



THE WISTAR INSTITUTE

TODAY'S DISCOVERIES – TOMORROW'S CURES

Personalized pre-clinical trials in BRAF inhibitor resistant patient derived xenograft models of melanoma identify c-Met as an effective second line combination therapy target

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The Wistar Institute, Philadelphia, PA; University of Pennsylvania Abramson Cancer Center, Philadelphia, PA; University of Texas MD Anderson Cancer Center, Huston, TX; Novartis Oncology Translational Medicine, Cambridge, MA

AACR Annual Meeting 2015

**Minisymposium- Molecular Mechanisms of Sensitivity or Resistance to Pathway-Targeted Agents
4/20/2015**

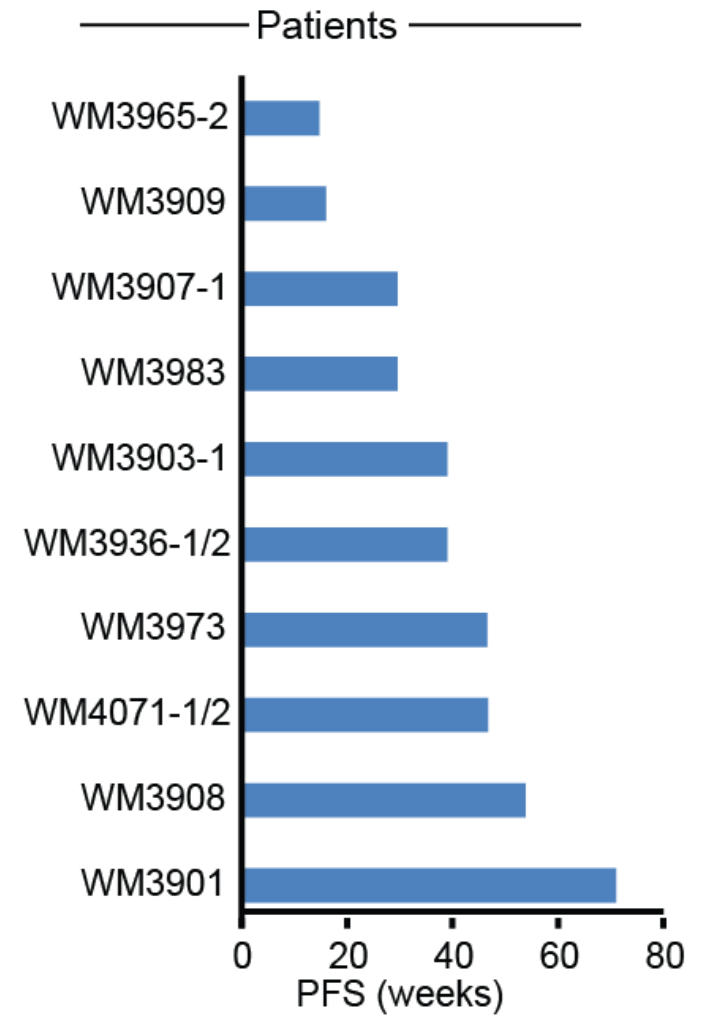
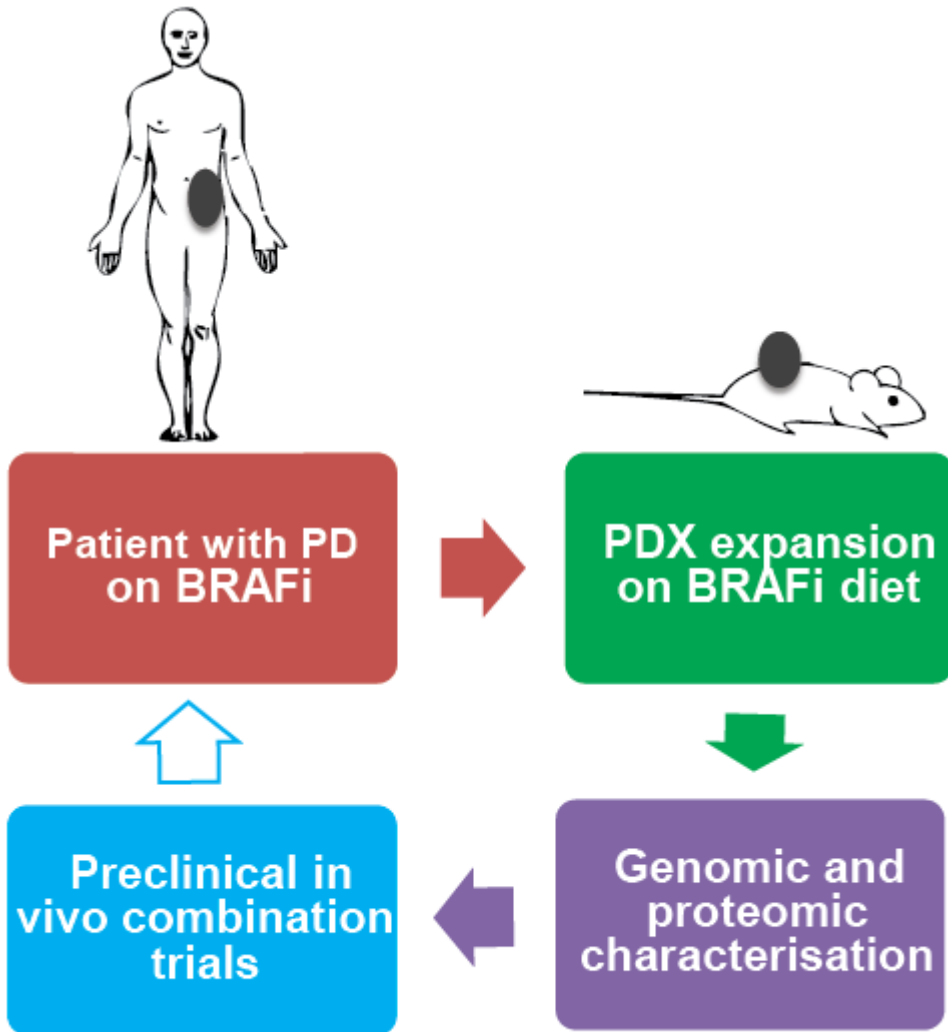
Disclosure Information
AACR Annual Meeting 2015
Clemens Krepler

I have the following financial relationships to disclose:

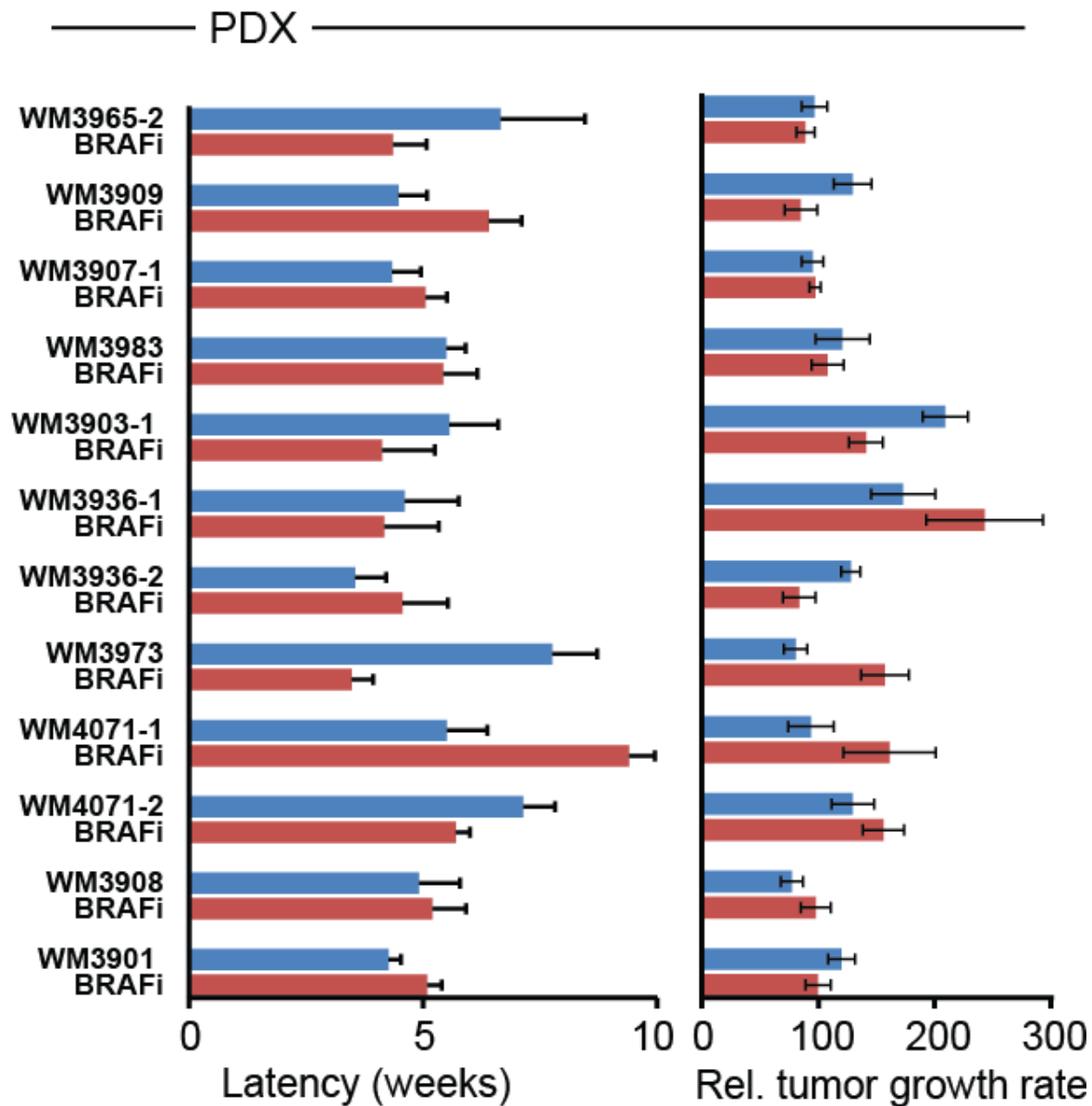
Part of the studies was supported by a grant from Novartis

I will not discuss off label use and/or investigational use in my presentation.

Establishment of BRAFi resistant PDX models

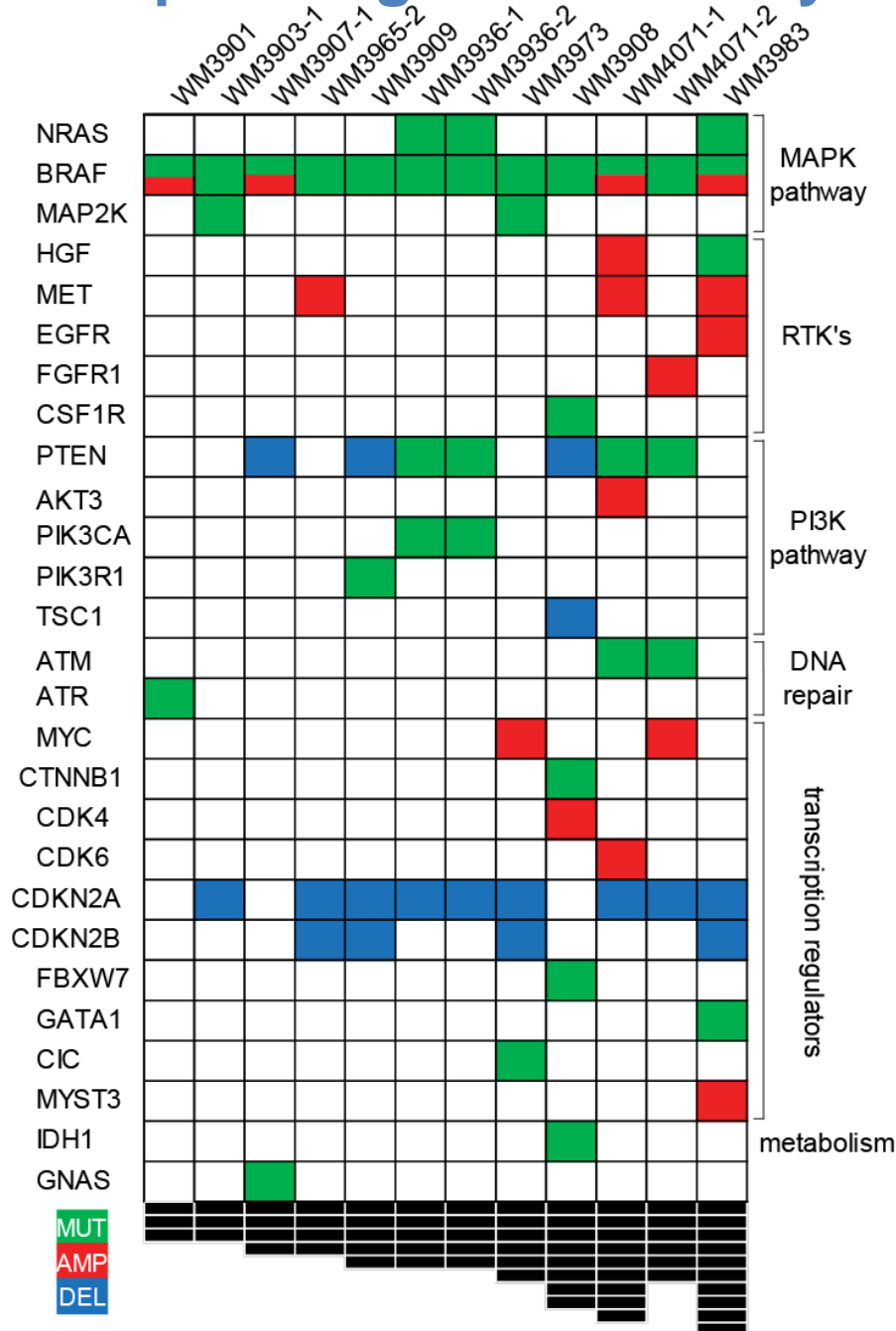


Tumorigenicity and resistant phenotype are preserved



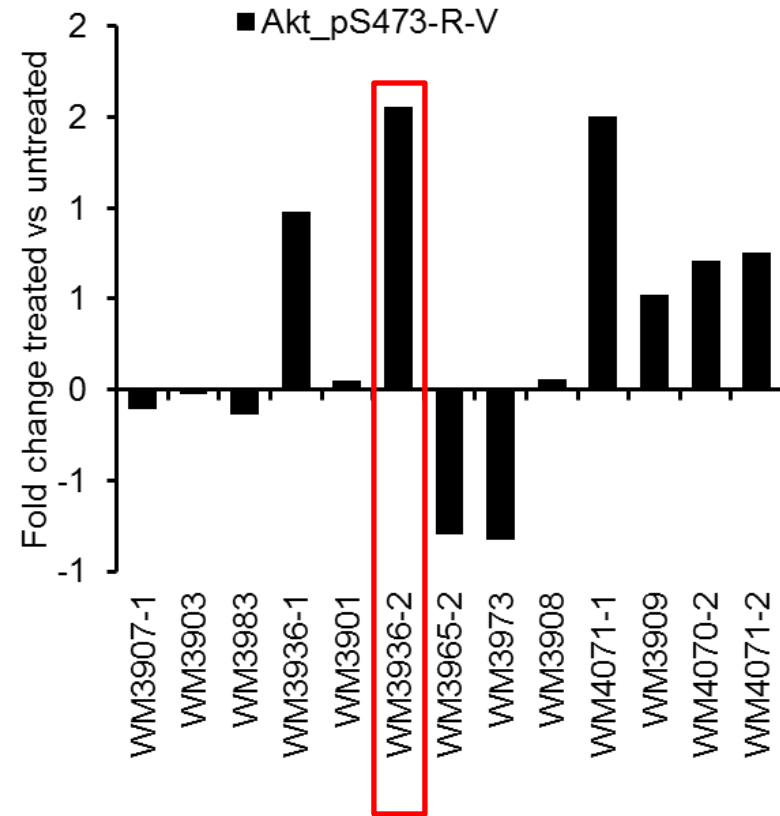
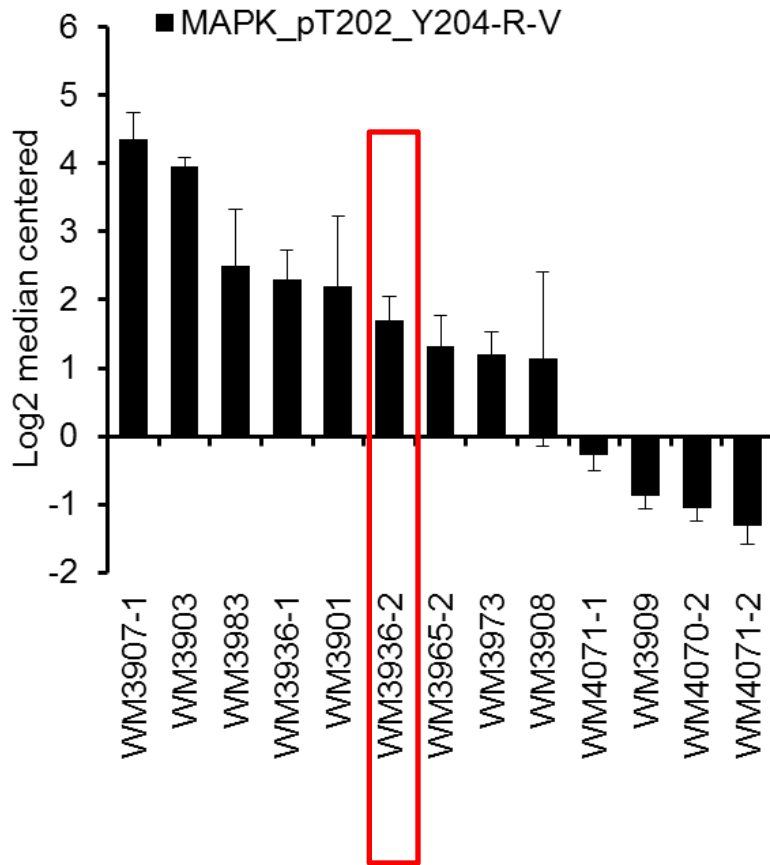
Targeted sequencing identifies key target lesions in PDX from BRAFi progressed patients

known somatic short-variants,
deletions and amplifications

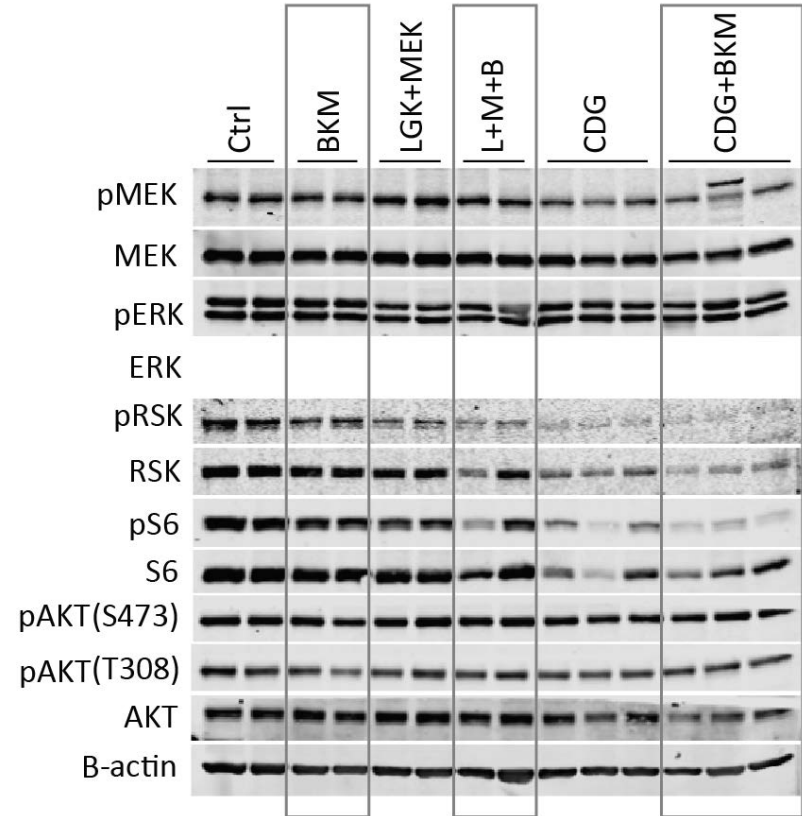
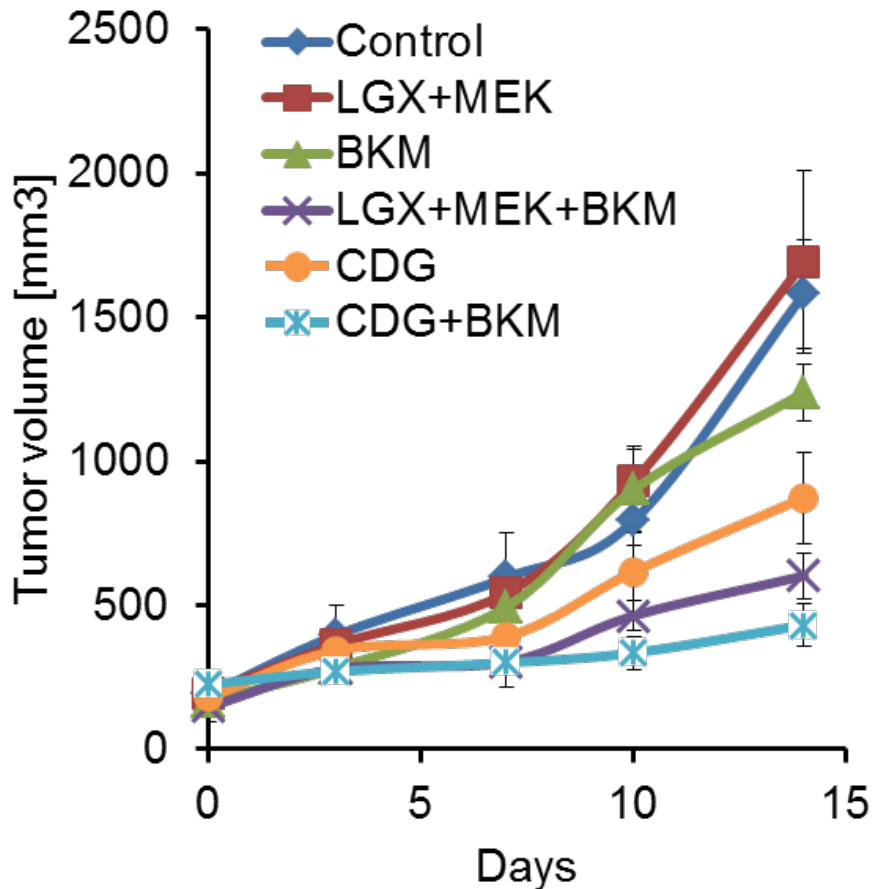


PDX from BRAFi progressed patients

RPPA analysis identifies MAPK and PI3K pathway reactivation under continuous drug pressure in vivo

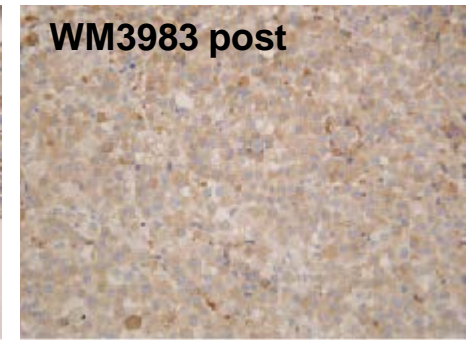
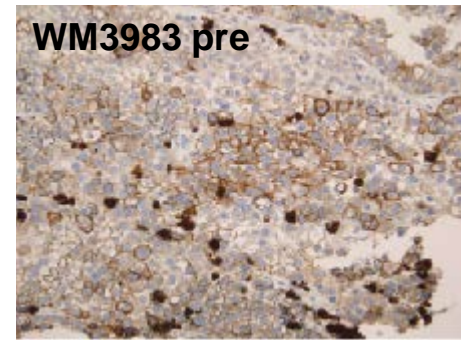
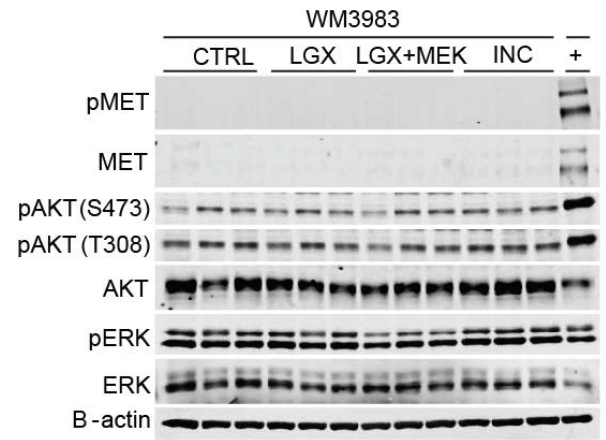
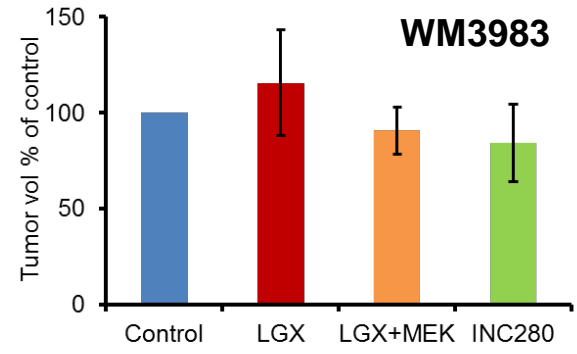
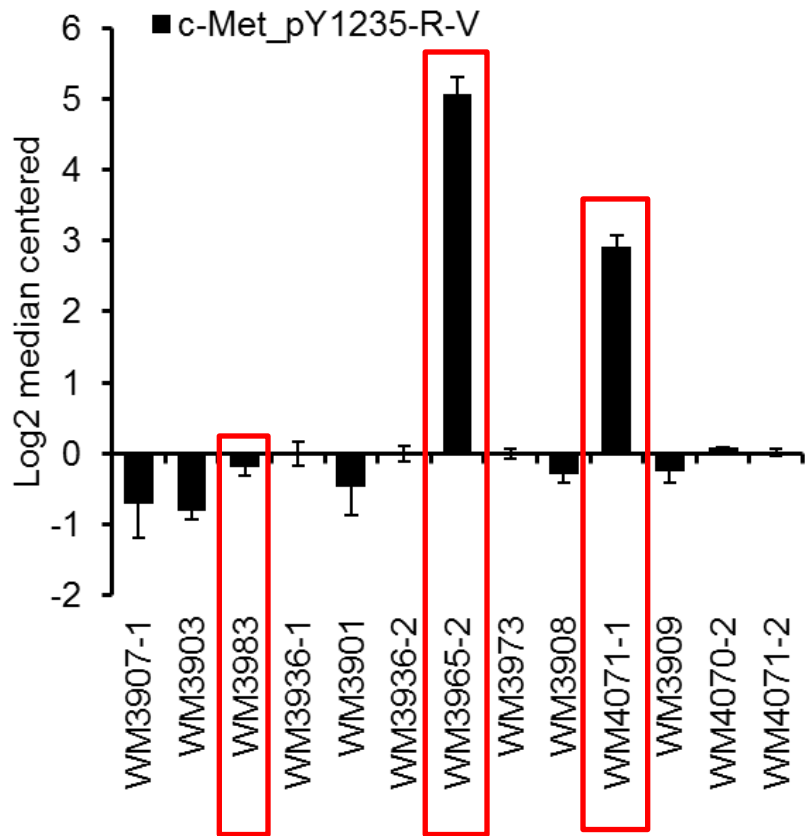


Rational second line combination therapy synergizes in vivo

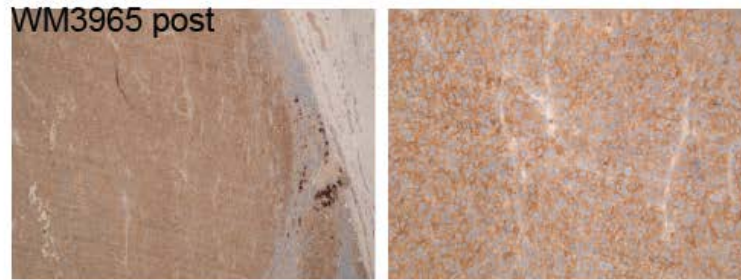
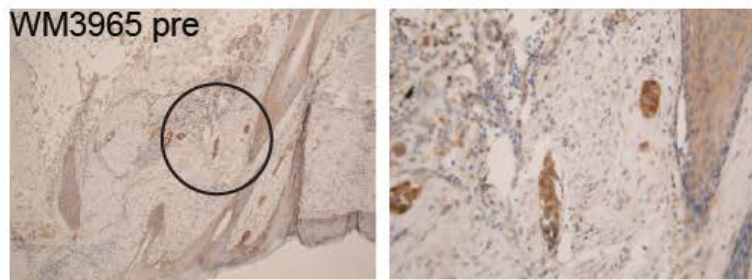
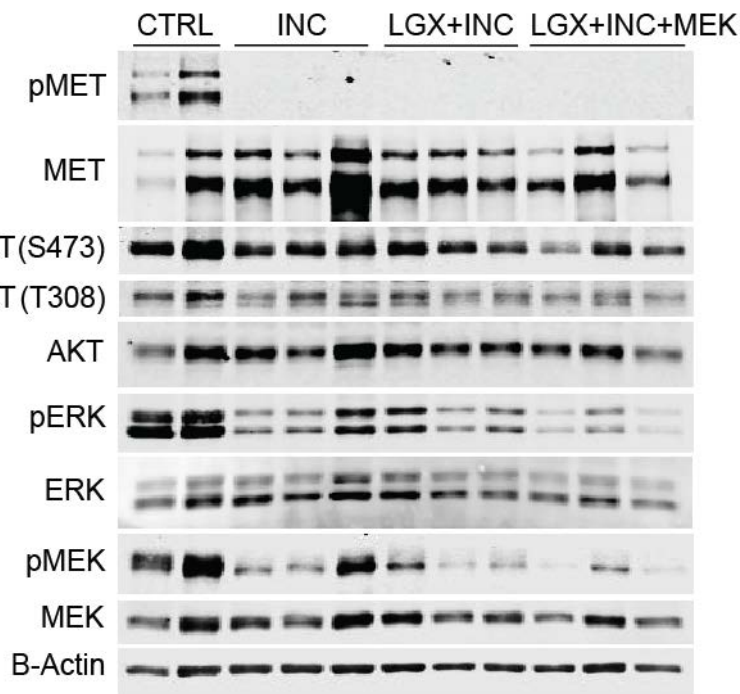
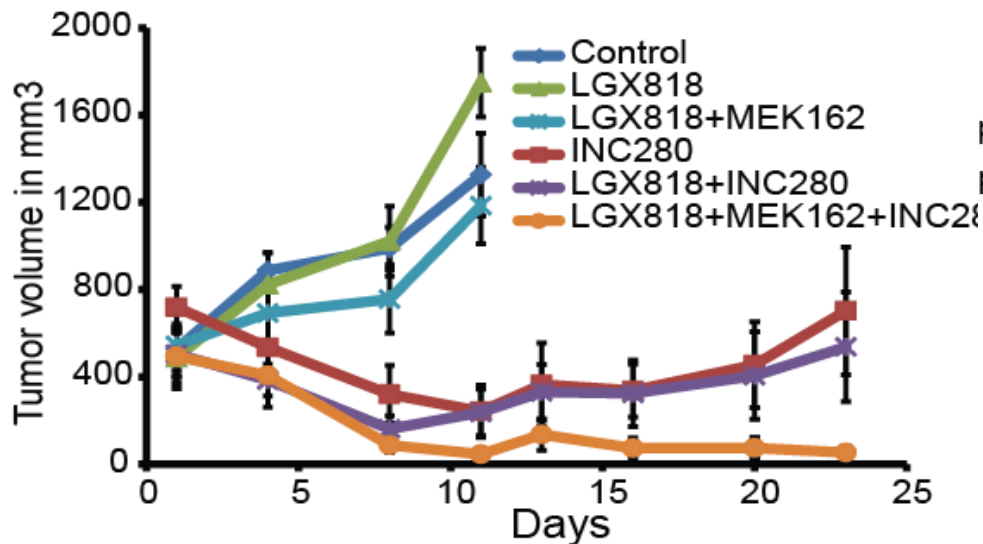


WM3936-2: Excellent clinical response on dabrafenib . After 9 months new s.c. thigh lesion with aggressive growth under therapy. NRASmut, PTENmut, and PIK3CA mut; high pERK and pAKT.

MET amplification confirmation on the protein level



C-Met inhibition leads to tumor regression, only the triple combination results in sustained MAPK inhibition



WM3965-2: aggressive disease with early PD in the right parotid gland after 3 months on vemurafenib

Summary

- ✓ **A collection of MAPKi resistant patient derived PDX was established.**
- ✓ **The kinase inhibitor resistant phenotype could be preserved in NSG mice.**
- ✓ **Mechanisms of resistance were be assessed using targeted sequencing and correlated with phospho protein levels.**
- ✓ **FFPE patient samples were used to confirm PDX findings.**
- ✓ **Rational combination therapies were effective as second line therapies in vivo.**
- ✓ **Integrating genomic and proteomic data may help to avoid incorrect decisions.**

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