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Molecular Profiling and Tumor Biomarker Analysis of RAMP 201: A Study Demonstrating Efficacy of Avutometinib in Combination With Defactinib in Recurrent Low-grade Serous Ovarian 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)*
AbbVie, AstraZeneca, BeiGene, BioNTech, Daiichi Sanyo, Eisai, Epitopea, Epsilogen, Gilead, GlaxoSmithKline, Genmab, Grey Wolf Therapeutics, Immunogen, Incyte, ITM Oncologics, Lilly, Merck Sharpe Dohme, Myriad, Sciensus, TORL BioTherapeutics, Zymeworks		X						
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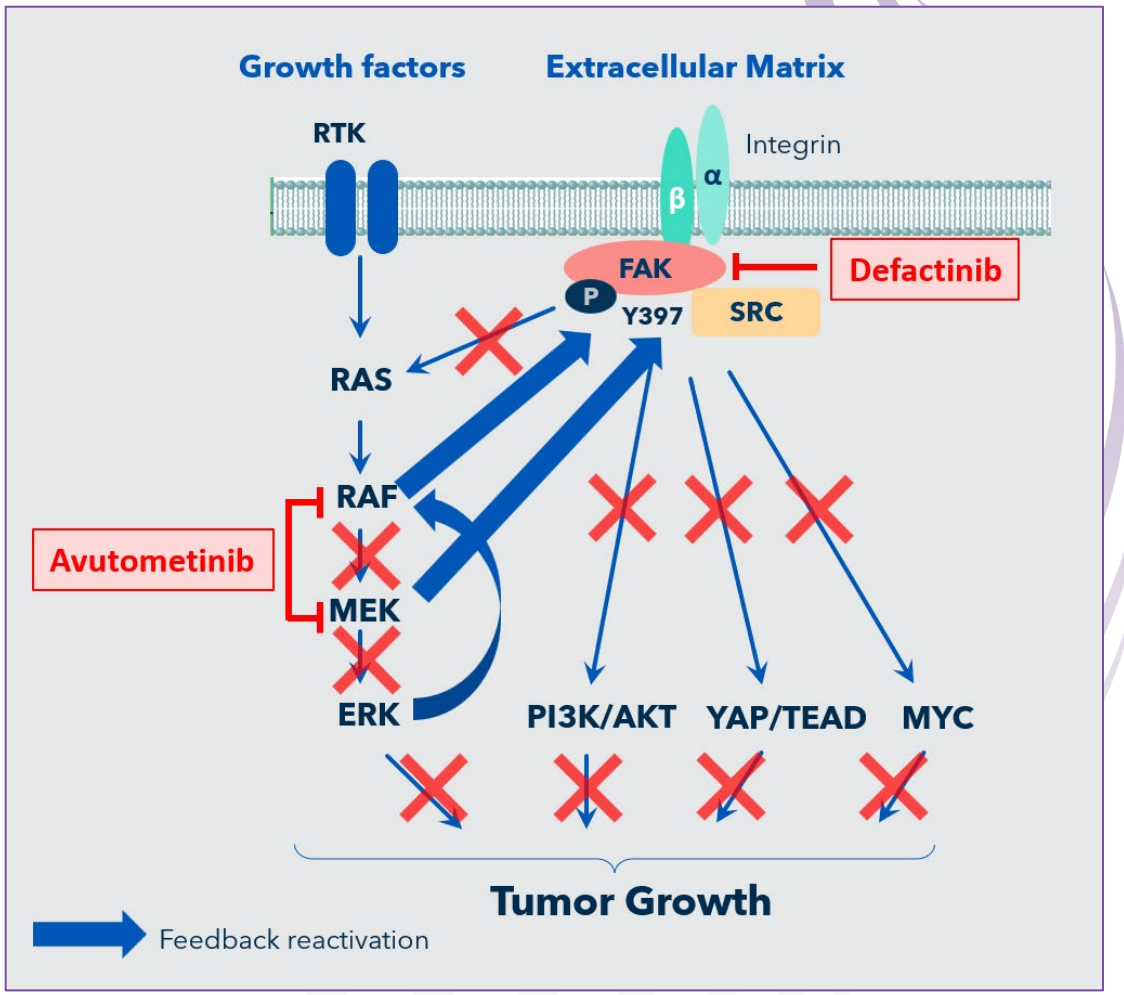
Avutometinib and Defactinib Mechanism of Action and Rationale for Combination

- Avutometinib is an oral dual inhibitor of RAF and MEK[1,2]
- Defactinib is a selective FAK inhibitor[3,4]
- Avutometinib + defactinib combination:
  - Inhibits MAPK pathway signaling[5]
  - **Inhibits putative mechanisms of resistance to avutometinib, including PI3K/AKT, YAP/TEAD and MYC signaling[5]**

  (Based on RNAseq analysis from a patient-derived xenograft model of KRAS mutant LGSOC)

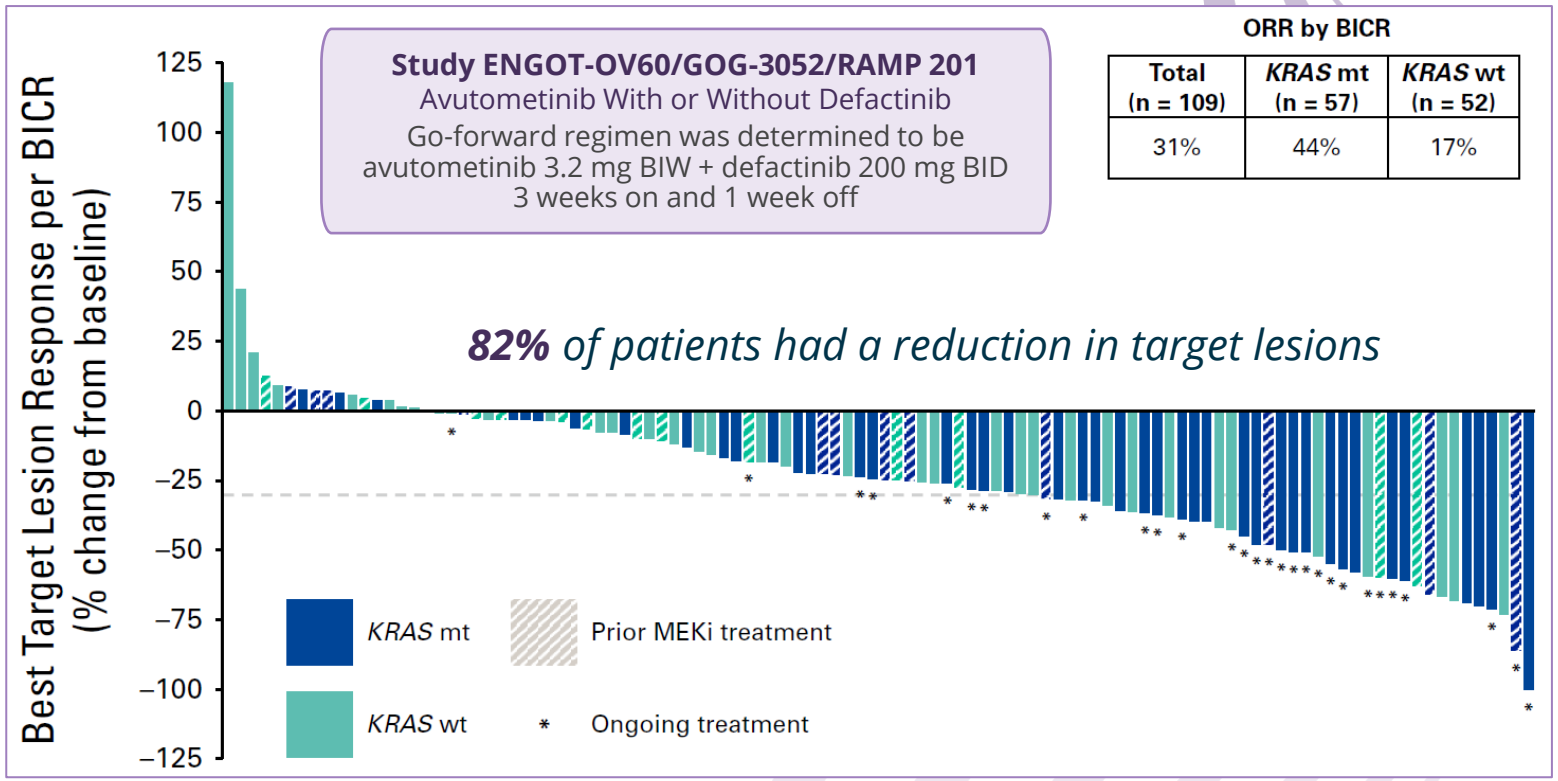


1. Ishi, et al. *Cancer Res*. 2013;73(13):4050–4060. **2**. Lito P, et al. *Cancer Cell*. 2014;25(5):697-710. **3**. Dawson JC, et al. *Nat Rev Cancer*. 2021;21(5):313-324. **4**. Kang Y, et al. *J Natl Cancer Inst*. 2013;105(19):1485-1495. **5.** Pickard et al. Abstract 6368. Presented at: AACR Annual Meeting; April 25-30, 2025; Chicago, IL.

LGSOC, low-grade serous ovarian cancer; AKT, protein kinase B; ERK, extracellular signal-regulated kinase; FAK, focal adhesion kinase; KRAS, Kirsten rat sarcoma viral oncogene homolog; MEK, mitogen-activated protein kinase kinase; PI3K, phosphatidylinositol 3-kinase; RAF, rapidly accelerated fibrosarcoma; RAS, rat sarcoma virus; RNAseq, RNA sequencing; RTK, receptor tyrosine kinase; YAP, yes-associated protein.

Avutometinib and Defactinib Received FDA Accelerated Approval for Adults With Recurrent *KRAS*-Mutated LGSOC

- LGSOC is a rare and clinically distinct cancer driven by *KRAS* mutations in approximately 30% of patients[1-4]
- Avutometinib + defactinib received **FDA accelerated approval for recurrent *KRAS*-mutated LGSOC** based on results from ENGOT-OV60/GOG-3052/RAMP 201[5]
- A phase 3 study is evaluating avutometinib + defactinib vs investigator's choice in patients with recurrent LGSOC (GOG-3097/ENGOT-ov81/GTG-UK/RAMP 301)[6]



Objective of this study

Perform molecular profiling of baseline tumors from RAMP 201 to determine activity of avutometinib with defactinib in subgroups within the *KRAS* wt population

1. Grisham RN, et al. *Int J Gynecol Cancer*. 2023;33(9):1331-1344. **2**. Matsuo K, et al. *J Gynecol Oncol*. 2018;29(1a):e15. **3.** Manning-Geist B, et al. *Clin Cancer Res*. 2022;28(20):4456-4465. **4**. ElNaggar A, et al. *Gynecol Oncol*. 2022;167(2):306-313. **5**. Banerjee S, et al. *JCO*. 2025;43(25):2782-2792. **6.** Grisham et al. *Int J Gynecol Cancer*. 2025;35(11):101832.

BID, twice per day; BIW, twice per week; BIRC, blinded independent central review; FDA, US Food and Drug Administration; *KRAS*, Kirsten rat sarcoma viral oncogene homolog; LGSOC, low-grade serous ovarian cancer; MEKi, mitogen-activated protein kinase kinase inhibitor; mt, mutant; ORR, overall response rate; wt, wild-type.

In *KRAS* Wild-Type LGSOC With or Without *NRAS* or *BRAF* Mutations, Avutometinib + Defactinib Showed Clinically Meaningful Activity

Avutometinib + Defactinib (RAMP 201 study)

Parameter	*KRAS/NRAS/BRAF* wild-type
	Avutometinib + defactinib
ORR, % (95% CI) [n/N]	**18** (7.5–34) [7/39]
Median PFS, months (95% CI)	**13** (6–13)

For *KRAS* wild-type LGSOC with *NRAS* or *BRAF* mutations, avutometinib + defactinib showed a confirmed ORR of 22% (2/9; 95% CI: 2.8%–60%)

Trametinib vs Standard of Care (GOG 281 study[1])

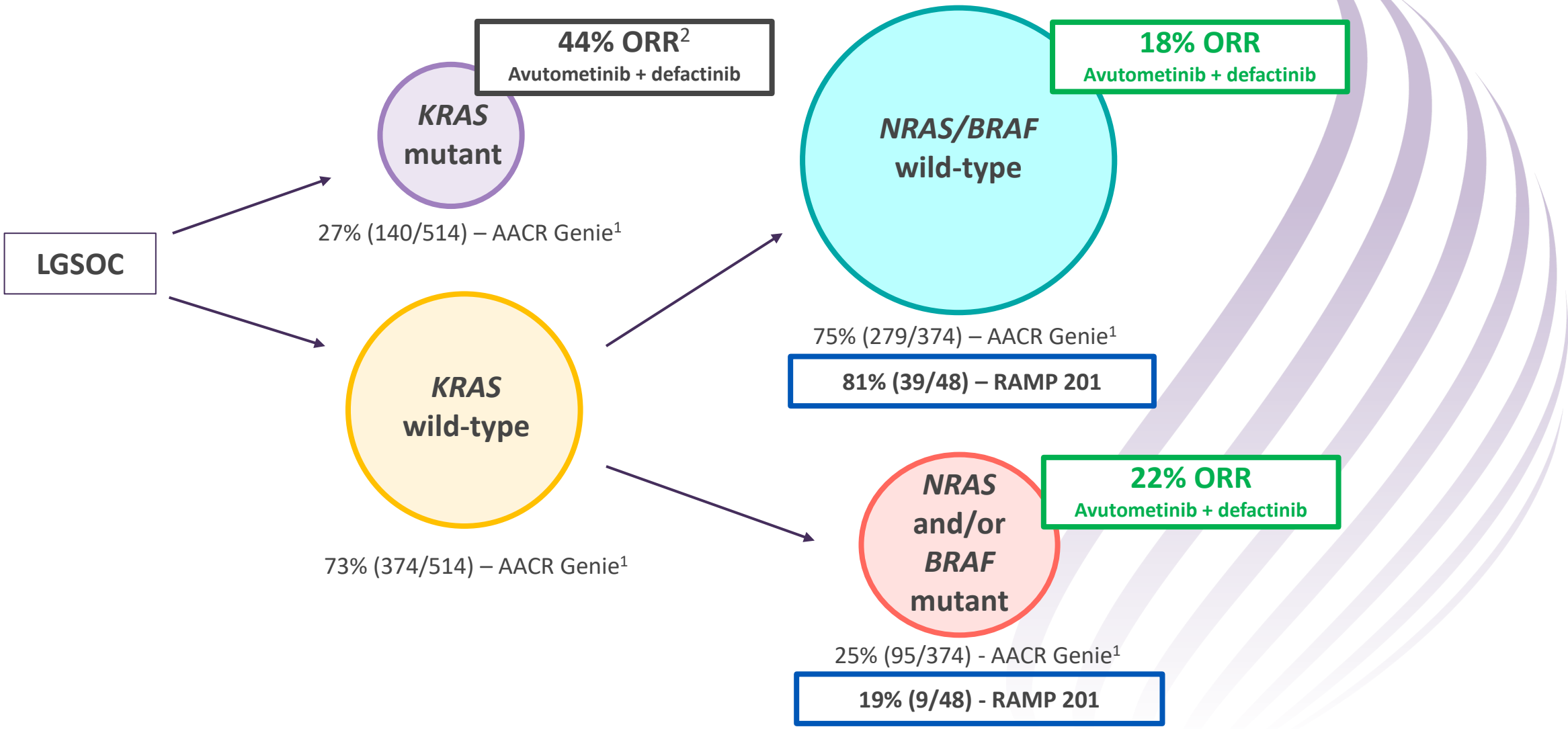
Parameter	*KRAS/NRAS/BRAF* wild-type	
	Trametinib	Standard of care*
ORR, % (95% CI) [n/N]	**8** (2.3–20) [4/48]	**7** (1.5–19) [3/42]
Median PFS, months (95% CI)	**7** (5.6–12.7)	**6** (3.7–9.9)

**Standard of care included paclitaxel, pegylated liposomal doxorubicin, topotecan, letrozole, or tamoxifen*

1. Gershenson DM, et al. *Lancet*. 2022;399(10324):541-553.

BRAF, B-Raf proto-oncogene, serine/threonine kinase; *KRAS*, Kirsten rat sarcoma viral oncogene homolog; LGSOC, low-grade serous ovarian cancer; MEK, mitogen-activated protein kinase kinase; *NRAS*, neuroblastoma rat sarcoma virus viral oncogene homolog; ORR, overall response rate; PFS, progression-free survival.

Majority of Patients With *KRAS* Wild-Type LGSOC (76%–81%) Also Had Wild-Type for *NRAS* and *BRAF*

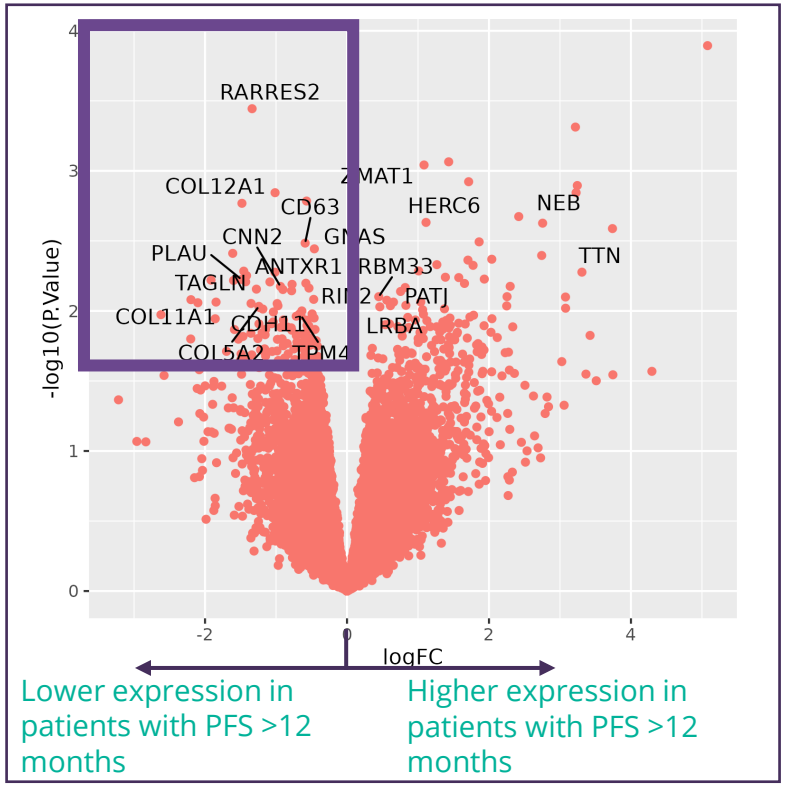


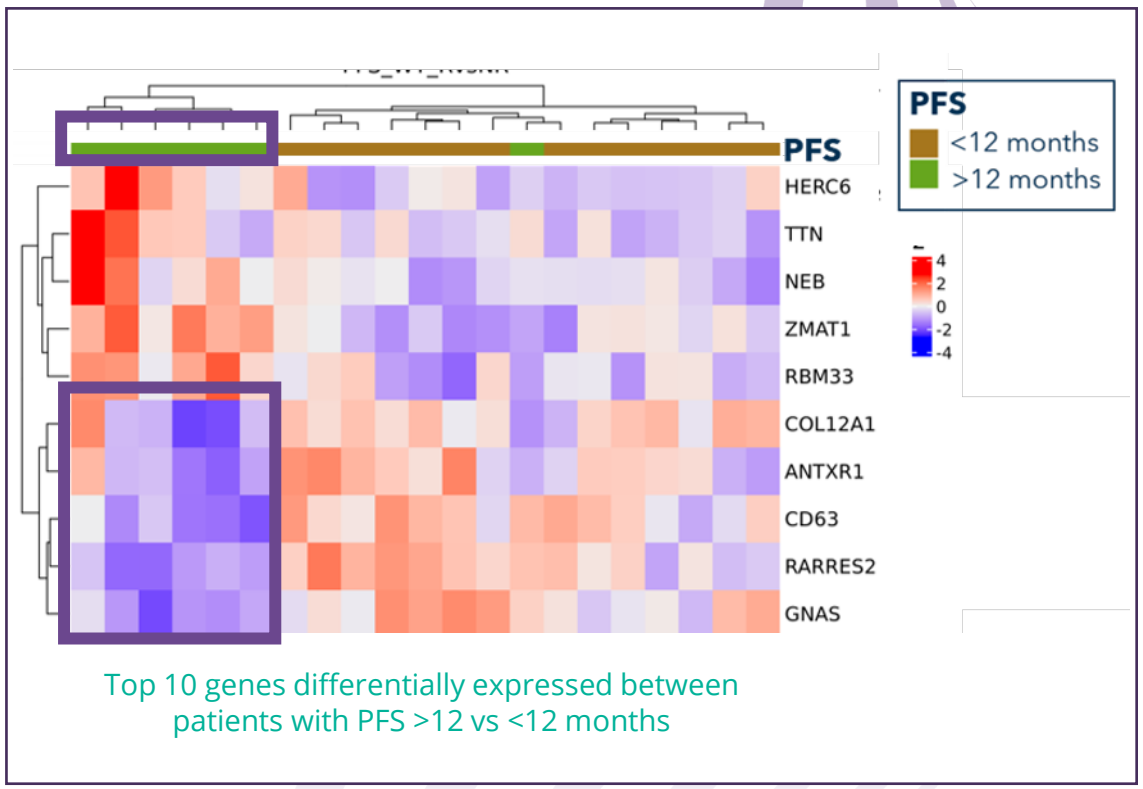
1. AACR Project GENIE Consortium. AACR Project GENIE v20.0. American Association for Cancer Research; 2024. Available from: AACR Project GENIE. **2.** Banerjee S, et al. *J Clin Oncol*. 2025;43(25):2782-2792.

AACR Genie, American Association for Cancer Research Genomics Evidence Neoplasia Information Exchange; *BRAF*, B-Raf proto-oncogene, serine/threonine kinase; *KRAS*, Kirsten rat sarcoma viral oncogene homolog; LGSOC, low-grade serous ovarian cancer; *NRAS*, neuroblastoma rat sarcoma virus viral oncogene homolog; ORR, overall response rate.

In *KRAS/NRAS/BRAF* Wild-Type LGSOC, Patients With Longer PFS Showed Lower Expression of Genes Associated With Fibroblast Activation and Extracellular Matrix Remodeling

- Baseline tumor samples were collected from patients in RAMP 201
- RNA profiling was performed with Tempus xR assay
- RNA data were available from 21 patients with *KRAS/NRAS/BRAF* wild-type tumors
- Showing differentially expressed (P<0.05) genes between patients with PFS >12 months vs <12 months





Patients with PFS >12 months exhibited lower expression of genes associated with fibroblast activation and extracellular matrix remodeling, including *COL12A1*, *ANTXR1* (TEM8), *RARRES2* (chemerin), and *CD63*

BRAF, B-Raf proto-oncogene, serine/threonine kinase; *KRAS,* Kirsten rat sarcoma viral oncogene homolog; LGSOC, low-grade serous ovarian cancer; *NRAS*, neuroblastoma rat sarcoma virus viral oncogene homolog; ORR, overall response rate; PFS, progression-free survival.

Conclusions

- Among patients with *KRAS* wild-type LGSOC
  - Majority (81%) were also wild-type for *NRAS* and *BRAF*
- Clinically meaningful efficacy was observed with avutometinib + defactinib in *KRAS* wild-type subpopulations
  - *KRAS*/*NRAS*/*BRAF* wild-type (ORR, 18%; 13-month mPFS)
  - *KRAS* wild-type LGSOC with *NRAS* or *BRAF* mutations (ORR, 22%)

Targeting RAF, MEK and FAK with avutometinib + defactinib enables efficacy beyond patients harboring *KRAS*, *NRAS*, or *BRAF* mutations and offers a clinically meaningful therapy for patients with *KRAS* wild-type LGSOC

BRAF, B-Raf proto-oncogene, serine/threonine kinase; FAK, focal adhesion kinase; *KRAS*, Kirsten rat sarcoma viral oncogene homolog; LGSOC, low-grade serous ovarian cancer; MEK, mitogen-activated protein kinase kinase; mPFS, median progression-free survival; *NRAS*, neuroblastoma rat sarcoma virus viral oncogene homolog; ORR, overall response rate; RAF, rapidly accelerated fibrosarcoma.

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Thank you!