesonephric and Mesonephric-like Gynecologic Cancers are rare cancers that **commonly recur** and **frequently metastasize to the lung**
- Most cases **(96%) will harbor a MAPK alteration**, usually ***KRAS***
- **Avutometinib with Defactinib was recently FDA approved** for patients with recurrent **low grade serous ovarian cancer harboring a KRAS mutation**
- This Investigator Initiated Single Arm Phase 2 Study of Avutometinib with Defactinib in patients with MA/MLA has **met its primary endpoint, with an ORR of 25%, median PFS of 6.8 months**
- **Responses** were seen **in MA/MLA across all histologic sites of origin (cervical, endometrial, ovarian)**
- The combination was well tolerated and grade 3 toxicity was rare
- Expansion phase of 20 additional patients currently enrolling (NCT05787561)