第68回
日本婦人科腫瘍学会学術講演会

# A Phase 2 Trial of the Combination Therapy of Avutometinib and Defactinib in Japanese Patients With Recurrent Low-Grade Serous Ovarian Cancer

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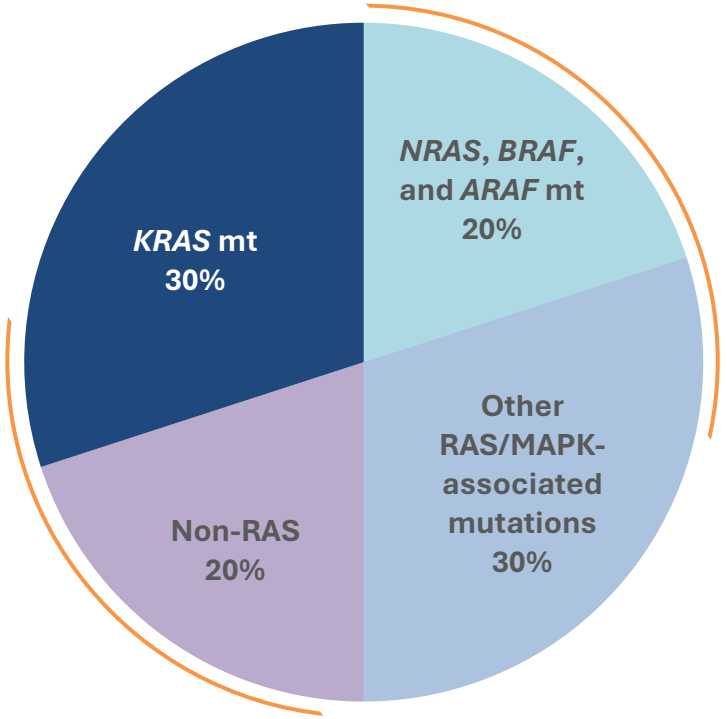
# Low-Grade Serous Ovarian Cancer

- Low-grade serous ovarian cancer (LGSOC) is a rare, histopathologic, molecular, and clinically distinct cancer subtype 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 for patients with recurrent disease has shown limited efficacy (ORR, 0%–13%)[5,6]

**Mutations in patients with LGSOC[3,4,7,8]**



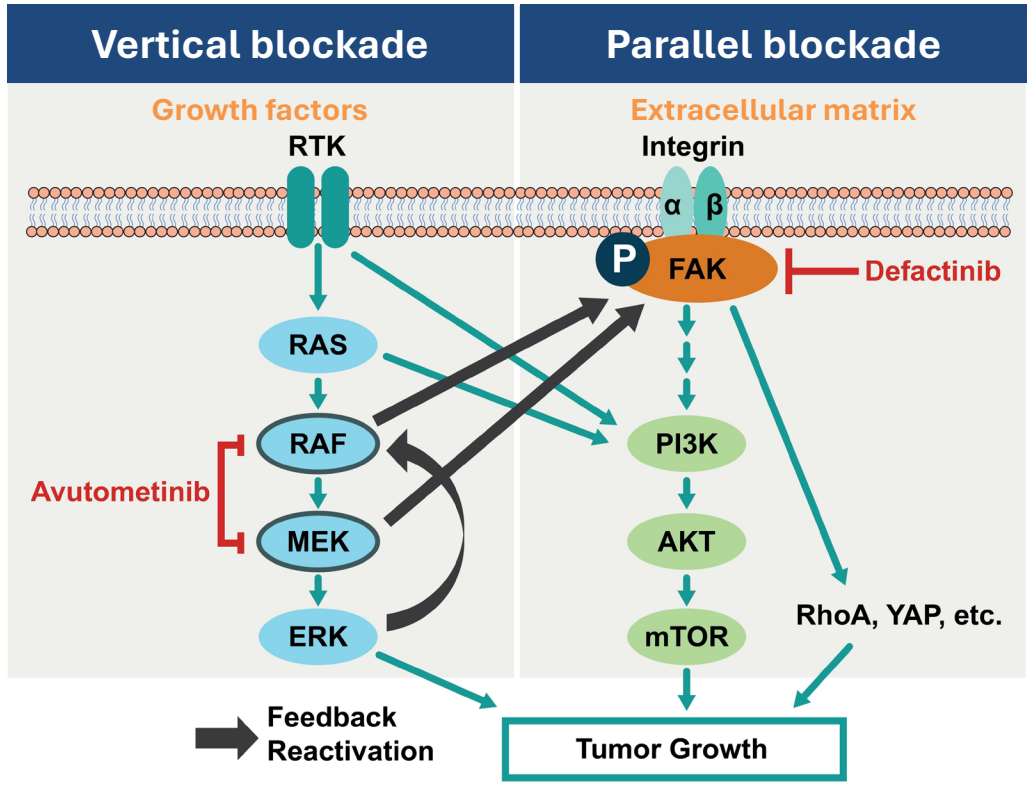

**1**. Grisham RN, et al. *Int J Gynecol Cancer*. 2023;33(9):1331-1344. **2**. Matsuo K, et al. *J Gynecol Oncol*. 2018;29(1):e15. **3.** Manning-Geist B, et al. *Clin Cancer Res*. 2022;28(20)4456-4465. **4**. ElNaggar A, et al. *Gynecol Oncol*. 2022;167(2):306-313. **5**. Gershenson DM, et al. *Lancet*. 2022;399(10324):541-553. **6**. Monk BJ, et al. *J Clin Oncol*. 2020;38(32):3753-3762. **7.** Thomson JP, et al. *Gynecol Oncol*. 2023;174:157-166. **8.** Gershenson DM, et al. *Gynecol Oncol*. 2022;165(3):560-567.

*ARAF*, A-Raf proto-oncogene, serine/threonine kinase; *BRAF*, v-raf murine sarcoma viral oncogene homolog B1; *KRAS*, Kirsten rat sarcoma virus; LGSOC, low-grade serous ovarian cancer; MAPK, mitogen-activated protein kinase; mt, mutant; *NRAS*, neuroblastoma RAS viral oncogene homolog; ORR, objective response rate; RAS, rat sarcoma virus.

# Avutometinib + Defactinib Mechanism of Action

- Avutometinib is a 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[3-5]

**Avutometinib + defactinib mechanism of action**

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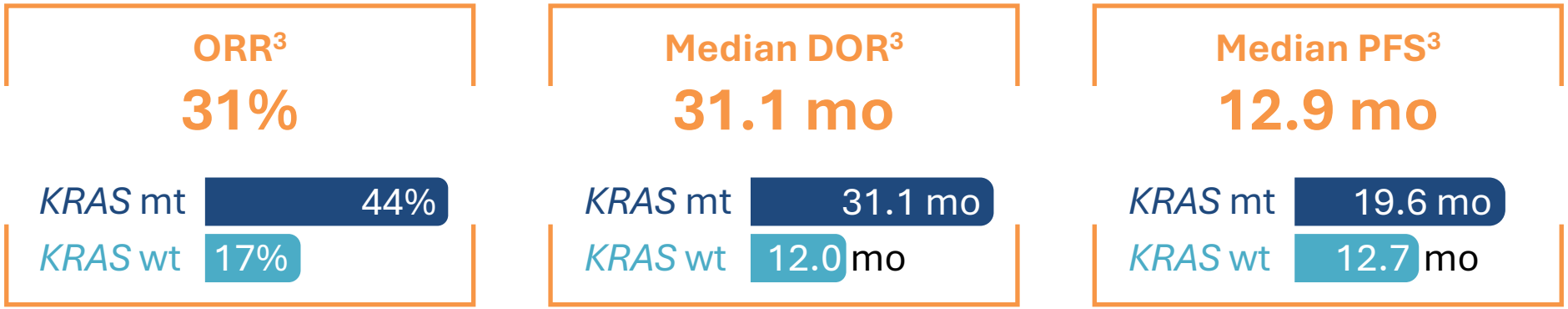
**1.** Lito P, et al. *Cancer Cell*. 2014;25(5):697-710. **2.** Gonzalez-Del Pino GL, et al. *Proc Natl Acad Sci U S A*. 2021;118(36):e2107207118. **3.** Dawson JC, et al. *Nat Rev Cancer*. 2021;21:313-324. **4.** Shinde R, et al. *Cancer Res*. 2020;80(suppl 16):CT143. **5.** Kang Y, et al. *J Natl Cancer Inst*. 2013;105(19):1485-1495.

AKT, protein kinase B; ERK, extracellular signal-regulated kinase; FAK, focal adhesion kinase; MEK, mitogen-activated protein kinase kinase; mTOR, mechanistic target of rapamycin; PI3K, phosphoinositide 3-kinase; RAF, rapidly accelerated fibrosarcoma; RAS, rat sarcoma; RhoA, Ras homolog family member A; RTK, receptor tyrosine kinase; YAP, yes-associated protein.

# Avutometinib + Defactinib Clinical Data in Patients With Recurrent LGSOC

- Avutometinib + defactinib combination therapy was approved by the FDA for treatment the of patients with recurrent *KRAS*-mutated LGSOC based on the RAMP 201 single-arm international trial conducted in the US, Europe, and Canada[1-3]
- A long-term RAMP 201 analysis (median follow-up, >24 mo) demonstrated that avutometinib + defactinib treatment, along with AE management, had clinically meaningful disease response in patients with recurrent LGSOC, regardless of *KRAS* mutation status[3]




**1.** Verastem, Inc. AVMAPKI™ FAKZYNJA™ CO-PACK. Prescribing Information. 2025. **2.** Banerjee SN, et al. *J Clin Oncol. 2025;43(25):2782-2792*. **3.** Grisham RN et al. 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. Presented at: Society of Gynecologic Oncology Annual Meeting on Women's Cancer; April 10-13, 2026; San Juan, Puerto Rico.

AE, adverse event; DOR, duration of response; FDA, Food and Drug Administration; *KRAS*, Kirsten rat sarcoma virus; LGSOC, low-grade serous ovarian cancer; mt, mutant; ORR, objective response rate; PFS, progression-free survival; US, United States; wt, wild-type.

# RAMP 201J Study Design

## Avutometinib 3.2 mg BIW + Defactinib 200 mg BID

- This phase 2 study (RAMP 201J) is designed to evaluate the efficacy, pharmacokinetics, and safety of avutometinib + defactinib in Japanese patients with recurrent LGSOC
- Patients with recurrent LGSOC (*KRAS* mt or wt) who progressed on prior platinum-based chemotherapy received avutometinib 3.2 mg PO BIW + defactinib 200 mg PO BID for the first 3 weeks of each 4-week cycle

### Key eligibility criteria

- Confirmed LGSOC diagnosis
- Recurrent disease after prior platinum therapy
- Documented *KRAS* mutation status
- Measurable disease per RECIST v1.1

### Safety run-in (n=6)

- Avutometinib 3.2 mg PO BIW + defactinib 200 mg PO BID 3 weeks on, 1 week off for 1 full cycle (28 days)

No dose-limiting toxicities occurred among 6 patients enrolled and reviewed to confirm safety dose

### Treatment phase (N=16 total[a])

- Avutometinib 3.2 mg PO BIW 3 weeks on, 1 week off + defactinib 200 mg PO BID 3 weeks on, 1 week off

Pharmacokinetic assessment comparing Japanese to Western patients to ensure exposure equivalency[b]

- The primary endpoint of the final analysis is ORR by BICR
- The data cutoff date for this ad hoc interim analysis of investigator-assessed response was May 29, 2026
- The study is ongoing

[a]Includes 6 patients from the safety run-in. [b]Includes all patients (N=16).

BICR, blinded independent central review; BID, twice daily; BIW, twice weekly; *KRAS*, Kirsten rat sarcoma virus; LGSOC, low-grade serous ovarian cancer; mt, mutant; PO, orally; ORR, objective response rate; RECIST v1.1, Response Evaluation Criteria in Solid Tumors - Version 1.1; wt; wild-type.

# Patient Baseline Characteristics

## Avutometinib 3.2 mg BIW + Defactinib 200 mg BID

- At data cutoff, 16 patients were enrolled
  - 7 patients with *KRAS* mt tumors
  - 9 patients with *KRAS* wt tumors
- Median (range) age was 47 (23-72) years
- 44% of patients had ≥4 prior lines of therapy
  - All patients received prior platinum-based chemotherapy
  - Other prior therapies[a]
    - Bevacizumab (63%)
    - PARP inhibitor (38%)
    - Hormonal therapy (31%)
    - MEK inhibitor (0%)

| Characteristic | All patients (N=16) |
|---|---|
| Age, median (range), y | 47 (23-72) |
| ECOG PS, n (%) | |
| 0 | 14 (88) |
| 1 | 2 (13) |
| *KRAS* status, n (%) | |
| *KRAS* mt | 7 (44) |
| *KRAS* wt | 9 (56) |
| Time since last recurrence, median (range), mo | 3.8 (1-21) |
| Number of prior lines of therapy, n (%) | |
| 1 | 3 (19) |
| 2 | 3 (19) |
| 3 | 3 (19) |
| ≥4 | 7 (44) |
| Prior therapy, n (%)[a] | |
| Platinum | 16 (100) |
| Bevacizumab | 10 (63) |
| PARP inhibitor therapy | 6 (38) |
| Hormonal therapy | 5 (31) |
| MEK inhibitor therapy | 0 |

Data cutoff date of May 29, 2026.

[a]Medications used as prior therapies are consistent with the Japanese health insurance system. MEK inhibitors were not approved for LGSOC treatment in Japan at the time of study enrollment.

BID, twice daily; BIW, twice weekly; ECOG PS, Eastern Cooperative Oncology Group performance status; *KRAS*, Kirsten rat sarcoma virus; LGSOC, low-grade serous ovarian cancer; MEK, mitogen-activated extracellular signal-regulated kinase; mt, mutant; PARP, poly(ADP-ribose) polymerase; wt, wild-type.

# Patient Disposition

## Avutometinib 3.2 mg BIW + Defactinib 200 mg BID

**At the time of data cutoff, the median (range) duration of follow-up was 12.4 (5.4-18.1) mo**

| Patient disposition, n (%) | All patients (N=16) |
|---|---|
| Patients treated | 16 (100) |
| Patients on treatment at data cutoff | 11 (69) |
| Patients discontinued treatment | 5 (31) |
| Primary reason for discontinuation | |
| Clinical progression | 3 (19) |
| Radiographic progression (RECIST 1.1) | 1 (6) |
| Other reason | 1 (6) |
| AEs | 0 |

- Of the 16 patients enrolled, 11 (69%) remain on treatment
- No patients discontinued for an AE

Data cutoff date of May 29, 2026.

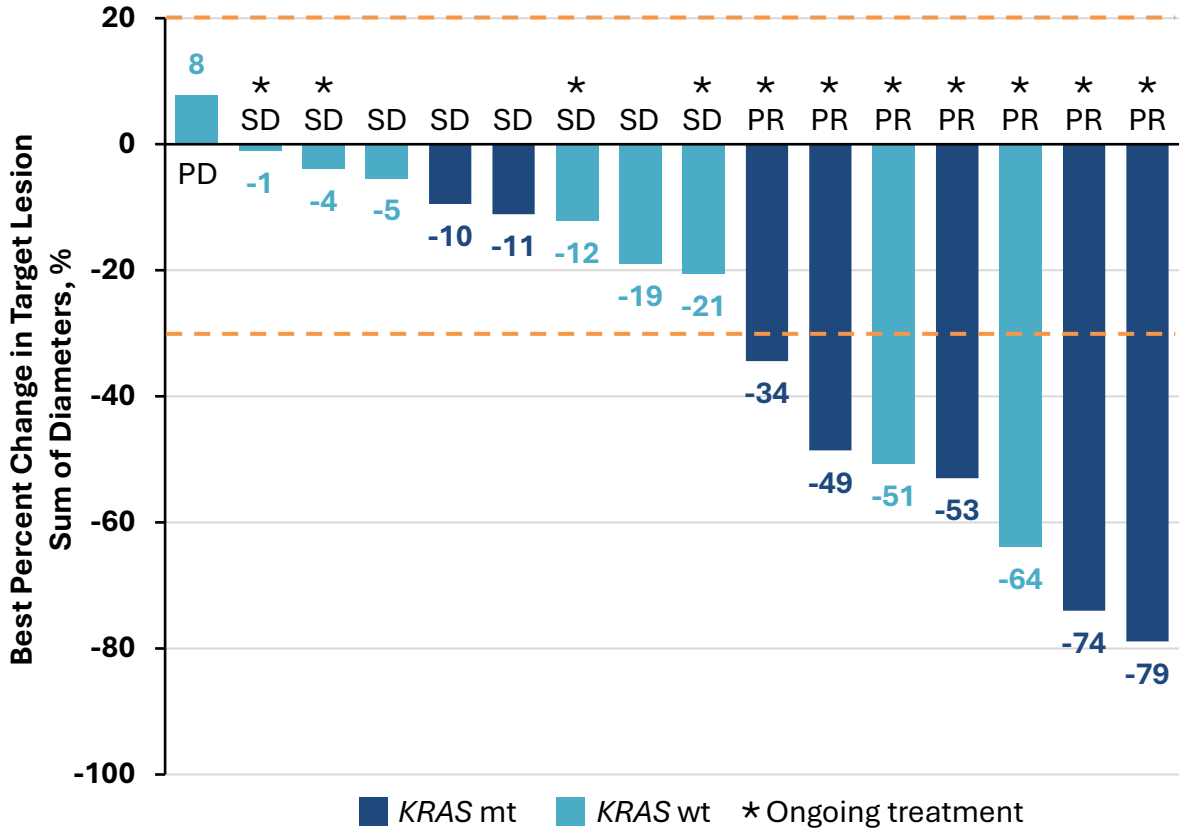
AE, adverse event; BID, twice daily; BIW, twice weekly; RECIST v1.1, Response Evaluation Criteria in Solid Tumors - Version 1.1.

# ORR and Best Percent Change in Target Lesions and Response (by Investigator Assessment)

Avutometinib 3.2 mg BIW + Defactinib 200 mg BID

| Response rates, n (%) | *KRAS* mt (n=7) | *KRAS* wt (n=9) | All patients (N=16) |
|---|---|---|---|
| Confirmed ORR | 5 (71) | 2 (22) | 7 (44) |
| CR | 0 | 0 | 0 |
| PR | 5 (71) | 2 (22) | 7 (44) |
| SD[a] | 2 (29) | 6 (67) | 8 (50) |
| PD | 0 | 1 (11) | 1 (6) |
| DCR | 7 (100) | 8 (89) | 15 (94) |

- 44% (7/16) of patients had confirmed ORR
- 94% (15/16) of patients had a decrease in target lesions



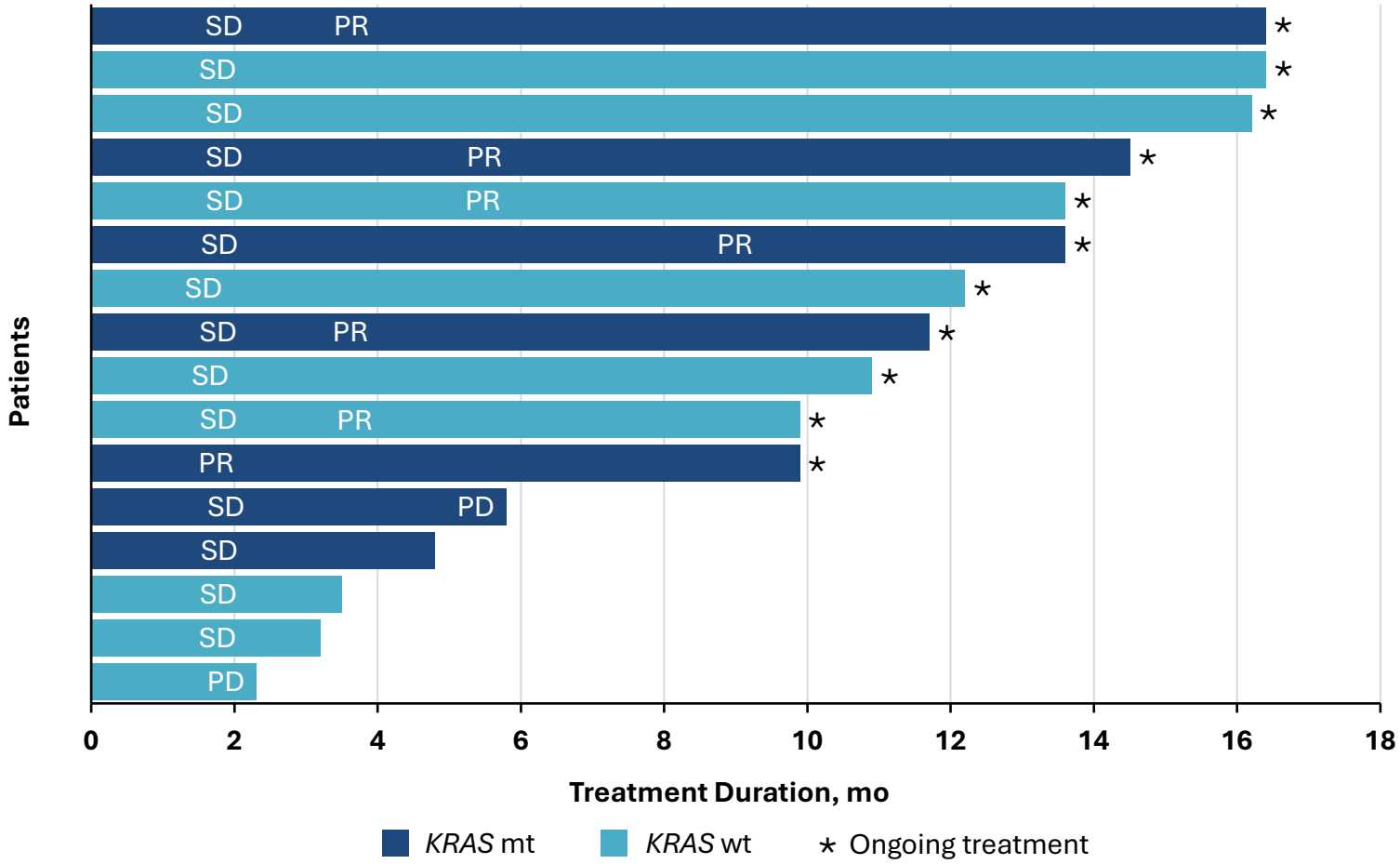

Data cutoff date of May 29, 2026. Orange dashed lines indicate thresholds for ≥20% increase and ≥30% decrease.

[a]Includes SD, unconfirmed PR, and unconfirmed CR.

BID, twice daily; BIW, twice weekly; CR, complete response; DCR, disease control rate; *KRAS*, Kirsten rat sarcoma virus; mt, mutant; ORR, objective response rate; SD, stable disease; wt, wild-type. PD, progressive disease; PR, partial response; SD, stable disease; wt, wild-type.

# Duration of Treatment (by Investigator Assessment)

## Avutometinib 3.2 mg BIW + Defactinib 200 mg BID



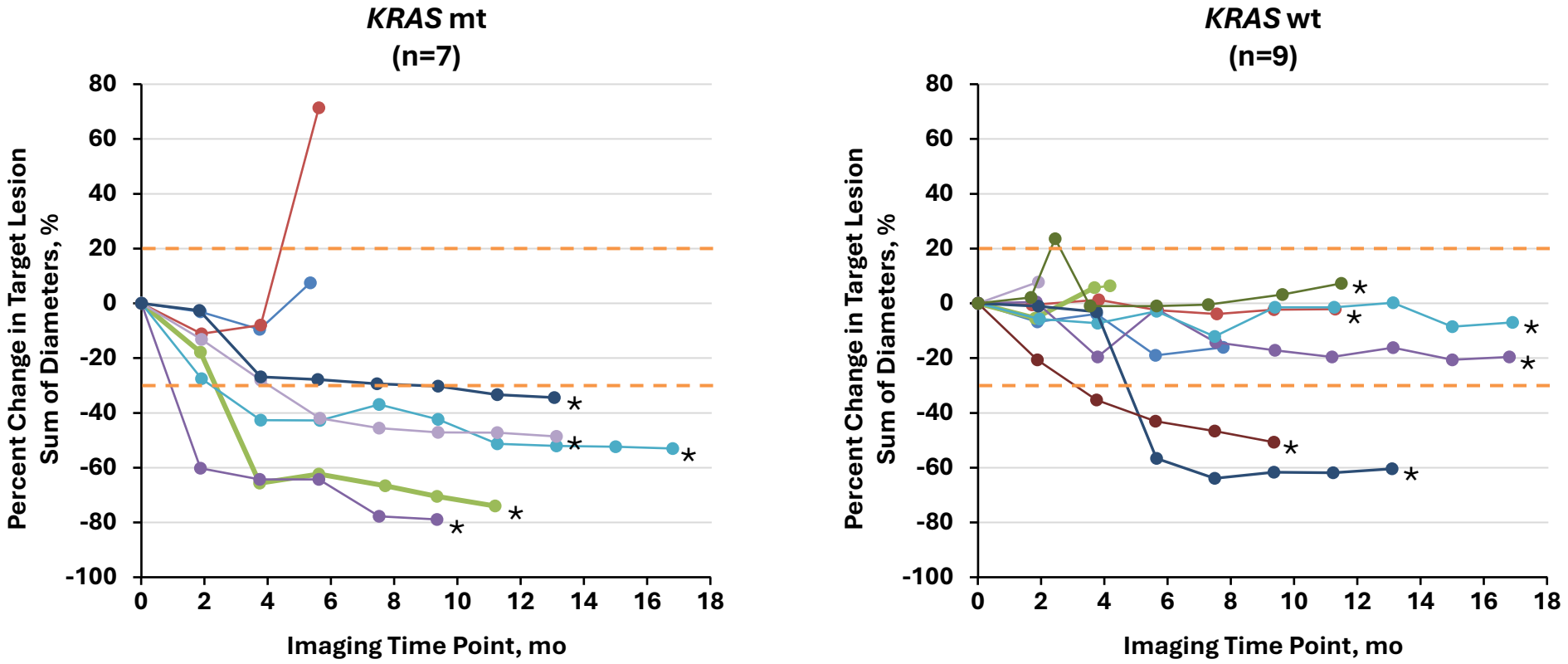

- 44% (7/16) of patients received treatment for >12 mo
- Median (range) duration of treatment was:
  - 11.7 (4.8-16.4) mo for *KRAS* mt
  - 10.9 (2.3-16.4) mo for *KRAS* wt

Data cutoff date of May 29, 2026.

BID, twice daily; BIW, twice weekly; *KRAS*, Kirsten rat sarcoma virus; mt, mutant; PD, progressive disease; PR, partial response; SD, stable disease; wt, wild-type.

# Disease Control in Avutometinib + Defactinib in Patients With *KRAS* mt and *KRAS* wt LGSOC

Avutometinib 3.2 mg BIW + Defactinib 200 mg BID




* Ongoing treatment

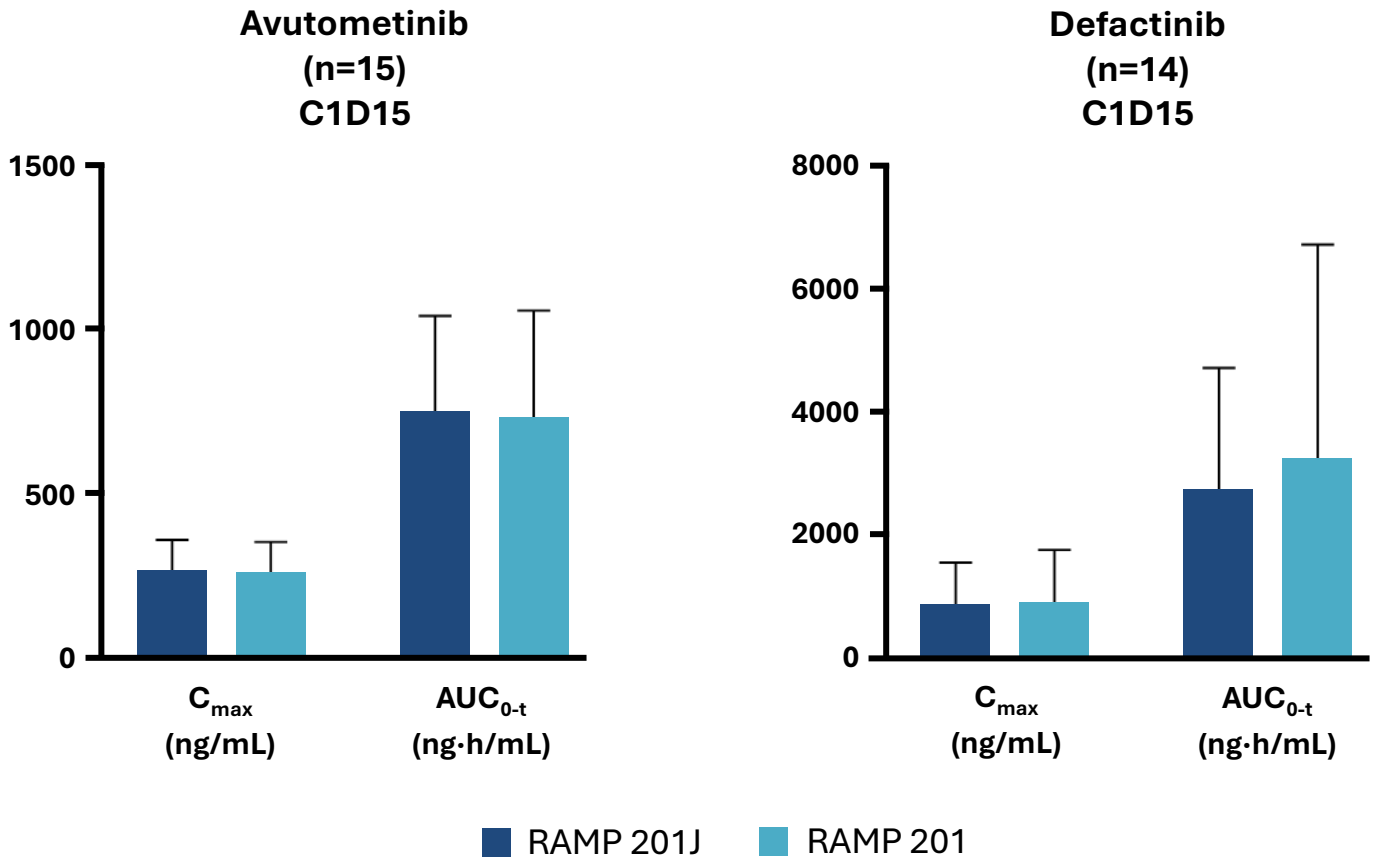
Prolonged disease control was observed in patients with *KRAS* mt and *KRAS* wt LGSOC

Data cutoff date of May 29, 2026. All patients received ≥1 postbaseline assessment; therefore, the mITT and efficacy evaluable populations are the same. Orange dashed lines indicate thresholds ≥20% increase and ≥30% decrease.

BID, twice daily; BIW, twice weekly; *KRAS*, Kirsten rat sarcoma virus; LGSOC, low-grade serous ovarian cancer; mITT, modified intent-to-treat; mt, mutant; wt, wild-type.

# Pharmacokinetics of Avutometinib and Defactinib in RAMP 201J and RAMP 201

## Avutometinib 3.2 mg BIW + Defactinib 200 mg BID




The pharmacokinetic profile was similar between patients in RAMP 201J and RAMP 201, with comparable $C_{max}$ and steady-state exposure

Includes all patients (N=16).

$AUC_{0-t}$, area under the curve from time zero to time t; BID, twice daily; BIW, twice weekly; C1D15, cycle 1 day 15; $C_{max}$, maximum concentration.

# Safety Profile: No New Safety Signals Observed

## Avutometinib 3.2 mg BIW + Defactinib 200 mg BID

- Most treatment-related AEs were grade 1 or 2
- The most common grade 3 treatment-related AEs were increased blood CPK and rash
- AEs were managed with conservative treatment and dose interruptions (and resuming at same dose) or reductions
  - 15 patients (93%) had ≥1 AE that led to dose interruption
    - The most common were rash and increased blood CPK in 4 patients (25%) each
  - 5 patients (31%) had ≥1 AE that led to dose reduction
    - The most common were rash in 2 patients (13%) and malaise, anemia, and elevated ALT in 1 patient (6%) each
- There were no discontinuations due to AEs
- No grade 4 or grade 5 treatment-related AEs were observed; there were 3 deaths, all due to progressive disease

| Treatment-related AEs, [a] n (%) | All patients (N=16) | |
|---|---|---|
| **Preferred term** | **All grades** | **Grade 3[b]** |
| Any treatment-related AE | 16 (100) | 9 (56) |
| Treatment-related AEs (≥25% of patients) | | |
| Nonlaboratory AEs | | |
| Peripheral edema | 9 (56) | 0 |
| Stomatitis | 9 (56) | 0 |
| Diarrhea | 8 (50) | 0 |
| Nausea | 8 (50) | 0 |
| Rash | 8 (50) | 3 (19) |
| Malaise | 7 (44) | 2 (13) |
| Paronychia | 6 (38) | 0 |
| Vision blurred | 5 (31) | 0 |
| Rash maculopapular | 5 (31) | 1 (6) |
| Acne | 4 (25) | 0 |
| Dermatitis acneiform | 4 (25) | 1 (6) |
| Dry eye | 4 (25) | 0 |
| Laboratory-related AEs | | |
| CPK blood elevations | 15 (94) | 3 (19) |
| ALT increased | 5 (31) | 2 (13) |
| Increased blood bilirubin | 5 (31) | 0 |

Data cutoff date of March 29, 2026.

[a]Most common AEs (preferred term) considered by the investigator to be related to study drug (either avutometinib or defactinib).
[b]Other grade 3 events included back pain, neck pain, anemia, hypoalbuminemia, and pyogenic granuloma (1 patient each).

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

# Efficacy, Pharmacokinetic, and Safety Profiles of Avutometinib + Defactinib in Japanese Patients are Comparable to the Larger International RAMP 201 Study

- Avutometinib + defactinib (median follow-up, 12.4 mo) demonstrated promising preliminary efficacy in Japanese patients with recurrent LGSOC
  - ORR by investigator assessment: 44% overall (71% in *KRAS* mt and 22% in *KRAS* wt)
  - DCR by investigator assessment: 94% overall (100% in *KRAS* mt and 89% in *KRAS* wt)
- The drug combination was generally well tolerated and resulted in no treatment discontinuations due to AEs
- The pharmacokinetic profiles of both avutometinib and defactinib in patients with recurrent LGSOC were similar between Japanese patients and Western patients following the same dosing regimen

**The efficacy, pharmacokinetic, and safety profiles of avutometinib + defactinib in Japanese patients with recurrent LGSOC were similar to the results observed in the international RAMP 201 study, suggesting this combination therapy may be an effective treatment option for Japanese patients with recurrent LGSOC**

**The phase 3 study, RAMP 301 (NCT06072781), is ongoing and enrolling in Japan**

AE, adverse event; BID, twice daily; BIW, twice weekly; DCR, disease control rate; *KRAS*, Kirsten rat sarcoma virus; mt, mutant; LGSOC, low-grade serous ovarian cancer; ORR, overall response rate; wt, wild-type.

# Acknowledgements

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