Session 5: Translational Approaches to Breast Cancer Prevention: *Developing and Testing Strategies Women are Likely to Use*

Carol Fabian MD
University of Kansas Medical Center

Co-Chairs

Andrea DeCensi MD
Galliera Hospital, Genoa, Italy

Advocate

Valerie Frasier

Despite Substantial Risk Reduction <5% of Risk Eligible Women will take full dose Tamoxifen for Prevention Primarily due to Side Effect Concerns

Need New Intervention Approaches

- Lower Doses Standard Drugs or New ones with Minimal Sx
- Interventions Targeting a Current Problem + Breast Ca Risk
- Cohort and Intervention-Centric Biomarkers to measure success

Improve Risk Knowledge and Prevention Opportunities in Diverse Populations

- Trials Designed to Accrue Understudied Populations
- Population based approaches to dissemination of risk and prevention interventions

Session 5 Oral Presentations and Posters

Preventing Breast Cancer with Molecules Targeting the Estrogen Receptor: SERMs, SERDs & TSECs

An Excursion into Translational Drug Development

BARRY KOMM PHD

Effect of Low Dose SERMs/TSECS on Biomarkers of Efficacy

SHORT ORAL

1. Hewitt: RECAST: Change in Surveillance MRI Background Parenchymal Enhancement (BPE) with SERMs/SERDS in DCIS

2. Khan: Renaissance: Assessing Efficacy of Low Dose Tamoxifen (LDTAM) with Mammographic Density change in Premenopausal Women

3. Giles: Beneficial Effects of Bazedoxifene + Conjugated Estrogens (TSEC) in a Rat Model of Obesity Menopause and Breast Cancer .

Advocate Comments and Audience Q & A

BREAKING THE OBESITY-BREAST CANCER LINK: DIET, DRUG, AND SURGICAL STRATEGIES

Stephen D Hursting PhD

Exercise, Short Fast + Metformin, LDTAM + Caloric Restriction

SHORT ORAL

1. Jennifer Ligibel MD: Effects of Exercise on Risk Biomarkers in Women with Dense Breasts

- *Primary Endpoint is Change in Irisin*

2. Irene Briata PhD: TEAM: Time Restricted Eating and Metformin vs control Window of Opportunity Trial 4-6 weeks in DCIS and Invasive Cancer

- *Primary Endpoint is change in Ki-67*

3. Matteo Lazzeroni MD: TOLERANT: Phase II trial of LDTAM +/- intermittent caloric restriction or Step counters (goal 10K/day) + /-intermittent caloric restriction

- *Primary Endpoint Change in SHBG*

Advocate Comments and Audience Q & A

Session 5 Posters

NEW APPROACHES & BIOMARKERS TO MEASURE SUCCESS

1. Behbod: Carnosic Acid (Rosemary Extract) activity in MIND preclinical model of DCIS (NCI PREVENT)

2. King: Phase II Baby Tam vs Baby Exemestane

3. Nye: Phase II LDTAM +/- Hi Dose Omega-3 FA in Obese Postmenopausal Women

4. Kimler: Phase II Trial Acolbifene vs LDTAM in Premenopausal Women

5. Fabian: Phase II Trial Bazedoxifene & Conjugated Estrogen vs Control

6. Sardesai: Lasofoxifene in DCIS (Concept)

7. Jing: RECAST: Evaluating new Endocrine agents in reducing DCIS Progression

8. Ramalingam: Shift in interferon and cytokine signaling in women with DCIS progressing to IC

DIET, WEIGHT LOSS, TRIAL DIVERSITY IMPLEMENTATION

1. Strahan-Inflammatory Diet

2. Beaver: Tirzepatide effects on benign breast tissue

3. Nandini: VA recruitment to improve trial diversity

4. Liberty: Effects of gender affirming hormone exposures in benign breast tissue (LIBRA-X)

5. West: Low rate of discussion of meds with high-risk women (Australia)Liberty

6. Latham: Risk Stratification and results dissemination

7. Price: Legislation reducing environmental chemicals

8. Casco: Optimizing workflow for Rx change in I Spy 2.2

Preventing Breast Cancer with Molecules Targeting the Estrogen Receptor: SERMs, SERDs & TSECs

An Excursion into Translational Drug Development

Rise Up

San Francisco

Barry Komm, PhD

Just so you know--Disclaimers

- Consultant for Sermonix Pharmaceuticals
- Consultant for Pfizer Pharmaceuticals
  - Former Employee: Women's Health Medical Affairs

Endocrine Therapy for Treatment and/or Prevention

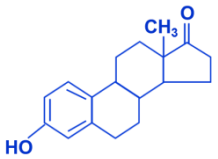
Candidates that potentially qualify for this "Drug Discovery"

- The target is the **Estrogen Receptor** (ESR1)
- SERMs or SERDs or TSECs
  - Call them by any name—Function via binding and activation/inactivation/degradation of the ER

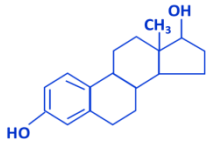
Estrogens vs SERMs vs SERDs: Commonality

All Bind with High Affinity to the ER

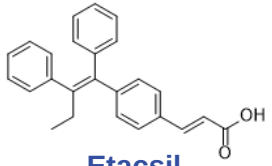
Unique Pharmacologic Profiles



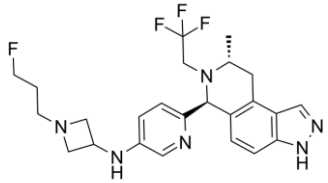
Estrone



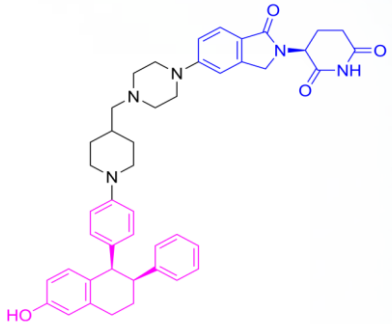
17β-Estradiol



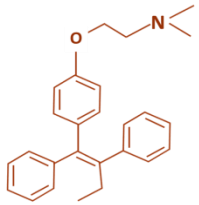
Etacsil



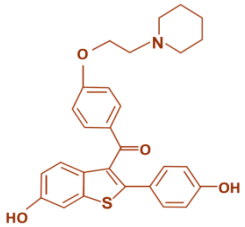
Camizestrant



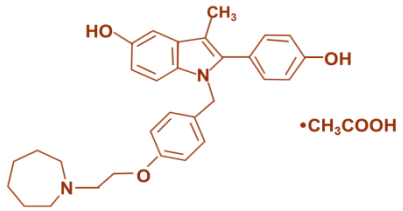
Vepdegestrant



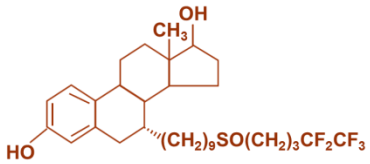
Tamoxifen



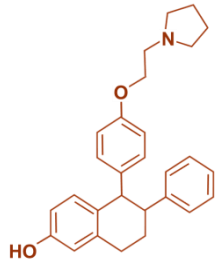
Raloxifene



Bazedoxifene



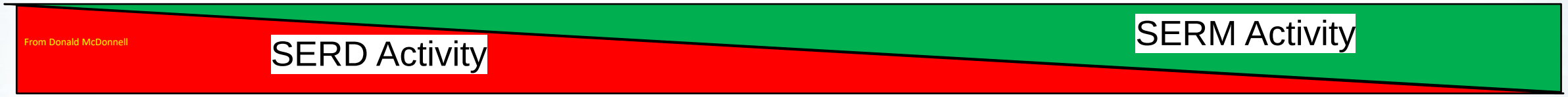
Fulvestrant



Lasofoxifene

Dive Deeper: These molecules don't all fit into one class bucket

SERMs, SERDs and Mixed



Fulvestrant*
RU58668

Elacestrant*

Vepdegestrant**

Camizestrant
Giredestrant
Imlunestrant
Palazestrant

Taragestrant
AC0682

Etacstil***

Bazedoxifene**
Acolbifene**

Raloxifene*
Lasofoxifene**
Arzoxifene***

Tamoxifen*
Toremifene*
Endoxifen**
Idoxifene***
Droloxifene***

- Approved for clinical use *
- Currently in Clinical Development **
- No Longer in Development ***

Considerations for the use of this group of compounds

Pre-menopausal (estrogen rich) vs Post-menopausal (estrogen poor) Antagonist vs Agonist vs Neutral

- Block estradiol binding and game over--**Anti-estrogens**
  - 1st anti-estrogen for adjuvant treatment: tamoxifen led to keoxifene (raloxifene)
  - Class name change to Selective Estrogen Receptor Modulators (Lilly didn't want a drug called anti-anything for use as a menopausal therapy)
- Multiple component (**TSEC**) approach to menopausal therapy where breast and uterine safety is baked in as absolutely necessary
- Eradicate the ER: Degrade the receptor (SERD), but what about the liver, the uterus, the brain, the bone, the intestine, the lymphatics…….
  - Not going to consider as candidates for use in the Prevention of Breast Cancer!!
- Definitely different issues to consider if taking the estrogen receptor out of the game in a pre-menopausal woman vs a post-menopausal woman

Are We Preventing Breast Cancer?

How do we rationally choose efficacious, tolerable molecules that qualify as "Endocrine Therapy"?

Where is the ER Expressed? Perhaps a better question is where isn't it expressed?

Compound

Biological Activity

- ER-ERE-Luciferase
- C3 Promoter-Luciferase
- Ligand Binding (Competition)

Profile Assignment

Ovariectomized Rat Model
6-week

- Bone mineral density
- Bone strength
- Collagen x-links
- Histomorphometry
- Total Cholesterol
- Uterine Weight/histology

Tissue Selectivity

In vitro

- MCF-7 Cells
- Bone marrow
- HepG2
- GT-1
- D12
- Endothelial

In vivo:

- Uterine: 3 day immature rat
- Lipid/uterine: 4 day ovx rat
- Hypothalamus: PR expression

Ancillary Pharmacology

- GR: liver glycogen/thymus weight
- PR: uterine decidualization
- AR: ventral prostate weight

Consider the expectations from one compound……..

Developing the "Ideal" SERM

Positive Effects	Without Negative Effects
• **Skeleton** – Bone-sparing or ↑ BMD – ↓ Fracture • **Lipid profile/Metabolism** – ↓ LDL, ↑ HDL, ↓ total cholesterol – No weight gain – Neutral or improve insulin sensitivity/glucose regulation • **Central nervous system** – ↓ or neutral vasomotor effects	• **Reproductive system** – ↓ or neutral uterine stimulation – ↑ or neutral amenorrhea • **Breast** – ↓ Breast cancer risk – Does not prime breast tissue – ↓ or neutral on breast density

There is no SERM (or any other molecule) that comes close to achieving this pharmacologic profile…..So

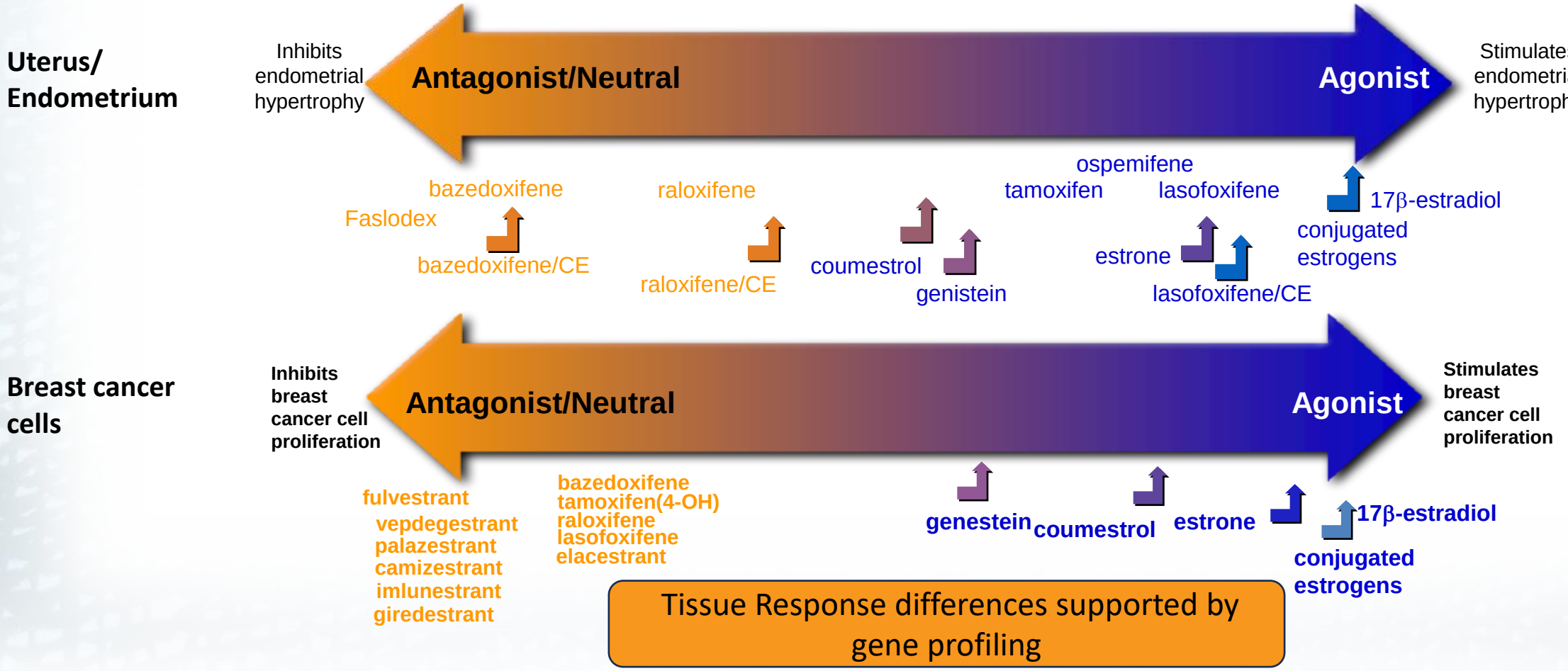
Rationale for Development of Tissue-Selective Estrogen Complexes (TSECs)

TSEC

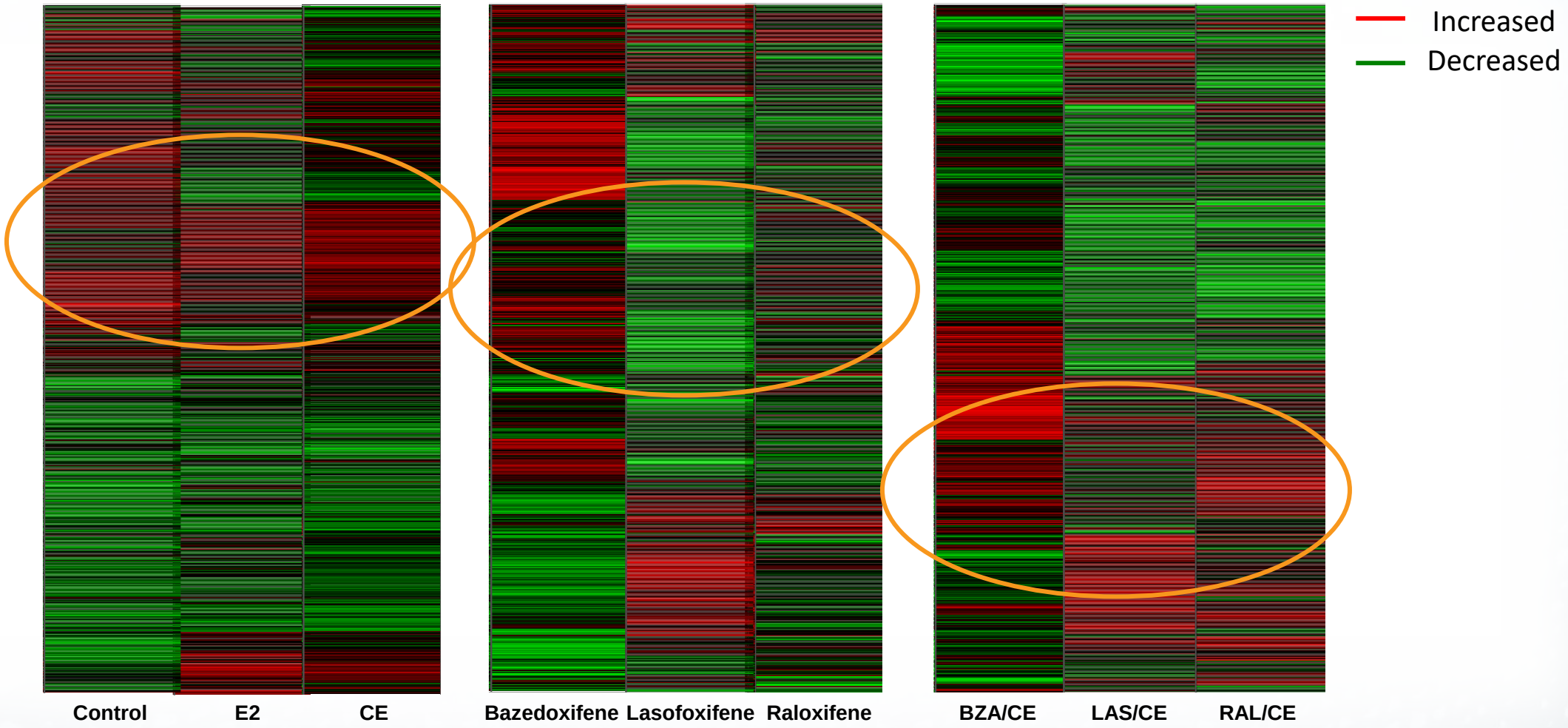
The partnering of a **SERM** with one or more **estrogens** to achieve pharmacologic results based on their blended tissue-selective activity profile

We Call Them SERMs or SERDs
Compare their Pharmacology: Critical Endpoints to Consider

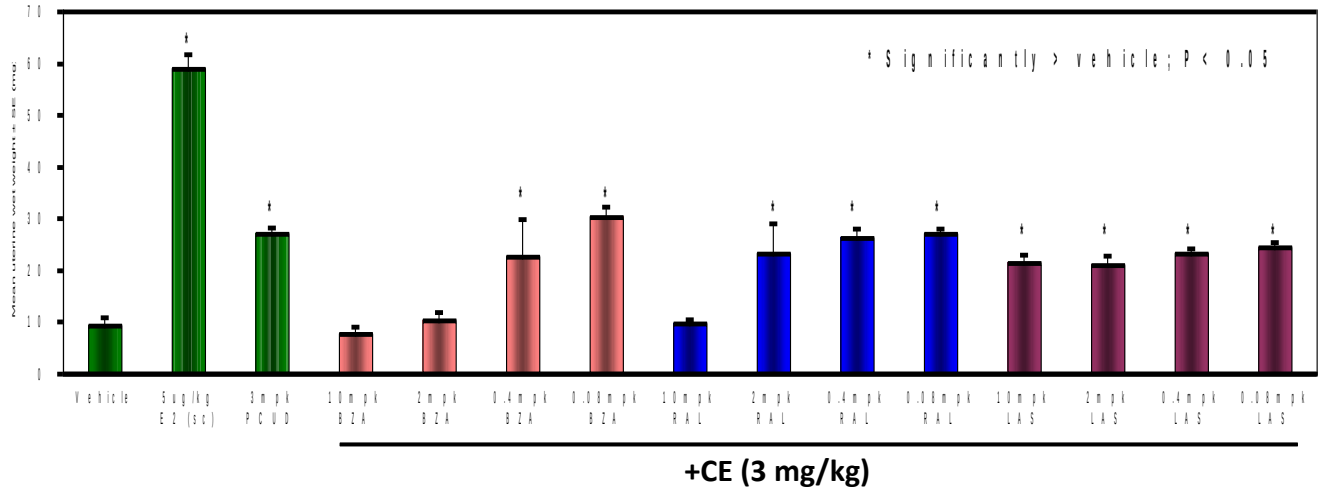
SERMs were developed to be used in the menopausal population as the "better" Hormone Therapy—No progestin

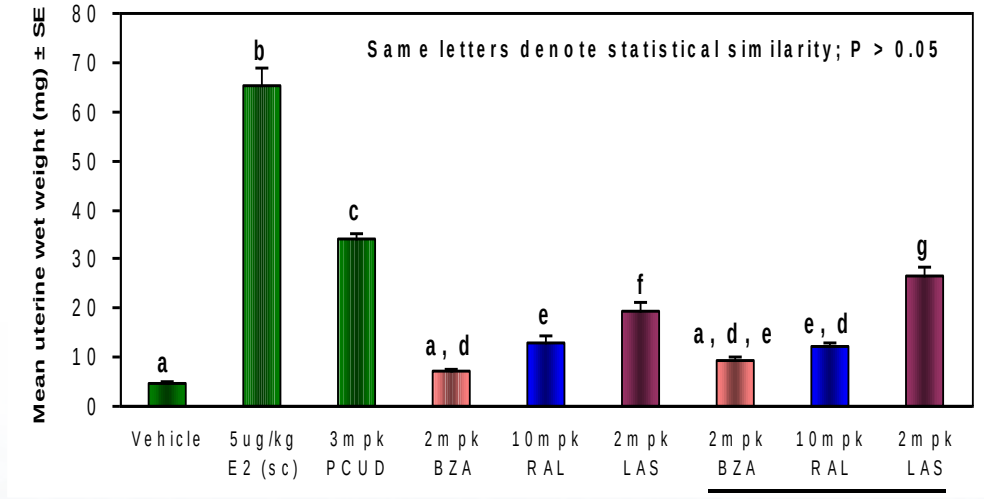


Uterine Gene Expression Profiles
Comparing 3 SERMs and 3 TSECs: Clearly Different



Uterine Response
SERM Pharmacology vs TSEC Pharmacology

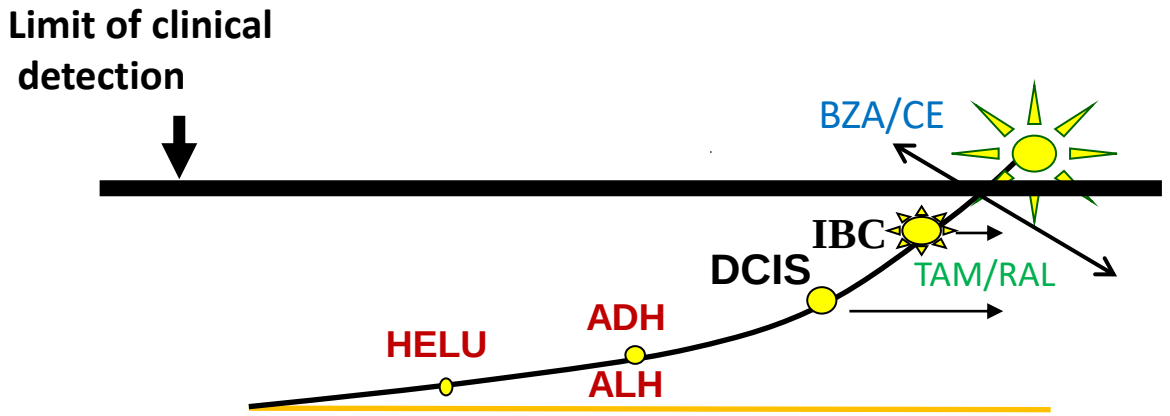




Prevention of Breast Cancer

Just What is Our Hypothesis?

- All of these molecules (SERMs, SERDs, TSECs) target the estrogen receptor (no matter where it is!!), so in the breast (occult breast cancer):
  - **If we reduce estrogen receptor activity then we will reduce the incidence of breast cancer (prevent breast cancer)**
- Is it a matter of detection vs preventing initiation or both?

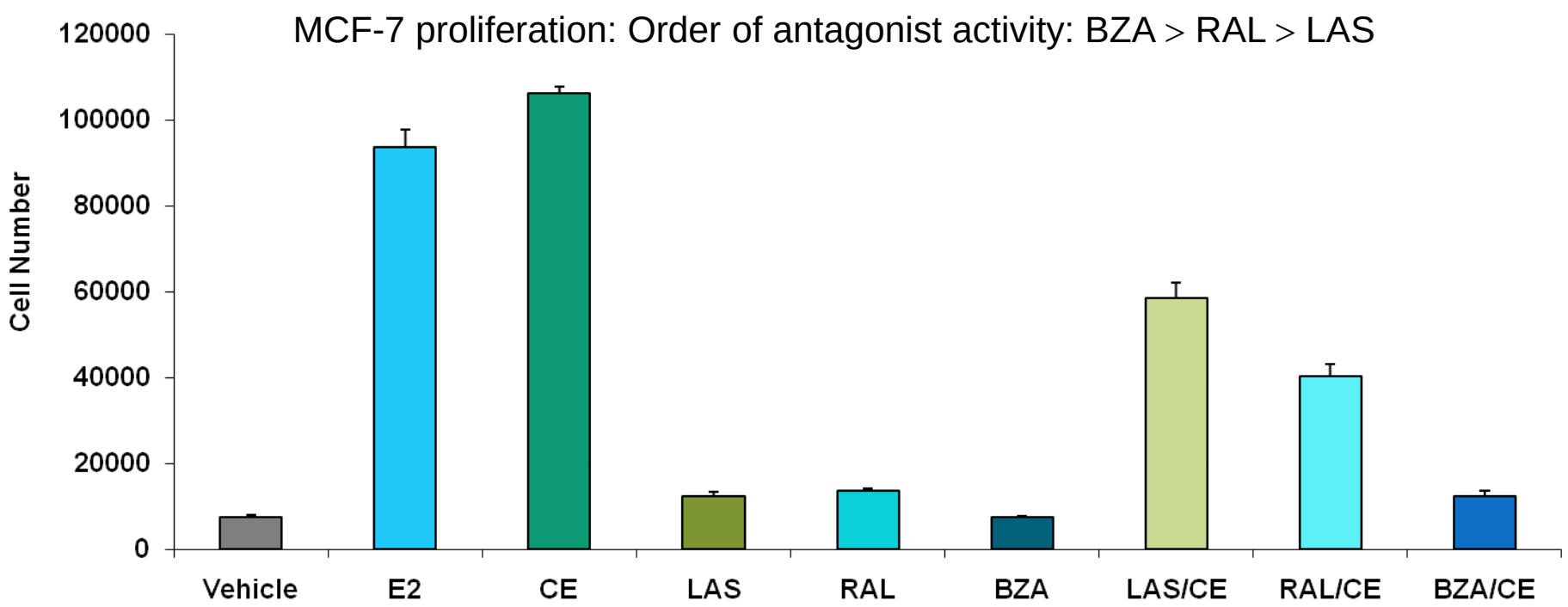


From Richard J.Santen

SERM vs TSEC on breast cancer cell proliferation

Breast Cancer Cell Proliferation:

Estrogens vs SERMs vs TSECs

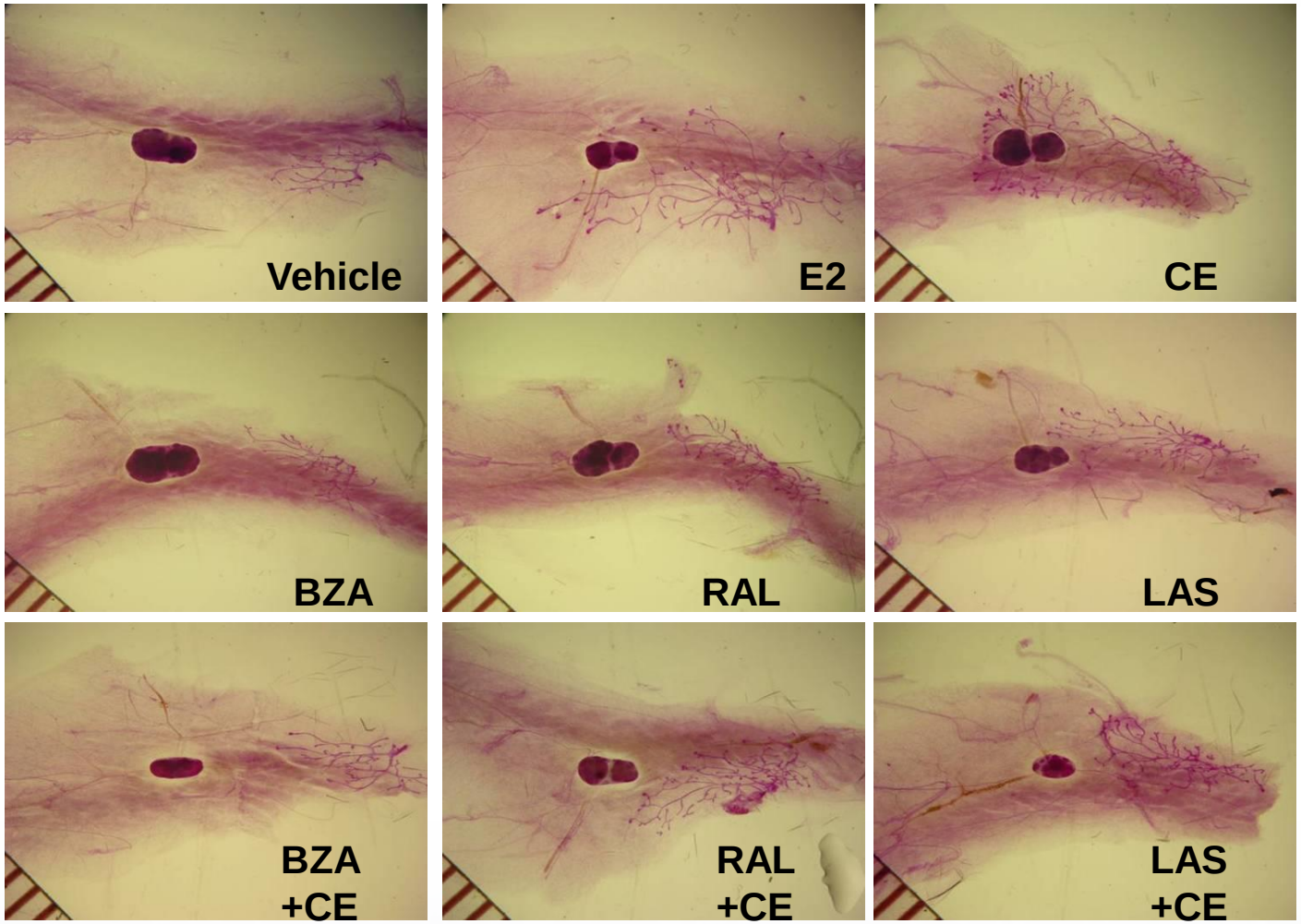


Only 1 nM tested. However, binding IC_{50}s are not too different for the 3 SERMs.

Why the difference in combination?

Mammary Gland Whole Mounts:

Early Fat Pad Infiltration



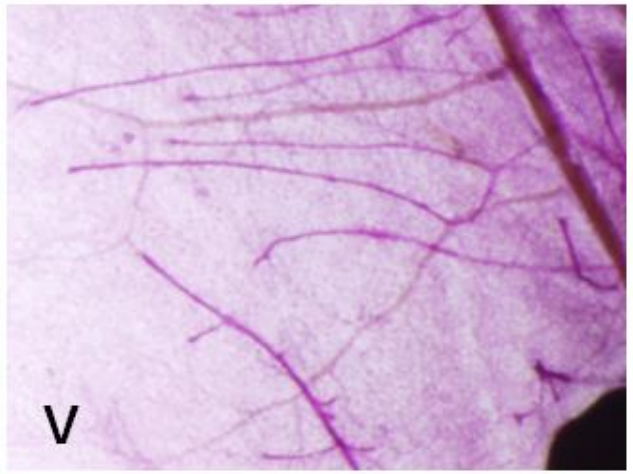
Tissue response: End bud proliferation and duct number

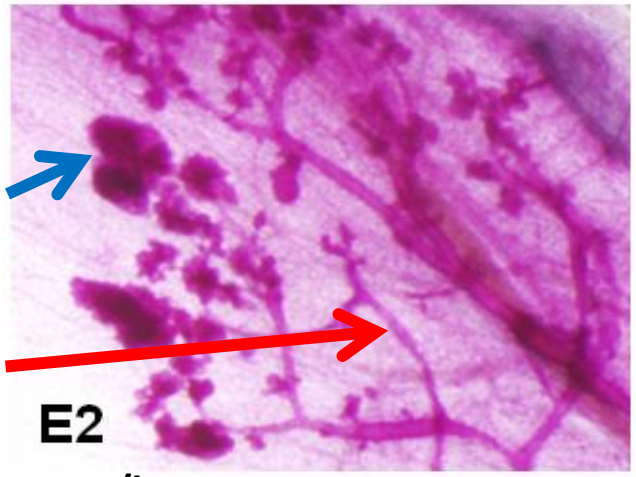
BZA Inhibits Mammary Duct Elongation and Endbud Proliferation

Endbuds

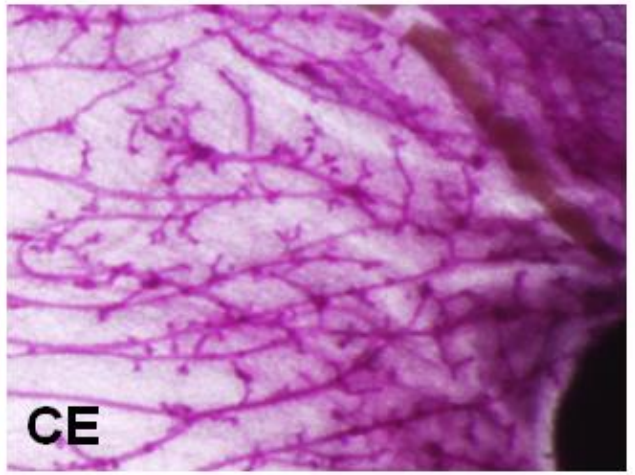
Ducts

Same magnification (50x) for all micrographs

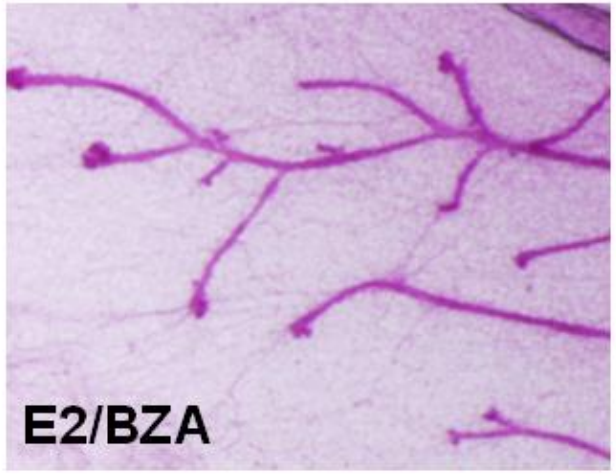




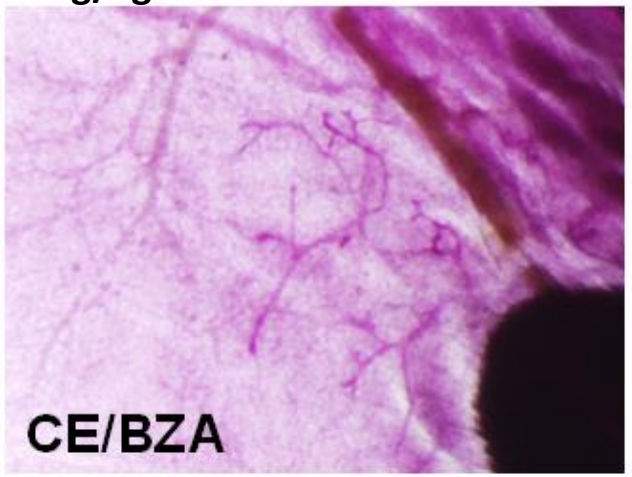
5 µg/kg



3 mg/kg



5 µg/kg + 2 mg/kg



3 mg/kg + 2 mg/kg

V, vehicle.

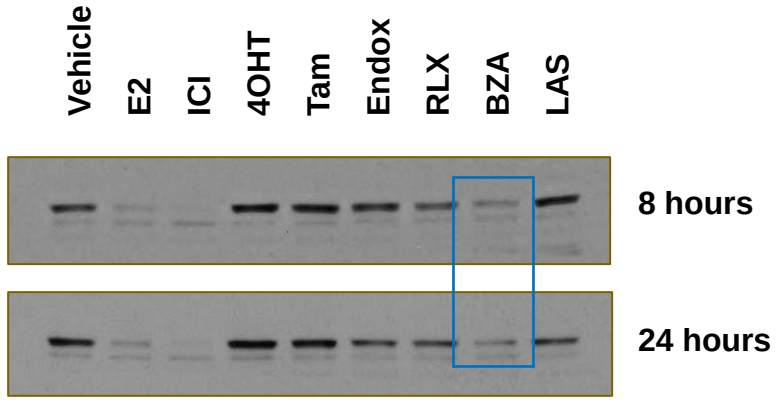
Song Y, et al. *Endocrinology.* 2012;153:5706–5715.

Images courtesy of Richard J. Santen, MD; University of Virginia, Charlottesville.

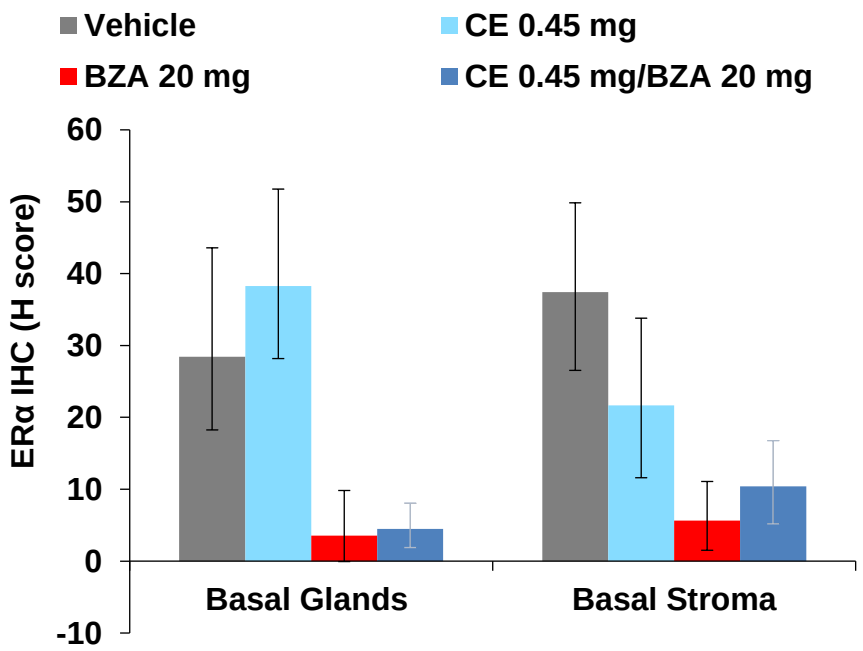
What is BZA doing that RAL and LAS are not?

BZA Facilitates Degradation of ER in Breast, Uterus and Breast Cancer

Human Breast Cancer Cells: ER protein Expression[1]



Nonhuman Primate Uterus: ER Protein Expression[2]



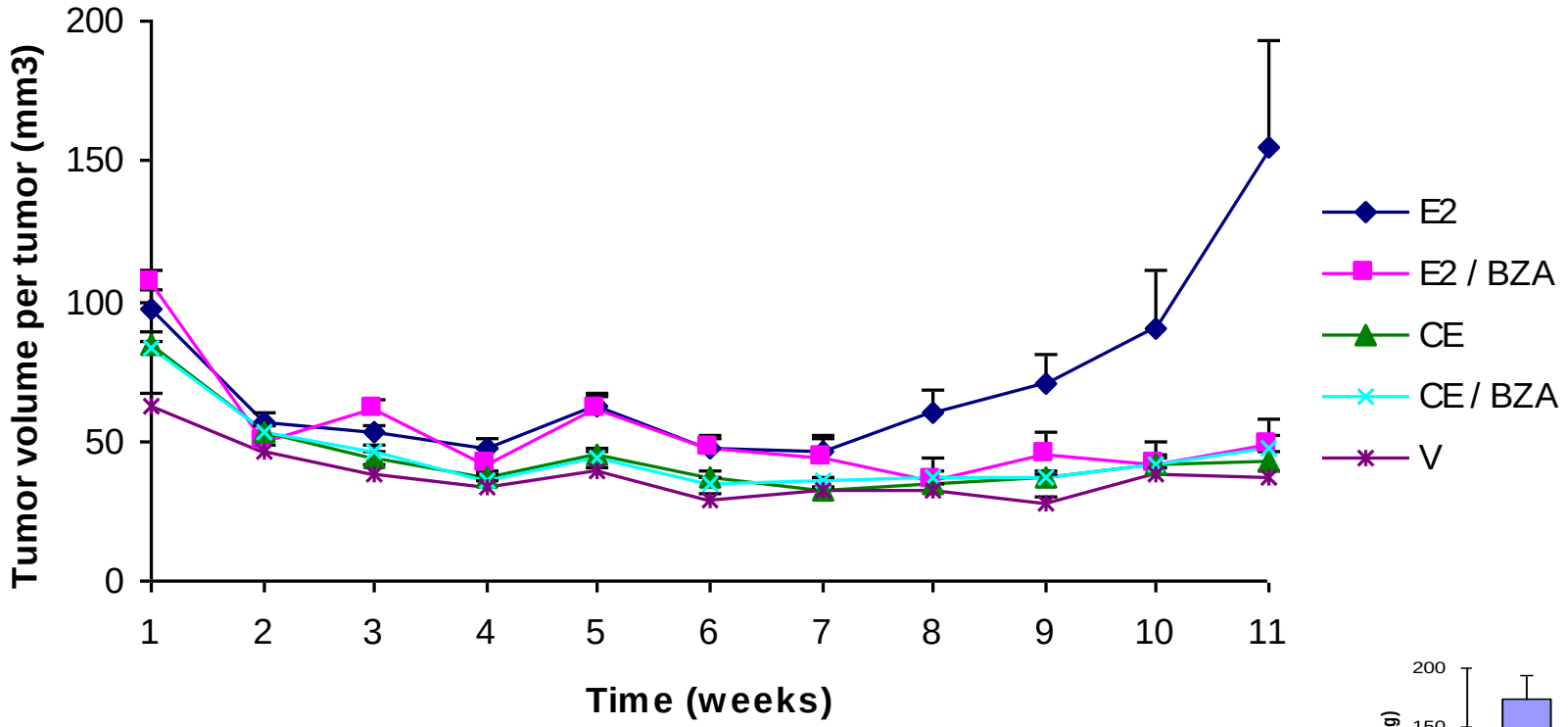
Unlike the SERDs, BZA demonstrates selective degradation of ER—Is that the magic?

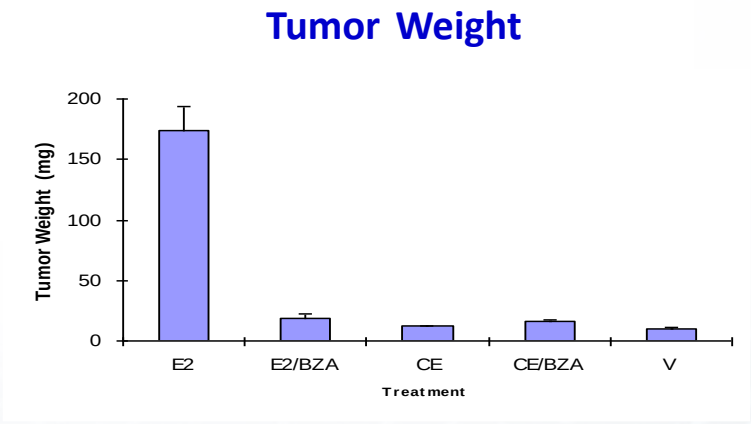
4OHT, 4-hydroxytamoxifen; BZA, bazedoxifene; CE, conjugated estrogens; E2, 17β-estradiol ; Endox, endoxifen; ER, estrogen receptor; ICI, fulvestrant; IHC, immunohistochemistry; LAS, lasofoxifene; RLX, raloxifene; Tam, tamoxifen.

1. Wardell SE, et al. *Clin Cancer Res.* 2013;19:2420–2431. 2. Ethun KF, et al. *Menopause.* 2013;20(7):777–784.

Occult Tumor Model

This is what we are looking for a drug to do





Courtesy of Richard J Santen

Clinical Data Support for Use of Duavee for Prevention in all Qualifying Women

- First: SERMs used alone in pre-menopausal women are associated with an increase in hot flashes, vaginal dryness, loss of bone mass and negative quality of life
- The TSEC, Duavee
  - 3-month treatment resulted in no change in gonadotropins and no ovarian cysts in 20-25 y.o. women
  - Reduced endometriotic lesion size and associated pain without use of Lupron
  - In Menopausal Women
    - No change in breast density or pain compared to placebo
    - Reduced hot flashes
    - No increase in endometrial hyperplasia
    - No reduction in amenorrhea (no bleeding)
    - Maintained or increased bone mineral density
    - Reduced LDL, increased HDL with no statistical change in triglycerides

Target	SERMs	Estrogens	E + P	TSECs
Breast	Positive	Not acceptable	Not acceptable	Neutral
Uterus	Neutral	Not acceptable	Neutral	Neutral
Hot Flush	Not acceptable	Positive	Positive	Positive
Vagina	Not acceptable	Positive	Positive	Positive
Bone	Positive	Positive	Positive	Positive

Neutral Positive Not acceptable

Considerations and Conclusions

- Critical to assess each molecule's pharmacology as thoroughly as possible: Perhaps side effect profile more so than efficacy profile
- Which SERM or TSEC will provide the desired pharmacologic profile with more than acceptable safety and tolerability? After all we are talking prevention not treatment of breast cancer.
  - Each SERM, SERD and TSEC are pharmacologically distinct
    - Target is the same, but……..
  - Gene expression profiles distinct: Subtlety vs sledgehammer
  - **Combinations, at this point in time, are the only way to achieve the optimal drug profile or perhaps we should say acceptable, but not perfect**

The RECAST DCIS study

Re-Evaluate Conditions for Active surveillance Suitability as Treatment

PIs: Kelly Hewitt MD, Laura Esserman, MD
Sponsor: Quantum Leap Healthcare Collaborative
Participating Companies:
Atossa Therapeutics, HavaH Therapeutics, Menarini-Stemline

Kelly Hewitt, MD, FACS
Associate Professor of Surgery
University of Utah, Huntsman Cancer Center

DCIS: Gateway for Prevention

- Identifies women at elevated risk for developing breast cancer
- The current approach is likely **NOT NECESSARY** in the majority patients
- The diagnosis covers a range of biology
- The risk of progression or new cancer development varies widely
- **There is no emergency and no one's life is threatened by DCIS only**
  - There is some risk of upstaging to invasive cancer, reduced by use of MRI
- There is a window of opportunity to test risk reduction strategies
  - The same neoadjuvant approach has accelerated treatment advances in IDC

Active Surveillance Prospective Imaging Study

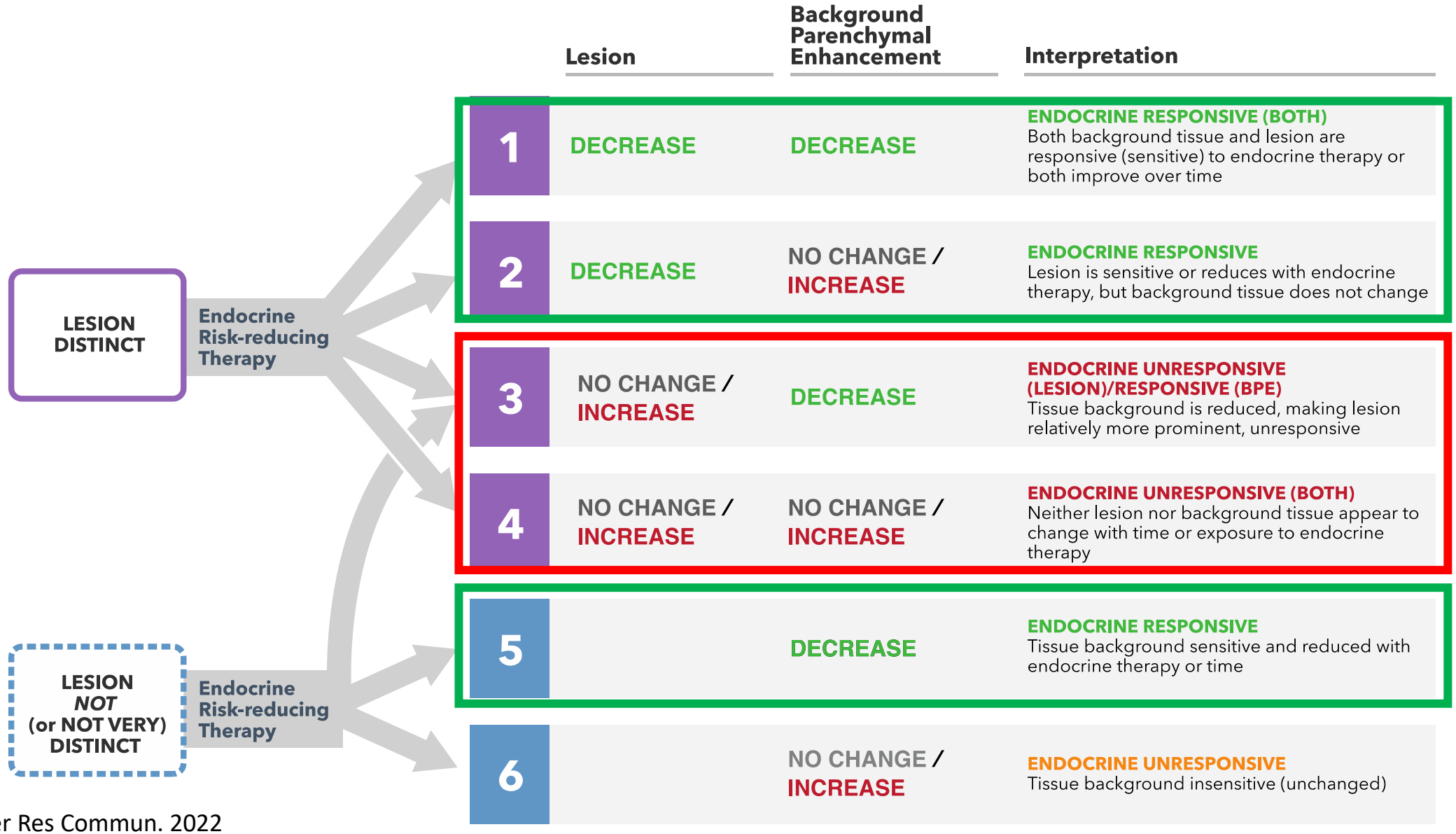
Cohort

- Prospective imaging study of 71 patients who chose not to start with surgery, mean follow up 8.5 years
  - range of risk features
- HR + , Endocrine risk reduction recommended
  - Accepted in 90%
- Patients were followed and recommended to have surgery if there was progression of lesions
- Imaging features were used to classify low and high risk for IDC progression

- **Main findings**
  - 60% did not have a distinct lesion above background
  - Imaging features at 3- 6 months can stratify risk and guide decision for active surveillance
    - Reduction in Background enhancement (BPE) and lesion (if present)→low risk
    - Persistence or increase in lesion→ higher risk

Glencer. Cancer Res Commun. 2022

Baseline/Response to Endocrine therapy:



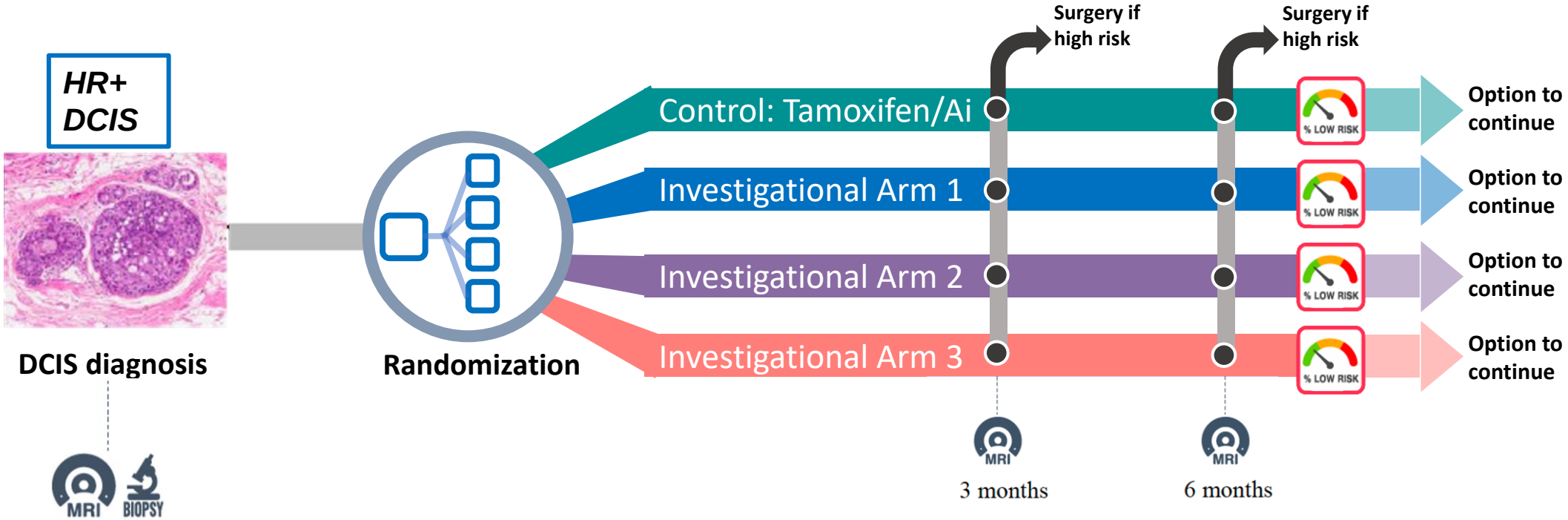
Glencer. Cancer Res Commun. 2022

What is DCIS:RECAST

- An adaptive platform trial that offers women with DCIS 6 months of neoadjuvant ET with the intent to determine their suitability for long term active surveillance

RECAST DCIS Study schema

Re-Evaluate Conditions for Active surveillance Suitability as Treatment



Agent 1: Elacestrant

Agent 2: Testosterone+Ai implant

Agent 3: z-Endoxifen

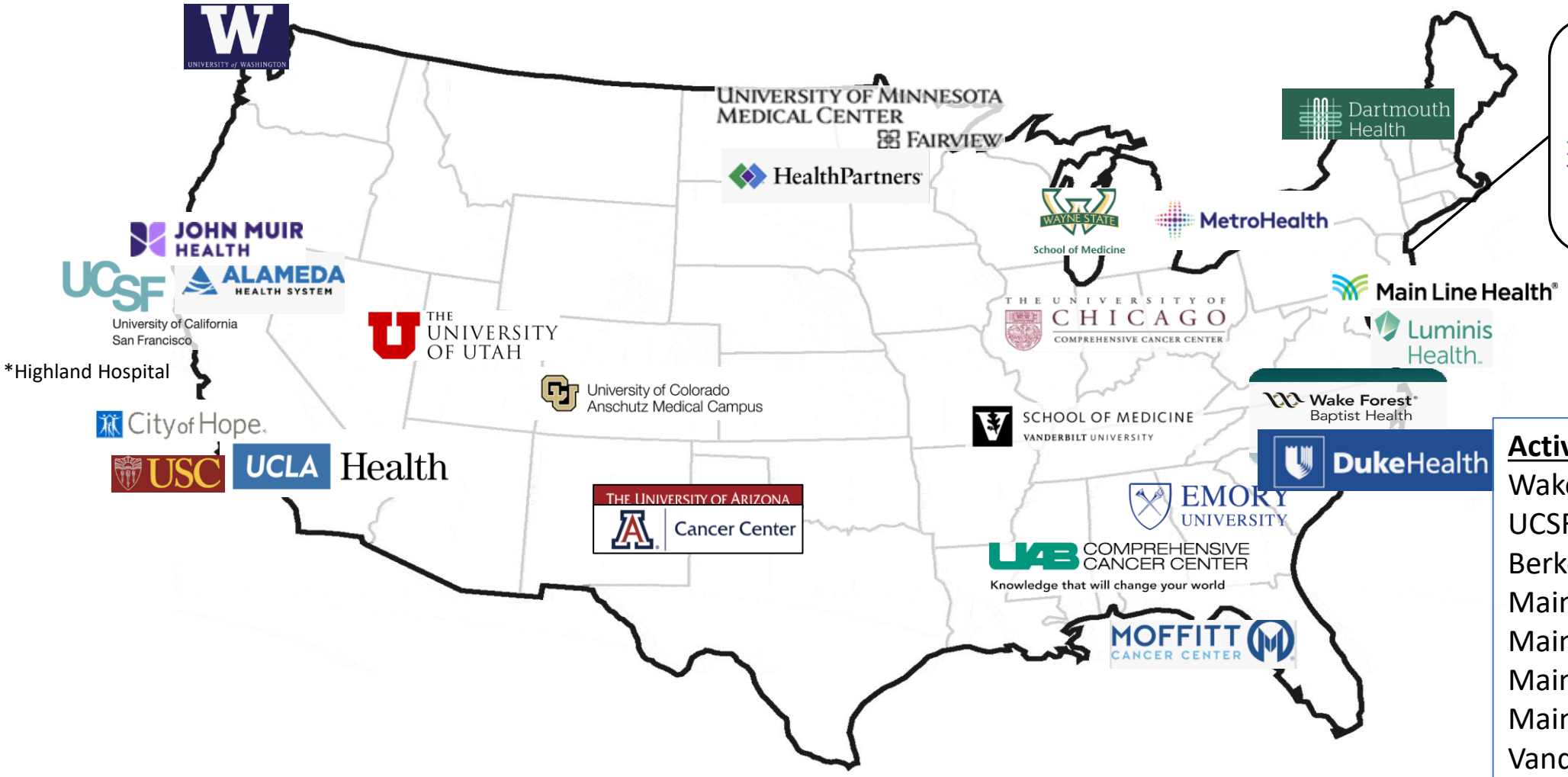
Primary Objective

- To determine whether novel endocrine therapy increases the fraction of patients who will be suitable for long term surveillance
  - Fraction of patients on active surveillance at 7 months of treatment

Secondary Objectives

- To determine whether novel ET increases the fraction of patients suitable for long-term active surveillance as measured by fraction of patients deemed to be low risk for IDC after 3 months compared to control
- Associate rate of progression to IDC with risk of categorization after 6 months of treatment at 3 years
- Asses the QOL impact of novel ET compared to standard ET using PROMIS and FACT-ES composite score
- Additional imaging objectives

30+ Institutions planned for DCIS RECAST
12 are already part of the I SPY network



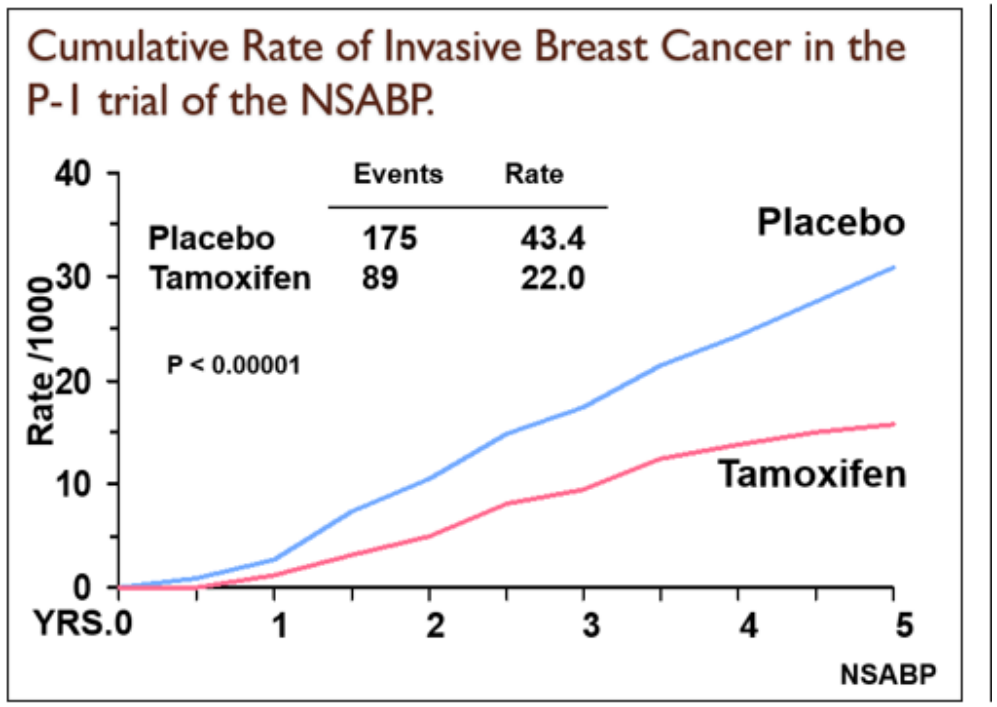
Activated:
Wake Forest
UCSF
Berkeley Outpatient Ctr
Main Line Lankenau
Main Line Bryn Mawr
Main Line Paoli
Main Line Riddle
Vanderbilt

Refining tamoxifen dose for premenopausal breast cancer risk reduction (RENAISSANCE): a Phase II single arm CPCT-Net trial. INT 23-04-01

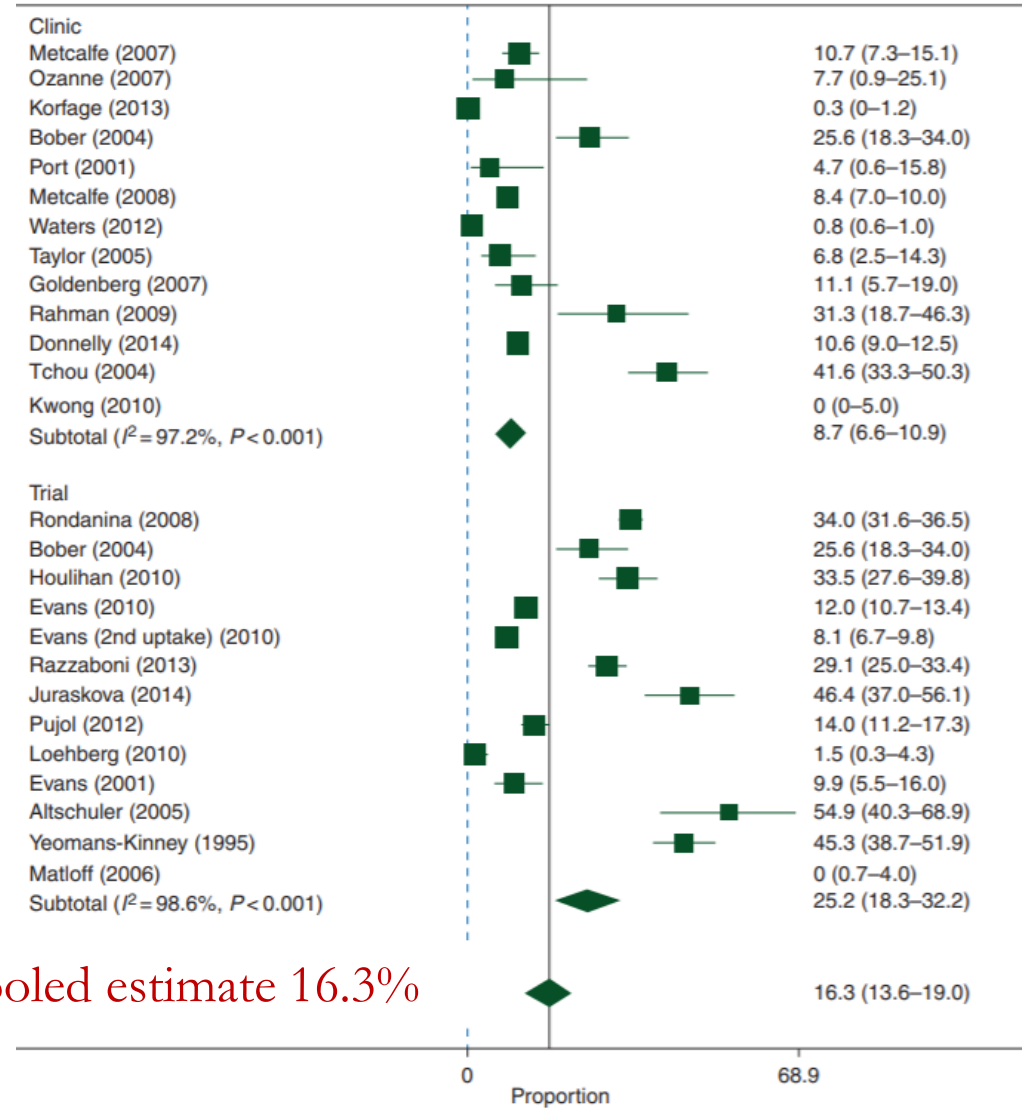
Seema Ahsan Khan	Northwestern University
Amanda L. Amin	Case Western Reserve
H.H. Sherry Chow	University of Arizona
Carol Fabian	University of Kansas
Kent Hoskins	University of Illinois Chicago
Kevin Hughes	Medical Univ of South Carolina
Tari King	Dana-Farber Cancer Institute
Melissa Pilewskie	Univ of Michigan, Ann Arbor
Parijatham Thomas	MD Anderson Cancer Center
Adetunji Toriola	Washington University
Gretchen Gierach	NCI/DCP

Tamoxifen reduces the risk of ER+ breast cancer

Tamoxifen 20 mg daily



Bernard Fisher et. al. 1998

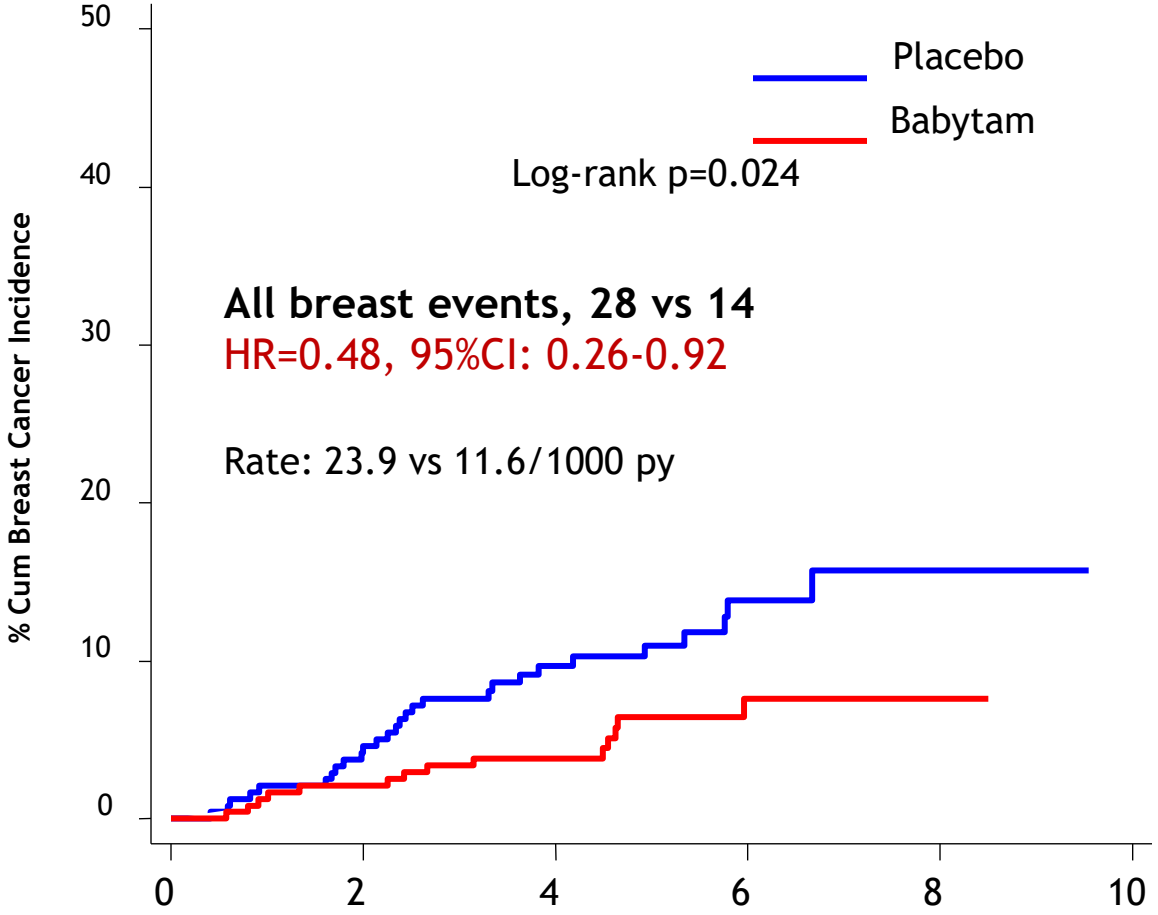


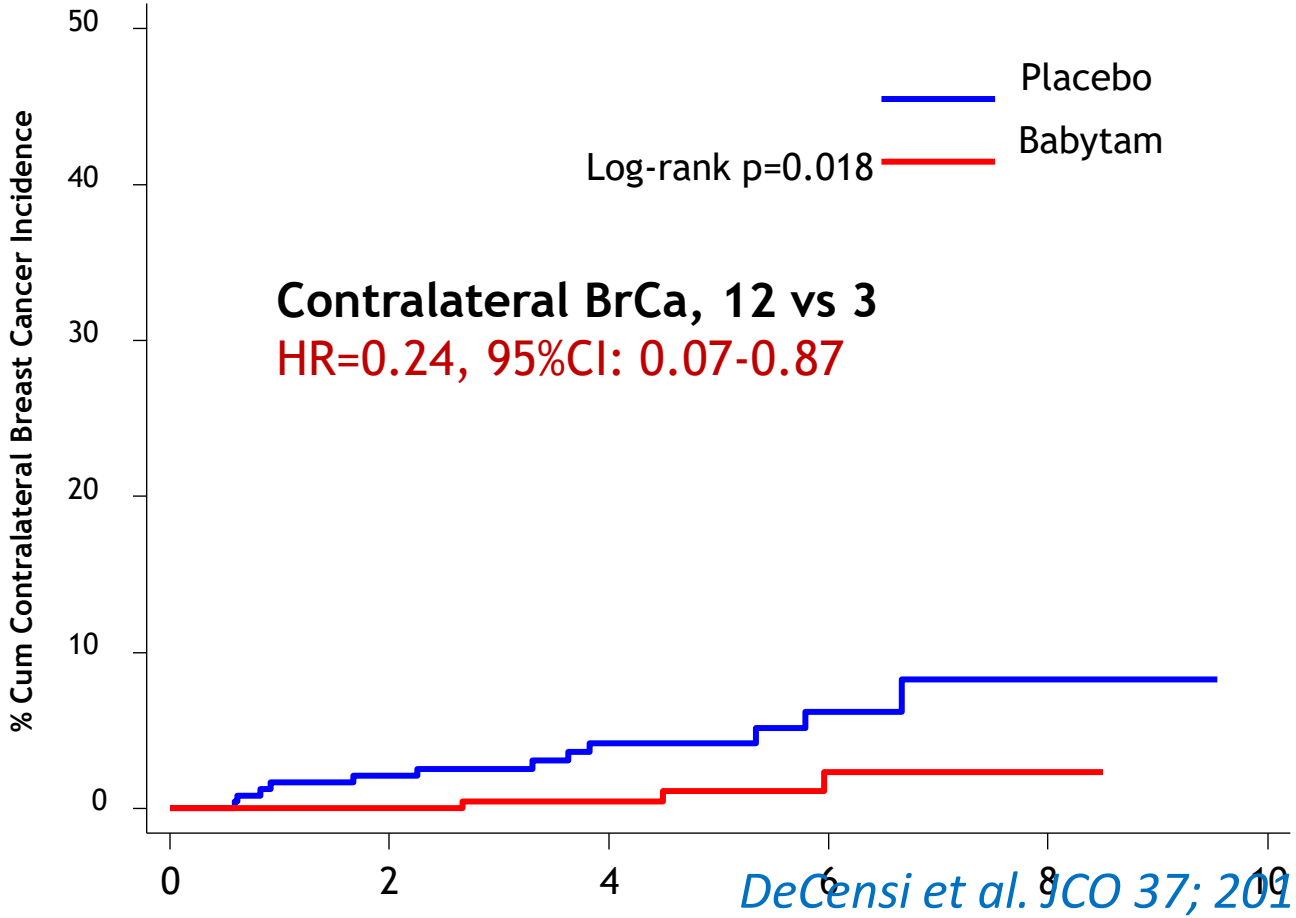
Pooled estimate 16.3%

SG Smith et. al., Annals Oncol 2016

Solution to low acceptance

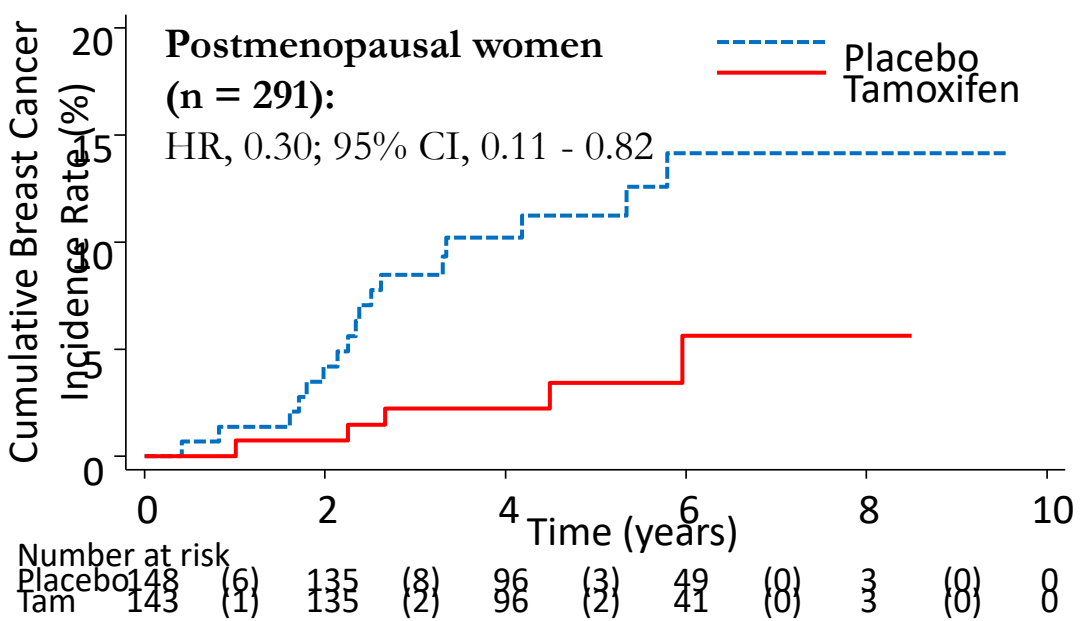
Find the minimal effective dose: Decensi et. al. TAM01 trial

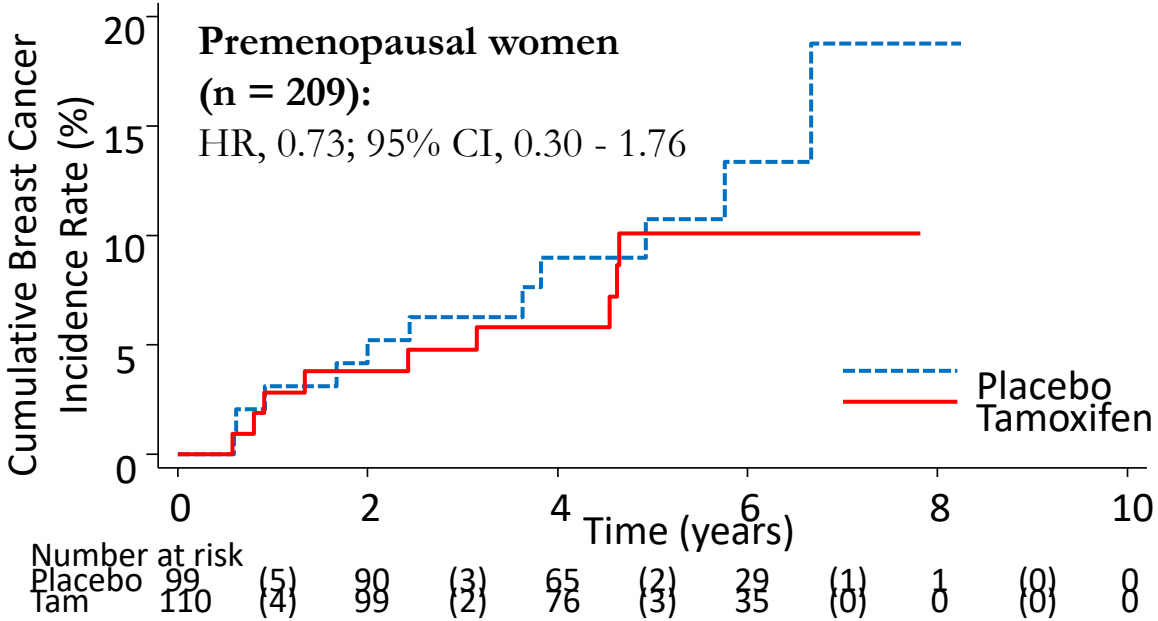




DeCensi et al. JCO 37; 2019

TAM-01 trial of low dose (5 mg) tamoxifen for breast cancer risk reduction
Results by allocated arm and menopausal status





Is this a dose effect? Do premenopausal women require a higher dose?

De Censi A et al. Clin Cancer Res. 2021 Feb 19. Online ahead of print.

TAM-01 trial of low dose (5 mg) tamoxifen for breast cancer risk reduction
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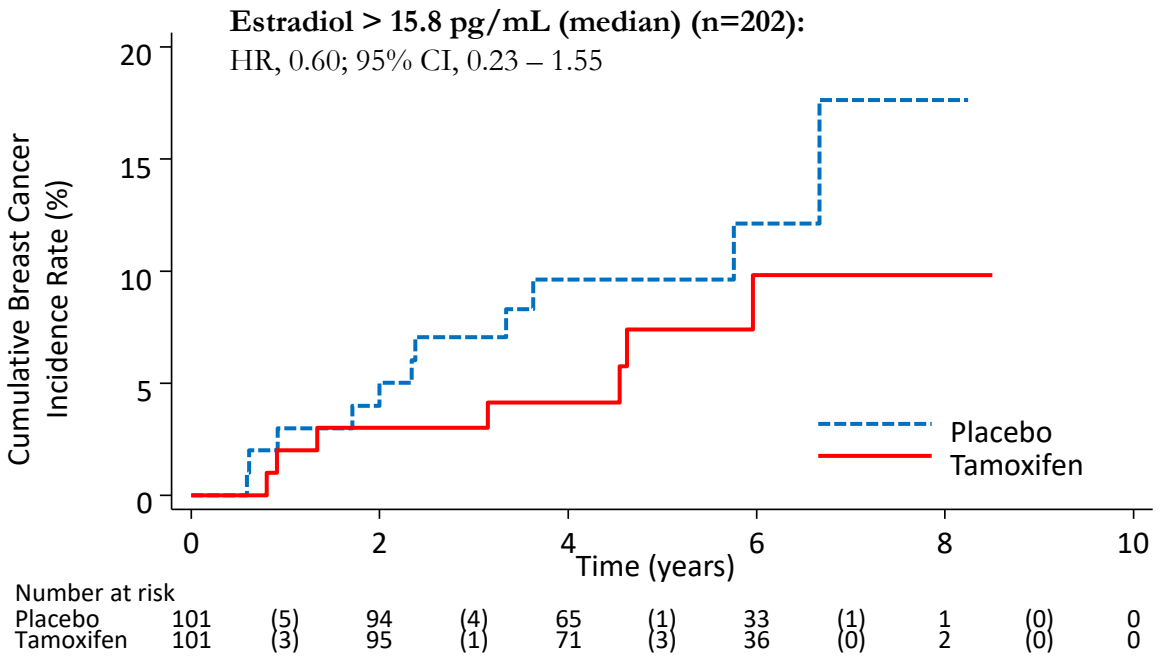

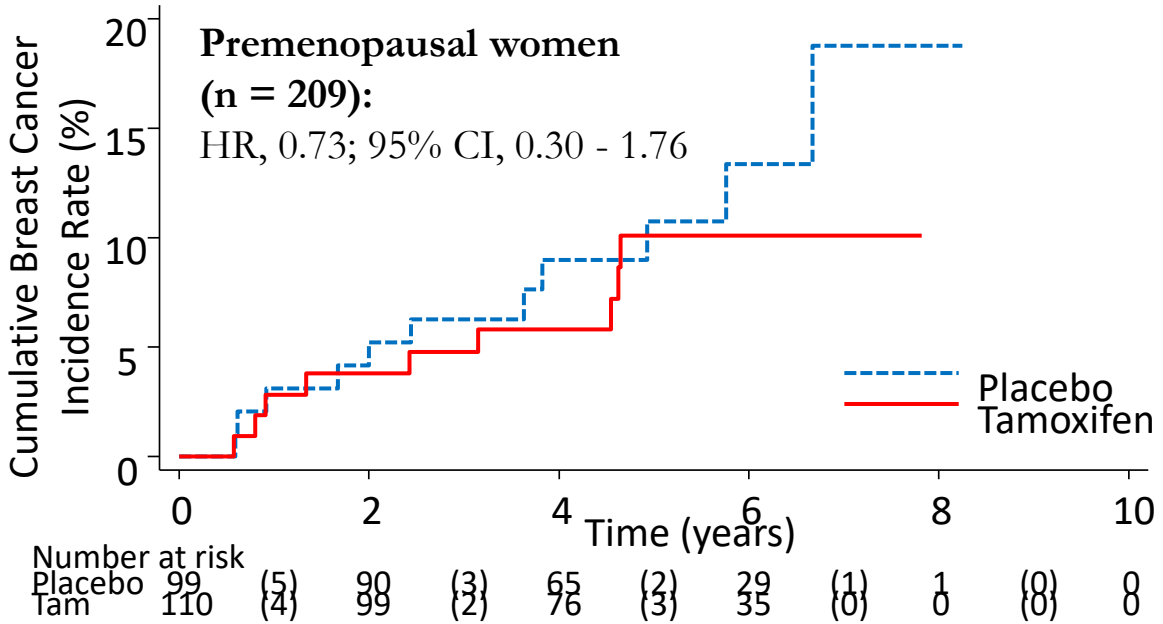

Is this a dose effect? Do premenopausal women require a higher dose?

De Censi A et al. Clin Cancer Res. 2021 Feb 19. Online ahead of print.

Tamoxifen-Induced Reduction in Mammographic Density and Breast Cancer Risk Reduction: A Nested Case–Control Study

Jack Cuzick, Jane Warwick, Elizabeth Pinney, Stephen W. Duffy, Simon Cawthorn, Anthony Howell, John F. Forbes, Ruth M. L. Warren

Manuscript received July 30, 2010; revised February 3, 2011; accepted February 18, 2011.

Table 3. Odds ratios (ORs) associated with categories of change in breast density in the tamoxifen and placebo arms*

	Tamoxifen group			Placebo group		
Change in breast density, No. (%)	Case subjects (N = 51)	Control subjects (N = 456)	OR (95% CI)	Case subjects (N = 72)	Control subjects (N = 486)	OR (95% CI)
Increase	4 (8)	16 (3)	2.13 (0.64 to 7.20)	9 (12)	57 (12)	1.23 (0.54 to 2.81)
No change	20 (39)	141 (31)	1.00 (referent)	27 (38)	206 (42)	1.00 (referent)
Reduction 5%	12 (24)	82 (18)	0.90 (0.40 to 2.04)	21 (29)	98 (20)	1.35 (0.71 to 2.58)
Reduction ≥10%	15 (29)	217 (48)	0.32 (0.14 to 0.72)	15 (21)	125 (26)	0.69 (0.34 to1.41)
P_{trend}		.001		.51		

* Odds ratios adjusted for age, breast density at baseline, history of atypical hyperplasia or lobular carcinoma in situ, and body mass index. *P* values are two-sided. CI = confidence interval.

- **Premenopausal ≥10% density decrease OR=0.27 (0.11 to 0.66)**
- Postmenopausal ≥10% density decrease OR=0.53 (0.22 to 1.28)

Tamoxifen-Induced Reduction in Mammographic Density and Breast Cancer Risk Reduction: A Nested Case–Control Study

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Low-Dose Tamoxifen for Mammographic Density Reduction: A Randomized Controlled Trial

KARISMA TRIAL,
Karolinska Institute

Premenopausal	All	placebo	1 mg	2.5 mg	5 mg	10 mg	20 mg
N completing study	474	74	85	76	78	82	70
Mean dense area change, % (95% CI)	-11.0 (-14, -8)	1.4 (-6, 9)	1.0 (.6, 8)	-13.4 (-21, -6)	-19.6 (-27, -12)	-17.0 (-24, 10)	-18.5 (-26, -11)

Eriksson M et. al. *JCO* 2021

Refining tamoxifen dose for premenopausal breast cancer prevention (RENAISSANCE)

IBIS

Tamoxifen **20 mg** causes a ≥10% breast density reduction ~50% of women which is associated with prevention success.

Density assessed by a single radiologist: dense tissue to the nearest 5%.

Density reduction is a surrogate for risk reduction

TAM 01

Tamoxifen **5 mg** daily results in a non-significant decrease in breast cancer risk in premenopausal women (HR, 0.73; 95% CI, 0.30–1.76).

No density assessment reported.

Non-significant risk reduction with 5 mg dose; do some premenopausal women need a higher dose?

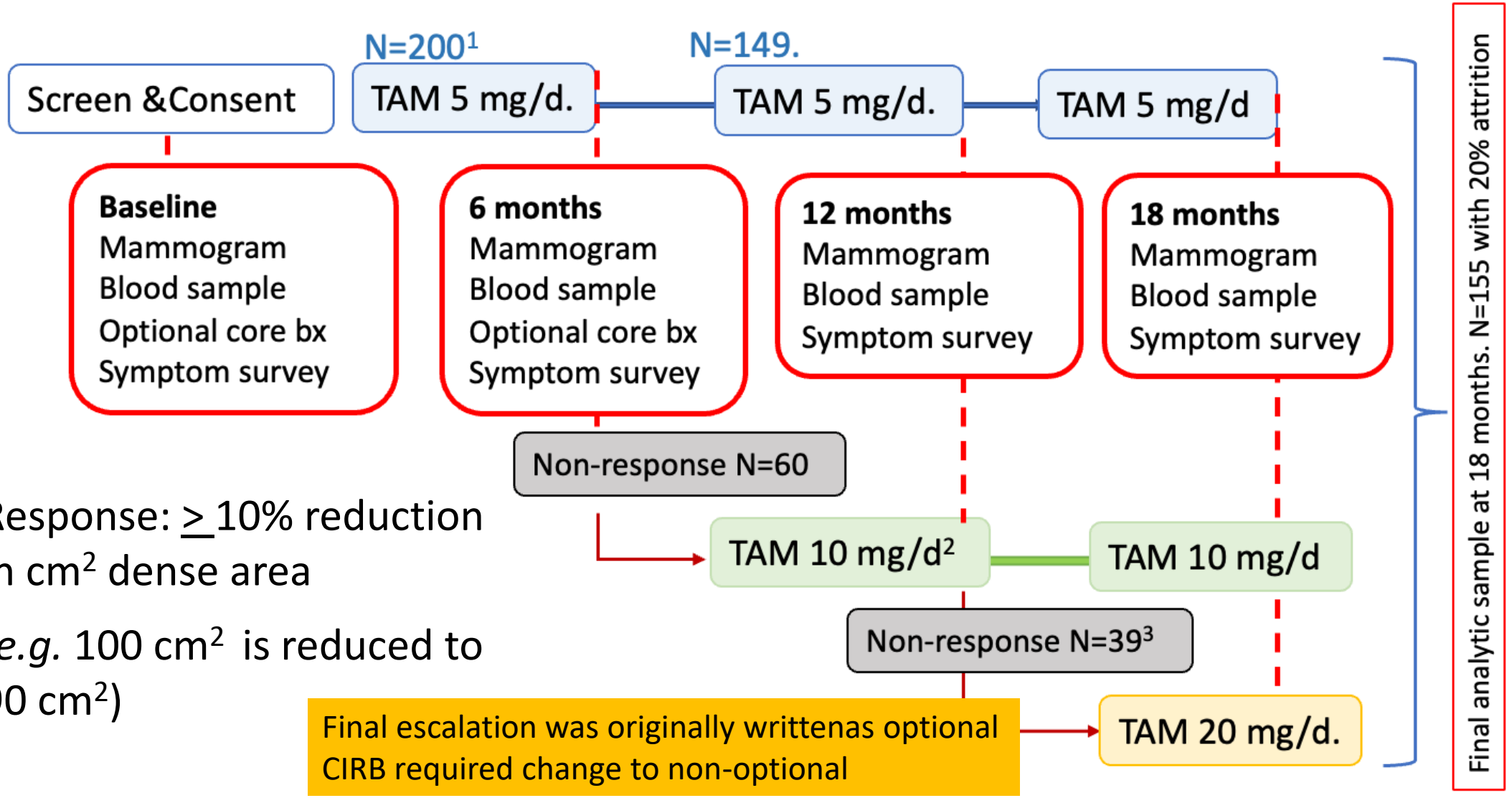
KARISMA

Tamoxifen **2.5 mg** daily is equivalent to higher doses for breast density reduction in 95% of premenopausal women

Density assessed by STRATUS; ≥10% decrease in dense area in 70% of women receiving 5 mg dose.

Can we use dense area reduction (DAR) as a surrogate endpoint for tamoxifen efficacy to personalize the tamoxifen dose for premenopausal women?

RENAISSANCE: premenopausal women eligible for tamoxifen to reduce breast cancer risk



Response: ≥ 10% reduction in cm^2 dense area

(*e.g.* 100 cm^2 is reduced to 90 cm^2)

Imaging workflow for density measurement

Institutional server?

TRIAD
ACR IMAGE AND INFORMATION EXCHANGE

Transfer of Images and Data
An American College of Radiology
cloud-based platform,
Supports the exchange of images
and associated data for clinical trials.

IMS

Information Management Systems,
NCI data repository
Supports clinical trials.

Study site & participant

REDCap
Research Electronic Data Capture

Karolinska Institutet

Density read

Endpoints and statistical plan

- **The primary endpoint is the proportion of women who respond to treatment at 18 months**.
- Response: **10% reduction in absolute dense area** measured on processed mammogram images.
- Expect a **10% absolute improvement in response rates**, from 70% to 80% through dose escalation.
- A sample size of **n=155 evaluable women** would provide 82% power with two-sided α=0.05 to detect such a difference based on the exact test for one proportion
- Allowing for attrition, **enrollment of 200 women will be required**

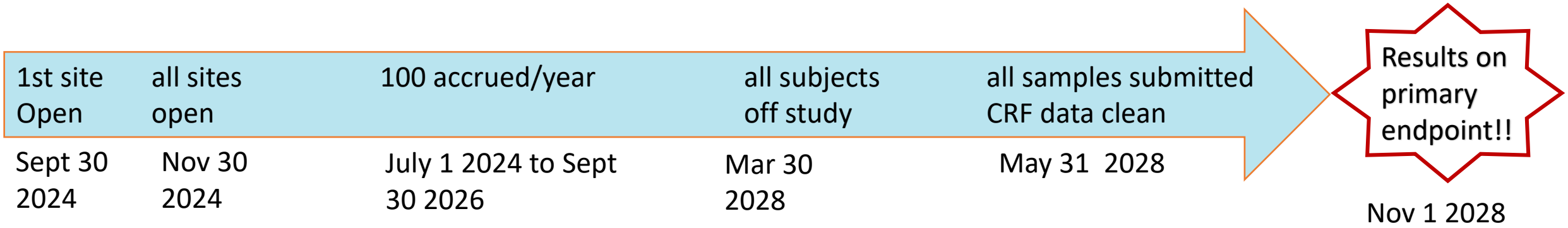
Advancing the science: secondary endpoints

- **Radiomics**…. Assessing **risk reduction** following tamoxifen intervention
- **Breast tissue correlates** (biopsies at entry and 6 months in 30% of subject)
  - Collagen feature analysis (Sherry Chow)
  - Gene expression profiles (collaboration with Tunji Toriola)
- Polymorphisms related to **tamoxifen metabolism** ….. May be more important at lower doses
- **Polymorphisms common to breast density and breast cancer risk** may influence density response
- **Intrinsic resistance to tamoxifen**…. Dose may make no difference
- **Treatment duration** and density reduction…. increase over time?
- Effect of dose on **symptoms**

Accrual goals

- 200 participants, 10 sites
  - **3 open so far: Northwestern, Michigan, Arizona**

- 20/site, 1/month, 24 months
  - **6 enrolled at Northwestern in 1st month**



eringile@umich.edu
https://cancer.kines.umich.edu
@erindgiles

Beneficial effects of bazedoxifene plus conjugated estrogens (Duavee®) on breast cancer risk and metabolic biomarkers in a rat model of obesity, menopause, and breast cancer

Erin Giles, Katherine Cook, Ramsey Jenshcke, Katherine Sanchez, Karen Corleto, Stephen Hursting, Bruce Kimler, and Carol Fabian

Menopause & Breast Cancer Risk

Menopause transition:

↑ vasomotor symptoms, weight / visceral fat, & insulin resistance

Tamoxifen: effective for prevention, but causes vasomotor symptoms; possible detrimental metabolic effects in women with excess body weight

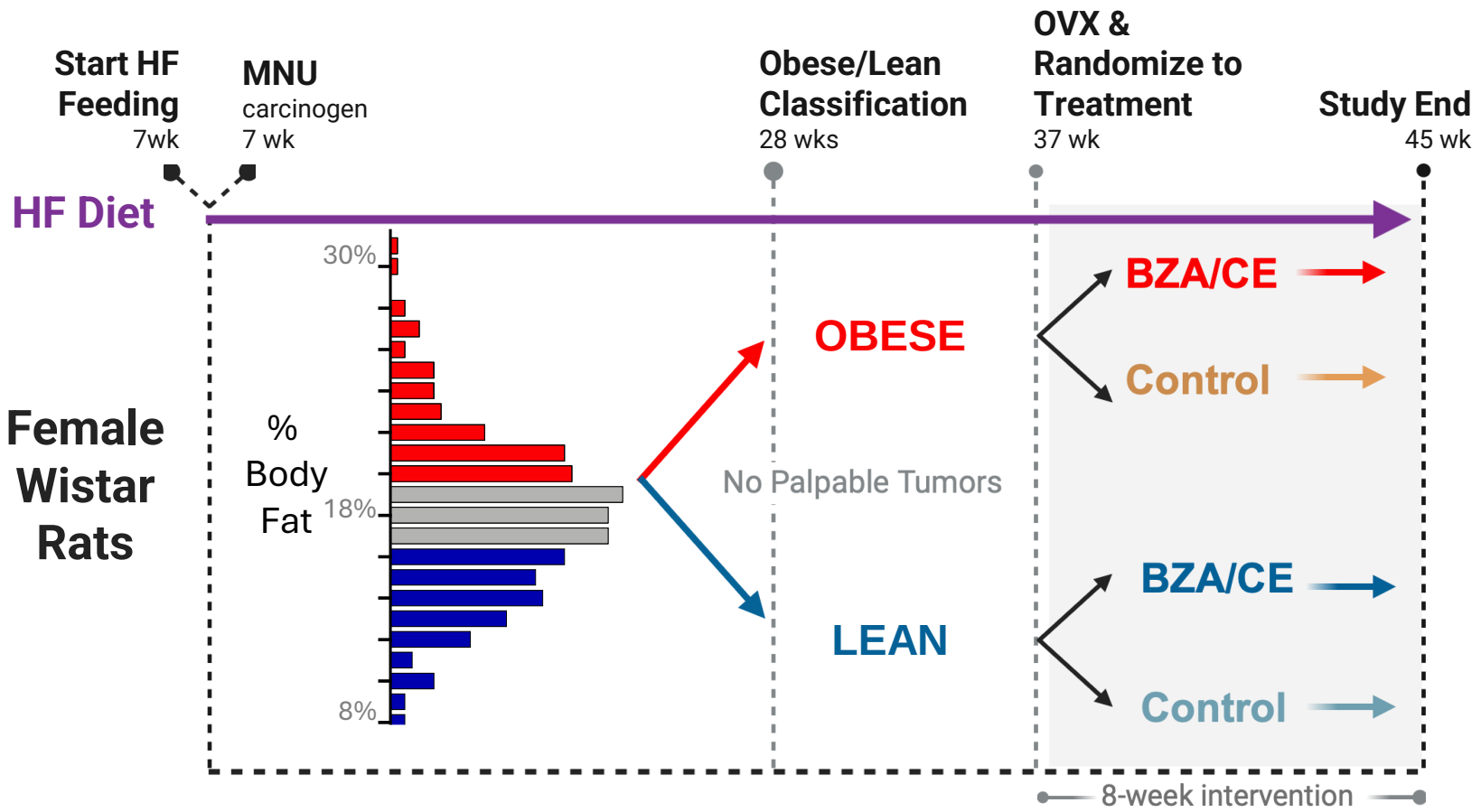
Duavee®: Bazedoxifene (20mg) + conjugated estrogen (0.45mg)

- FDA approved for relief of hot-flashes
- Preclinical & early phase human studies suggest potential for cancer prevention
  - ↓ mammographic fibroglandular volume *(Fabian et al, Cancer Prevention Res 2019)*
  - ↓ benign breast tissue proliferation

Goal: To identify effects of BZA/CE (Duavee®) on metabolic outcomes under lean and obese conditions using a rat model of postmenopausal breast cancer risk

(*parallel to an ongoing clinical trial)*

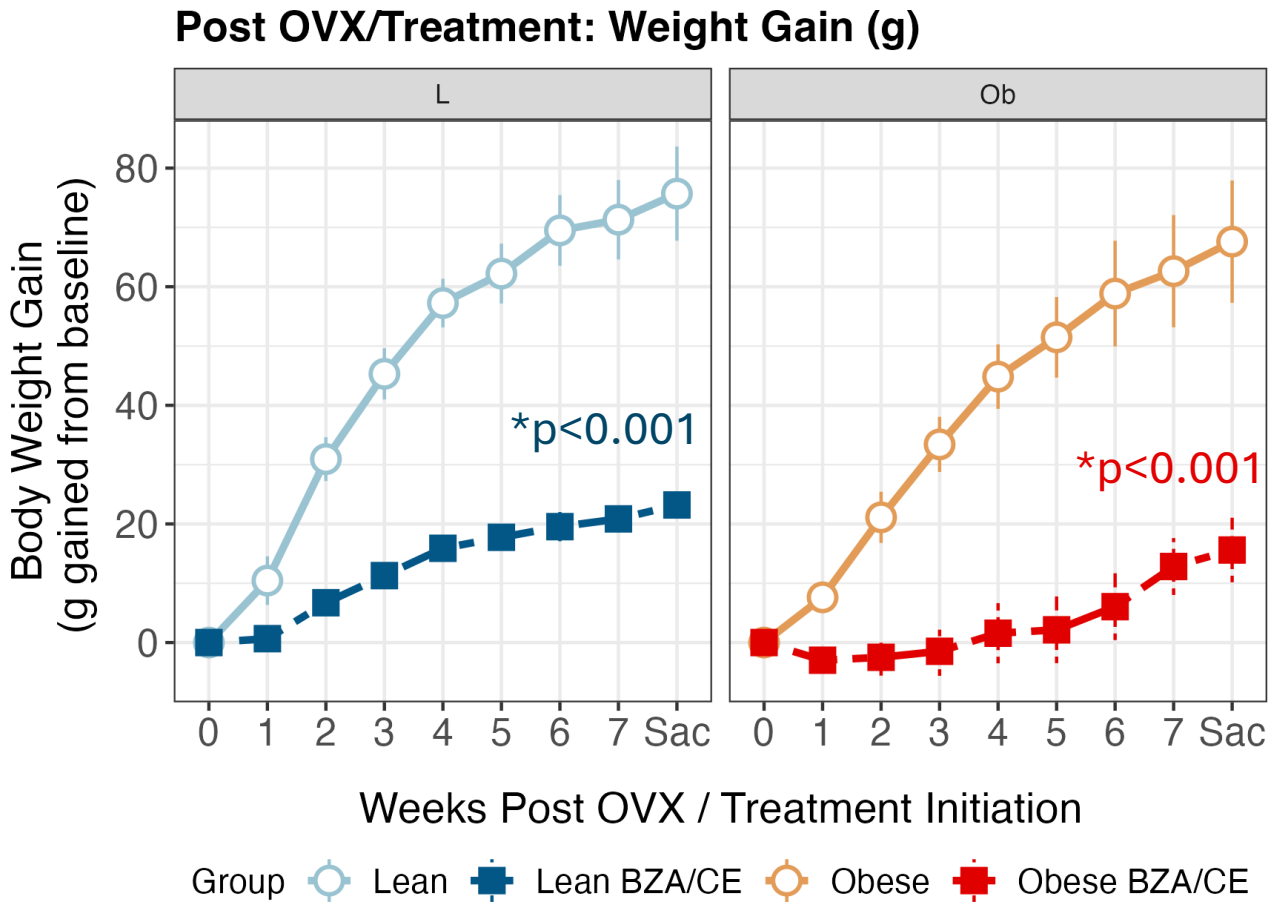
Study Design

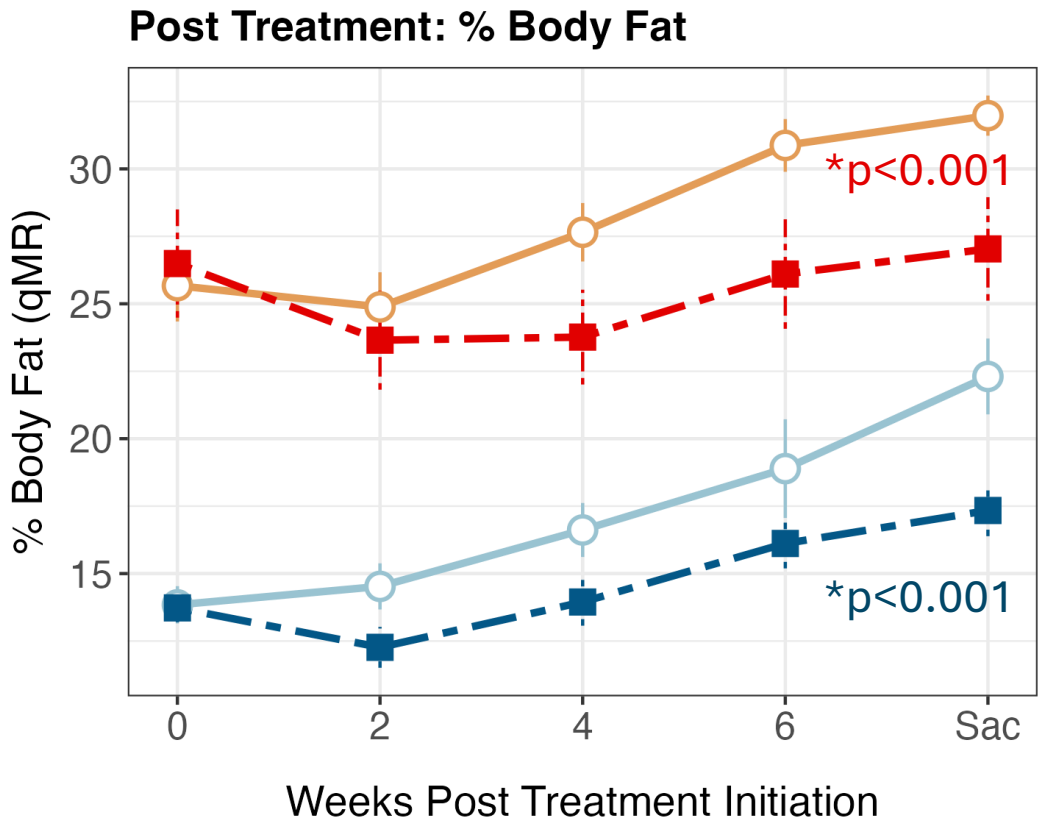


Assessed:

- Food Intake
- Body Weight
- Body Composition (qMR)
- Plasma Metabolites
- Tumor Growth
- Body Fat Distribution (Fat Pad Weights)

BZA/CE: Blunted OVX-Induced Weight Gain & Adipose Deposition in both Lean and Obese Rats



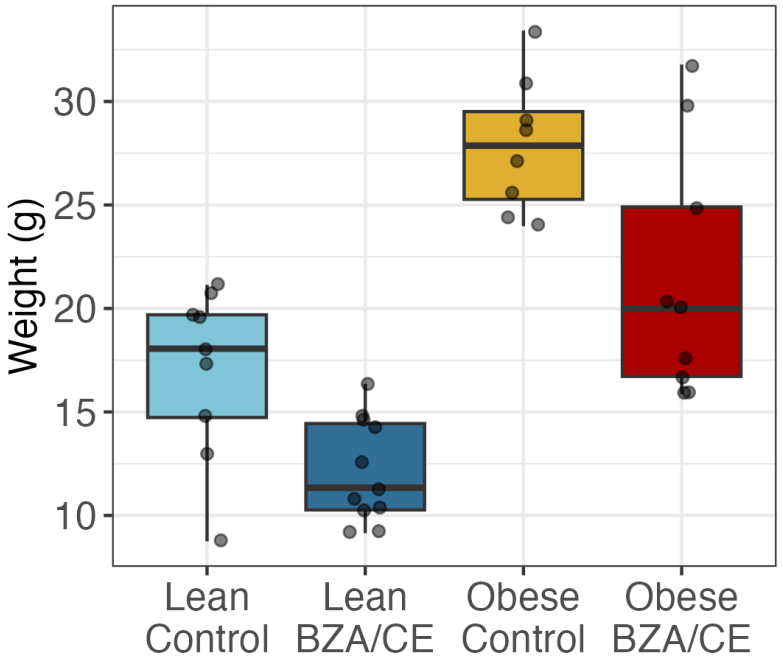


Unpublished Data

BZA/CE: Preferentially Blunted Adipose Tissue Deposition

↓ Visceral, Mammary, and Gonadal adipose depot weights

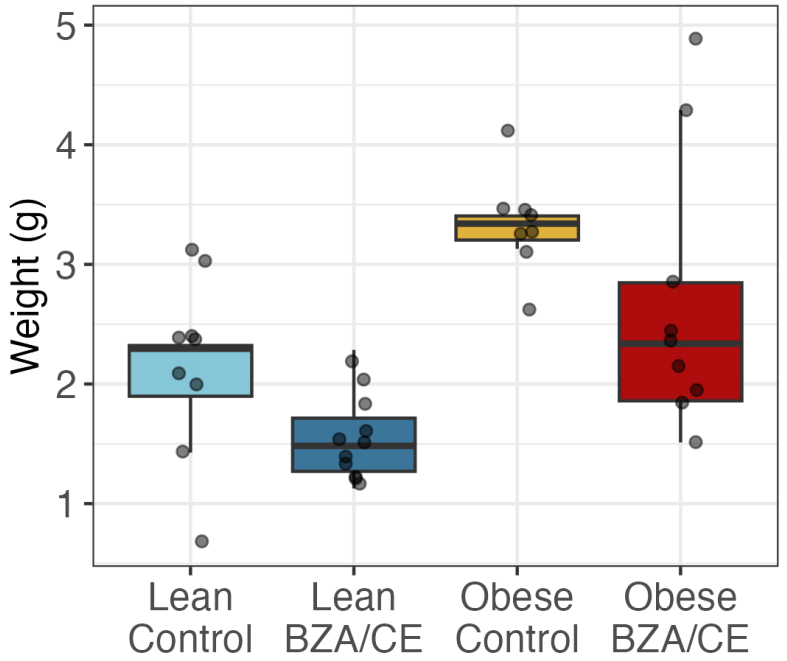
Visceral Adipose



2-Way Anova, Treatment: p<0.001
Obesity: p<0.001

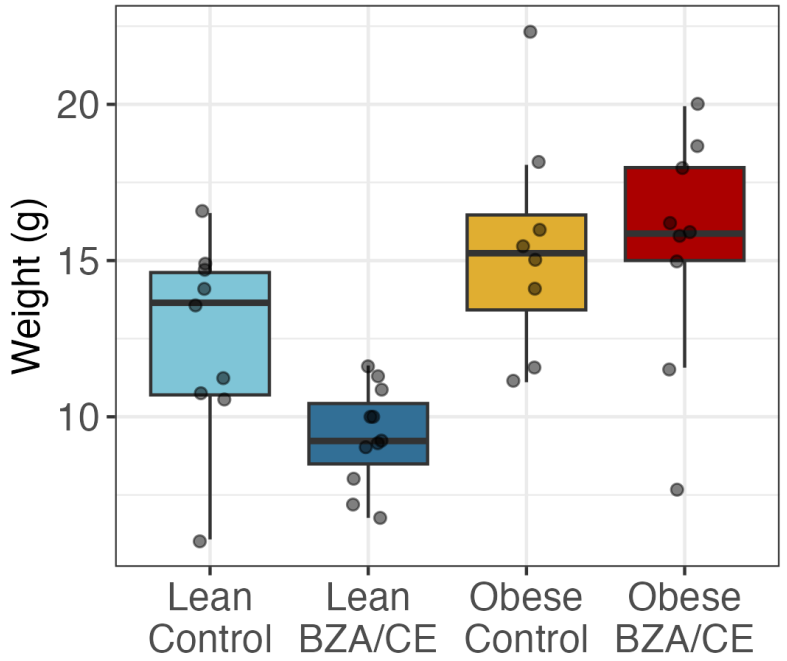
(mesenteric, retroperitoneal, pericardial)

Mammary Adipose



2-Way Anova, Treatment: p<0.05
Obesity: p<0.001

Gonadal Adipose

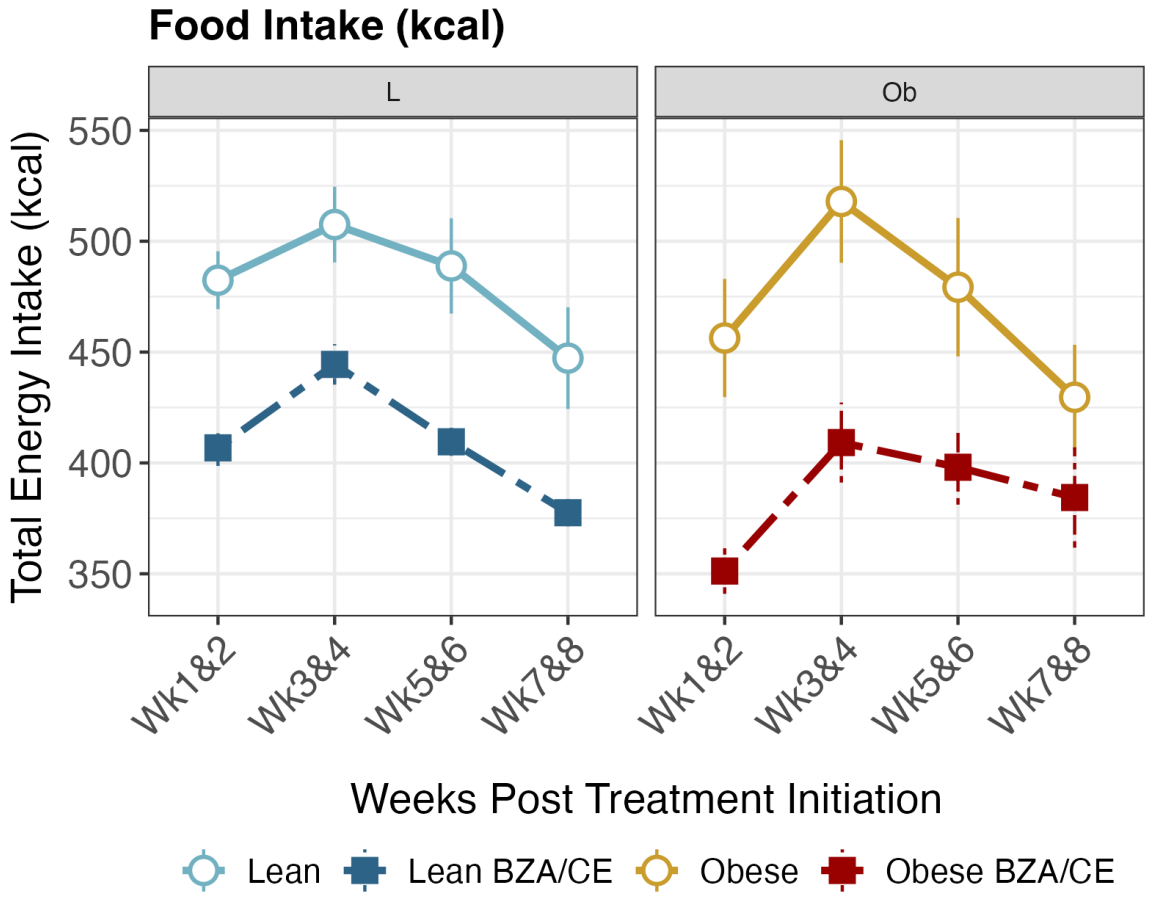


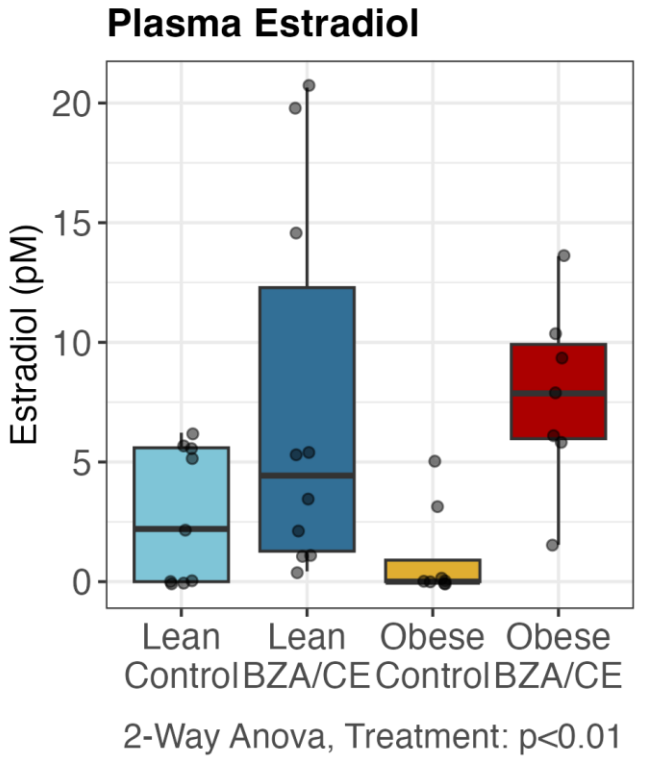
2-Way Anova, Treatment: p<0.08
Obesity: p<0.001

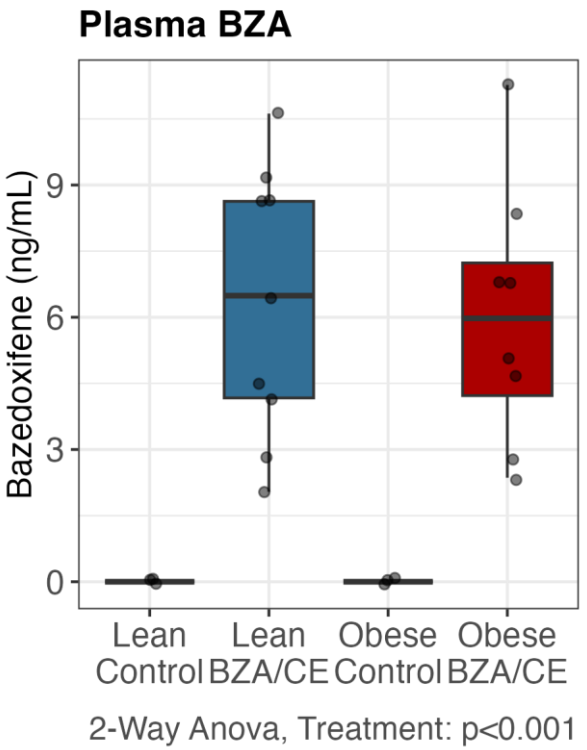
Unpublished Data

Weight difference likely driven, at least in part, by reduced food intake

Due to higher circulating E2 and/or BZA





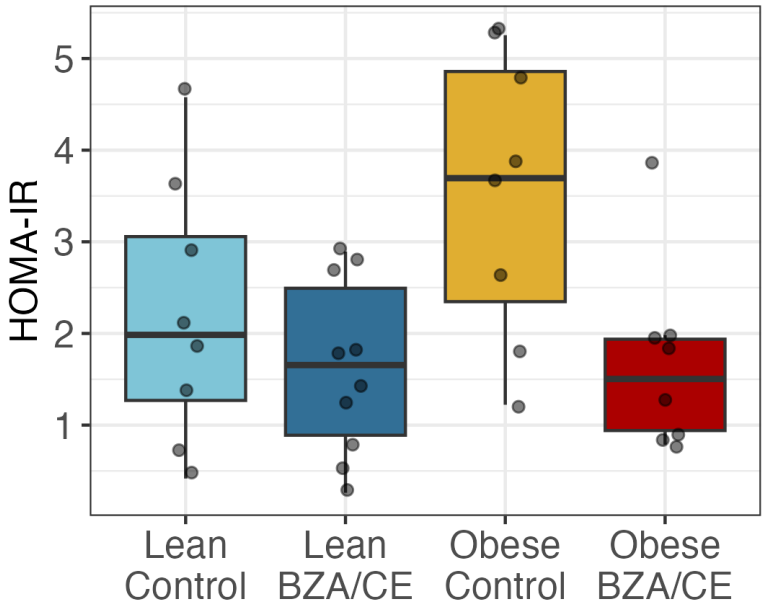


Unpublished Data

BZA/CE: Improved markers of metabolic health

Circulating markers: ↓ HOMA-IR & Cholesterol; Does not increase TG (as does Tamoxifen)

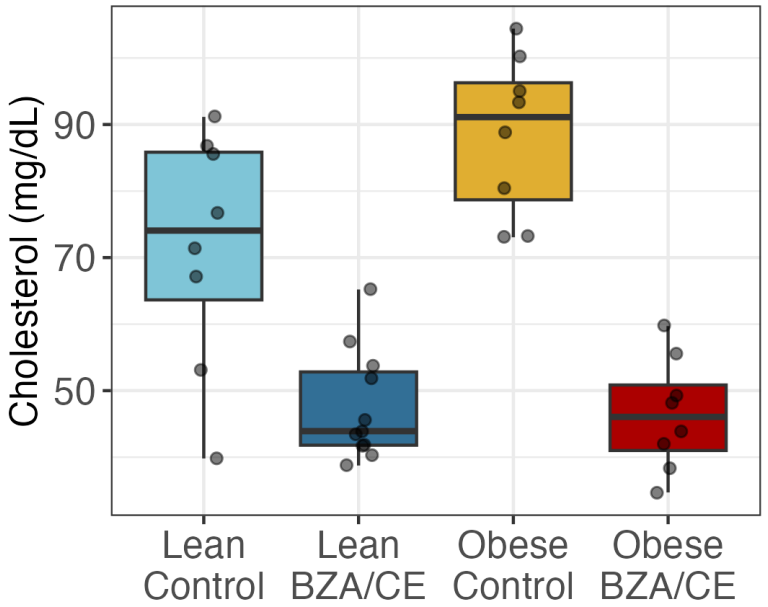
HOMA-IR



2-Way Anova, Treatment: p=0.01

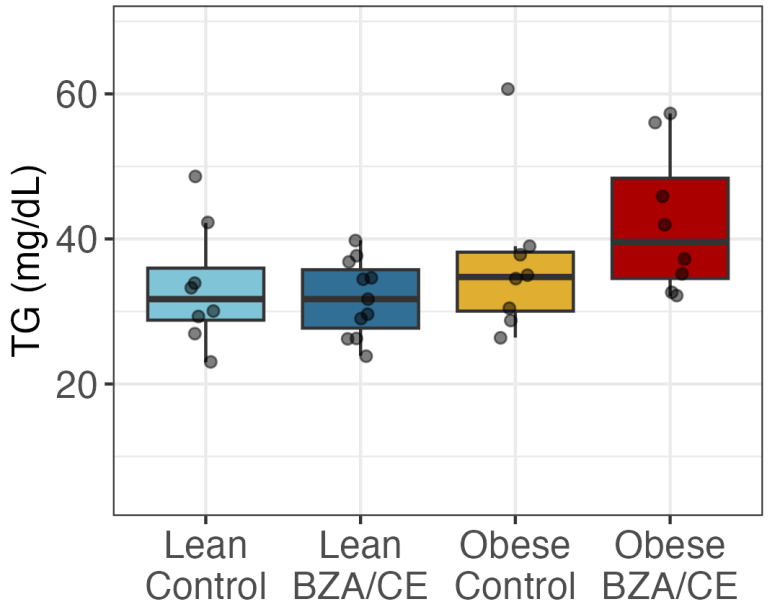
Due to ↓ in both insulin & glucose

Cholesterol



2-Way Anova, Treatment: p<0.001
Obesity: p=0.08
Interaction: p<0.01

TG

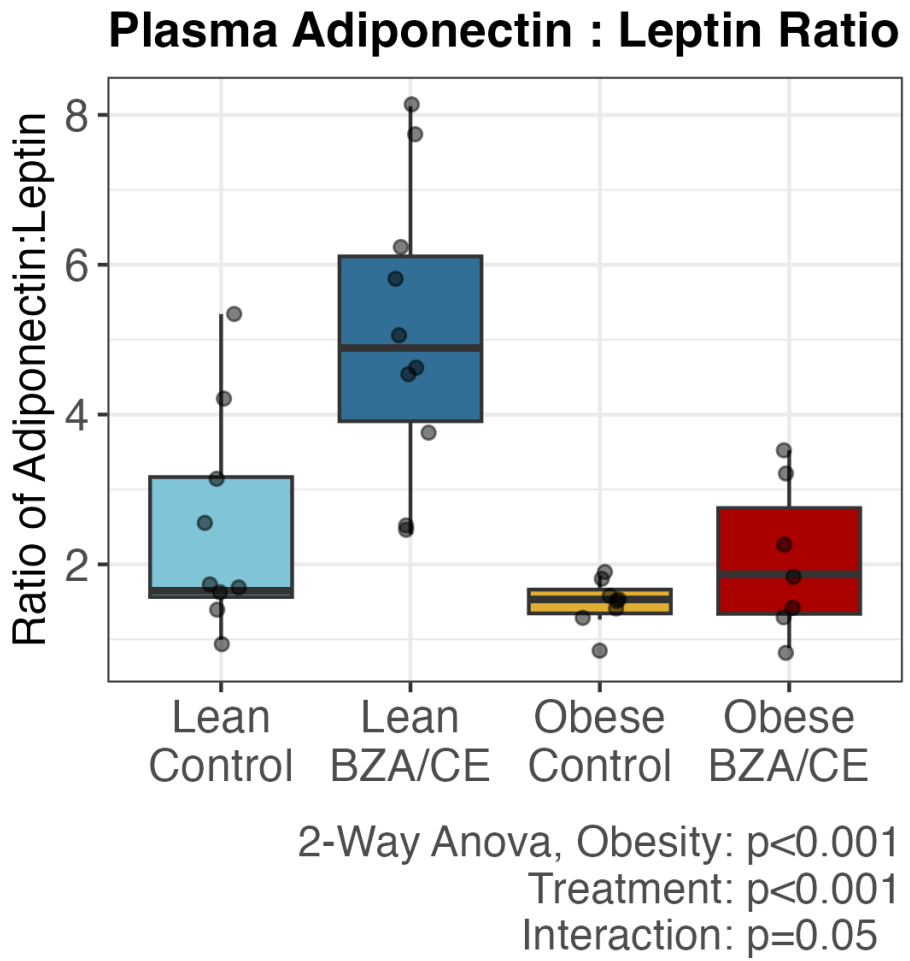


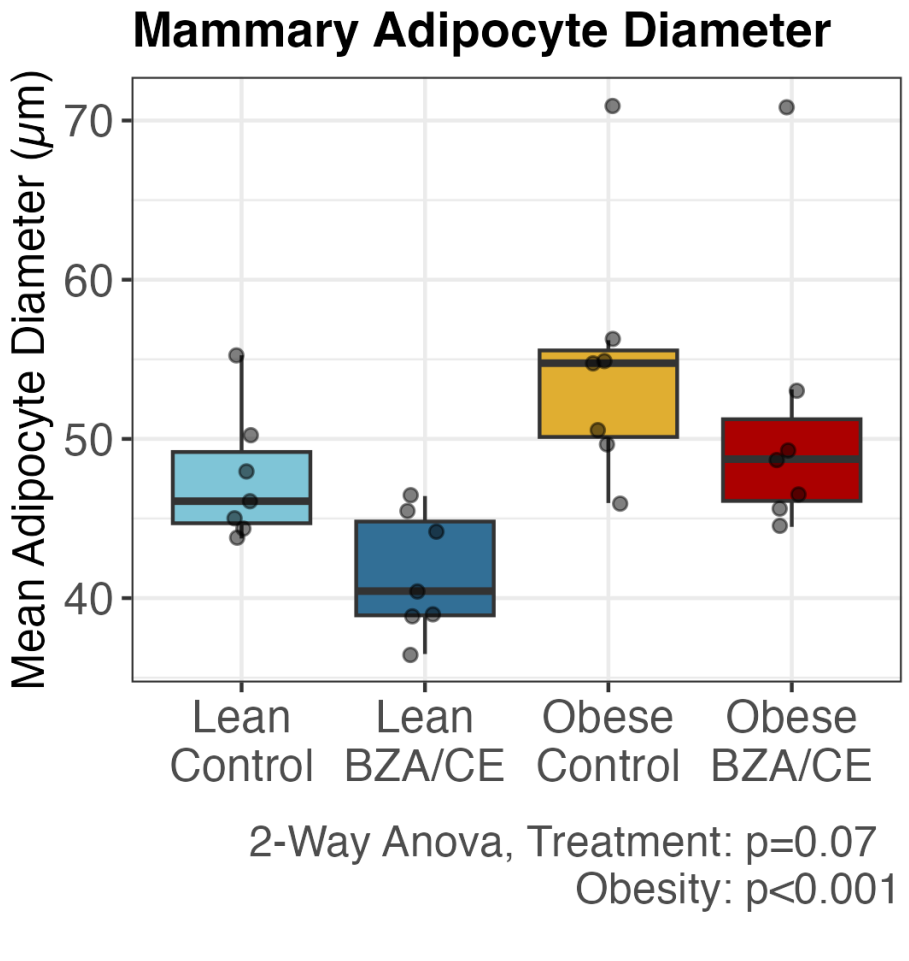
2-Way Anova, Obesity: p<0.05

Unpublished Data

BZA/CE: Improved markers of metabolic health

Mammary Adipose (Tumor Microenvironment): ↑ A:L Ratio, ↓ Adipocyte Size





Unpublished Data

BZA/CE: Beneficial changes in gene expression in the MG

Suggest reduced tumorigenic environment

BZA/CE vs Control:

Obese:

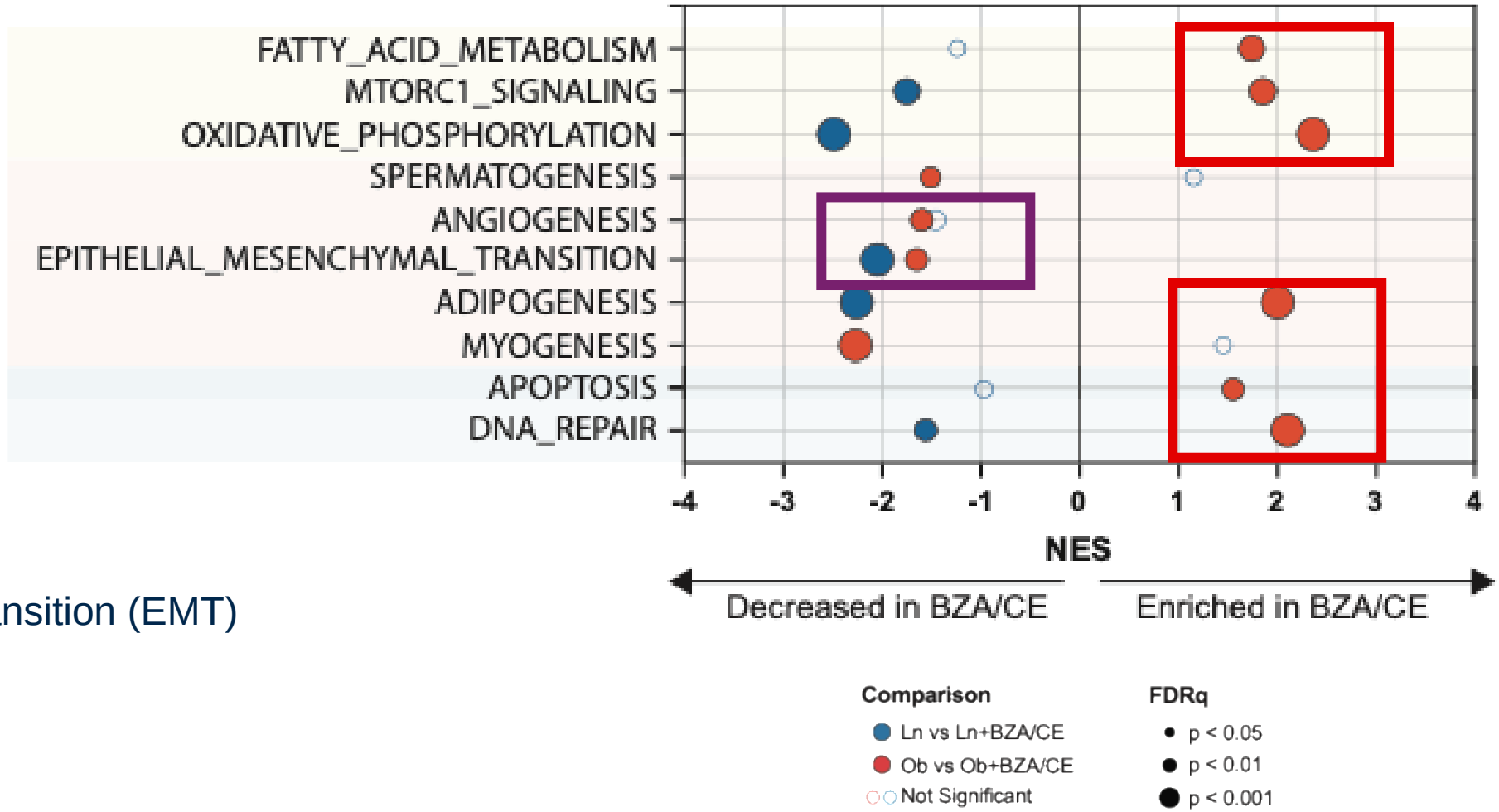
- ↑ Fatty Acid Metabolism
- ↑ Oxidative phosphorylation
- ↑ Adipogenesis
- ↑ Apoptosis & DNA Repair

Both Lean & Obese

- ↓ Angiogenesis
- ↓ Epithelial-Mesenchymal transition (EMT)

Gene Set Enrichment Analysis (GSEA)

Pathways Altered in Response to BZA/CE



Unpublished Data

Summary & Conclusions

In the rat model, **Bazedoxifene + Conjugated Estrogens** (Duavee ®)

- ✓ Blunted OVX-induced weight gain & fat deposition
- ✓ Improved metabolic health
- ✓ Beneficial gene expression changes in the mammary gland
  - No evidence that BZA/CE promoted tumor development

These data support BZA/CE as an agent with potential beneficial effects on **breast cancer risk reduction** & **improvements in metabolic health** in women with obesity

Parallel study in older, ovary-intact rats shows similar beneficial effects (modeling perimenopausal women)

Giles Lab

Karen Corleto
Ramsey Jenschke
Danilo Landrock
Katherine Sanchez
Emma Kortmansky
Taylor Daniels
Charlotte Gibson
Amanda Kucinskas

Samantha Foster
Tara Mahmood
Sarina Obeid
Grace Qian
Kaycee Khuat
Grace Suter
Emma Bailey

Carol Fabian & Bruce Kimler (KUMC)

Steve Hursting (UNC-Chapel Hill)

Katherine Cook (Wake Forest)

NIH NATIONAL CANCER INSTITUTE

TREC Transdisciplinary Research on Energetics and Cancer Centers

American Institute for Cancer Research

Center for Women's Health Research

CancerCure

Cancer Prevention & Research Institute of Texas

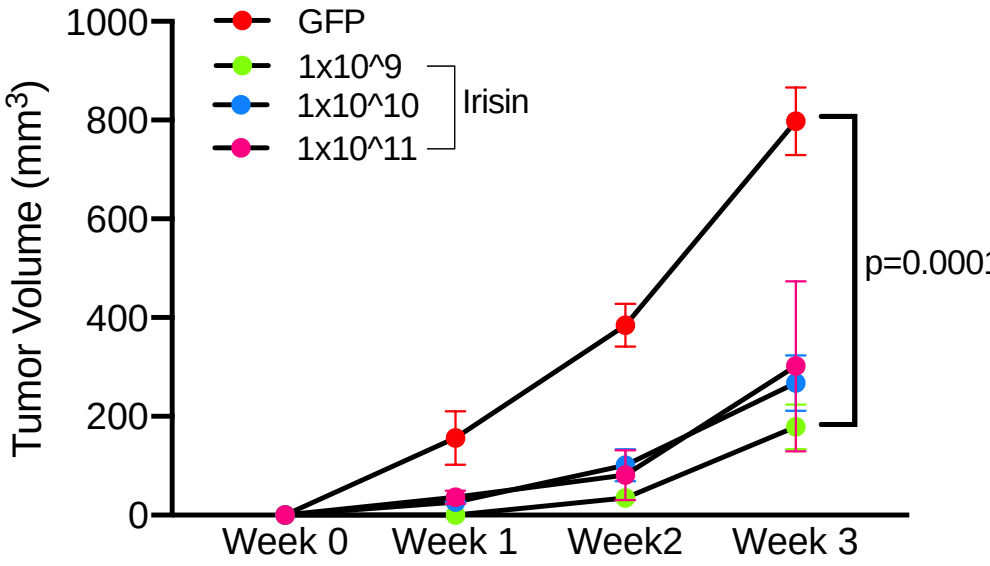
Resistance and aerobic Exercise for Prevention in women with Dense breasts (REP-D)

Jennifer Ligibel, MD

Co-PI's: Bruce Spiegelman, PhD; Rinath Jesselsohn, MD

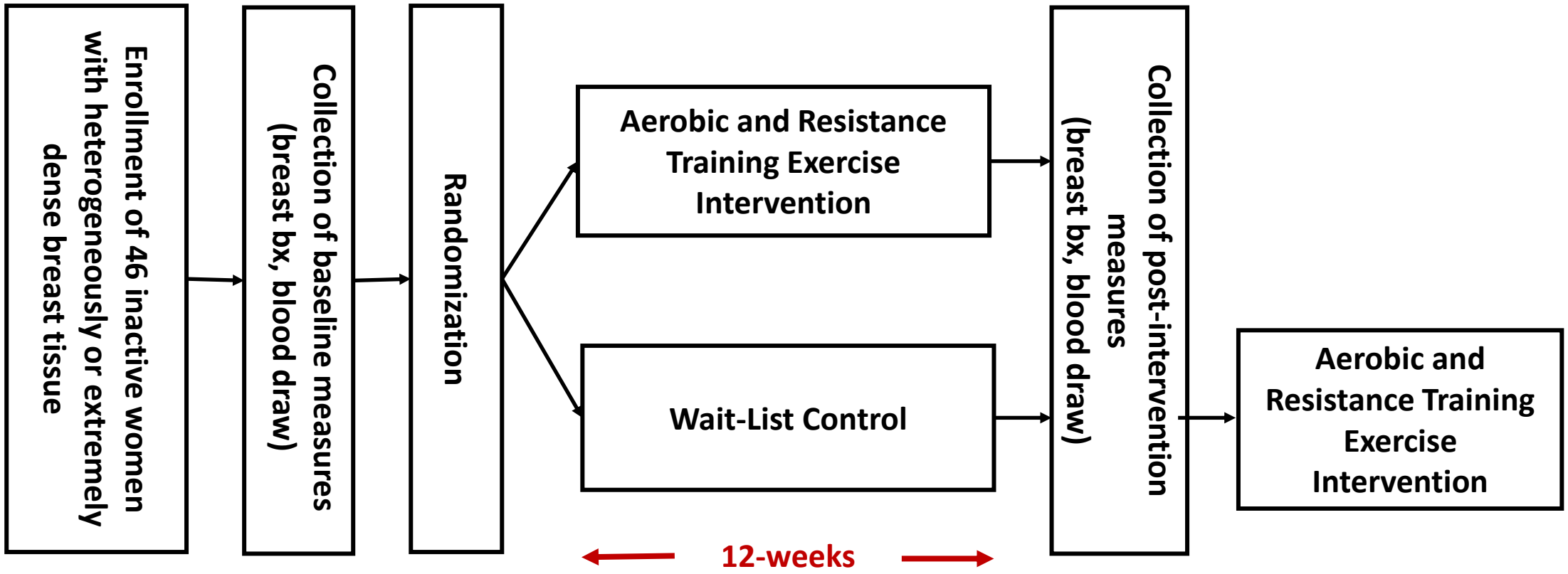
Physical activity is linked to lower breast cancer risk

- Observational evidence demonstrates an inverse relationship between physical activity and breast cancer risk
- Animal models show that physical activity reduces cancer incidence and suppresses tumor growth
- Mechanistic studies suggest that physical activity leads to upregulation of immune and inflammatory pathways in murine models
- Data from Spiegelman's lab suggest that effects of exercise may be mediated through the myokine irisin



Thompson et al. Cancer Prev Res (Phila). 2010 Nov; 3(11): 1484–1492; Adapted from Pedersen et al, Cell Metabolism, 2016; Lahart et al. Acta Oncol. 2015 May;54(5):635-54

Resistance and endurance Exercise for Prevention in women with Dense breasts (REP-D)



Clinical Objectives

- **Evaluate the impact of an exercise intervention (vs. wait-list control) on the following in women at increased risk of breast cancer by virtue of increased breast density:**
  - Circulating irisin (primary outcome)
  - Immune and proliferative markers in benign breast tissue
  - Circulating inflammatory and immune biomarkers
- **Explore the relationship between changes in circulating irisin and changes in immune and proliferative markers in benign breast tissue in women with increased breast density.**

Patient Population

Eligibility Criteria:

- Women under the age of 60
- Heterogeneously dense/extremely dense (BIRADS C or D) breast tissue on most recent mammogram
- Physically inactive; engaging in <60 minutes of moderate or vigorous intensity physical activity/week
- No prior history of breast cancer
- Not using oral contraceptives, endocrine therapy, or hormone replacement therapy
- Not pregnant or breastfeeding

Exercise Intervention

- Supervised, 12-week program aerobic and strength training program
- Delivered through 2 in-person or remotely supervised sessions per week plus additional home-based aerobic exercise
    - Zoom-based training
- Participants receive Fitbit/bike/weights
- Intervention goals:
    - 150 minutes of moderate/vigorous intensity aerobic activity
    - 40 minutes strength training

Study Measures

Measures collected at baseline and 12-weeks

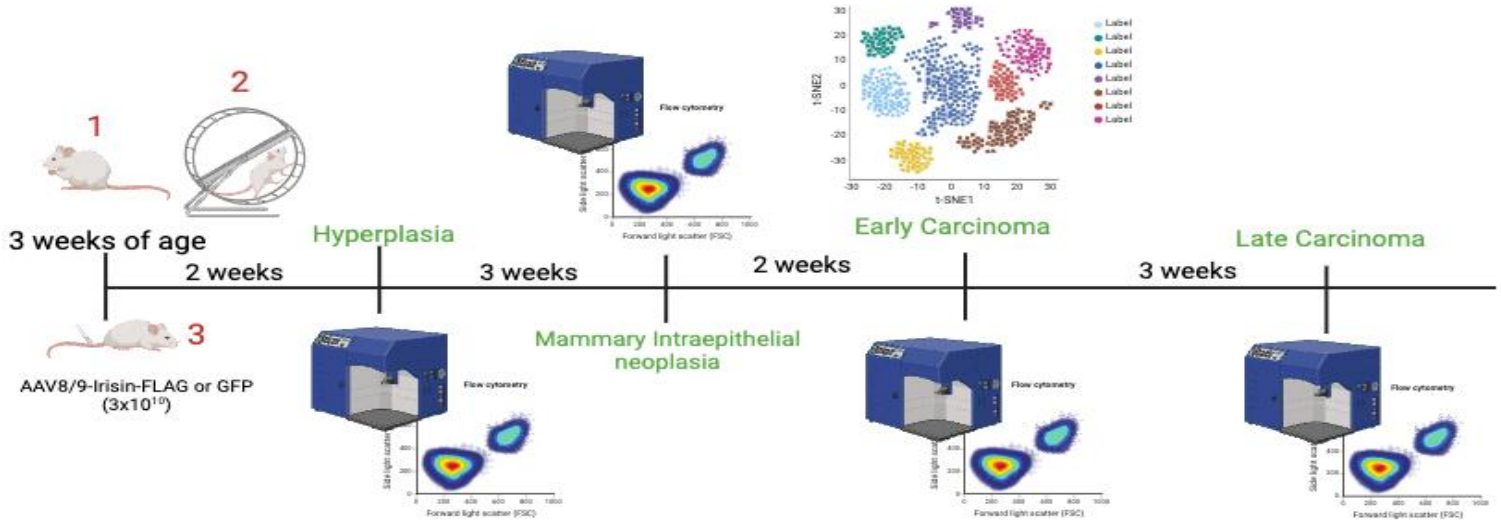
Measure	Screening	Baseline	After 1st Ex Session (Ex group only)	12-weeks
Screening exercise assessment	x			
Mammogram*	x			
Biopsy of benign breast tissue**		x		x
Medical history and demographic questionnaires		x		
7-Day Physical Activity Recall		x		x
Submaximal treadmill test		x		x
10-Rep Max test		x		x
Anthropometric measures		x		x
Blood draw		x	x	x

***Mammogram must be within 12 months**

****Biopsy collected under ultrasound guidance; luteal phase if premenopausal; mirror-image site in contralateral breast biopsied post-intervention**

Pre-Clinical Aims

- **Evaluate the immuno-modulatory role of irisin in mammary tissue of high-risk female mice, prior to tumor initiation.**
  - Evaluate the effect of irisin in high risk and early mammary atypia
  - Identify unique, population-level genomic signatures of irisin exposure using fluorescently activated cell sorting (FACS) and subsequent RNA sequencing.



- **Evaluate translational potential of irisin in immune recruitment using patient derived organoids**

Study Status and Acknowledgements

Study Status

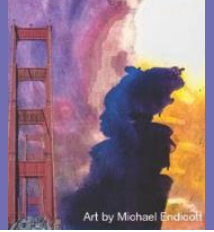
- Activated in July 2024
- Current enrollment: 8 patients
- Three patients have completed the program, 5 on-going

Investigators

- Bruce Spiegelman
- Rinath Jesselsohn
- Tari King
- Judy Garber
- Doug Rousso
- Kate Blackmore
- Anita Giobbie-Hurder
- Nelly Polyak
- Myles Brown

Study Team

- Anna Tanasijivik
- Kaedryn Digugliemo
- Chris Maples-Campbell
- Nancy Campbell
- MaryBeth Hans



RISE UP for Breast Cancer

Time restricted Eating And Metformin (TEAM) in invasive breast cancer or DCIS: a randomized window of opportunity trial. Preliminary safety analysis.

Irene Maria Briata
Medical Oncology –
E.O. Ospedali Galliera, Genoa

IEO Istituto Europeo di Oncologia

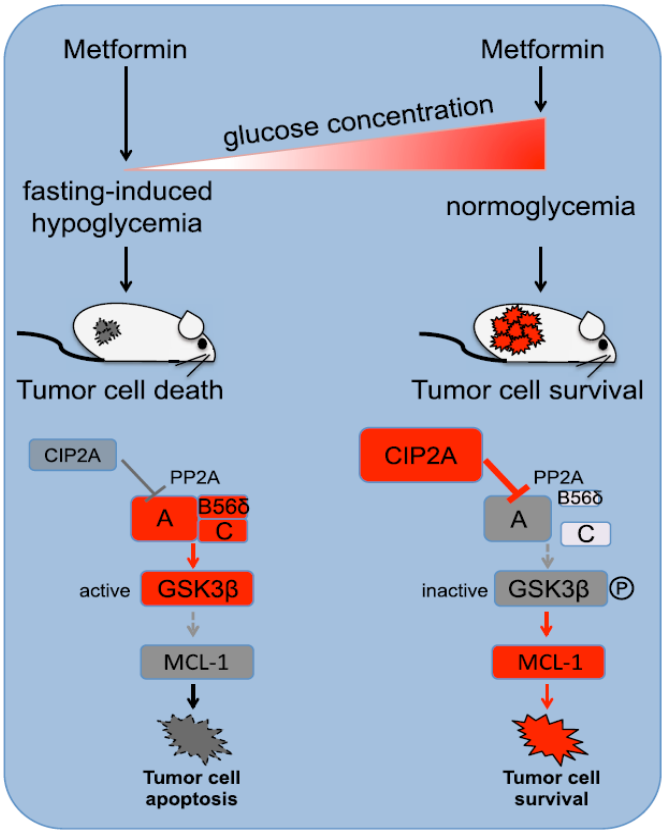
Ente Ospedaliero Ospedali Galliera Genova
Ospedale di rilievo nazionale e di alta specializzazione

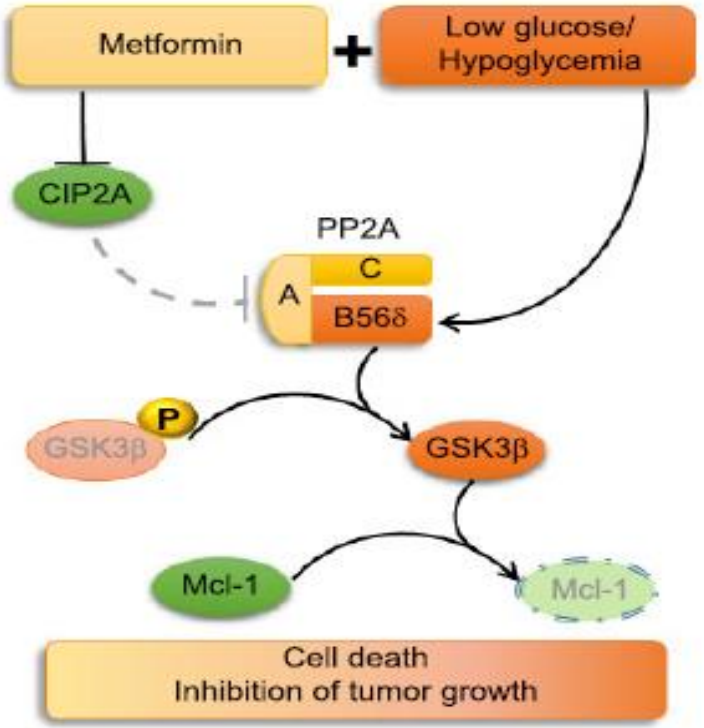
Asl3 Sistema Sanitario Regione Liguria

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

NIH NATIONAL CANCER INSTITUTE

Combining intermittent fasting with metformin leads to tumor cell death





Elgendy M et al., *Cancer Cell*. 2019

TEAM TRIAL

Trial Design

Women with histologically confirmed luminal (ER+ve and/or PgR+ve ≥1%) operable IBC or DCIS

N = 120

R

EXPERIMENTAL ARM

≥16 hrs Nightly fasting
+ Metformin
+ Nutritional counseling
+ Blinded Continuous Glucose Monitoring

CONTROL ARM

Blinded Continuous Glucose Monitoring

SURGERY

4-6 WEEKS

Both groups will receive the WCRF/AICR recommendations

Funded by NIH National Institutes of Health; Ministero della Salute

Endpoints

Primary

- **Pre/post-treatment change of Ki67 labeling index (LI) in cancer tissue** (**IBC or DCIS**, if IBC is absent) between biopsy and surgical specimen.

Co-primary

- **difference in post-treatment Ki67 in cancer adjacent DCIS** (in the presence of IBC), **or IEN** (ADH or ALH or LCIS) between the active and the control group.
- **change** (pre/post treatment) of **Ki67 in IEN** will be evaluated **only if present** in the **pretreatment biopsy specimen**

→ With a sample size of 120 **women,** the study will be **96% powered** to detect a **6% absolute difference** in the **change between arms**.

Endpoint - Safety Cohort

Primary safety endpoint

Incidence of **Dose Limiting Toxicities** (DLTs) in the first **14 patients** in the **exp arm.**

DLT= hypoglycemic event requiring permanent discontinuation of study treatment **or** any **grade ≥ 3 AE** possibly, probably, or definitely related to the study drug

SAE	Maximum Acceptable SAE Rate τ									
k	0.01	0.02	0.03	0.04	0.05	0.06	0.07	0.08	0.09	0.10
2	35	18	12	9	7	6	5	4	4	3
3	82	41	27	21	16	14	12	10	9	8
4	137	69	46	34	28	23	20	17	16	14
5	198	99	66	50	40	33	29	25	22	20

Note: $\alpha = 0.05$ for each analysis.

- If **4 or more** out of 14 participants experience a DLT→ **Trial stop** because the rate of G3 events is significantly higher that 10%
- If **3 or fewer** out of 14 participants experience a DLT→ **Trial continuation**

Kramar A, et al. *Med Decis Making* 2009

SAFETY ANALYSIS
Main AEs in the Experimental Arm

Adverse Event	Experimental arm (n = 14)	
	Grade 1	Grade 2
Diarrhea	9	1
Fatigue	5	1
Nausea	4	-
Headache	2	-
Dizziness	2	-
Tremor	2	-
Hyperhidrosis	2	-
Other	23	3
Total	**49**	**5**

SAFETY ANALYSIS
AEs in the Experimental Arm by Grade/Relationship

Grade	Attribution	Number of events, n (%)
		Experimental arm
1	Unrelated	26 (53%)
	Unlikely	1 (2%)
	Possible	15 (31%)
	Probable	7 (14%)
Grade 1 totals		**49 (100%)**
2	Unrelated	3 (60%)
	Unlikely	0 (0%)
	Possible	1 (20%) *(fatigue)*
	Probable	1 (20%) *(diarrhea)*
Grade 2 totals		**5 (100%)**

Accrual (updated September 30, 2024)

- **Date first potential study participant was contacted**: January 10, 2023
- **Projected monthly accrual rate**: 4 per month
- **Actual accrual**: 3 per month

	MDACC	EOG	EIO	Total
Pre-screening	267	66	86	419
Consented/Registered	20	35	8	63
Withdrew Consent (prior to starting study agent) /Screen Failed	5	1	0	6
Enrolled/Randomized	15	34	8	57
• *Experimental arm*	*8*	*18*	*4*	*30*
• *Control arm*	*7*	*16*	*4*	*27*
Early Drop Out	1	1	0	2

withdrew consent after randomization (control arm)

clinical team decided to start neoadjuvant chemo

Sub-study funded by Italian MoH in Italian participants

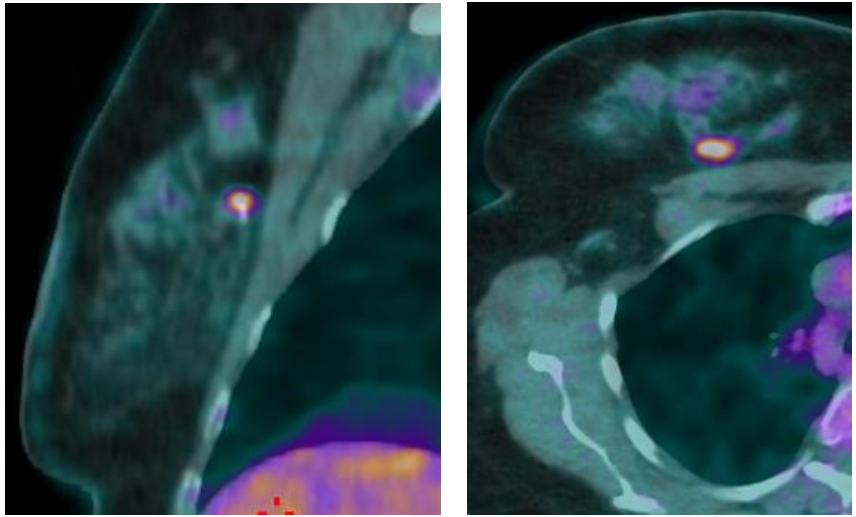
FDG-PET/CT scan performed at baseline and before surgery in 8 patients

Change in median SUV: exp arm, -0.64, control arm: -0.3

PRE

Sagittal

Axial

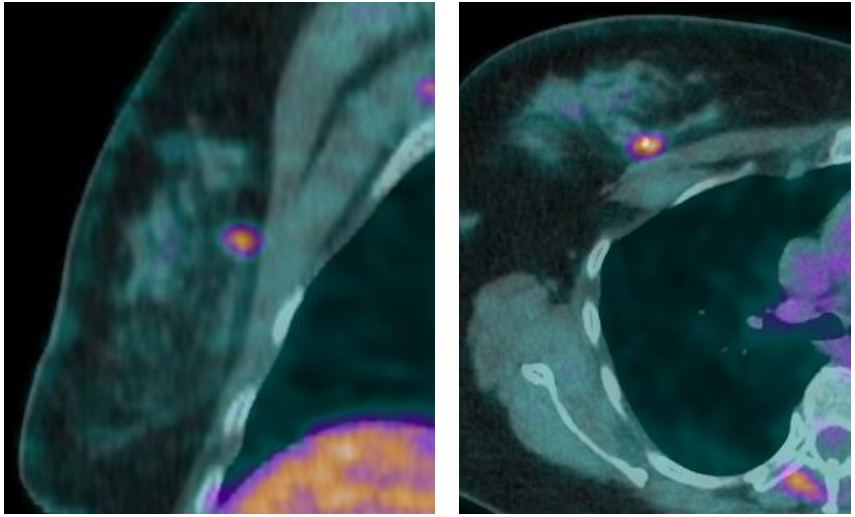


SUVmax 5.8

POST

Sagittal

Axial



SUVmax 3.9

Preliminary Conclusions

- **No Dose Limiting Toxicities** were reported in the experimental arm →
- **The Study can continue**
- The proposed intervention is **safe and feasible**
- New metformin schedule implemented without ramp-up to allow women to be on full treatment dosage after the first 3 days (Protocol v 8.2)
- Accrual is increasing with IEO activation

TEAM Trial - Staff

Galliera/ASL3

- **Andrea De Censi**, Principal Investigator
- **Mauro D'Amico,** Local Sub-Investigator
- **Irene Maria Briata**, Study Coordinator/Nutritionist
- **Tania Buttiron Webber**, Research Nurse
- **Mariangela Rutigliani**, Pathologist
- **Flavio Guasone**, Breast surgeon
- **Stefano Spinaci**, Breast surgeon
- **Emma Firpo,** Breast surgeon
- **Andrea Rattaro**, Breast surgeon
- **Nicoletta Gandolfo,** Radiologist

MD Anderson Cancer Center

- **Eduardo Vilar,** Consortium Principal Investigator
- **Lana Vornik,** Director, Research Planning and Development
- **Parijatham Thomas**, Local Principal Investigator
- **Alejandro Contreras**, Local Pathologist
- **Araceli Garcia Gonzalez**, Local Study Coordinator
- **Maria Lozano,** Local Study Coordinator
- **J. Jack Lee**, Consortium Statistician
- **Diane Liu**, Consortium Statistician
- **Tawana Castile**, Data Manager
- **James Kim**, Project Coordinator

Istituto Europeo di Oncologia

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- **Matteo Lazzeroni,** Local Sub-Investigator
- **Davide Serrano**, Local Sub-Investigator
- **Aliana Guerrieri Gonzaga**, Local Study Coordinator
- **Harriet Johansson,** Lab Investigator
- **Saverio Minucci**, Lab Investigator
- **Gianmaria Frigè**, Lab Investigator
- **Paolo Veronesi**, Breast surgeon
- **Sara Gandini,** Study Statistician

Division of Cancer Prevention, NCI

- **Brandy Heckman-Stoddard,** Scientific Lead
- **Edward Sauter,** Medical Monitor
- **Eileen Dimond,** Nurse Consultant
- **Eva Szabo,** Consortium Lead
- **Leslie Ford,** Associate Director of Clinical Research

RISE UP for Breast Cancer

A new interdisciplinary breast cancer conference
November 1-3, 2024
San Francisco, CA

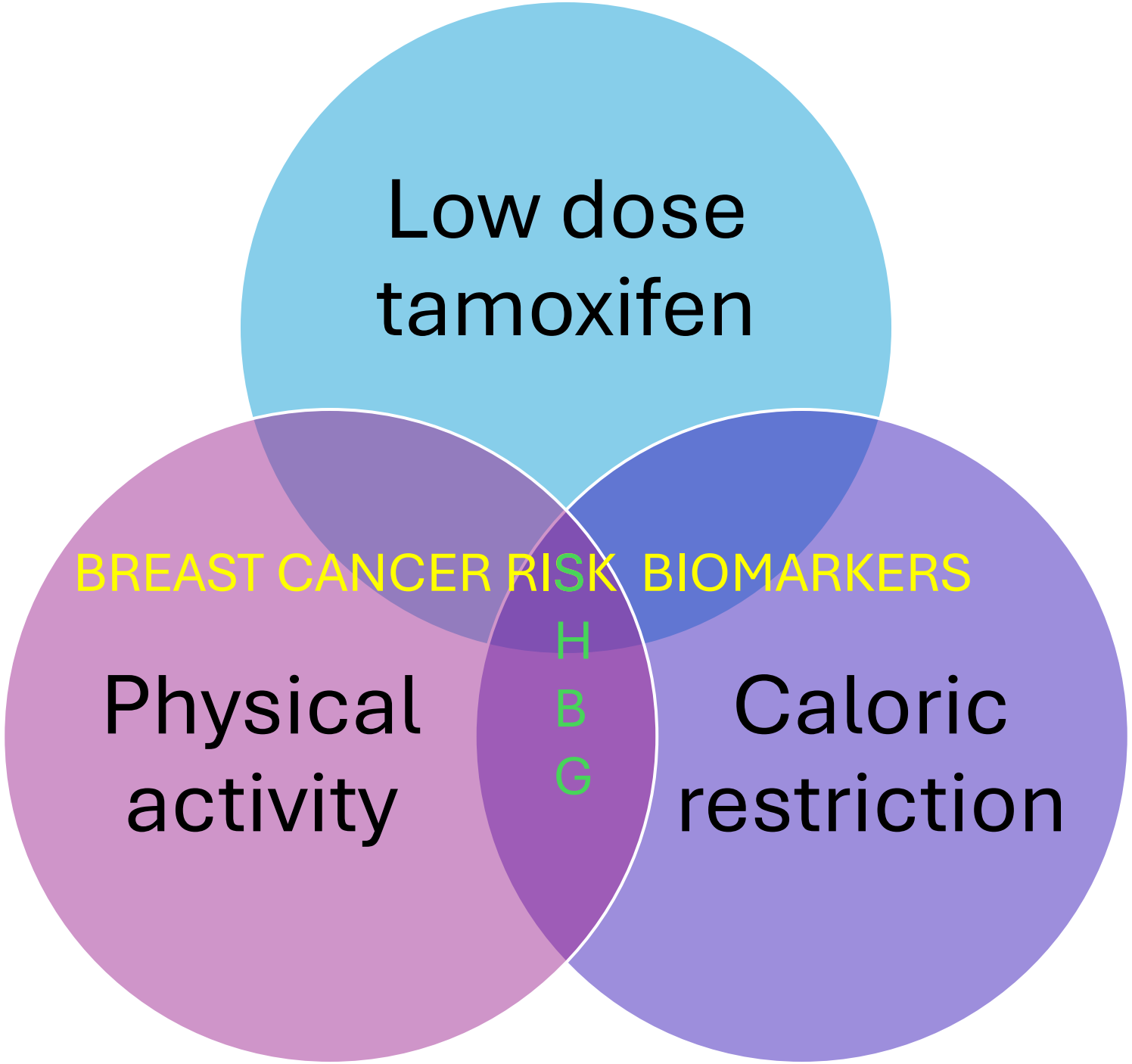
THANK YOU

RISE UP for Breast Cancer November 1-3, 2024. San Francisco, CA.

Low dose TamOxifen and LifestylE changes for bReast cANcer prevenTion: a randomized phase II biomarker trial in subjects at increased risk (TOLERANT Study)

Matteo Lazzeroni, MD
Division of Cancer Prevention and Genetics
European Institute of Oncology
Milan, Italy

no conflict of interest related to the content of this presentation


Low dose tamoxifen
BREAST CANCER RISK BIOMARKERS
H
B
G
Physical activity
Caloric restriction

Randomized, 4-arm phase II trial (1:1:1:1)

200 Women

- ✓ Unaffected carriers of high/moderate penetrance gene variants (C4-C5)
- ✓ Healthy women with > 5% Tyrer-Cuzick BC risk at 10 yrs
- ✓ Women with a history of Intraepithelial Neoplasia (IEN)

IEN:

ADH
LCIS
DCIS (Er_{pos})

BRCA1
BRCA2
PALB2
ATM
CHEK2
CDH1
RAD51C
RAD51D

6M Tx

ARMS:

1. Low dose Tamoxifen (LDT).
2. LDT + Intermittent Caloric Restriction (ICR).
3. Lifestyle intervention (LI) only.
4. LI + ICR.

Stratification: center and disease status (high risk vs IEN)

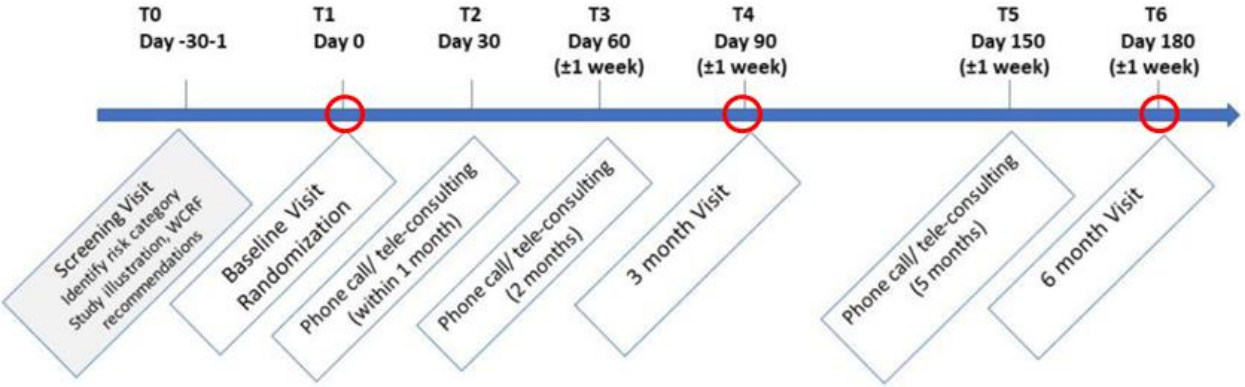
Primary Objective:

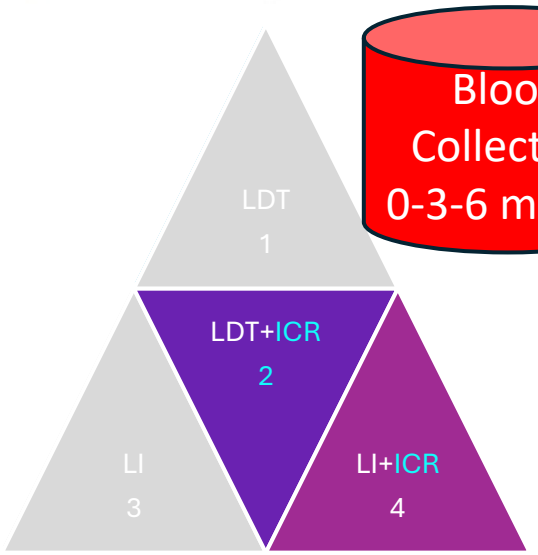
- Effect of Low dose Tamoxifen and lifestyle interventions on biomarkers.

Secondary Objectives:

- Monitor safety, toxicity, quality of life, and body composition changes.
- Evaluate immune modulation and microbiome impact.

Further details …





ARMS:

1. Low dose tamoxifen (LDT).
2. LDT + 5:2 Intermittent Caloric Restriction (ICR).
3. Lifestyle intervention (LI) only (step counter).
4. LI + ICR.

Blood Collection 0-3-6 month

Stool collection: 0-6 month

Self reporting questionnaire: 0-3-6

Effect of IC

(Exploratory)

ARMS:

- Low Dose Tamoxifen (LDT): 10 mg every other day
- Intermittent Caloric Restriction (ICR): 5:2 Diet with 75% caloric reduction on 2 days/week + personalized meal plans
- Lifestyle Intervention: step counter (10,000 steps per day)

Primary Endpoint:

- Changes in Sex Hormone Binding Globulin (SHBG).

Secondary Endpoints:

- Biomarkers (HOMA-index, Lipids, IGF, hs-CRP, adiponectin, leptin).
- Immune modulation by gene expression profile in mononuclear blood cells, microbiome analysis, BMI and body composition; mammographic breast density
- Safety and toxicity
- Quality of life

Tolerant Study

Innovation:

- Multimodal approach.
- Improve women's quality of life.
- LDT in healthy women at genetic risk for breast cancer

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Finanziato dall'Unione europea
NextGenerationEU

PNRR
MISSIONE 6 –SALUTE

Ministero della Salute

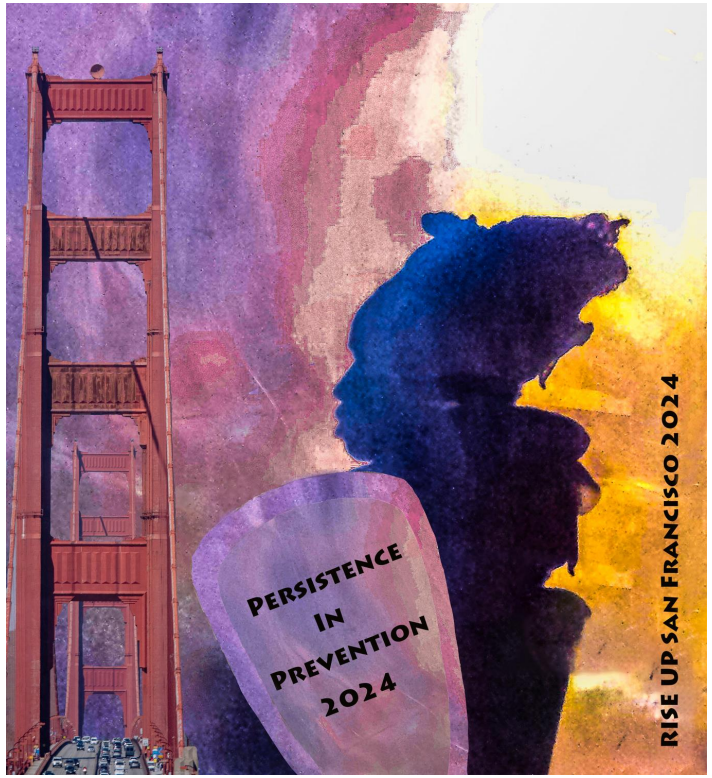
Persistence in Prevention

CAROL FABIAN

Carol J. Fabian, MD

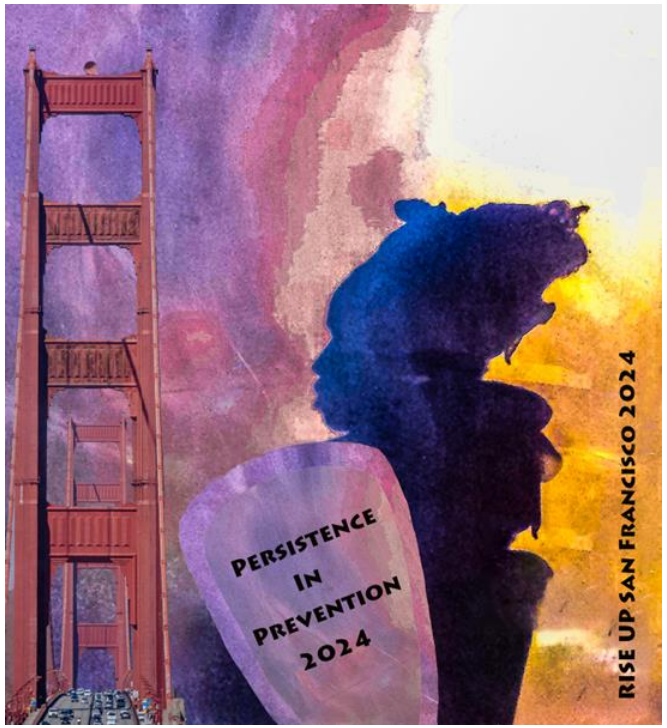
- Trained at the University of Kansas School of Medicine in Kansas City, KS
- Mark and Bette Morris Family Professor in Cancer Prevention at the University of Kansas Medical Center
- Director of the Breast Cancer Prevention and Survivorship Centers
- Leads the Cancer Prevention Research Program
- In 1989, founded the clinic for women at increased risk of breast cancer
- Endowed professorship has been established in her honor in Cancer Prevention at the University of Kansas

- Fellow of the American Society of Clinical Oncology
- Past chair or co-chair of the ASCO Prevention Committee, ASCO Prevention Workforce Pipeline, ASCO Pharmacologic intervention in Breast Cancer Risk Reduction
- Served on ASCO committees developing position statements on Obesity, Prevention and Monitoring of Cardiac Dysfunction in Cancer Survivors
- Co-chair SWOG Cancer Survivorship Committee



Carol J. Fabian, MD

- **Carol Fabian is a world-renowned translational researcher** focused on short-term risk assessment and prevention of breast cancer. She has more than 170 publications, has led numerous NCI grants including Prevention Consortia as well as foundation grants from BCRF and others.
- Developed Random Periareolar Fine Need Aspiration (**RPFNA**), a procedure for collecting breast tissue that can be used to evaluate changes over time and as a result of interventions for breast cancer risk-reduction. She and her team have trained researchers around the country and the world in this technique
- Validated the use of RPFNA specimens for breast cancer risk assessment
- Carol has led numerous innovative clinical trials balancing reducing breast cancer risk and improving menopause symptoms. She has studied lignans, Omega-3-fatty acids, SERMS, behavioral weight loss interventions, bazedoxifene/conjugated estrogens, lazefoxifene and others, continuously pushing the envelope.



Carol J. Fabian, MD

Carol J. Fabian is a true leader in breast cancer prevention. Her inclusive approach has trained numerous clinicians and researchers at the University of Kansas and beyond. Her rigorous approach to the science, her fierce pursuit of novel agents and other interventions to advance the field, and her commitment to accelerating progress in breast cancer prevention over a remarkable career makes her the perfect choice as the first recipient of the **Persistence in Prevention** award.