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# Long-Term Efficacy and Safety of Avutometinib + Defactinib in Patients With Recurrent Low-Grade Serous Ovarian Cancer: Results From ENGOT-ov60/GTG-UK/GOG-3052

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# Disclosures



Consulting: AZ, GSK, Merck, Verastem, Corcept, Incyte, Incyclix, GenMab.

DOR, duration of response; FAK, focal adhesion kinase; KRAS, Kirsten rat sarcoma virus; LGSOC, low-grade serous ovarian cancer; MEK, mitogen-activated extracellular signal-regulated kinase; RAF, rapidly accelerated fibrosarcoma.

# Unlabeled/Investigational Uses



I will be discussing unlabeled or investigational uses of pharmaceutical products.

The combination of avutometinib + defactinib received accelerated approval by the FDA and is indicated for the treatment of adult patients with *KRAS*-mutated recurrent low-grade serous ovarian cancer who have received prior systemic therapy.

The accelerated approval was based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

DOR, duration of response; FAK, focal adhesion kinase; KRAS, Kirsten rat sarcoma virus; LGSOC, low-grade serous ovarian cancer; MEK, mitogen-activated extracellular signal-regulated kinase; RAF, rapidly accelerated fibrosarcoma.

# Low-Grade Serous Ovarian Cancer



- 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]
- Molecular alterations may influence patient outcomes.[5] *KRAS* mutations/MAPK alterations are associated with improved prognosis[1,3,6]
- Traditional treatment options for recurrent disease including chemotherapy options have shown limited efficacy ORR (0%-13%)[6,7]
- Response rates of 26% and 16% were observed with trametinib and binimetinib, respectively, but with discontinuation rates of 36% and 31% due to toxicity[6,7]
- Therefore, there is a need for therapies that offer durable efficacy with limited side effects to allow patients to benefit from long-term treatment

*KRAS*, Kirsten rat sarcoma virus; LGSOC, low-grade serous ovarian cancer; MAPK, mitogen-activated protein kinase; ORR, objective response rate; RAS, rat sarcoma virus.

**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**. Manning-Geist BL, et al. *Clin Adv Hematol Oncol*. 2024:22(5):205-226. **6.** Gershenson DM, et al. *Lancet.* 2022;399(10324):541-553. **7.** Monk BJ, et al. *J Clin Oncol.* 2020;38(32):3753-3762.

# Avutometinib + Defactinib Treatment in Patients With LGSOC

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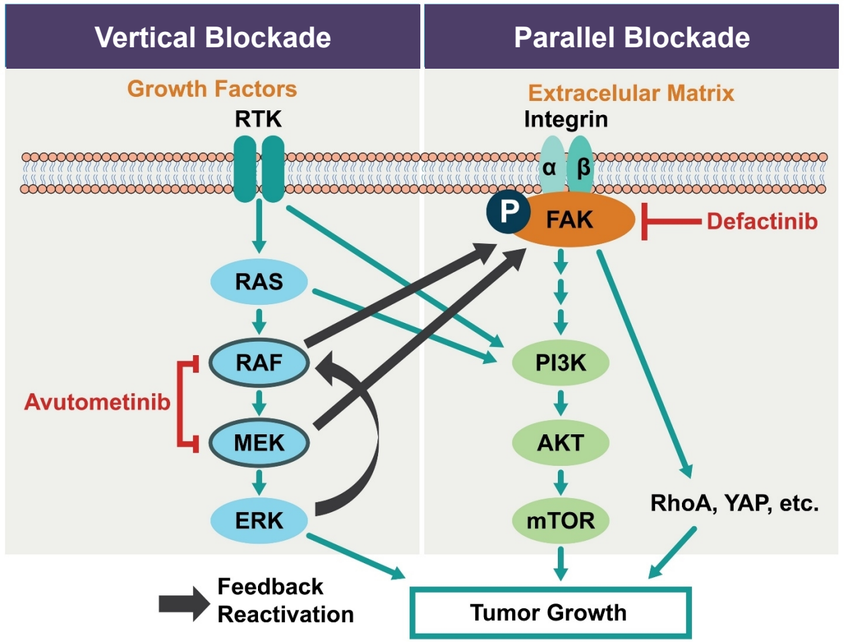
- Avutometinib is a first-in-class oral RAF/MEK clamp that potently inhibits MEK while also blocking the compensatory reactivation of MEK by upstream RAF[1,2]
- Defactinib is a selective inhibitor of FAK, a key adaptive resistance mechanism to the RAS/MAPK pathway[3-5]
- In the ENGOT-ov60/GOG-3052/RAMP 201 study, the combination of avutometinib plus defactinib demonstrated[6]
  - ORR of 31% overall (44% in *KRAS* mt and 17% in *KRAS* wt)
  - 10% discontinuation rate due to adverse events
- The results of RAMP 201 led to the accelerated approval of avutometinib + defactinib by the FDA for *KRAS*-mutated recurrent LGSOC[7]

The purpose of this analysis is to provide an update on the long-term safety and efficacy of avutometinib + defactinib in RAMP 201 with 1 additional year of follow-up since the primary analysis.

**Avutometinib + Defactinib Mechanism of Action**




**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.** Banerjee SN, et al. *J Clin Oncol*. 2025;43(25):2782-2792. **7.** Verastem, Inc. AVMAPKI™ FAKZYNJA™ CO-PACK. Prescribing Information. 2025.

AE, adverse event; FAK, focal adhesion kinase; FDA, Food and Drug Administration; *KRAS*, Kirsten rat sarcoma virus; LGSOC, low-grade serous ovarian cancer; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated extracellular signal-regulated kinase; ORR, objective response rate; RAF, rapidly accelerated fibrosarcoma; RAS, rat sarcoma virus; US, United States.

# ENGOT-ov60/GOG-3052/RAMP 201 Study Design

## Avutometinib 3.2 mg BIW and Defactinib 200 mg BID

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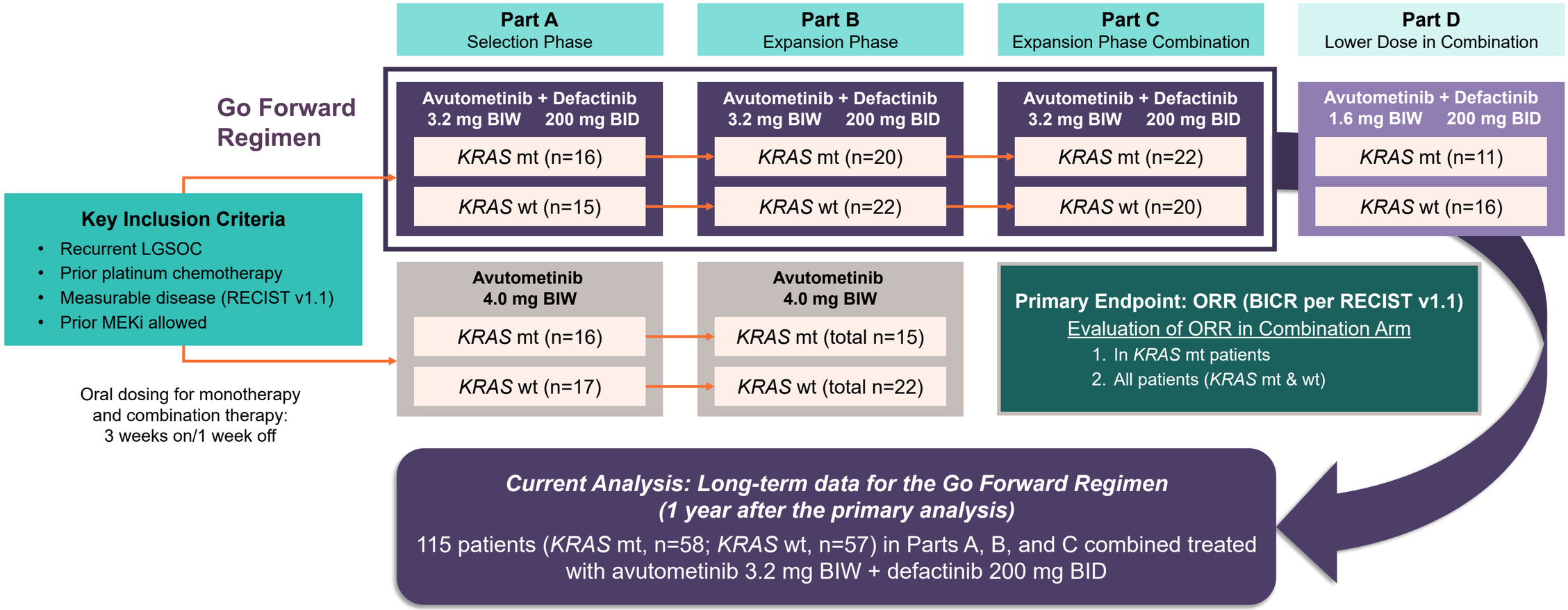


N-values represent patients who were treated in the study. Figure adapted from Banerjee SN, et al. *J Clin Oncol*. 2025;43(25):2782-2792.

BICR, blinded independent central review; BID, twice daily; BIW, twice weekly; ctDNA, circulating tumor DNA; *KRAS*, Kirsten rat sarcoma virus; LGSOC, low-grade serous ovarian cancer; MEK, mitogen-activated extracellular signal-regulated kinase; MEKi, mitogen-activated protein kinase Accad inhibitor; mt, mutant; ORR, objective response rate; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; wt, wild-type.

# Detection of *KRAS* Mutations Using Blood ctDNA vs Tumor Tissue Screening



- In RAMP 201, *KRAS* mutation status was based on tumor tissue analysis
- A separate analysis of RAMP 201 was conducted to determine if blood samples could reliably detect *KRAS* mutations in LGSOC[1]
- 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) showed KRAS mutation in blood samples
  - 56% (28/50) of patients showed a false negative blood KRAS mutation detection result

These findings suggest that blood (ctDNA) screening is not a sufficiently robust method for detecting KRAS mutations in patients with LGSOC

**1.** Van Nieuwenhuysen E, et al. Poster presented at: ESMO Gynaecological Cancers Annual Congress; June 19-21, 2025; Vienna, Austria.

# Baseline Characteristics

## Avutometinib 3.2 mg BIW and Defactinib 200 mg BID



| Baseline characteristic | All patients (N=115) | *KRAS* mt (n=58) | *KRAS* wt (n=57) |
|---|---|---|---|
| Age, median (range), y | 54 (21 to 87) | 60 (29 to 87) | 45 (21 to 80) |
| ECOG PS, n (%) | | | |
| 0 | 78 (68) | 42 (72) | 36 (63) |
| 1 | 37 (32) | 16 (28) | 21 (37) |
| Number of prior systemic regimens, median (range) | 3 (1 to 9) | 3 (1 to 9) | 3 (1 to 9) |
| Prior platinum-based chemotherapy, n (%)[a] | 114 (99) | 58 (100) | 56 (98) |
| Prior hormonal therapy, n (%) | **99 (86)** | 49 (85) | 50 (88) |
| Prior bevacizumab, n (%) | **59 (51)** | 23 (40) | 36 (63) |
| Prior MEKi therapy, n (%) | **25 (22)** | 12 (21) | 13 (23) |

- Overall, 53% and 47% of patients were from the United States and Europe, respectively
- The majority of patients were White (White, 77%; not reported, 11%; Asian, 4%; Black or African American, 4%; other, 4%)

Avutometinib and defactinib dosing was 3 weeks on and 1 week off.

[a]One patient without prior platinum received anastrozole only.

BID, twice daily; BIW, twice weekly; ECOG PS, Eastern Cooperative Oncology Group performance status; *KRAS*, Kirsten rat sarcoma virus; MEKi, mitogen-activated extracellular signal-regulated kinase inhibitor; mt, mutant; wt, wild-type.

# Patient Disposition

## Avutometinib 3.2 mg BIW and Defactinib 200 mg BID

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Median (range) follow-up for ongoing patients was **24.9 mo** (22.4 to 52.5)
Median (range) duration of treatment was **9.0 mo** (<1.0 to 52.2)
Mean relative dose intensity **0.8** for avutometinib and defactinib

| All patients treated (N=115) | | *KRAS* mt treated (n=58) | | *KRAS* wt treated (n=57) | |
|---|---|---|---|---|---|
| **Discontinued treatment (n=98; 85%)** | | **Discontinued treatment (n=46; 79%)** | | **Discontinued treatment (n=52; 91%)** | |
| Primary reason | | Primary reason | | Primary reason | |
| RECIST v1.1 disease progression | 59 (51%) | RECIST v1.1 disease progression | 27 (47%) | RECIST v1.1 disease progression | 32 (56%) |
| AE/unacceptable toxicity | 14 (12%) | AE/unacceptable toxicity | 6 (10%) | AE/unacceptable toxicity | 8 (14%) |
| Withdrawal of consent | 10 (9%) | Withdrawal of consent | 4 (7%) | Withdrawal of consent | 6 (11%) |
| Other[a] | 10 (9%) | Other[a] | 6 (10%) | Other[a] | 4 (7%) |
| Clinical deterioration | 5 (4%) | Clinical deterioration | 3 (5%) | Clinical deterioration | 2 (4%) |
| Death | 0 | Death | 0 | Death | 0 |
| **Continuing on treatment (n=17; 15%)** | | **Continuing on treatment (n=12; 21%)** | | **Continuing on treatment (n=5; 8%)** | |

Data cutoff date of August 12, 2025.

[a]Other includes clinical progression (n=5) and progression confirmed by biopsy/pathology report, patient noncompliance, patient withdrawal with agreement to follow-up, physician decision, patient decision (1 each).

AE, adverse event; BID, twice daily; BIW, twice weekly; *KRAS*, Kirsten rat sarcoma virus; mt, mutant; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; wt, wild-type.

# ORR (RECIST v1.1) by BICR – Primary Analysis

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| | All patients (N=109) | *KRAS* mt (n=57) | *KRAS* wt (n=52) |
|---|---|---|---|
| Confirmed[a] ORR, n (%) | 34 (31) | 25 (44) | 9 (17) |
| Complete response | 2 (2) | 2 (4) | 0 |
| Partial response | 32 (29) | 23 (40) | 9 (17) |
| Stable disease[b], n (%) | 62 (57) | 28 (49) | 34 (65) |
| Progressive disease, n (%) | 9 (8) | 2 (4) | 7 (14) |
| Not evaluable, n (%) | 4 (4) | 2 (4) | 2 (4) |

[a]By BICR. [b]Includes unconfirmed partial response; stable disease (or unconfirmed partial response) must occur ≥53 days after first dose date.

BICR, blinded independent central review; BID, twice daily; BIW, twice weekly; *KRAS*, Kirsten rat sarcoma virus homologue; mt, mutant; NE, not evaluable; ORR, objective response rate; RECIST v1.1, Response Evaluation Criteria in Solid Tumors - Version 1.1; wt, wild-type.

# Duration of Response 1 Year Post Primary Analysis

## Avutometinib 3.2 mg BIW and Defactinib 200 mg BID

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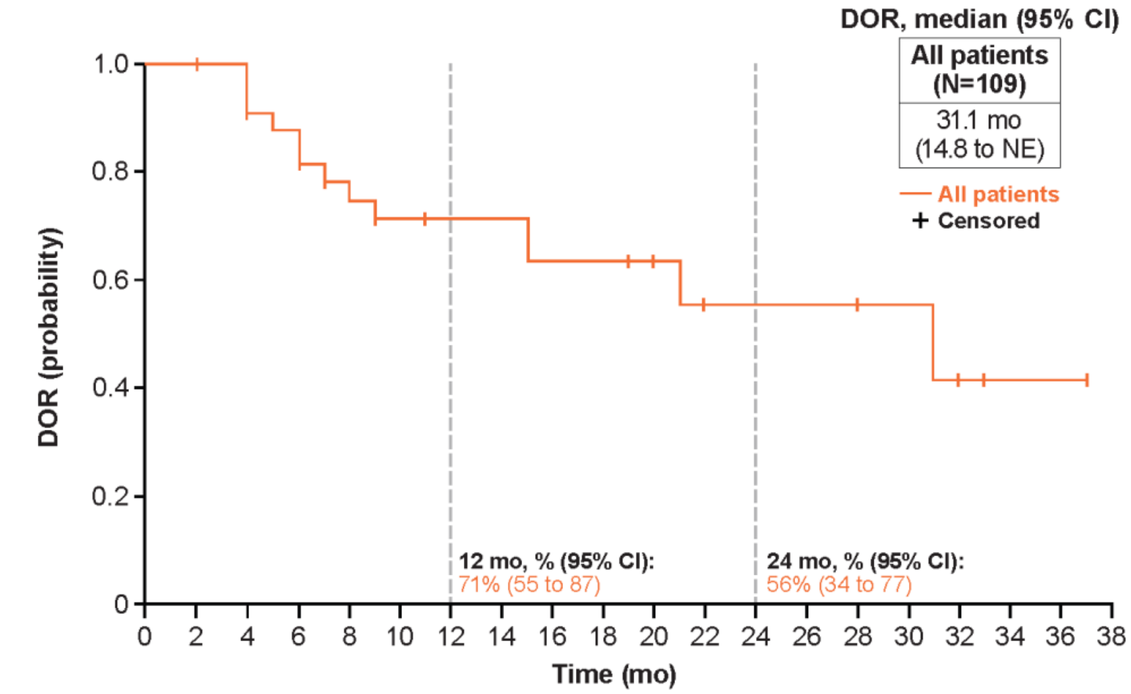


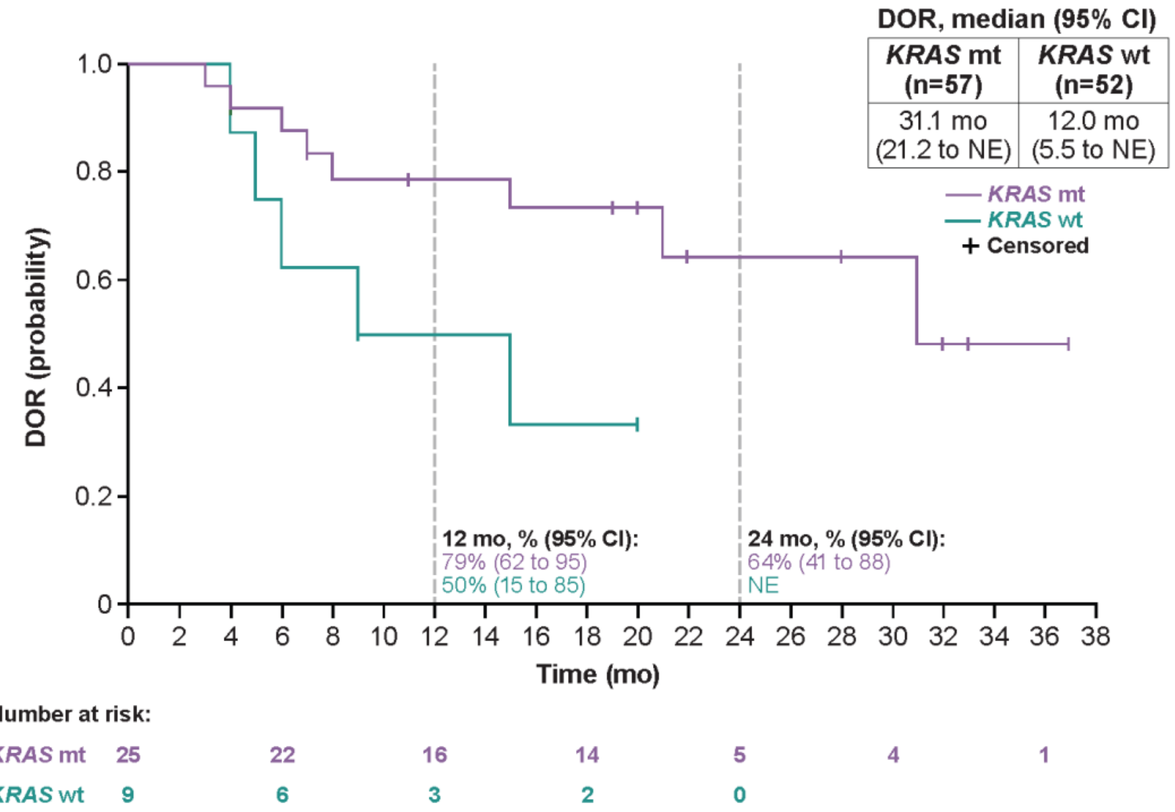


Data cutoff date of August 12, 2025. All patients have had an opportunity for ≥18 mo of follow-up.

BID, twice daily; BIW, twice weekly; DOR, duration of response; *KRAS*, Kirsten rat sarcoma virus homologue; mt, mutant; wt, wild-type.

# Treatment Duration and Response Time in Patients With *KRAS* mt Tumors

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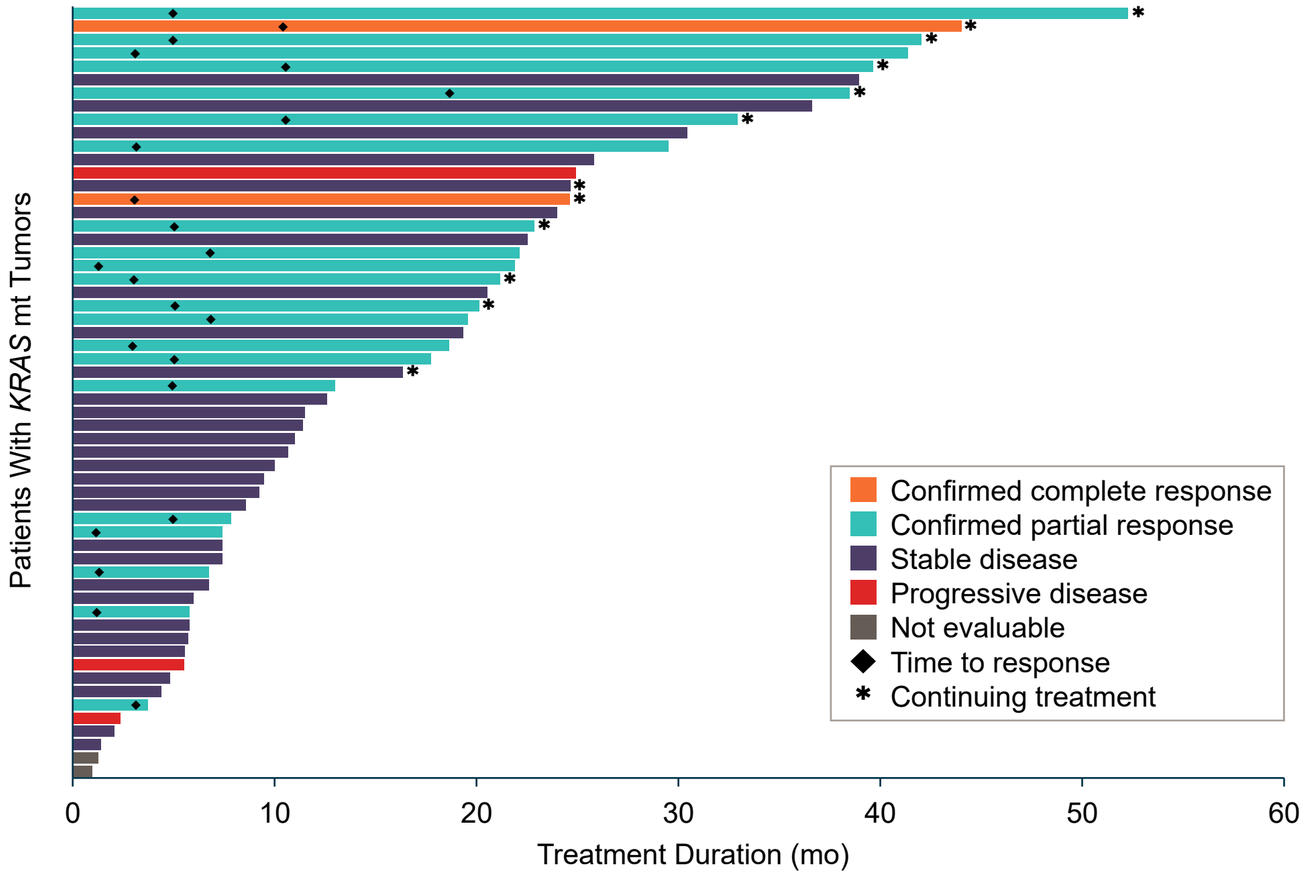
## Avutometinib 3.2 mg BIW and Defactinib 200 mg BID



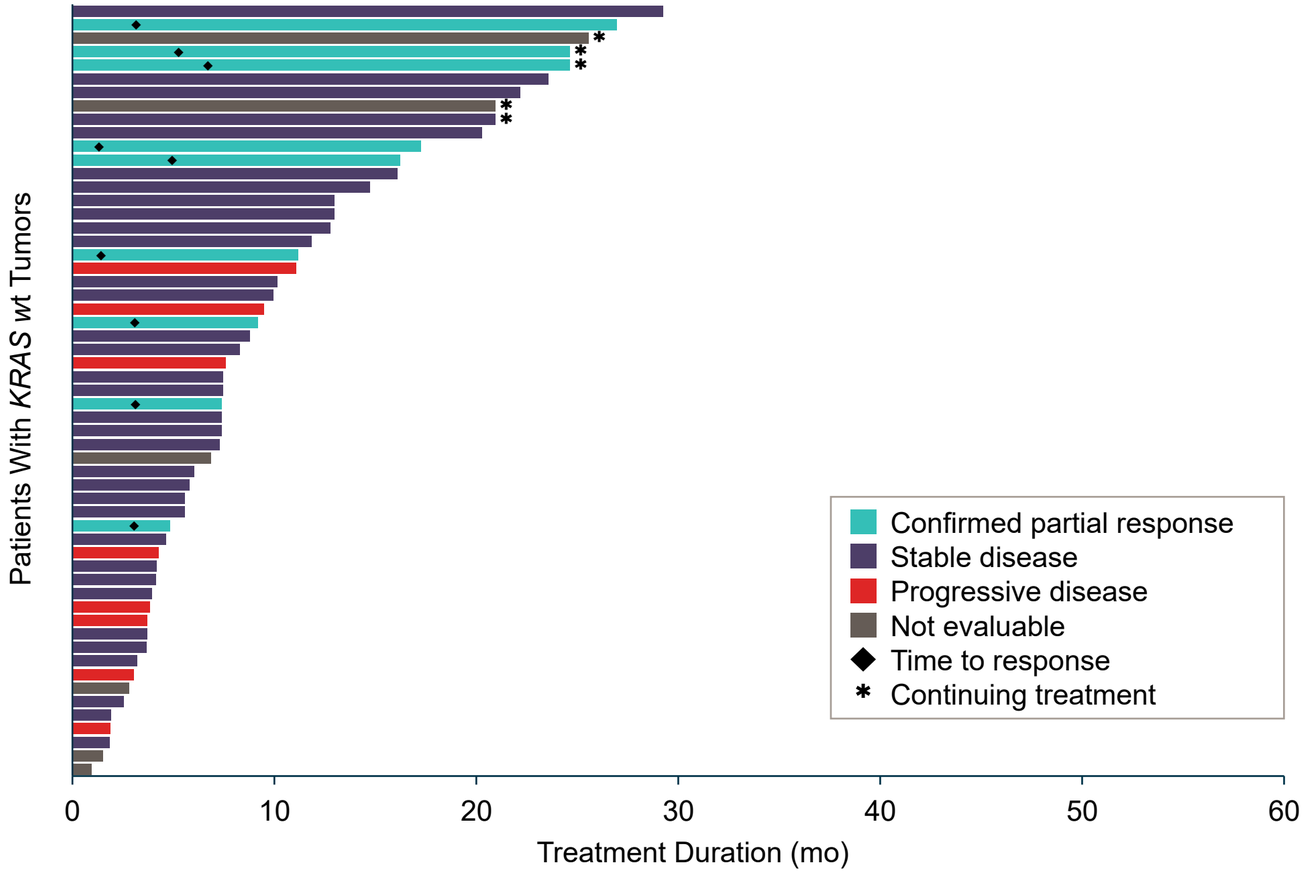

In Patients with *KRAS* mt tumors:

- Median (range) duration of treatment was 12.6 mo (9.2 to 21.9)
- Median (range) time to response was 3.7 mo (1.7 to19.2)
- 52% (30/58) remained on therapy for >1 y

BID, twice daily; BIW, twice weekly; *KRAS*, Kirsten rat sarcoma virus; mt, mutant.

# Treatment Duration and Response Time in Patients With *KRAS* wt Tumors

## Avutometinib 3.2 mg BIW and Defactinib 200 mg BID



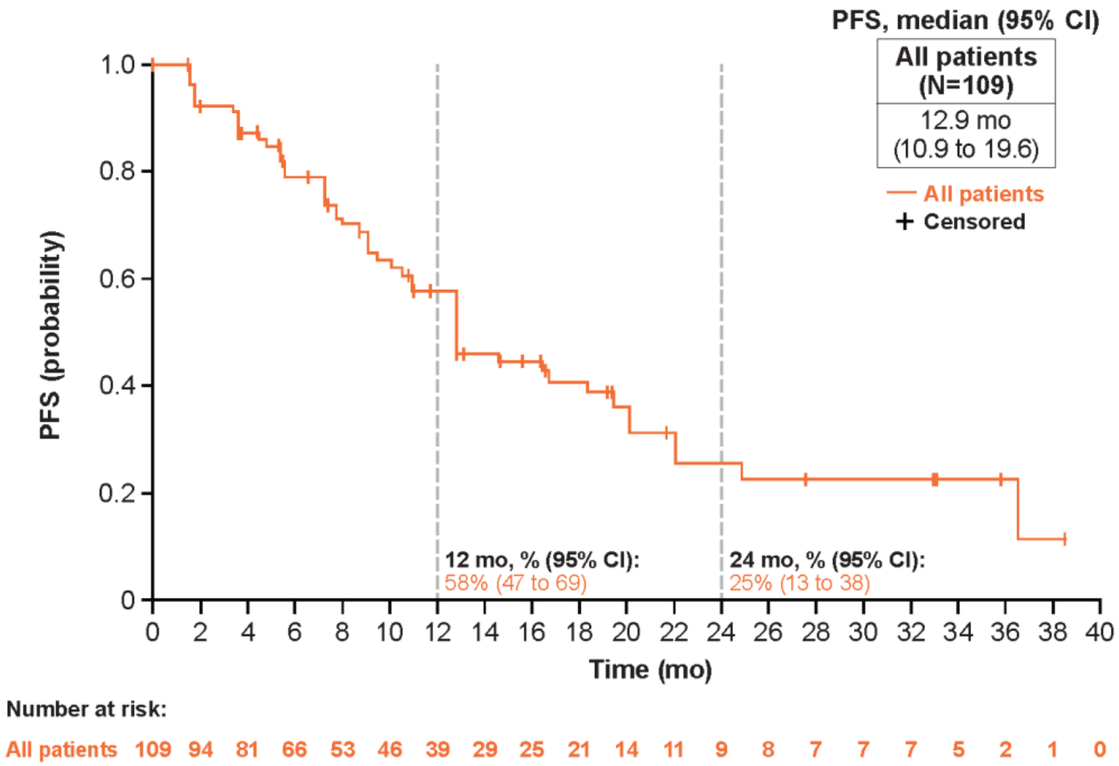

In Patients with *KRAS* wt tumors:

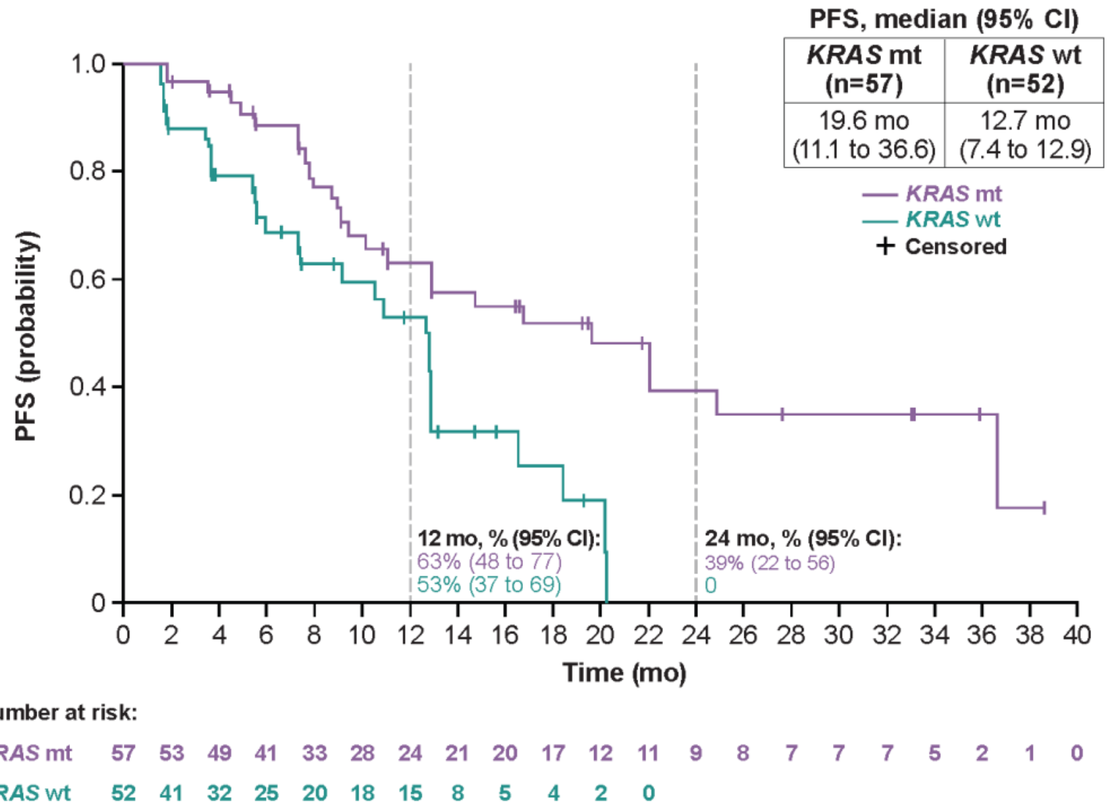
- Median (range) duration of treatment was 7.2 mo (<1 to 29.2)
- Median (range) time to response was 3.6 mo (1.8 to 7.2)
- 30% (17/57) remained on therapy for >1 y

BID, twice daily; BIW, twice weekly; *KRAS*, Kirsten rat sarcoma virus; wt, wild-type.

# Progression-Free Survival in Patients With *KRAS* mt and *KRAS* wt Tumors

## Avutometinib 3.2 mg BIW and Defactinib 200 mg BID




Data cutoff date of August 12, 2025.

BID, twice daily; BIW, twice weekly; *KRAS*, Kirsten rat sarcoma virus; mt, mutant; PFS, progression-free survival; wt, wild-type.

# Most Common Treatment-Related AEs at the Time of the Primary Analysis and With 1 Additional Year of Follow-up

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## Avutometinib 3.2 mg BIW and Defactinib 200 mg BID

| Preferred term, n (%) | Primary analysis[a] (N=115) | | Updated analysis[b] (N=115) | |
|---|---|---|---|---|
| | All grades | Grade ≥3 | All grades | Grade ≥3 |
| **Nonlaboratory AEs** | | | | |
| Nausea | 77 (67) | 3 (3) | 78 (68) | 3 (3) |
| Diarrhea | 67 (58) | 9 (8) | 68 (59) | 9 (8) |
| Peripheral edema | 61 (53) | 1 (1) | 61 (53) | 1 (1) |
| Rash[c] | 58 (50) | 3 (3) | 59 (51) | 5 (4) |
| Fatigue | 50 (44) | 3 (3) | 51 (44) | 3 (3) |
| Vomiting | 49 (43) | 3 (3) | 50 (44) | 3 (3) |
| Vision blurred | 47 (41) | 0 | 48 (42) | 0 |
| Dermatitis acneiform | 39 (34) | 5 (4) | 39 (34) | 5 (4) |
| Dry skin | 30 (26) | 0 | 31 (27) | 0 |
| Anemia | 26 (23) | 6 (5) | 27 (24) | 8 (7) |
| **Laboratory-related AEs** | | | | |
| Increased blood CPK | 69 (60) | 28 (24) | 69 (60) | 30 (26) |
| Increased blood bilirubin/ hyperbilirubinemia | 38 (33) | 5 (4) | 38 (33) | 5 (4) |
| Increased AST | 36 (31) | 2 (2) | 36 ( 31) | 2 (2) |
| Increased ALT | 25 (22) | 2 (2) | 26 ( 23) | 2 (2) |

- Frequency and nature of AEs were generally consistent with findings from the primary analysis
- No new safety signals and few new-onset AEs

Most common AEs (preferred term) considered by the investigator to be related to study drug (either avutometinib or defactinib).

[a]Data cutoff of June 30, 2024. [b]Data cutoff of August 12, 2025. [c]Treatment-related AEs for "rash" include the preferred terms butterfly rash, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, and rash pruritic.

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, twice daily; BIW, twice weekly; CPK, creatine phosphokinase.

# Management of Adverse Events

## Avutometinib 3.2 mg BIW and Defactinib 200 mg BID

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AEs were managed with dose modifications (dose interruptions or reductions) and prophylaxis for skin reactions*

**At the time of the current analysis**

### ⏸ Dose Interruptions

- 84% of patients had AEs leading to dose interruption (80% at primary analysis)
- The most common treatment-related AEs managed with dose interruptions (≥5% of patients) were:
  - Elevated blood CPK (25%)
  - Elevated blood bilirubin/ hyperbilirubinemia (22%)
  - Diarrhea (10%)
  - Vomiting (7%)
  - Peripheral edema (6%)
  - Blurred vision (6%)
  - Nausea (5%)
  - Fatigue (5%)

### ▼ Dose Reductions

- 37% of patients had AEs leading to dose reduction (37% at primary analysis)
- The most common treatment-related AEs managed with dose reductions (≥5% of patients) were:
  - Elevated blood CPK (8%)
  - Dermatitis acneiform (5%)

### ■ Discontinuations

- 12% of patients discontinued for AEs (10% at primary analysis)

*Prophylactic medication for rash was mandatory during the first 2 cycles (ie, hydrocortisone cream, moisturizer, sunscreen, and systemic antibiotic) and optional at the discretion of the investigator thereafter.

Data cutoff of August 12, 2025

AE, adverse event; BID, twice daily; BIW, twice weekly; CPK, creatine phosphokinase.

# Summary and Conclusions



- With 1 additional year of follow-up in RAMP 201, DOR and PFS with the combination of avutometinib and defactinib were comparable to the primary analysis
  - **Median DOR:** 31 months overall; 31 months in *KRAS* mt and 12 months in *KRAS* wt
  - **Median PFS**: 12.9 months overall; 19.6 months in *KRAS* mt and 12.7 months in *KRAS* wt
- Patients remaining on therapy for >1 year: 52% in *KRAS* mt and 30% in *KRAS* wt
- The types of AEs observed, frequency, and severity were also similar to earlier reports, indicating few new-onset AEs with longer-term treatment and no new safety signals
    - Most AEs were grade 1 or 2
    - The discontinuation rate for AEs was 12%

The combination of AE management and durable efficacy, including objective responses and stable disease in patients with and without a *KRAS* mutation, allowed patients to stay on long-term avutometinib + defactinib combination therapy

AE, adverse event; DOR, duration of response; *KRAS*, Kirsten rat sarcoma virus; PFS, progression-free survival.

# We thank the patients and their families, the trial teams at the participating centers, ENGOT, and GOG for supporting this study

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