Targeting The PI3K Pathway in Women's Cancers

Lewis Cantley, Gordon Mills, Charles Sawyers

Eric Winer – Clinical Trial Leader

Potential Conflicts

Agios Pharmaceuticals
Aveo Pharmaceuticals
Vertex
Transmolecular
Cell Signaling Technologies

BMS
Alnylam
Infinity
Perkin Elmer
Neurophage

GSK
Novartis
Merck
Genentech
Amgen
Millennium
Takeda
Biogen
Affymetrix
Infinity

Beth Israel Deaconess
Lewis Cantley
Gerburg Wulf
Pier Paolo Pandolfi
Andrea Myers

Dana Farber
Tom Roberts
Eric Winer
Ursula Matulonis
Jean Zhao
Ian Krop
Andrea Richardson
David Livingston
Joyce Liu
Dirk Iglehart
Nancy Lin
Don Watson

MGH
Jose Baselga
Michael Birrer
Jeff Engelman

Sloan Kettering
Charles Sawyers
Carol Aghajanian
Douglas Levine
David Solit
Neal Rosen
Robert Soslow
Chris Sander
Alex Lash
Nicholas Socci
Nikolaus Schultz
Karuna Garg

Vanderbilt
Carlos Arteaga
Ingrid Mayer
Melinda Sanders

MD Anderson
Gordon Mills
Yisheng Li
Don Berry
Rob Coleman
Russel Broaddus
Funda Meric-Bernstam
Ana Gonzalez-Angulo
Karen Lu
Pricilla McAuliffe

Vall d'Hebron
Jose Baselga
Jordi Rodon
Josep Tabernero
Yasir Ibrahim
Violeta Serra

Columbia
Ramon Parsons
Matthew Maurer

THIS IS WHERE THE END OF CANCER BEGINS

STAND UP TO CANCER™

Advocates

Janet Price (HICC), Elizabeth Frank (DFCI), Don Listwin (MDACC), Jane Perlmutter (MDACC), Ruth Fax (DFCI), Judi Hirshfield-Bartec (MSN/BIDMC), Patricia Lee (VICC), Piru Cantarell (Vd'H)

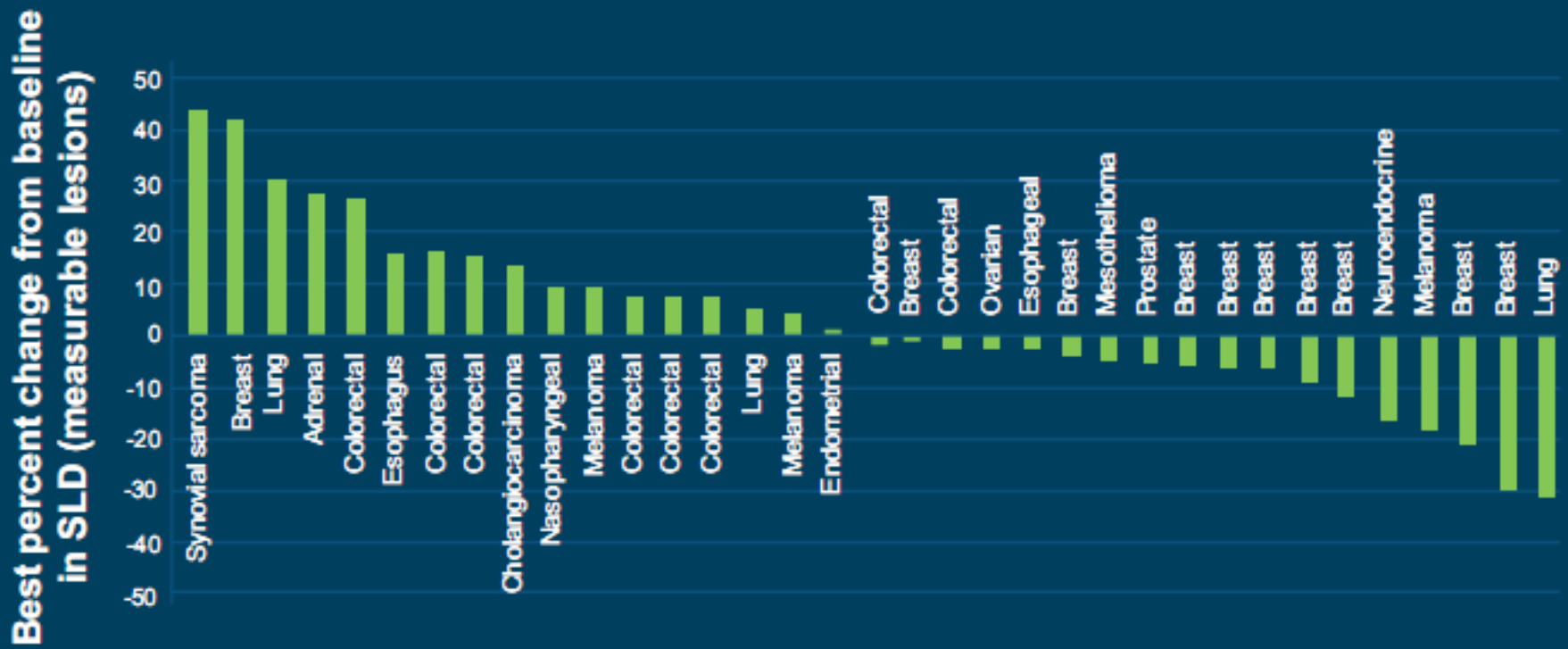
THIS IS WHERE THE END OF CANCER BEGINS

STAND UP TO CANCER™

Tumor Type	PIK3CA	AKT1	PTEN	PTEN	INPP4B	PDK1	RAS/RAF	HER2	p53
	Mutations	Mutation	Mutation	Protein loss	deletion	Amplification	Mutation	Amplification	Mutation
Breast Total	339/1261 **(26.9%)**	27/1008 (2.6%)	6/209 (2.3%)	25/110 **(22.7%)**	**~20%**	27/129 **(20.9%)**	2/406 (0.5%)	15%	46/121 **(38%)**
Breast HR+	101/305 **(33.1%)**	6/232 (2.6%)	4/131 (3.4%)	10/69 (14.5%)	rare	16/79 **(23.2%)**		0	18/73 **(24.6%)**
Breast HER2+	24/98 **(24.5%)**	0/75	0/33	2/18 (11%)	rare	5/19 **(26.3%)**		**100%**	14/23 **(60.9%)**
Breast TN	21/262 (8.0%)	0/111	2/41 (4.9%)	11/21 **(52%)**	**60%**	2/15 (13.3%)		0	14/22 **(63.6%)**
Ovarian	2/332 (0.6%)	2/332 (0.6%)	4/132 (3%)	**40%**	**~20%**	rare	12/428 (2.8%)	8%	90/132 **(68%)**
Endometrial*	**73/246 (30%)**	3/150 (2.0%)	**20/76 (26%)**	**>50%**	8.00%	rate	**44/206 (21%)**	rare	9/96 (9%)
Where patient numbers are present represents data from consortium.									
*** in Endometrial cancer, of the RAS mutant tumors half are Pik3CA or PTEN mutant.**									
In endometrial tumors 60% of the PIK3CA and PTEN mutant tumors are Ras mutant.									
Other mutations tested in breast include: CTNNB1, Jak2, PDGFRA, EGFR, KIT, FBXW7,									
Other mutations tested in ovarian and endometrial include: CTNNB1, FGFR2									

BEZ235 Phase I: Reduction in tumor burden as per CT

CT SCAN



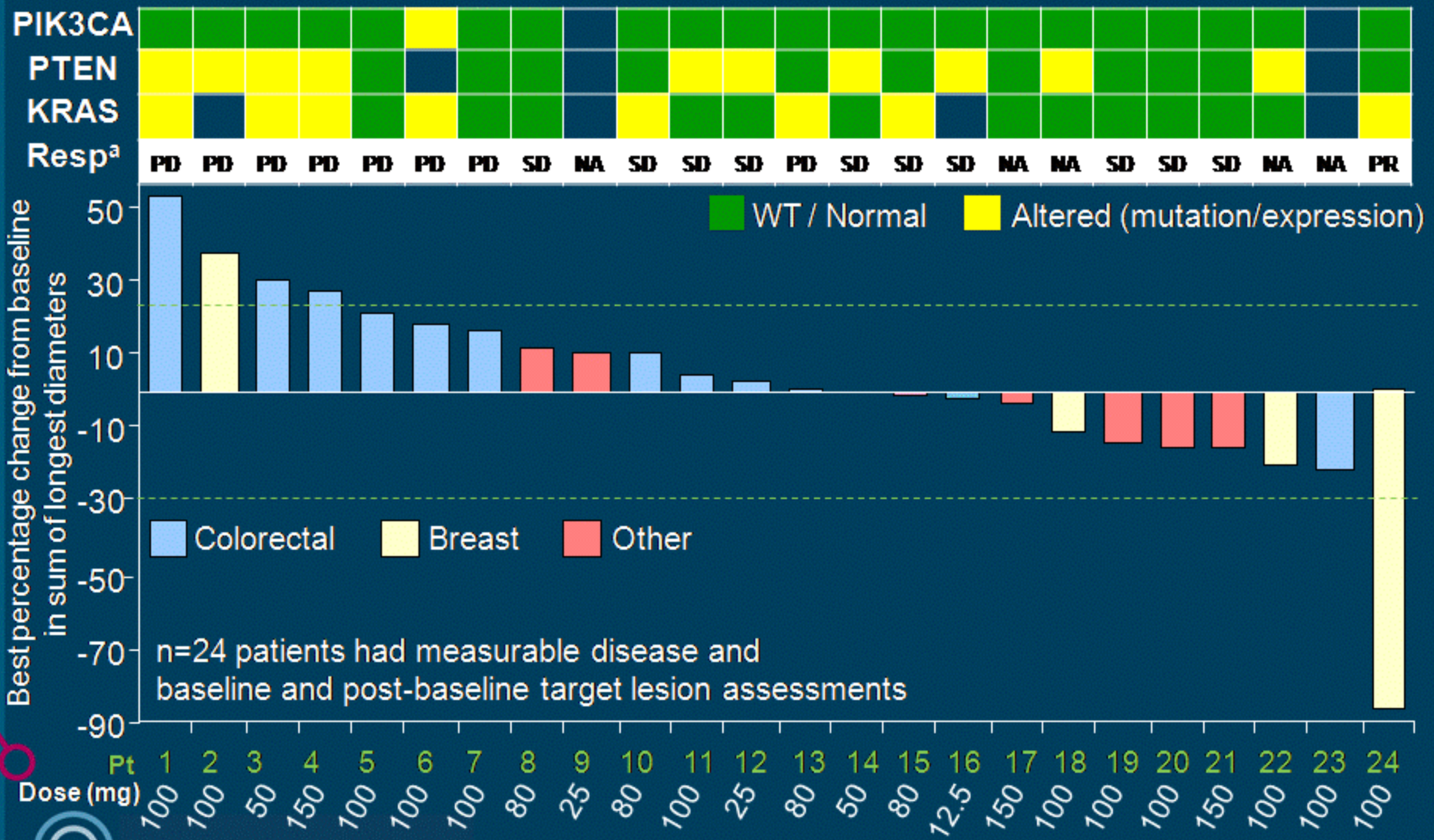
- 18 out of 35 evaluable patients had tumor shrinkage ≥ -5% as per central review

ASCO Annual '10 Meeting

Baselga, Rodon

BKM120 Phase I: clinical efficacy by radiologic assessment and overall respo e

CT SCA N



[a]Response as per investigator; NA, not available

General Approach To Clinical Trials in Stand Up To CancerPI3K Dream Team

- Inclusive of almost all Women's Cancers
  - Breast
    - HER2+
    - Triple Negative
    - ER+
  - GYN
    - Endometrial
    - Ovarian

All trials require surgical material and/or biopsies that will be interrogated for mutations, amplifications and deletions of known oncogenes and tumor suppressor genes!!

Animal Models

We are generating mouse models engineered to replicate the same mutational events that are frequently observed in breast, endometrial and ovarian cancers.

The mice are being subjected to the same drug treatments that are being used in the human trials

When resistance is observed, the mutational changes in the mouse tumors before and after resistance are examined. The ability of these mutations to drive resistance are evaluated

These results lead to hypotheses for innate resistance or acquired resistance to PI3K inhibitors in the human trials and suggest combination therapies.

Guiding Principles (1)

- **Develop limited number of molecularly driven single-agent trials**
- **Combine PI3 kinase inhibitors with other established targeted therapies (endocrine therapy for ER+ breast cancer and anti-HER2 therapy for HER2+ disease)**
- **Explore combinations of novel targeted agents (e.g. PI3K inhibitor and MEK inhibitor in:**
  - **Endometrial cancer**
  - **Triple negative breast cancer**

Guiding Principles (2)

- **COLLECT TISSUE**: All trials obtain tissue (FFPE and fresh research biopsies) + re-bx at progression
- **INCORPORATE NOVEL IMAGING**: Functional imaging used when promising and feasible
- **PURSUE COLLABORATIONS**: Agents obtained from both industry and CTEP. Accrual facilitated by interactions with TBCRC, GOG, other indivudal centers
- **LEVERAGE COMPLEMENTARY TRIALS**: Opportunity for tissue acquisition
- **USE NOVEL STATISTICAL DESIGNS**

Progress in enrolling patients

Phase 2: mTOR and/or MEK inhibitors in inoperable endometrial cancers: 168 patients enrolled

Phase 2: PI3K inhibitor/Herceptin in metastatic HER2+ breast cancers: 29 patients enrolled

Phase 2: PI3K inhibitor/Letrozole in metastatic ER/PR+ breast cancers: 26 patients enrolled (2 trials)

Phase 1b: AKT inhibitor/(Paclitaxel) in metastatic breast cancers: 6 patients enrolled

Trials that have just opened or will open later this year

Phase 2: AKT inhibitor in endometrial cancers
Phase 2: PI3K inhibitor in endometrial cancers
Phase 2: mTOR/MEK inhibitor in endometrial cancers
Phase 2: AKT inhibitor in ovarian cancers
Phase 2: PI3K inhibitor in triple negative breast cancers

In planning stage:
PI3K/MEK inhibitor combination in endometrial cancers

For information on our trials go to:

http://pi3k.org/

Progress in enrolling mice

Breast Cancers:

- PIK3CA H1047R driven breast cancers (ER+)
- PIK3CA H1047R/HER2 driven breast cancers (HER2+)
- PTEN-/- breast cancers (triple negative)
- Brca1-/-, p53+/- breast cancers (triple negative)
- Human explants into mouse breast (all types).

Endometrial Cancers:

- PTEN-/-
- PTEN-/-, PIK3R1-/-

Ovarian Cancers:

- Human explants into mouse plural cavity

All models being treated with drugs used in our human trials

Several hundred mice have been treated

Clinical Trials Team

- BREAST
  - Eric Winer DF/HCC
  - Ian Krop DF/HCC
  - Nancy Lin DF/HCC
  - Jose Baselga DF/HCC-VdH
  - Jordi Radon VdH
  - Carlos Arteaga Vanderbilt
  - Ingrid Mayer Vanderbilt
  - Funda Meric-Berstrom MDACC
  - Ana-Maria Gonzalez MDACC
- GYN
  - Carol Agajanian MSKCCC
  - Rob Coleman MDACC
  - Ursula Matulonis DF/HCC
  - Joyce Liu DF/HCC
  - Andrea Myers DF/HCC/BID
  - Michael Birrer DF/HCC/MGH

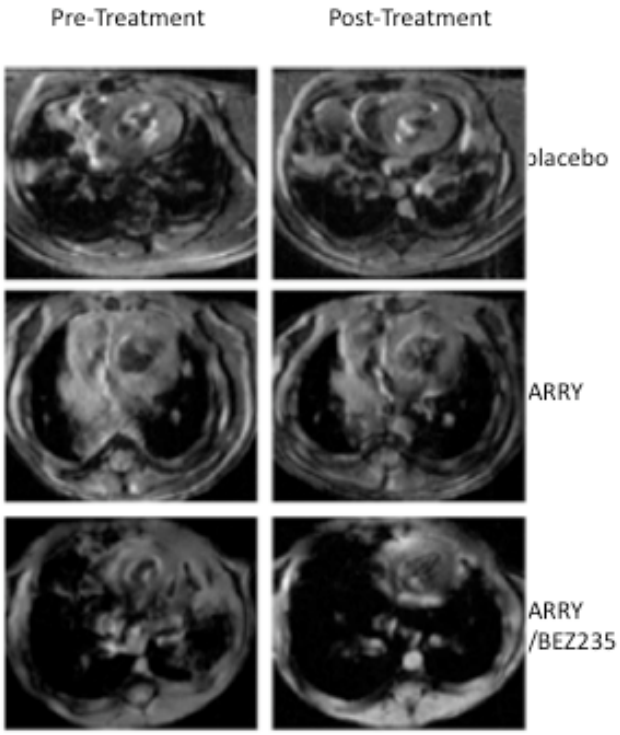
Mouse Clinical Trials Team:

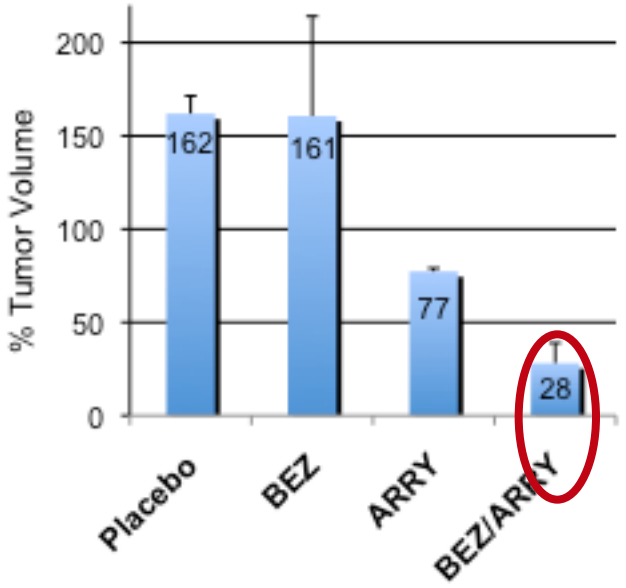
Breast:
Tom Roberts
Jean Zhao
Gerburg Wulf*
Andrea Myers*
Pier Paolo Pandolfi
Ramon Parsons
Carlos Arteaga*
Yasir Ibraham
Violeta Serra

Gyn:
Joyce Liu*
Jean Zhao
Andrea Myers*
Gordon Mills

*On both mouse and human trials teams

The K-Ras lung tumors are sensitive to combination therapy

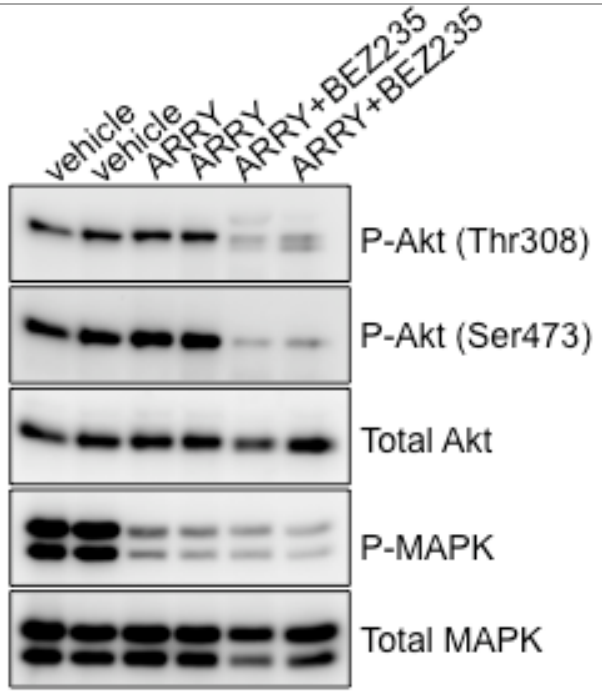


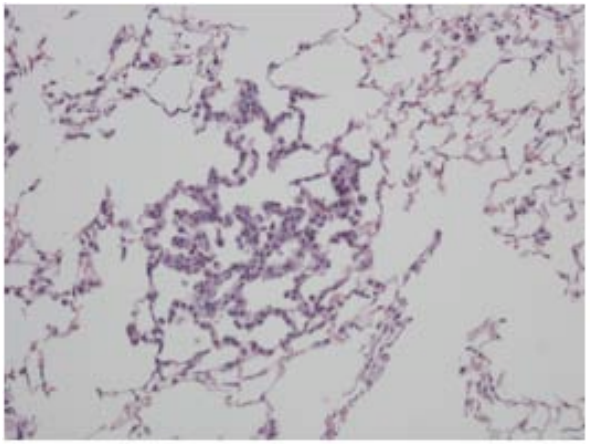


Combined PI3K and MEK inhibition has efficacy in:
KRAS mutant lung cancer, KRAS mutant colorectal cancer, basal breast cancer, EGFR mutant lung cancer

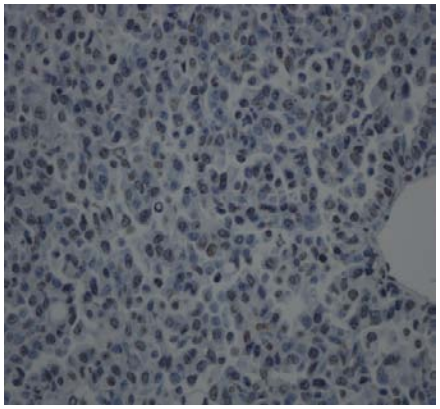
Engelman et al, Nature Medicine, 2008

Combination of PI3K and MEK inhibitors is effective in KRAS mutant cancers



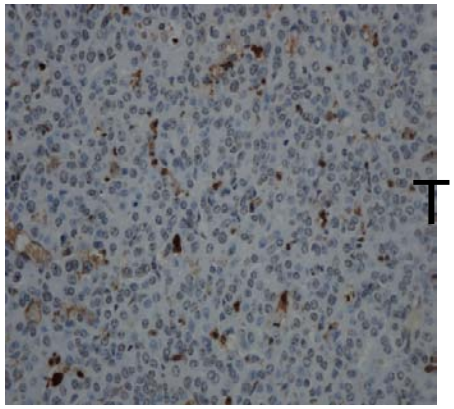


One of the larger remnant nodules after 2 weeks of combo treatment



Vehicle

TUNEL



ARRY +BEZ235 (after 2 doses)

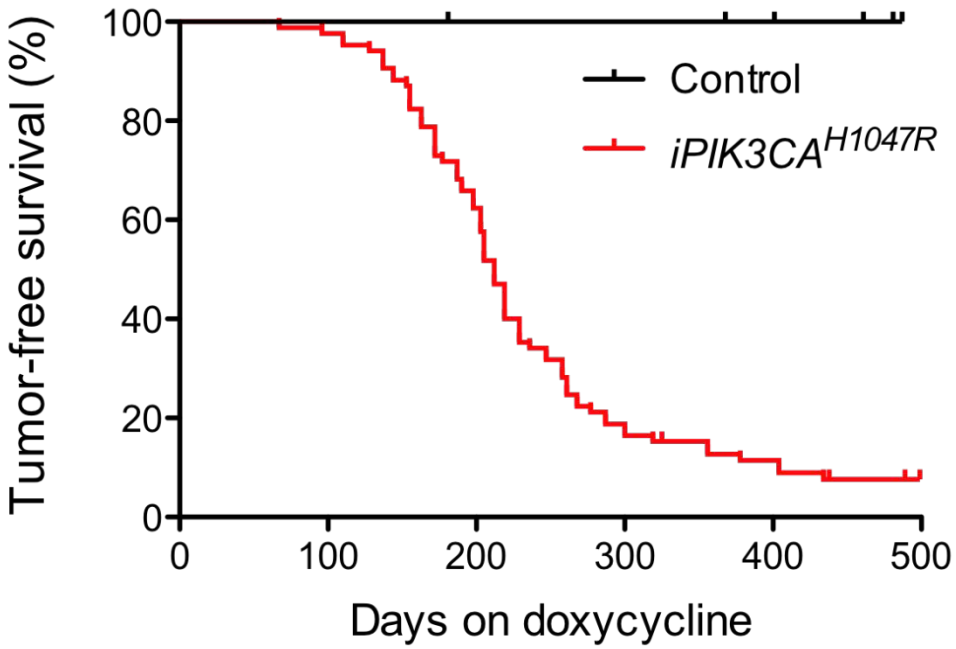
Engelman et al, Nature Medicine, 2008

Our Team has invested $500,000 to purchase 50-100 gram quantities of 10 different investigational drugs that recently entered phase II clinical trials and that were of interest to us for combination therapies.

Our policy is to test these drugs as single agents and in combinations and to immediately inform the companies who make these drugs if we observe efficacy in any of our mouse models.

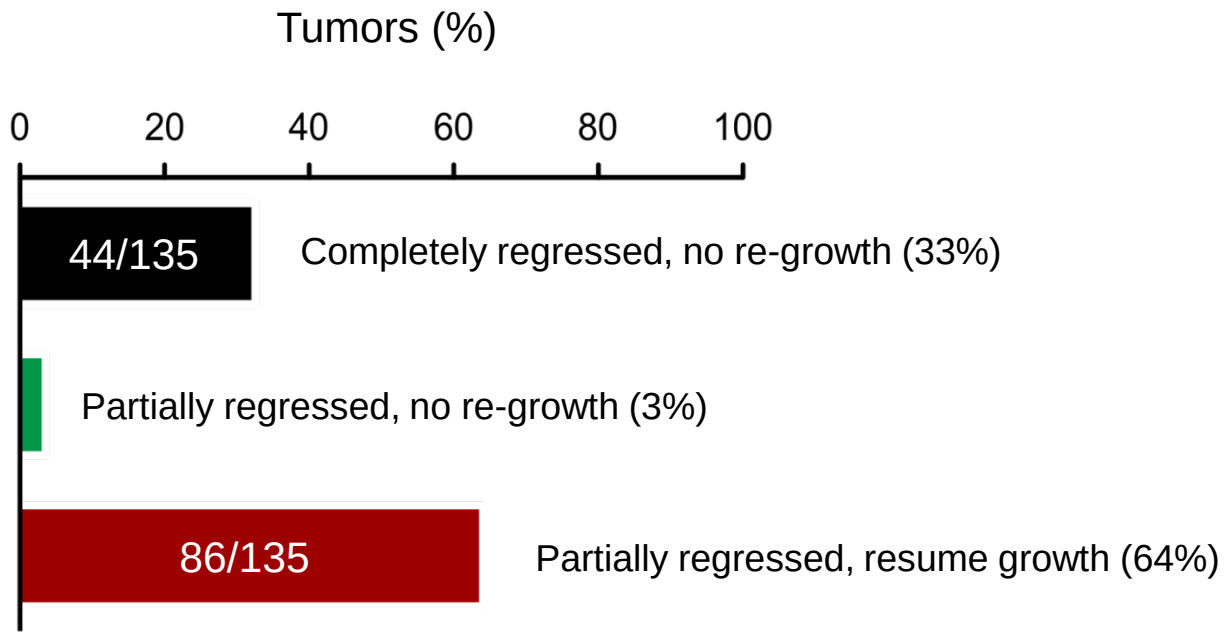
We then work with the companies that make the drugs to facilitate biomarker-driven combination trials (sometimes involving two companies).

Tumor-free survival curve of iPIK3CA^{H1047R} Mice



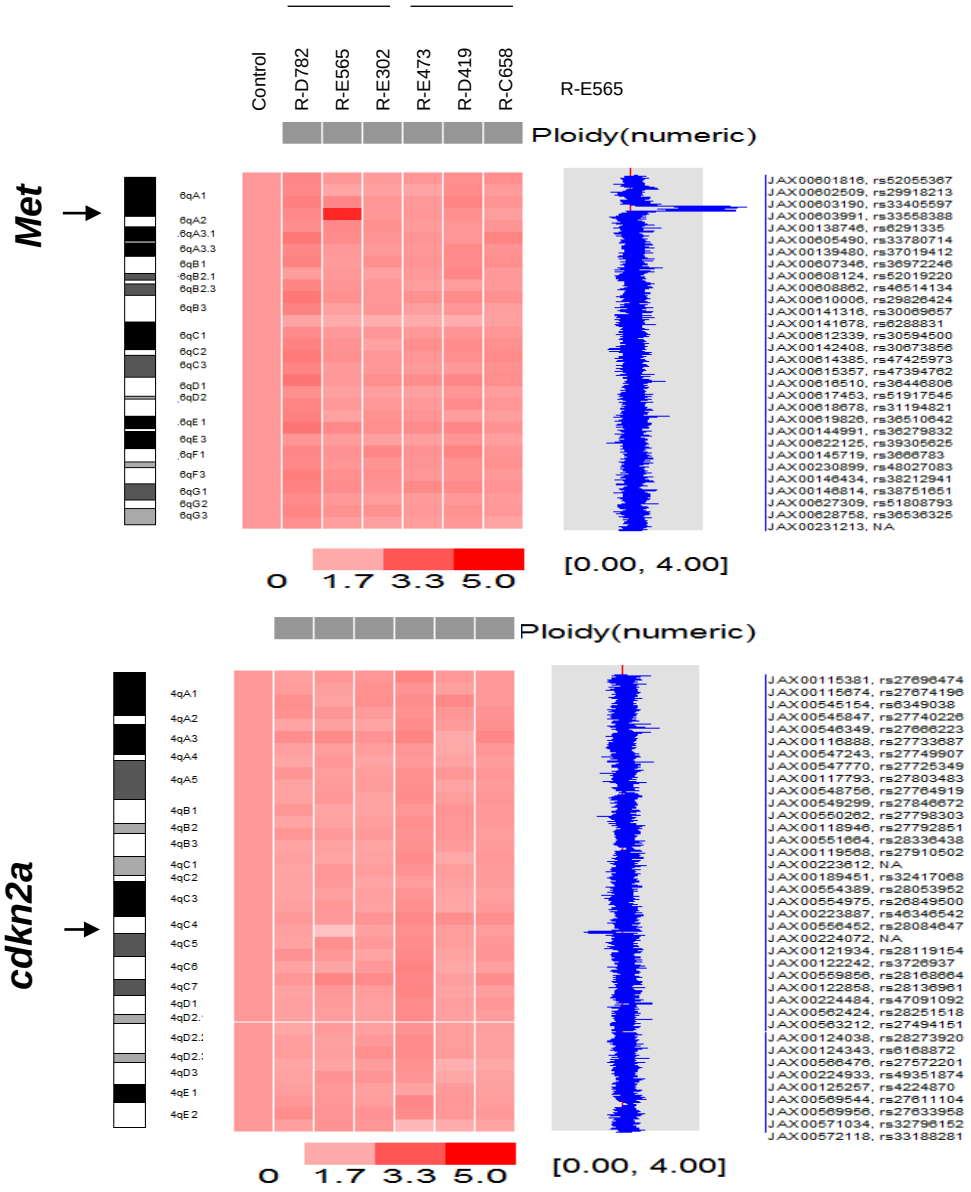
Length of Observation Period: ~500 days (17months);
Penetrance: ~95%;
Median Latency: ~200 days (7 months)

PIK3CA^{H1047R}-induced tumors frequently recur After doxy withdrawl or PI3Ki treatment

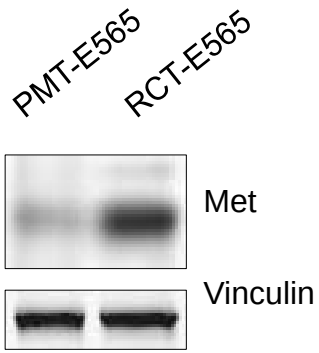


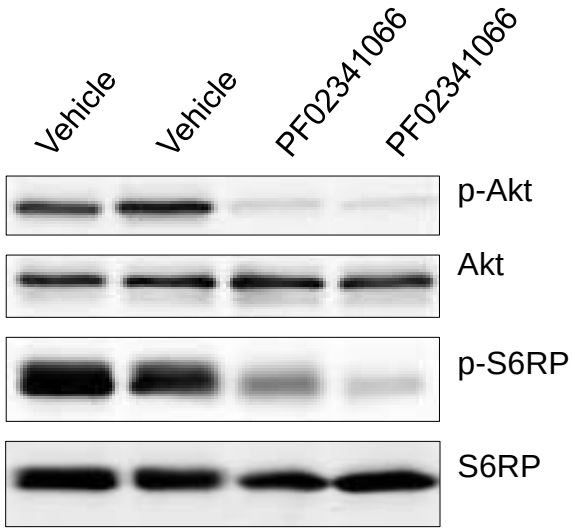
H. Cheng & P. Liu

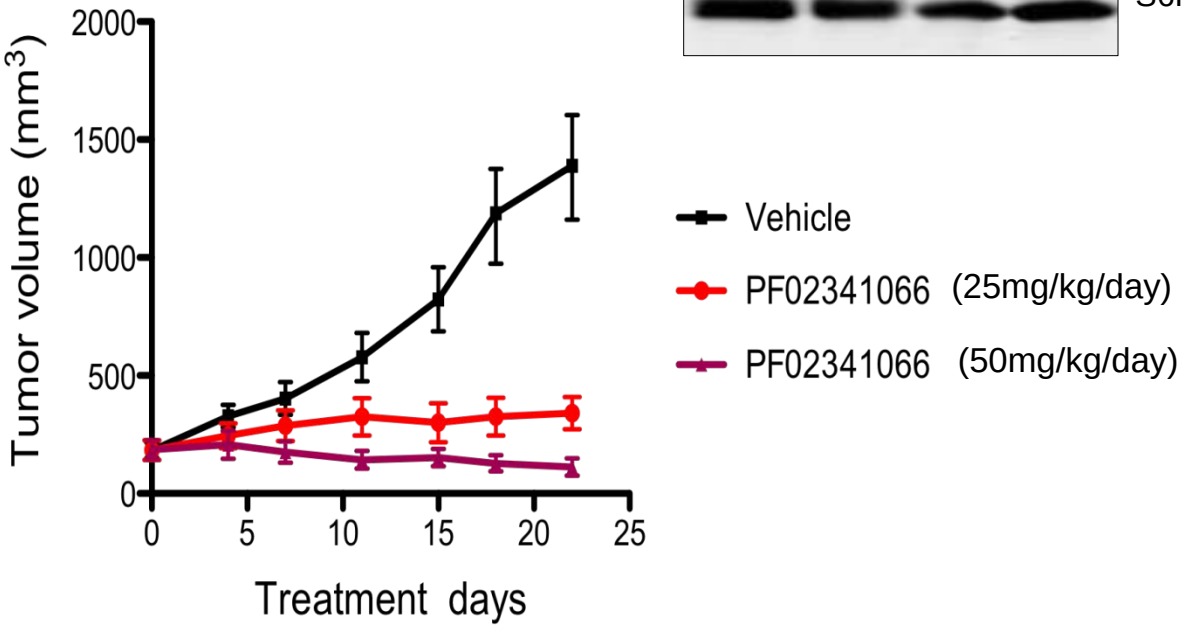
Met amplification found in recurrent tumors



Met contributes to PI3K activation and tumor recurrence when PIK3CA^{H1047R} is inactivated as judged by sensitivity to a MET inhibitor

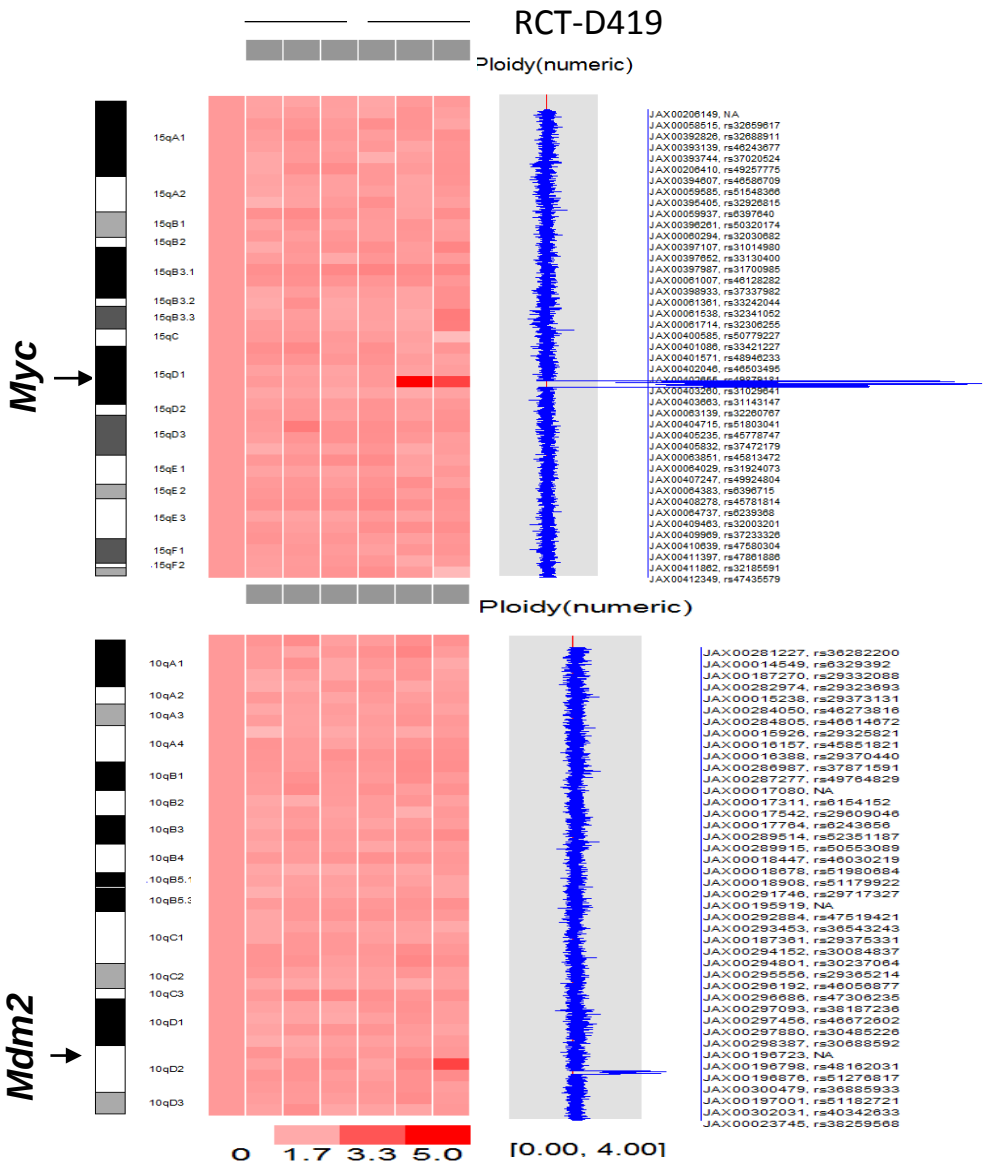






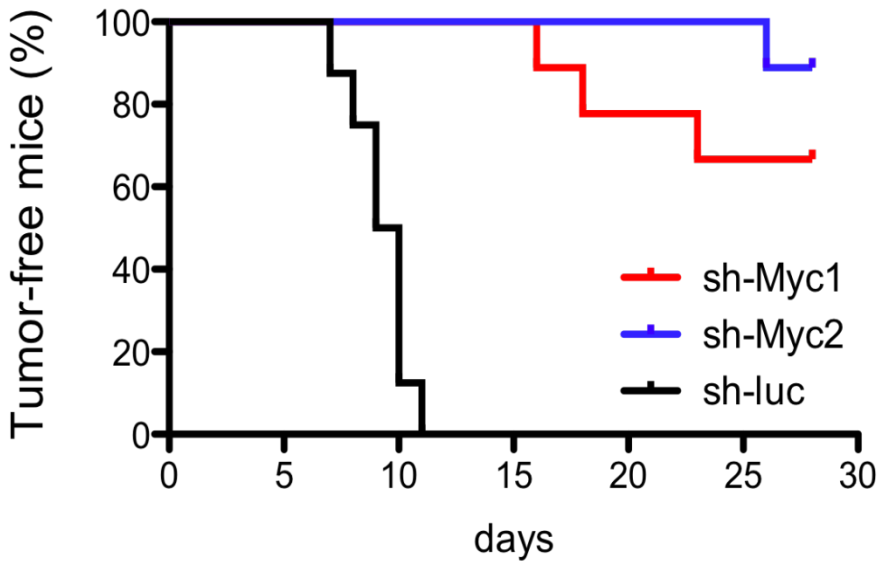
H. Cheng & P. Liu

Amplification of c-Myc found in recurrent tumors



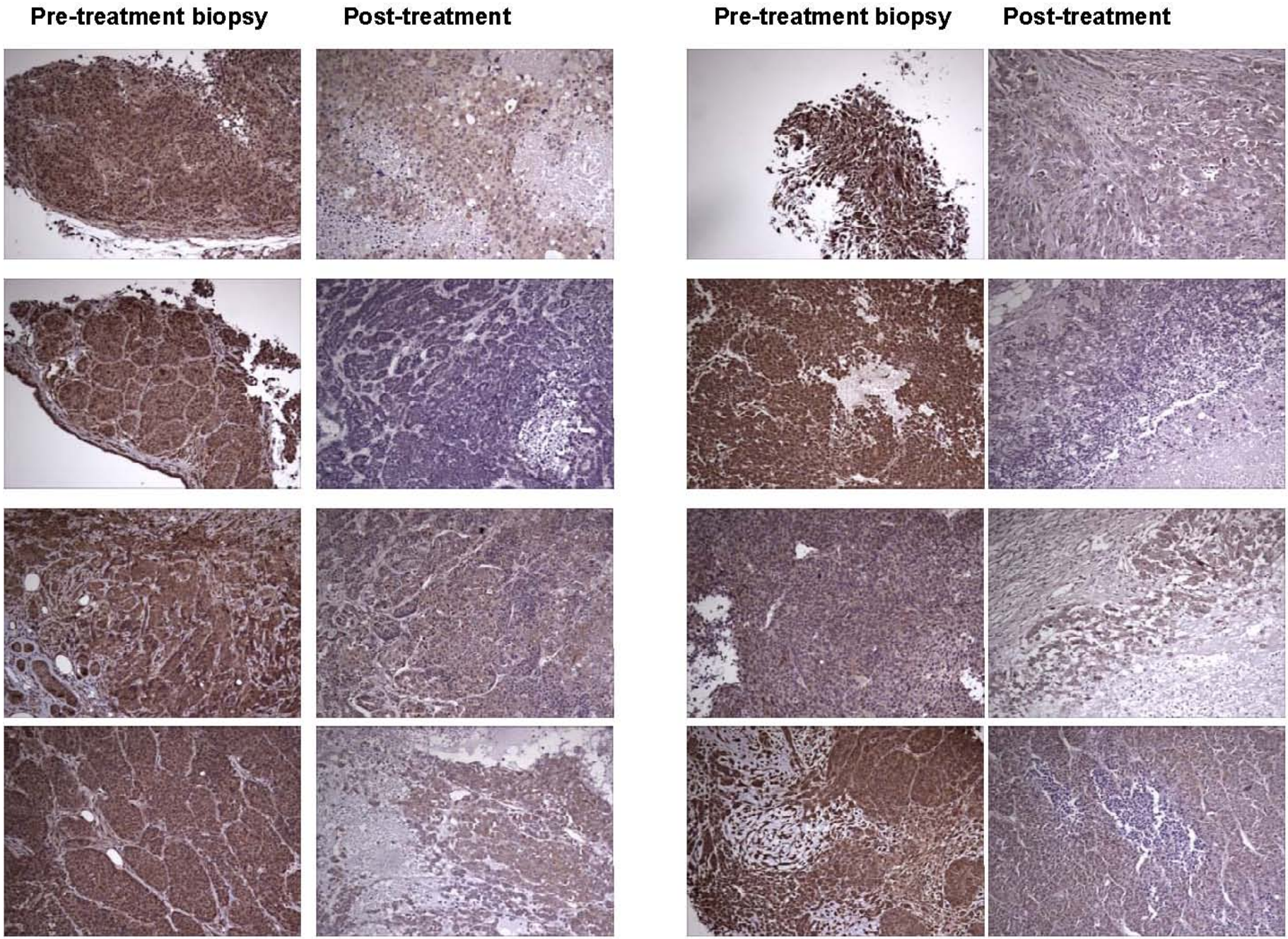
E Fox , J Yang

Myc knockdown impaired tumor formation



H. Cheng & P. Liu

Treatment of BRCA1-/-p53+/- murine BC with PI3K-Inhib: p-akt response

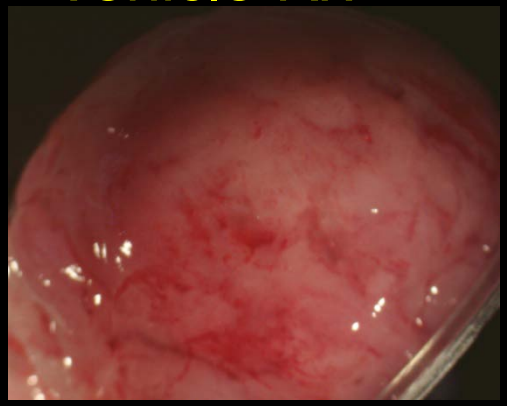


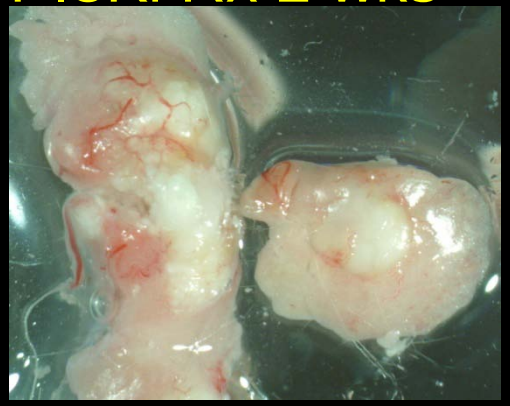
Gerburg Wulf

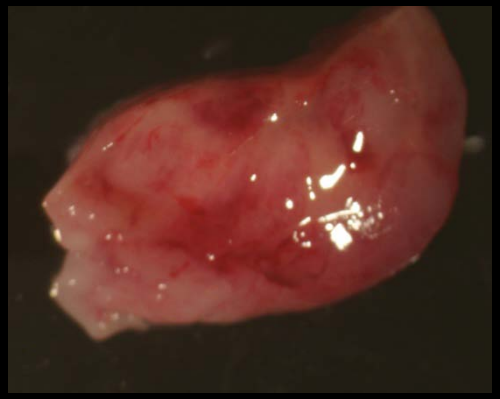
Tumor Morphology

vehicle Rx

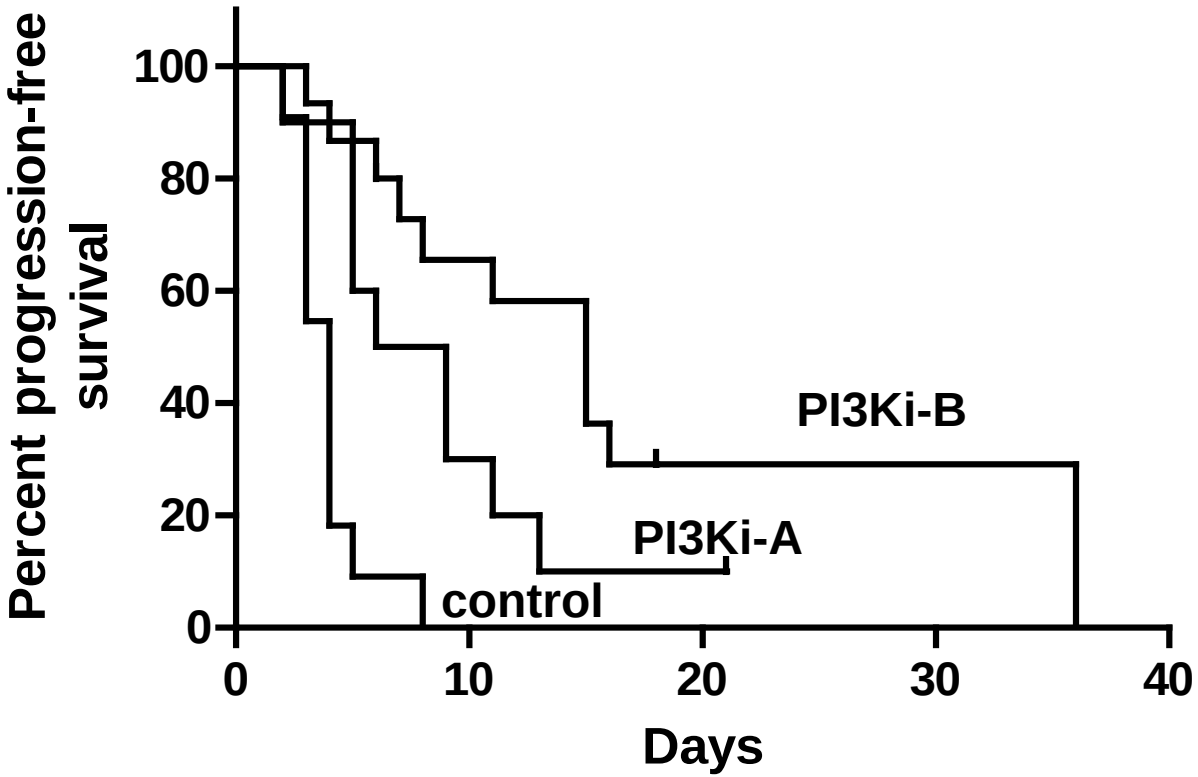
PI3Ki Rx 2 wks







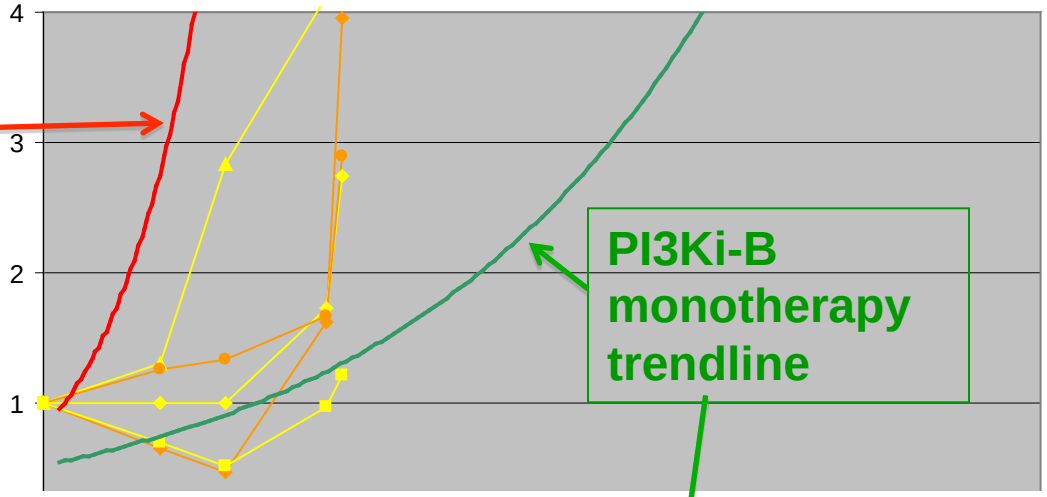
Treatment of BRCA1-/-p53+/- murine BC with PI3K-Inhibitors: survival response



Note: A MEK inhibitor had no single agent response and did not add to the effect of PI3Ki-B.

Combination of PI3Ki-B plus Investigational Drug Z flatlines BRCA-/-, p53+/- breast tumors

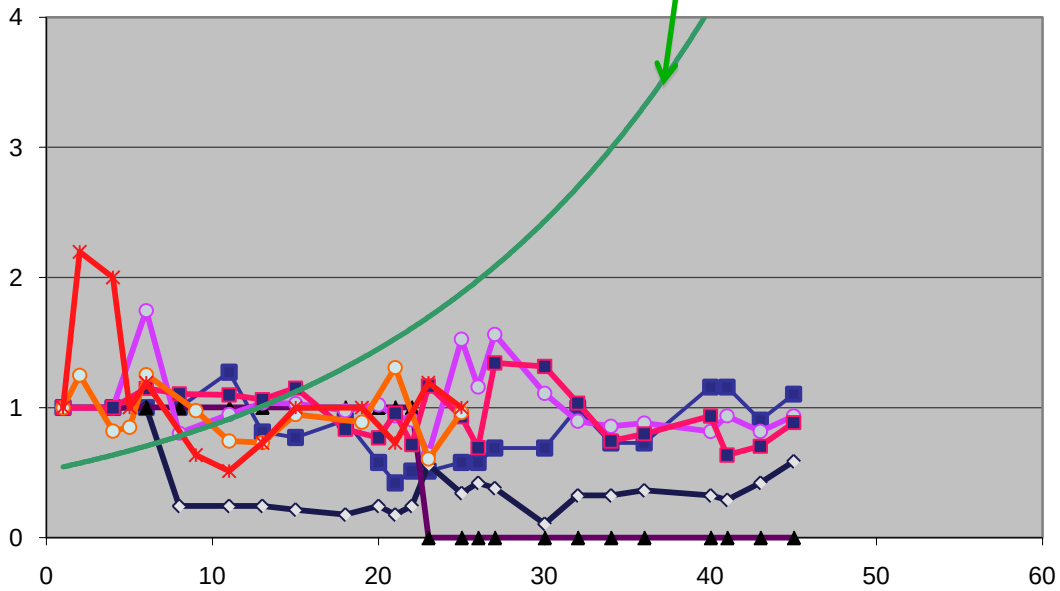
vehicle control trendline



PI3Ki-B monotherapy trendline

Drug Z: 50 mg/kg/day ip

n = 5



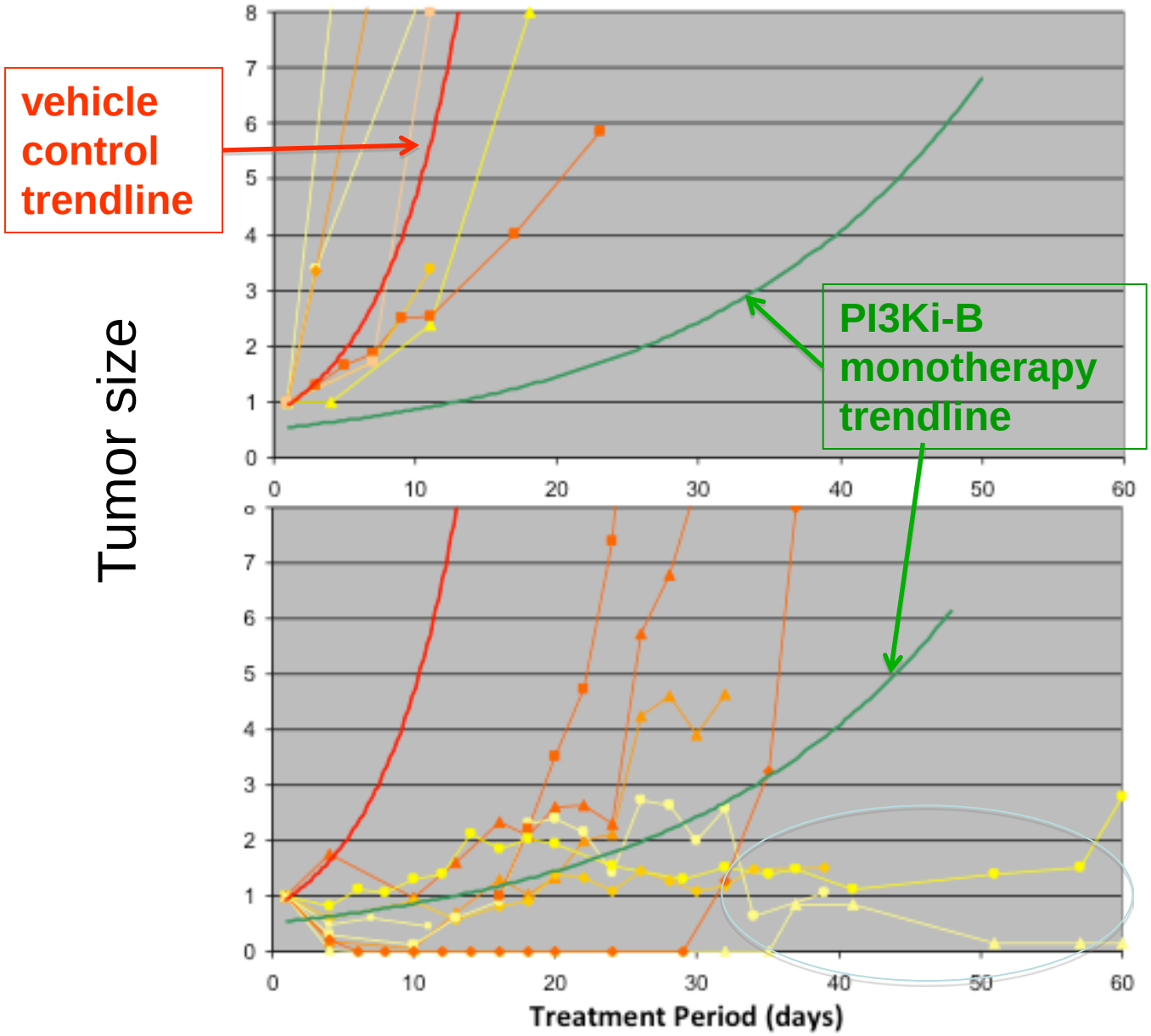
Drug Z 50 mg/kg/day ip

+ PI3Ki-B

30 mg/kg/day po

n = 7

Drug Y has no single agent effect, but when combined with PI3Ki-B may provide synergy in a subset of BRCA-/-, p53+/- breast tumors

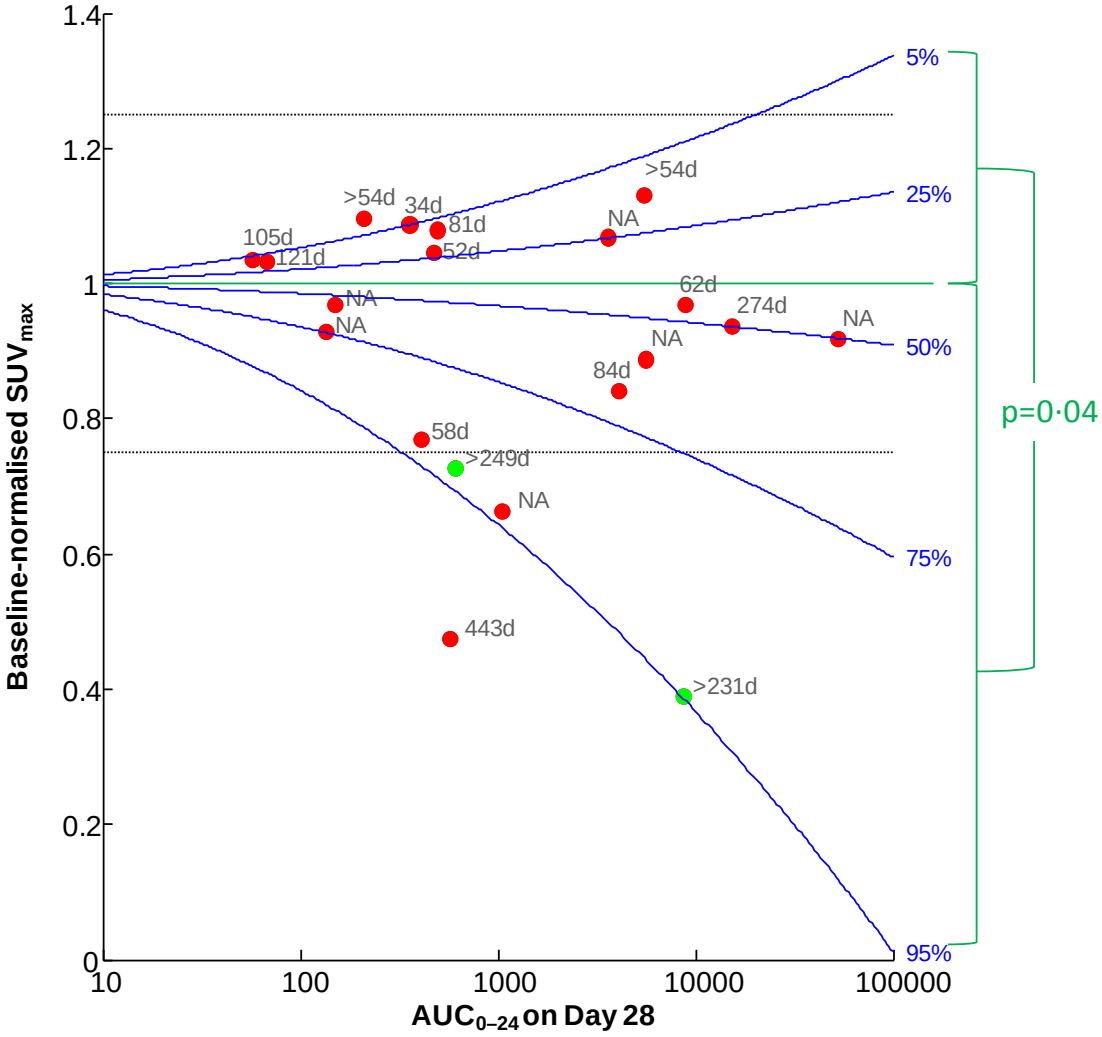


Drug Y 50 mg/kg/day
n = 7

Drug Y 50mg/kg/day
+ PI3Ki-B 60mg/kg/day
N = 9

Repeat FDG-PET studies of patients on BEZ235 suggest that an early decrease in glucose uptake predicts clinical outcome

Dose–response relationship between fluoro-deoxy glucose (FDG)-uptake and BEZ235 exposure on Day 28 post-dose



Jose Baselga

Clinical Trial Development In PI3K Dream Team

Eric P. Winer, MD

Dana-Farber Cancer Institute

Harvard Medical School

January, 2011

Diseases of Interest (1)

- **Endometrial cancer**
  - Frequent PIK3CA mutations and/or PTEN loss
  - Established single agent activity of mTOR inhibitors
  - PLAN: Explore single agent followed by combination therapy with MEK inhibitor
- **Ovarian Cancer**
  - Frequent loss of PTEN and/or INPP4B
  - PLAN: Explore single agent with consideration of potential combinations

Diseases of Interest (2)

- **ER+ Breast Cancer**
  - PIK3CA mutations common
  - Limited activity of mTOR inhibition in combination with endocrine therapy
  - PLAN: Minimal single agent exploration with focus on combinations with endocrine therapy in randomized phase II designs
- **Triple Negative Breast Cancer**
  - PTEN or INPP4B loss common
  - PLAN: Single agent trial with plan to move on to combinations with other targeted agents

Diseases of Interest (3)

- **HER2+ Breast Cancer**
  - Strong preclinical data
  - PIK3CA mutations (and associated with resistance to anti-HER2 therapy)
  - Activity of mTOR inhibition with trastuzumab
  - HOWEVER, there is already extensive work going on in this area, and therefore NOT a present focus of our trials program

Approach in ER+ Breast Cancer

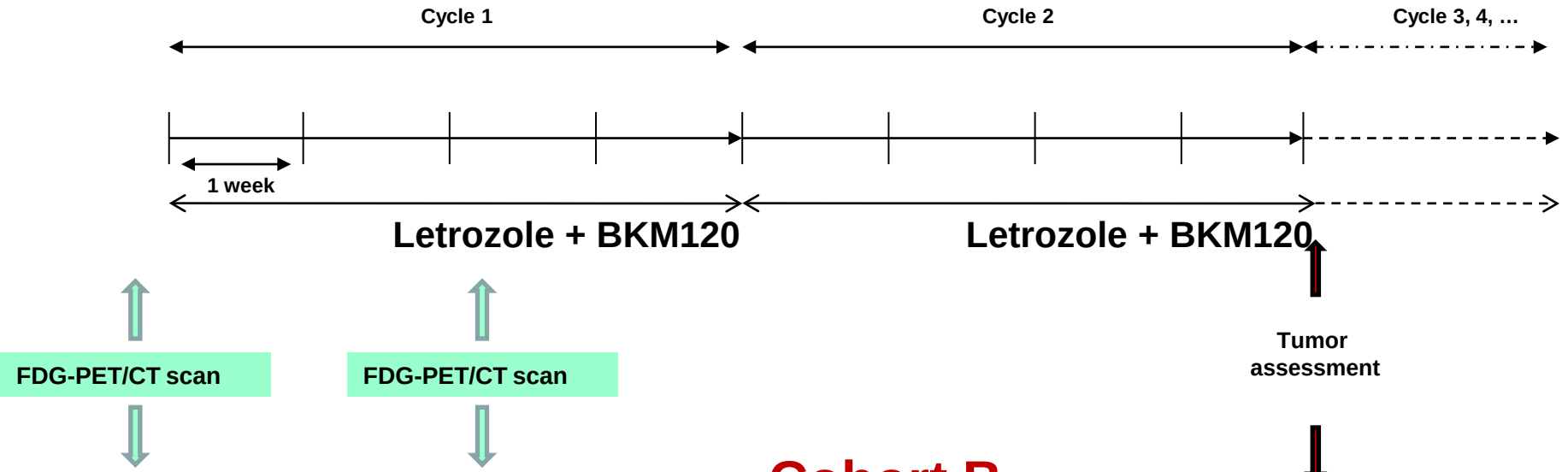
- Identification of tolerable regimen with BEZ235 (PI3Ki/mTORi) or BKM120 (PI3Ki) with letrozole
- Randomized preoperative trial in patients with tumors that have PIK3CA mutations of letrozole +/- PI3K inhibitor
- Metastatic trial of tamoxifen vs tamoxifen + BEZ235

Study Schema

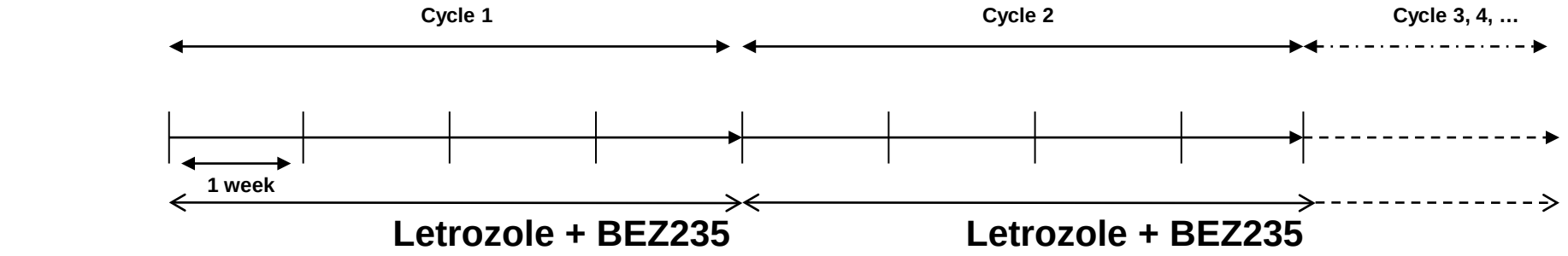
PI: Ingrid Mayer

Post-menopausal patients with hormone receptor-positive metastatic breast cancer

Cohort A



Cohort B



GOAL: TO IDENTIFY TOLERABLE REGIMEN FOR PREOPERATIVE TRIAL

Status

- **Study activated at Vanderbilt on 11/29/10**
- **Participating sites: Vanderbilt, DFCI, Columbia and UAB. Regulatory docs sent to all these other institutions**
- **Predicted completion of trial: June 2011**

Objectives
(facilitated by large amount of tissue collection)

Primary

- To evaluate rate of complete pathological response (pCR) after 24-week treatment with neoadjuvant Letrozole +/- BEZ235 in patients with ER and/or PR-positive tumors with mutations on PIK3CA

- To determine the percentage of Ki67-positive tumor cells (determined by immunohistochemistry) in core biopsies performed at 2 weeks after initiation of neoadjuvant Letrozole +/- BEZ235

Secondary

- To evaluate rate of tumor response in each arm, as measured by ultrasound (US) prior to definitive surgery

- To perform the following correlative studies on all patients enrolled in the trial:
  - Mutational analysis of PIK3CA (exons 9 and 20), PTEN, and Akt1
  - Quantitative ER
  - Immunohistochemistry for PTEN
  - Reverse phase protein array (RPPA; Gordon Mills) analysis in protein lysates from fresh biopsies.
  - To explore the relationship between Ki67 changes and FDG-PET/CT response (at 2 weeks)

Summary

- **Wide array of trials in breast and gyn cancers, all developed with extensive laboratory collaborations**
- **Large and enthusiastic clinical group to support the trials, including high level of advocacy involvement**
- **Collaborations with industry have offset many costs**
- **Brisk accrual expected once studies activated**