This presentation includes forward-looking statements about, among other things, Verastem Oncology’s products and product candidates, including anticipated regulatory submissions, approvals, performance and potential benefits of Verastem Oncology products and product candidates, that are subject to substantial risks and uncertainties that could cause actual results to differ materially from those expressed or implied by such statements. Applicable risks and uncertainties include the risks and uncertainties, among other things, regarding: the satisfaction of closing conditions with respect to the sale of the COPIKTRA assets to Secura Bio; the ability of Secura Bio to achieve the clinical and sales milestones necessary to result in additional consideration payable to Verastem.

Additional information regarding these factors can be found in Verastem Oncology’s Annual Report on Form 10-K for the fiscal year ended December 31, 2019 and in any subsequent filings with the SEC, including in the sections thereof captioned “Risk Factors” and “Forward-Looking Information and Factors that May Affect Future Results,” as well as in our subsequent reports on Form 8-K, all of which are filed with the U.S. Securities and Exchange Commission (SEC) and 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.
### Well Positioned to Capitalize on Growth Opportunities

**New lead clinical program has best-in-class potential**

VS-6766 (RAF/MEKi) and defactinib (FAKi) are clinically active against KRAS mutant cancers

**Rapid development paths to market**

Validating clinical results achieved in KRAS mutant low-grade serous ovarian cancer (LGSOC), strong signal in KRAS mutant G12V NSCLC; registration-directed trials initiated in 2020

**Significant downstream market opportunity and blockbuster potential**

30% of all human cancers are driven by mutations in RAS family of genes; VS-6766 combinations broadly applicable across a variety of tumor types

**Strong balance sheet**

Monetization of COPIKTRA® (duvelisib) provides funding until at least 2024

Proforma Cash Balance of $168.3 million, after Hercules Debt Repayment

Starting in 2021, annual operating expense forecast $50 million
VS-6766 is a Unique Small Molecule RAF/MEK Inhibitor

- VS-6766 inhibits both MEK & RAF kinase activities
- MEK inhibitors paradoxically induce MEK phosphorylation (pMEK) by relieving ERK-dependent feedback inhibition of RAF
- By inhibiting RAF phosphorylation of MEK, VS-6766 has advantage of not inducing pMEK
- VS-6766 inhibits ERK signaling more completely; may confer enhanced therapeutic activity

# Robust Pipeline Targeting the RAS Pathway and Multiple Growth Opportunities

<table>
<thead>
<tr>
<th>Combinations</th>
<th>PRECLINICAL</th>
<th>PHASE 1 / 1B</th>
<th>PHASE 2</th>
<th>PHASE 3</th>
<th>MARKET</th>
</tr>
</thead>
<tbody>
<tr>
<td>FRAME study in advanced LGSOC(^1,2) with defactinib</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FRAME study in advanced KRAS mt NSCLC(^1,2) with defactinib</td>
<td></td>
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<tr>
<td>FRAME study in advanced CRC(^1,2) with defactinib</td>
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</tr>
<tr>
<td>FRAME study in advanced KRAS-G12V mt NSCLC(^1,2) with defactinib</td>
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<tr>
<td>FRAME study in advanced pancreatic cancer(^1,2) with defactinib</td>
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<tr>
<td>FRAME study in advanced KRAS mt endometrial cancer(^2,2) with defactinib</td>
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<tr>
<td>RAMP registration-directed study in recurrent LGSOC(^3) monotherapy and in combination with defactinib</td>
<td></td>
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</tr>
<tr>
<td>RAMP registration-directed study in recurrent KRAS mt NSCLC(^4) monotherapy and in combination with defactinib</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metastatic uveal melanoma(^1) with defactinib</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KRAS mt NSCLC(^1) \underline{VS-6766 + everolimus}</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^1\) Investigator-sponsored trial  
\(^2\) NCT03875820  
\(^3\) NCT04625270  
\(^4\) NCT04620330

*Pre-clinical studies ongoing in multiple KRAS mutant tumors
Updated Phase 1/2 FRAME Study Data in Low-Grade Serous Ovarian Cancer
# RAF/MEK Inhibitor VS-6766 in Gynecological Malignancies

<table>
<thead>
<tr>
<th></th>
<th>PHASE 1 / 1B</th>
<th>PHASE 2</th>
<th>PHASE 3</th>
<th>MARKET</th>
</tr>
</thead>
<tbody>
<tr>
<td>FRAME study in LGSOC(^1,2) VS-6766 + defactinib</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FRAME study in KRASm endometrial cancer(^1,2) VS-6766 + defactinib</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAMP registration-directed study in recurrent LGSOC(^3) monotherapy and in combination with defactinib</td>
<td></td>
<td></td>
<td></td>
<td>Registration-directed study commenced November 30, 2020</td>
</tr>
</tbody>
</table>

\(^1\) Investigator-sponsored trial  
\(^2\) NCT03875820  
\(^3\) NCT04625270
What is Low-Grade Serous Ovarian Cancer (LGSOC)?

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.

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

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

Favorable Tolerability Profile for Novel Intermittent Dosing Regimen of VS-6766 plus Defactinib

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade ≥3</th>
<th>Grade ≥3</th>
<th>Grade ≥3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash related</td>
<td>3 (50%)</td>
<td>5 (19%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>CK elevation</td>
<td>1 (17%)</td>
<td>2 (8%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>-</td>
<td>1 (4%)</td>
<td>-</td>
</tr>
<tr>
<td>Mucositis</td>
<td>-</td>
<td>1 (4%)</td>
<td>-</td>
</tr>
<tr>
<td>Fatigue</td>
<td>-</td>
<td>1 (4%)</td>
<td>-</td>
</tr>
<tr>
<td>Nausea</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Daily at MTD
N=6
28-day cycle

4mg twice weekly
N=26
28-day cycle

RP2D
(VS-6766 3.2mg twice weekly + defactinib 200mg twice daily)
N=26
21 days of 28-day cycle

VS-6766 in Combination with Defactinib Shows Robust ORR with Durability in Refractory LGSOC with Expanded Number of Patients (n=17)

- **KRAS-G12 mutations ORR = 56% (5/9); data still maturing**
- **Current ORR = 41% (7/17); data still maturing**
- **5/9 PRs in pts who had previous MEKi**
- **9/17 (53%) still on study**
- **3 pts on treatment for ~2 yrs or more**

1. Patients came off prior MEKi treatment primarily for progression
2. Data cutoff date August 17, 2020
VS-6766 in Combination with Defactinib Shows Robust ORR with Durability in Refractory LGSOC at Phase 2 Dose Level

All patients on RP2D: 3.2 mg VS-6766 (2x/wk) + 200 mg Defactinib (BID) q3/4 wks

- ORR in KRAS mt = 50% (3/6); data still maturing
- Current overall ORR = 45% (5/11); data still maturing
- 9/11 (82%) still on study at RP2D
- 2 pts on treatment for 2.5 yrs

1 Data cutoff date August 17, 2020
KRAS Mutated (mt) and Wild Type (wt), Phase 2, Recurrent LGSOC Adaptive Design for Potential Accelerated Approval

**Selection Phase**
- Recurrent LGSOC
- Measurable disease (RECIST 1.1)
- Prior MEKi allowed
- Approximately 32 subjects

**Expansion Phase**
- Defactinib+VS-6766
  - Defactinib 200 mg PO BID 21/28 days + VS-6766 3.2 mg PO 2x/wk 21/28 days
- VS-6766 Mono
  - VS-6766 4.0 mg PO 2x/wk 21/28 days
- Selected Regimen based on ORR
  - Additional 20-30 subjects with KRAS mt
  - Additional 36-56 subjects with KRAS wt
- Total Range of Subjects: 88 - 118

**Primary Endpoint ORR**
- Hierarchical evaluation of:
  1) In KRAS mt subjects
  2) All subjects (KRASmt & wt)

FDA Was Supportive of Development Strategy and Adaptive Design

This Registration-directed Phase 2 Study Commenced in November 2020 with an estimated Primary Completion Date for the Expansion Phase of June 2023 (clinicaltrials.gov)

* Selection Phase – KRAS mt only
** Expansion Phase – final sample size to be adjusted based on adaptive design
Low-Grade Serous Ovarian Cancer

Market Opportunity
LGSOC: Key Drivers Are KRAS/NRAS/BRAF Mutations

<table>
<thead>
<tr>
<th>Incidence</th>
<th>10 Yr Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worldwide</td>
<td>~15,000 – 30,000</td>
</tr>
<tr>
<td>US</td>
<td>~1,000 – 2,000</td>
</tr>
</tbody>
</table>

32% of LGSOC Patient Have KRAS Mutations

- Wild-type KRAS includes NRAS and BRAF mutations, among others

*Based on LGSOC representing 5-10% of epithelial ovarian cancer*
LGSOC: Limited Treatment Options With High Unmet Need

Low-Grade Ovarian Cancer – Treatment Algorithm⁴

Stage IA-IB

Observe only

Stage IC

Pt Chemo Combo: Carbo-Pt + Paclitaxel (preferred) + Beva for Stage II-IV (incl maintenance Beva) OR Hormonal Tx (2B)

Stage II-IV

Recurrence

Pt-Sensitive
- Pt-Chemo combo +/- Beva
- Trametinib
- Fulvestrant

Pt-Resistance
- Taxane or gemcitabine, or doxorubicine, or topotecan +/- Beva
- Trametinib
- Fulvestrant

Limited Response Rates for Available Treatments:

- Chemotherapy: <10%²
- Letrozole: 14%²
- Selumetinib: 15%³
- Binimetinib: 24%⁴
- Trametinib: 26%²

- 31-35% discontinuation rate with MEK inhibitors due to AEs
- No discontinuations in the FRAME study due to AEs

¹ NCCN guidelines
Validating Clinical Data in LGSOC
VS-6766 ± Defactinib Represents Best in Class Market Opportunity in LGSOC

Key Takeaways

- KRAS mutations account for 32%\(^1\) of LGSOC cases
- No FDA-approved therapy; limited treatment options
- Unmet medical need creates large market opportunity
- ~6,000 patients living with the disease; ultra-orphan opportunity
- FRAME study: 56% ORR in KRAS-G12m LGSOC and 41% ORR in overall LGSOC represents best-in-class opportunity
- FDA supportive of development strategy and registration trial design

Next Steps

- Phase 2 registration-directed trial has commenced in Nov 2020
- Report updated data from FRAME LGSOC cohort in mid-2021

\(^1\) AACR Project Genie, cBioportal
Other Program Updates
High Unmet Need in Refractory KRASm NSCLC Adenocarcinoma

NSCLC Adenocarcinoma

US Annual Incidence\(^1,\)\(^2\): 92K
WW Annual Incidence\(^1,\)\(^2\): 836K

KRAS Mutations Represent 25% of Lung Cancer Adenocarcinoma (EGFR 17%, ALK 7%)\(^4\)

KRAS Mutation

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

- EGFR/ALK/ROS1/B RAF (targeted) Non-targeted
- PD-(L)1 \(\geq 1\%\)
- Non-Targeted PD-(L)1 < 1%

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

Prior PD-(L)1
- Chemotherapy
  - Docetaxel
  - Gemcitabine
  - Pemetrexed

No Prior PD-(L)1
- PD-(L)1

Chemotherapy or clinical trials

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

---

\(^1\) Globocan, 2018
\(^2\) https://www.ncbi.nlm.nih.gov/books/NBK519578/
\(^3\) TCGA PanCancer Atlas (cBioPortal analysis)
\(^4\) www.thelancet.com Vol 389 January 21, 2017
\(^5\) Adapted from NCCN Non-small cell lung cancer guidelines Version 3.2020
Preclinical evidence suggests combination with Defactinib may improve efficacy in KRAS\textsuperscript{G12V} mutant patients.

Activity of VS\textsuperscript{-6766} as a single agent and in combo with Defactinib in KRAS\textsuperscript{G12V} NSCLC has been confirmed.

1 additional confirmed PR in KRAS\textsuperscript{G12V} mutant patient as of Mar-2020.

Source: 1 Guo, et al Lancet Oncology 2020 2 Banerji, AACR VM 1, April 27, 2020, CT143
NSCLC Clinical Strategy: KRAS Mutant (mt), Enriched G12V, Phase 2, Recurrent NSCLC for Potential Accelerated Approval

Selection Phase

- Recurrent NSCLC
- 1-2 prior regimens
- 1 prior platinum-containing chemo;
- Prior CPI unless contraindicated
- Measurable disease (RECIST 1.1)
- Appropriate approved therapy for other relevant mutations
- No prior MEKi, no prior KRAS-specific targeted therapy
- No untreated CNS metastases
- ECOG OS 0-1

Defactinib + VS-6766

1. KRAS mt G12V
   - N=16

VS-6766

2. KRAS mt G12V
   - N=16

Defactinib + VS-6766

1. KRAS mt non-G12V
   - N=25, maximum

Expansion Phase

KRAS Mutant – G12V

- Selected Regimen based on ORR

KRAS Mutant – non-G12V

- Final G12V sample size to be discussed with FDA
- Non-G12V Cohorts TBD based on results of exploratory analysis

This Registration-directed Phase 2 Study commenced December 2020 with an estimated Primary Completion Date for the Expansion Phase of March 2023 (clinicaltrials.gov)

1 Defactinib 200 mg PO BID (21/28 days) + VS-6766 3.2 mg PO 2x/wk (21/28 days)
2 VS-6766 4.0 mg PO 2x/wk (21/28 days)
Vertical Blockade: Establishing VS-6766 as the backbone of therapy for RAS pathway-driven tumors

### Current Challenges
- Blocking any single target in the pathway is insufficient for maximum depth and duration of anti-tumor efficacy
  - e.g., SHP2i, KRAS-G12Ci, RAFi, MEKi, ERKi
- Vertical inhibition concept is now well established
  - Necessary to block more than 1 target in the pathway
- Many of these agents (e.g., SHP2i, MEKi) have poor tolerability as monotherapy and in combination

### Solutions offered by VS-6766
- Vertical inhibition (RAF and MEK blockade) in a single drug
- Best-in-class tolerability with established twice weekly dosing regimen
  - Should enable tolerable combinations
- Compelling synergy data (preclinical) emerging for VS-6766 combinations (e.g., with KRAS-G12C inhibitors)

References: ¹ Chen, Mol Cancer Res 2018; ² Banerji, BTOG Dublin, Jan 23, 2019
Parallel Pathway Blockade: Establishing VS-6766 as the backbone of therapy for RAS pathway-driven tumors

### Current Challenges
- Blocking Ras pathway can be circumvented through parallel pathways
  - e.g., PI3K/AKT/mTOR, FAK, RhoA, YAP
- Combinations of MEKi + AKTi have shown poor tolerability

### Solutions offered with VS-6766
- Good tolerability with twice weekly VS-6766 opens up intermittent dosing options for combinations
- Compelling preclinical synergy data with VS-6766 in combination with FAK inhibition and with AKT pathway inhibition (e.g., everolimus)
- RP2D established for VS-6766 + defactinib and for VS-6766 + mTORi (everolimus) with twice weekly regimen (Udai Banerji, 3Q20)

References: 1 Chen, Mol Cancer Res 2018; 2 Banerji, BTOG Dublin, Jan 23, 2019
Continuing to Move VS-6766 Forward Aggressively With Additional Opportunities

**NSCLC**
- Go-forward strategy is to focus primarily on KRAS G12V patients in NSCLC given clinical signals to-date
- KRAS G12V cohort added to ongoing FRAME study
- Completing Phase 1 investigating VS-6766 in combination with everolimus; plan to advance to Phase 2 in KRASm non-G12V NSCLC
- Reported new preclinical data demonstrating strong synergy and tumor regression with G12C inhibitors in combination with VS-6766 and FAK inhibitor *in vitro* and *in vivo*

**Other Tumor Areas**
- Expanded FRAME study to include pancreatic and KRASm endometrial patient cohorts to provide early efficacy signals
- VS-6766 enhances efficacy of anti-PD-1 in preclinical models
High Priority Lead Indications with Multiple Growth Opportunities

High Priority Indications Supported by Initial Data
Registration-Directed Trials Initiating in 4Q20
- LGSOC\(^1,2\)
- KRAS\(^{G12V}\) NSCLC\(^1,2\)

Expansion Opportunities
- Pancreatic\(^1,2\) (10 pt cohort initiated)
- KRAS mt endometrial\(^1\) (10 pts initiated)
- Uveal Melanoma\(^2\) (IST initiating)
- BRAF mt melanoma\(^1,2\)
- NRAS mt melanoma
- BRAF mt prostate\(^2\)

Other Mutation Opportunities
- GNAQ mutations in uveal melanoma\(^2\)
- NF1 mutations in melanoma
- MAP3K1 mutations in breast cancer

Other Combinations
- Anti-PD-1\(^1,2\)
- KRAS\(^{G12C}\) inhibitors\(^2\)
- Everolimus\(^1,2\)
- SHP2 inhibitors

1 Supported by clinical data
2 Supported by preclinical data
Selling COPIKTRA® (duvelisib) Rights to Secura Bio

- Total Deal Value Up to $311 Million, Plus Royalties
- Provides Cash Runway Through at Least 2024
- New Verastem Headcount of ~50
- Beginning in 2021 Annual OPEX Expected to be ~$50 Million
- Secura Bio Has Assumed All Operational and Financial Responsibilities, Including Existing Royalty Obligations
# Key Financial Statistics

## As of September 30, 2020

<table>
<thead>
<tr>
<th>Description</th>
<th>Amount</th>
</tr>
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<tbody>
<tr>
<td>Cash, cash equivalents &amp; short-term investments as of 9/30/2020</td>
<td>$205.7M</td>
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<tr>
<td>Shares fully diluted as of 9/30/2020</td>
<td>190.2M</td>
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<tr>
<td>Hercules Term Loan Facility as of 9/30/2020</td>
<td>$35.0M</td>
</tr>
<tr>
<td>5.00% Convertible Senior Notes Due 2048 (2018 Notes) as of 9/30/2020</td>
<td>$28.3M</td>
</tr>
<tr>
<td>Insider ownership (outstanding / vested) as of 9/30/2020</td>
<td>9.2% / 5.0%</td>
</tr>
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</table>

## Revised to include Hercules Debt Repayment

<table>
<thead>
<tr>
<th>Description</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proforma Cash after Hercules Repayment</td>
<td>$168.3M</td>
</tr>
<tr>
<td>5.00% Convertible Senior Notes Due 2048 as of 11/09/2020</td>
<td>$28.3M</td>
</tr>
</tbody>
</table>
High Unmet Needs in RAS/RAF/MEK/ERK-Driven Cancers

<table>
<thead>
<tr>
<th>KRAS-mutant Cancers¹</th>
<th>NSCLC Incidence³: 194K</th>
<th>Pancreatic Incidence⁵: 58K</th>
<th>Uterine Endometrioid Incidence⁴,⁵: 59K</th>
<th>Colorectal Incidence⁵: 105K</th>
<th>Ovarian Incidence⁵: 22K</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>31%</td>
<td>98%</td>
<td>21%</td>
<td>45%</td>
<td>5%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NRAS-mutant Cancers¹</th>
<th>Melanoma Incidence⁵: 108K</th>
<th>Multiple Myeloma Incidence⁵: 32K</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>28%</td>
<td>20%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BRAF-mutant Cancers²</th>
<th>Melanoma Incidence⁵: 108K</th>
<th>Ovarian Incidence⁵: 22K</th>
<th>Papillary Thyroid Incidence⁵: 42K</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>60%</td>
<td>35 – 60%</td>
<td>30 – 80%</td>
</tr>
</tbody>
</table>

Breadth of potential opportunity

- 30% of all human cancers are driven by mutations of the RAS family of genes

Established prognostic significance

- Patients with mutations of the RAS family have an overall worse prognosis

Challenges with conventional approaches

- Modest progress; limited number of approved therapies
- Single agent therapies (e.g., MEK inhibitors) associated with resistance
- Tolerable combination regimens with MEK inhibitors have been challenging
- Current RAS inhibitors in development address only a minority of all RAS mutated cancers

Incidence Sources:

³85% of lung cancer is NSCLC (Lu et. al. Cancer Manag Res. 2019); ⁴90% of all uterine cancers are of the endometrial type (ACS); ⁵Cancer Statistics 2020, Siegel et. al. CA Cancer J Clin 2020;70:7-30; ⁶8 out of 10 thyroid cancers are of the papillary type (ACS)

References:

KRAS G12V and G12D Represent ~50% of KRAS Mutations across Human Cancers

% frequency in a total of 780 cancer patients with KRAS mutations¹

- 21.40% G12V
- 25.30% G12D
- 5.10% G12A
- 13.30% G12C
- 2.70% Q61H
- 32.20% Others

Pancreatic Adenocarcinoma¹

- Annual Incidence³: 58K

Uterine Endometrioid Carcinoma¹

- Annual Incidence²,³: 59K

¹ TCGA PanCancer Atlas (cBioPortal analysis)
² 90% of all uterine cancers are of the endometrial type (ACS)
³ Cancer Statistics 2020 (Siegel et al. CA Cancer J Clin 2020; 70:7-30)
More Complete Shutdown of Tumor Growth Requires Addressing Multiple Resistance Mechanisms

- BRAF inhibition induces compensatory activation of pFAK\(^1\)
- MEK inhibition induces compensatory activation of pFAK preclinically and clinically\(^2\)
  - Trametinib induced ↑ pFAK (Y397) preclinically in KRAS mt NSCLC cell lines
  - Also observed in patients
    - VS-6766 induced ↑ pFAK (Y397) as a potential resistance mechanism in the majority of patients
    - Combination with defactinib reduced this compensatory pFAK signal
- Upon MEK blockade, ERK feeds back to activate RAF kinase

References:
1. Chen, Mol Cancer Res 2018
2. Banerji, BTOG Dublin, Jan 23, 2019
Combination of defactinib with VS-6766 or trametinib shows synergy in KRAS mt and BRAF mt cell lines.
VS-6766 and FAK inhibitor combination leads to more robust anti-tumor efficacy \textit{in vivo}

Ovarian cancer model (TOV-21g KRAS(G13C) mutant)

NSCLC cancer model (H2122 KRAS(G12C) mutant)

Uveal melanoma model (92.1 GNAQ mutant)

J. Paradis, AACR 2020
VS-6766 Inhibits CRAF - The key driver of KRAS-G12V mutant NSCLC

A Precision Approach to KRAS-G12V Driven NSCLC

- KRAS\(^{G12V}\) signals mainly through RAF/MEK in contrast to other variants, such as KRAS-G12D, which signal more through PI3K/AKT
- KRAS\(^{G12V}\) models are especially dependent on CRAF

CRAF, but not BRAF, ablation improves survival of mice with KRAS\(^{G12V}\) induced lung cancer \textit{in vivo}

Synergy of VS-6766 + G12C inhibitor AMG 510 across G12C mutant NSCLC and CRC cell lines

<table>
<thead>
<tr>
<th>Cell line</th>
<th>Indication</th>
<th>Sensitivity to G12C inhibitors</th>
<th>AMG 510 + VS-6766 (H2122 KRAS G12C mt NSCLC)</th>
<th>VS-6766 + AMG 510</th>
<th>VS-6766 + MRTX849</th>
</tr>
</thead>
<tbody>
<tr>
<td>H2122</td>
<td>NSCLC</td>
<td>Moderately sensitive</td>
<td>43.9</td>
<td>46.9</td>
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<tr>
<td>H358</td>
<td>NSCLC</td>
<td>Sensitive</td>
<td>14.5</td>
<td>11.9</td>
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<tr>
<td>H2030</td>
<td>NSCLC</td>
<td>Moderately sensitive</td>
<td>12.1</td>
<td>ND</td>
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</tr>
<tr>
<td>H1373</td>
<td>NSCLC</td>
<td>Sensitive</td>
<td>9.3</td>
<td>9.6</td>
<td></td>
</tr>
<tr>
<td>SW1573</td>
<td>NSCLC</td>
<td>Insensitive</td>
<td>5</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>SW837</td>
<td>CRC</td>
<td>Sensitive</td>
<td>14.9</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>SW1463</td>
<td>CRC</td>
<td>Moderately sensitive</td>
<td>11.5</td>
<td>ND</td>
<td></td>
</tr>
</tbody>
</table>

ND: not determined

AMG 510 + VS-6766 (H2122 KRAS G12C mt NSCLC)

Synergy Score (Loewe model)

AMG 510 + VS-6766 (% change from baseline) for KRAS G12C mt NSCLC in vivo; Tumor regression in all mice with triple combination

Doses Tested
- Trametinib: 0.3 mg/kg QD
- VS-6766: 0.3 mg/kg QD
- FAKi: 50 mg/kg BID
- AMG 510: 30 mg/kg QD

Presented at RAS-Targeted Drug Development Summit (Sept 16, 2020)
We are testing VS-6766 combos with several key agents/mechanisms in KRAS G12V, G12D and G12C mt NSCLC and pancreatic cancer preclinical models

- To inform clinical directions and in-licensing efforts

Head-to-head 3D proliferation assays in progress

- Objective is to test best combinations with VS-6766 (e.g., with G12Ci) in patients
FRAME\(^1\): Focusing on Low Grade Serous Ovarian Cancer

Dr. Udae Banerji
Royal Marsden Hospital

**Phase I**

Advanced Solid Cancers

- **VS-6766 (V)** oral twice wkly x 3 wks every 4 wks
- Defactinib (D) oral BID daily x 3 wks q 4 wks
- 3 cohorts with increasing doses explored

**LGSOC\(^*\)**

Advanced NSCLC KRAS mutant\(^a\)

Advanced CRC RAS mutant\(^a\)

Advanced Solid Tumors Enriched for RAS\(^*\) (Biopsy Amenable)

---

**Patient Disposition**

<table>
<thead>
<tr>
<th>Dose Escalation: Disclosed at AACR &amp; Verastem Investor Meeting</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VS-6766/Defactinib</strong></td>
</tr>
<tr>
<td>-------------------------</td>
</tr>
<tr>
<td>Escalation</td>
</tr>
<tr>
<td>3.2mg/200mg</td>
</tr>
<tr>
<td>4.0mg/200mg</td>
</tr>
<tr>
<td>3.2mg/400mg</td>
</tr>
<tr>
<td>Biopsy</td>
</tr>
<tr>
<td>4.0mg/200mg</td>
</tr>
<tr>
<td>Expansion</td>
</tr>
<tr>
<td>4.0mg/200mg</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
</tr>
</tbody>
</table>

**RP2D dose**

Ongoing Dose Expansion cohorts; data not mature

<table>
<thead>
<tr>
<th><strong>VS-6766/Defactinib</strong></th>
<th><strong>LGSOC</strong></th>
<th><strong>NSCLC</strong></th>
<th><strong>Other</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Expansion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.2mg/200mg</td>
<td>Goal</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Apr-20</td>
<td>9</td>
<td>4(^e)</td>
</tr>
</tbody>
</table>

\(^a\) Refractory to conventional treatment or for which no conventional treatment exists

\(^b\) Includes one KRASm mucinous ovarian carcinoma

\(^c\) Non LGSOC or NSCLC phase 1 patients included to determine recommended dose or PD modeling

\(^d\) Response rate data reported for NSCLC at AACR 2020

\(^e\) Response rate data reported for NSCLC at AACR 2020; one patient not evaluable for response, included in time on treatment

\(^*\) Data not disclosed, except for one NSCLC\(^\text{G12V}\) patient as part of combined analysis

References: Banerji. AACR VM 1. April 27, 2020, CT143; Data on file

\(^1\) Investigator-initiated Phase 1 / 2 Study
### Dose Escalation Phase

<table>
<thead>
<tr>
<th>Adverse Event Details</th>
<th>VS-6766 3.2mg Def 200mg Cohort 1 n=3</th>
<th>VS-6766 4mg Def 200mg Cohort 2a n=6</th>
<th>VS-6766 3.2mg Def 400mg Cohort 2b n=3</th>
<th>Total N=46</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gr1/2</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Gr3/4</td>
<td>6</td>
<td>1</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>Rash</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>CK Elevation</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>AST Elevation</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Visual Disturbance</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>ALT Elevation</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Oral Mucositis^</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Nausea</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Peripheral Edema</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

### Dose Expansion Phase

<table>
<thead>
<tr>
<th>VS-6766 3.2mg Def 200mg Cohort 1 n=17</th>
<th>VS-6766 4mg Def 200mg Cohort 2a n=17</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gr1/2</td>
<td>19</td>
</tr>
<tr>
<td>Gr3/4</td>
<td>3</td>
</tr>
<tr>
<td>Rash</td>
<td>16</td>
</tr>
<tr>
<td>CK Elevation</td>
<td>16</td>
</tr>
<tr>
<td>AST Elevation</td>
<td>16</td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td>16</td>
</tr>
<tr>
<td>Visual Disturbance</td>
<td>16</td>
</tr>
<tr>
<td>ALT Elevation</td>
<td>16</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>16</td>
</tr>
<tr>
<td>Fatigue</td>
<td>16</td>
</tr>
<tr>
<td>Oral Mucositis^</td>
<td>16</td>
</tr>
<tr>
<td>Nausea</td>
<td>16</td>
</tr>
<tr>
<td>Peripheral Edema</td>
<td>16</td>
</tr>
</tbody>
</table>

### Treatment Related Adverse Events Occurring in ≥ 10 Patients (Total) Q4 2019 Update

**Most Adverse Events (AE) were Grade 1/2**
- All changes were reversible
- No DLTs in Cohort 1 or 2a
- DLTs Cohort 2b: Gr 2 rash in 2/3 of patients; MTD not reached
- Due to chronic Grade 2 AEs in patients on treatment > 6 months

**References:** Banerji, AACR VM 1, April 27, 2020, CT143; Data on file

*AEs were graded by NCI CTC v4; highest grade only recorded for each patient; data preliminary and subject to change; *also includes glossitis/mouth ulcers
Overcoming Key Resistance Mechanisms to MEK Inhibitors

- MEK inhibition induces compensatory activation of pFAK preclinically and clinically
  - Trametinib induced ↑ pFAK (Y397) preclinically in KRAS mt NSCLC cell lines
  - Also observed in patients
    - VS-6766 induced ↑ pFAK (Y397) as a potential resistance mechanism in the majority of patients
    - Combination with defactinib reduced this compensatory pFAK signal

References:
Banerji, BTOG Dublin, Jan 23, 2019
Banerji, AACR VM 1, April 27, 2020, CT143
Pharmacokinetic Profiles of VS-6766 + Defactinib in Combination Similar to that seen in Single Agent Studies

**VS-6766**

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Dose (mg)</th>
<th>N</th>
<th>Subject</th>
<th>AUC$_{0-24h}$ (h*ng/mL)</th>
<th>C$_{max}$ (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.2 (with 200mg VS)</td>
<td>3</td>
<td></td>
<td>Mean: 6179</td>
<td>354</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CV%: 32.1</td>
<td>30.4</td>
</tr>
<tr>
<td>2a</td>
<td>4 (with 200mg VS)</td>
<td>5</td>
<td></td>
<td>Mean: 5353</td>
<td>289</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CV%: 15.8</td>
<td>16.0</td>
</tr>
<tr>
<td>2b</td>
<td>3.2 (with 400mg VS)</td>
<td>1</td>
<td>FRA101-007</td>
<td>3302</td>
<td>229</td>
</tr>
</tbody>
</table>

**Defactinib**

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Dose (mg)</th>
<th>N</th>
<th>Subject</th>
<th>AUC$_{last}$ (h*ng/mL)</th>
<th>C$_{max}$ (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>200 (with 3.2mg RO)</td>
<td>3</td>
<td></td>
<td>Mean: 2071</td>
<td>273</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CV%: 103</td>
<td>80</td>
</tr>
<tr>
<td>2a</td>
<td>200 (with 4mg RO)</td>
<td>5</td>
<td></td>
<td>Mean: 2252</td>
<td>318</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CV%: 124</td>
<td>117</td>
</tr>
<tr>
<td>2b</td>
<td>400 (with 3.2mg RO)</td>
<td>3</td>
<td></td>
<td>Mean: 2807</td>
<td>360</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CV%: 31</td>
<td>32</td>
</tr>
</tbody>
</table>

Reference: Banerji, AACR VM 1, April 27, 2020, CT143
Efficacy – KRAS mutant NSCLC

Best response by RECIST

![Graph showing best response by RECIST for different KRAS mutations.]

**Time on treatment**

- 3 patients received treatment for 24 weeks
- Median time on treatment for this cohort was approximately 18 weeks (range 4-38 weeks)

14/20 pts enrolled in KRAS mt NSCLC cohort;
1 additional confirmed PR in KRAS-G12V mutant patient

Reference: Banerji, AACR VM 1, April 27, 2020, CT1
VS-6766 Monotherapy Active in Refractory KRAS Mutant NSCLC Adenocarcinoma

Best Response by RECIST v1.1

Progression Free Survival

Guo, et al Lancet Oncology 2020
VS-6766 Monotherapy Shows Activity Across RAS Pathway Mutations in Refractory Gynecologic Cancers

Best Response by RECIST v1.1

- G12o: LGSOC (KRAS<sup>mut</sup>)
- G12V: Endometrial (KRAS<sup>mut</sup>)
- BRAFV600E: LGSOC (BRAF<sup>mut</sup>)
- G12V: Endometrial (KRAS<sup>mut</sup>)
- G12D: LGSOC (KRAS<sup>mut</sup>)

% Change from Baseline

Progression Free Survival

- Ovarian (KRAS<sup>mut</sup>): PFS (Weeks)
- Ovarian (BRAF<sup>mut</sup>):
- Endometrial (KRAS<sup>mut</sup>):
- Ovarian (KRAS<sup>mut</sup>):
- Endometrial (KRAS<sup>mut</sup>):

Best Response

- Partial Response
- Stable Disease
- Progressive Disease

Reason Off Study

- PD

Source: Guo, et al Lancet Oncology 2020

G12o = G12D, R or S
**VS-6766 + Defactinib has a Confirmed 58% ORR in KRAS\textsuperscript{G12V} Tumors**

Best Response by RECIST in KRAS\textsuperscript{G12V} Tumors

- Endometrial (50%; N=2)
- NSCLC (57% ORR; N=7)
- OvC (66% ORR; N=3)

Time on Treatment for KRAS\textsuperscript{G12V} Tumors

- Days on Treatment

**Best Response by RECIST in KRAS\textsuperscript{G12V} Tumors**

- All PRs confirmed with subsequent scan per RECIST

 Mono = VS-6766 Monotherapy\textsuperscript{1}
 Combo = VS-6766 + Defactinib

**March 2020**

Source: \textsuperscript{1}Guo, et al Lancet Oncology 2020
Strong Patent Protection for VS-6766 ± Defactinib

- COM for VS-6766 to 2027 & defactinib to 2028, Hatch Waxman should extend to 2032
- VS-6766 intermittent dosing regimen until 2038 if granted
- FAK/MEK combination to 2035
- VS-6766/defactinib combination until 2040 if granted
- Method of manufacture for VS-6766 to 2032
- Other activity related to patent protection is ongoing and will continue into the future
Experienced Senior Management Team

Brian Stuglik  
Chief Executive Officer
- Global VP & Chief Marketing Officer – Lilly Oncology
- Founding Member – Proventus Health Solutions

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

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

Rob Gagnon  
Chief Business and Financial Officer
- CFO – Harvard Bioscience, Clean Harbors
- VP of Finance – Biogen Idec

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

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