Ovatars: Using Patient-Derived Xenografts for Selecting Best Therapies

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Learning Objectives

After reading and reviewing this material, the participant should be able to:

- Define PDX and Avatar Models
- Understand how Avatar models may be used for drug development
- Understand why Ovarian Cancer may be a good cancer type for using Avatars
- Explain how Avatars are being used to direct therapy and individualize therapy.

Outline

- Project Overview
- Characterization
  - Gross, Histological, Molecular
- Novel Therapy development
  - PARP inhibitor
  - Use of US for monitoring
  - Potential for Collaborations
- Avatar Directed Therapy

Barriers to Better Ovarian Cancer Outcomes

- Screening
  - Neither common nor rare
  - Imaging/serum markers- disappointing
- Vague symptoms
  - No longer the ‘silent killer’, but…
- Late stage at diagnosis
- Treatment not customized

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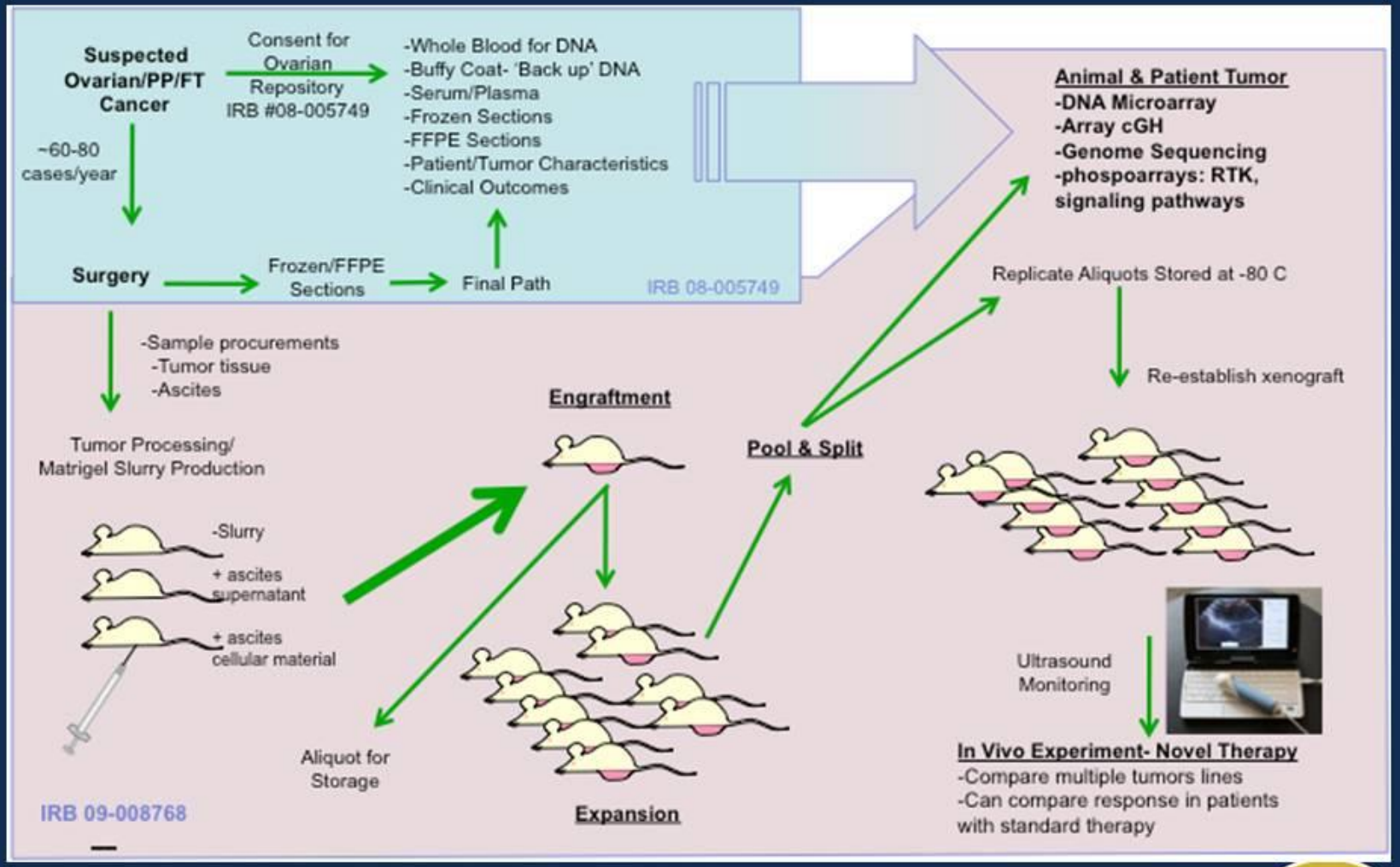
Ovarian Avatar Project



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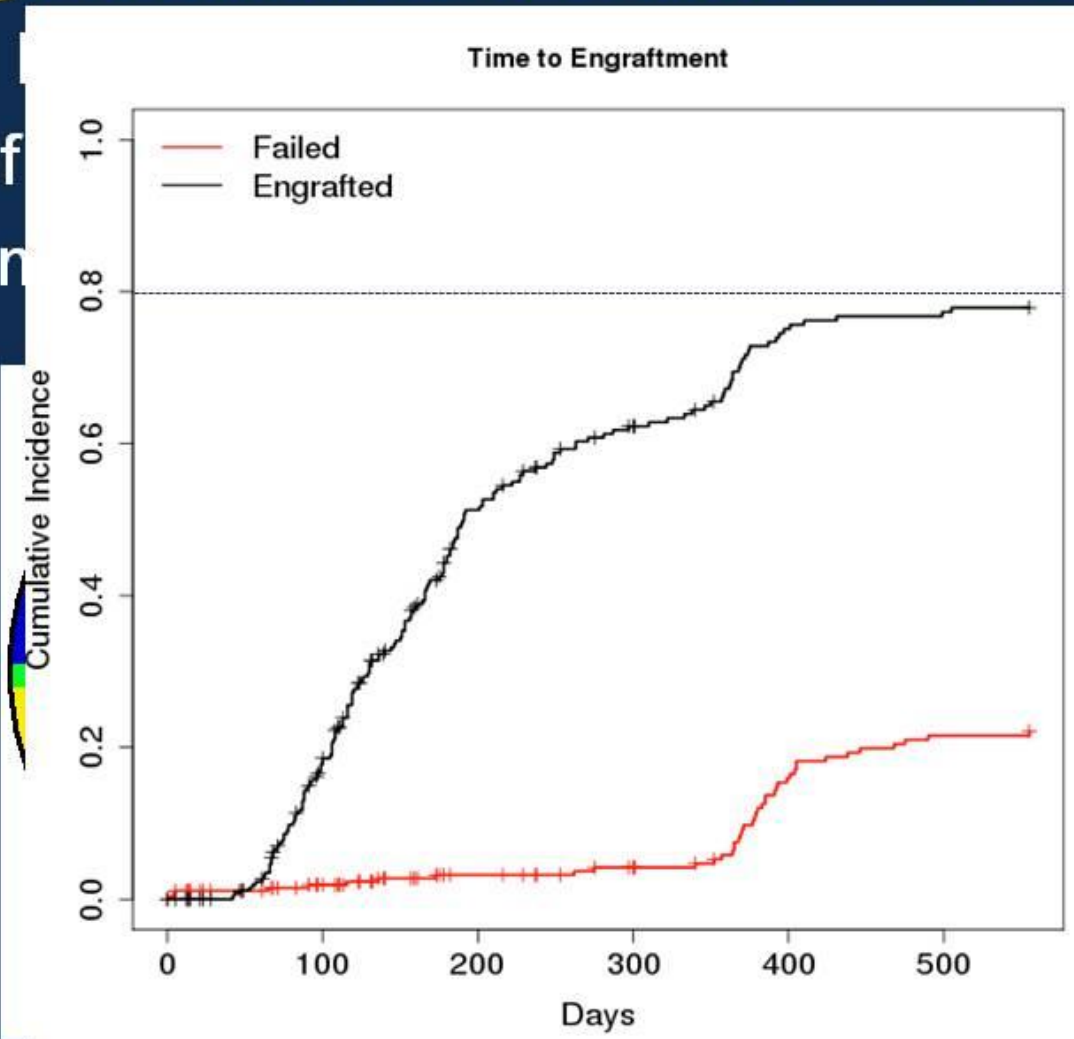
Definitions

- Xenografts- tumors from one species implanted in another
  - Most commonly human in mouse
- Orthotopic- in the natural location
- Patient-derived xenografts- xenografts implanted directly from patients (i.e.- no plastic)
- Avatars- Orthotopic, treatment-naïve PDX's
- Ovatars- Our Ovarian Avatar modeling system

Engraftment & Tumor Diversity

- First
- As of
- 239 n



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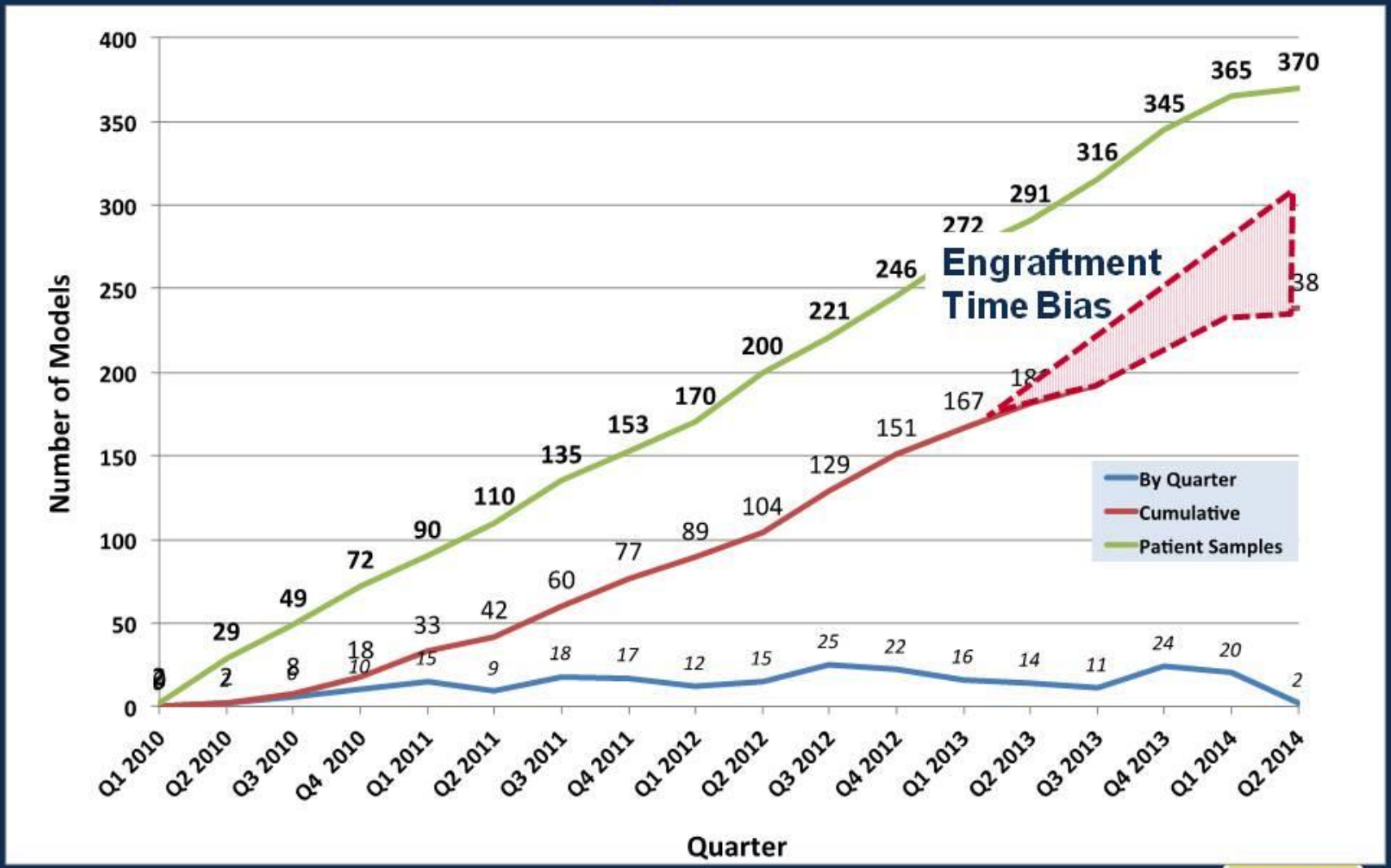
Avatar Program Status



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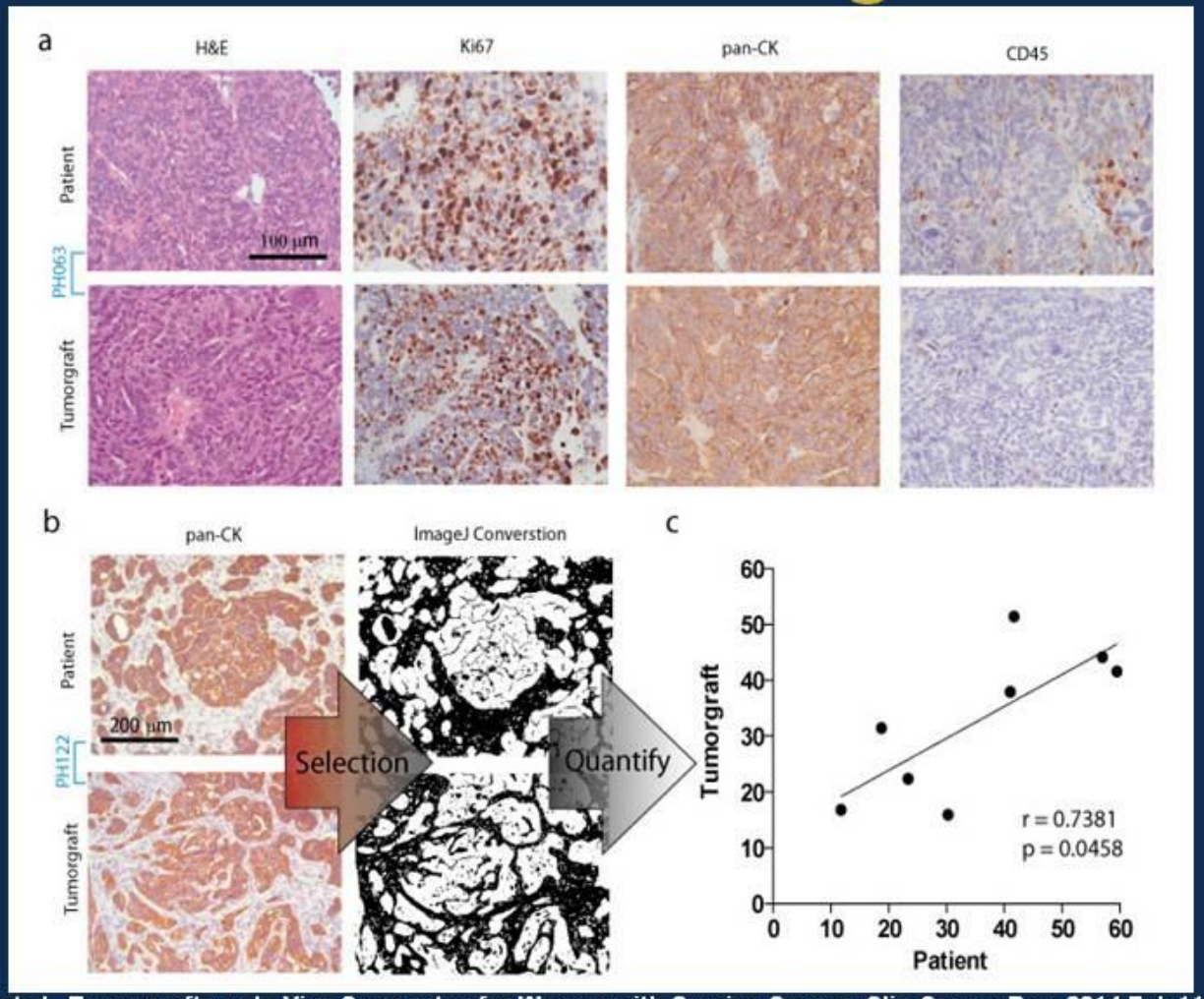
Histological Comparison: Patient →Xenograft



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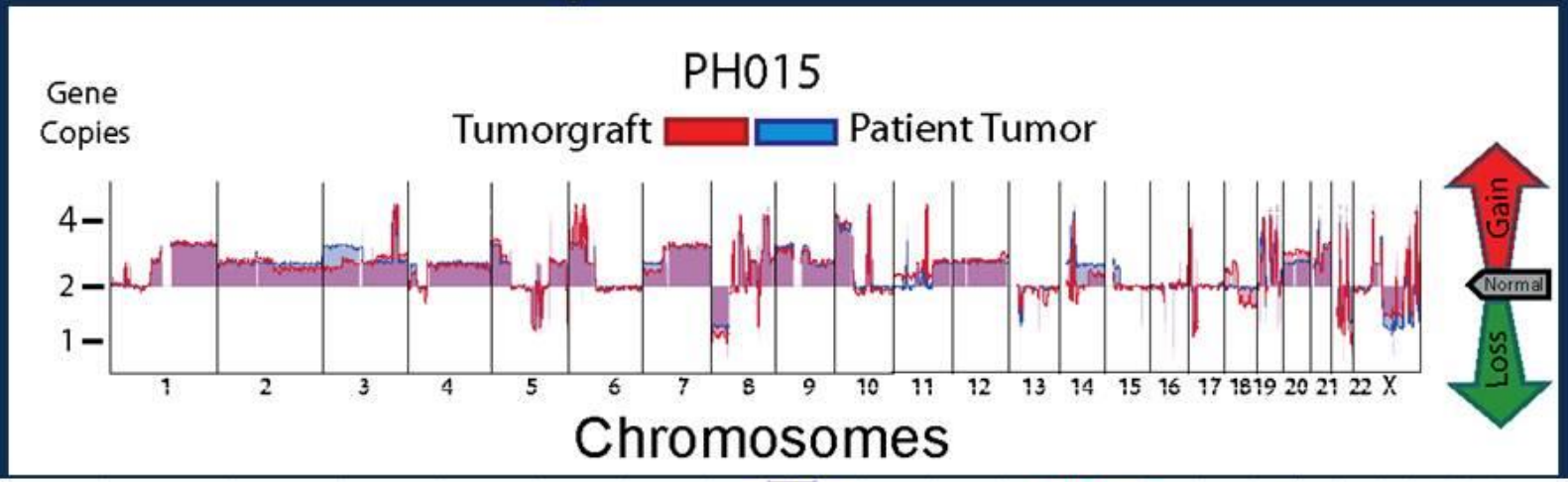
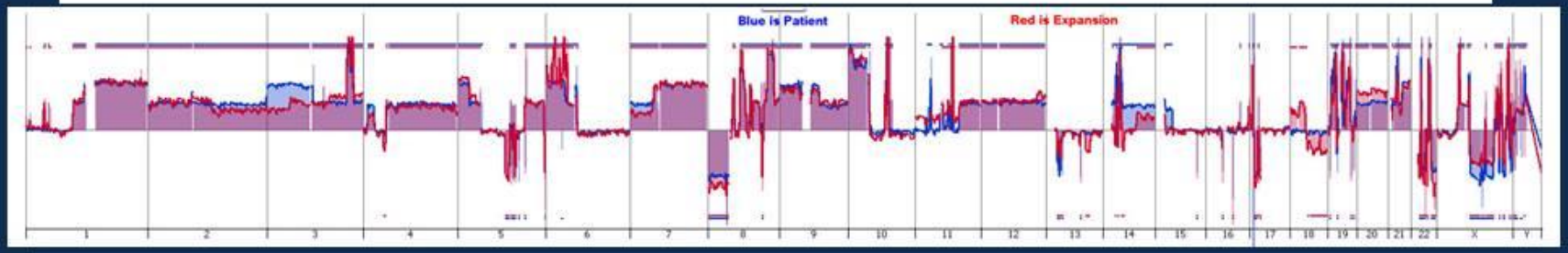
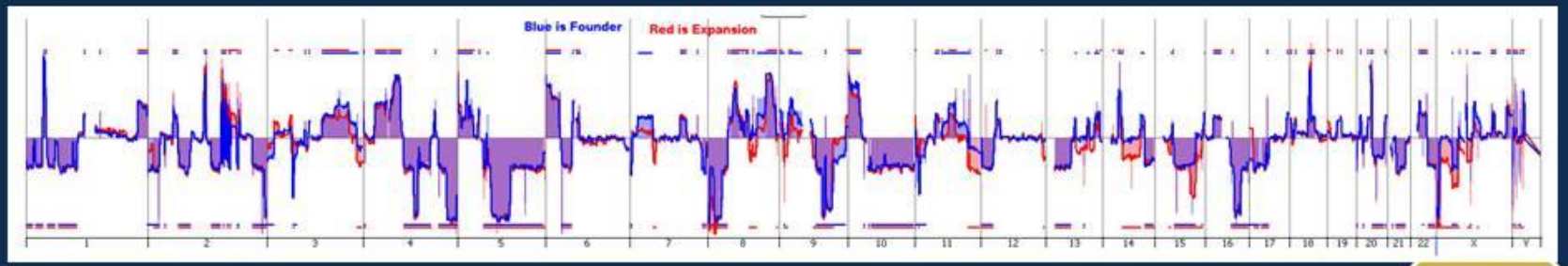
Ovatars recapitulate heterogeneity of donor patient tumors







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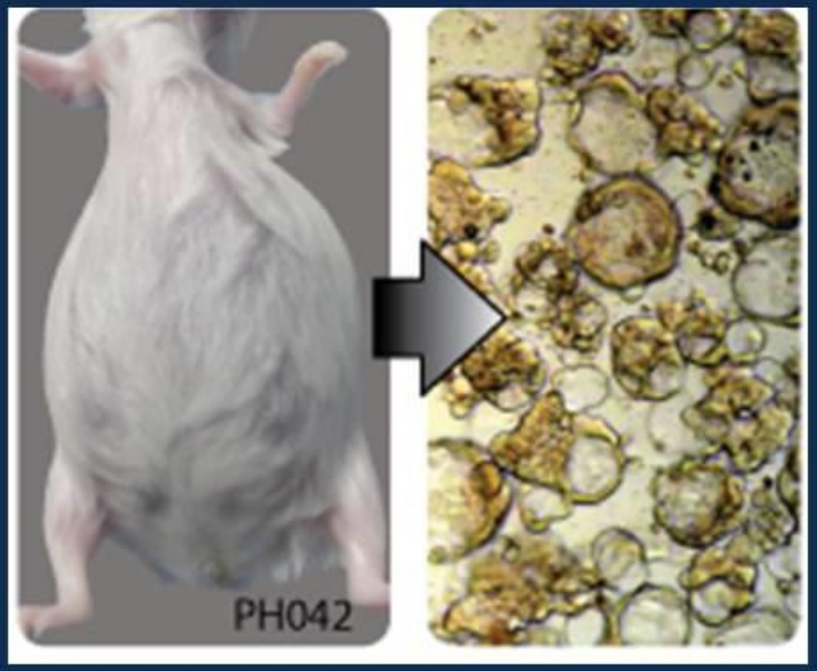
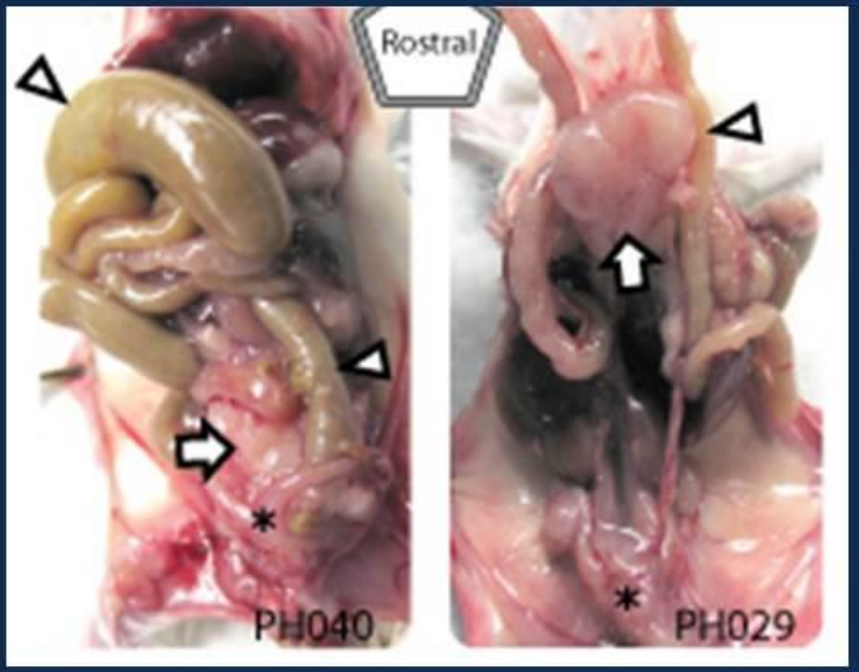
Ovarian avatars recapitulate clinical complications of donor patient tumors





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Criticism:

“While cell lines are not predictive of therapeutic response, neither are xenografts”

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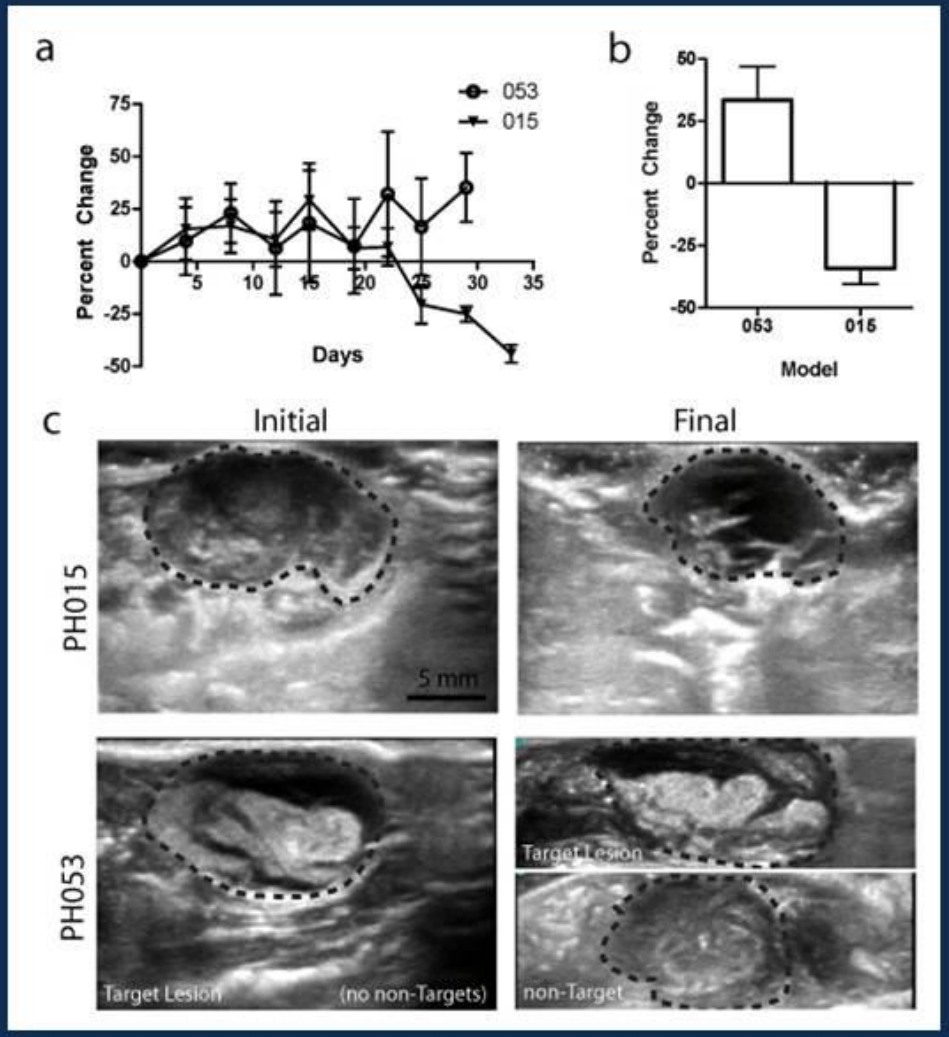
Avatar Predictive for Platinum Response



PH053

-Stage IIIC serous OC

-Received TC x 6

-Recurred within 6 mo

PH015

-Stage IIIC serous OC

-Received TC x 6

-Disease free >2 yrs

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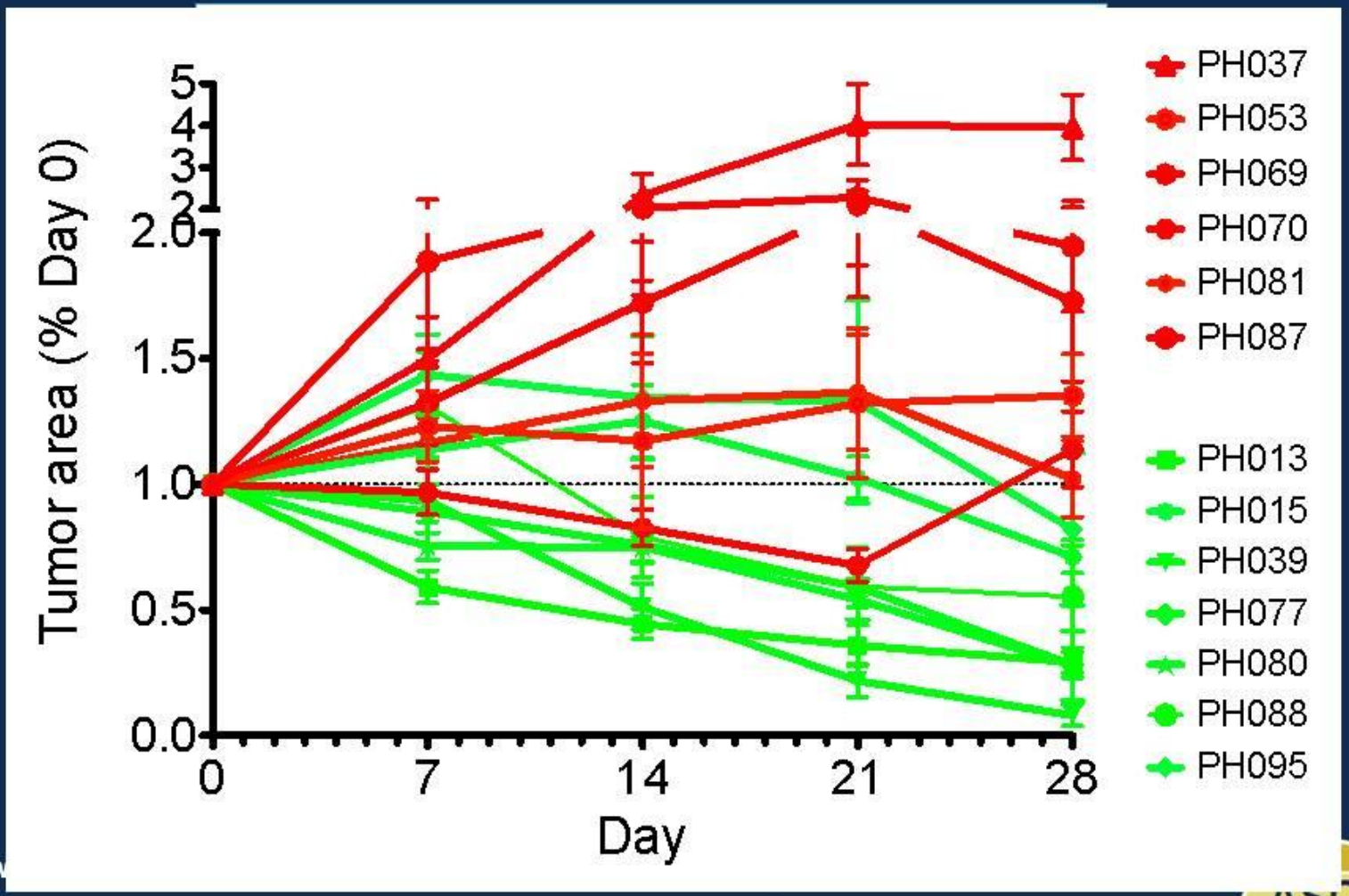
Avatar Predictive for Platinum Response



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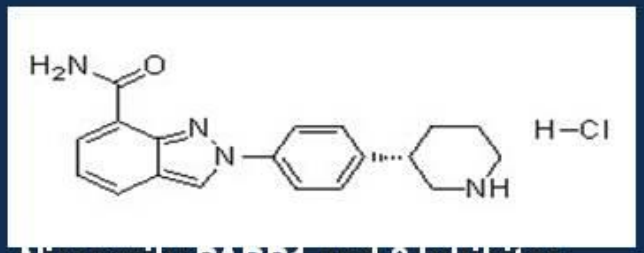
Drug Development Example

1. Test Hypothesis that HR-Deficient models most sensitive to PARP inhibition

- *HR deficient vs. HR proficient*
  - *Genotyping: BROCA*
  - *Functional: RAD51 foci*
  - *In-vivo: Avatars*

MK-4827



Niraparib: PARP1 and 2 Inhibitor

Al Hilli et al., Clin Cancer Res October 1, 2013 19:PR05

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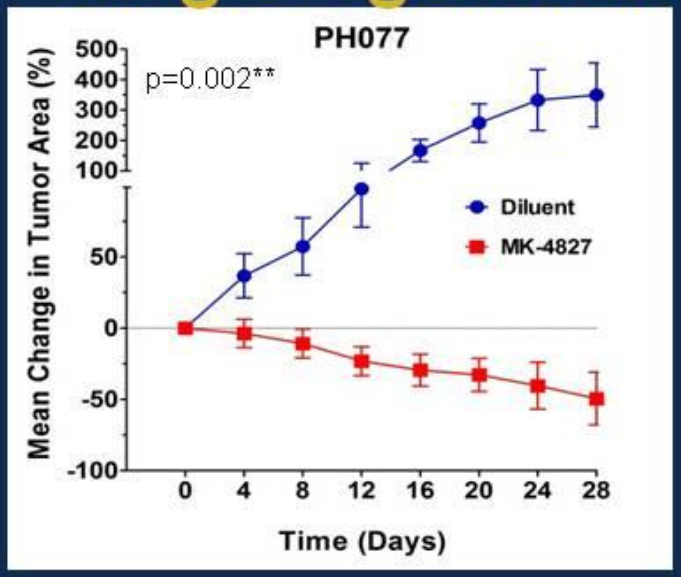
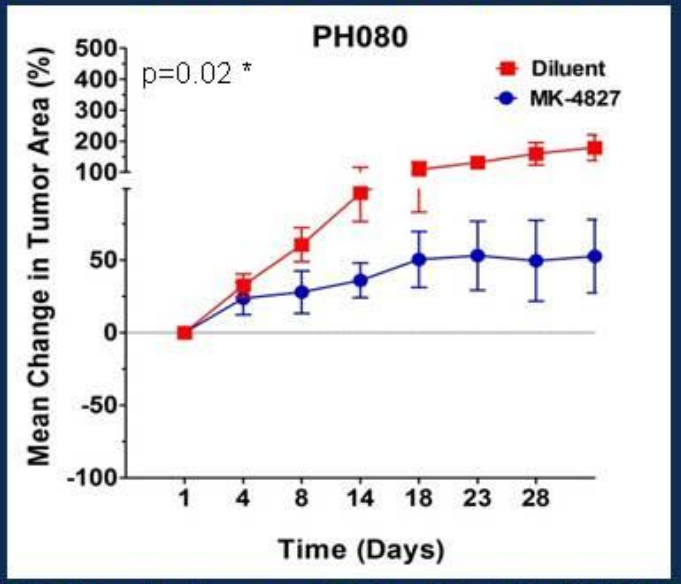
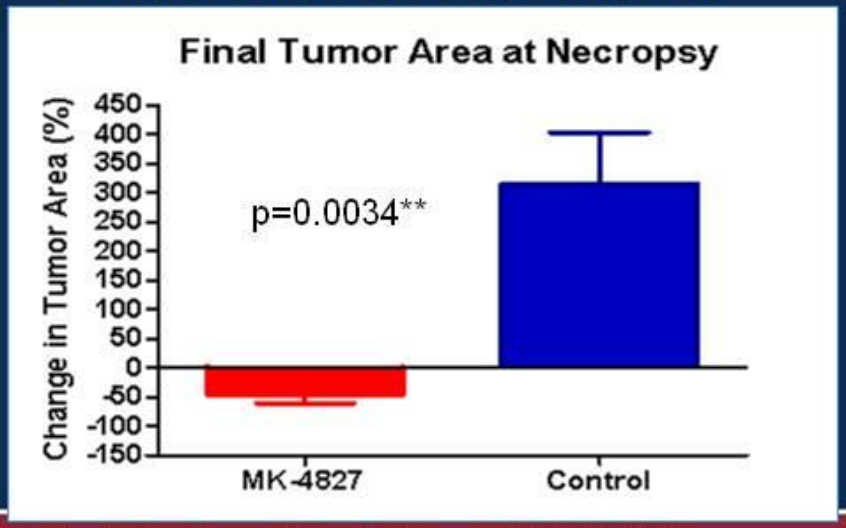
Single Agent Niraparib- "HR Deficient"

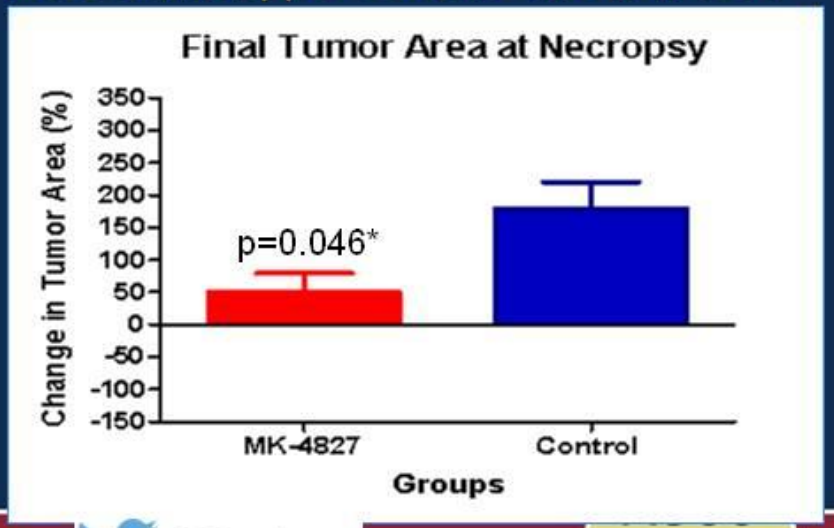


SOMATIC BRCA2 MUTATION



BRCA wildtype CDK12 MUTATION





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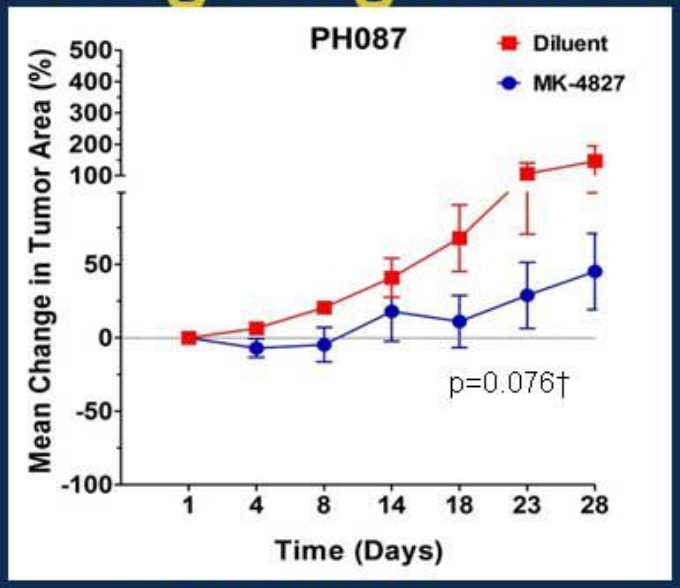
Single Agent Niraparib- "HR Proficient"



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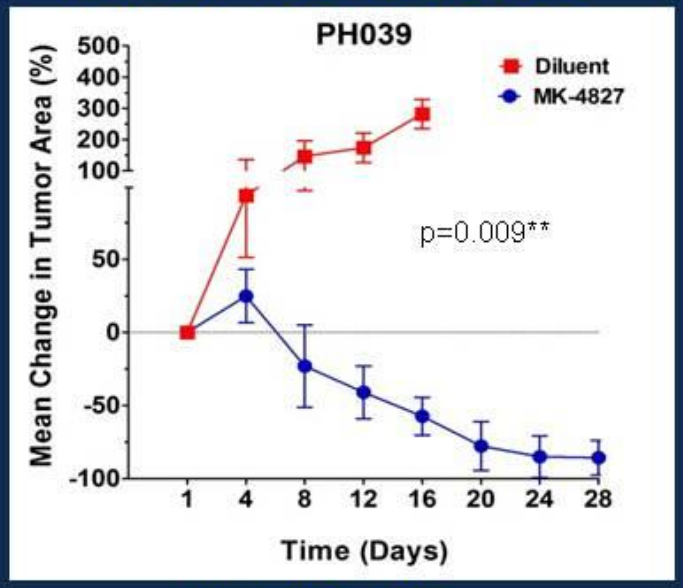

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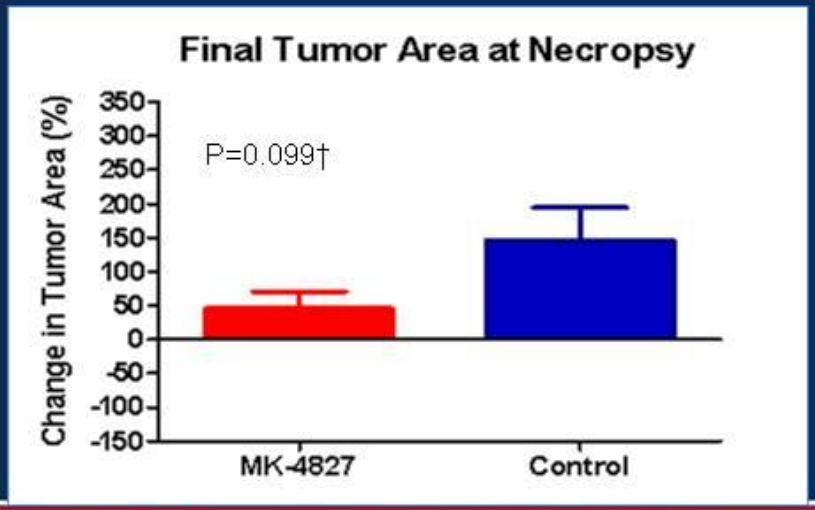

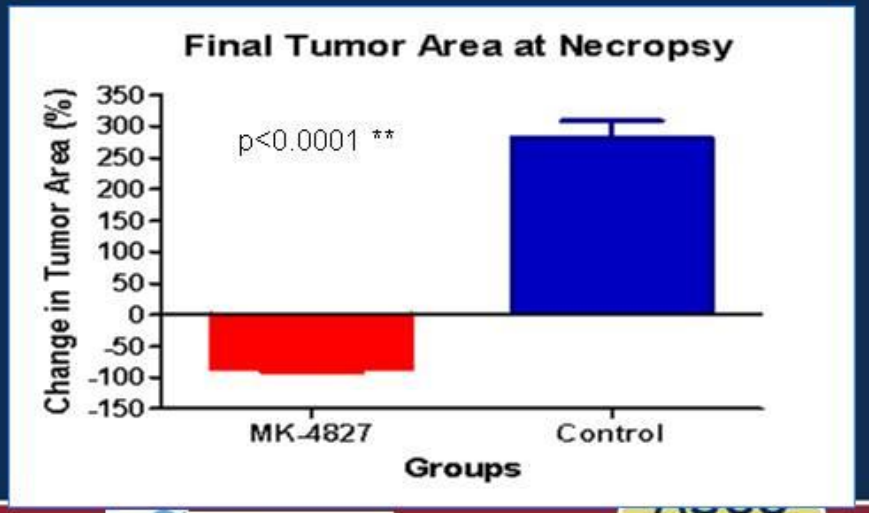

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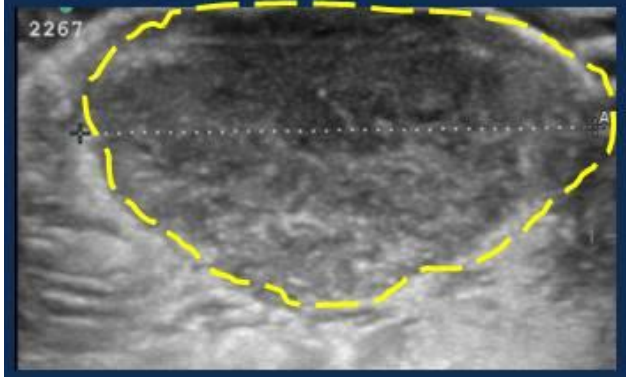
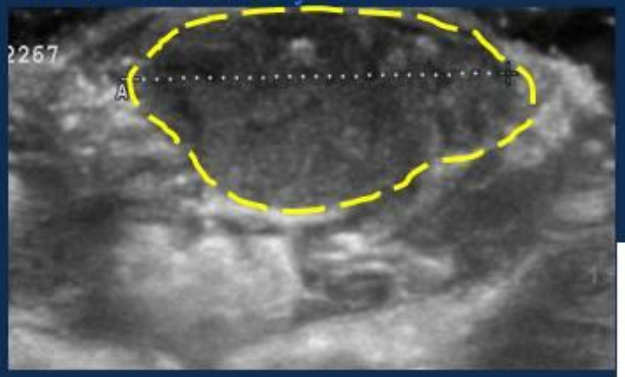
In-vivo Imaging: PH039 Ultrasound

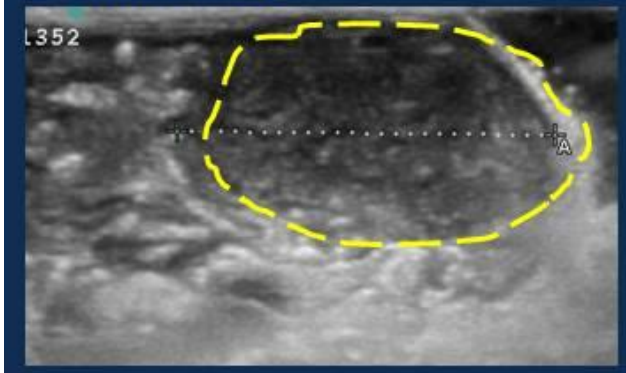
MK-4827: Day 1



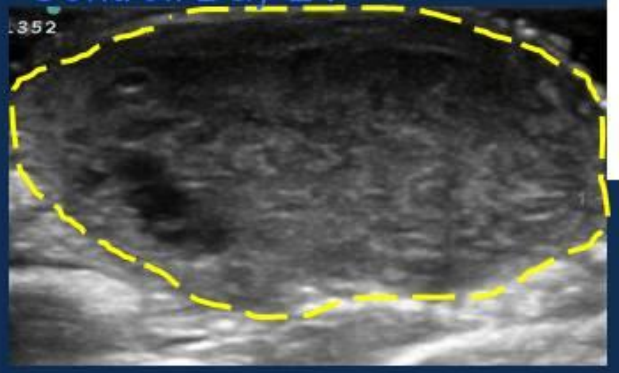
MK-4827: Day 24

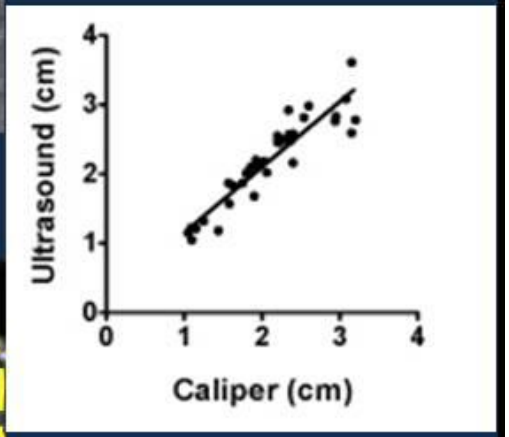


Control: Day 1



Control: Day 24





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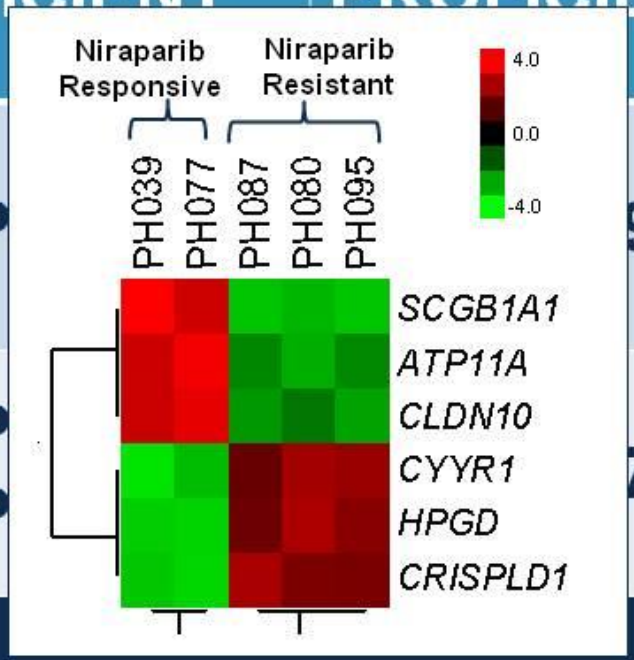
Challenging DOGMA

	HR DEFICIENT	HR PROFICIENT
PARP inhib Responsive	P	9
PARP inhib Non-Responsive	P P	7



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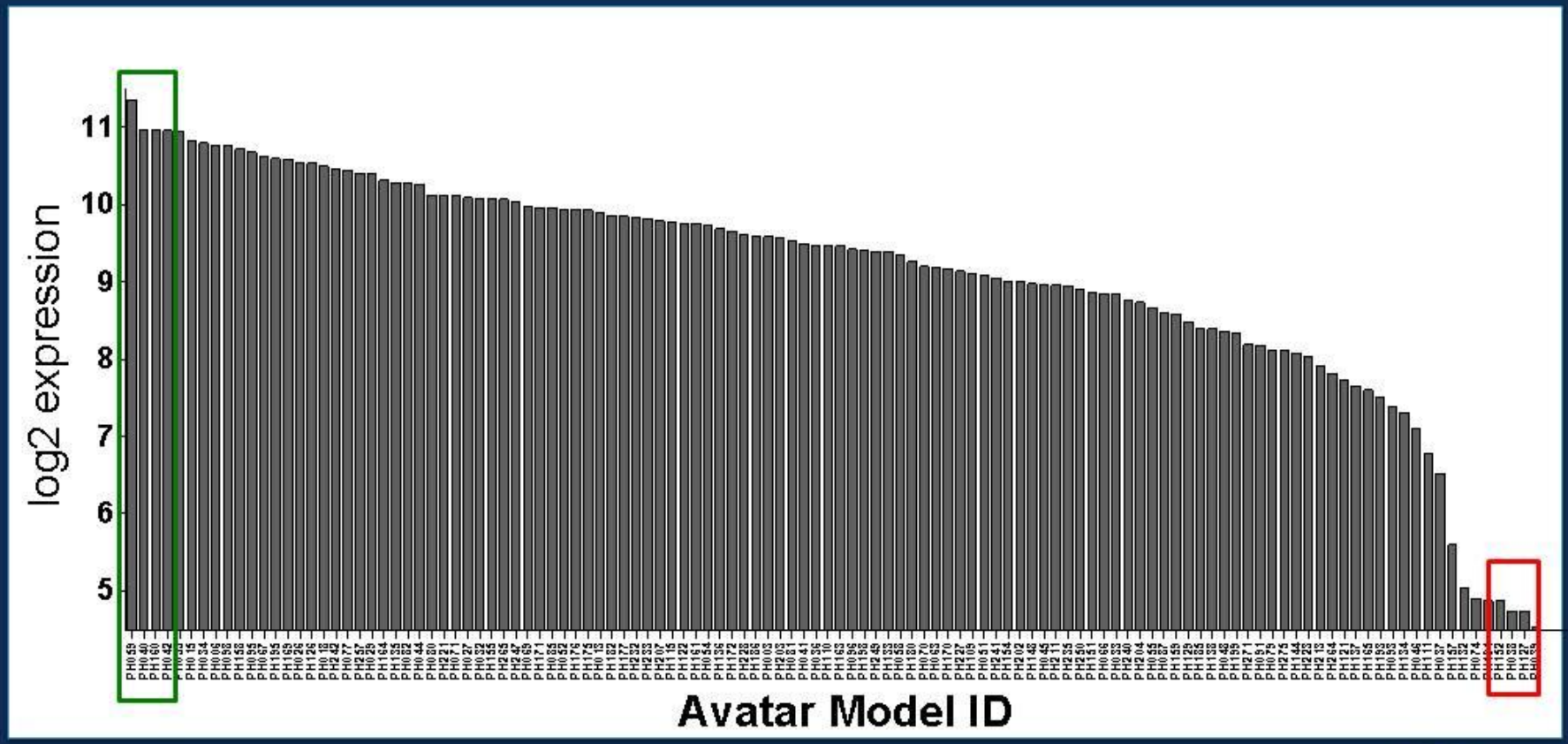
PKC iota Expression in Avatars



Collaboration with Alan Fields, Ph.D. (Mayo Clinic Florida)

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Next Step:

Directing Patient Therapy

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Modulation of Effective Response Rate

Topotecan
9-18% RR

Gemzar

Doxil

Taxol

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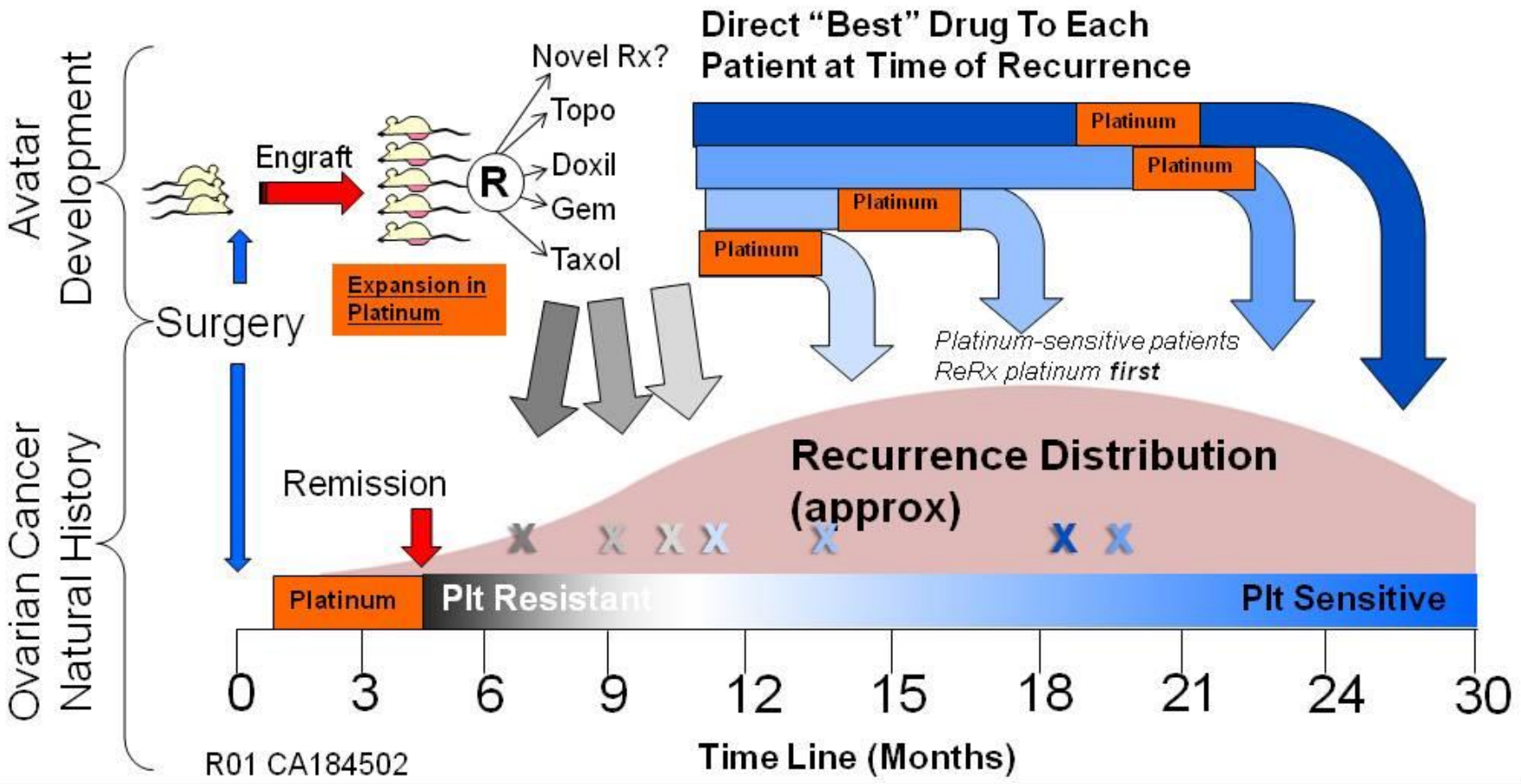
MC1463- Avatar Trial

-each patient's Avatar directs her own therapy



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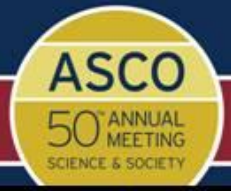
Ovarian Cancer Practice and Natural History

- Excellent tumor type for this approach
- LOTS of tumor tissue available
- High engraftment rate
  - Non-engrafters→ Do well
- Frontline treatment fairly uniform
  - Still surgery first…mostly
- Most go into remission
- Most come back, but median PFS (>20 mo) allows for model development
- No clear 'winning' standard salvage
- No clear predictive marker

PRESENTED AT:



Avatar Directed Therapy

- First Ovarian Trial with Xenograft-Directed Therapy
  - Enterprise wide… other US sites next?
- Truly individualize- Each woman's Avatar will help her!
- Idea: The best predictor of response… is response!
  - Genotyping too complex in *most cases*
  - Treatment relevant subtypes unlikely
- Do we really know our 'standard' therapies?
  - Do same patients respond to each?
  - Can we predict resistance?
  - We will be able to determine the genotype of responders to each type of chemo
  - We will also be able to determine genotype on non-responders
- Pilot SuperAvatars- Avatars w/ source patient Immune system

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Conclusions

- Generating Avatars in ovarian cancer is feasible
  - High engraftment rate
  - Recapitulate patient disease
    - Histology, Biology, Molecularly, Therapeutically…
- Useful as drug development tool
  - Large number of models can sort on marker of interest
- Natural history of ovarian cancer lends well to the idea of directed therapy

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Acknowledgements

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  - Sergio Enderica
  - Sean Harrington
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  - Marla Sommerfield
  - Susan Rogers (TRAG)

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