Rebastinib, a selective TIE2 kinase inhibitor, decreases TIE2-expressing macrophages, reduces metastasis, and increases survival in murine cancer models.
REBASTINIB: FIRST-IN-CLASS TIE2 KINASE INHIBITOR

Rebastinib is a small molecule potent inhibitor of TIE2 kinase

TIE2 expression largely restricted to endothelial cells and subsets of monocytes/macrophages

Interest in TIE2 microenvironment mechanisms:
  o effects on tumor vascularization (angiogenic switching)
  o effects on tumor invasion/dissemination/metastasis
  o effect on tumor immunotolerance

A Phase 1 study in metastatic solid tumors in combination with approved agents is planned for Q4 2014
1. Vascularization
2. Invasiveness
3. Metastasis
4. Immunomodulation

5. Tumor cell
   (ANG2 secretion)

Joyce and Pollard 2009
Rebastinib (DCC-2036)

- First in class TIE2 inhibitor
- Phase 1 trial completed in 2013
  - MTD: 150 mg twice daily
  - Activity observed in resistant / refractory CML (as BCR-ABL drug)
  - Safe and tolerable
  - TIE2 targeting demonstrated in patients
- Further clinical development is based on TIE2 inhibition
  - 70-fold increased potency against TIE2 vs. BCR-ABL
  - Companion diagnostic in development
  - Indications: tumor microenvironment – breast, pancreatic, ovarian, HCC cancers
IC\textsubscript{90} of Rebastinib for TIE2 In ECs
Well below plasma levels achieved in Phase 1

IC\textsubscript{90} TIE-2 (HUVEC/endothelial cells) = 0.36 ng/mL

Suggests that a lower daily dose and/or less frequent dosing of rebastinib may be feasible to target TIE-2 versus BCR-ABL.
Rebastinib Phase 1: Increased circulating ANG2 demonstrates TIE2 targeting

Fold Change in Plasma Angiopoietin-2 in Rebastinib Patients Pre and Post Treatment

- Patient ID
- Fold Change in pg Ang-2/mg Total Protein (Day 22/Day 1)
- Patient ID

Copyright © 2014 Deciphera Pharmaceuticals, LLC. All rights reserved
Picomolar potency of rebastinib for blocking cellular TIE2 in endothelial cells

Rebastinib – EA.hy926 Cells

<table>
<thead>
<tr>
<th>Rebastinib</th>
<th>- ANG1 Control</th>
<th>+ ANG1 Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 nM</td>
<td>6.7 nM</td>
<td>2.2 nM</td>
</tr>
<tr>
<td>0.74 nM</td>
<td>0.25 nM</td>
<td>0.082 nM</td>
</tr>
<tr>
<td>0.027 nM</td>
<td>0.0091 nM</td>
<td>0.0031 nM</td>
</tr>
<tr>
<td>0.0010 nM</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

EA.hy926 pTIE2 Western Blot

IC$_{50}$ = 0.077 nM
Long residency times lead to robust cellular inhibition of TIE2 by rebastinib

$t_{1/2}$ off-rate $\sim 10$ h

Attribute of Deciphera’s Switch Pocket Platform for Kinase Inhibition

IC$_{50} = 0.63$ nM
- TEMs exist within the primary tumor and metastatic sites to facilitate invasion, streaming, and intravasation of tumor cells (into blood vessels)

- In addition, TEMs in metastatic sites facilitate extravasation of tumor cells (out of blood vessels) to further the metastatic process
TMEM function in tumor cell dissemination

- TMEM density increases with tumor grade in mouse and human mammary tumors.

**TMEM density in mouse PyMT mammary tumor and human breast cancer**

- **Mouse PyMT mammary tumor**

  - EC
  - LC

- **Human breast cancer**

  - Well
  - Moderate
  - Poor

(Courtesy of John Condeelis, PhD, Albert Einstein College of Medicine)

See J. Joans poster on TMEM as a marker for metastatic risk in BC
Rebastinib inhibits growth of breast tumors (PyMT) alone and in combination with paclitaxel

Rebastinib
- 75% TGI*

Rebastinib plus Paclitaxel
- 90% TGI*

Paclitaxel
- 49% TGI*

*TGI Normalized to starting tumor size
Rebastinib Targets Perivascular TEMs

Vehicle | Paclitaxel | Rebastinib
Rebastinib Inhibits Lung Metastases in PyMT Model

Vehicle

Rebastinib
Intermittent dosing of Rebastinib is sufficient to cause ablation in BC lung metastases (PyMT resection model)

**MI 1869 PyMT - Lung Mets Cohort B**

**μCT Day 111**

**Average number of lung nodules**

- **Vehicle**
- **Paclitaxel 10 mg/kg every five days**
- **Rebastinib 10 mg/kg once weekly + Paclitaxel**
- **Rebastinib 10 mg/kg twice weekly + Paclitaxel**
- **Rebastinib 5 mg/kg twice weekly + Paclitaxel**

**Average volume of lung nodules**

- **Vehicle**
- **Paclitaxel 10 mg/kg every five days**
- **Rebastinib 10 mg/kg once weekly + Paclitaxel**
- **Rebastinib 10 mg/kg twice weekly + Paclitaxel**
- **Rebastinib 5 mg/kg twice weekly + Paclitaxel**
Rebainib exhibits survival benefit even with intermittent dosing in combination with Eribulin

MI 1869 PyMT
Percent Survival by Group

- Rebainib 10 mg/kg once weekly + Eribulin 0.1 mg/kg three times weekly
  \( p = 0.029 \) vs. Eribulin

- Rebainib 10 mg/kg twice weekly + Eribulin 0.1 mg/kg three times weekly
  \( p = 0.013 \) vs. Eribulin

- Vehicle

- Eribulin 0.1 mg/kg three times weekly
Rebastinib as First-In-Class TIE2 Inhibitor

- Supported by preclinical data
- Targets tumor microenvironment
  - Targeting of tumoral TEM population
  - Targeting of tumoral vasculature
  - Targeting of tumor immunotolerance (in progress)
- Phase 1B/2 trial Q4 2014
  - Breast cancer or other cancer driven by significant TIE2 microenvironment component
  - Single agent and as adjuvant combination with standard-of-care therapy