PHASE 2 NEOADJUVANT STUDY OF VS-6063, A FAK INHIBITOR, IN SUBJECTS WITH SURGICALLY RESECTABLE MALIGNANT PLEURAL MESOTHELIOMA

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The International Mesothelioma Program
Conflicts and Support

• Peer Reviewed Funding
  • NCI (RO1 CA120528)

• Industry Funding:
  • Castle Biosciences
  • Genentech
  • HTG
  • Merck
  • Novartis
  • Siemens
  • Verastem

• Patents and licenses:
  • Castle Biosciences
Defactinib (VS-6063) Window of Opportunity: Neo-adjuvant Proof of Mechanism (POM) study in malignant mesothelioma

**Assessments**
- Biological proof of mechanism evaluated in all cohorts by biomarkers in paired tumor biopsies
- Tumor response evaluated in all cohorts by PET/CT

**Trial status**
- **Cohort 1 (12 days treatment):** Complete (10 patients enrolled, reported at iMig 2014)
- **Cohort 2 (35 days treatment):** Complete (10 patients enrolled)
Cohort 1: Tumor response in newly diagnosed MPM patients following 12 days of treatment with defactinib

PET/CT performed to guide biopsy
Tumor response assessed using RECIST modified for mesothelioma

Source: Bueno et al., iMig 2014
Early signs of favorable immunomodulation in Cohort 1: Defactinib treatment increases CD8+ T cells and decreases exhaustion markers PD-1 & LAG-3

<table>
<thead>
<tr>
<th>Preclinical</th>
<th>Clinical – Cohort 1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SCC 7.1 tumors</strong></td>
<td><em>Mesothelioma patients treated with VS-6063</em></td>
</tr>
<tr>
<td>CD8+ T cells</td>
<td></td>
</tr>
<tr>
<td><strong>Fold change</strong></td>
<td></td>
</tr>
<tr>
<td>FAK WT</td>
<td>FAK -/-</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PD-1+ LAG-3+ cells</th>
<th>Mean RNA expression (3 patients, 12 days treatment)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>% Memory T cells</strong></td>
<td><strong>Normalized expression</strong></td>
</tr>
<tr>
<td>(CD8+ CD44^hi)</td>
<td>Pre</td>
</tr>
</tbody>
</table>

Bueno, iMig 2016
The composition of the tumor microenvironment is highly variable in mesothelioma: Could this lead to variability in tumor response to treatment?

- The mesothelioma patient population has a wide range of tumor immune cells prior to treatment
- Favorable modulation of tumor immune cells may lead to tumor regression
- High variability in baseline mesothelioma tumor microenvironment may result in variability to response to immune-modulating agents

**Flow Cytometry Analysis on surgical tumor samples from untreated mesothelioma patients**

- % CD3+ T cells
- % CD19+ B cells
- % CD56+ NK cells
- % CD33+ Monocytes
- % CD66b+ Granulocytes
- % CD123+ Dendritic cells

**Cases ordered by increasing numbers of T cells**

Source: Belfer Institute
Comparable patient demographics were maintained in expansion to Cohort 2

<table>
<thead>
<tr>
<th>Patients</th>
<th>400 mg defactinib BID</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cohort 1 (n = 10)</td>
<td>Cohort 2 (n = 10)</td>
<td>Total N = 20</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>8 (80%)</td>
<td>8 (80%)</td>
<td>16 (80%)</td>
</tr>
<tr>
<td>Female</td>
<td>2 (20%)</td>
<td>2 (20%)</td>
<td>4 (20%)</td>
</tr>
<tr>
<td>Median age, years (range)</td>
<td>71 (55-83)</td>
<td>66.5 (47 – 78)</td>
<td>70 (47 – 83)</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epithelial</td>
<td>4 (40%)</td>
<td>7 (70%)</td>
<td>11 (55%)</td>
</tr>
<tr>
<td>Biphasic</td>
<td>2 (20%)</td>
<td>3 (30%)</td>
<td>5 (25%)</td>
</tr>
<tr>
<td>Sarcomatoid</td>
<td>4 (40%)</td>
<td>0 (0%)</td>
<td>4 (20%)</td>
</tr>
<tr>
<td>ECOG</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>7 (70%)</td>
<td>8 (80%)</td>
<td>15 (75%)</td>
</tr>
<tr>
<td>1</td>
<td>3 (30%)</td>
<td>2 (20%)</td>
<td>5 (25%)</td>
</tr>
</tbody>
</table>

Unlocked, in progress data as of 14Mar2016
Defactinib continues to be well tolerated across Cohorts 1 and 2

<table>
<thead>
<tr>
<th>Treatment Emergent Adverse Event, ≥ 10%</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
<th>Total (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnoea</td>
<td>9 (45.0)</td>
<td>1 (5.0)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>10 (50.0%)</td>
</tr>
<tr>
<td>Blood bilirubin increased</td>
<td>4 (20.0)</td>
<td>2 (10.0)</td>
<td>1 (5.0)</td>
<td>-</td>
<td>-</td>
<td>7 (35.0%)</td>
</tr>
<tr>
<td>Cough</td>
<td>7 (35.0)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>7 (35.0%)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>6 (30.0)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>6 (30.0%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>5 (25.0)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>5 (25.0%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>4 (20.0)</td>
<td>1 (5.0)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>5 (25.0%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>3 (15.0)</td>
<td>1 (5.0)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>4 (20.0%)</td>
</tr>
<tr>
<td>Headache</td>
<td>2 (10.0)</td>
<td>2 (10.0)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>4 (20.0%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>-</td>
<td>2 (10.0)</td>
<td>2 (10.0)</td>
<td>-</td>
<td>-</td>
<td>4 (20.0%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3 (15.0)</td>
<td>1 (5.0)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>4 (20.0%)</td>
</tr>
<tr>
<td>Back pain</td>
<td>1 (5.0)</td>
<td>2 (10.0)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3 (15.0%)</td>
</tr>
<tr>
<td>Hyperhidrosis</td>
<td>3 (15.0)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3 (15.0%)</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>3 (15.0)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3 (15.0%)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>3 (15.0)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3 (15.0%)</td>
</tr>
<tr>
<td>Abdominal distension</td>
<td>2 (10.0)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2 (10.0%)</td>
</tr>
<tr>
<td>Abdominal pain upper</td>
<td>2 (10.0)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2 (10.0%)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>1 (5.0)</td>
<td>1 (5.0)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2 (10.0%)</td>
</tr>
<tr>
<td>Musculoskeletal chest pain</td>
<td>1 (5.0)</td>
<td>1 (5.0)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2 (10.0%)</td>
</tr>
<tr>
<td>Oroparyngeal pain</td>
<td>2 (10.0)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2 (10.0%)</td>
</tr>
<tr>
<td>Tumour pain</td>
<td>1 (5.0)</td>
<td>1 (5.0)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2 (10.0%)</td>
</tr>
</tbody>
</table>
Early tumor response seen in Cohort 1 is continued in Cohort 2, consisting of an additional 10 patients treated with defactinib for 35 days prior to surgery.

Tumor regression after 12 days (Cohort 1) or 35 days (Cohort 2) of treatment:

- PET/CT performed to guide biopsy
- Tumor response assessed using RECIST modified for mesothelioma
- Unlocked, in progress data as of 14Mar2016

Bueno, iMig 2016
Modified RECIST
Decrease of 36%

SUV max
Decrease of 69%

Tumor Volume
Decrease of 365cc3
Higher stromal/immuno-suppressive tumors (by ESTIMATE score) correlate with greater tumor reduction following defactinib treatment in Cohorts 1 and 2.

Epithelial mesothelioma patients in Cohorts 1 & 2

![Graph showing correlation between Pre-Treatment ESTIMATE Score and Tumor change (% baseline)](image)

- $R^2 = 0.751$

(High score reflects high baseline stromal/immuno-suppressive environment)

Estimation of Stromal and Immune cells in Malignant Tumours using Expression data [Yoshihara et al., Nature Commun. 2013]

Bueno, iMig 2016
IL-10 decreases are seen in Cohorts 1 and 2, suggesting further favorable modulation of an immuno-suppressive environment by defactinib treatment.

- Circulating IL-10 measured in matched samples at baseline and day 12 on therapy.
- IL-10 (pro-tumor) cytokine shows significant decrease at day 12 on therapy.
Summary and Next Steps

- Defactinib treatment in neoadjuvant setting is generally well-tolerated with mostly Grade 1/2 adverse events.
- Six out of 20 patients demonstrate an encouraging tumor reduction after brief treatment with defactinib in this uncontrolled pilot study.
- High baseline stromal/tumor immunosuppression may be associated with tumor reduction after defactinib treatment:
  - FAK pathways may influence stromal and tumor immune microenvironments.
- Changes in immune modulation markers and immune cells are associated with defactinib treatment:
  - CD8+ T cell influx
  - Decrease of exhaustion markers in tumor (PD-1, LAG3)
  - IL-10 (immunosuppressive cytokine) reduction in plasma
- Further evaluation of immune and stromal populations is warranted; Study is continuing with third Cohort (n=10 patients) with collection of tumor tissue for Flow Cytometry.
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TCGA
NCI (Schrump)