



**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**

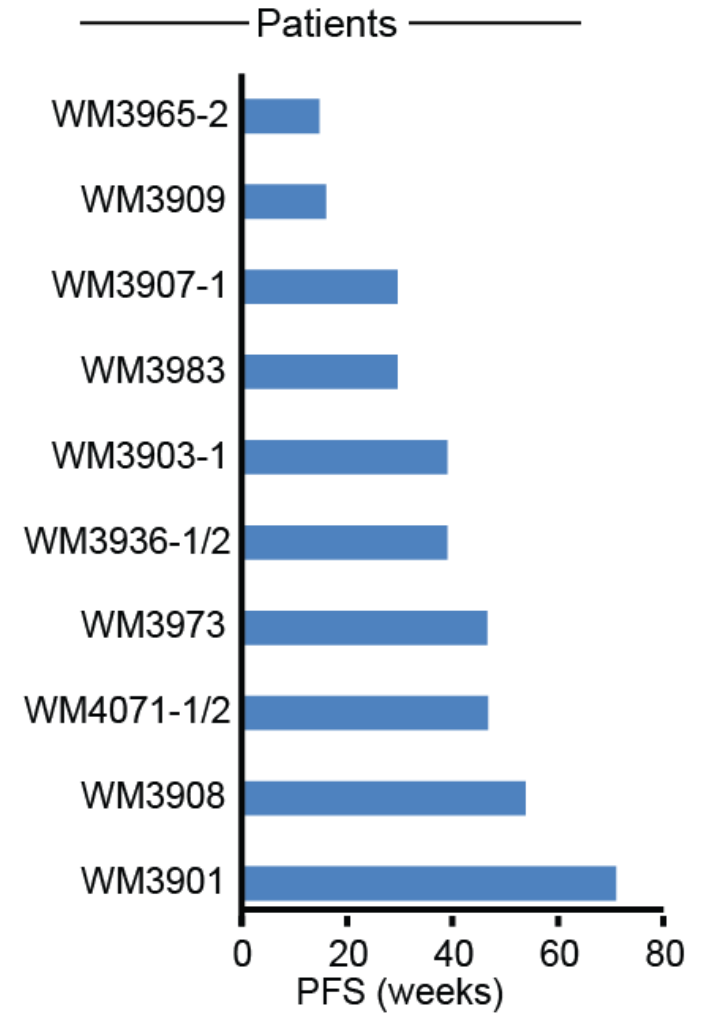
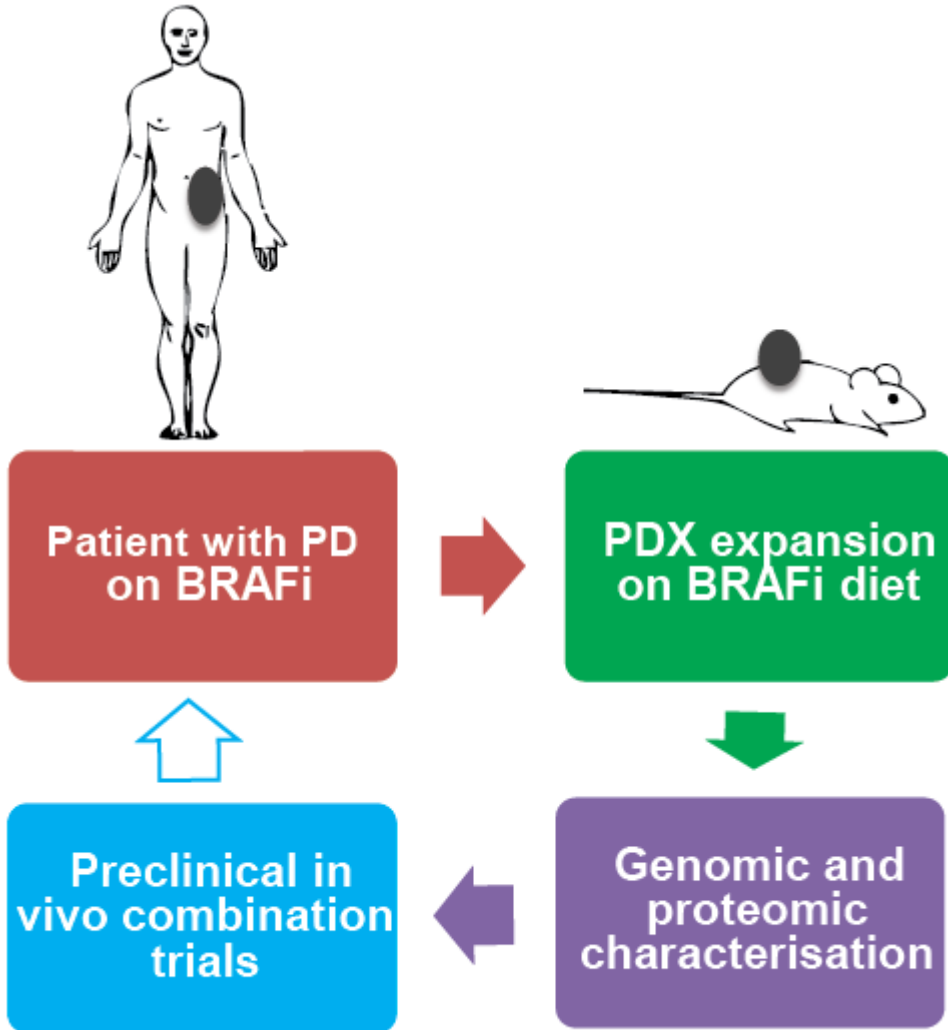
**Disclosure Information**  
**AACR Annual Meeting 2015**  
**Clemens Krepler**

**I have the following financial relationships to disclose:**

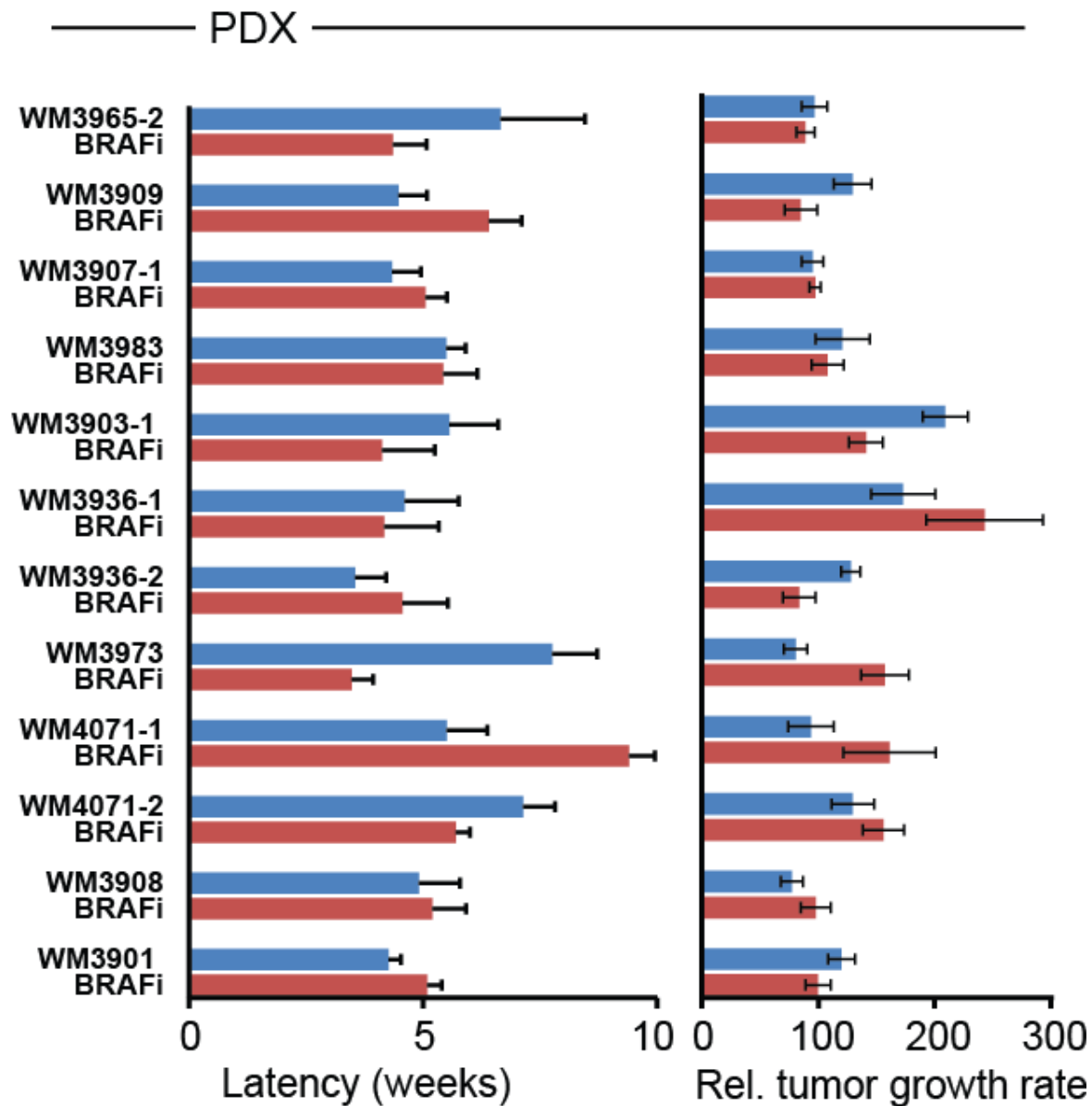
**Part of the studies was supported by a grant from Novartis**

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

# Establishment of BRAFi resistant PDX models

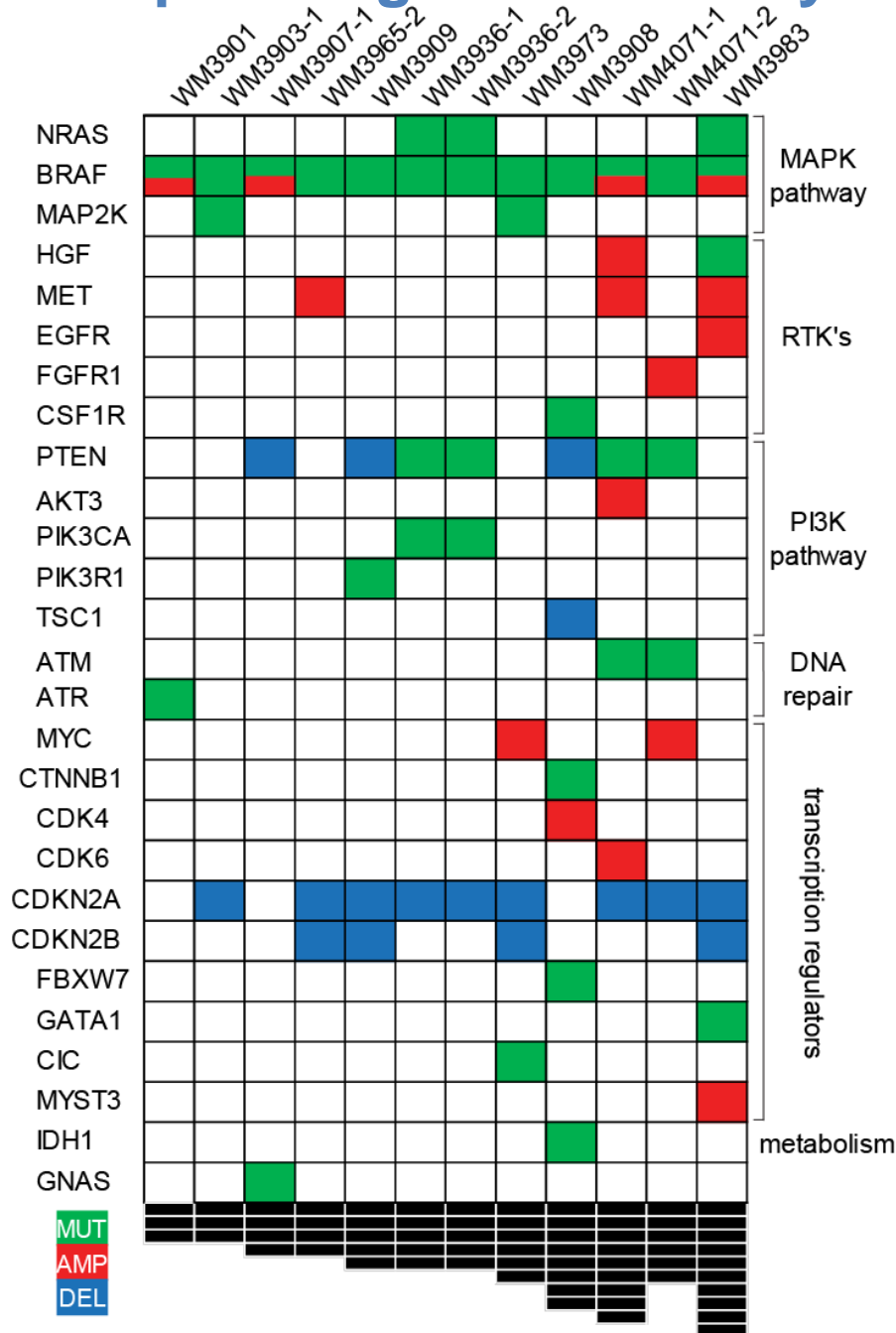


# Tumorigenicity and resistant phenotype are preserved



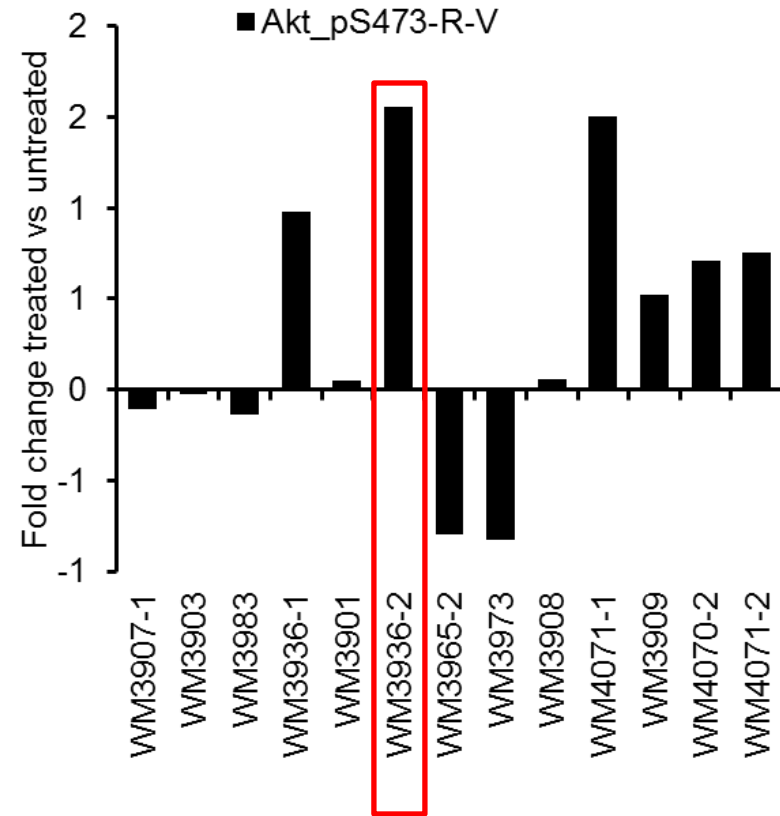
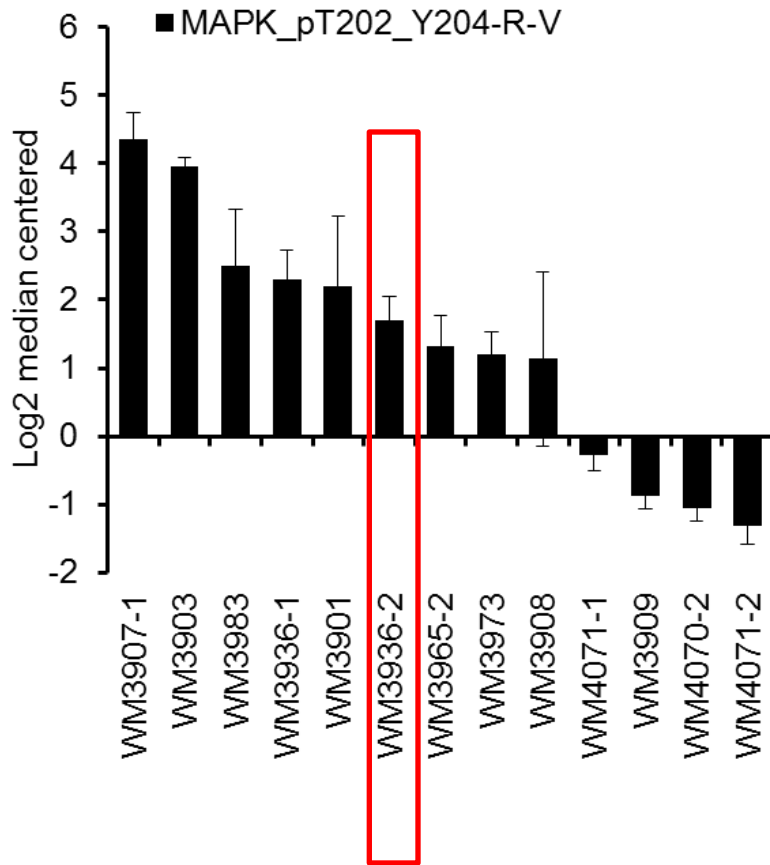
# Targeted sequencing identifies key target lesions in PDX from BRAFi progressed patients

known somatic short-variants,  
deletions and amplifications

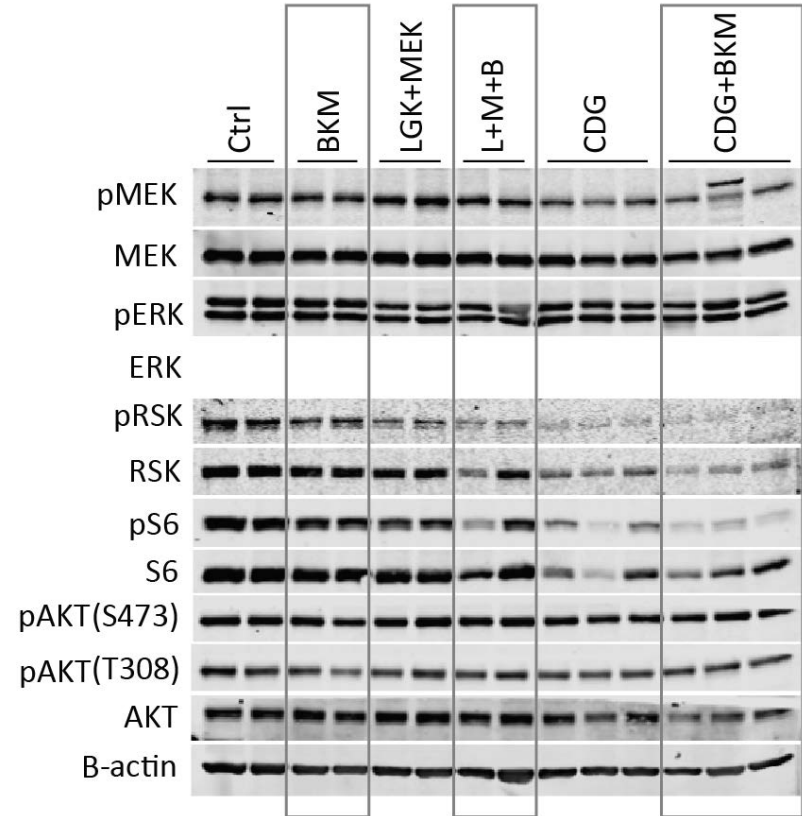
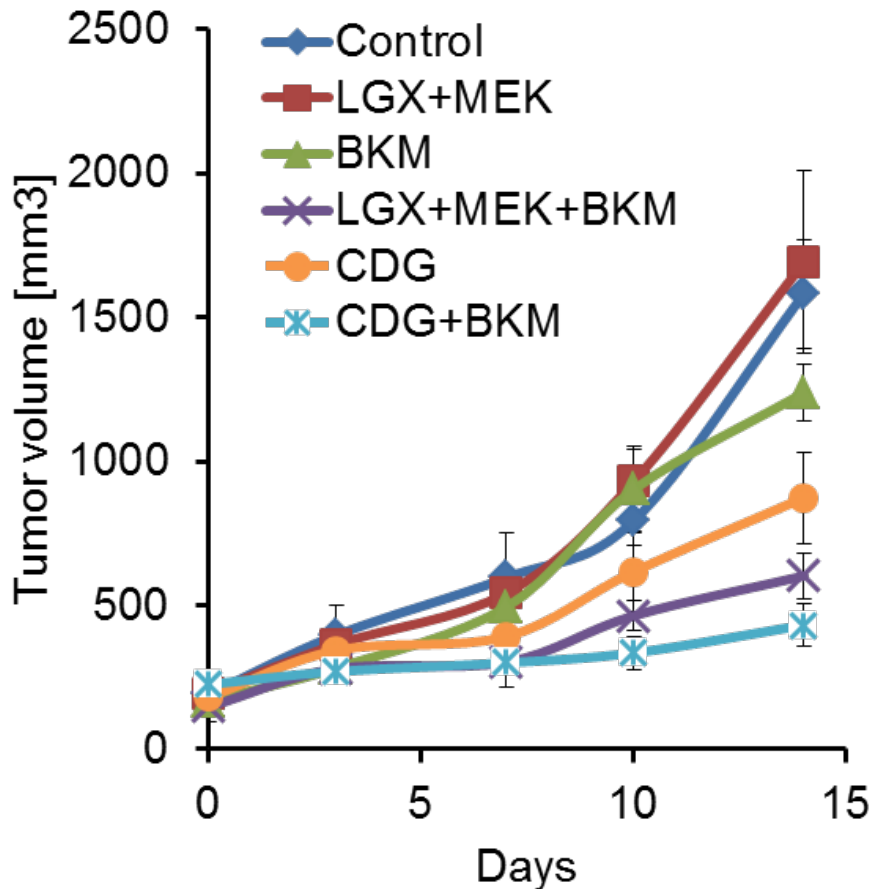


PDX from BRAFi progressed patients

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

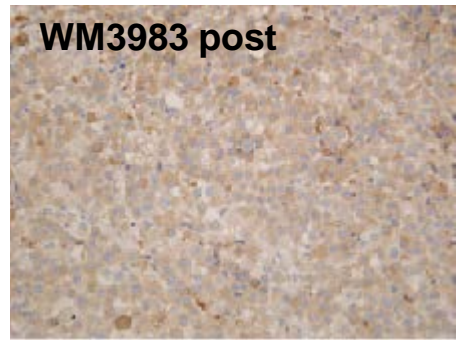
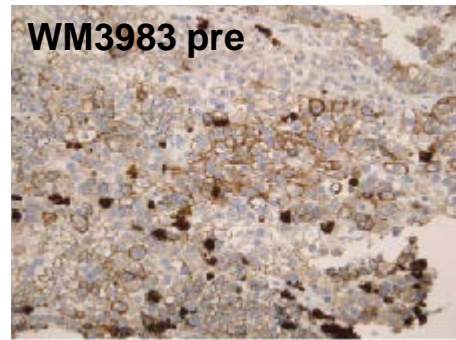
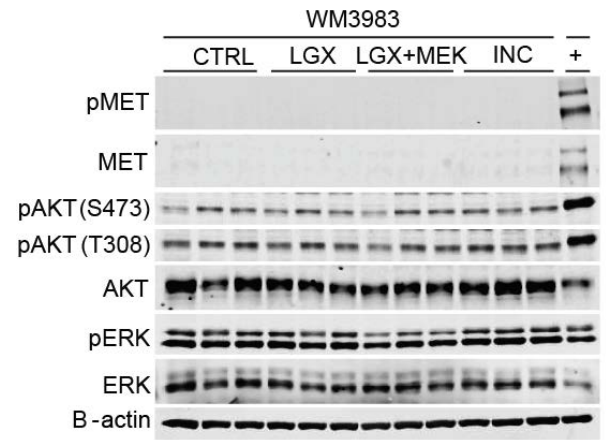
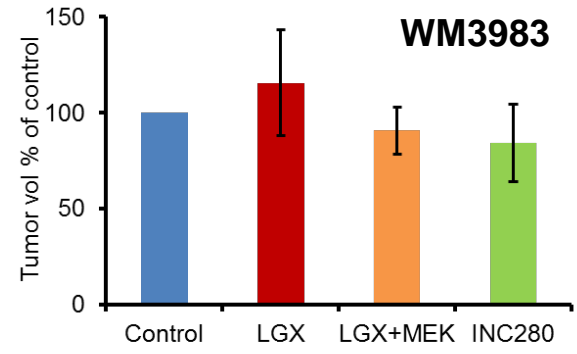
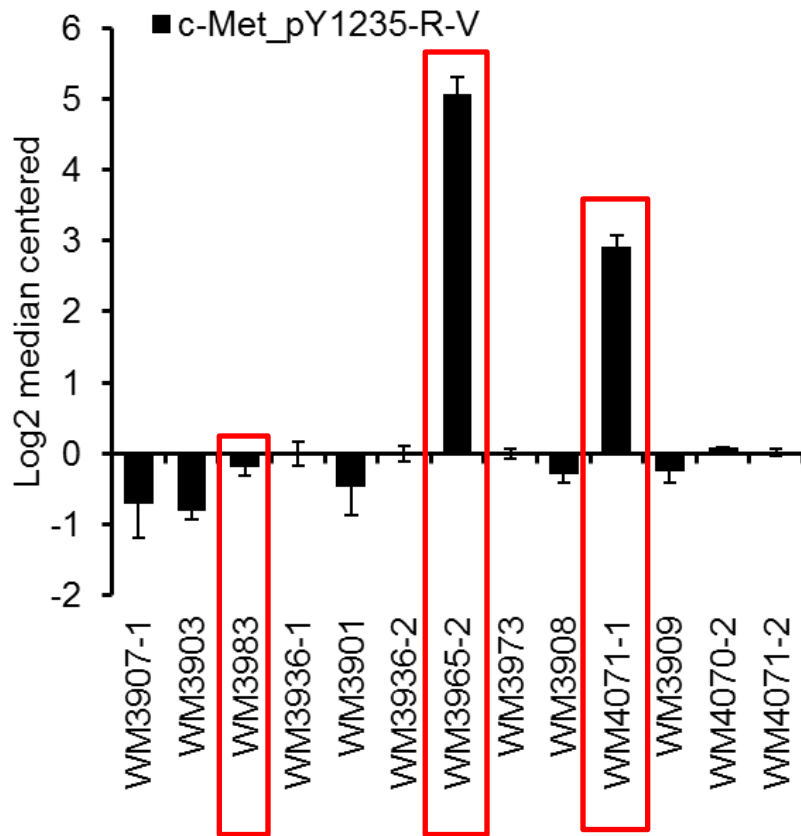


# Rational second line combination therapy synergizes in vivo



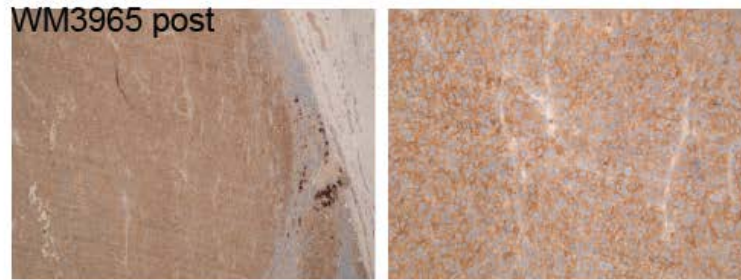
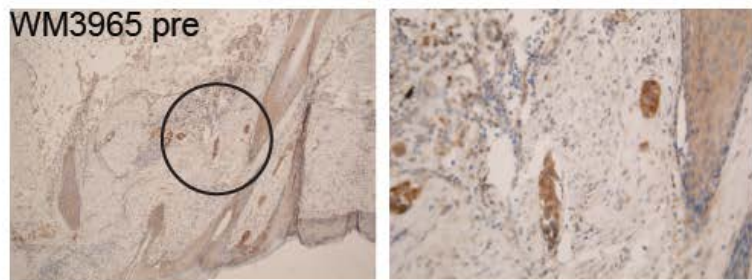
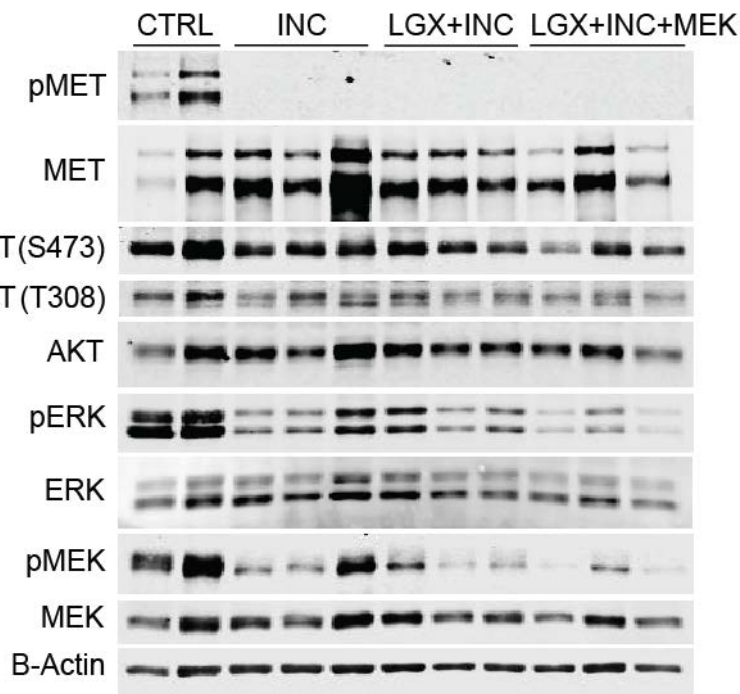
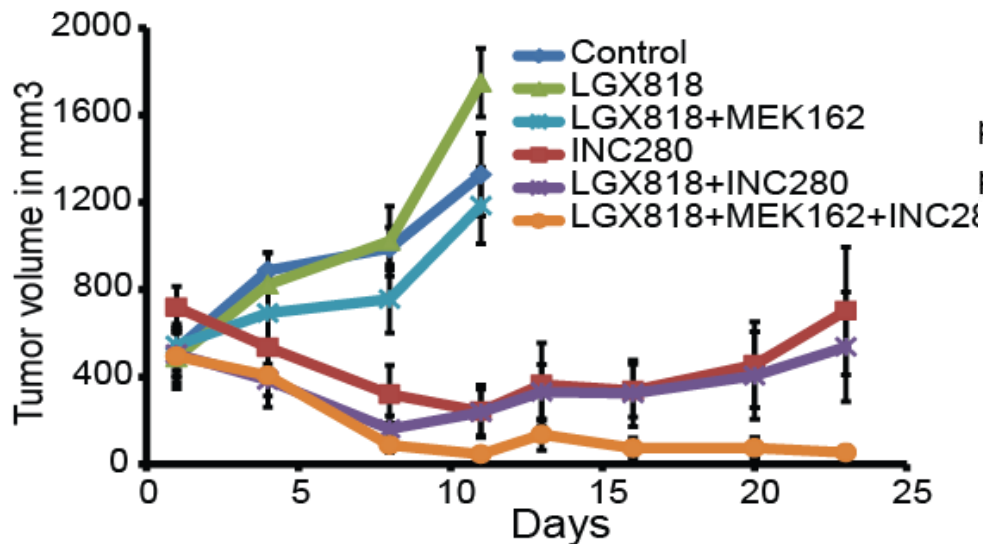
**WM3936-2: Excellent clinical response on dabrafenib . After 9 months new s.c. thigh lesion with aggressive growth under therapy. NRASmut, PTENmut, and PIK3CA mut; high pERK and pAKT.**

# 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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