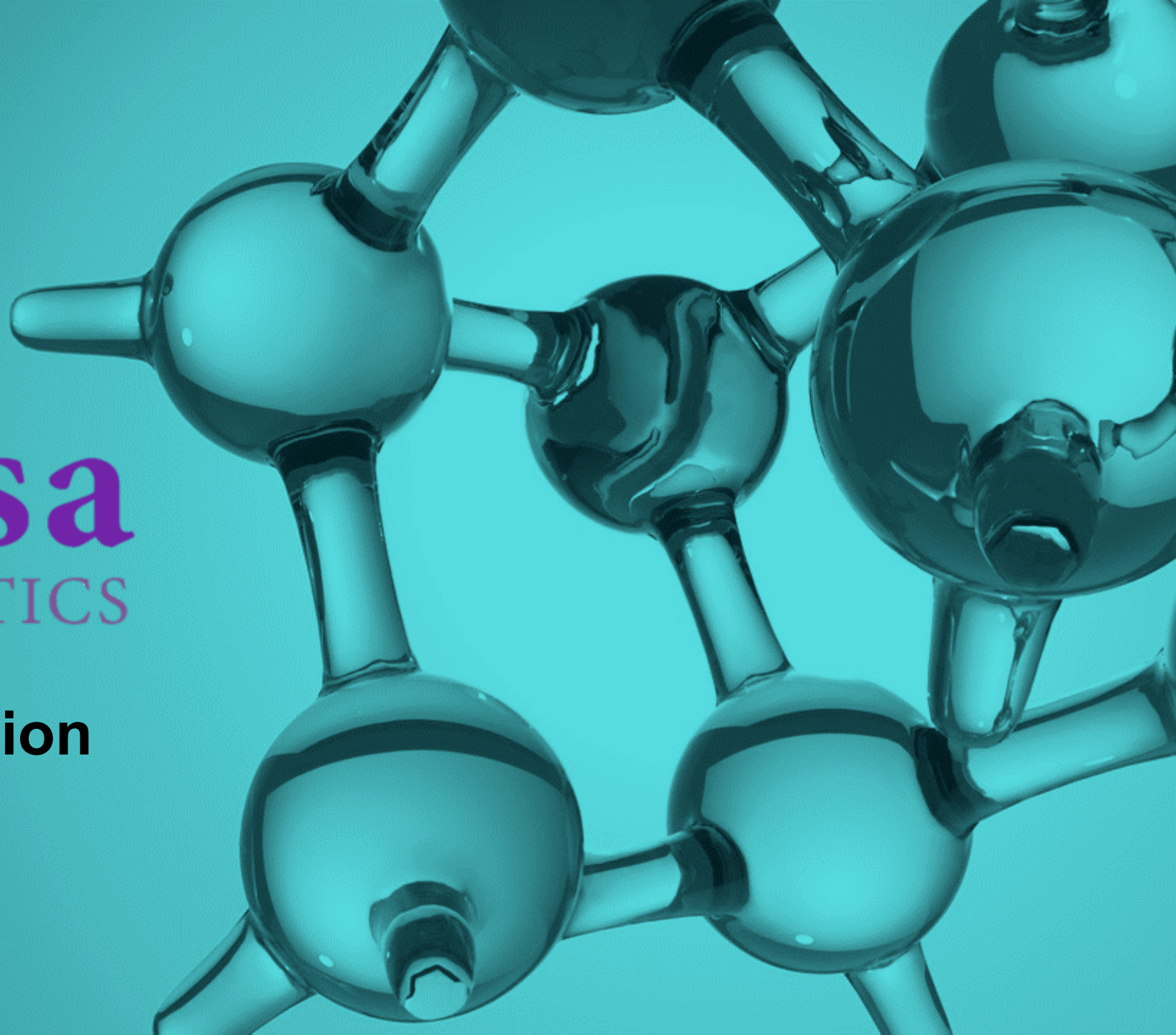

Atossa THERAPEUTICS

Investor Presentation

May 2024

NASDAQ: ATOS

www.atossatherapeutics.com

Forward Looking Statements

Some of the information presented herein may contain projections or other forward-looking statements regarding future events or the future financial performance of the Company. These statements, which Atossa undertakes no obligation to update, are subject to risks and uncertainties that may cause actual results, outcomes, or the timing of actual results or outcomes, to differ materially from those projected or anticipated, including risks and uncertainties associated with: macroeconomic conditions and increasing geopolitical instability; the expected timing of releasing data; any variation between interim and final clinical results; actions and inactions by the FDA and foreign regulatory bodies; the outcome or timing of regulatory approvals needed by Atossa, including those needed to continue our planned (Z)-endoxifen trials; our ability to satisfy regulatory requirements; our ability to successfully develop and commercialize new therapeutics; the success, costs and timing of our development activities, including our ability to successfully initiate or complete our clinical trials, including our (Z)-endoxifen trials; our anticipated rate of patient enrollment; our ability to contract with third-parties and their ability to perform adequately; our estimates on the size and characteristics of our potential markets; our ability to successfully defend litigation and other similar complaints and to establish and maintain intellectual property rights covering our products; whether we can successfully complete our clinical trial of oral (Z)-endoxifen in women with mammographic breast density and our trials of (Z)-endoxifen in women with breast cancer, and whether the studies will meet their objectives; our expectations as to future financial performance, expense levels and capital sources, including our ability to raise capital; our ability to attract and retain key personnel; our anticipated working capital needs and expectations around the sufficiency of our cash reserves; and other risks and uncertainties detailed from time to time in Atossa's filings with the Securities and Exchange Commission, including without limitation its Annual Reports on Form 10-K and Quarterly Reports on 10-Q. Forward-looking statements are presented as of the date of this presentation. Except as required by law, we do not intend to update any forward-looking statements, whether as a result of new information, future events or circumstances or otherwise.

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Chairman, CEO and President

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Heather Rees, CPA
VP, Finance and Accounting

Avalara | gettyimages

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Matthew Goetz, M.D.
EVANGELINE Principal Investigator

MAYO CLINIC

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Weill Cornell Medicine

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Consultant

Lumanity

The Breast Cancer Problem

50%
of women have dense breasts[1]

1 in 8
women experience breast cancer[2]

310,000
women diagnosed in US annually[2]

80%
of US Breast cancer is ER+[2]

(1) Sprague BL, Gangnon RE, Burt V, et al. Prevalence of mammographically dense breasts in the United States. J Natl Cancer Inst. 106(10), 2014.
(2) American Cancer Society, Inc.

Clinical Positioning In Breast Cancer

Atossa THERAPEUTICS

Prevention Setting → **Neoadjuvant/Window of Opportunity** → **Adjuvant Setting**

Mammographic Breast Density

DCIS

(Z)-endoxifen

Value Proposition

- Earlier detection in patients with dense breast tissue
- Prevention of cancer in at-risk patients

Suspicious Lump

Biopsy

Diagnosis

Surgery and Radiation/ Chemotherapy

(Z)-endoxifen

Value Proposition

- Potential Improvement in Breast Conservation Rate
- Premenopausal women avoid ovarian function suppression (OFS), which results in higher use and compliance

Tamoxifen (5-10 years)

(Z)-endoxifen

Value Proposition

- Many patients are refractory to Tamoxifen / contraindicated for aromatase inhibitors
- Improved safety / tolerability profile and avoid OFS

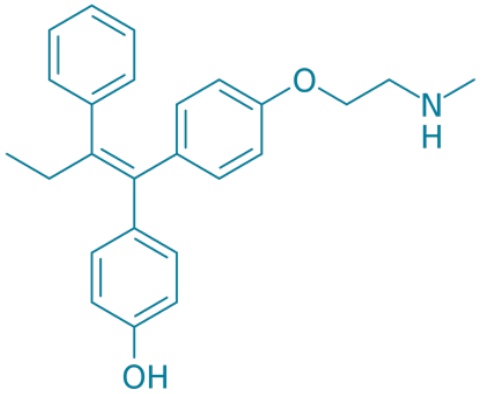
(Z)-endoxifen may also play an important role in the metastatic setting

Large Market Opportunities

PROGRAM	OPPORTUNITY
Mammographic Breast Density	**27 Million** Women in U.S. with dense breasts[1]
Ductal Carcinoma In Situ (DCIS)	**60,0000** DCIS diagnoses annually in U.S.[2]
Neoadjuvant	**250,000** ER+ Breast Cancers/Yr. in U.S.[2]

(1) Journal of the National Cancer Institute: Prevalence of Mammographically Dense Breasts in the United States
(2) American Cancer Society; WebMD: Types of Cancer

Novel SERM, De-risked, Strong IP



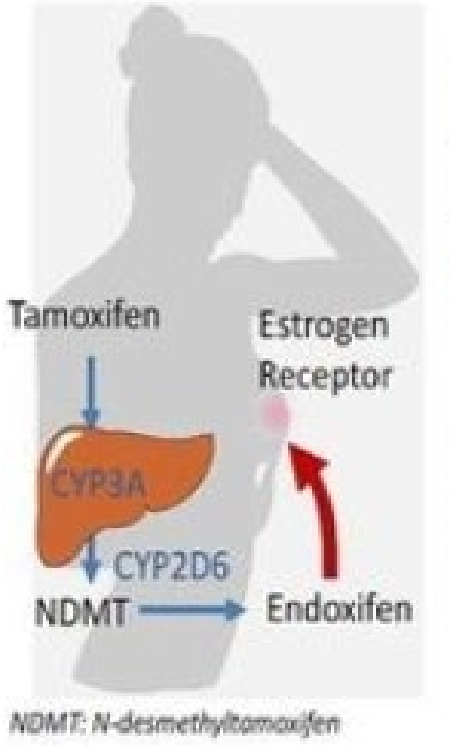
- **(Z)-endoxifen:**
  - Competitive inhibitor of ERα and represses ERα transcriptional activity
  - 100-fold more potent in anti-estrogen activity compared to other SERMs(1)
  - Binds to and disrupts protein kinase C beta one function (PKCb1, a known oncogenic protein)
- **De-risked**
  - The National Cancer Institute (NCI) and others have demonstrated promising results in the treatment of breast cancer and other solid tumors
  - Studied in numerous non-clinical studies and in four completed Ph1 or 2 studies at various doses with an acceptable safety profile
- **May have improved safety profile**
  - Opportunity to avoid ovarian function suppression and off target effects associated with tamoxifen and remaining metabolites and may potentially increasing adherence
- **Strong IP**
  - Patented (Z)-endoxifen chemical process and composition of matter → enhanced stability of (Z)-endoxifen on the shelf
  - Patented oral enteric capsule formulation of (Z)-endoxifen → enhanced stability following oral administration
  - Patented suspension formulation of (Z)-endoxifen → enhanced ease of delivery, increased bioavailability of drug dosage

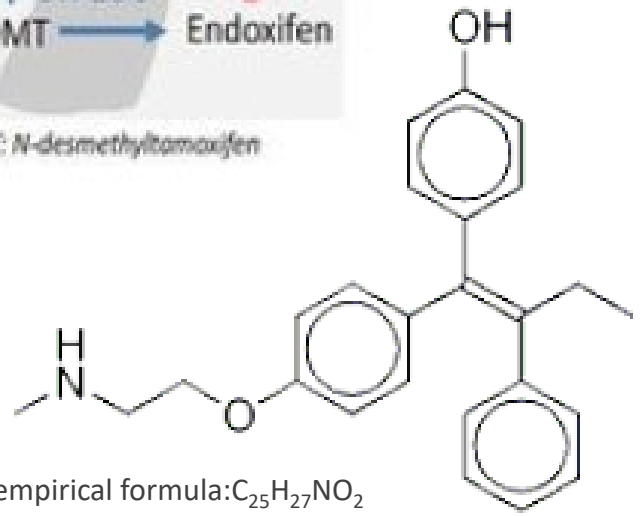
(1) Source: National Center for Biotechnology Information – “Endoxifen and fulvestrant regulate estrogen-receptor α and related DEADbox proteins” https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7774761/

Advantage of (Z)-endoxifen

Tamoxifen is a “pro-drug,” in that it must be metabolized by cytochrome P450 enzymes, primarily via CYP2D6, into active metabolites (~22) to have pharmacological activity

- **Endoxifen** is the most active metabolite of tamoxifen
- **Endoxifen** consists of two isomeric forms: (E) and (Z) and ***the (Z)-endoxifen isomer is the active anti-estrogenic form***
- **(Z)-endoxifen** is 100-fold more potent as an ER-targeted therapy when compared to the parent drug tamoxifen
- **(Z)-endoxifen** does not require first pass metabolism to reach target tissue and achieve therapeutic concentrations





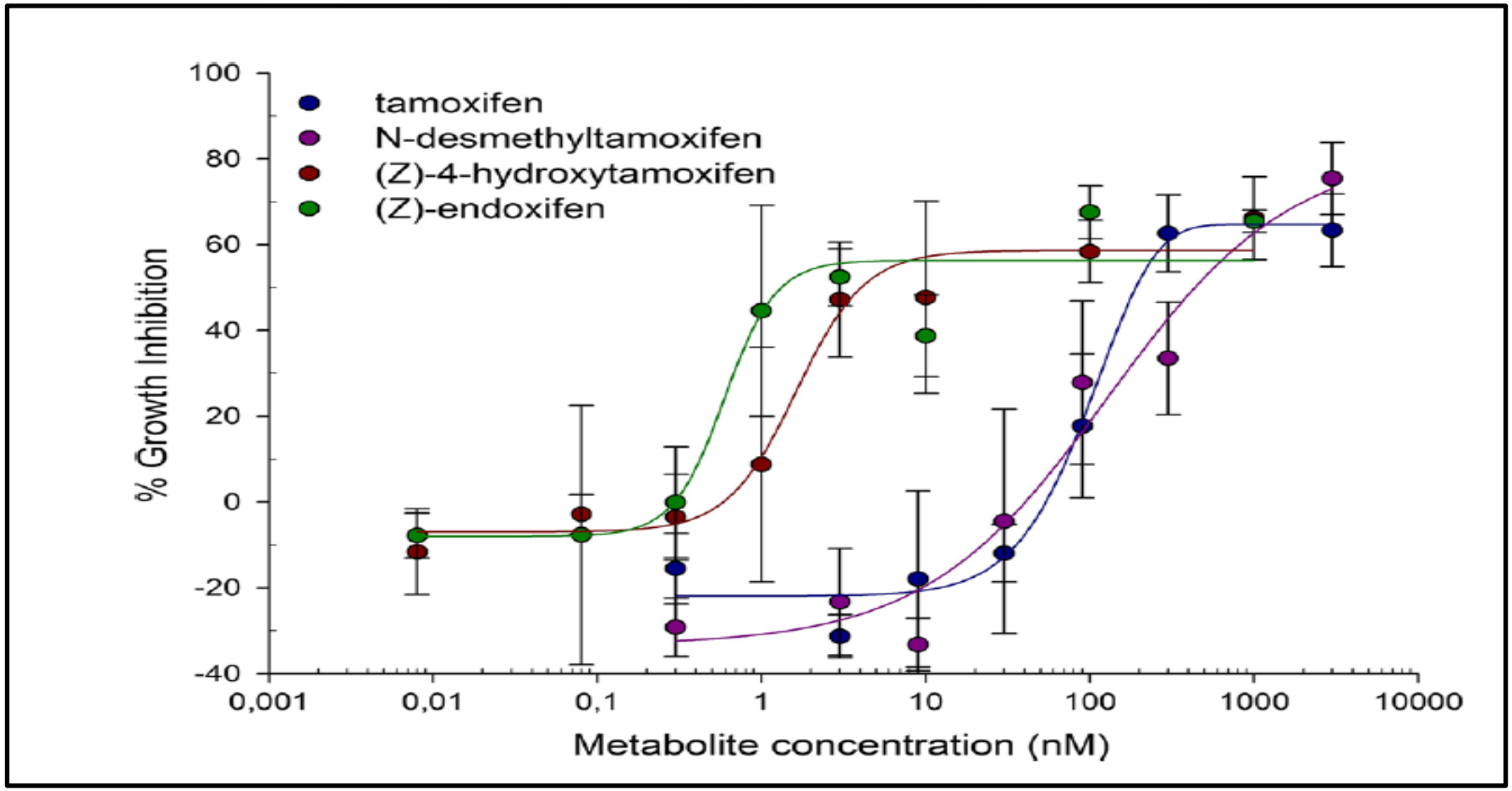
empirical formula: $C_{25}H_{27}NO_2$
molecular weight: 373.49 g/mol

Image Credit: *J. Pers. Med.* **2022**, *12*(4), 511; https://doi.org/10.3390/jpm12040511

(Z)-Endoxifen: A Potent Novel SERM

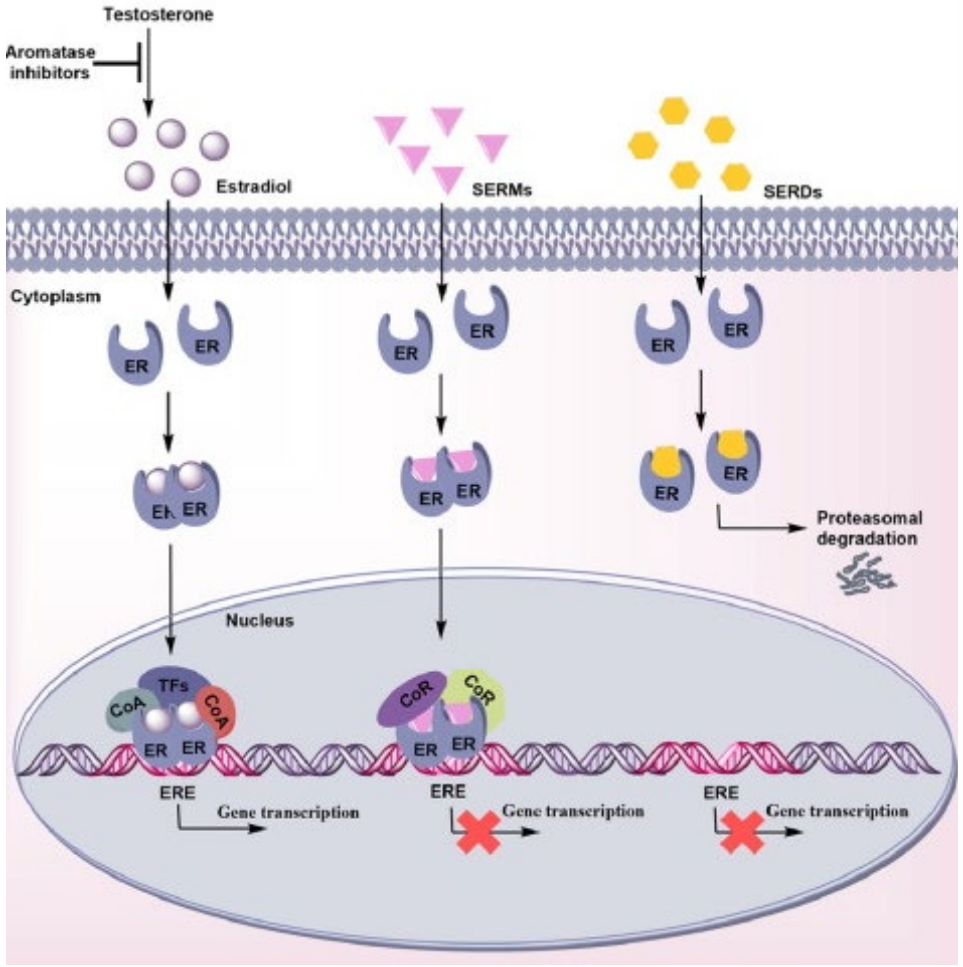
(Z)-endoxifen inhibits cancer cell growth:

- Best among tamoxifen-related molecules
- Better than tamoxifen itself



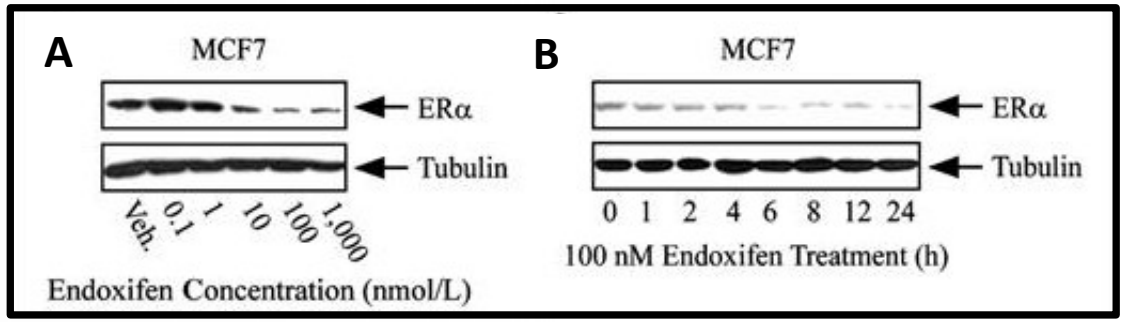
Endoxifen-Induced ER-α Degradation is Potent & Rapid

Traditional mechanisms of estrogen receptor inhibition with SERMs vs SERDs



(Z)-endoxifen:

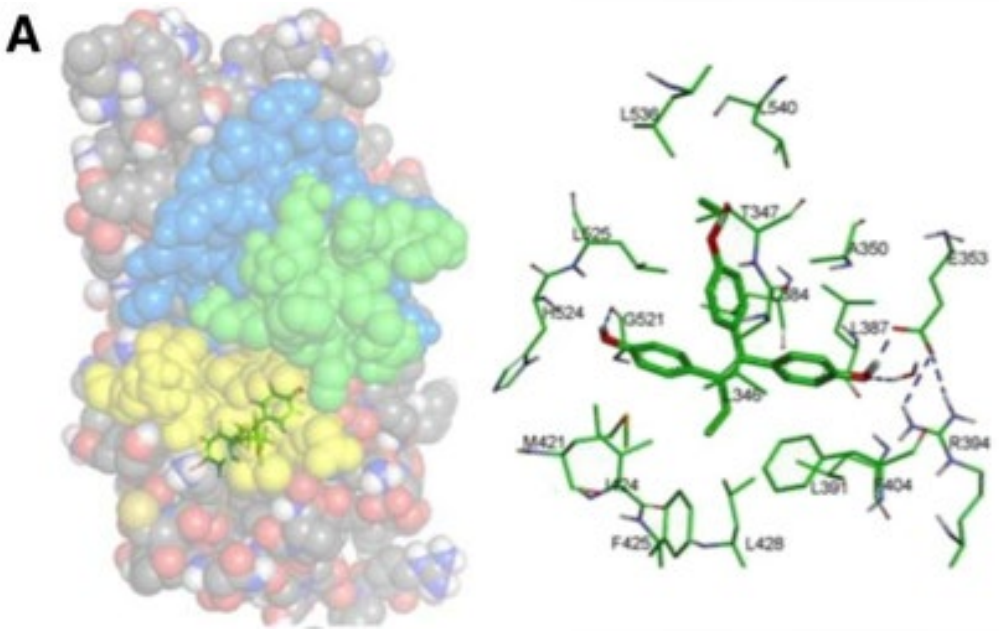
- Novel selective estrogen receptor modulator (SERM) with degradation activity (SERD)
- Competitive inhibitor of ER-α and represses ER-α transcriptional activity



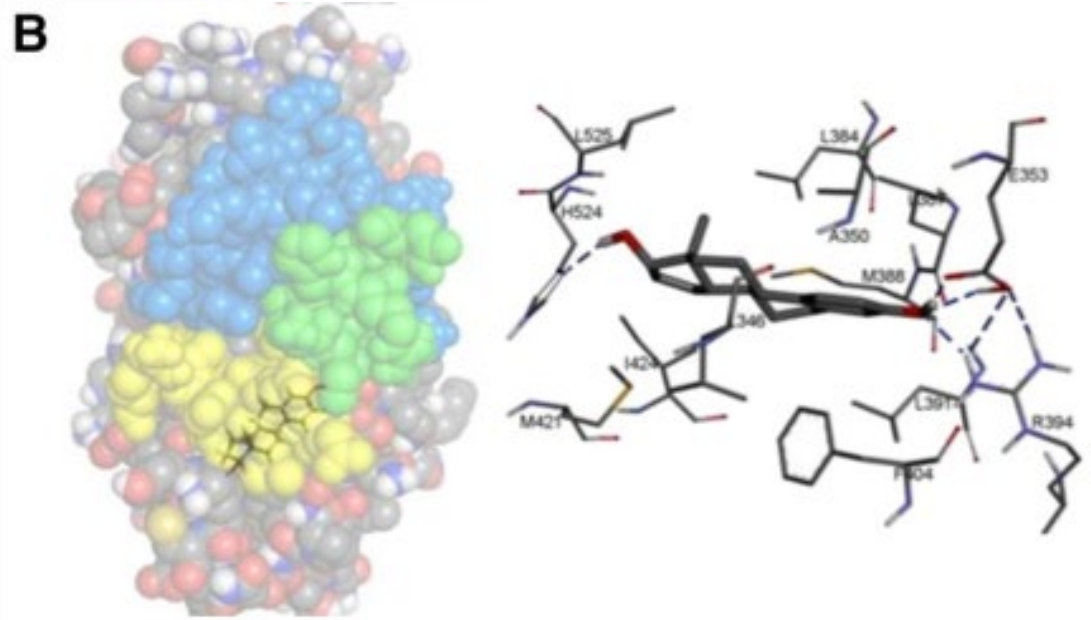
Degradation begins at the low concentration of 10 nM (panel A) and is complete within 24 hours (panel B)

Estrogen & Endoxifen Bind the Estrogen Receptor-alpha

Estrogen binds the ER-α



Endoxifen binds the ER-α

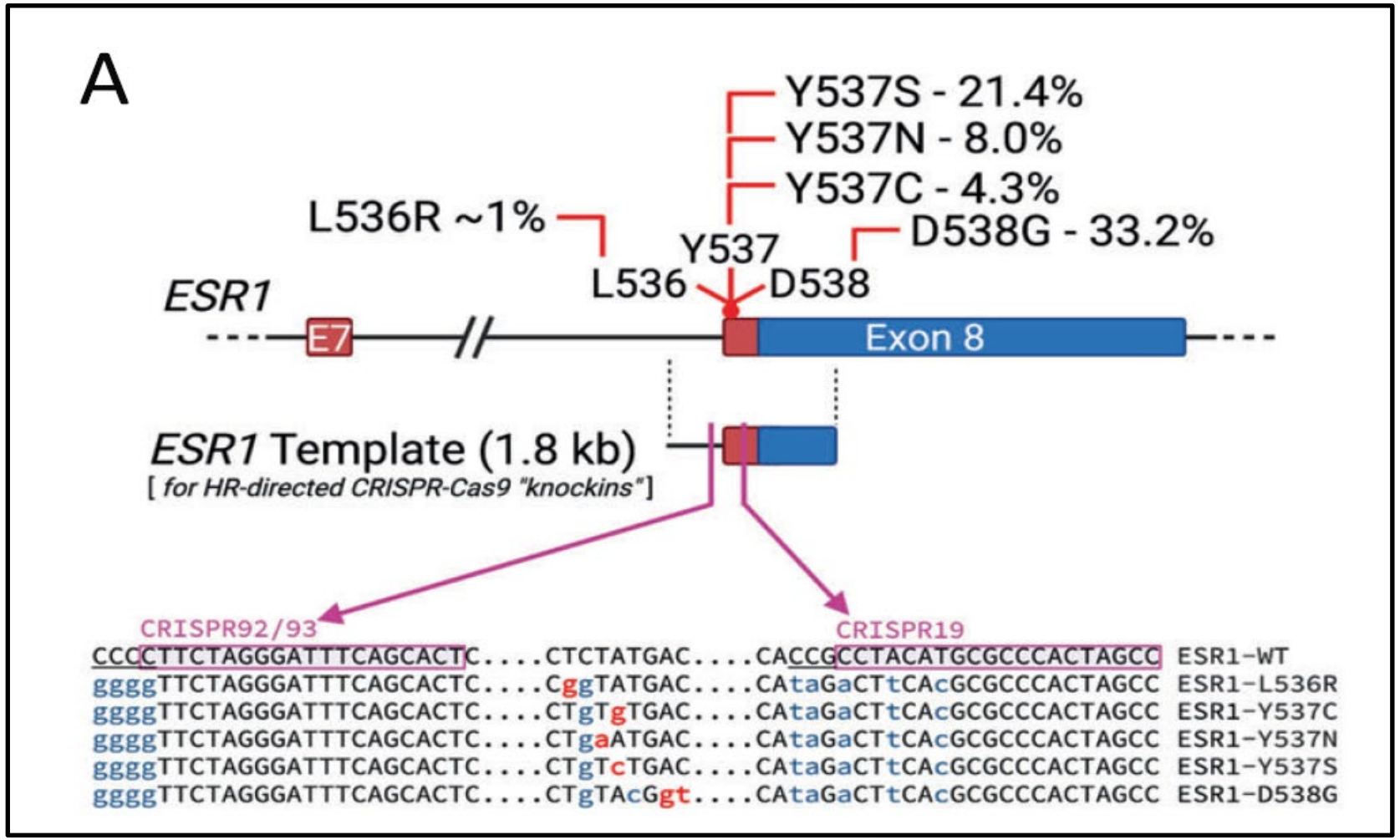


Maximov PY, et al., Endoxifen, 4-Hydroxytamoxifen and an Estrogenic Derivative Modulate Estrogen Receptor Complex Mediated Apoptosis in Breast Cancer. Mol Pharmacol. 2018 Aug;94(2):812-822. doi: 10.1124/mol.117.111385. Epub 2018 May 8. PMID: 29739819; PMCID: PMC6022805.

Treatment-Emergent ER-α Mutations

68% of all Treatment-Emergent ER Mutations occur at:

- **L536 (~1%)**
- **L537 (33.7%)**
- **L538 (33.2%)**



Endoxifen Inhibits Ligand Binding Domains of Mutant ER-α Phenotypes

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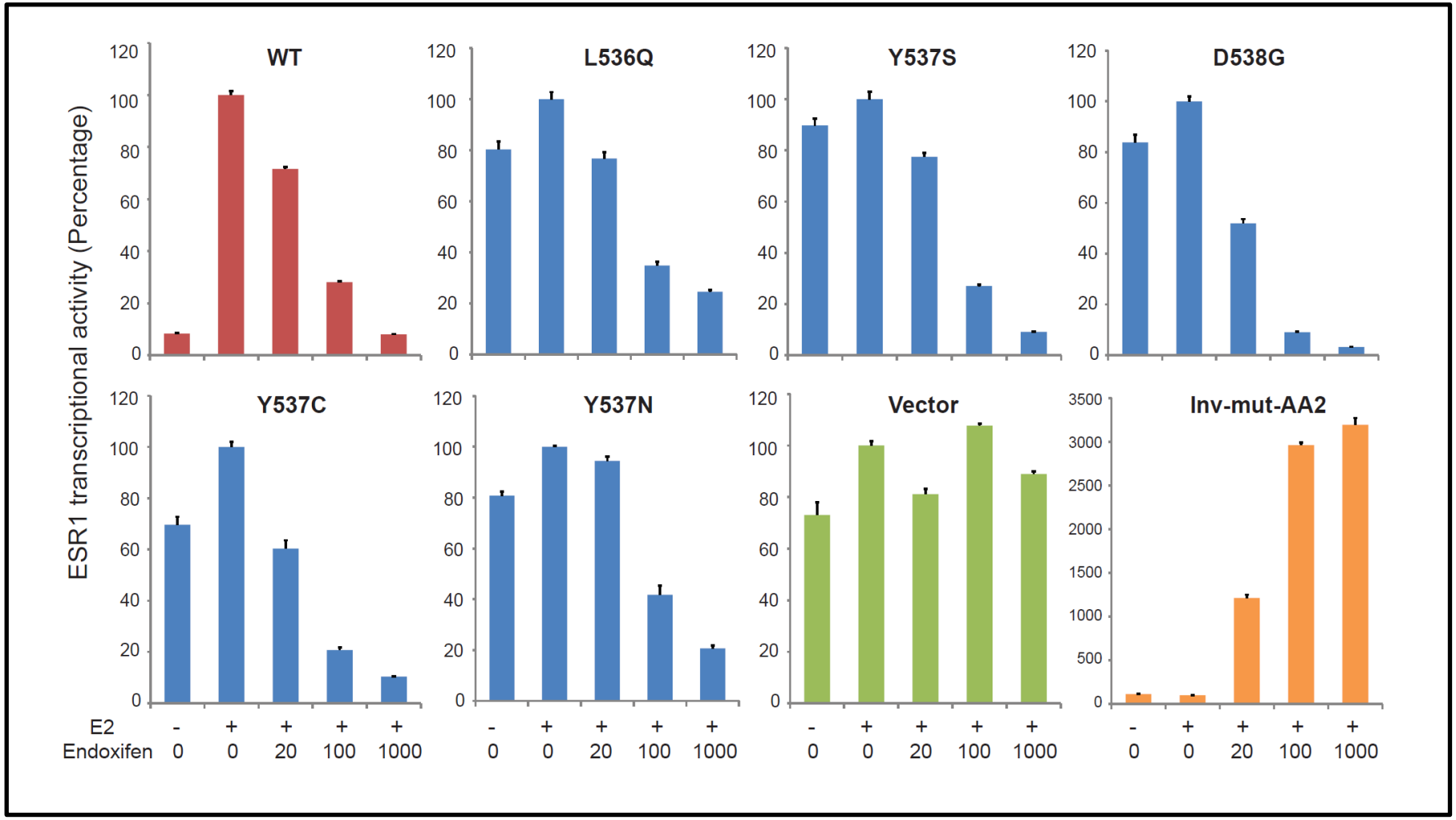
Estrogen stimulation is inhibited by endoxifen in a dose-dependent manner

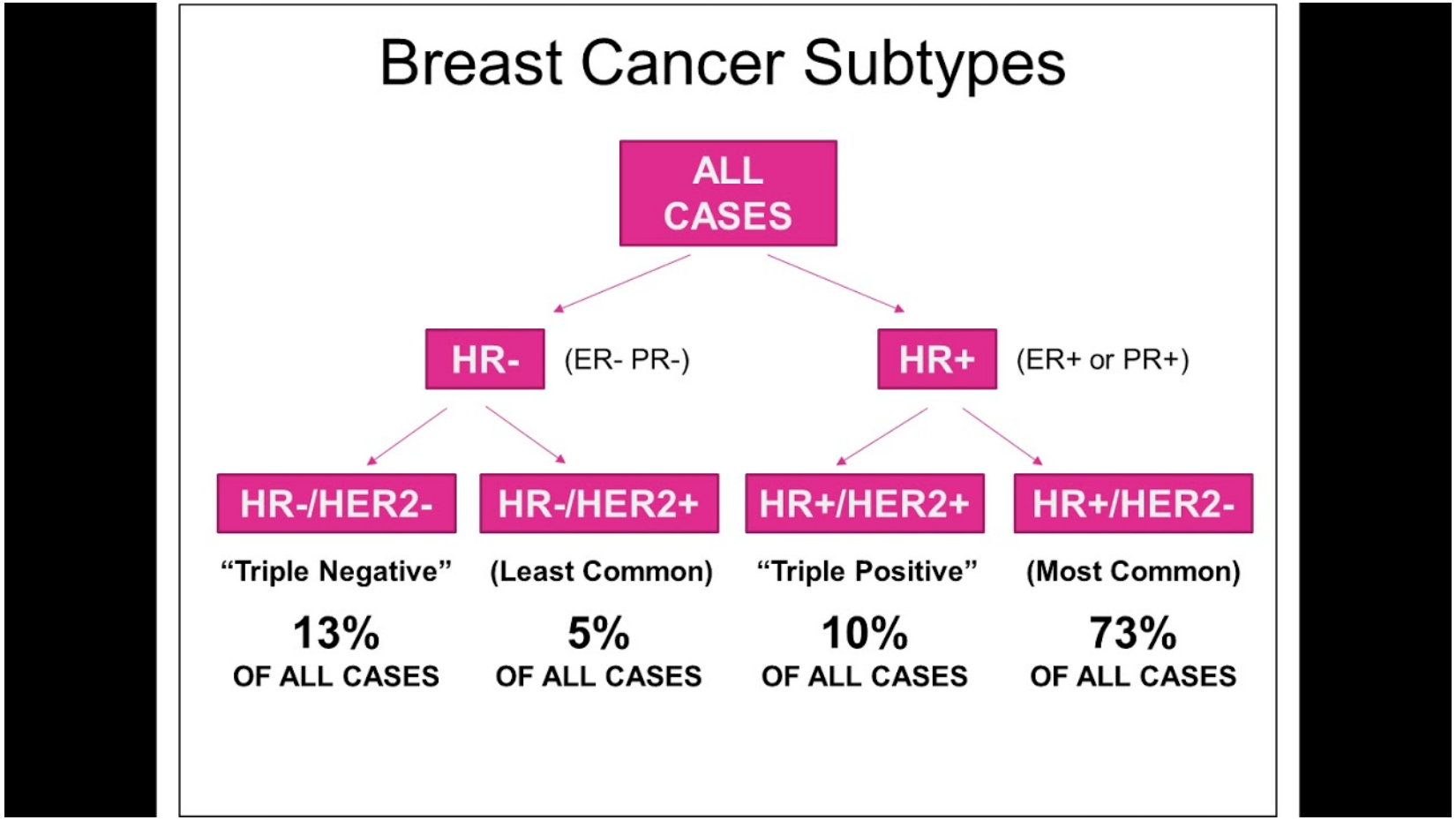
Top Row: Amino Acid changes in positions 536, 537, and 538 show a non-estrogen stimulated baseline expression which is again also inhibited by endoxifen

Bottom Left: The additional 537 amino acid changes continue to be inhibited by endoxifen.
Note: the endoxifen used in these experiments is Z/E-endoxifen



ER+ Breast Cancer Is 83% of Subtypes

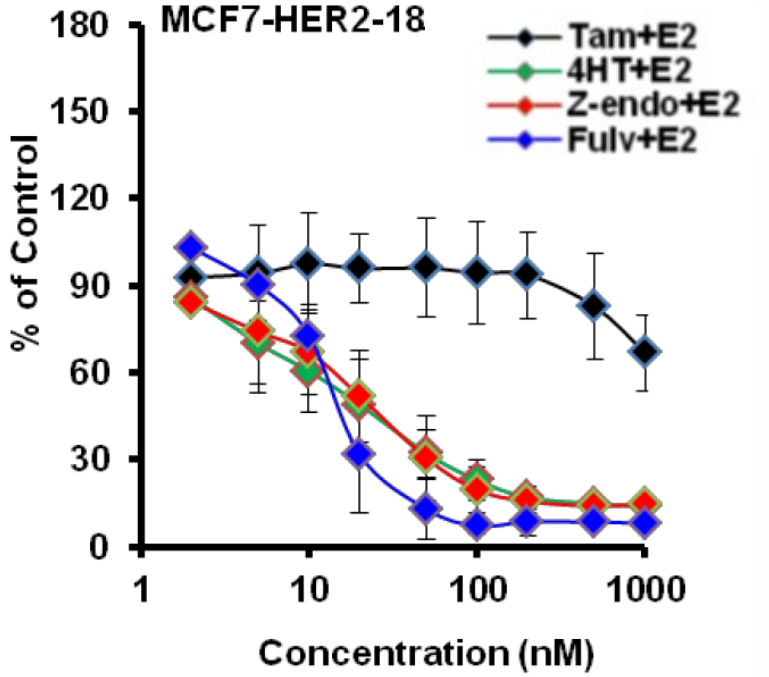
These studies thus far have been conducted in the ER+/HER2- breast cancer subtype, comprising 73% of all cases



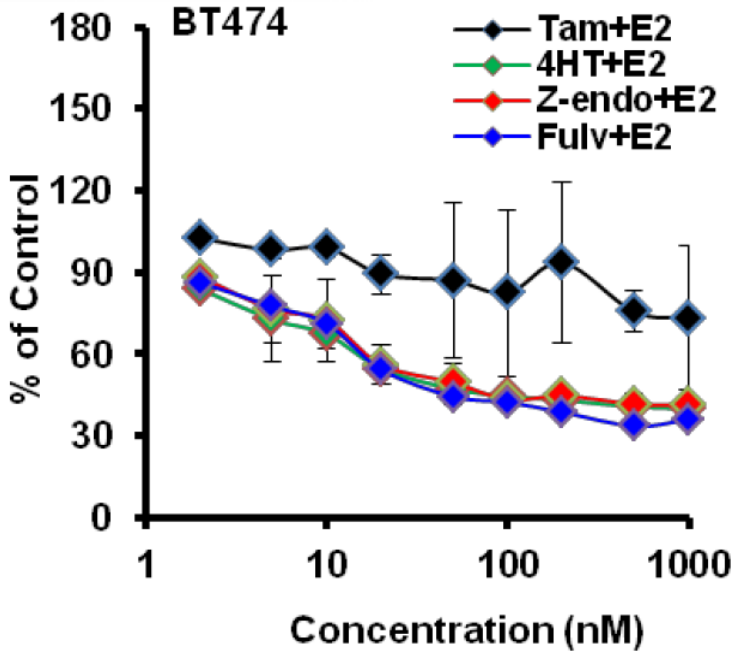
Endoxifen Inhibits Growth of ER+/HER2+ Breast Cancer

Endoxifen and fulvestrant (standard of care) effects on cancer cell growth were equivalent in both cell lines (MCF7-HER2-18 and BT474) and superior to tamoxifen

(Z)-endoxifen inhibits cell growth in cell lines overexpressing HER2



(Z)-endoxifen inhibits cell growth in cell lines with endogenous HER2



Endoxifen superior to tamoxifen in inhibiting growth in cancer cell lines

Validation of PKCβ1 as a Breast Cancer Target

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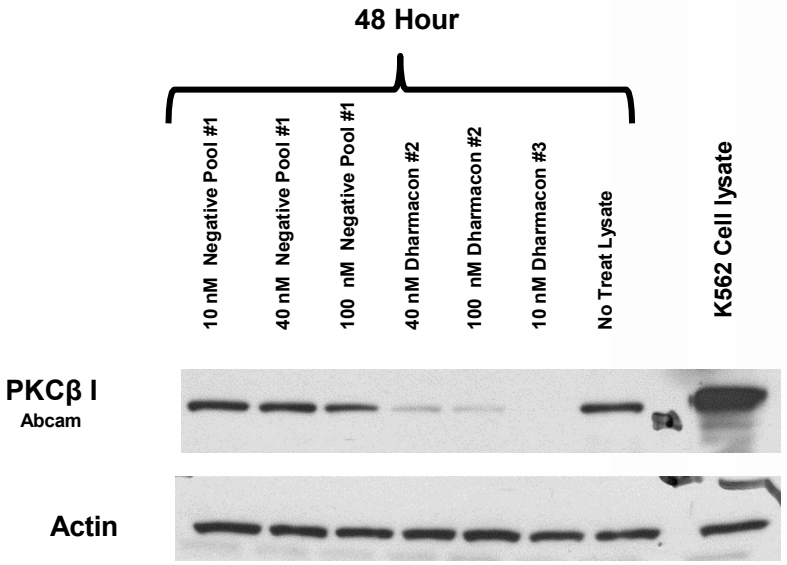
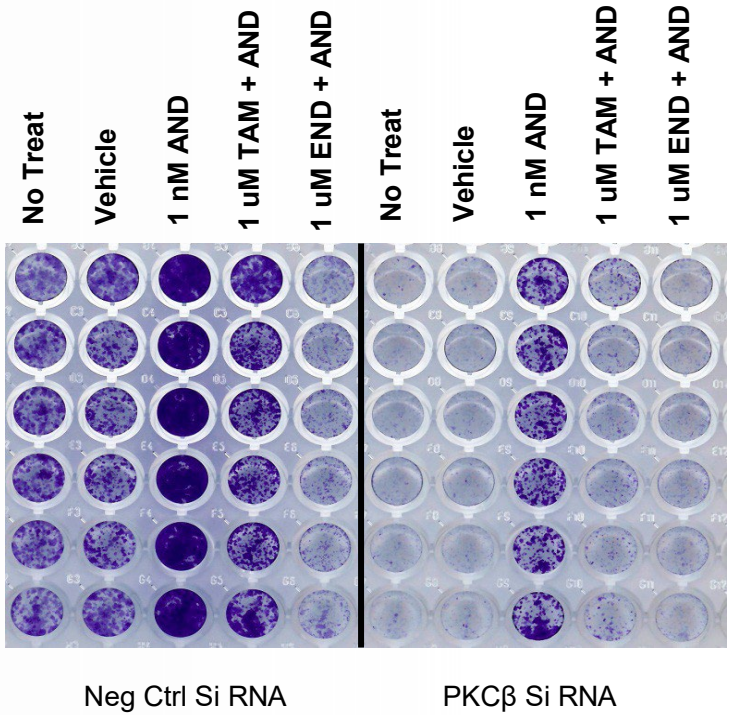
PKCβ1 Knockdown



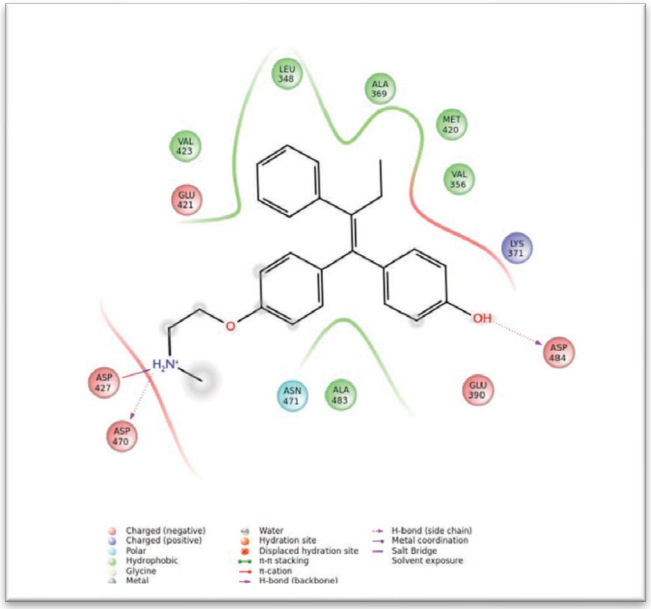
Proliferation



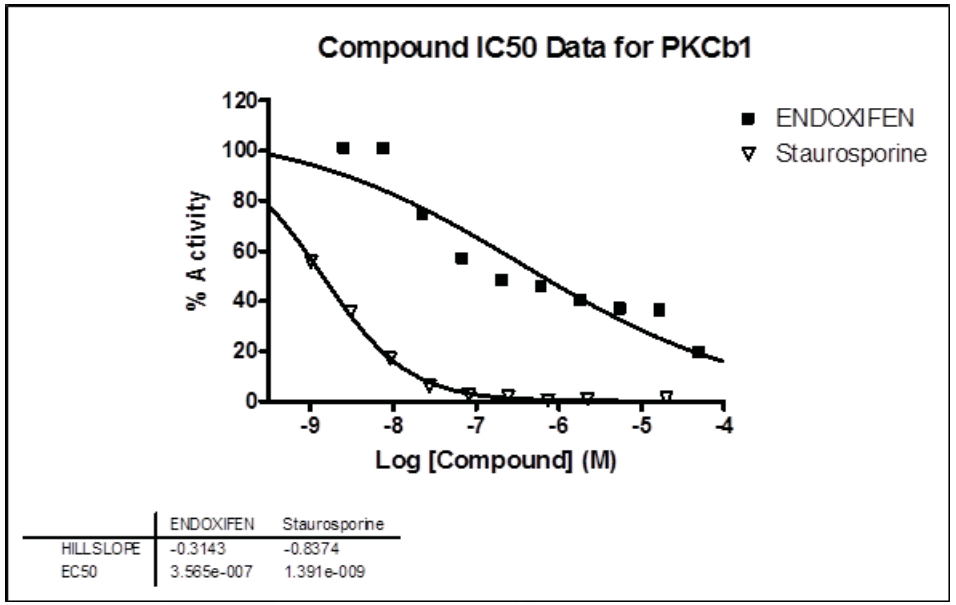
Figures: Anti-proliferative effects of PKCβ1 Knockdown and SERM administration on MCF7 ER+ cell line

Goetz et al.

Endoxifen Binds & Inhibits PKCβ1 Kinase Activity



Docking model of PKC beta with endoxifen. Several H-Bonds formed between endoxifen and Asp427, Asp470 and Asp484 of PKC beta at the ATP binding pocket. Endoxifen also formed hydrophobic interactions with PKC beta with Val356, Met420, Ala369 and Leu348.



	ENDOXIFEN	Staurosporine
HILLSLOPE	-0.3143	-0.8374
EC50	3.565e-007	1.391e-009

Enzyme screen (IC50) demonstrates endoxifen inhibits PKCβ1 (350 nM) (tamoxifen 5 micromolar).

	Endoxifen	Tamoxifen
PKC Beta 1	0.1 uM	2.06 uM

Goetz et al.

Nature Pub – Dec ‘23 – Endoxifen Induces Apoptosis

npj | breast cancer

www.nature.com/npjbcancer

REVIEW ARTICLE OPEN

Check for updates

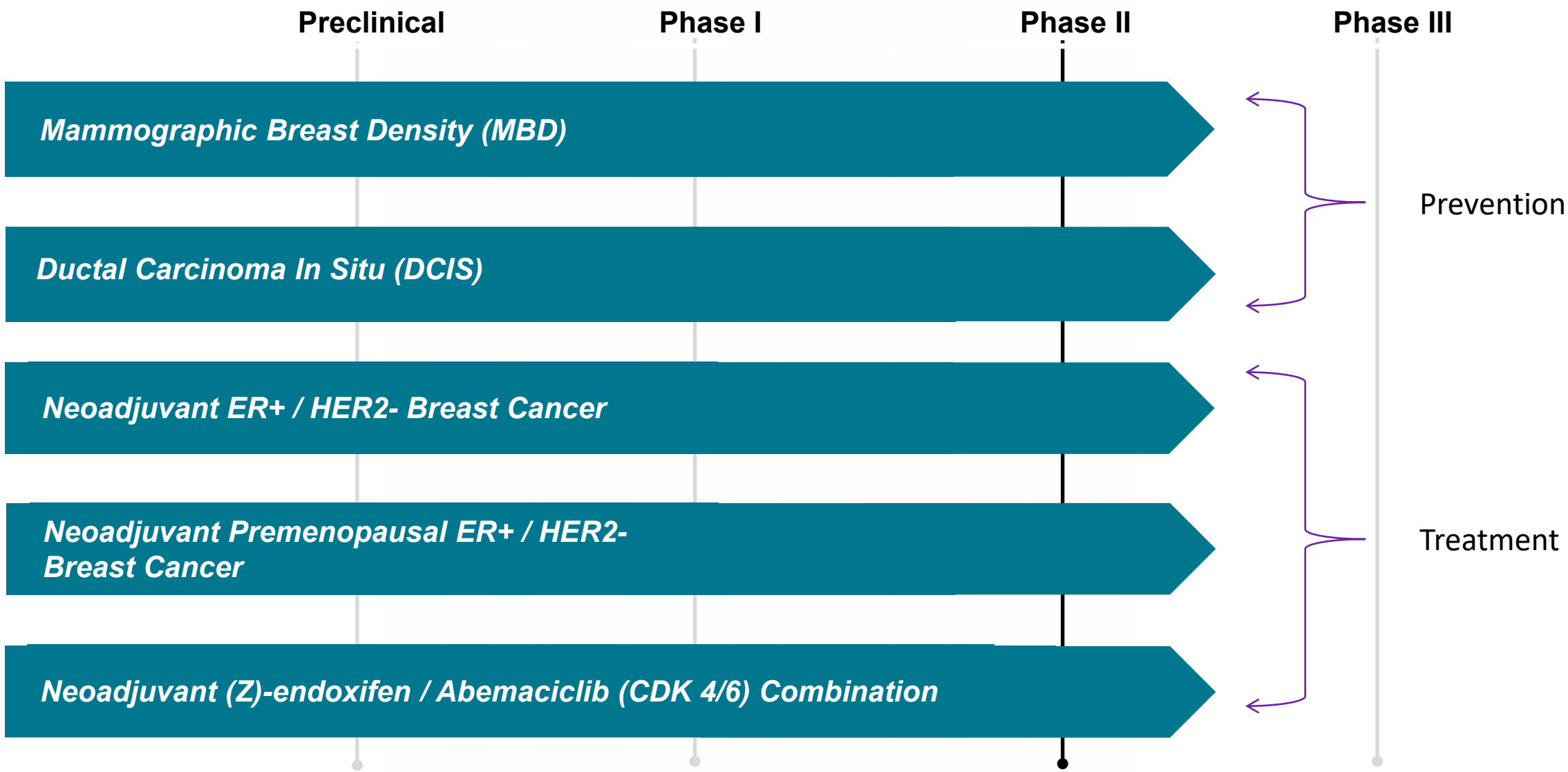
Endoxifen downregulates AKT phosphorylation through protein kinase C beta 1 inhibition in ERα+ breast cancer

Swaathi Jayaraman[1,8], Xinyan Wu[2,3,8], Krishna R. Kalari[4], Xiaojia Tang[4], Mary J. Kuffel[1], Elizabeth S. Bruinsma[5], Shahrzad Jalali[1], Kevin L. Peterson[1], Cristina Correia[1,3], Rachel A. Kudgus[1], Scott H. Kaufmann[1,3], Santosh Renuse[2], James N. Ingle[1], Joel M. Reid[1], Matthew M. Ames[1,3], Alan P. Fields[6], Matthew J. Schellenberg[5], John R. Hawse[5,7], Akhilesh Pandey[2,9] and Matthew P. Goetz[1,3,9]✉

Endoxifen, a secondary tamoxifen metabolite, is a potent antiestrogen exhibiting estrogen receptor alpha (ERα) binding at nanomolar concentrations. Phase I/II clinical trials identified clinical activity of Z-endoxifen (ENDX), in endocrine-refractory metastatic breast cancer as well as ERα+ solid tumors, raising the possibility that ENDX may have a second, ERα-independent, mechanism of action. An unbiased mass spectrometry approach revealed that ENDX concentrations achieved clinically with direct ENDX administration (5 μM), but not low concentrations observed during tamoxifen treatment (<0.1 μM), profoundly altered the phosphoproteome of the aromatase expressing MCF7AC1 cells with limited impact on the total proteome. Computational analysis revealed protein kinase C beta (PKCβ) and protein kinase B alpha or AKT1 as potential kinases responsible for mediating ENDX effects on protein phosphorylation. ENDX more potently inhibited PKCβ1 kinase activity compared to other PKC isoforms, and ENDX binding to PKCβ1 was confirmed using Surface Plasma Resonance. Under conditions that activated PKC/AKT signaling, ENDX induced PKCβ1 degradation, attenuated PKCβ1-activated AKT^{Ser473} phosphorylation, diminished AKT substrate phosphorylation, and induced apoptosis. ENDX's effects on AKT were phenocopied by siRNA-mediated PKCβ1 knockdown or treatment with the pan-AKT inhibitor, MK-2206, while overexpression of constitutively active AKT diminished ENDX-induced apoptosis. These findings, which identify PKCβ1 as an ENDX target, indicate that PKCβ1/ENDX interactions suppress AKT signaling and induce apoptosis in breast cancer.

npj Breast Cancer (2023)9:101 ; https://doi.org/10.1038/s41523-023-00606-2

Development Pipeline



Karisma-Endoxifen Study

Issue

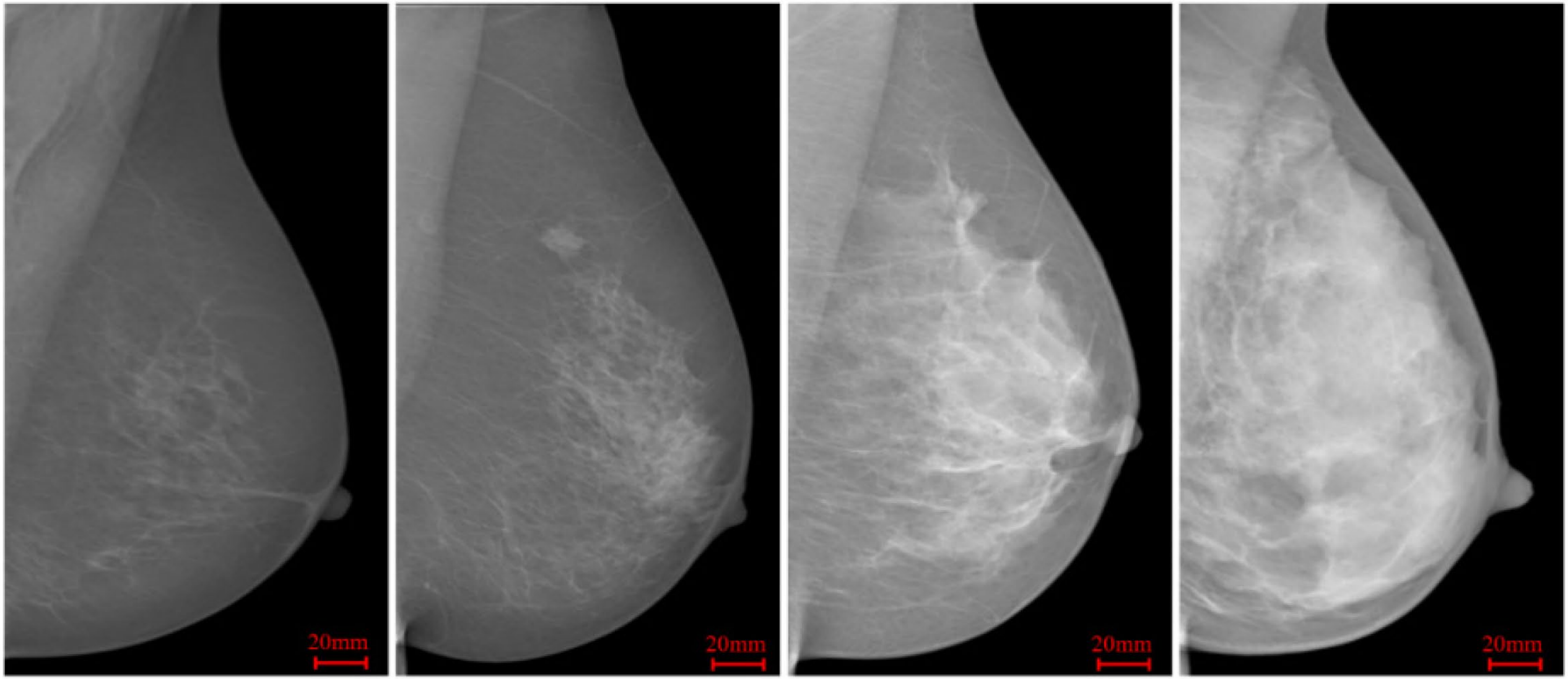
- 50% of the women in the world have dense breast tissue
  - Elevated density is a significant independent risk factor for developing breast cancer
  - Elevated density make mammograms less effective
  - Federal legislation goes into effect Sept. ‘24 requiring notification of density

Study

- Phase 2, randomized, double-blind, placebo-controlled, study of (Z)-endoxifen in premenopausal women with Measurable Breast Density (MBD)
  - (Z)-endoxifen 1 or 2 mg/day (or PBO) for 6 months
  - Endpoints – change from baseline in MBD at 3 and 6 months and durability of change at 24 months
  - Fully enrolled (n=240) Nov. ’23
  - Six-month density reduction data 2H ‘24

*NCT05068388

Mammographic Breast Density



BI-RADS I | BI-RADS II | BI-RADS III | BI-RADS IV

EVANGELINE – Neoadjuvant

Issue

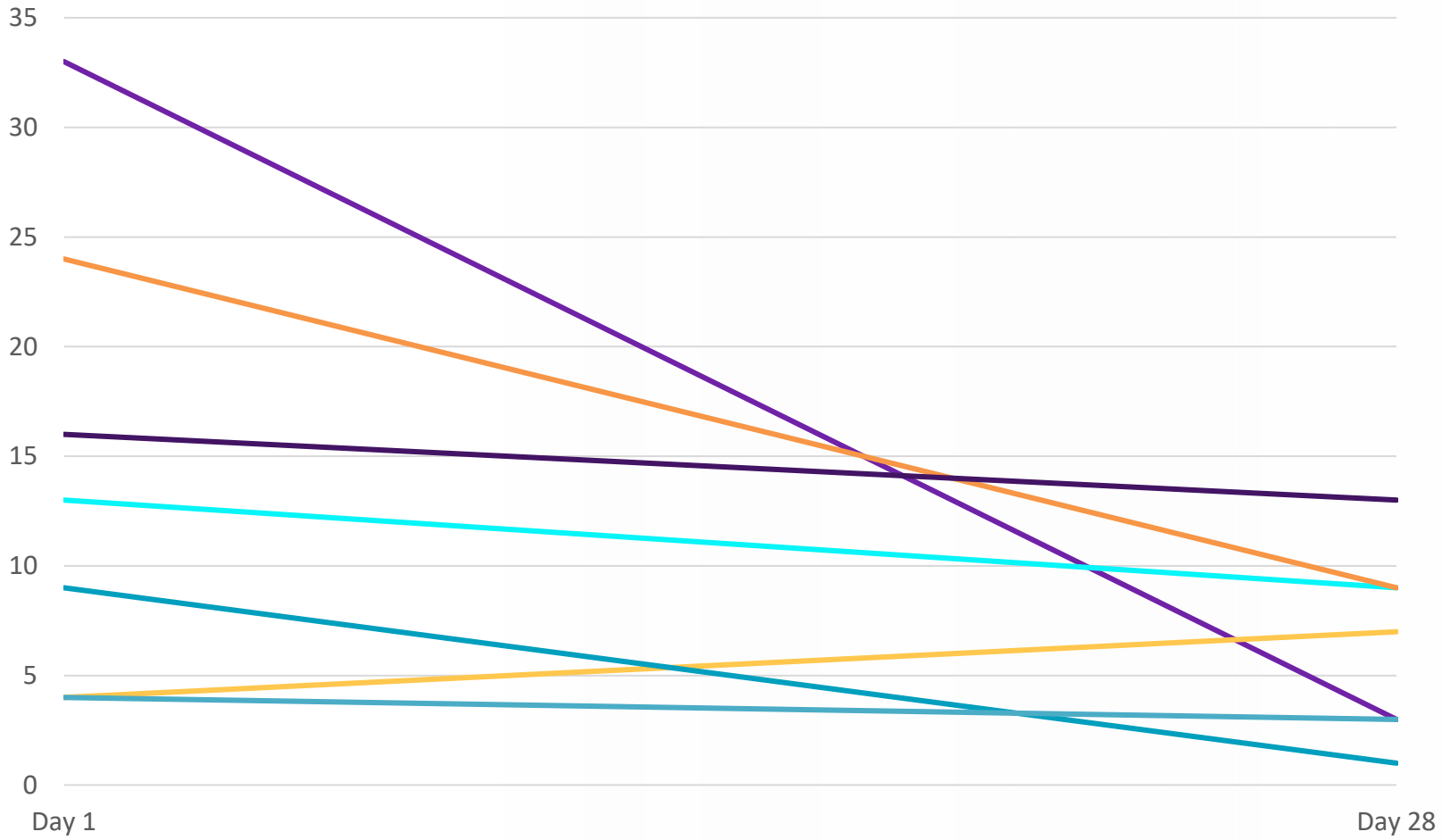
- No effective neoadjuvant therapies for premenopausal ER+ BC
  - Endocrine therapies require ovarian suppression in premenopausal women
  - Adverse event profile leads to compliance challenges
  - Lack of safe and effective neoadjuvant treatment options reduces effectiveness of surgery and increases risk of recurrence

Study

- Phase 2 study of (Z)-endoxifen in premenopausal women with ER+ / HER2- BC
  - Participants receive (Z)-endoxifen daily for six months
  - Began with PK run-in to determine optimal dose to target PKCβ1 inhibition
  - 40mg PK run-in cohort completed in ‘23
  - Endpoints – Ki-67 reduction and objective response – assessed by MRI and pathology
  - 40mg safety and efficacy data presented at AACR (April 2024)
  - 80mg PK data expected Q2 ‘24

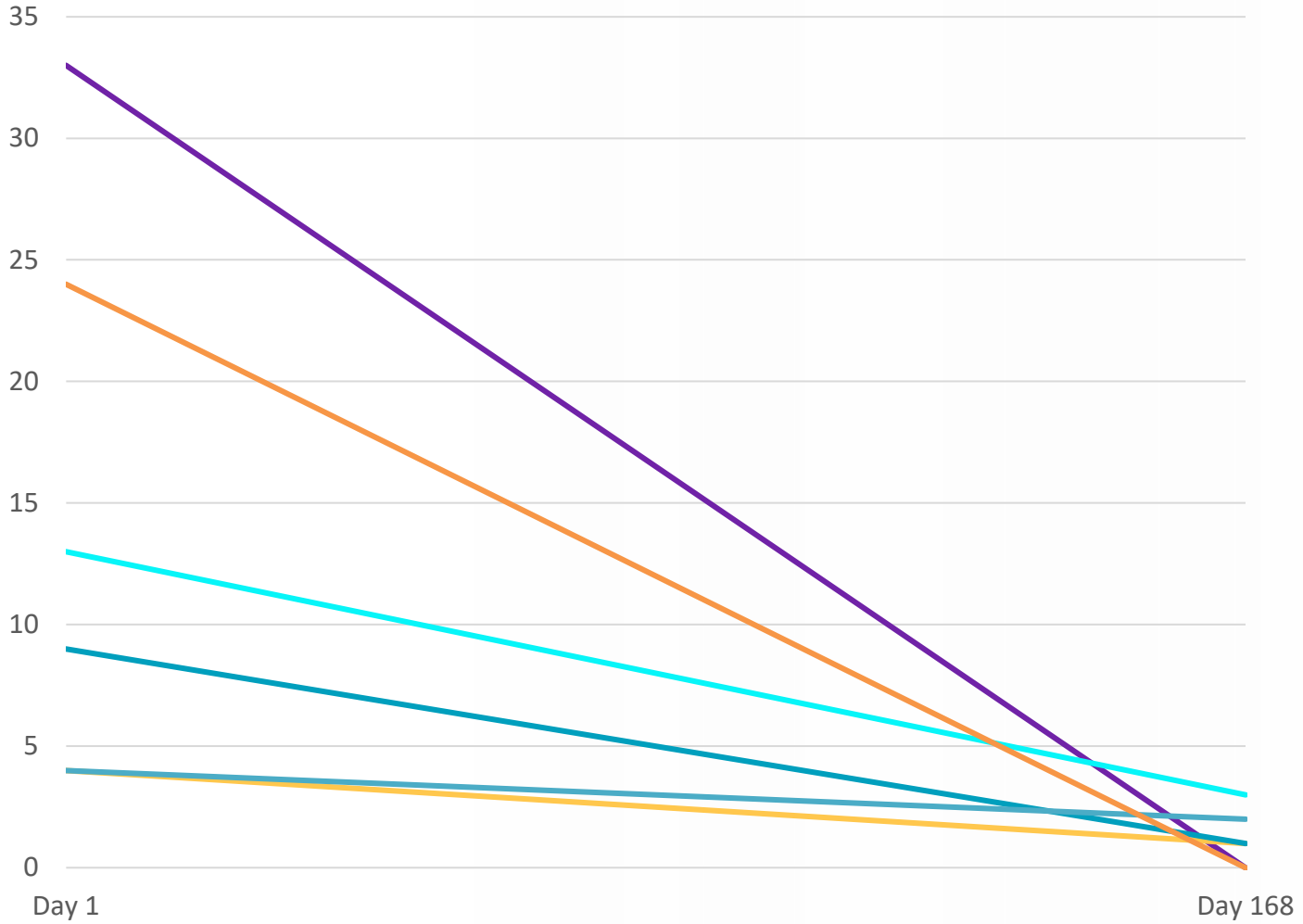
*NCT05607004

KI-67 Reduction - Baseline to Day 28



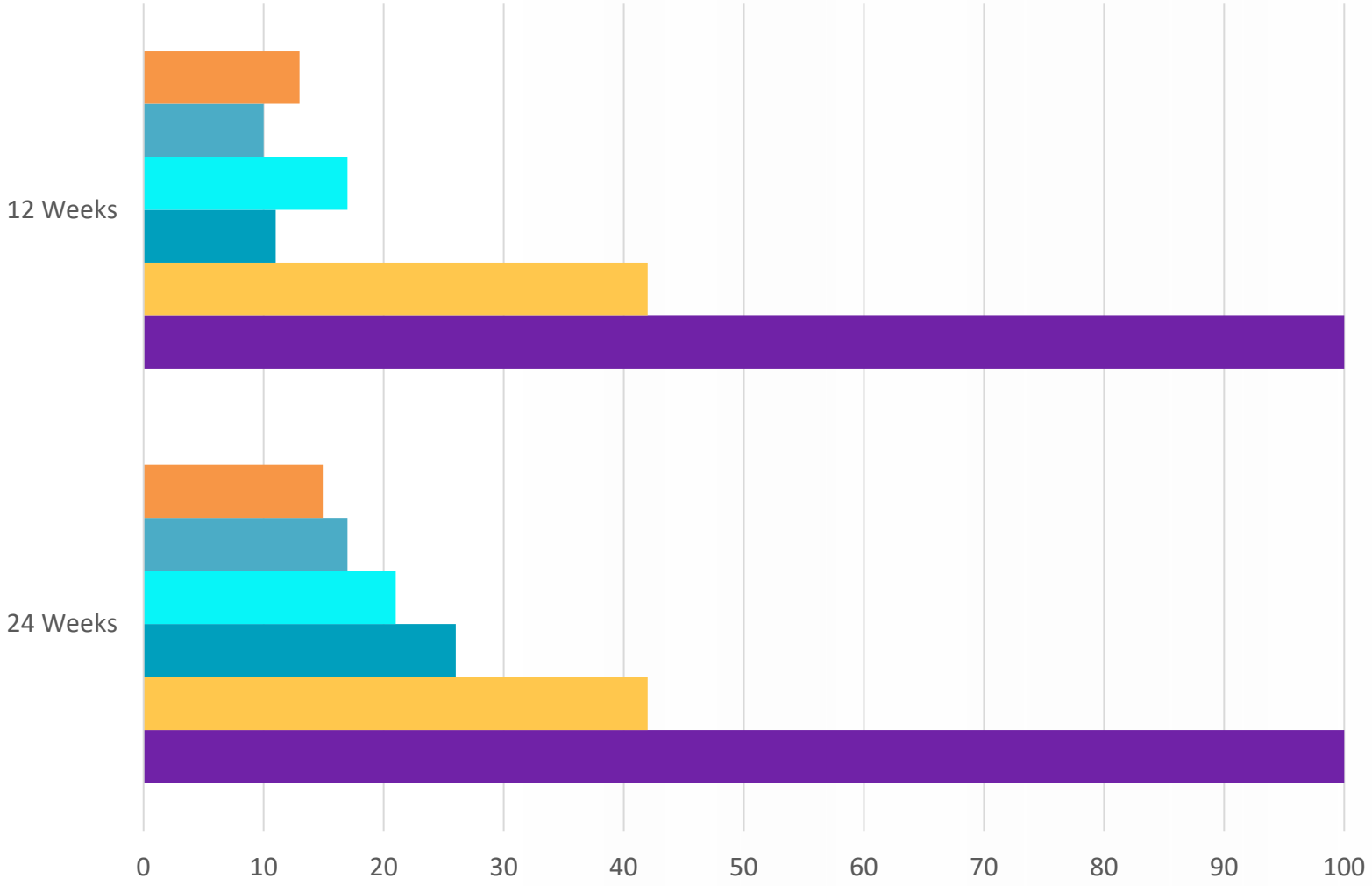
Patient	Ki-67 Day 1	Ki-67 Day 28	% Change
1	33	3	91%
2	4	7	75%
3	9	1	89%
4	13	9	31%
5	4	3	25%
6	24	9	63%
7	16	13	19%
Total	103	45	56%

KI-67 Reduction - Baseline to Six Months



Patient	Ki-67 Day 1	Ki-67 @ 6 Months	% Change
1	33	0	100%
2	4	1	75%
3	9	1	89%
4	13	3	77%
5	4	2	50%
6	24	0	100%
Total	87	7	92%

% Decrease in Tumor Size



Average target lesion reduction at 12 weeks = 32%

Average target lesion reduction at 24 weeks = 37%

Adverse Event	Grade			
	2	3	4	5
Headache	0	1 (14.3%)	0	0
Amenorrhea	1 (14.3%)	0	0	0
Hot Flashes	1 (14.3%)	0	0	0

I-SPY 2 – Neoadjuvant Combination

Issue

- Women with high clinical stage but less proliferative tumors are particularly challenging to treat
  - High risk of late recurrence
  - Currently approved CDK 4/6 combination therapies have sub-optimal safety profile

Study

- Phase 2 neoadjuvant study of (Z)-endoxifen in combination with *abemaciclib* (VERZENIO) in women diagnosed with ER+ / HER2- invasive breast cancer
  - Co-sponsored by Atossa and Eli Lilly & Company
  - Part of the largest and most successful platform trail in history
  - Participants receive 40mg (Z)-endoxifen and 150mg *abemaciclib* daily for six months
  - Endpoints – Ki-67 reduction and objective response – assessed by MRI and pathology
  - Initiated April ‘24

*NCT01042379

Near Term Catalysts / Capital Table

Near Term Catalysts

- Mammographic Breast Density
  - Density reduction data available 2H ’24
- I-Spy
  - 10mg neoadjuvant data available 2H ‘24
- EVANGELINE
  - 80mg PK run-in cohort completion 2Q ‘24
  - Treatment arm initiated – 2H ’24
- DCIS
  - Enrollment updates throughout ‘24
- Combinations
  - CDK 4/6 - enrollment updates throughout ’24
  - ADC – clinical start TBD

Key Metrics

- Cash (as of 12/31/23)
  - $88.5M – represents approx. three years working capital
  - Zero debt
- Nasdaq: ATOS (as of 4/26/24)
  - Market Cap - $192M
  - Share Price - $1.53
  - 52 Week Range - $0.59 - $2.31
- Outstanding Warrants / Options (as of 12/31/23)
  - 11.0M warrants exercisable at $1.00 or $1.05/share
  - 10.5M warrants exercisable at $2.88/share
  - 13.7M options exercisable at average $2.04/share

Atossa THERAPEUTICS

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