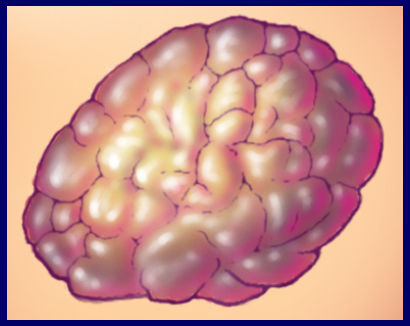
Sheikh Khalifa bin Zayed Al Nahyan Institute for Personalized Cancer Therapy

John Mendelsohn Gordon Mills
Funda Meric-Bernstam Kenna Mills Shaw

DELIVERING ON THE PROMISE OF PERSONALIZED MOLECULAR MEDICINE

Targeting the Genetic Changes Specific to Each Patient's Cancer

Small molecules and immune therapy



Tumor

Capitalizing on the vulnerabilities (Achilles Heel) of cancer

Khalifa Institute for Personalized Therapy

MDACC patients without curable disease 20,000
5-9000 per year

↓

Actionable mutations
Targetable
Predict patient outcomes
(Paraffin compliant)

↙ ↘

Targetable aberration present

↙ ↓ ↘

Standard of care

N of 1 trials

Clinical trial cohorts

No Targetable Aberration

↓

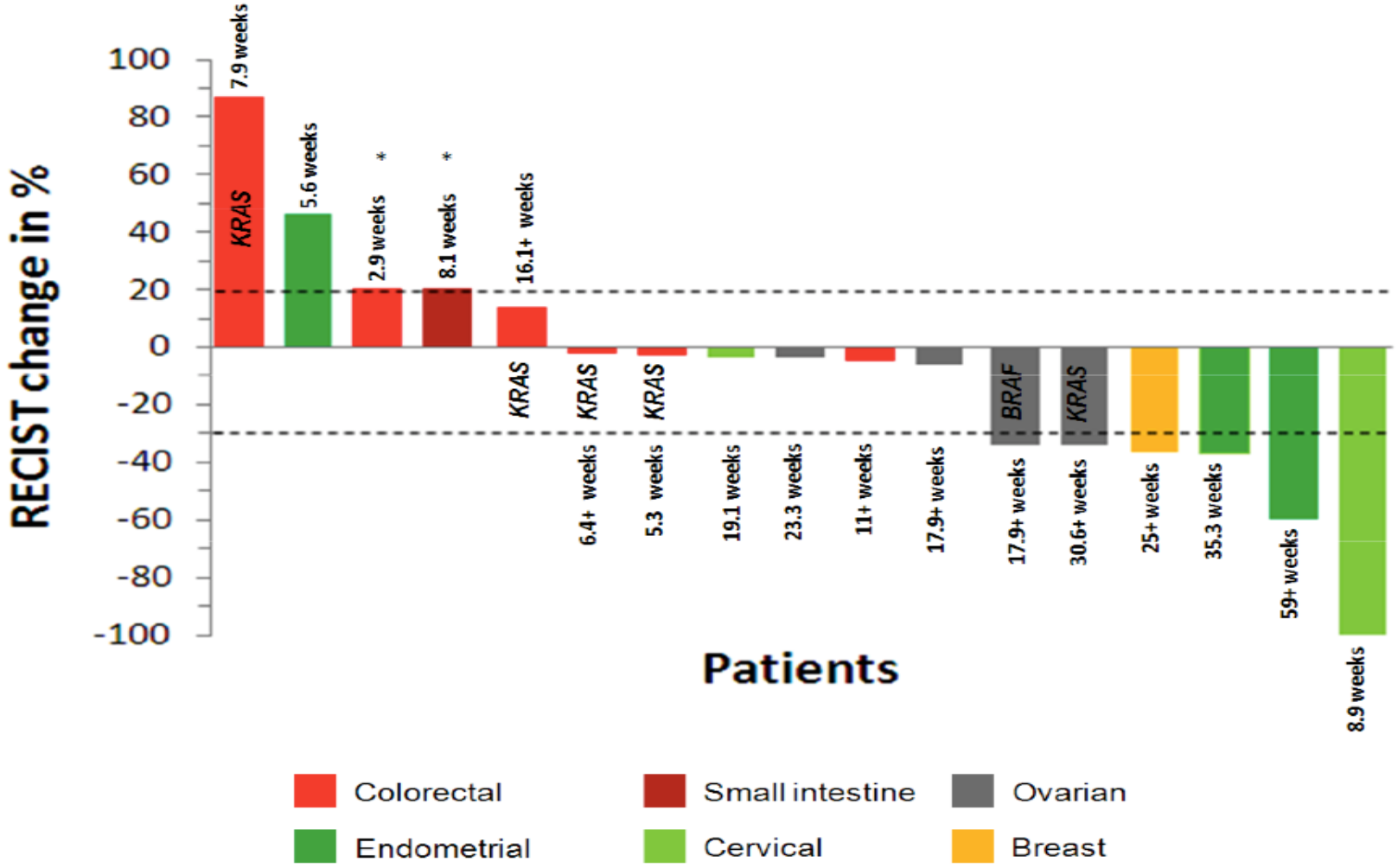
Deep characterization

↓

High throughput biological validation

Deep learning from each patient; Real time adaptive treatment

Efficacy of targeted therapy conditioned by mutation, comutation and tissue lineage BRAF in melanoma and bowel



* Clinical progression

\+ Continuing response

Janku et Mol Can Ther

CAN WE ACHIEVE TRULY PERSONALIZED THERAPY?

N of one problem

Precision Medicine?

Stratified Medicine

Homogenous patient groups

Ductal Breast Cancer

8 subclasses

A set of orphan diseases

Rare aberration populations

AKT mutant tumors

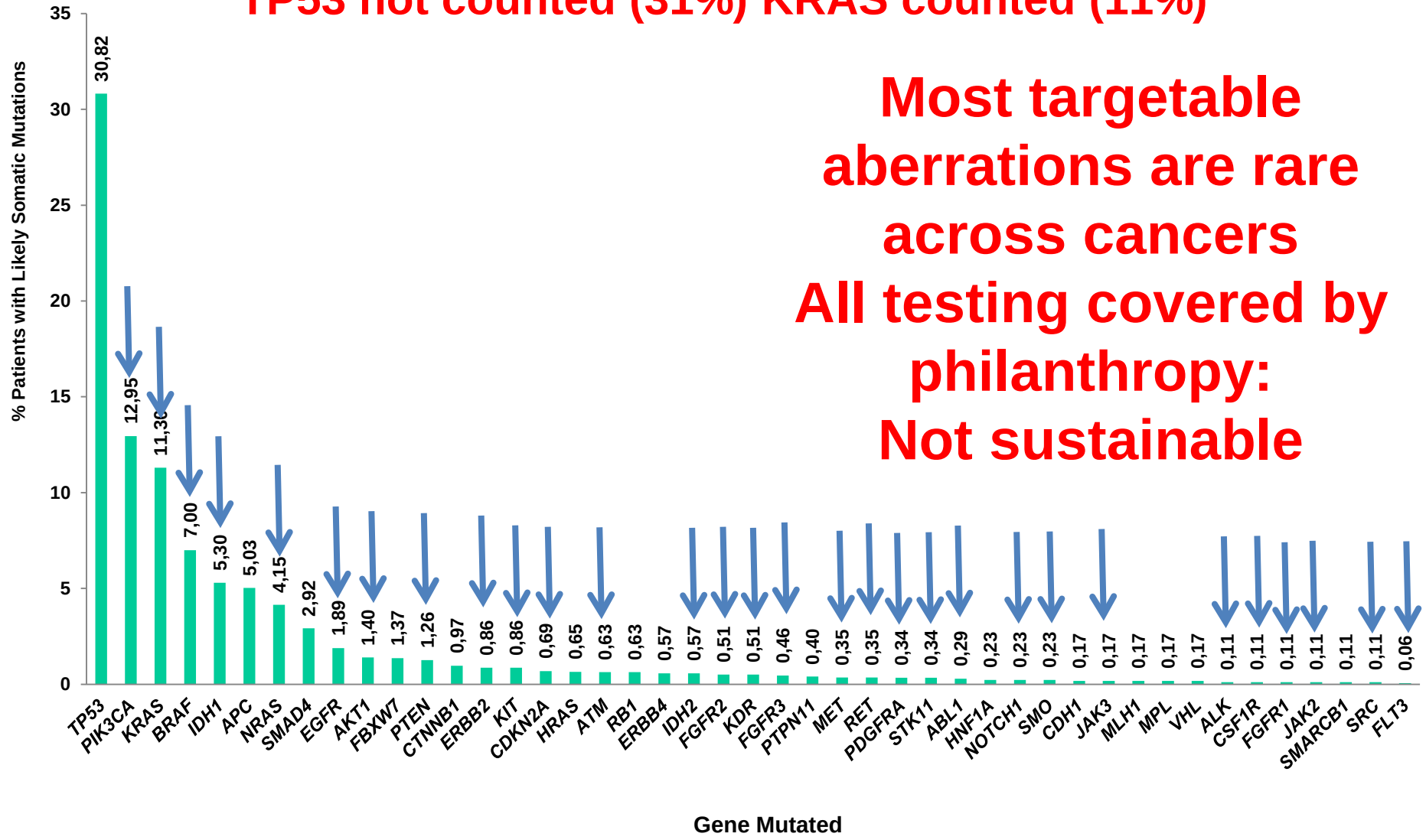
2-3% in any major lineage

0.7% in trial sets

Multiplex analysis of multiple aberrations allows “amortization” of costs across multiple trials

CHALLENGES TO PERSONALIZED TARGETED THERAPY

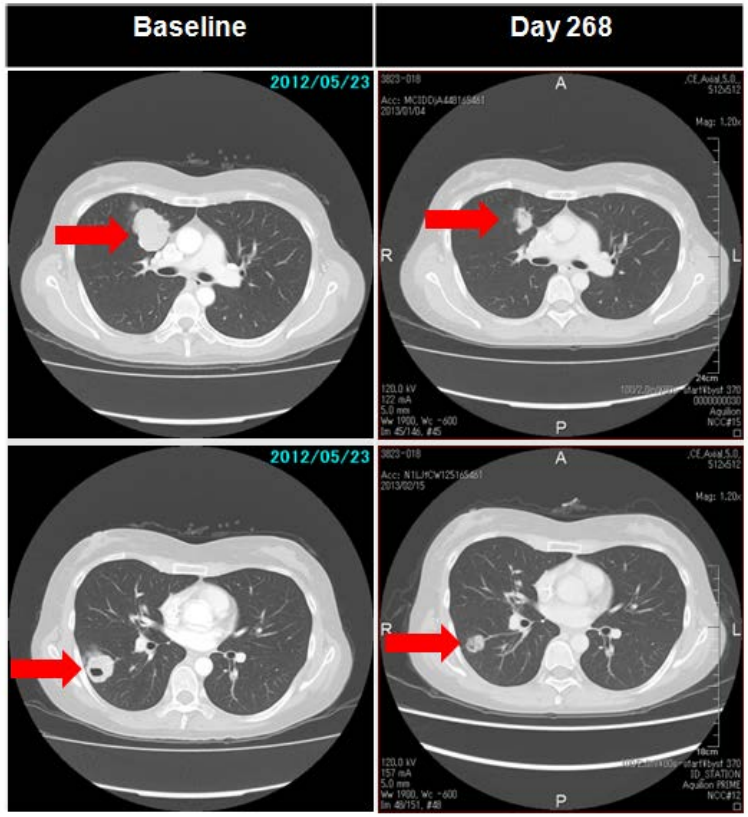
19000 (2000 in set) patients likely to enter trials
Hot Spot Mutation CMS46 (Ion Torrent)
Potentially actionable 39%
TP53 not counted (31%) KRAS counted (11%)



Most targetable aberrations are rare across cancers

All testing covered by philanthropy: Not sustainable

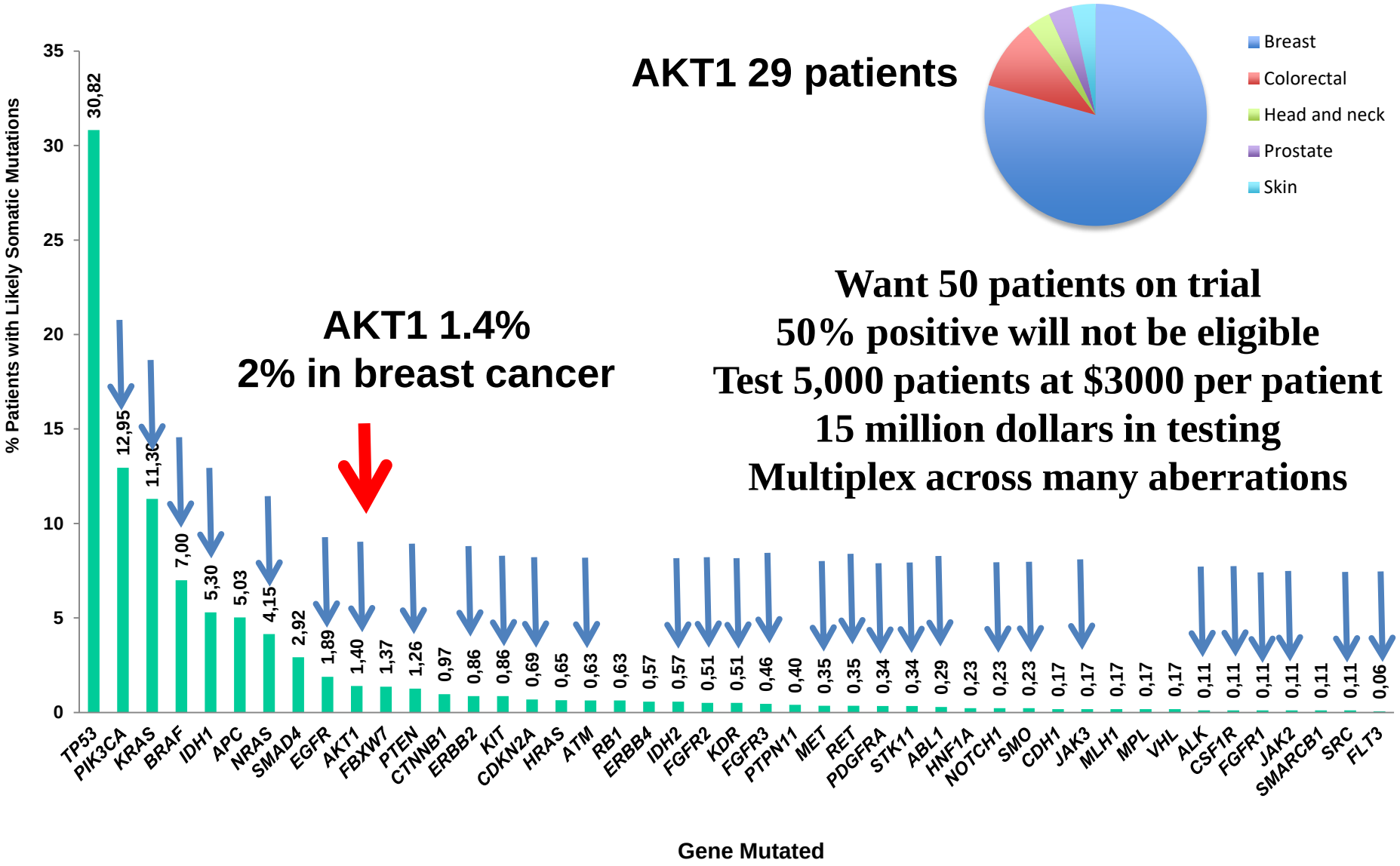
19000 (2000 in set) li
Hot Spot Mutation CI
Potentially acti
TP53 not counted (31%) KRA



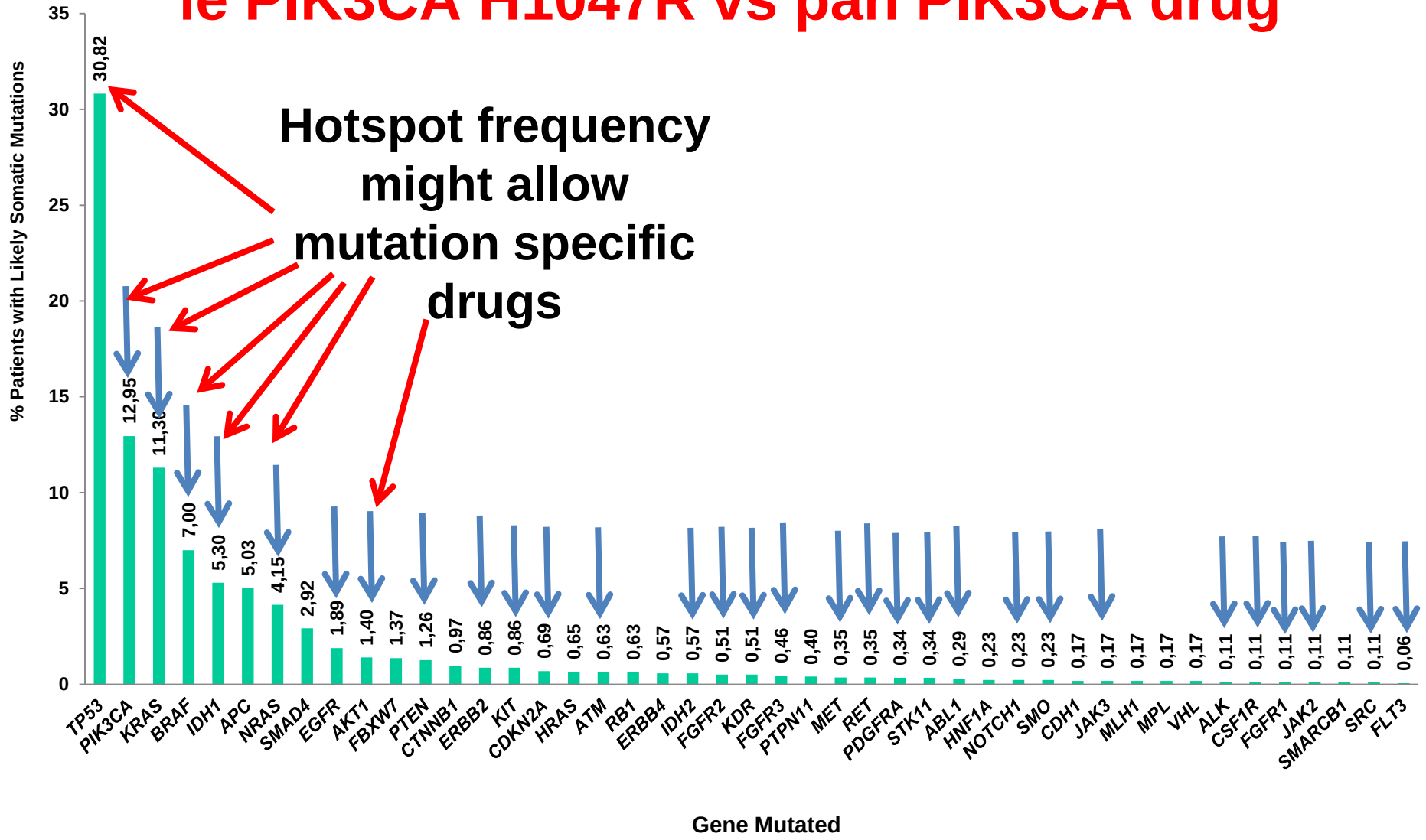
AKT mutant tumors respond to AKT targeted drugs

Endometrioid ovarian primary, 480mg BD 4d on/3d off Confirmed RECIST PR (maximum reduction 55%). Ongoing in study (more than 600 days on drug).

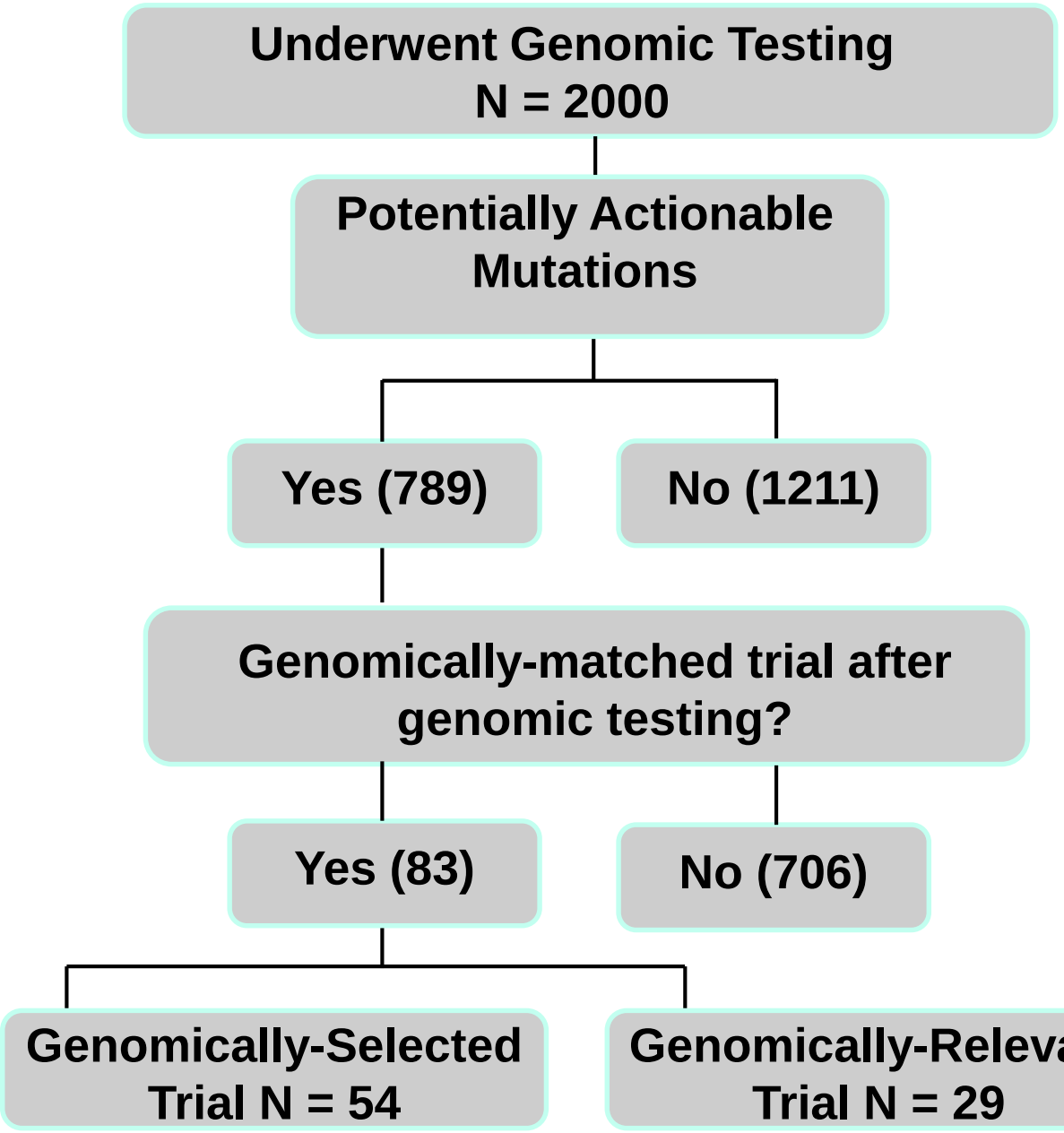
HOW DO WE DETERMINE WHETHER RARE MUTATIONS INDICATE VULNERABILITY



THERAPEUTIC INDEX IS LIMITING FACTOR
COULD WE IMPLEMENT MUTATION SPECIFIC DRUGS (1-2% frequency)
ie PIK3CA H1047R vs pan PIK3CA drug



Outcomes for first 2000 patients



4% of patients tested were ultimately treated with "matched" agent

39% of patients had aberration in actionable gene

11% of pts with mutations in actionable genes went on genotype-matched trials

What did we learn Goal 25% of patients to trials

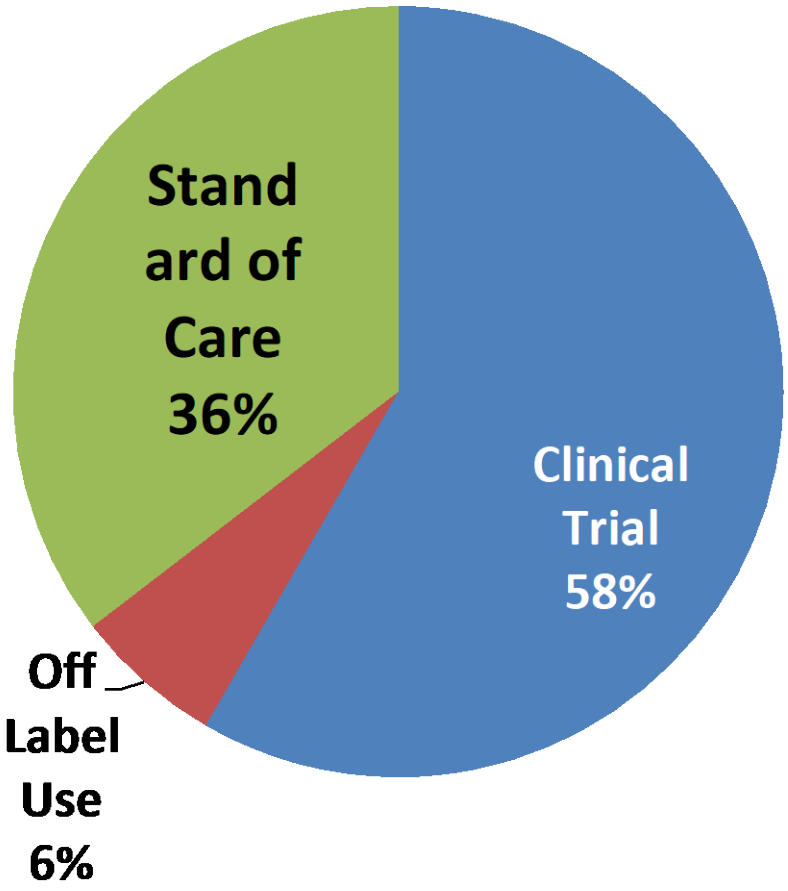
- Increasing scope of testing increases rate of actionable events modestly (39-53%):
  - 90% of actionable aberrations are in limited set of genes
- Time to results critical in Phase I due to patient deterioration
  - Test when likely to need information and have therapeutic options
- Physician decision support is critical
  - Aberration level information
  - Not all alterations in actionable genes are actionable
  - Clinical trials alert to curated results and eligible clinical trials
- The utility of genomic testing is dependent on availability and efficacy of therapeutic agents
  - Increase number of molecular marker driven trials
  - Develop basket trials to deal with rare events AKT, TRK
- Move from single aberrations to pathways and networks
- Circulating DNA allows for proximal analysis of metastases

Value of Molecular Testing

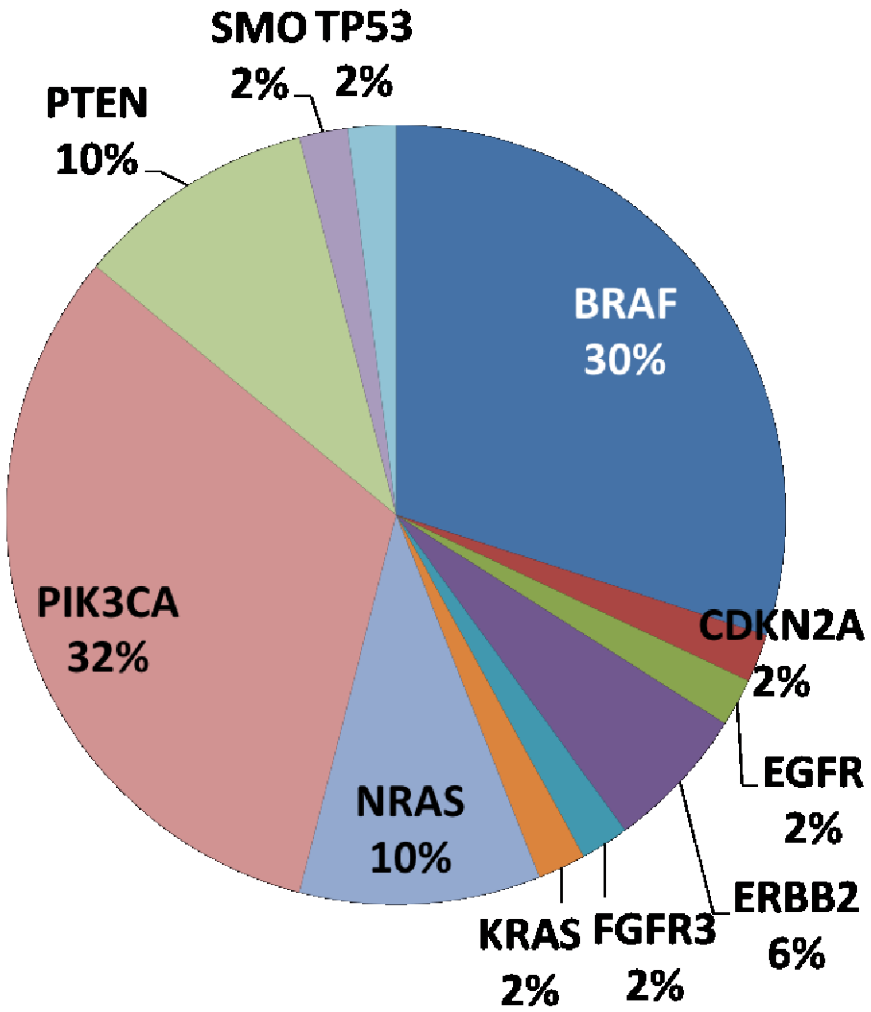
- Directing patients to standard of care or off label use is important outcome
- Rapid approval of effective drugs
- Reputational event to recruit patients
- Recruit high quality information rich trials
- Consider testing a “loss-leader”
  - Added cost of multiplex testing modest
- Critical to convince payors of value
  - Philanthropy non sustainable

ENTRY INTO CLINICAL TRIALS UNDERESTIMATES UTILITY OF MOLECULAR TESTING

Types of Genotype Matched Treatment Received



Gene Alterations for Which Patients Received Treatment



Medical Decision-Support

Personalized Cancer Therapy Website https://pct.mdanderson.org

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

Personalized Cancer Therapy

Knowledge Base for Precision Oncology

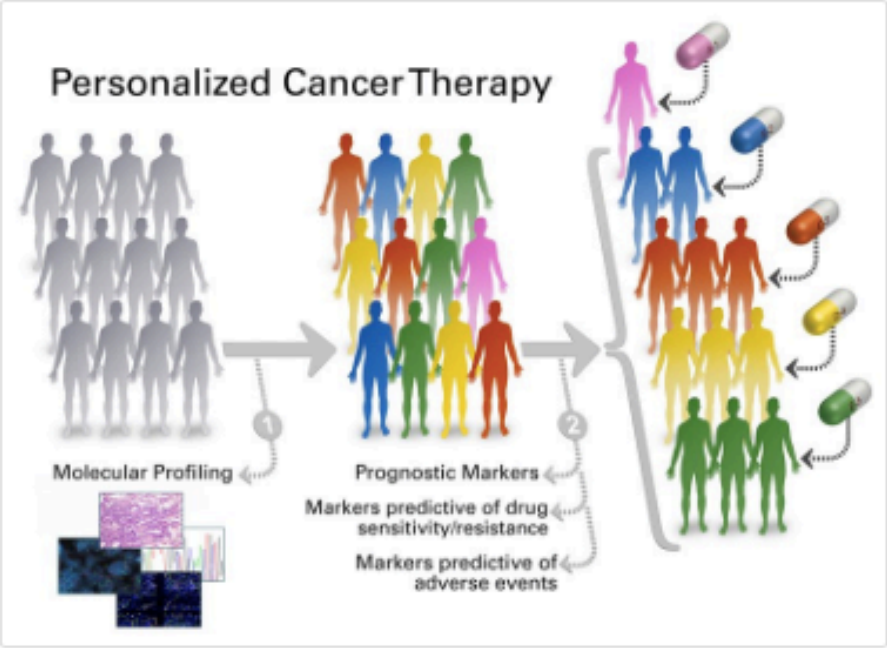
Who We Are | What We Do | Vision and Mission | Knowledge Base Generation | Contact Us

Search for gene information

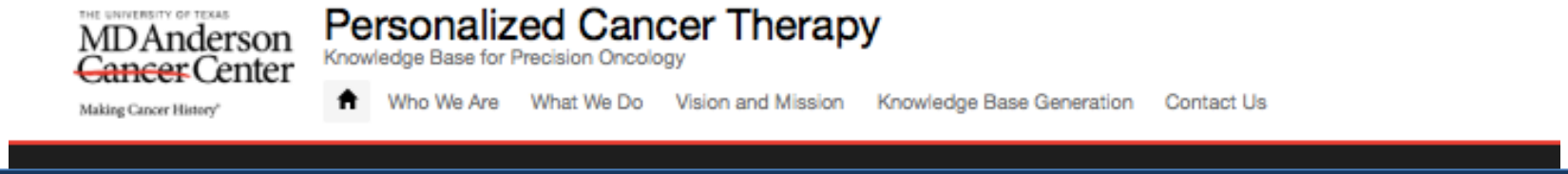
Select gene

Personalized cancer therapy is a treatment strategy centered on the ability to predict which patients are more likely to respond to specific cancer therapies. This approach is founded upon the idea that tumor biomarkers are associated with patient prognosis and tumor response to therapy. In addition, patient genetic factors can be associated with drug metabolism, drug response and drug toxicity. Personalized tumor molecular profiles, tumor disease site and other patient characteristics are then potentially used for determining optimum individualized therapy options.

Tumor biomarkers can be DNA, RNA, protein and metabolomic profiles that predict therapy response. However, the most recent approach is the sequencing of tumor DNA, which can reveal genomic alterations that have implications for cancer treatment. This Personalized Cancer Therapy website was specifically developed as a tool for physicians and patients to assess potential therapy options based on specific tumor biomarkers.



Personalized Cancer Therapy Website https://pct.mdanderson.org



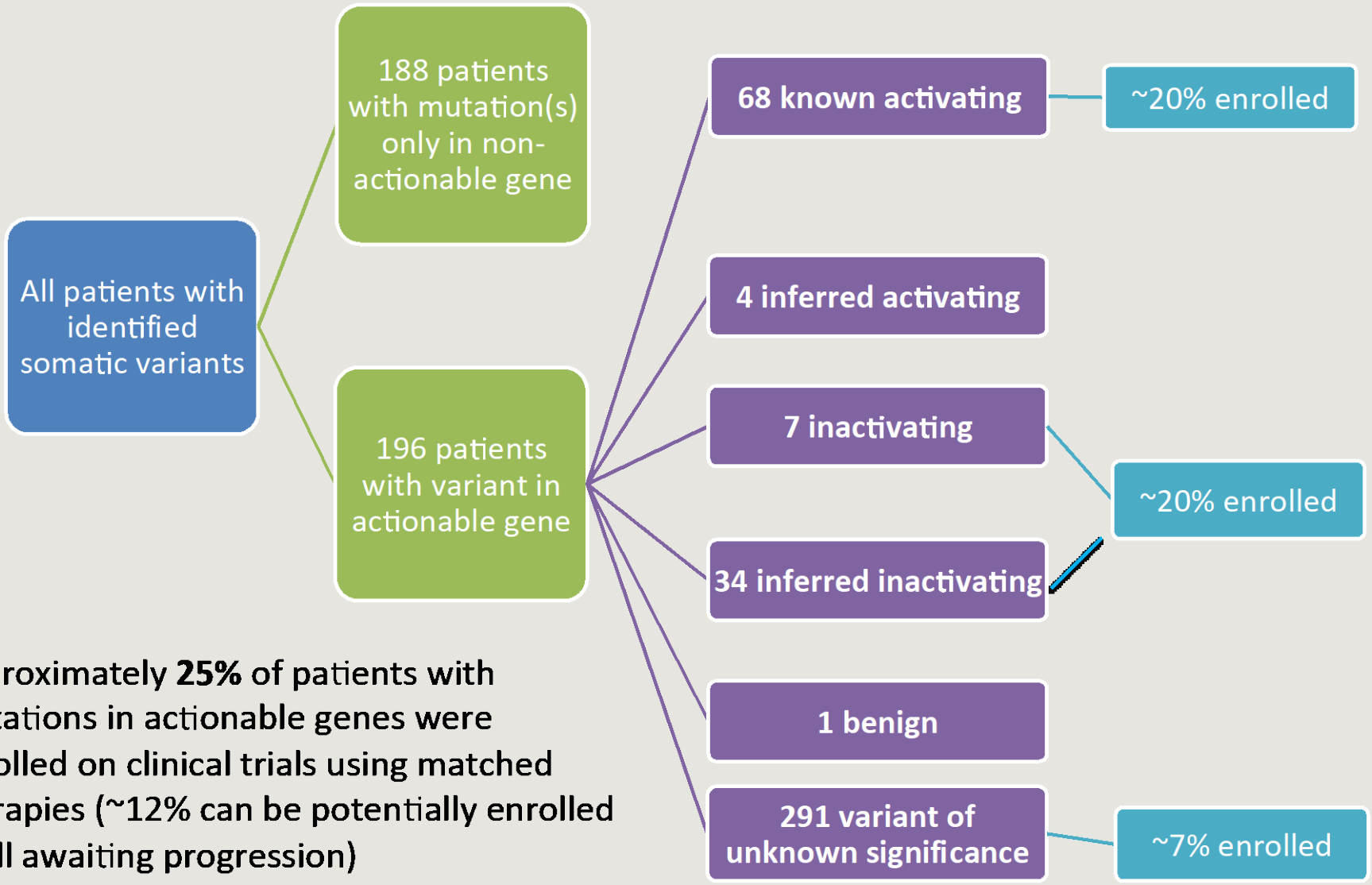
27 potentially actionable genes fully annotated

- Mutations
- Copy number changes
- Fusions
- Germline alterations if relevant

- Interactive: Physician determines level of information
- Therapeutic implications and the level of evidence for each therapy
- Clinical trials available by location

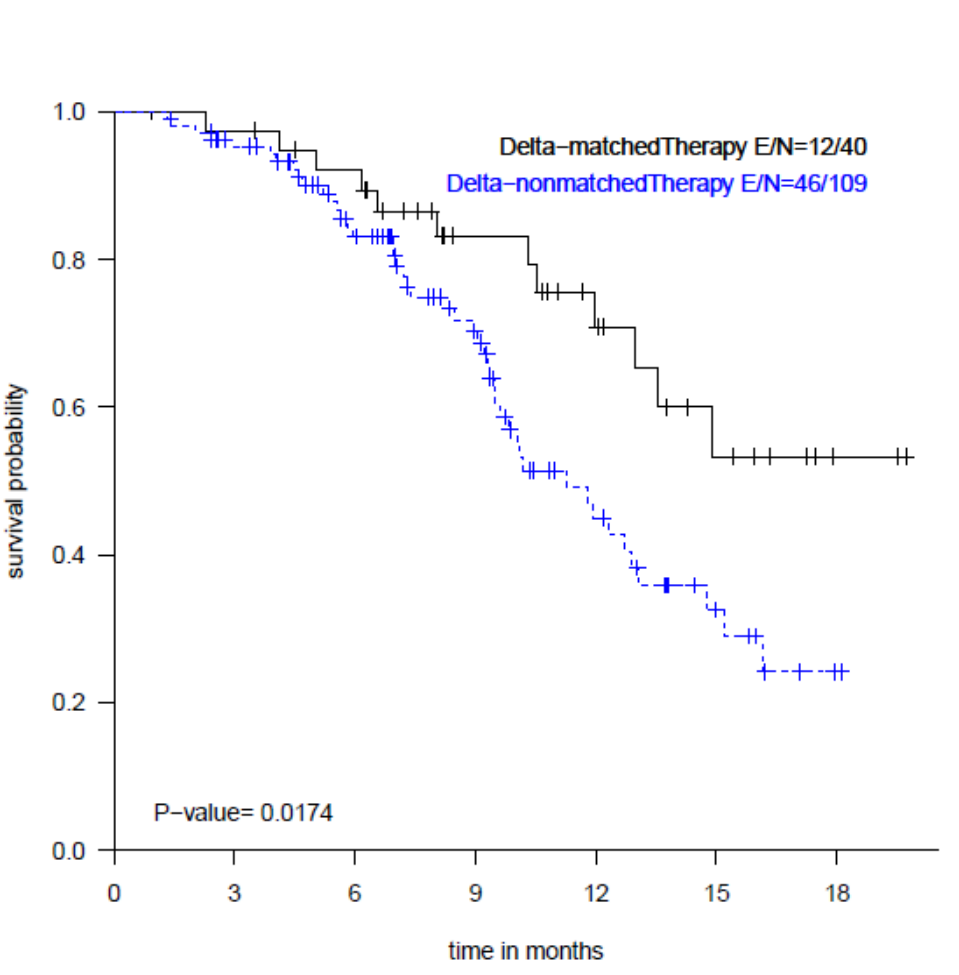
tumor biomarkers.

Decision Support in Real Time Improves 'Matching' to 'Right' Drug



Approximately **25%** of patients with mutations in actionable genes were enrolled on clinical trials using matched therapies (~12% can be potentially enrolled - still awaiting progression)

‘Matching’ to ‘Right’ Drug Improves Patient Outcomes



Unpublished data from S. Kopetz, J. Lee, R. Broaddus & K. Shaw.

UNEXPECTED HIGH RATE OF FAILURE OF TARGETED THERAPEUTICS

Even for patients with the biomarker only subpopulations of patients benefit from monotherapy: Usually short term

Resistance is almost universal

- Intrinsic (Genetic)
- Selected (Genetic)
- Adaptive (Homeostatic loops, cross talk and bypass)
- Heterogeneity

Rationale combinatorial therapy will be required to fulfill the promise of targeted therapy

Yossi Yarden Arthur Lander

CHALLENGES TO PERSONALIZED TARGETED THERAPY

A PLATFORM TO FACILITATE TARGETING ADAPTIVE RESISTANCE TO INCREASE UTILITY OF TARGETED THERAPEUTICS

Cells in 2D, 3D, in vivo, or patient tumors

Add drug

Early time points: target engagement

Medium time points: adaptive responses

Late time points: genomic resistance

Harvest cells for Omic analysis

DNA, RNA, protein metabolomics

G. Gao

HUMAN PROTEOMICS ATLAS: RPPA

Quantitative high throughput multiplexed inexpensive ELISA

300 validated antibodies

Dot blot: less sensitive to degradation

Requires high quality validated antibodies and robotics

No Spatial orientation: combined tumor and stromal signature

>10,000 TCGA and internal patient samples with extensive DNA, RNA, miRNA, and clinical data

Tcpaportal.org

Search Cancer Proteome Atlas

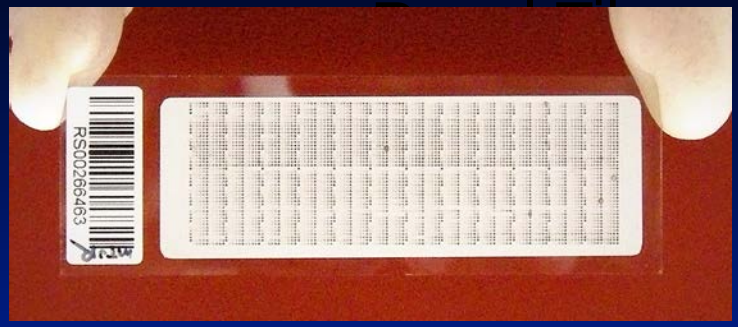
Cell lines with RNASeq and drug data

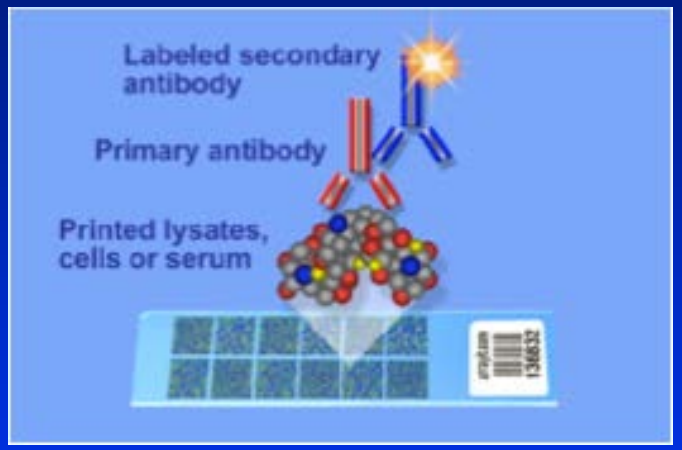
700 lines in house

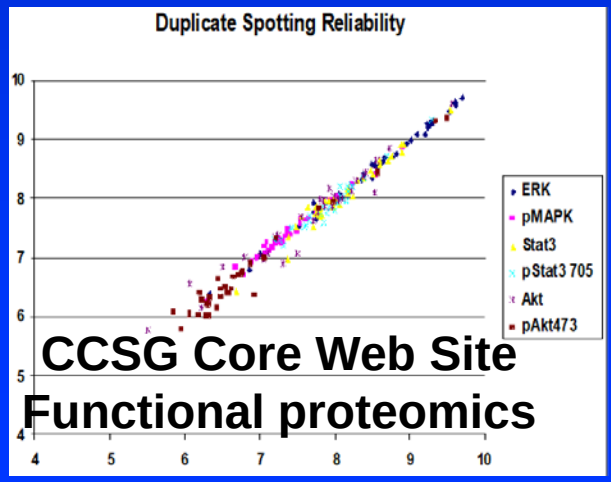
http://tcpaportal.org/mclp/#/

Broad Cancer Cell Line Encyclopedia

130,000 samples in total







PARP inhibitors induce **synthetic lethality** in homologous recombination-deficient (HRD) cancer cells

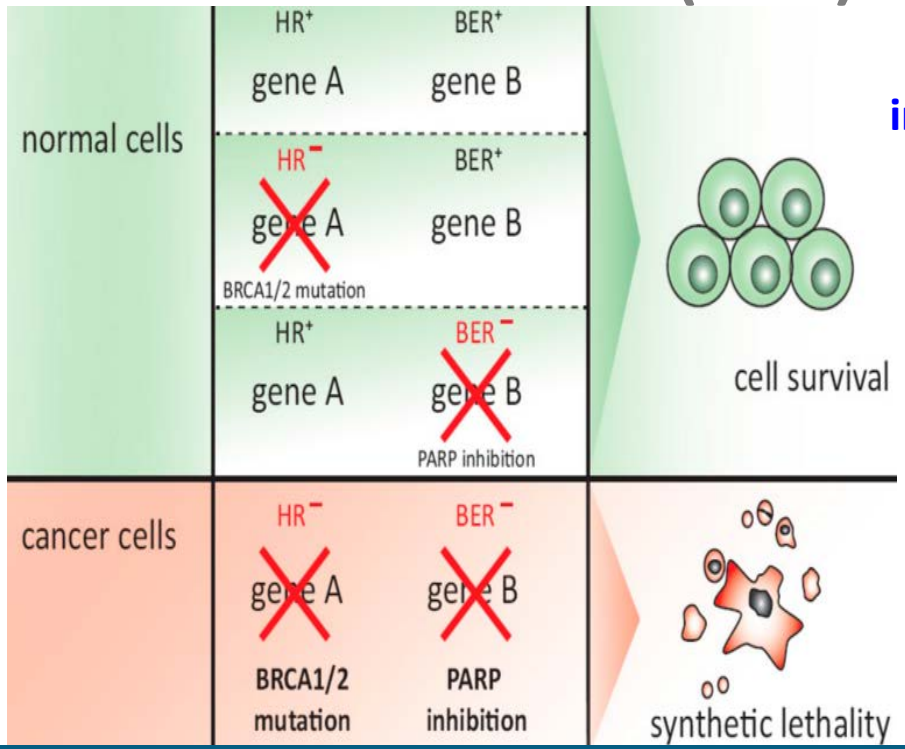
DNA damage occurs **constantly**

↓

DNA damage induces cell cycle checkpoints to allow DNA damage repair

↓

Normal cells have **many** DNA Repair Pathways

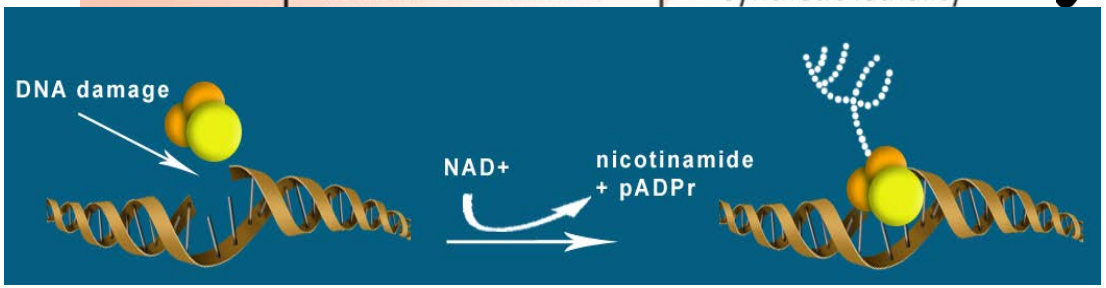


PARP inhibitors **induce** DNA damage

↓

HRD cells do not accurately repair damage

↓



Three PARP inhibitors have been approved for ovarian cancer and OLYMPIAD Phase III trial in breast cancer has met its goals

Despite high response rate, duration of response remains short

Rank-Sum Analysis of AZD2281 and BMN673

5 representative cell lines were treated with 2 doses for 72 and 96 hours in 2D and 3D cultures. Lysates were collected and analyzed by RPPA for 191 antibodies. High levels are represented in Red. >50,000 data points

Data is ratio of treated to untreated

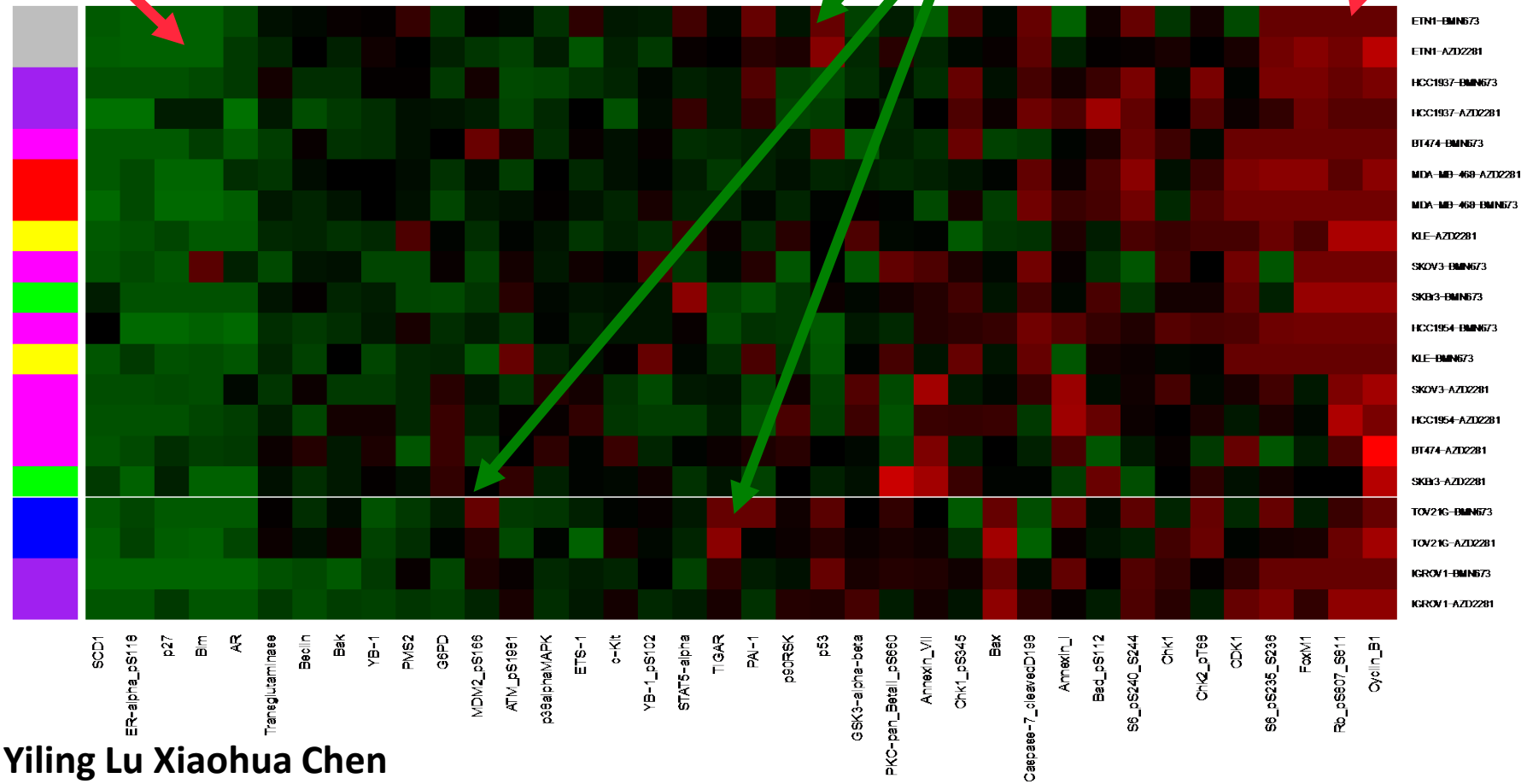
Samples are ordered based on adding all antibody scores

Only significant changes presented

Private

Public

Public



Yiling Lu Xiaohua Chen

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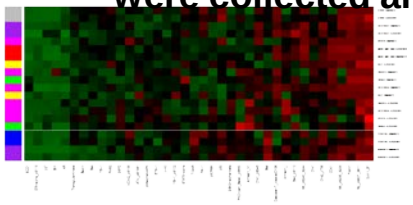
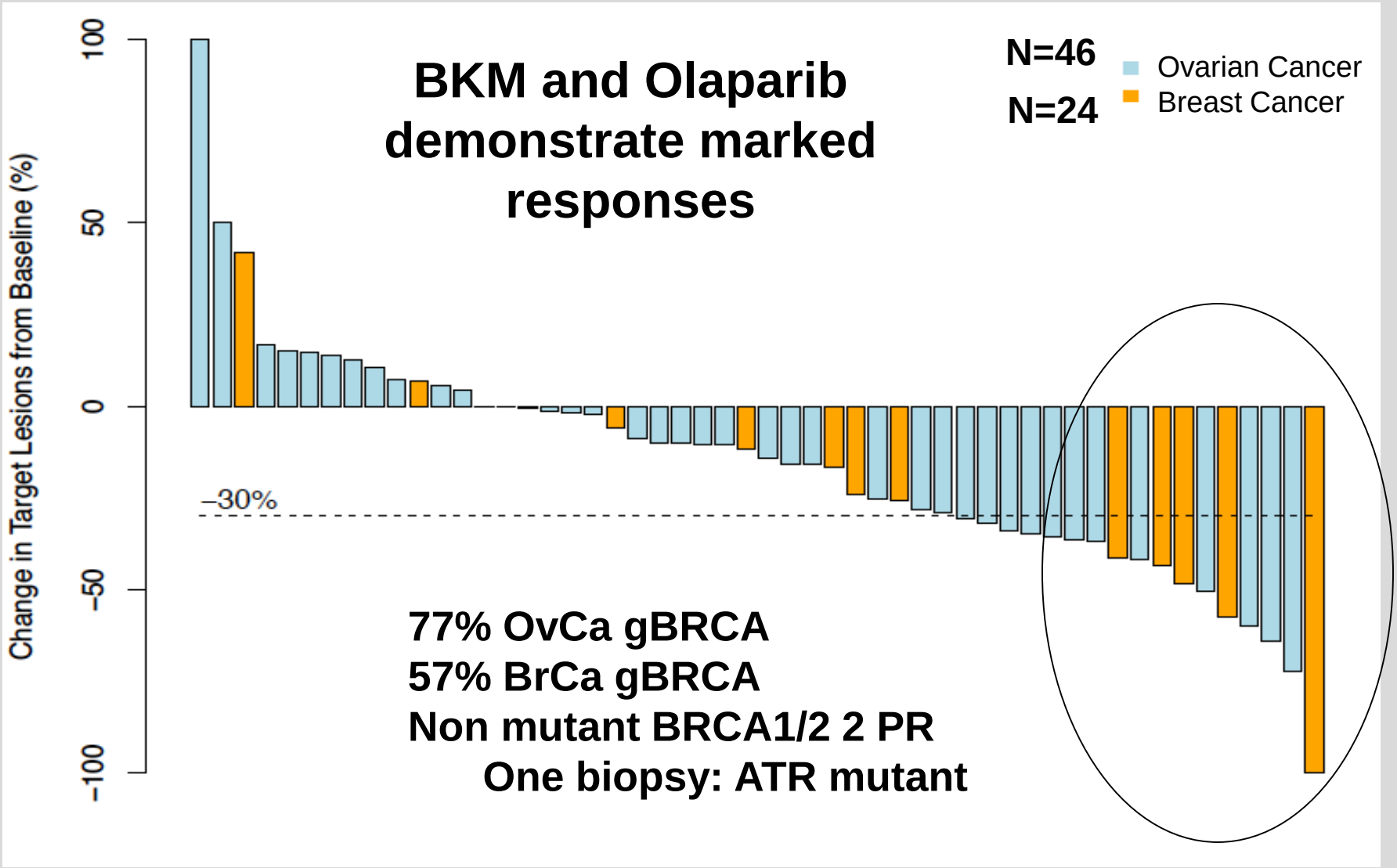


Yiling Lu Xiaohua Chen



Ursula Matulonis
Shannon Westin

STAND UP TO CANCER

PI3K Dream Team
http://pi3k.org

AACR American Association for Cancer Research

Ursula Matulonis
Shannon Westin

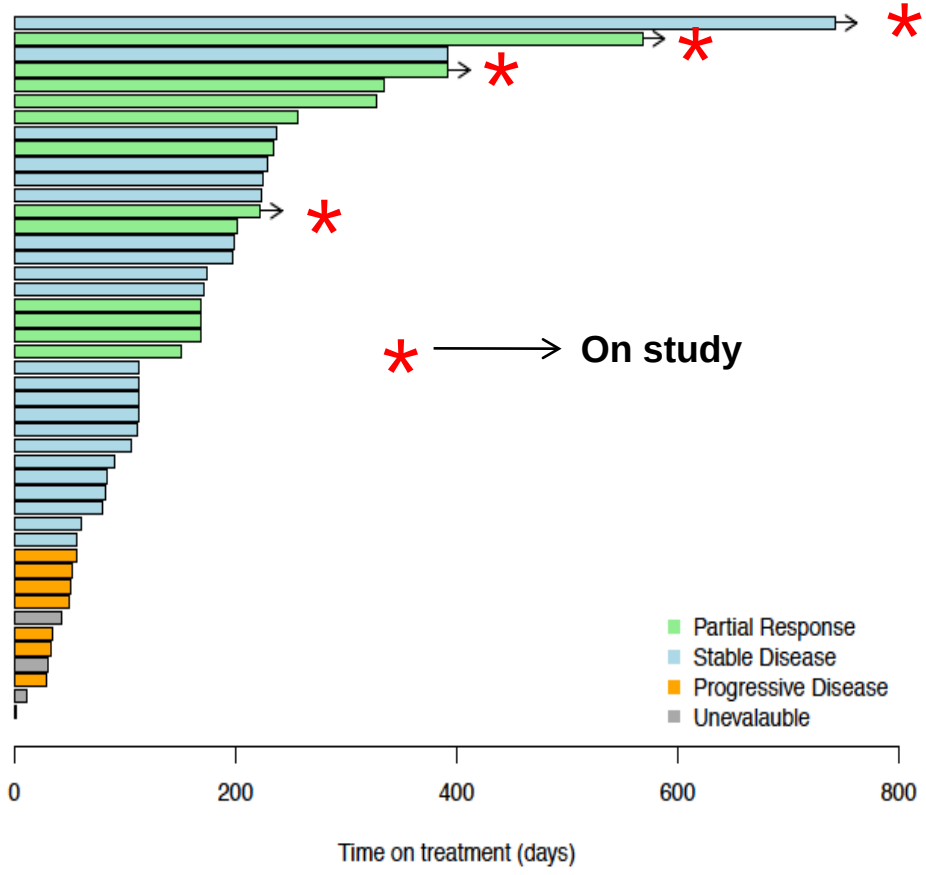
Time on Treatment

Olaparib, BKM120 Pan PI3K

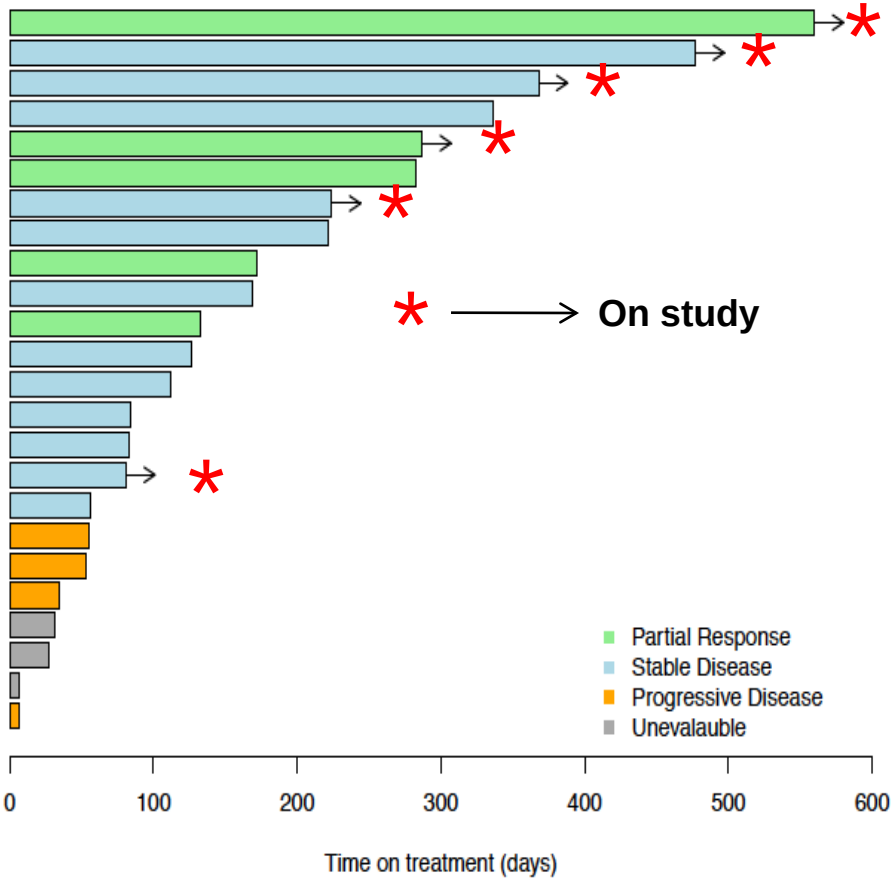
PI3K alpha, mTOR and AKT in progress

Up to 24 months response: 50% of endometrial cancers

Ovarian Cancer



Breast Cancer



STAND UP TO CANCER

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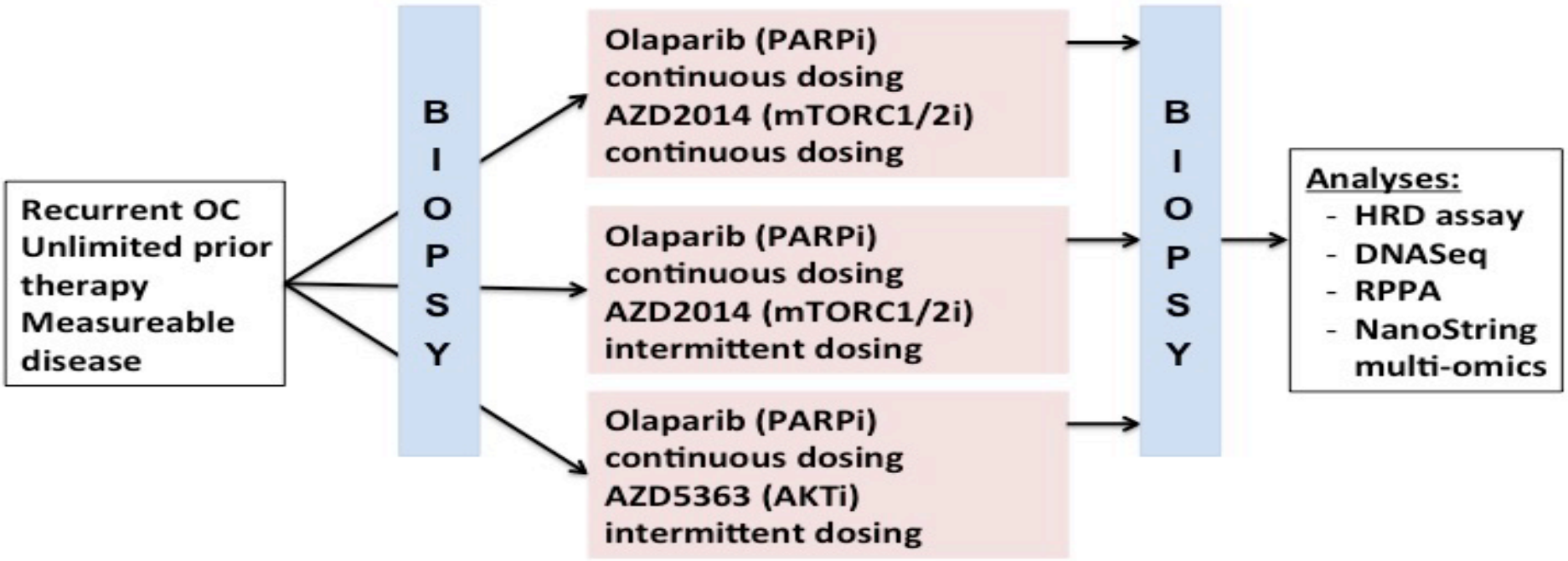
http://pi3k.org

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

AACR American Association for Cancer Research

OCTOPUS – PARP/PI3K pathway combinations



> 70 patients accrued

RR ~ 30% for OC, 50% for EC

Rank-Sum Analysis of AZD2281 and BMN673

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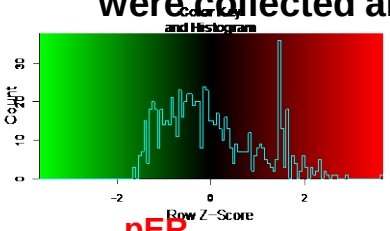
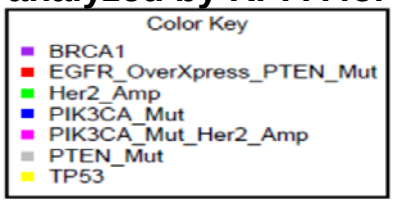




Joan Brugge

ATR, ATM, WEE1/CHK1/2 PI3K CDK1 CDK4/6

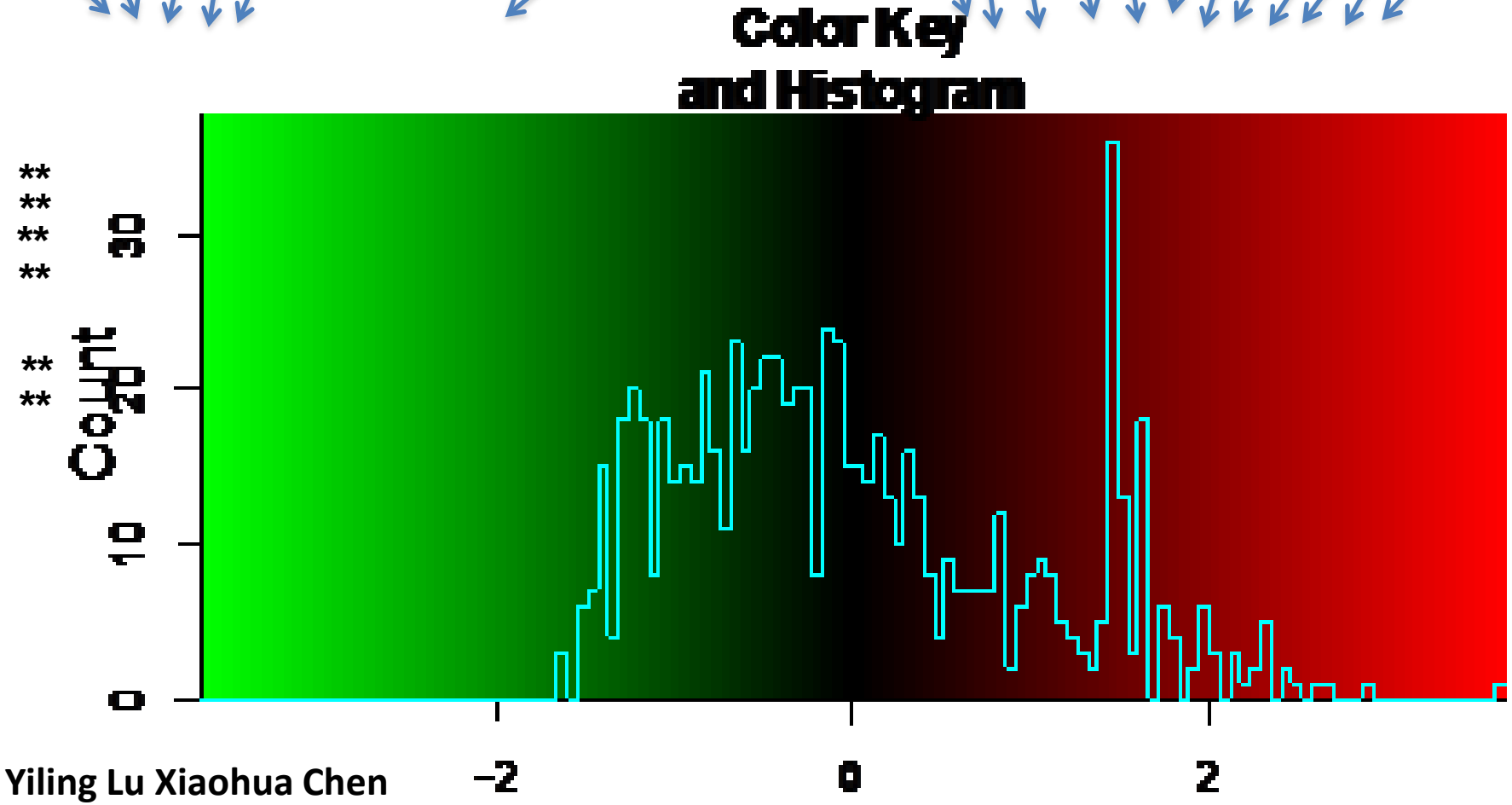
pCHK1 Casp7 pCHK2 pS6 FoxM1

BAX pBAD pS6 CHK1 CDK1 pRB

Cyclin B1

pER Bim Mek

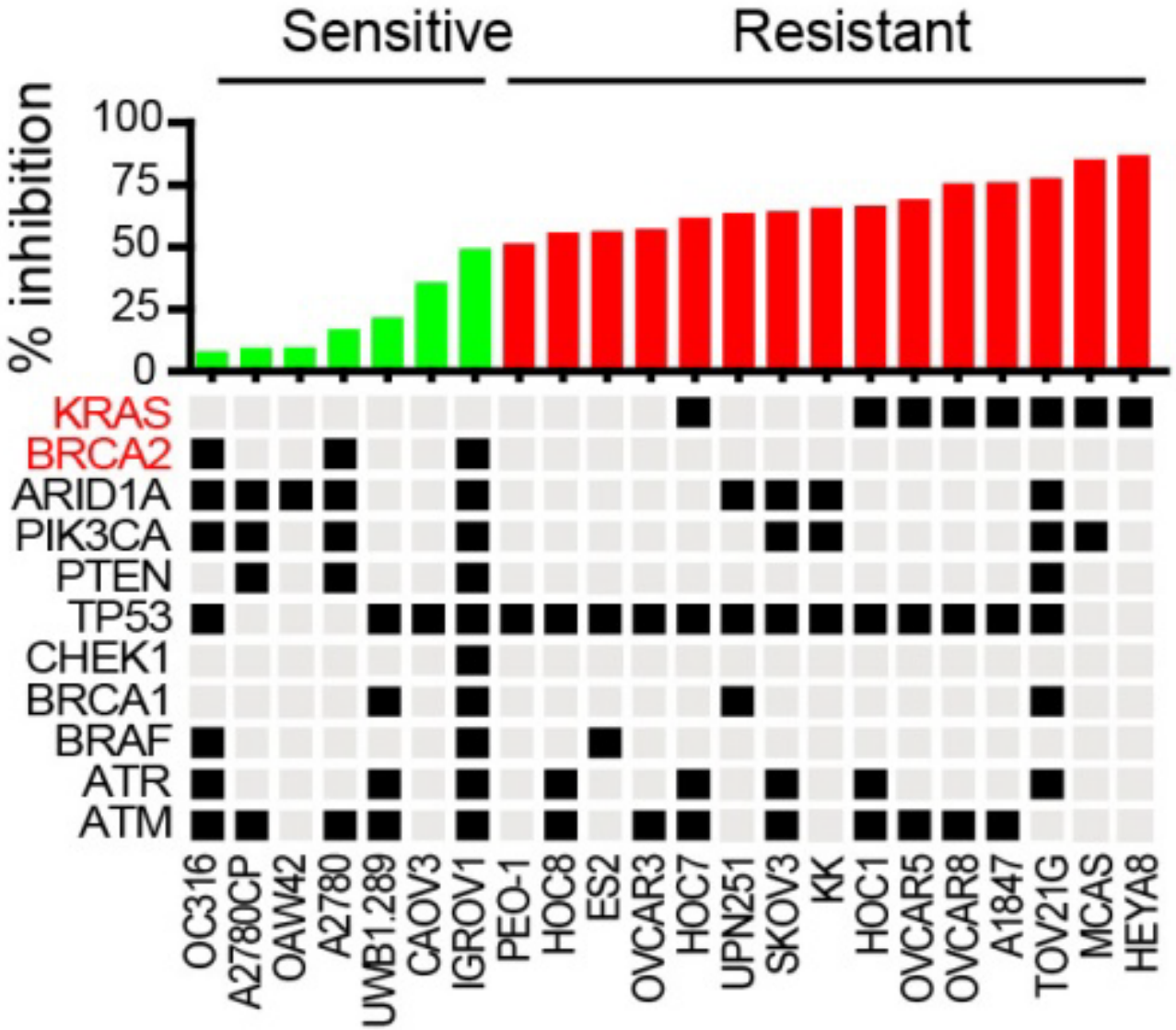
SCD1 p27 AR pATM



Yiling Lu Xiaohua Chen

SERENDIPITY IS CRITICAL

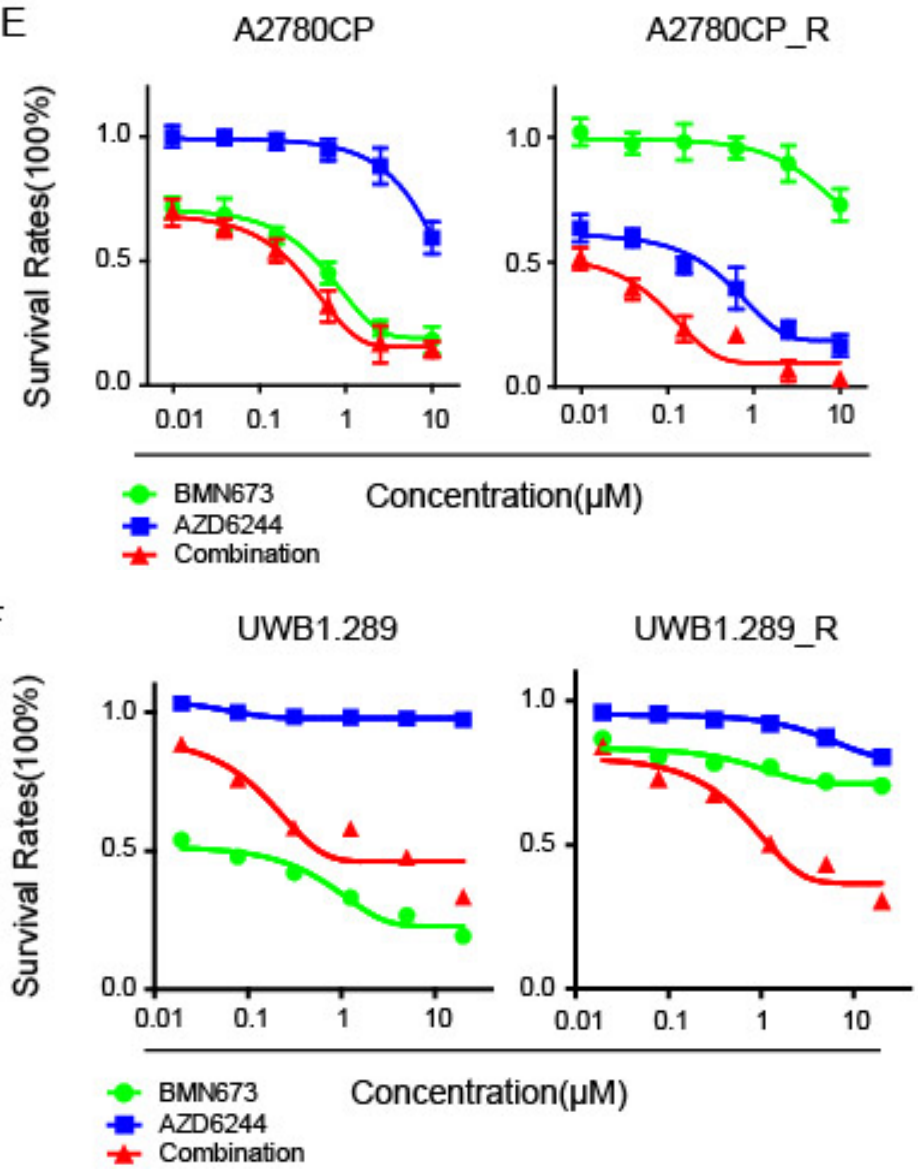
KRAS mutation is a marker for BMN673 resistance: markedly improved HR DNA repair in RAS mutant lines

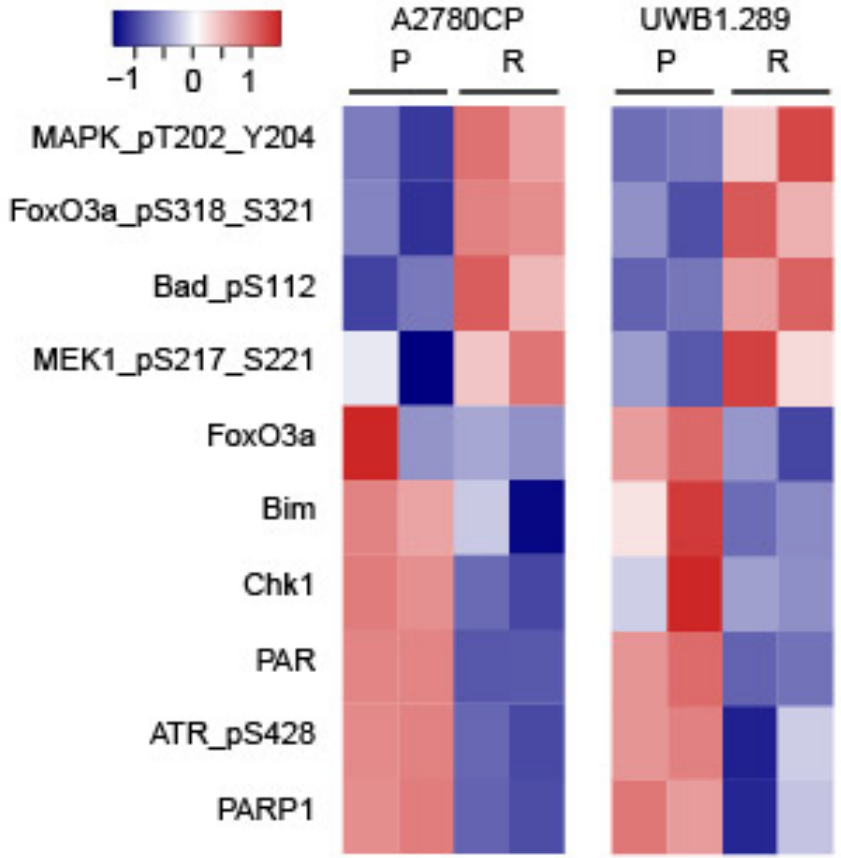


PARPi

Chaoyang Sun

Acquired PARPi resistance is associated with RAS MAPK pathway activation, acquisition of RAS mutations and sensitization to combination therapy





Acquired RAS mutation

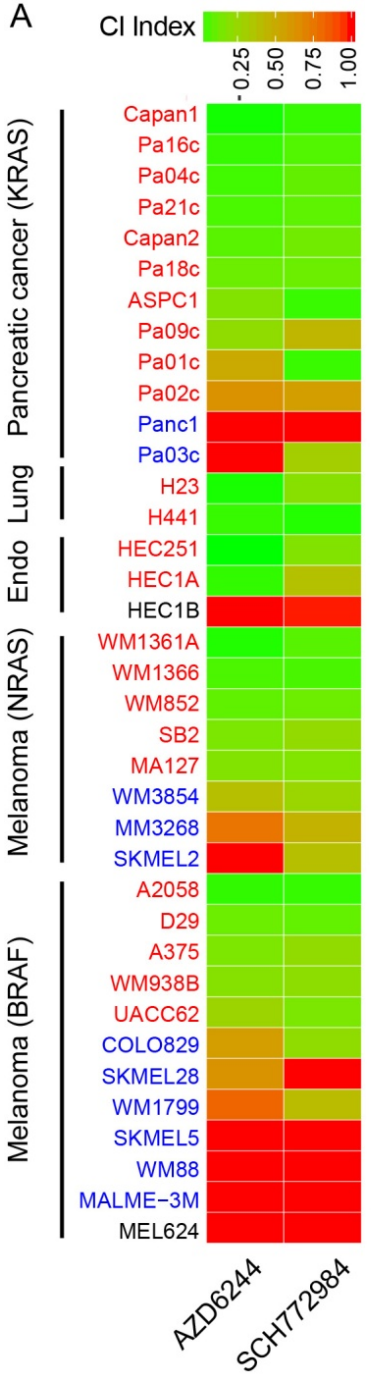
BRCA1 mutant

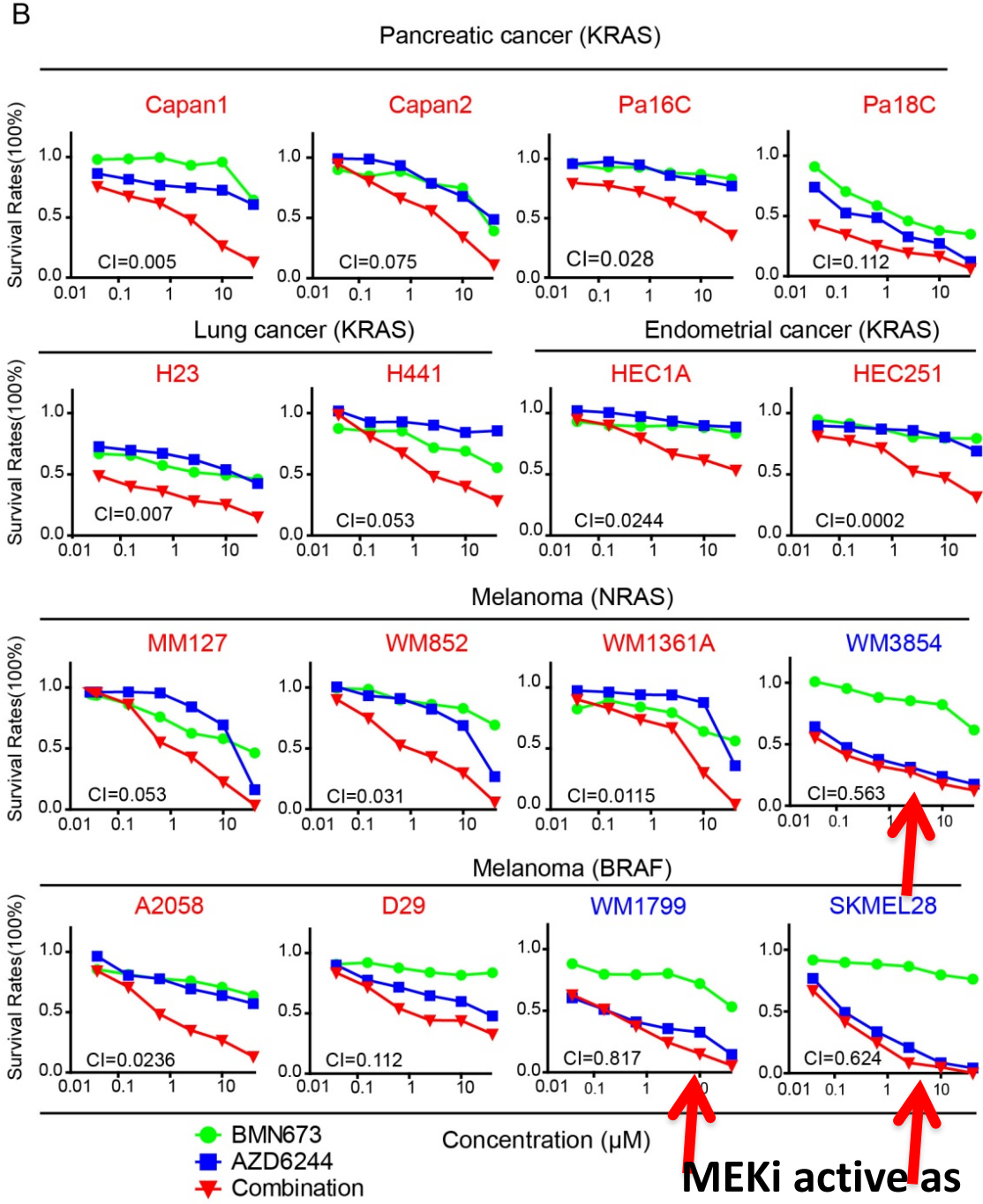
Chaoyang Sun

Synergistic effect of PARP and MEK/ERK inhibition is lineage independent and observed with KRAS/NRAS /BRAF mutations.

35/37 models

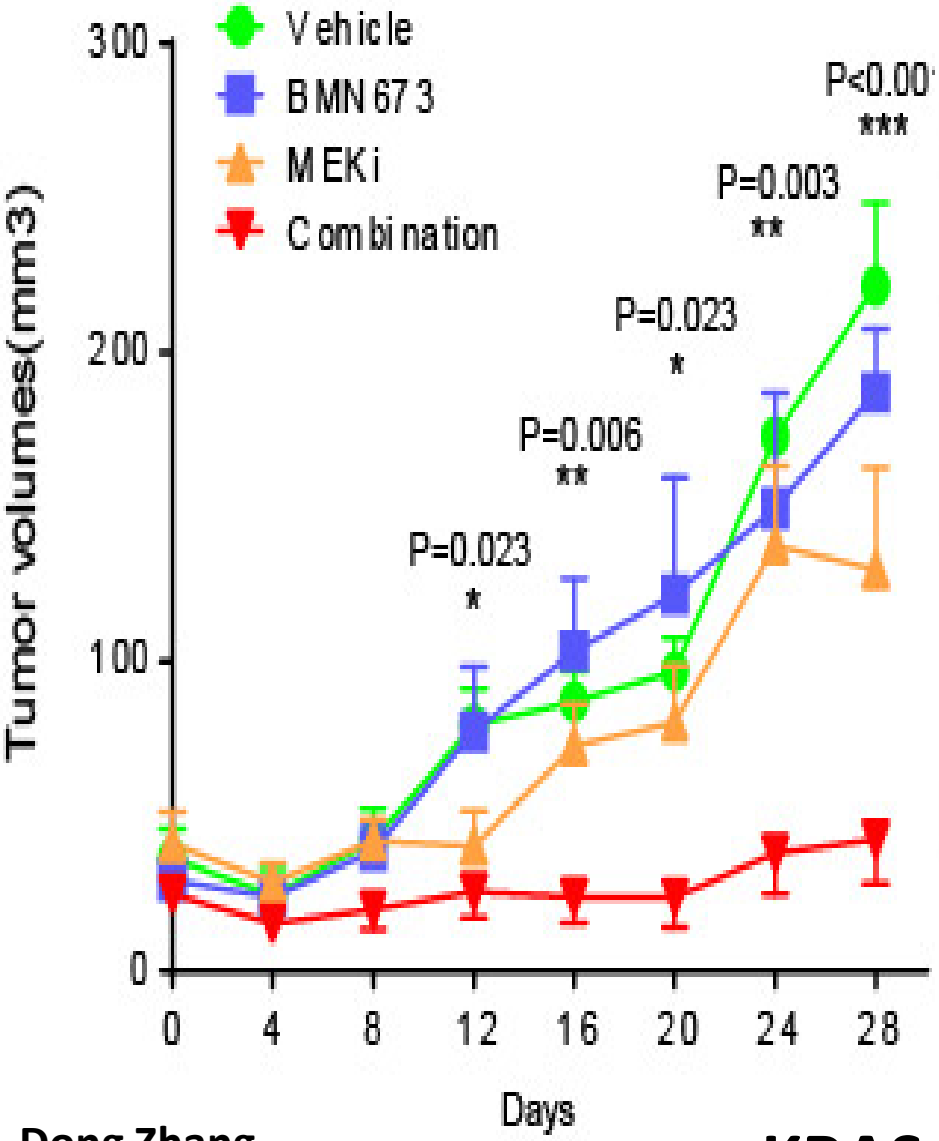
Dong Zhang
Yong Fang
Chaoyang Sun

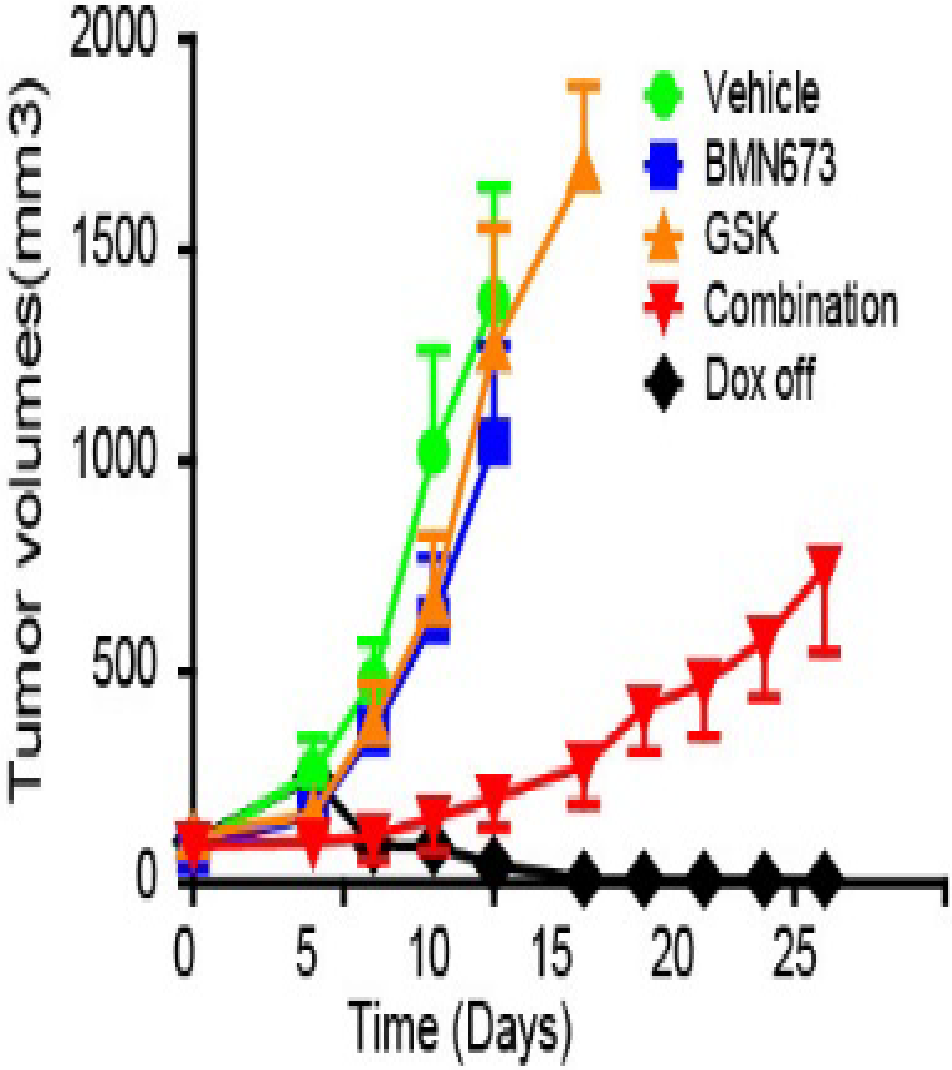




MEKi active as monotherapy

PARP plus MEK inhibitors are synergistic in vivo



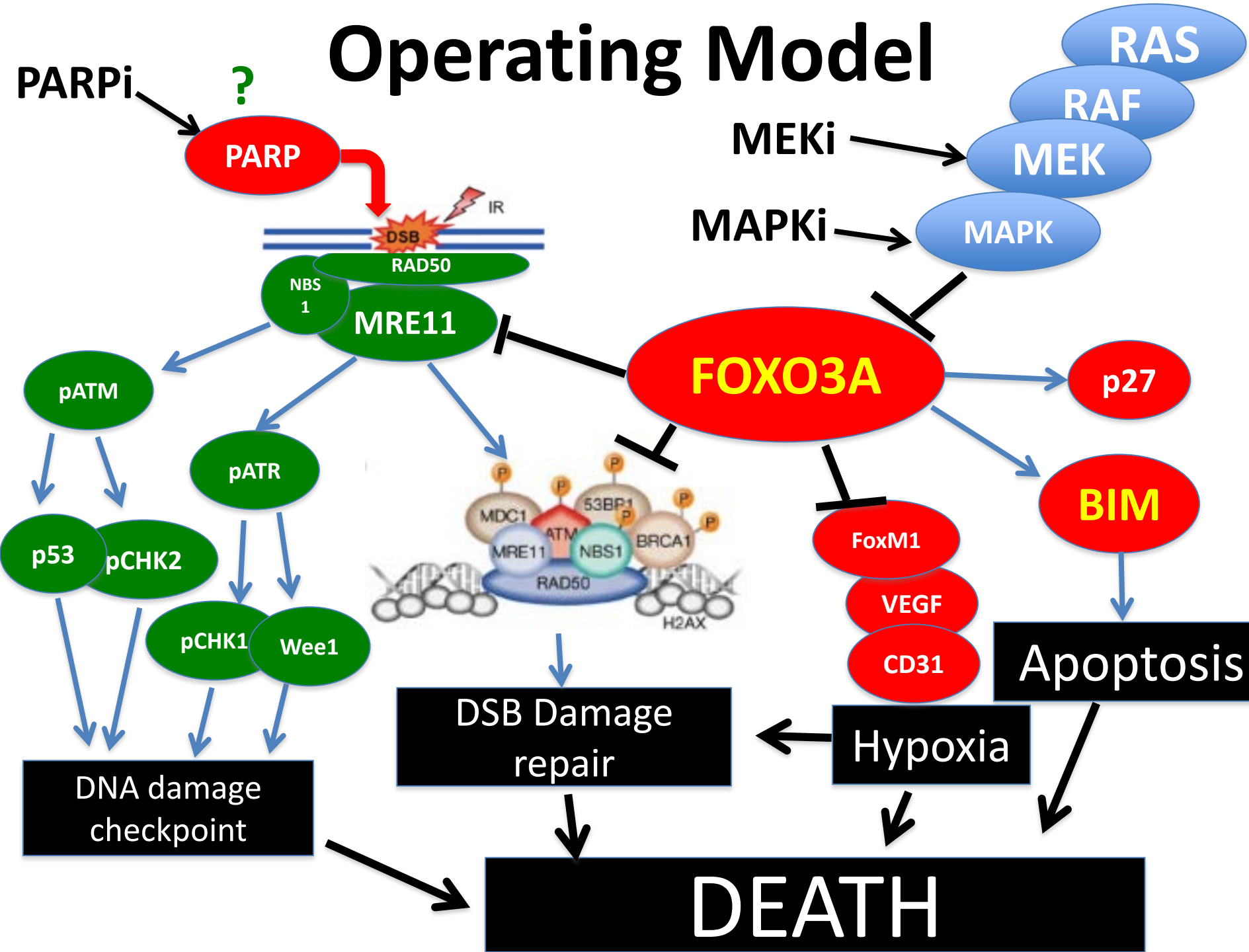


Dong Zhang
Yong Fang
Chaoyang Sun

KRAS OVCAR8

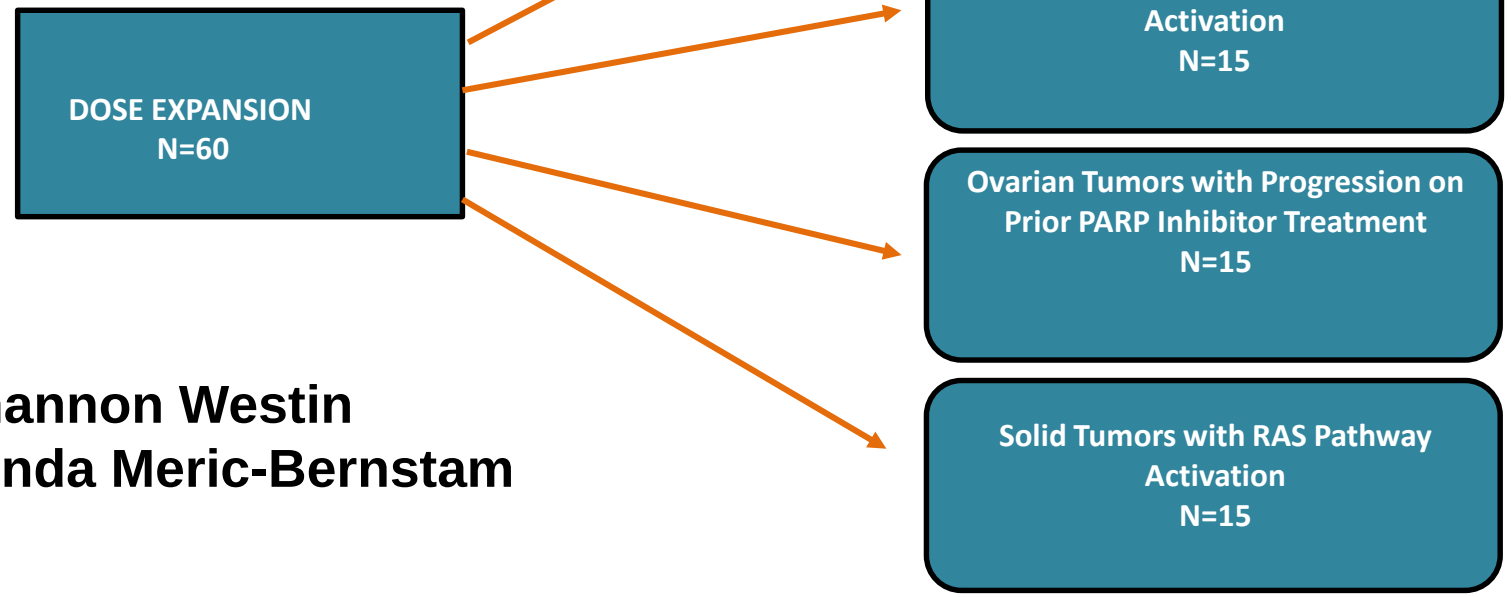
KRAS HPDE Pancreas

Operating Model



SOLAR study: selumetinib and olaparib in RAS activated tumors

Original observation 4/8/2015
CRC Approved, IRB 3/1/17
FDA no Objection
SIV May 30 2017
First in human August 2017



Shannon Westin
Funda Meric-Bernstam

Immune system contributes to response to PARP plus MEK

Dong Zhang
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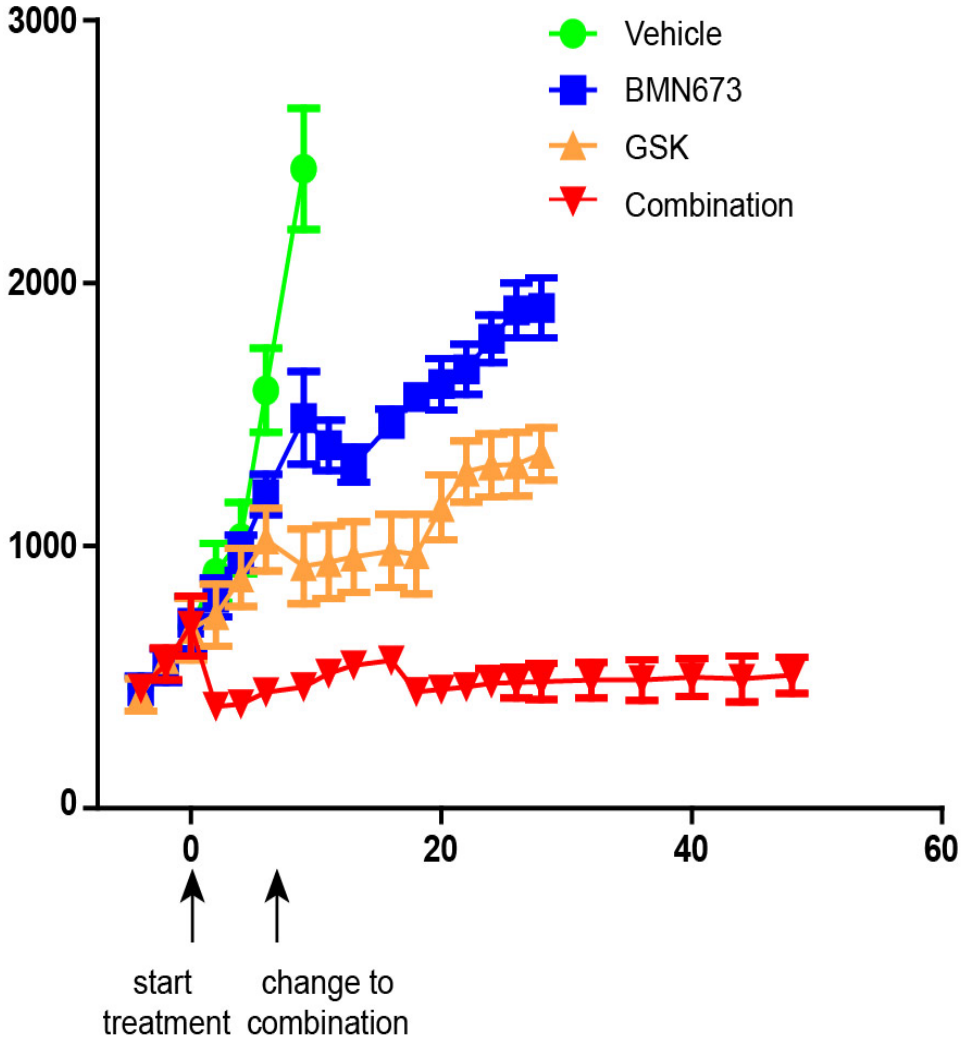
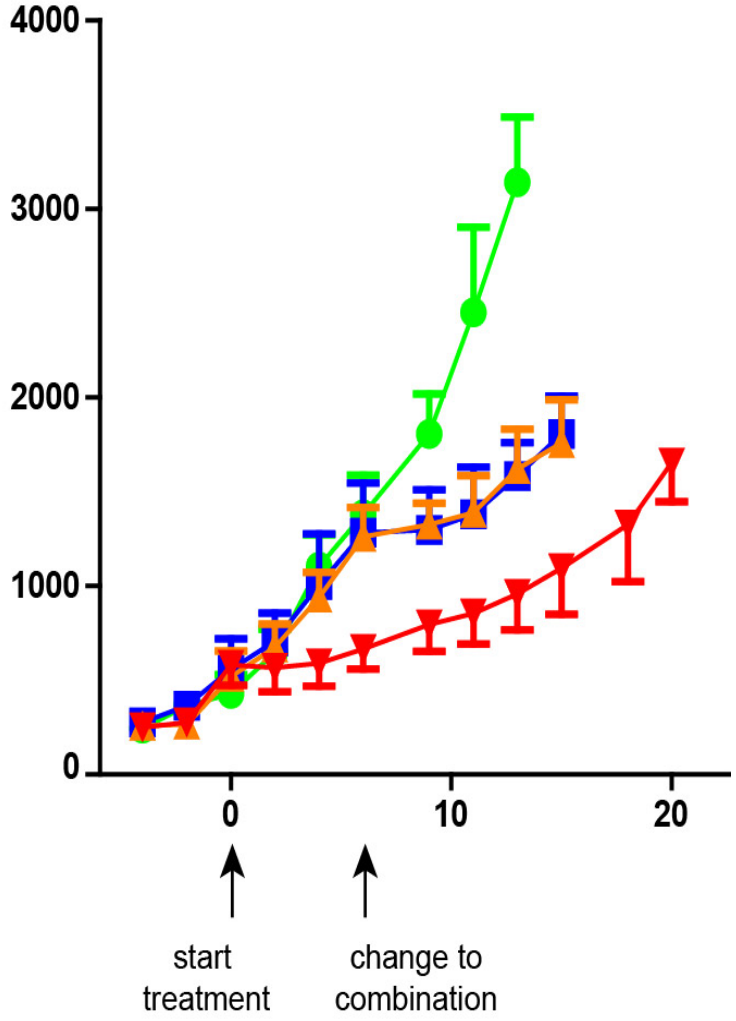
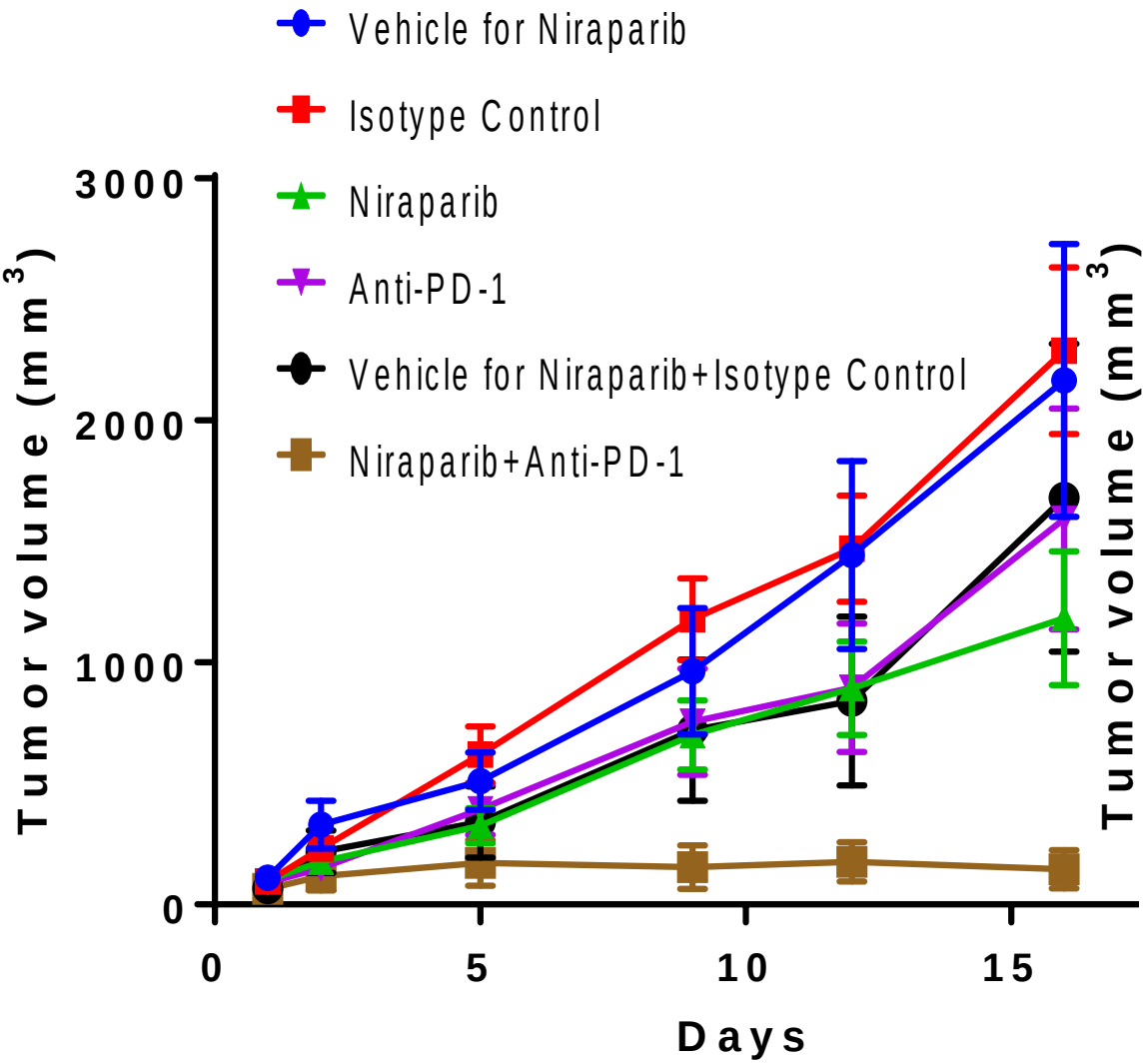


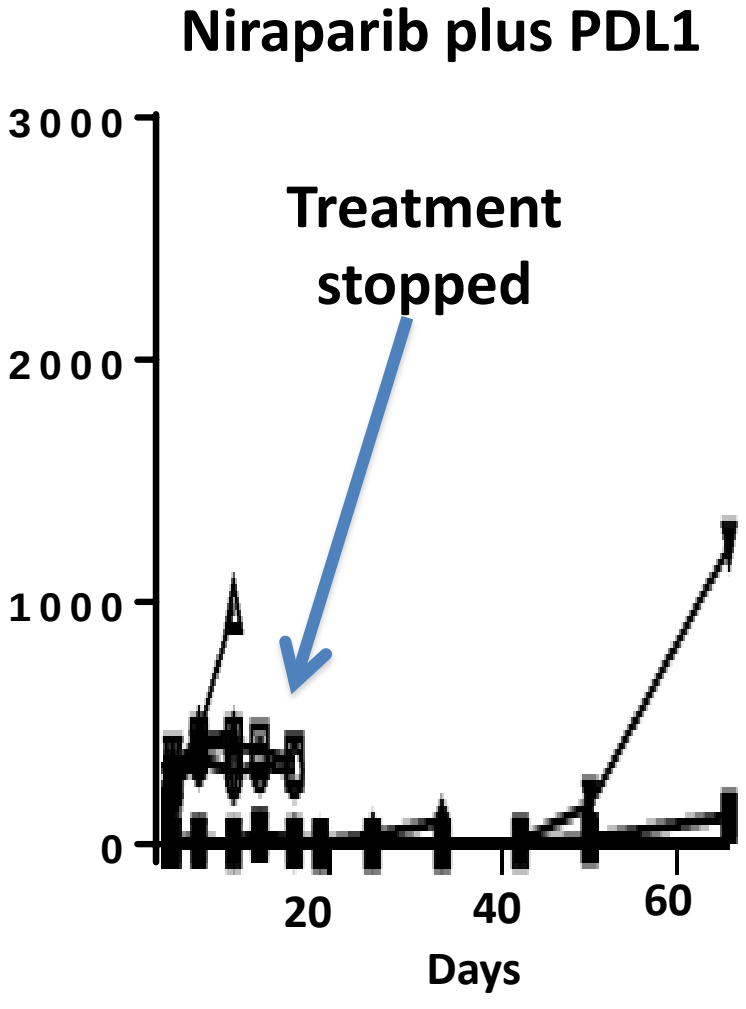
MDX in immune competent mouse



MDX in immunoincompetent mouse

Niraparib plus anti-PD1 is effective in MDX T22 model

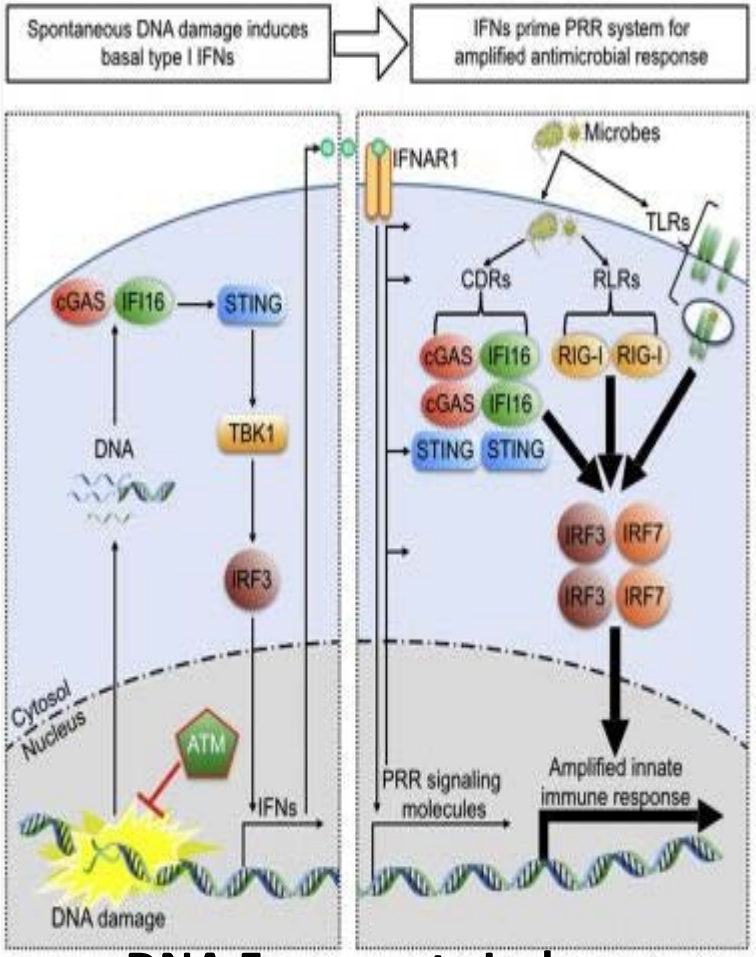




CCCT Collaboration with Tesaro

STING / Type I IFN and immune priming

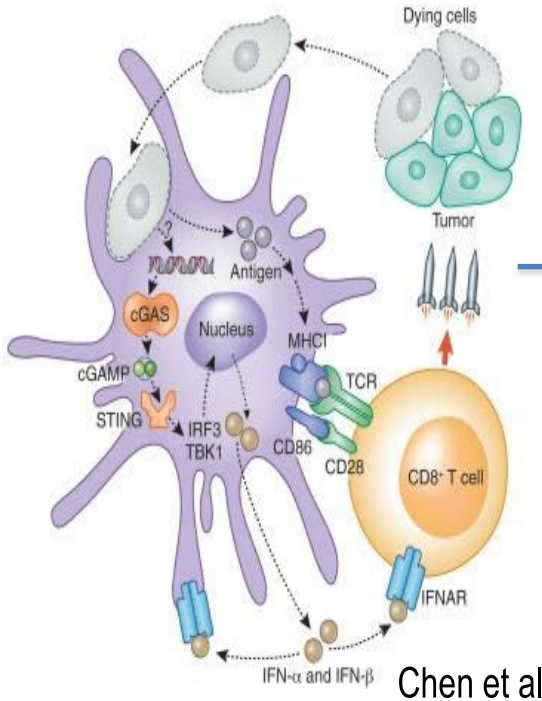
DNA fragments in response to PARPi induces immune activation



DNA Fragments Induce a Sting Response as Protection from Virus and Bacteria

Hartlova et al., Immunity 2015

- Activation of STING by cGAMP in response to cytoplasmic dsDNA results in secretion of Type I IFNs (IFNα, IFNβ)
- IFNα/β promotes DC maturation and cross-presentation of tumour antigens to CD8+ T cells



Immune activation

Chen et al., Nat Immunol, 2016

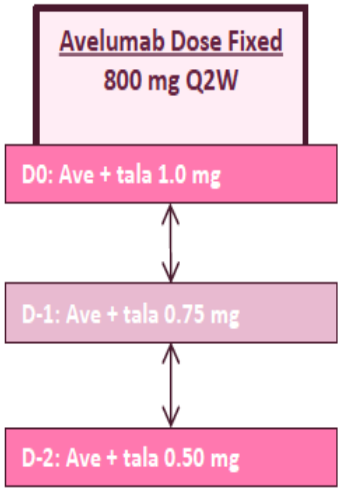
Phase I Trial of Talazoparib + Avelumab in Advanced Cancers

Currently enrolling in ICT (PI: Tim Yap)

Eligibility:

- Advanced or metastatic solid tumors including NSCLC, breast, ovarian, bladder, and prostate.
- PARP refractory excluded
- PD-1/PD-L1 treatment naïve
- ECOG 0 and 1
- Prior platinum eligibility varies by tumor type

1. Dose escalation



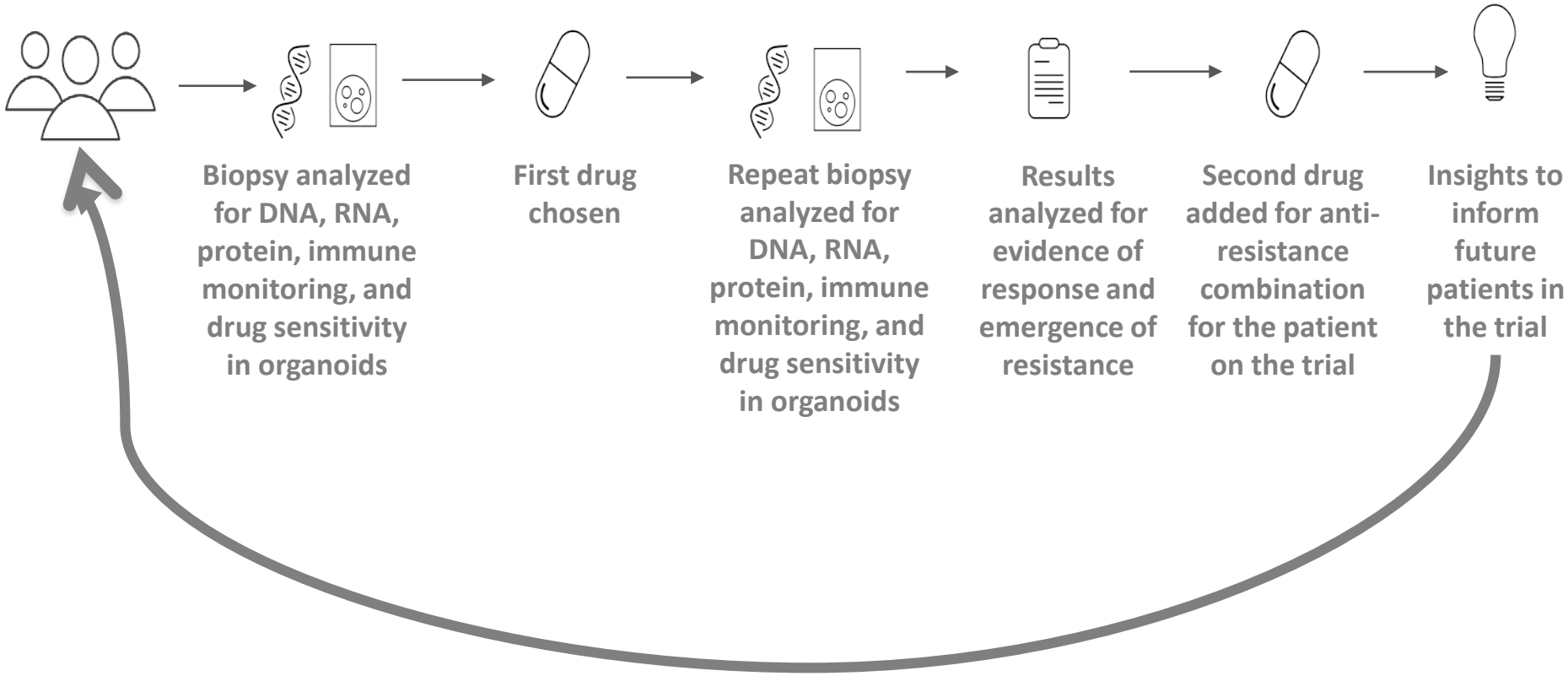
- Tumor types permitted as per those defined for the dose expansion cohorts
- Dose escalation as per mTPI
- Each dose level will have 3-12 pts
- No backfill
- DLT Observation period=28 days
- N=12-36 total

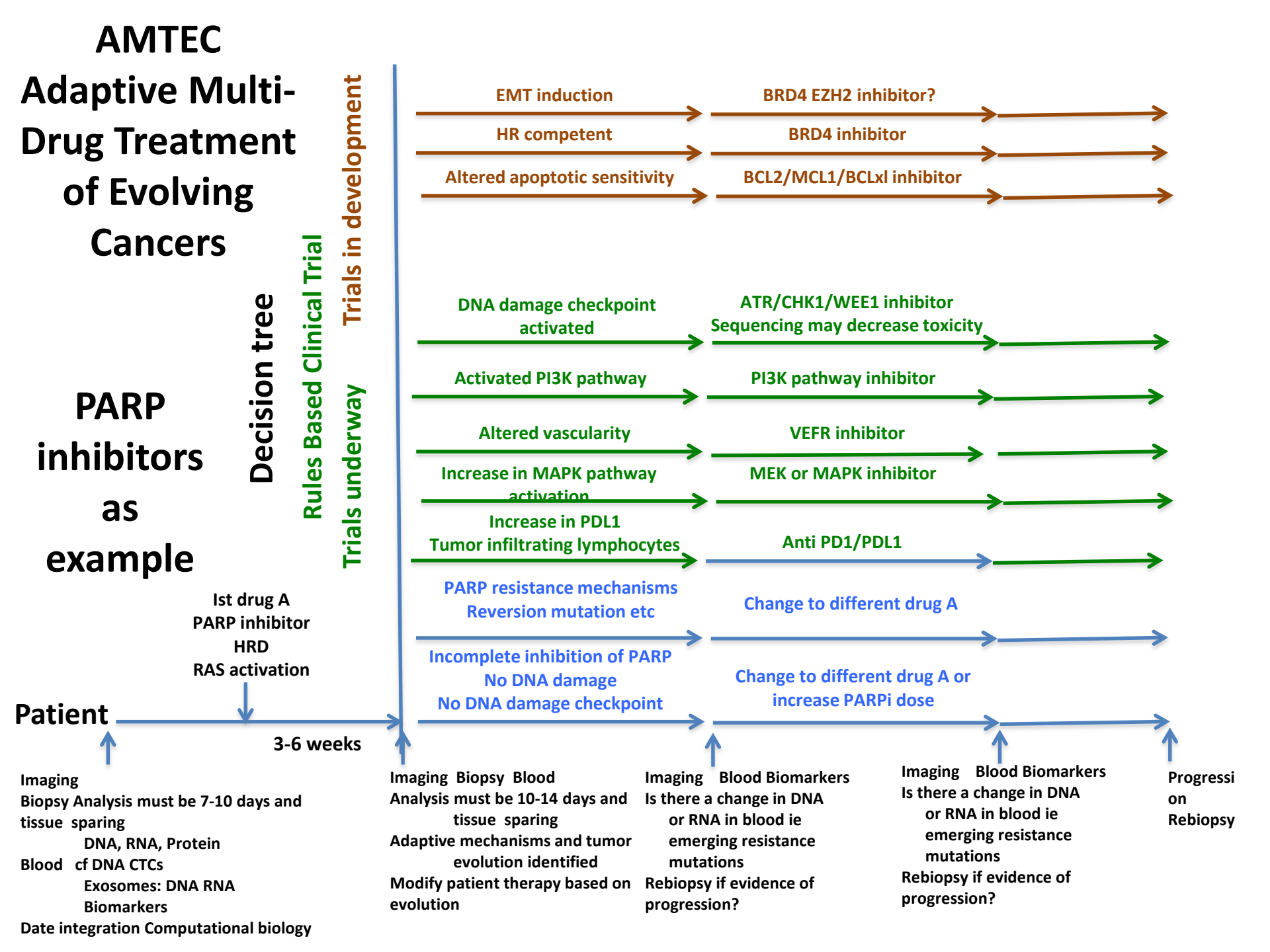
2. Dose expansion

- A1. NSCLC N=40
- A2. NSCLC PD-L1 TPS ≥ 50% N=40
- B1. TNBC N=20
- B2. HR+ BC DDR Defect + assay N=20
- C1. Ovarian Recurrent platinum-sensitive N=40
- C2. Ovarian Recurrent platinum-sensitive BRCA defect N=20
- D. Urothelial N=40
- E1. CRPC N=20
- E2. CRPC DDR Defect + assay N=20

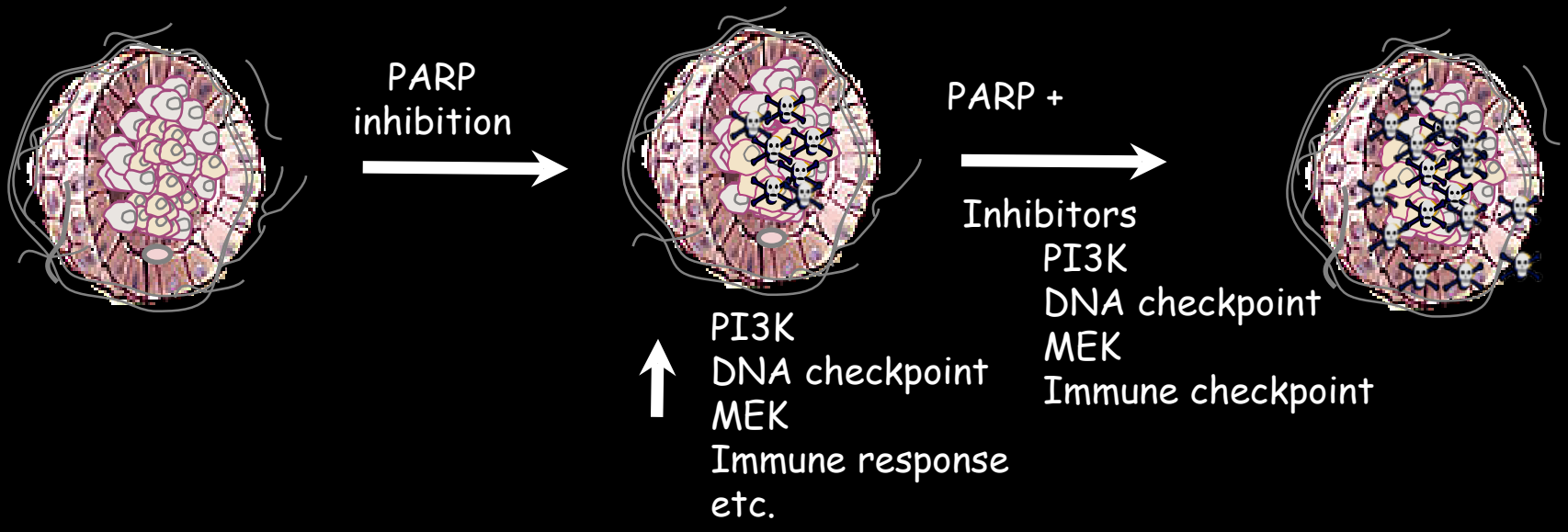
AMTEC
Adaptive Multi-Drug Treatment of Evolving Cancers

AMTEC will be designed to reveal the complexity of each individual's cancer and its evolution under therapeutic stress, implementing uniquely designed therapeutic strategies that evolve concomitantly benefiting the patient we are treating while identifying underlying mechanisms of resistance to guide new drug combinations.




AMTEC
Adaptive Multi-Drug Treatment of Evolving Cancers
PARP inhibitors as example
Decision tree
Rules Based Clinical Trial
Trials underway
Trials in development
EMT induction
BRD4 EZH2 inhibitor?
HR competent
BRD4 inhibitor
Altered apoptotic sensitivity
BCL2/MCL1/BCLxl inhibitor
DNA damage checkpoint activated
ATR/CHK1/WEE1 inhibitor
Sequencing may decrease toxicity
Activated PI3K pathway
PI3K pathway inhibitor
Altered vascularity
VEFR inhibitor
Increase in MAPK pathway activation
MEK or MAPK inhibitor
Increase in PDL1
Tumor infiltrating lymphocytes
Anti PD1/PDL1
PARP resistance mechanisms
Reversion mutation etc
Change to different drug A
Incomplete inhibition of PARP
No DNA damage
No DNA damage checkpoint
Change to different drug A or increase PARPi dose
Ist drug A
PARP inhibitor
HRD
RAS activation
Patient
3-6 weeks
Imaging
Biopsy Analysis must be 7-10 days and tissue sparing
DNA, RNA, Protein
Blood cf DNA CTCs
Exosomes: DNA RNA Biomarkers
Date integration Computational biology
Imaging Biopsy Blood
Analysis must be 10-14 days and tissue sparing
Adaptive mechanisms and tumor evolution identified
Modify patient therapy based on evolution
Imaging Blood Biomarkers
Is there a change in DNA or RNA in blood ie emerging resistance mutations
Rebiopsy if evidence of progression?
Imaging Blood Biomarkers
Is there a change in DNA or RNA in blood ie emerging resistance mutations
Rebiopsy if evidence of progression?
Progression Rebiopsy

Rational Strategy for Combination Therapies



Blocking critical signaling nodes "rewires" signaling pathways

Rewired networks contribute to cellular resistance to targeted therapeutics

Induced signaling events represent "vulnerabilities" that can be exploited leading to synthetic lethality

Adaptive responses can be restricted to specific tumor subpopulations

AMTEC
Adaptive Multi-Drug Treatment of Evolving Cancers

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Breast Cancer Research Foundation, Ionis, Tarveda

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