Delivering Novel Therapies in RAS/MAPK Pathway Driven Cancers

March 2024
Corporate Presentation
This presentation includes forward-looking statements about Verastem Oncology's programs and product candidates, strategy, future plans and prospects, including statements related to the expected outcome and benefits of collaborations, including with GenFleet, the potential clinical value of various of its clinical trials, the timing of commencing and completing trials, including topline data reports, interactions with regulators, the potential for and timing of commercialization of product candidates and potential for additional development programs involving Verastem Oncology's lead compound. The words "anticipate," "believe," "estimate," "expect," "intend," "may," "plan," "predict," "project," "target," "potential," "will," "would," "could," "should," "continue," "can," "promising" and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. Each forward-looking statement is subject to risks and uncertainties that could cause actual results to differ materially from those expressed or implied in such statement.

Other risks and uncertainties include those identified under the heading "Risk Factors" in the Company's Annual Report on Form 10-K for the year ended December 31, 2023, as filed with the Securities and Exchange Commission (SEC) on March 14, 2024, and in any subsequent filings with the SEC, which are available at www.sec.gov and www.verastem.com.

The forward-looking statements in this presentation speak only as of the original date of this presentation, and we undertake no obligation to update or revise any of these statements. This presentation contains references to our non-GAAP operating expense, a financial measure that is not calculated in accordance with generally accepted accounting principles in the US ("GAAP"). This non-GAAP financial measure excludes certain amounts or expenses from the corresponding financial measures determined in accordance with GAAP. Management believes this non-GAAP information is useful for investors, taken in conjunction with the Company’s GAAP financial statements, because it provides greater transparency and period-over-period comparability with respect to the Company's operating performance and can enhance investors' ability to identify operating trends in the Company’s business. Management uses this measure, among other factors, to assess and analyze operational results and trends and to make financial and operational decisions. Non-GAAP information is not prepared under a comprehensive set of accounting rules and should only be used to supplement an understanding of the Company’s operating results as reported under GAAP, not in isolation or as a substitute for, or superior to, financial information prepared and presented in accordance with GAAP. In addition, this non-GAAP financial measure is unlikely to be comparable with non-GAAP financial information provided by other companies. The determination of the amounts that are excluded from GAAP information is not prepared under a comprehensive set of accounting rules and should only be used to supplement an understanding of the Company’s operating results as reported under GAAP, not in isolation or as a substitute for, or superior to, financial information prepared and presented in accordance with GAAP. In addition, this non-GAAP financial measure is unlikely to be comparable with non-GAAP financial information provided by other companies. The determination of the amounts that are excluded from non-GAAP financial measures is a matter of management judgment and depends upon, among other factors, other risks and uncertainties include the risks and uncertainties, among other things, regarding: the success in the development and potential commercialization of our product candidates, including avutometinib in combination with other compounds, including defactinib, LUMAKRAS™ and others; the uncertainties inherent in research and development, such as negative or unexpected results of clinical trials, the occurrence or timing of applications for our product candidates that may be filed with regulatory authorities in any jurisdictions; whether and when regulatory authorities in any jurisdictions may approve any such applications that may be filed for our product candidates, and, if approved, whether our product candidates will be commercially successful in such jurisdictions; our ability to obtain, maintain and enforce patent and other intellectual property protection for our product candidates; the scope, timing, and outcome of any legal proceedings; decisions by regulatory authorities regarding trial design, labeling and other matters that could affect the timing, availability or commercial potential of our product candidates; whether preclinical testing of our product candidates and preliminary or interim data from clinical trials will be predictive of the results or success of ongoing or later clinical trials; that the timing, scope and rate of reimbursement for our product candidates is uncertain; that third-party payors (including government agencies) may not reimburse; that there may be competitive developments affecting our product candidates; that data may not be available when expected; that enrollment of clinical trials may take longer than expected; that our product candidates will cause adverse safety events and/or unexpected concerns may arise from additional data or analysis, or result in unmanageable safety profiles as compared to their levels of efficacy; that our product candidates may experience manufacturing or supply interruptions or failures; that any of our third-party contract research organizations, contract manufacturing organizations, clinical sites, or contractors, among others, who we rely on fail to fully perform; that we face substantial competition, which may result in others developing or commercializing products before or more successfully than we do which could result in reduced market share or market potential for our product candidates; that we will be unable to successfully initiate or complete the clinical development and eventual commercialization of our product candidates; that the development and commercialization of our product candidates will take longer or cost more than planned, including as a result of conducting additional studies; that we may not have sufficient cash to fund our contemplated operations; that we may not attract and retain high quality personnel; that we or Chugai Pharmaceutical Co., Ltd. will fail to fully perform under the avutometinib license agreement; that our target market for our product candidates might be smaller than we are currently estimating; that Secura Bio, Inc. will fail to fully perform under the asset purchase agreement with Secura Bio, Inc., including in relation to milestone payments; that we will not see a return on investment on the payments we have and may continue to make pursuant to the collaboration and option agreement with GenFleet Therapeutics (Shanghai), Inc. (“GenFleet”) or that GenFleet will fail to fully perform under the agreement; that we may be unable to obtain adequate financing in the future through product licensing, co-promotional arrangements, public or private equity, debt financing or otherwise; that we will not pursue or submit regulatory filings for our product candidates; and that our product candidates will not receive regulatory approval, become commercially successful products, or result in new treatment options being offered to patients.

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Verastem Oncology

**Strong progress in 2023 sets up multiple value-creation opportunities**

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**Well-Positioned To Deliver on 2024 Catalysts**

- **On track to deliver the first approved therapy in LGSOC**
  - Data at ASCO 2023 of avutometinib, a RAF/MEK Clamp in combination with defactinib, a FAK inhibitor, demonstrated robust responses in patients with recurrent low-grade serous ovarian cancer (LGSOC)
  - Phase 3 confirmatory study underway with plans to report updated topline data from RAMP 201 trial in H1 2024
  - Commence rolling NDA for Accelerated Approval in H1 2024

- **Ongoing studies in additional indications including Pancreatic Cancer and NSCLC**
  - Report initial safety and efficacy results from RAMP 205 trial of avutometinib + gemcitabine/nab-paclitaxel + defactinib in first-line metastatic pancreatic cancer in H1 2024
  - Report updated data from both non-small cell lung cancer (NSCLC) trials - RAMP 203 (sotorasib-Amgen) and RAMP 204 (adagrasib-Mirati) trials in Mid-2024

- **GenFleet collaboration furthers pipeline potential in RAS/MAPK driven cancers**
  - GenFleet expected to submit IND for GFH375/VS-7375, a potential best-in-class oral KRAS G12D (ON/OFF) inhibitor in China in H1 2024
  - Initiate Phase 1 trial for GFH375/VS-7375 in China in H2 2024
  - Ongoing discovery/lead optimization for second and third programs

- **Strong balance sheet to support ongoing programs and operations**
  - Company ended Q4 2023 with $137.1M in cash and investments and $31.1 million GAAP operating expenses ($29.5 million non-GAAP operating expenses*)

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*Q4 2023 GAAP operating expenses - $31.14M less Q4 2023 stock compensation of $1.60M = $29.54M Q4 2023 non-GAAP operating expenses; IND: investigational new drug; NDA: new drug application*
## Driving Momentum in 2024: Recap of Recent Key Achievements

<table>
<thead>
<tr>
<th>Avutometinib + Defactinib: Recurrent LGSOC</th>
<th>Avutometinib + Defactinib: Metastatic Pancreatic Cancer</th>
<th>Avutometinib + KRAS G12C Inhibitors: NSCLC</th>
<th>GFH375/VS-7375: Oral G12D (ON/OFF) Inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>✓ Received FDA Orphan Drug Designation</td>
<td>✓ Initiated RAMP 205 combo avutometinib + gemcitabine/nab-paclitaxel + defactinib</td>
<td>✓ Received FDA Fast Track Designation for avutometinib in combo with Amgen’s G12C inhibitor sotorasib</td>
<td>✓ Established discovery and development collaboration with GenFleet</td>
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<tr>
<td>✓ Initiated Phase 3 confirmatory study</td>
<td></td>
<td>✓ Presented initial results from Phase 1/2 RAMP 203 trial of avutometinib + sotorasib in KRAS G12C mutant NSCLC</td>
<td>✓ Selected GFH375/VS-7375, a potential best-in-class oral KRAS G12D (ON/OFF) inhibitor</td>
</tr>
<tr>
<td>✓ Presented planned subgroup analysis of Part A RAMP 201 trial</td>
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<td>✓ Added defactinib to avutometinib and sotorasib combination in the RAMP 203 trial</td>
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<tr>
<td>✓ RAMP 201 FDA meeting – combination selected as go-forward regimen</td>
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**Clinical Program Designed for Success in LGSOC, Signal Generation**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>IND-Enabling/Preclinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Anticipated Milestones</th>
<th>Collaboration</th>
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<tbody>
<tr>
<td><strong>Avutometinib + Defactinib: Recurrent LGSOC</strong></td>
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<tr>
<td>RAF/MEK Clamp + FAKi</td>
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<td>RAMP 301 Ongoing Enrollment</td>
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<tr>
<td>RAF/MEK Clamp + FAKi</td>
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<td></td>
<td></td>
<td>RAMP 201 Topline Data; Rolling NDA Submission Accelerated Approval: H12024</td>
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<tr>
<td><strong>Avutometinib + KRAS G12C Inhibitors: NSCLC</strong></td>
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<tr>
<td>RAF/MEK Clamp + KRAS G12Ci + FAKi</td>
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<td></td>
<td></td>
<td>RAMP 203 Updated Data Mid-2024</td>
<td>Amgen</td>
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<tr>
<td>RAF/MEK Clamp +KRAS G12Ci</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>RAMP 204 Updated Data Mid-2024</td>
<td>Mirati/BMS</td>
</tr>
<tr>
<td><strong>Avutometinib + Defactinib: Metastatic Pancreatic Cancer</strong></td>
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<tr>
<td>RAF/MEK Clamp + FAKi + gemcitabine, nab-paclitaxel</td>
<td></td>
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<td></td>
<td></td>
<td>RAMP 205 Initial Safety/Efficacy H12024</td>
<td>PanCAN</td>
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<tr>
<td><strong>GFH375/VS-7375</strong></td>
<td></td>
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<tr>
<td>G12D (ON/OFF) inhibitor</td>
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<td></td>
<td>GenFleet expected to submit IND in China in H12024; Initiate Phase 1 in H22024</td>
<td>GenFleet</td>
</tr>
</tbody>
</table>
Avutometinib RAF/MEK Clamp
Program Overview
Avutometinib is a Differentiated Agent with the Potential to Serve as the Backbone for Combinations Across RAS Pathway-Driven Cancers

- Unique RAF/MEK clamp mechanism of action
- Novel intermittent dosing schedule; convenient oral regimen
- Orphan Drug Designation for avutometinib alone or in combination with defactinib in recurrent LGSOC
- Breakthrough Therapy Designation for combination of avutometinib and defactinib for treatment of recurrent LGSOC after one or more prior lines of therapy including platinum-based chemotherapy
- Received FDA Fast Track Designation for avutometinib in combination with Amgen’s G12C inhibitor sotorasib in KRAS G12C-mutant NSCLC
- Potential best-in-class safety & tolerability profile relative to marketed MEK inhibitors, with potential for combinability with agents from multiple target classes
- Promising signals of clinical activity in various RAS pathway-driven cancers, including in patients whose tumors previously progressed on other MEK inhibitors

RAF-Rapidly accelerated fibrosarcoma, MEK-Mitogen-activated protein kinase kinase, RAS-Rat sarcoma virus MAPK-Mitogen-activated protein kinase KRAS-Kirsten rat sarcoma virus; NRAS-Neuroblastoma RAS viral oncogene homolog, BRAF-v-raf murine sarcoma viral oncogene homolog B1, NF1-Neurofibromatosis type I
Avtometinib is a Unique Small Molecule RAF/MEK Clamp
Contrasting Mechanism of Action vs. MEK-Only Inhibitors

Avtometinib induces dominant negative RAF/MEK complexes
Avtometinib inhibits both RAF and MEK activities

The RAF/MEK clamp mechanism avoids the compensatory activation of pMEK enabling more complete pERK inhibition

Avutometinib conc. (µmol/L)

DMSO      Tram      Avuto

% Inhibition

Collaboration with Deborah Morrison, NCI

Coma et al., ACR 2022; Ishii et al., Cancer Res, 2013; Lito et al., Cancer Cell, 2014
Avutometinib Inhibits Cell Proliferation Across Multiple RAS/MAPK Pathway Alterations and Multiple Solid Tumor Histologies
Strong Scientific Rationale for Avutometinib and FAK Inhibitor Combination

Anti-Tumor Efficacy in KRAS Mutant and Wild-Type LGSOC models

Growth factors Extracellular Matrix

RTK β α Integrin

FAK Y397 SRC

defactinib

RAS

FAK avutometinib

integrin

Ras

RAF

MEK

ERK AKT YAP RhoA

Feedback Reactivation

Tumor Growth

KRAS mutant LGSOC PDX model

pFAK

H-Score

Days after first dose

Tumor volume (mm$^3$ +/- SEM)

vehicle FAKi avutometinib avutometinib + FAKi

KRAS wild-type LGSOC PDX model

Pre dose Post avutometinib Post avutometinib + defactinib

Tumor volume (mm$^3$ +/- SEM)

Days after first dose

vehicle FAKi avutometinib avutometinib + FAKi

Banerji, BTOG Dublin, Jan 23, 2019; Banerji, AACR VM 1, April 27, 2020, CTI 43; Banerji, unpublished; Santin, unpublished
Optimized Dosing Schedule Defined: Favorable Tolerability Profile with Novel Intermittent Dosing Regimen

Summary of Adverse Events Grade ≥ 3 Occurring in ≥ 5% of patients

<table>
<thead>
<tr>
<th>Treatment Related Adverse Event</th>
<th>Grade ≥3</th>
<th>Grade ≥3</th>
<th>Grade ≥3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td>3 (50%)</td>
<td>5 (19%)</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>CK elevation (Creatine phosphokinase)</td>
<td>1 (17%)</td>
<td>2 (8%)</td>
<td>2 (5%)</td>
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</tbody>
</table>

Avutometinib monotherapy
Daily at MTD
N=6
28-day cycle

RP2D
Avutometinib monotherapy
4mg twice weekly
N=26
28-day cycle

RP2D
(Avutometinib 3.2mg twice weekly + defactinib 200mg twice daily)
N=38
21 days of 28-day cycle

1 Chenard-Poirier, et al. ASCO 2017; References: Banerji, Q4 2020 report; Data on file; RP2D: recommended phase 2 dosing
RAS Pathway-Driven Cancers and Rational Avutometinib Combinations
# Ongoing Comprehensive Approach to Establish More Complete Blockade of RAS Pathway & Resistance Pathways

<table>
<thead>
<tr>
<th>Indication</th>
<th>Incidence/Prevalence</th>
<th>Regimen</th>
<th>Setting</th>
<th>Collaborator</th>
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</thead>
<tbody>
<tr>
<td><strong>Gynecologic Cancers</strong></td>
<td></td>
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<tr>
<td>RAMP301 LGSOC</td>
<td>Incidence: 114K</td>
<td>Avutometinib + defactinib</td>
<td>Relapsed Refractory molecularly profiled LGSOC</td>
<td></td>
</tr>
<tr>
<td>RAMP201 LGSOC</td>
<td>Incidence: 6K</td>
<td>Avutometinib + defactinib</td>
<td>Relapsed Refractory molecularly profiled LGSOC</td>
<td></td>
</tr>
<tr>
<td>Gynecologic Basket*</td>
<td>Incidence: 85K</td>
<td>Avutometinib + defactinib</td>
<td>Recurrent RAS Pathway-driven (RAS/RAF/NF1) endometrioid cancer, mucinous ovarian cancer, high-grade serous ovarian cancer or cervical cancer</td>
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<td><strong>NSCLC Adenocarcinoma</strong></td>
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<tr>
<td>RAMP203 and 204 KRAS G12C</td>
<td>Incidence: 114K</td>
<td>Avutometinib + sotorasib ± defactinib</td>
<td>Recurrent KRAS G12C with prior KRAS G12C inhibitor(i) treatment or KRAS G12C-naïve</td>
<td>AMGEN</td>
</tr>
<tr>
<td>RAMP203 and 204 KRAS G12C</td>
<td>Incidence: 114K</td>
<td>Avutometinib + adagrasib</td>
<td>Recurrent KRAS G12C with prior KRAS G12Ci treatment</td>
<td>MIRATI</td>
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<tr>
<td><strong>Pancreatic</strong></td>
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<tr>
<td>RAMP205 PDAC</td>
<td>Incidence: 58K</td>
<td>Avutometinib + defactinib + gemcitabine/nab-paclitaxel</td>
<td>Previously untreated (front-line) metastatic pancreatic ductal adenocarcinoma (PDAC)</td>
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<tr>
<td><strong>CRC</strong></td>
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<tr>
<td>KRAS mt*</td>
<td>Incidence: 148K</td>
<td>Avutometinib + cetuximab</td>
<td>Recurrent metastatic KRAS mt</td>
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<tr>
<td><strong>Breast Cancer</strong></td>
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<tr>
<td>ER+*</td>
<td>Incidence: 279K</td>
<td>Avutometinib + abemaciclib + fulvestrant</td>
<td>Recurrent ER+/HER2- breast cancer following progression on CDK4/6i + aromatase inhibitor</td>
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<tr>
<td><strong>Thyroid</strong></td>
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<tr>
<td>MAPK alterations**</td>
<td>Incidence: 44K</td>
<td>Avutometinib + defactinib</td>
<td>Differentiated &amp; anaplastic thyroid cancer</td>
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</tbody>
</table>

*IST
**excluding BRAFV600E

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## Robust Clinical Program: Avutometinib in Multiple Combinations Across RAS/MAPK Pathway-Driven Tumors

<table>
<thead>
<tr>
<th>INDICATION</th>
<th>REGIMEN</th>
<th>STUDY NAME</th>
<th>PRECLINICAL</th>
<th>PHASE 1</th>
<th>PHASE 2</th>
<th>PHASE 3</th>
<th>CLINICAL COLLABORATION WITH</th>
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<tbody>
<tr>
<td>LGSOC¹</td>
<td>Avutometinib + defactinib</td>
<td>RAMP 301</td>
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<td></td>
<td>Confirmatory Randomized Controlled Trial</td>
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<tr>
<td>LGSOC¹</td>
<td>Avutometinib + defactinib</td>
<td>RAMP 201</td>
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<td></td>
<td>Registration-directed trial: accelerated approval cohort fully enrolled</td>
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<td>R/R LGSOC</td>
<td>Avutometinib + defactinib</td>
<td>IST-FRAME</td>
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<tr>
<td>Gynecological Cancers (RAS Pathway-driven)</td>
<td>Avutometinib + defactinib</td>
<td>IST</td>
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<tr>
<td>Mesonephric²</td>
<td>Avutometinib + defactinib</td>
<td>IST</td>
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<tr>
<td>R/R NSCLC (KRAS G12C)</td>
<td>Avutometinib + sotorasib ± defactinib</td>
<td>RAMP 203</td>
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<tr>
<td>R/R NSCLC (KRAS G12C)</td>
<td>Avutometinib + adagrasib</td>
<td>RAMP 204</td>
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<tr>
<td>Pancreatic Ductal Adenocarcinoma</td>
<td>Avutometinib + gemcitabine/nab-paclitaxel + defactinib</td>
<td>RAMP 205</td>
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<tr>
<td>R/R Colorectal Cancer (KRAS mt)</td>
<td>Avutometinib + cetuximab (EGFRi)</td>
<td>IST</td>
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<tr>
<td>ER+ Breast Cancer</td>
<td>Avutometinib + abemaciclib + fulvestrant</td>
<td>IST</td>
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<tr>
<td>Thyroid Cancer²</td>
<td>Avutometinib + defactinib</td>
<td>IST</td>
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¹ FDA Breakthrough Therapy Designation and Orphan Drug Designation
² Imminent initiation
Avutometinib ± Defactinib in Low-Grade Serous Ovarian Cancer
LGSOC Unmet Need & Opportunity

- **LGSOC** is a less common type of ovarian cancer that is often diagnosed in younger women
  - LGSOC is a unique disease that is distinct from high-grade serous ovarian cancer (HGSOC) in its pathology, protracted clinical course and low response to chemotherapy and thus requires a more tailored therapeutic approach
  - An estimated 1,000-2,000 patients are diagnosed with LGSOC per year in the U.S., with prevalence of ~6,000

- There are currently **no** approved therapies specifically indicated for recurrent LGSOC
  - Recent clinical trials in recurrent LGSOC showed that standard-of-care chemo and hormonal therapy are relatively ineffective (6-13% ORR).
  - LGSOC has a chemo-resistant nature and optimal treatment has not yet been defined. NCCN guidelines include clinical trials and observation highlighting the lack of approved & effective therapies

- **LGSOC** is known to be driven by the MAPK (RAS) pathway in ≥70% of patients

- A phase I/II study in the UK (FRAME) evaluated the combination of avutometinib and defactinib
  - Results in recurrent LGSOC showed a 42% confirmed ORR with durable responses and favorable safety/tolerability

- **RAMP 201:** A registration-directed Phase 2 trial of avutometinib and avutometinib + defactinib in recurrent LGSOC
  - Updated data from ASCO 2023 showed a 45% confirmed ORR in the combination arm with tumor shrinkage in 86% of evaluable patients

- **RAMP 301:** A confirmatory Phase 3 trial evaluating the combination of avutometinib and defactinib versus standard chemotherapy or hormonal therapy for the treatment of recurrent LGSOC

- **Orphan Drug Designation** for avutometinib alone or in combination with defactinib in recurrent LGSOC
- **Breakthrough Therapy Designation** granted for avutometinib and defactinib in recurrent LGSOC after one or more prior lines of therapy

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LGSOC is a type of ovarian cancer that disproportionately affects younger women.

1,000 to 2,000 patients in the U.S. and 15,000 to 30,000 worldwide diagnosed with LGSOC each year.

A slow growing cancer, that has a median survival of almost 10 years, so patients remain in treatment for a long time (10-yr prevalence ~80,000 worldwide, ~6,000 US).

Patients often experience significant pain and suffering from their disease over time.

Prior research has focused primarily on high grade serous ovarian cancer (HGSOC). However, LGSOC is clinically, histologically and molecularly unique from HGSOC with limited treatments available.

~30% of LGSOC Patients Have KRAS mt
~70% of LGSOC Shows RAS Pathway-Associated mts

References: AACR Project GENIE Cohort v9.0-public and Verastem unpublished analysis

Low-Grade and High-Grade Serous Ovarian Cancer Are Different Diseases

<table>
<thead>
<tr>
<th>Variable</th>
<th>LGSOC</th>
<th>HGSOC</th>
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<tbody>
<tr>
<td>Nuclear atypia</td>
<td>Uniform round to oval with little variation</td>
<td>+++ Marked variation</td>
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<tr>
<td>Mitotic Index</td>
<td>&lt;12 mitoses per 10 hpf</td>
<td>&gt;12 mitoses per 10 hpf</td>
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<tr>
<td>Chromatin and variation in size of nucleus</td>
<td>Little</td>
<td>Marked (nuclear size ratio ≥3)</td>
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<tr>
<td>Mutation</td>
<td>KRAS ++</td>
<td>P53 +++</td>
</tr>
<tr>
<td></td>
<td>BRAF +</td>
<td>BRCA1/2 +</td>
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<tr>
<td></td>
<td>ER/PR +++</td>
<td></td>
</tr>
<tr>
<td>Precursor</td>
<td>Serous borderline tumor</td>
<td>Tubal intraepithelial neoplasia</td>
</tr>
</tbody>
</table>

Malpica et al., Am J. Surg Pathol 2007
Recurrent Low-Grade Ovarian Cancer – Treatment Guidelines

**RECURRENCE THERAPY**

| Clinical trial |
| Trametinib |
| Binimetinib (category 2B) |
| Dabrafenib + trametinib (for BRAF V600E-positive tumors) |
| Hormonal therapy |
| Chemotherapy (if not previously used), see OV-C (6 of 11) |
| Other systemic therapy |
| • For platinum-sensitive disease, see OV-C (8 of 11) |
| • For platinum-resistant disease, see OV-C (9 of 11) |

**Preferred Regimens**

- Paclitaxel/carboplatin q3weeks + maintenance letrozole (category 2B) or other hormonal therapy (category 2B)
- Paclitaxel/carboplatin/bevacizumab + maintenance bevacizumab (ICON-7 & GOG-218)
- Hormone therapy (aromatase inhibitors: anastrozole, letrozole, exemestane) (category 2B)

---

No Category 1 recommendations (high-level evidence). Category 2a (lower-level evidence with uniform NCCN consensus) unless otherwise indicated.

f: There is no standard sequencing of drugs for recurrent disease. Considerations include prior therapies, disease burden, relative efficacy, and relative toxicity profile.

t: An aromatase inhibitor (i.e., letrozole, anastrozole, exemestane) is preferred if not used previously. Fulvestrant, tamoxifen, or leuprolide acetate is recommended if an aromatase inhibitor was given previously.
## Recent LGSOC Trials Highlight High Unmet Need

<table>
<thead>
<tr>
<th>Trial</th>
<th>Number of Prior Systemic Therapies Median (range)</th>
<th>Prior MEK allowed</th>
<th>Prior Bevacizumab</th>
<th>Therapy</th>
<th>Response Rate ORR</th>
<th>Image Assessment</th>
<th>Median PFS Months (95% CI)</th>
<th>Discontinuation Rate due to AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOG 281¹</td>
<td>2 (1-10)</td>
<td>No</td>
<td>* Low %</td>
<td>SoC (n=130)</td>
<td>6% 95% CI: (3%, 12%)</td>
<td>INV</td>
<td>7.2 (5.6-9.9)</td>
<td>30%</td>
</tr>
<tr>
<td>MILO²</td>
<td>2 (1-8)</td>
<td>No</td>
<td>* Low %</td>
<td>SoC (n=101)</td>
<td>13% 95% CI: (7%, 21%)</td>
<td>BICR</td>
<td>10.6 (9.2 - 14.5)</td>
<td>17%</td>
</tr>
<tr>
<td>MILO²</td>
<td>2 (1-8)</td>
<td>No</td>
<td>* Low %</td>
<td>Binimetinib² (n=198)</td>
<td>16% 95% CI: (11%, 22%)</td>
<td>BICR</td>
<td>9.1 (7.3-11.3)</td>
<td>31%</td>
</tr>
</tbody>
</table>

¹ Study GOG 281 trial Gershenson et al., Lancet 2022  
² MILO Study Monk et al., J Clin Oncol 2020.

* Low historical use of bevacizumab during trial conduct. % not reported  
MILO: no more than 3 lines of prior chemotherapy

SoC = Standard of Care  
(endocrine / chemotherapy)  
INV = Investigator  
BICR = Blinded independent central review  
PFS = Progression free survival  
CI = confidence interval  
NR = Not reached
FRAME Study: High Rate of Durable Responses with the Combination of Avutometinib and Defactinib in Recurrent LGSOC (n=26)

- Overall response rate (ORR) = 42% (11 confirmed PRs/26)
  - KRAS mutant ORR = 58% (7 confirmed PRs/12)
  - KRAS wild-type ORR = 33% (4 confirmed PRs/12)
- Median DoR 26.9 months (95% CI 8.5–47.3) across all LGSOC patients
- Median PFS 20.0 months (95% CI 11.1–31.2) across all LGSOC per RECIST 1.1
- Median 3.5 prior lines of treatment (n=26)
- Responses observed in patients previously treated with MEK inhibitor
- 19% (5/26) patients still on treatment as of July 2023 (minimum follow up: ~17 months)
- No new safety findings with continued follow-up
- 1 patient discontinued for adverse events as of July 2023 (skin AE)

Response by RECIST

- 28-day cycles
- DoR: Duration of Response
- PFS: Progression free survival
- NR: Not reached

Denis, 5th Annual RAS-Targeted Drug Development Sept 2023; (Data cut off July 2023: Data on file)
RAMP 201 (ENGOTov60/GOG3052): Registration-Directed Phase 2 Trial of Avutometinib ± Defactinib in Patients with Recurrent LGSOC

**Recurrent LGSOC**
- Prior chemotherapy
- Measurable disease (RECIST 1.1)
- Prior MEKi allowed

**Part A**
- Selection Phase*
  - Avutometinib + Defactinib
    - KRAS mt (n=16)
    - KRAS wt (n=16)
    - N=32

**Part B**
- Expansion Phase*
  - Avutometinib + Defactinib
    - KRAS mt (Total n=36)
    - KRAS wt (Total n=36)
    - N=72 (incl Part A+B)

**Part C**
- Expansion Phase* Combo
  - Avutometinib + Defactinib
    - KRAS mt
    - KRAS wt (Total n=36)

**Part D**
- Expansion Phase** (Combo Lower Dose)
  - Avutometinib + Defactinib
    - KRAS mt
    - KRAS wt

**Completed Enrollment**

**Primary Endpoint:**
Objective Response Rate (blinded independent review)

Evaluation of ORR in Combination Arm:
1) In KRAS mt patients
2) All patients (KRAS mt & wt)

**Combination Arm:**
- Target Enrollment Reached (N=72)
- Expanded Enrollment Ongoing (Lower Dose)

---

*Dosing: Avutometinib + Defactinib combo: Avutometinib 3.2 mg PO 2x/wk 21/28 days + Defactinib 200 mg PO BID: 21/28 days; Avutometinib monotherapy: Avutometinib 4.0 mg PO 2x/wk 21/28 days

**Lower Dose:** Avutometinib + Defactinib combo: Avutometinib 1.6 mg PO 2x/wk 21/28 days + Defactinib 200 mg PO BID: 21/28 days; Completed Enrollment
These results demonstrate avutometinib in combination with defactinib can deliver high response rates for patients with recurrent LGSOC with a promising safety profile to date. It is particularly encouraging to see extensive tumor shrinkage in women who have had several treatment lines, including prior MEK inhibitors. These latest findings suggest the combination may offer a new treatment option for women with this hard-to-treat cancer, and we are hopeful it will become the new standard of care.”

—Dr. Susana Banerjee, MBBS, MA PhD, FRCP, global and lead investigator of the study, Consultant Medical Oncologist at The Royal Marsden NHS Foundation Trust and Team Leader in Women’s Cancers at The Institute of Cancer Research, London

### ASCO 2023 data

#### Updated Data from Part A of RAMP 201

<table>
<thead>
<tr>
<th></th>
<th>Avutometinib + Defactinib</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total (n=29)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>ORR, % (n)</strong></td>
<td></td>
</tr>
<tr>
<td>KRAS mt</td>
<td>60% (9/15)</td>
</tr>
<tr>
<td>KRAS wt</td>
<td>29% (4/14)</td>
</tr>
<tr>
<td><strong>Tumor shrinkage, % (n)</strong></td>
<td>86% (25)</td>
</tr>
<tr>
<td><strong>Median Time to Response</strong></td>
<td>5.5 months (range 1.6-14.7 months)</td>
</tr>
<tr>
<td><strong>Relative avutometinib Dose Intensity</strong></td>
<td>83% ± 20%</td>
</tr>
</tbody>
</table>

- 29 patients were evaluable for efficacy with a minimum follow-up of 12 months and 13 (45%) patients remain on study treatment
- Patients were heavily pretreated with a median of 4 prior systemic regimens (up to 11)
  - 3 out of 4 patients who received prior MEK inhibitors responded to the combination
- Median duration of response and median progression free survival have not been reached
- Safety and tolerability continued to be favorable and consistent with previously reported data
  - The discontinuation rate due to ≥ 1 adverse event was 12% in the combination overall to date (4.9% due to elevated blood CPK)
Recent LGSOC Trials with Standard of Care Highlight High Unmet Need: Current Trials with Avutometinib + Defactinib Show Overall Response Rate >40%

<table>
<thead>
<tr>
<th>Trial</th>
<th>Median Number of Prior lines of Therapy</th>
<th>Prior MEK Allowed</th>
<th>Prior Bevacizumab</th>
<th>Therapy</th>
<th>Response Rate ORR</th>
<th>Image Assessment</th>
<th>Median PFS Months (95% CI)</th>
<th>Discontinuation Rate Due to AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOG 281(^1)</td>
<td>2 (1-10)</td>
<td>No</td>
<td>* Low %</td>
<td>Standard of Care</td>
<td>6% (^\wedge)</td>
<td>INV</td>
<td>7.2 (5.6-9.9)</td>
<td>30%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Trametinib</td>
<td>95% CI: (3%, 12%)</td>
<td>INV</td>
<td>13.0 (9.9-15.0)</td>
<td>36%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Bevacizumab</td>
<td>(26%)</td>
<td>INV</td>
<td>95% CI: (19%, 35%)</td>
<td></td>
</tr>
<tr>
<td>MILO(^2)</td>
<td>2 (1-8)</td>
<td>No</td>
<td>* Low %</td>
<td>Standard of Care</td>
<td>13%</td>
<td>BICR</td>
<td>10.6 (9.2 to 14.5)</td>
<td>17%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Binimetinib</td>
<td>16%</td>
<td>BICR</td>
<td>9.1 (7.3-11.3)</td>
<td>31%</td>
</tr>
<tr>
<td>FRAME(^3)</td>
<td>3.5</td>
<td>Yes</td>
<td>19 %</td>
<td>Avutometinib + Defactinib</td>
<td>42% (^\wedge)</td>
<td>INV</td>
<td>20 (11 - 31)</td>
<td>4%</td>
</tr>
<tr>
<td>RAMP 201 Part A (ASCO 2023 data)(^4)</td>
<td>4</td>
<td>Yes</td>
<td>65%</td>
<td>Avutometinib + Defactinib</td>
<td>45%</td>
<td>BICR</td>
<td>Not Yet Reached</td>
<td>10%**</td>
</tr>
</tbody>
</table>

\(^1\)Study GOG 281 trial Gershenson et al., Lancet 2022
\(^2\)MILO Study Monk et al., J Clin Oncol 2020.
\(^3\)Banerjee et al., ESMO Sept 2021
\(^4\)Banerjee et al., ASCO June 2023

* Low historical use of bevacizumab during trial conduct. % not reported
MILO: no more than 3 lines of prior chemotherapy

SoC = Standard of Care
GOG 281: (chemotherapy / endocrine therapy)
PLD (liposomal doxorubicin), paclitaxel, topotecan, letrozole or tamoxifen
MILO: (chemotherapy only)
PLD (liposomal doxorubicin), paclitaxel or topotecan

INV = Investigator
BICR = Blinded independent central review
PFS = Progression free survival
CI = confidence interval

**12% discontinuation in all combination pts (Part A + B (n=81): 4.9% due to elevated blood CPK)

*** Confirmed + Unconfirmed Objectives responses
RAMP 201 Part A: Heavily Pre-Treated Patient Population

Prior Platinum-Based Chemotherapy, Endocrine Therapy, Bevacizumab in Most Patients; Prior MEK Inhibitor Therapy was Permitted

<table>
<thead>
<tr>
<th></th>
<th>Avutometinib Monotherapy</th>
<th>Avutometinib + Defactinib</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>KRAS mt (n=16)</td>
<td>KRAS wt (n=17)</td>
</tr>
<tr>
<td>Age (yrs), median (min, max)</td>
<td>58 (27, 72)</td>
<td>48 (27, 74)</td>
</tr>
<tr>
<td>ECOG PS, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>8 (50)</td>
<td>15 (88)</td>
</tr>
<tr>
<td>1</td>
<td>8 (50)</td>
<td>2 (12)</td>
</tr>
<tr>
<td>Number of Prior Systemic Regimens, median (min, max)</td>
<td>4 (1, 10)</td>
<td>3 (1, 9)</td>
</tr>
<tr>
<td>Prior platinum-based chemotherapy, n (%)</td>
<td>15 (94)</td>
<td>17 (100)</td>
</tr>
<tr>
<td>Prior MEK inhibitor therapy, n (%)</td>
<td>5 (31)</td>
<td>5 (29)</td>
</tr>
<tr>
<td>Prior Bevacizumab, n (%)</td>
<td>8 (50)</td>
<td>8 (47)</td>
</tr>
<tr>
<td>Prior Hormonal therapy, n (%)</td>
<td>11 (69)</td>
<td>13 (76)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**RAMP 201 Part A: Evaluable Patient Population**

Positive ORR Confirmed by Blinded Independent Central Review (BICR) Support Avutometinib + Defactinib as Go Forward Regimen in LGSOC - Regardless of KRAS Status

<table>
<thead>
<tr>
<th></th>
<th>Avutometinib</th>
<th>Avutometinib + Defactinib</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>KRAS mt (n=15)</td>
<td>KRAS wt (n=14)</td>
</tr>
<tr>
<td>Confirmed ORR, n (%)</td>
<td>2 (13)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>CR, n (%)</td>
<td>1 (7)</td>
<td>0</td>
</tr>
<tr>
<td>PR, n (%)</td>
<td>1 (7)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>SD, n (%)</td>
<td>12 (80)</td>
<td>13 (81)</td>
</tr>
<tr>
<td>Disease control rate***, n (%)</td>
<td>14 (93)</td>
<td>14 (88)</td>
</tr>
<tr>
<td>PD, n (%)</td>
<td>1 (7)</td>
<td>2 (13)</td>
</tr>
<tr>
<td>Confirmed + unconfirmed ORR, n (%)</td>
<td>2 (13)</td>
<td>1 (6)</td>
</tr>
<tr>
<td></td>
<td>9 (60)</td>
<td>4 (29)</td>
</tr>
<tr>
<td></td>
<td>95% CI (2%, 24%)</td>
<td>95% CI (26%, 64%)</td>
</tr>
</tbody>
</table>

**Evaluable for Efficacy: At least one blinded imaging assessment in 31 of 33 and 29 of 31 patients enrolled in respective treatment arms**

**Includes patient deepened to CR at last assessment; CR not yet confirmed**

***Disease control rate (SD + PR + CR) at 8 weeks.
Combination of Avutometinib and Defactinib
High Disease Control Rate + Tumor Reduction in Recurrent LGSOC

**Part A (Evaluable for Efficacy *)**

Confirmed ORR: 45%

Confirmed/Unconfirmed ORR: 52%

Disease Control Rate (SD+PR): 90%

Patients still on study treatment: 45%

Minimum follow-up: 12 months

* Evaluable for Efficacy: At least one blinded imaging assessment
Combination of Avutometinib and Defactinib
*Initial Data from RAMP 201 Trial Reinforce Findings from FRAME Trial*

**RAMP 201 (Part A)**
Interim Analysis - Blinded ICR
N=29

**FRAME**
Investigator Assessment
N=26

---

**Best Response (% change from baseline)**

- **KRAS mutant**
- **KRAS wild-type**
- **Still on treatment**

**ASCO 2023 data**

-80  -60  -40  -20  0  20

- **KRAS mutant**
  -100%

- **KRAS wild-type**
  -100%

- **Still on treatment**
  +117.7%

---

Reference: Banerjee et al., ESMO Sept 2021
RAMP 201: Safety and Tolerability Profile of Avutometinib + Defactinib
No New Safety Signals; Few Discontinuations Due to Adverse Events

Most Common Treatment-Related Adverse Events (>20%) in All Treated Patients

• Majority of adverse events are mild to moderate and manageable/reversible\(^1\)

• Few discontinuations due to adverse events (12.3% in combo due to ≥ 1 TEAE 4.9% due to elevated blood CPK\(^*)\)

* No association to date with clinically significant toxicities, including rhabdomyolysis

{AVUTOMETINIB + DEFACTINIB (n=81)}

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Any Grade</th>
<th>Grade ≥3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea, n (%)</td>
<td>50 (61.7)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea, n (%)</td>
<td>40 (49.4)</td>
<td>3 (3.7)</td>
</tr>
<tr>
<td>Blood CPK increased, n (%)</td>
<td>39 (48.1)</td>
<td>15 (18.5)</td>
</tr>
<tr>
<td>Oedema peripheral, n (%)</td>
<td>34 (42.0)</td>
<td>1 (1.2)</td>
</tr>
<tr>
<td>Vomiting, n (%)</td>
<td>30 (37.0)</td>
<td>0</td>
</tr>
<tr>
<td>Vision blurred, n (%)</td>
<td>29 (35.8)</td>
<td>0</td>
</tr>
<tr>
<td>Dermatitis acneiform, n (%)</td>
<td>28 (34.6)</td>
<td>2 (2.5)</td>
</tr>
<tr>
<td>Fatigue, n (%)</td>
<td>27 (33.3)</td>
<td>3 (3.7)</td>
</tr>
<tr>
<td>Rash, n (%)</td>
<td>25 (30.9)</td>
<td>2 (2.5)</td>
</tr>
<tr>
<td>Dry skin, n (%)</td>
<td>18 (22.2)</td>
<td>0</td>
</tr>
<tr>
<td>Anemia, n (%)</td>
<td>14 (17.3)</td>
<td>3 (3.7)</td>
</tr>
</tbody>
</table>

\(^1\) J Clin Oncol 41, 2023 (suppl 16; abstr 5515)

\(^*\) No association to date with clinically significant toxicities, including rhabdomyolysis
RAMP-301: Avutometinib + Defactinib

Phase 3 Confirmatory Trial – Randomized Controlled Trial (RCT)

- Recurrent LGSOC
  - KRAS mt+wt
- Prior platinum chemotherapy
- Prior MEKi allowed
- Prior Bev allowed
- Measurable disease (RECIST 1.1)

Randomized 1:1 Strat Factors include:
KRAS Mut Status (KRAS mt vs wt)

Avutometinib + Defactinib*

Recurrent LGSOC (N=135)
Avutometinib + Defactinib*

Crossover upon PD

Investigator’s Choice Treatment (ICT)*

Recurrent LGSOC (N=135)
ICT*

Primary Endpoint:
Progression-Free Survival (PFS) by BICR**

Secondary Endpoints include:
- Objective Response Rate (ORR)
- Duration of Response (DoR)
- Disease Control Rate (DCR)
- Safety / Tolerability
- Patient Reported Outcomes
- Overall Survival

Primary Analysis: Hierarchical Evaluation
1) KRAS mutant LGSOC only
2) All recurrent LGSOC

*A+D Dosing: Avutometinib 3.2 mg PO 2x/wk 21/28 days + Defactinib 200mg PO BID: 21/28 days
*Chemo Hormonal ICT: Liposomal doxorubicin (PLD), Paclitaxel, Topotecan, Letrozole, Anastrozole

**BICR: Blinded Independent Central Review
### Patient-months of Therapy Per Year² (across all 2L+ patients)

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>US Prevalence</th>
<th>Worldwide Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSCLC KRAS G12C²</td>
<td>~4K</td>
<td>~80K</td>
</tr>
<tr>
<td>Pancreatic Cancer³</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LGSOC³</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endometrioid Cancer³</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metastatic uveal melanoma³</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


² Patient-months of Therapy metric calculated by multiplying relevant incidence/prevalence rate times estimated duration of therapy; represents US market opportunity only; patient population estimates from Globocan 2020, American Cancer Society 2021, AACR Genie Cohort V9.0 public, and scientific publications. Duration of therapy estimates from clinical studies and clinician experience. Patient-months on therapy is for 2nd-line+ patients

³ NSCLC KRAS G12C 2nd line patients (incidence); Pancreatic RAS/RAF mutant 2nd-line patients (incidence); LGSOC KRAS mutant and wild-type patients (prevalence); Endometrioid RAS/RAF mutant 2nd-line patients (incidence); Uveal melanoma RAS/RAF mutant 2nd-line patients (incidence)
Plan to File for Accelerated Approval with Mature RAMP 201 and FRAME Study Results

- Encouraging efficacy results include independently confirmed responses (FRAME study)
- RAMP 201 Part A data at ASCO 2023 demonstrated ORR of 45% (13/29) and tumor shrinkage in 86% (25/29) of evaluable patients
- No new safety signals; few discontinuations due to adverse events
- Initiated RAMP 301, a Phase 3 confirmatory trial
- High unmet need in rare ovarian cancer with no currently FDA approved therapies specifically for recurrent LGSOC
- Received FDA Breakthrough Therapy Designation and Orphan Drug Designation for avutometinib in combination with defactinib in LGSOC

Next Milestones

- Plan to file for accelerated approval based on the totality of the data from the RAMP 201 and FRAME studies
- Report updated topline data from RAMP 201 trial in H1 2024
- Continue site activation (sites currently open in US and Australia) and enrollment of RAMP 301, a Phase 3 confirmatory study
Avutometinib with KRAS G12C Inhibitors in Non-Small Cell Lung Cancer
High Unmet Need in Refractory NSCLC Adenocarcinoma

**NSCLC Adenocarcinoma**

US Annual Incidence\(^7,8\): 114K
WW Annual Incidence\(^1,2\): 882K

**Advanced or Metastatic NSCL Cancer**
Recommend Histologic and Molecular Subtyping\(^5\)

- **EGFR/ALK/ROS1/BRAF/KRAS G12C (targeted)**
- **Non-targeted PD-(L)1 ≥ 1%**
- **Non-Targeted PD-(L)1 < 1%**

**Appropriate targeted agent**
- **PD-(L)1 single agent or PD-(L)1 + chemo**
- **Chemo ± PD-(L)1**

**Recurrence**
- SOC in recurrent disease is chemotherapy
- Pre-PD-(L)1 era, chemotherapy response rate ~10% in recurrent disease; 12w PFS of 30–45%

**Verastem Clinical Trials:**
- **RAMP 203:** Avutometinib + sotorasib in KRAS G12C NSCLC
- **RAMP 204:** Avutometinib + adagrasib in KRAS G12C NSCLC

**KRAS Mutations**
- KRAS Mutations Represent 25% of Lung Adenocarcinoma & BRAF Mutations Represent ~4% (EGFR 17%, ALK 7%)\(^4,6\)

**References:**
1. Globocan, 2020
3. TCGA PanCancer Atlas (cBioPortal analysis)
5. Adapted from NCCN Non-small cell lung cancer guidelines Version 3.2020
7. 50% of NSCLC is adenocarcinoma (Pakkala and Ramalingam JCI Insight 2018)
Preclinical Synergy of Avutometinib + G12C Inhibitors in KRAS G12C Models

Synergy of avutometinib + G12C inhibitors across G12C mutant NSCLC, CRC & Pancreatic cancer cell lines

<table>
<thead>
<tr>
<th>Cell line</th>
<th>Indication</th>
<th>Sensitivity to G12C inhibitors</th>
<th>Avutometinib + sotorasib</th>
<th>Avutometinib + adagrasib</th>
</tr>
</thead>
<tbody>
<tr>
<td>H2122</td>
<td>NSCLC</td>
<td>Moderately sensitive</td>
<td>44.7</td>
<td>44.6</td>
</tr>
<tr>
<td>H1373</td>
<td>NSCLC</td>
<td>Sensitive</td>
<td>10.0</td>
<td>3.4</td>
</tr>
<tr>
<td>SW1573</td>
<td>NSCLC</td>
<td>Insensitive</td>
<td>8.6</td>
<td>12.0</td>
</tr>
<tr>
<td>H358</td>
<td>NSCLC</td>
<td>Sensitive</td>
<td>6.9</td>
<td>5.4</td>
</tr>
<tr>
<td>H2030</td>
<td>NSCLC</td>
<td>Moderately sensitive</td>
<td>5.1</td>
<td>ND</td>
</tr>
<tr>
<td>SW837</td>
<td>CRC</td>
<td>Sensitive</td>
<td>16.1</td>
<td>18.5</td>
</tr>
<tr>
<td>MIAPACA2</td>
<td>Panc</td>
<td>Sensitive</td>
<td>2.3</td>
<td>5.3</td>
</tr>
</tbody>
</table>

ND: not determined

Avutometinib + sotorasib yields deeper and more sustained inhibition of ERK signaling pathway

H2122 KRAS G12C NSCLC

Concentrations Tested
Sotorasib: 100 nM
Avutometinib: 100 nM

Doses Tested
Sotorasib: 30 mg/kg PO QD
Avutometinib: 0.3 mg/kg PO QD
FAKi: 50 mg/kg PO BID
Trametinib: 0.3 mg/kg PO QD

Response @ Day 10 (% change from baseline)

Reference: Coma et al., AACR 2021
Avutometinib ± FAKi Restores Anti-Tumor Efficacy of Sotorasib in G12Ci-Resistant KRAS G12C Models

Avutometinib is effective against acquired KRAS mutations that occur clinically upon progression on G12C inhibitors

Addition of avutometinib + FAK inhibitor to sotorasib increases tumor growth inhibition in a sotorasib-resistant KRAS G12C/Y96D model

Addition of avutometinib + FAKi restores anti-tumor activity after progression on sotorasib monotherapy in a KRAS G12C NSCLC GEMM model

<table>
<thead>
<tr>
<th>Cell Line</th>
<th>Sotorasib</th>
<th>Adagrasib</th>
<th>Avutometinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>G12C</td>
<td>29</td>
<td>3</td>
<td>14</td>
</tr>
<tr>
<td>G12D</td>
<td>435</td>
<td>382</td>
<td>7</td>
</tr>
<tr>
<td>G12C/R68S</td>
<td>157</td>
<td>85</td>
<td>13</td>
</tr>
<tr>
<td>G12C/H95D</td>
<td>11</td>
<td>235</td>
<td>10</td>
</tr>
<tr>
<td>G12C/Y96C</td>
<td>438</td>
<td>216</td>
<td>4</td>
</tr>
<tr>
<td>G12C/Y96D</td>
<td>&gt;5000</td>
<td>578</td>
<td>17</td>
</tr>
</tbody>
</table>

<30 nM | 30-150 nM | >150 nM

Reference: Coma et al., AACR RAS meeting 2023

Collaboration with Mariano Barbacid, CNIO (Spain)

Collaboration with Chiara Ambrogio, U Turin (Italy)

Collaboration with Andy Aguirre, DFCI
Patients must have a KRAS G12C mutation determined using validated test

Treatment with at least 1 but no more than 3 prior systemic regimens, for Stage 3B-C or 4 NSCLC*

Patient may have previously received adjuvant chemotherapy for earlier-stage disease

Measurable disease according to RECIST 1.1

ECOG performance status ≤ 1

*may include patients with or without prior G12C therapy

**Recommended Phase 2 Dose (RP2D): 4mg avutometinib / 960mg sotorasib

Collaboration with Amgen

DLT = dose-limiting toxicity; n = number of patients; ORR = overall response rate; RP2D = recommended phase 2 dose
RAMP 203: Objective Responses in KRAS G12C NSCLC Sotorasib + Avutometinib Combination

*On treatment at time of data cutoff; + Patient with -38.4% tumor reduction classified as SD due to disease progression prior to confirmatory scan.

Reference: Awad et al., EORTC- NCI – AACR Conference Oct 2023
RAMP 204: Phase 1/2 Trial of Avutometinib + KRAZATI™ (Adagrasib) in KRAS G12C Advanced NSCLC

- Patients must have a KRAS G12C mutation determined using validated test
- Treatment with at least 1 but no more than 3 prior systemic regimens, for Stage 3B-C or 4 NSCLC
- Patient must have received prior therapy with a KRAS G12C inhibitor and experience progressive disease
- Measurable disease according to RECIST 1.1
- ECOG performance status ≤ 1

Part A: Dose Evaluation
(3+3 DLT Assessment)

Part B: Dose Expansion
(Primary endpoint ORR)

Stage 1: 19 patients (including Part A patients) treated with RP2D
Stage 2: expand to 55 patients

Avutometinib + Adagrasib
Dose Finding Cohorts (n=3-6)

RP2D Selection

Collaboration with Mirati Therapeutics

NCT05375994

DLT = dose-limiting toxicity; n = number of patients; ORR = overall response rate; RP2D = recommended phase 2 dose
Avutometinib Combinations in Pancreatic Cancer and Colorectal Cancer
Addition of Avutometinib + FAKi to Chemotherapy Induces Tumor Regression and Increases Survival in a KRAS/p53 Pancreatic Cancer Mouse Model

✓ The combination of avutometinib + FAKi induces tumor growth inhibition and increases survival but does not induce tumor regression

✓ Addition of chemo (gemcitabine + paclitaxel) to avutometinib/FAKi induces tumor regression
RAMP 205: Phase 1/2 Trial of Avutometinib/Defactinib + GEMZAR™ (Gemcitabine)/ABRAXANE™ (Nab-paclitaxel) in Front Line Metastatic Pancreatic Cancer

- Patients with confirmed metastatic pancreatic ductal adenocarcinoma
- Eligible for treatment in the first-line setting with standard gemcitabine and nab-paclitaxel
- Prior adjuvant or neoadjuvant chemotherapy, radiotherapy or surgery is permitted if the last intervention/dose was ≥ 12 months prior to the diagnosis of metastatic disease
- Measurable disease according to RECIST 1.1
- ECOG performance status ≤ 1

Part A: Dose Evaluation (3+3 DLT Assessment)
- Avutometinib + Defactinib + Gemcitabine + Nab-paclitaxel
- Dose Finding Cohorts (n=3-6)

Part B: Dose Expansion at RP2D (Primary endpoint ORR)
- Patients with PDAC
  - KRAS G12D
  - KRAS G12V
  - KRAS G12R
  - Others
  - Treated with RP2D
  - Stage 1: 17 patients
  - If ≥4 responders, then
  - Stage 2: expand to 29 patients

NCT05669482

DLT = dose-limiting toxicity; n = number of patients; ORR = overall response rate; RP2D = recommended phase 2 dose

Collaboration with PanCAN
Combination of Avutometinib with anti-EGFR mAb Induces Tumor Regression in a KRAS mt Colorectal PDX Model

- Avutometinib + anti-EGFR (panitumumab) induces tumor regression in a KRAS mutant CRC patient-derived xenograft model
- G12Ci + anti-EGFR (sotorasib + panitumumab and adagrasib + cetuximab) have shown partial responses in KRAS G12C CRC (Fakih et al. ESMO 2021; Weiss et al. ESMO 2021)
- These data support the ongoing clinical evaluation of avutometinib + cetuximab (anti-EGFR) for treatment of KRAS mt CRC (NCT05200442)
Discovery Efforts and Financials
Discovery and Development Collaboration with GenFleet Strengthens Pipeline Targeting RAS Pathway-Driven Cancers

• Increases the breadth of Verastem’s oncology pipeline with strategically-aligned RAS pathway focus
  o Exclusive option for Verastem to license up to 3 programs with development and commercialization rights outside China
  o Potential development in combination with Verastem’s current pipeline
  o Completed IND enabling studies for oral KRAS G12D (ON/OFF) inhibitor GFH375 (VS-7375) as lead program; GenFleet expected to submit IND for GFH375/VS-7375 in China in H1 2024 and initiate Phase 1 trial for GFH375/VS-7375 in China in H2 2024
  o Programs 2 & 3 in discovery phase
  o Small molecule programs focused on anti-cancer targets related to the RAS/MAPK pathway or surrounding cancer cell signaling

• Strategic collaboration builds on Verastem Oncology and GenFleet’s experience in RAS pathway-driven cancers
  o Collective worldwide strengths in RAS pathway discovery and development
  o Established network of collaborators, including leading scientific and clinical experts
  o Leverages experience from GenFleet’s KRAS G12C inhibitor program and Verastem’s avutometinib/defactinib program

• Risk-sharing structure of the collaboration with milestone-based options provides capital efficient approach
  o At execution, Verastem paid GenFleet an upfront payment to obtain exclusive option right to 3 programs
  o Combined with the upfront amount, payments for future annual R&D support, development milestones and option payment for first program through completion of Phase I trial could equal up to $11.5 million
  o Potential total deal size across all 3 programs up to $625.5 million excluding royalties if Verastem exercises its in-license options
  o Includes exclusive rights for Verastem to obtain a license to each of the compounds after successful completion of pre-determined milestones in Phase 1 trials
### Key Financial Statistics

**As of and for the quarter ended December 31, 2023**

<table>
<thead>
<tr>
<th>Description</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cash, cash equivalents &amp; investments</td>
<td>$137.1M</td>
</tr>
<tr>
<td>GAAP Operating Expenses</td>
<td>$31.1M</td>
</tr>
<tr>
<td>Non-GAAP Operating Expenses*</td>
<td>$29.5M</td>
</tr>
<tr>
<td>Shares Outstanding</td>
<td>25.3M**</td>
</tr>
</tbody>
</table>

**Sources of Non-Dilutive Capital**

- **Oxford Finance LLC Credit Facility**
  - Up to $150M available in a series of term loans
  - $40M term loans outstanding
  - Remaining $110M available upon achievement of pre-defined milestones or at lender’s discretion
  - Floating interest rate, subject to a floor and a cap; 5% final payment charge, and loan subject to 1-3% early payment fee
  - Interest only payments through April 2025
  - No financial covenants

- **Secura Bio, Inc. (Secura) Asset Purchase Agreement – COPIKTRA**
  - Regulatory and commercial milestone payments up to $95M
  - Entitled to receive 50% of royalties, milestones, and sublicensee revenue payments made to Secura related to COPIKTRA
  - Low double-digit royalties on annual net sales over $100M in US, EU, and UK

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* Q4 2023 GAAP operating expenses - $31.14M less Q4 2023 stock compensation of $1.60M = $29.54M Q4 2023 non-GAAP operating expenses

**Excludes Series A Preferred (0.8M Shares on as-converted basis), Series B Preferred (4.2M Shares on as-converted basis), and outstanding unexercised pre-funded warrants (1.5M Shares).
Avutometinib Patent Exclusivity

Composition of Matter

Method of Making

Dosing Protocol

Combination w/ Defactinib

Solid Form

Methods or Treating; Combinations

PTE

Feb 2027 + 5 yrs (PTE) = 2032

Sept 2032

May 2038

Sept 2040

Dec 2042

2041 - 2042 if issued
Experienced Senior Management Team

Daniel Paterson  
President and Chief Executive Officer  
- CEO – The DNA Repair Co. (now On-Q-ity)  
- PharMetrics (now IMS), Axion

Mike Crowther  
Chief Commercial and Business Strategy Officer  
- CBO, Minerva Biotechnologies  
- Interim US lead and VP of US Marketing, Kite Pharma  
- Celgene

Dan Calkins  
Chief Financial Officer  
- Technical Accounting Consultant-CFGI  
- PwC LLP

Jonathan Pachter, Ph.D.  
Chief Scientific Officer  
- Head of Cancer Biology – OSI (now Astellas)  
- Schering-Plough

Cathy Carew  
Chief Organizational Effectiveness Officer  
- Principal – HR Collaborative  
- Ironwood, ActiveBiotics, Dynogen, Tufts Health Plan

Hagop Youssoufian, MSc, M.D.  
Head of Medical Strategy  
- CMO, BIND Therapeutics, EVP, Progenics,  
- CMO & EVP, Ziopharm Oncology, SVP, Imclone
THANK YOU