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Single Arm Phase II Study of Avutometinib and Defactinib in Advanced or Recurrent Mesonephric or Mesonephric-like (MLA) Gynecologic Cancer: Interim Results

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NCT05787561

Financial Disclosure for:
[Insert Name]

I have the following financial relationships with ACCME defined ineligible companies to report over the past 24 months:

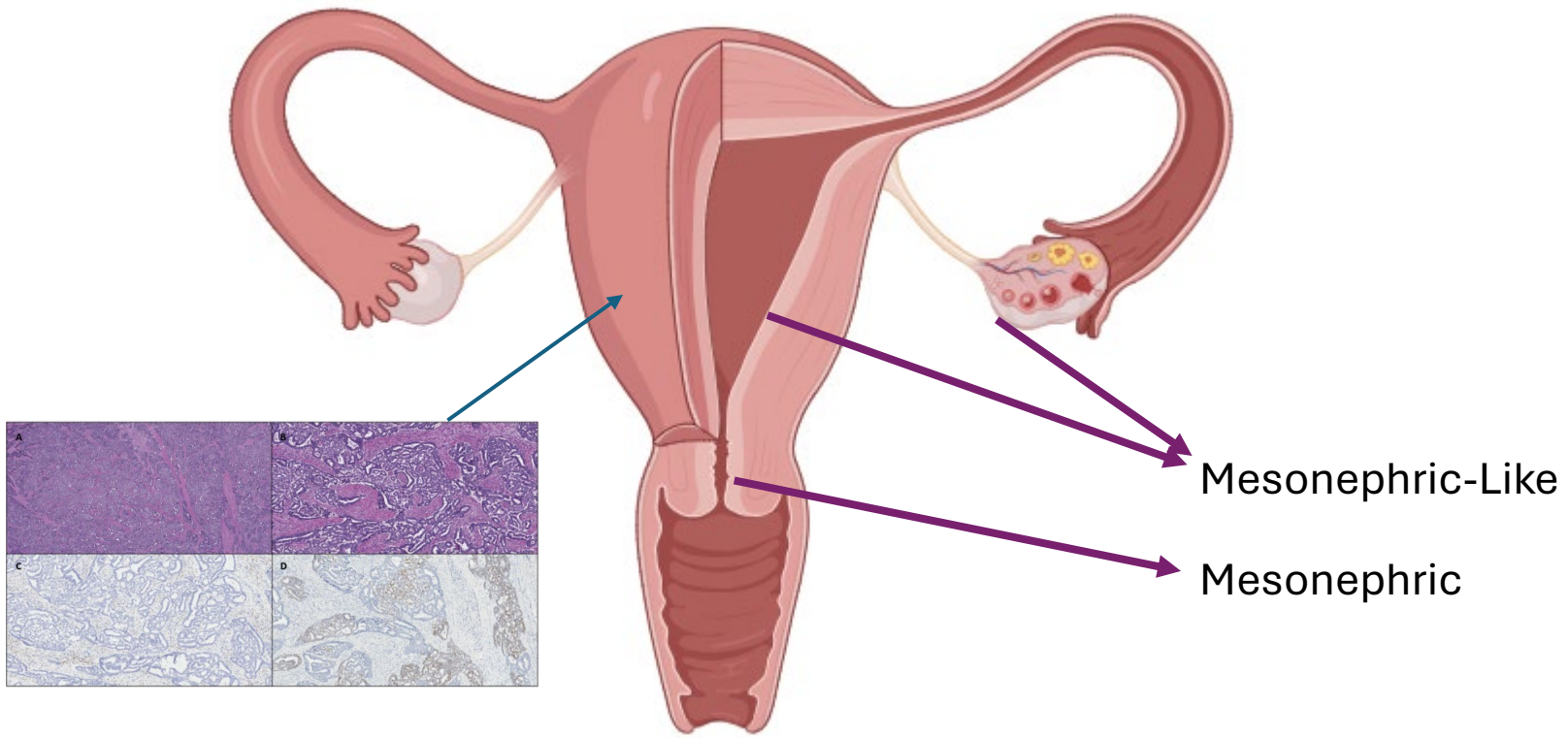
- AZ (ended), GSK (ended), Verastem (ended), Cardinal Health (ended), Genmab (ended), Incyte (ended), Incyclix (ended)

Unlabeled/Investigational Uses

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

Avutometinib and defactinib are not currently FDA approved for any indication

Mesonephric and Mesonephric-like Adenocarcinomas Can Arise From Multiple Gyn Sources

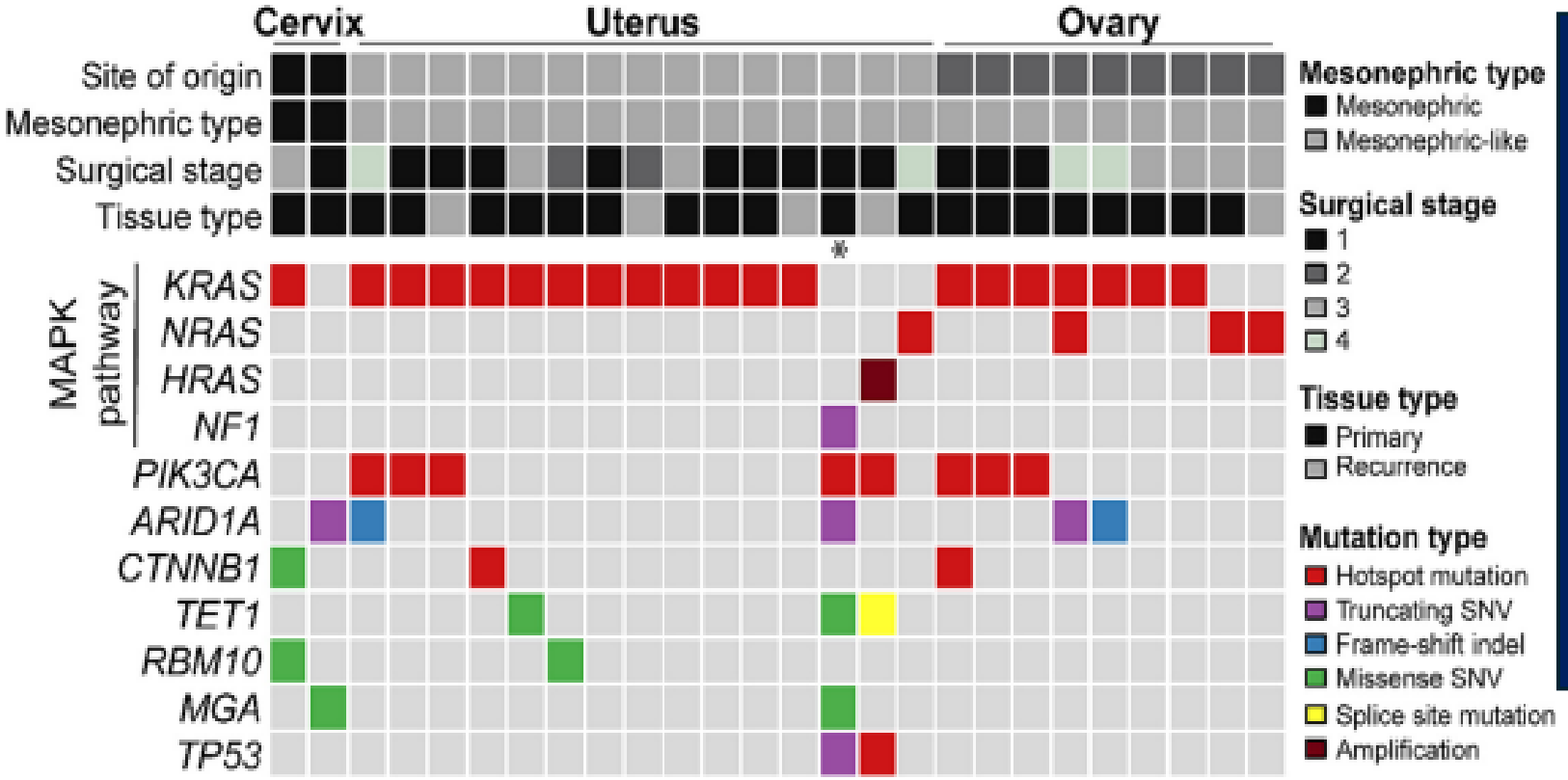


- Often GATA3 +, TTF1 +, ER-, PR-
- MA arises from Wolffian duct remnant within deep cervical walls (not HPV associated)
- MLA typically not associated with Wolffian remnant, thought to arise from trans-differentiation of mullerian epithelium
- Majority of cases recur
- Lung is most common site of metastases

Praiss, White, Iasonos, Selenica, Zivanovic, Chi, Abu-Rustum, Weigelt, Aghajanian, Girshman, Park, Grisham. Gyn Onc. 2024.
Pors, Segura, Chiu, Almadani, Ren, Fix, Howitt, Kolin, McCluggage, Mirkovic, Gilks, Park, Hoang. Am J Surg Pathol. 2022

MA= Mesonephric Adenocarcinoma; MLA= Mesonephric-like Adenocarcinoma

Mesonephric and MLA Cancers Commonly Harbor Somatic KRAS mutations



96% of Patients Harbored MAP Kinase Pathway Alterations

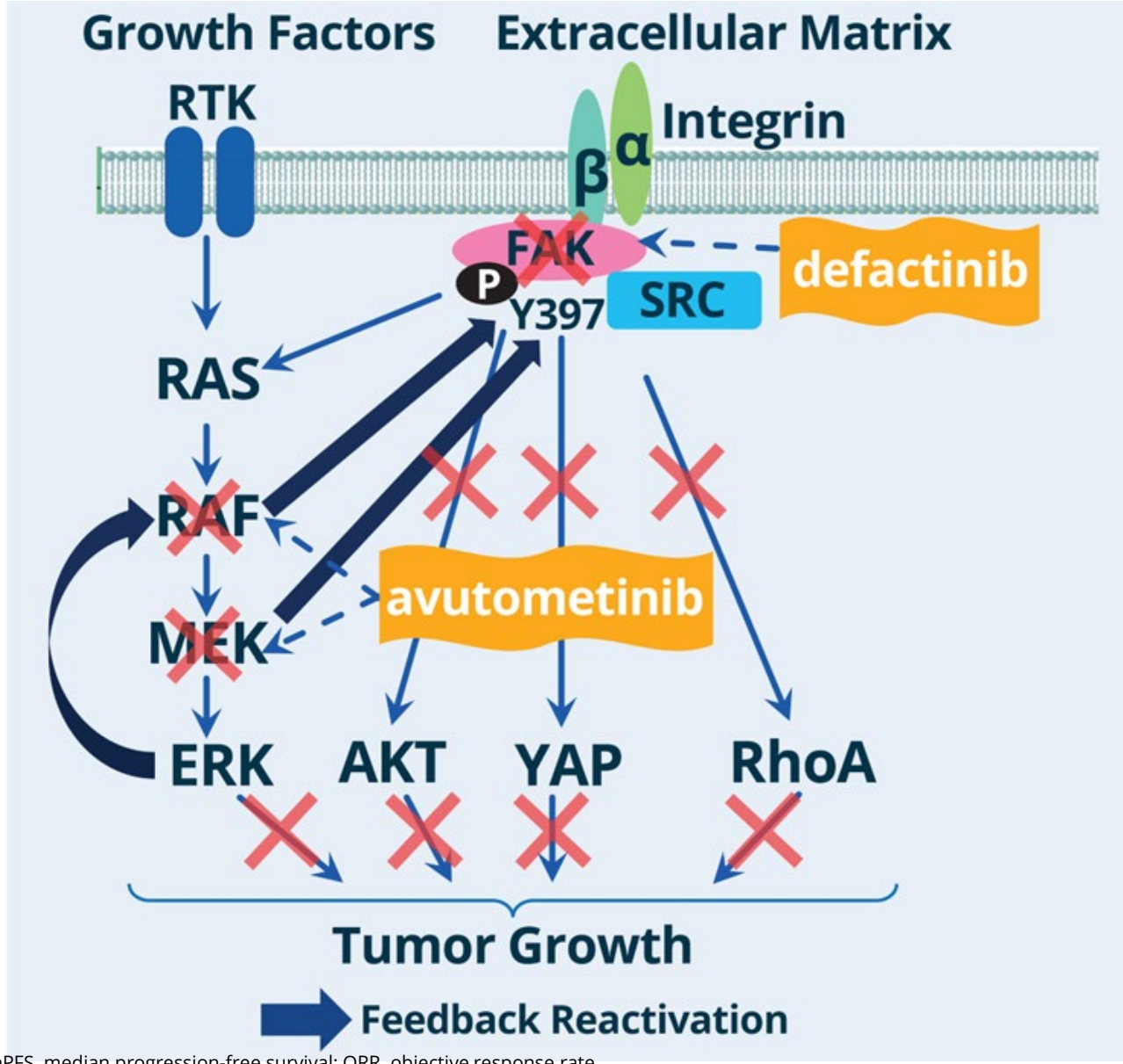
KRAS * (n = 20, 77%)
NRAS * (n = 3, 11%)
HRAS amplification (n = 1, 4%)
NF1 truncating mutation (n = 1, 4%)

*Hotspot missense mutation

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

Avutometinib and Defactinib

- **Avutometinib** is a first-in-class oral RAF/MEK clamp that potently inhibits MEK kinase activity, while also blocking the compensatory reactivation of MEK by upstream RAF[1-4]
- **Defactinib** is a selective inhibitor of FAK, a signaling target that has been shown to mediate resistance to multiple anticancer agents[5-7]
- Avutometinib + defactinib demonstrated an ORR of 42% (n/N=11/26), a mDOR of 26.9 months (95% CI, 8.5-47.3), and a mPFS of 20.0 months (95% CI, 11.1-31.2) in recurrent LGSOC in the FRAME study (NCT03875820)[8-10]
- Results of the FRAME study led to **FDA Breakthrough Therapy Designation** and rationale for the phase 2 ENGOT-ov60/GOG-3052/RAMP 201 (NCT04625270) and RAMP301 Studies[11-12]



FDA, US Food and Drug Administration; LGSOC, low-grade serous ovarian cancer; mDOR, median duration of response; mPFS, median progression-free survival; ORR, objective response rate.

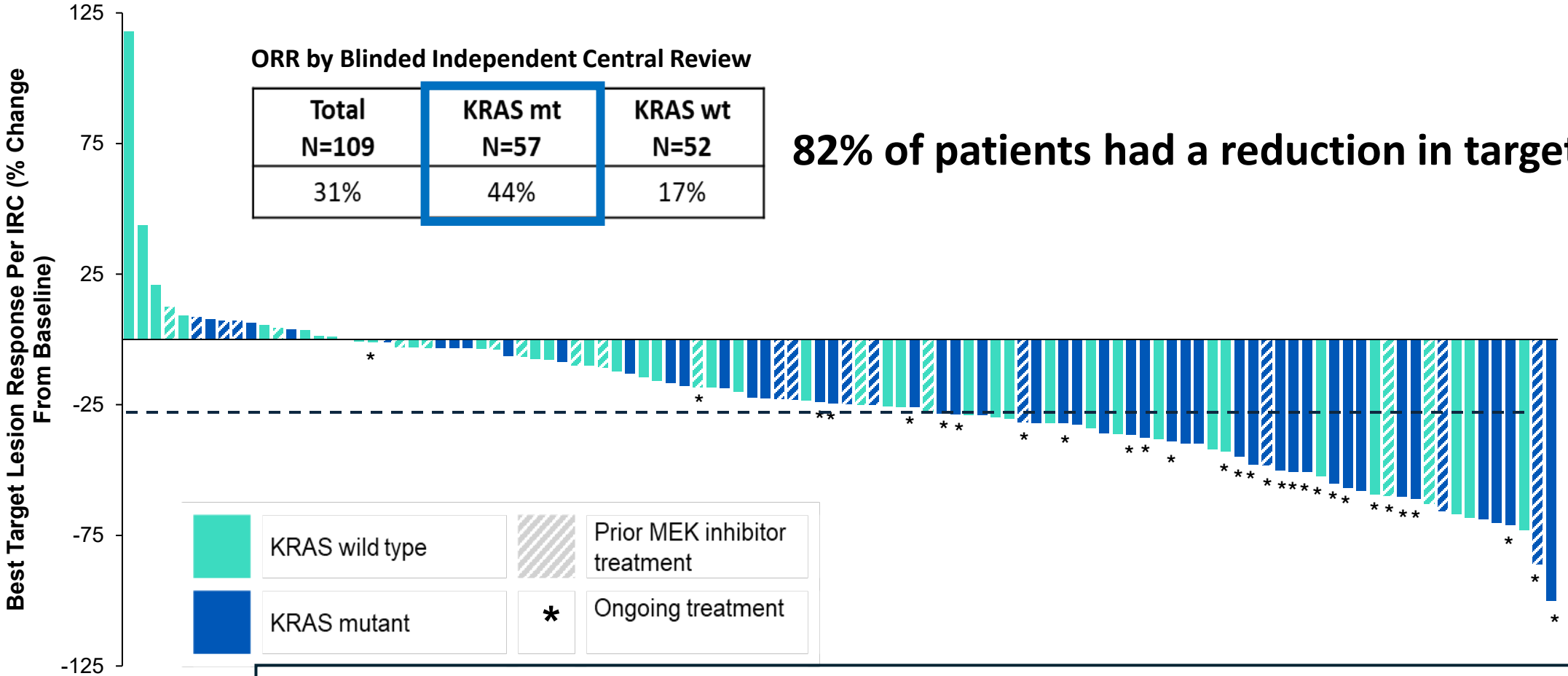
1. Martinez-Garcia C, et al. *Clin Cancer Res.* 2012;18:4806-4819; 2. Ishii N, et al. *Cancer Res.* 2013;73:4050-4060; 3. Lito P, et al. *Cancer Cell.* 2014;25:697-710; 4. Gonzalez-Del Pino GL, et al. *PNAS.* 2021;118:e2107207118; 5. Dawson JC, et al. *Nat Rev Cancer.* 2021;21:313-324; 6. Shinde R, et al. *Cancer Res.* 2020;80(suppl 16):CT143; 7. Kang Y, et al. *J Natl Cancer Inst.* 2013;105(19):1485-1495; 8. Banerjee S, et al. *Ann Oncol.* 2021;32(suppl_5):S725-S772; 9. Banerji Udai. Targeting RAS 2023 SYMPOSIUM. Proteomic profiling of KRAS signaling; Context, CAFs and Combinations; 10. Denis Louis. 5th RAS- Targeted Drug Development Summit. Introducing Rational Combinations of RAF/MEK Clamp Avutometinib: Breakthrough Designation & Beyond; 11. Banerjee SN, et al. *J Clin Oncol.* 2023;41(16 suppl):5515; 12. Verastem Oncology Receives Breakthrough Therapy Designation for VS-6766 with Defactinib in Recurrent Low-Grade Serous Ovarian Cancer. Press Release. Verastem Oncology. May 24, 2021. Accessed September 28, 2023. https://investor.verastem.com/node/12421/pdf.

RAMP 201 Phase 2 Study in Low Grade Serous Ovarian Cancer: Highest Response Rates Seen in Patients with KRAS Mutation

ORR by Blinded Independent Central Review

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

82% of patients had a reduction in target lesions



Primary Endpoint (ORR):

- **31%** overall; **44%** KRAS mt, **17%** KRAS wt
- **33%** without prior MEKi, **24%** with prior MEKi

Median Time to Response: 3.7 months (range, 1.7 – 19.2)

Median DoR: 31.1 months (95% CI, 14.8, 31.1)

IRC, independent review committee; KRAS, kirsten rat sarcoma virus; MEK, mitogen-activated protein kinase; RESULTS FROM PARTS A,B and C of RAMP201 study

Study Schema

Stage 1

Accrue 13 patients with measurable, advanced or recurrent MC

If ≥ 1 response is seen by RECIST 1.1 criteria then advance to stage 2

Stage 2

Accrue an additional 7 eligible patients

If ≥ 3 responses are seen out of the total cohort of 20 patients then the treatment will be considered active

Primary Endpoint:
Confirmed Response Rate (complete or partial response), as determined by RECIST 1.1 response, in patients with advanced or recurrent mesonephric or mesonephric-like gynecologic cancer

Key Secondary Endpoints:
Safety and Tolerability; duration of response, CBR, PFS, OS

Avutometinib 3.2 mg PO twice a week and Defactinib 200mg PO twice daily
Treatment is for the first 21 days of each 28 day cycle (3 weeks on/ 1 week off)

Key Eligibility Criteria

Inclusion Criteria

- Female patients ≥ 18 years of age
- Histologic confirmation of Mesonephric or Mesonephric-like cancer (MC). Patients with mixed histology are eligible if the disease at time of recurrence is deemed by the treating physician to be driven by the MC component.
- Measurable disease according to RECIST 1.1
- Patients must have persistent or recurrent disease

Exclusion Criteria

- Systemic anti-cancer therapy (other than endocrine therapy) within 4 weeks, 1 cycle, or 5 half-lives (whichever is shortest) of the first dose of study intervention; Endocrine therapy within 1 week of the first dose of study intervention.
- Major surgery within 4 weeks , minor surgery within 2 weeks, or palliative radiotherapy within 1 week of the first dose of study intervention.
- Prior treatment with a MEK or RAF or FAK inhibitor
- Patients with the inability to swallow oral medications or impaired gastrointestinal absorption due to gastrectomy or drainage PEG tube

Interim Results For Stage I Patients: Baseline Characteristics

Patient Characteristics (n=13)	
Median Age (range)	66 years (53-85)
Site of Origin :	
Cervix	5 (38.5 %)
Ovary	5 (38.5 %)
Endometrium	3 (23 %)
Median Prior Lines of Therapy (range)	3 (0-7)
Prior Radiation	10 (77 %)

All Patients Had Reduction in Target Lesions

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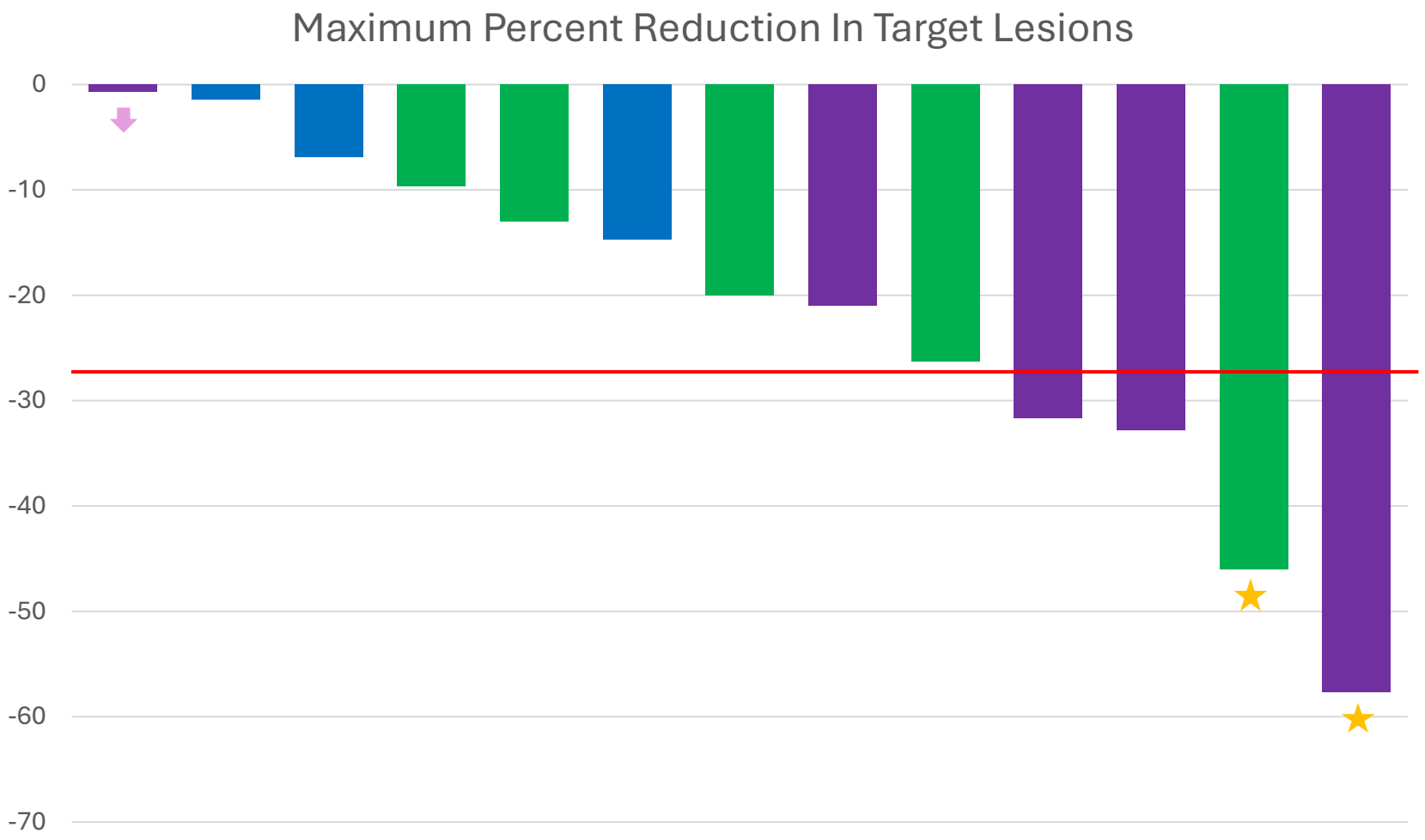


= Cervix

= Endometrium

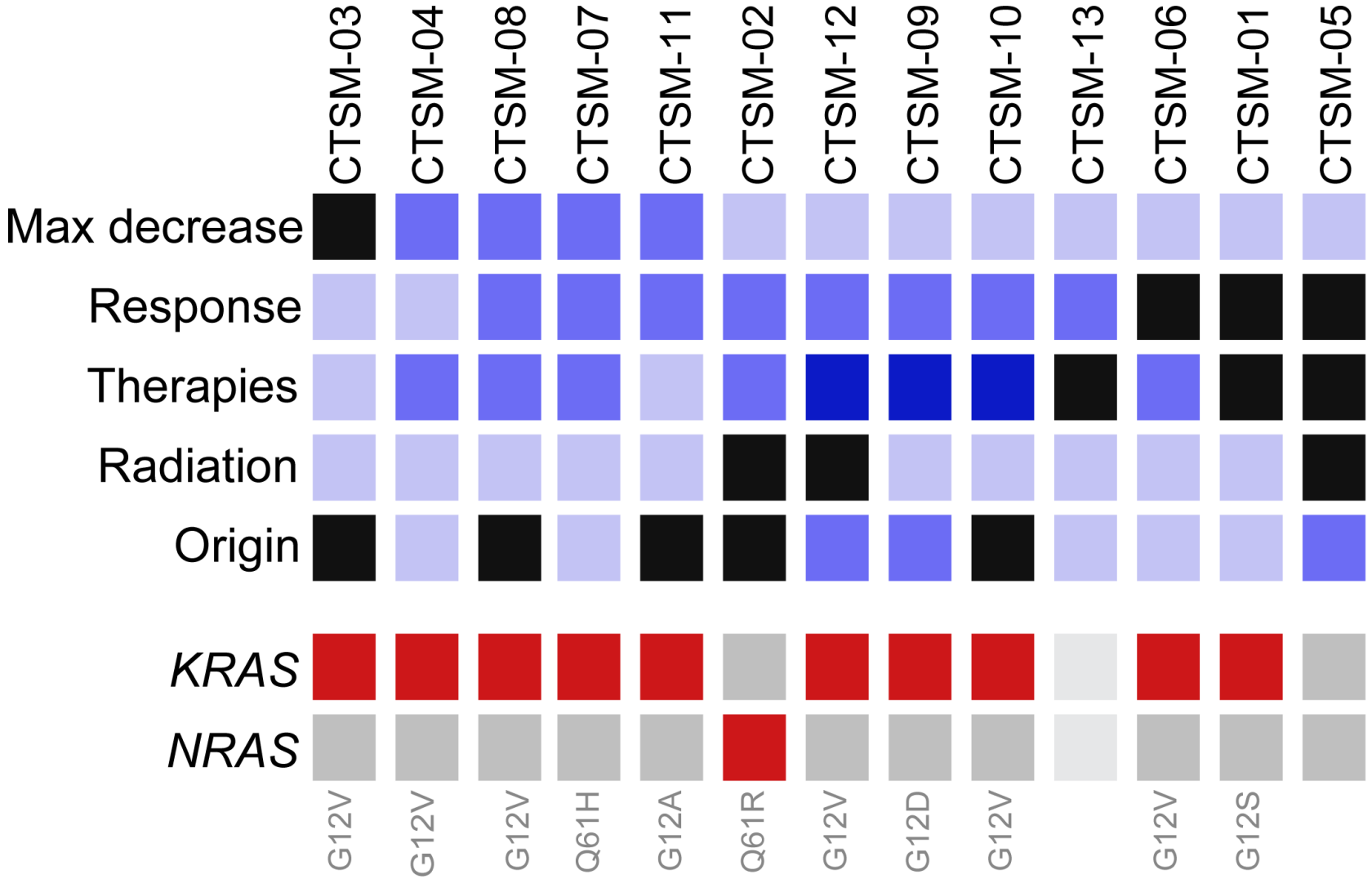
= Ovary

★ = Confirmed Partial Response

= Remains on Treatment

Reasons For Discontinuation (n=12)	
RECIST POD	9
Withdrawal of Consent (travel logistics)	1
Clinical POD (SBO)	1
Non-Compliance	1

Molecular Results and Clinical Features



Maximum decrease
- 0-25%
- 26-50%
- 51-75%

Radiation
- Yes
- No

Response
- PR
- SD
- PD

Site of origin
- Cervix
- Endometrium
- Ovary

Prior therapies
- 7
- 3
- 2
- 0-1

Mutation type
- Hotspot mutation
- Wild-type
- Not performed

Figure Courtesy of Britta Weigelt and Pier Selenica

Interim Results For Stage I Patients: Adverse Laboratory Events Related to Treatment

Laboratory Toxicities			
	Grade 1	Grade 2	Grade 3
Alkaline phosphatase elevation	1 (8%)	0	1 (8%)
Anemia	0	0	0
Aspartate aminotransferase elevation	1 (8%)	0	0
Bilirubin increased	6 (46%)	3 (23%)	1 (8%)
CPK increased	9 (69%)	5 (38%)	2 (15%)
Lymphocyte count decreased	0	1 (8%)	0

Interim Results For Stage I Patients: Adverse Events Related to Treatment Occurring in >1 Patient (non-lab)

	Grade 1	Grade 2	Grade 3
Rash Maculopapular	4 (31%)	1 (8%)	1 (8%)
Diarrhea	8 (62%)	2 (15%)	1 (8%)
Edema limb	7 (54%)	3 (23%)	1 (8%)
Fatigue	8 (63%)	3 (23%)	1 (8%)
Pruritis	5 (38%)	2 (15%)	
GERD	1 (8%)	3 (23%)	
Nausea	2 (15%)	1 (8%)	
Rash Acneiform	4 (31%)	1 (8%)	
Dyspepsia	3 (23%)	1 (8%)	
Nausea	3 (23%)	1 (8%)	
Vomiting	4 (31%)	1 (8%)	
Alopecia	2 (15%)		
Nail changes	2 (15%)		
Dry skin	2 (15%)		
Constipation	2 (15%)		
Arthralgia	2 (15%)		
Mucositis	2 (15%)		
Blurred vision	2 (15%)		

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 in combination with defactinib has previously shown activity in patients with LGSOC, with highest response rates seen in those patients with a *KRAS* mutation (44% response rate)
- This Investigator Initiated Simon 2-Stage Phase 2 Study has **exceeded the response threshold needed to advance to Stage 2**
- The study has reached its original accrual goal, and was recently amended to allow for an additional 20 patients
- **Expansion phase enrolling now**! (NCT05787561)

Thank You to our Patients and Their Supporters Who Make This Research Possible

This study was funded by Verastem Oncology