A First-in-class Phase 1 Dose-escalation Study of the Novel Oral ERK 1/2 Kinase Inhibitor BVD-523 (ulixertinib) in Patients with Advanced Solid Tumors

I have no personal financial relationship to disclose
Targeting the MAPK pathway

- MAPK pathway mutations causally drive many cancers
- RAF and MEK inhibitors are approved but limited by intrinsic and acquired resistance
- ERK inhibition has the potential to overcome or avoid resistance from upstream mutations

• BVD-523: Highly potent, selective and reversible ATP-competitive ERK1/2 inhibitor
BVD-523 (ulixertinib): A Potent & Selective ERK Inhibitor

**Highly potent**
- ERK1 $K_i < 300$ pM
- ERK2 $K_i = 40$ pM

**Highly selective**
- $> 1,000$-fold vs CDK1, CDK2, CDK5, CDK6, GSK3b
- $> 10,000$-fold vs 70 other kinases

- Tumor growth regression in BRAF and KRAS-mutant xenograft models
- Single agent inhibition in patient-derived xenograft models cross-resistant to BRAFi and MEKi
BVD-523: Patient-derived Xenografts that Progressed on BRAF and MEK Inhibitors

Tumors that escape BRAFi and MEKi may remain sensitive to ERKi
RSK1/2 Phosphorylation as a BVD-523 Activity Clinical Biomarker

BVD-523 inhibits RSK1/2 phosphorylation using an ex vivo human whole blood assay

EC$_{50}$ ~450 nM (200 ng/mL)
BVD-523: FIH Study Objectives

**Primary objective:** To define the safety and tolerability of BVD-523, the maximum tolerated dose (MTD), and the recommended Phase 2 Dose (RP2D).

**Secondary objectives:** To determine the pharmacokinetic profile of BVD-523 and selected metabolites. To investigate any preliminary clinical efficacy.

**Exploratory objective(s):** To evaluate pharmacodynamic marker (biomarker) measures. To investigate any preliminary clinical effects on tumor response assessed by FDG-PET as indicated.
Study Design: Dose Escalation Phase

First-in-human starting dose
(10 mg, BID)

Accelerated
Dose Titration
(1 patient per cohort)

> Grade 2
Related AE

Recommended Phase 2 Dose

Standard
“3 + 3”
Dose Escalation

- PK collection, pre-dose through 12 hours post-dose, on Days 1 and 15
- PD collection, at pre-dose and 4 hours post-dose, on Days 1 and 15
BVD-523: Key Eligibility

• **Inclusion Criteria**
  – Patients with metastatic or advanced-stage malignant tumor, for whom no therapy exists that would be curative
  – ECOG performance status of 0 or 1
  – Adequate renal, hepatic, bone marrow, and cardiac function

• **Exclusion Criteria**
  – A history or current evidence/risk of retinal vein occlusion or central serous retinopathy
  – Concurrent therapy with drugs known to be strong inhibitors of CYP1A2, CYP2D6, and CYP3A4, or strong inducers of CYP3A4
BVD-523: Dose-Limiting Toxicity Criteria

- BVD-523 related toxicity in the first 21 days (Cycle 1) of treatment
  - ≥ Grade 4 hematologic toxicity > 1 day
  - Grade 3 hematologic toxicity with complications
  - ≥ Grade 3 non-hematologic toxicity (except untreated nausea, vomiting, constipation, pain and rash unless they persist with adequate treatment), including a doubling of AST/ALT in patients with grade 2 ALT/AST at baseline
  - A treatment interruption exceeding 5 days (or > 7 days for rash, despite adequate treatment) in Cycle 1 (or inability to begin Cycle 2 for ≥ 7 days) due to BVD-523-related toxicity
## BVD-523: Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All Patients (n=27)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Age (yr), median (range)</strong></td>
<td>61 (33-86)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>13</td>
</tr>
<tr>
<td>Male</td>
<td>14</td>
</tr>
<tr>
<td><strong>ECOG Performance Status (Initial)</strong></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>10 (37)</td>
</tr>
<tr>
<td>1</td>
<td>17 (63)</td>
</tr>
<tr>
<td><strong>Tumor Types</strong></td>
<td></td>
</tr>
<tr>
<td>Melanoma</td>
<td>8 (30)</td>
</tr>
<tr>
<td>BRAF mt</td>
<td>7</td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
</tr>
<tr>
<td>Colorectal Cancer</td>
<td>5 (18)</td>
</tr>
<tr>
<td>Papillary Thyroid Cancer</td>
<td>4 (15)</td>
</tr>
<tr>
<td>Non-small Cell Lung Cancer</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Others*</td>
<td>8 (30)</td>
</tr>
<tr>
<td><strong>Prior Systemic Therapy</strong></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1 (4)</td>
</tr>
<tr>
<td>1</td>
<td>2 (7)</td>
</tr>
<tr>
<td>2-3</td>
<td>11 (41)</td>
</tr>
<tr>
<td>&gt;3</td>
<td>13 (48)</td>
</tr>
</tbody>
</table>

*2 Pancreatic, 1 Appendiceal, 1 NSGCT, 1 Ovarian, 3 Unknown
**BVD-523: Dose Escalation and DLT**

**Dose-limiting Toxicities in Cycle 1 (21 days)**

<table>
<thead>
<tr>
<th>Dose (mg, BID)</th>
<th>DLT Frequency (%)</th>
<th>DLT Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>0/1</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>0/1</td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>0/1</td>
<td></td>
</tr>
<tr>
<td>75</td>
<td>0/1</td>
<td></td>
</tr>
<tr>
<td>150</td>
<td>0/1</td>
<td></td>
</tr>
<tr>
<td>300</td>
<td>0/4</td>
<td></td>
</tr>
<tr>
<td>600</td>
<td>1/7 (14)</td>
<td>• Rash G3</td>
</tr>
</tbody>
</table>
| 750*          | 2/4 (50)          | • Rash G3, diarrhea G2  
• Hypotension G2, elevated creatinine G2, anemia G2, delay to cycle 2 dosing |
| 900           | 2/7 (29)          | • Pruritis G3, elevated AST G3  
• Diarrhea G3, vomiting G3, dehydration G3, elevated creatinine G3 |

* Intermediate dose

**MTD defined as 600 mg po BID continuously**
## Adverse Events Possibly Related/Related to BVD-523 in ≥ 10% of Patients

**Analysis cut-off date of 13 March 2015**

<table>
<thead>
<tr>
<th>Category</th>
<th>All Patients (N=27)</th>
<th>All Grade (%)</th>
<th>Grade 1/2</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood and Lymphatic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>5 (18)</td>
<td>3</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>3 (11)</td>
<td></td>
<td>3</td>
<td></td>
</tr>
<tr>
<td><strong>Diarrhea</strong></td>
<td>14 (52)</td>
<td>12</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>14 (52)</td>
<td>14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>8 (30)</td>
<td>7</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td><strong>General</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral Edema</td>
<td>5 (18)</td>
<td></td>
<td>5</td>
<td></td>
</tr>
<tr>
<td><strong>Fatigue</strong></td>
<td>16 (59)</td>
<td>15</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>3 (11)</td>
<td></td>
<td>3</td>
<td></td>
</tr>
<tr>
<td><strong>Laboratory Values</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased Creatinine</td>
<td>5 (18)</td>
<td>4</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Increased LFTs (ALT/AST)</td>
<td>4 (15)</td>
<td>1</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td><strong>Metabolism and Nutrition</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anorexia</td>
<td>6 (22)</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Dehydration</td>
<td>4 (15)</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td><strong>Ophthalmological</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blurry/Dimmed Vision</td>
<td>3 (11)</td>
<td></td>
<td>3</td>
<td></td>
</tr>
<tr>
<td><strong>Skin and Subcutaneous</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erythema Multiforme</td>
<td>3 (11)</td>
<td></td>
<td>3</td>
<td></td>
</tr>
<tr>
<td><strong>Rash</strong></td>
<td>19 (70)</td>
<td>17</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Pruritis</td>
<td>6 (22)</td>
<td></td>
<td>6</td>
<td></td>
</tr>
</tbody>
</table>
BVD-523: Pharmacokinetics (Cycle 1 Day 15)

- BVD-523 is absorbed slowly, \( T_{\text{max}} \) 2 – 4 hours post dose
- \( C_{\text{max}} \) and AUC generally dose related, up to 600 mg BID
- Moderate accumulation in plasma (1.3 to 4.0 fold at doses >75 mg BID)
- Moderate inter-patient variability.
BVD-523: Pharmacodynamic inhibition of ERK substrate phosphorylation

Concentration-dependent inhibition of ERK activity in whole blood; ≥80% target inhibition at tolerated doses/exposures

Day 15 Trough Data

Avg ± Std Dev
(no error bars n < 2)
BVD-523: Pharmacodynamic / Radiographic Response

- Metabolic response observed by FDG-PET in 5/16 evaluable patients

- Patient: 61 y/o V600E BRAF mutant melanoma
  - Post-vemurafenib & dabrafenib progression
  - Confirmed CT Partial Response on BVD-523, on-study > 500 days
BVD-523: Radiographic Response

Note: All patients with disease measured by RECIST v1.1 who received ≥ 1 dose of study treatment and had > 1 on-treatment tumor assessment (n=25 of 27; 2 did not receive both scans of target lesions)

* Evaluated with calipers
Analysis cut-off date of 13 March 2015

BVD-523: Duration on Study

Melanoma; BRAF V600E; Refractory

Off-study: PD
Off-study: other
Partial Response

10 mg BID
20 mg BID
40 mg BID
75 mg BID
150 mg BID
300 mg BID
450 mg BID
600 mg BID
750 mg BID
900 mg BID

NSCLC/ERCC1
Appendiceal/KRAS

PTC/BRAF
Ovarian/KRAS

Melanoma; BRAF V600K; BRAF/MEK Inhibitor naïve

Melanoma; BRAF V600E; Intolerant to other BRAF/MEK Inhibitors

100 days
200 days
300 days
400 days
500 days
600 days
700 days

Melanoma

18

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Conclusions

- BVD-523 showed manageable tolerability in 27 patients with solid tumors
- The MTD and preliminary RP2D is 600 mg BID
- PK was generally linear and dose-dependent up to 600 mg BID
- In patients’ peripheral blood, phosphorylation of the ERK substrates RSK1/2 was shown to be inhibited at doses ≥75 mg BID
- 3 PR and 7 SD >3 months
**BVD-523 Clinical Program**

**Accelerated Dose Titration**
- FIH (10 mg, BID)
- > Grade 2 Related AE

**Standard “3 + 3” Dose Escalation**

**Solid Tumor RP2D**

**Advanced Solid Tumor Protocol (NCT01781429)**

- **Group 1:** BRAF mutant cancers (except CRC and NSCLC), inhibitor naïve
- **Group 2:** BRAF mutant CRC, inhibitor naïve
- **Group 3:** BRAF mutant melanoma, progressed/refractory to BRAFi &/or MEKi
- **Group 4:** NRAS mutant melanoma, inhibitor naïve
- **Group 5:** MEK mutant cancers, inhibitor naïve
- **Group 6:** BRAF mutant NSCLC, inhibitor naïve

**Current Status**
- **Enrollment to Date**
  - Dose Escalation: n=27, complete
  - Cohort Expansion: n=21, ongoing
Thank You to the patients and their families

Howard A Burris
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Michael Shearer
Melissa Rivera

Anthony W. Tolcher
Amita Patnaik
Kyri Papadopoulos

Johanna C. Bendell
Manish R. Patel
Terri Peterson
Michael Shearer
Melissa Rivera

Howard A Burris
Todd Bauer
Johanna C. Bendell
Manish R. Patel
Terri Peterson
Michael Shearer
Melissa Rivera

Key Partners

Washington University in St. Louis
Andrea Wang-Gillam
Craig Lockhart
Rebecca Nieman

Vanderbilt University Medical Center
Jeffrey Alan Sosman
Jordan Berlin
Igor Puzanov

Yale Cancer Center
Mario Szol
Harriet Kluger

Massachusetts General Hospital
Keith Flaherty
Ryan J. Sullivan
Rebecca Heist

Biomed Valley
Amanda Collins, Gary DeCresenzo, Anna Groover, Maria Miller, Saurabh Saha, Mary Varterasian, Dean Welsch

Key Partners

Amanda Collins, Gary DeCresenzo, Anna Groover, Maria Miller, Saurabh Saha, Mary Varterasian, Dean Welsch

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