2025 ESMO GYNAECOLOGICAL CANCERS
Annual Congress

BLOOD ctDNA VS TUMOR TISSUE SCREENING FOR THE DETECTION OF *KRAS* MUTATIONS IN LOW-GRADE SEROUS OVARIAN CANCER

ENGOT-OV60/GOG-3052/RAMP 201

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19 June 2025

EUROPEAN SOCIETY FOR MEDICAL ONCOLOGY

DECLARATION OF INTERESTS

Els Van Nieuwenhuysen, MD

Financial Interests

- AstraZeneca, Advisory Board, Institutional
- GSK, Expert Testimony, Institutional
- MSD, Expert Testimony, Institutional
- Oncoinvent, Advisory Board, Institutional
- Regeneron, Advisory Board, Institutional
- Astrazeneca, Coordinating PI, Institutional
- Astrazeneca, Steering Committee Member, Institutional
- Bioncotech Therapeutics, Local PI, Institutional
- Merck, Local PI, Institutional
- Merck Serono, Trial Chair, Institutional
- Novartis, Local PI, Institutional
- Oncoinvent, Local PI, Institutional
- Regeneron, Local PI, Institutional
- Roche, Local PI, Institutional
- Seagen, Local PI, Institutional
- Verastem Oncology, Local PI, Institutional
- Verastem Oncology, Steering Committee Member, Institutional

Non-Financial Interests

- Eli Lilly, Product Samples

Other

- GSK, Other, Travel
- MSD, Other, Travel

Low Grade Serous Ovarian Cancer (LGSOC)

- LGSOC is a rare, histopathologically, molecularly, and clinically distinct cancer accounting for <10% of new epithelial ovarian cancers[1,2]
- LGSOC is commonly driven by alterations in the RAS/MAPK pathway, including *KRAS* mutations, which occur in approximately 30% of patients[3,4]
- Chemotherapy options have shown limited efficacy in LGSOC (ORR 0%–13%)[5,6]
- Response rates of 26% and 16% were observed with the MEK-only inhibitors trametinib and binimetinib, respectively, but with discontinuation rates of 36% and 31% due to toxicity[5,6]

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**. Gershenson DM, et al. *Lancet.* 2022;399(10324):541-553; **6**. Monk BJ, et al. *J Clin Oncol.* 2020;38(32):3753-3762.

KRAS, Kirsten rat sarcoma virus; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated protein kinase kinase; ORR, objective response rate; RAS, rat sarcoma virus.

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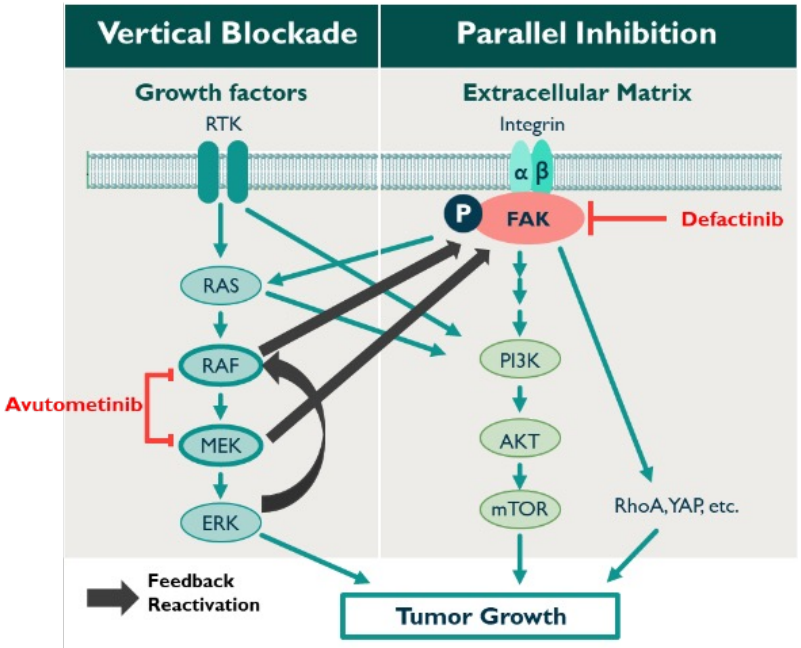
Avutometinib and Defactinib Mechanism of Action

- Avutometinib is a first-in-class oral RAF/MEK clamp that potently inhibits MEK while also blocking the compensatory reactivation of MEK by upstream RAF[1,2]
- Defactinib is a selective inhibitor of FAK, a key adaptive resistance mechanism to the RAS/MAPK pathway[3-5]
- **Avutometinib + defactinib received accelerated approval by the FDA on May 8, 2025, for adult patients with *KRAS*-mutated recurrent LGSOC who have received prior systemic therapy[6]**
  - Based on phase 2 and phase 1 studies
    - ENGOT-OV60/GOG-3052/RAMP 201[7]
    - FRAME[8]
- A Phase 3 study is evaluating avutometinib + defactinib versus investigator's choice of treatment in patients with recurrent LGSOC
    - GOG-3097/ENGOT-ov81/GTG-UK/RAMP 301[9]



1. Lito P, et al. *Cancer Cell.* 2014;25(5):697-710; **2**. Gonzalez-Del Pino GL, et al. *Proc Natl Acad Sci U S A.* 2021;118(36):e2107207118; **3**. Dawson JC, et al. *Nat Rev Cancer.* 2021;21:313-324; **4**. Shinde R, et al. *Cancer Res.* 2020;80(suppl 16):CT143; **5**. Kang Y, et al. *J Natl Cancer Inst.* 2013;105(19):1485-1495; **6.** Verastem, Inc. AVMAPKI™ FAKZYNJA™ CO-PACK. Full Prescribing Information. 2025; **7.** Banerjee S, et al. IGCS 2024; **8.** Banerjee S, et al. *Ann Oncol.* 2021;32(suppl 5):S728; **9.** Grisham et al. *Int J Gynecol Cancer*. 2025; DOI: 10.1136/ijgc-2024-005919.

AKT, protein kinase B; ERK, extraceulluar signal-regulated kinase; FAK, focal adhesion kinase; KRAS, Kirsten rat sarcoma viral oncogene homologue; LGSOC, low-grade serous ovarian cancer; MEK, mitogen-activated protein kinase kinase; mTOR, mechanistic target of rapamycin; PI3K, phosphatidylinositol 3-kinases; RAF, rapidly accelerated fibrosarcoma; RAS, Rat sarcoma virus; RhoA, Ras homolog family member A; RTK, receptor tyrosine kinases; YAP, yes-associated protein.

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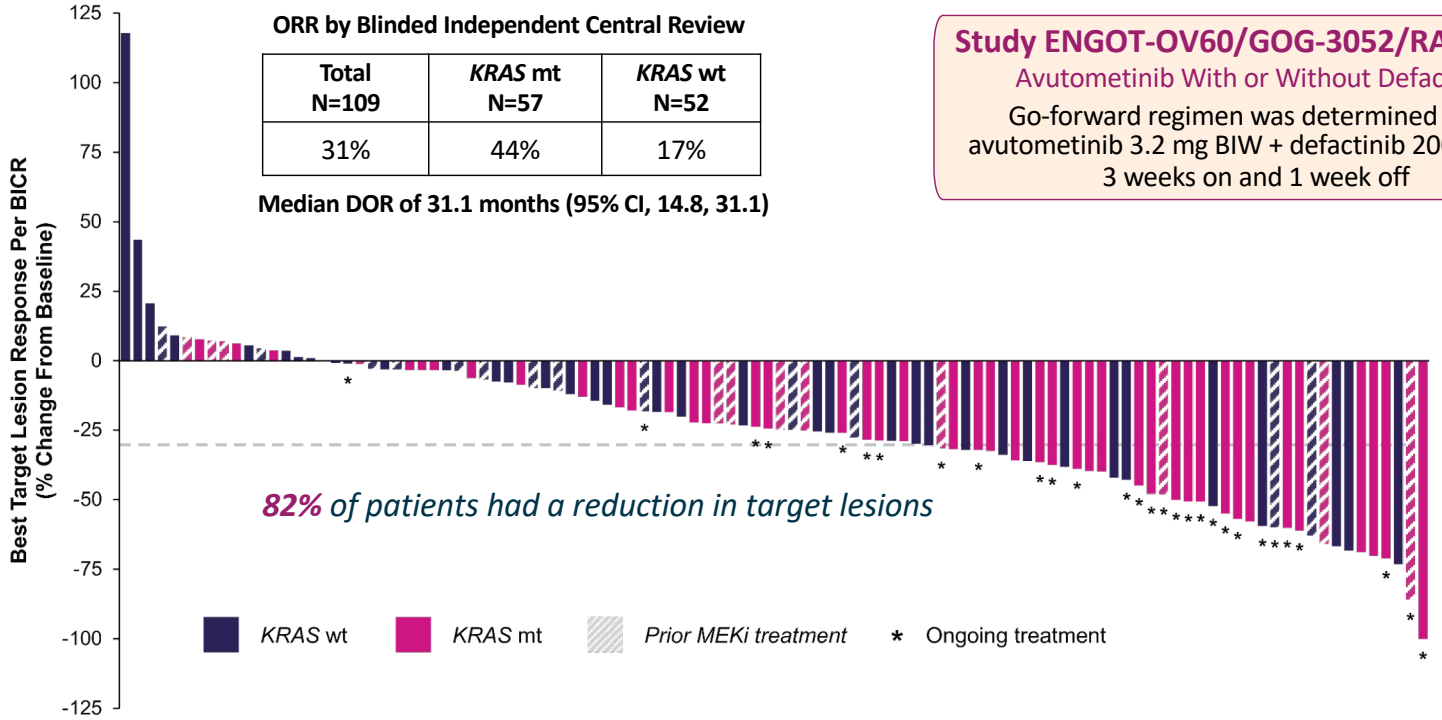
Responses Observed in both *KRAS* Mutant and *KRAS* Wild-Type Recurrent LGSOC with Avutometinib 3.2 mg BIW + Defactinib 200 mg BID

ORR by Blinded Independent Central Review

Total N=109	*KRAS* mt N=57	*KRAS* wt N=52
31%	44%	17%

Median DOR of 31.1 months (95% CI, 14.8, 31.1)

Study ENGOT-OV60/GOG-3052/RAMP 201
Avutometinib With or Without Defactinib
Go-forward regimen was determined to be avutometinib 3.2 mg BIW + defactinib 200 mg BID 3 weeks on and 1 week off



BICR, blinded independent central review; KRAS, Kirsten rat sarcoma virus; LGSOC, low-grade serous ovarian cancer; MEKi, mitogen-activated protein kinase kinase inhibitor; mt, mutant; wt, wild type; ORR, objective response rate.

Visit cutoff date: 30 June 2024

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Background and Objective

- Molecular profiling is becoming standard practice for patients with ovarian cancer
  - US guidelines, including ASCO, NCCN and SGO, recommend germline/somatic tumor testing for all patients with ovarian cancer
  - In Europe, there is no standardized guidance for germline/somatic tumor testing
- For determination of *KRAS* status in patients with LGSOC, tumor tissue-based biopsy procedures are most commonly employed
  - In ENGOT-OV60/GOG-3052/RAMP 201, *KRAS* status was determined by tumor-tissue based testing in 98% (113/115) of patients
- In a prior report in patients with LGSOC, 6/13 (46%) patients with a *KRAS* mutation detected in tissue showed a *KRAS* mutation detected in blood[1]

Here, using samples from ENGOT-OV60/GOG-3052/RAMP 201, we evaluated whether blood samples, which offer less invasive testing than tumor biopsies, could reliably detect *KRAS* mutations in patients with LGSOC

1. Hasson, et al. *Int J Gynecol Cancer*. 2024; 34 (suppl 3): A72-A73 (abstract PR057/#745).

ASCO, American Society of Clinical Oncology; KRAS, Kirsten rat sarcoma virus; LGSOC, low-grade serous ovarian cancer; NCCN, National Comprehensive Cancer Network; SGO, Society of Gynecologic Oncology.

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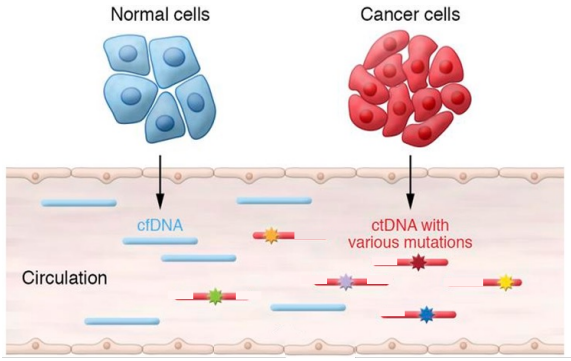
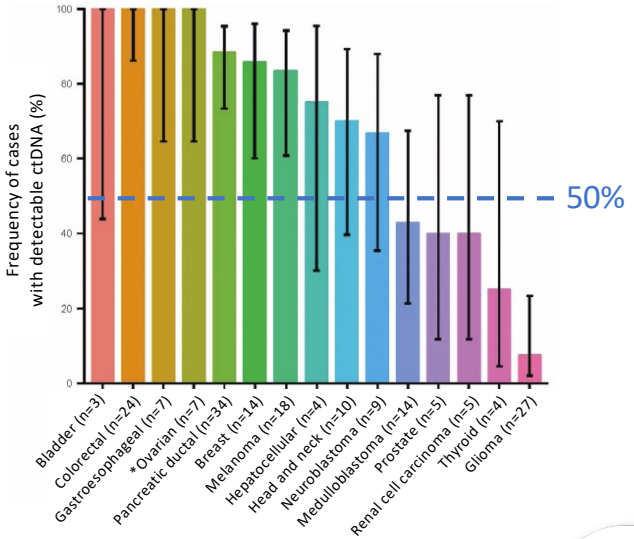
Circulating Tumor DNA (ctDNA)

- Tumor cells release/shed ctDNA into the bloodstream by apoptosis, necrosis and secretion
- ctDNA can be differentiated based on shorter length relative to cell-free DNA (cfDNA), which comes from normal cells
- ctDNA tumor fraction measures the % of ctDNA relative to total DNA present in the blood (ctDNA + cfDNA)
  - ctDNA is present in small amounts (0.1-10% of total circulating DNA)
  - The detection of ctDNA requires highly sensitive detection methods, typically next generation sequencing
- Not all tumor types shed enough ctDNA to be detected
  - In high shedding tumor types, ctDNA can serve as a tool for cancer diagnosis, monitoring, prognosis and mutation detection (e.g. *KRAS* mutations)





*Stage III ovarian; not specific to LGSOC.
Reference: Adapted from Bettegowda, et al. 2014 & Dang and Park, 2022.

cfDNA, cell-free DNA; ctDNA, circulating tumor DNA; LGSOC, low-grade serous ovarian cancer.

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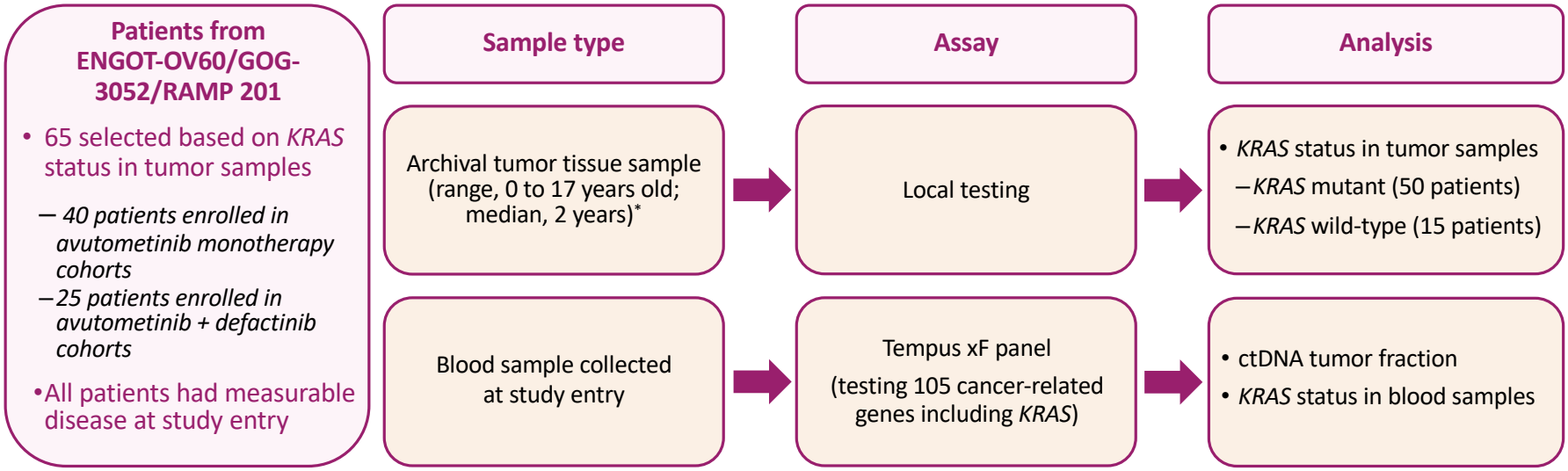
Methods



Goals

- Determine % of patients with LGSOC with detectable ctDNA
- Determine concordance between *KRAS* detection in tumor vs blood samples

**KRAS* status has been shown not to change over time (Manning-Geist, et al. *Clin Cancer Res.* 2022;28:4456–65)

ctDNA, circulating tumor DNA; KRAS, Kirsten rat sarcoma virus.

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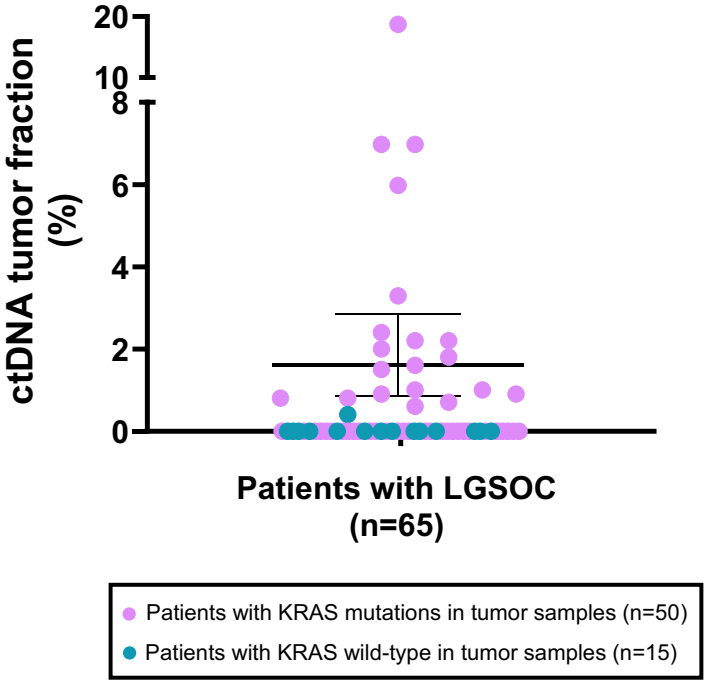
32% (21/65) of Patients With LGSOC Have Detectable ctDNA in Blood Samples Collected at Study Entry

- Out of 65 patients with LGSOC included in the analysis
  - 21 patients (32%) showed ctDNA tumor fraction above the limit of detection of 0.25% (ranging from 0.4% to 19%)
  - In 44 patients (68%), ctDNA tumor fraction was not above the limit of detection of 0.25%



ctDNA, circulating tumor DNA; LGSOC, low-grade serous ovarian cancer.

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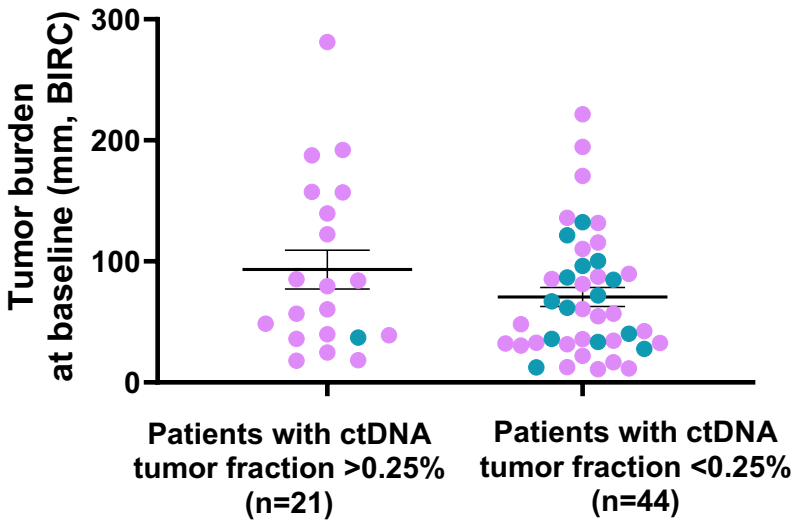
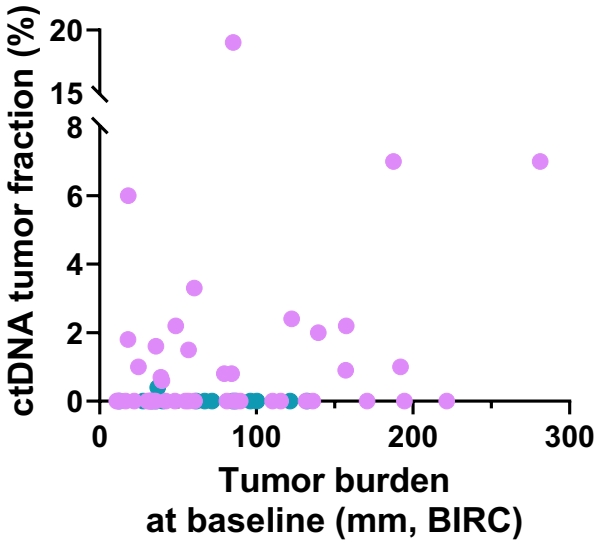
No Correlation Seen Between Tumor Burden at Baseline and ctDNA Tumor Fraction





Patients with KRAS mutations in tumor samples (n=50)
Patients with KRAS wild-type in tumor samples (n=15)

Tumor burden at baseline is defined as the sum of diameters of target lesions assessed by BIRC.

ctDNA, circulating tumor DNA; BIRC, blinded independent review committee.

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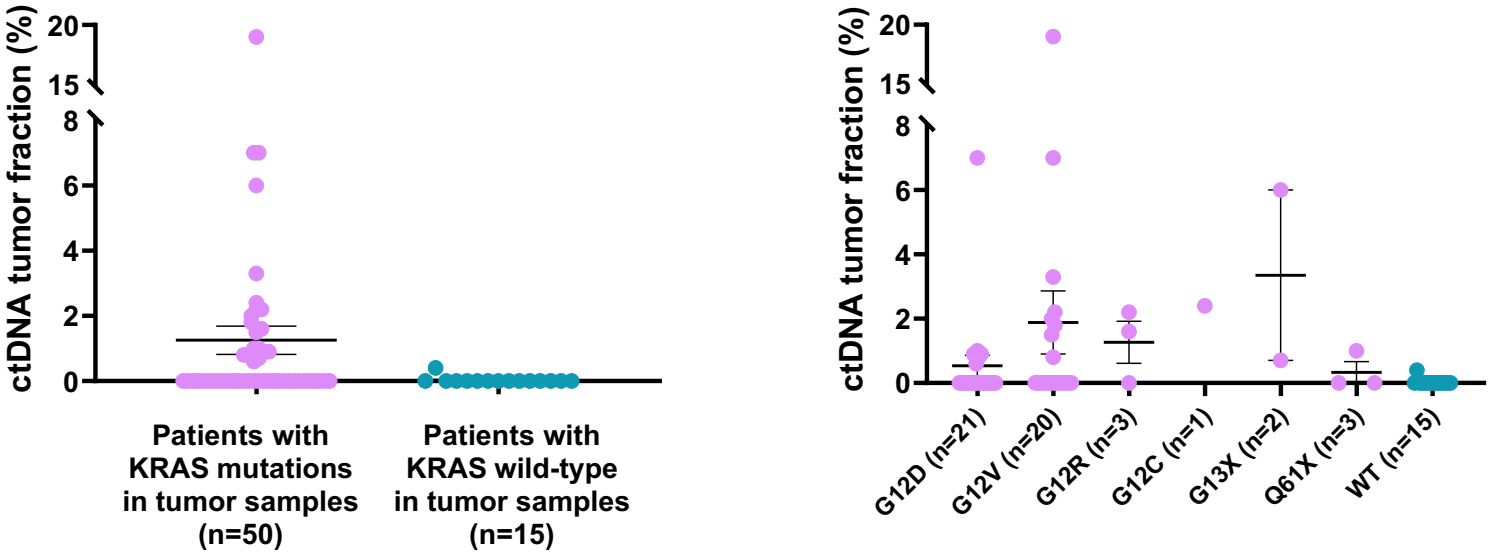
Similar ctDNA Tumor Fraction Between Patients With Different *KRAS* Mutation Variants Detected in Tumor Samples



ctDNA, circulating tumor DNA; KRAS, Kirsten rat sarcoma virus; LGSOC, low-grade serous ovarian cancer; VAF, variant allele frequency; WT, wild type.

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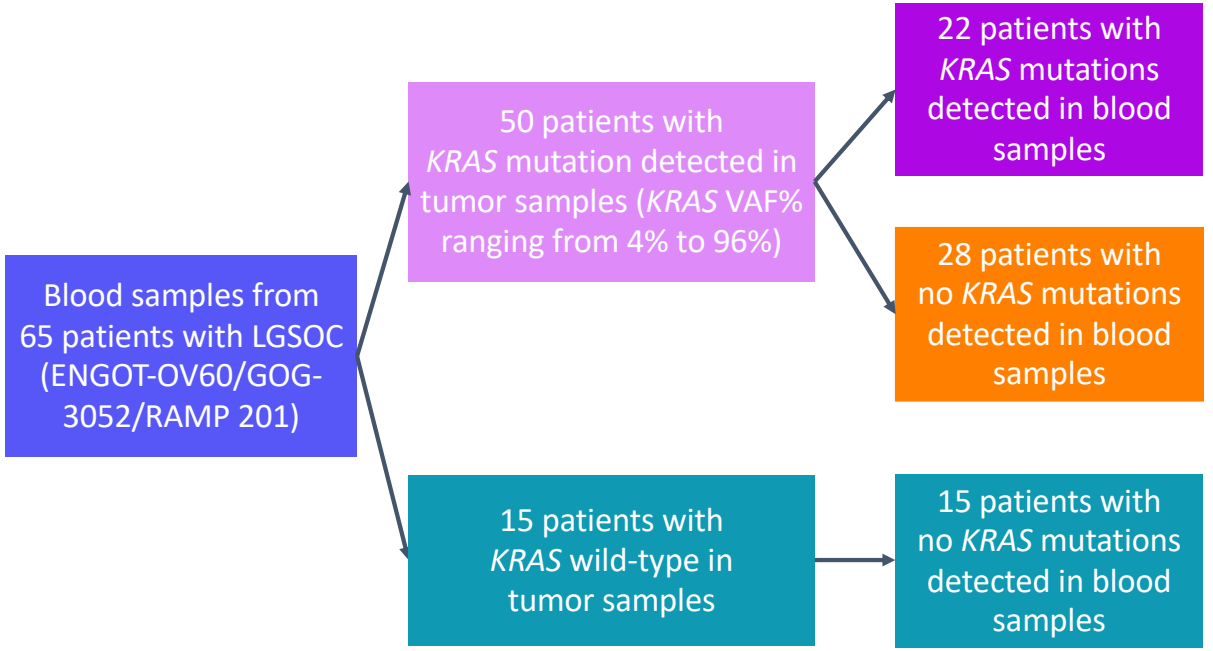
In Patients With *KRAS* Mutations Detectable in Tumor Samples, 44% (22/50) Concordance Between *KRAS* Detection in Tumor vs Blood Samples



- 44% (22/50) concordance between tumor vs blood samples
  - For these 22, the same *KRAS* variant was detected in tissue vs blood samples
- 56% (28/50) of patients showed a false negative result from ctDNA testing
- No *KRAS* mutations detected by ctDNA testing in patients with *KRAS* wild-type in tumor samples

ctDNA, circulating tumor DNA; KRAS, Kirsten rat sarcoma virus; LGSOC, low-grade serous ovarian cancer; VAF, variant allele frequency.

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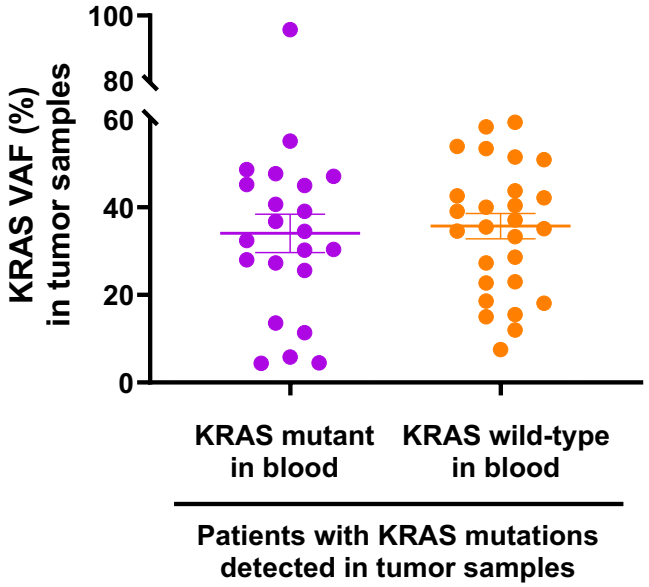
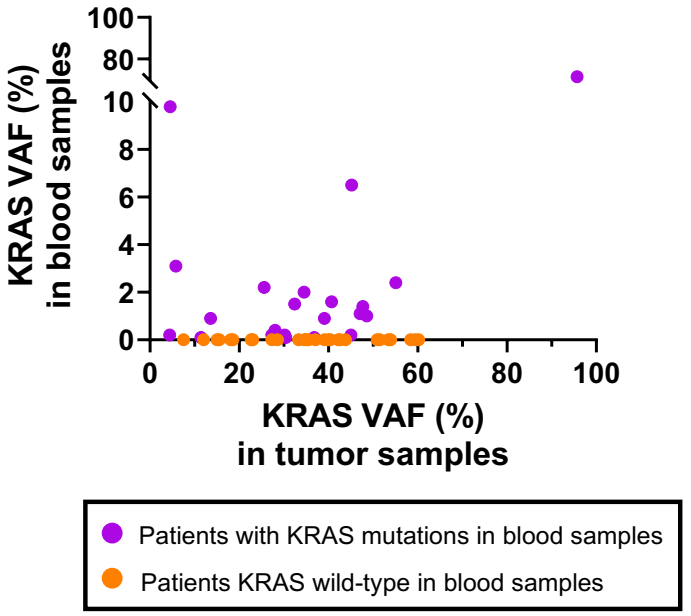
In Patients With *KRAS* Mutations Detectable in Tumor Samples, No Correlation Between *KRAS* VAF in Tumor and *KRAS* VAF in Blood





KRAS, Kirsten rat sarcoma virus; VAF, variant allele frequency.

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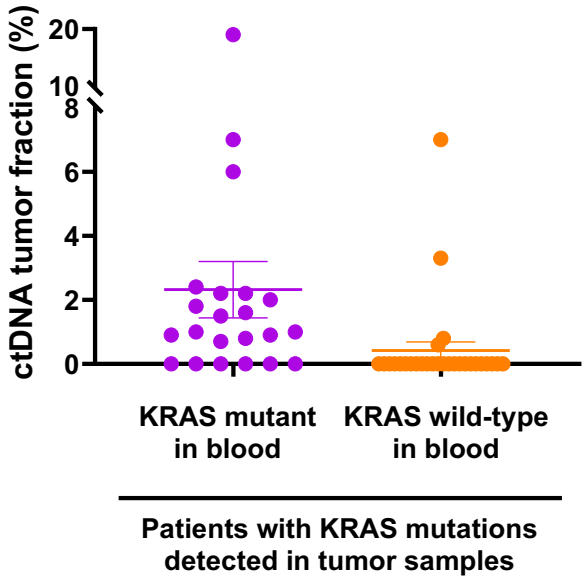
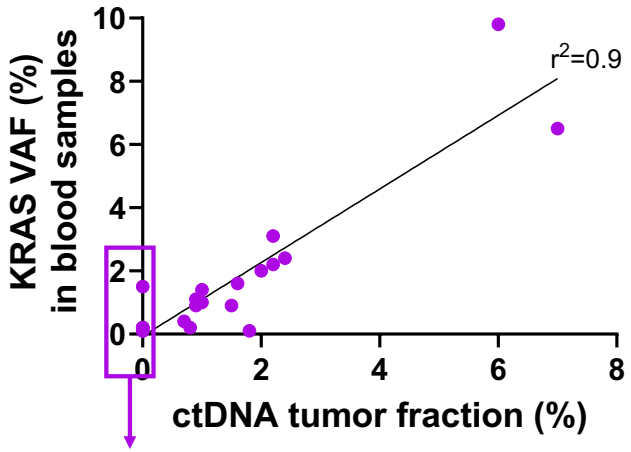
In Patients With *KRAS* Mutations Detectable in Tumor Samples, Correlation Between ctDNA Tumor Fraction and *KRAS* VAF in Blood





6 patients with ctDNA <0.25%, but with *KRAS* mutations detected in blood samples

ctDNA, circulating tumor DNA; KRAS, Kirsten rat sarcoma virus; VAF, variant allele frequency.

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Conclusions

- In the ENGOT-OV60/GOG-3052/RAMP 201 study, only 32% (21/65) of patients with LGSOC exhibited a ctDNA tumor fraction above the limit of detection, suggesting that LGSOC is a low shedding tumor
- In patients with *KRAS* mutations detectable in tumor samples (N=50/65),
  - 44% (22/50) concordance was observed between *KRAS* mutation detection in blood vs tumor samples
    - In the 22 patients with a *KRAS* mutation detected in both blood and tumor samples, the same *KRAS* variant was detected in blood vs tumor samples
  - 56% (28/50) of patients showed a false negative blood *KRAS* mutation detection result
- In patients with no *KRAS* mutations detectable in tumor samples (N=15/65),
  - No *KRAS* mutations were detected in blood samples
- These findings suggest that blood (ctDNA) screening is not a sufficiently robust method for detecting *KRAS* mutations in patients with LGSOC
  - Treatment decisions should not be made based on lack of *KRAS* mutation detection in blood

ctDNA, circulating tumor DNA; KRAS, Kirsten rat sarcoma virus; LGSOC, low-grade serous ovarian cancer.

Els Van Nieuwenhuysen, MD

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