VS-6766, a unique RAF/MEK Clamp, for treatment of KRAS mutant NSCLC

Novel combinations targeting G12V or G12C variants

Jonathan Pachter, Chief Scientific Officer
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Precision Lung Cancer Summit
Outline

• Mechanism of action of VS-6766 (RAF/MEK Clamp)
• Clinical activity of VS-6766 monotherapy in RAS/RAF mutant cancers
• VS-6766 + defactinib (FAK inhibitor) in KRAS G12V mutant NSCLC
• VS-6766 + G12Ci inhibitor in KRAS G12C mutant NSCLC
• VS-6766 + everolimus (mTOR inhibitor) in KRAS mutant NSCLC
VS-6766 is a Unique Small Molecule RAF/MEK Clamp

- VS-6766 inhibits both MEK & RAF kinase activities by trapping them in inactive complexes
- 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

References: Ishii et al., Cancer Res, 2013; Lito et al., Cancer Cell, 2014
VS-6766 is a unique RAF/MEK Clamp which induces inactive complexes of MEK with ARAF, BRAF & CRAF

Contrasting mechanism of action vs. trametinib

Deborah Morrison unpublished
VS-6766 monotherapy has shown clinical activity in several cancer indications, including NSCLC

Confirmed responses especially in patients with KRAS G12V mutation

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Change in tumour size or paraprotein concentration from baseline (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>KRAS G12V</td>
<td>NSCLC</td>
</tr>
<tr>
<td>KRAS G13D</td>
<td>Gynaecological malignancy</td>
</tr>
<tr>
<td>KRAS G12V</td>
<td>Colorectal cancer</td>
</tr>
<tr>
<td>KRAS G12V</td>
<td>Melanoma</td>
</tr>
<tr>
<td>KRAS G12V</td>
<td>Multiple myeloma</td>
</tr>
</tbody>
</table>

Guo et al., Lancet Oncology 2020
Combination of VS-6766 with FAK Inhibitor Leads to More Robust Anti-Tumor Efficacy \textit{In vivo} & Suppresses pFAK in Patients’ Tumors

VS-6766 induces pFAK in patients’ tumors

Ovarian cancer model (TOV21G KRAS mutant)

NSCLC cancer model (H358 KRAS mutant)

U. Banerji, AACR 2020
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>VS-6766 monotherapy Daily at MTD N=6 28-day cycle</td>
<td>3 (50%)</td>
<td>5 (19%)</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>RP2D VS-6766 monotherapy 4mg twice weekly N=26 28-day cycle</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RP2D (VS-6766 3.2mg twice weekly + defactinib 200mg twice daily) N=38 21 days of 28-day cycle</td>
<td></td>
<td></td>
<td></td>
</tr>
<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>
</tr>
</tbody>
</table>

Summary of FRAME Safety Profile
Most Adverse Events (AE) were Grade 1/2
Few patients have discontinued due to AEs in the study

1 Chenard-Poirier, et al. ASCO 2017
References: Banerji, Q4 2020 report; Data on file
RP2D: recommended phase 2 dosing
High Unmet Need in Refractory KRAS mt NSCLC Adenocarcinoma

NSCLC Adenocarcinoma

US Annual Incidence¹²: 92K
WW Annual Incidence¹²: 836K

KRAS Mutation

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

Advanced or Metastatic NSCL Cancer
Recommend Histologic and Molecular Subtyping⁵

- 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

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

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

Recurrence

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%

References:
¹ Globocan, 2018
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
VS-6766 Inhibits CRAF - The key driver of KRAS G12V mt 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 in vivo

VS-6766 +/- FAKi induces significant tumor regression in KRAS G12V mt NSCLC in vivo model, with clear differentiation from trametinib

- VS-6766 monotherapy caused tumor regression
- VS-6766 + FAKi showed stronger regression
- No significant anti-tumor effect of trametinib at same dose level

Reference: Coma et al. AACR 2021

Collaboration with Mariano Barbacid
Case Study: Response to VS-6766 + defactinib in a patient with KRAS G12V mutant NSCLC

May 2019: Diagnosed with NSCLC

June 2019 - Sept 2019: Treated with first line Carboplatin + Pemetrexed + Pembrolizumab

Oct 2019: Progression, palliative RT to right hip

Nov 2019 – present: On treatment in FRAME study VS-6766 + Defactinib

Reference: Krebs et al. AACR 2021
Strong Signal Identified in KRAS G12V NSCLC

VS-6766 ± Defactinib Has a Confirmed 57% ORR in KRAS G12V mt NSCLC in Integrated Analysis

Best Response by RECIST in KRAS G12V mt NSCLC

NSCLC (57% ORR; N=7)

-80 -70 -60 -50 -40 -30 -20 -10 0 10 20 30 40 50

Best Response (% change from baseline)

Mono: VS-6766 monotherapy
Combo: VS-6766 + Defactinib

-80 -70 -60 -50 -40 -30 -20 -10 0 10

Time on Treatment for KRAS G12V mt NSCLC

Weeks on treatment

Mono: VS-6766 monotherapy
Combo: VS-6766 + Defactinib

-4.0 mg VS-6766/200 mg defactinib
* Continuing on treatment


- Preclinical evidence suggests combination with Defactinib may improve efficacy in KRAS G12V mt NSCLC
- Activity of VS-6766 as a single agent and in combo with Defactinib in KRAS G12V mt NSCLC
RAMP 202: Registration-directed Phase 2 Trial of VS-6766+/- Defactinib in KRAS Mutant (mt), G12V Enriched Advanced NSCLC

Selection Phase
- Defactinib+VS-6766\(^1\)
  - KRAS mt G12V
  - N=16
- VS-6766\(^2\)
  - KRAS mt G12V
  - N=16

Expansion Phase
- KRAS Mutant – G12V
  - Selected Regimen based on ORR
- KRAS Mutant – non-G12V
  - Exploratory mutation-specific cohort analyses for ORR

• Advanced 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

This Registration-directed Phase 2 Study commenced December 2020 with an estimated Primary Completion Date for the Expansion Phase of March 2023 (NCT04620330)

References:
\(^1\) 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)
Preclinical synergy of VS-6766 + G12C inhibitors in KRAS G12C mt models

Synergy of VS-6766 + G12C inhibitor AMG 510 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>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>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

VS-6766 + AMG 510 yields deeper and more sustained inhibition of ERK signaling pathway

H2122 KRAS G12C mutant NSCLC

Concentrations Tested
AMG 510: 100 nM
VS-6766: 100 nM

Response: Coma et al., AACR 2021
Acquired resistance mechanisms to KRAS G12Ci treatment in patients further support combination of KRAS G12Ci with VS-6766

Summary of Putative Mechanisms of Acquired Resistance to Adagrasib Treatment

- Mechanisms of acquired resistance to KRAS G12Ci adagrasib treatment in patients recently reported\(^1,2\)
- The main resistance alterations occurred in
  - RTK mts or amplifications
  - KRAS mts or amplification
  - NRAS mt
  - BRAF V600E mt, BRAF or CRAF fusions
  - MAP2K1 (MEK1) mt/deletion
- VS-6766 is expected to be effective against these KRAS, NRAS, BRAF and CRAF modifications

VS-6766 inhibits cell proliferation across multiple MAPK pathway alterations and multiple solid tumor indications

Reference: Pachter RAS-Targeted Drug Discovery, Sep 2021 3D proliferation assay
RAMP 203: Phase 1/2 Trial of VS-6766 + LUMAKRAS™ (sotorasib) in KRAS G12C-mutated advanced NSCLC

- Patients must have known G12C KRAS 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

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

**Part B: Dose Expansion at RP2D (Primary endpoint ORR)**

Cohort 1
- Patients without Prior KRAS G12C Inhibitor Treatment
- Stage 1: ~20 patients
- Stage 2: expand

Cohort 2
- Patients whose NSCLC Progressed on KRAS G12C Inhibitor Treatment
- Stage 1: ~20 patients
- Stage 2: expand

VS-6766 + Sotorasib Dose Finding Cohorts (N= 3-6 pts)

RP2D Selection

Part A (Dose Evaluation) portion of study expected to be initiated in 1Q 2022 (NCT05074810)
Combination of VS-6766 with Everolimus (mTOR inhibitor) now being evaluated in patients with KRAS mt NSCLC

Resistance to MAPK pathway blockade can occur through PI3K/AKT/mTOR pathway activation and this can be overcome by dual MAPK-PI3K pathway inhibition

VS-6766 + Everolimus are synergistic across multiple KRAS mutant NSCLC models

A well-tolerated RP2D for VS-6766 + everolimus has been established with intermittent dosing of both agents (twice weekly; 3 wks on/1 wk off)

KRAS mutant NSCLC expansion cohort is currently ongoing with VS-6766 + everolimus

**PI:** Udai Banerji, Institute of Cancer Research, UK
Conclusions: VS-6766 as potential backbone of therapy for KRAS mutant NSCLC

• For KRAS G12V mt NSCLC
  • VS-6766 ± FAKi induces tumor regression in KRAS G12V mt NSCLC genetically engineered mouse model: Consistent with the strong dependence of KRAS G12V mt NSCLC on CRAF
  • VS-6766 ± defactinib has elicited confirmed responses in patients with KRAS G12V mt NSCLC (4/7 pts; 57% ORR)
  • A registration-directed trial of VS-6766 ± defactinib is ongoing with focus on recurrent KRAS G12V mt NSCLC (NCT04620330)

• For KRAS G12C mt NSCLC
  • Preclinical synergy of VS-6766 with G12C inhibitors across KRAS G12C mt cell lines correlates with deeper/sustained pERK inhibition and tumor regressions in KRAS G12C mt NSCLC xenograft models
  • Clinical data show that acquired resistance to G12Ci in patients with KRAS G12C mt NSCLC is largely mediated by additional RAS and/or RAF mutations – predicted to be sensitive to VS-6766
  • Working with Amgen & Mirati to assess clinical combination of VS-6766 with sotorasib or adagrasib in KRAS G12C NSCLC

• For other KRAS mutations
  • A cohort is currently ongoing testing a RP2D of VS-6766 + everolimus (mTOR inhibitor) in patients with KRAS mutant NSCLC
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Thanks for your attention!