ESR1 mutations: A Mechanism for Acquired Endocrine Resistance

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- Introduction
- New insights for ESR1 mutations in MBC
- New diagnostic strategies
- Therapeutic strategies
- Summary

Endocrine Therapy: The 1st Target Tx

Dr. Schinziner &
Sir. Beatson GT

1870

1st description of surgical oophorectomy

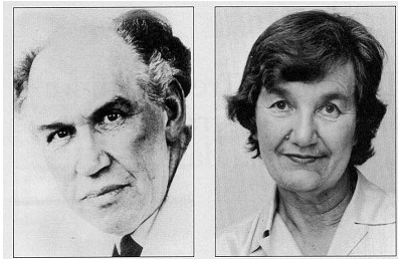
1940's

Full range of ablative hormonal therapy developed

1950's

Era of Additive hormonal therapy

Dr. Arthur Walpole/Dr. Dora Richardson



1970's

Development of Tamoxifen

1980's

ER/PR detection and resurgence in interest in endocrine Rx

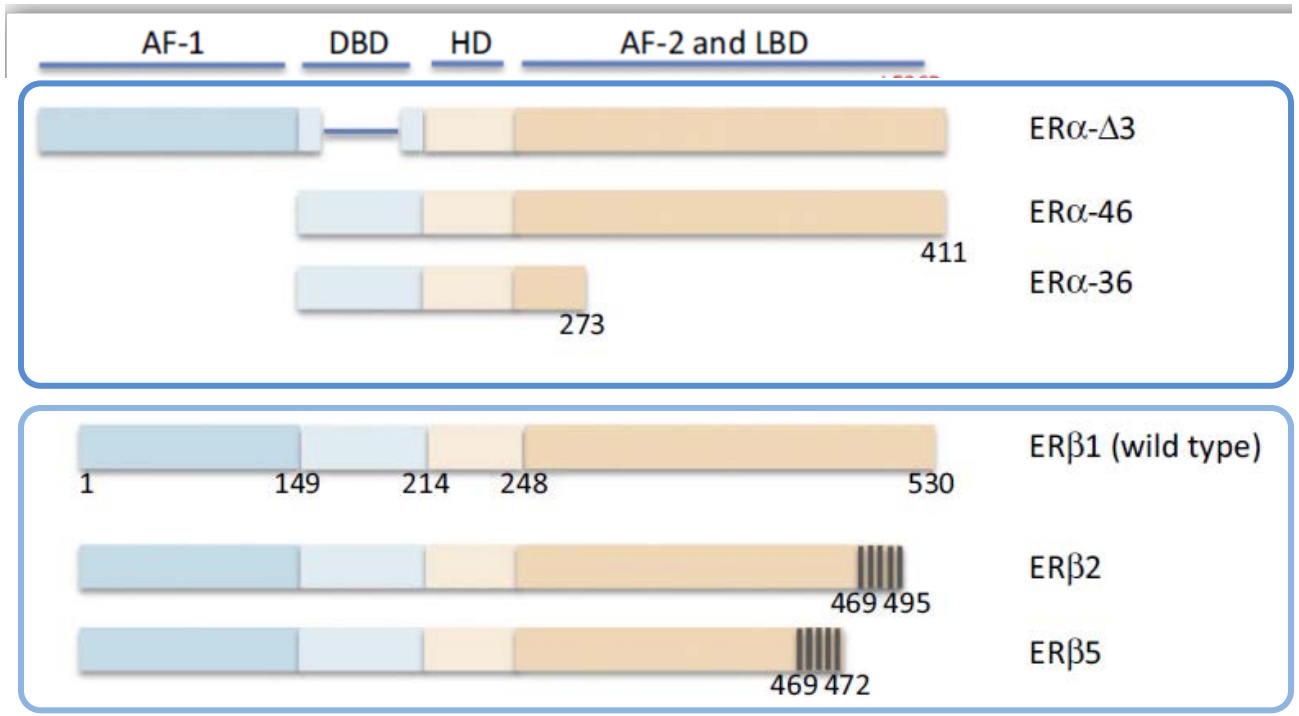
IHC Detection

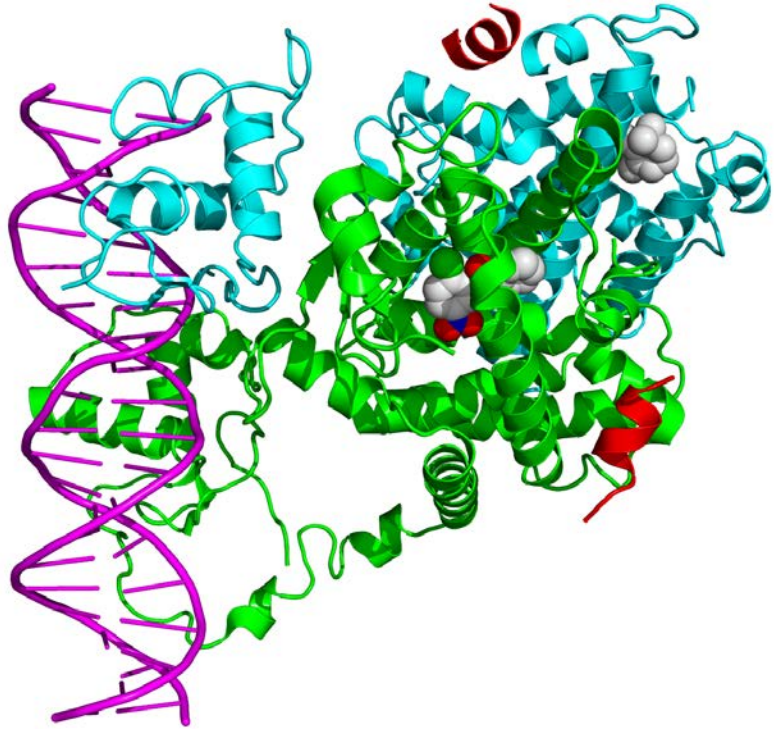
1990's

Demonstration of the therapeutic efficacy of Tamoxifen

Lancet 1896;2:104–7.

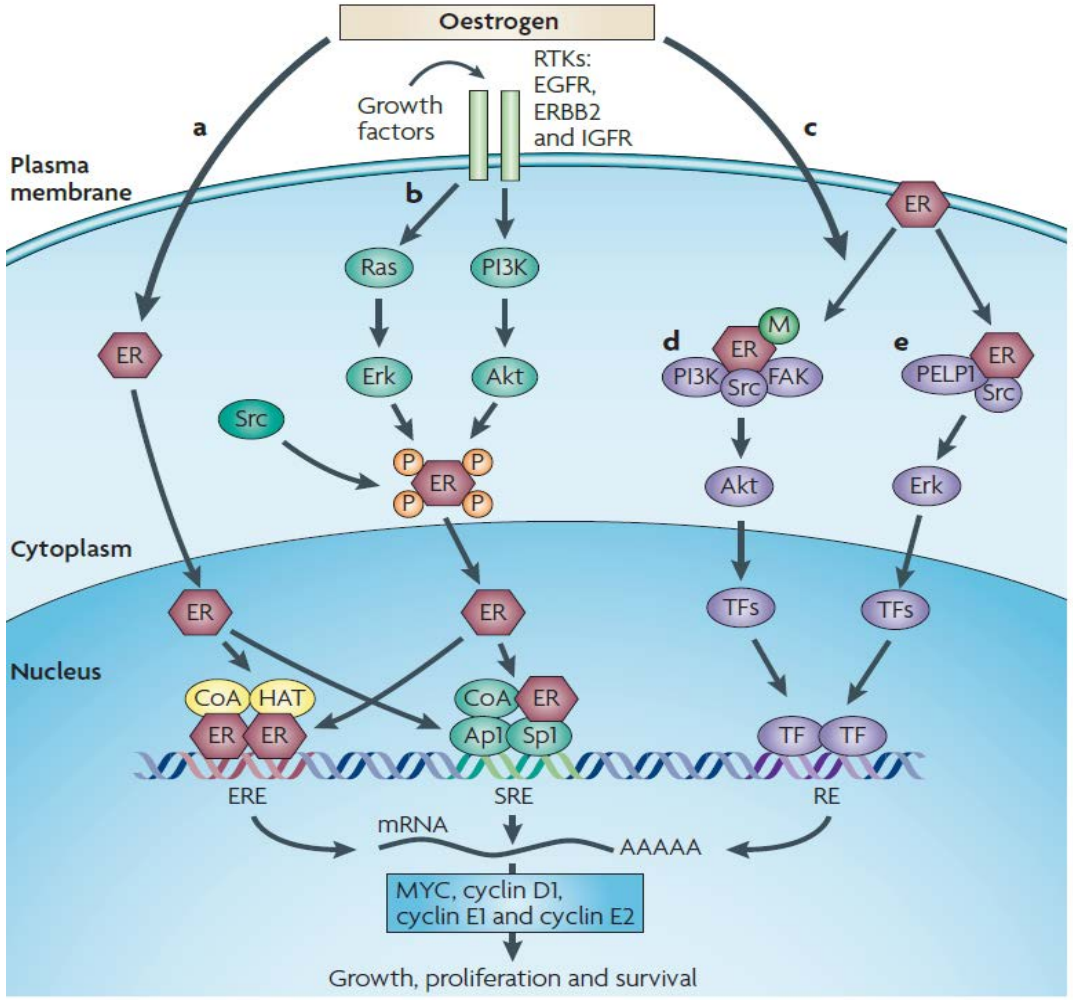
Genomic & Functional Structure of Estrogen Receptors





Trends in Endocrinology and Metabolism, September 2015

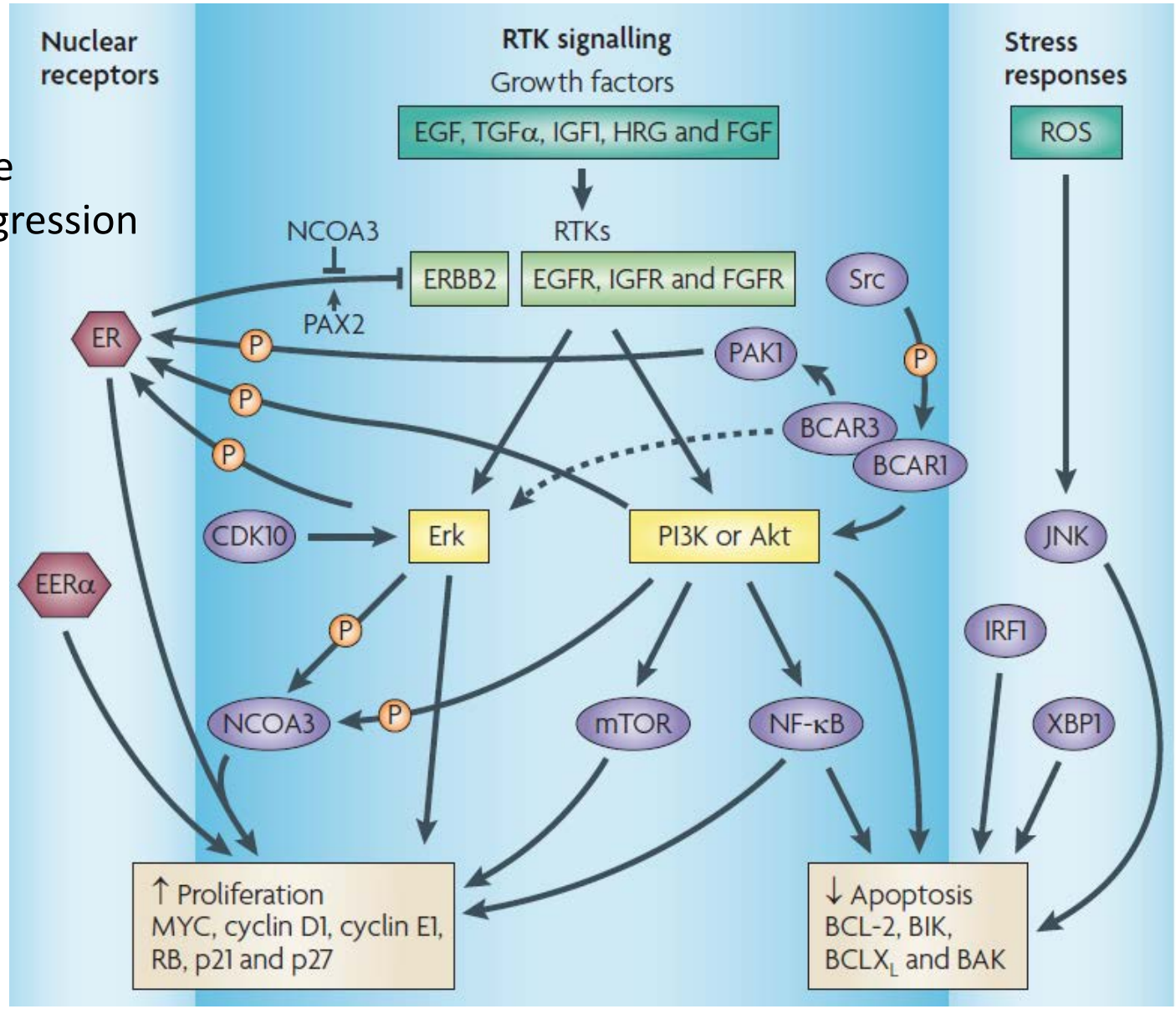
Signaling through ER



Nat Rev Cancer

Molecular Mechanisms of Endocrine Resistance

EBC: ~25% Resistance
MBC: ~30% initial regression

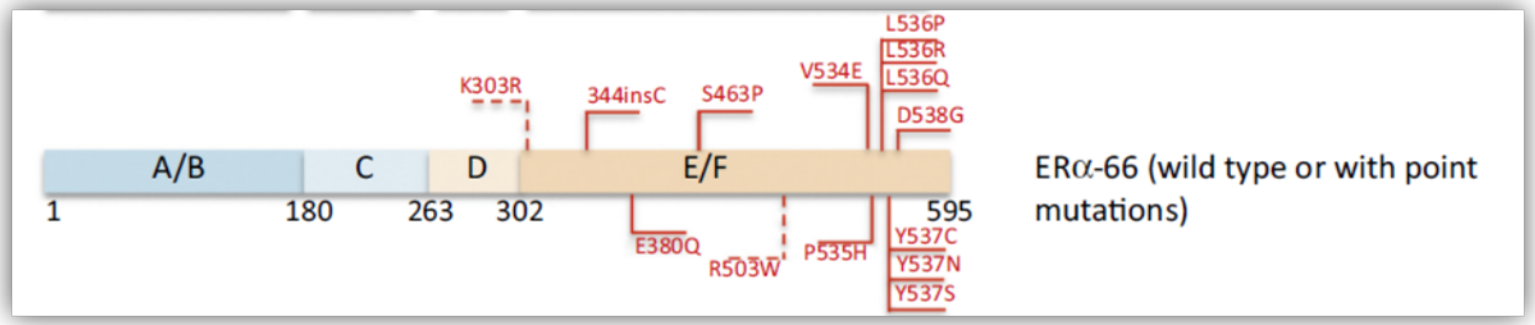


Nat Rev Cancer

TCGA data

- **N=962** breast cancer samples
- Frequency > 5% in Luminal types: *PIK3CA, TP53, MAP3K1, MAP2K4, GATA3, MLL3, CDH1*, and *PTEN*

- **ESR1 genes**: mutations 0.5%, amplifications 2.6%



MSKCC. The cBioPortal for Cancer Genomics [online], http://www.cbioportal.org/ (2015)

Nature 490, 61–70 (2012)

ESR-1 Genomic Alterations in MBC

- ***ESR1* amplifications**: 0-23%
  - mechanism for endocrine resistance and treatment failure

- ***ESR1* Genomic rearrangements**: *ESR1-CCDC170, YAP1-ESR1*
  - transcriptional dysregulation
  - ↑motility, tumorigenecity, resistance to fulvestrant

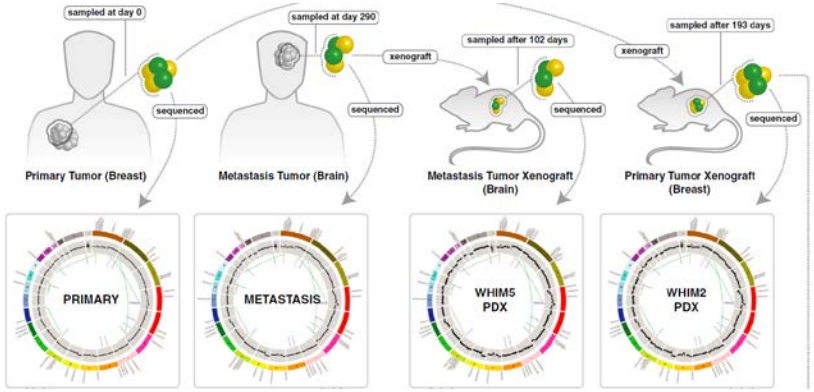
- ***ESR1* missense mutations**

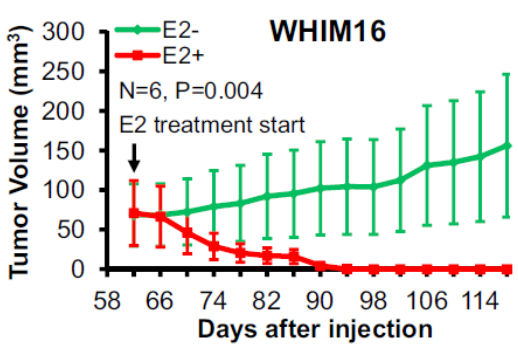
Genomic Characterization of *ESR1* Variants by Breast cancer PDX

PDXs study

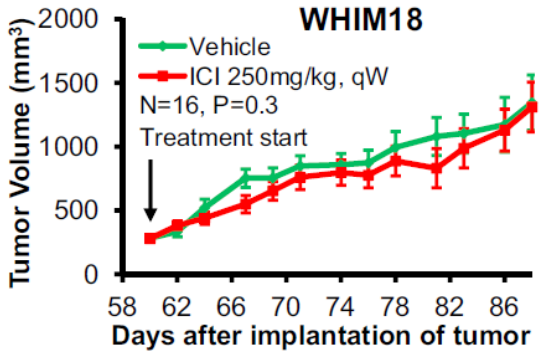
7 ER+ PDXs/Met

3*/7

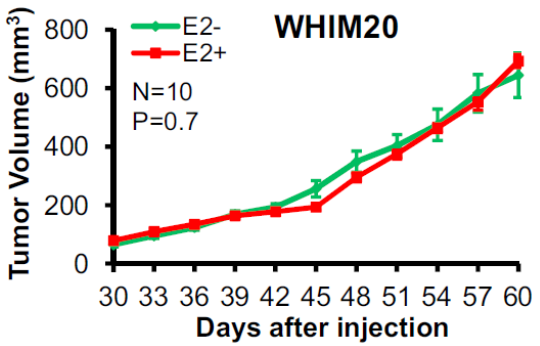




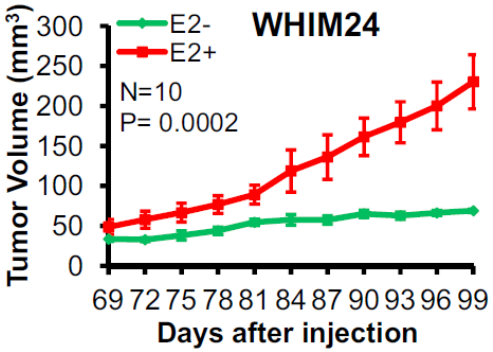
ESR1 amplification



ESR1-YAP1



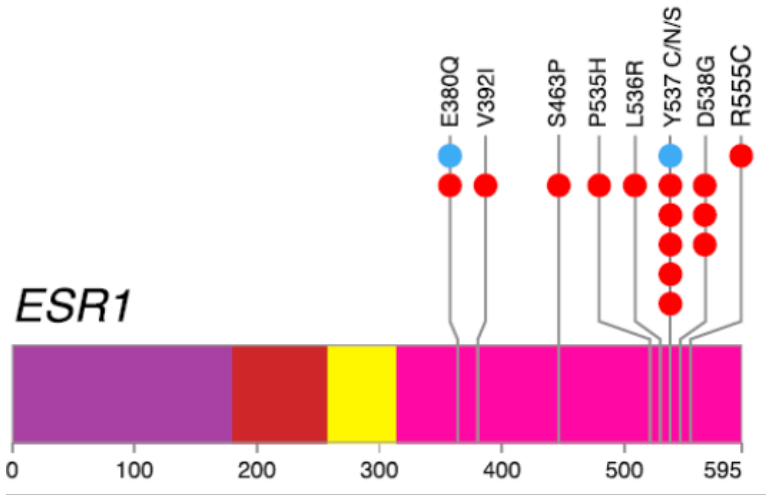
ESR1-Y537S

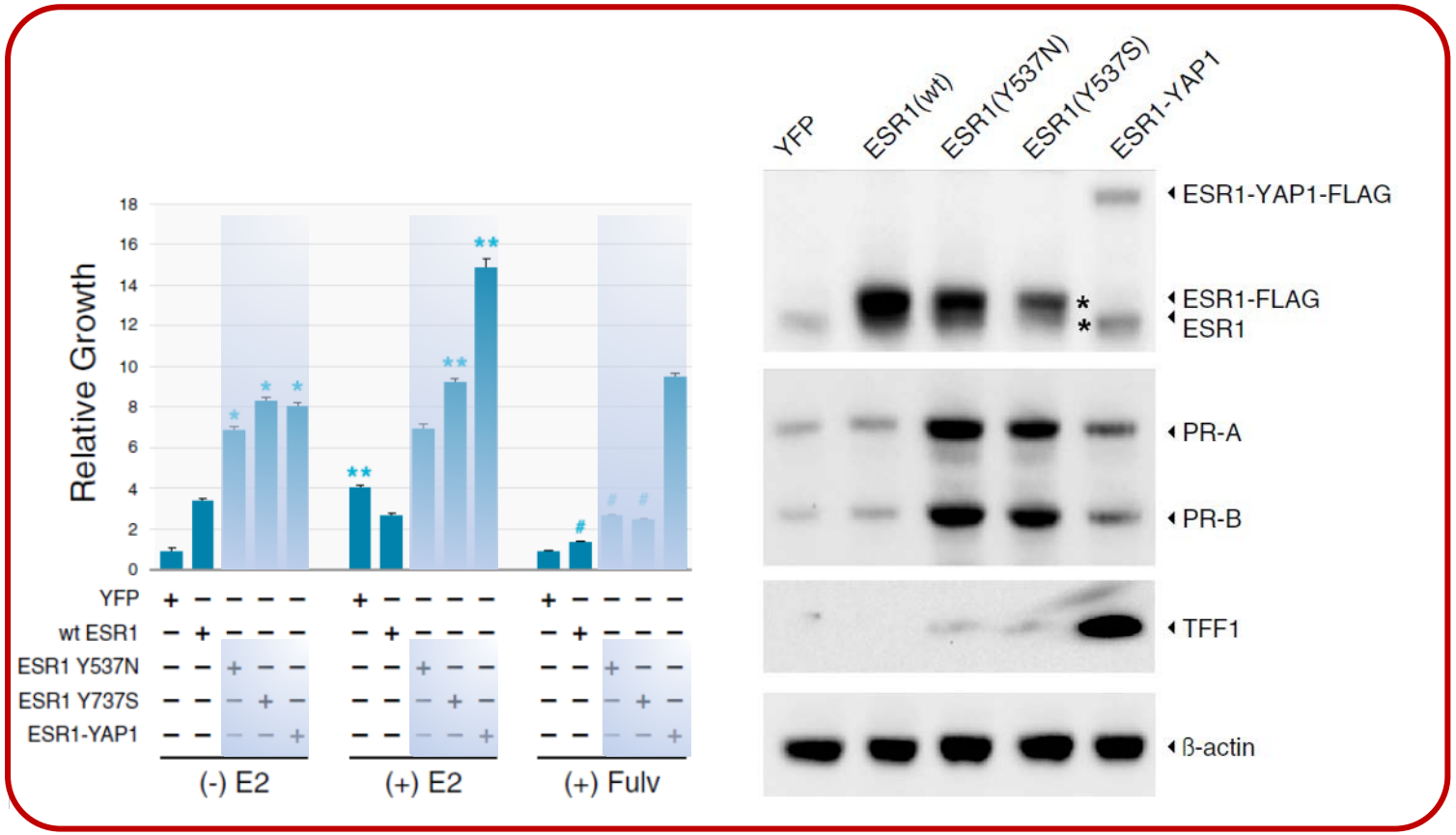


ESR1-E380Q

Cell Reports 4, 1116–1130, September 26, 2013

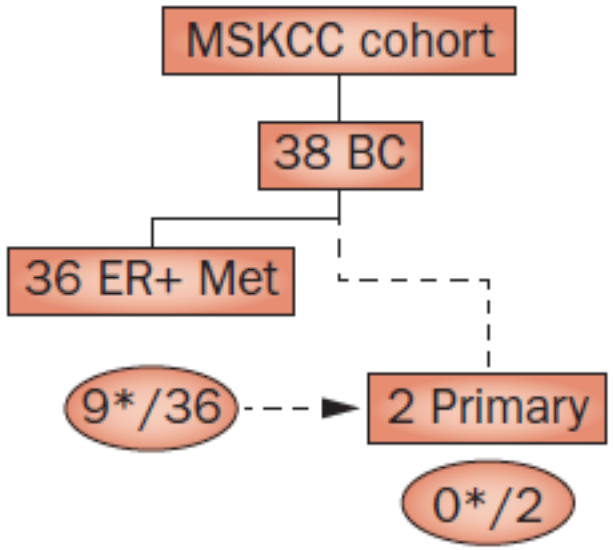
Biologic Consequences

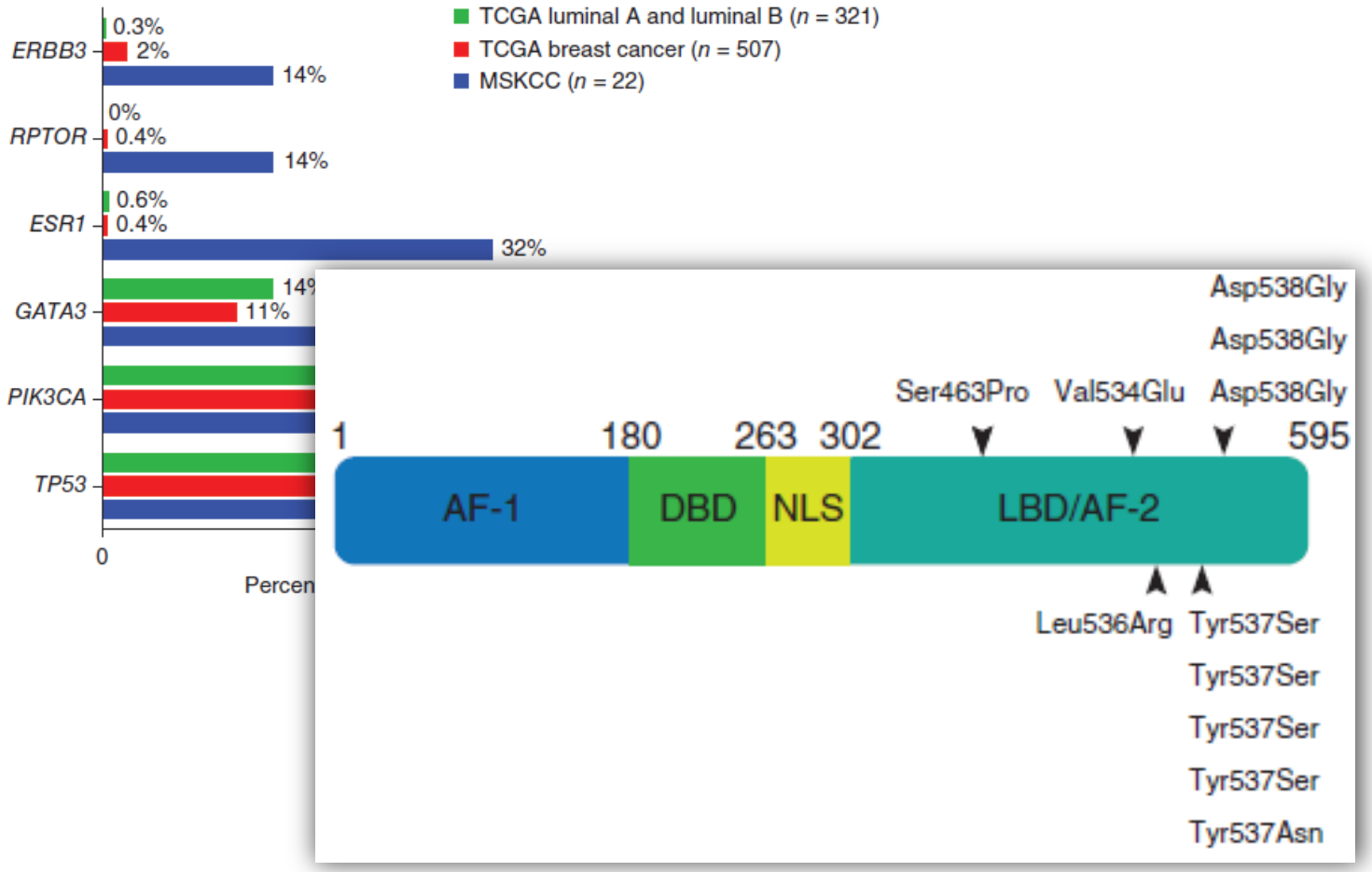




Cell Reports 4, 1116–1130, September 26, 2013

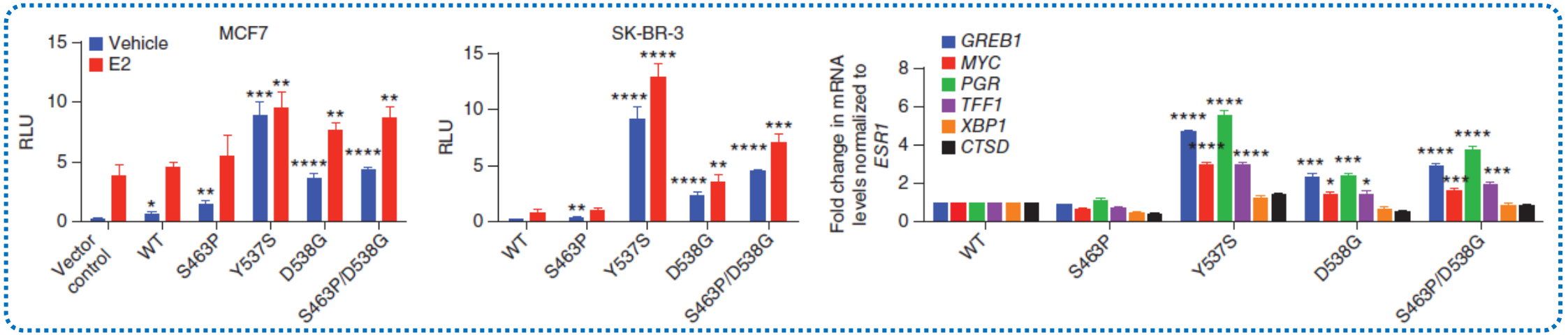
ER-LBD-activating *ESR1* mutations

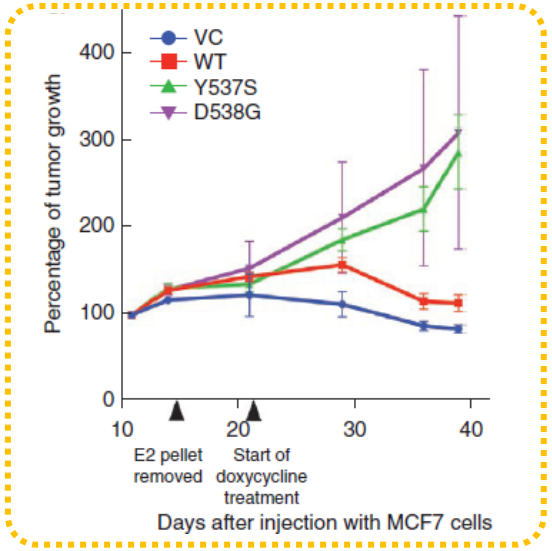


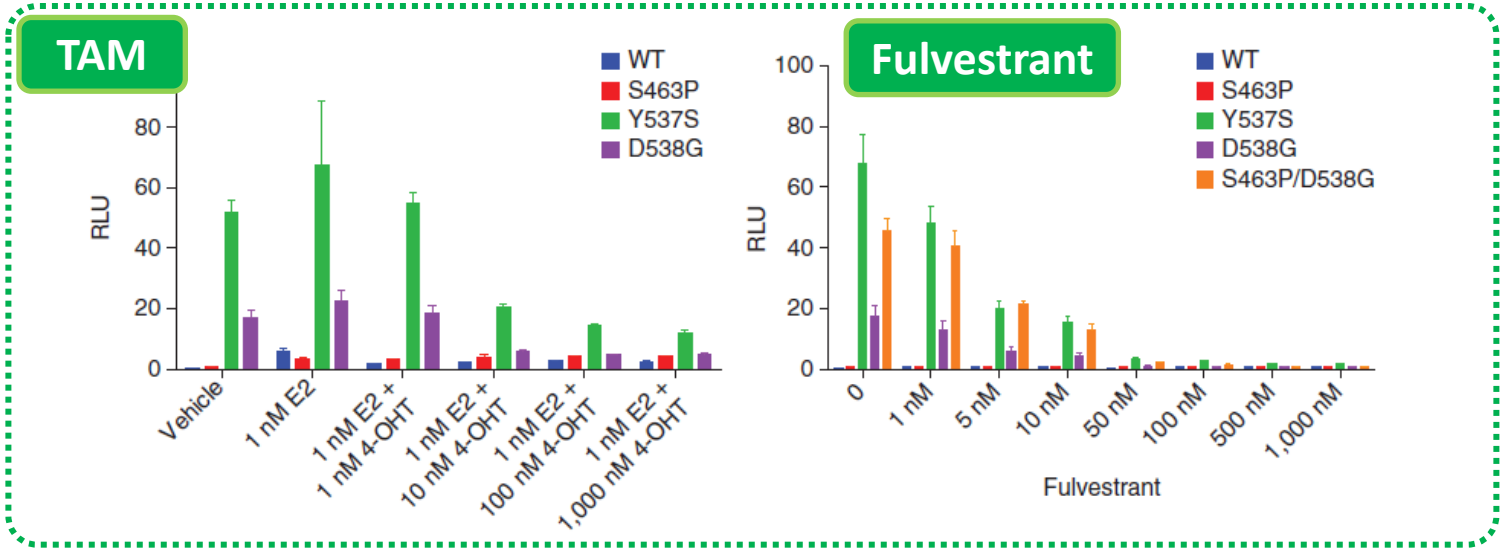


2013 Nat Genet

Endocrine resistant Biology

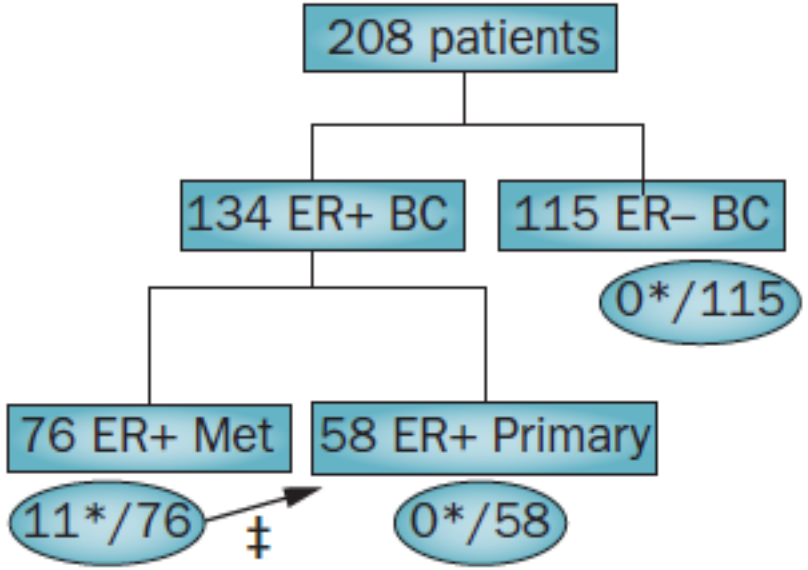


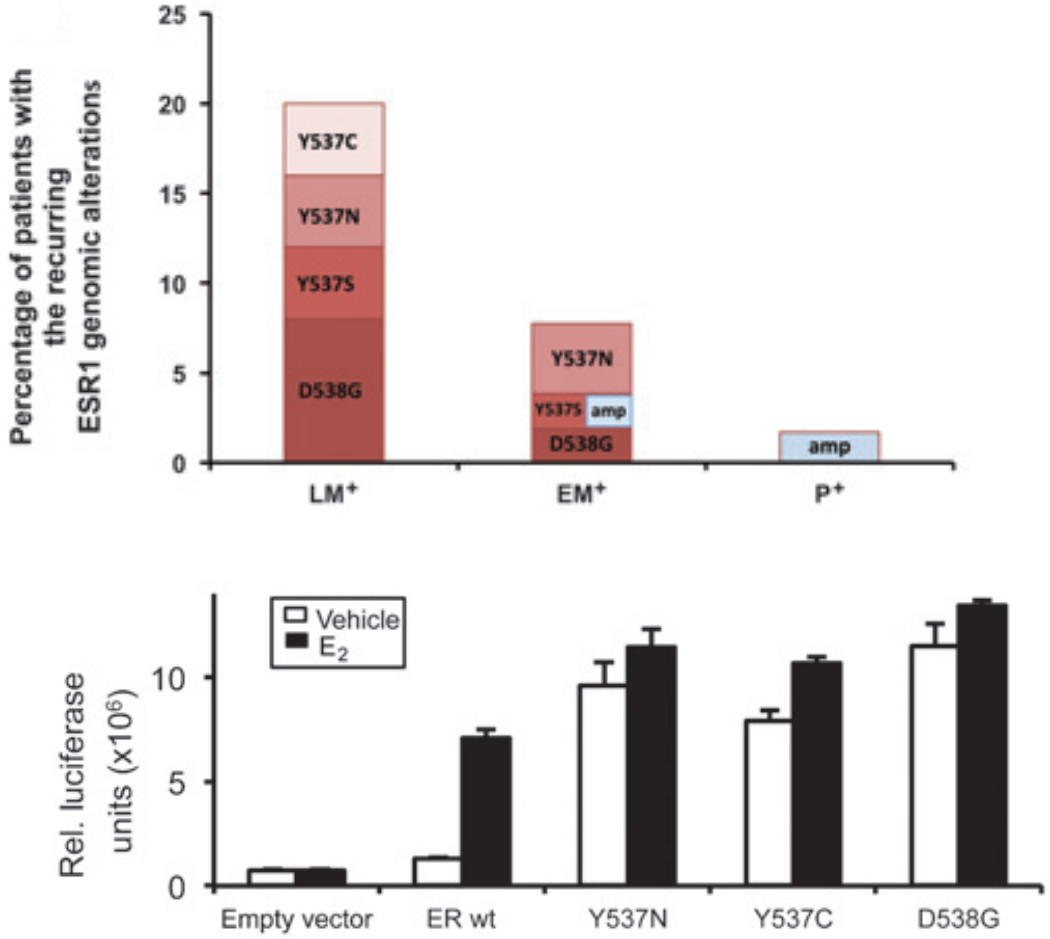




2013 Nat Genet

Emergence of Constitutively Active *ESR1* Mutations in Pretreated ABC

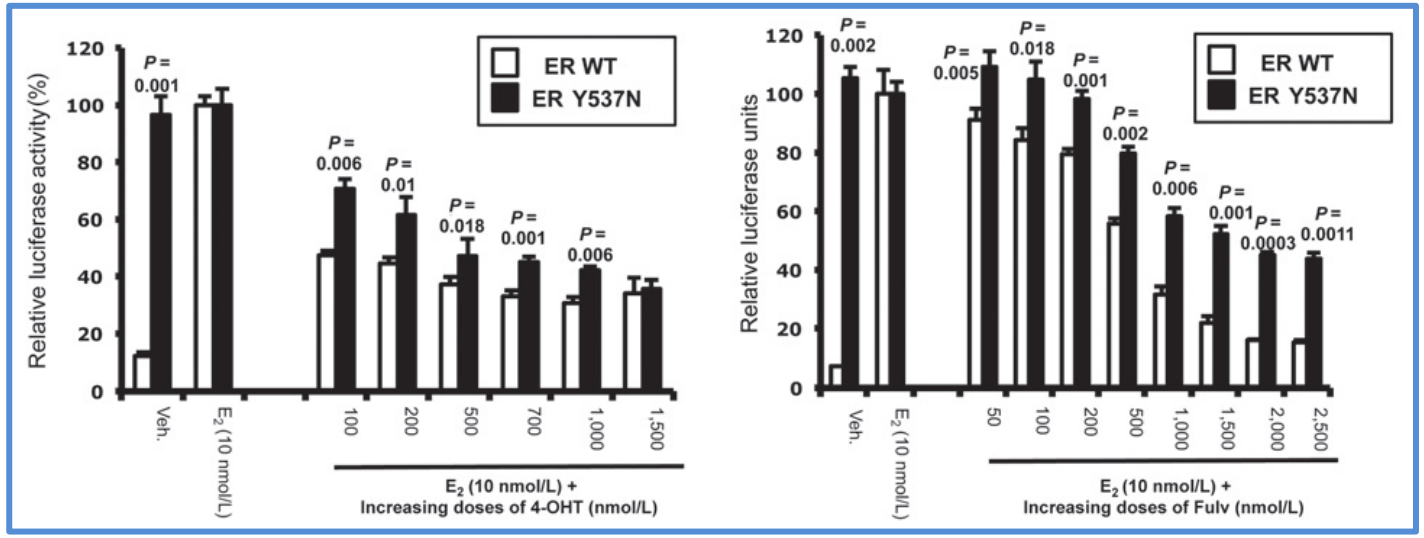




Clin Cancer Res; 20(7) April 1, 2014

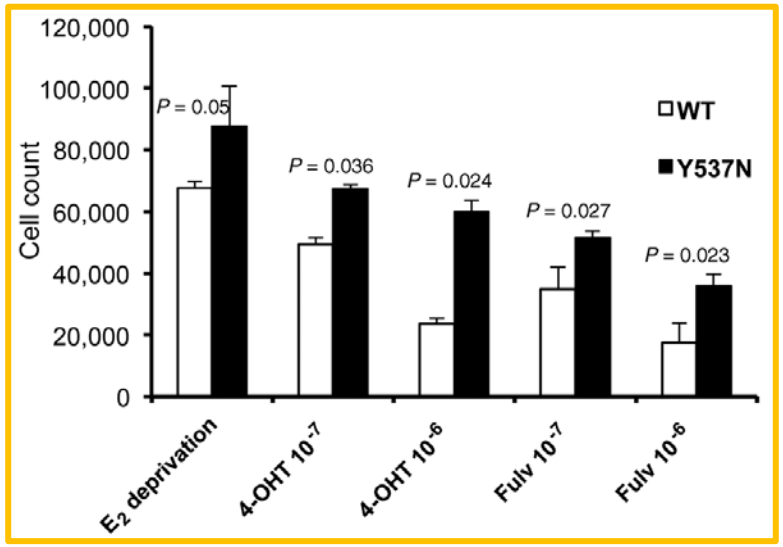
LBD mutations and Endocrine Resistance

Tamoxifen



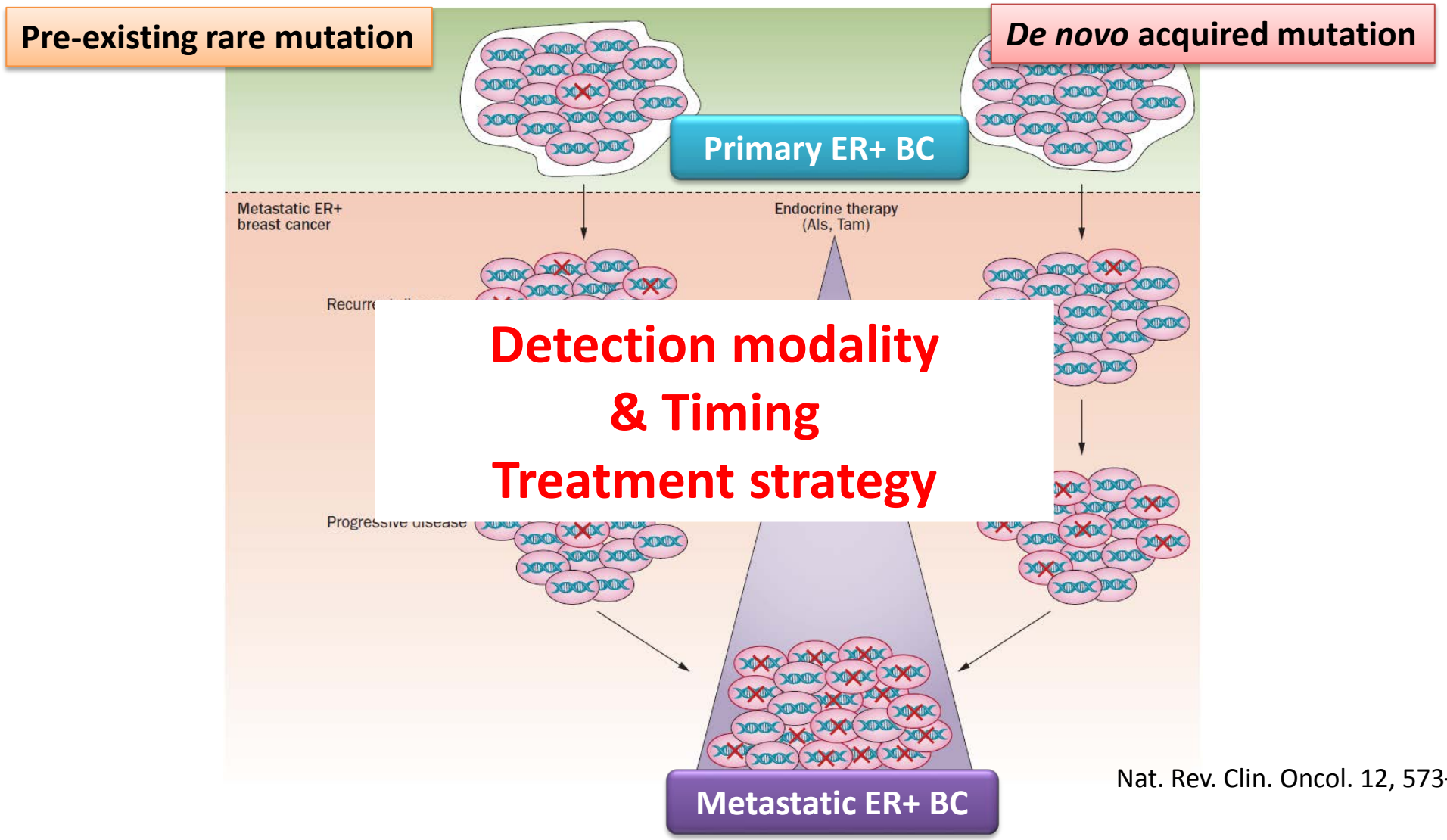
Fulvestrant

Cell Survival



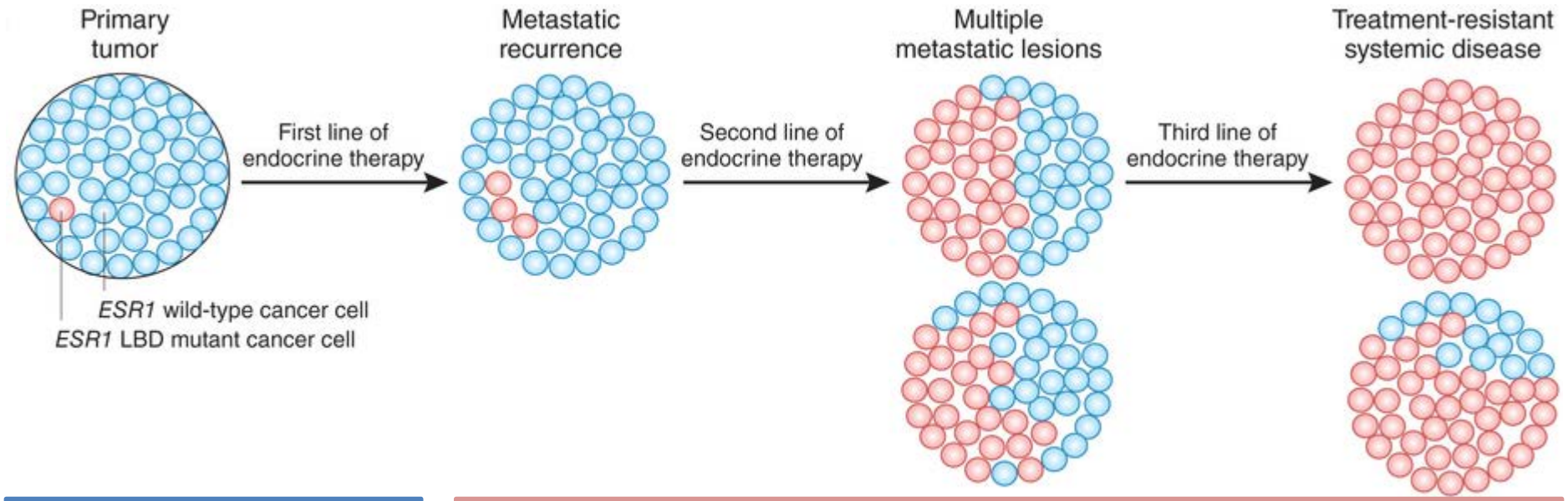
Clin Cancer Res; 20(7) April 1, 2014

Scenarios for Clonal Selection of rare *ESR1* Mutation



Nat. Rev. Clin. Oncol. 12, 573–583 (2015);

Detection of rare *ESR1* Mutation



- Very low mutational frequency

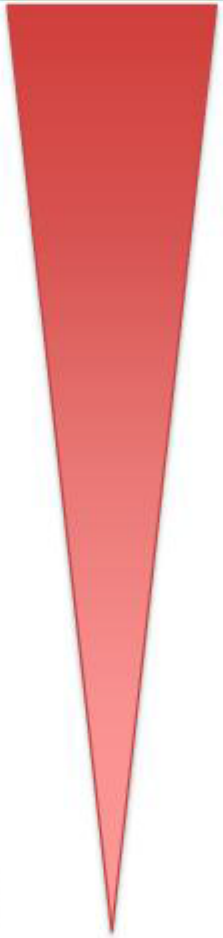
- Limited availability of tissue
- Monitoring by repeated test

More sensitive platform & Liquid biopsy

Nature Medicine 20, 344–346 (2014)

Emerging detection Platforms

ctDNA detection method	Detection limit
Sanger sequencing	>10%
Pyrosequencing	10%
Whole exome sequencing	**5%**
Whole genome sequencing	**1%**
Allele-specific PCR	0.1-1%
Digital PCR (BEAMing, ddPCR, etc.)	0.01%
Targeted NGS (CAPP-Seq, Safe-SeqS, etc.)	**≤0.01%**



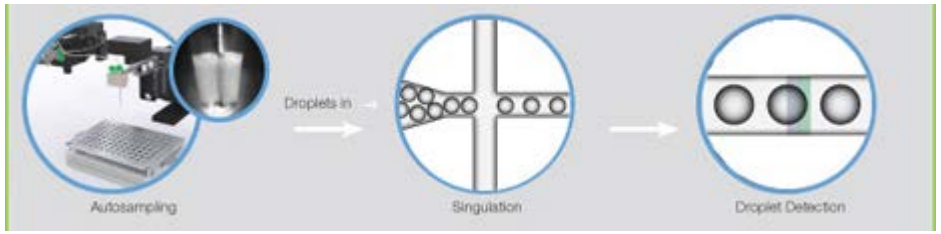
Diehn M. 2015 SABCS

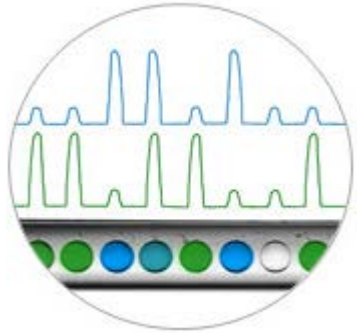
Droplet Digital PCR

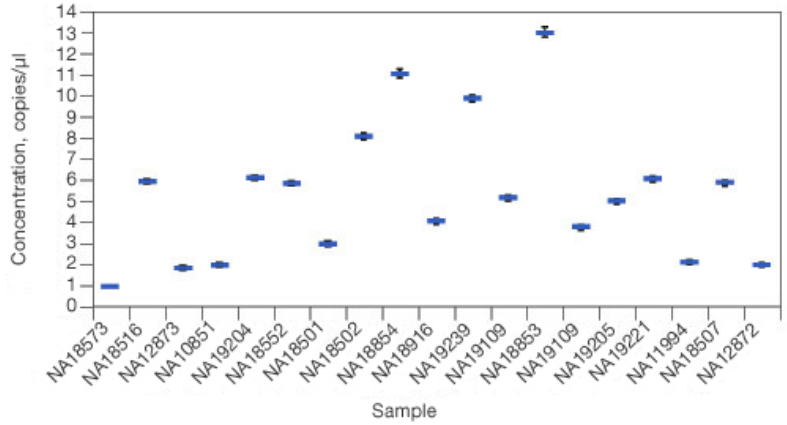
One measurement

Nanodroplet PCR reactions are independent, single amplification events

Many thousands of discrete measurements

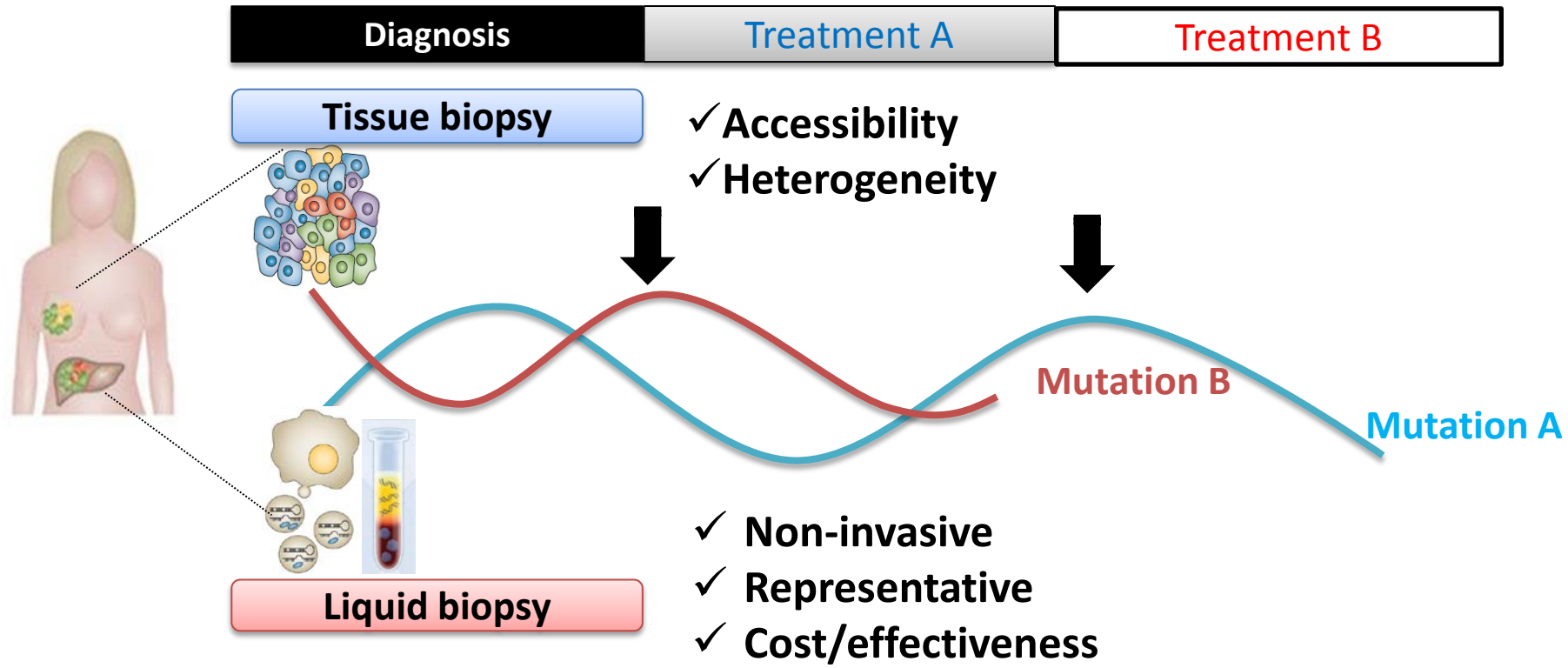






www,bio-rad.com

Application of Sensitive Detection Platforms

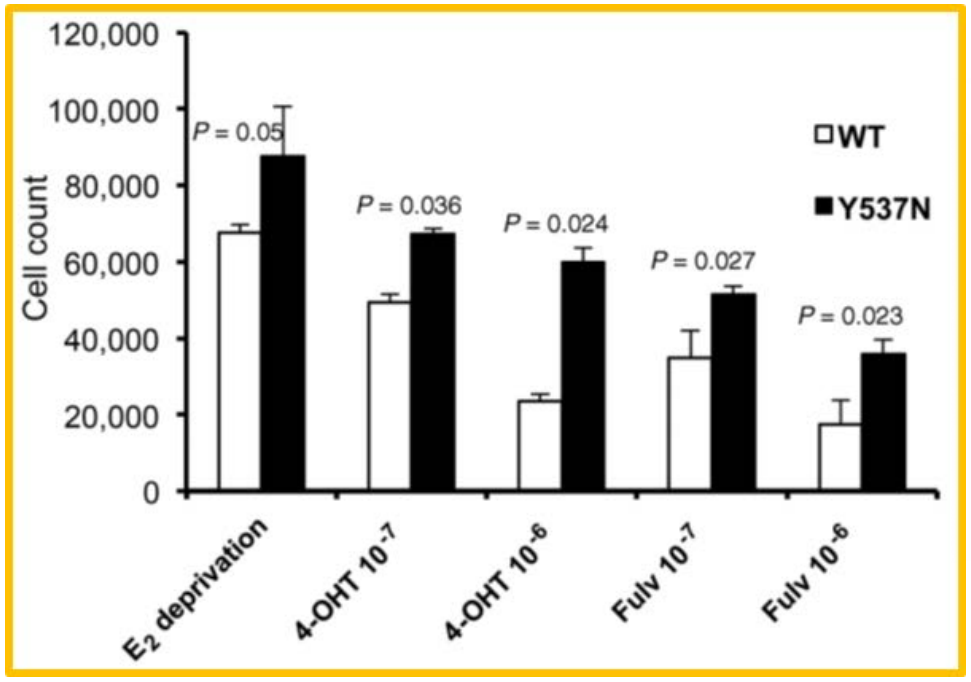


Non-invasive Genotyping of cancer

→ Prognosis/ Section of Treatment/ Disease monitoring (MRD)

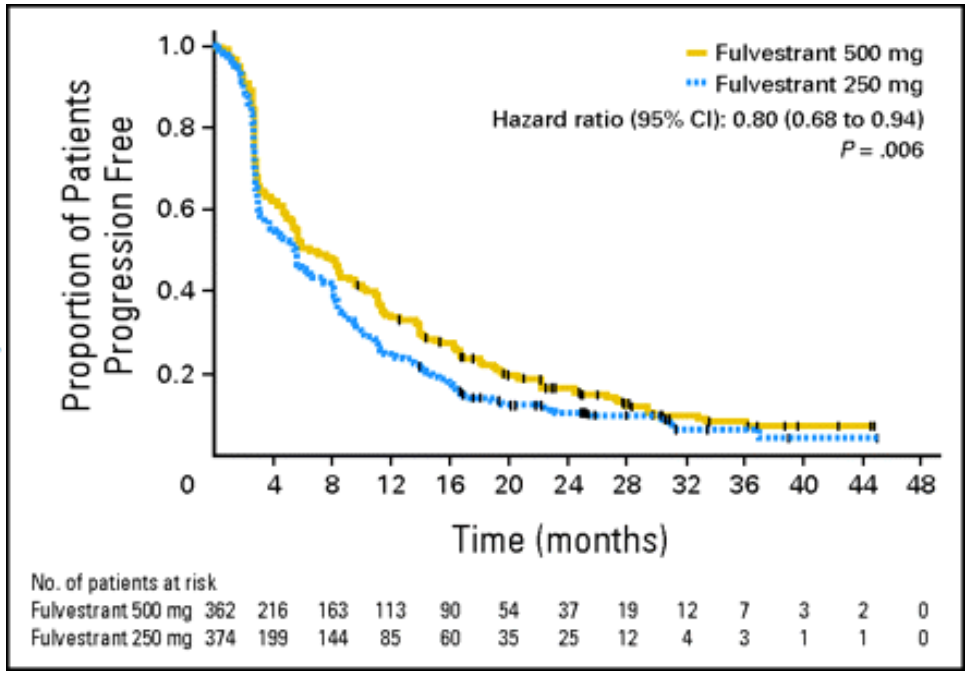
New Treatment Strategies: HD Endocrine

In vitro Study



CONFIRM Study

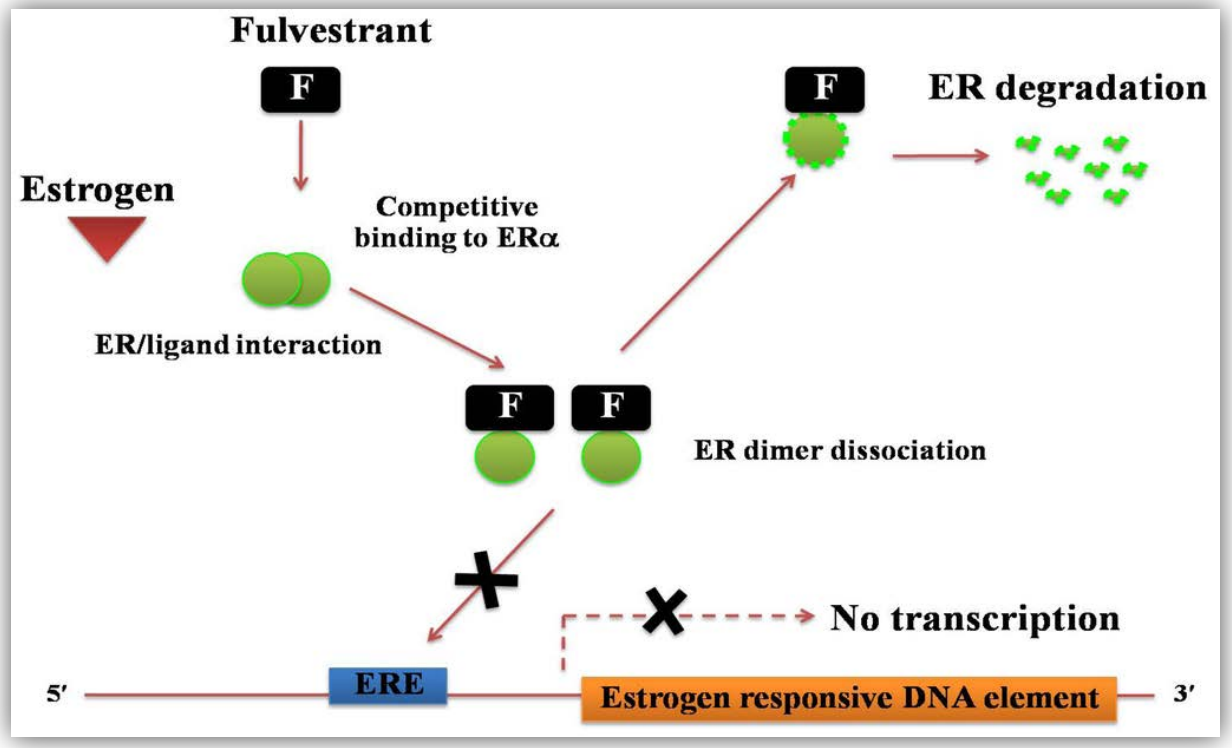
: Fulvestrant 250mg vs 500mg



Clin Cancer Res; 20(7) April 1, 2014

J Clin Oncol. 2010 Oct 20;28(30):4594-600

New Treatment Strategies: New SERD



Steroidal	Non-Steroidal	
	Acrylic Acids	Bases
ICI 182,780 (fulvestrant)	GW7604	bazedoxifene
		OP-1074
RU 58668	GDC-0810	pipendoxifene
	AZD9496	acolbifene (EM-652)
		arzoxifene

J. Med. Chem. 2015, 58, 4883−4887

Estrogen-Receptor Degrader GDC-0810 Active in Metastatic Breast Cancer

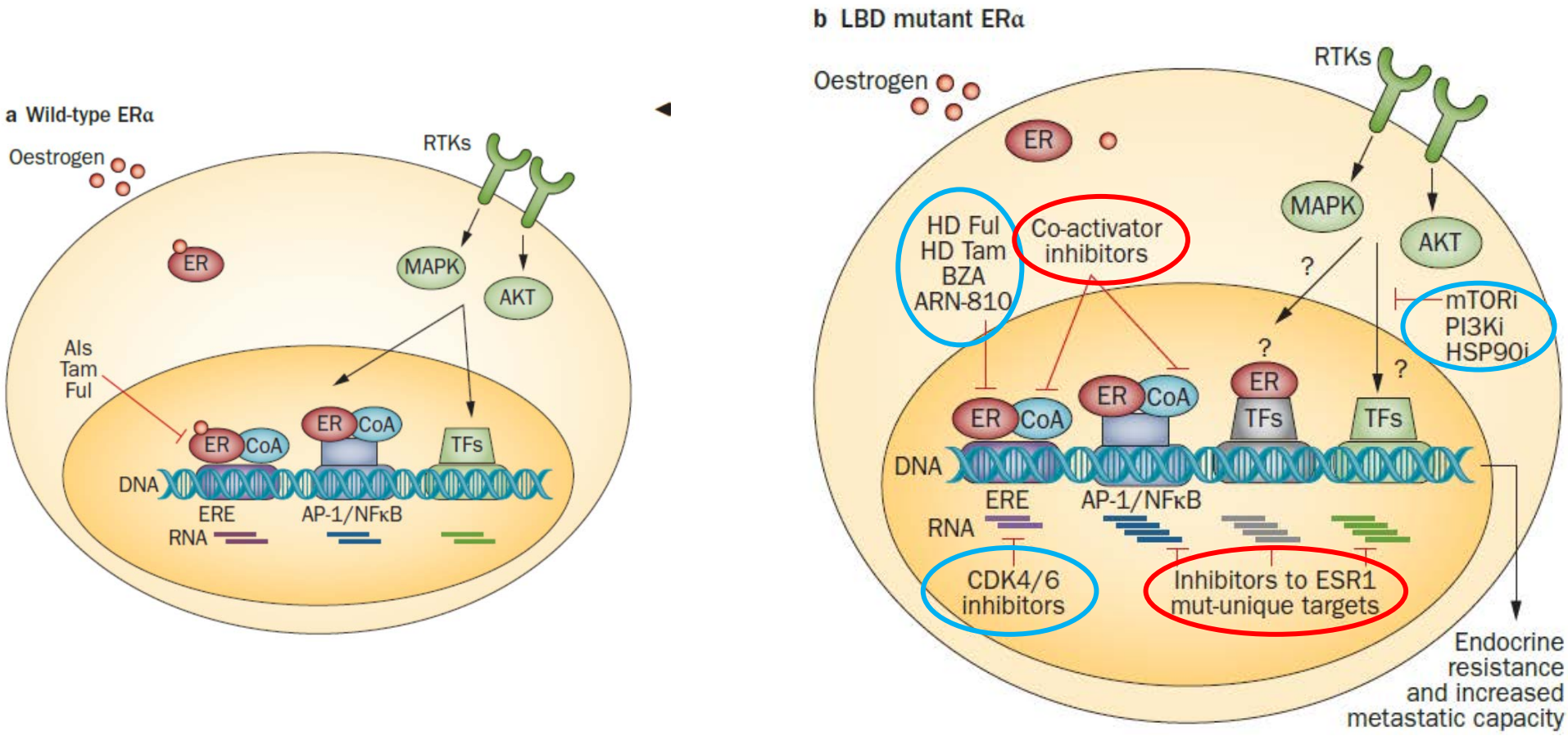
- **GDC-0810 (ARN-0810):** ER antagonism and degradation, non-steroidal and orally bioavailable
- Active in TAM-sensitive, resistant & *ESR1*-wild, mutant

- Phase I dose-escalation study (n=41)
- *ESR1* mutation: positive (n=9, 22%), wild type (n=10, 24%), unknown (n=22, 54%)
- **Response: SD (42%)**

Phase IIa study: GDC-0810 in postmenopausal women with ER-positive advanced or m etastatic breast cancer who have been previously treated with an aromatase inhibitor, **including tumors with *ESR1* mutations.**

2015 AACR (Abstract CT231)

New Treatment Strategies: Summary



Summary

- Endocrine resistance after treatment is a case for Darwinian tumor evolution.
- *ESR1*-LBD mutations confer endocrine resistance and ligand independent tumor growth.
- New technologies with better sensitivity: Safe-Seq, ddPCR
- Application of liquid biopsy
- New strategies: HD endocrine therapy, New SERD