Rebastinib, a selective TIE2 kinase inhibitor, decreases TIE2-expressing macrophages, reduces metastasis, and increases survival in murine cancer models

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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:

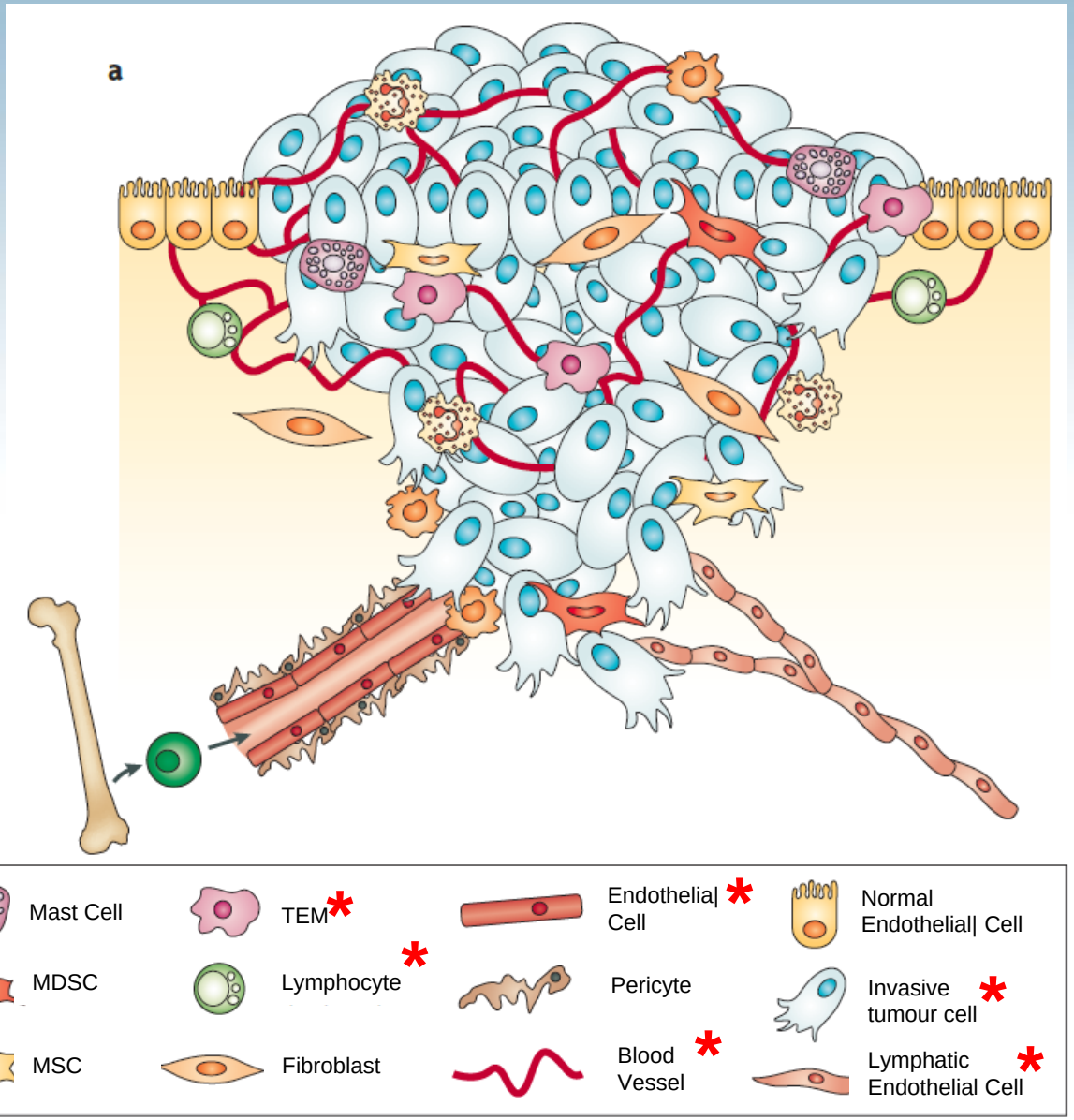
- effects on tumor vascularization (angiogenic switching)
- effects on tumor invasion/dissemination/metastasis
- effect on tumor immunotolerance

A Phase 1 study in metastatic solid tumors in combination with approved agents is planned for Q4 2014

Rebastinib Focus on Tumor Cell/Microenvironment

1. Vascularization
2. Invasiveness
3. Metastastis
4. Immunomodulation

5. Tumor cell
   (ANG2 secretion)



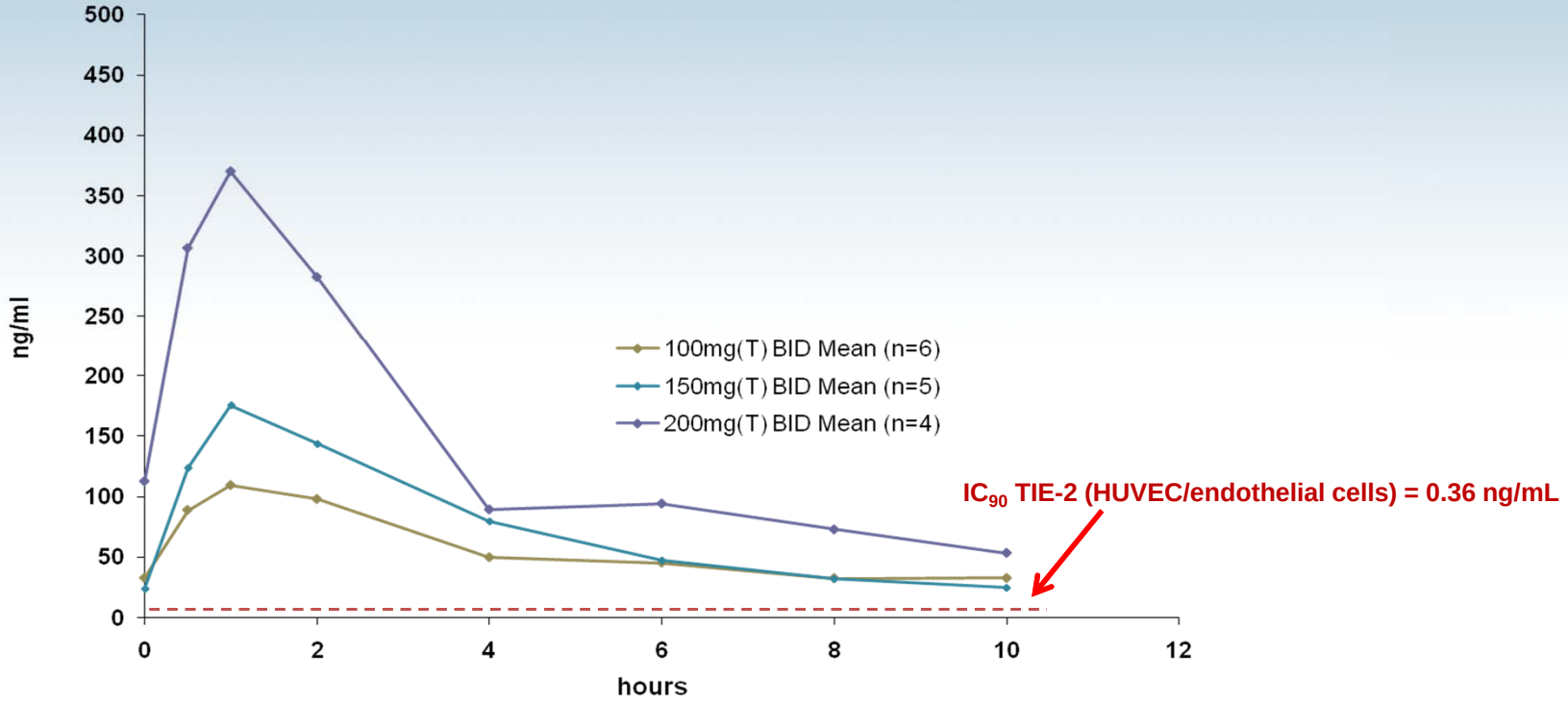
Joyce and Pollard 2009

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_{90} of Rebastinib for TIE2 In ECs

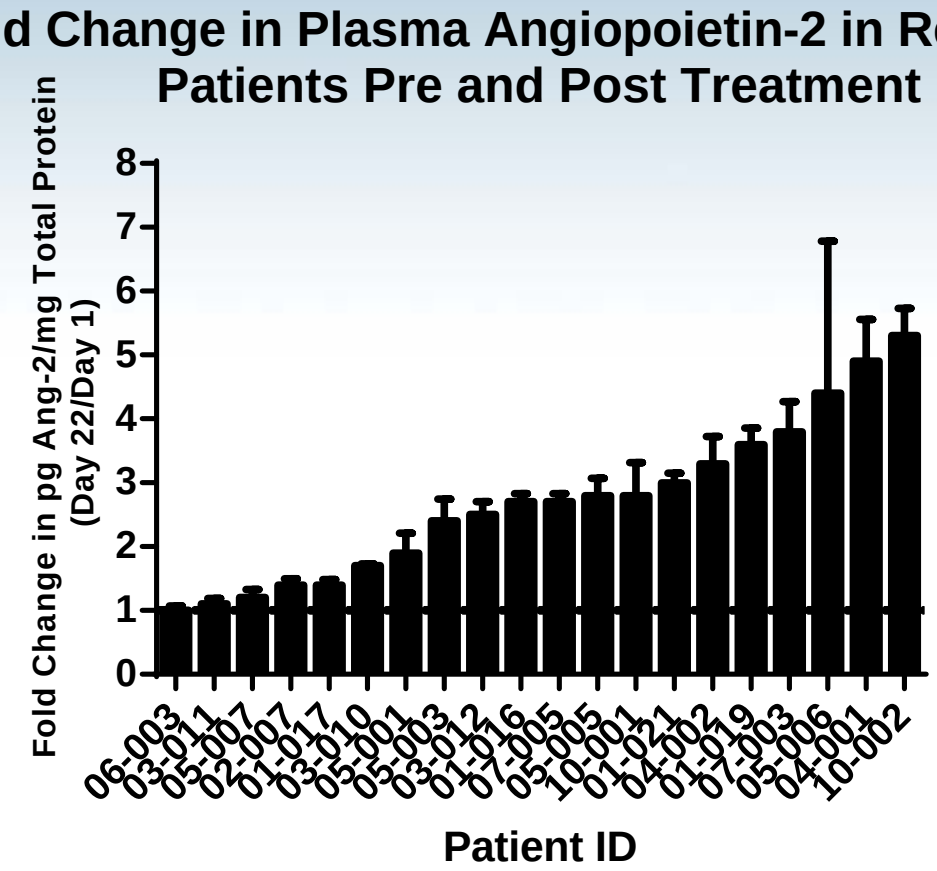
Well below plasma levels achieved in Phase 1



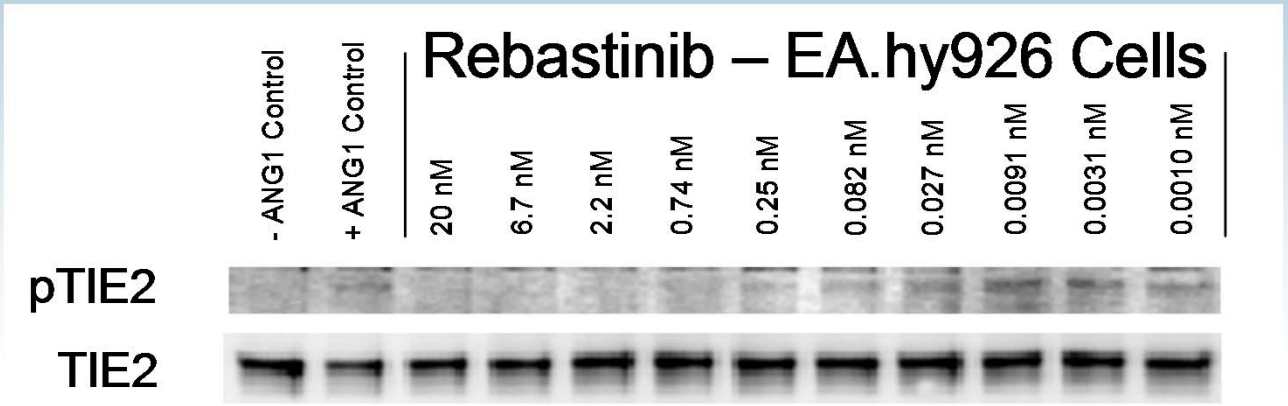
Suggests that a lower daily dose and/or less frequent dosing of rebastinib may be feasible to target TIE-2 versus BCR-ABL.

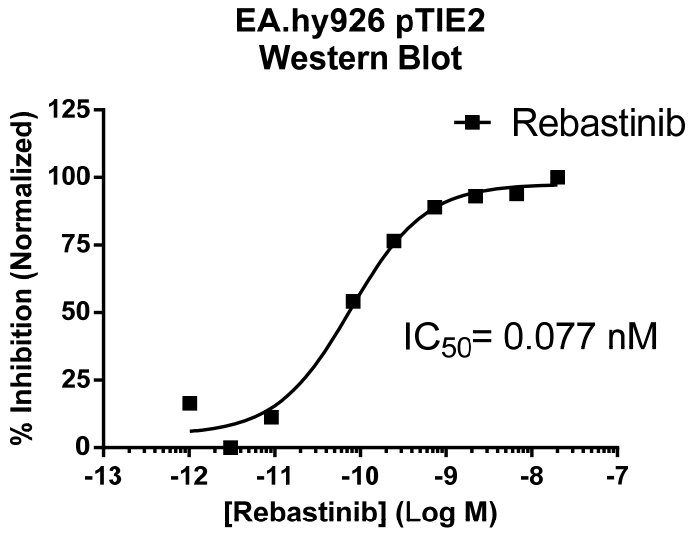
Rebastinib Phase 1:

Increased circulating ANG2 demonstrates TIE2 targeting



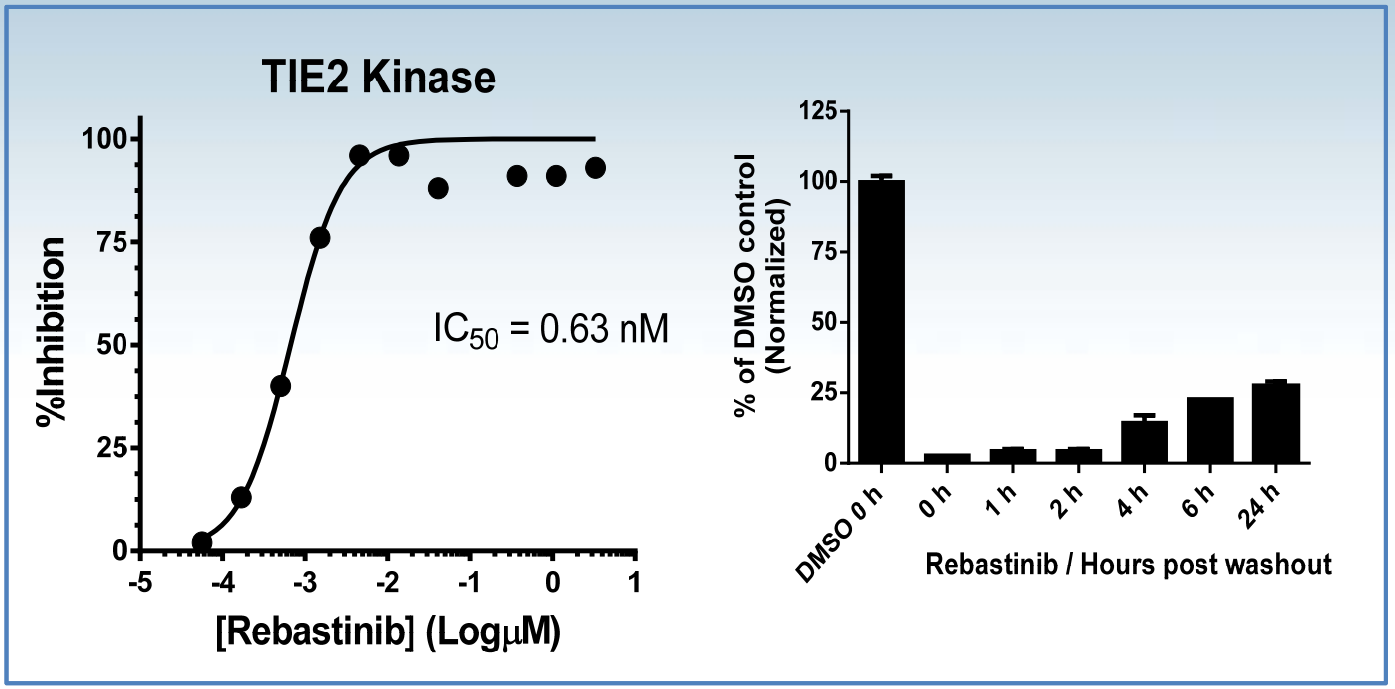
Picomolar potency of rebastinib for blocking cellular TIE2 in endothelial cells





Confidential

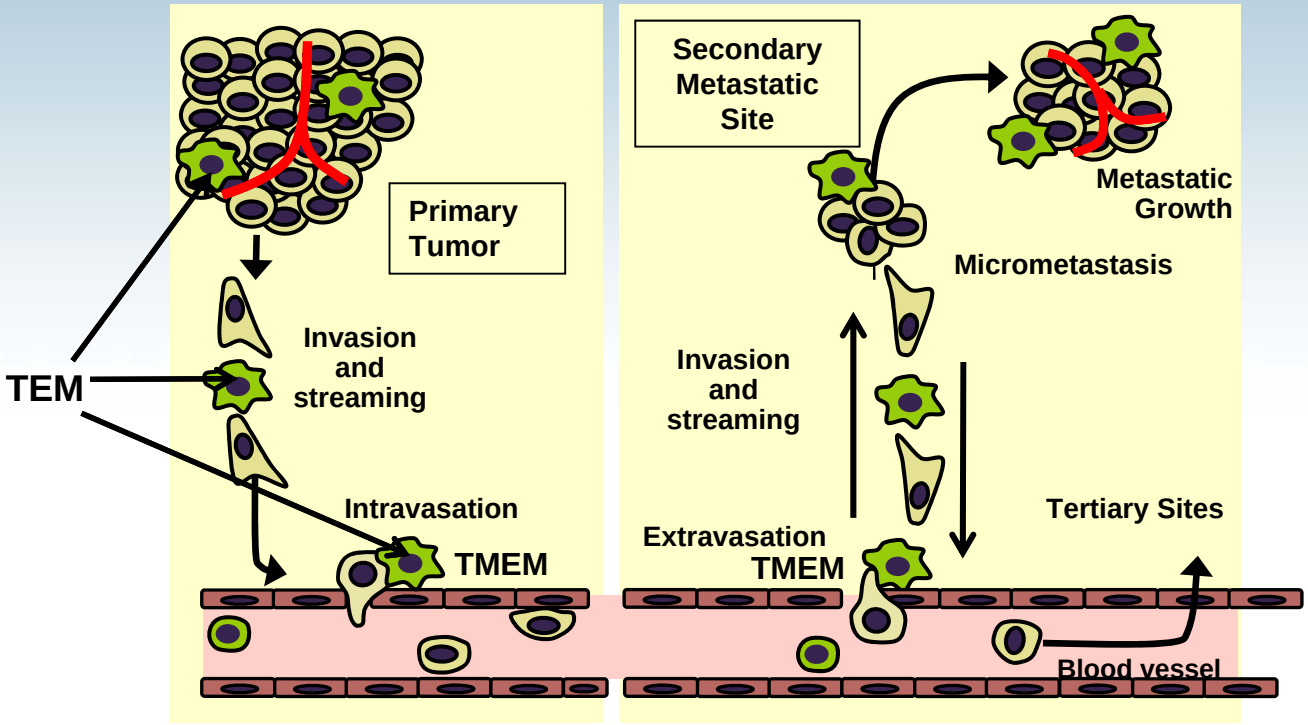
Long residency times lead to robust cellular inhibition of TIE2 by rebastinib



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

Attribute of Deciphera's Switch Pocket Platform for Kinase Inhibition

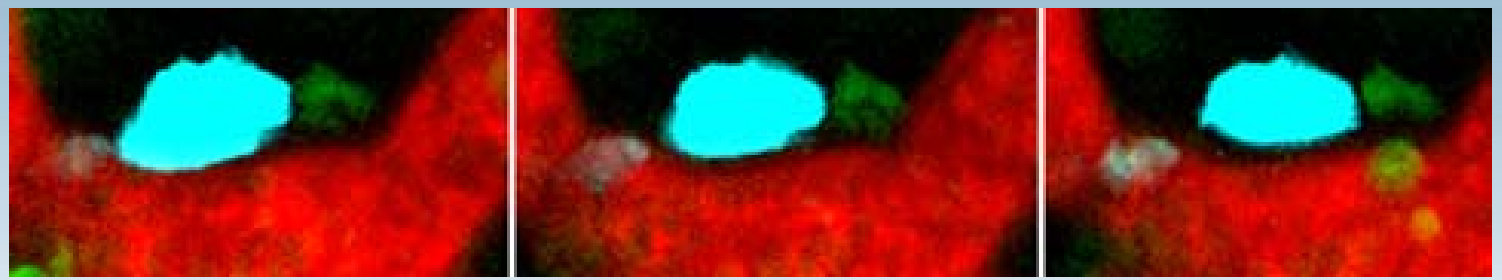
TIE2-expressing macrophages (TEM)-mediated tumor dissemination



Courtesy of John Condeelis, PhD Albert Einstein College of Medicine

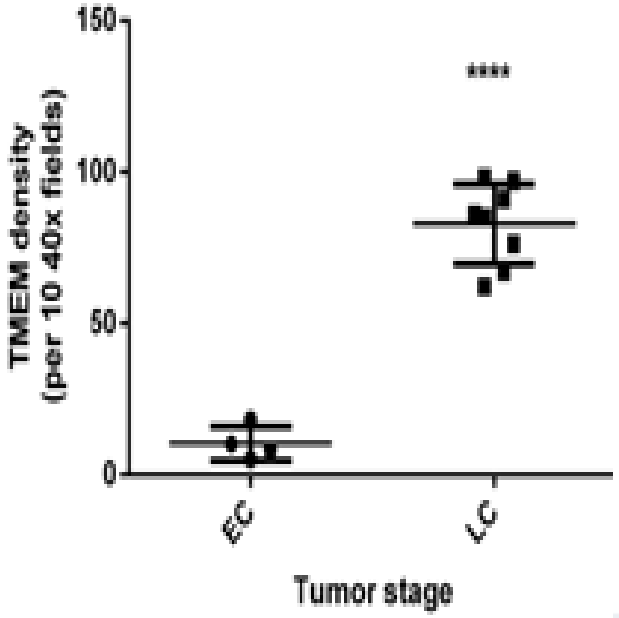
- TEMs exist within the primary tumor and metastatic sites to facilitate invasion, streaming, and intravasation of tumor cells (into blood vessels)
- In addition, TEMs in metastatic sites facilitate extravasation of tumor cells (out of blood vessels) to further the metastatic process

TMEM function in tumor cell dissemination

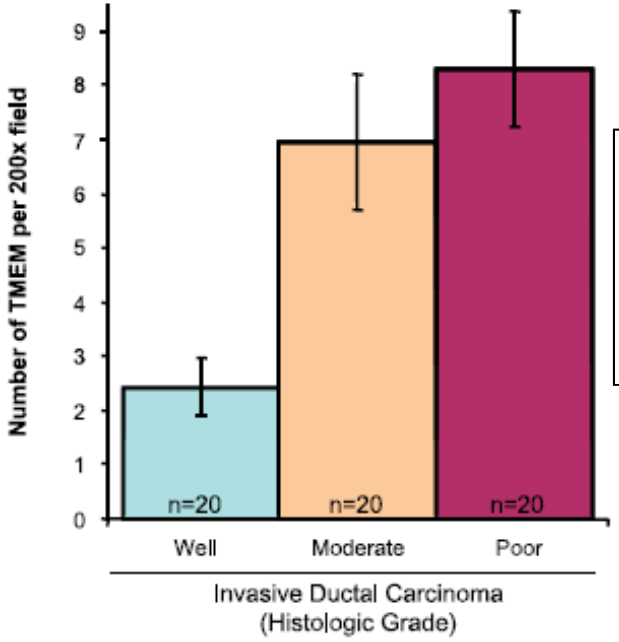


- TMEM density increases with tumor grade in mouse and human mammary tumors.

Mouse PyMT mammary tumor



Human breast cancer



Courtesy of John Condeelis, PhD Albert Einstein College of Medicine

See J. Joans poster on TMEM as a marker for metastatic risk in BC

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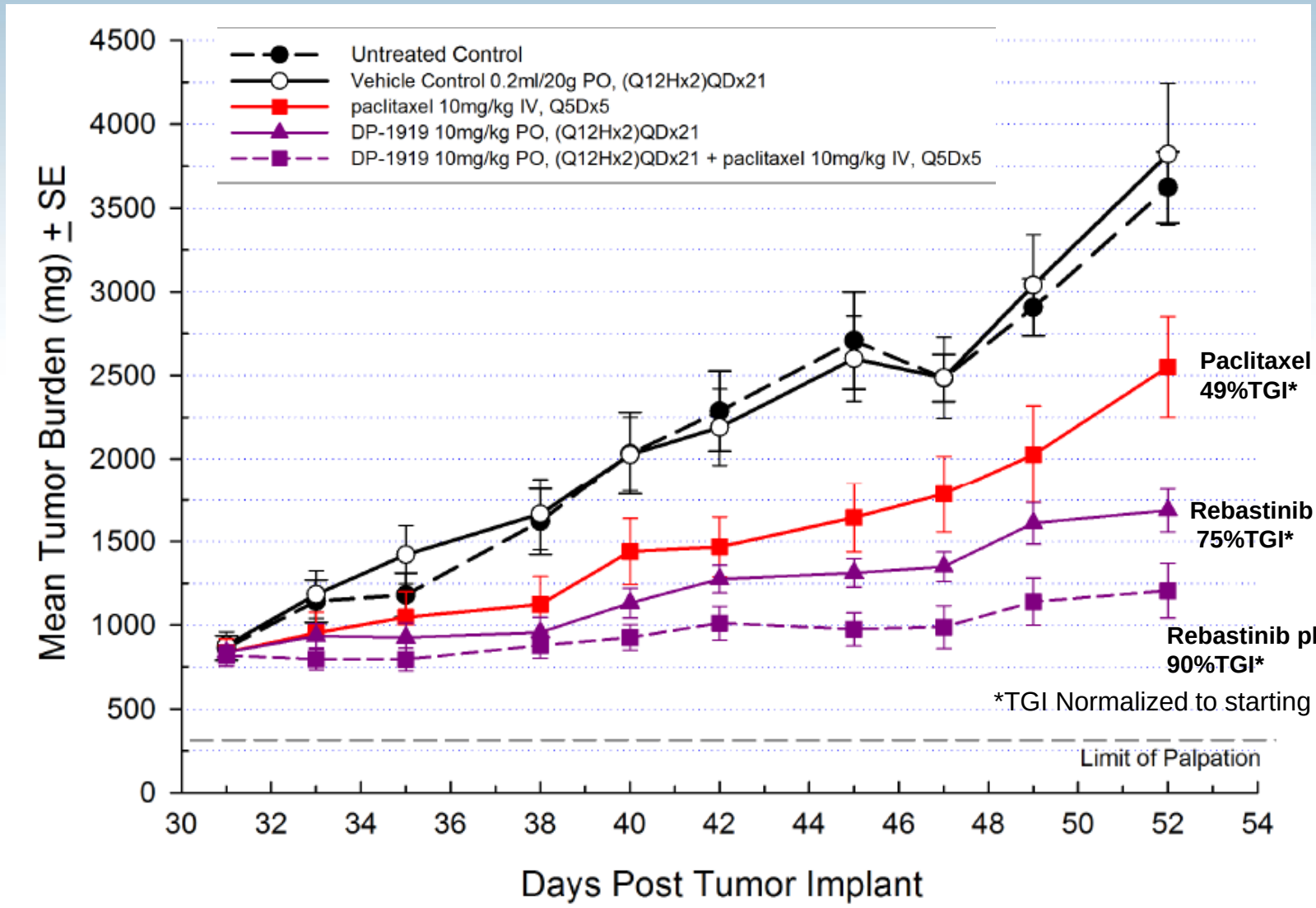
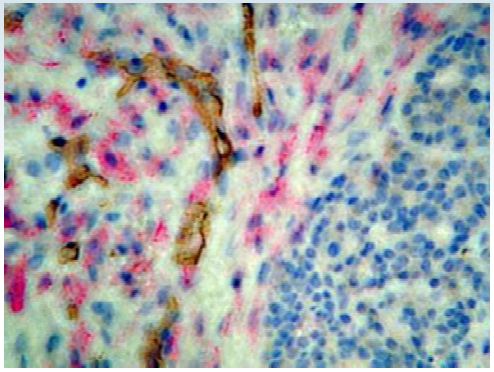
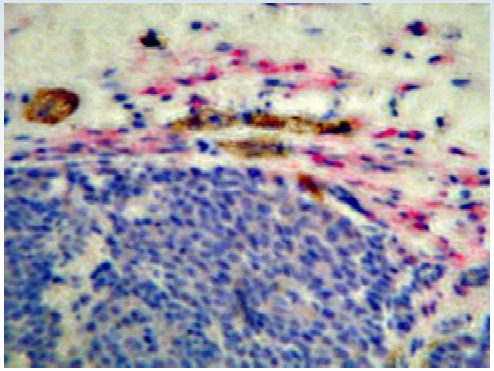
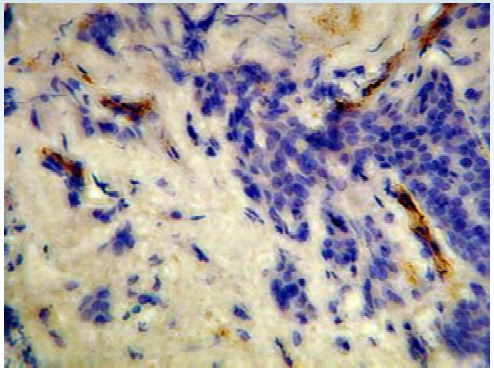
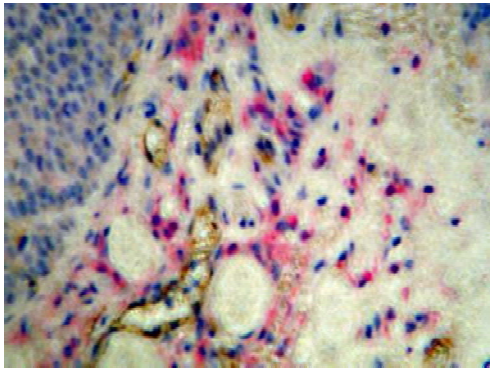
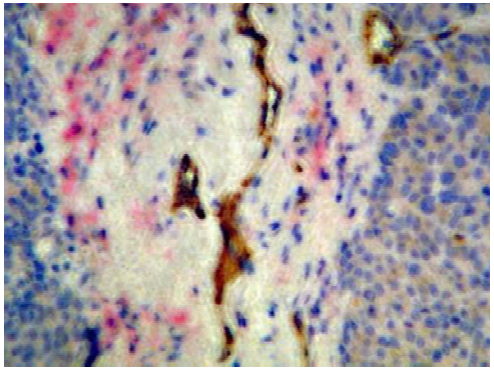
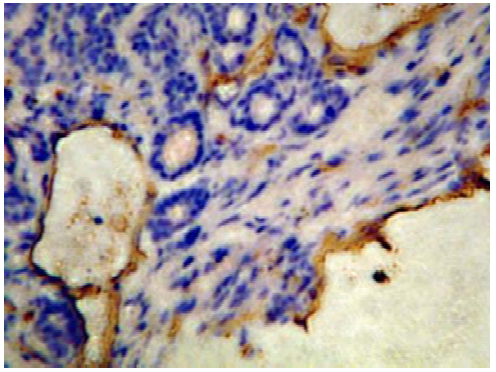
Rebastinib inhibits growth of breast tumors (PyMT) alone and in combination with paclitaxel

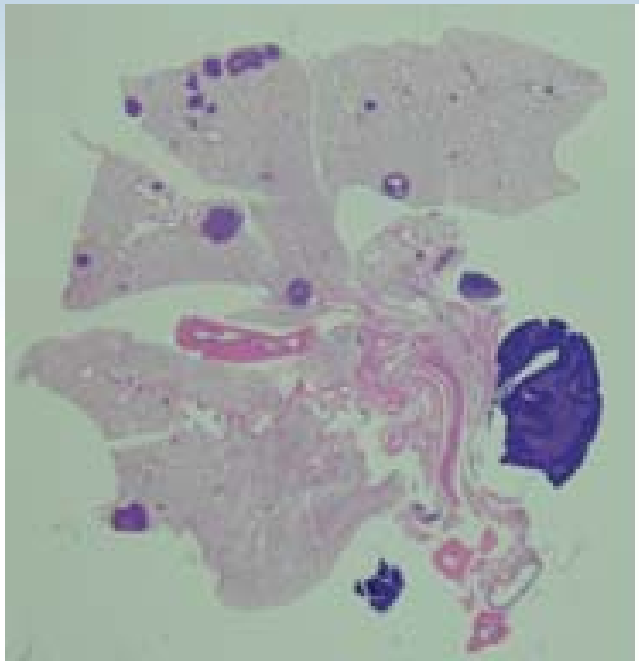


Rebastinib Targets Perivascular TEMs

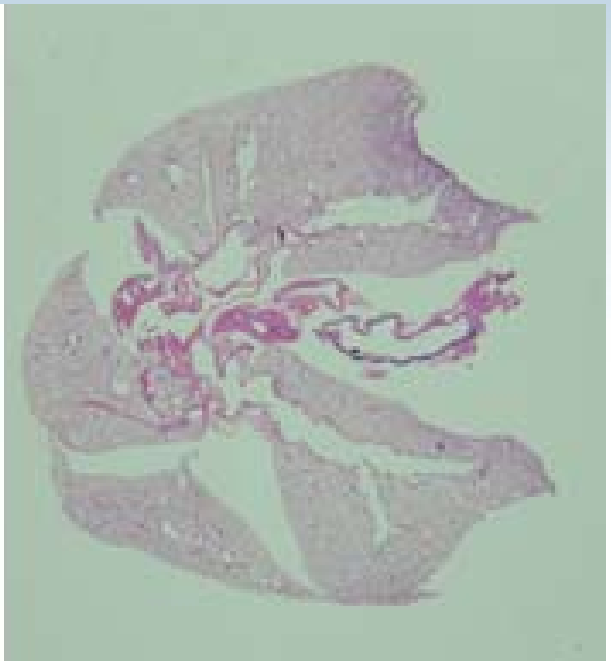
Vehicle	Paclitaxel	Rebastinib
		
		

Rebastinib Inhibits Lung Metastases in PyMT Model

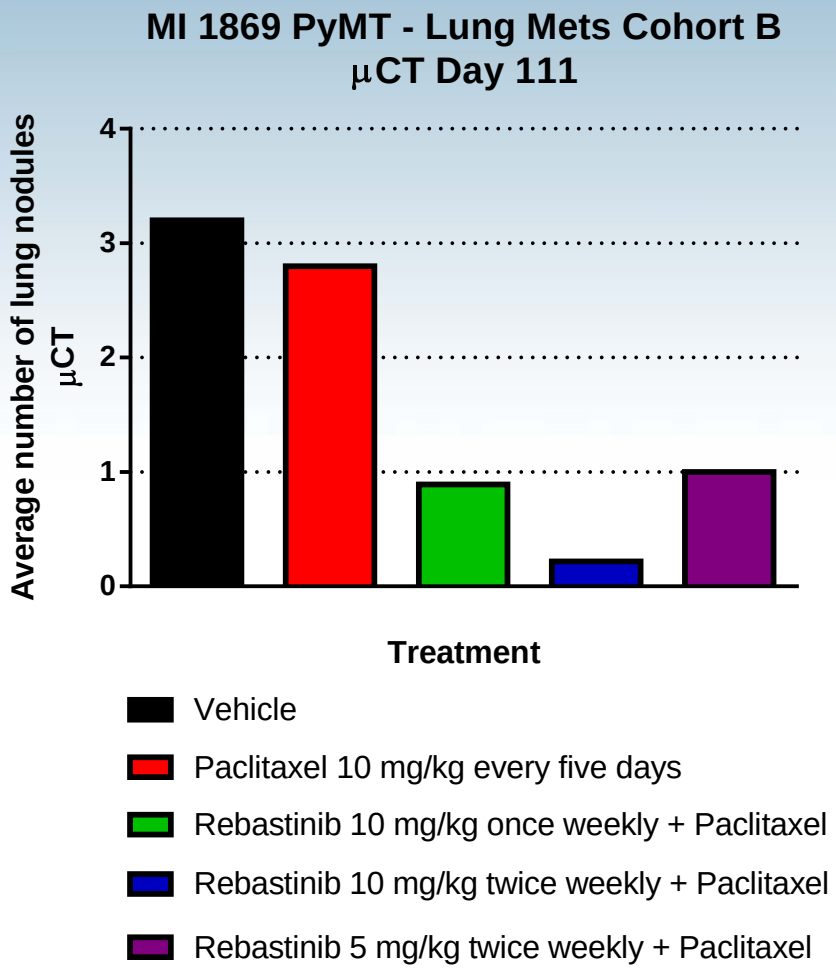
Vehicle

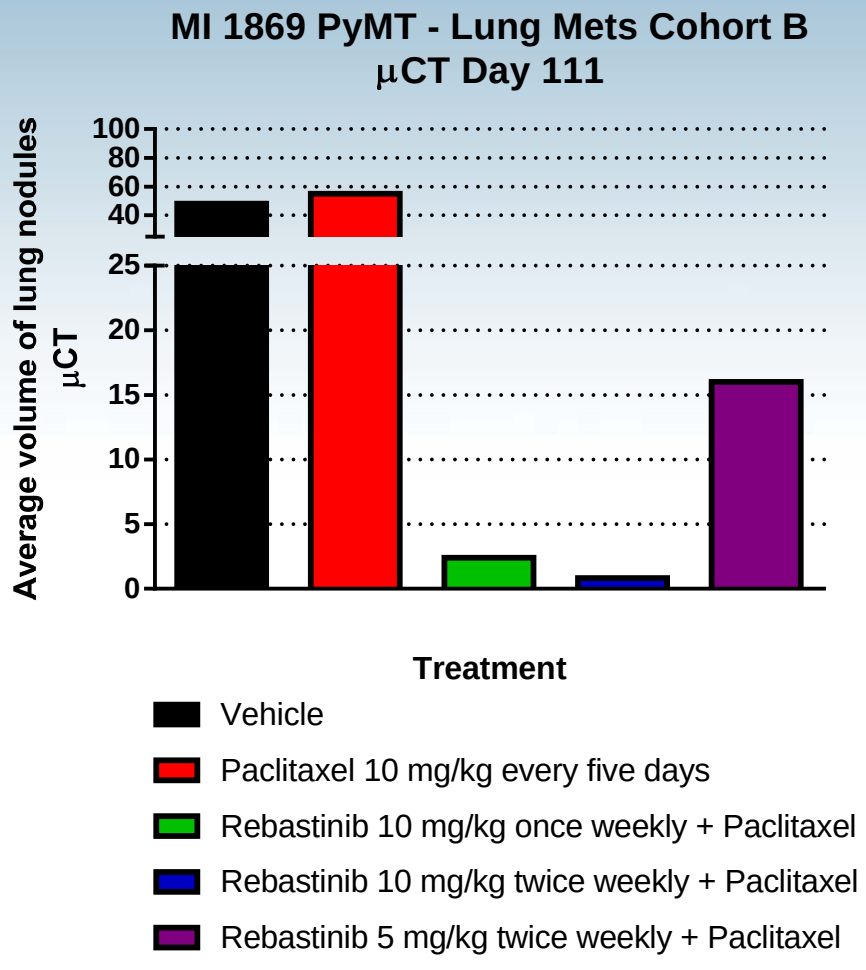


Rebastinib

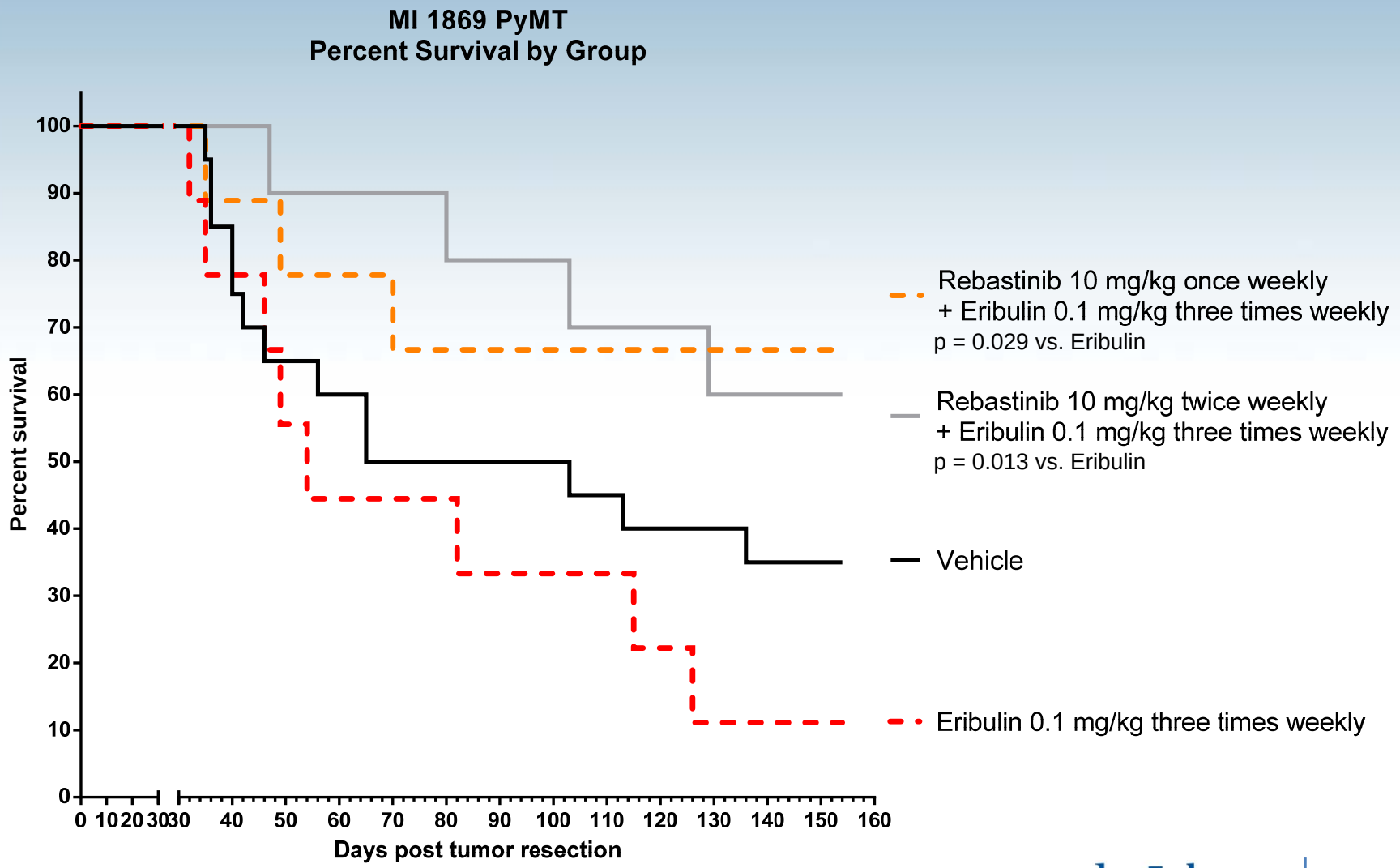


Intermittent dosing of Rebastinib is sufficient to cause ablation in BC lung metastases (PyMT resection model)





Rebastinib exhibits survival benefit even with intermittent dosing in combination with Eribulin



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