Interesting faces of cancer treatment

Some overwhelming developments in Breast Cancer Chemotherapy

Natural history –if untreated

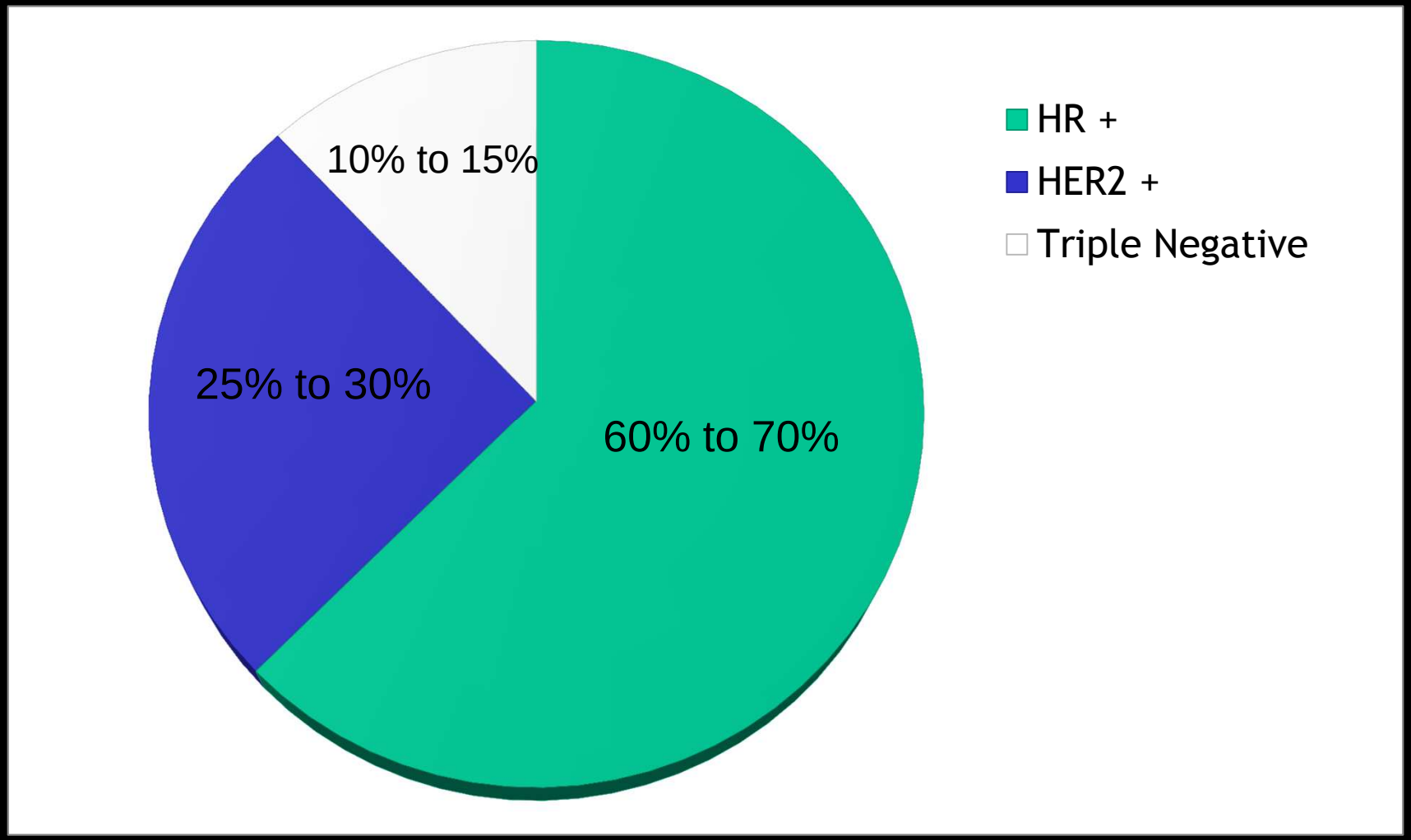
- Average survival from 1st symptom- 44 months
- Median survival- 2.5 years
- 5 year survival- 22%
- 10 year survival – 5%
- Above data on the basis of tumor doubling time
- Biology of breast cancer-Aggressive or slowly progressive

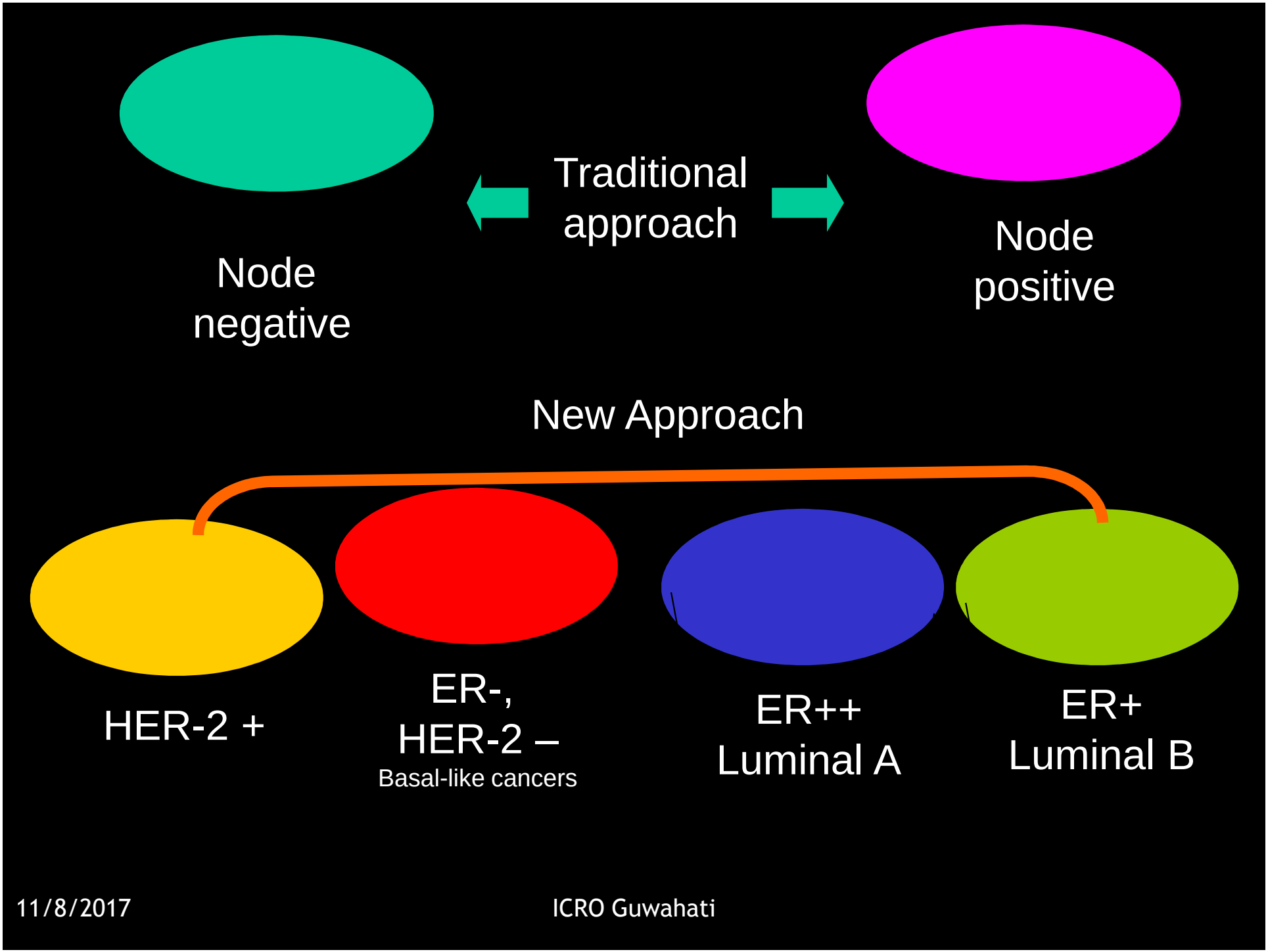
Treatment Options..General View

Standard treatments used are-

- Surgery
  - *Breast-conserving surgery (BCT)*
  - *Mastectomy(MRM)*
- Radiation therapy
- Chemotherapy
- Hormone therapy
- Targeted therap**y**

Invasive Breast Cancer Subsets defined by IHC




Traditional approach
Node negative
Node positive
New Approach
HER-2 +
ER-, HER-2 –
Basal-like cancers
ER++ Luminal A
ER+ Luminal B

Prognostic and Predictive Factors

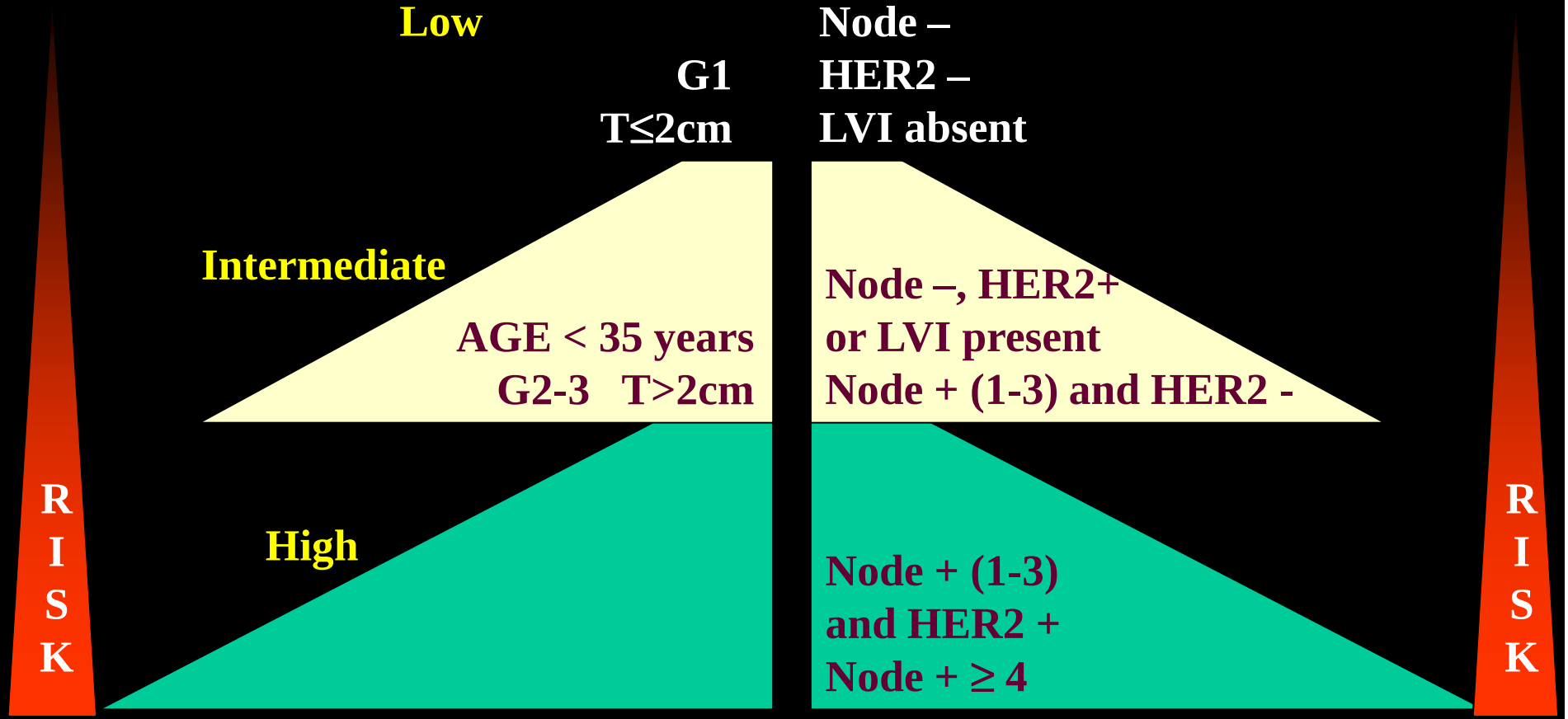
- Prognostic factors
  - Predict natural history
    - Nodal status
    - Tumor size
    - LVI
    - Grade
    - HER2 status*
    - ER/PgR*
    - Age
    - Recurrence score*
- Predictive factors
  - Predict response to therapy
    - ER/PgR*
    - HER2*
    - Recurrence score*

*Both prognostic and predictive

LVI = lymphovascular invasion; ER = estrogen receptor; PgR = progesterone receptor.

Rugo. ASCO; 2005. Abstract 3009. Adapted from slide presentation.

How to predict risk of recurrence & death



T = size G = grade LVI = lympho-vascular invasion

Oncotype DX 21 Gene Recurrence Score (RS) Assay

16 Cancer and 5 Reference Genes From 3 Studies

PROLIFERATION
Ki-67
STK15
Survivin
Cyclin B1
MYBL2

ESTROGEN
ER
PR
Bcl2
SCUBE2

GSTM1

BAG1

CD68

INVASION
Stromolysin 3
Cathepsin L2

HER2
GRB7
HER2

REFERENCE
Beta-actin
GAPDH
RPLPO
GUS
TFRC

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

Category	RS (0 – 100)
Low risk	RS < 18
Int risk	RS ≥ 18 and < 31
High risk	RS ≥ 31

Chemotherapy in breast cancer

- Adjuvant
- Neo-adjuvant
- Metastatic

Goals Of Breast Cancer Treatment

- **Palliation**
  - **relieve symptoms caused by the tumor**
- **Neo-adjuvant therapy**
  - **easy operability / down staging**
- **Adjuvant therapy**
  - **micro metastases**

Adjuvant chemotherapy

- **CMF, first generation, 1970s**
  - Cyclophosphamide
  - Methotrexate
  - 5-FU
- Benefit in
  - Older individual with early stage carcinoma Breast
  - Distant recurrence
  - Survival

Adjuvant chemotherapy

- **CAF or CEF, 2nd generation, 1980s**
  - Cyclophophamide
  - Adramycin(or Epirubicin)
  - 5-FU
- More toxic than CMF
- CAF better than CMF in high-risk group
  - Axilla LN+
  - LN-, but tumor large or other risk factor

What have we learned?

- Standard regimens are CMF and CAF
- Anthracycline (e.g. Adriamycin) containing regimens are superior to those that lacks it
- High dose therapy did not improve overall survival
  - Increased morbidity and mortality

Hamilton, et al., J Clin Oncol 23:1760, 2005.

After 200+ RCTs -

- Combination therapy is superior to single agents
- 4 to 6 months produced optimal results
  - Longer treatment with the same regimen did NOT provide incremental gains
- Hormone receptor-positive patients benefit from sequential chemotherapy plus endocrine therapy
  - Additive therapeutic effect

Third Generations Regimen

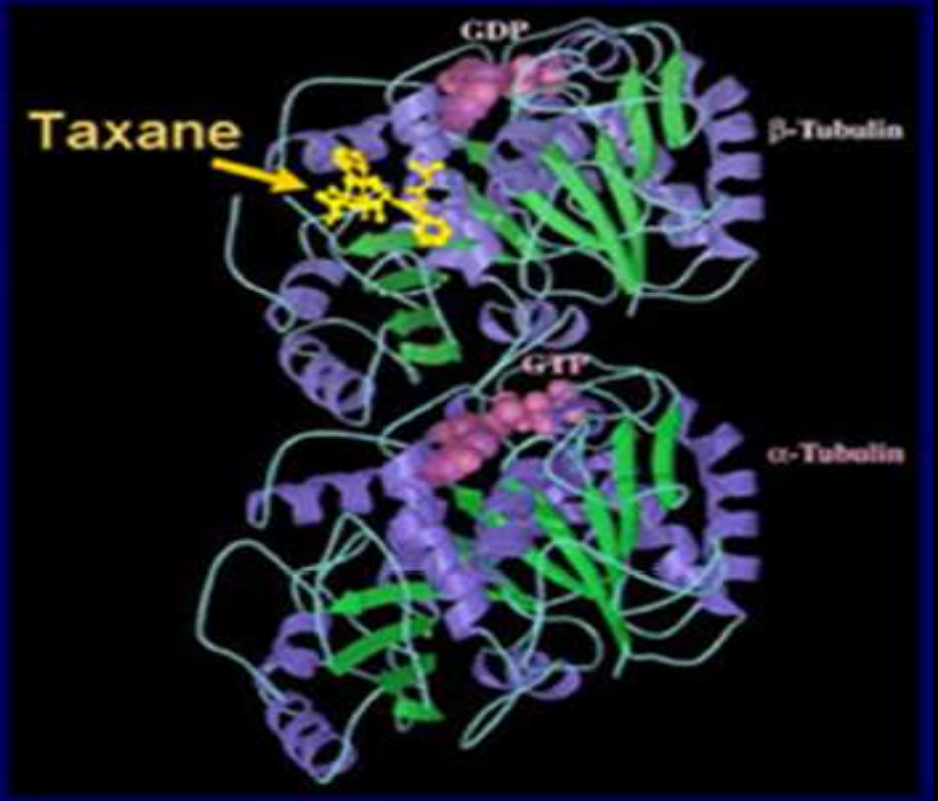
Taxanes as Adjuvant Therapy in BC

- Taxane use in stage I-III BC significantly improves disease-free survival and overall survival
  - Recurrence is still a substantial problem
- Emergence of molecular resistance to taxanes:
  - Increases population requiring alternate therapy
  - Decreases efficacy to other chemotherapies by cross-resistance

BC = breast cancer.

Taxane Mechanism of Action (Paclitaxel, Docetaxel)

- Stabilize microtubules and promote polymerization
- Arrest cellular division at G2/M checkpoint, inducing apoptosis
- Reversibly bind β-tubulin subunits



Downing and Nogales. *Cell Struct Funct*. 1999;24:269.
Esteva et al. *Oncologist*. 2001;6:133.

Taxanes

- 1st Trial CALGB 9344: AC ± placlitaxel(T)
- 3,121 node-positive patients
- Median follow-up of 69 months
  - 5 yr DFS: 70% v 65%, p=0.0023
  - 5 yr OS: 80% v 77%, p=0.0064

Henderson, et al., J Clin Oncol 21:976, 2003

Docetaxel (Taxotere) Trial

- BCIRG 001 Trial
  - 1,491 node-positive patients
  - TAC X6 v FAC X6
  - 5 yr outcome
    - DFS: 75% v 68%
    - OS: 87% v 81%
  - Increased morbidity
    - Febrile neutropenia 10X control arm
    - Neurotoxicity

Nabholz, et al., Proc ASCO 21:36, 2002

Dose-dense Regimen

- Theoretical premise:
  "Full doses of drug, given at the highest possible frequency, will produce the highest degree of cell kill"
- CALGB 9741
  - 2,005 node-positive patients
  - 2 X 2 factorial design
    - A → T → C every 3 weeks
    - A → T → C every 2 weeks + G-CSF
    - AC → T every 3 weeks
    - AC → T every 2 weeks + G-CSF

CALGB 9741

- Median follow-up of 36 months
- Dose dense regimen
  - 4 yr DFS: 82% v 75%
  - Significant OS in favor of dose-dense arm
  - Low rate of neutropenic fever and cardiac toxicity
  - Increased rate of anemia

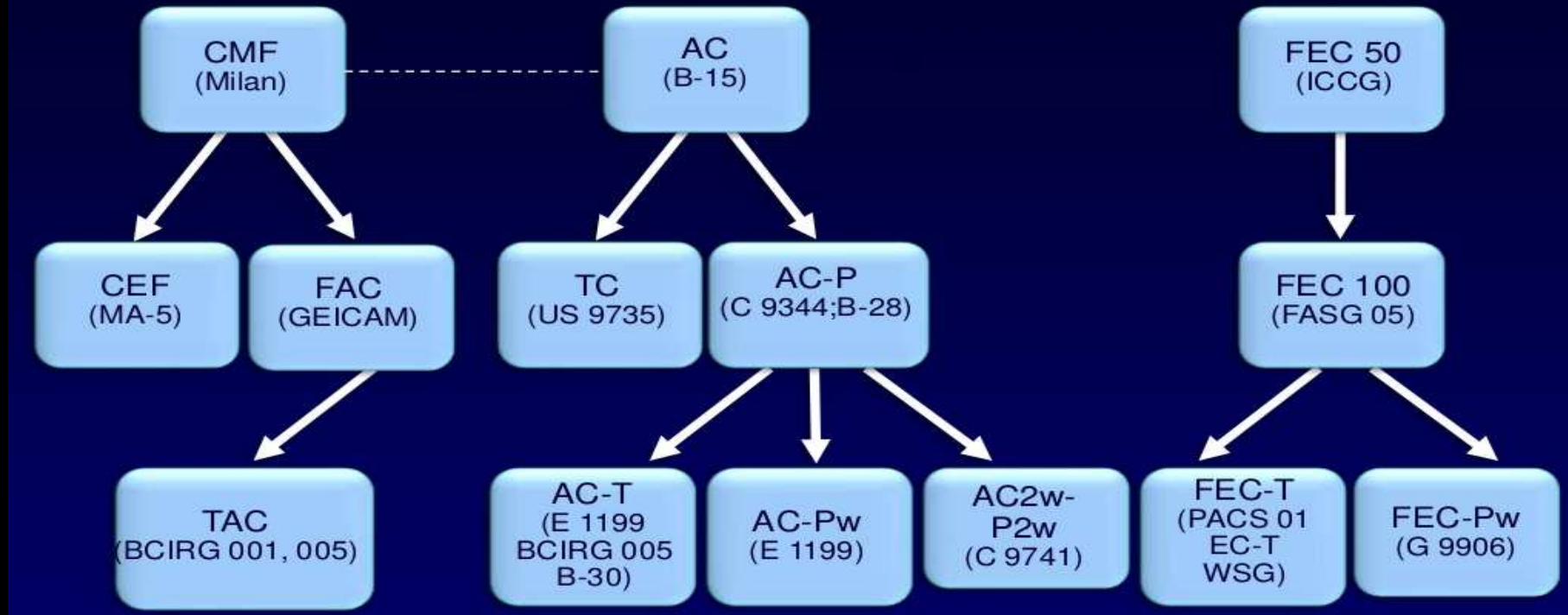
Citron, et al., J Clin Oncol 21:1431,2003.

Overall survival in the paclitaxel adjuvant trials

Trial	No.	Follow-up	Regimen	Overall survival HR	Overall survival *p*	5-year absolute OS (%)
CALGB 9344	3121	69	AC x 4 → T x 4	0.82 (0.71–0.98)	0.006	80 77
NSABP B-28	3060	64	AC x 4 → T x 4 AC x 4	0.93 (0.78–1.12)	0.46	85 85

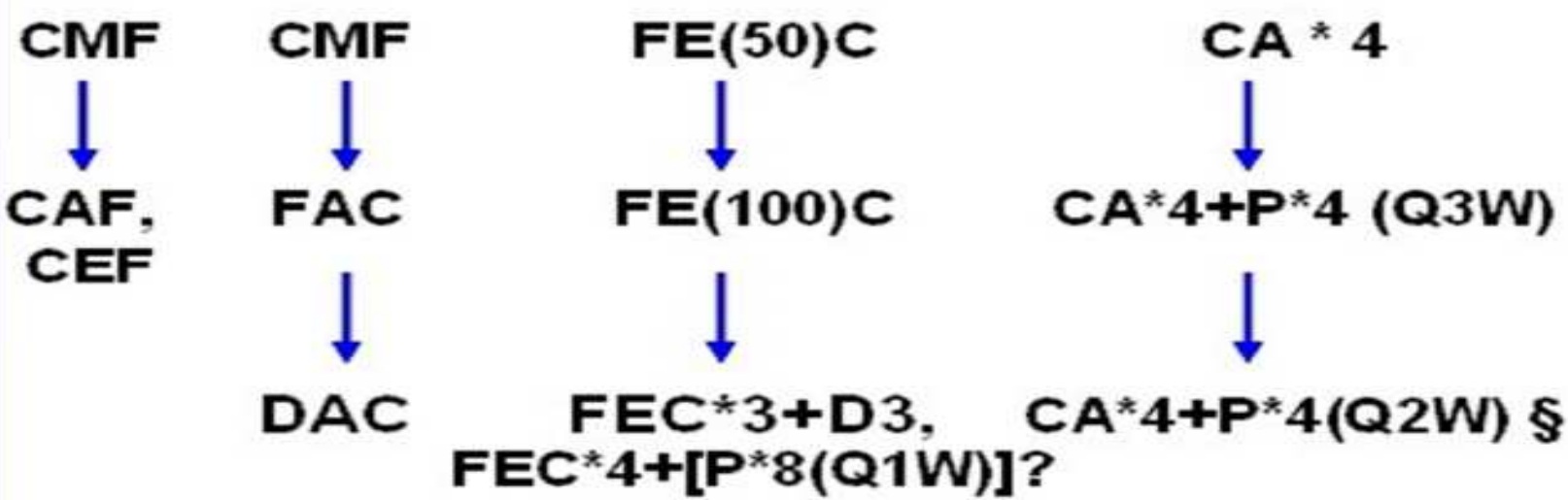
- TAC is a very effective adjuvant regimen for patients with node-positive breast cancer:
  - Significant improvement of DFS and OS over FAC
  - TAC significantly improved DFS irrespective of nodal, menopausal, HER2 and hormonal status

Evolution of Adjuvant Chemotherapy



Walshe et al, 2006; Ellis, 2006; Fumoleau et al, 2003; Roche et al, 2006; Eiermann et al, 2008; Mamounas, 2005; Joensuu et al, 2009.

The Generations
(Lineages and Chains of Inference)



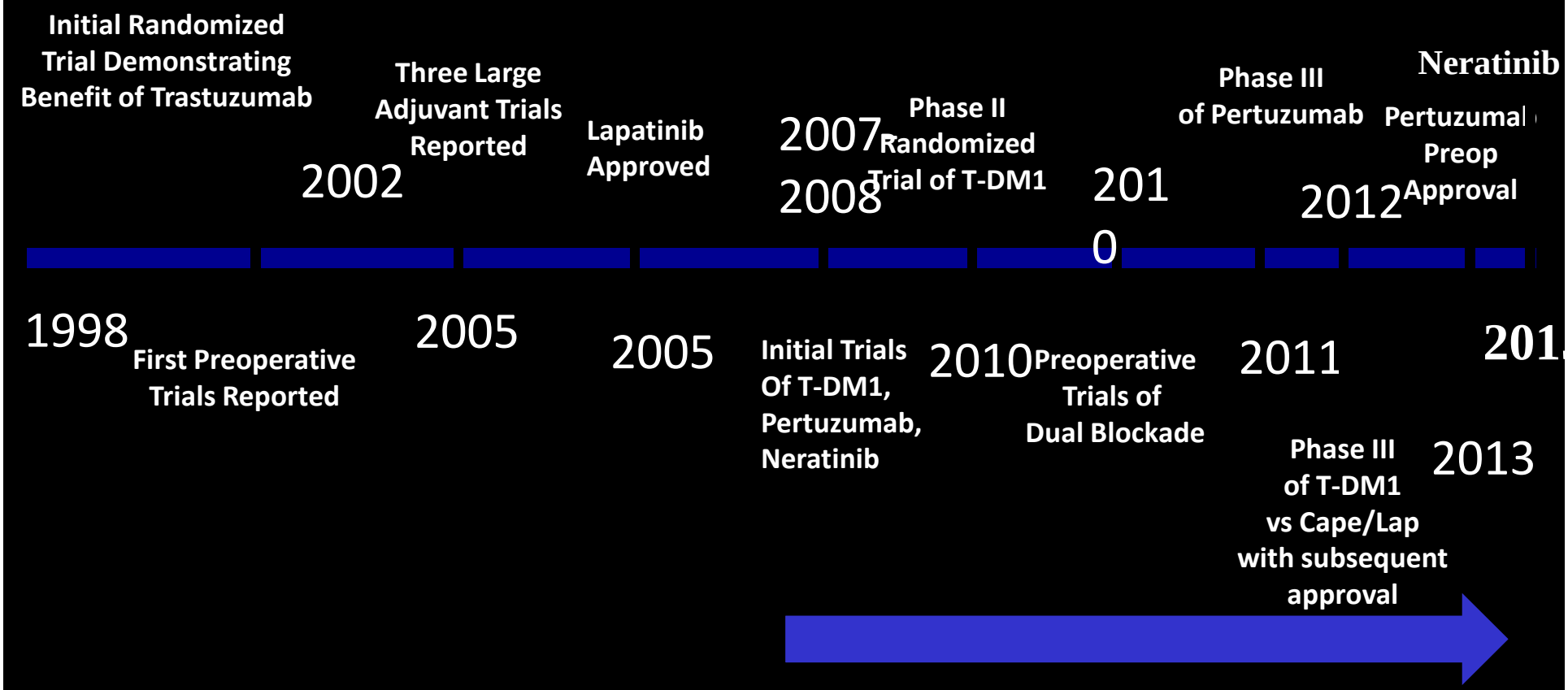
P = paclitaxel; D = docetaxel; A = doxorubicin; E = epirubicin

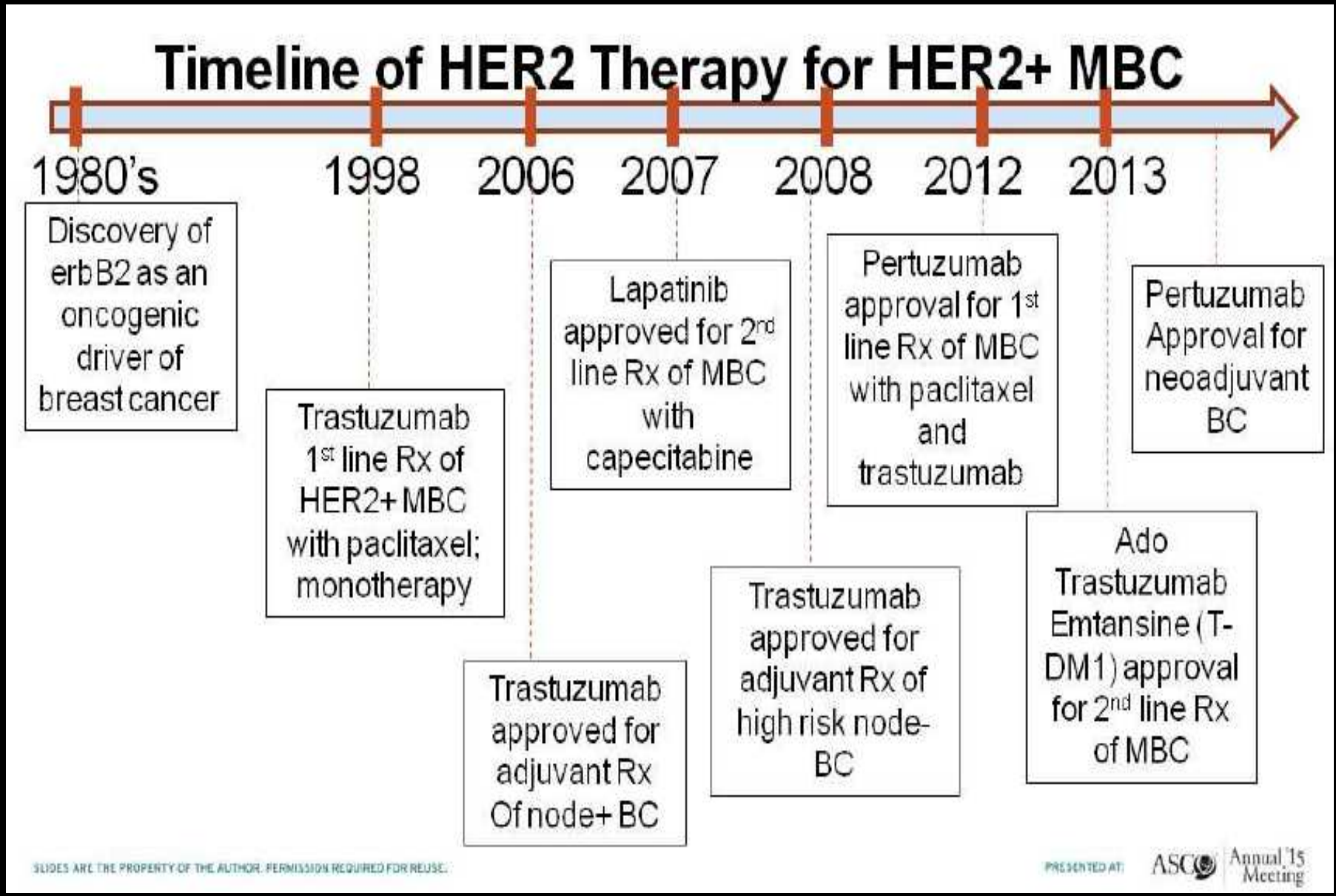
§ Exploratory analyses suggest may be less effective in ER+ cases

? Hazard ratios consistent with designation but p values for OS not < 0.05

Targeted therapy in cancer

HER2+ Disease: Major Clinical Advances Over The Past 15+ Years




Timeline of HER2 Therapy for HER2+ MBC
1980's
Discovery of erbB2 as an oncogenic driver of breast cancer
1998
Trastuzumab 1st line Rx of HER2+ MBC with paclitaxel; monotherapy
2006
Trastuzumab approved for adjuvant Rx Of node+ BC
2007
Lapatinib approved for 2nd line Rx of MBC with capecitabine
2008
Trastuzumab approved for adjuvant Rx of high risk node- BC
2012
Pertuzumab approval for 1st line Rx of MBC with paclitaxel and trastuzumab
2013
Ado Trastuzumab Emtansine (T-DM1) approval for 2nd line Rx of MBC
Pertuzumab Approval for neoadjuvant BC
SLIDES ARE THE PROPERTY OF THE AUTHOR. PERMISSION REQUIRED FOR REUSE.
PRESENTED AT: ASCO Annual '15 Meeting

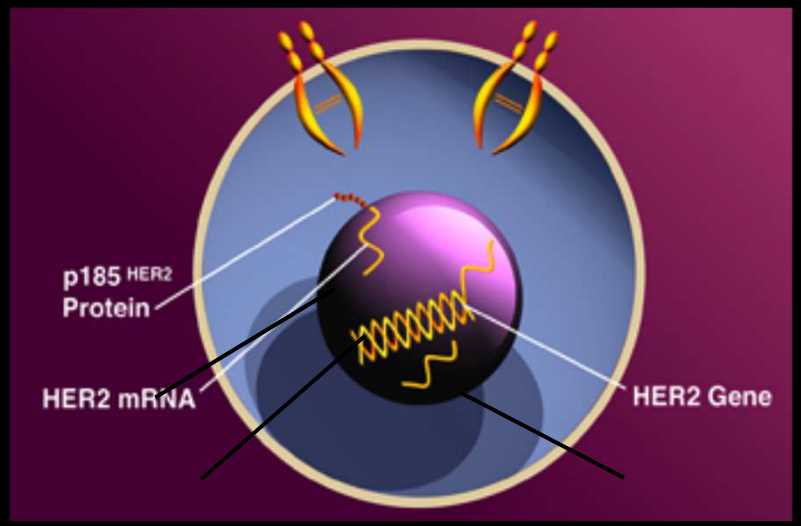
The HER2 Timeline

1981	*neu* described as a transforming oncogene in rat brain tumor carcinogenesis model
1985	a) *neu* is homologous to the v-erb B viral oncogene b) "EGFR-like" gene amplified in a human breast cancer cell line – named "HER2"
1986	HER2 found to have tyrosine kinase activity similar to EGFR
1987	HER2 amplification correlated with poor OS in human breast cancer
1989	Discovery of HER3
1993	Discovery of HER4
1998	**FDA approval of trastuzumab**
2007	**FDA approval of lapatinib**
2012	**FDA approval of pertuzumab**
2013	**FDA approval of trastuzumab emtansine (T-DM1)**

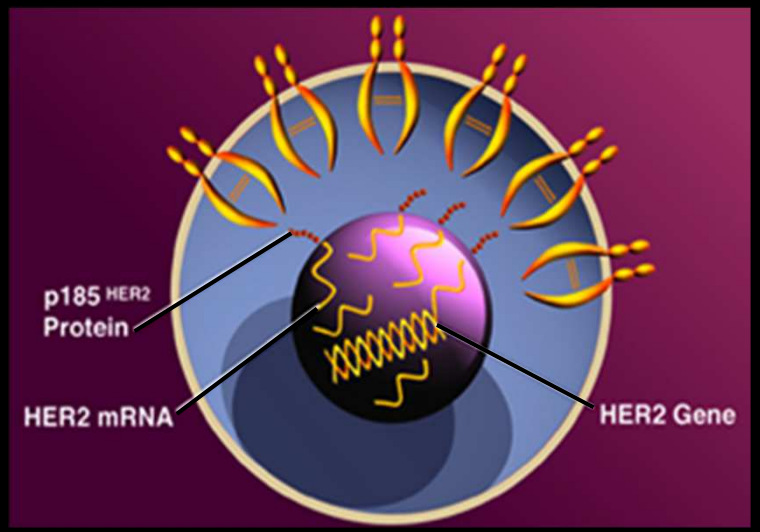
HER-2 Positivity in Breast Cancer

- OVEREXPRESSION: marked increase in number of HER2 receptors on the cell surface
- AMPLIFICATION: increase in number of HER2/neu gene copies in the nucleus

HER2-normal (HER2-) breast epithelium cell (~20,000 receptors)

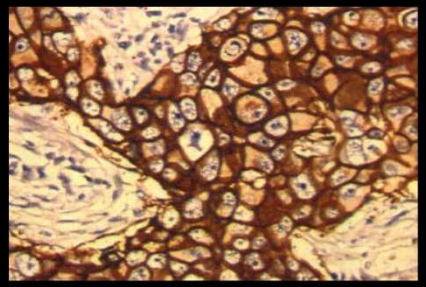


HER2-positive breast cancer cell (up to 1-2 million receptors)



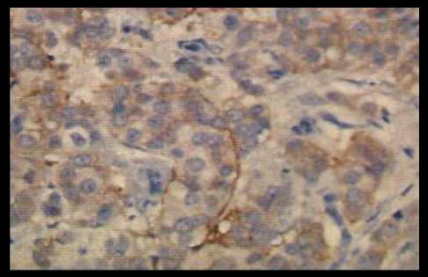
HER2-positive status shortens survival

- **Women whose breast cancers are HER2 positive have a shorter overall survival**



Median survival

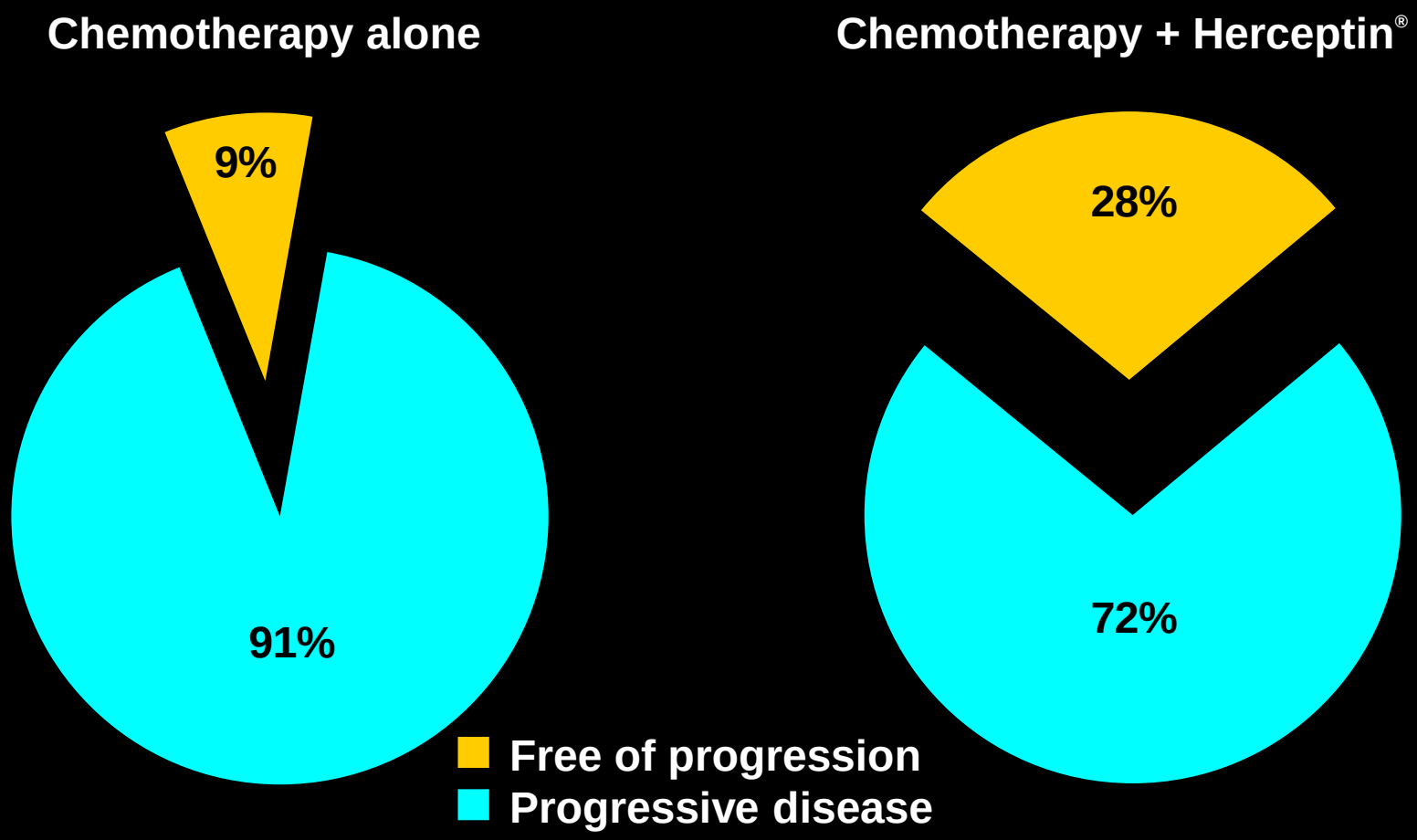
HER2 positive **3 years**



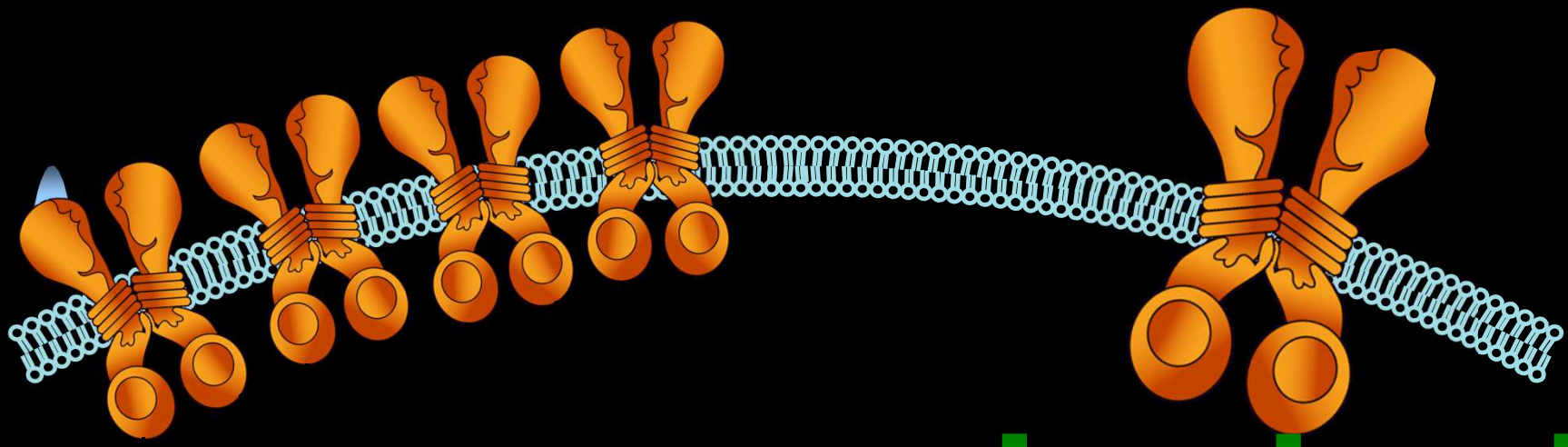
HER2 negative **6–7 years**

Slamon DJ et al. Science 1987;235:177–82

Herceptin + chemotherapy
Disease progression at 1 year



Anti-HER2 Antibodies: Mechanism of Action



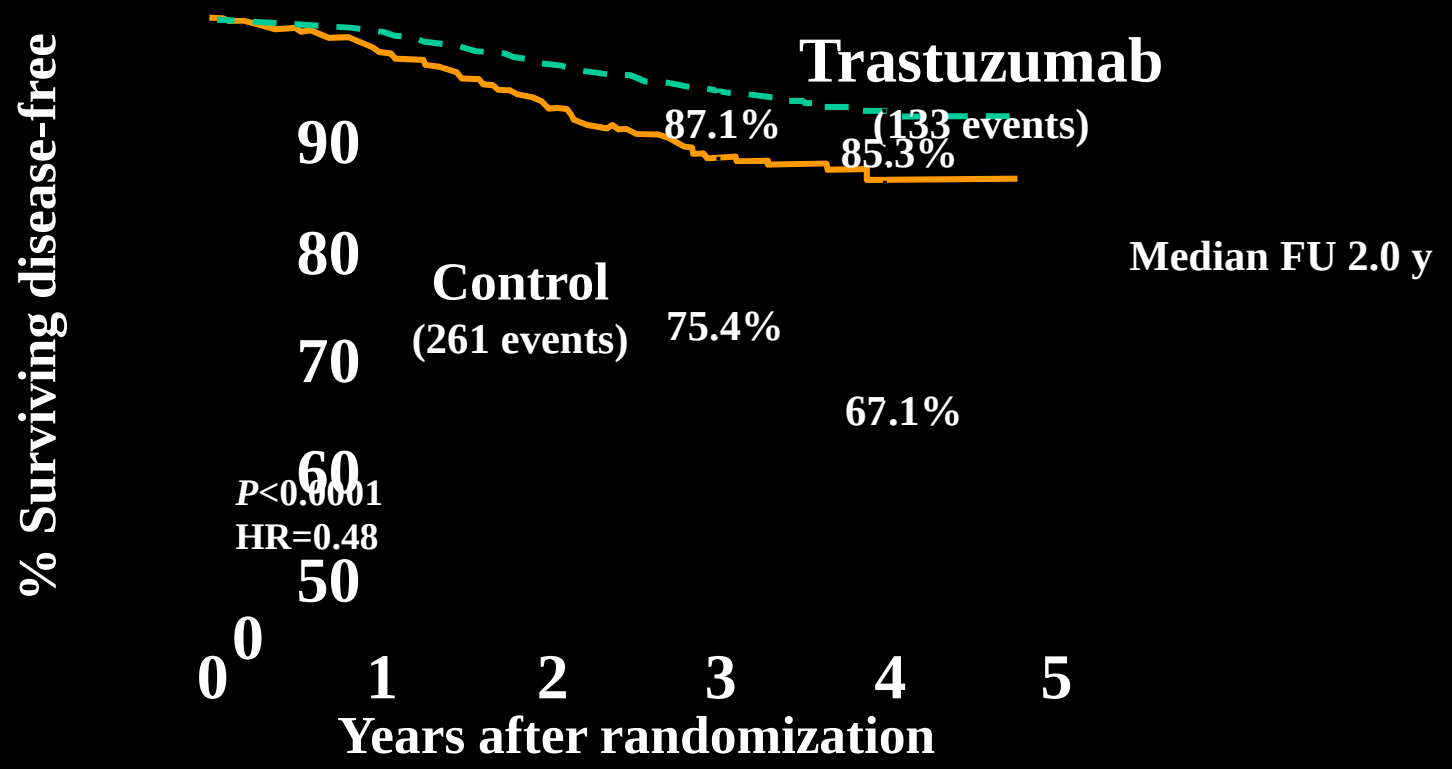
Excessive cell proliferation, survival, and angiogenesis

Potentiation of chemotherapy

Inhibition of tumor cell proliferation

Facilitation of immune function

NSABP B-31/N9831 Joint Analysis: Impact of Adding Trastuzumab to AC → Paclitaxel on Disease-Free Survival*



Control	1679	1162	689	374	59	0
Trastuzumab	1672	1217	766	427	74	0

* N9831 arm B (sequential trastuzumab after AC→P) not included in joint analysis.

Romond et al. *N Engl J Med.*, 2005;353:1673.

Adjuvant Trastuzumab: Room to Improve

- Generally well tolerated
- Some patients will still recur
- Intravenous infusion q1-3 wks for one year
- Serious side effect: cardiotoxicity

Study	Regimen	Symptomatic CHF
B31/NCCTG	AC→ TH	3.5 – 4.1%
NCCTG	AC→ T → H	2.5%
HERA	Chemo → H	0.6%
BCIRG 006	TCH	0.4%
FinHER	H → chemo	0%

Piccart-Gephardt, ASCO 2006

Early Stage Disease

Hormones

Premenopausal

Tamoxifen

Postmenopausal

Tamoxifen

Aromatase Inhibitors

Herceptin

IV

3wkly for 1 year

Cardiac monitoring

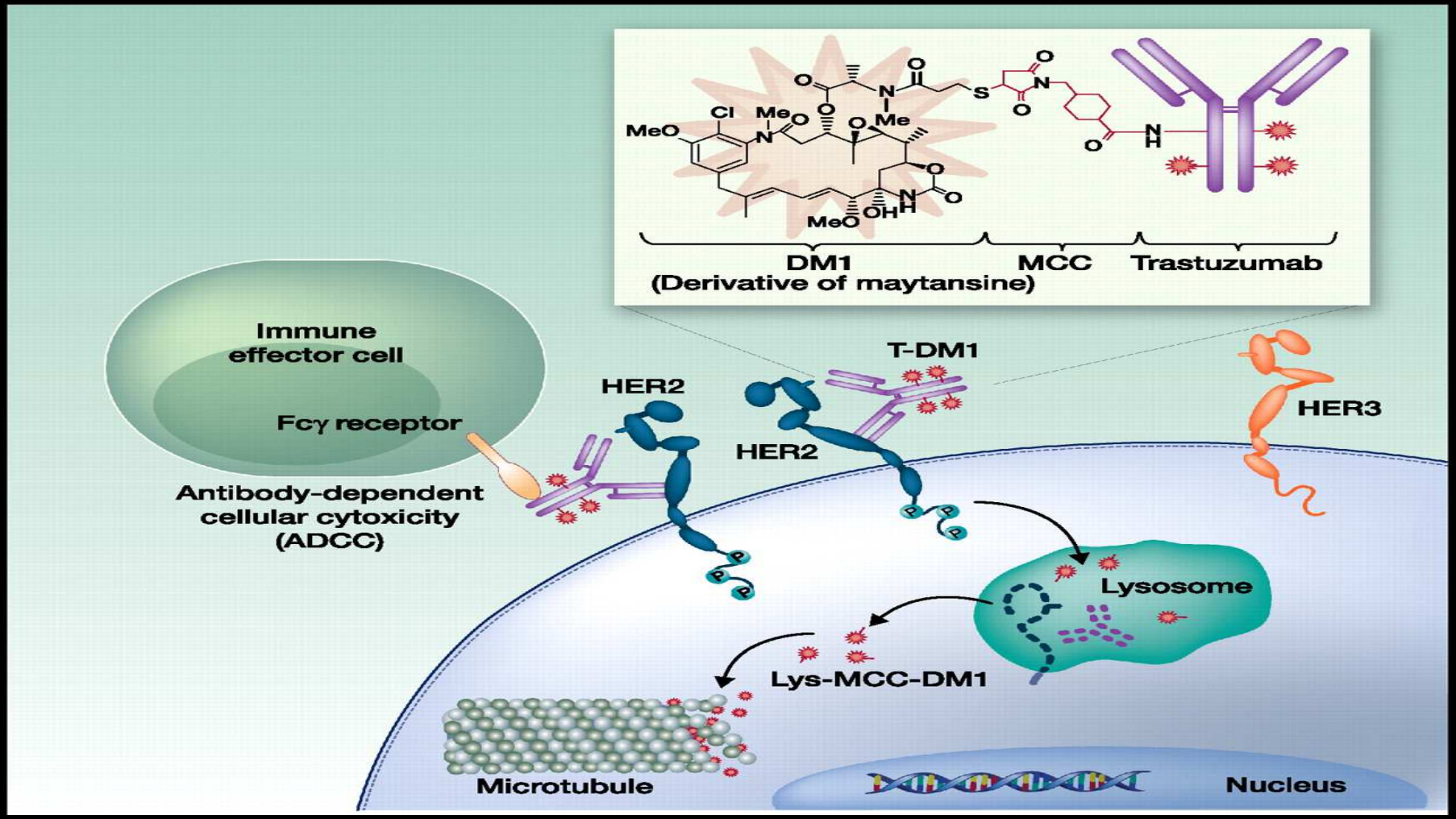
Chemo

Multiple regimens

4-6 months

Alopecia / Mucositis / Sepsis

ADVANCED DISEASE
- TRASTUZUMAB EMTANSINE (T-DM1) -



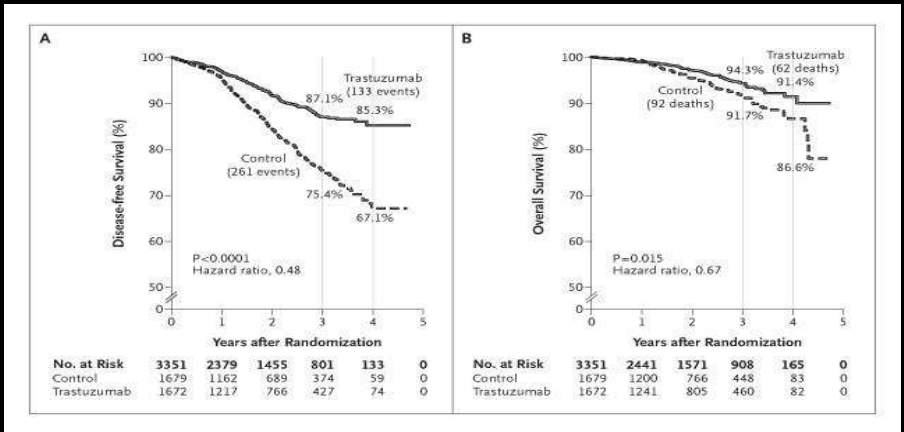
ADJUVANT THERAPY
- TRASTUZUMAB (Herceptin) -

All patients with HER2-positive tumors ≥ T1c or N+

- ❑ Administer concurrently with Taxane, then complete 1 year of treatment
- ❑ <u>OUTCOMES</u> → DFS increase of 12% at 3 years; 33% reduction in the risk of death
- ❑ Monitor heart function (ECG, ejection fraction)

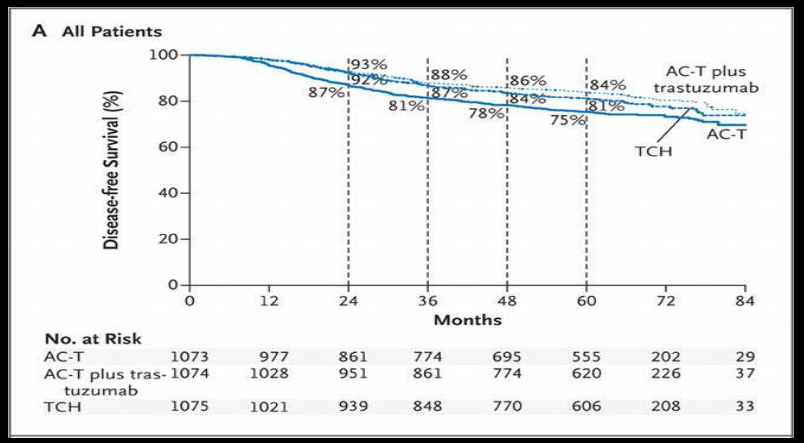
REGIMEN
➢ EC (or AC) → Taxane + H → H
➢ FEC (or FAC) → Taxane + H → H
➢ Docetaxel + Carboplatin + Trastuzumab (**TCH**) → H

NSABP trial B-31 + NCCTG trial N9831



Romond EH, NEJM 2005

BCIRG 006 study



Slamon D, NEJM 2011

A summary of four adjuvant trials of trastuzumab at time of interim analysis

Study	Eligibility – all patients HER-2$^+$ and had adjuvant chemotherapy	No.	Study design	Median follow-up
NSABP-31	LN-positive	1021 1022	**Group 1**: AC x 4 → paclitaxel x 4 **Group 2**: AC x 4 → paclitaxel x 4 plus weekly trastuzumab for 12 months	28 months
N9831	LN-positive and high risk LN-negative	1633 1633	**Group A**: AC x 4 → weekly paclitaxel x 12 **Group B**: AC x 4 → weekly paclitaxel x 12 → weekly trastuzumab for 12 months* **Group C**: AC x 4 → weekly paclitaxel x 12 *plus* weekly trastuzumab for 12 months	18 months
HERA	LN-positive or LN-negative (tumour >1 cm) and completed adjuvant chemotherapy	1694 1694 1693	**Group A**: 3 weekly trastuzumab for 24 months* **Group B**: 3 weekly trastuzumab for 12 months **Group C**: observation	12 months
BCIRG-006	LN-positive or high-risk node negative disease	1073 1074 1075	**Group 1**: AC x 4 → docetaxel x 4 **Group 2**: AC x 4 → docetaxel x 4 *plus* weekly trastuzumab then 3 weekly for 12 months **Group 3**: docetaxel plus carboplatin x 6 *plus* weekly trastuzumab then 3 weekly for 12 months	23 months

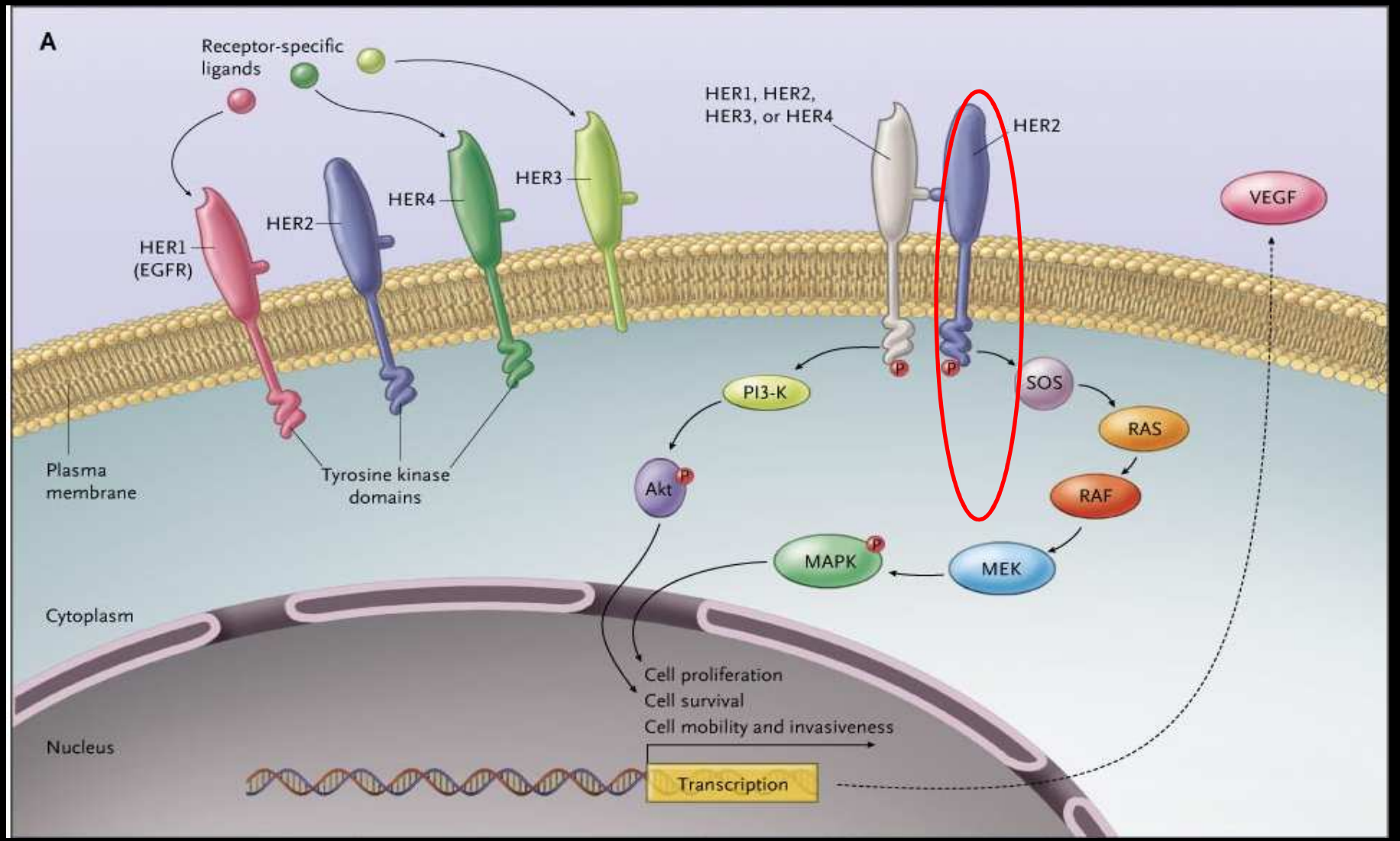
A summary of the endpoints of the adjuvant trials (NSABP B-31 and N9831, and HERA)

Endpoints	Number of events		HR	*p* value
	T	Control		
B-31 and N9831*				
DFS	133	261	0.48 (0.39–0.59)†	<0.0001
OS	62	92	0.67 (0.48–0.93)‡	0.015
HERA				
DFS	127	220	0.54 (0.43–0.67)	<0.0001
OS	29	37	–	NS

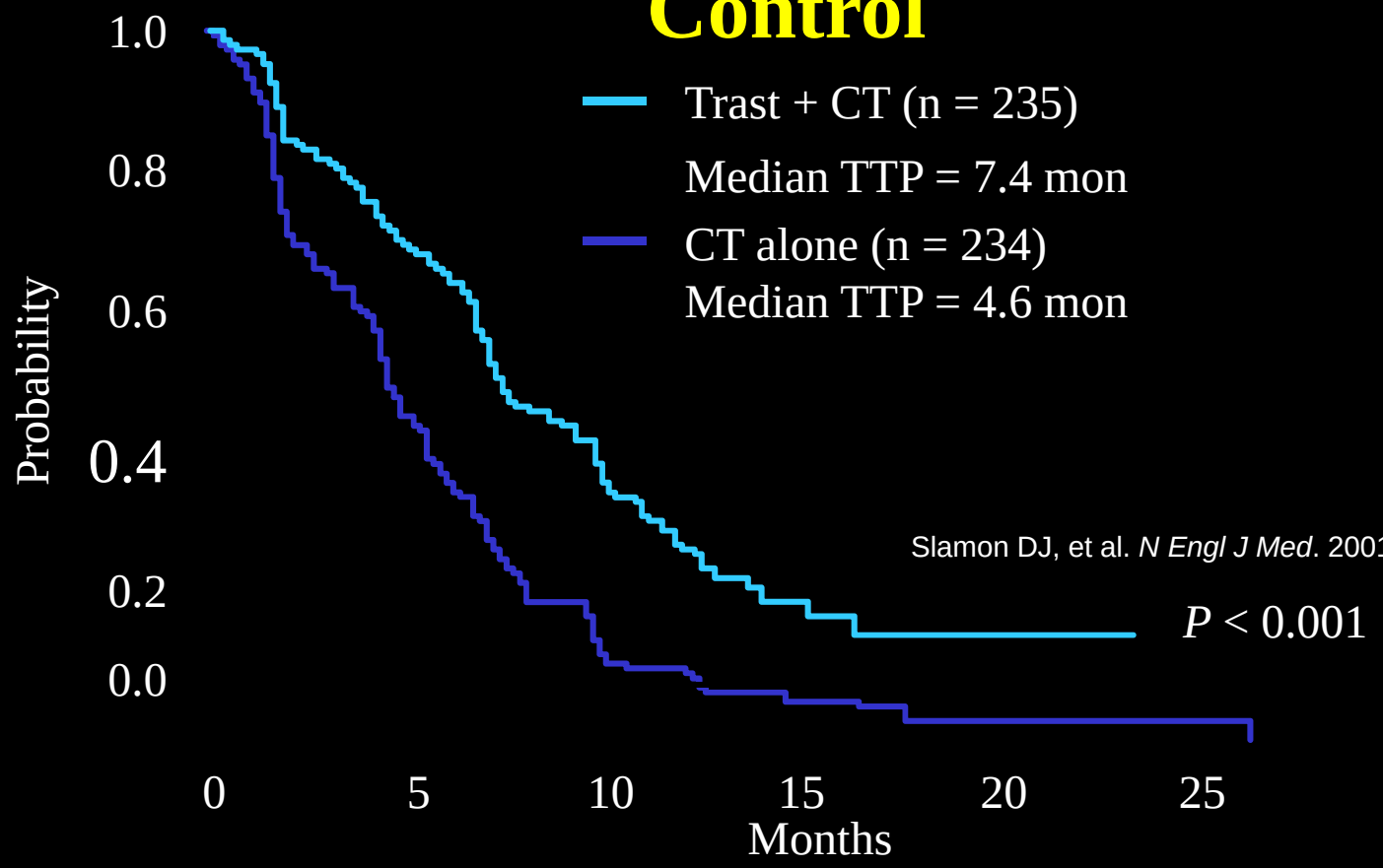
Treatment Advances in HER2+ Breast Cancer

In 1995, HER2+ breast cancer was one of the most aggressive types of breast cancer and was very difficult to treat.

HER Family Signaling



Chemotherapy +/- Trastuzumab: Proportion of Patients with Cancer Under Control



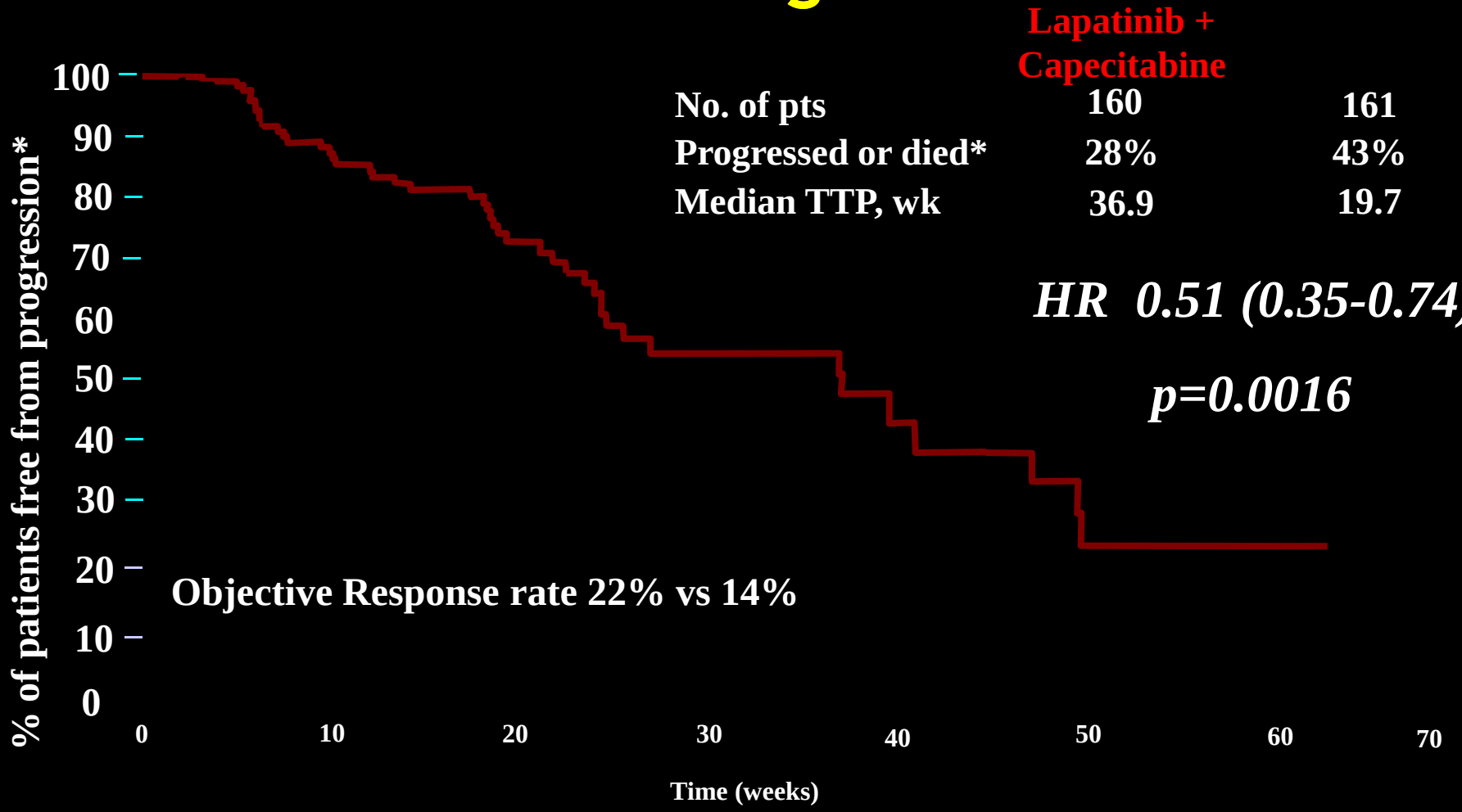
Slamon DJ, et al. *N Engl J Med*. 2001;344(11):783-792.

When trastuzumab was first approved based on the results above, few thought it would have such a profound effect on the course of HER2+ breast cancer

Critical Observation: HER2 Addiction

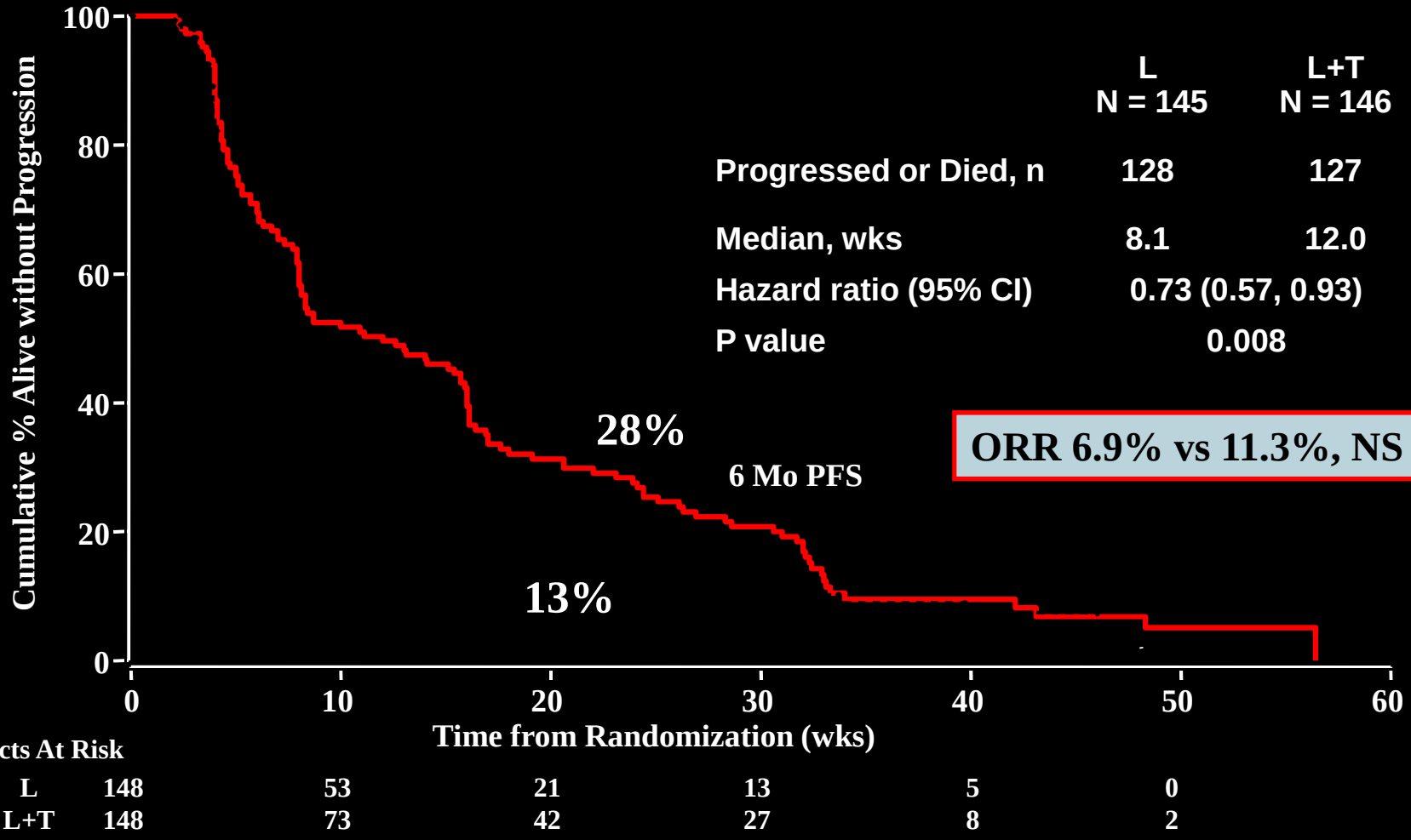
This means that HER2+ breast cancer is dependent on HER2 signaling even when the cancer gets worse after initial treatment with trastuzumab

Capecitabine +/- Lapatinib
Time to Progression



* Censors 4 patients who died due to causes other than breast cancer

Progression-Free Survival: Lapatinib vs Lapatinib + Trastuzumab

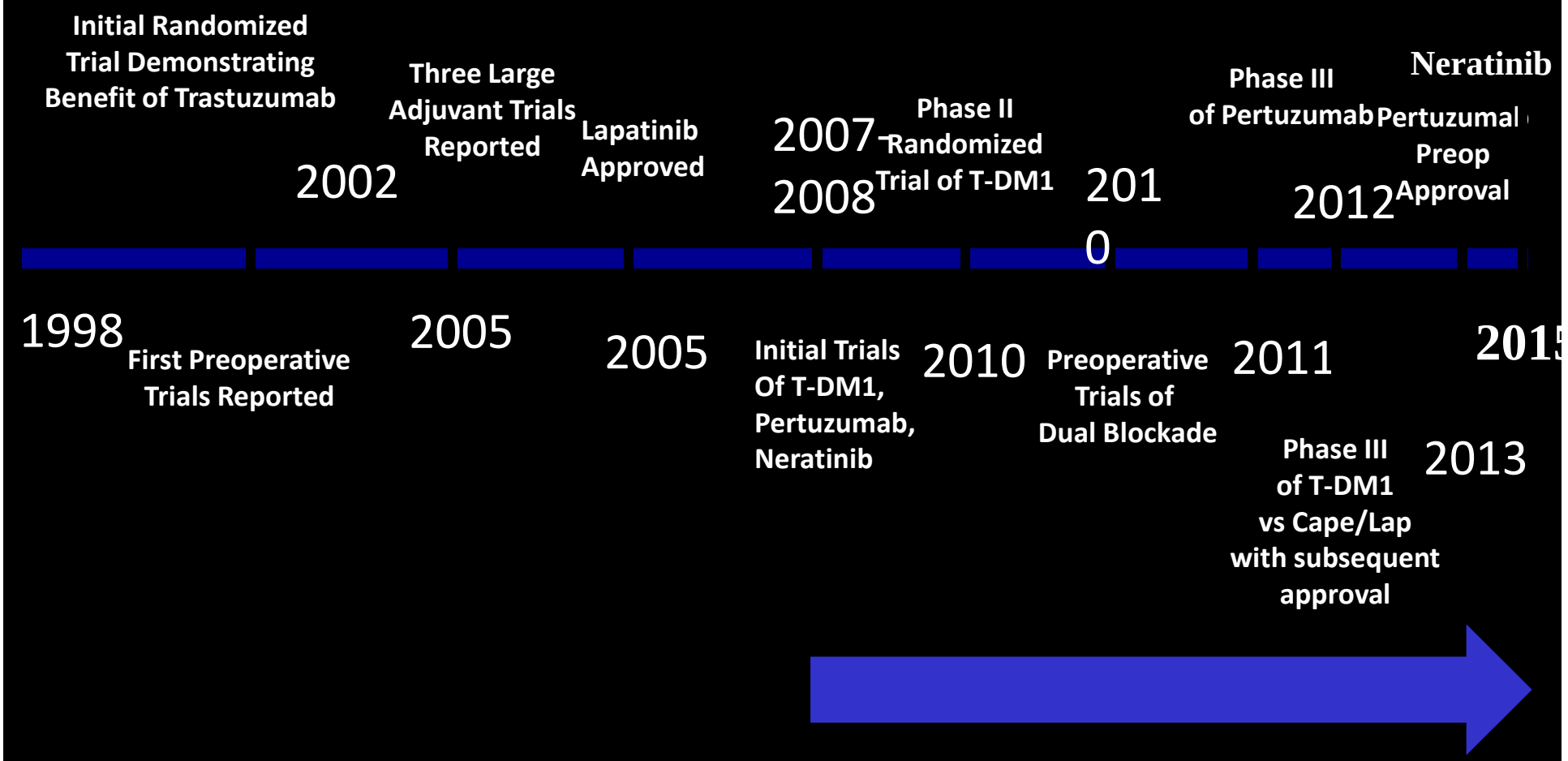


	L N = 145	L+T N = 146
Progressed or Died, n	128	127
Median, wks	8.1	12.0
Hazard ratio (95% CI)	0.73 (0.57, 0.93)	
P value	0.008	

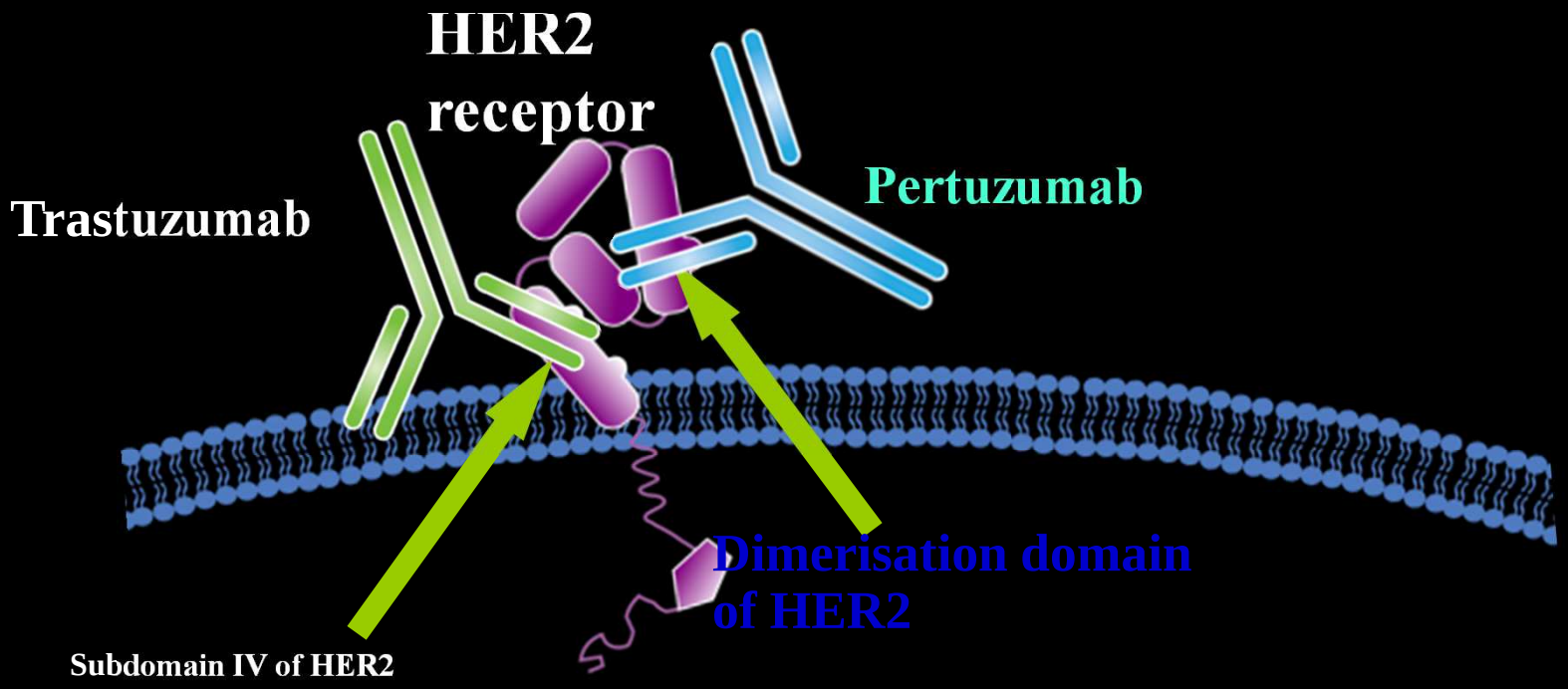
ORR 6.9% vs 11.3%, NS

Significant improvement in overall survival also seen

HER2+ Disease: Major Clinical Advances Over The Past 15+ Years



Trastuzumab and Pertuzumab Bind to Different Regions on HER2 and Have Synergistic Activity



CLEOPATRA:
Phase III Trial of Docetaxel + Trastuzumab vs Docetaxel + Trastuzumab + Pertuzumab

N=800

HER2-positive MBC

(53% no prior chemo
10% prior trastuzumab)

1:1

Docetaxel + trastuzumab + placebo

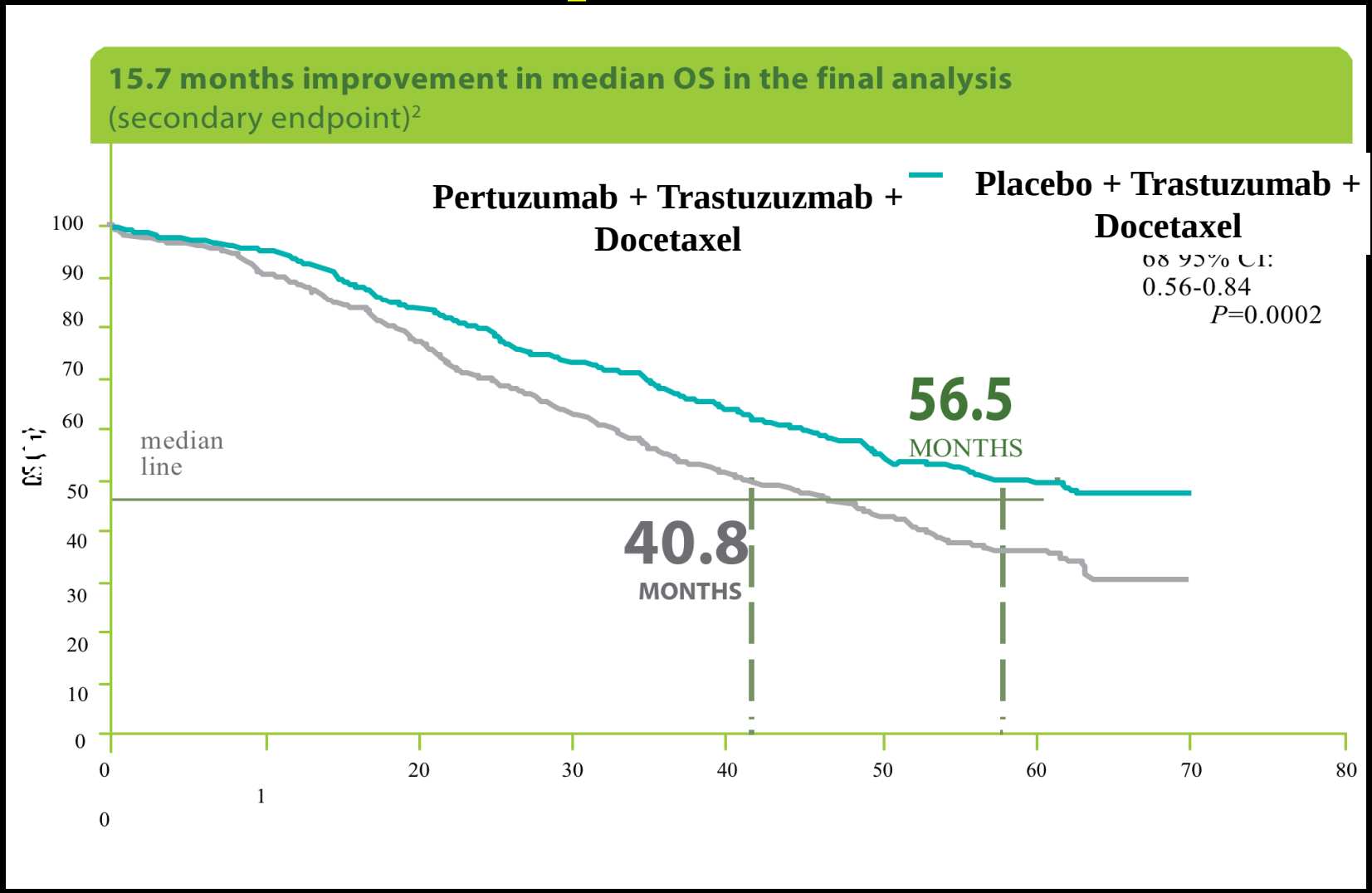
Docetaxel + trastuzumab + pertuzumab

- End points
  - PFS and OS
  - quality of life
  - biomarker analysis

Improvement with Pertuzumab in Cleoapatra

- Disease control (progression free survival)
  - 6 months
- Overall survival
  - 15 months (biggest benefit ever seen)

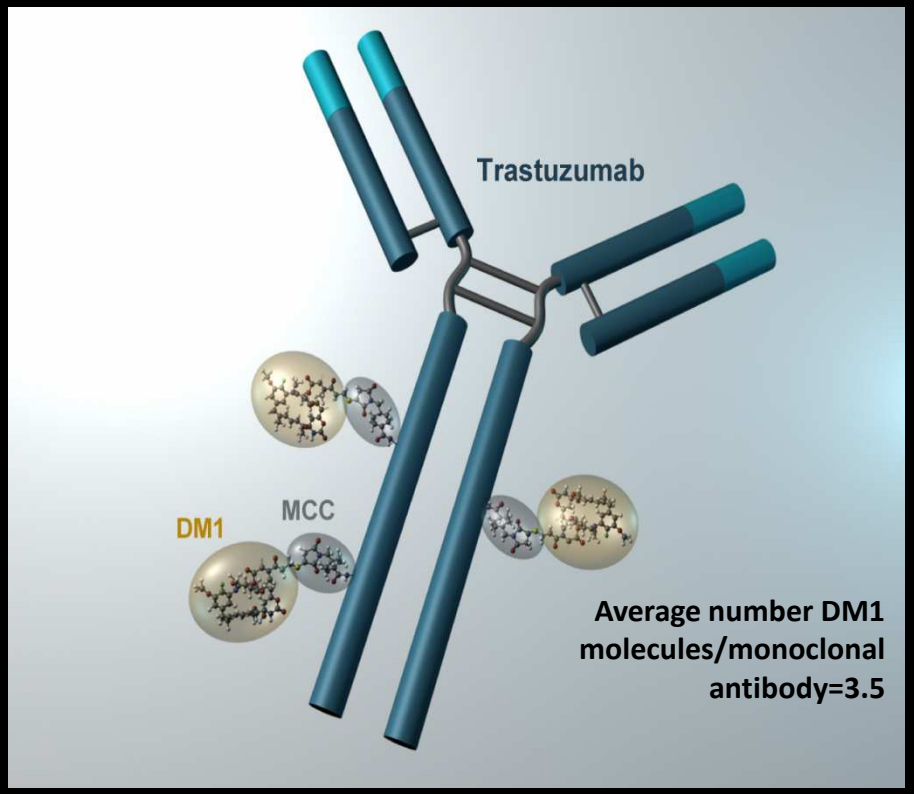
CLEOPATRA: Updated Survival Data

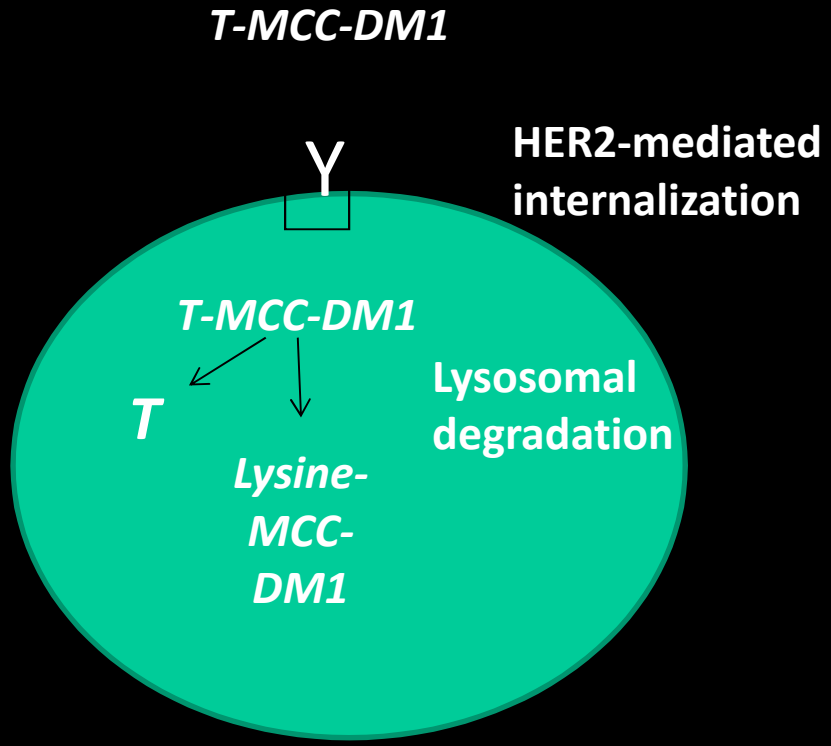


Swain et al, ESMO, 2014
NEJM 2015

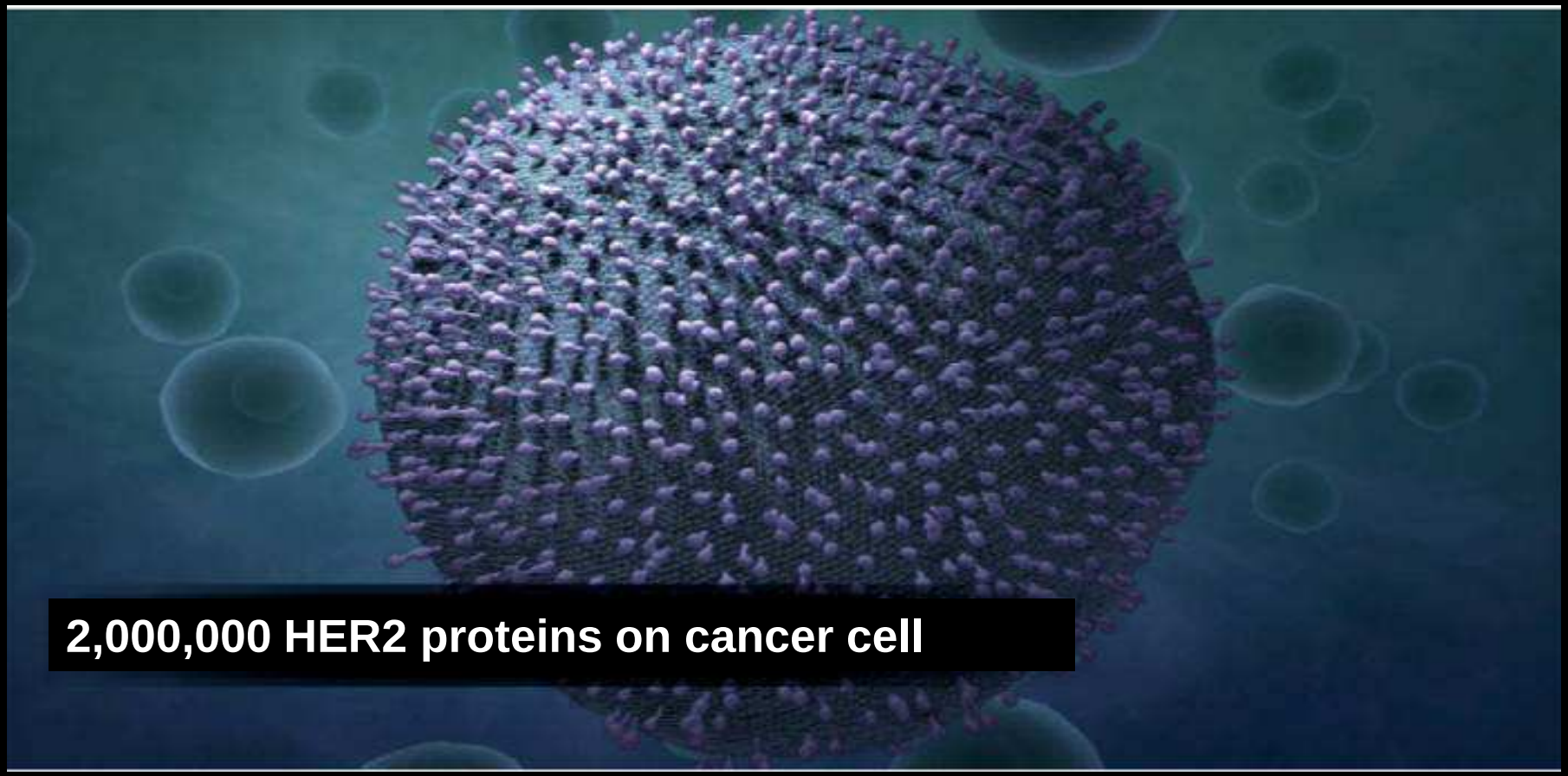
Trastuzumab-DM1 (T-DM1), a HER2 Antibody-Drug Conjugate

- Maytansine analogue DM1 (antitubule akin to vincas) conjugated to trastuzumab – similar to gemtuzumab (Myelotarg)

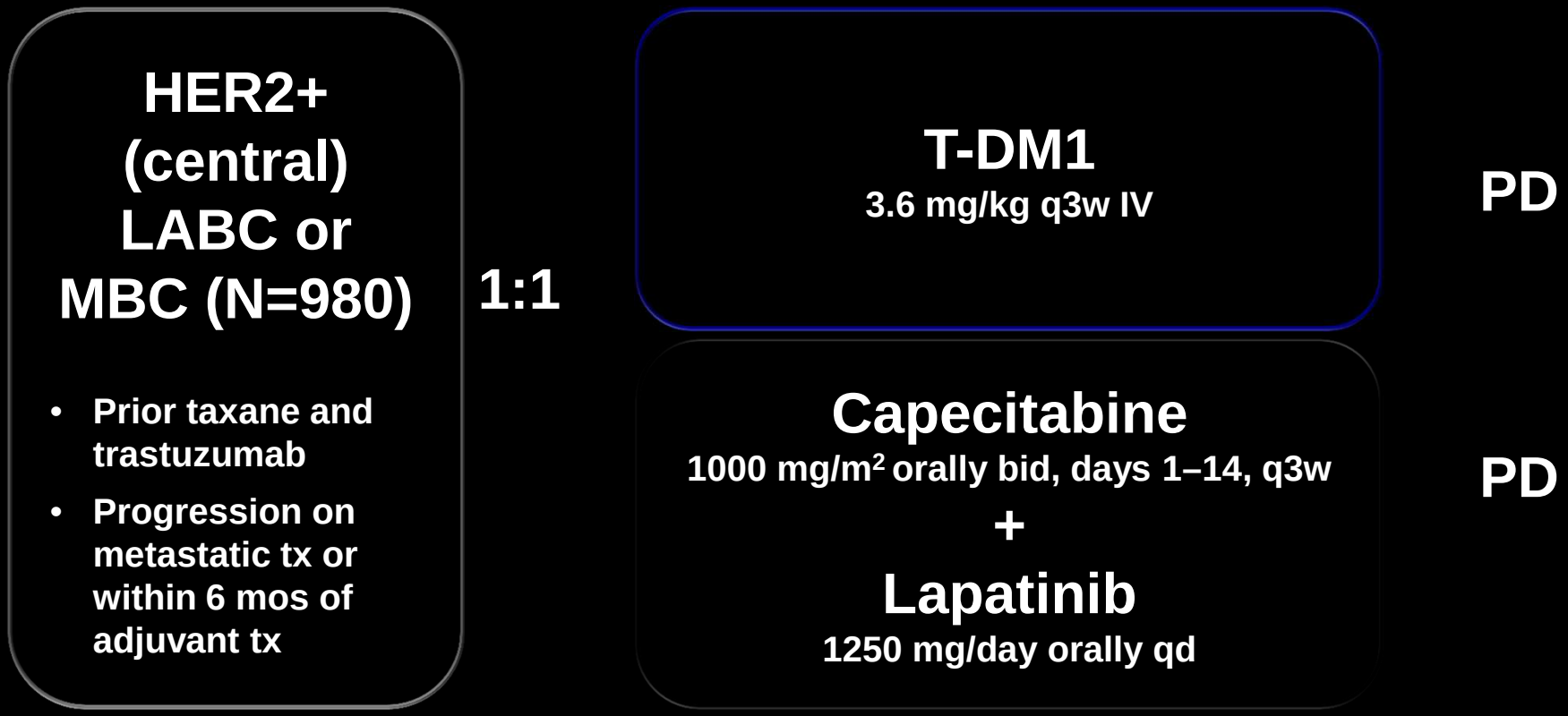




HER2 Gene Amplification Results in Marked Overexpression of HER2 Proteins *(and therefore a great target)*



EMILIA Study Design



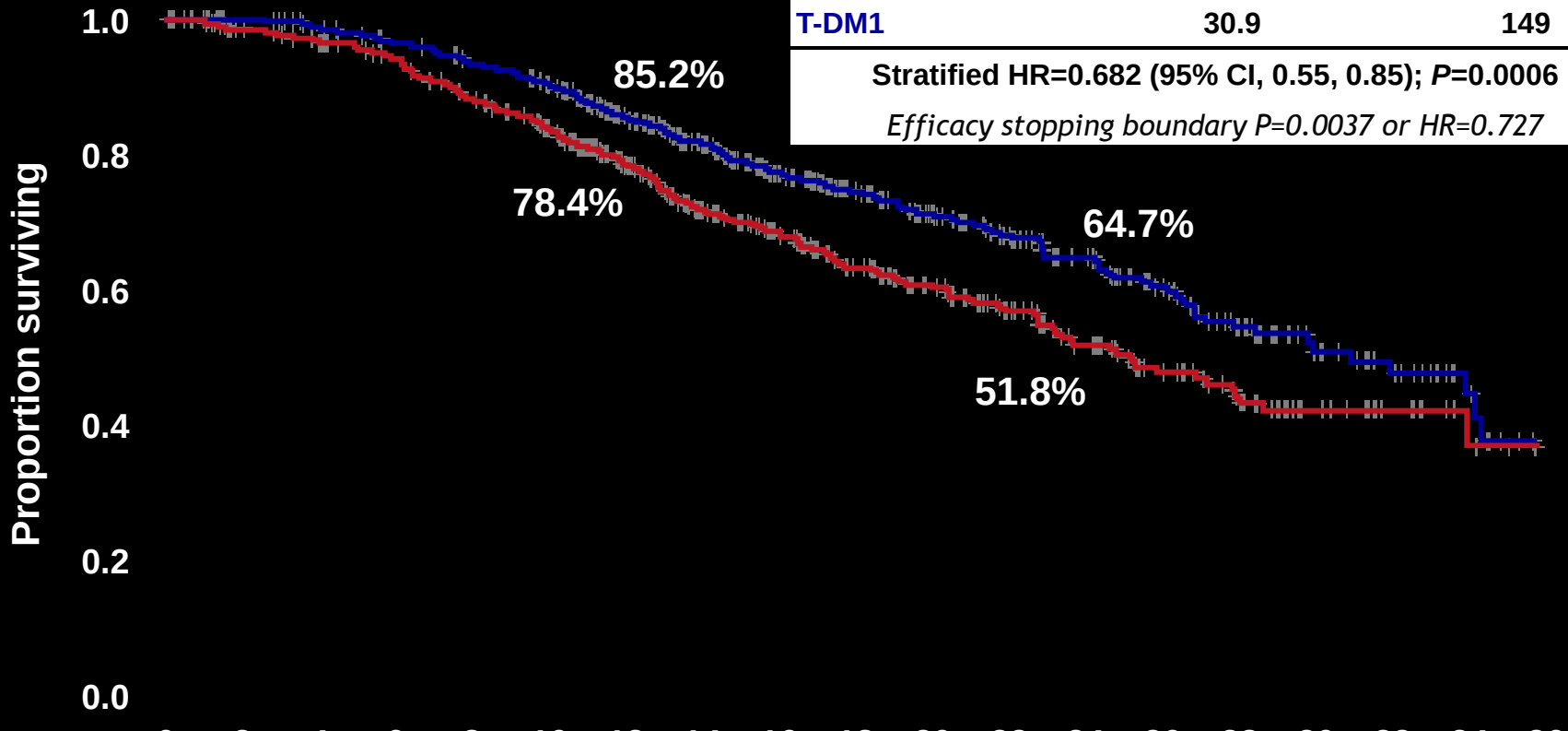
- **Primary end points:** PFS by independent review, OS, and safety
- **Key secondary end points:** PFS by investigator, ORR, duration of response, time to symptom progression

Overall Survival

	Median (months)	No. of events
Cap + Lap	25.1	182
T-DM1	30.9	149

Stratified HR=0.682 (95% CI, 0.55, 0.85); *P*=0.0006

Efficacy stopping boundary P=0.0037 or HR=0.727



No. at risk:

Cap + Lap	496	471	453	435	403	368	297	240	204	159	133	110	86	63	45	27	17	7	4
T-DM1	495	485	474	457	439	418	349	293	242	197	164	136	111	86	62	38	28	13	5

Adverse Events

Grade ≥3 AEs With Incidence ≥2%

	Cap + Lap (n=488)		T-D	
Adverse Event	All Grades, %	Grade ≥3, %	All	3, %
Diarrhea	79.7	20.7		
Hand-foot syndrome	58.0	1		
Vomiting	29.3			
Neutropenia	8.6			2.0
Hypokalemia				2.2
Fatigue			35.1	2.4
Nausea			39.2	0.8
Muco		.3	6.7	0.2
Thron		0.2	28.0	12.9
Increas	.4	0.8	22.4	4.3
Increased	8.8	1.4	16.9	2.9
Anemia	8.0	1.6	10.4	2.7

T-DM1 Far Better Tolerated Than Cape/Lap

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Verma et al, ESMO 2012
Blackwell, NEJM 2012

Treatment Approach For Patient Presenting With HER2+ MBC in 2016

First Line:
Taxane +
Trastuzumab +
Pertuzumab

Second Line:
TDM-1

Third, Fourth….Line
Capecitabine + Lap
Capecitabine + Trast
Vinorelbine + Trast
Lapatinib + Trast
Other chemo + Trast
Endocrine Therapy + Trast

(Some patients with ER+/PR+ disease can be treated up front with hormonal therapy +/- anti-HER2 therapy)

Neo-adjuvant therapy

- Refers to the
  - systemic treatment of breast cancer prior to definitive surgical therapy (ie, preoperative therapy).

Neo-adjuvant chemotherapy

- Introduced in the early 1970s as part of an integrated therapeutic approach to treat inoperable locally advanced breast cancer, primary, anterior, induction or Neoadjuvant chemotherapy (NACT) resulted in
  - high responses and sufficient down-staging to allow mastectomy in some patients
  - The small number of pathological complete responders, which was contrary to expectations, is now the prime focus of NACT trials

NACT - Objective

- To improve surgical outcomes in patients with breast cancer for whom a
  - primary surgical approach is technically not feasible and
  - for patients with operable breast cancer who desire breast conservation, but for whom either a mastectomy is required or a partial mastectomy would result in a poor cosmetic outcome

NACT - Objective

- In addition, appropriate for patients with human epidermal growth factor 2 (HER2) - positive or triple-negative breast cancer (ie, estrogen receptor [ER]-negative, progesterone receptor [PR]-negative, and HER2- negative) who are most likely to have a good locoregional response to treatment, regardless of the size of their breast cancer at presentation

NACT: Advantages and Disadvantages
Theoretically!?

Advantages	Disadvantages
Reduction in tumor volume	Clinical/radiological staging imprecise
Tumor down-staging	Overtreatment of small favorable tumors
In vivo assessment of tumor response	Extent of surgery not confirmed
Less-extensive surgical resection	Loss of prognostic significance of axillary nodal status
Postsurgical growth spurt abrogated	Unknown relevance of surgical margins
Earlier introduction of a systemic therapy	Large number of drugresistant cells present
Response to chemotherapy serves as a marker for long-term outcome	Delays effective local therapy
Multiple sequential sampling of primary tumor allows evaluation of biologic changes during chemotherapy	Response of primary tumor may not correlate with response of micrometastases

Indian J Med Paediatr Oncol. 2010 Jan-Mar; 31(1): 8–17

DOES NACT IMPROVE OVERALL SURVIVAL?

- Neoadjuvant vs adjuvant
- The largest and most important trial was the *National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18* trial which compared 4 cycles of doxorubicin plus cyclophosphamide (AC) given either preoperatively or postoperatively
- 1,523 women with a median tumor size of 3.5 cm were included independent of hormone receptor status
- In the neoadjuvant arm, the objective clinical response (ORR) rate was 78% with clinical partial response (cPR) in 43% and a clinical complete response (cCR) in 36%
- A pathologic complete response (pCR) was documented in 13% of patients

Journal of Oncology Volume 2013
Article ID 732047, 12 pages

DOES NACT IMPROVE OVERALL SURVIVAL?

- The two main findings in *NSABP B-18* however were
- (1) no difference in overall survival (HR = 0.99; 95% CI, 0.85 to 1.16; P = .90) and disease free survival (HR = 0.93; 95% CI, 0.81 to 1.06; P = .27) between pre- and postoperative chemotherapy;
- (2) patients achieving a pCR had a superior DFS and OS compared to patients not achieving a pCR (DFS: HR = 0.47, P < .0001; OS:HR = 0.32, P < .0001).

Journal of Oncology Volume 2013
Article ID 732047, 12 pages

Trials comparing the same chemotherapeutic regimen pre- and postoperatively

Trial	Phase (*n*)	Tumors	NA versus adjuvant	Primary endpoint	Other outcomes
IBBGS	III (272)	T2 > 3 cm or T3 N0-1	3 × EVM → 3 × ETV	BCT 63% (33% RT only, 30% S + RT) versus 0%	No difference in DFS or OS; 34% local recurrence with RT only
Institut Curie S6	III (390)	T2-3, N0-1	4 × FAC	BCT 82 versus 77% (ns) (S only if no cCR after RT)	No difference in DFS and OS, short-term OS benefit (P = .02) for NA
Royal Marsden	III (293)	T0–4, N0-1	4 × 2MT	BCT 89 versus 78% (P = .004)	No difference in DFS, OS, and local recurrence; pCR 7%
NSABP B-18	III (1493)	T1–3, N0-1	4 × AC	5 y-OS: 80 versus 81% (ns); 5 y-DFS: 67 versus 67% (ns)	BCT 68 versus 60% (P = .001); LRR 13 versus 10% (P = .21); ORR 78%, pCR 13%; pCR associated with better 9 y-DFS (75 versus 58%) pCR associated with better 9 y-OS (85 versus 73%); trends in favor of NA for DFS and OS in women <50 y
EORTC 10902	III (698)	T1c–T4b	4 × FEC	4 y-OS 82 versus 84% (P = .38)	4 y-PFS 65 versus 70% (P = .27); LRR 5 versus 5% (ns); pCR 4%; downstaging to BCT in 23%
ABCSG-7	III (423)	T1–3, N0-1 HR− + high risk HR+	3 × CMF	RFS better with adjuvant therapy (HR 0.7; P = .02); no difference in OS (HR 0.8; P = .21)	cORR 56%, pCR 6%; LRR 13 versus 8% (P = .1)
Meta-analysis	IV (3946)	9 randomized trials	Same regimen	No difference in OS (RR 1.0); no difference in DFS (RR 0.99)	LRR higher for NA (RR 1.22; P = .015) especially if no S was done; pCR range 4–29%

EVM: epirubicin, vincristin, methotrexat; ETV: mitomycin, thiotepa, vindesine; FAC: 5-FU, doxorubicin, cyclophosphamide; 2MT: mitoxantrone, methotrexat tamoxifen; AC: doxorubicin, cyclophosphamide; FEC: 5-FU, epirubicin, cyclophosphamide; CMF: cyclophosphamide, methotrexat, 5-FU.

Neo-adjuvant versus Adjuvant

- In summary, the primary objective to show an advantage due to earlier systemic therapy was not met, but it has been shown that neoadjuvant chemotherapy is as effective as adjuvant chemotherapy

- Additionally, the rate of breast conservation in operable disease can be increased, even if the risk of local recurrence might be slightly higher

Addition of Taxanes

- The rate of pCR in these early trials was quite low with a range from 4 to 29%. Therefore, the addition of taxanes to the classical anthracycline-based chemotherapy was investigated in several phase-III trials

Journal of Oncology Volume 2013
Article ID 732047, 12 pages

Randomized trials incorporating either concurrent or sequential taxane-based neoadjuvant therapy

Trial	Phase (n)	Tumors	Treatment	Primary endpoint	Other outcomes
Aberdeen trial	III (162)	≥3 cm	4 × CVAP → PR/CR: 4 × CVAP versus 4 × Doc; SD/PD: 4 × Doc	pCR 16 versus 34%; $P = .04$	cORR 66 versus 94%, $P = .001$; BCT 48 versus 67%; 5 y-OS (78 versus 93%, $P = .04$); 5 y-DFS (72 versus 90%, $P = .04$)
NSABP B-27	III (2411)	T1c–3 N0, T1–3 N1; (median 9 cm)	4 × AC → S versus 4 × AC → 4 × Doc → S versus 4 × AC → S → 4 × Doc	DFS (arm 2 versus 1) HR 0.92 ($P = .29$); OS (P across all 3 arms = .76); RFI (arm 2 versus 1: HR 0.83, $P = .04$)	LRR (arm 2/3 versus 1) HR 0.67 ($P = .02$); BCT 62 versus 64% (ns), ORR 86 versus 91% ($P < .001$); pCR 9 versus 19% ($P = .0001$), pCR associated with better DFS (HR 0.49, $P < .0001$) and OS (HR 0.36, $P < .0001$)
ACCOG	III (363)	≥3 cm or T4d	6 × AC versus 6 × ADoc	pCR 24 versus 21% ($P = .61$); cORR 61 versus 70% ($P = .06$)	No difference in RFS ($P = 17$); no difference in OS ($P = .57$)
Diéras et al.	III (200)	T2-3 N0-1	4 × APac versus 4 × AC	pCR 16 versus 10% (P = NA)	cORR 89 versus 70%; BCT 58 versus 45%; DFS (18 MO: 87 versus 79%); pCR associated with better DFS (31 MO: 91 versus 70%)
Meta-analysis	IV (2455)	7 randomized trials	Anthracycline-based therapy ± taxane	pCR better with sequential (RR 1.73, $P = .013$), but not with concomitant taxanes (RR 1.04, $P = .77$); BCT higher with taxanes (RR 1.11, $P = .012$)	No difference in DFS (RR 0.91, $P = .12$)

CVAP: cyclophosphamide, vincristin, doxorubicin, prednisone; Doc: doxetaxel; AC: docorubicin, cyclophosphamide; Pac: paclitaxel.

Journal of Oncology Volume 2013
Article ID 732047, 12 pages

Addition of Taxanes

- Seven randomized trials including 2,455 patients were summarized in a literature-basedmeta-analysis in order to answer the question if the addition of taxanes to an anthracyclines-based chemotherapy provides an advantage in the primary treatment for early breast cancer
- The rate of BCT was significantly higher for patients receiving taxanes, with an absolute difference (AD) of 3.4% (P = .012)
- The rate of pCR was higher for patients receiving taxanes, but only statistically significant if used in a sequential schedule with an AD of 2.4% (P = .013)

Journal of Oncology Volume 2013
Article ID 732047, 12 pages

Neo-tAnGo study

- Addressed the value of addition of gemcitabine to paclitaxel, and the sequencing of epirubicin and cyclophosphamide and paclitaxel (with or without gemcitabine) blocks

- The investigators concluded that no advantage was provided in terms of pCR rate by addition of gemcitabine: 70 (17%) of 404 patients given epirubicin and cyclophosphamide then paclitaxel had pCR compared with 71 (17%) of 408 patients who received additional gemcitabine (p=0.98).

Lancet oncology Published **Online** December 19, 2013

Neo-tAnGo study

- Conversely, improved pCR was seen with taxane first sequencing for neoadjuvant chemotherapy: 82 (20%) of 406 patients given paclitaxel with or without gemcitabine followed by epirubicin and cyclophosphamide achieved pCR compared with 59 (15%) of 406 patients who received epirubicin and cyclophosphamide first (p=0.03)

Lancet oncology Published **Online** December 19, 2013

Neo-tAnGo study

- The improved pCR reported in Neo-tAnGo with the taxane-first sequence did not translate into improved disease-free survival and overall survival
- This finding might be related to the small, albeit significant, difference noted in the pCR (20% *vs* 15%)
- The overall low pCR (17%) was possibly related to the heterogeneous population, which included patients with inflammatory breast cancer

Lancet oncology Published **Online** December 19, 2013

Taxane first in NACT

- Overall, a taxane-first sequence can be regarded as a reasonable option in neoadjuvant chemotherapy for locally advanced breast cancer

Lancet oncology Published **Online** December 19, 2013

NACT – Choice

- Doxorubicin and cyclophosphamide followed by weekly paclitaxel (**Grade 2C**)
- For patients with a contraindication to anthracycline treatment, docetaxel and cyclophosphamide (**Grade 2C**)
- For patients with a triple-negative (ER, PR, and HER2 negative) breast cancer (TNBC), the addition of carboplatin to standard NACT is reasonable.

NACT – Choice

- For patients whose breast cancer is HER2-positive, the addition of HER2-directed therapy to NACT over chemotherapy alone (**Grade 1B**)
  - NACT with trastuzumab alone until further data are available to inform whether the addition of pertuzumab in this setting also improves survival outcomes.
  - Other prefer to administer dual HER2-blockade (using pertuzumab with trastuzumab) and NACT based on an increased rate of pathologic complete responses with combined treatment compared with trastuzumab alone
  - In this scenario, trastuzumab alone without pertuzumab would be continued after surgery

NACT – Choice

- For women with hormone receptor-positive, HER2-negative breast cancers who are candidates for neoadjuvant therapy,
  - chemotherapy rather than endocrine therapy

- For patients with HR-positive, HER2-negative breast cancers who are not candidates for chemotherapy, endocrine therapy is reasonable
  - an aromatase inhibitor rather than tamoxifen
  - premenopausal women who desire neoadjuvant endocrine therapy rather than chemotherapy should be informed of the lack of data to inform the benefits of this treatment approach

NACT – Surgical approach

- The surgical approach following neoadjuvant treatment depends upon the pretreatment evaluation, clinical response, and patient preference

- Management of the axilla may be influenced by clinical nodal stage at presentation and, in patients with clinically or pathologically positive lymph nodes at baseline, by clinical and pathologic response of the axillary nodes to neoadjuvant therapy

NACT - Monitoring

- Patients receiving neoadjuvant systemic therapy should be followed by clinical exam at regular intervals during treatment to ensure that disease is not progressing

- At the end of treatment, the assessment of tumor response is important to help guide the surgical approach

NACT - Monitoring

- For patients on NACT perform a clinical examination every two to four weeks (ie, prior to each cycle of treatment)
  - include evaluation of the affected breast and ipsilateral axilla
- For those undergoing neoadjuvant endocrine therapy, response to treatment is expected to take a longer time to become evident
  - As such, we perform clinical evaluations every four to eight weeks while on treatment
- Imaging studies should only be performed if disease progression is suspected based on clinical exam

Adjuvant following neoadjuvant

- Recommendations regarding adjuvant treatment depend on the pretreatment tumor characteristics, efficacy of treatment as defined at final pathology, and the neoadjuvant treatment administered
  - Regarding postoperative radiation therapy (RT) on the tumor characteristics prior to the start of neoadjuvant therapy
  - In general, postoperative RT for all patients treated with breast conserving surgery, for patients with locally advanced breast cancer (stage III disease) treated with mastectomy, and for the majority of patients with histologically positive lymph nodes remaining after preoperative chemotherapy

Adjuvant following neoadjuvant

- not administering adjuvant chemotherapy after neoadjuvant treatment
- For patients with HER2 positive breast cancer, wadjuvant trastuzumab rather than observation (**Grade 1B**)
- trastuzumab be administered for a total treatment duration of one year rather than for a shorter duration (**Grade 2B**)
- For patients with HR positive breast cancer, recommend adjuvant endocrine therapy (**Grade 1A**)
- For patients with HER2-positive and HR positive breast cancer, initiate endocrine therapy concurrent with trastuzumab

Prognosis

- For patients with aggressive breast cancer subtypes such as triple-negative breast cancer, HER2-positive breast cancer, and high-grade hormone receptor-positive/HER2-negative breast cancer who undergo NACT, prognosis correlates with pathologic response in the breast and the axilla at the time of surgery

- Patients with hormone receptor-positive breast cancers rarely achieve a pathologic complete response following neoadjuvant endocrine therapy. Until we can validate other ways to quantitate response to this treatment, such as the preoperative endocrine prognostic index (PEPI) score, its efficacy is assessed by clinical response and patient eligibility for breastconserving surgery

Neoadjuvant therapy

- Goals
  - Decrease tumor size
  - Minimize surgery
  - Establish tumor sensitivity
- Appropriate treatments
  - Chemotherapy
  - Tamoxifen or aromatase inhibitors
  - Radiation therapy

Neoadjuvant therapy

Advantages

- Higher rate of breast conservation
  - Convert some "inoperable" breast cancer to potentially curative surgical candidates
- Response in real time
  - Lack of response – change regimen
- Prognosis can be refined by degree of residual disease
  - Pathologic clinical response had much higher DFS and OS

Wolmark, et al., JNCI 30:96, 2001.

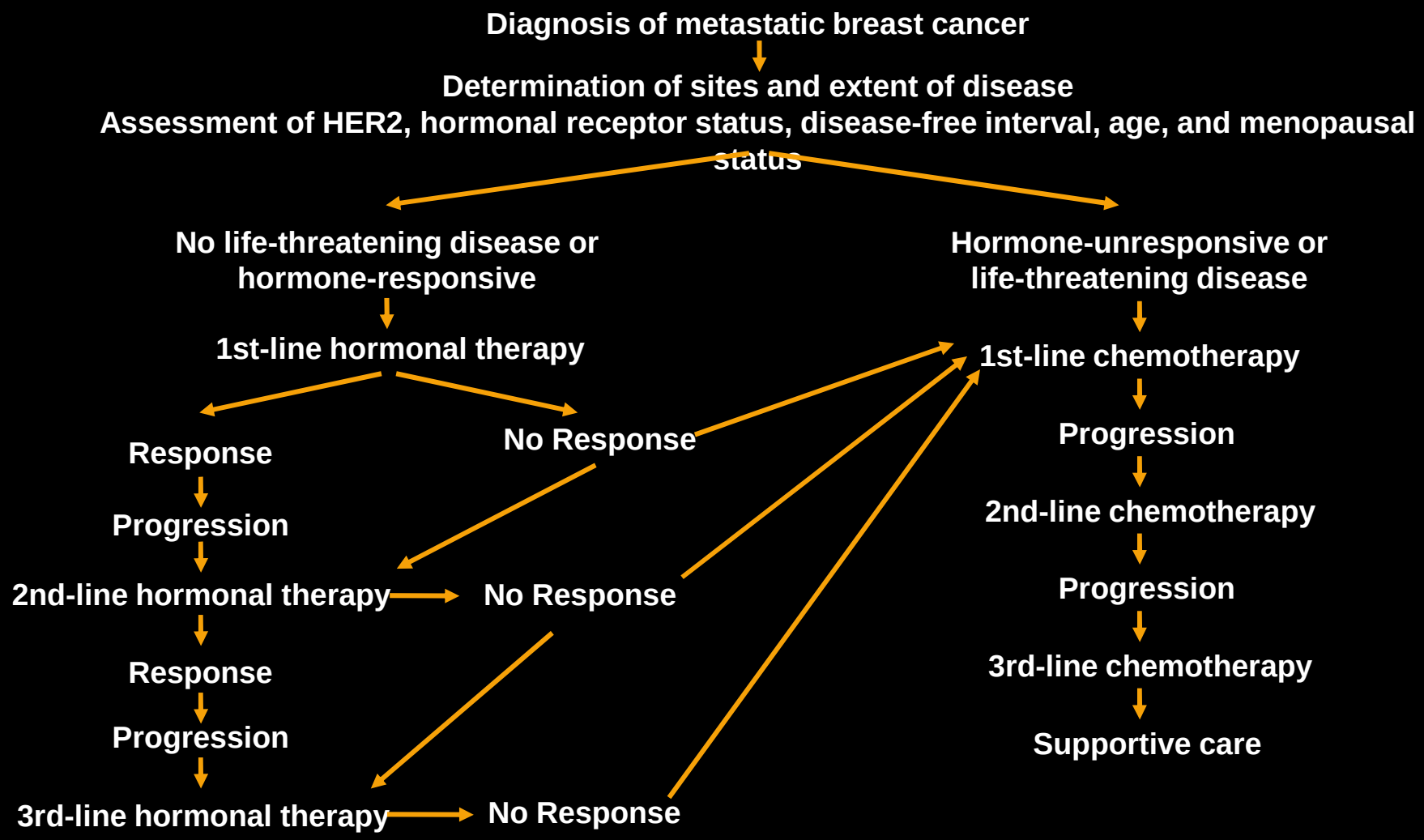
Neoadjuvant therapy

- **Conclusions**
- Neoadjuvant chemotherapy is recommended for patients with locally advanced disease
- A taxane should be included in the regimen

Metastatic Breast Cancer

- Chronic disease
- MS of MBC-2 to 3 yrs/5-10% live more than10yr.
- 3% to 25% can achieve CR/PR and can be rendered disease free and progression free for more than 5 yrs.
- Optimal sequential use of all modalities can lead to maximum palliation, delay progression and death as much as possible

Metastatic Breast Cancer: Management



When to initiate chemotherapy (CT) in MBC ?

- Difficult decision
- There is no evidence that CT should be initiated as soon as MBC is identified
- Optimal duration of CT also varies on the basis of clinical situation and patient preferences

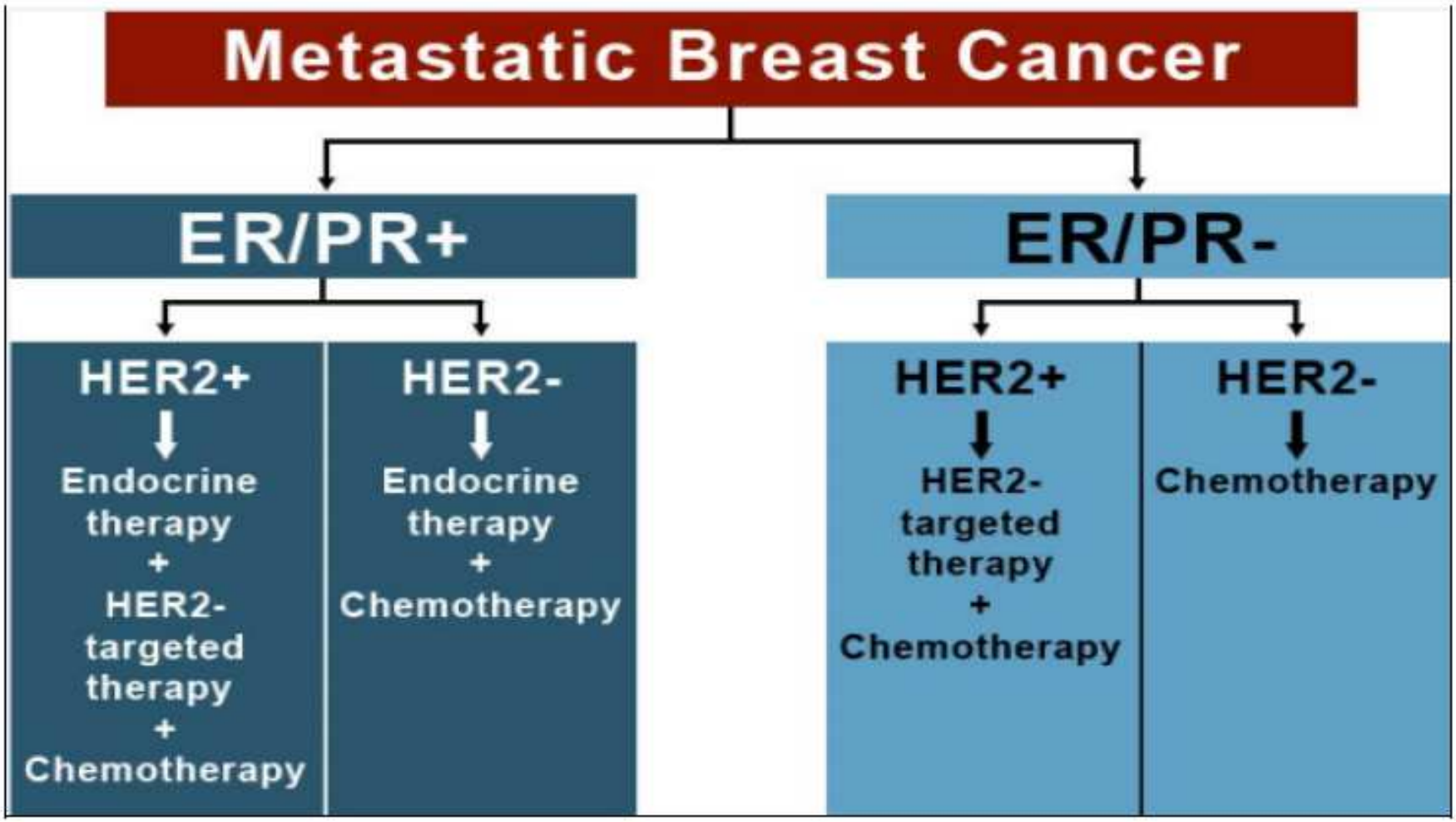


Figure. Determining treatment for metastatic breast cancer.
ER = estrogen receptor; PR = progesterone receptor.

Drug Approvals for Metastatic Breast Cancer

	Year Approval	First-Line	OS Benefit	Biomarker
Cytotoxics				
Paclitaxel (antitubulin)	1994	-	-	-
Docetaxel (antitubulin)	1996	-	Yes	-
Capecitabine (antimetabolite)	1998	-	-	-
Nab-paclitaxel (antitubulin)	2005	-	-	-
Gemcitabine (antimetabolite)	2004	Yes	-	-
Ixabepilone (antitubulin)	2007	-	-	-
Eribulin (antitubulin)	2010	-	Yes	-
Biologics				
Trastuzumab (anti-HER2)	1998	Yes	Yes	Yes
Lapatinib (anti-HER2)	2006	Yes	-	Yes
Bevacizumab (antiangiogenic)	2008-2011*	Yes	-	-
Pertuzumab (anti-HER2)	2012	Yes	Yes	Yes
Ado-trastuzumab emtansine (anti-HER2 immunoconjugate)	2013	-	Yes	Yes

**Approval revoked in 2011*

Cortazar P, et al.[13]

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2016
Invasive Breast Cancer

NCCN Guidelines Index
Breast Cancer Table of Contents
Discussion

CHEMOTHERAPY REGIMENS FOR RECURRENT OR METASTATIC BREAST CANCER[1]

Preferred single agents:

Anthracyclines
- Doxorubicin
- Pegylated liposomal doxorubicin

Taxanes
- Paclitaxel

Anti-metabolites
- Capecitabine
- Gemcitabine

Other microtubule inhibitors
- Vinorelbine
- Eribulin

Other single agents:
- Cyclophosphamide
- Carboplatin
- Docetaxel
- Albumin-bound paclitaxel
- Cisplatin
- Epirubicin
- Ixabepilone

Chemotherapy combinations:
- CAF/FAC (cyclophosphamide/doxorubicin/fluorouracil)
- FEC (fluorouracil/epirubicin/cyclophosphamide)
- AC (doxorubicin/cyclophosphamide)
- EC (epirubicin/cyclophosphamide)
- CMF (cyclophosphamide/methotrexate/fluorouracil)
- Docetaxel/capecitabine
- GT (gemcitabine/paclitaxel)
- Gemcitabine/carboplatin
- Paclitaxel/bevacizumab[2]

Preferred first-line agents for HER2-positive disease:
- Pertuzumab + trastuzumab + docetaxel (category 1)[5]
- Pertuzumab + trastuzumab + paclitaxel[5]

Other agents for HER2-positive disease:
- Ado-trastuzumab emtansine (T-DM1)
- Trastuzumab + paclitaxel ± carboplatin
- Trastuzumab + docetaxel
- Trastuzumab + vinorelbine
- Trastuzumab + capecitabine

Agents for trastuzumab-exposed HER2-positive disease:
- Lapatinib + capecitabine
- Trastuzumab + capecitabine
- Trastuzumab + lapatinib (without cytotoxic therapy)
- Trastuzumab + other agents[3,4,5]

[1]There is no compelling evidence that combination regimens are superior to sequential single agents.

[2]Randomized clinical trials in metastatic breast cancer document that the addition of bevacizumab to some first- or second-line chemotherapy agents modestly improves time to progression and response rates but does not improve overall survival. The time-to-progression impact may vary among cytotoxic agents and appears greatest with bevacizumab in combination with weekly paclitaxel.

[3]Trastuzumab given in combination with an anthracycline is associated with significant cardiac toxicity. Concurrent use of trastuzumab and pertuzumab with an anthracycline should be avoided.

[4]Trastuzumab may be safely combined with all non-anthracycline containing preferred and other single agents listed above for recurrent or metastatic breast cancer.

[5]Patients previously treated with chemotherapy plus trastuzumab in the absence of pertuzumab in the metastatic setting may be considered for one line of therapy including both trastuzumab plus pertuzumab in combination with or without cytotoxic therapy (such as vinorelbine or taxane). Further research is needed to determine the ideal sequencing strategy for anti-HER2 therapy.

For patients in whom a **combination regimen** is preferred, the patient's health status also can help choose the most appropriate regimen. As examples (see 'Combination chemotherapy' below):

- Ideal candidates for an anthracycline-containing regimen include women with chemotherapy naive, stage IV breast cancer (ie, no prior cytotoxic therapy and those who received endocrine therapy initially) and those who did not previously receive an anthracycline (eg, those who received docetaxel plus cyclophosphamide in the adjuvant setting). These are among of the most active regimens for metastatic breast cancer. (See 'Anthracycline-containing regimens' below.)

- Patients with a cardiac history (including prior anthracycline-induced cardiac injury) should not be treated with an anthracycline. Our preference is to administer a taxane-based regimen (eg, gemcitabine plus paclitaxel or docetaxel). (See 'Non-anthracycline, taxane-based regimens' below.)

For patients in whom a **single agent** is recommended, an understanding of the patient's health status also may influence the appropriate selection of agents. As examples (see 'Single agent chemotherapy' below):

- Patients with a history of cardiac disease or heart failure and those who are felt to be at a greater risk for cardiac injury (eg, elderly patients) should not be treated with an anthracycline. There are multiple appropriate alternatives (eg, paclitaxel or capecitabine).
- Patients with symptomatic peritoneal metastases, those who have difficulty swallowing pills, or those who are not able to follow instructions required to use a daily regimen may not be good candidates for oral therapies (eg, capecitabine).
- Patients at risk for hyperglycemia (eg, patients with diabetes) and those who cannot tolerate steroids for whatever reason may derive more of a benefit from agents that do not require premedication (eg, nanoparticle albumin bound [nAb]-paclitaxel, capecitabine, and gemcitabine).

Toxicities Associated With Approved Therapies

	Hematologic	Non-Hematologic
Cytotoxics		
Paclitaxel	++	Neuropathy
Docetaxel	+++	Asthenia, neuropathy
Capecitabine	+	Hand-foot syndrome
Nab-paclitaxel	++	Neuropathy
Gemcitabine	++	Asthenia
Ixabepilone	++	Neuropathy, asthenia
Eribulin	+++	Neuropathy
Biologics		
Trastuzumab	-	Cardiac dysfunction
Lapatinib	-	Diarrhea
Bevacizumab	-	Hypertension
Pertuzumab	-	Rash, diarrhea
Ado-trastuzumab emtansine	+	Asthenia, neuropathy, thrombocytopenia

- Patients who received doxorubicin or epirubicin in the adjuvant setting, even years previously, may not be good candidates for repeat anthracycline therapy due to increasing risk of cardiac toxicity at higher cumulative doses. Of the available alternative agents, we typically administer a taxane in these patients. (See 'Taxanes' below.)

- Patients with a history of myelosuppression with prior therapy that resulted in dose modification or treatment delay may not be good candidates for combination chemotherapy, particularly those using agents or schedules with significant myelotoxicity risks (eg, ixabepilone, gemcitabine, and every three-week docetaxel). In these situations, single agent treatment using a weekly anthracycline, capecitabine, or a weekly taxane may be more appropriate. (See 'Taxanes' below and 'Anthracyclines' below.)

- Patients with baseline or a history of serious (grade 3/4) neuropathy may not be good candidates for microtubulin-directed agents (eg, taxanes, ixabepilone, eribulin, or vinorelbine). These patients are appropriate candidates for anthracyclines, especially in the first-line setting in a patient who was never treated with an anthracycline. Alternatives to anthracyclines include capecitabine, etoposide, or gemcitabine. (See 'Anthracyclines' below and 'Other agents' below.)

For patients in whom chemotherapy is recommended, the choice of regimen (ie, single agent or a combination) and selection of a specific therapy depends on multiple factors, including the tumor burden (both in tumor volume and the presence of disease-related symptoms), general health status, prior treatments and toxicities, and patient preferences. These factors can help in the formulation of an individualized treatment plan in the first- or later-line setting. (See 'Factors influencing chemotherapy choice' above.)

For patients with a limited tumor burden and/or limited or minimal cancer-related symptoms, we suggest single agent chemotherapy administered sequentially rather than combination chemotherapy (Grade 2B).

For select patients with symptomatic disease due to the location of specific metastatic lesions (eg, right upper quadrant pain due to expanding liver metastases, or dyspnea related to diffuse lung metastases) and a large tumor burden, we suggest a combination regimen rather than a single agent (Grade 2B).

Combination therapy results in a greater likelihood of a response compared with single agent therapy, which may be of a sufficient benefit to justify the risks of treatment.

Careful assessment for response to treatment requires serial clinical examination, repeat lab evaluation (including tumor markers), and radiographic imaging. (See 'Monitoring therapy' above.)

Unlike in the adjuvant setting, there is no predetermined duration of treatment. For the young patient who is responding to treatment, we suggest continuation of chemotherapy beyond best response (Grade 2B). However, for patients who experience side effects to treatment or prefer not to continue treatment for whatever reason, discontinuation of treatment is reasonable. (See 'Duration of treatment' above.)

Some criteria that we use to define treatment failure include any of the following: clinical deterioration during treatment (ie, increasing disease-related symptoms, intolerable treatment toxicity, a decline in performance status), appearance of new metastases, and increasing size of previously documented metastatic lesions. (See 'Definition of treatment failure' above.)

Cytotoxic Therapy for Metastatic Breast Cancer: Summary

Antitubulin agents have generally supplanted anthracyclines for first-line therapy

- Adjuvant anthracycline therapy commonly used
- Cumulative cardiotoxicity limits rechallenge after recurrence
- Taxanes have comparable or greater efficacy
- Patients who are anthracycline naive may still be treated with anthracyclines as first line

First-line antitubulin therapy

- Weekly paclitaxel or every 3 week docetaxel most effective
- Weekly ixabepilone or *nab*-palictaxel not more effective than paclitaxel when combined with bevacizumab
- Neurotoxicity most common with weekly paclitaxel and ixabepilone
- Combination with anti-HER2 therapy in HER2 overexpressing disease improves survival

Second-line or greater antitubulin therapy

- Eribulin associated with overall survival advantage in heavily pretreated patients
- No advantage for eribulin over capecitabine overall

ADVANCED DISEASE
- HER2-NEGATIVE -

- First-line:
  - Endocrine Therapy (Tamoxifen, AIs, Fulvestrant)
  - Anthracyclines
  - Taxanes
  - Bevacizumab + Paclitaxel
  - Vinorelbine
  - Carboplatin (in TNBC)

- Further lines:
  - Endocrine Therapy
  - Everolimus + Exemestane
  - Anthracyclines
  - Taxanes
  - Vinorelbine
  - Eribulin
  - Gemcitabine
  - Capecitabine
  - Nab-Paclitaxel
  - Metronomic chemotherapy

MEDIAN SURVIVAL 3 YEARS

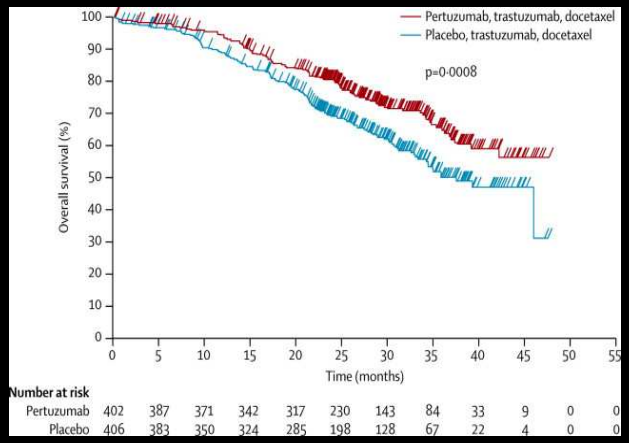
ADVANCED DISEASE
- HER2-POSITIVE (ASCO GUIDELINES 2014) -

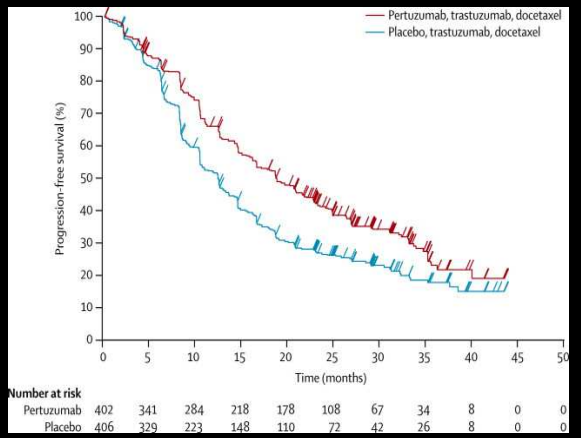
First-line:
Pertuzumab + Trastuzumab + Taxane

OUTCOMES

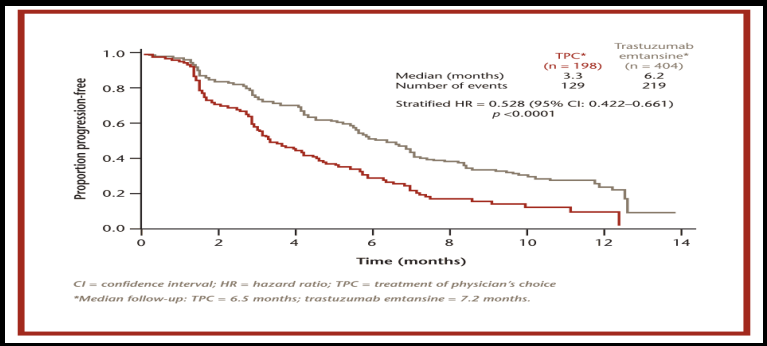
- **OS**: 37.6 months (placebo) VS not reached (Pertuzumab)
- **PFS**: 12.4 months (placebo) VS 18.7 months (Pertuzumab)

CLEOPATRA trial
Swain SM, Lancet Oncol 2013





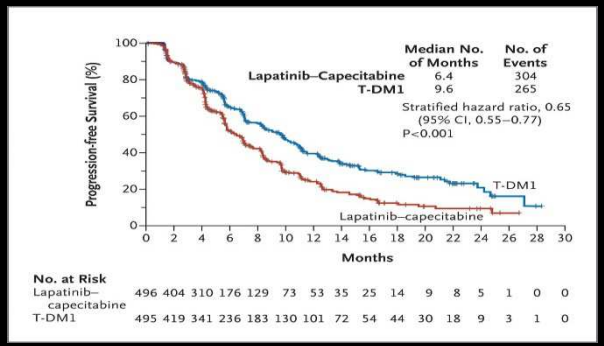
Second-line:
T-DM1
Trastuzumab + chemotherapy
Trastuzumab + Lapatinib



TH3RESA trial

- *Third-line*:
  T-DM1
  Trastuzumab + chemotherapy
  Trastuzumab + Lapatinib

- Further lines:
  Chemotherapy ± anti-HER2
  ET ± anti-HER2



EMILIA trial

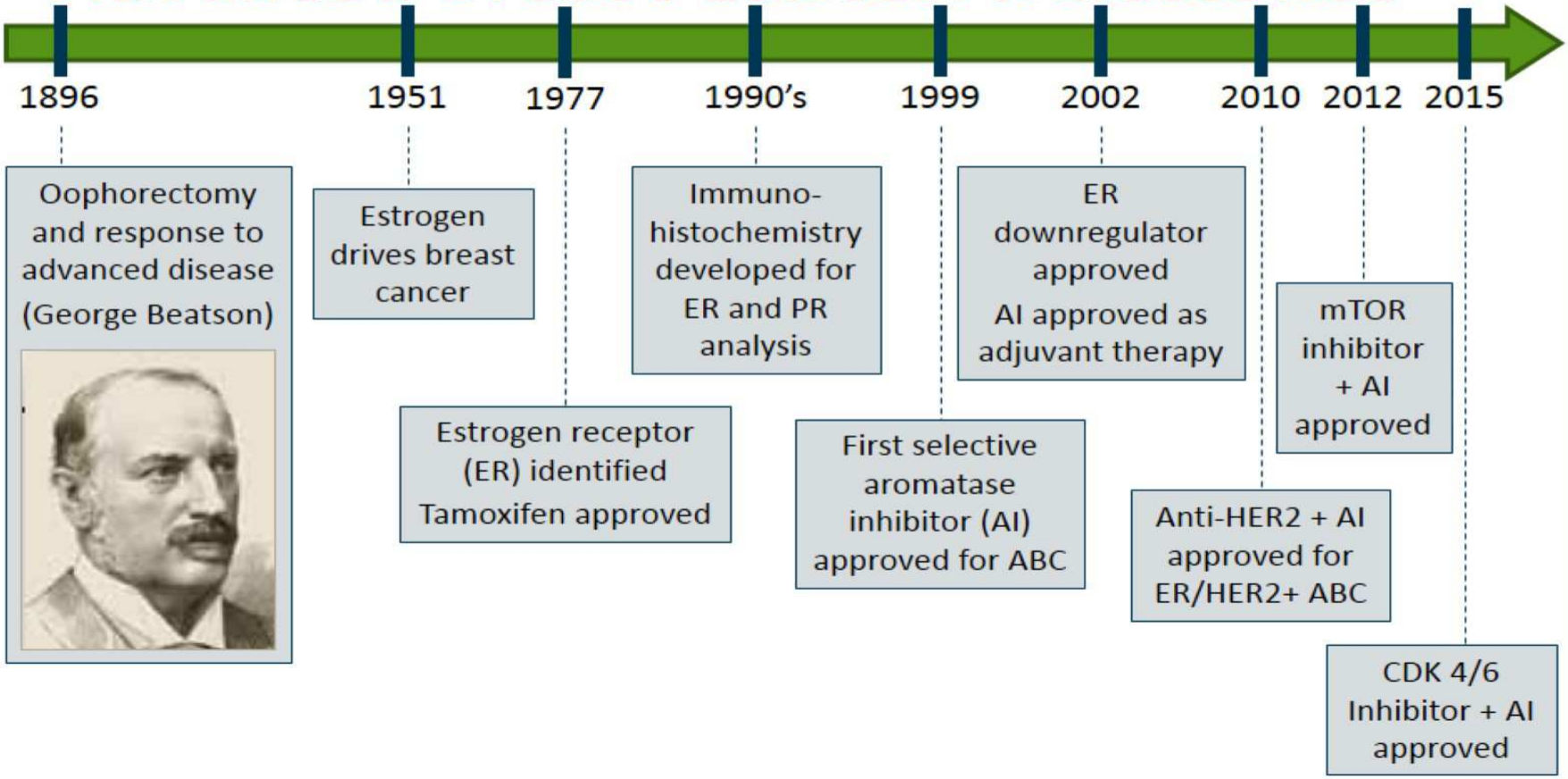
Krop IE, Lancet Oncol 2014

Verma S, NEJM 2013

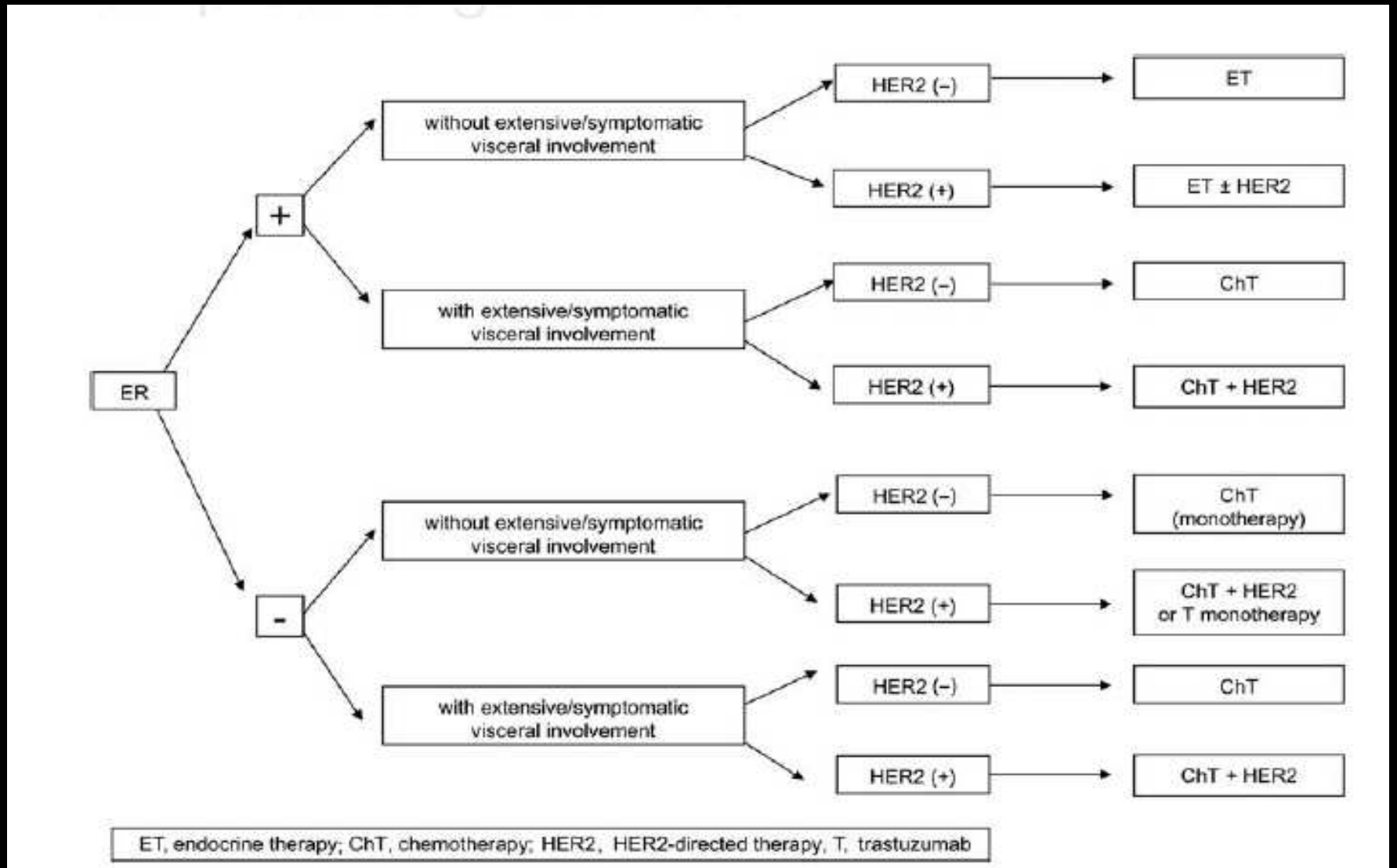
Therapy for Advanced ER+ Breast Cancer

- Strong preference to begin treatment using endocrine (hormone) therapy, unless cancer is causing significant symptoms/problems
- At least 4+ choices ("lines") of therapy; generally can be very effective at controlling the cancer with minimal side effects
- New approaches are needed to improve efficacy of endocrine therapy and delay onset of resistance

Hormonal Therapy for Advanced Breast Cancer: Milestones



Love RR, Philips J. *J Natl Cancer Inst*. 2002;94:1433-1434; Allred DC, et al. *Mod Pathol.* 1998;11:155-168; Bross PF, et al. *Oncologist*. 2002;7:477-480; Cohen MH, et al. *Oncologist*. 2001;6:4-11.



gure 2 First-line systemic therapy for advanced breast cancer.

Table 3. Available endocrine therapies for MBC

Class of agent	
Selective estrogen receptor modulators	Tamoxifen; toremifene
Estrogen receptor down-regulator	Fulvestrant
Luteinizing hormone-releasing hormone analogues	Goserelin, leuprorelin, triptorelin
Third-generation aromatase inhibitors	
Non-steroidal	Anastrozole, letrozole
Steroidal	Exemestane
Progestins	Medroxyprogesterone acetate; megestrol acetate
Anabolic steroids	Nandrolone decanoat
Estrogens	Estrogens

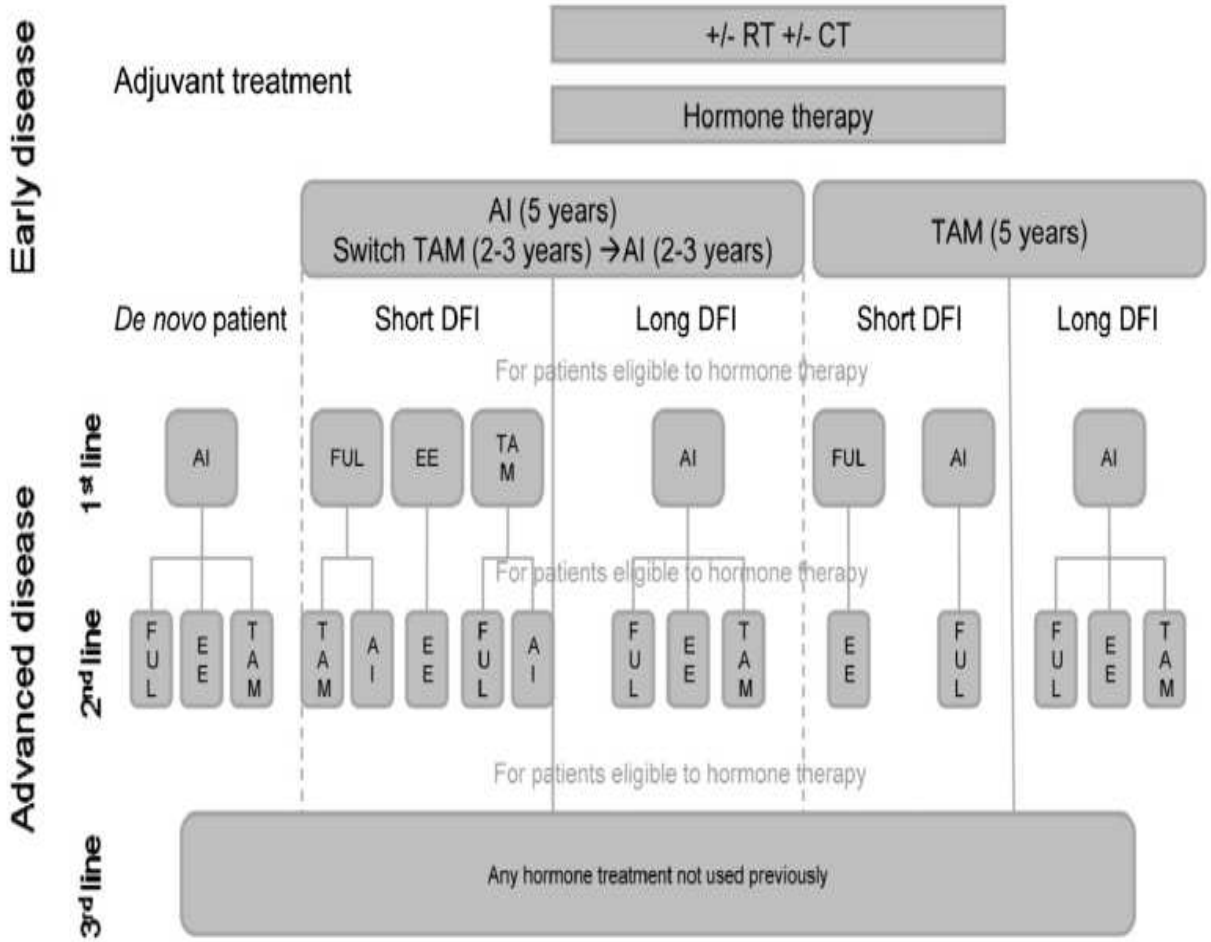


Fig. 2. Treatment algorithm for postmenopausal patients with hormone receptor-positive and HER2-negative breast cancer.* AI: aromatase inhibitor; CT: chemotherapy; DFI: disease-free interval; EE: exemestane plus everolimus; FUL: fulvestrant; HER2: human epidermal growth factor receptor type 2; HR: hormone receptor; RT: radiotherapy; TAM: tamoxifen. Short DFI: relapse occurs during adjuvant treatment administration or within the first 12 months after finishing it. Long DFI: relapse occurs after 12 months from the end of adjuvant hormonal treatment administration. *All treatment decisions should take into account the toxicity profile of different drugs and patient preferences.

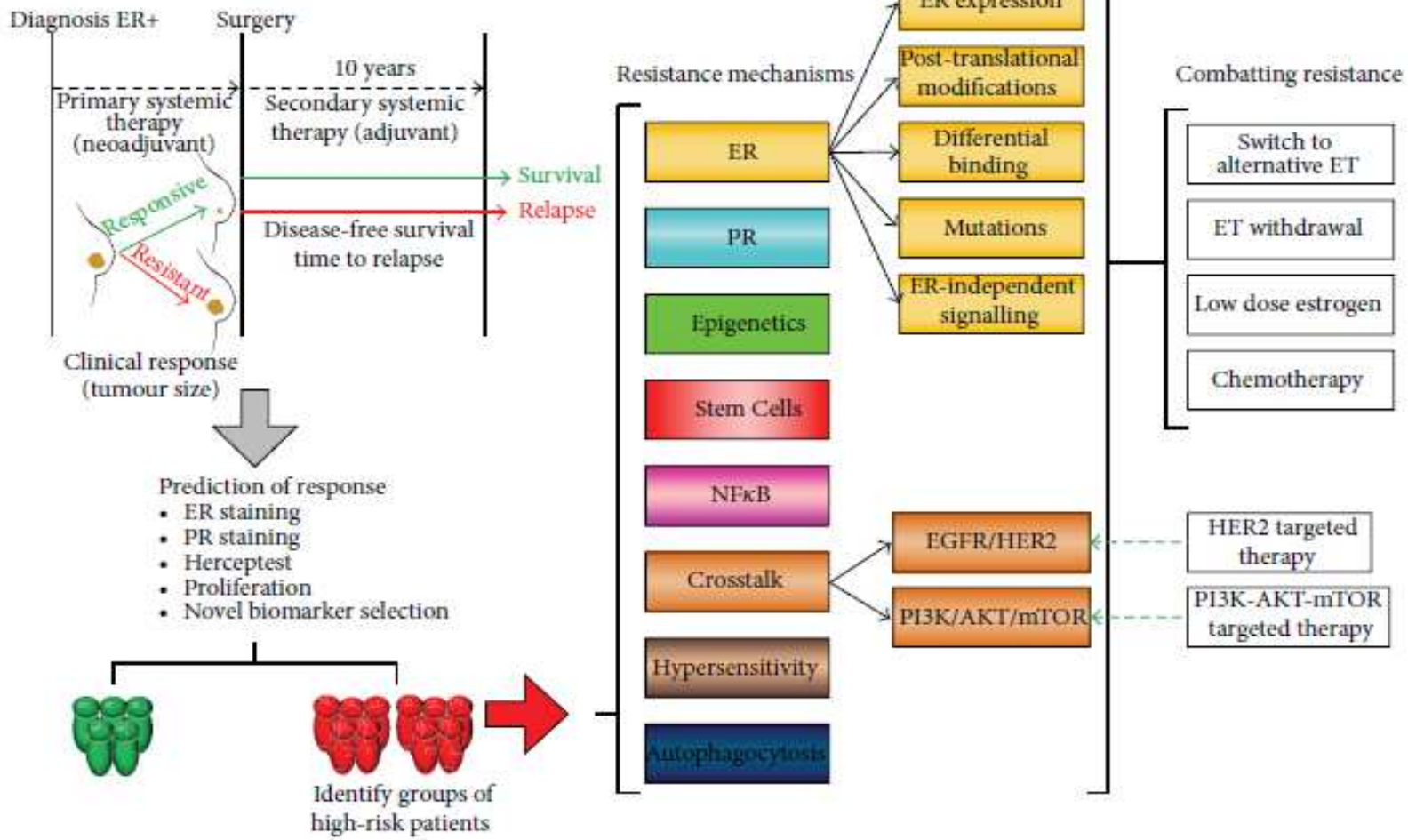
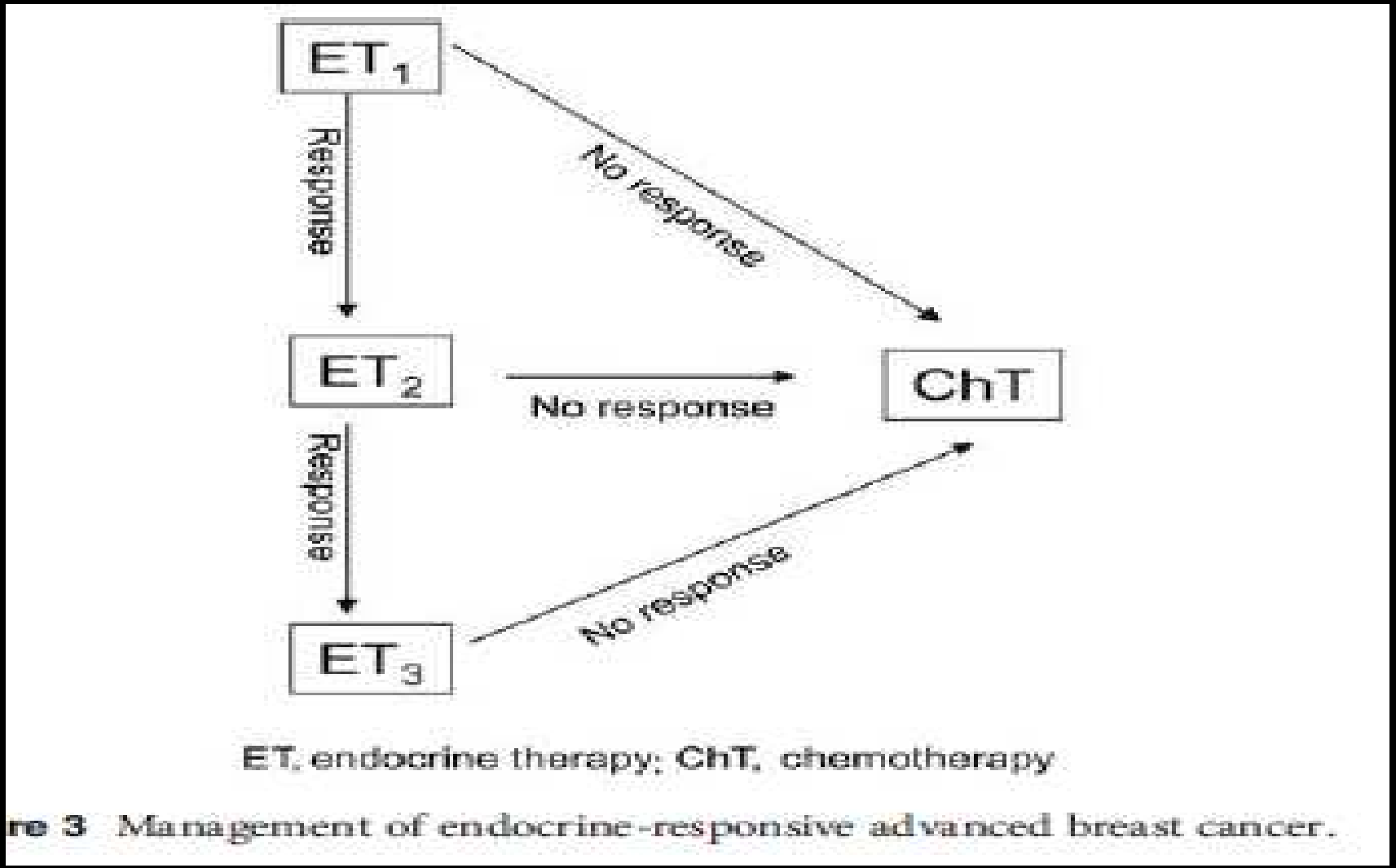


FIGURE 3: Summary of resistance in breast cancer showing the clinical manifestations of resistance in the neoadjuvant and adjuvant settings, the clinical need to accurately identify high risk patients, an overview of some of the best described resistance mechanisms and potential treatments and therapeutic strategies currently under investigation to combat resistance.

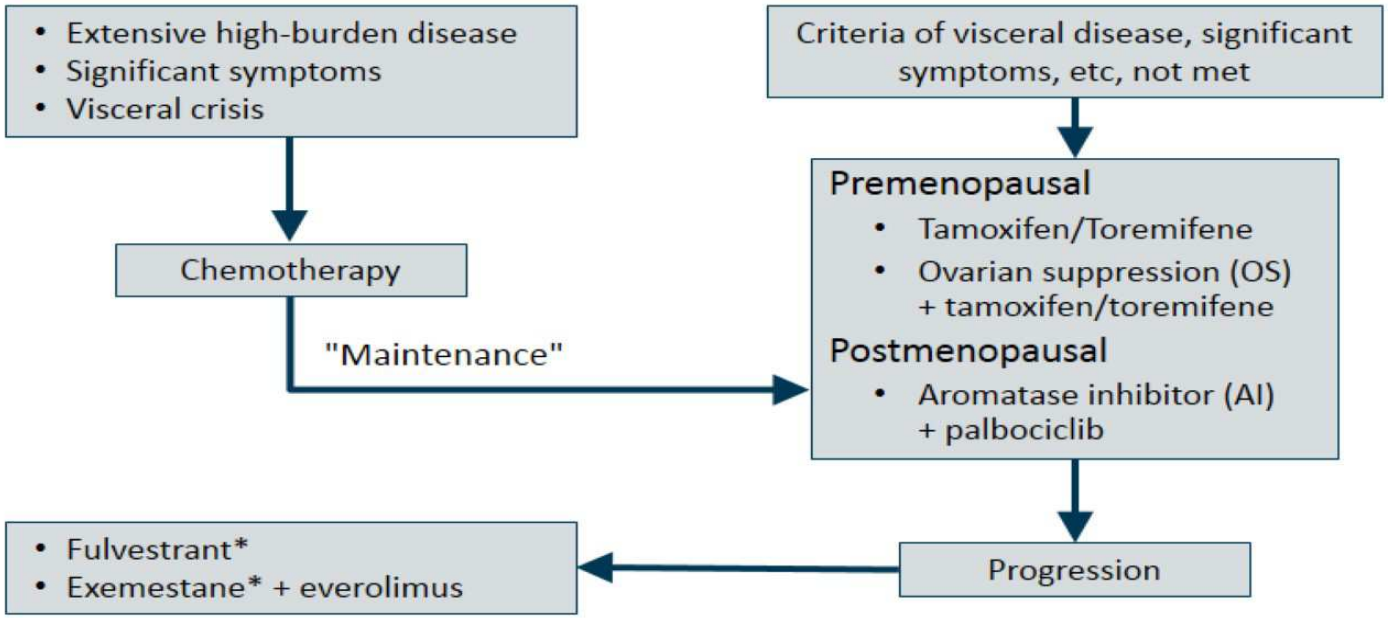


ET, endocrine therapy; ChT, chemotherapy

re 3 Management of endocrine-responsive advanced breast cancer.

Diagnosis and Treatment of HR+ mBC

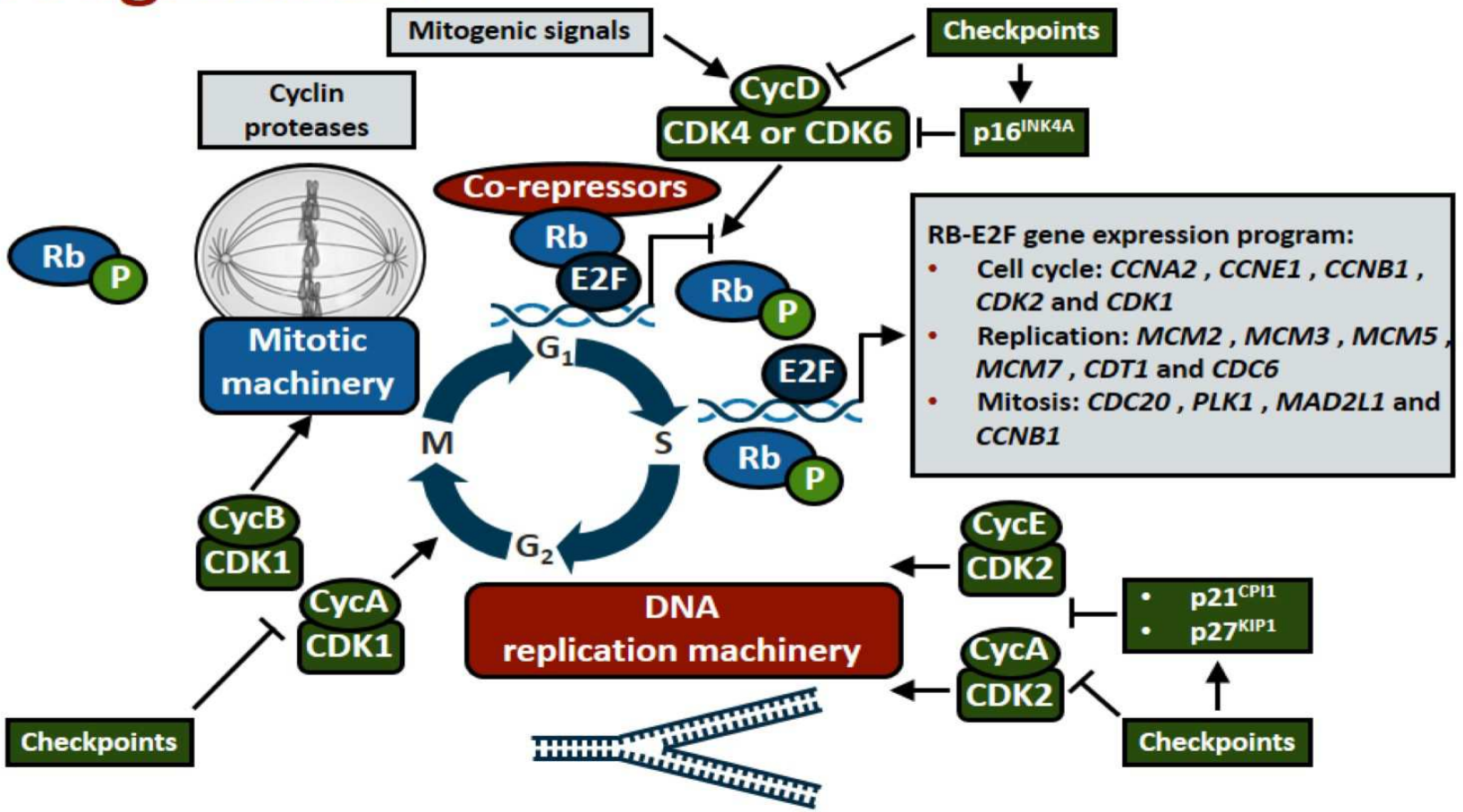
- Staging with CT chest/abdomen/pelvis and bone scan or PET/CT
- Confirmation of histology, if biopsy is feasible
- Determination of ER, PR, and HER2 status
- Review of prior treatments, comorbidities, preferences



*OS if **premenopausal**, and if so, can use AI after tamoxifen/toremifene.

Senkus E, et al. *Ann Oncol.* 2015;26:v8-v30.

Cyclin-Dependent Kinases and Cell Cycle Progression

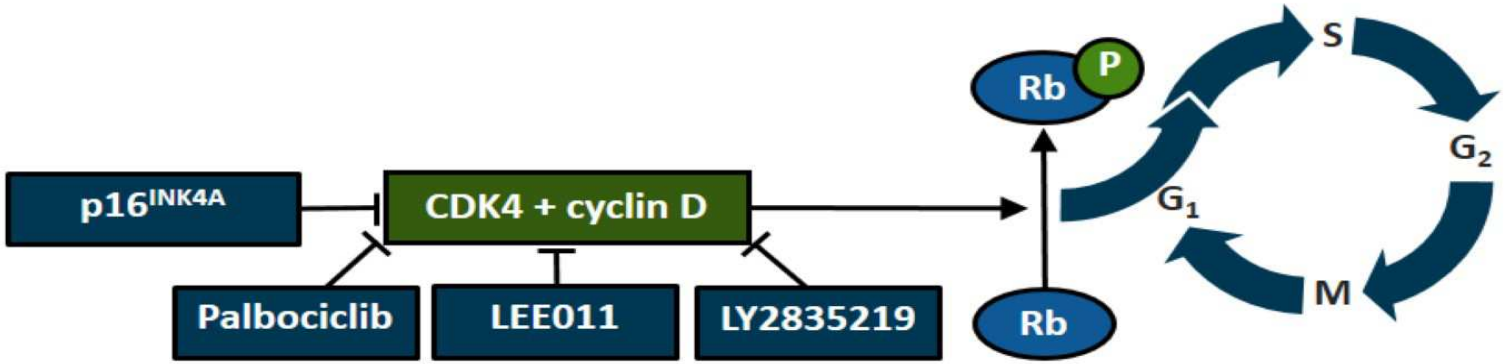


Asghar U, et al. *Nat Rev Drug Discov*. 2015;14:130-146.

CDK 4/6 Inhibition Is Most Effective in ER+/Luminal Breast Cancer Cells

Activity Is Initiated in an Rb-Dependent Fashion

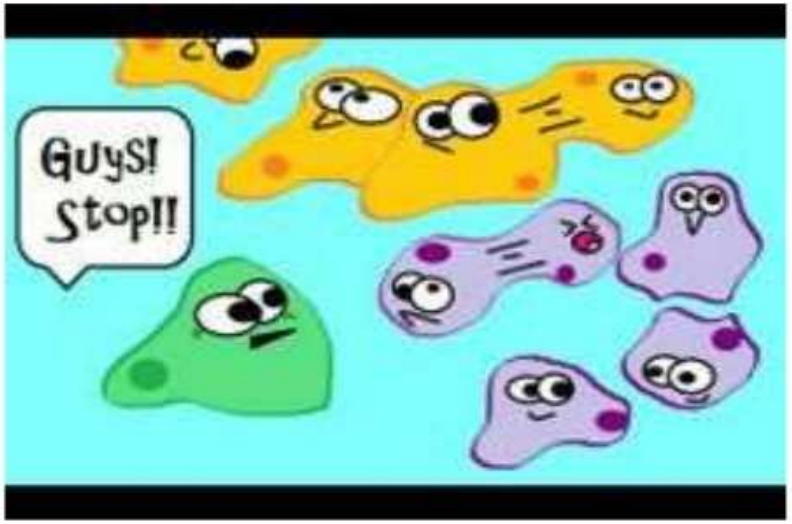
In vitro studies of cyclin D kinase inhibitor activity against ER+ luminal cell lines showed significant correlation between molecular subtype and sensitivity to the inhibitor. ($\chi^2 < 0.05$). The subtypes most sensitive to growth inhibition by the inhibitor were ER-positive.



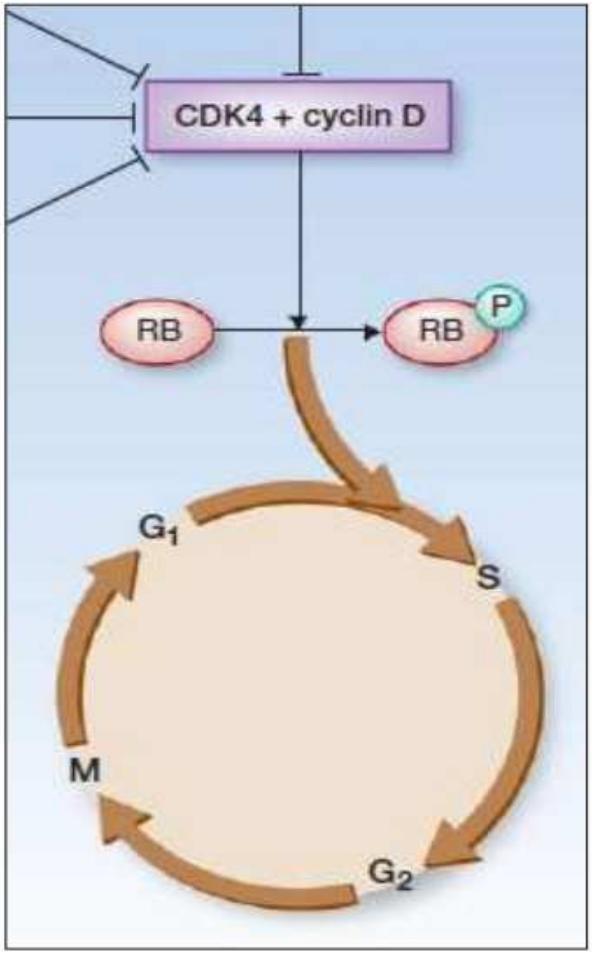
Finn RS, et al. *Breast Cancer Res*. 2009;11:R77; Dickson MA. *Clin Cancer Res*. 2014;20:3379-3383.

Cyclin Dependent Kinase (CDK 4/6) inhibition

- A classic feature of breast cancer is uncontrolled growth

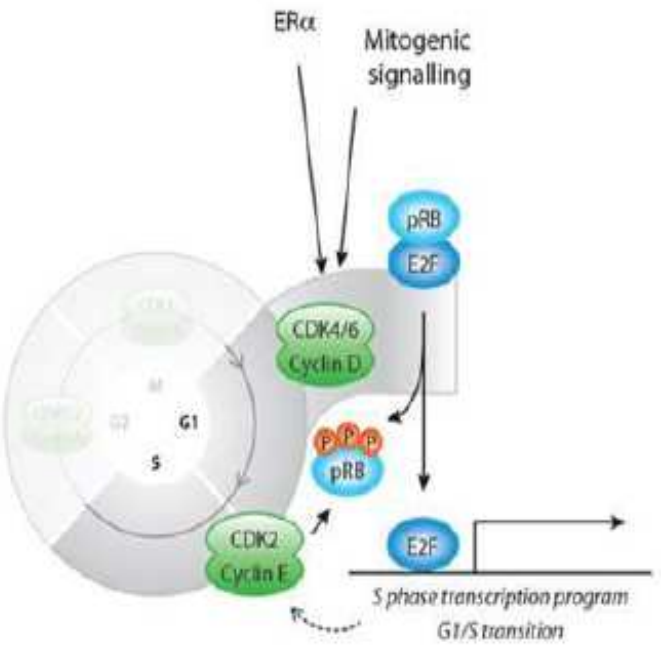


- In ER+ breast cancer, out-of-control growth may be due to a failure in the braking system: overactive CDK4/6



CDK4/6 in Breast Cancer

- **Resistance to endocrine therapy presents a major clinical challenge.**
- **The growth of HR+ breast cancer is dependent on Cyclin D1, a direct transcriptional target of ER.**
- **Cyclin D1 activates CDK 4/6 resulting in G1–S phase transition and entry into the cell cycle.[1]**
- **Cell line models of endocrine resistance remain dependent on Cyclin D1 and CDK4/6.[2,3]**

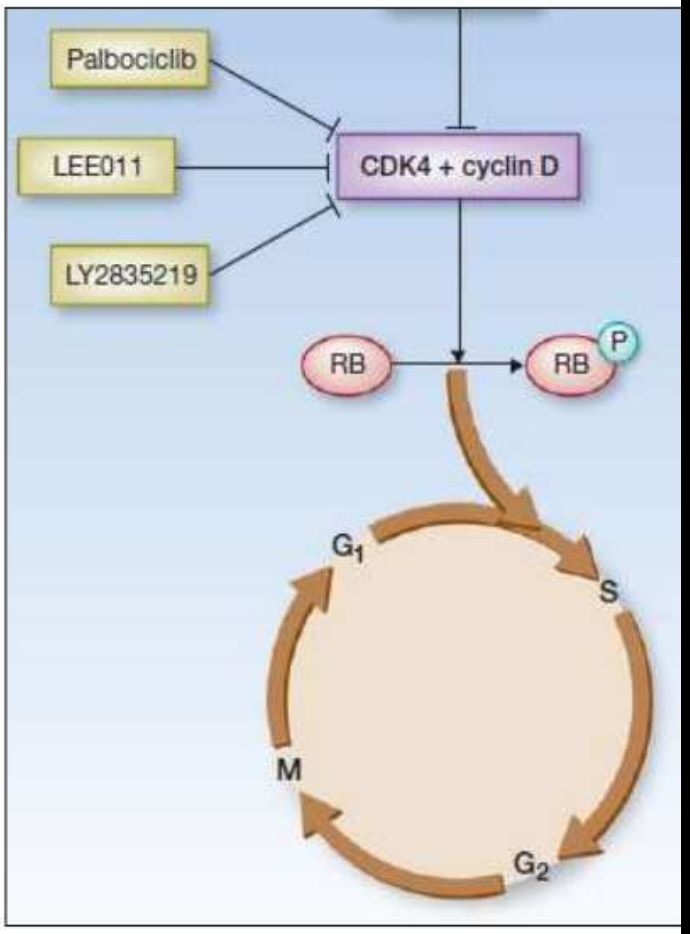


CDK=cyclin-dependent kinase; ER=estrogen receptor; HR+=hormone receptor-positive.

1. Asghar U, et al. *Nat Rev Drug Discov*. 2015;14:130-46.
2. Miller T, et al. *Cancer Discov*. 2011; 1:338-51.
3. Thangavel C, et al. *Endocr Relat Cancer*. 2011;18:333-45.

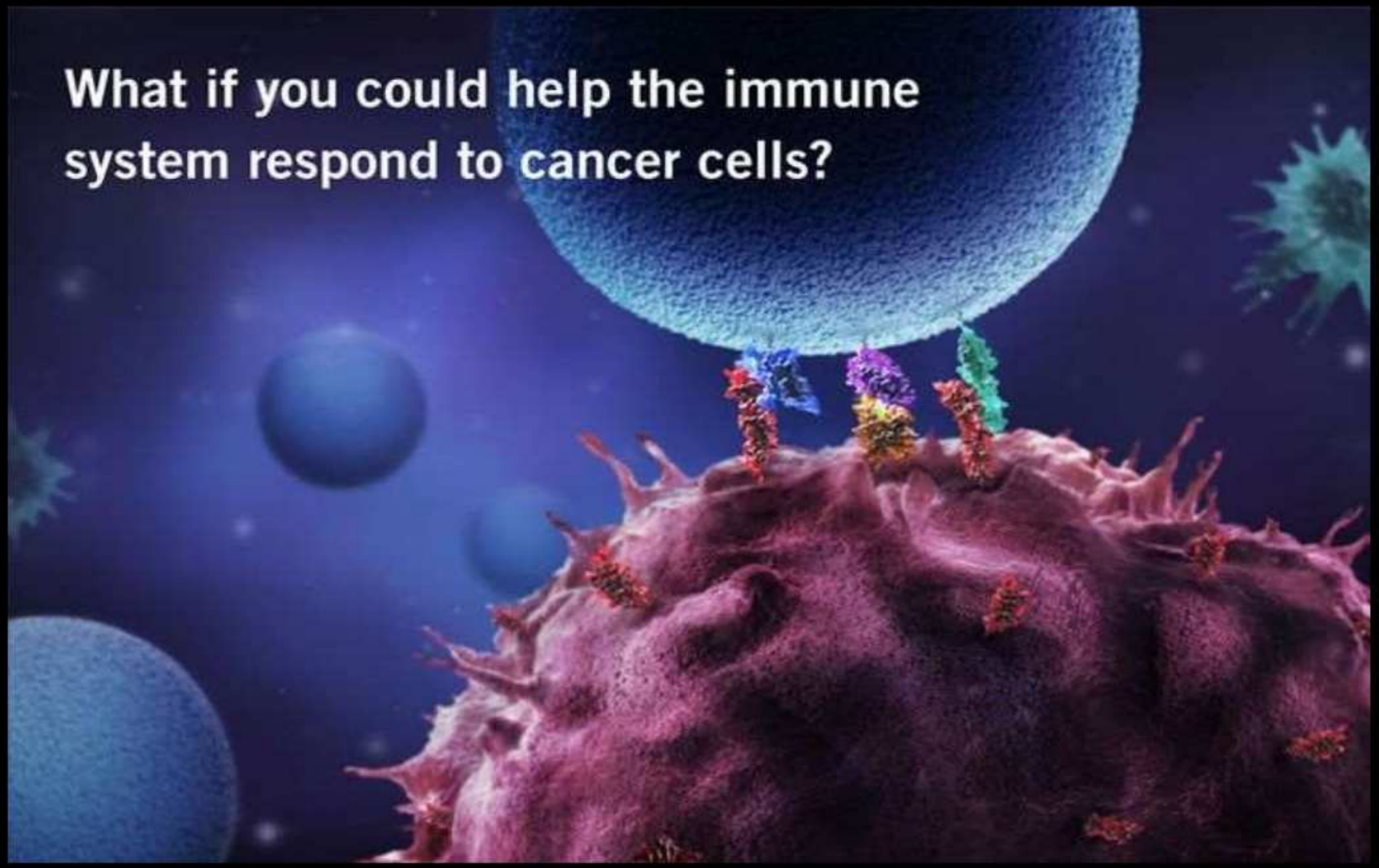
What's Hot for ER+ Breast Cancer?
CDK 4/6 inhibition

- CDK 4/6 Inhibition:
  - puts the brakes on cell growth
  - pushes cancer cells towards cell death



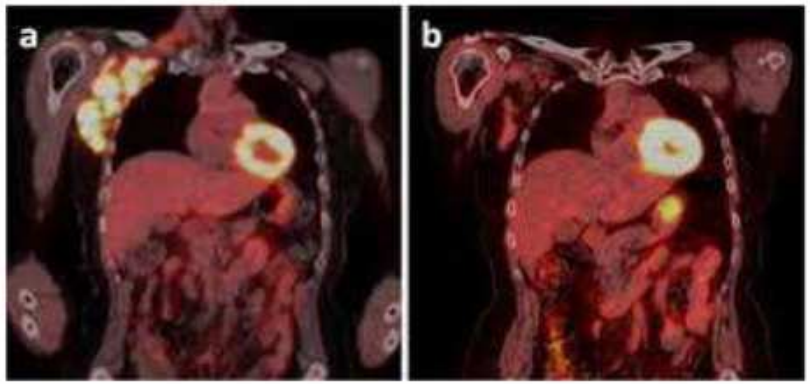
Palbociclib (Ibrance)

- Palbociclib: oral inhibitor of CDK 4/6
- Taken daily, 3 weeks on, 1 week off
- Most common toxicities: low white blood cell count (but no infections), fatigue, mild hair thinning


What if you could help the immune system respond to cancer cells?

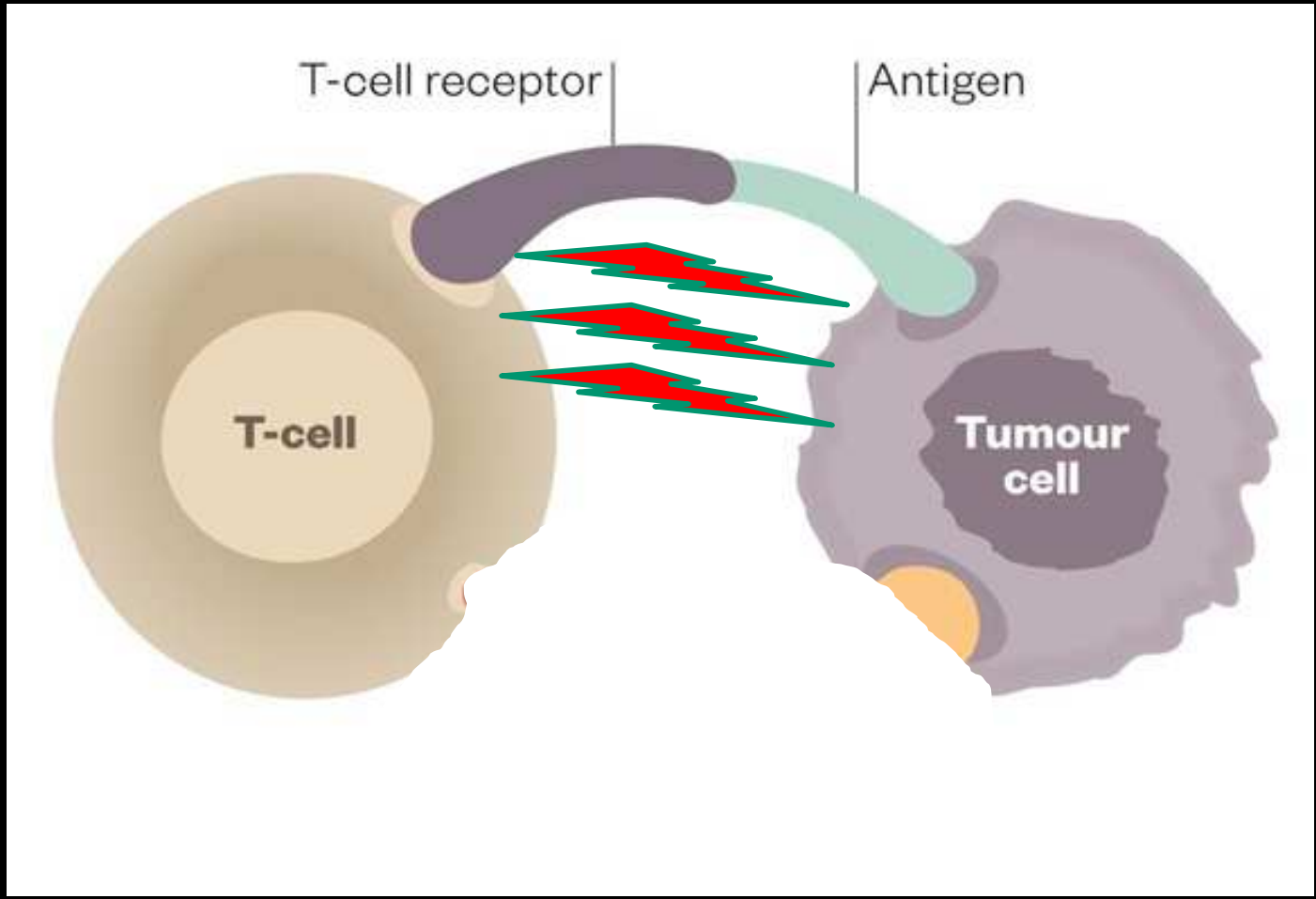
Immunotherapy in Cancer

- First generation (anti-CTLA4)
  - Ipilumumab: approved for melanoma
- Second generation (anti-PD1 or PDL1)
  - Nivolumab: approved for melanoma, lung cancer
  - Pembrolizumab: approved for melanoma

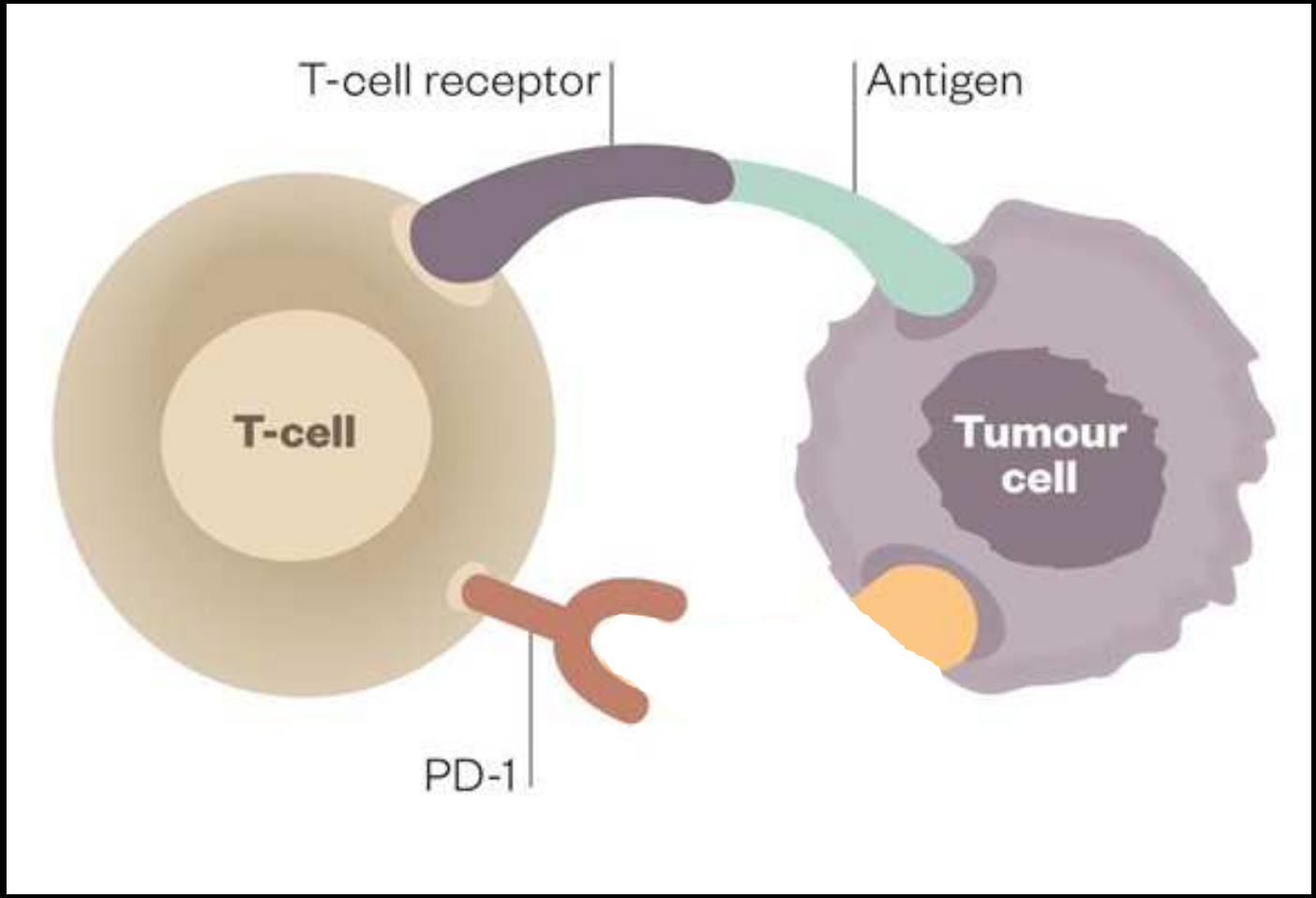


What about breast cancer?

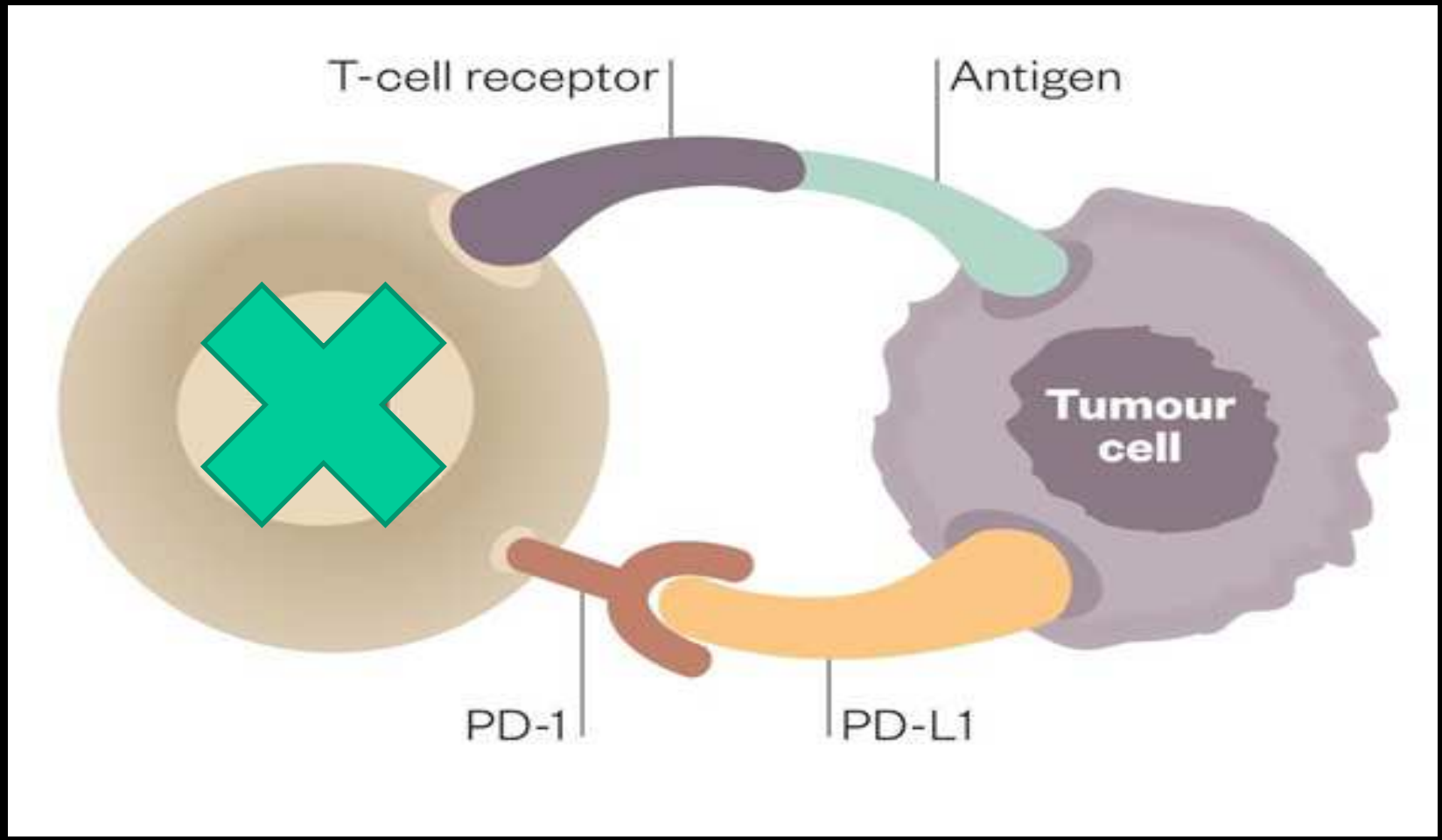
T-cells are designed to recognize and kill tumor cells



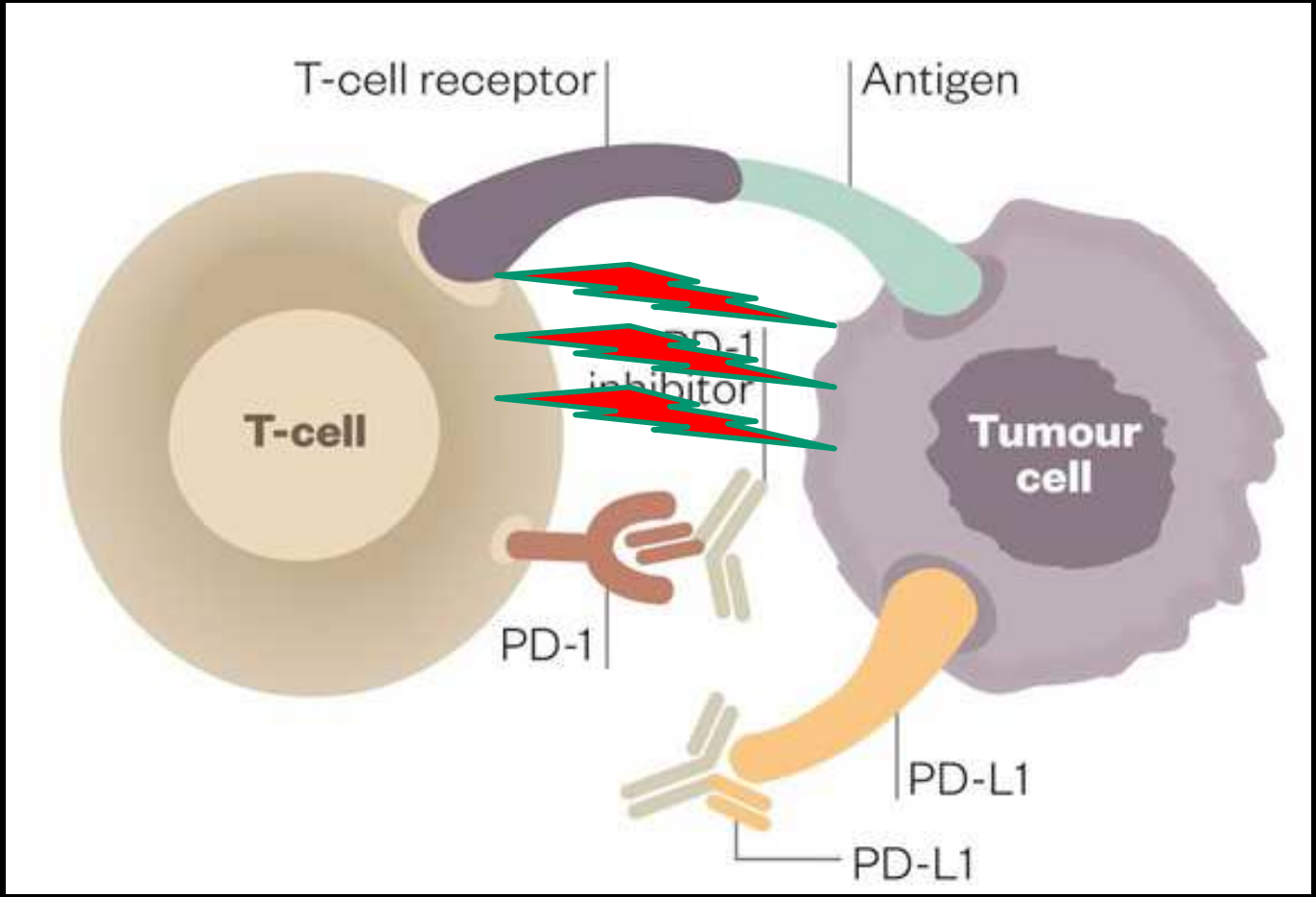
PD-1 acts as an “off-switch” for T-Cells



PD-1/PD-L1 inactivates T-Cells



Antibodies to PD-1 or PD-L1 prevent tumor cells from inactivating T-cells



Early PD1/PDL1 Experience in Breast Cancer

- Immune cells often found infiltrating triple negative breast cancer – potentially indicates candidacy for immune therapy!
- Two Phase 1 trials completed in patients with advanced triple negative breast cancer
  - More response seen than expected with chemotherapy
  - Will tolerated
- Phase 2 and 3 trials opening now
- Many questions need to be figured out:
  - Is immunotherapy for everyone or can we find tumor markers that predict who will get more benefit?
  - Do we need to test tumor for PDL1
  - Will immunotherapy have benefit in other types of breast cancer, ie HR+, HER2+?

New Concepts

- Triple Negative
- Chemotherapy resistance
- Hormonal resistance
- Dose Dense Schedule
- Metronomic Therapy

Major Problems

- Drug resistance
- Brain metastases
- Treatment-related toxicities (includes venous access)
- Cost of therapy

Thank you for your patient hearing