BRINGING CHANGE FOR FEMALE CANCERS

R&D Webinar

Highlights from AACR 2022

April 13, 2022

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Agenda

Welcome	**Martin Lehr, CEO**	**11:00 a.m. – 11:05 a.m.**
Introduction	Dr. Evan Dick, SVP of R&D	11:05 a.m. – 11:10 a.m.
ONA-XR		
• Immunomodulation	Lauryn Werner, MD, PhD Candidate*	11:10 a.m. – 11:20 a.m.
• PDx Combination Studies	Elisabetta Marangoni, PhD*	11:20 a.m. – 11:30 a.m.
• STAT3 Signaling and Stemness	Antonio D'Assoro, MD, PhD	11:30 a.m. – 11:40 a.m.
Claudin 6 x CD3		
• Bispecific optimalization	Joseph Rucker, PhD*	11:40 a.m. – 11:50 a.m.
Summary and Q&A	**Dr. Evan Dick, SVP of R&D**	**11:50 a.m. – 12:05 p.m.**

*Receives support from Context Therapeutics

Introduction

Martin Lehr, CEO

Dr. Evan Dick, SVP R&D

Upcoming Milestones

Cancer	Clinical Indication	Research	Phase 1	Phase 2	Phase 3	Upcoming Milestones	FDA Fast Track
ONA-XR (PR antagonist)[1]							
Breast Cancer	1L ER+,PR+,HER2- ctDNA^{high}			Phase 1b/2 Trial		• Phase 1b data Mid 2022	
	2L/3L ER+,PR+,HER2- Post-CDK4/6 inhibitor			Phase 2 Trial		• Preliminary data 2H 2022	
Ovarian Cancer	Recurrent PR+ Granulosa Cell			Phase 2 Trial		• Preliminary data 2H 2022	✓
Endometrial Cancer	Recurrent PR+ Endometrioid			Phase 2 Trial		• Preliminary data Mid 2022	
CLDN6xCD3 bispecific antibody							
	Ovarian & Endometrial Cancer					• IND enabling studies 2H 2022	

(1) Tyligand Biosciences Ltd licensed rights to ONA-XR in China, HK, Macau

ONA-XR

- Currently in Phase 2 development
- PR oncogenic signaling is associated with breast and gynecologic cancer
- Onapristone is a progesterone receptor (PR) antagonist that suppresses PR oncogenic signaling
- Onapristone extended release (ONA-XR) is a proprietary, oral, extended-release form of onapristone
- Potential for combination with SERD, CDK4/6, or PI3Kα inhibitors
- Exclusive ownership ex-Greater China

Claudin 6 x CD3

- Currently in preclinical development
- Developing a highly selective Claudin 6 (CLDN6) x CD3 bispecific antibody
- CLDN6 is an oncofetal protein enriched in gynecologic cancers
- CLDN6 binding arm is >100X more selective for CLDN6 versus CLDN9
- Internal studies and published data suggest we may be 10X more selective than competitive anti-CLDN6 mAbs and bispecifics
- Exclusive worldwide license to bispecific development of CLDN6 antibody from Integral Molecular

Our Presenters

Lauryn Werner

MD, PhD Candidate

University of Kansas

Ms. Werner is an MD/PhD candidate in the laboratory of Dr. Christy Hagan. Her thesis project focuses on the role of PR as an immunomodulatory agent.

Elisabetta Marangoni, PhD

Scientific Director

Translational Research Dept

Institut Curie (France)

Dr. Marangoni runs a translational research department focused on *in vivo* evaluation of novel therapeutics in patient-derived (PDx) models.

Antonio D'Assoro, MD, PhD

Associate Professor

Mayo Clinic

Dr. D'Assoro studies the role of PR in STAT3 signaling and breast cancer stemness.

Joseph Rucker, PhD

VP of R&D

Integral Molecular

Dr. Rucker co-founded Integral Molecular in 2006 and is an expert in antibody discovery.

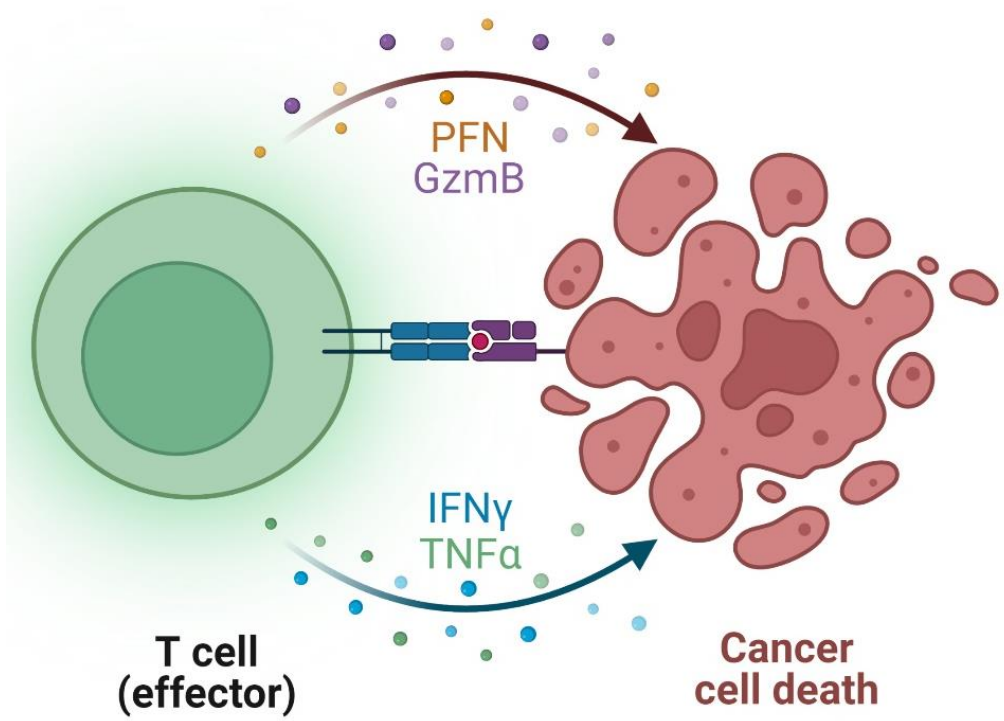
Progesterone Promotes Immunomodulation and Tumor Development in the Murine Mammary Gland

AACR 2022 Poster Recap

Lauryn Werner, M.D./Ph.D. Candidate
Christy Hagan Laboratory

THE UNIVERSITY OF KANSAS
CANCER CENTER

Anti-tumor Immune Responses Play a Key Role in Controlling Tumor Growth and Response to Immunotherapies



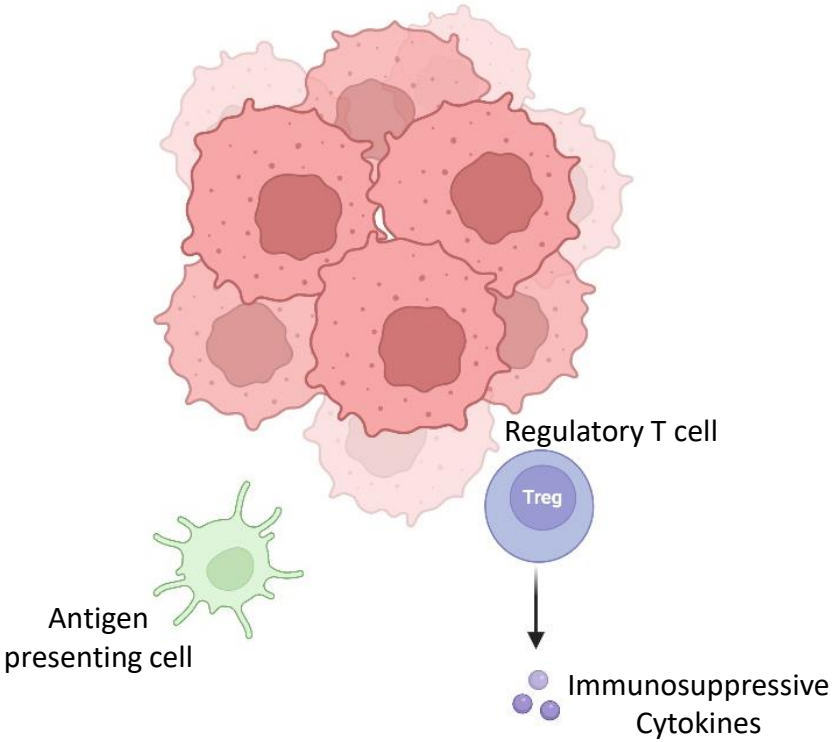
Anti-tumor immune responses are key in preventing the development and growth of human tumors, including breast cancer

Anti-tumor Immune Responses Play a Key Role in Control of Tumor Growth and Therapeutic Response

Hormone receptor positive breast cancers have "immune cold" microenvironments, which makes them poor responders to immune-based therapies

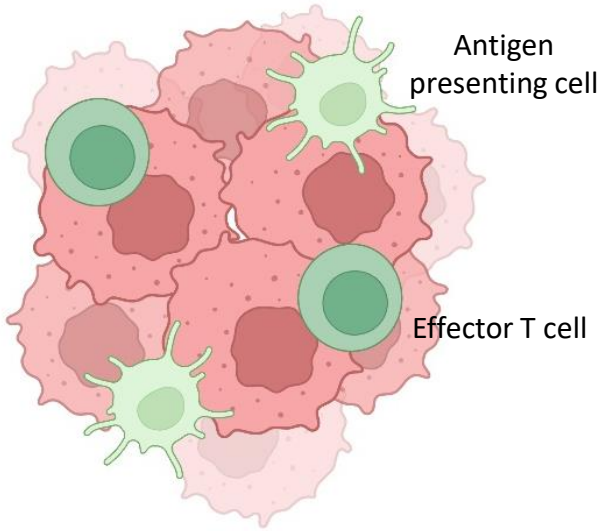
"Immune Cold" Tumor

Poor response to immunotherapy

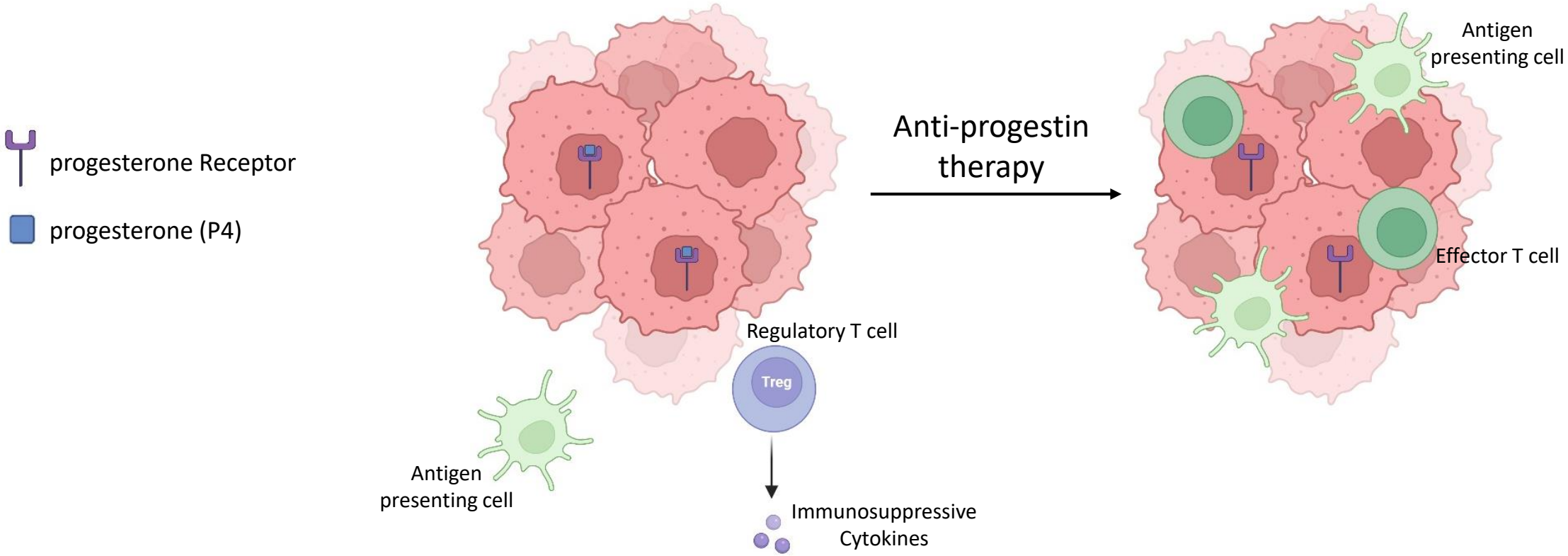


"Immune Hot" Tumor

Good response to immunotherapy

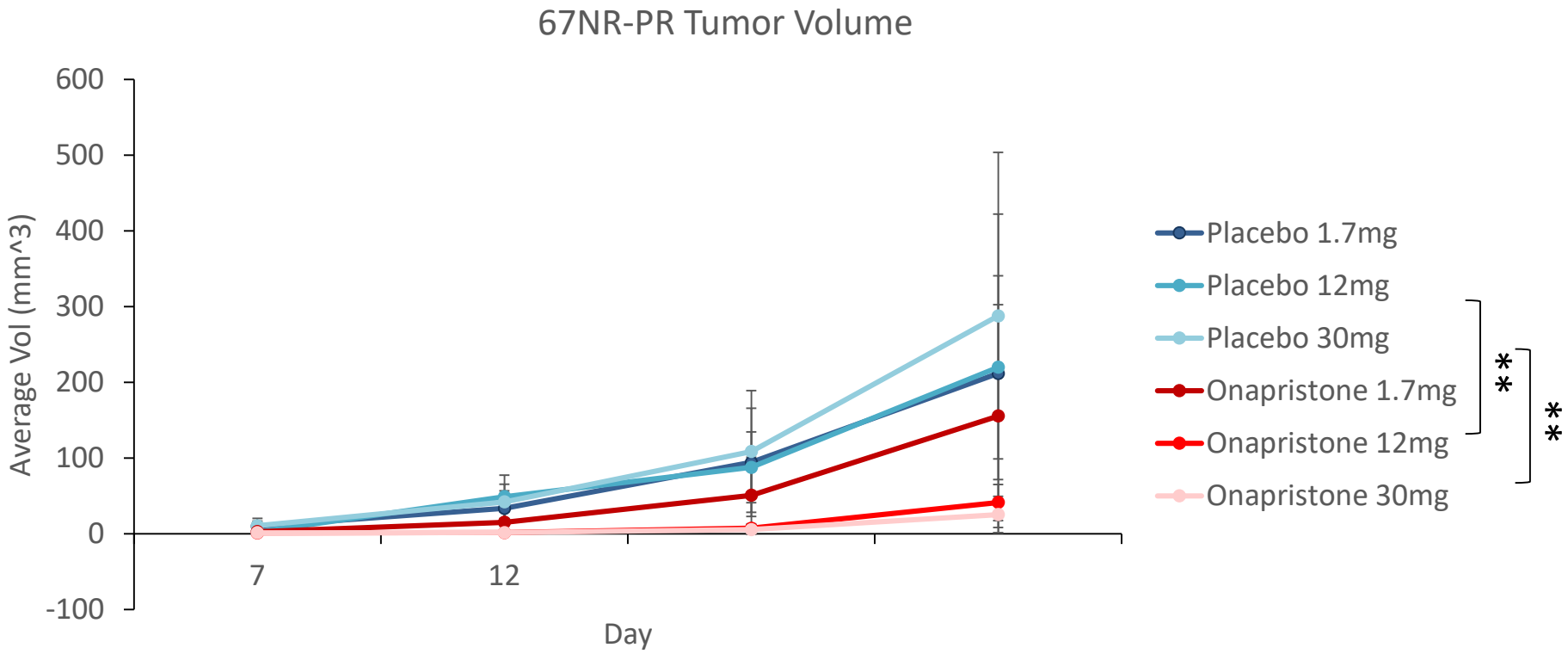


Working Hypothesis: Anti-progestins Enhance the Response to Immunotherapy by Altering Immune Microenvironment



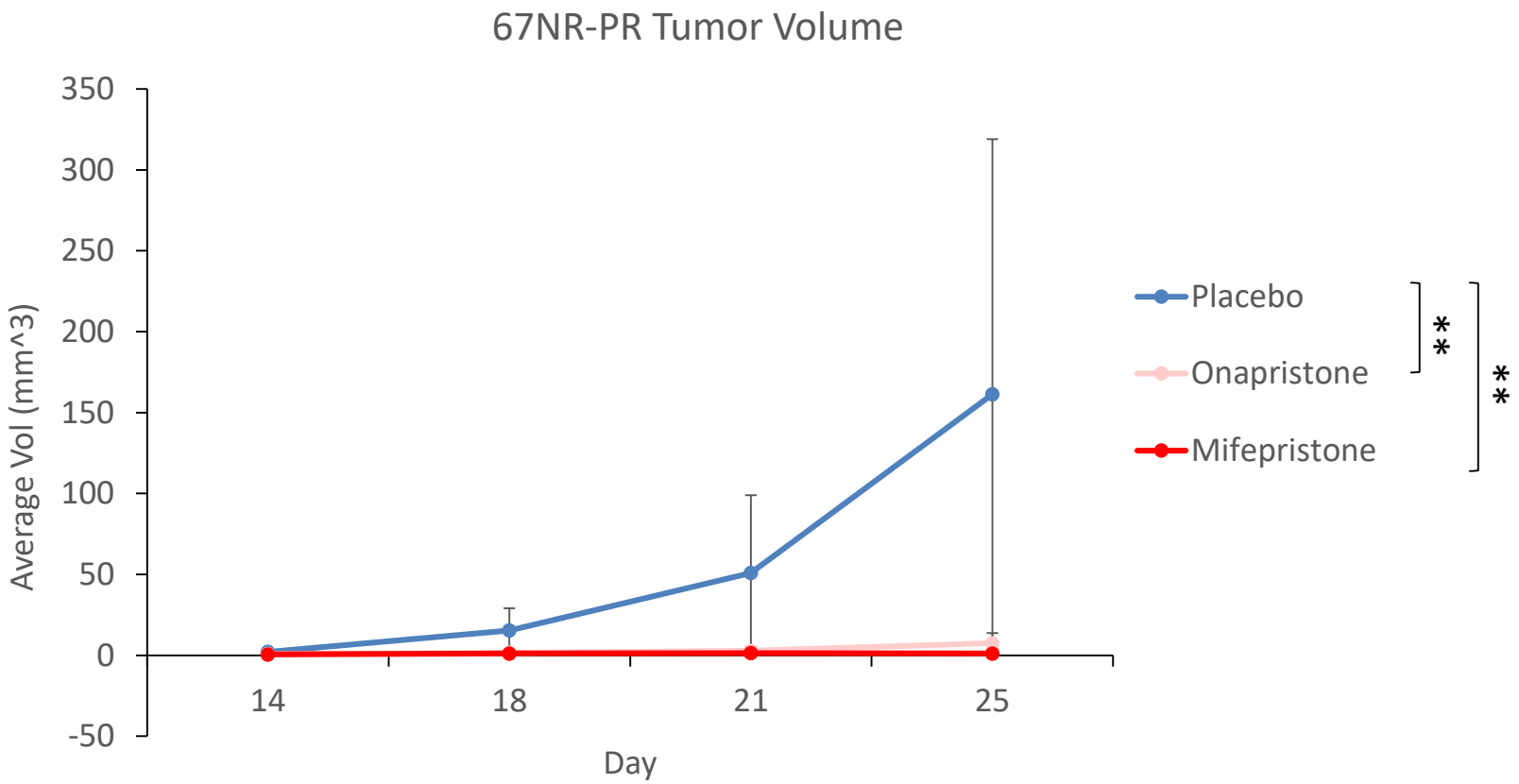
If PR/P4 signaling in tumor cells contributes to immune cold environment, anti-progestins could convert PR+ immune cold tumors into immune hot tumors, leading to enhanced immunotherapy responses

Effect of Onapristone Treatment on Growth of PR+ Mammary Gland Tumors



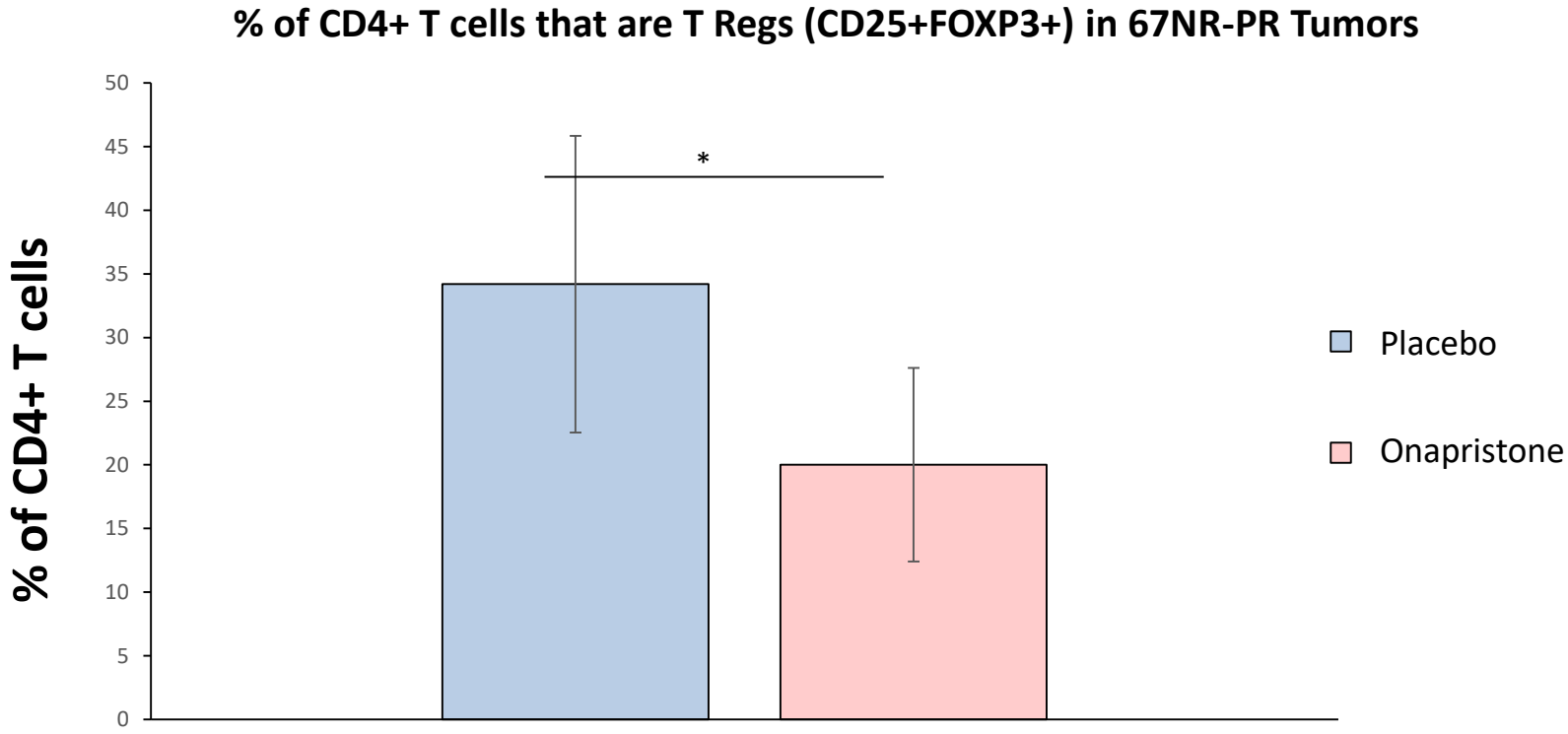
Both 12mg and 30mg doses of Onapristone were able to induce nearly complete growth inhibition of PR+ mammary gland tumors

Effect of Anti-Progestin Treatment on Growth of Mammary Gland Tumors



Both onapristone and mifepristone (anti-progestins) significantly inhibited the growth of 67NR-PR tumors

Effect of Anti-Progestin Treatment on Tumor Growth and Immune Infiltration of Mammary Gland Tumors

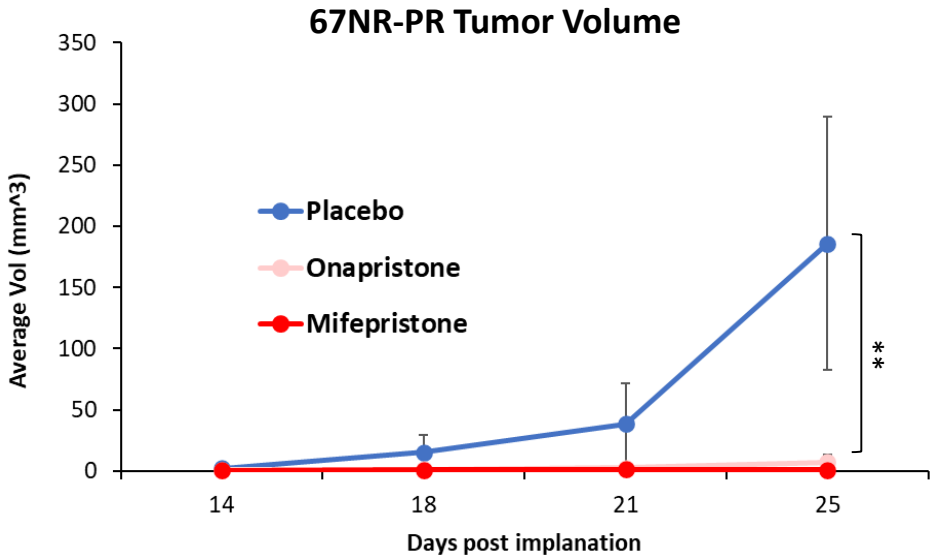


Onapristone treatment led to significantly decreased numbers of regulatory T cells (T regs) in 67NR-PR mammary gland tumors

Anti-progestins Only Achieved Complete Growth Inhibition in Immunocompetent Mice

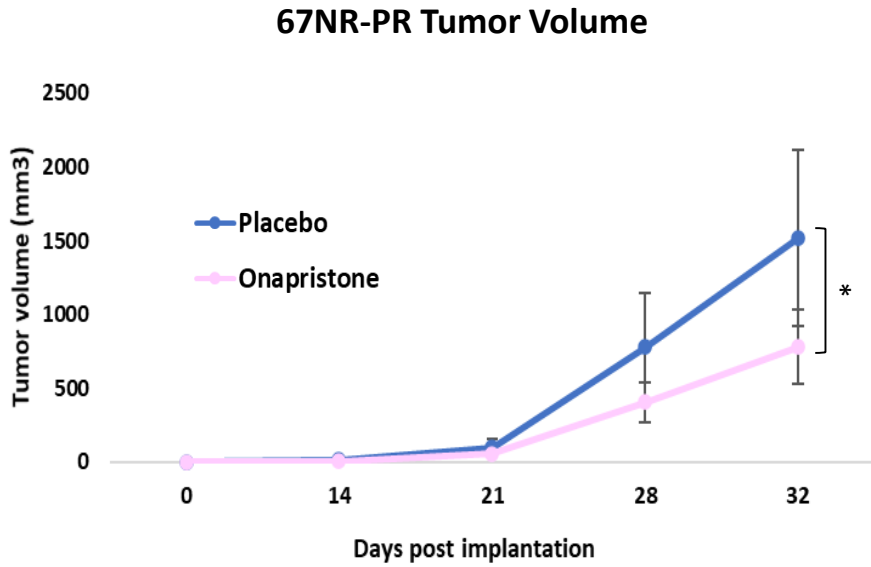
BALB/c mice

immunocompetent



SCID beige mice

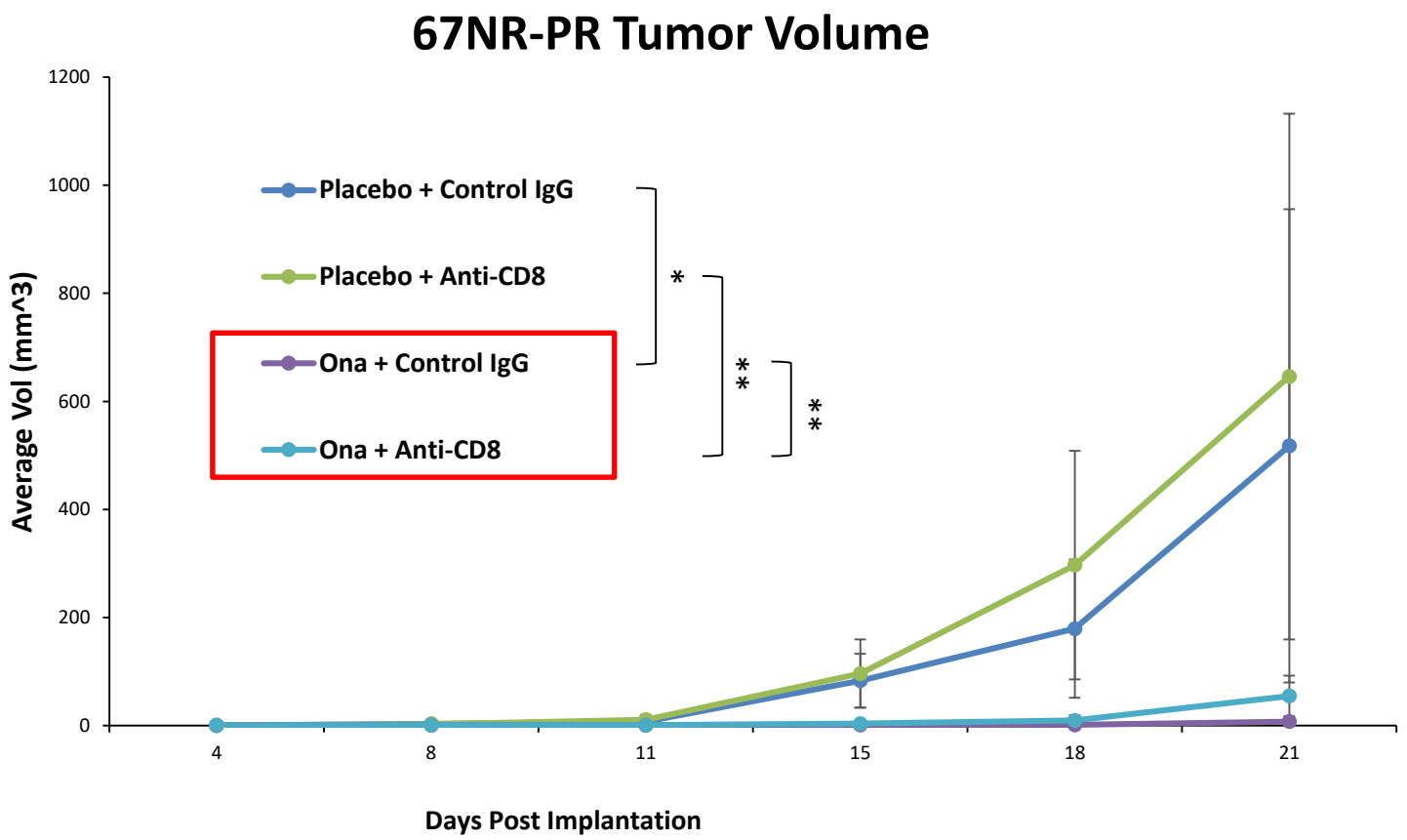
immunodeficient



In SCID (immunocompromised) mice, anti-progestins inhibited the growth of 67NR-PR tumors, but had a lesser impact than that seen in immunocompetent mice

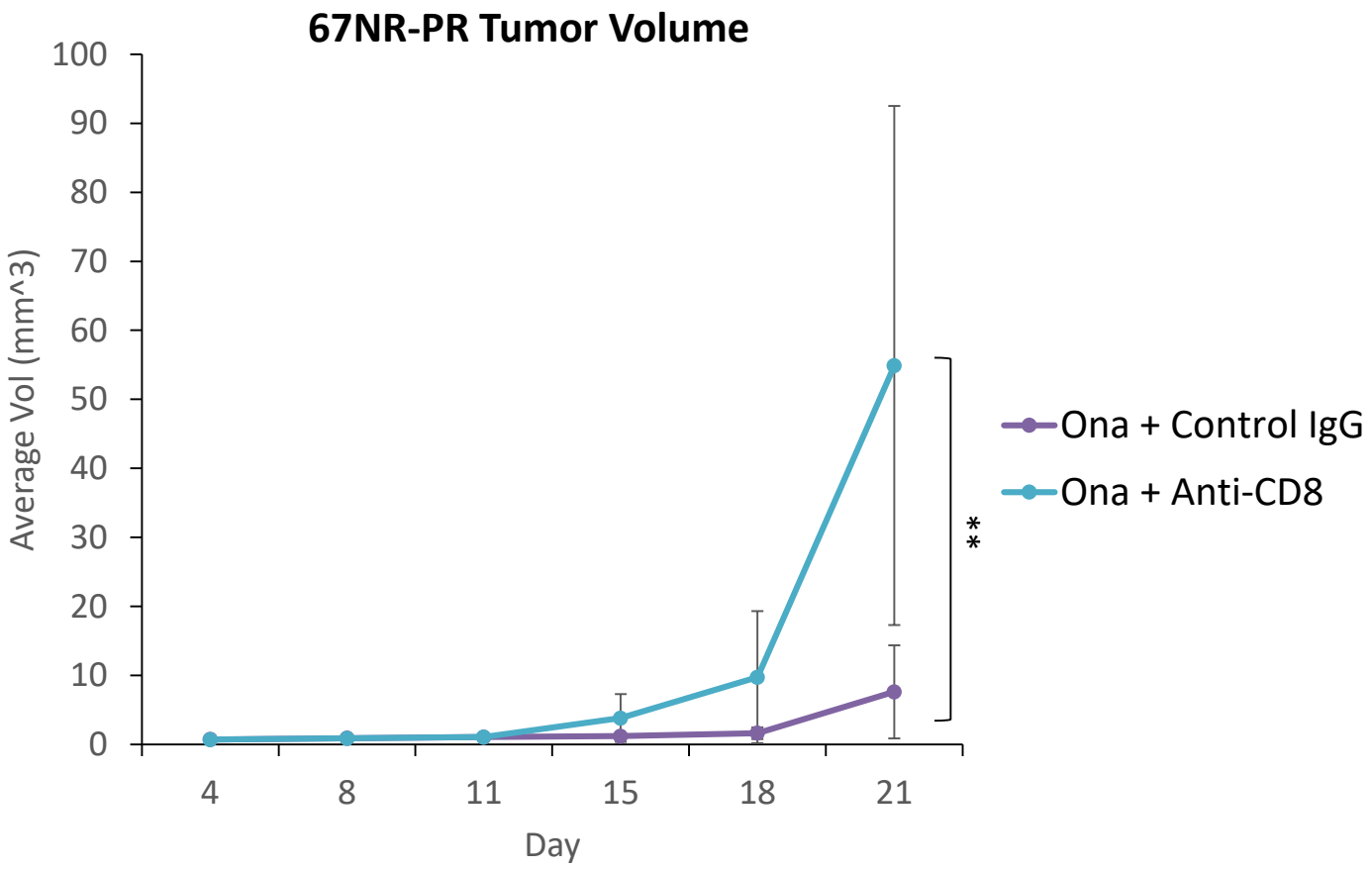
Inhibition is partially immune-mediated

Depletion of T cells Decreased the Efficacy of Onapristone



Onapristone was superior to placebo in tumors with or without CD8 T cells, but depletion of CD8 T cells reduced the ability of Onapristone to control growth of PR+ mammary gland tumors

Depletion of T cells Decreased the Efficacy of Onapristone



Depletion of CD8 T cells reduced the ability of Onapristone to control growth of PR+ mammary gland tumors

Summary

- Our previous data demonstrated P4 increased tumor growth and infiltration of suppressive regulatory T cells in PR+ mammary gland tumors
- Onapristone was able to completely inhibit the growth of PR+ mammary gland tumors and reverse the effect of P4 on tumor-infiltrating regulatory T cells
- Complete growth inhibition with Onapristone relies on an intact immune system, as only partial inhibition was achieved in immunocompromised mice
- Growth inhibition by Onapristone is diminished upon deletion of CD8 T cells

Overall, our studies provide a strong rationale to further investigate whether Onapristone treatment can promote immune-mediated elimination of mammary gland tumors and enhance the response of tumors to immunotherapies

Acknowledgements

Hagan Lab
Emma Helm

(Former Members)
Sean Holloran
Katie Walter
Gloria Trinca
Merit Goodman
Katelin Gibson
Jade Hall
Luke Majeske

Committee Members & Experts
Timothy Fields
Joseph Fontes
Christy Hagan
Mary Markiewicz
Jeroen Roelofs
Chad Slawson
Shane Stecklein
Sufi Thomas

KUMC
Mary Markiewicz
Prabhakar Chalise
Chad Slawson
Rashna Madan

Biospecimen Repository Core:
Tara Meyer
Marsha Danley

Flow Core:
Richard Hastings
Tykeemi Manor

Funding:

KUMC BRTP Fellowship

NCI R00CA166643
V Foundation V2015-025
Komen CCR16376147
DOD BCRP W81XWH-16-1-0320
NCI P30 CA168524
KUMC SOM Funding

Vanderbilt
Justin Balko
Melinda Sanders

UW – Madison
James Shull

Duke
Zachary Hartmann

KUMC Department of Biochemistry and Molecular Biology
KUMC MD/PhD Program

AACR American Association for Cancer Research ANNUAL MEETING 2022 New Orleans

institut Curie

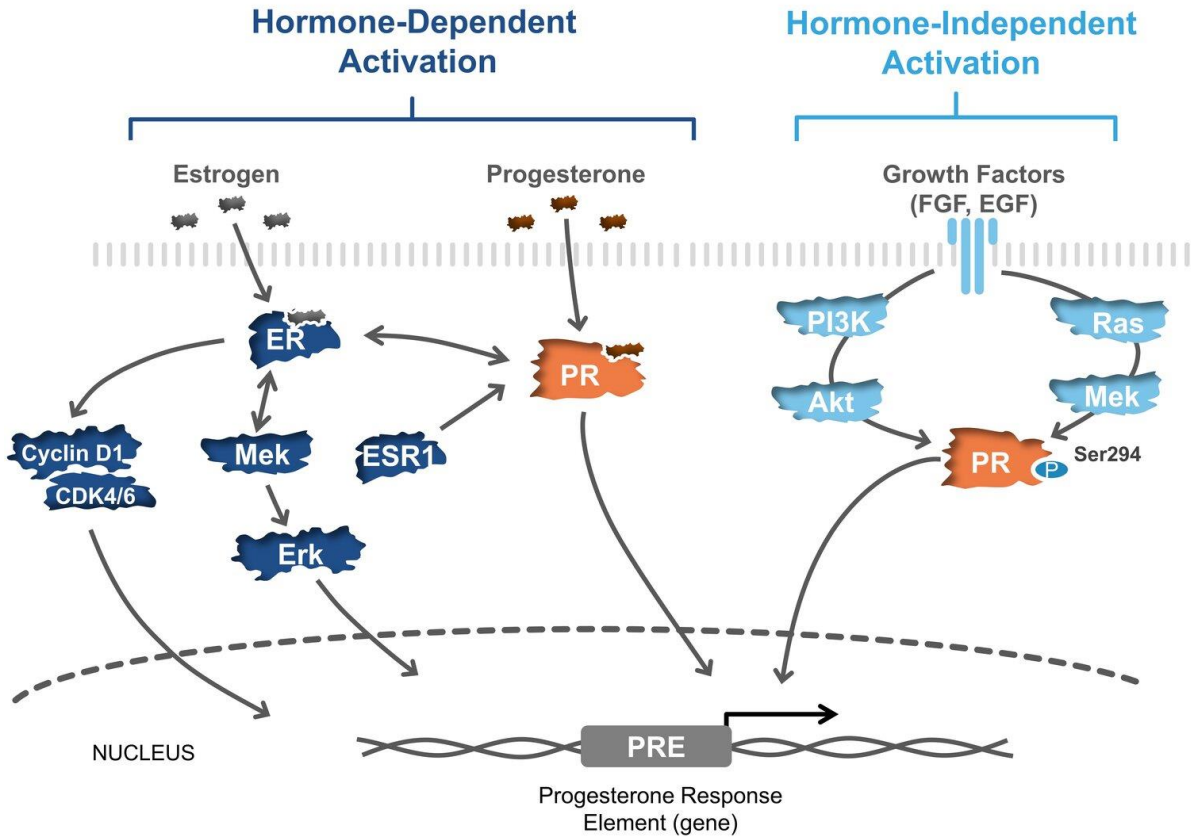
Targeting progesterone receptor (PR) with the antiprogestin onapristone in PDX models of ER+,PR+ bone metastasis of breast cancer

ELISABETTA MARANGONI, PHD

INSTITUT CURIE, PARIS

Progesterone receptor in breast cancer

- Progesterone receptor is expressed in approximately 70 % of breast cancers (luminal A and B)
- It can be activated in hormone-dependent and independent ways
- Interacts with ER and is a target of ER dependent transcription

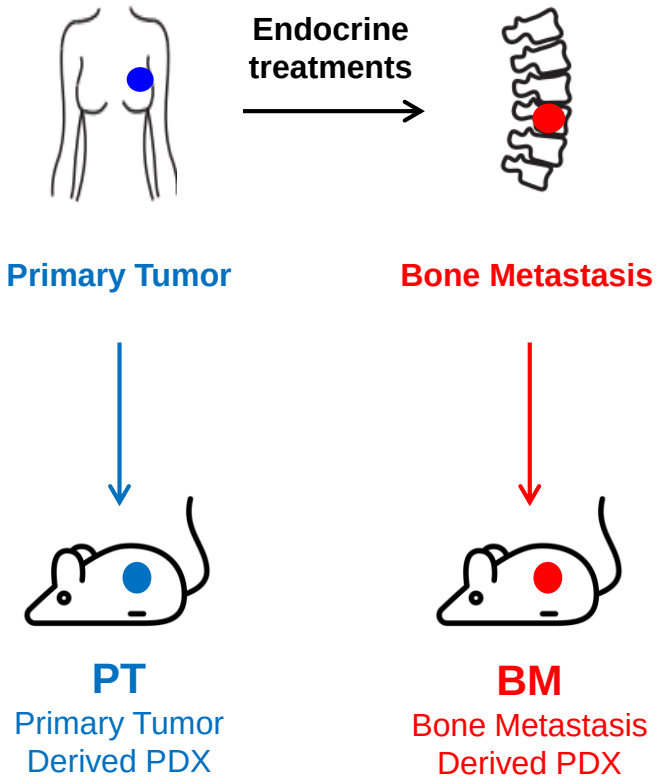


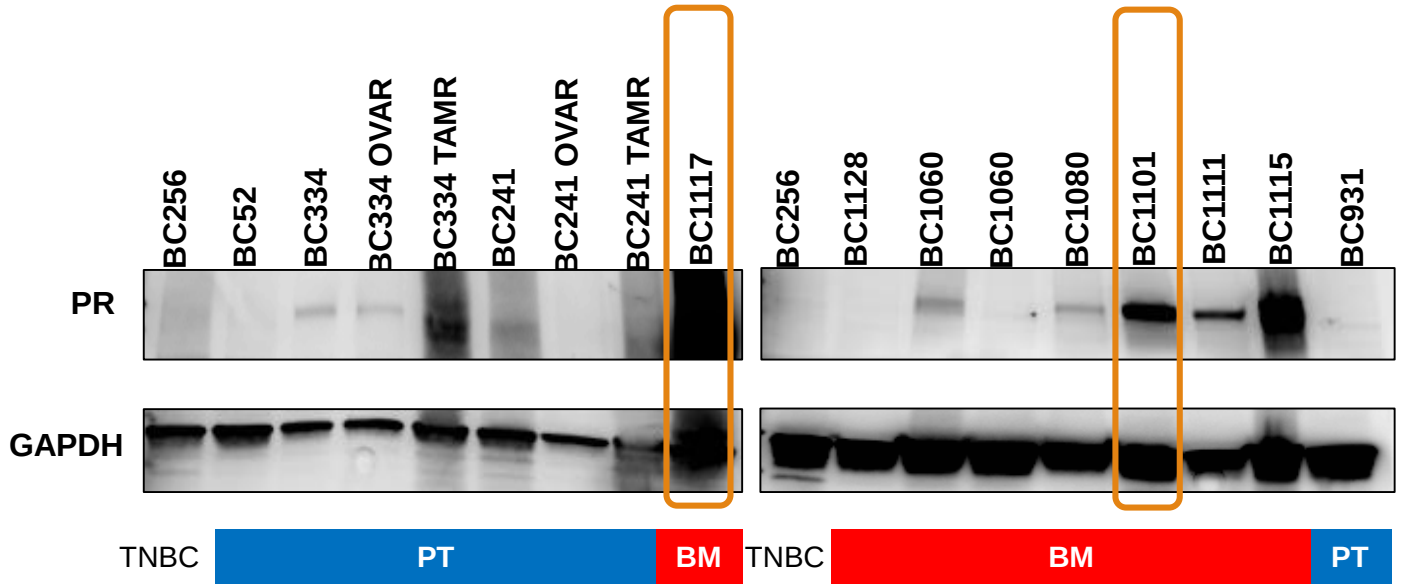
Objectives

1. To determine the anti-tumor activity of onapristone combined with endocrine treatments, CDK4/6, and/or PI3K inhibitors in PDX models of ER+,PR+ breast cancer

2. To analyze transcriptional modifications in onapristone-treated xenografts

PDX models of breast cancer

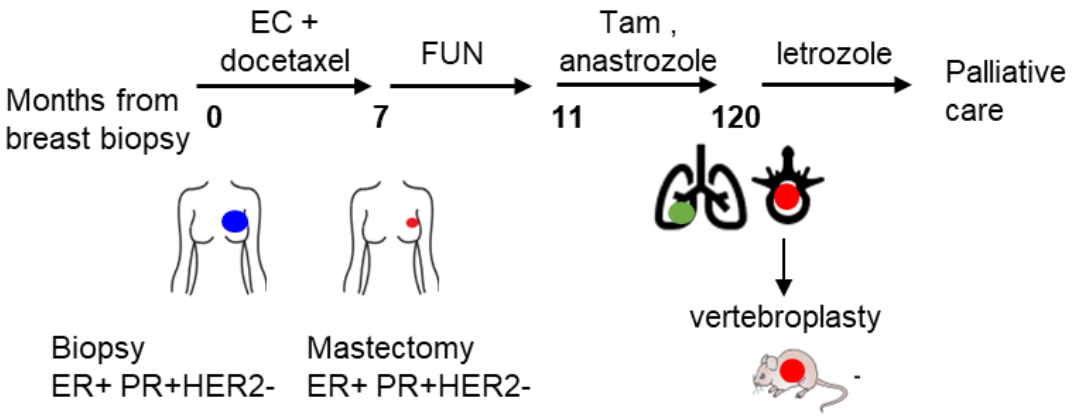




TNBC = triple negative breast cancer (ER-,PR-, HER2-)
PT = primary tumor
BM = bone metastasis derived PDX

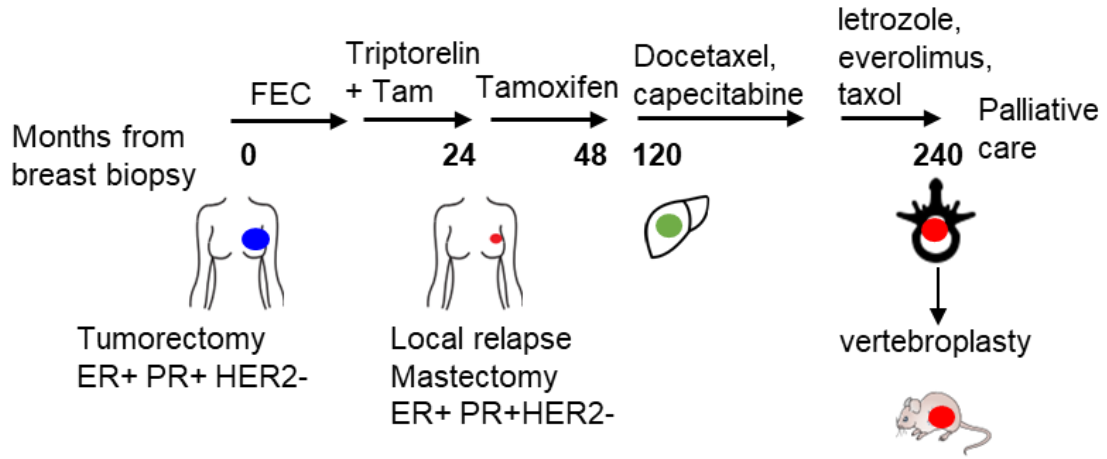
Clinical history of patients and PDX characteristics

BC1101 PDX Model
Low PR Expression



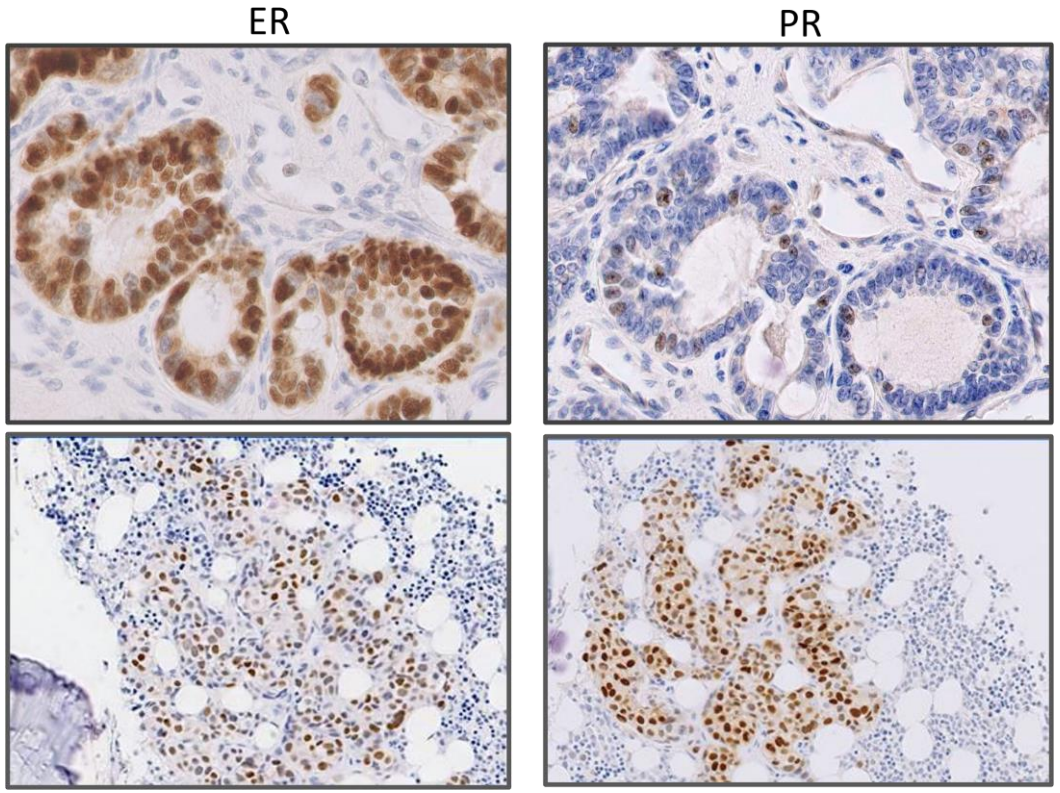
PDX	Primary tumor	IHC bone metastasis	IHC PDX	Mutations amplification
BC1101	ER+ PR+	ER+ PR+ **PR score 4**	ER+ PR+	FGFR1 CCND1

BC1117 PDX Model
High PR Expression



PDX	Primary tumor	IHC bone metastasis	IHC PDX	Mutations amplification
BC1117	ER+ PR+	ER+ PR+ **PR score 8**	ER+ PR+	PIK3CA PAK1 CCND1 CCNB1

ER and PR expression in PDX models



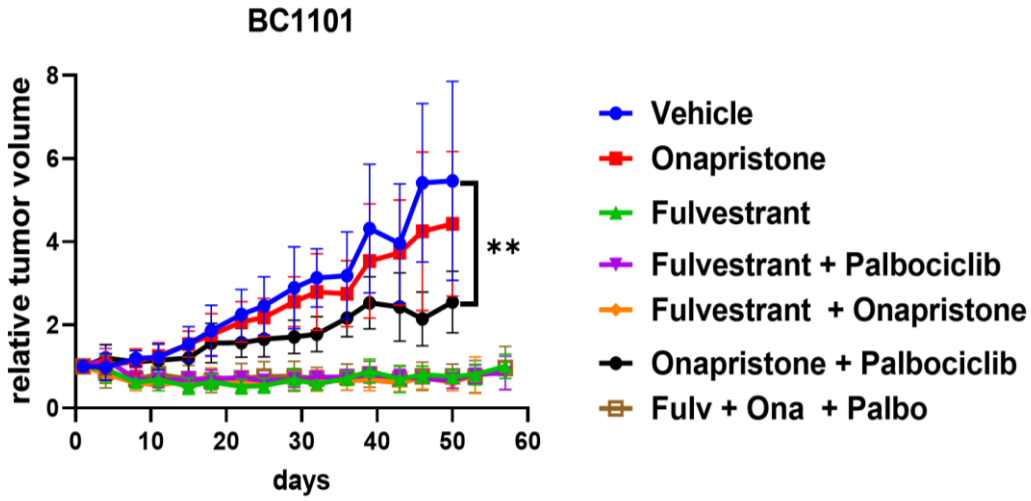
BC1101 PDX Model

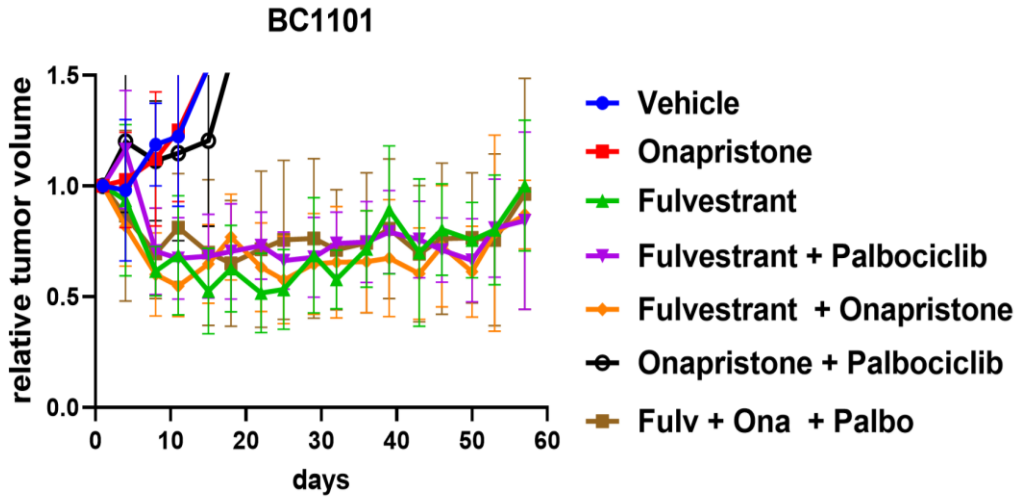
Low PR expression

BC1117 PDX Model

High PR expression

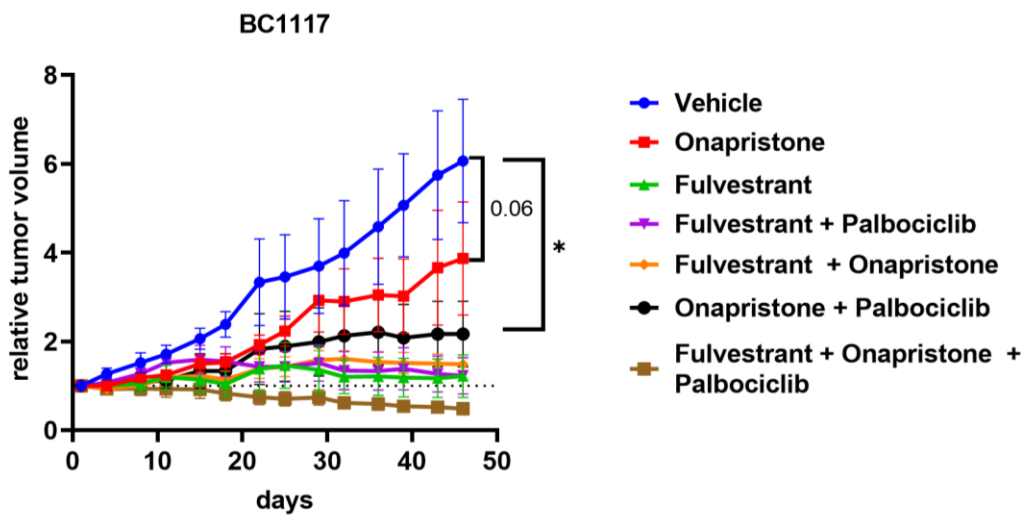
PDX with Low PR Expression (BC1101 Model)

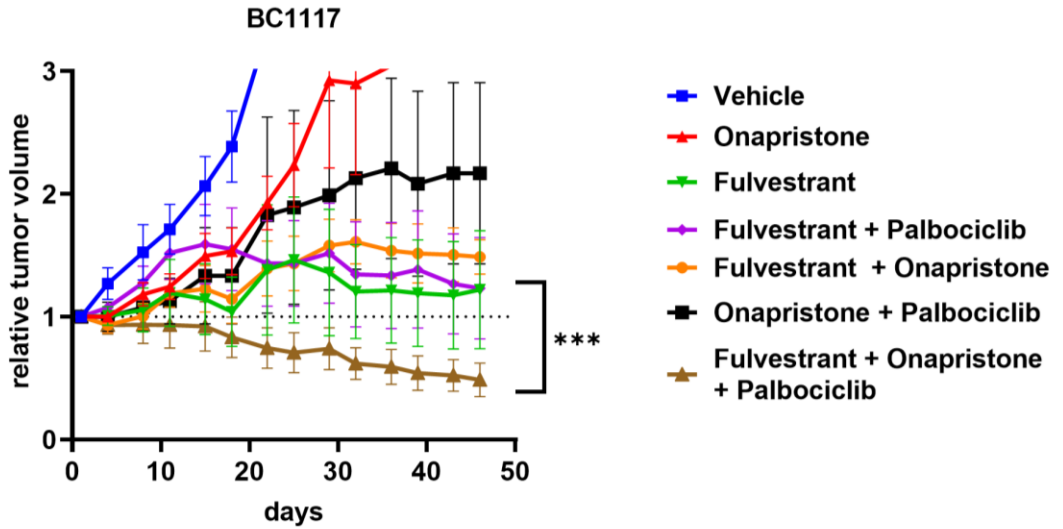




- No effect of onapristone alone
- Tumor growth inhibition of onapristone + CDK4/6 inhibitor palbociclib
- No benefit of adding onapristone to fulvestrant or fulvestrant + palbociclib

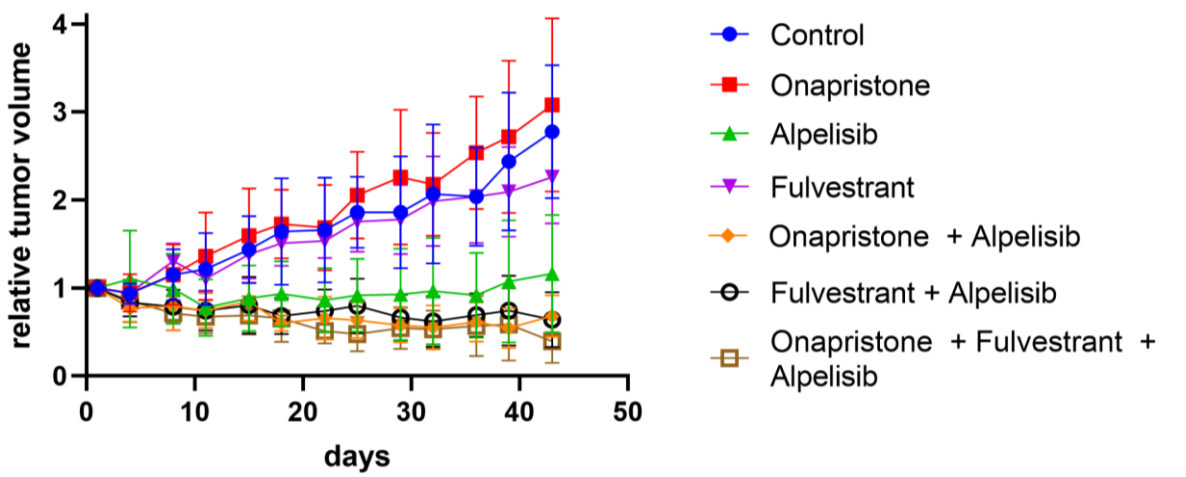
PDX with High PR Expression (BC1117 Model)

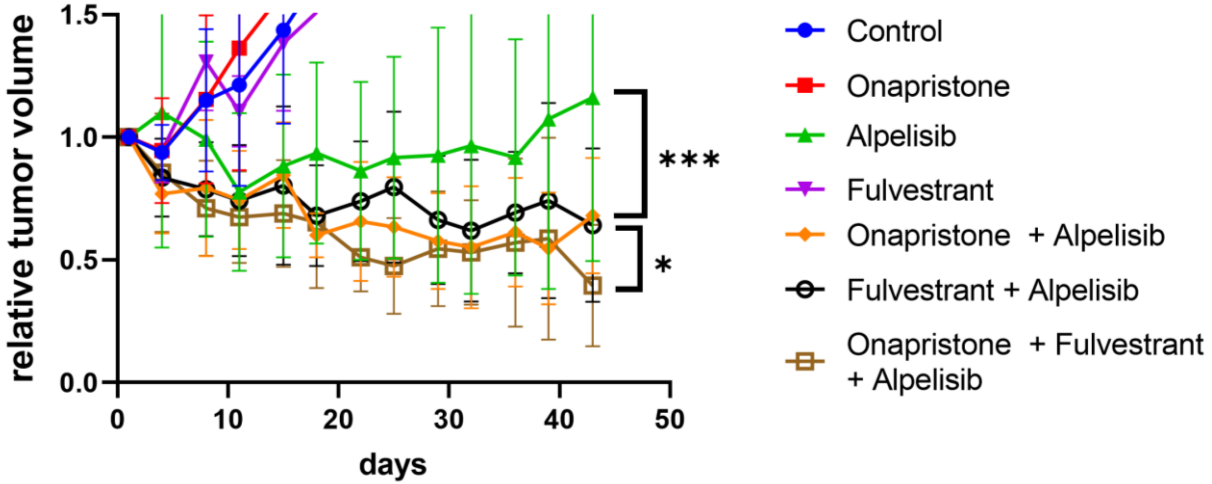




- Weak effect of onapristone alone
- Tumor growth inhibition of onapristone + palbociclib
- Increased response of the triple combination of fulvestrant + onapristone + palbociclib

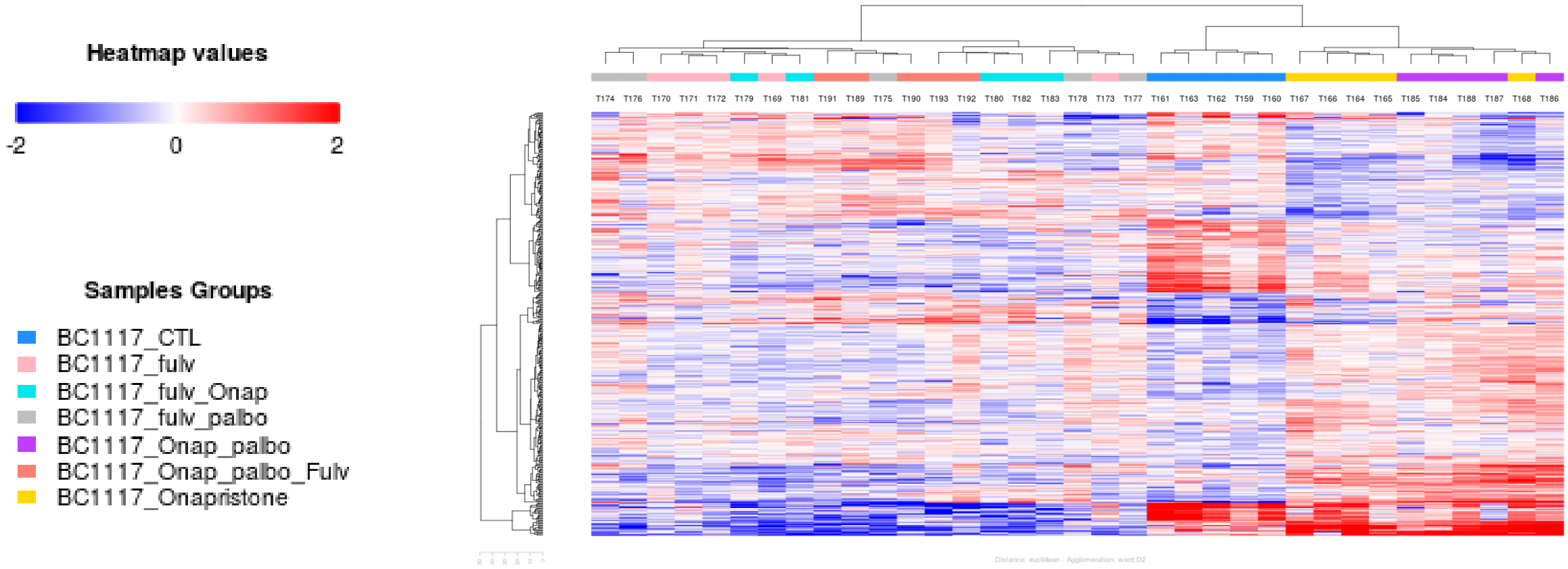
PDX with High PR Expression (BC1117 Model)





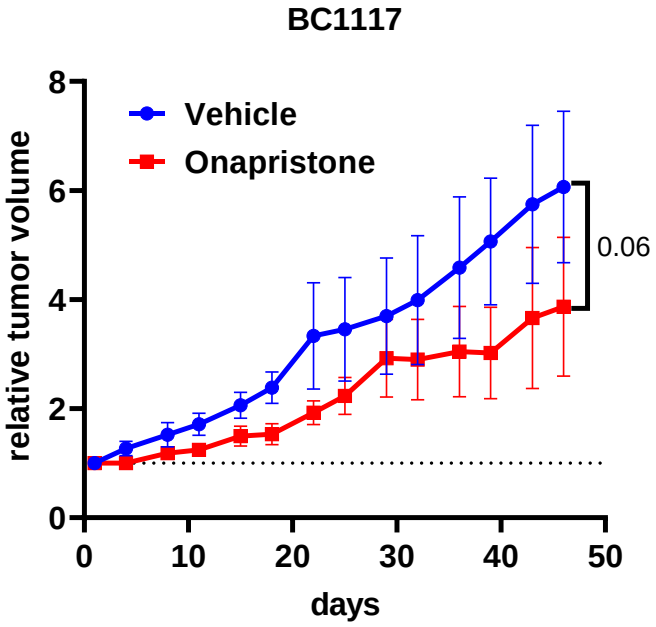
- Onapristone increases response to the PI3K inhibitor alpelisib
- Onapristone increases the response to fulvestrant + alpelisib
- Onapristone + alpelisib is as efficient as fulvestrant + alpelisib

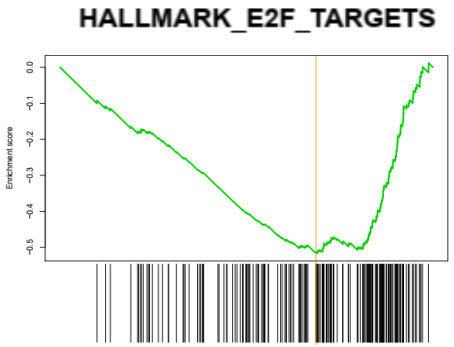
RNAseq analysis of treated tumors

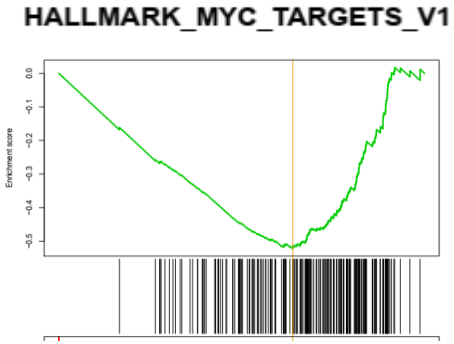


Comprehensive RNAseq analysis of all BC1117 (PR high) groups

Gene set enrichment analysis of tumors treated by onapristone as compared to control



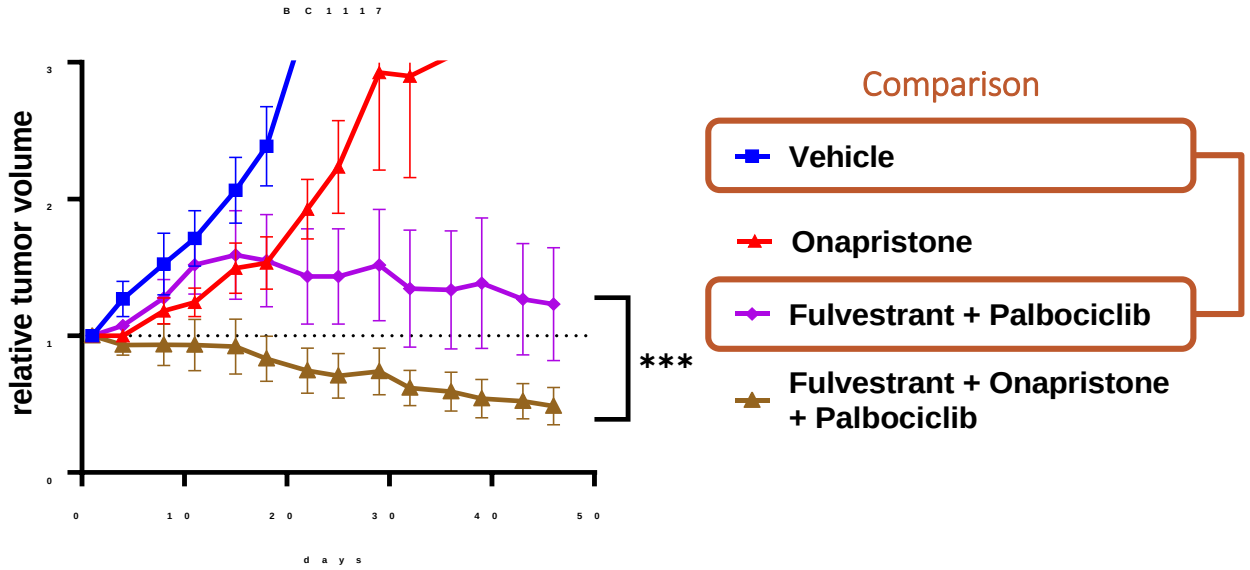


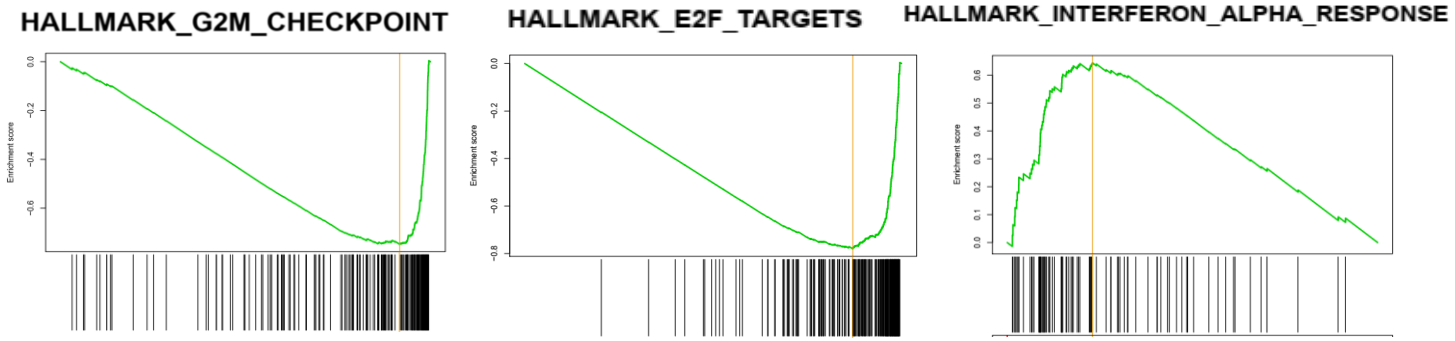


Top Enriched Gene Sets

Gene Set Description	Normalized Enrichment Score
cell cycle progression: E2F targets	-2.10
MYC targets, variant 1	-2.11
MYC targets, variant 2	-2.08
TNFA signaling via NF_KB	-1.84
IL6 STAT3 signaling during acute phase response	-1.75
KRAS signaling, upregulated genes	-1.76
early estrogen response	1.87
late estrogen response	1.81
p53 pathway	-1.76
cell cycle progression: G2/M checkpoint	-1.66
reactive oxygen species pathway	-1.59
response to hypoxia; HIF1A targets	-1.57
androgen response	-1.55
oxidative phosphorylation and citric acid cycle	-1.54
inflammation	-1.47
mTORC1 signaling	-1.47
KRAS signaling, downregulated genes	1.51
cholesterol homeostasis	-1.44
epithelial mesenchymal transition	1.46
IL2 STAT5 signaling	-1.35

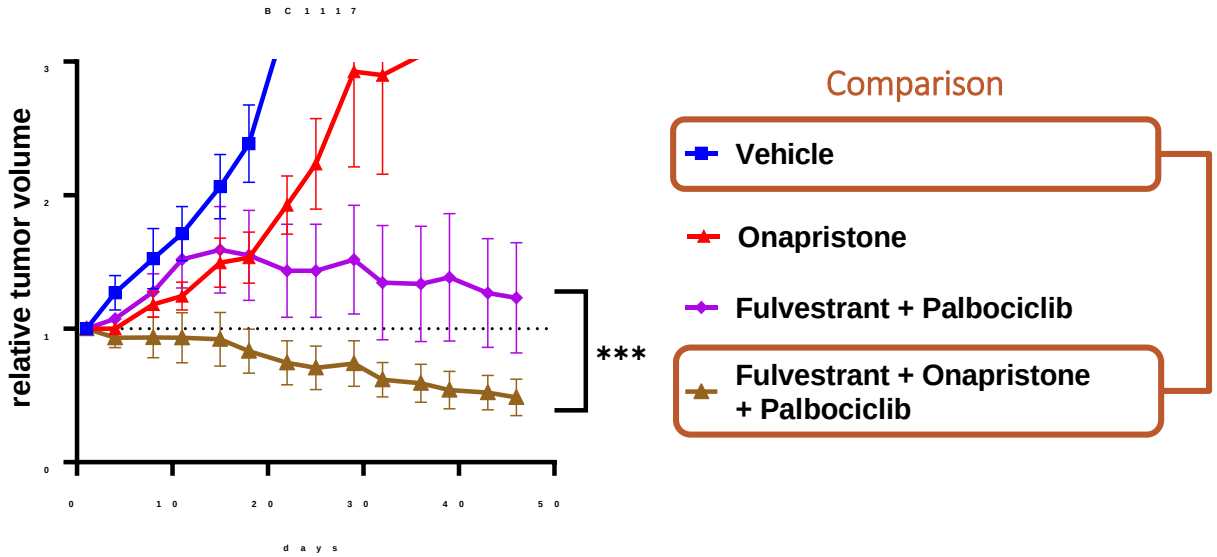
Gene set enrichment analysis of tumors treated by fulvestrant + palbociclib as compared to control

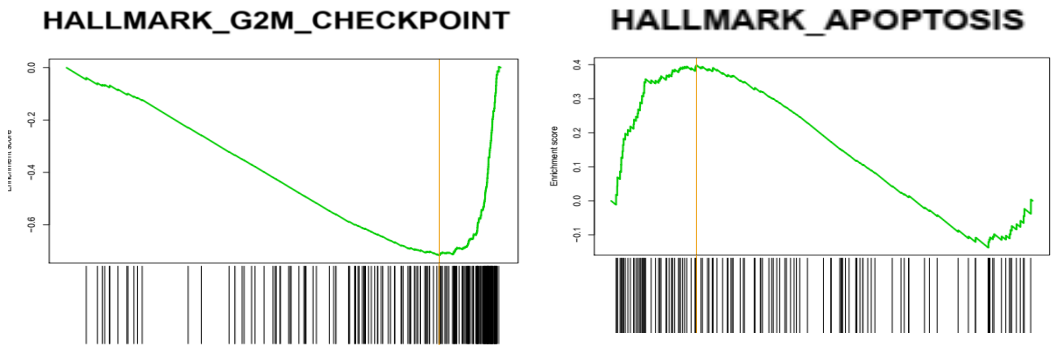




Gene Set Description	Normalized Enrichment Score
interferon alpha response	2.28
blood coagulation cascade	1.94
TNFA signaling via NF_KB	1.99
MYC targets, variant 1	-2.34
cell cycle progression: mitotic spindle assembly	-2.45
cell cycle progression: G2/M checkpoint	-2.87
cell cycle progression: E2F targets	-3.05
KRAS signaling, upregulated genes	1.86
interferon gamma response	1.79
mTORC1 signaling	-1.79
sperm development and male fertility	-1.76
inflammation	1.69
MYC targets, variant 2	-1.64
IL2 STAT5 signaling	1.60
KRAS signaling, downregulated genes	1.52
complement cascade	1.53
muscle differentiation	1.43
IL6 STAT3 signaling during acute phase response	1.43
DNA repair	-1.42

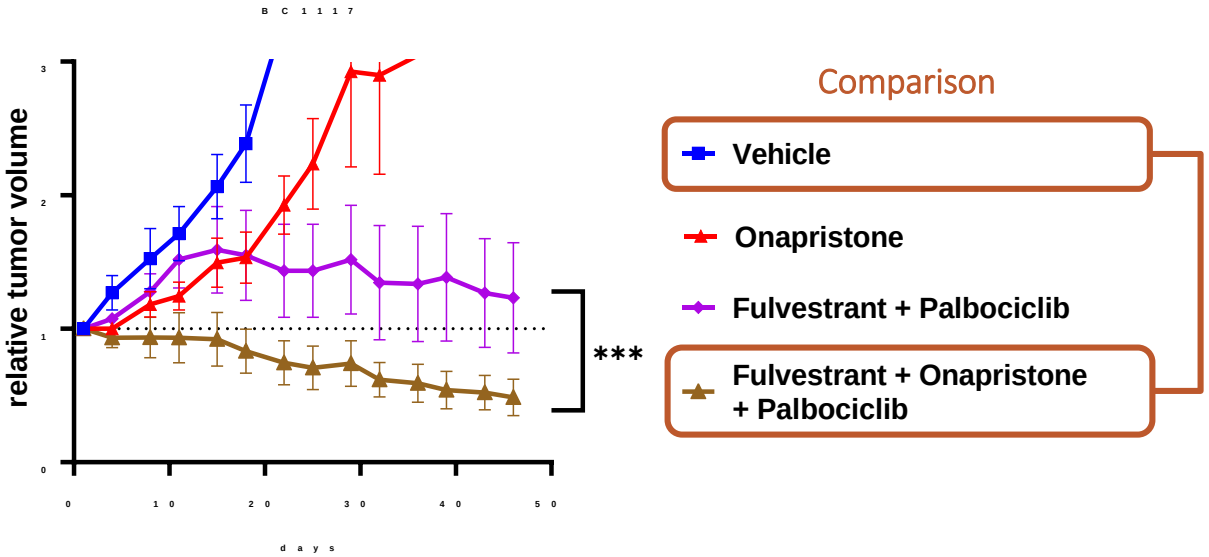
Gene set enrichment analysis of tumors treated by fulvestrant + palbociclib + onapristone as compared to control

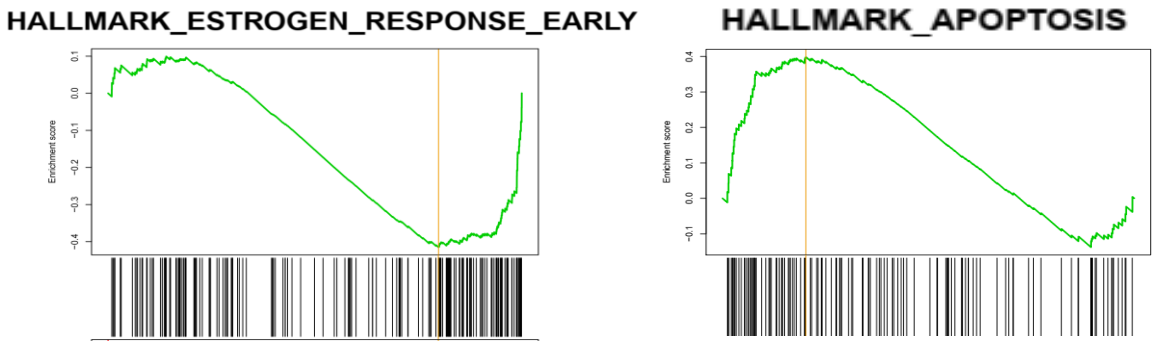




Gene Set Description	Normalized Enrichment Score
interferon alpha response	2.35
interferon gamma response	2.31
inflammation	2.00
TNFA signaling via NF_B	2.11
KRAS signaling, upregulated genes	2.00
MYC targets, variant 1	-2.27
cell cycle progression: mitotic spindle assembly	-2.38
cell cycle progression: G2/M checkpoint	-2.77
cell cycle progression: E2F targets	-2.88
complement cascade	1.94
allograft rejection	1.86
MYC targets, variant 2	-1.88
cholesterol homeostasis	1.71
KRAS signaling, downregulated genes	1.72
epithelial mesenchymal transition	1.64
IL2 STAT5 signaling	1.58
IL6 STAT3 signaling	1.46
mTORC1 signaling	-1.50
p53 pathway	1.46
programmed cell death; caspase pathway	1.44
early estrogen response	-1.43
DNA repair	-1.33

Gene set enrichment analysis of xenografts treated by fulvestrant + palbociclib + onapristone as compared to fulvestrant + palbociclib

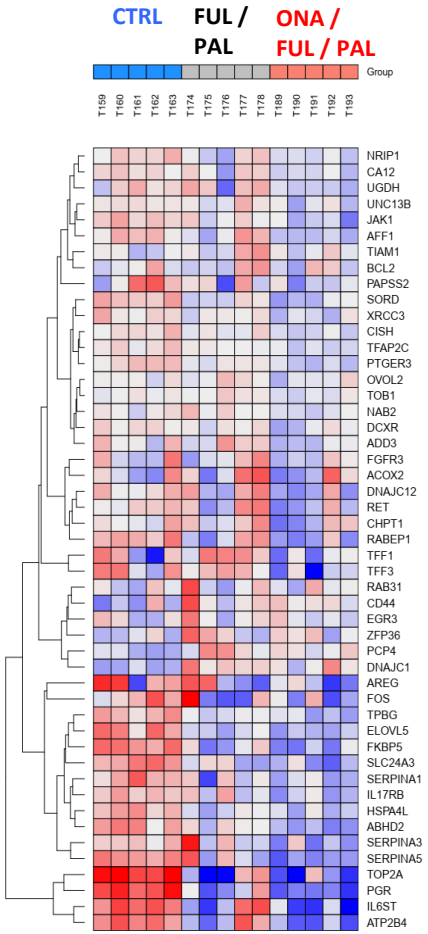




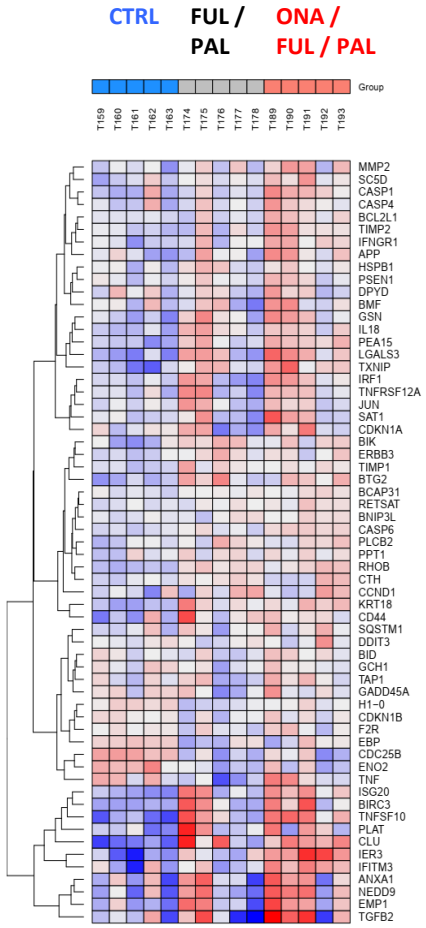
Gene Set Description	Normalized Enrichment Score
interferon alpha response	2.39
interferon gamma response	2.39
inflammation	2.30
epithelial mesenchymal transition	2.01
cholesterol homeostasis	1.94
response to hypoxia; HIF1A targets	1.88
KRAS signaling, downregulated genes	1.80
TNFA signaling via NF_KB	1.77
KRAS signaling, upregulated genes	1.77
muscle differentiation	1.71
glycolysis and gluconeogenesis	1.67
early estrogen response	-1.66
programmed cell death; caspase pathway	1.51
IL6 STAT3 signaling	1.50
IL2 STAT5 signaling	1.37
fatty acid metabolism	1.35
late estrogen response	-1.34
cell cycle progression: G2/M checkpoint	1.32
cell cycle progression: mitotic spindle assembly	-1.36
p53 pathway	1.28

Gene set enrichment analysis of xenografts treated by fulvestrant + palbociclib + onapristone as compared to fulvestrant + palbociclib

Late Estrogen Response

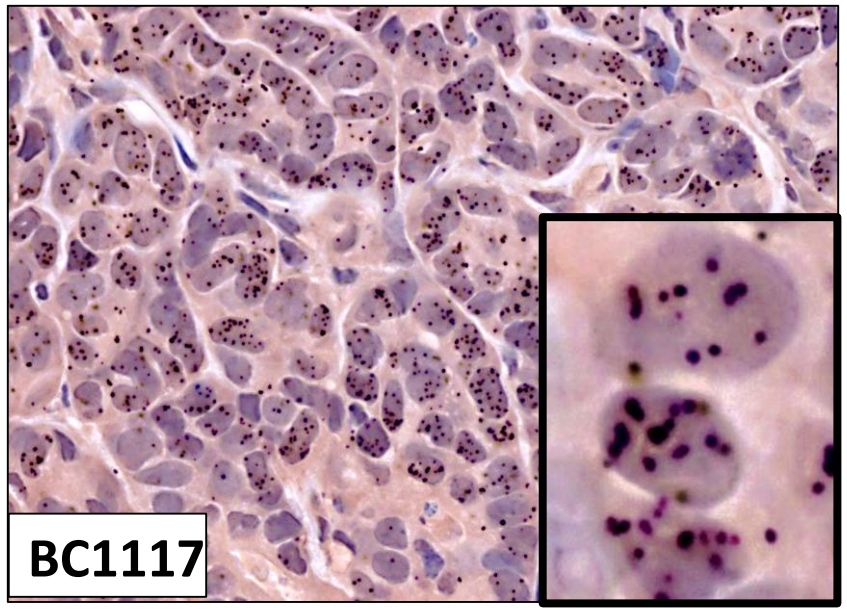


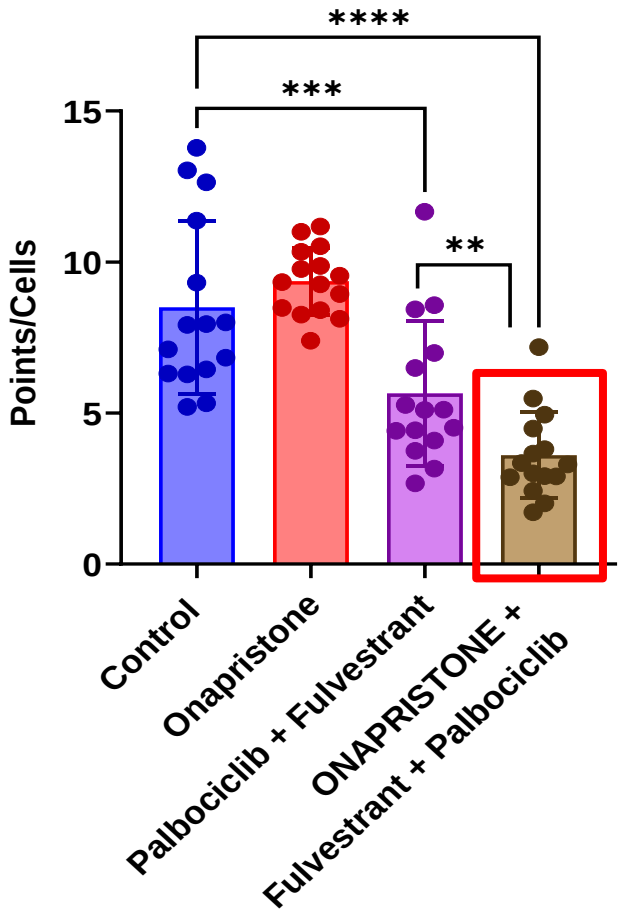
Apoptosis



Gene Set Description	Normalized Enrichment Score
interferon alpha response	2.39
interferon gamma response	2.39
inflammation	2.30
epithelial mesenchymal transition	2.01
cholesterol homeostasis	1.94
response to hypoxia; HIF1A targets	1.88
blood coagulation cascade	1.87
KRAS signaling, downregulated genes	1.80
TNFA signaling via NF_KB	1.77
KRAS signaling, upregulated genes	1.77
glycolysis and gluconeogenesis	1.67
early estrogen response	-1.66
programmed cell death; caspase pathway (APOPTOSIS)	1.51
IL6 STAT3 signaling	1.50
IL2 STAT5 signaling	1.37
fatty acid metabolism	1.35
late estrogen response	-1.34
cell cycle progression: G2/M checkpoint	1.32
cell cycle progression: mitotic spindle assembly	-1.36
p53 pathway	1.28

In situ detection of ER-PR interaction by the Duolink Proximity Ligation Assay





Treatment by onapristone alone does not affect ER-PR interaction

A **significant decrease in ER-PR interaction** is observed in tumors treated by the triple combination onapristone + fulvestrant + palbociclib as compared to the palbociclib + fulvestrant treated group

Summary

- Onapristone increases response to fulvestrant + palbociclib in a PDX of metastatic breast cancer with high expression of PR (BC1117)
- Treatment by the triple combination onapristone + fulvestrant + palbociclib led to downregulation of estrogen response and proliferation genes and up-regulation of genes involved in cell death, interferon responses, KRAS, TNFA and STAT3/5 signaling
- The anti-tumor activity of the triple combination is associated with a decreased interaction between PR and ER
- Additional PDX models should be treated to identify predictive biomarkers of onapristone activity (PR expression)

Acknowledgements

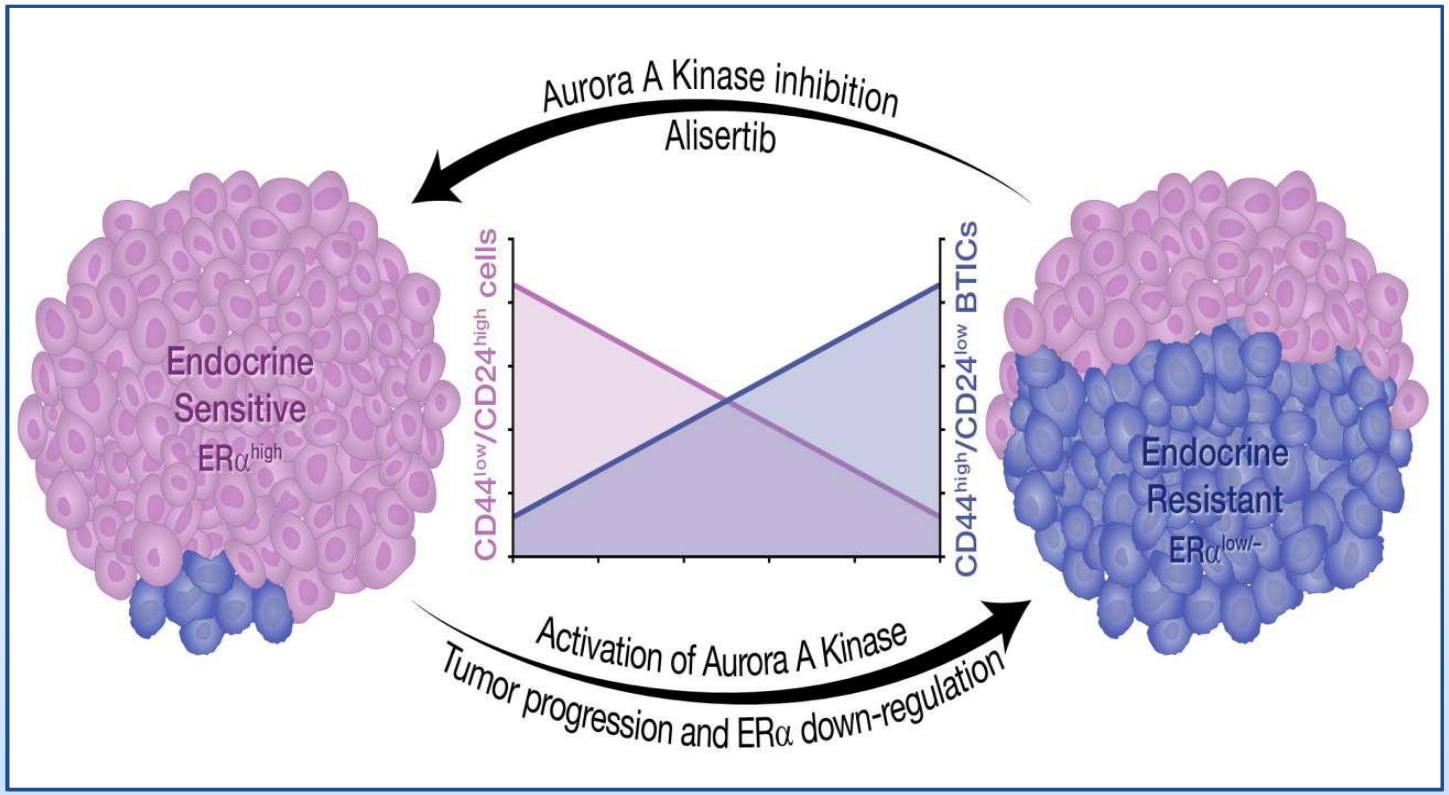
- Iodie Montaudon, Ahmed Dahmani, Léa Huguet, Rania EL Botty (Translational Research Department of Institut Curie)
- Paul Cottu, Guillaume Dutertre, Anne Salomon (Institut Curie Hospital)
- Muriel Le Romancer, Charlène Thiebaut (Centre Léon Bérard)
- Pierre de la Grange, Ariane Jolly (Genosplice)
- Context Therapeutics
- PATIENTS

MAYO CLINIC

AUKRA And Progesterone Receptor Pharmacologic Co-targeting in Endocrine Resistant ER+ Breast Cancer

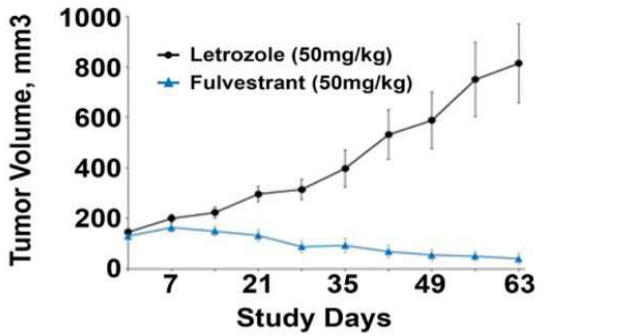
Tony B. D'Assoro, M.D., Ph.D

Working Model

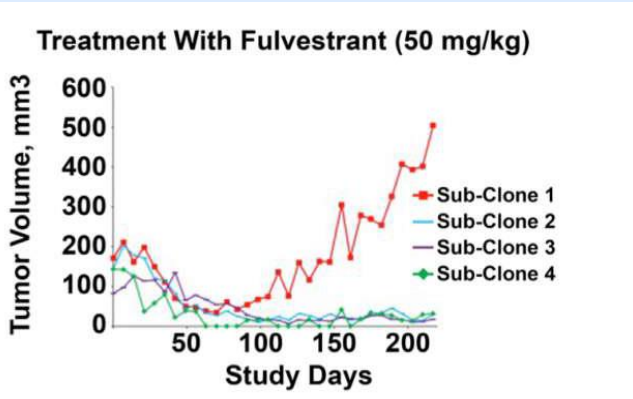


- **In endocrine sensitive breast tumors, the majority of bulk cancer cells exhibit a luminal $CD44^{low}/CD24^{high}/ER^{high}$ phenotype with nominal ALDH1 activity.**
- **Aberrant activation of AURKA signaling pathway induces cancer plasticity and the enrichment of a sub-population of endocrine resistant cancer cells harboring a basal-like $CD44^{high}/CD24^{low}/ER^{low}$ phenotype with high ALDH1 activity that promotes intrinsic (de novo) endocrine therapy resistance and tumor progression.**

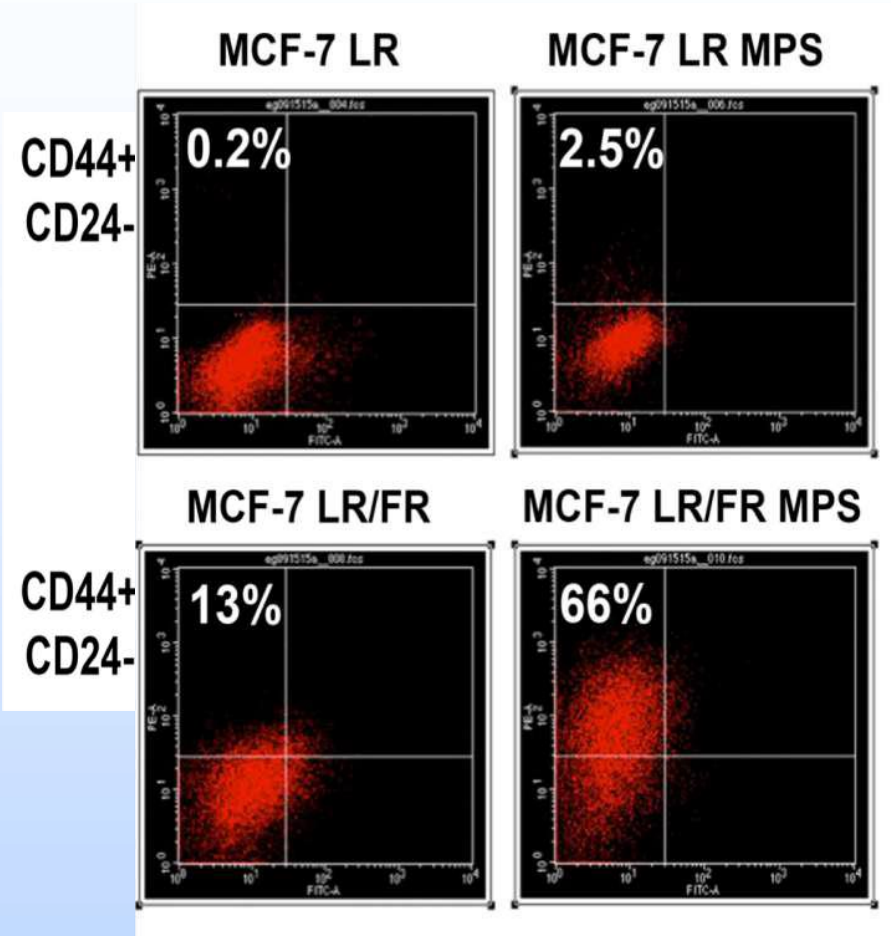
Development of Endocrine Resistant Breast Cancer Cells



Identification of letrozole resistant (LR) MCF-7 sub-clone to create MCF-7 LR



Identification of fulvestrant resistant (FR) MCF-7 LR sub-clone to create MCF-7 LR/FR

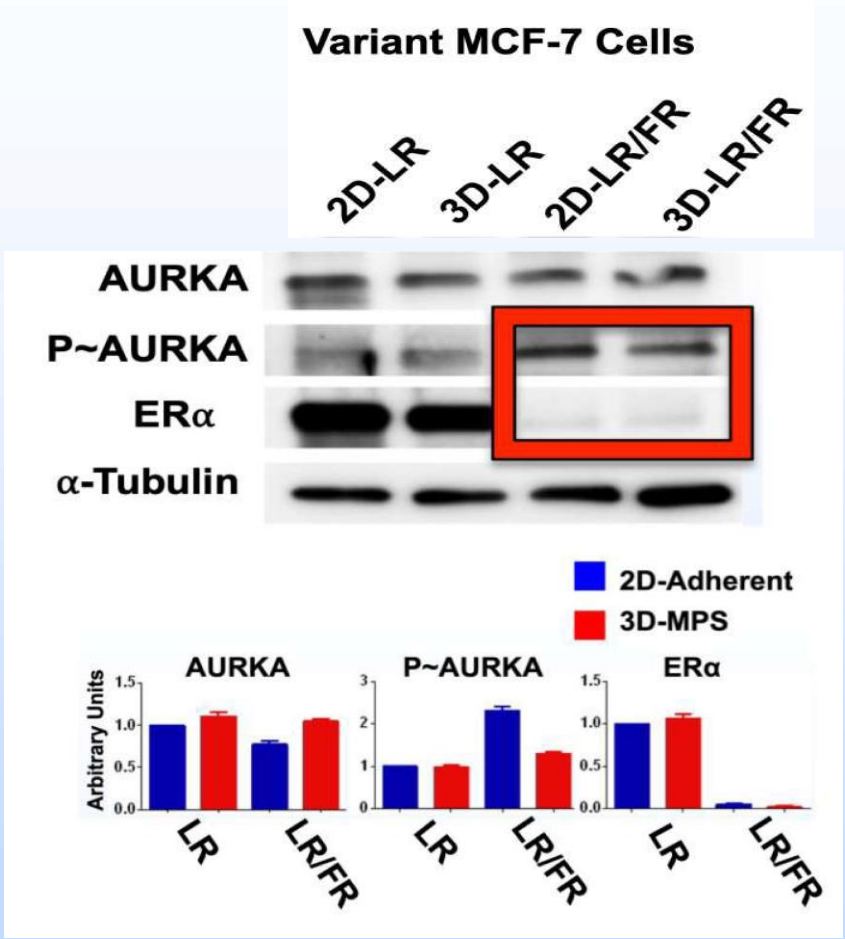


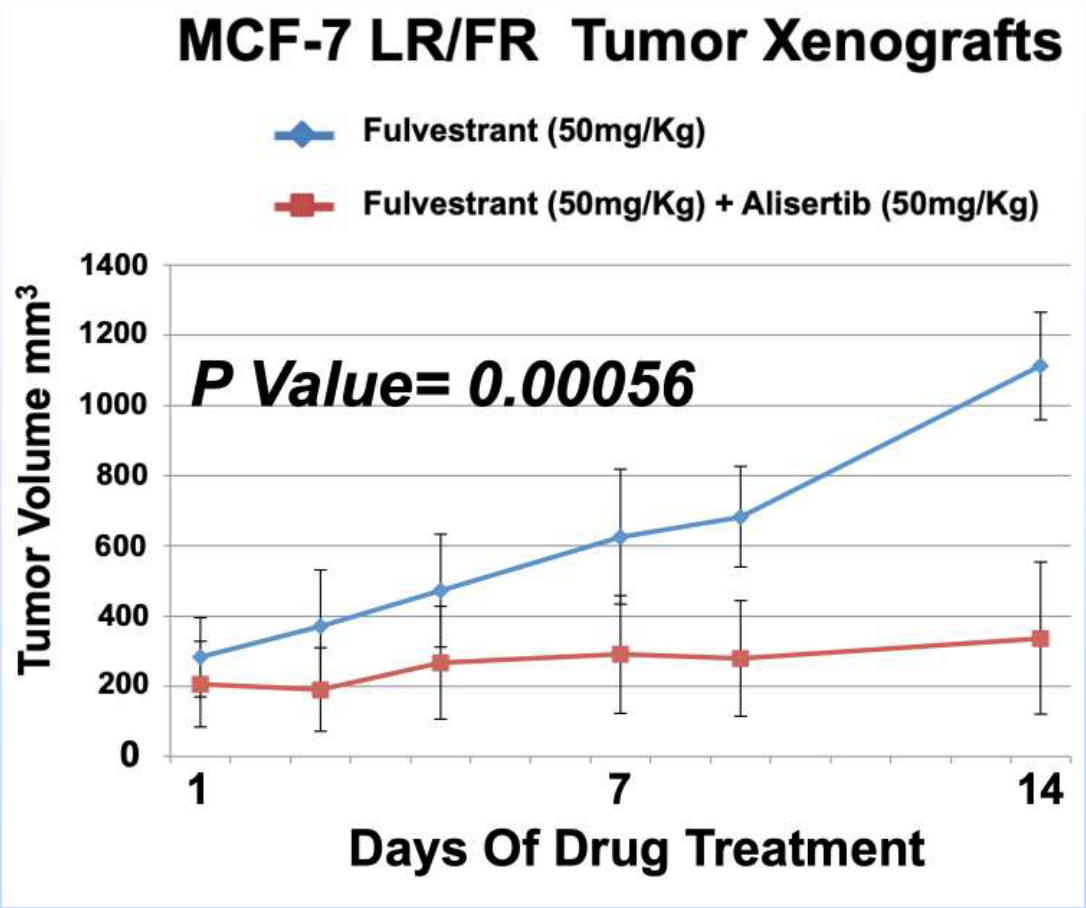
FACS analysis showing the percentage of CD44+/CD24- BTICs in MCF-7 LR and MCF-7 LR/FR breast cancer cells in 2D or 3D cultures.

Three independent experiments were performed with comparable results.

Alisertib (AURKA inhibitor) inhibits MCF7 LR/FR tumor xenograft growth

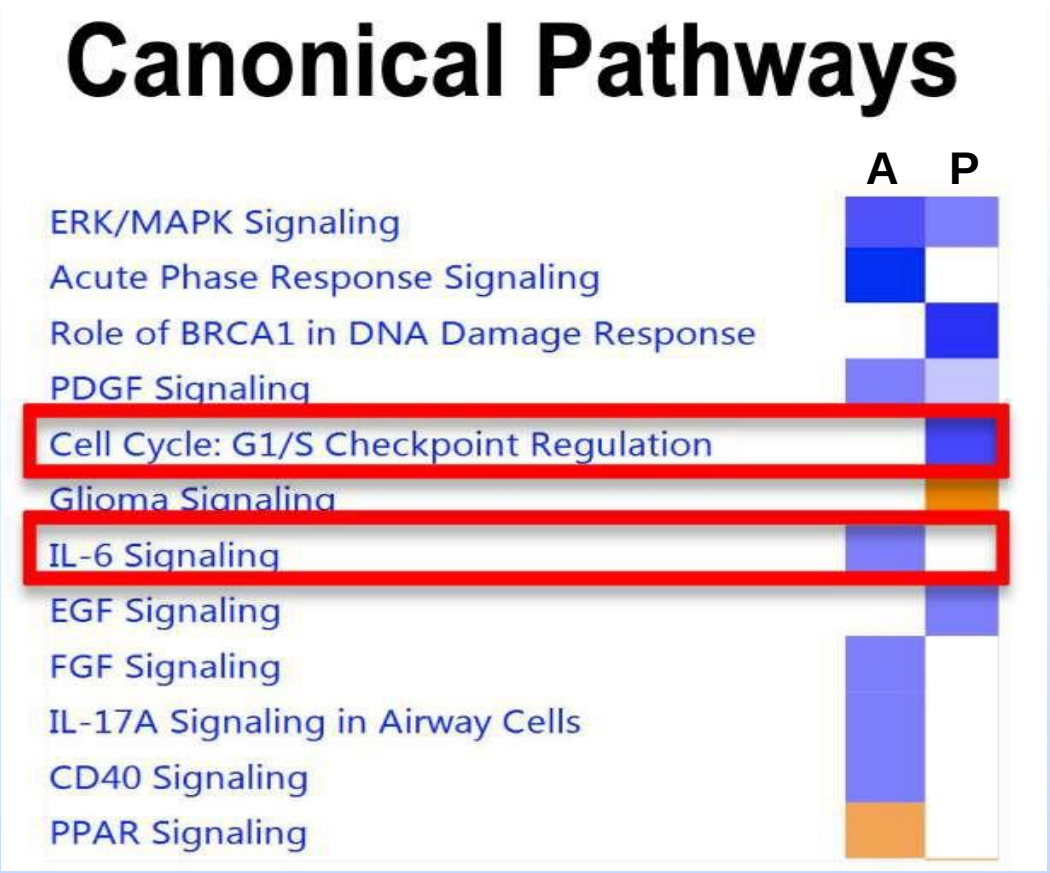
Development of Endocrine Resistant Breast Cancer Cells

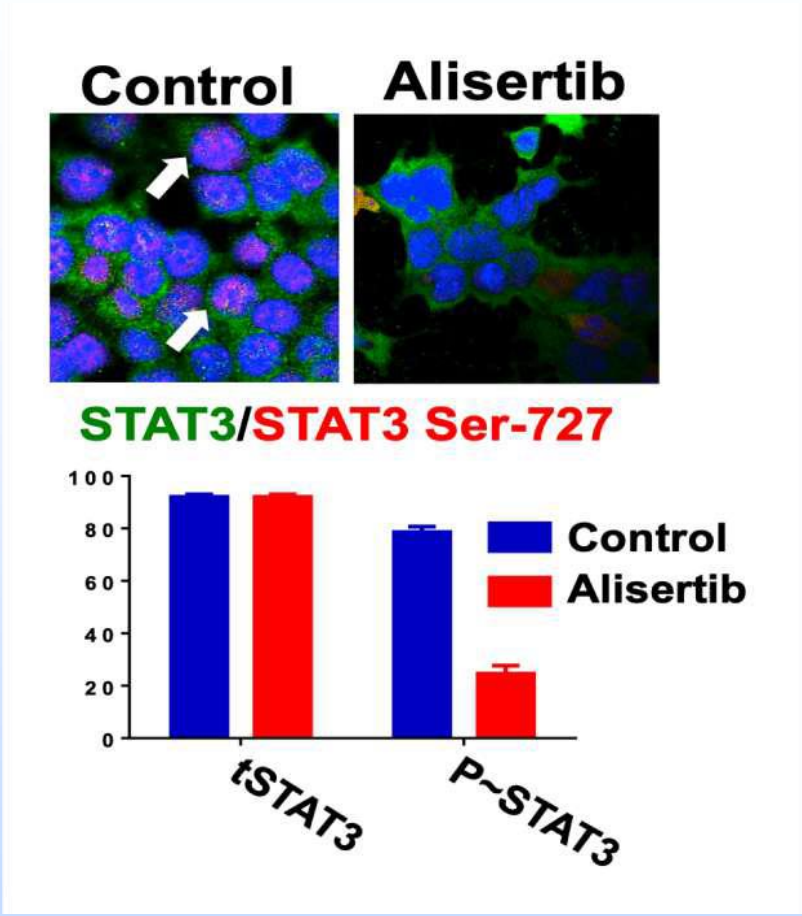




Alisertib (AURKA inhibitor) inhibits MCF-7 LR/FR tumor xenograft growth

AURKA Activity Induces STAT3 Phosphorylation

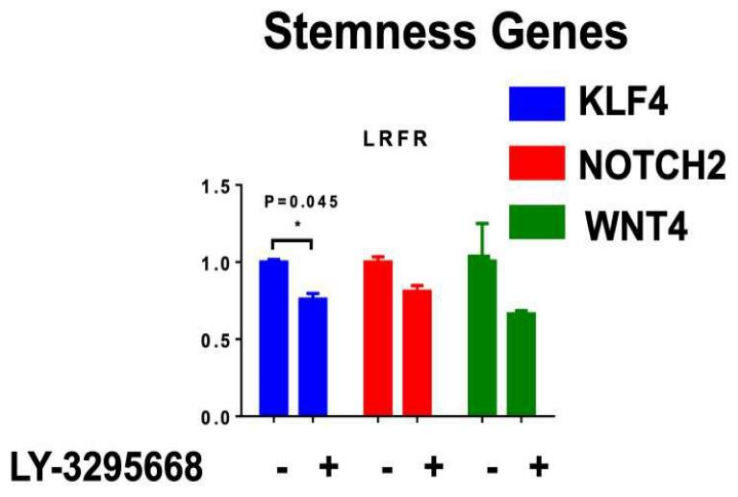




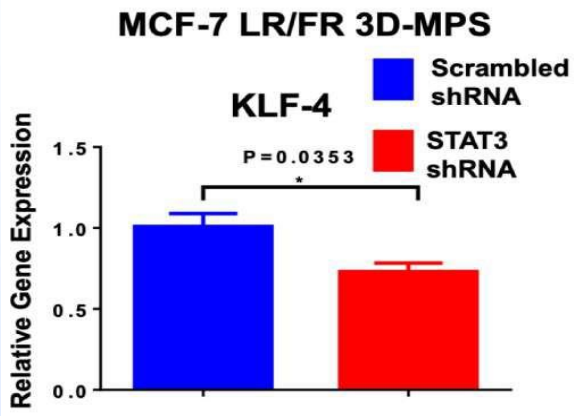
A = alisertib (AURKA inhibitor)
P = palbociclib (CDK4/6 inhibitor)

AURKA targeting reduced the phosphorylation of STAT3 transcription factor at the *serine-727* site

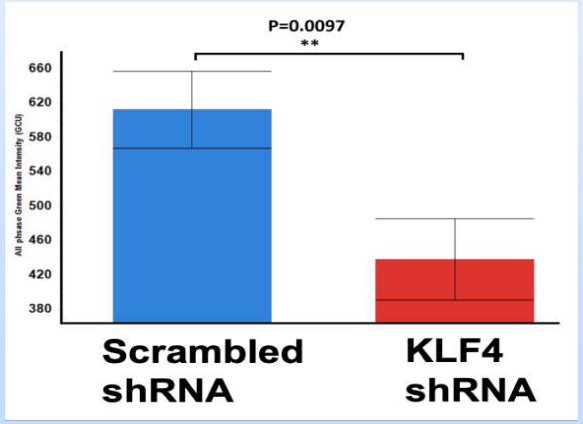
STAT3 Genetic Targeting in Endocrine Resistant (MCF7 LR/FR) Breast Cancer Cells



Real-Time Quantitative RT-PCR showing expression of KLF4, NOTCH2 and WNT4 stemness genes in MCF-7 LR/FR (letrozole and fulvestrant resistant) cells.



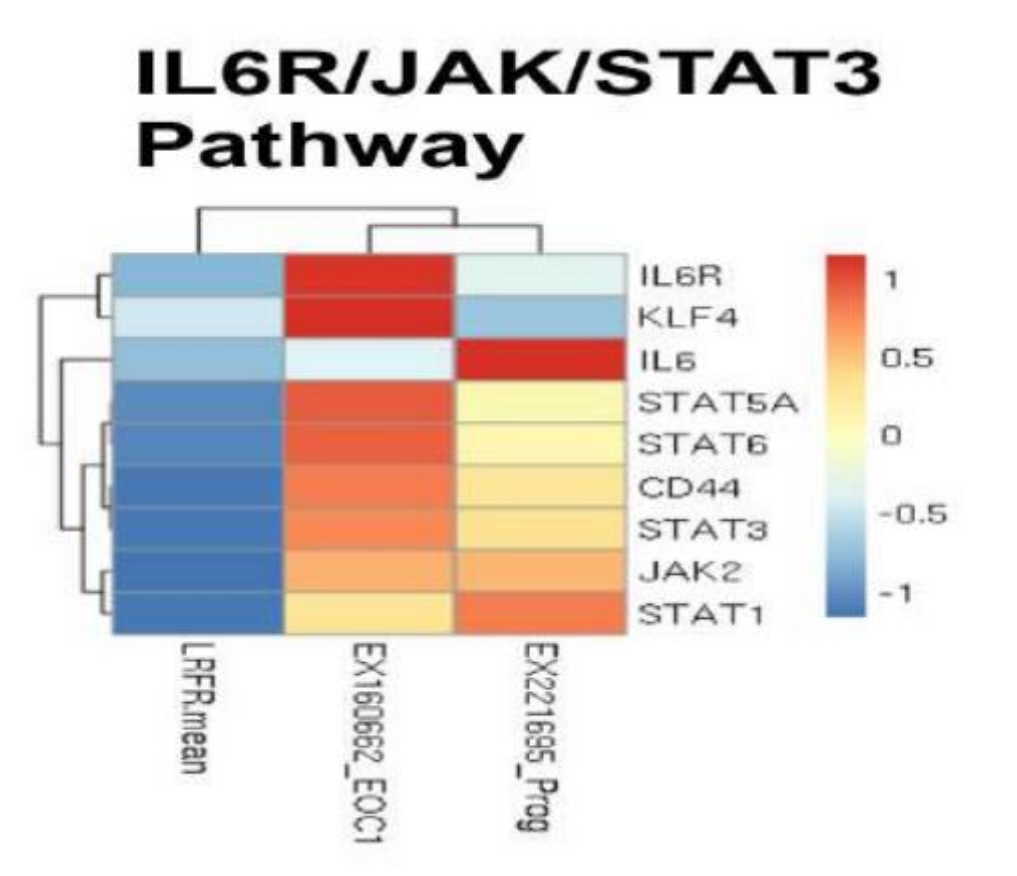
Real-Time Quantitative RT-PCR showing expression of KLF4 stemness transcription factor

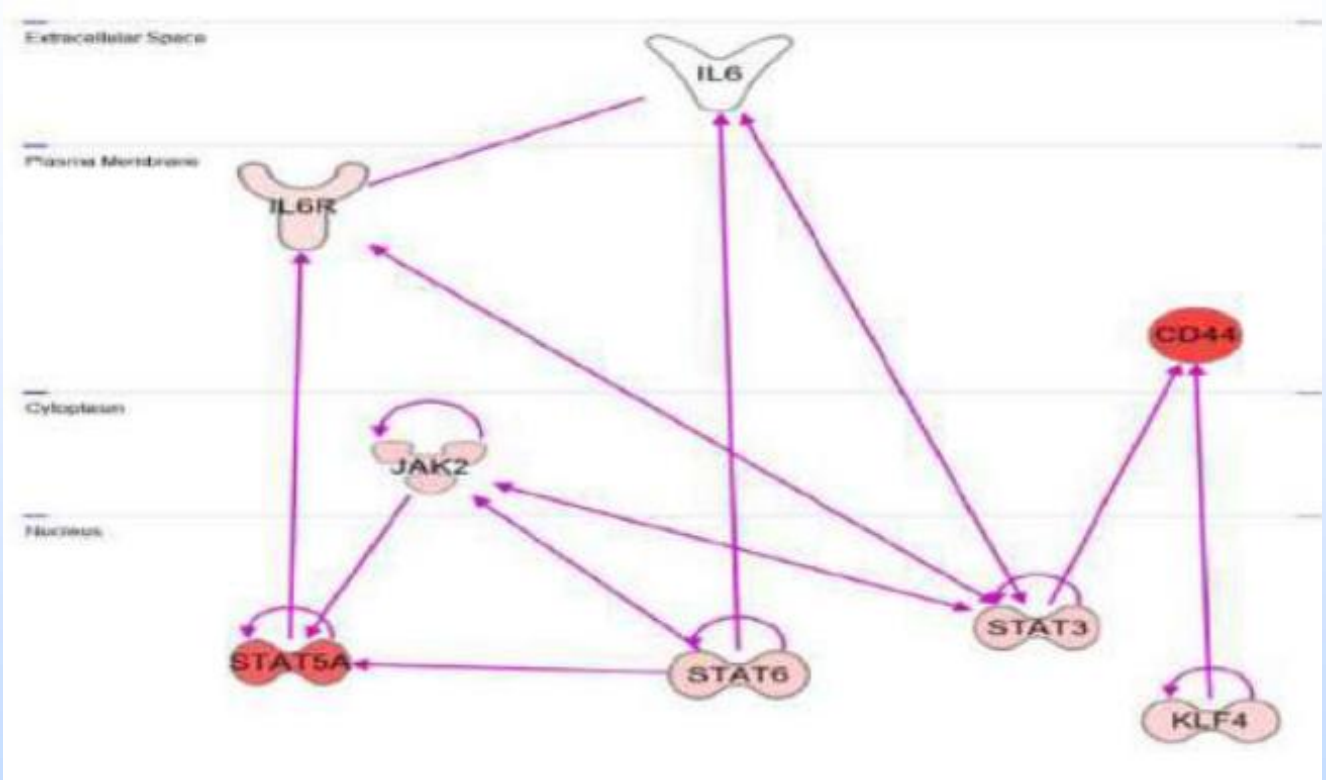


Real-Time 3D-Mammosphere growth following KLF4 genetic targeting

AURKA regulates KLF4, NOTCH2, and WNT4 stemness genes in MCF-7 LR/FR cells

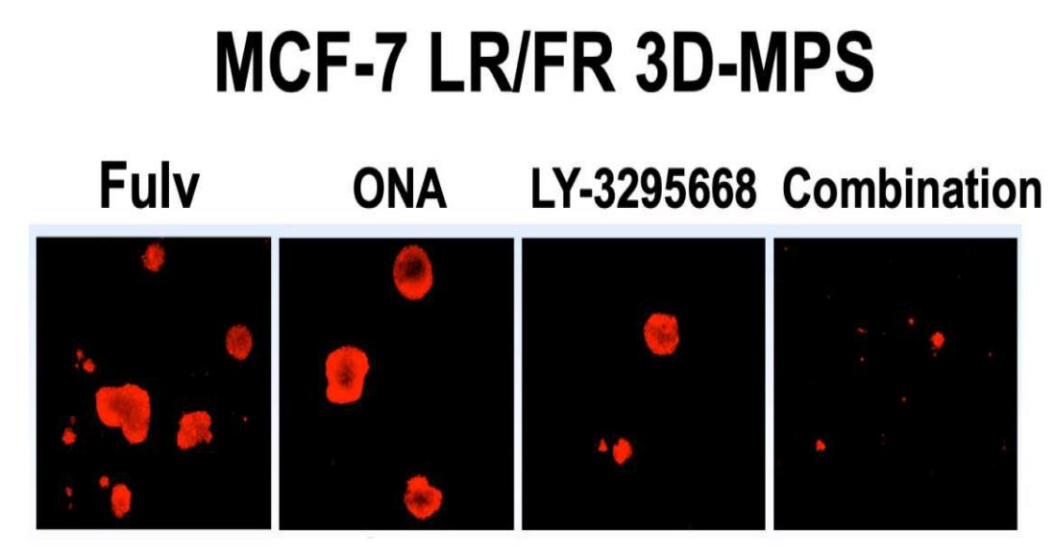
Alisertib Modulates Stemness Gene Network



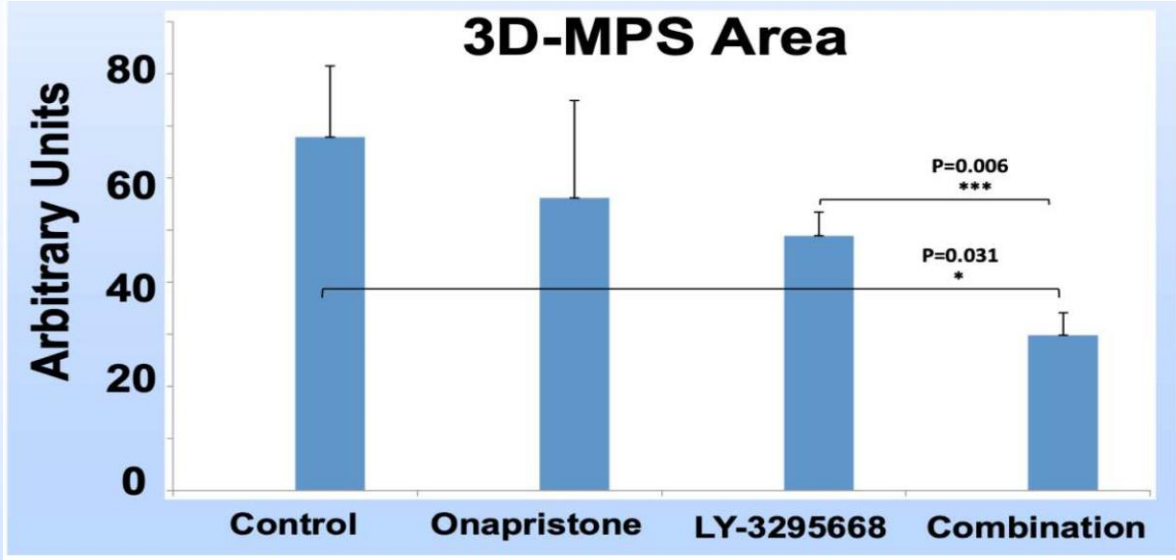


Tumor enrichment of the *IL6/STAT3/KLF4/CD44* stemness gene network in patients with endocrine and CDK4/6 inhibitor resistant breast cancer receiving alisertib

AURKA/PR Targeting in Endocrine Resistant Breast Cancer



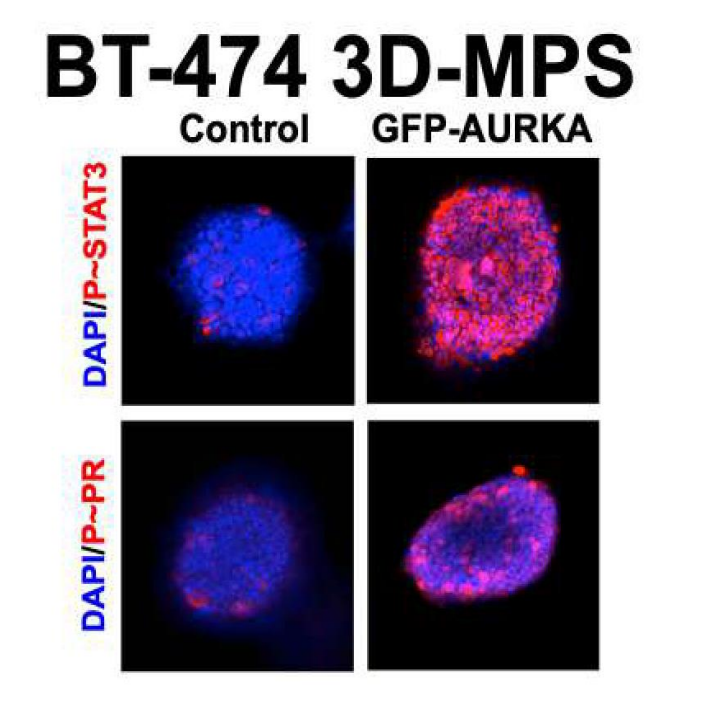
5000 cells derived from letrozole and fulvestrant (LR/FR) resistant 3D-MPS were treated with 50nM fulvestrant as monotherapy and in combination with 50nM onapristone (ONA) and/or 50nM LY-3296668 (AURKA inhibitor) and were incubated for 8 days to monitor 3D-MPS growth.



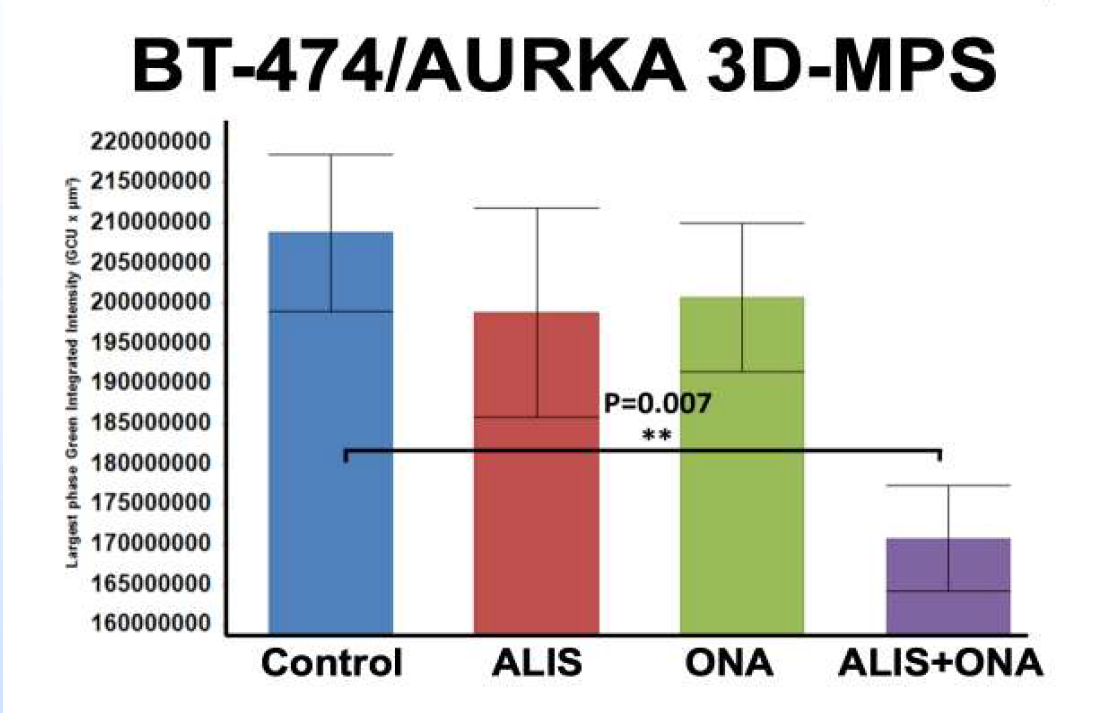
Graph showing the average of 3D-MPS growth from three independent experiments (+/- s.d.).

Dual pharmacologic targeting of AURKA and PR signaling pathways is additive/synergistic in endocrine resistant model

AURKA/PR Targeting in Breast Cancer Cells



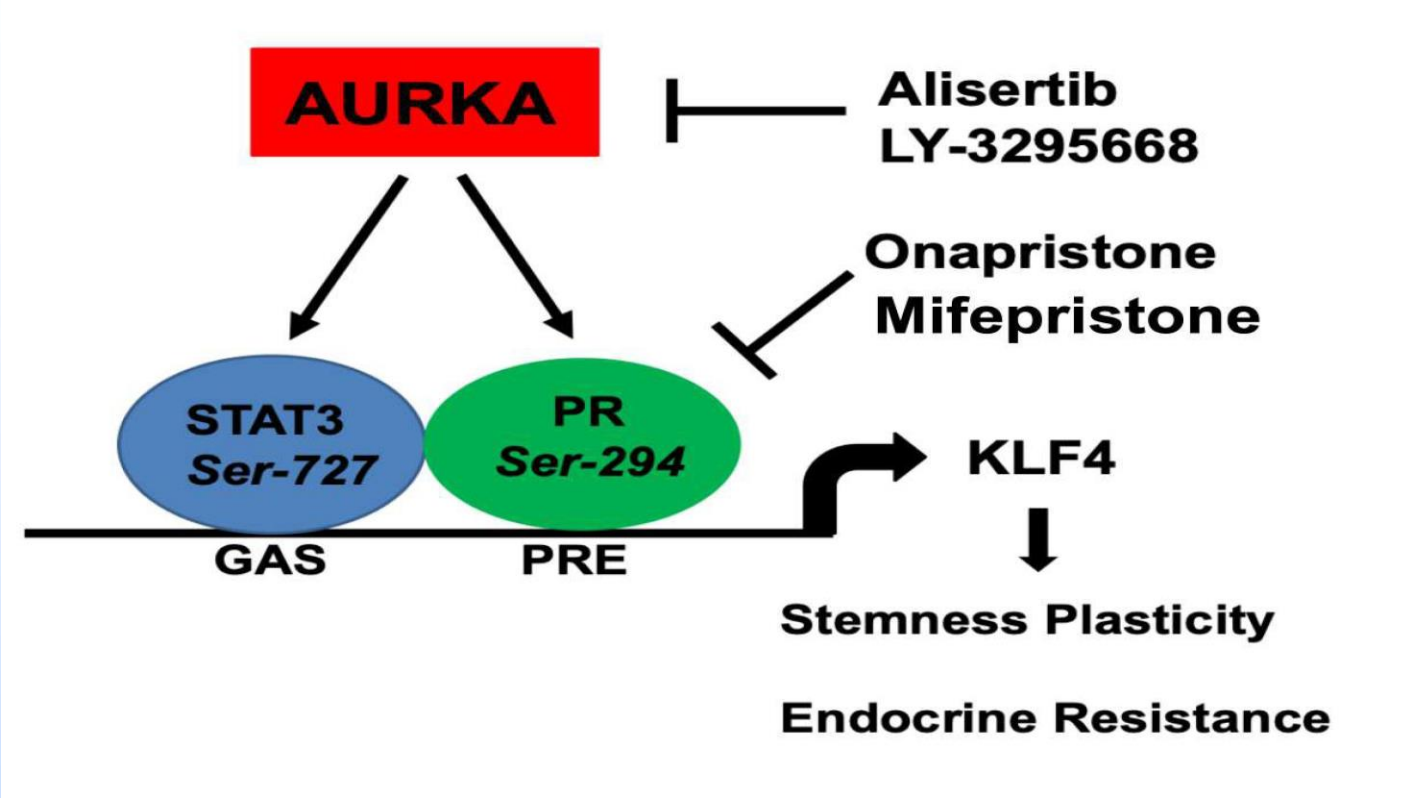
Development of AURKA overexpression cell line grown in 3D (BT-474 3D-MPS). Model resistant to palbociclib (data not shown).



Treatment of AURKA overexpression cell line grown in 3D. Graph showing the average of 3D-MPS growth from three independent experiments (+/- s.d.).

Dual pharmacologic targeting of AURKA and PR signaling pathways is additive/synergistic in palbociclib-resistant model

AURKA And PR Pharmacologic Co-Targeting



- AURKA-induced cancer plasticity and endocrine therapy resistance is mediated through phosphorylation of S727-STAT3 and S294-PR transcription factors that favors their co-recruitment in the promoter region of KLF4 stemness reprogramming gene.
- Dual pharmacologic targeting of AURKA and PR signaling pathways will efficiently rewire nuclear reprogramming to a more differentiated luminal phenotype and enhance endocrine therapy sensitivity.

Ongoing Studies

***In vivo* preclinical ER+ breast cancer models to test the combination of AURKA-targeted therapy with onapristone**

1. Endocrine resistant breast cancer cells
   (MCF-7 LR/FR, MCF-7 LR/FR-PalboR, BT474/AURKA)

2. Unique PDX-derived tumor xenografts from the alisertib Phase II clinical trial (NCT02860000)

Acknowledgements

Mayo Clinic

- James Ingle M.D.
- Matthew Goetz M.D.
- Tufia Haddad M.D.
- Vera Suman Ph.D.

U of Minnesota

- Carol Lange Ph.D.

- **Proteomic Core Facility**
- **Grants**
- NIH R01
- Minnesota Partnership
- Randy Shaver Foundation
- Nan Sawyer Funds

integral molecular

Membrane Protein Solutions

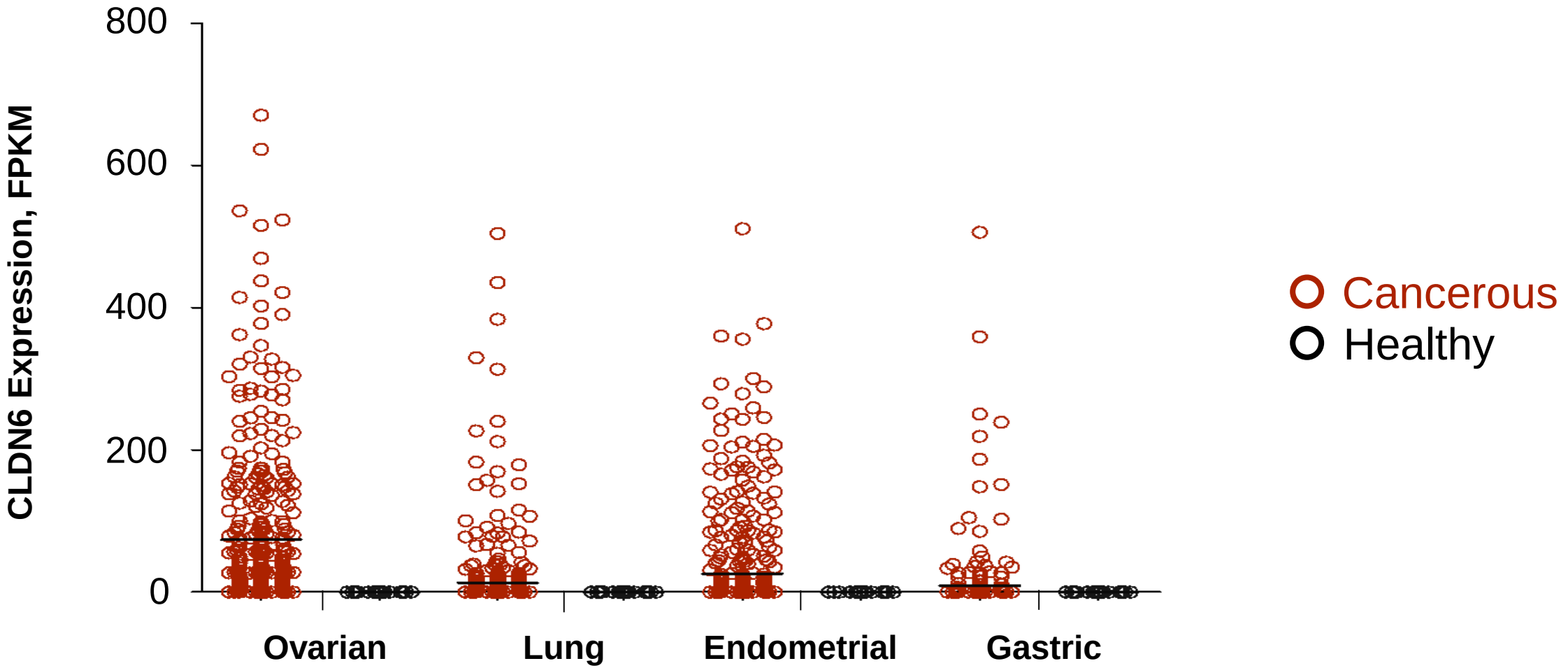
Development of CLDN6 x CD3 Bispecific Antibodies for Gynecological Cancers

Joseph Rucker, Ph.D.

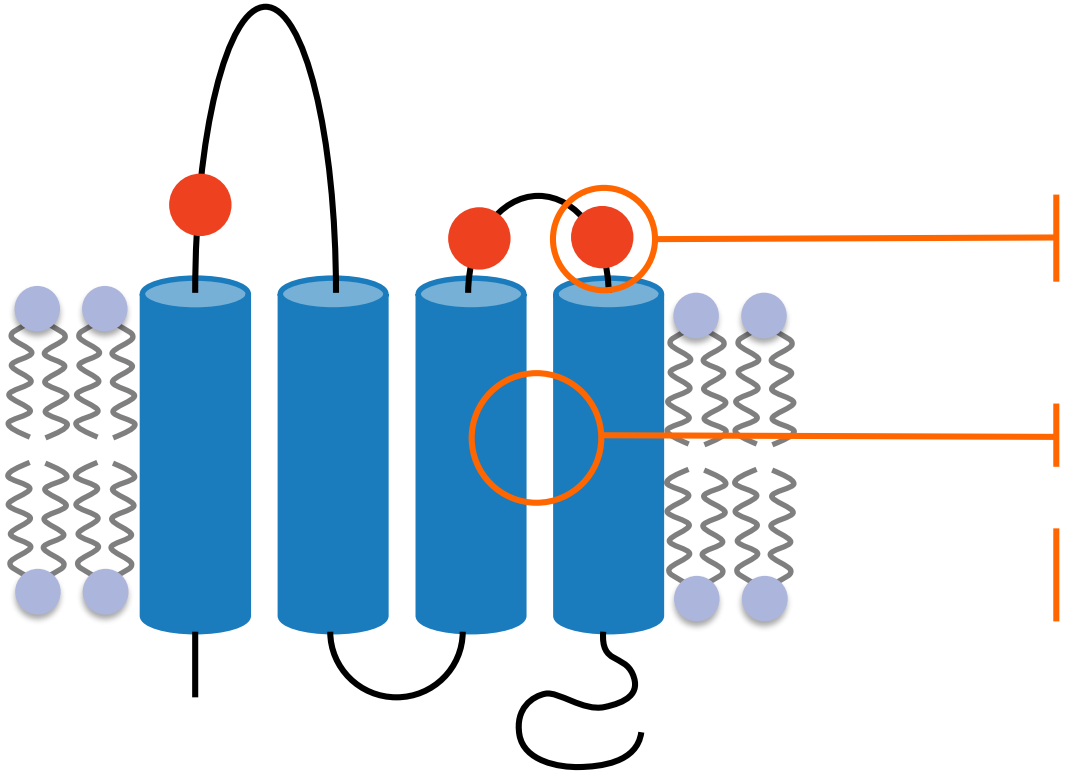
Talk Overview

1. CLDN6 as a Therapeutic Target for Multiple Cancer Types
2. Development of Ultra-Specific CLDN6 Antibodies
3. CLDN6 Bispecifics
4. Current Status and Future Steps

CLDN6 is Overexpressed in Multiple Cancers



Therapeutic Potential of CLDN6



Challenges

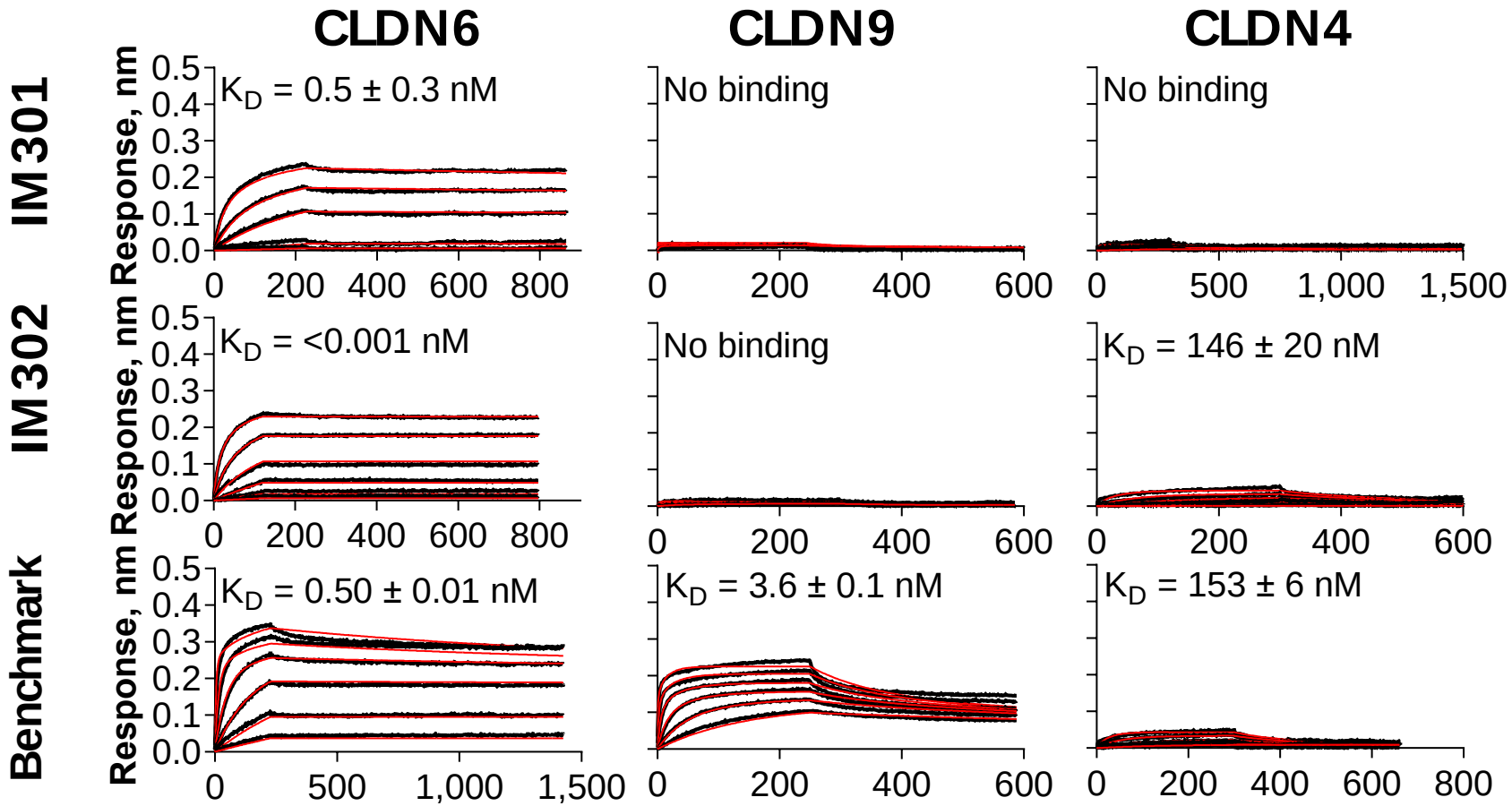
Only 3 extracellular residues different from CLDN9 (widely expressed)

Structurally complex antigen

95% conserved to mouse

- Expressed in ovarian, endometrial, and multiple other solid tumors
- Not expressed in normal adult tissues
- Excellently suited for use in a T-cell engaging bispecific antibody

CLDN6 Antibodies



Integral CLDN6 antibodies show specificity for CLDN6 over other claudins

Benchmark = IMAB027 (Astellas / Ganymed)

CLDN6xCD3 Bispecific Library

Highly specific CLDN6 MAbs generated by Integral Molecular

Well characterized anti-CD3gd partner arms

Highly diverse molecular properties:

Stoichiometry

Affinity

Specificity

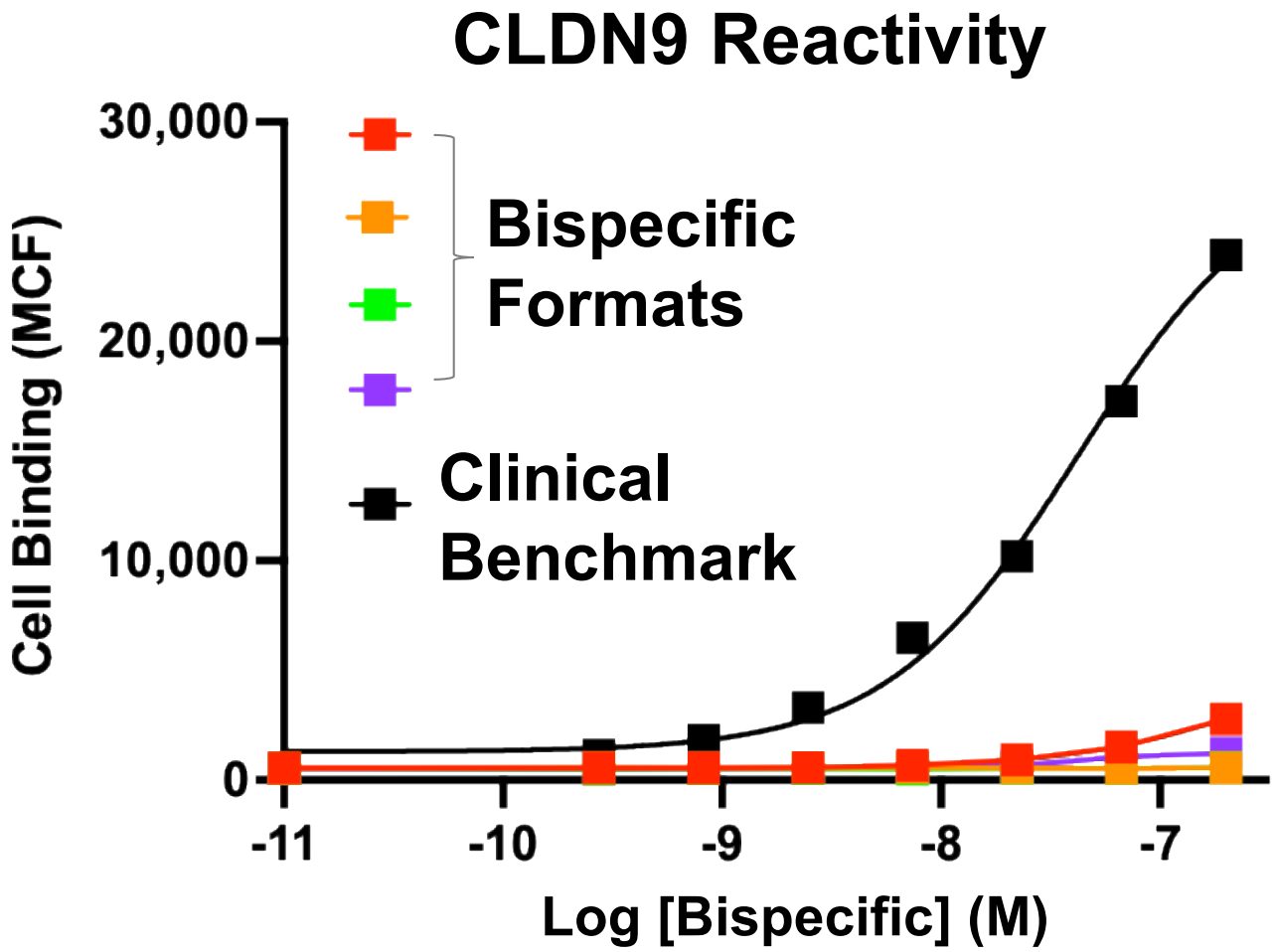
54
Bispecific candidates

Geometry

Size

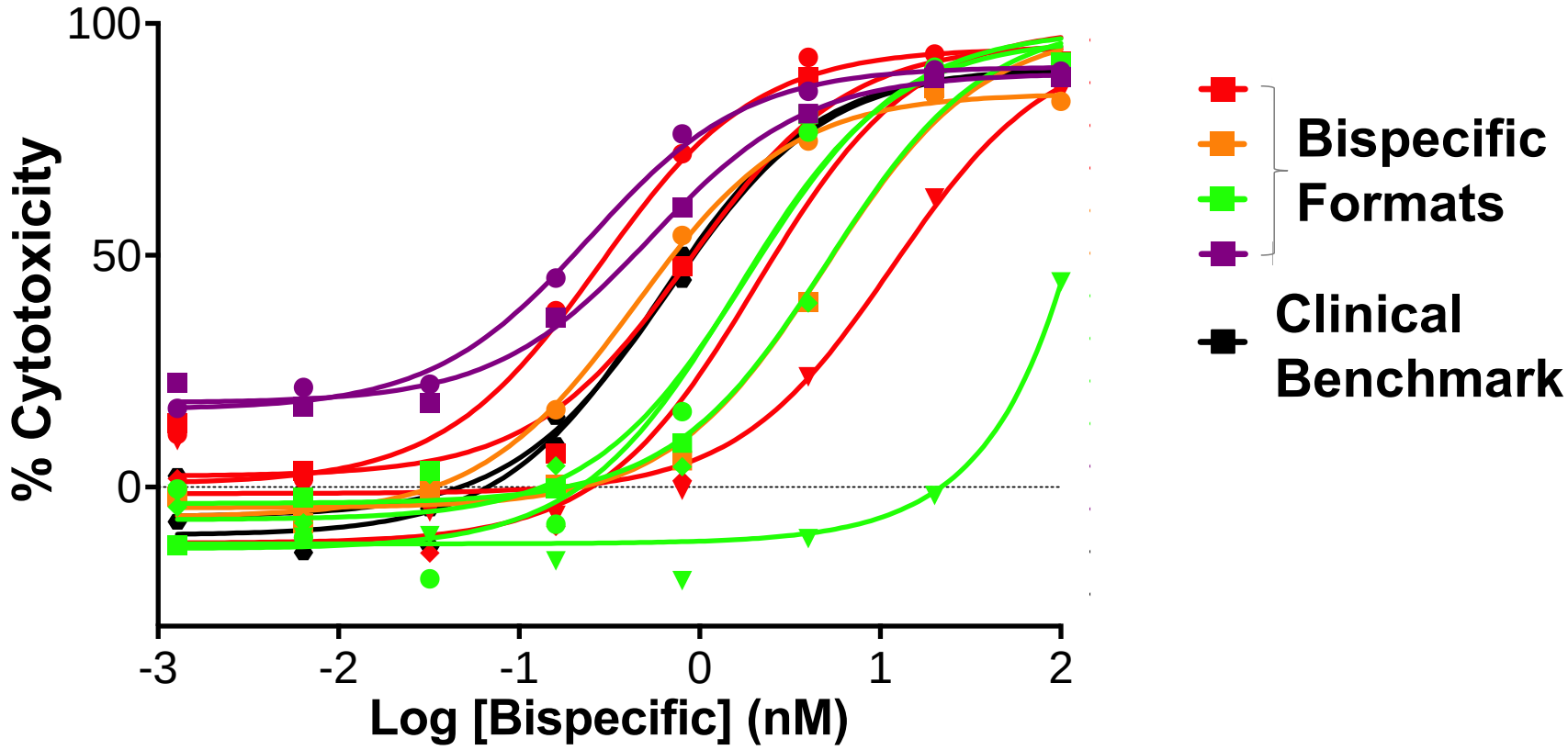
Function

Bispecific antibodies retain high CLDN6 specificity



Benchmark = IMAB027 (Astellas / Ganymed)

T-cell Dependent Cytotoxicity



CLDN6xCD3 bispecifics induce robust T-cell dependent cytotoxicity

Benchmark = IMAB027 (Astellas / Ganymed)

Summary

Completed in vitro characterization of a panel of 54 CLDN6 x CD3 bispecifics

- Diverse across bispecific backbone and CD3 sequence
- Retain CLDN6 selectivity of parent CLDN6 monoclonal antibody
- CLDN6 bispecifics redirect T-cells to kill CLDN6-expressing cells at picomolar concentrations

Candidate panel of 12 bispecifics chosen to undergo scale-up and additional developability te

Summary

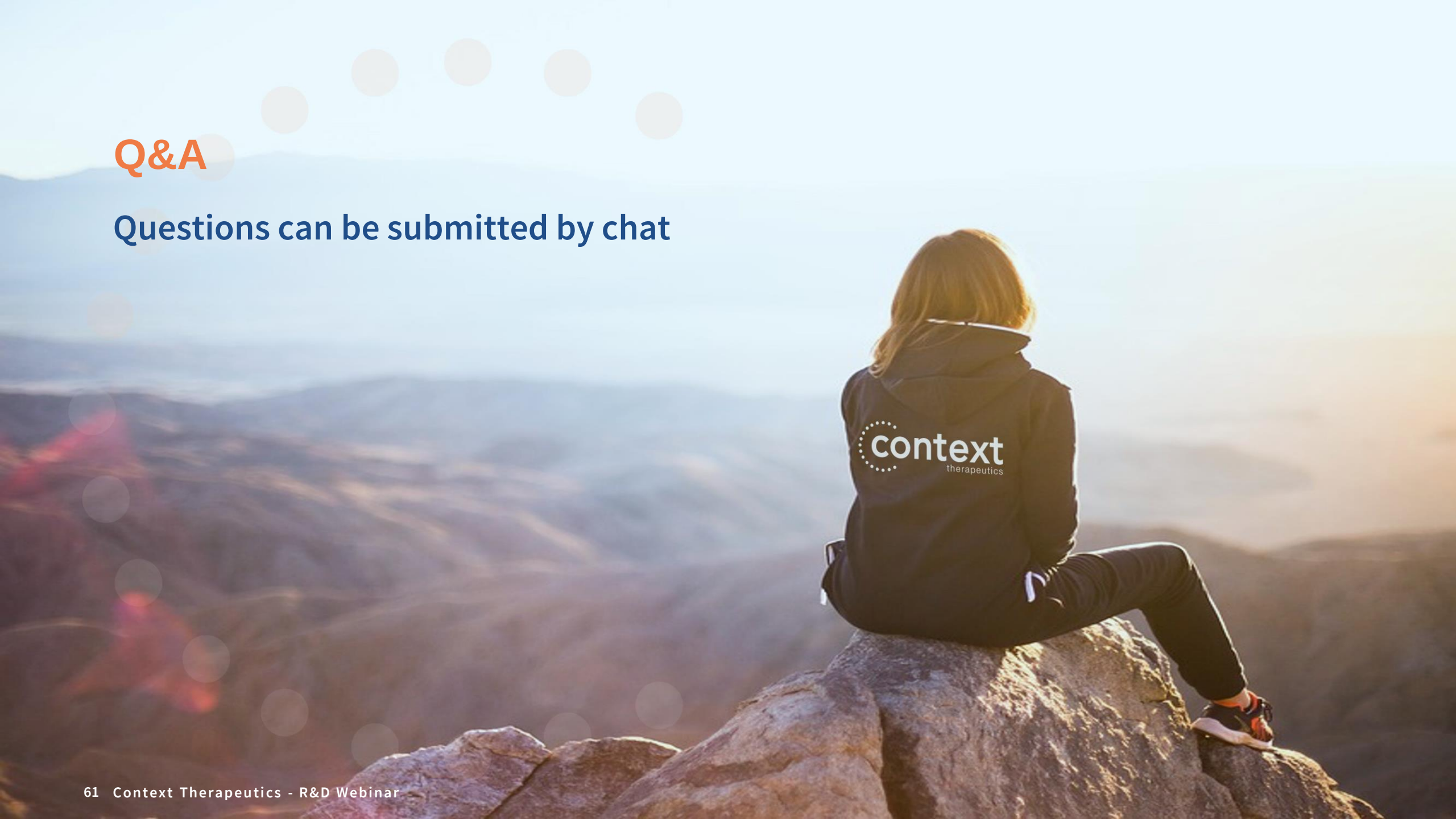
Evan Dick, PhD – SVP R&D

Summary

- Onapristone facilitates breast cancer cell transition from immunologically cold to hot, providing a rationale for future checkpoint inhibitor combinations
- Pharmacologic targeting of AURKA/STAT3/PR oncogenic axis impairs self-renewal capacity of breast cancer cells that show resistance to antiestrogen and/or CDK4/6 inhibitor therapy
- Onapristone enhances therapeutic activity of antiestrogen, CDK4/6, and/or PI3K inhibitors in PDX models of breast cancer
- First presentation of CLDN6xCD3 bispecific data, highlighting CLDN6 selectivity and T-cell activation

Q&A

Questions can be submitted by chat



context therapeutics

BRINGING CHANGE FOR FEMALE CANCERS