Targeting the PI3K-Akt-mTOR pathway with GDC-0068, a novel selective ATP competitive Akt inhibitor

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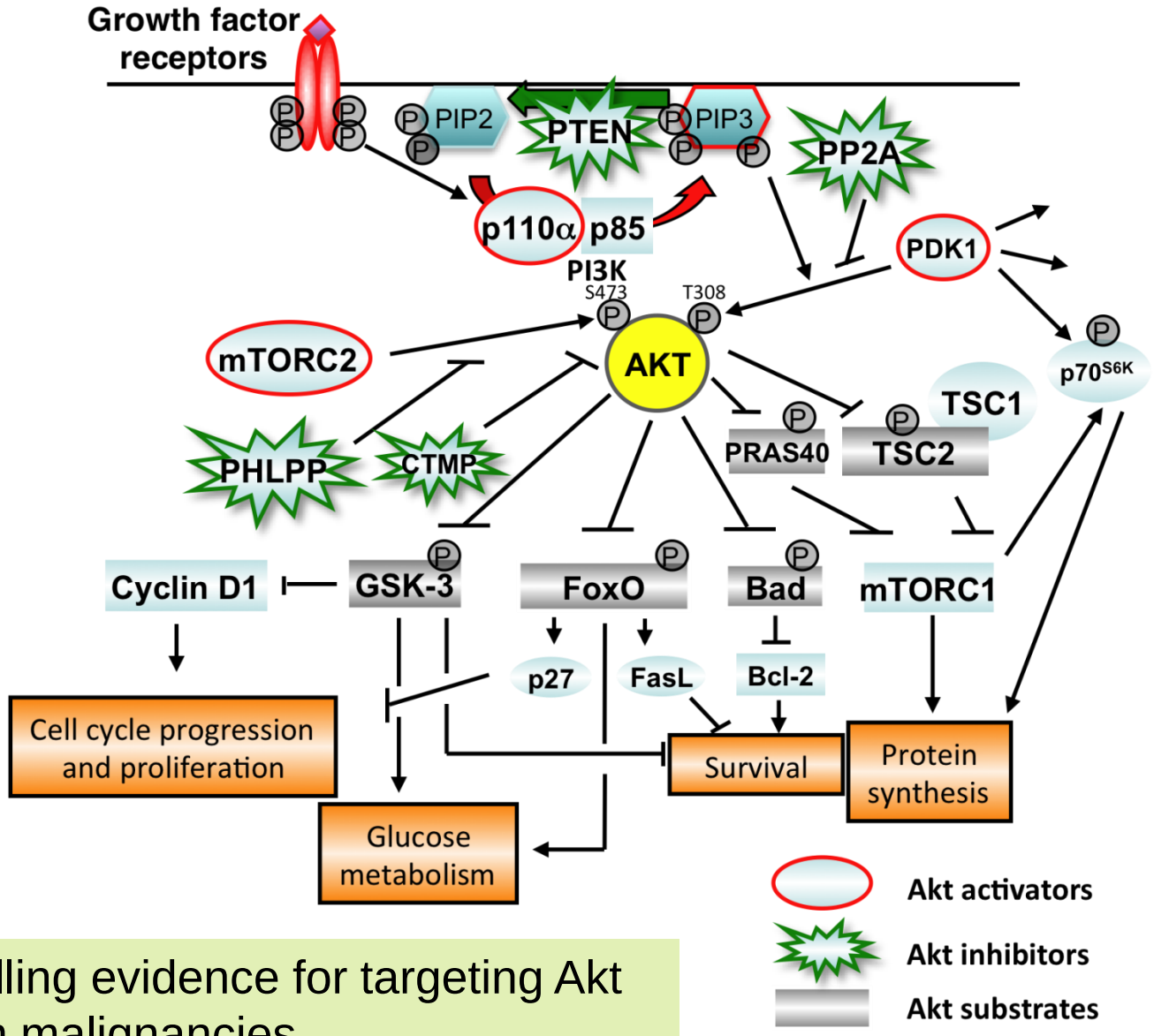
Akt pathway is frequently activated in cancer



- Compelling evidence for targeting Akt in human malignancies

GDC-0068: Novel, specific, ATP competitive Akt inhibitor

Enzymatic potency and selectivity of GDC-0068

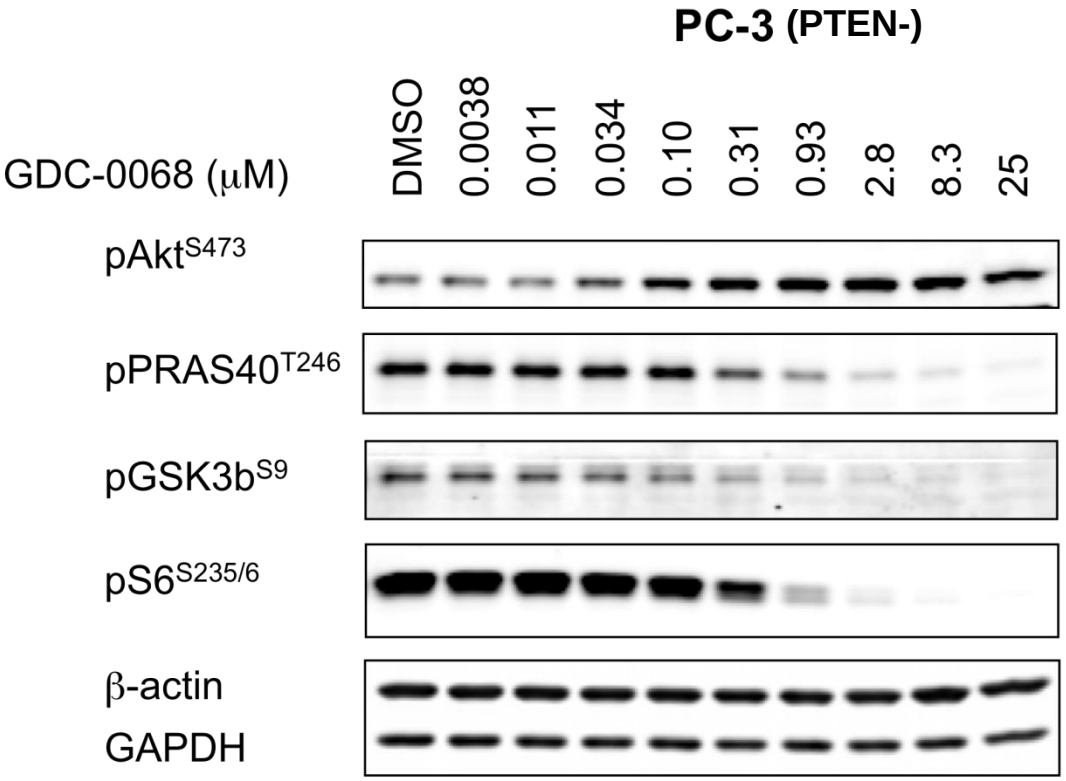
Kinase	IC50 (nM)
Akt1/2/3	5/18/8
PKG1a/b	98/69
p70S6K	860
PKA	3100
SGK	>1000*
PDK1	>1000*
AMPK	>1000*

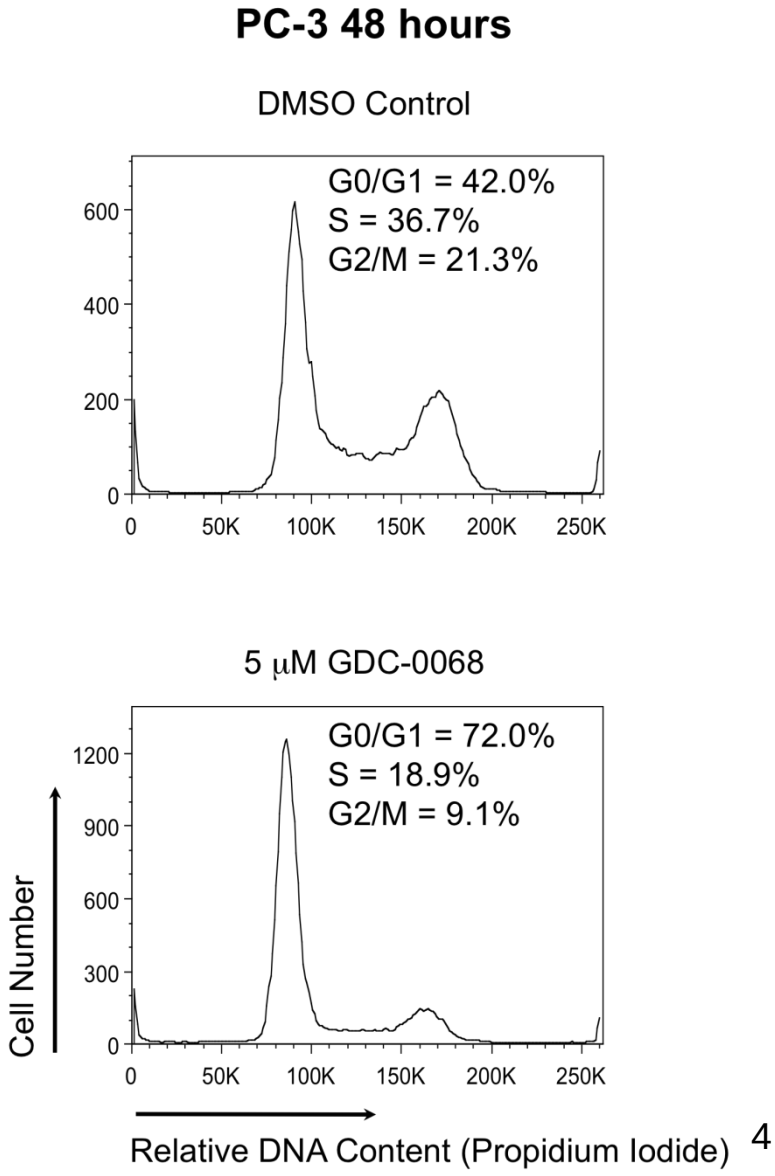
*No inhibition when screened at 1000 nM in a protein kinase panel

Cellular potency of GDC-0068

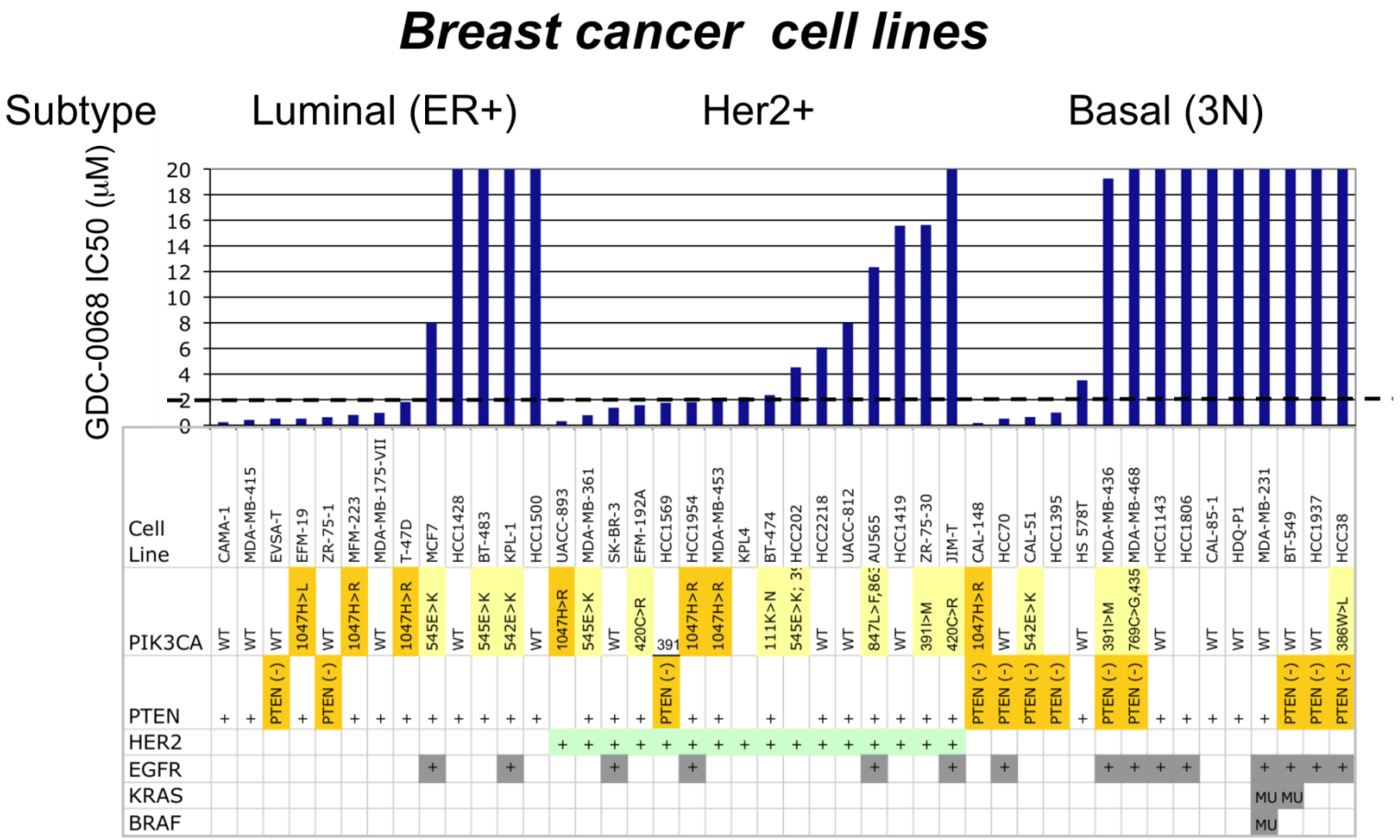
Cell line	pPRAS40 IC50 (nM)
LNCaP	157
BT474M1	208

GDC-0068: Effectively blocks Akt signaling and induces cell cycle arrest in human cancer cell lines in vitro





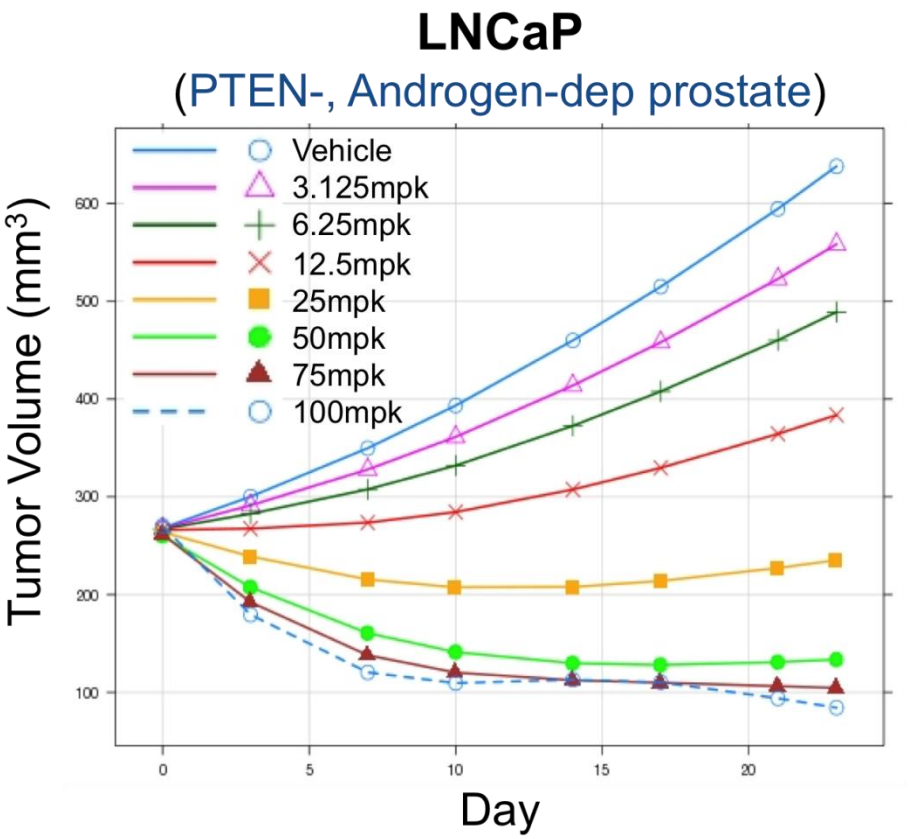
High Akt activity predicts sensitivity to GDC-0068

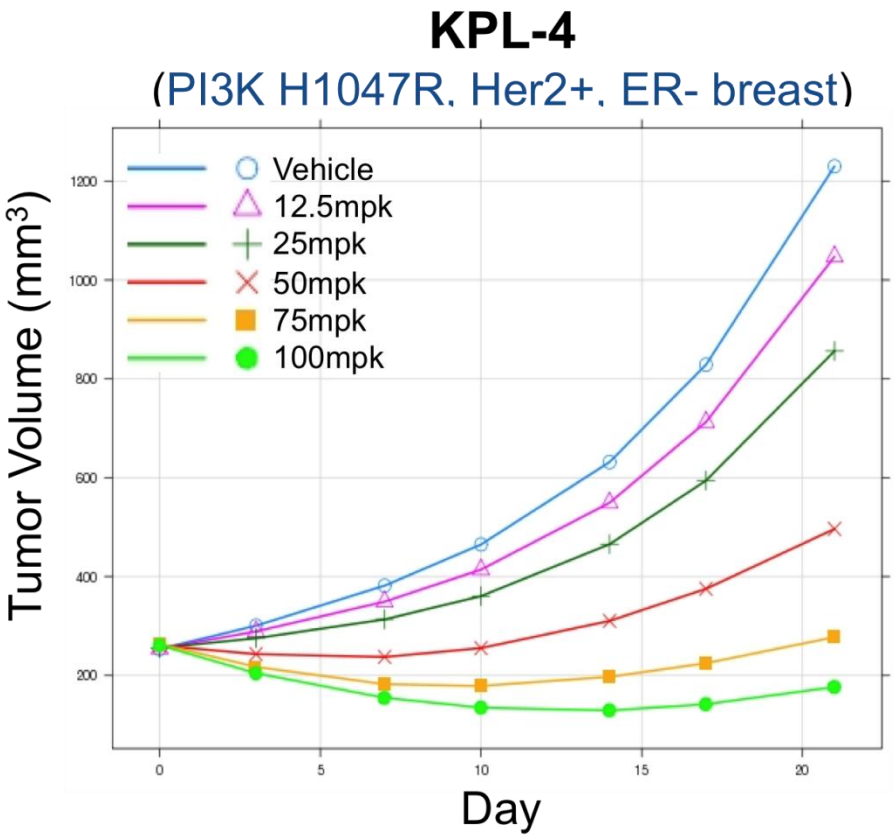


Sensitivity in breast cancer cell line panel:

- Strongest in HER2+ and Luminal subtypes.
- Driven by PI3K kinase domain mutations, PTEN loss and HER2 amplification.
- Negative association with KRas/BRaf mutations and EGFR expression.

GDC-0068 exhibits significant efficacy in PTEN- and PI3K mutant xenograft models



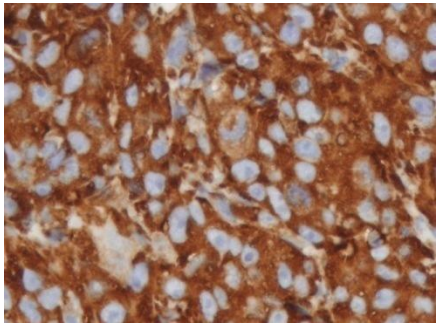


IHC/IF and RPPA: Complementary platforms to demonstrate PD changes

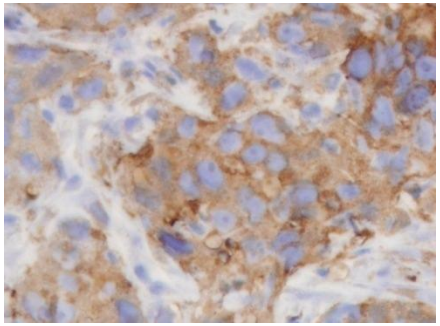
- GDC-0068 reduces pS6 and peIF4G levels in BT474-Tr xenografts

pS6 IHC

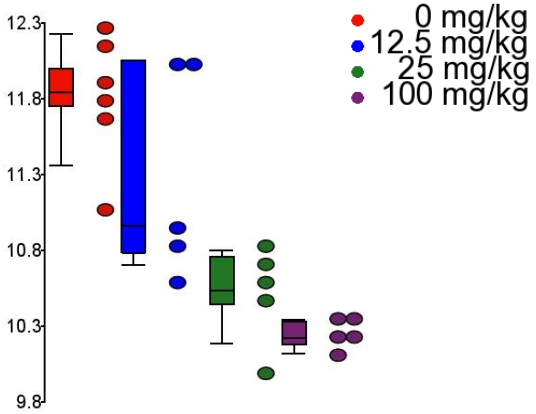
Vehicle



GDC-0068

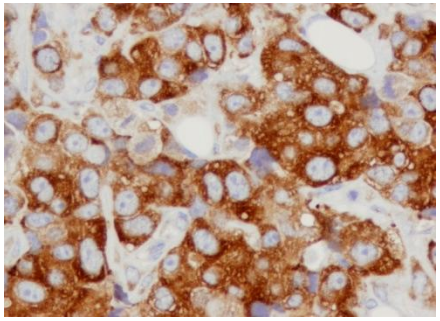


pS6 RPPA

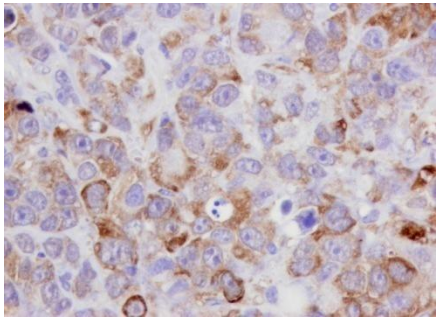


peIF4G IHC

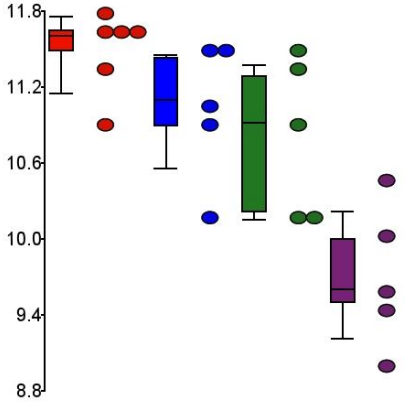
Vehicle



GDC-0068



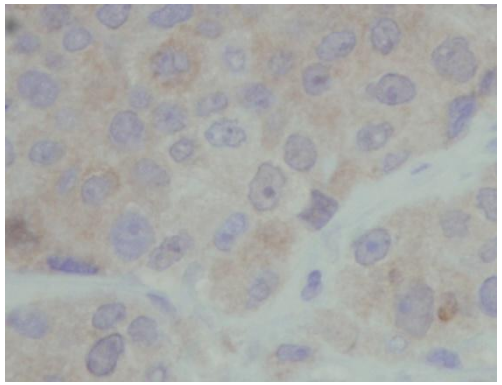
peIF4G RPPA



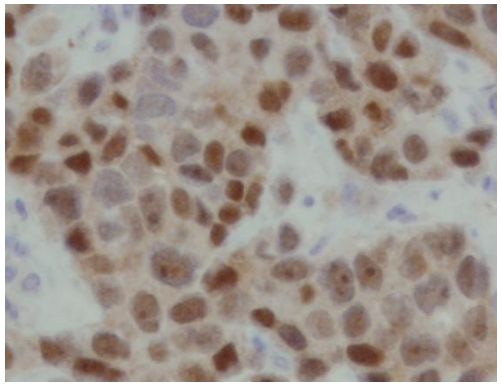
IHC/IF: Akt Inhibitor GDC-0068 relocalizes FOXO3a to nucleus

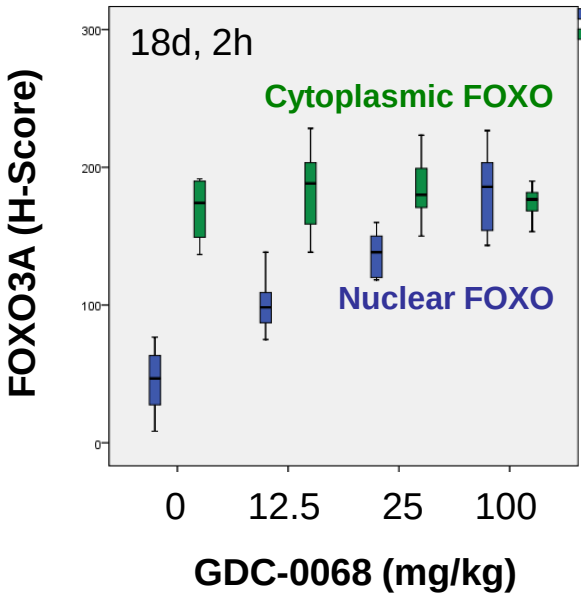
- Subcellular localization of FOXO3a regulated by phosphorylation by Akt
- Nuclear FOXO3a controls transcription of pro-apoptotic and cell cycle inhibitory genes

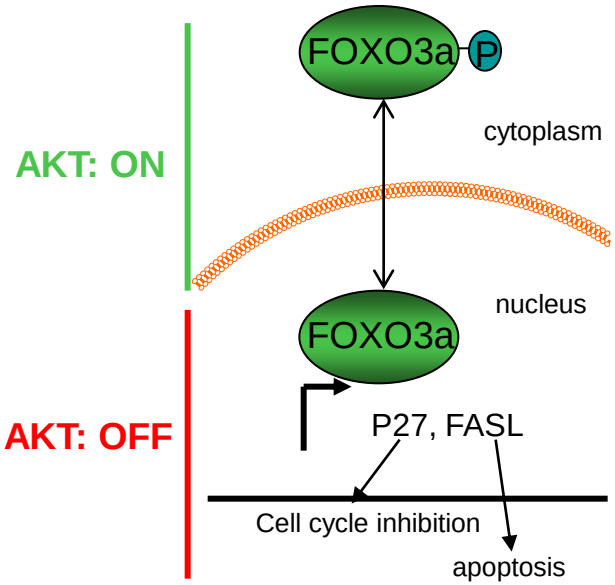
Vehicle



GDC-0068

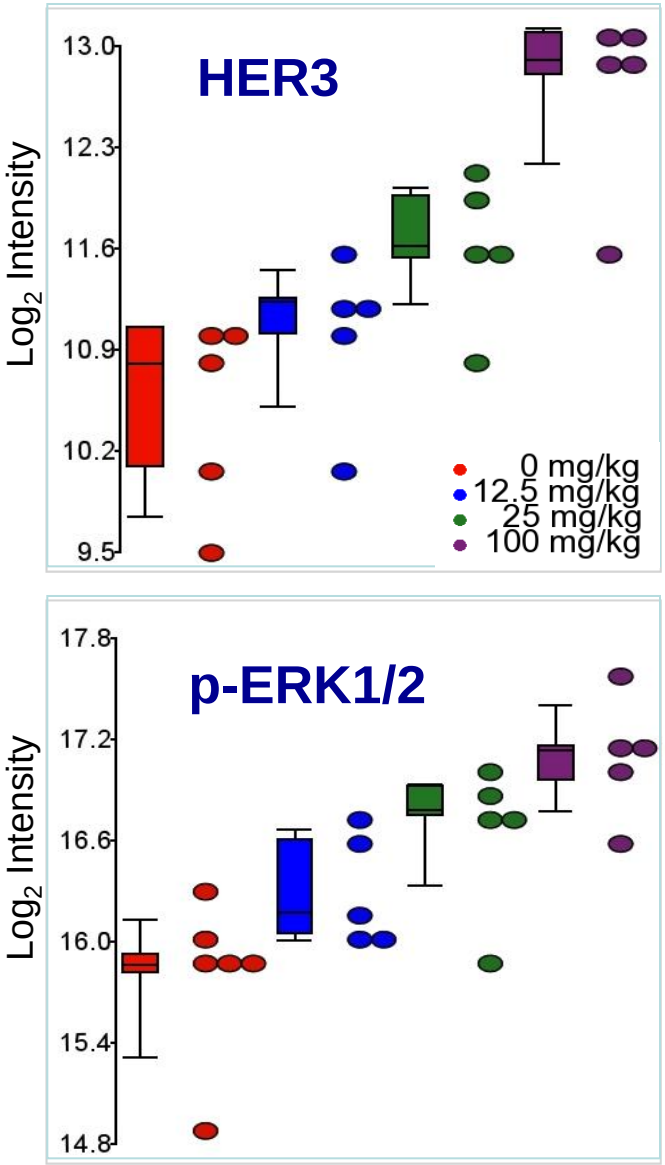


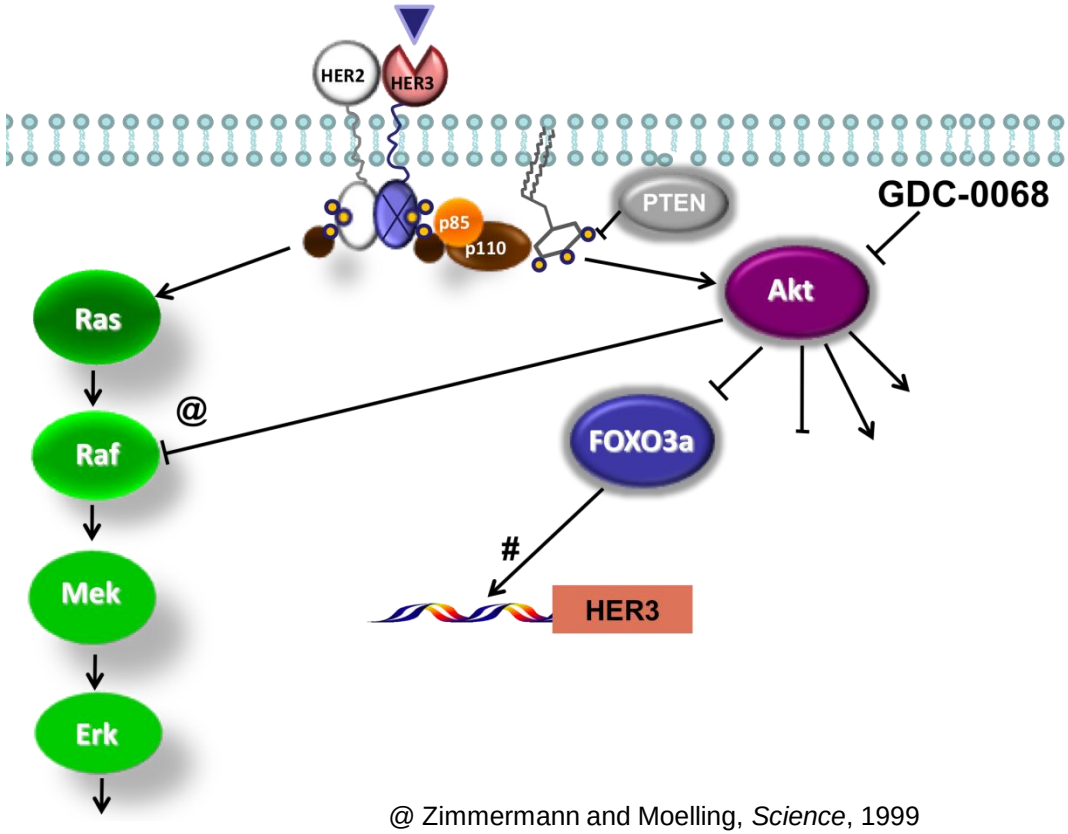




GDC-0068 treated BT474-Tr xenografts

RPPA analyses demonstrate feedback upregulation of HER3 and pERK induced by the Akt Inhibitor GDC-0068

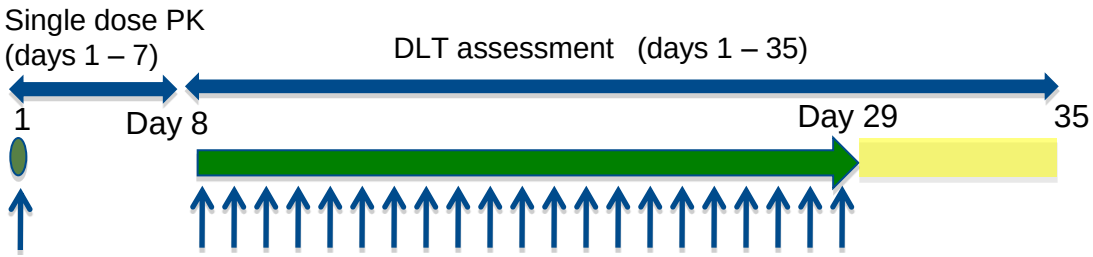




@ Zimmermann and Moelling, *Science*, 1999
# Serra et al., *Oncogene*, 2011; Makhija, et al., *J. Clin. Oncol.*, 2010; Garrett, et al., *Cancer Res.*, 2009

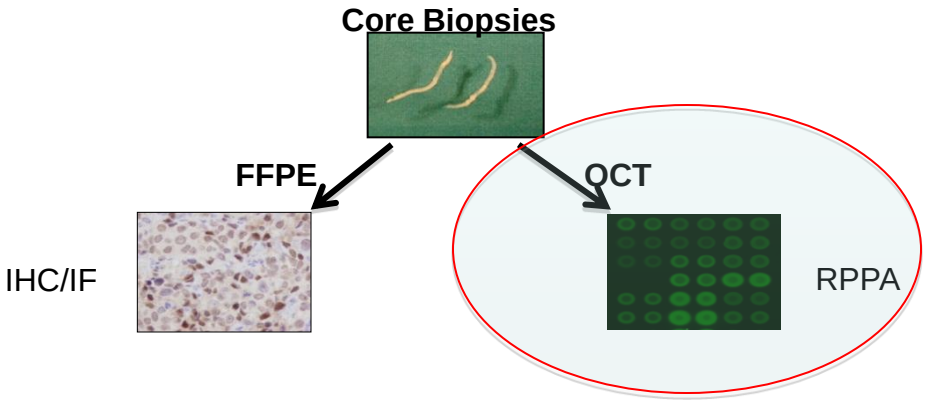
GDC-0068 treated BT474-Tr xenografts

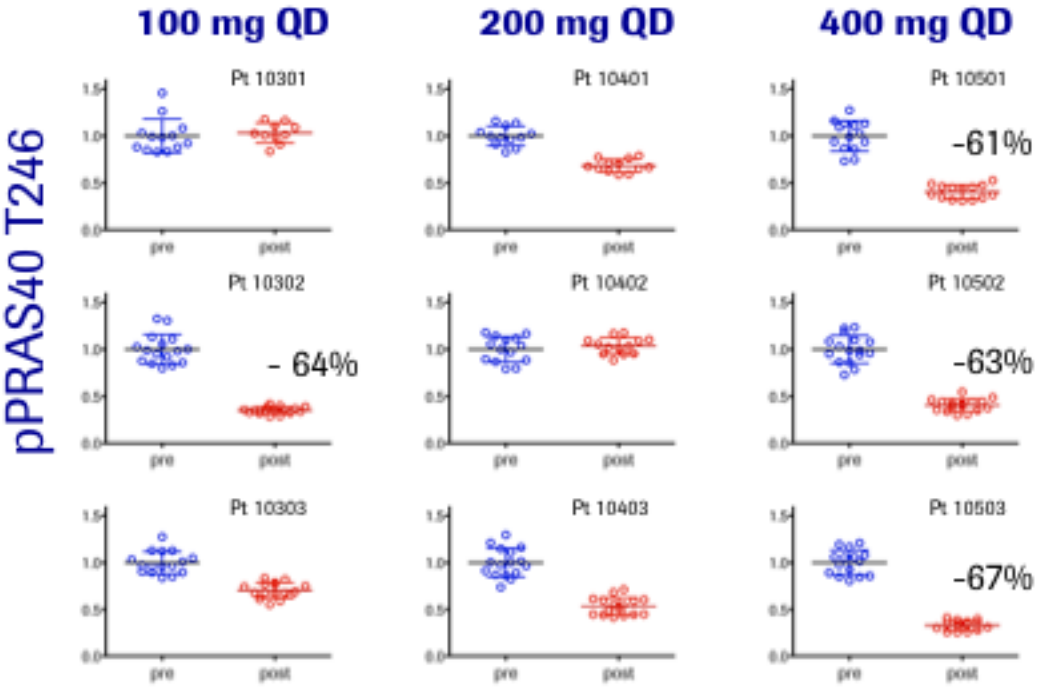
GDC-0068 Phase I dosing strategy



- **Dose:** oral daily x 21 days on/ 7days off
- **Schema:**
  - Single PK dose in week 1, then 21/28 day dosing
  - Dose GDC-0068 in am (post O/N fast) and fast 2 hrs post dose
  - Standard 3+3 design
- **PD:**
  - Surrogate tissue: AKT pathway evaluation in platelet-rich plasma
  - pre- and on-treatment skin biopsy of all patients
  - Tumor biopsy when ≥ 50% pathway knockdown achieved in surrogate tissue

Preliminary evidence for pathway knockdown in tumors





- All 3 patients in 400 mg cohort show >60% inhibition.

- Tumor biopsies were obtained from patients during screening (baseline) and once during Cycle 1 (between Days 15 and 21).

- Needle core biopsies were snap-frozen and evaluated by reverse phase protein array for epitopes, including pPRAS40.

- Decreases of 60%–70% in pPRAS40 (compared with baseline) were demonstrated in all 3 patients treated at 400 mg once daily

Conclusions

- GDC-0068 is a novel, oral, selective ATP-competitive AKT inhibitor
- Preclinical activity is most pronounced in models driven by PI3K kinase domain mutations, PTEN loss and HER2 amplification
- GDC-0068 treatment resulted in pronounced PD effects in tumor xenograft models as measured by RPPA and/or IHC, including dose-dependent suppression of P-S6 and P-eIF4G, as well as induction of FOXO nuclear localization
- GDC-0068 is currently in phase I develoment
- At well-tolerated doses, GDC-0068 results in >60% pathway knockdown in surrogate and tumor tissue

Acknowledgments

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