Breast Cancer

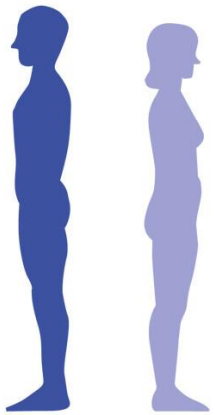
GSK Core Course

Sarat Chandarlapaty
Memorial Sloan Kettering Cancer Center
4/26/26

Hormone Dependent Tissues and Cancer

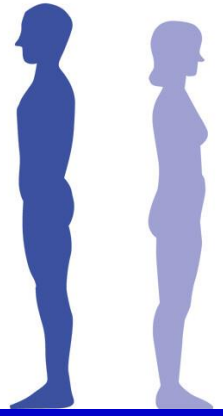
Estimated New Cases

Male			Female		
Prostate	333,830	31%	Breast	321,910	32%
Lung & bronchus	110,910	10%	Lung & bronchus	118,500	12%
Colon & rectum	84,160	8%	Colon & rectum	74,690	7%
Melanoma of the skin	65,400	6%	Uterine corpus	68,270	7%
Urinary bladder	64,730	6%	Melanoma of the skin	46,600	5%
Kidney & renal pelvis	50,770	5%	Non-Hodgkin lymphoma	35,550	3%
Non-Hodgkin lymphoma	43,770	4%	Pancreas	32,340	3%
Oral cavity & pharynx	43,070	4%	Thyroid	32,000	3%
Leukemia	39,070	4%	Kidney & renal pelvis	29,680	3%
Pancreas	35,190	3%	Leukemia	28,720	3%
All sites	**1,094,070**		**All sites**	**1,020,780**	



Estimated Deaths

Male			Female		
Lung & bronchus	63,040	19%	Lung & bronchus	61,950	21%
Prostate	36,320	11%	Breast	42,140	14%
Colon & rectum	30,110	9%	Pancreas	25,510	9%
Pancreas	27,230	8%	Colon & rectum	25,120	8%
Liver & intrahepatic bile duct	19,650	6%	Uterine corpus	14,450	5%
Leukemia	13,900	4%	Ovary	12,450	4%
Esophagus	12,940	4%	Liver & intrahepatic bile duct	11,330	4%
Urinary bladder	12,640	4%	Leukemia	10,010	3%
Non-Hodgkin lymphoma	11,710	4%	Brain & other nervous system	8,380	3%
Kidney & renal pelvis	10,200	3%	Non-Hodgkin lymphoma	8,260	3%
All sites	**327,290**		**All sites**	**298,850**	

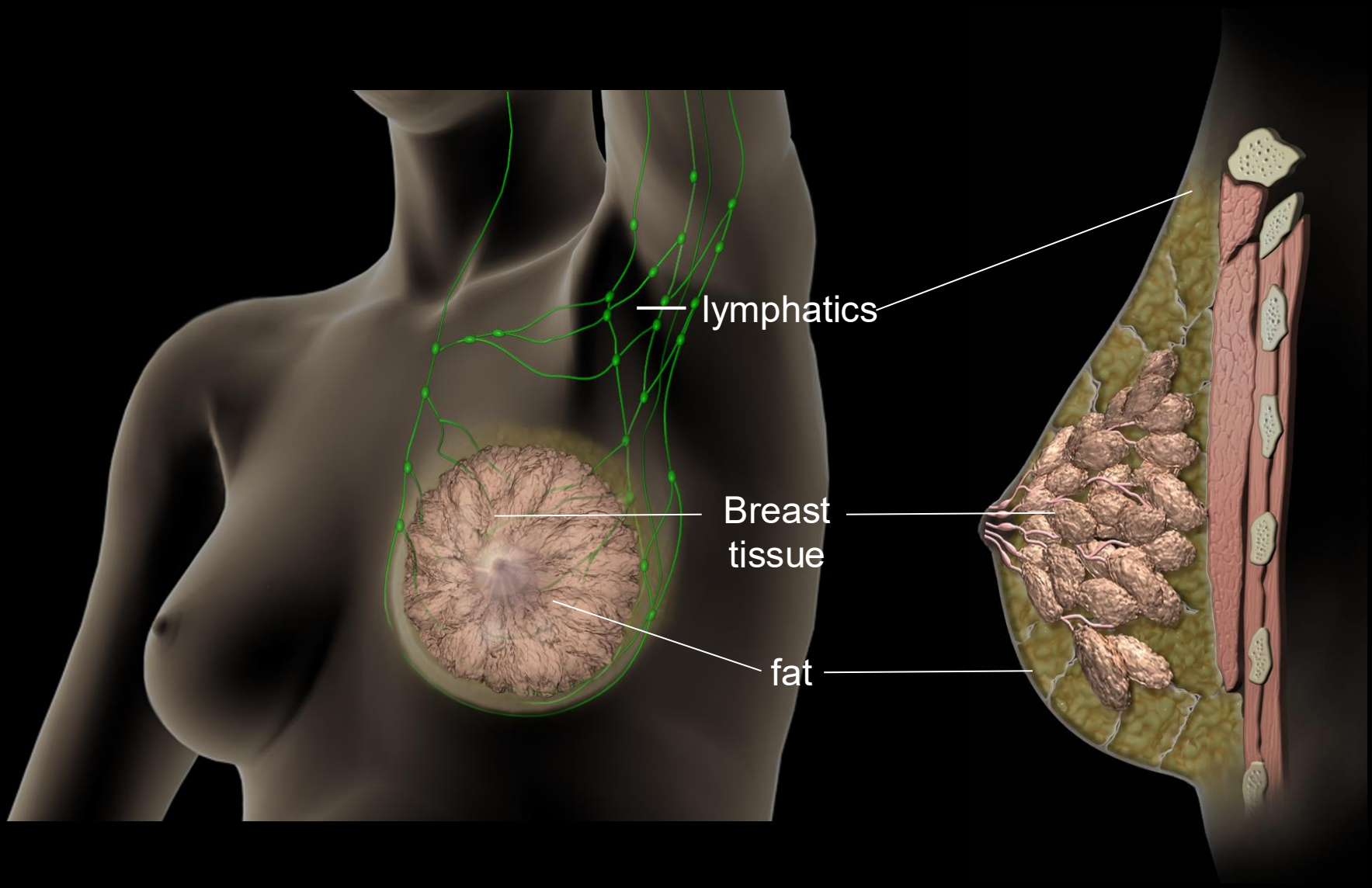


Siegel et al. 2026

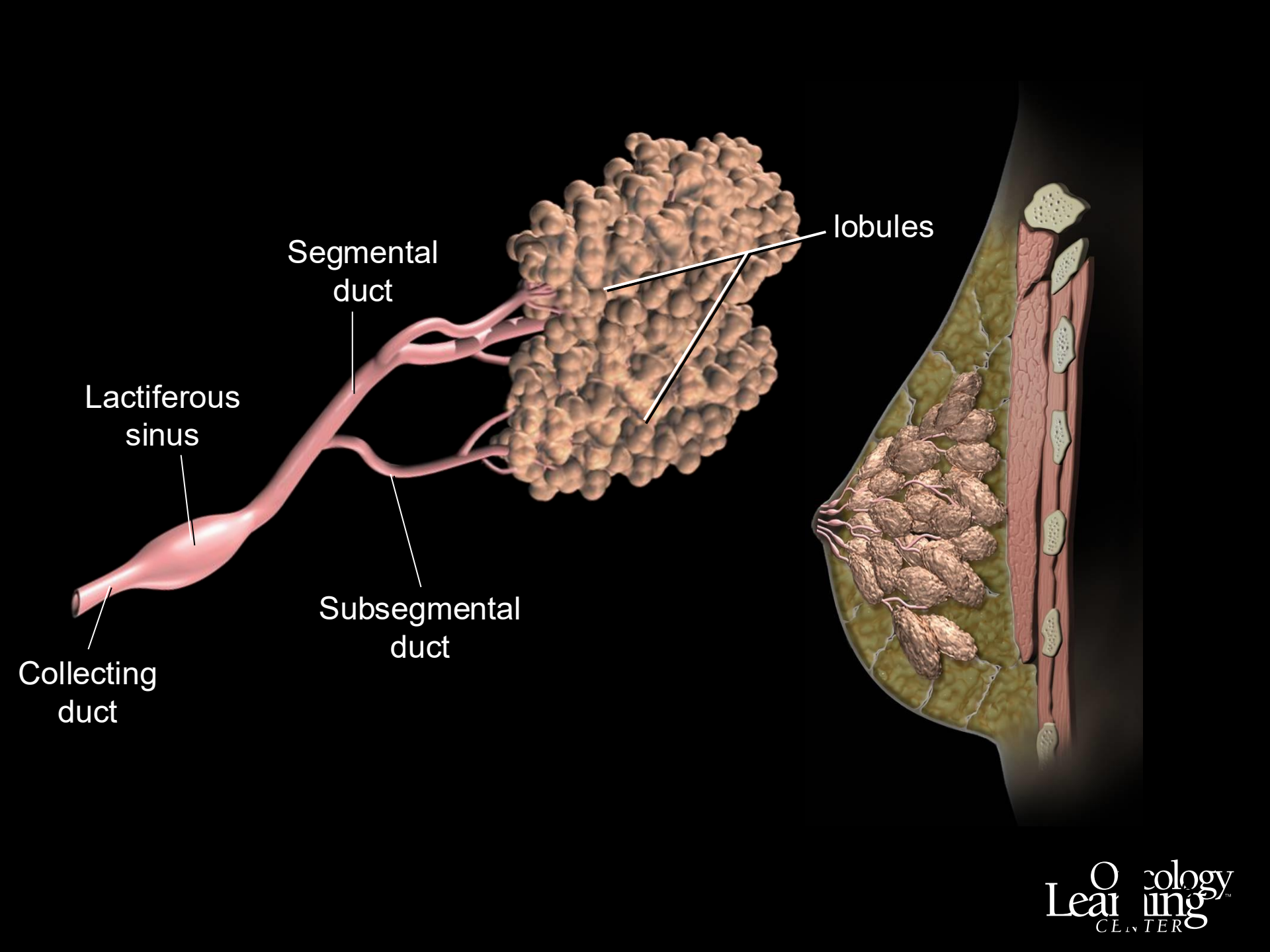
Declining US Mortality

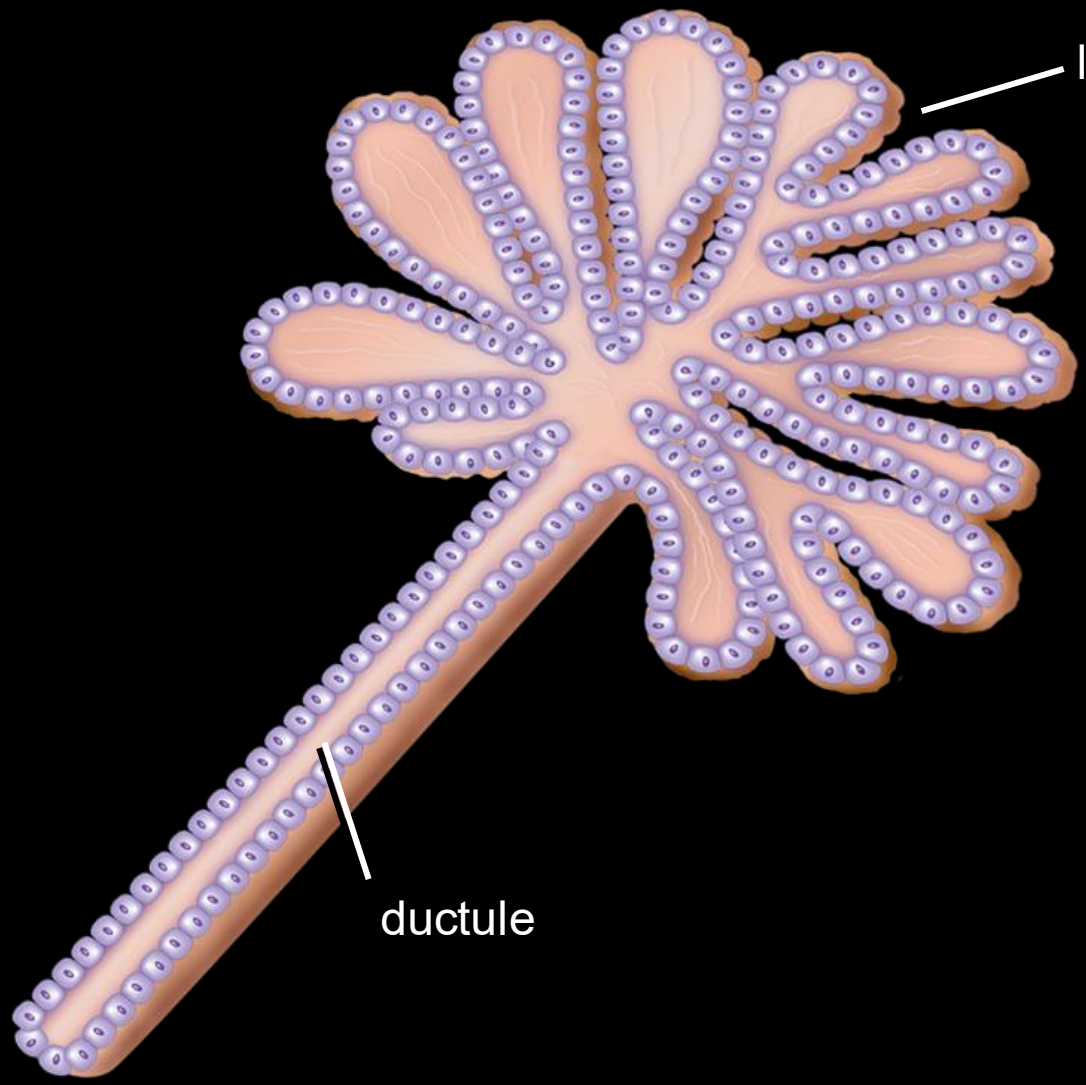
- Increased awareness and screening
- Early detection
- Improvements in treatment

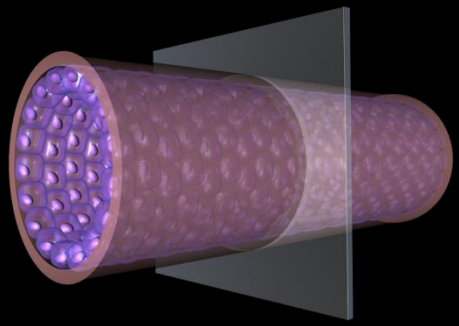
Anatomy of the Breast

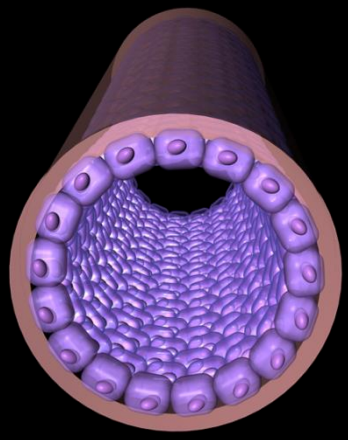


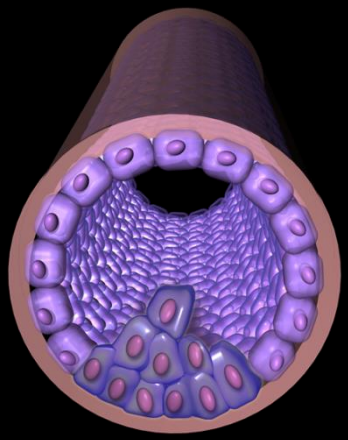
Oncology Learning CENTER

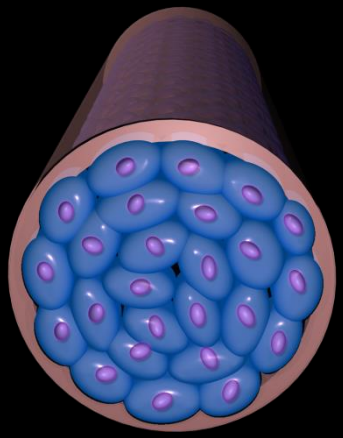

lobules
Segmental duct
Lactiferous sinus
Subsegmental duct
Collecting duct

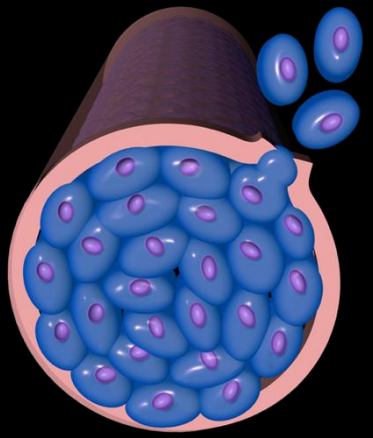

lobule
ductule











Normal Duct

Atypical Hyperplasia

DCIS

Invasive Ductal Carcinoma

Oncology Learning CENTER

Risk Factors for Breast Cancer

- Gender
- Age > 65
- Race
- Early onset of menses and late menopause
- Late or no pregnancies
- Family history (BRCA1, BRCA2, PALB2, TP53)
- Dense breast tissue
- Alcohol consumption
- Hormone supplementation
- Prior RT
- Prior lesions (ADH, ALH, LCIS, DCIS)

American Cancer Society. *Breast Cancer Facts and Figures 2019-2020.*

Staging of Breast Cancer

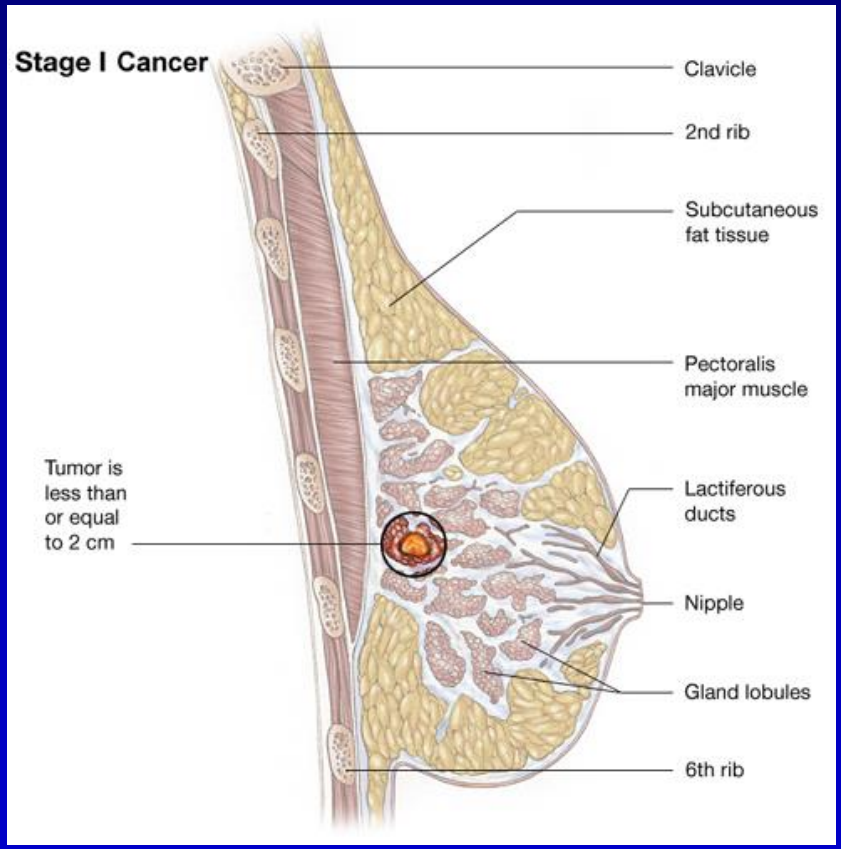
- Size and location of the tumor
- Determine if the cancer has spread beyond the breast
- Determine lymph node involvement
- Metastasis

Stage 0

- Noninvasive cancer
- Carcinoma in situ
  - Has not spread past the ducts or lobules of the breast
  - Ductal carcinoma in situ (DCIS)
    - Most common in situ breast cancer

Stage I

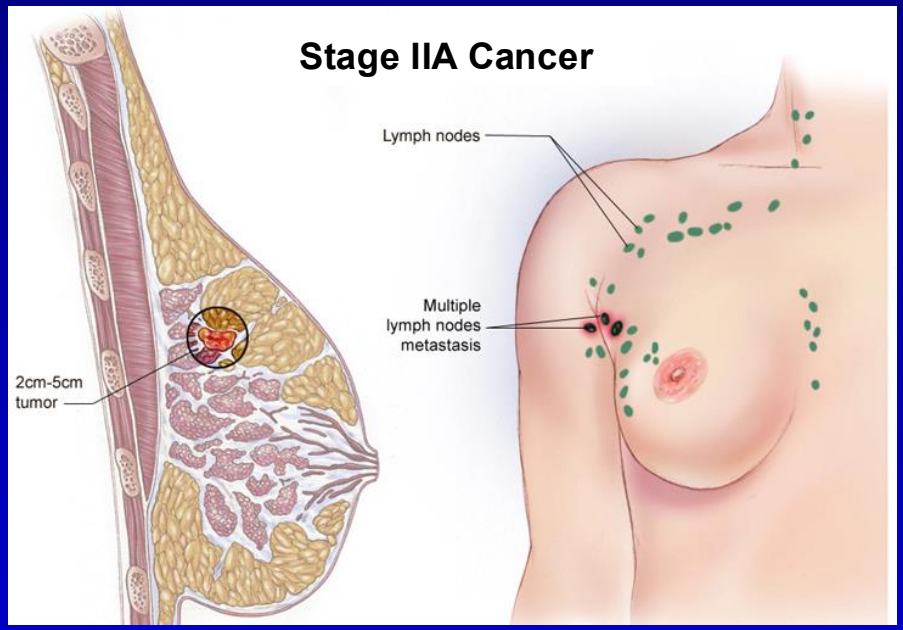
- Tumor is small
- Has not spread to lymph nodes



People Living With Cancer. 2006. ASCO Slide Deck Series: Understanding Breast Cancer.

Stage IIA

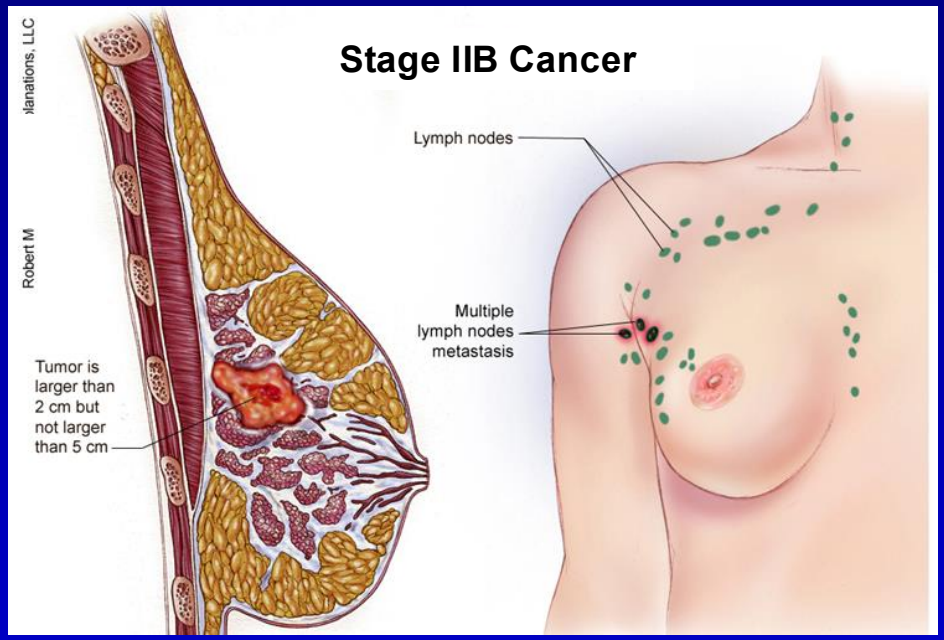
- One of the following
  - Smaller tumor that has spread to the axillary lymph nodes
  - Medium-sized tumor that has not spread to the axillary lymph nodes



People Living With Cancer. 2006. ASCO Slide Deck Series: Understanding Breast Cancer.

Stage IIB

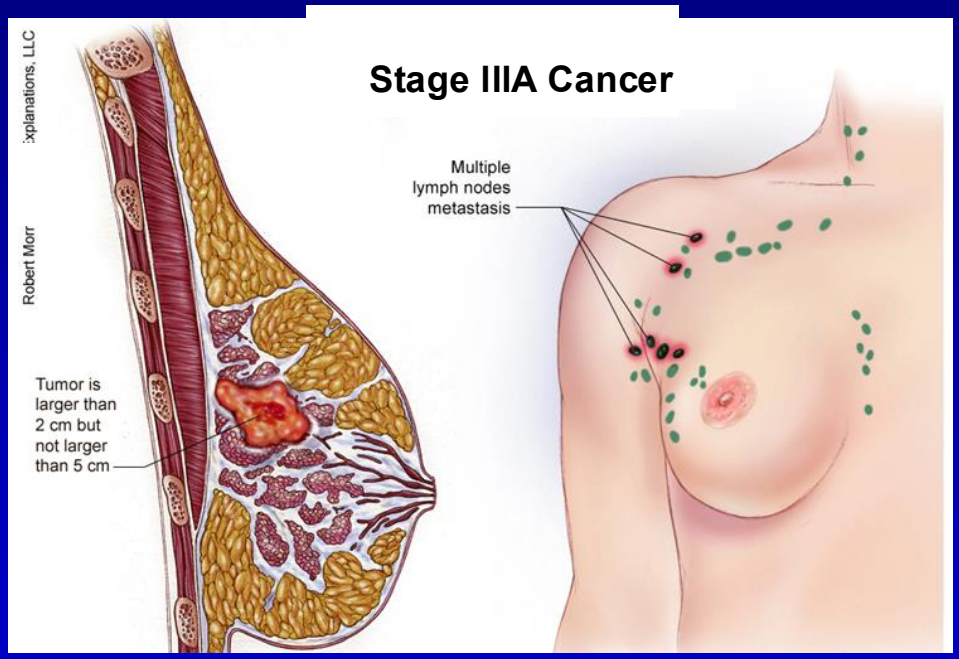
- One of the following
  - Medium-sized tumor that has spread to the axillary lymph nodes
  - Larger tumor that has not spread to the axillary lymph nodes



People Living With Cancer. 2006. ASCO Slide Deck Series: Understanding Breast Cancer.

Stage IIIA

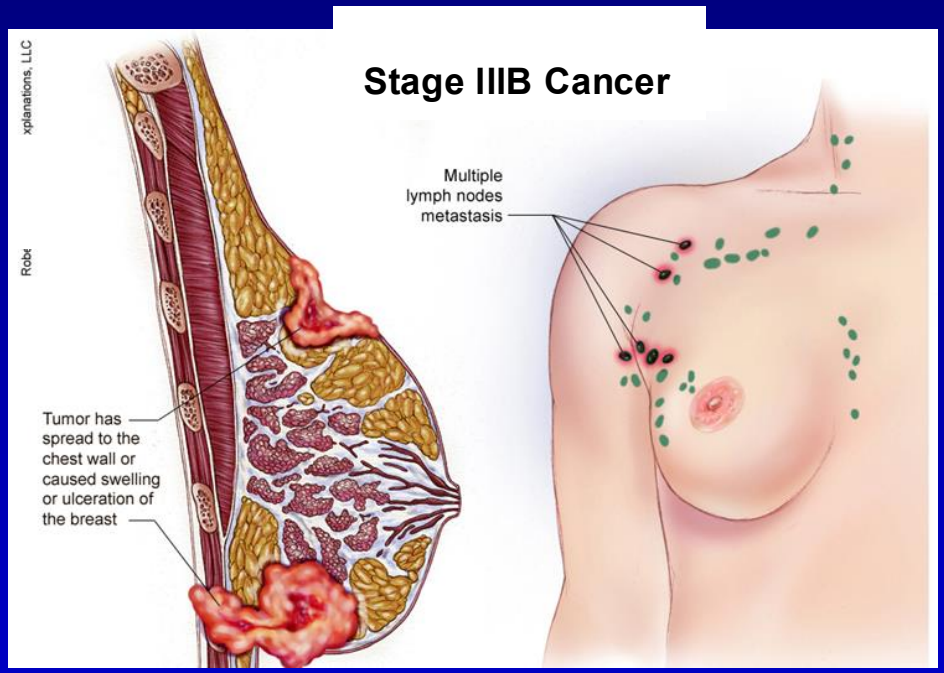
- Any size tumor that has spread to the lymph nodes



People Living With Cancer. 2006. ASCO Slide Deck Series: Understanding Breast Cancer.

Stage IIIB

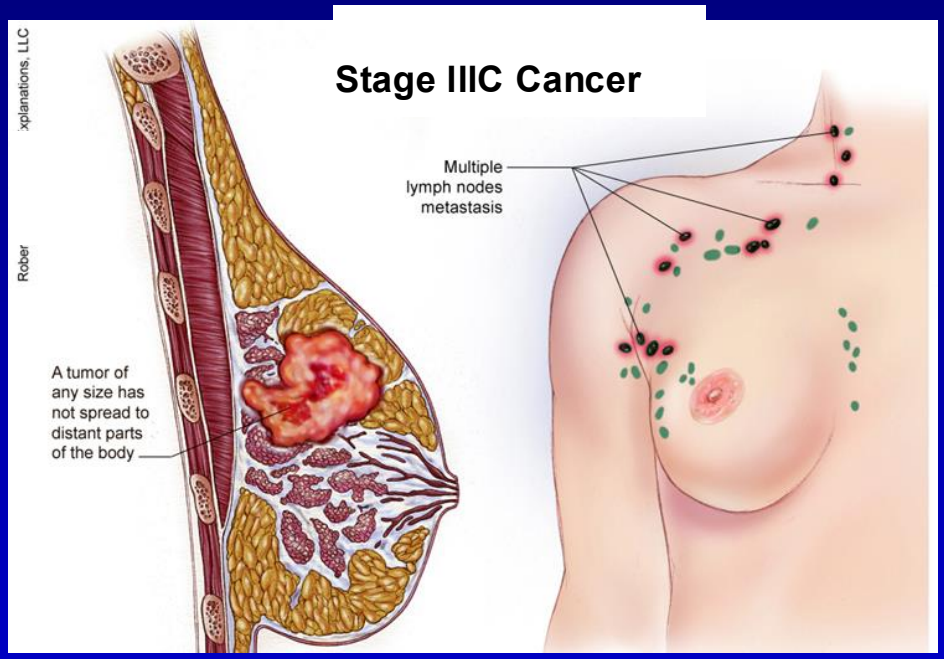
- Cancer has spread to the chest wall, caused swelling or ulceration of the breast, or is diagnosed as inflammatory breast cancer



People Living With Cancer. 2006. ASCO Slide Deck Series: Understanding Breast Cancer.

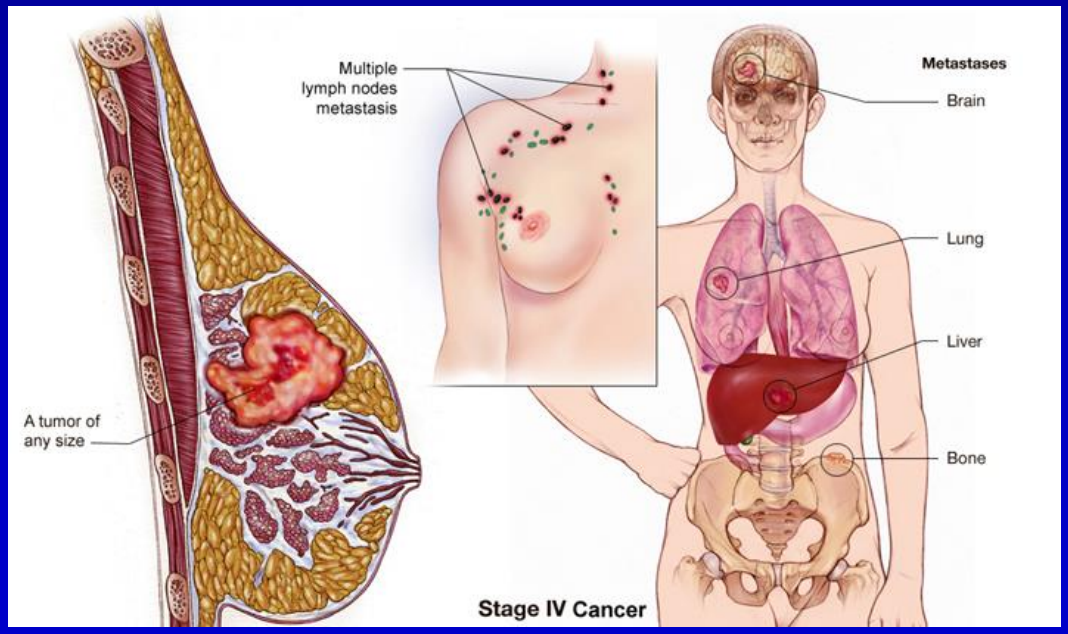
Stage IIIC

- Cancer has spread to distant lymph nodes but has not spread to distant parts of the body



Stage IV: Metastatic Breast Cancer

- Cancer of any size and has spread to distant sites in the body, usually the bones, lungs or liver, or chest wall



People Living With Cancer. 2006. ASCO Slide Deck Series: Understanding Breast Cancer.

Incidence of Metastatic Breast Cancer

- ~6% of patients have MBC at the initial diagnosis of breast cancer in USA
- MBC is more frequently represented by recurrent disease.

American Cancer Society. *Breast Cancer Facts and Figures 2019-2020*.

5-Year Survival Rates vs Breast Cancer Stage

Stage	Tumor Size	Lymph Node Involvement	Metastasis (Spread)	Survival Rate
0	N/A	No	No	100%
I	<2 cm	No	No	96%
II	2-5 cm	No or yes (on same side of breast only)	No	85%
III	>5 cm	Yes	No	52%
IV	N/A	N/A	Yes	**27%**

ACS

Breast Cancer Screening

- Mammogram
  - Annually 45-54 then annual or biennial >55
- Breast MRI for high risk (e.g. BRCA1/2, dense breast, etc)

American Cancer Society. *Breast Cancer Facts and Figures 2019-2020*

Breast Cancer
Local Therapy

- Surgery
- Radiation

Surgical Approaches to Breast Cancer

- Radical mastectomy
- Modified radical mastectomy
- Total mastectomy
- Partial mastectomy
- Lumpectomy

- Axillary lymph node dissection
- Sentinel lymph node biopsy (SLNB)

Goals of Surgery in Breast Cancer Treatment

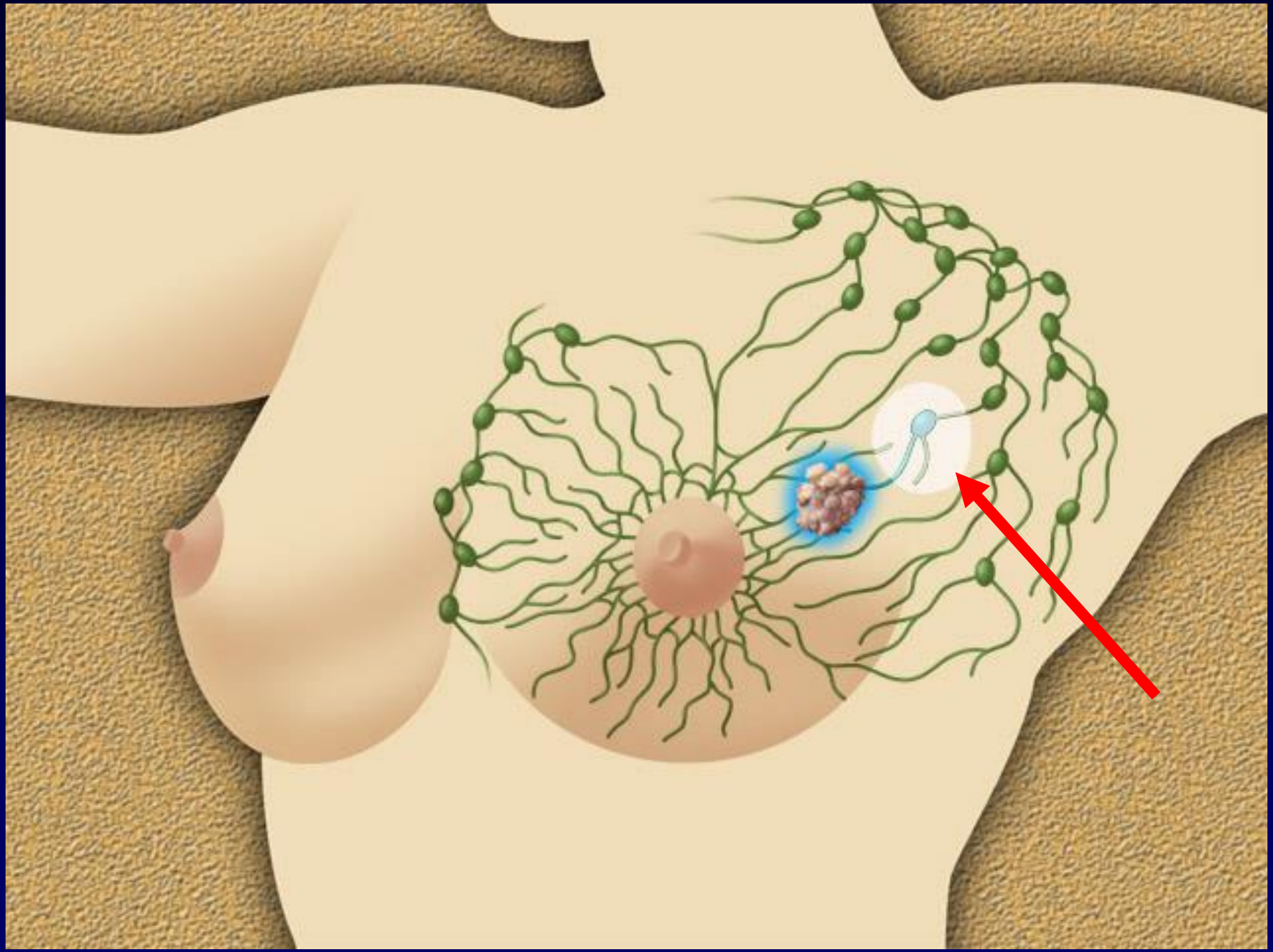
- Obtain the diagnosis and stage the patient.
- Achieve Local-Regional Control
- Contribute to long-term disease free state:
  - Stage O - 98%
  - Stage I - 80%
  - Stage IIa -75%
  - Stage IIb -30+%

Surgical Options

- **Mastectomy (with Immediate Reconstruction?)**
  - Tissue transfer vs. implant reconstruction
  - Skin sparing approach
- **Breast Conservation Therapy**
  - Tumor removal, Sentinel node biopsy, Radiation therapy.

Management of the Axilla

- **Axillary Dissection**
  - General anesthesia, Hospital admission
  - Clearance of 15-40 lymph nodes
  - Surgical drain week
  - Lymphedema in 20%
  - 5-15% false negative
- **Sentinel Node Biopsy**
  - Local anesthesia, outpatient surgery
  - Clearance of 1-4 nodes
  - No surgical drain
  - No lymphedema
  - 3-5% false negative
  - 20-35% reduction in charges

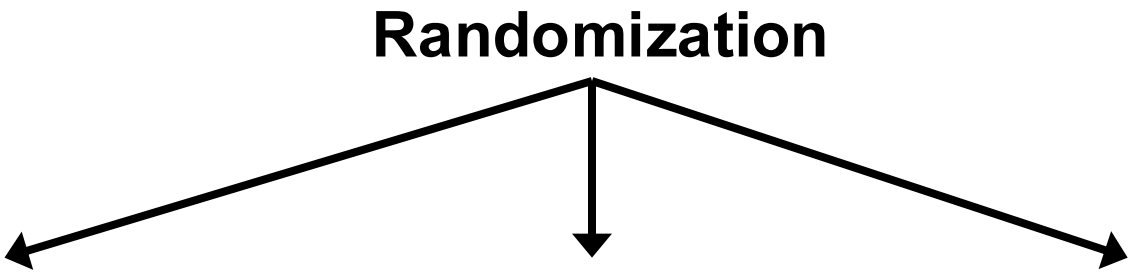


Sentinel Node Mapping

- **Enhanced evaluation of the axillary nodes.**
  - Serial sectioning
  - H&E staining
  - Immunohistochemistry
    - Cam 5.2 and AE1/3
- **Research Areas**
  - **PCR**
    - **EGFr, Muc1, ER**
  - **IHC Positive Nodes**
  - **Clonal derived from primary?**
  - **Viable/clonogenic?**
  - **Clinically significant?**

Radiation

NSABP B-06



Segmental Mastectomy + Axillary Dissection

Segmental Mastectomy + Axillary Dissection + RT

Total Mastectomy + Axillary Dissection

Breast Recurrence → Total mastectomy

Breast Recurrence → Total mastectomy

NSABP B-06
12 year results

	DFS	OS	LR
Total Mast.	50%	60%	8%
Seg. Mast.		59%	
(- Nodes)			*32%*
(+ Nodes)			*41%*
Seg. Mast. + RT	50%	62%	
(- Nodes)			*12%*
(+ Nodes)			*5%*

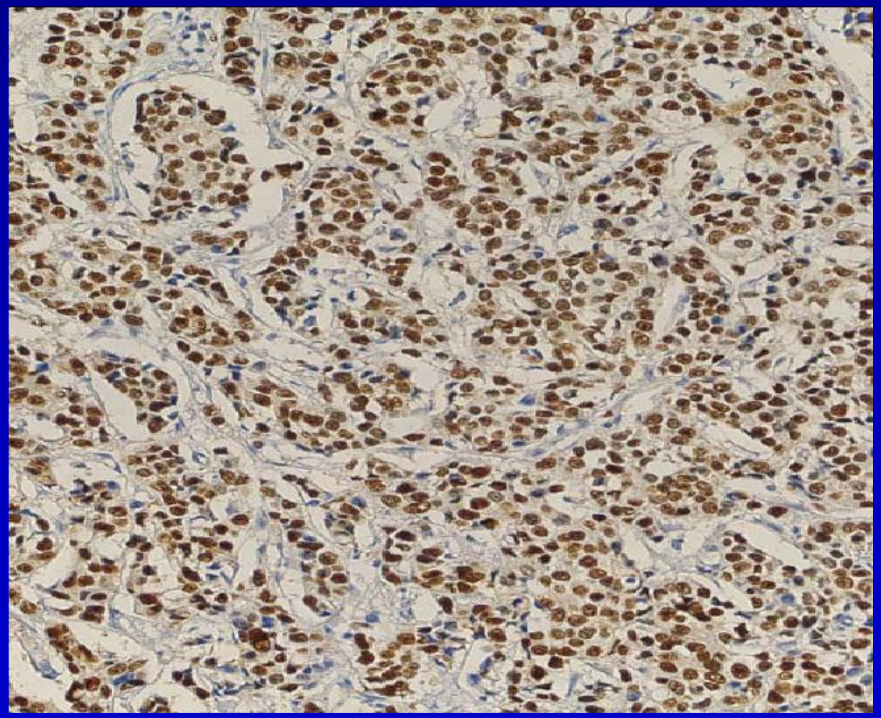
Systemic therapy

Prognostic Factors

- Axillary nodes
- Tumor size
- Histologic grade
- Estrogen and progesterone receptors
- HER-2/neu
- So many more (Ki67, TILs,….)

Biological Markers To Predict Therapeutic Response

- ER status is used to select for patients to receive or not hormone therapy



ER+

Estrogen modulation as a therapy

1896 GT Beatson - Oophorectomy in premenopausal women

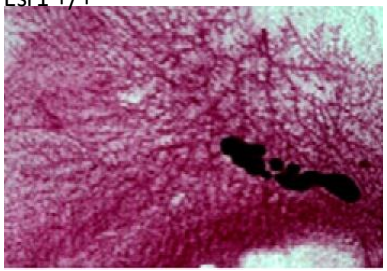
1944 A Haddow - Synthetic estrogen (stilbestrol) as treatment of breast cancer

1952 C Huggins - Adrenalectomy

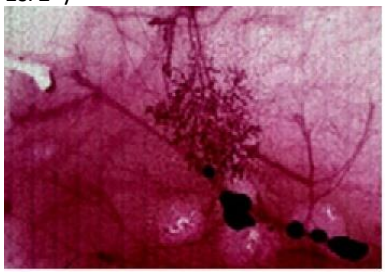
(1966 Wins Nobel Prize for development of endocrine therapy in prostate cancer)

Central role for estrogen receptor in normal and cancerous breast

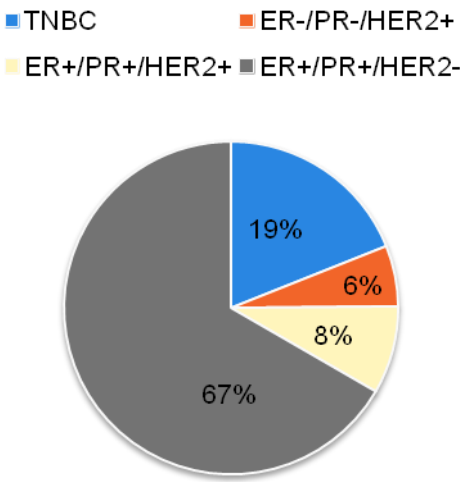
Esr1 +/+

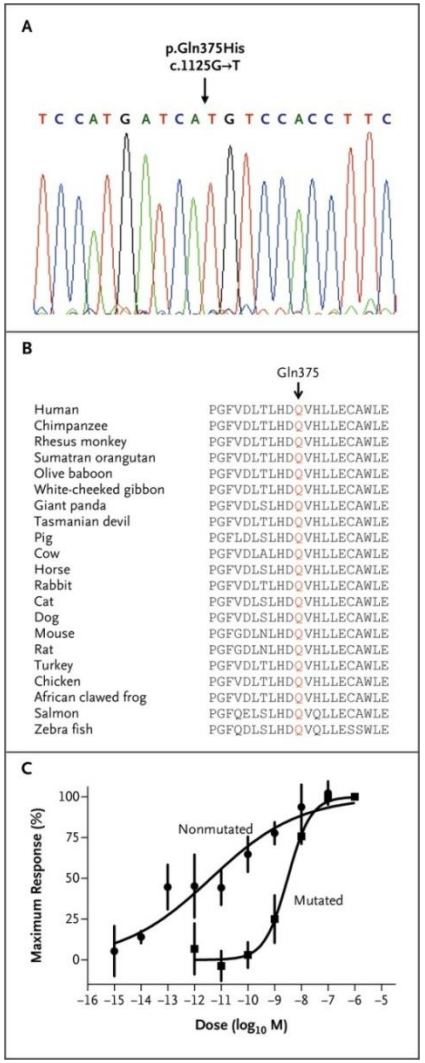


Esr1 -/-



Rumi et al. Endocrinology 2014

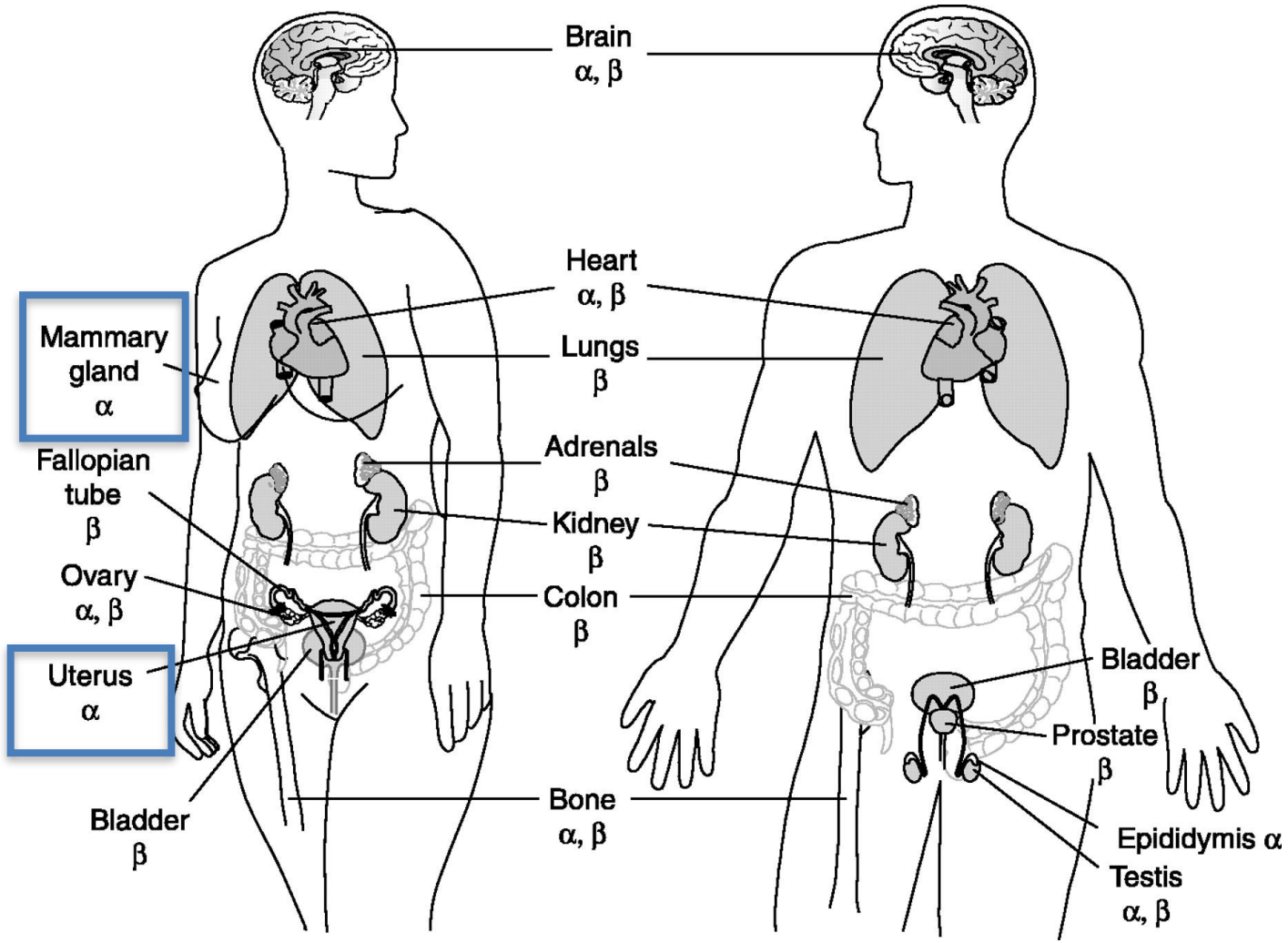




Quaynor et al. N Engl J Med 2013

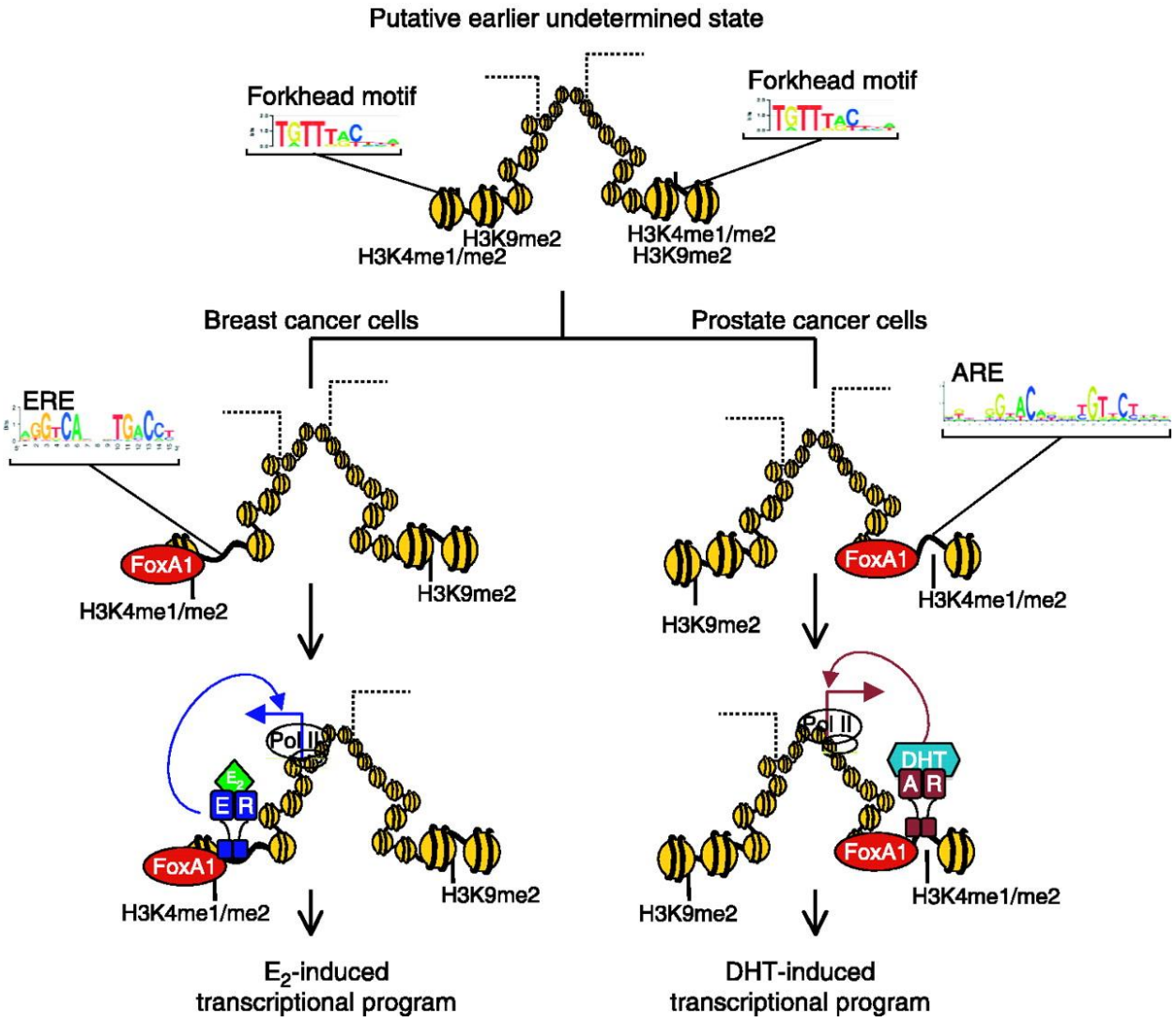
Memorial Sloan Kettering Cancer Center

Physiologic actions of estrogen receptors – distribution of receptor expression



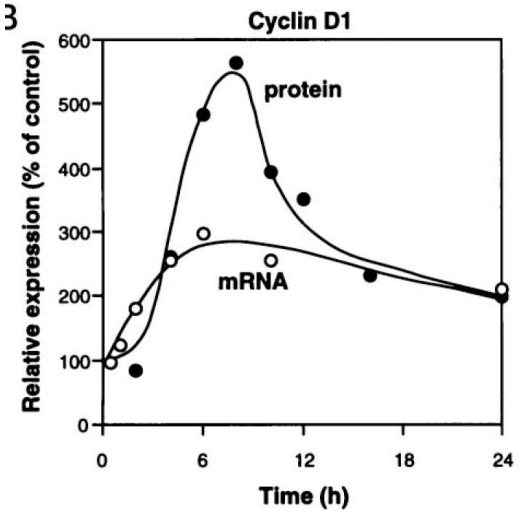
Drummond A E , and Fuller P J J Endocrinol 2010;205:15-23

FOXA1 as key pioneer in breast/prostate cancer

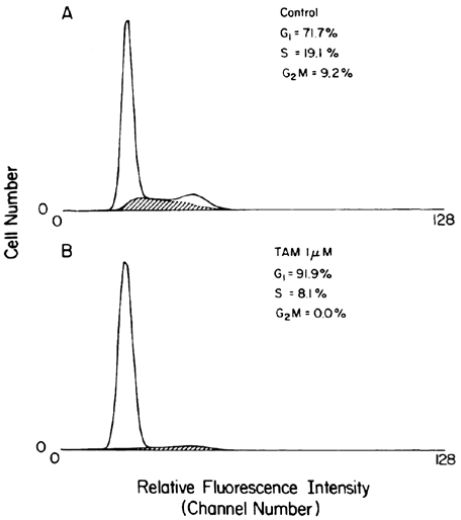


Lupien and Brown, 2009

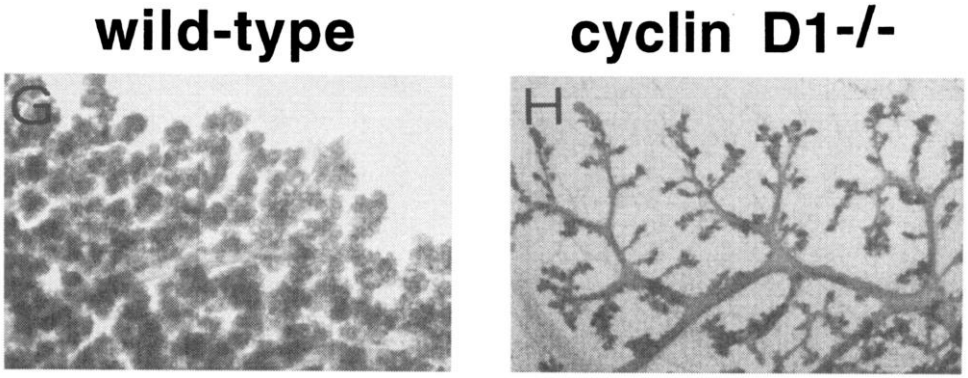
Estrogens and the G1 Checkpoint



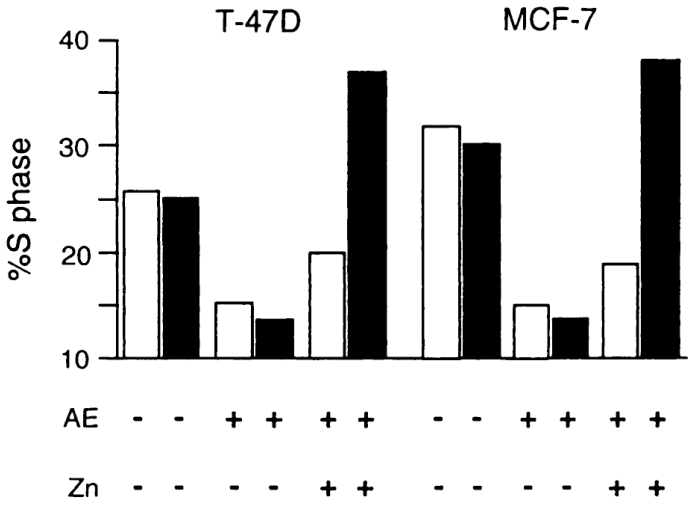
Prall et al, JBC 1997



Osborne et al, Can Res 1983



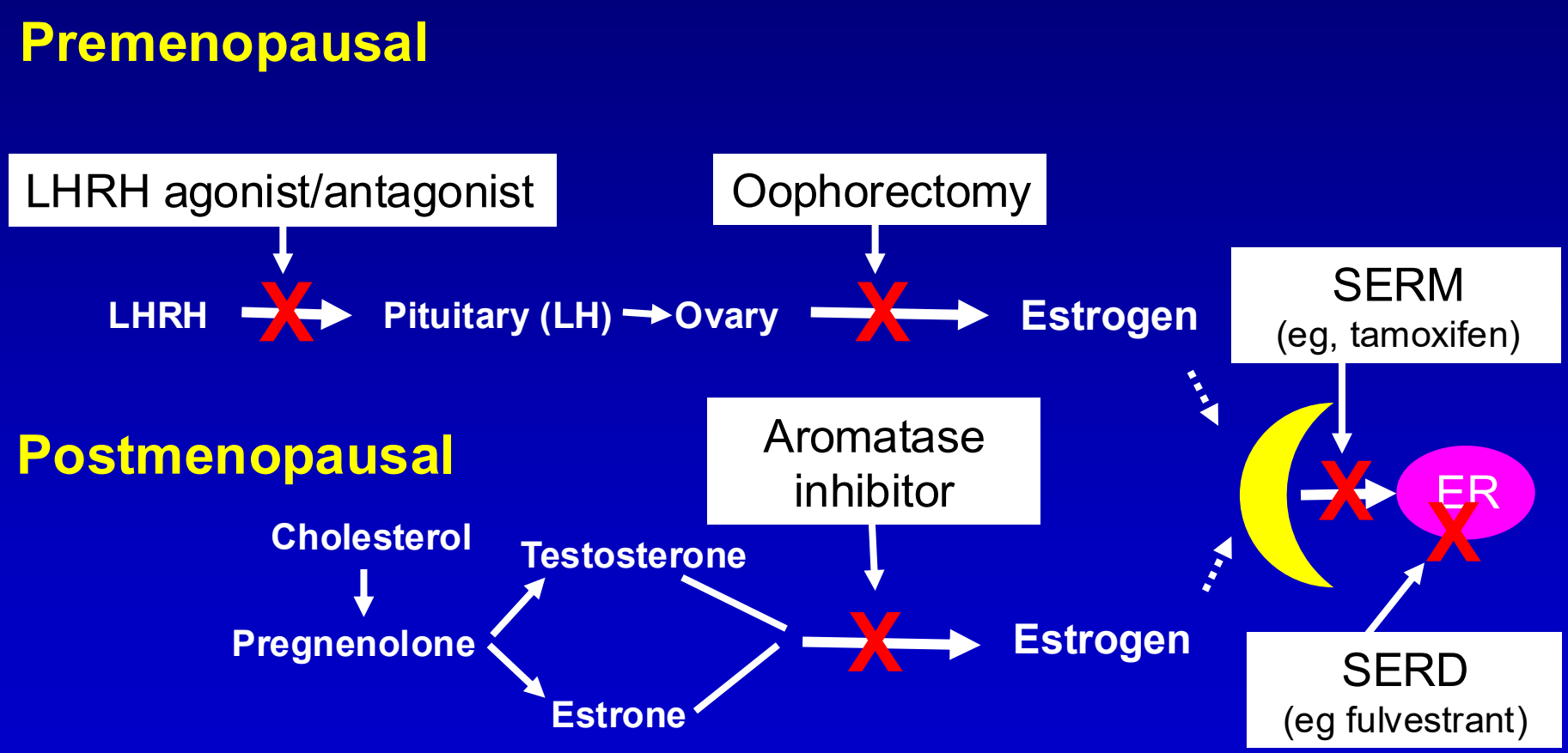
Sicinski et al, J Mammary Gland Biol 1997



Wilcken et al, CCR 1997

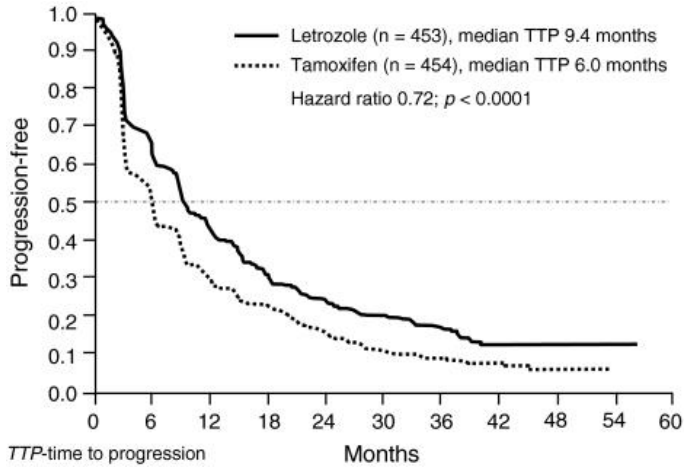
Memorial Sloan Kettering Cancer Center
1884

Targets of Inhibition

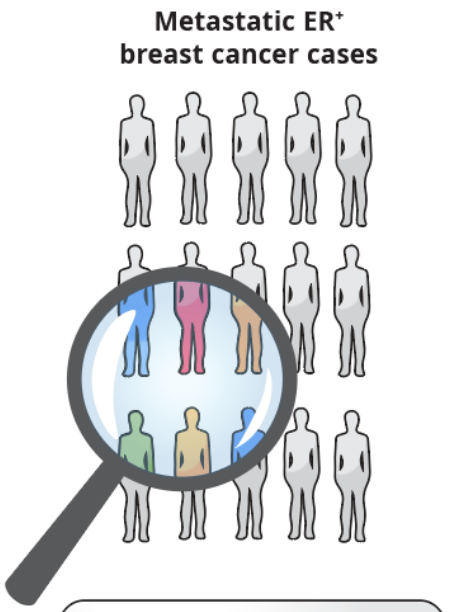


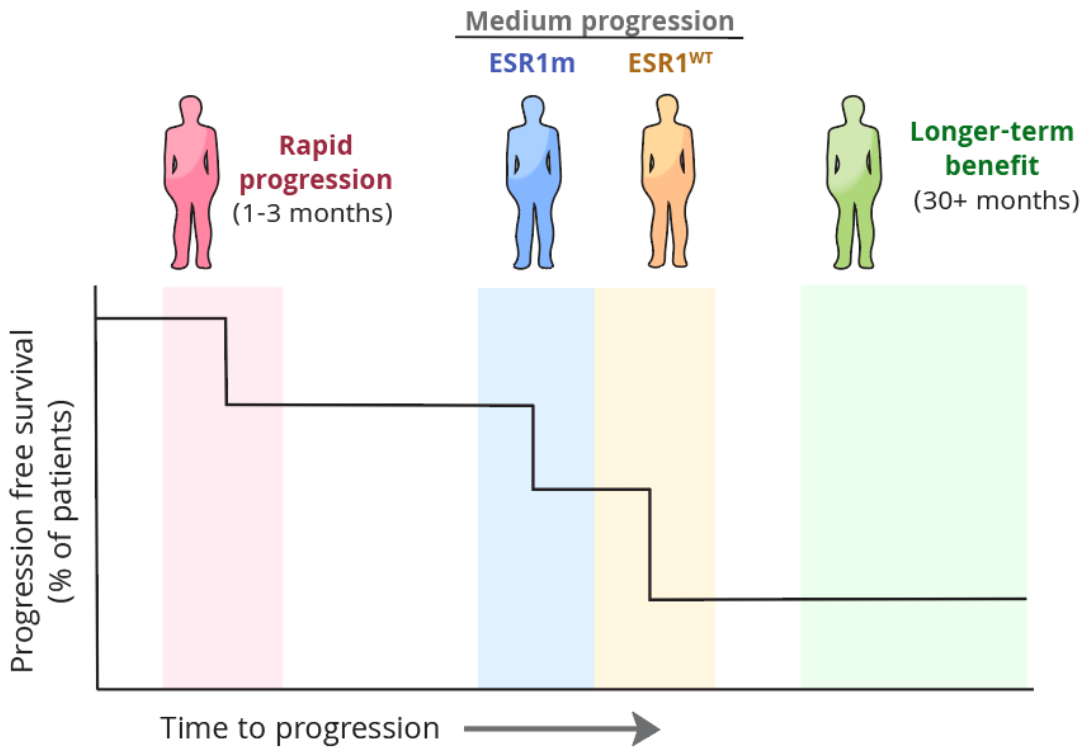
LH, luteinizing hormone; SERM, selective estrogen receptor modulator; SERD, selective estrogen receptor down-regulator.

Benefit of hormone therapy for ER+ metastatic breast cancer



Mouridsen H et al. JCO 2003





- Re-targeting of ER with a different type of drug is often effective after 1st line failure. This highlights the dependence of the tumor.

Phase III trials showing superiority of third-generation aromatase inhibitors to megestrol acetate as second-line therapy for patients with metastatic breast cancer resistant to tamoxifen

Table 2. Phase III trials showing superiority of third-generation aromatase inhibitors to megestrol acetate as second-line therapy for patients with metastatic breast cancer resistant to tamoxifen

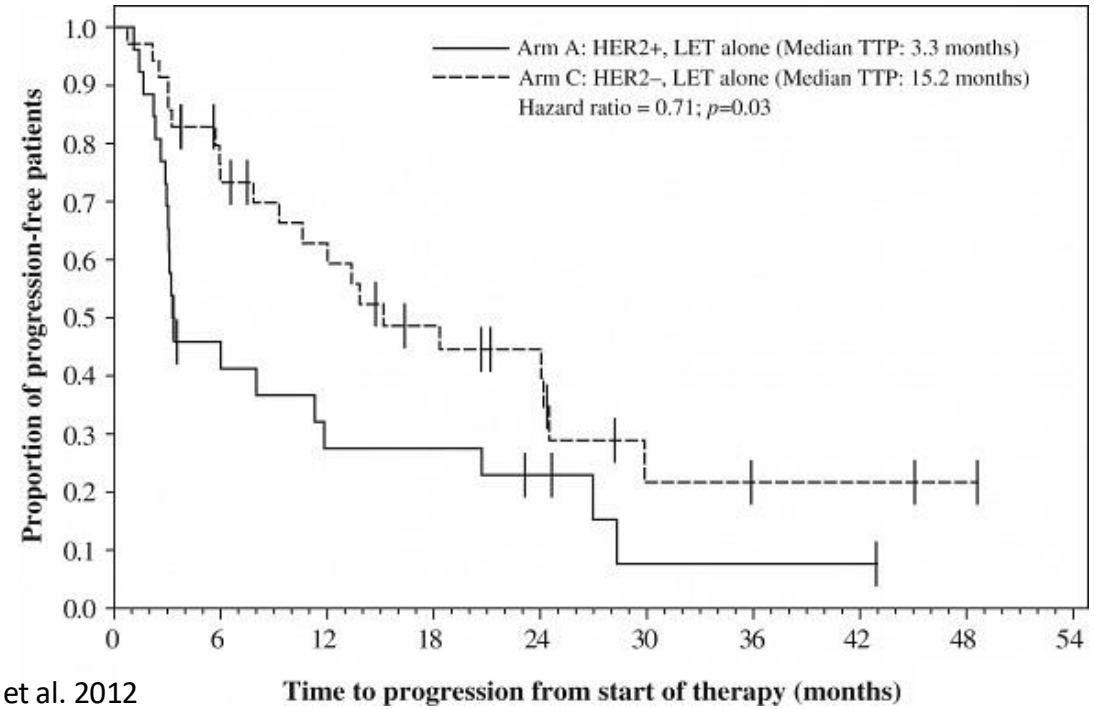
Study	AI	*n*	ORR (%)[a]	Clinical benefit (%)[a]	Median TTP (mo)[a]	Median OS (mo)[a]	MDR[a]
Jonat et al. [16]	Anastrozole	764	13 vs. 12	42 vs. 40	4.8 vs. 4.6	27 vs. 23 ($p = .02$)	–
Buzdar et al. [14]	Anastrozole	378	–	34 vs. 33	–	N/A	–
Dombernowsky et al. [15]	Letrozole	551	24 vs. 16 ($p = .04$)	24 vs. 15 ($p = .001$)	5.6 vs. 5.5	N/A	NR vs. 18 ($p = .02$)
Kaufmann et al. [18]	Exemestane	769	15 vs. 12	37 vs. 35 ($p = .025$)	4.7 vs. 3.8 ($p = .037$)	NR vs. 29 ($p = .039$)	18 vs. 17
Buzdar et al. [17]	Letrozole	602	16 vs. 15	27 vs. 23	3 vs. 3	N/A	25 vs. 30

[a]Second value is for megestrol acetate.
Abbreviations: AI, aromatase inhibitor; MDR, median duration of response; N/A, not applicable; NR, not reached; ORR, overall response rate; OS, overall survival; TTP, time to progression.

Altundag, K. et al. Oncologist 2006;11:553-562

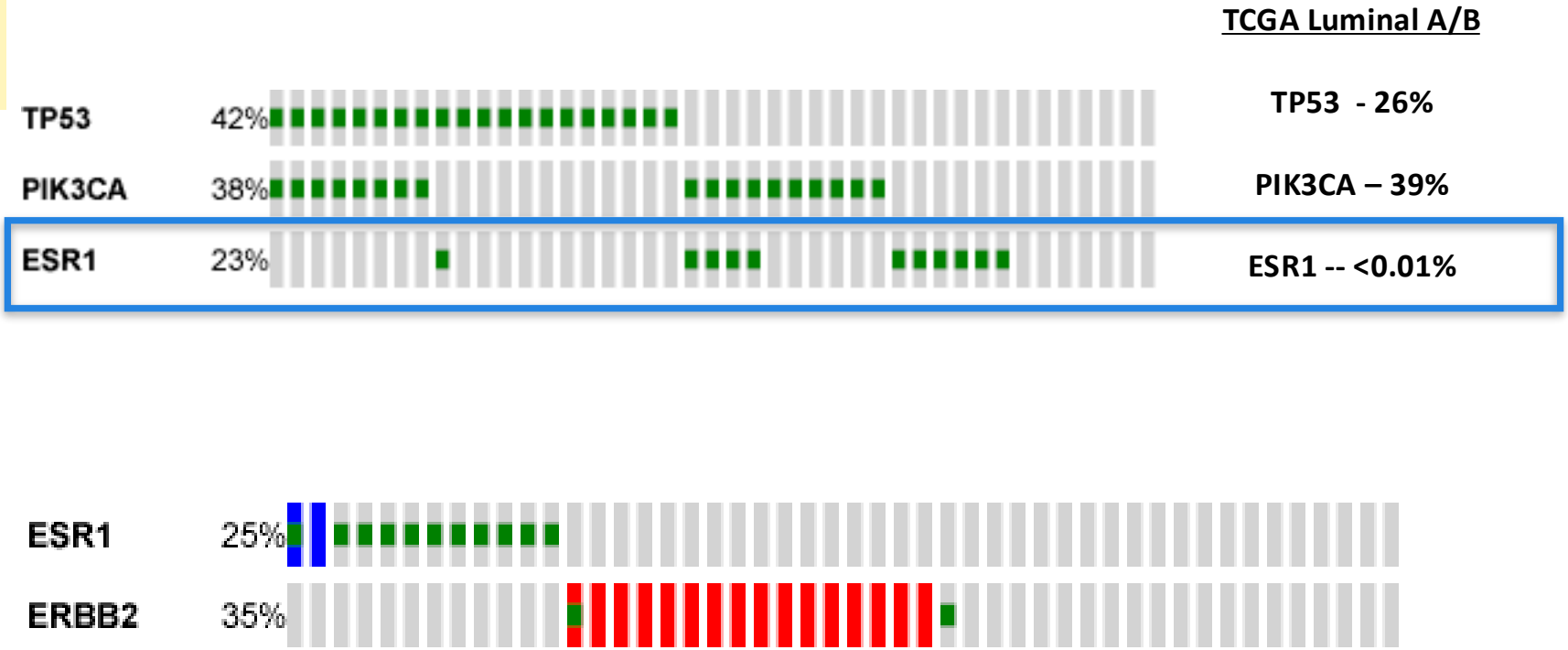
Genomic alterations in EGF signaling promote endocrine resistance

TCGA

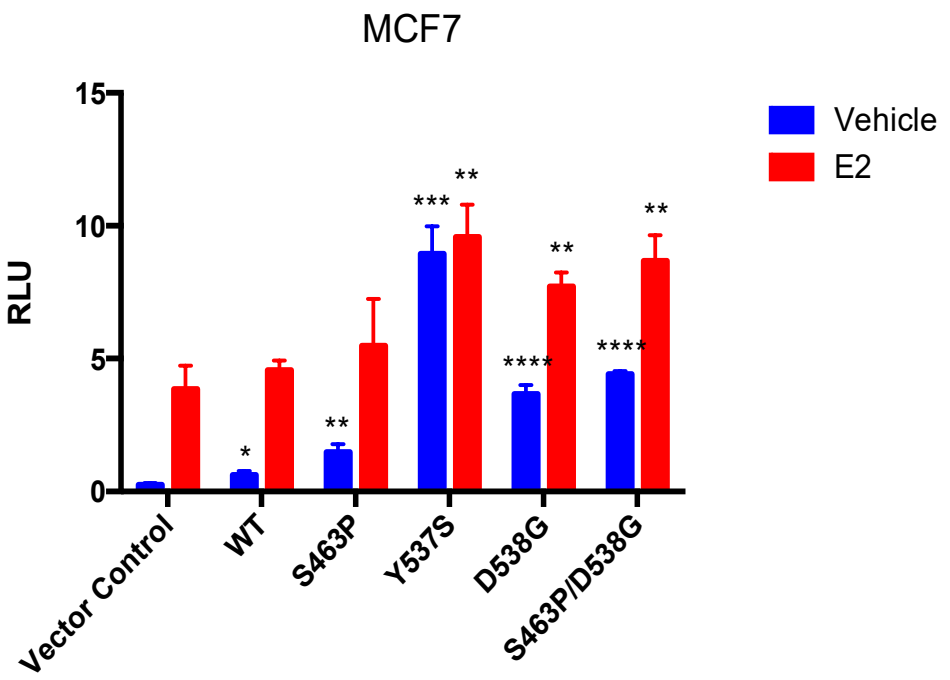


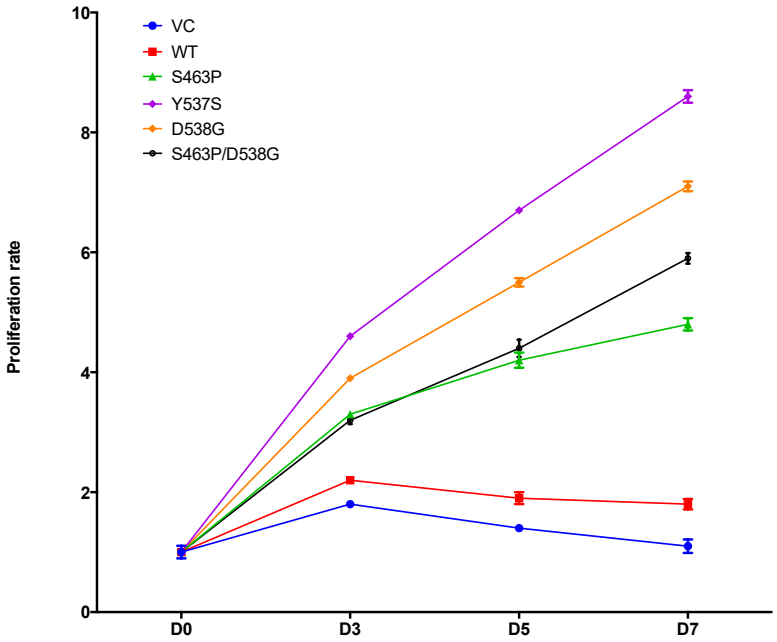
Huober et al. 2012

ESR1 mutations in metastatic breast cancer



ESR1 mutations promote E2-independent transcription and proliferation

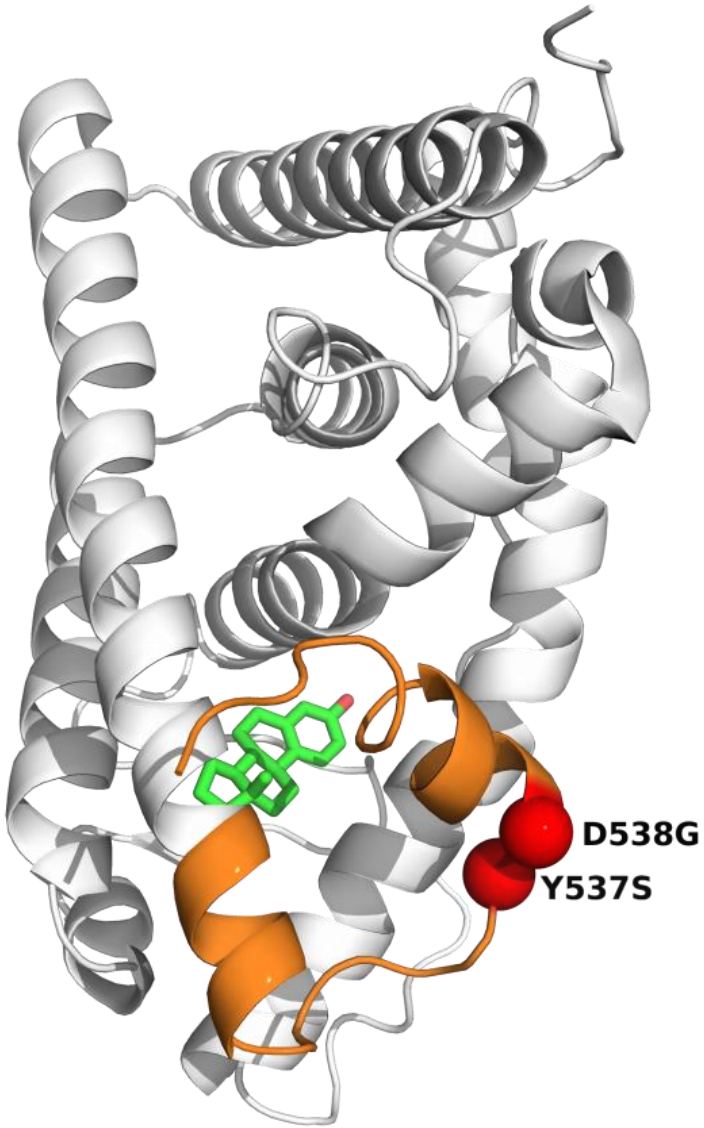




Memorial Sloan Kettering Cancer Center

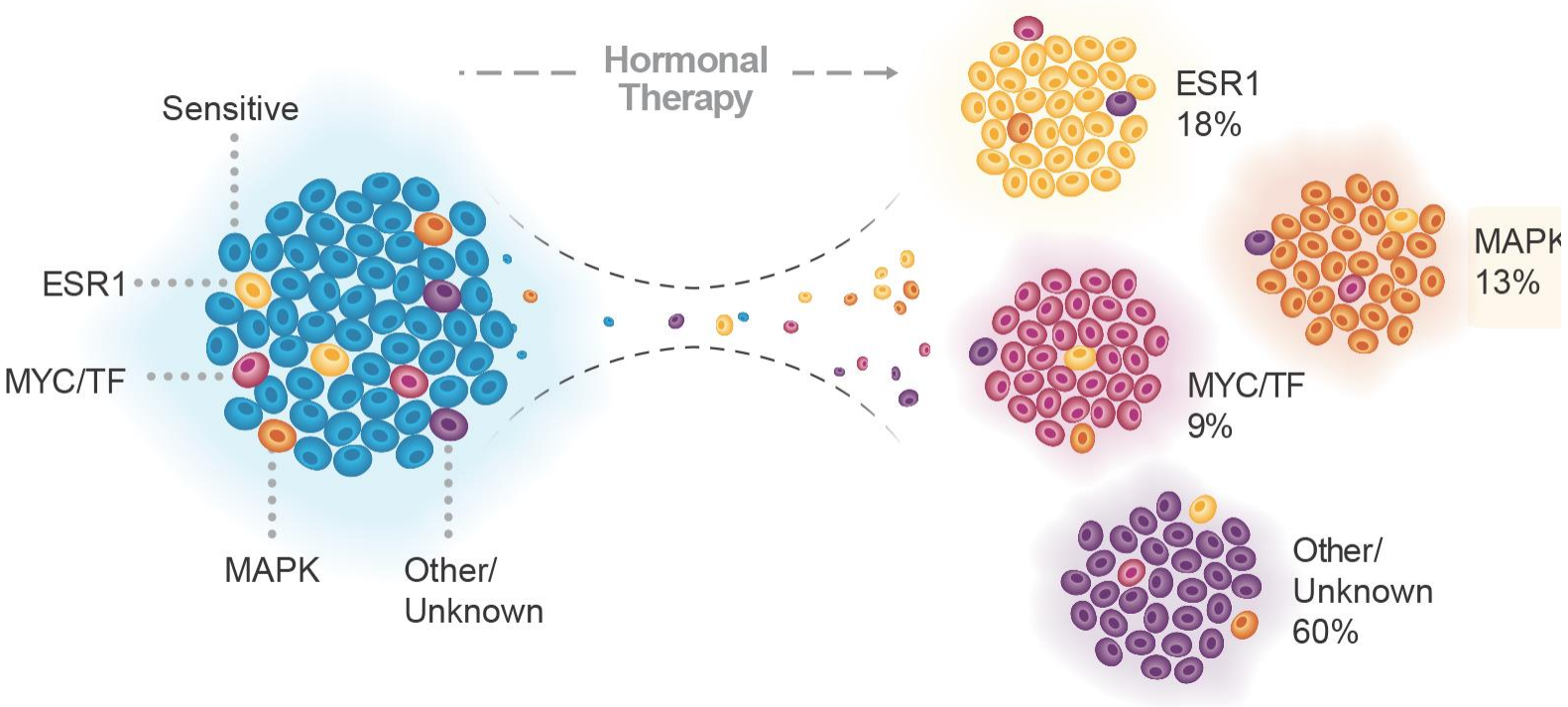
Common LBD mutations locate to region key to ER activation

Agonist structure

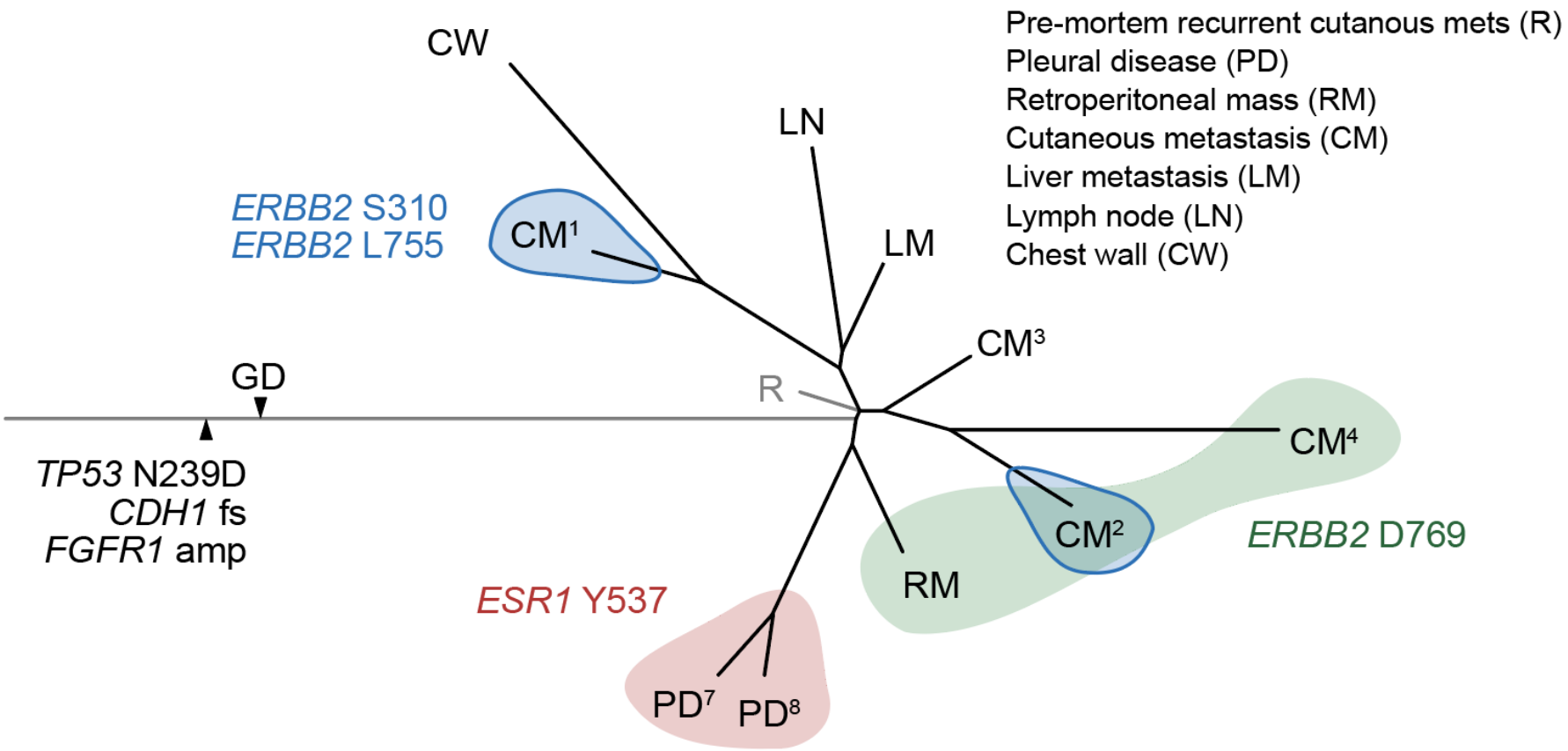


Sean Fanning and Geoffrey Greene

Polyclonal Endocrine Resistance



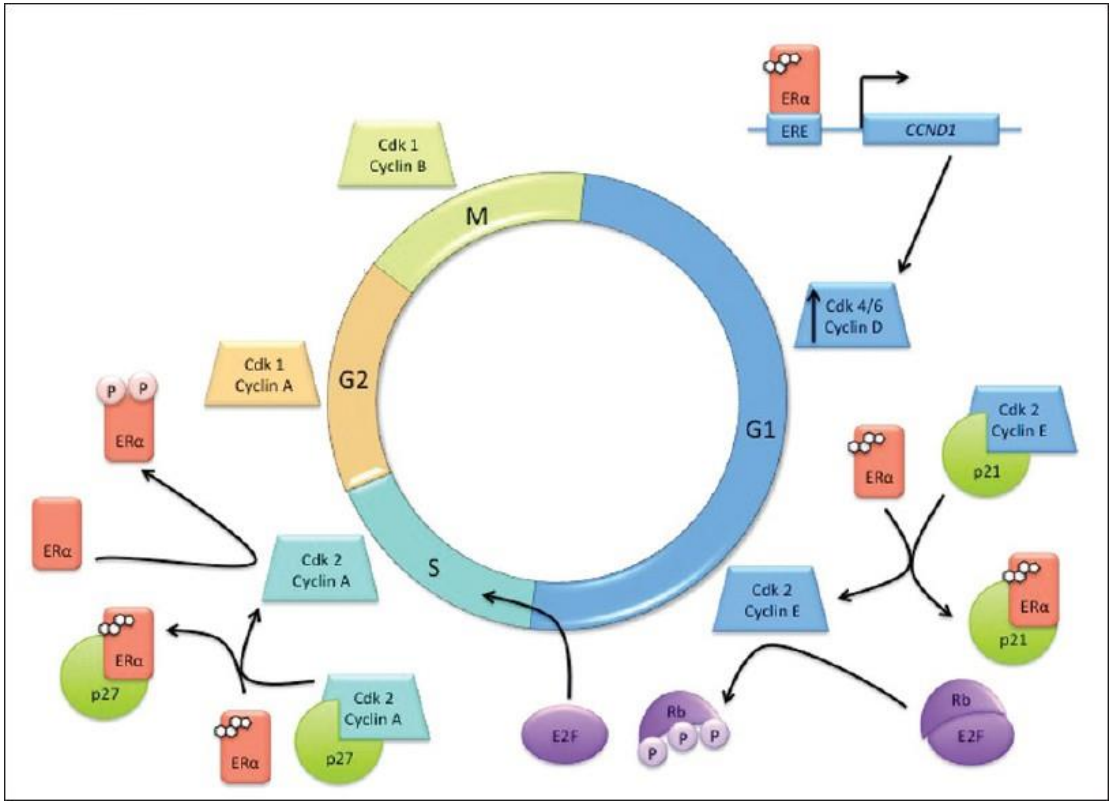
Heterogeneity in resistance mechanisms



Razavi et al., unpublished

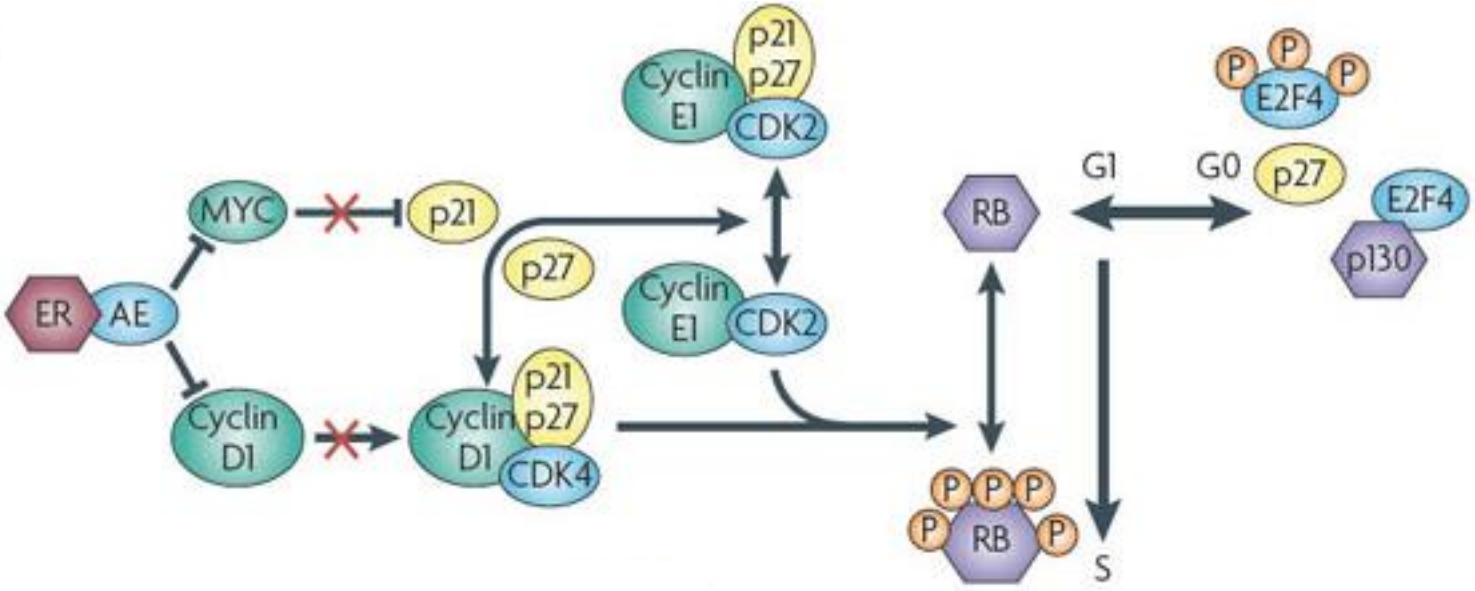
Memorial Sloan Kettering Cancer Center

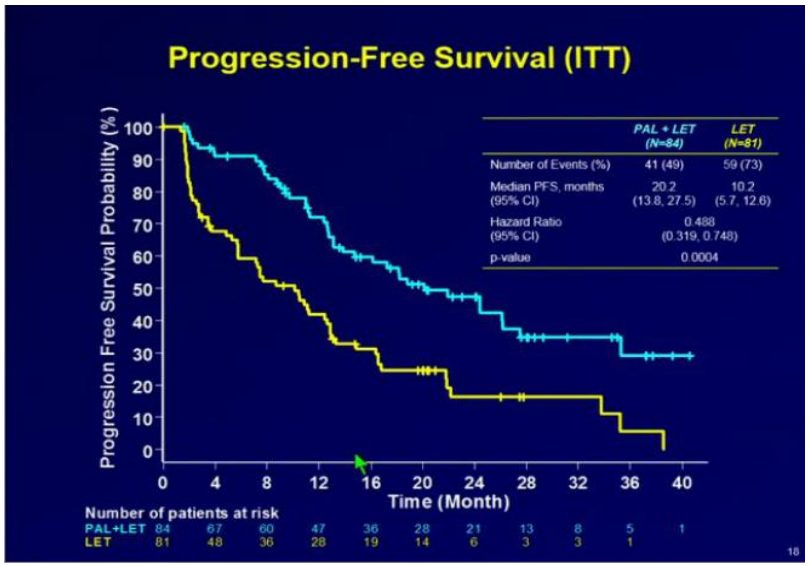
Mitogenic effects of estrogen via cell cycle regulation



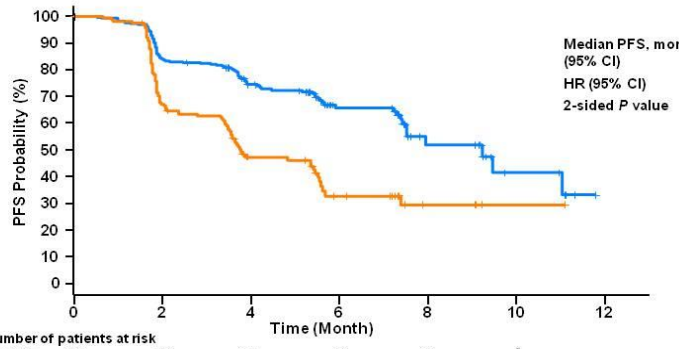
Moghadam et al. J Carcinogen 2013

Combined ER and CDK4/6 inhibition in breast cancer





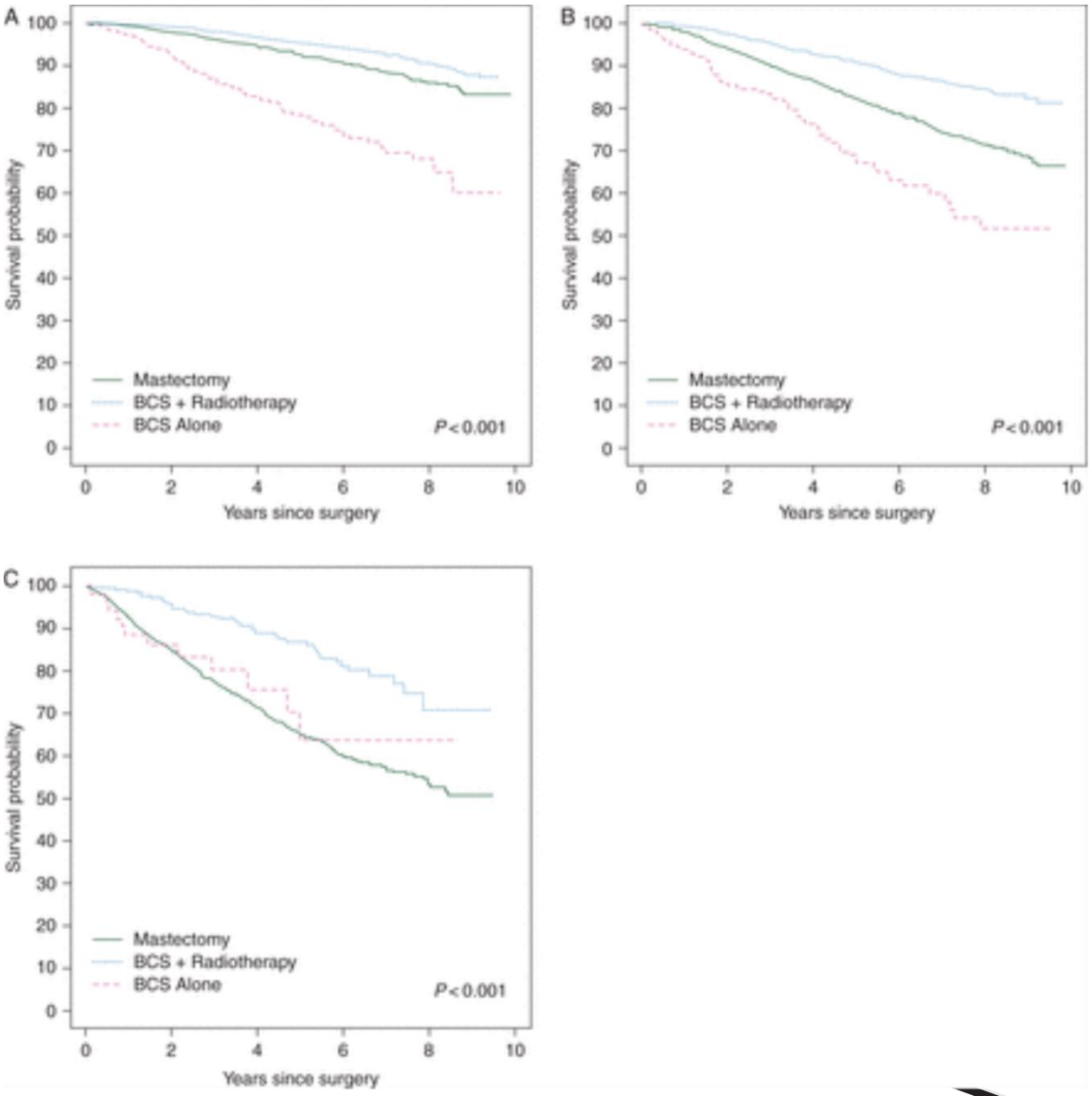
Primary Endpoint: PFS (ITT Population)



	Palbociclib + Fulvestrant n=347	Placebo + Fulvestrant n=174
Median PFS, months (95% CI)	9.2 (7.5, NE)	3.8 (3.5, 5.5)
HR (95% CI)	0.422 (0.318, 0.560)	
2-sided *P* value	<0.000001	

CI=confidence interval; HR=hazard ratio; ITT=intent-to-treat; NE=not estimable; PFS=progression-free survival.

Outcomes in early stage breast cancer



Ann Oncol. 2015;26(6):1161-1169. doi:10.1093/annonc/mdv107

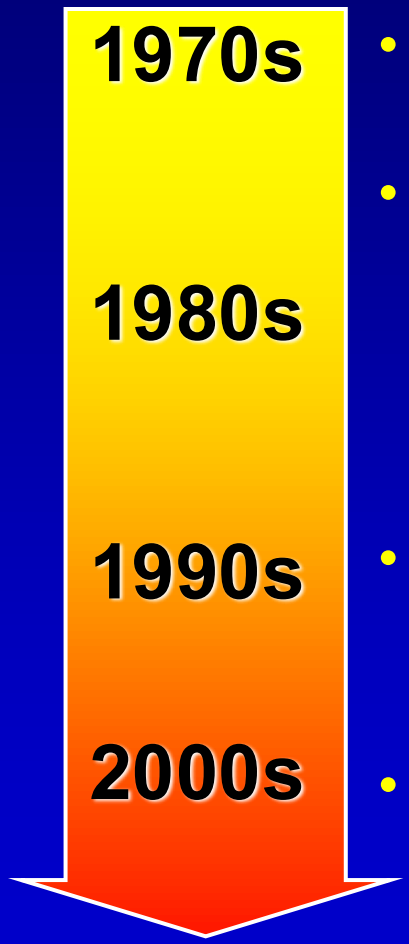
Memorial Sloan Kettering Cancer Center

Adjuvant Chemotherapy and Breast Cancer

- Adjuvant chemotherapy and/or hormonal therapy improve disease-free survival (DFS) and overall survival (OS)
- In an effort to improve outcome, further investigation has led to
  - Combination of agents
  - Sequencing of drug delivery
  - Dose escalation

Early Breast Cancer Trialists' Collaborative Group. *Lancet*. 1992;339:71-85.

Development Timeline: Breast Cancer Chemotherapy



- Pre-anthracyclines
  - CMF, CMFVP
- Anthracyclines
  - Combinations: AC, FAC, AVCMF, FEC, CEF
  - Sequence and alternating
  - Dose intensity, dose density, high-dose chemotherapy
- Taxanes (paclitaxel/docetaxel)
  - Sequential monotherapy
  - Combinations
- Biologic modifiers (trastuzumab)
  - Integration in chemotherapy strategies

Giordano SH, et al. *Cancer*. 2004;100:44-52.

15 years Follow-Up For Invasive Breast Cancer

Treatment:	Proportional Annual Recurrence Reduction:
Tamoxifen 5 yrs (ER +/Unk)	40% (+/- 3)
Combination Chemotherapy (CMF, AC, etc…)	24% (+/- 2)
Ovarian Ablation	31% (+/-8) [7% +/- 4% w/ chemo]

Prognostic Factor
Definition

- Reflect Natural History: predicts outcome in absence of systemic therapy
- Thus tell us when (not how) to treat a patient
- Reflect biological characteristics of the tumour such as ability to proliferate, invade, and induce angiogenesis

Routinely Accepted Prognostic Factors

Tumor

- Nodal status
- Tumor size
- Histology
- ER

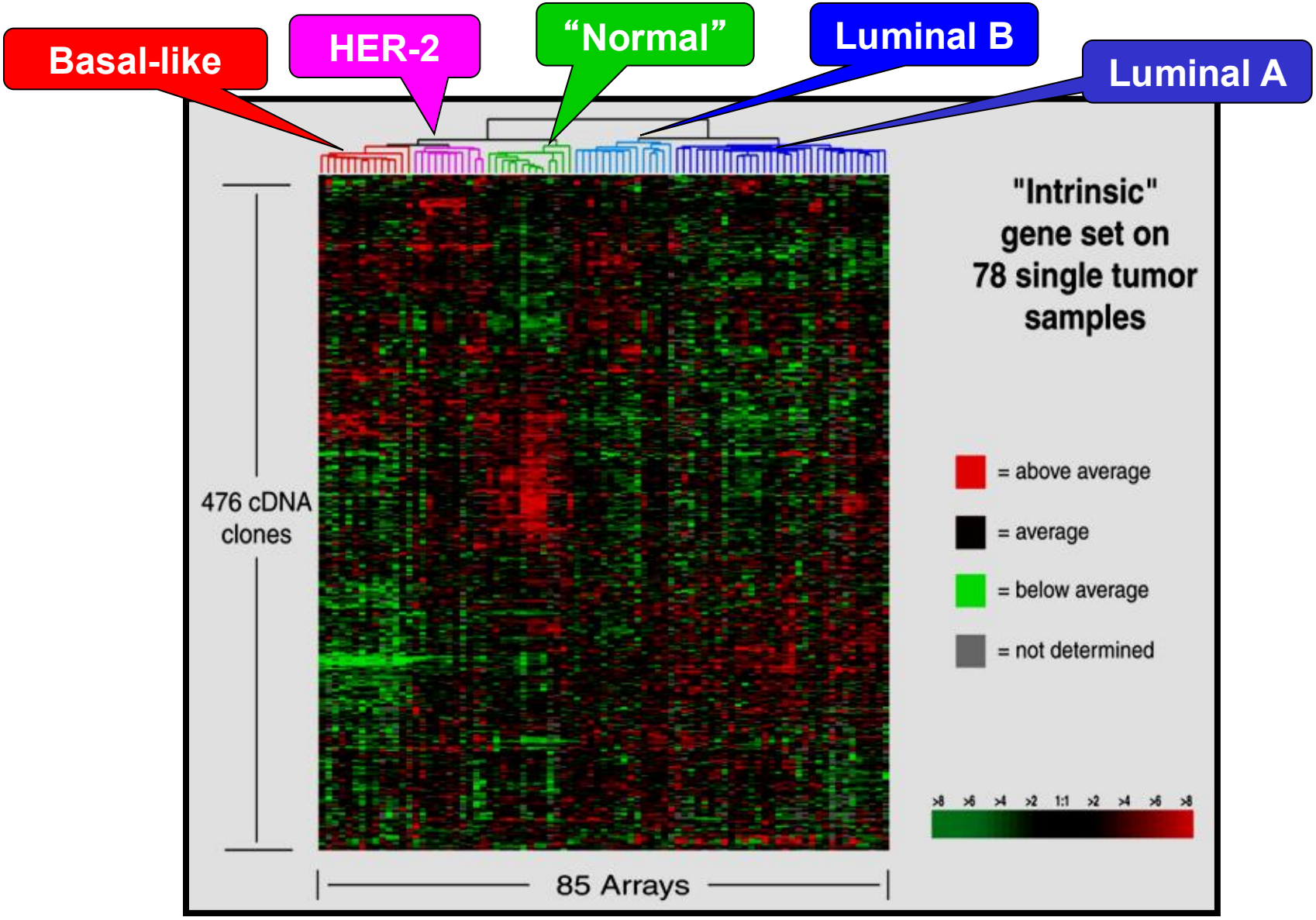
Patient

- Age

Ideal New Prognostic Factor

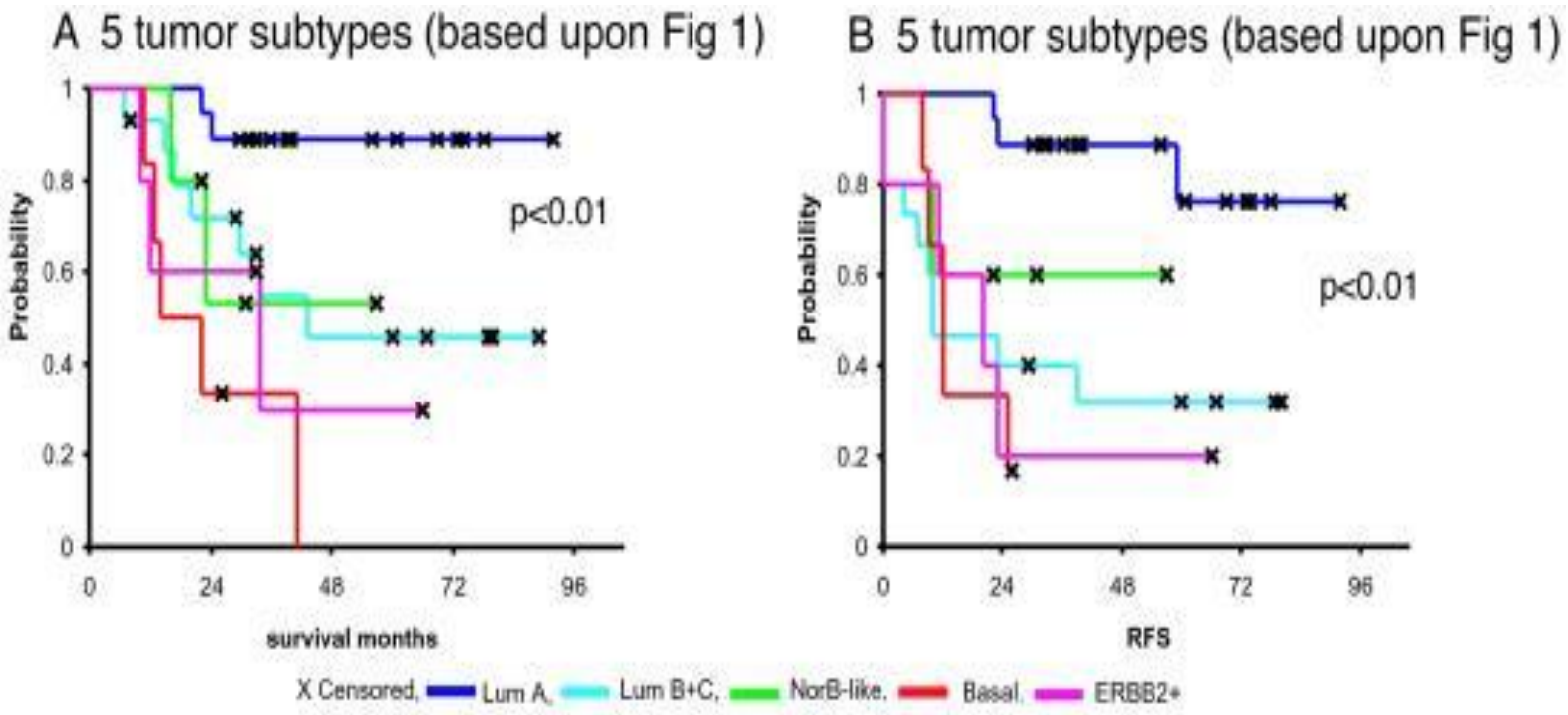
- Validated in prospective trials designed to address utility of prognostic factor in question
- Provides significant **independent value** on MVA including known prognostic factors
- Detectable by reproducible, feasible, standardized method
- Represents biologically plausible pathway

Molecular Portrait of Breast Cancers



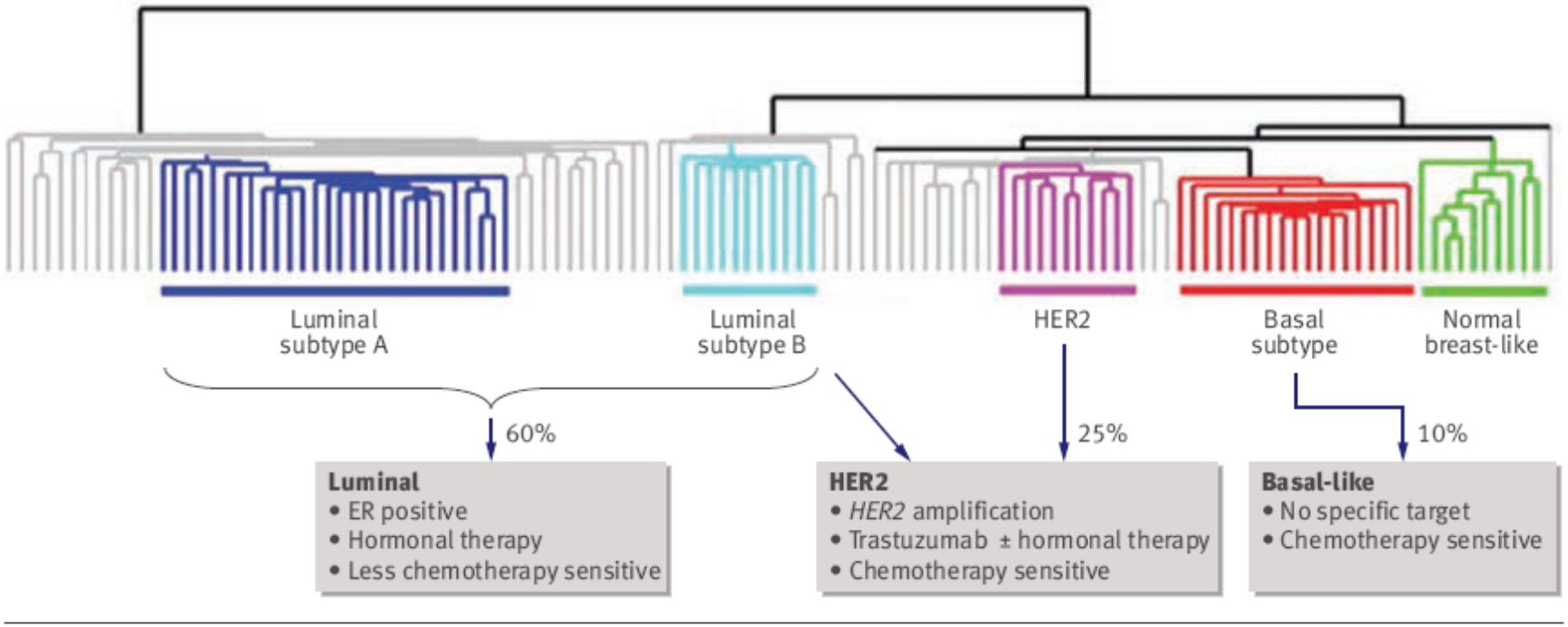
Sorlie T et al, PNAS 2001

DFS and OS by Subtype



Sorlie, PNAS 2001;2001 98:10869-874

Molecular Subtypes



Perou, Sorlie et al, Nature, 2000

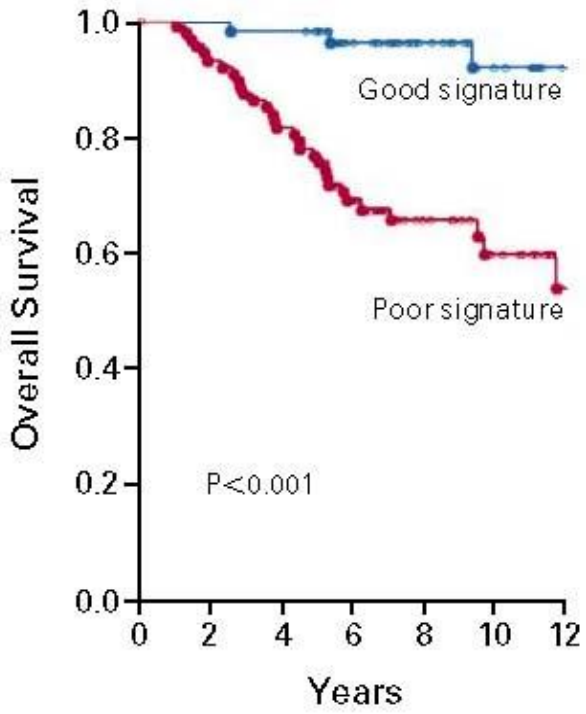
70 Gene Signature: Mammaprint™

- **Derived from 295 tumors**
  - T<5cm, age ≤ 52 yrs
  - 151 NO, 144 N+
  - 90 CTX, 20 hormonal, 20 both
  - Diagnosed 1984 – 1995

Van de Vijver, NEJM 2002 347:1999-2009

Overall Survival by Amsterdam Gene Signature

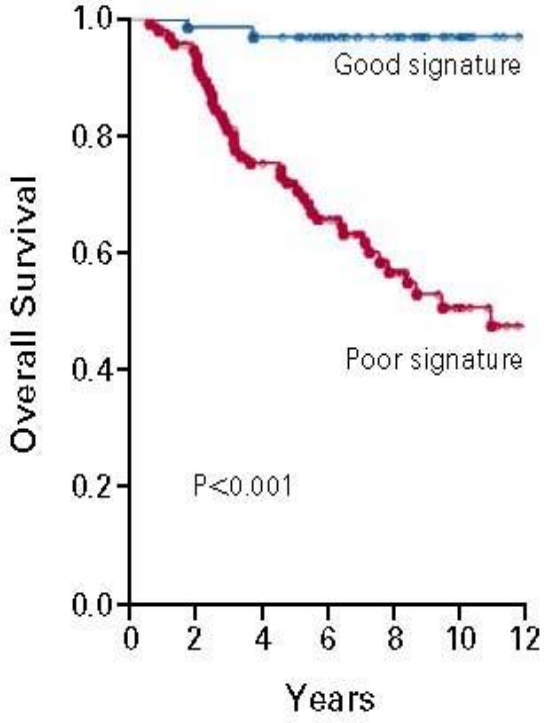
F Lymph-Node–Positive Patients



No. at Risk

Good signature	55	55	54	43	30	19	11
Poor signature	89	81	68	50	29	19	9

D Lymph-Node–Negative Patients



No. at Risk

Good signature	60	59	58	48	35	24	12
Poor signature	91	86	66	50	33	21	10

Van De Vijver MJ, NEJM 2002; 347:1999-2009

Oncotype DX™

16 Cancer and 5 Reference Genes

250 Candidate Genes, 3 Studies, 447 Pts

PROLIFERATION
Ki-67
STK15
Survivin
Cyclin B1
MYBL2

HER2
GRB7
HER2

ESTROGEN
ER
PGR
Bcl2
SCUBE2

INVASION
Stromolysin 3
Cathepsin L2

GSTM1
CD68
BAG1

REFERENCE
Beta-actin
GAPDH
RPLPO
GUS
TFRC

Best RT-PCR performance and most robust predictors

Paik S, NEJM 2004; 351:2817-26

Recurrence Score (RS) Algorithm

+ 1.04 x Proliferation Group Score
+ 0.47 x HER2 Group Score
- 0.34 x ER Group Score
+ 0.10 x Invasion Group Score
- 0.08 x GSTM1
- 0.07 x BAG1
+ 0.05 x CD68

Category	RS (0-100)	% Cases
Low risk	< 18	51
Inter risk	18 - 30	22
High risk	≥ 31	27

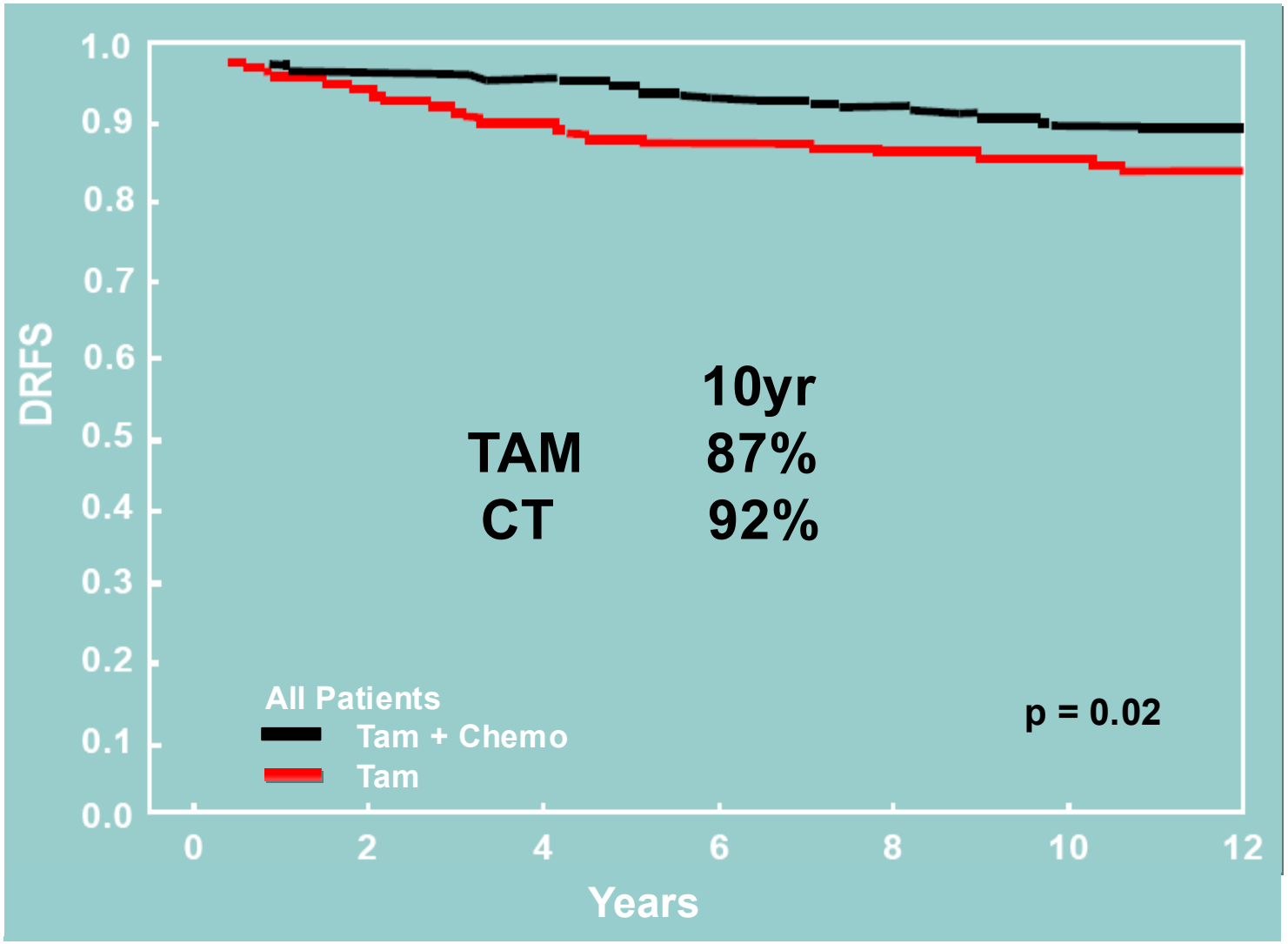
Prognosis vs Prediction

- Prognostic factors most useful if they identify patients with such a good prognosis that adjuvant treatment is NOT required

- A pure prognostic factor does not tell us how to best treat a patient in the poor prognosis group

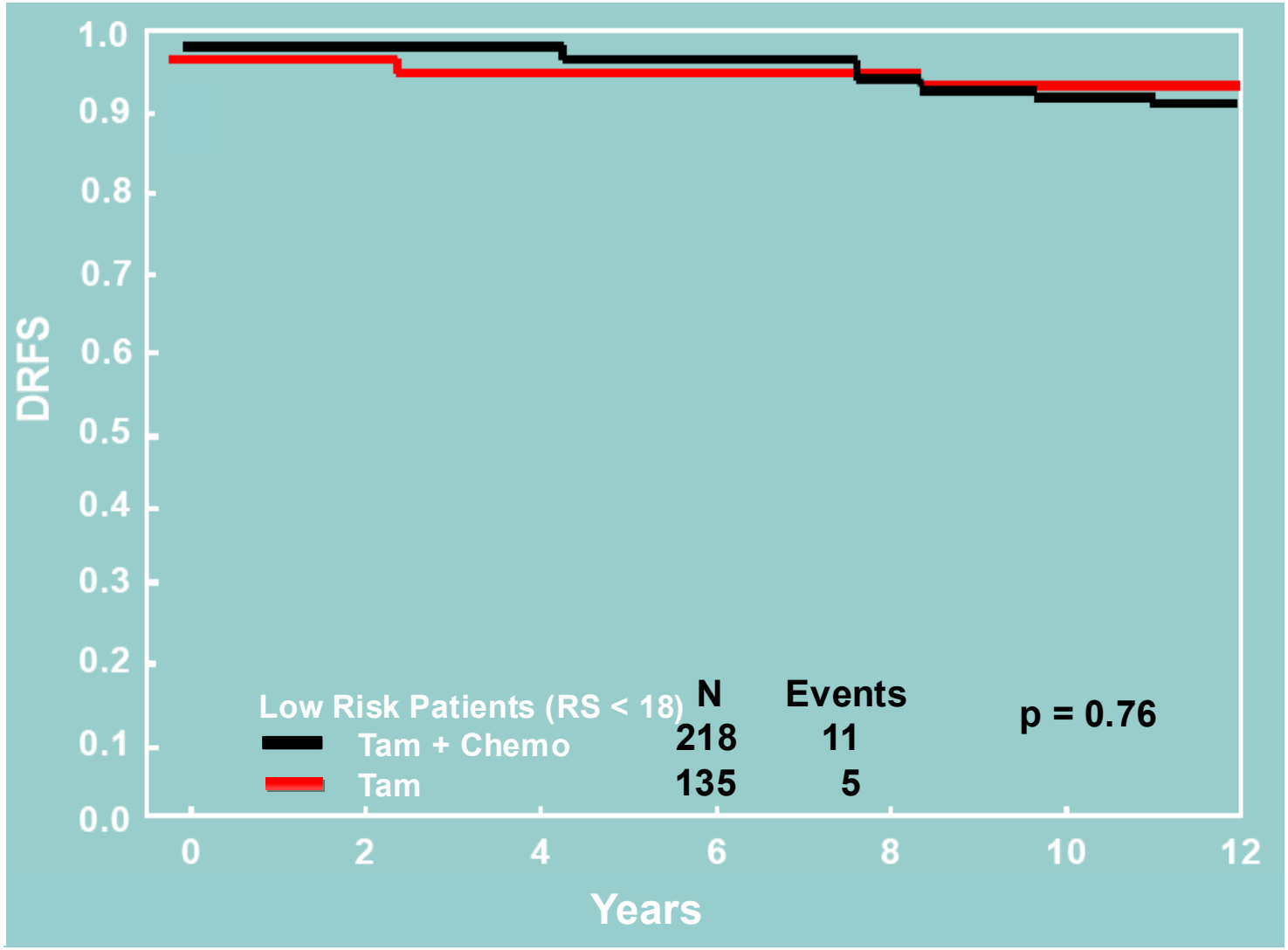
- It is increasingly clear that multiple tumor factors impact upon the success of therapy

B-20 All
Disease Free Survival



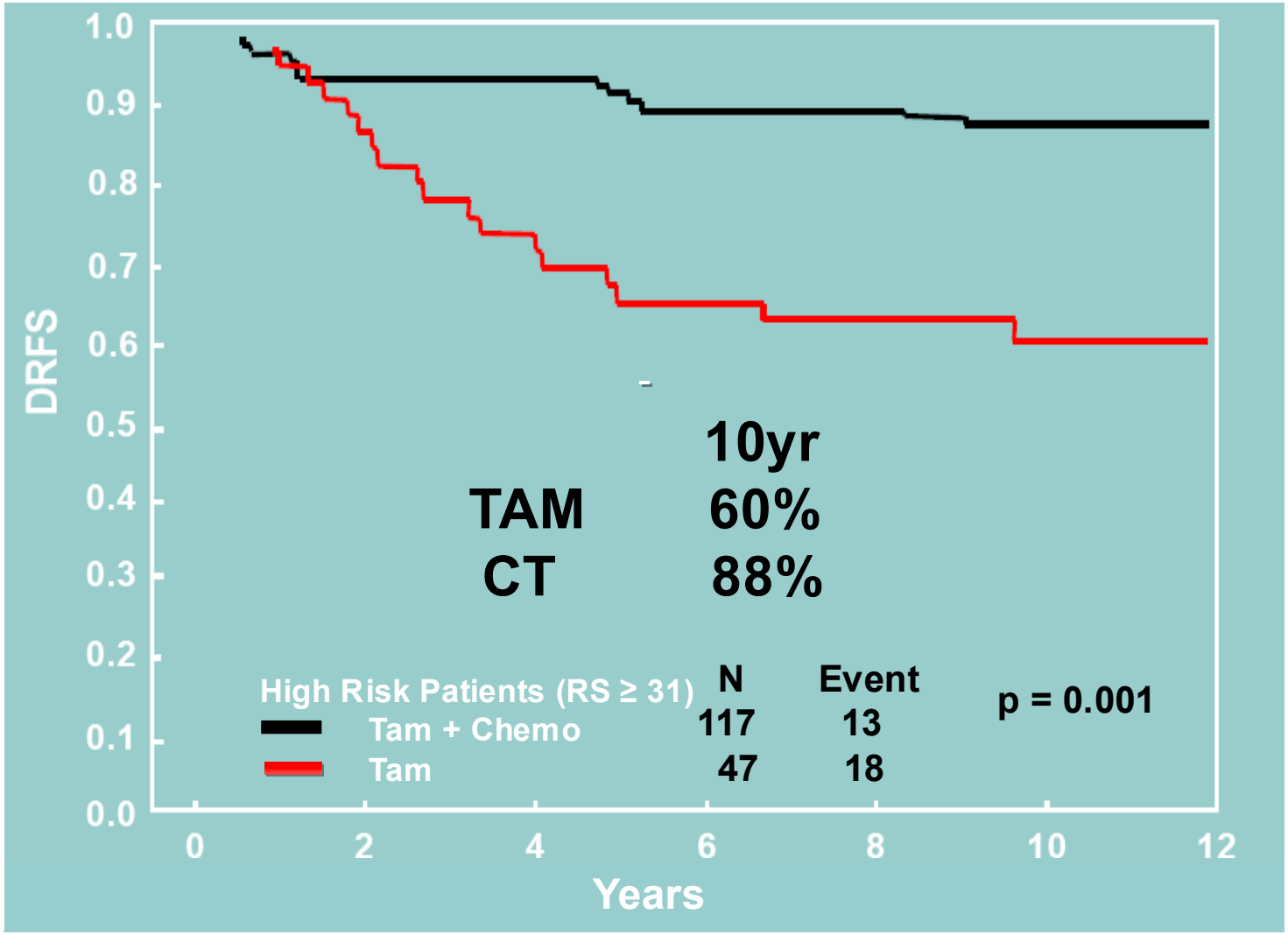
Paik S, JCO 2006; 24:3726-34

B-20 Low RS < 18
Disease Free Survival



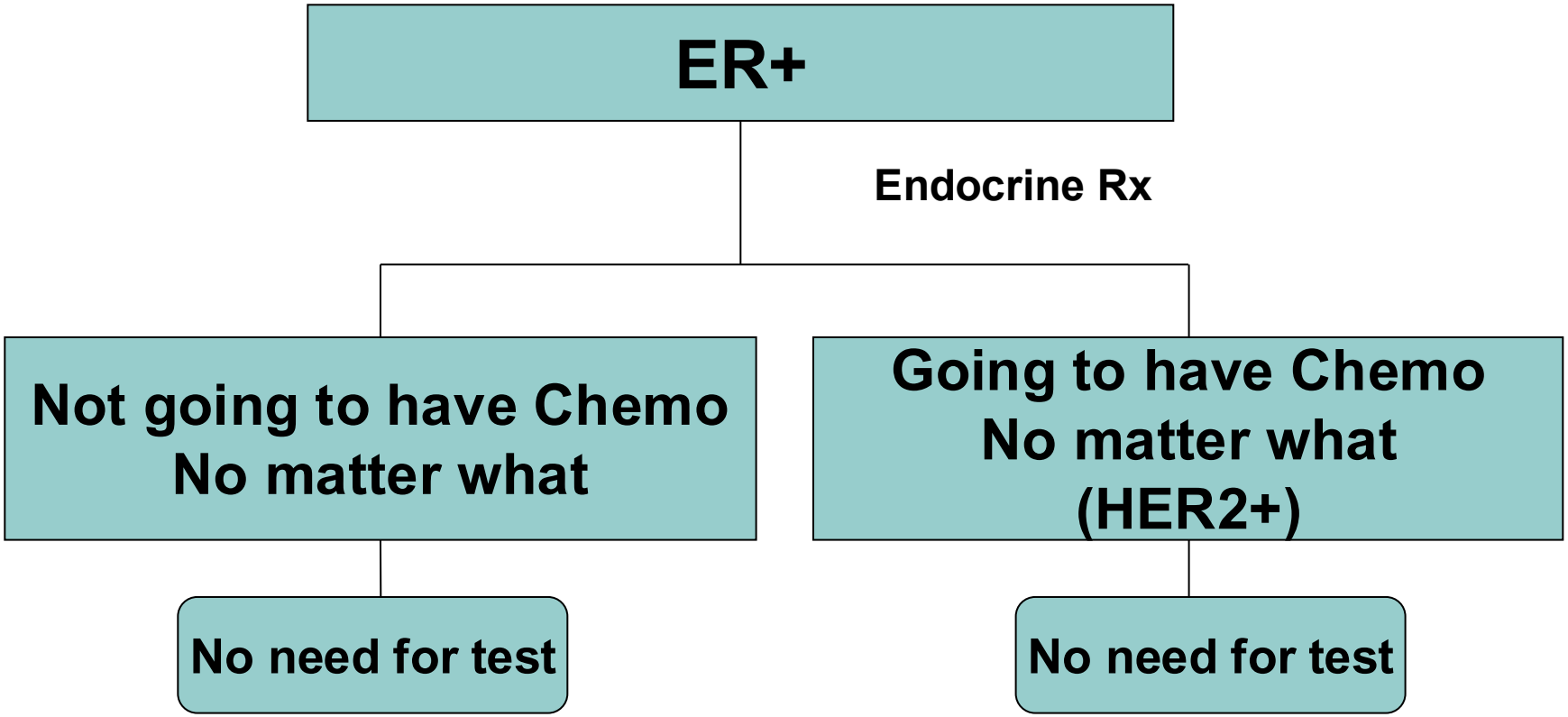
Paik S, JCO 2006; 24:3726-34

B-20 High RS ≥ 31 Disease Free Survival

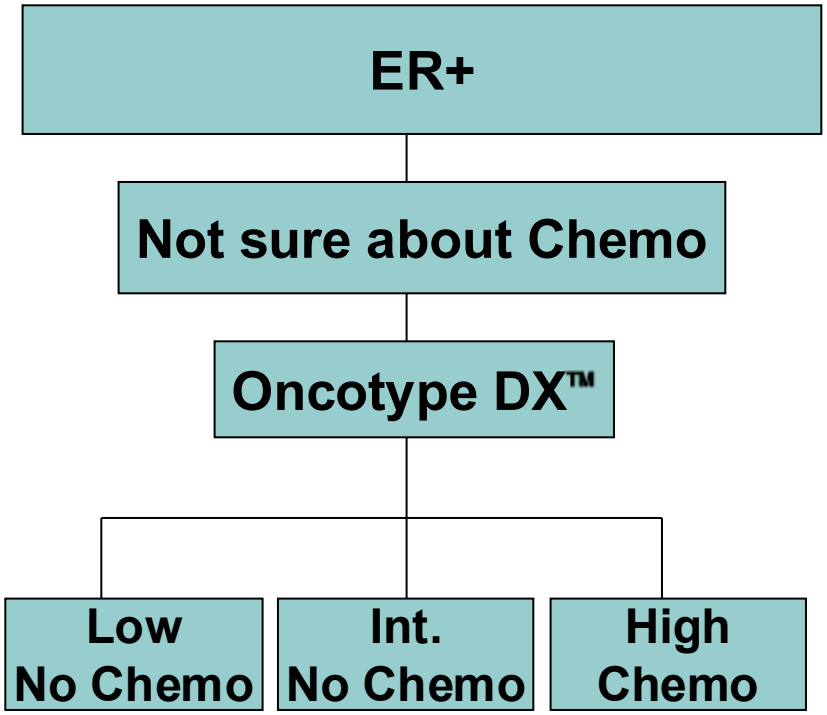


Paik, S JCO 2006;24:3726-34

Clinical Application of Oncotype DX™



Clinical Application of Oncotype DX™



Impact of Oncotype DX™ On Therapy

In practice		43% low risk
		47% int risk
		10% high risk
CTX →	E	22.5%
E →	CTX+E	3.4%
No Change		74.1%

Lo S. et al, JCO 2007;25:22S

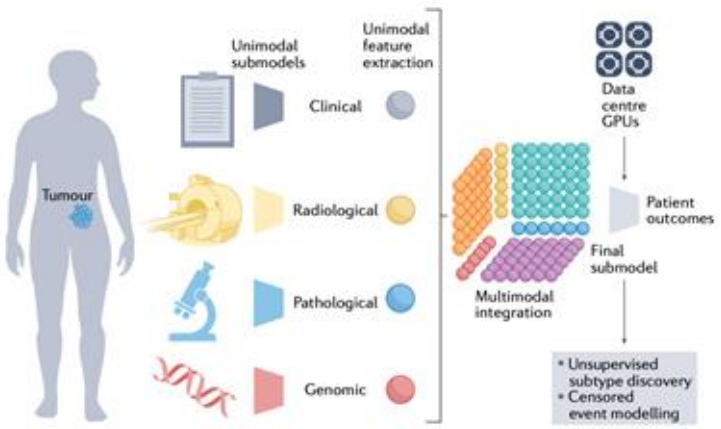
Multimodal data integration represents a frontier of Computational Oncology

Data Science -> Real World Data

- Combining information sources for increased predictive power
- Improving patient stratification & personalized medicine

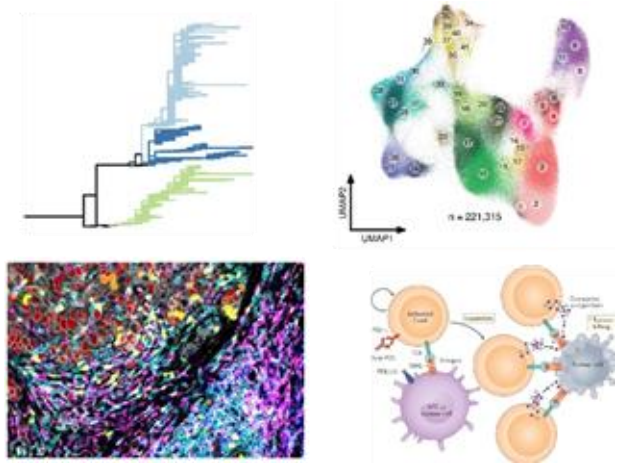
Discovery of new Tumor Biology

- Uncovering critical cellular states
- Tumor microenvironment composition, architecture and dynamics
- Tumor evolution, drug resistance, new therapeutics



Large patient n
Low molecular resolution

Small patient n
High molecular resolution



*Measuring & modeling the '**whole patient**'*

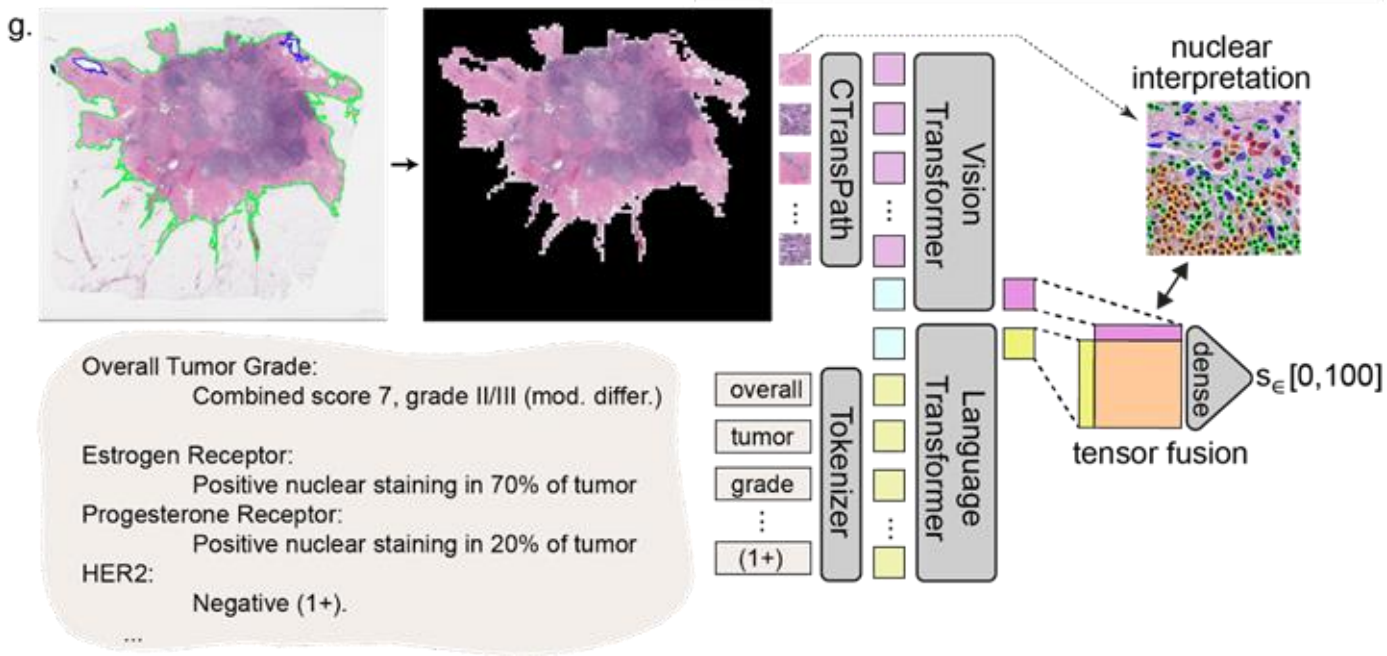
Boehm *et al* **Nat Rev Can** 2021
Vanguri *et al* **Nat Cancer** 2022
Boehm *et al* **Nat Cancer** 2022

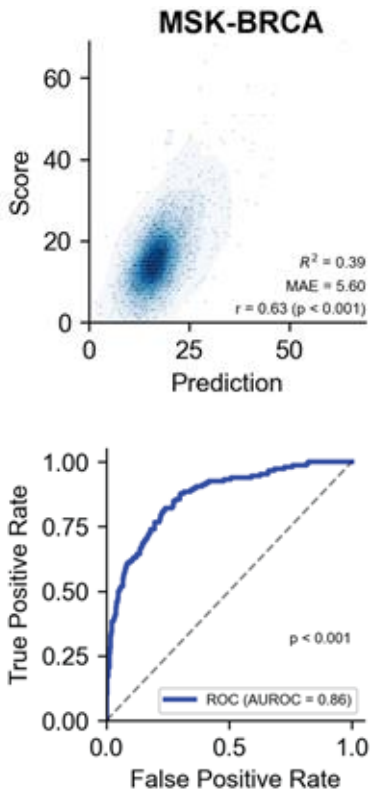
Kather et al **Nature Med** 2019
Sammut et al **Nature** 2022
Crispin-Ortuzar et al **Nature Comm** 2023
Truhn et al **NPJ Prec Oncology** 2024

*Measuring & modeling the '**whole tumor**'*

Shi et al **Nature Comm** 2024
Vazquez-Garcia *et al* **Nature** 2022

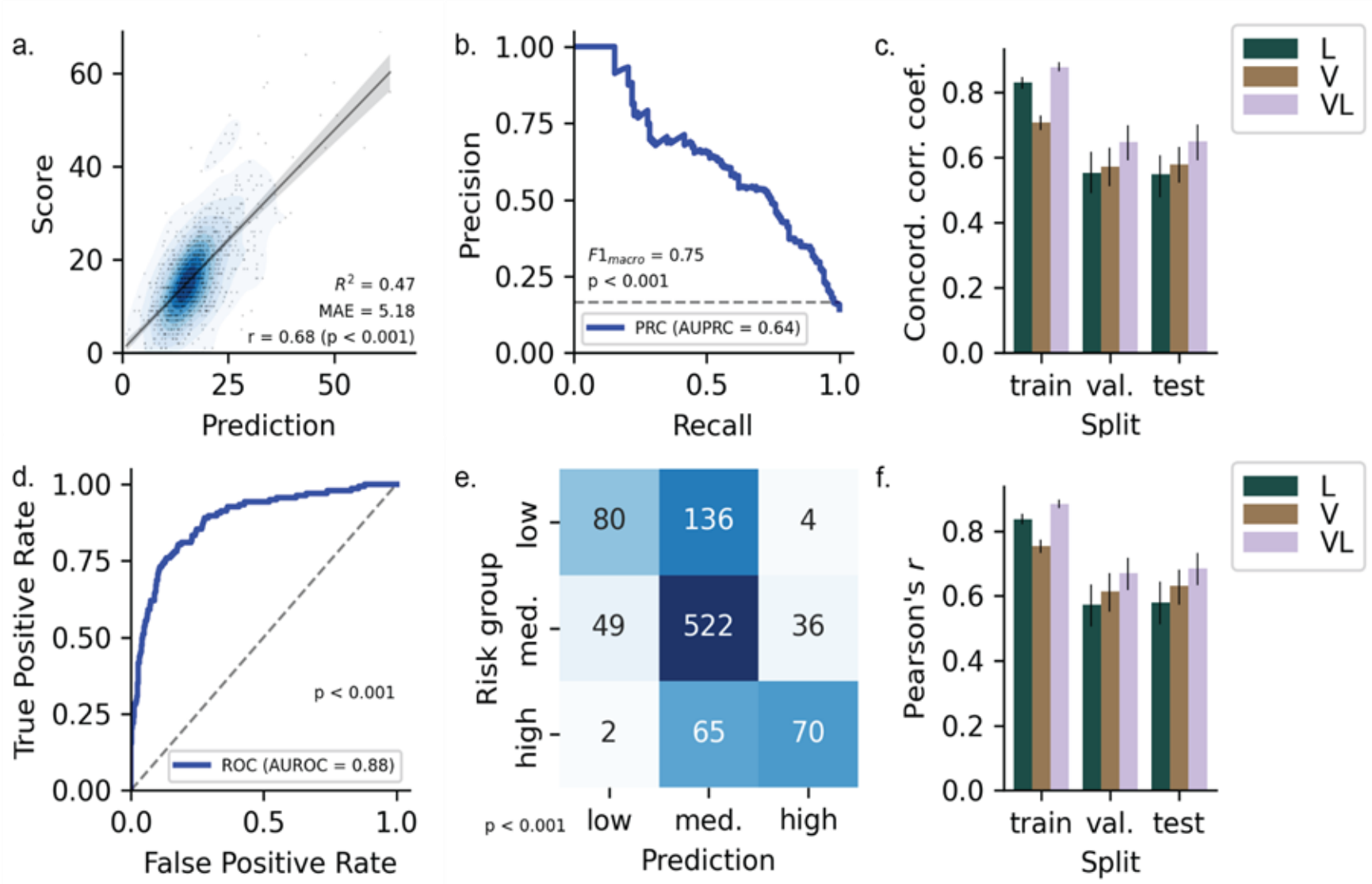
Predicting Oncotype ROR from H&E and path reports





Boehm, El Nahhas, Marra, Kather, et al, Nat Comm 2025

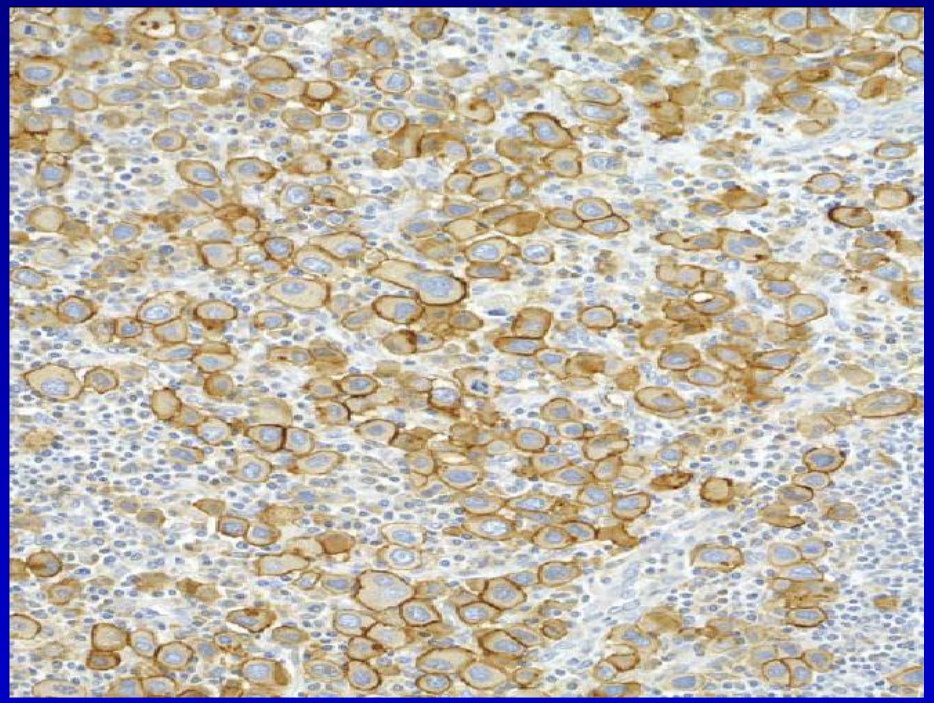
High and low risk strata cleanly modeled



Boehm, El Nahhas, Marra, Kather, et al, Nat Comm 2025

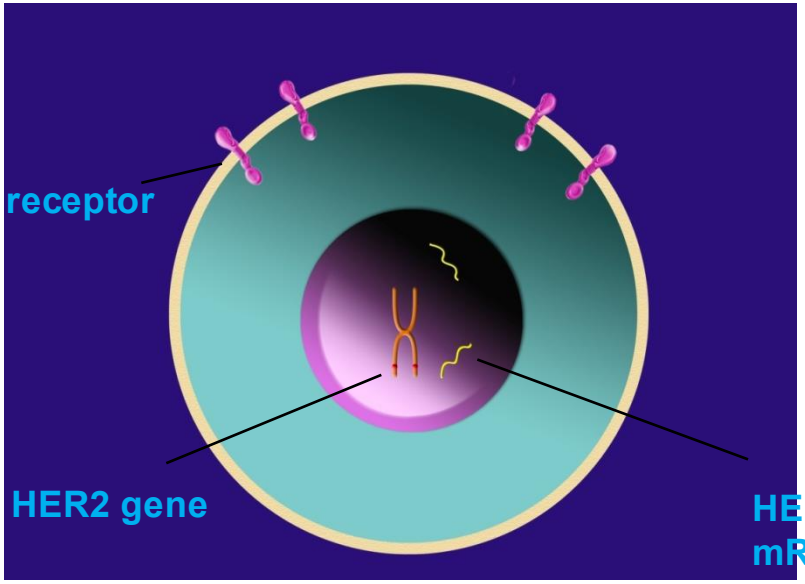
HER2 and Breast Cancer

- Overexpressed in nearly 20% of metastatic breast carcinomas
- HER2-positive breast cancer associated with worse outcomes

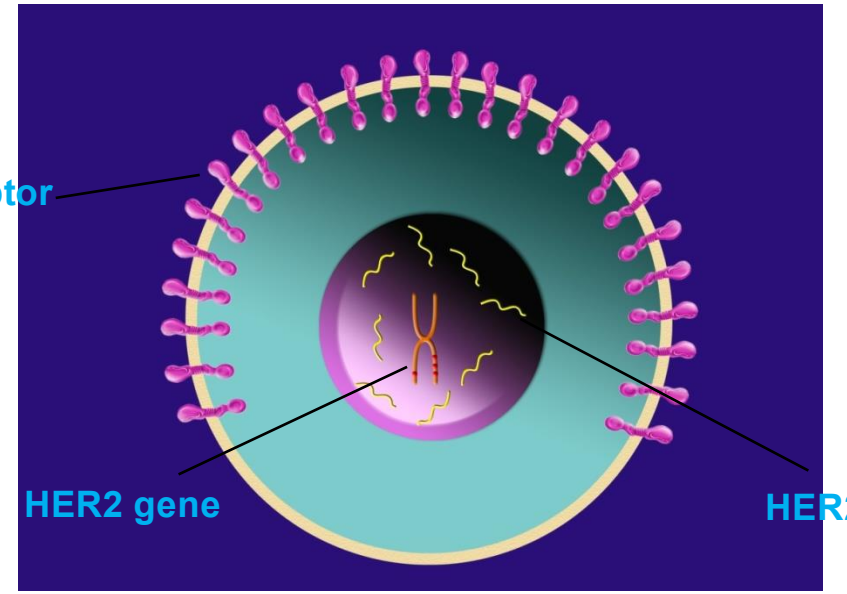


HER2+

HER2 amplification

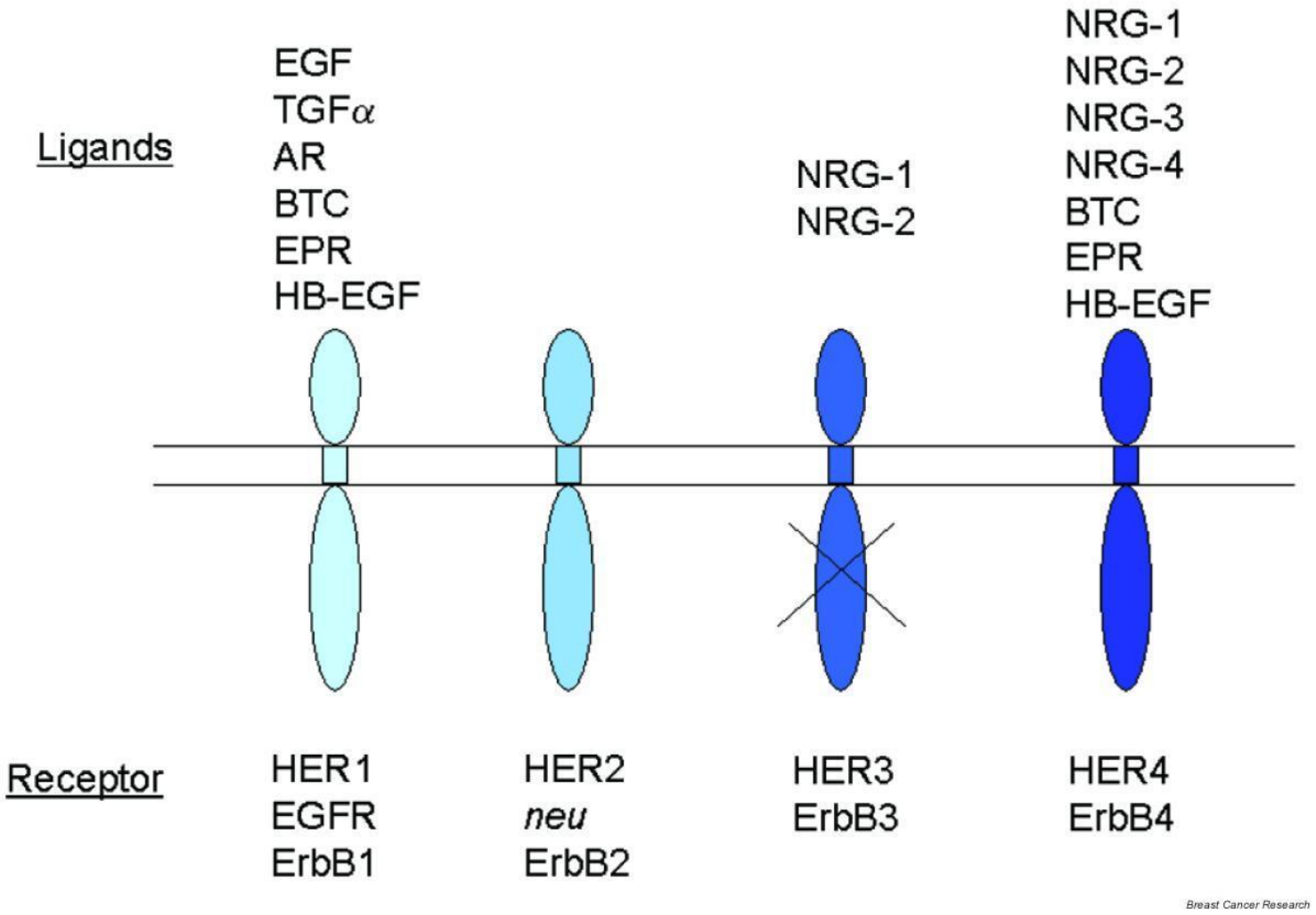


Normal
(~ 20,000-50,000 receptors)



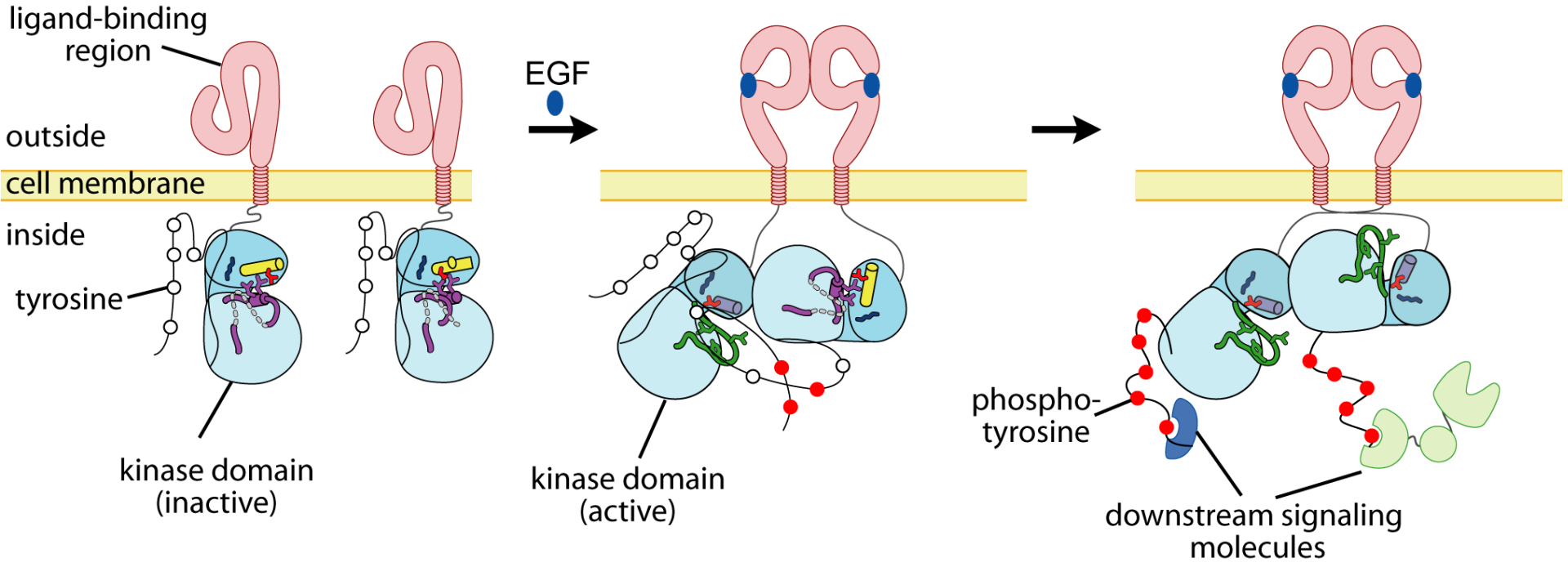
HER2-positive
(Up to 2 million receptor molecules)

ErbB receptors and ligands



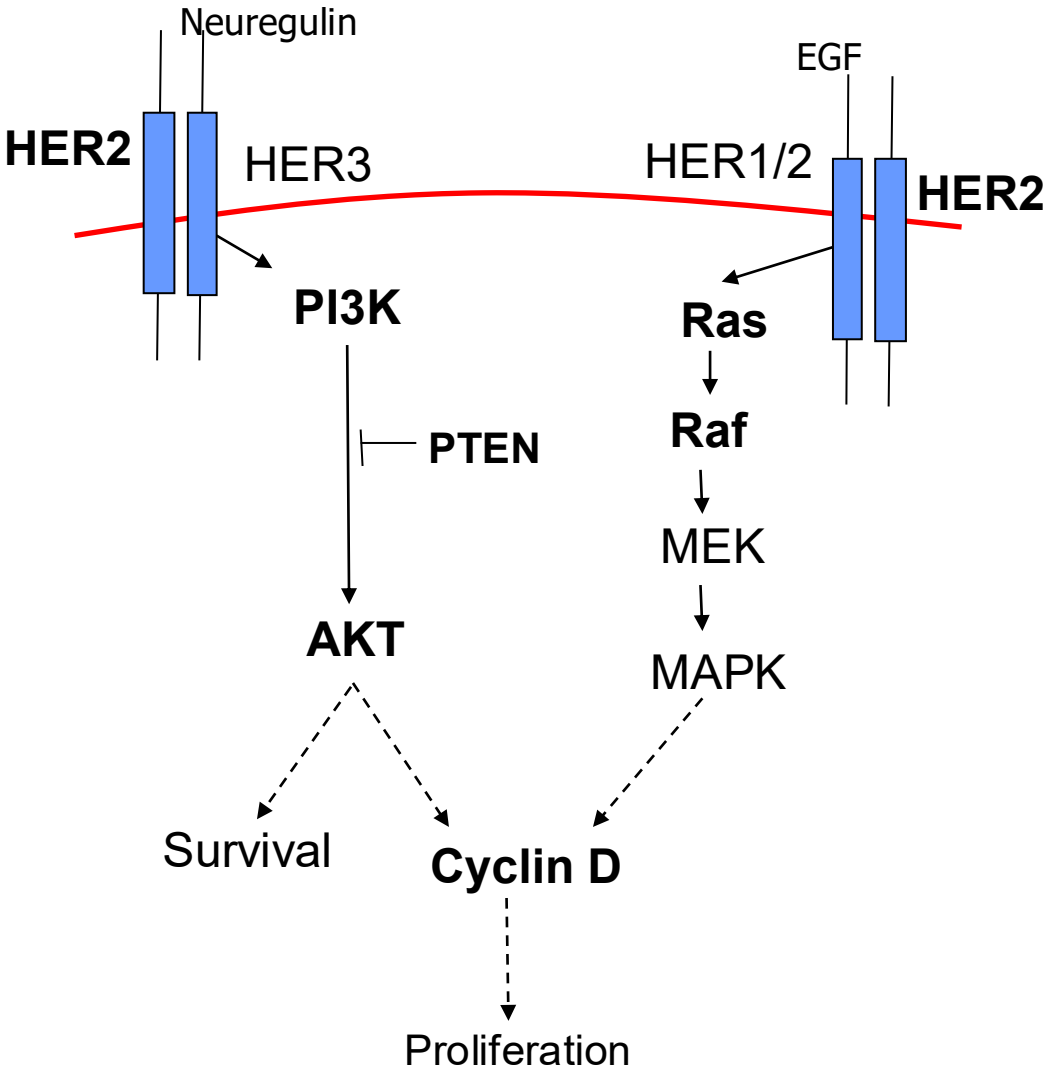
Lin 2004

Activation of ErbB receptors

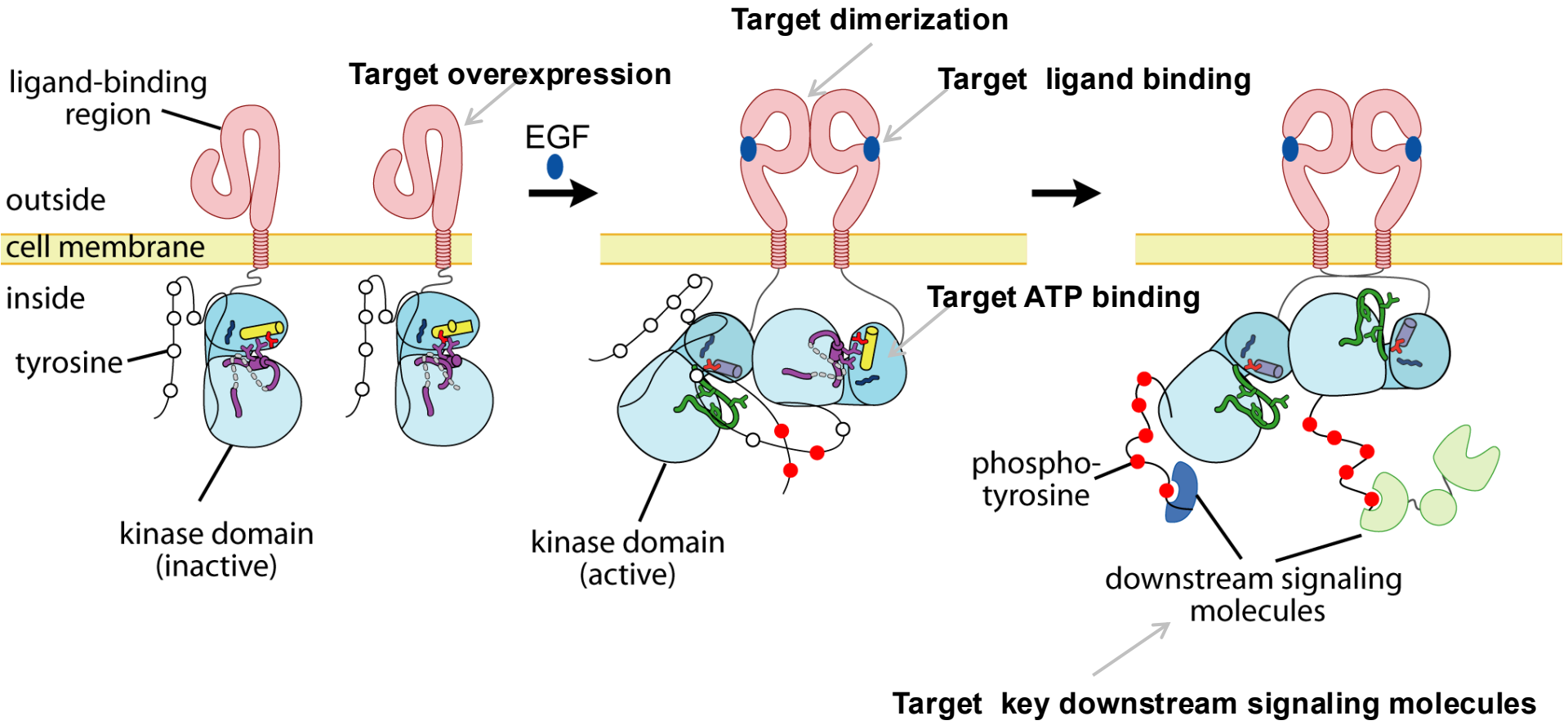


Kuriyan lab

ErbB receptor signaling cascades



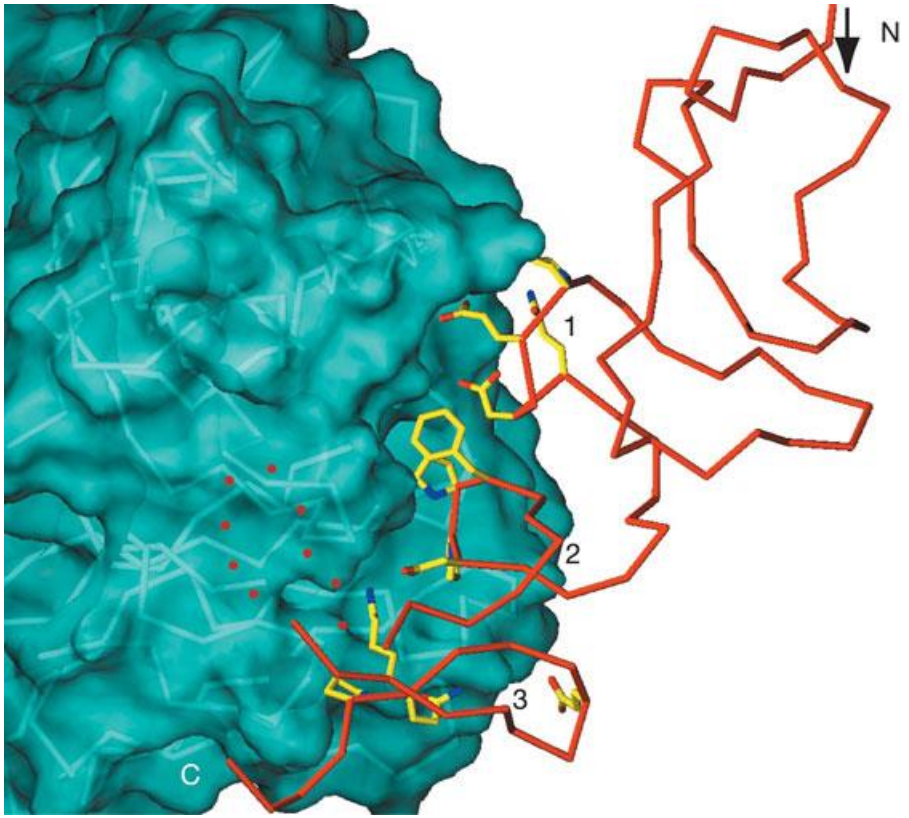
Strategies to target HER2 driven cancers



Trastuzumab: Humanized Anti-HER2 Antibody

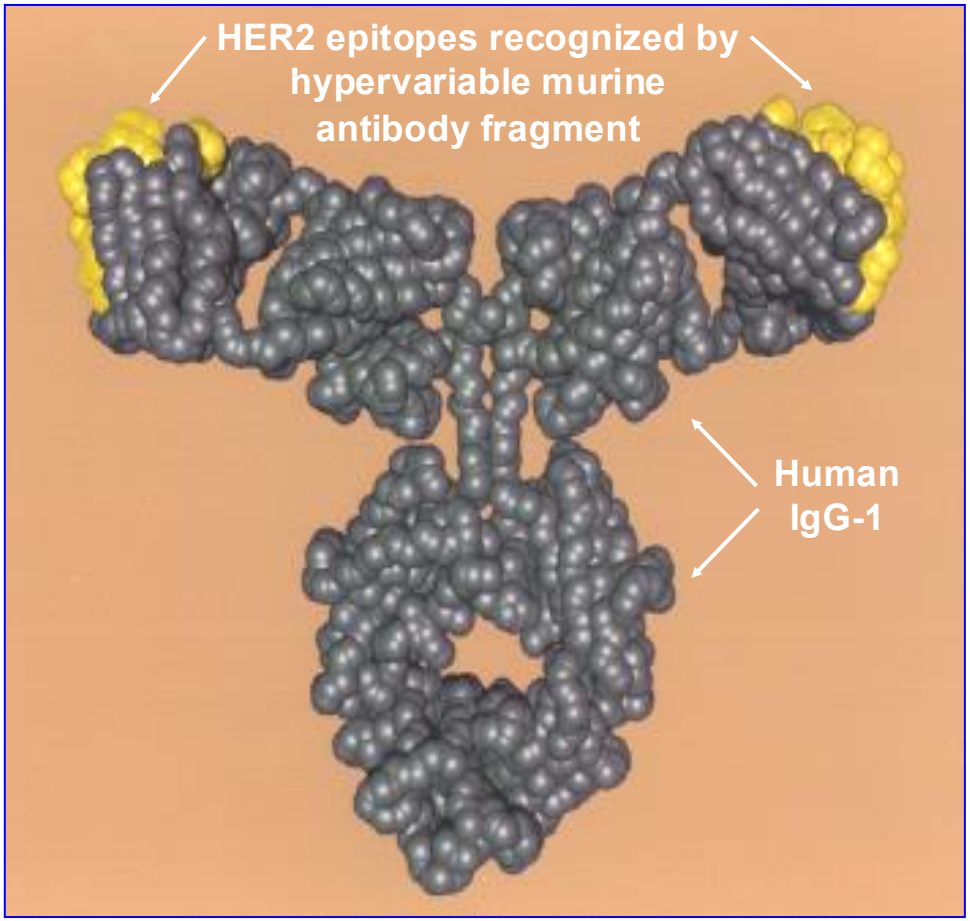
Trastuzumab = recombinant humanized monoclonal antibody to the extracellular domain of HER2. Antibody (shown in blue) contacts 3 extracellular loops of HER2 .

Contacts =1:557-561, 2: 570-573, 3:593-603



Choo et al. 2003.

Trastuzumab: Humanized Anti-HER2 Antibody



- High affinity & specificity
- 95% human, 5% murine
  - Decreases potential for immunogenicity
  - Increases potential for recruiting immune effector mechanisms

Trastuzumab First-Line Monotherapy in MBC: Response by HER2 status

(All Patients IHC 2+/3+)

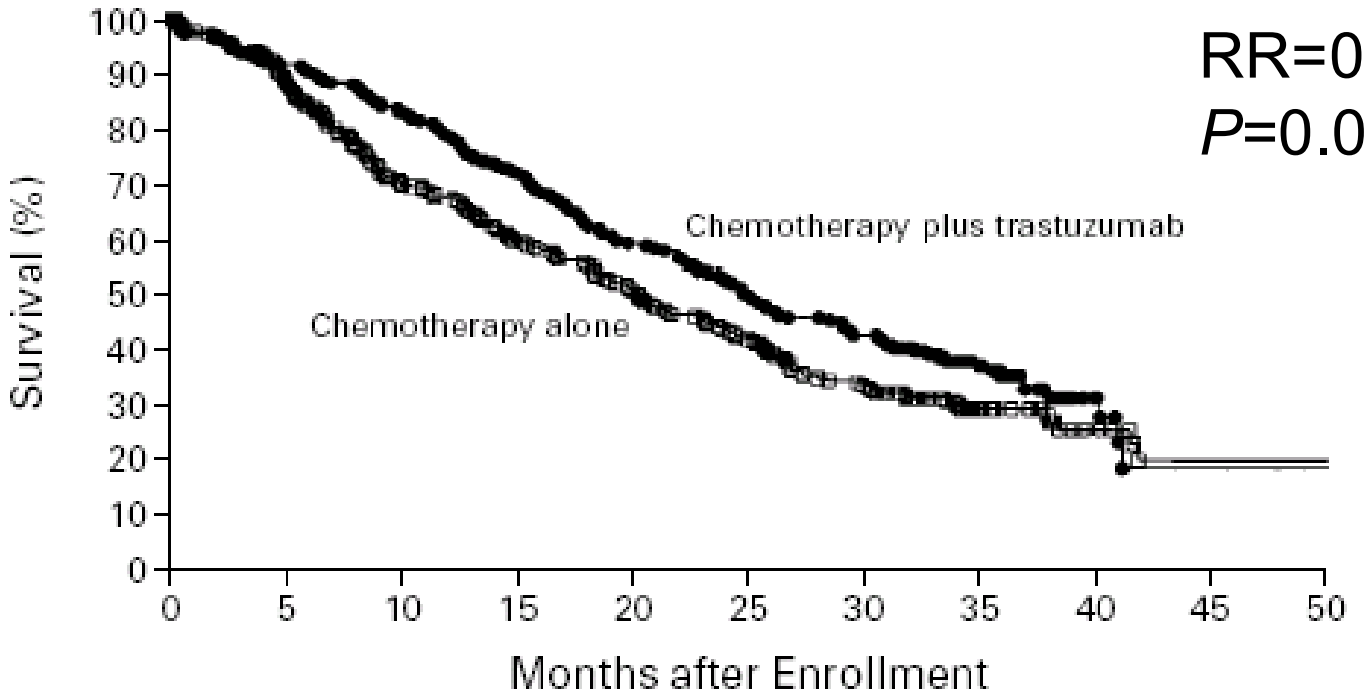
	3+ n (%)	2+ n (%)
No. of evaluable patients	84	27
ORR (%)	29 (35)	0 (0)

	FISH+ n (%)	FISH– n (%)
No. of evaluable patients	79	29
ORR (%)	27 (34)	2 (7)

Vogel et al: JCO 2002 20(3):719-726

Trastuzumab Added To ChemoRx Improves Survival In MBC

% w/trastuz.@ POD: 24 62 65

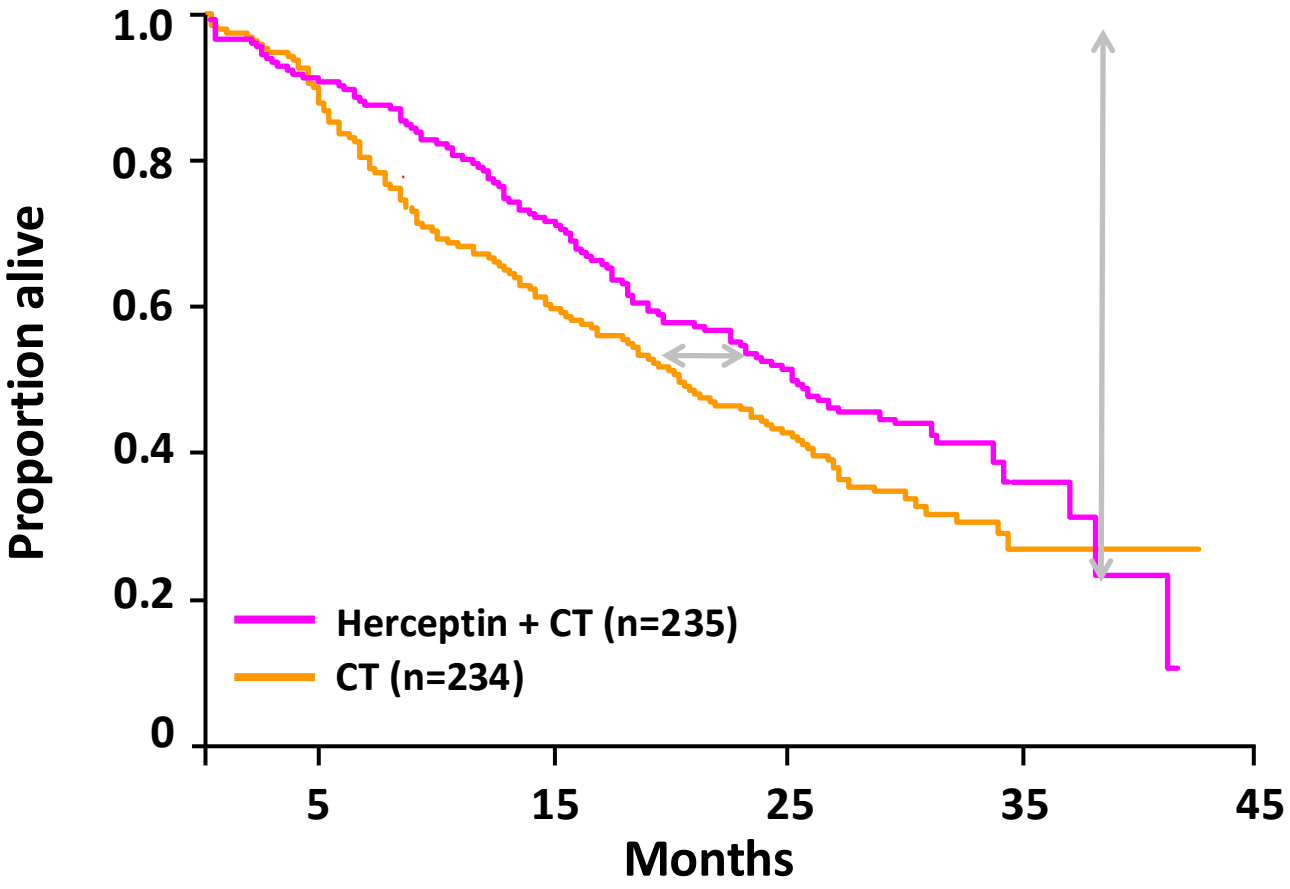


RR=0.76
P=0.025

No. at Risk									
Chemotherapy plus trastuzumab	235	214	192	165	134	114	96	47	11
Chemotherapy alone	234	205	160	136	116	97	76	37	13

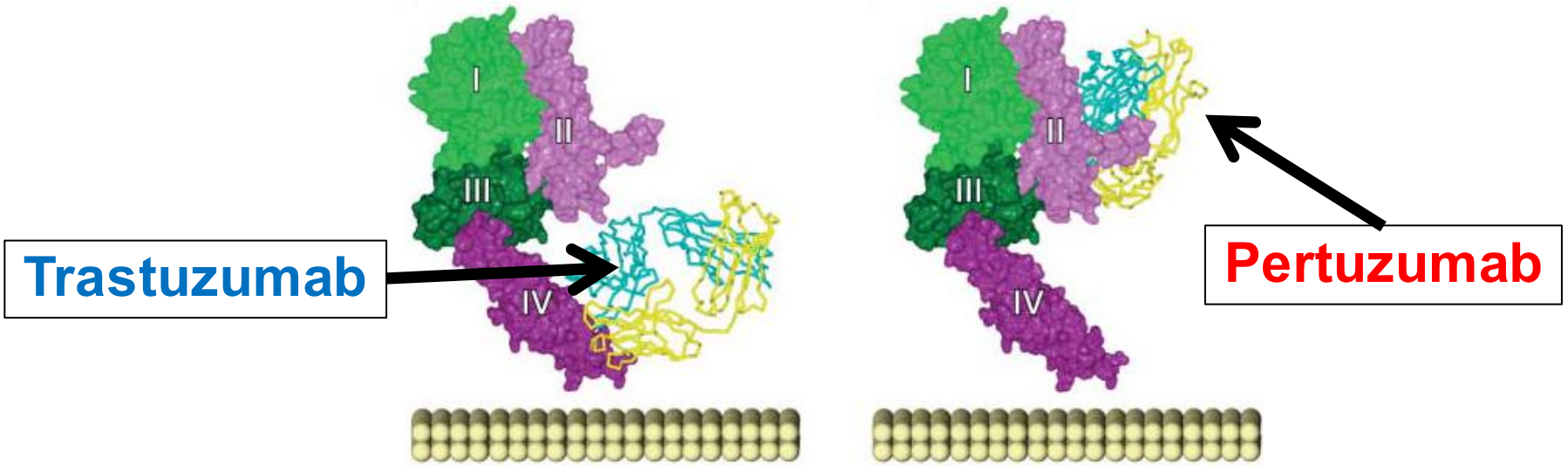
Slamon et al NEJM 2001; 344:783-92

Efficacy…. and resistance



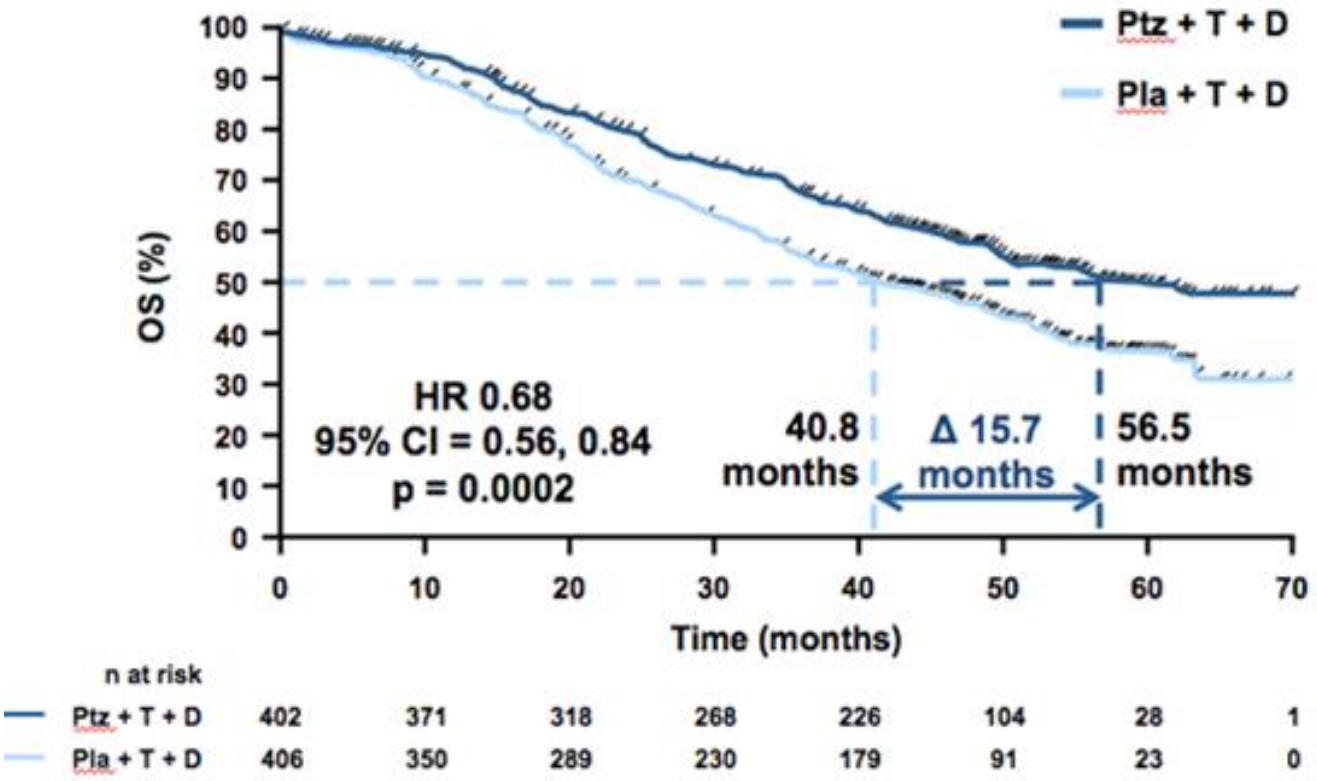
HER2-Targeted Therapy with Pertuzumab

- Monoclonal antibody and pan-HER inhibitor
- Binds to a distinct epitope on the HER2 extracellular domain-prevents dimerization
- Pertuzumab is approved w/ trastuzumab and docetaxel in MBC-1st-line



Final OS Analysis

Median follow-up 50 months (range 0–70 months)



n at risk								
Ptz + T + D	402	371	318	268	226	104	28	1
Pla + T + D	406	350	289	230	179	91	23	0

ITT population. Stratified by geographic region and neo/adjuvant chemotherapy.

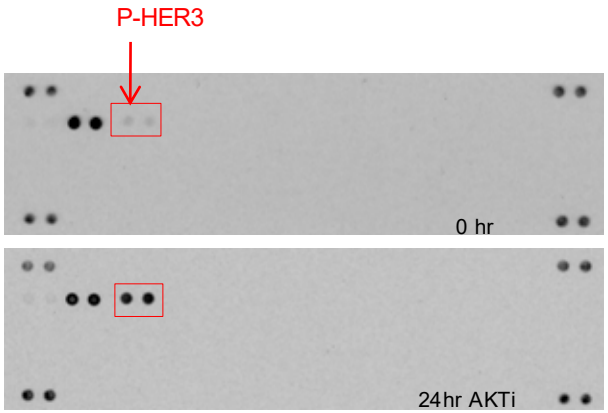
CI, confidence interval; D, docetaxel; HR, hazard ratio; OS, overall survival; Pla, placebo; Ptz, pertuzumab; T, trastuzumab.

Prognosis in MBC by HER2 Status and by Therapy With Trastuzumab

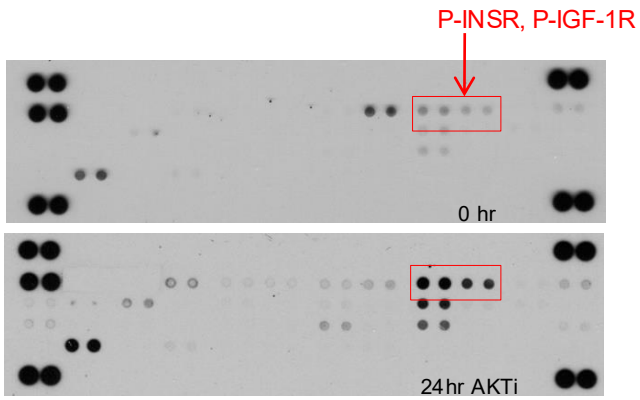
Breast Cancer Subtype (1st Line Setting)	Median Survival
HER2-positive (Slamon et al, NEJM 2001)	20.3 mo
ER+/HER2-negative (Finn et al, ASCO 2017)	37.5 mo
HER2-positive – treated with TP (Baslega et al, CLEOPATRA)	56.5 mo

T= trastuzumab P=pertuzumab

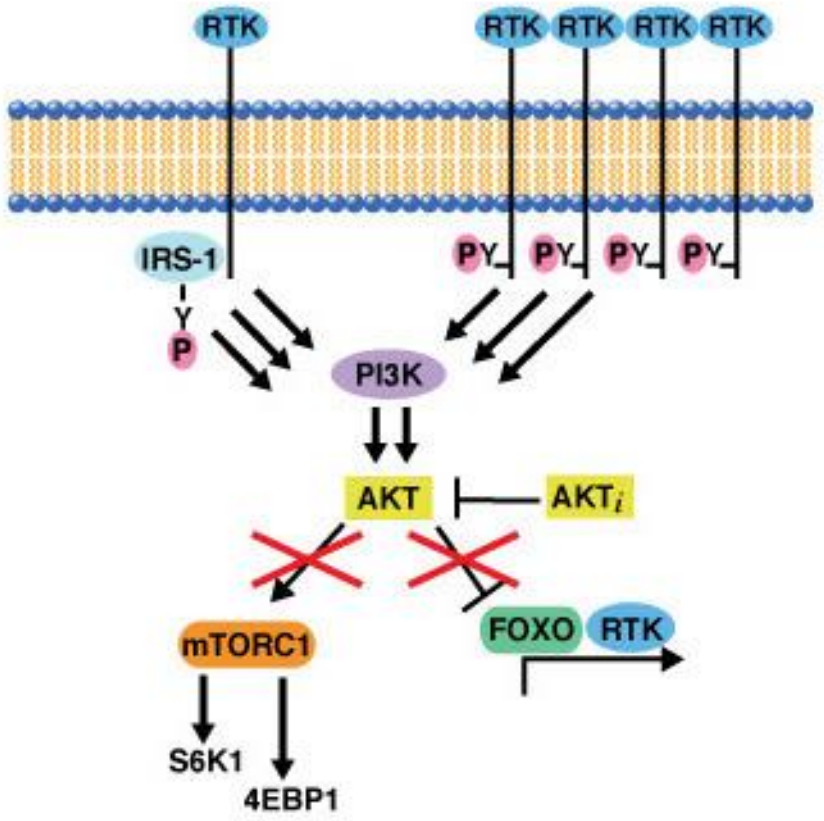
Inhibition of PI3K/AKT/mTOR activates RTK signaling: AKT inhibition



BT-474(light exposure)

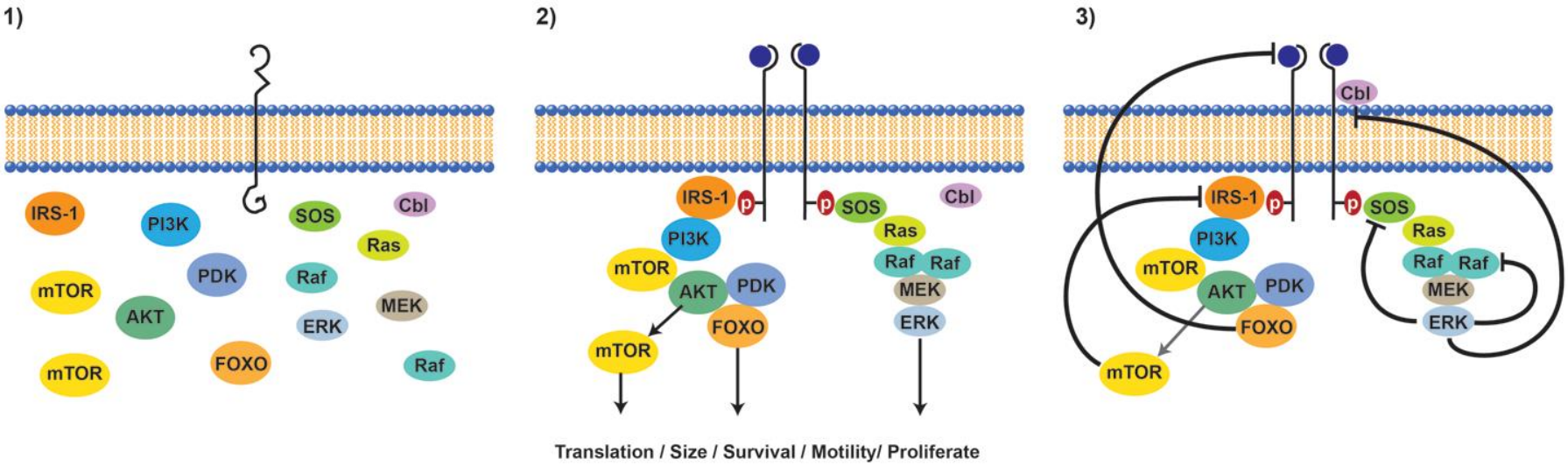


BT-474(dark exposure)



From Chandarlapaty, S. et al 2011 (Cancer Cell v19:58-71)

Relief of feedback limits antitumor efficacy



From Chandarlapaty S. 2012 (Cancer Discovery)

HER2 expression persists post-HER2 Tx: MSKCC Results

96 patients with HER2+ BC s/p HER2 targeted therapy in the adjuvant or metastatic setting who underwent biopsies

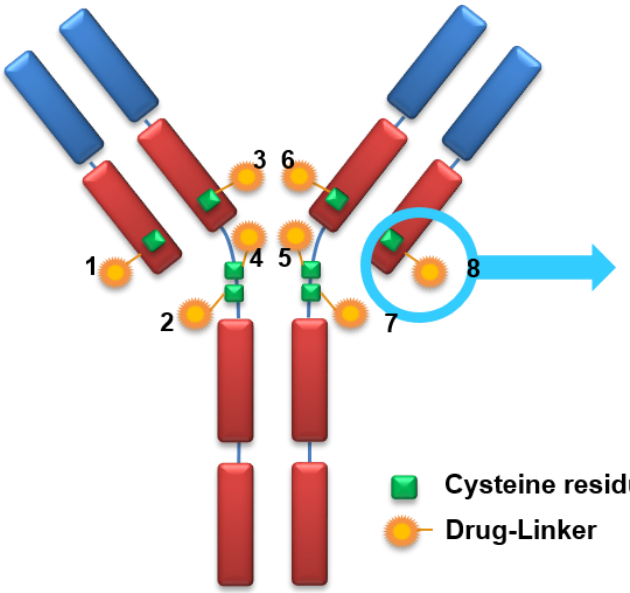
IHC/FISH RESULTS	No. Cases	(%)
Positive	74	77%
Negative	21	22%
Equivocal	1	1%

26 patients s/p treatment with both pertuzumab-based therapy and T-DM1

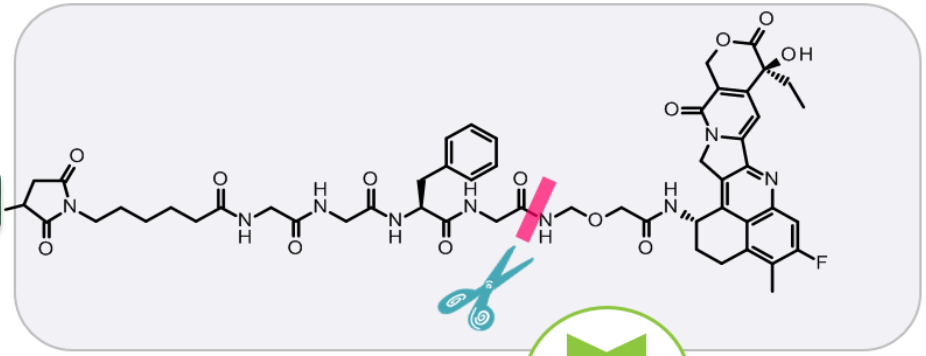
IHC/FISH RESULTS	No. Cases	(%)
Positive	20	77%
Negative	6	23%

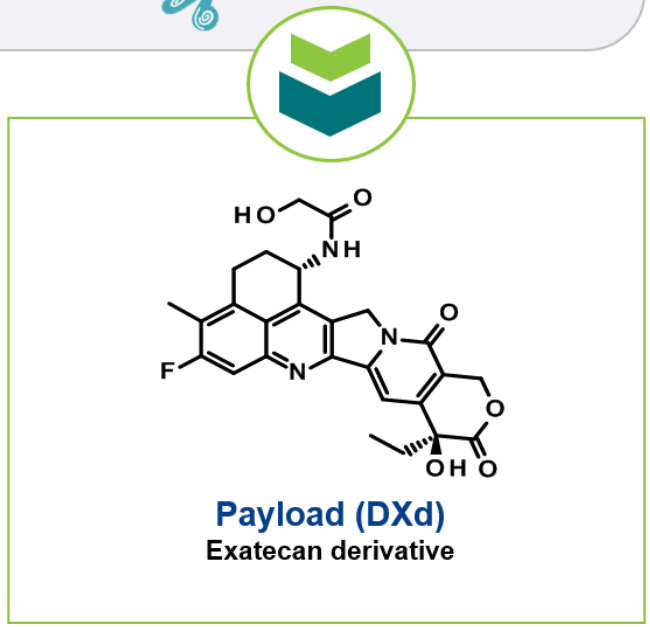
Data provided by Pedram Razavi, 2017

DS8201a: a novel anti-HER2 antibody drug conjugate (ADC)



Proprietary drug-linker





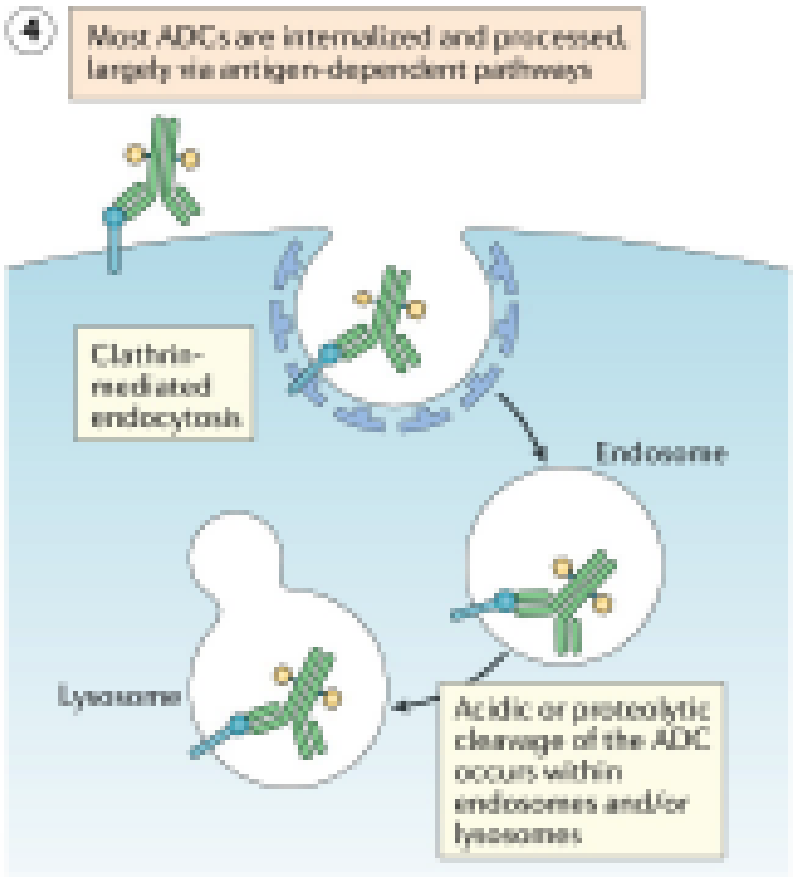
Payload (DXd)
Exatecan derivative

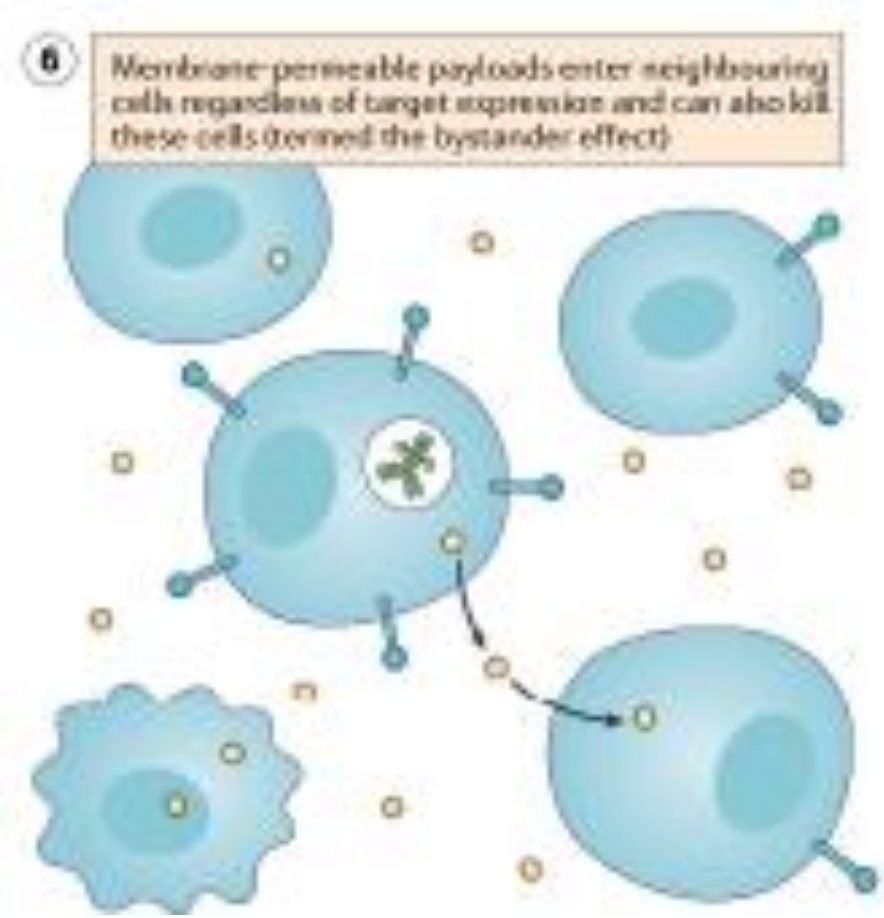
Conjugation chemistry
The linker is connected to cysteine residue of the antibody

DS8201a compared to T-DM1

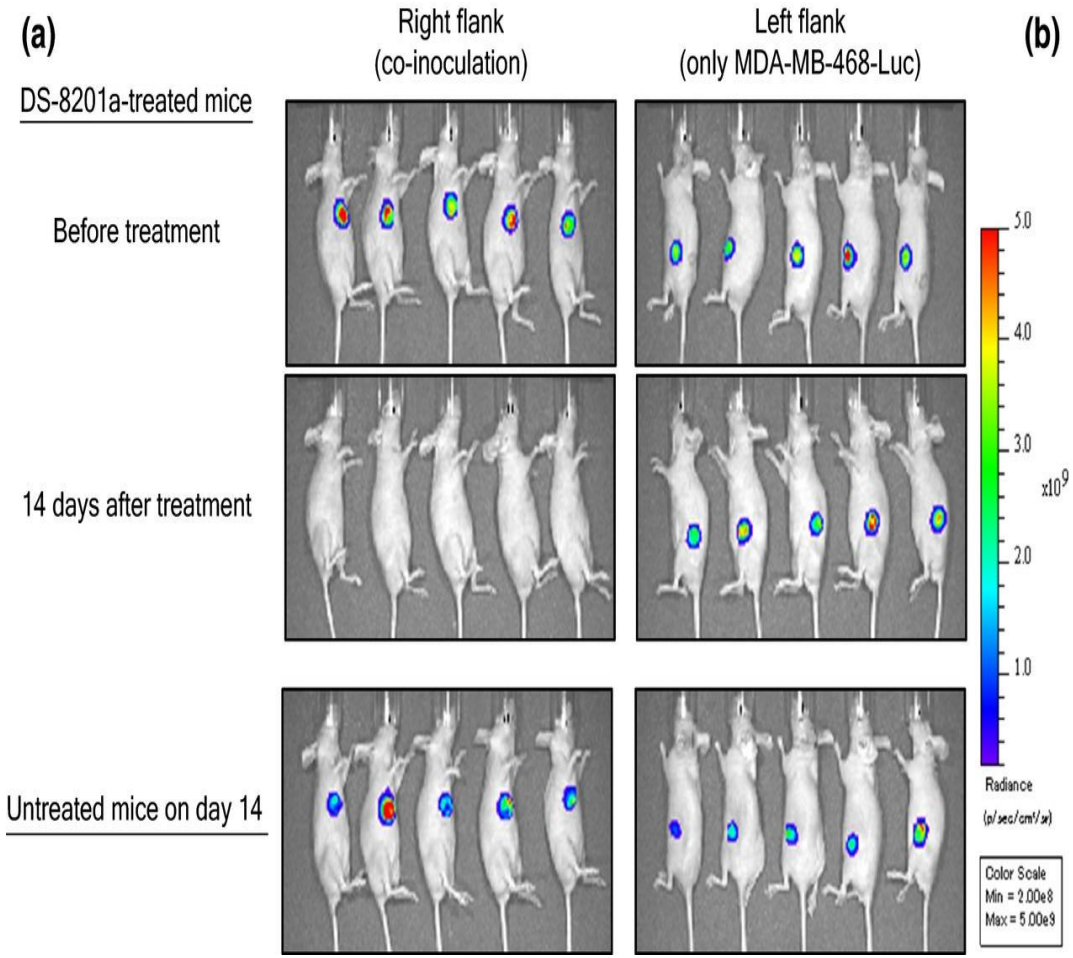
	DS-8201a	T-DM1
Antibody	Anti-HER2 mAb	Trastuzumab (Tmab)
Payload	Topoisomerase I inhibitor (DXd)	Tubulin inhibitor (DM1)
DAR*	7-8	3.5

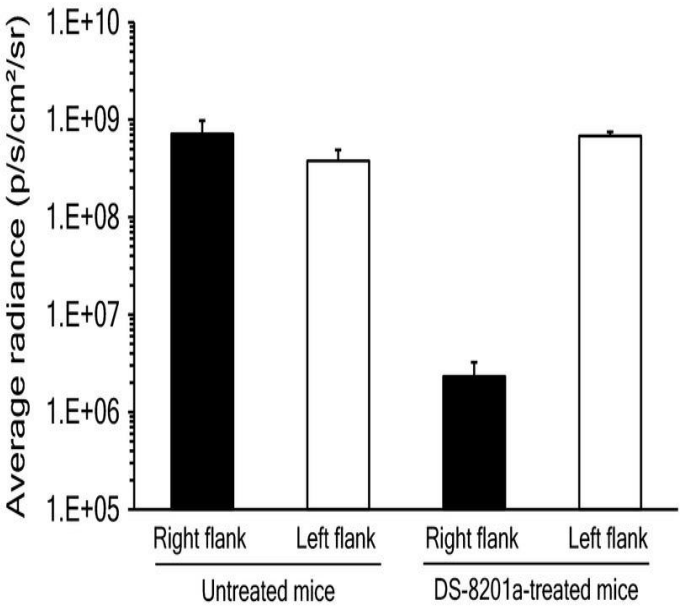
ADC direct and bystander effect





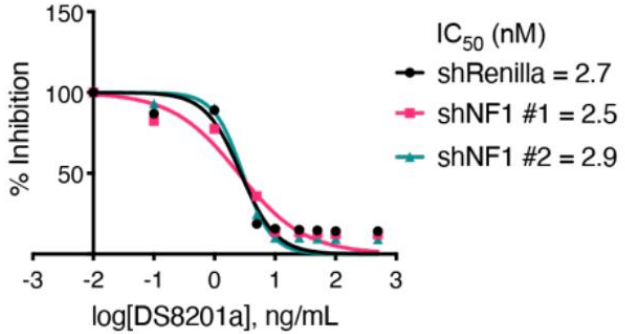
Bystander effect of TDXd



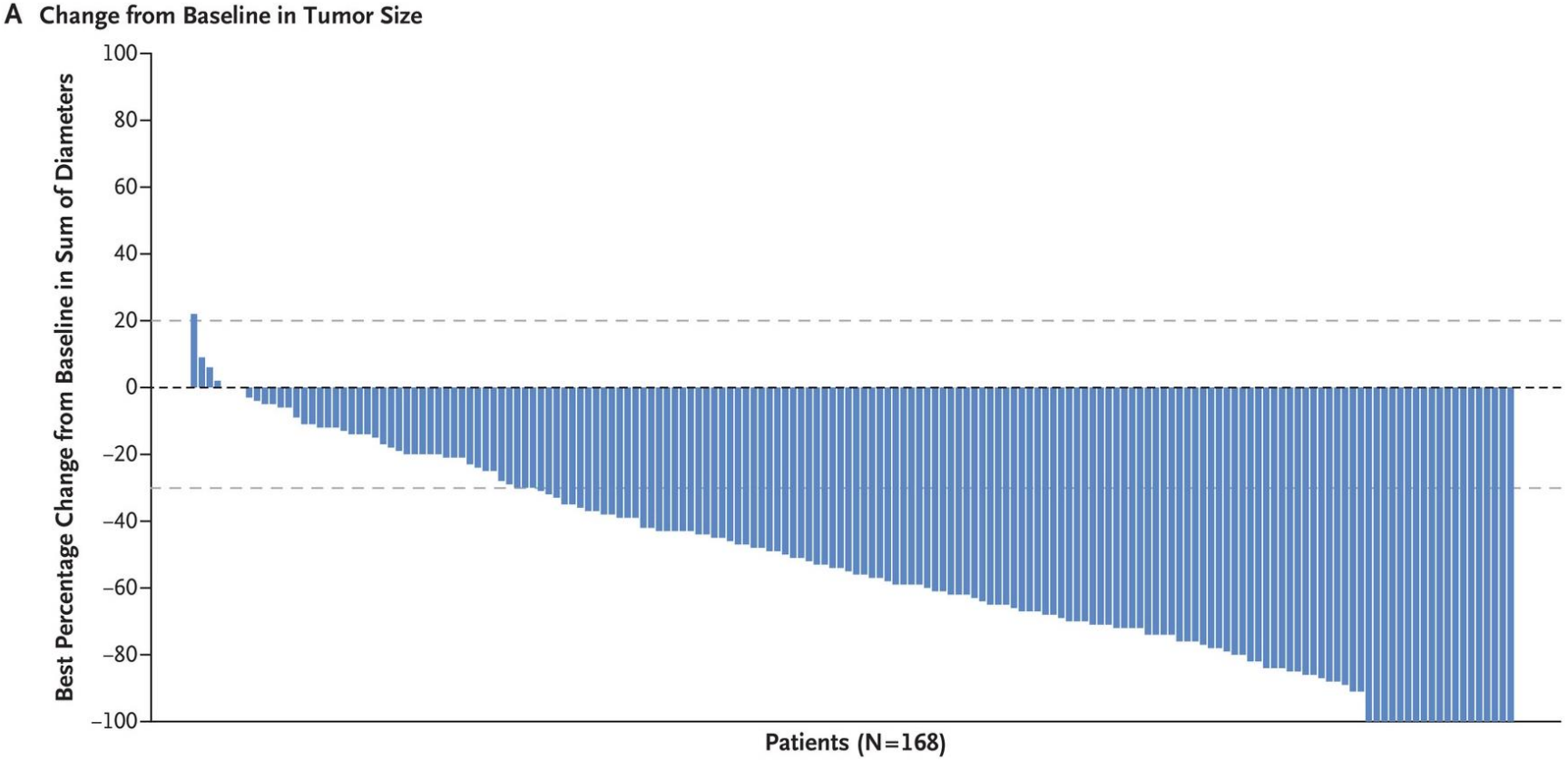


Cancer Science, Volume: 107, Issue: 7, Pages: 1039-1046, First published: 11 May 2016, DOI: (10.1111/cas.12966)

Striking efficacy of TDXd in resistant models and patients

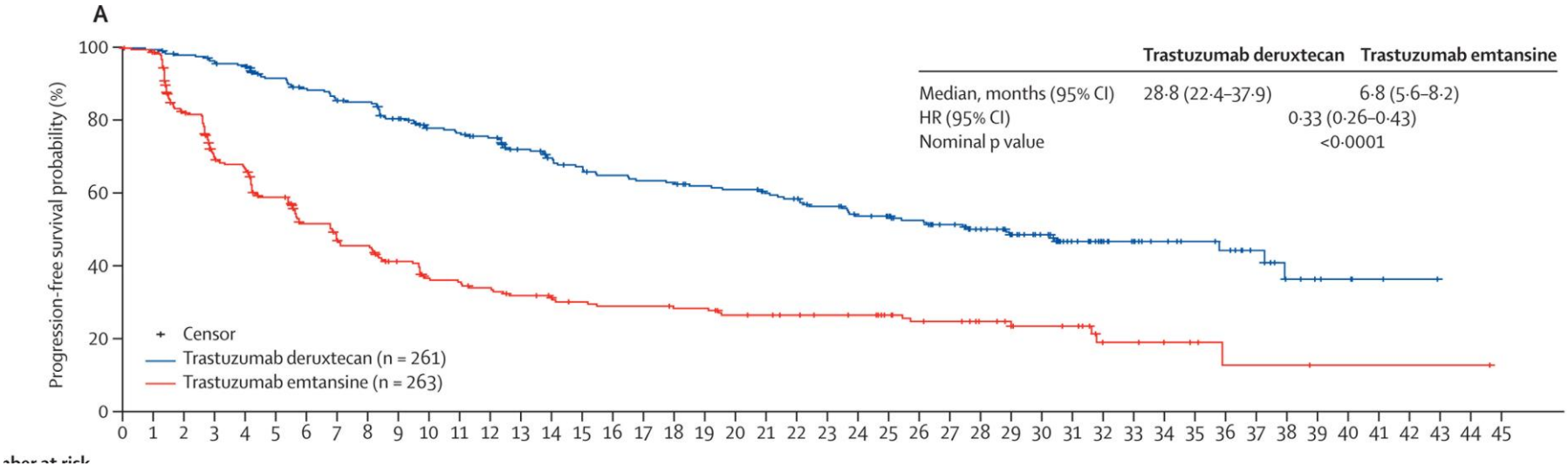


Smith et al., Nature Comm 2021



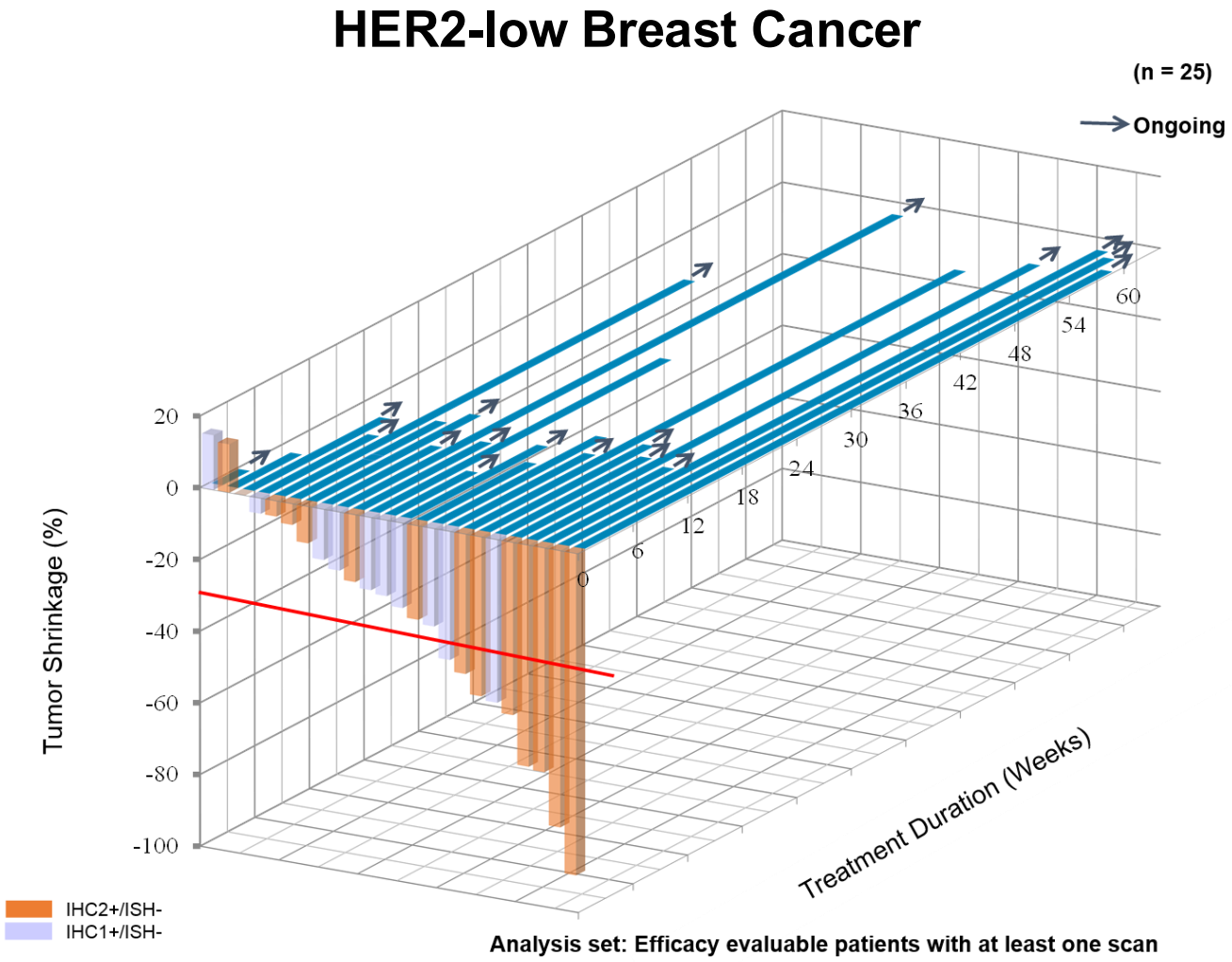
Modi et al., NEJM 2020

Striking efficacy of TDXd in HER2+ BC



Hurvitz, Lancet 2023

Response and Treatment Duration



HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization.