The selective ERK inhibitor BVD-523 is active in models of MAPK pathway-dependent cancers, including those with intrinsic and acquired drug resistance

Ursula Germann1, Brinley Furey2, Jeff Roix3, William Markland2, Russell Hoover2, Alex Aronov2, Michael Hale4, Guanjing Chen5, Gabriel Martinez-Botella6, Rossitza Alargova7, Bin Fan8, David Sorrell9, Kay Meshaw10, Paul Shapiro11, Michael J. Wick12, Cyril Benes13, Mathew Garnett14, Gary DeCrescenzo15, Mark Namchuk16, Saurabh Saha15, Dean J. Welsch15.

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Dr. Dean J. Welsch

I have the following financial relationship to disclose:
Employee of BioMed Valley Discoveries

I will not discuss off label use and/or investigational use in my presentation
MAPK pathway mutations causally drive many cancers.

- 3 MAPK drugs are approved but limited by intrinsic and acquired resistance.

- ERK inhibition has the potential to overcome or avoid resistance from upstream mutations.
BVD-523 Executive Summary

- Highly potent, selective and reversible ATP-competitive ERK1 and ERK2 inhibitor
- Tumor growth regression in BRAF- and KRAS-mutant xenograft models
- Single agent inhibition of a patient-derived xenograft cross-resistant to BRAFi and MEKi
- Phase 1 dose escalation completed with expansion cohorts in progress
BVD-523 (ulixertinib): A Potent & Selective ERK Inhibitor

Highly potent
• ERK1 $K_i < 300$ pM
• ERK2 $K_i = 40$ pM

Highly selective
• $\geq 1,000$-fold vs CDK1, CDK2, CDK5, CDK6, GSK3b
• $\geq 10,000$-fold vs 70 other kinases
MGH/Wellcome Genomics of Drug Sensitivity in Cancer Panel

Proliferation
IC50 [μM]

0.01
0.10
1
10
100

MAPK mut.

MAPK wt
BVD-523 Mechanism of Action and Enzyme Binding

Mechanism of Action

RTKs ➔ RAS ➔ RAF ➔ MEK ➔ ERK ➔ RSK

Enzyme: BVD-523 Binding

Differential Scanning Fluorimetry

BVD-523 (µM)

0 0.5 2

RKO (BRAF V600E) Colorectal Cancer Cell Line

MEK1/2

p*S217/S221

ERK1/2

p*T202/Y204

RSK1/2

p*T359/S363

ppERK2

ERK2

p38α

BVD-523 (µM)

0 0.01 0.1 1 10

ppERK2

ERK2

p38α
BVD-523 Anti-tumor Activity in Multiple In Vivo Cancer Models

• Single agent activity in xenografts with
  - BRAF mutation (Colo205 CRC, A375 Mel)
  - RAS mutation (MiaPaCa2 Panc)

• At least additive with other MAPK inhibitors
Response Correlates with Tumor PK and Dose

pERK Levels Correlate with Tumor PK - Timecourse

[pERK/Total ERK (%)]

<table>
<thead>
<tr>
<th>Time Post Dose (hrs)</th>
<th>pERK Levels Correlate with Tumor PK - Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0 hr post-dose</td>
</tr>
<tr>
<td>1</td>
<td>1 hr post-dose</td>
</tr>
<tr>
<td>3</td>
<td>3 hr post-dose</td>
</tr>
<tr>
<td>8</td>
<td>8 hr post-dose</td>
</tr>
<tr>
<td>16</td>
<td>16 hr post-dose</td>
</tr>
<tr>
<td>24</td>
<td>24 hr post-dose</td>
</tr>
</tbody>
</table>

Dose (mpk, P.O.)

- 0
- 25
- 50
- 75
- 100

100 mpk, P.O.

[BVD-523] Tumor (ng/mL)
RSK1/2 Phosphorylation as a BVD-523 Activity Clinical Biomarker

RSK1/2 is a substrate for ERK phosphorylation

BVD-523 inhibits RSK1/2 phosphorylation using an ex vivo human whole blood assay
BVD-523 inhibits ERK activity following oral dosing in canine GLP tox study

<table>
<thead>
<tr>
<th>Dose (mg/kg, BID)</th>
<th>ERK Inhibition (%)</th>
<th>BVD-523 Conc. (uM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>53</td>
<td>0.23</td>
</tr>
<tr>
<td>5</td>
<td>64</td>
<td>0.92</td>
</tr>
<tr>
<td>15</td>
<td>94</td>
<td>3.2</td>
</tr>
</tbody>
</table>

- Human and canine whole blood ERK activity assays established
- BVD-523 demonstrated significant ERK inhibition with chronic oral dosing in canine GLP toxicity study at tolerated doses, exposures
- ERK activity assay supporting clinical studies
BVD-523 Effective in Models of Acquired Resistance to BRAF and MEK Inhibitors

BVD-523 potency retained in cells cross-resistant to BRAFi & MEKi

<table>
<thead>
<tr>
<th>Cell Line</th>
<th>Dabrafenib</th>
<th>Trametinib</th>
<th>BVD-523</th>
<th>Paclitaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parental</td>
<td>2.1</td>
<td>0.2</td>
<td>129</td>
<td>1.9</td>
</tr>
<tr>
<td>BRAFi + MEKi-Resistant</td>
<td>17.9</td>
<td>2.7</td>
<td>323</td>
<td>4.7</td>
</tr>
<tr>
<td>Fold Increase</td>
<td>8.5</td>
<td>13.5</td>
<td>2.5</td>
<td>2.5</td>
</tr>
</tbody>
</table>
**BVD-523 Effective in Xenografts Derived from a Patient Who progressed on BRAF Inhibitor**

**BVD-523 sensitivity in patient-derived xenograft model**

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Intrinsic BRAFi Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle</td>
<td>Vemurafenib</td>
</tr>
<tr>
<td>Tumor Volume (mm$^3$)</td>
<td>0 7 14 21 28</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Post-Progression</th>
<th>BRAFi &amp; MEKi Insensitivity</th>
<th>ERKi Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle</td>
<td>Vemurafenib</td>
<td>Vehicle</td>
</tr>
<tr>
<td>Tumor Volume (mm$^3$)</td>
<td>0 7 14</td>
<td>0 7 14 21</td>
</tr>
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</table>

**Tumors that escape BRAFi and MEKi may remain sensitive to ERKi**
Safety Pharmacology

- No significant interaction in in vitro screens against 65 receptors, transporters, and ion channels
- Exhibited no significant genetic toxicology risks in reverse mutation and micronucleus assays
- Inhibits the hERG current ($\text{IC}_{50}$ 3.4 uM)
- Dog Purkinje fiber assays revealed no significant effects up to 10 ug/mL

Metabolism

- Recombinant human CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 capable of metabolizing BVD-523
- Metabolism predominantly via oxidation and de-alkylation
- Metabolic profile of BVD-523 across mouse, rat, dog, and human liver microsomes and hepatocytes very similar (monkey was unique in its metabolic profile)
- Rat & dog identified as appropriate species for toxicological evaluation

GLP Toxicity Studies

- No CV findings observed following 28 days of dosing with BVD-523
- 28-day studies, with reversal arms, conducted at doses ranging from 25-100 mg/kg/day and 4-30 mg/kg/day in rat and dog, respectively

Target Tissue Toxicities

- Findings are dose-dependent, and at least partially reversible
- Rat: tissue mineralization, skin lesions/rash
- Dog: gastrointestinal
- All toxicities consistent with MAPK pathway inhibitors, further demonstrating the exquisite selectivity of BVD-523

Starting Dose Justification

- Rat identified as most sensitive species
- Supported first-in-human starting dose of 10 mg, BID
BVD-523 Clinical Development Plan – Ongoing Studies

**Current Status**

**BVD-523 Clinical Development Plan – Ongoing Studies**

**Group 1:** BRAF V600E/K mutant melanoma, inhibitor naive

**Group 2:** BRAF non-V600E/K mutant melanoma, inhibitor naive

**Group 3:** BRAF mutant melanoma, progressed/refractory to BRAFi &/or MEKi

**Group 4:** NRAS mutant melanoma, inhibitor naive

**Group 5:** MEK mutant cancers, inhibitor naive

**Group 6:** BRAF mutant NSCLC, inhibitor naive

**Accelerated Dose Titration** (1 pt per cohort)

**FIH** (10 mg, BID)

**> Grade 2 Related AE**

**Solid Tumor RP2D**

**Standard “3 + 3” Dose Escalation**

**Advanced Solid Tumor Protocol (NCT01781429)**

**Group 1:** BRAF V600E/K mutant melanoma, inhibitor naive

**Group 2:** BRAF non-V600E/K mutant melanoma, inhibitor naive

**Group 3:** BRAF mutant melanoma, progressed/refractory to BRAFi &/or MEKi

**Group 4:** NRAS mutant melanoma, inhibitor naive

**Group 5:** MEK mutant cancers, inhibitor naive

**Group 6:** BRAF mutant NSCLC, inhibitor naive

**Advanced Solid Tumor Protocol (NCT01781429)**

**Acute Myelogenous Leukemia or Myelodysplastic Syndromes Protocol (NCT02296242)**

**Group 1:** AML/MDS w/o RAS mutation

**Group 2:** AML/MDS w/ RAS mutation

**AML/MDS RP2D**

**Solid Tumor RP2D X 0.5**

**Standard “3 + 3” Dose Escalation**
Possible Protocols

- BVD-523 + BRAFi, MEKi, or BRAFi & MEKi
- BVD-523 + BRAFi, MEKi, or BRAFi & MEKi after acquired resistance
- BVD-523 + non-MAPK pathway targeted agents
- BVD-523 + immune response modulators
- BVD-523 + chemotherapeutics
- BVD-523 + ???
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