

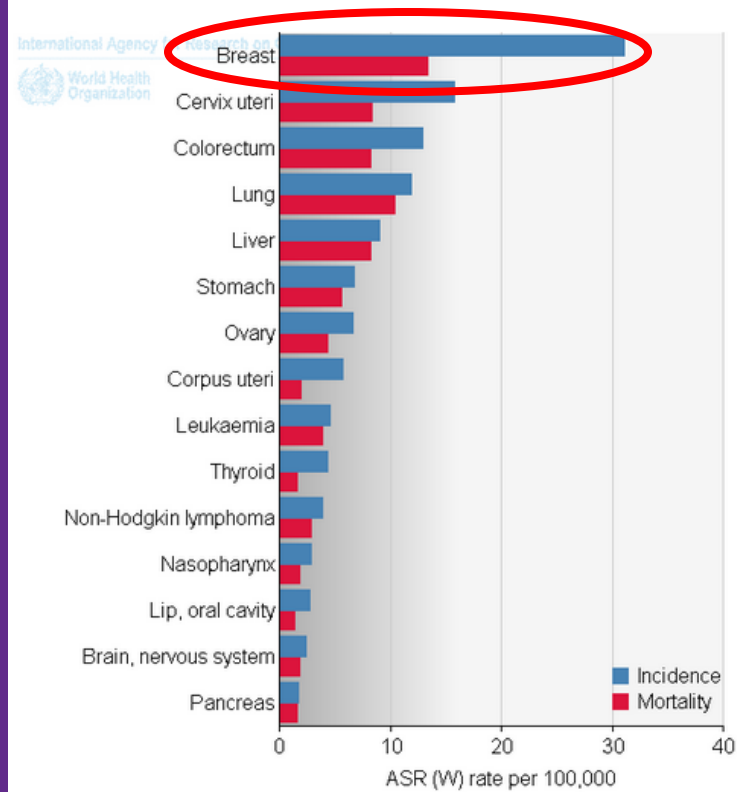
MANAGEMENT OF HER2-POSITIVE BREAST CANCER

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2nd Symposium Biomolecular Update On Cancer
May 18, 2013

- Introduction
- HER2-Positive Breast Cancer Treatment Guidelines
- Mechanism of Action Trastuzumab
- Trastuzumab as Standard of Care in EBC
- Trastuzumab as Standard of Care in MBC

Introduction

Estimated age-standardised incidence and mortality rates: women



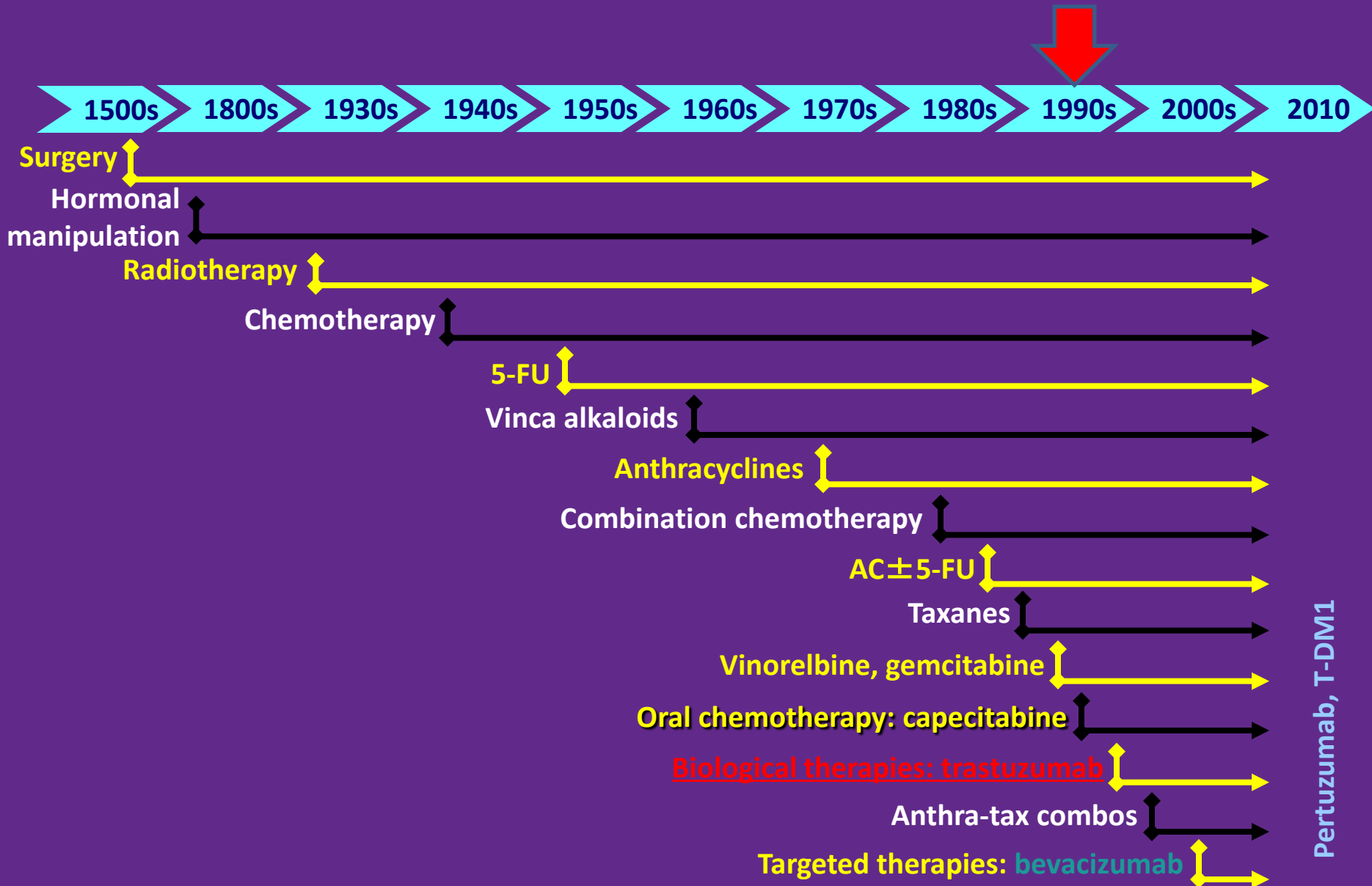
SOUTH-EASTERN ASIA

Estimated incidence, mortality and 5-year prevalence: women

Cancer	Incidence			Mortality			5-year prevalence		
	Number	(%)	ASR (W)	Number	(%)	ASR (W)	Number	(%)	Prop.
Lip, oral cavity	7294	1.9	2.7	3646	1.5	1.4	16186	1.8	7.7
Nasopharynx	7941	2.0	2.8	4921	2.0	1.8	20667	2.2	9.8
Other pharynx	2233	0.6	0.8	1663	0.7	0.6	5006	0.5	2.4
Oesophagus	3810	1.0	1.4	3374	1.4	1.3	3537	0.4	1.7
Stomach	18353	4.7	6.7	15303	6.3	5.6	23789	2.6	11.3
Colorectum	34523	8.9	12.9	22154	9.1	8.2	75564	8.2	35.9
Liver	23968	6.2	9.0	22215	9.2	8.3	14799	1.6	7.0
Gallbladder	3639	0.9	1.4	3126	1.3	1.1	4181	0.5	2.0
Pancreas	4672	1.2	1.8	4355	1.8	1.6	3298	0.4	1.6
Larynx	1157	0.3	0.4	655	0.3	0.2	2949	0.3	1.4
Lung	31651	8.1	11.9	27858	11.5	10.4	26676	2.9	12.7
Melanoma of skin	1858	0.5	0.8	1861	0.8	0.7	3618	0.4	1.7
Breast	86940	22.4	31.0	36775	15.2	13.4	308091	33.5	146.5
Cervix uteri	44367	11.4	15.8	22495	9.3	8.3	135277	14.7	64.3
Corpus uteri	15197	3.9	5.7	5146	2.1	2.0	57950	6.3	27.6
Ovary	18580	4.8	6.7	11913	4.9	4.4	47163	5.1	22.4
Kidney	4150	1.1	1.5	2722	1.1	1.0	8337	0.9	4.0
Bladder	3553	0.9	1.3	1861	0.8	0.7	9251	1.0	4.4
Brain, nervous system	6744	1.7	2.4	5102	2.1	1.8	9612	1.0	4.6
Thyroid	12524	3.2	4.3	4160	1.7	1.6	47392	5.2	22.5
Hodgkin lymphoma	1555	0.4	0.5	990	0.4	0.3	4256	0.5	2.0
Non-Hodgkin lymphoma	10683	2.7	3.9	7888	3.3	2.9	18082	2.0	8.6
Multiple myeloma	2052	0.5	0.8	1733	0.7	0.7	3618	0.4	1.7
Leukaemia	12407	3.2	4.5	10815	4.5	3.9	11072	1.2	5.3
All cancers excl. non-melanoma skin cancer	388757	100.0	141.6	242464	100.0	89.4	918832	100.0	437.0

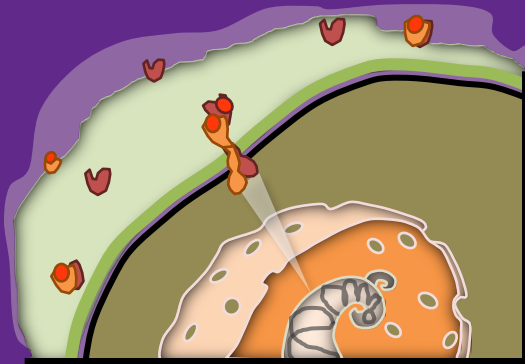
*Incidence and mortality data for all ages. 5-year prevalence for adult population only.
ASR (W) and proportions per 100,000.*

Key milestones in breast cancer treatment

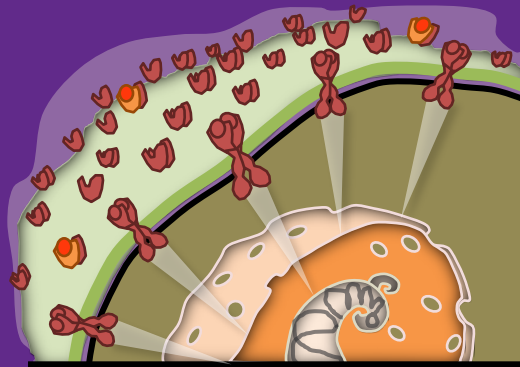


HER2 Overexpression in Breast Cancer

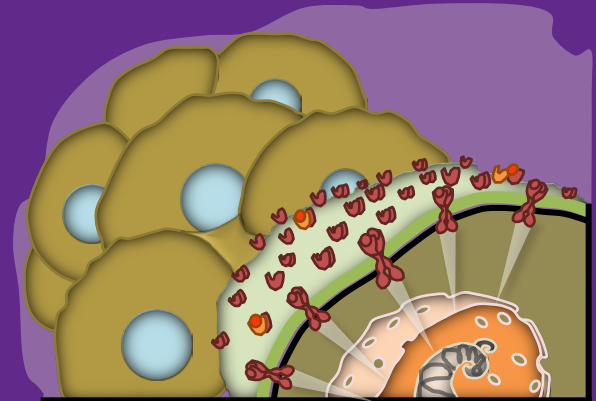
HER2 is overexpressed in
~ 25% of breast cancers



Normal (1x)
~ 25,000-50,000 HER2
receptors



**Overexpressed
HER2 (10-100x)**
up to ~ 2,000,000
HER2 receptors



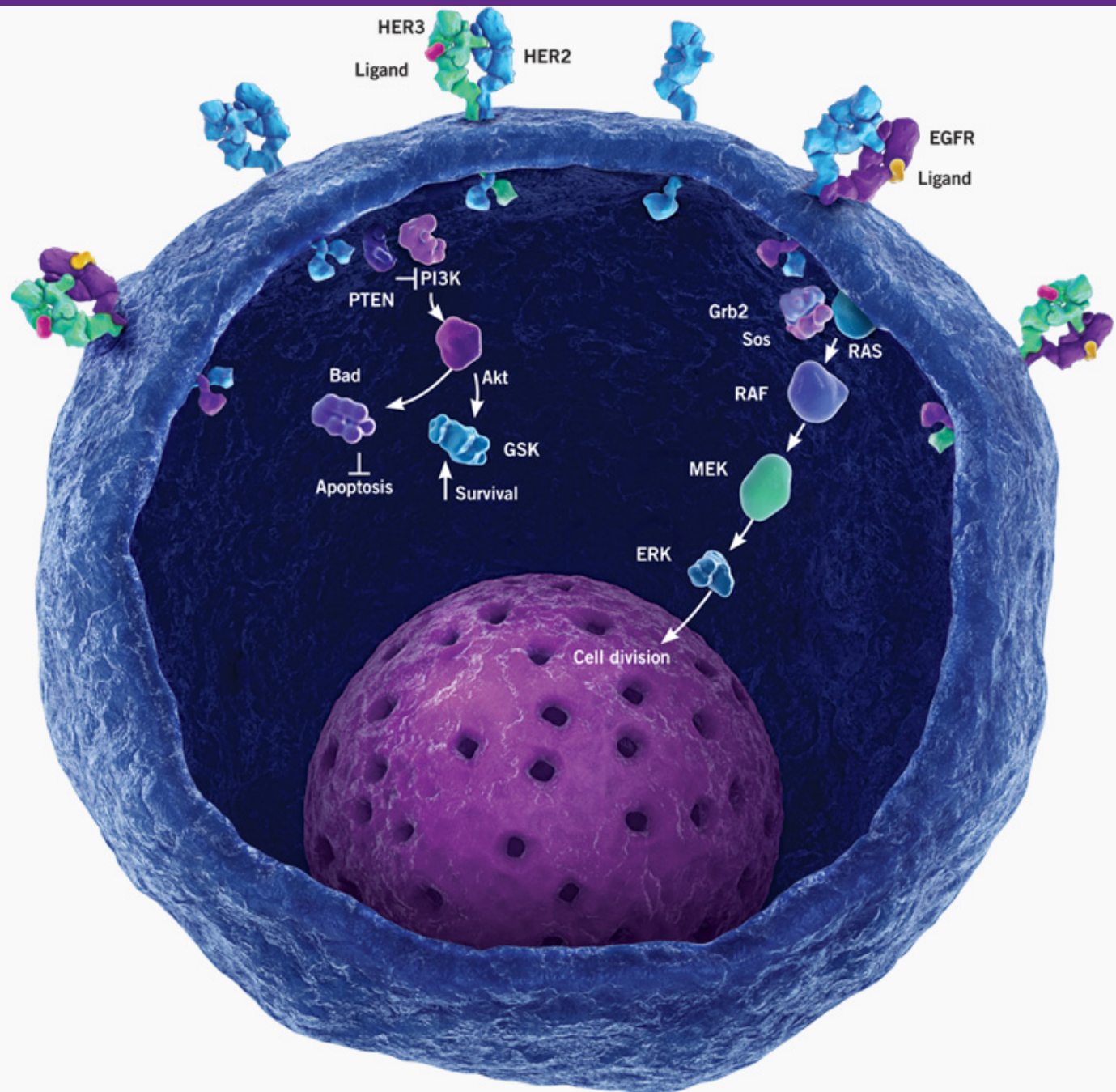
Excessive cellular division

Pegram MD, et al. Cancer Treat Res. 2000;103:57-75.

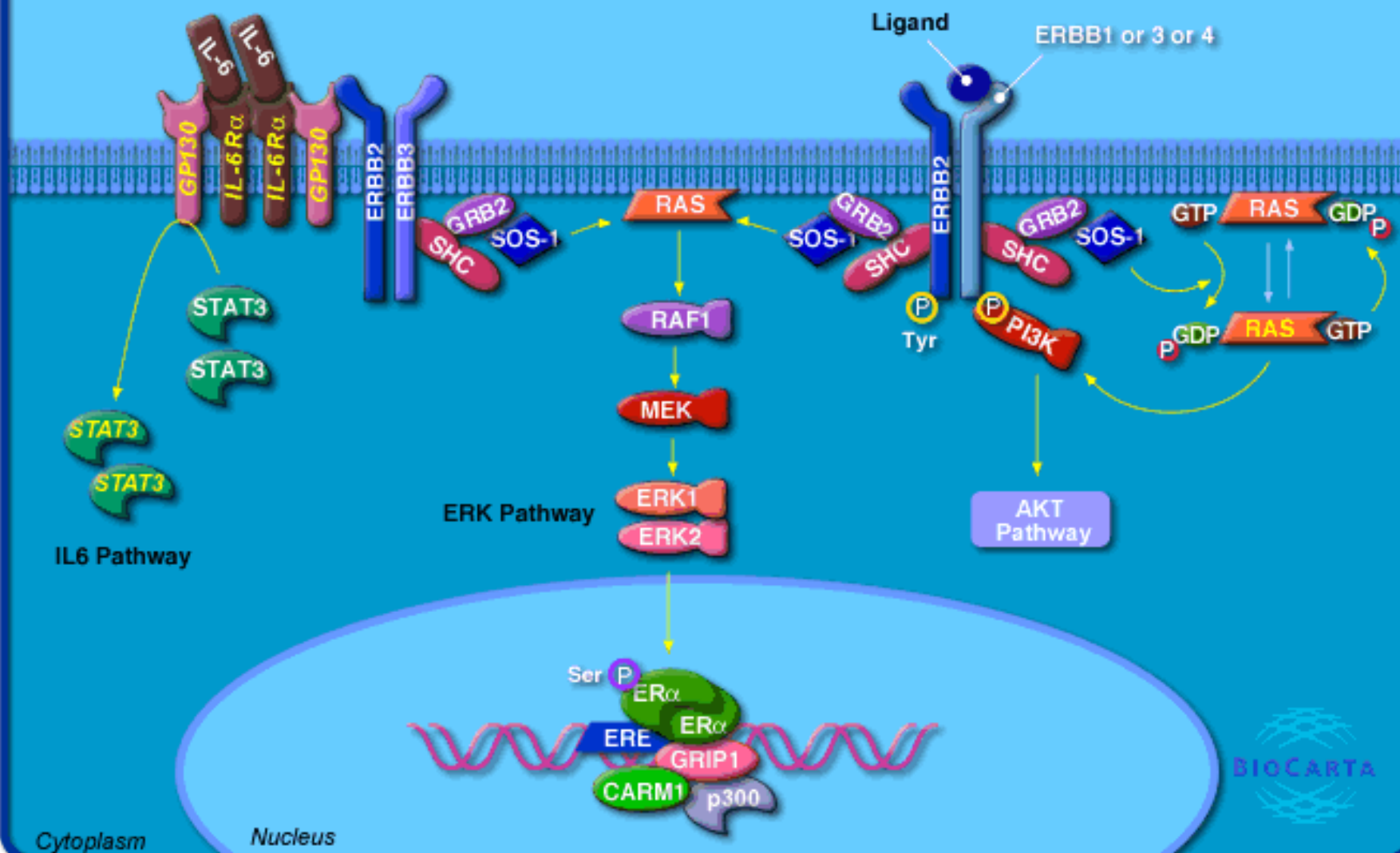
Ross JS, et al. Am J Clin Pathol. 1999;112(suppl 1):S53-S71.

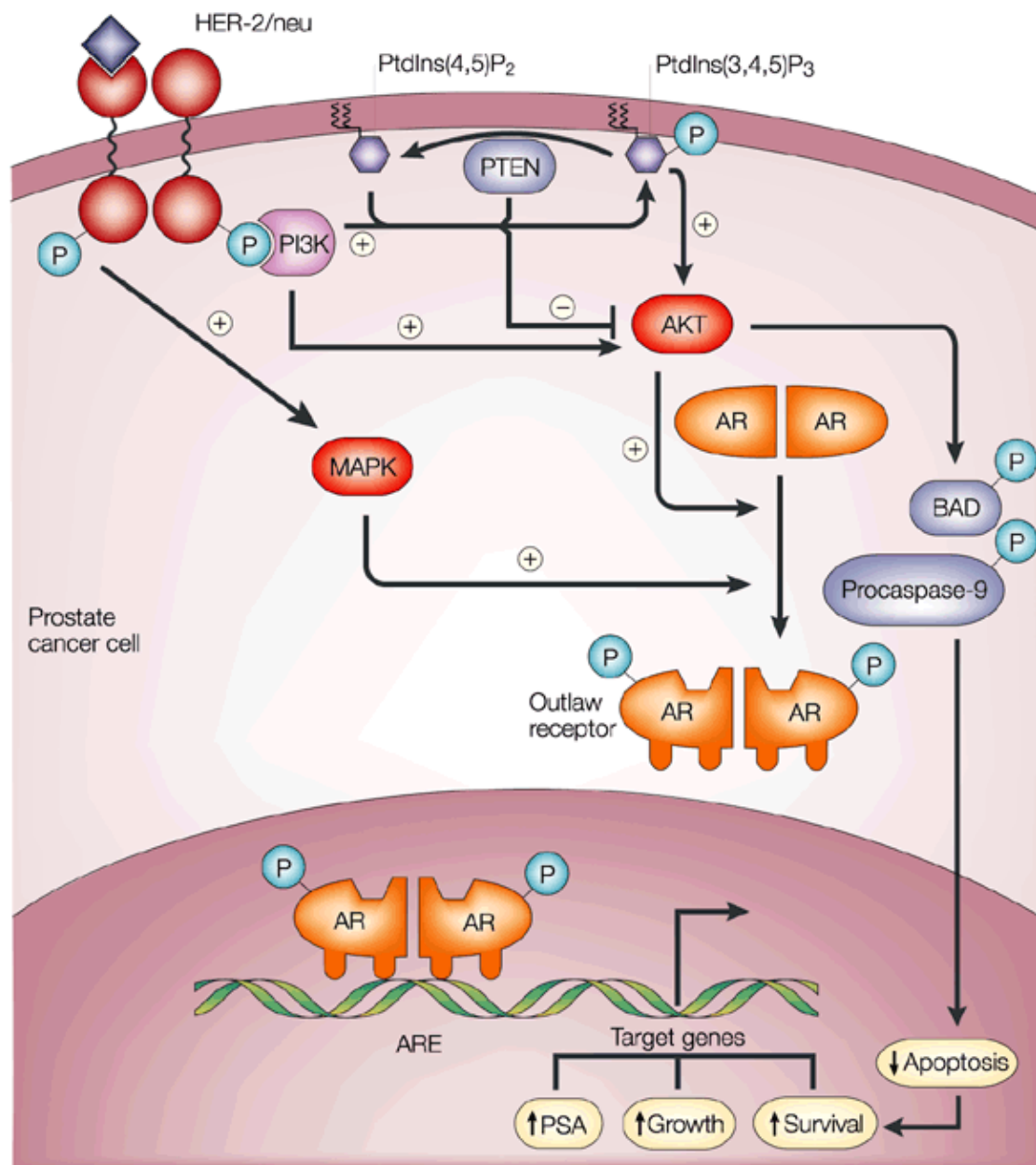
Slamon DJ, et al. Science. 1987;235:177-182.

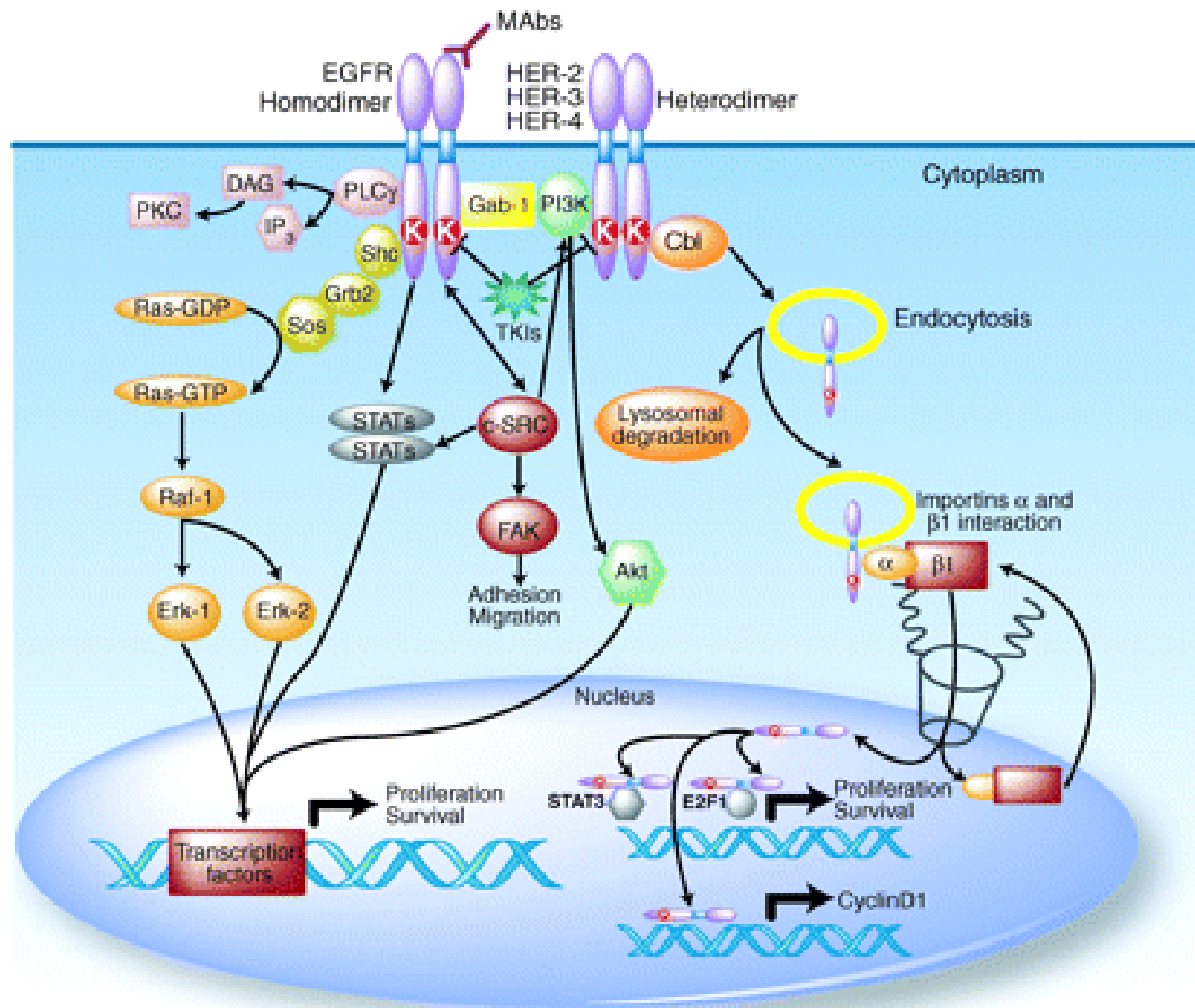
Mechanism of Action Trastuzumab

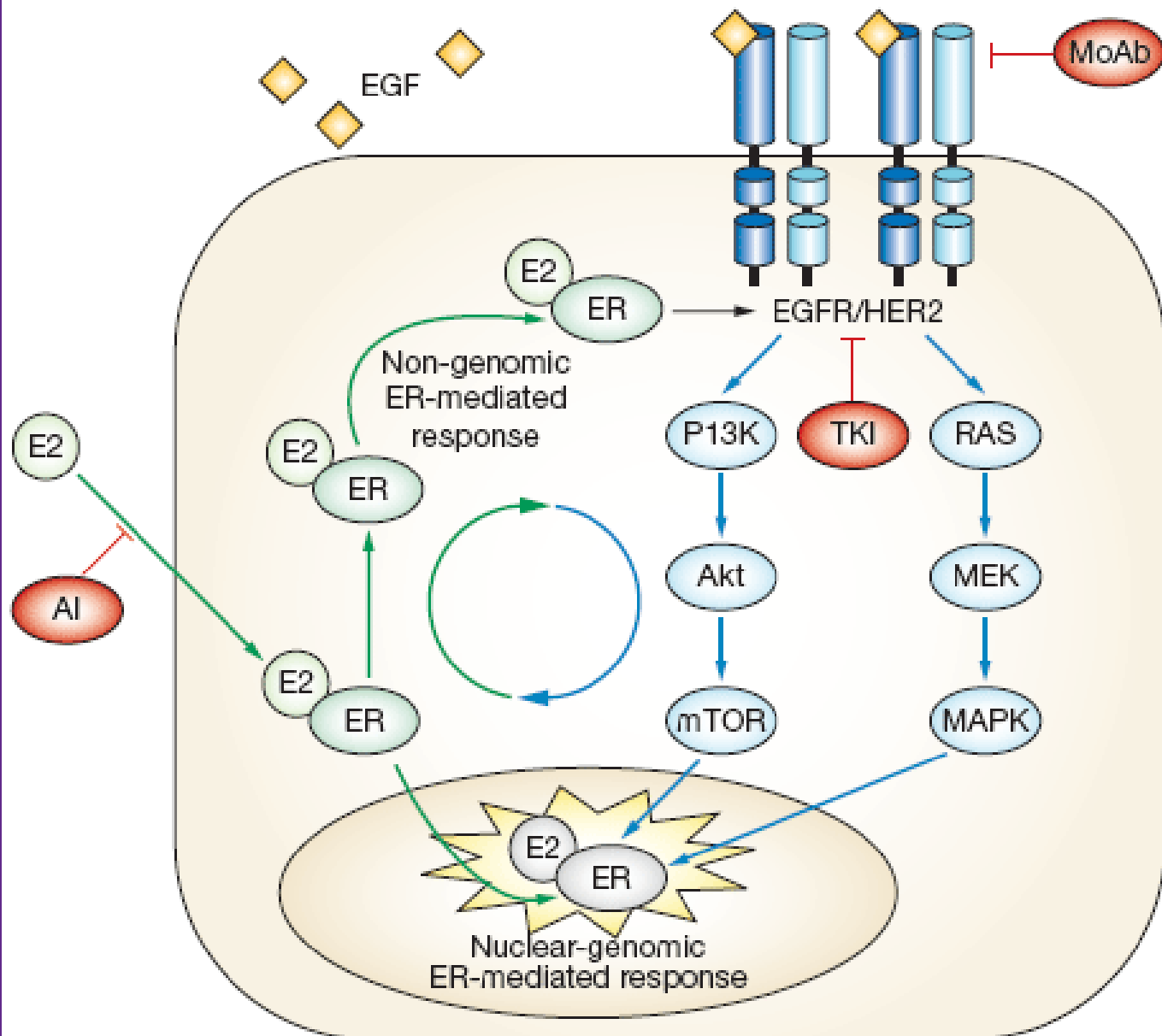


Extracellular



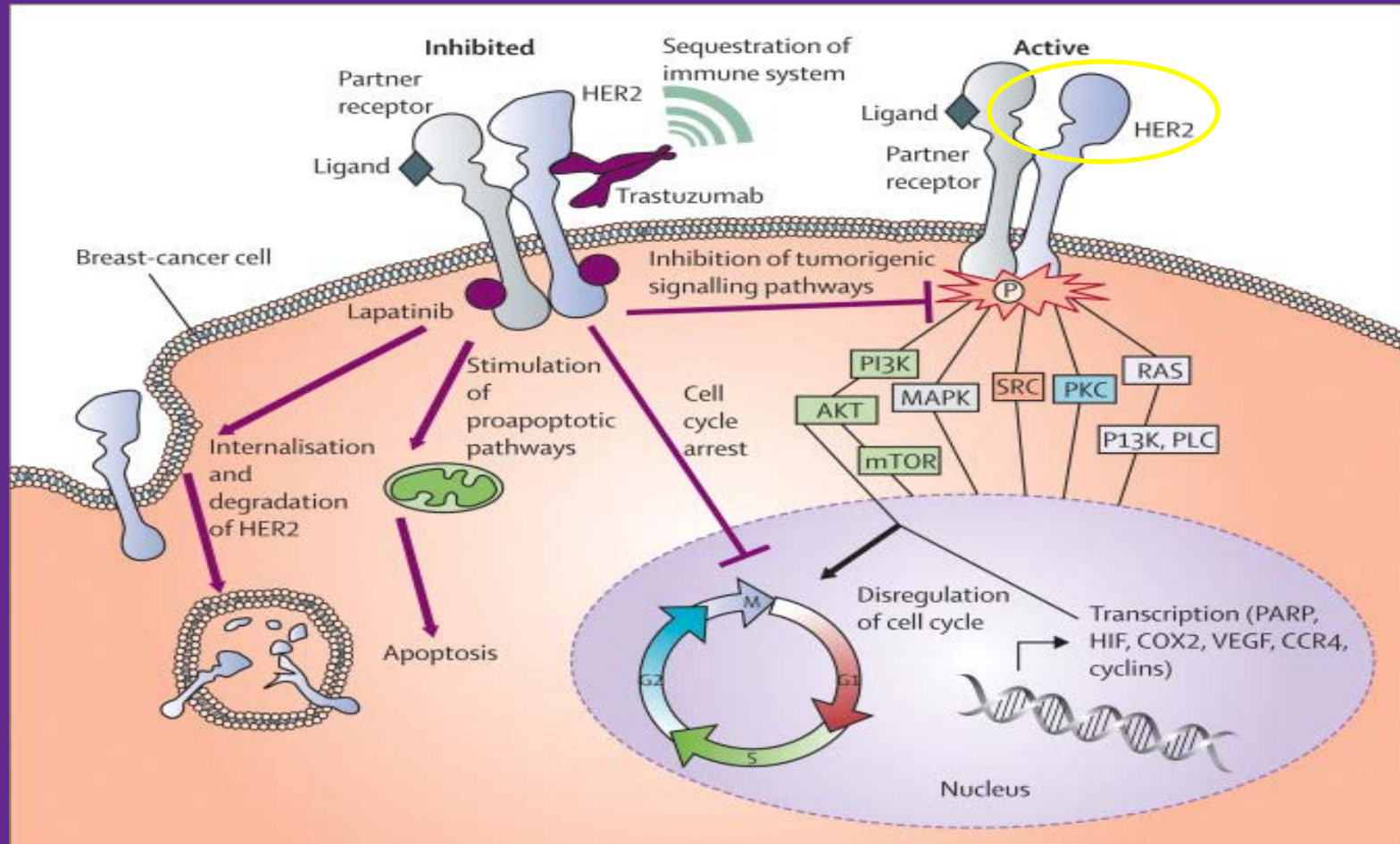




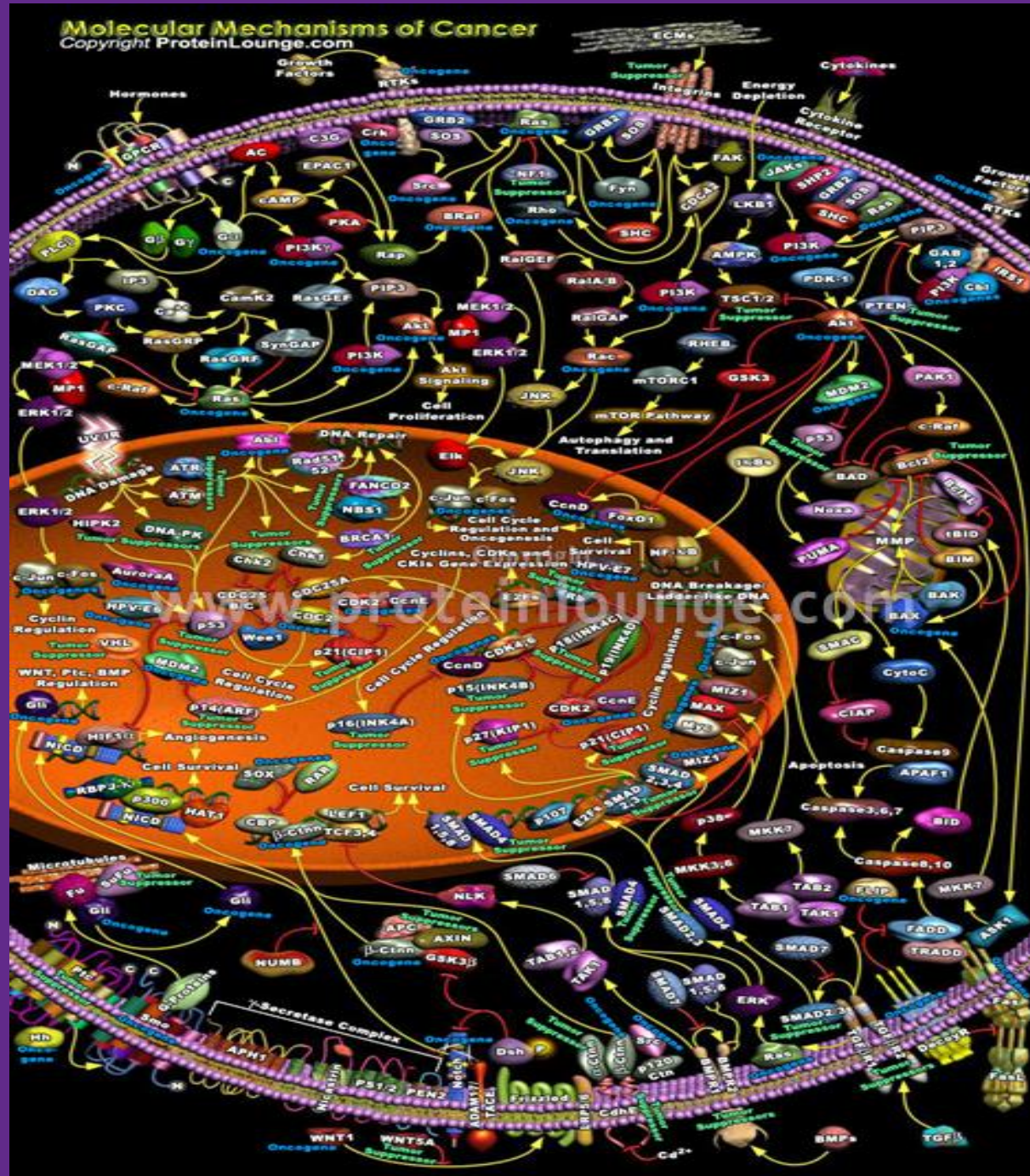


TRASTUZUMAB

- A recombinant, humanized monoclonal antibody against the extracellular domain of the HER2 protein







HER2-Positive Breast Cancer Treatment Guidelines

Trastuzumab recommended across international guidelines

Guideline	Early Breast Cancer ^{1,2,4}		Metastatic Breast Cancer ^{1,2,3}
	Adjuvant Therapy	Recommended Patients	
Consensus St. Gallen 2013	1 year of Trastuzumab	<ul style="list-style-type: none"> Her2-positive tumours ≥1 cm Her2-positive node negative tumours 0.5-1.0 cm (pT1b) Excludes : Her2-positive node negative tumours 0.1-0.5 cm (pT1a) 	
ESMO	1 year of Trastuzumab	<ul style="list-style-type: none"> Her2-positive tumours ≥1 cm Use of Herceptin® (Trastuzumab) should be discussed with patients with small node negative her2-positive breast cancer. 	PATIENTS with HER2-POSITIVE BREAST CANCER : <ul style="list-style-type: none"> Patients should be treated with Trastuzumab with or without chemotherapy. Trastuzumab should be offered early to all HER2-Positive MBC Patients. Continuing Trastuzumab, associated with a different chemotherapy regimen, after the first disease progression is superior to the discontinuation of this agent. Combination of Trastuzumab and lapatinib seems to be superior to lapatinib monotherapy in patients progressing on anthracyclines, taxanes, and trastuzumab.
NCCN 2013	1 year of Trastuzumab	<ul style="list-style-type: none"> Category 1 recommendation : patients with her2-positive tumours >1cm. Category 2A recommendation : patients with her2-positive node-negative tumours 0.6-1cm Her2-positive node negative pT1a or pT1b tumours : use of Herceptin® (Trastuzumab) to be based on individual benefit:risk. 	PREFERRED FIRST-LINE AGENTS FOR HER2-POSITIVE DISEASE : Trastuzumab with : <ul style="list-style-type: none"> Paclitaxel ± Carboplatin Docetaxel Vinorelbine Capecitabine PREFERRED AGENTS FOR TRASTUZUMAB-EXPOSED HER2-POSITIVE DISEASE <ul style="list-style-type: none"> Lapatinib + Capecitabine Trastuzumab + Capecitabine Trastuzumab + Lapatinib without cytotoxic therapy Trastuzumab + other first line agents

Trastuzumab as Standard of Care in HER2 Positive EBC

PHARE: 6 vs 12 Months of Adjuvant Trastuzumab in HER2+ EBC

- Subset analysis of the randomized, noninferiority phase III trial

Stratified by ER status (positive vs negative), chemotherapy + trastuzumab timing (concurrent vs sequential)



Patients with HER2-positive invasive early breast cancer who underwent at least 4 cycles of (neo)adjuvant chemotherapy + trastuzumab initiation in the previous 12 mos (N = 3384)



**Trastuzumab for 12 Mos
(trastuzumab continued for 6 more mos)
(n = 1690)**

**Trastuzumab for 6 Mos
(trastuzumab stopped)
(n = 1690)**

Left ventricular ejection fraction values every 3 mos; mammography every 6 mos up to 60 mos

PHARE: DFS After 6 vs 12 Months of Adjuvant Trastuzumab in HER2+ EBC

- DFS HR for **12 vs 6 mos of trastuzumab** was 1.28 (95% CI: 1.05-1.56; $P = .29$), with 95% CI that included prespecified noninferiority margin of 1.15, making results inconclusive regarding noninferiority

DFS Probability, %	Trastuzumab for 12 Mos (n = 1690)	Trastuzumab for 6 Mos (n = 1690)
1 yr	97.0	95.5
2 yrs	93.8	91.2
3 yrs	90.7	87.8
4 yrs	87.8	84.9

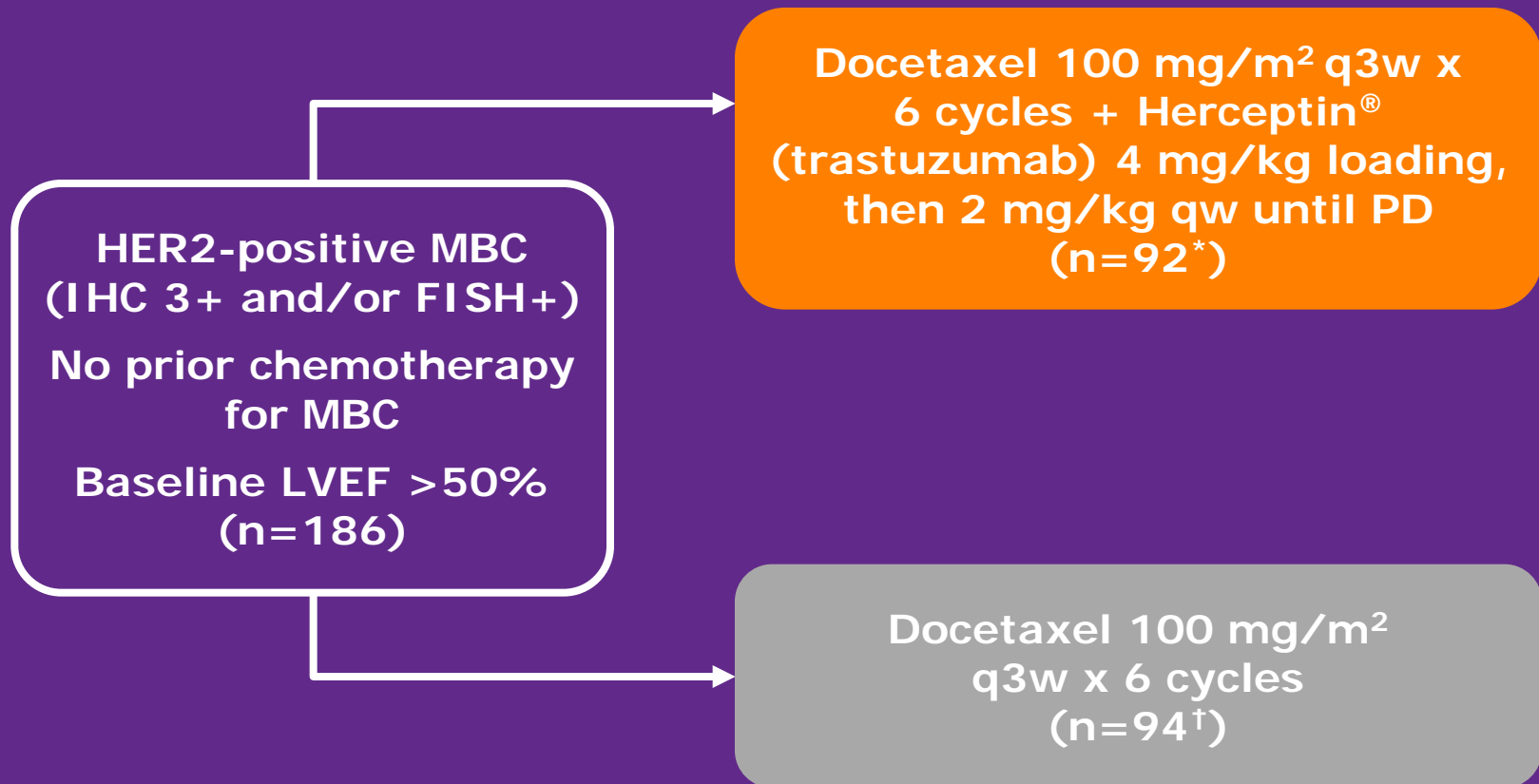
- Patients receiving **six months of Trastuzumab had a 28% higher risk of dying** or their cancer returning compared to patients receiving one year of Herceptin (HR=1.28; 95%CI: 1.05-1.56)

Optimal Duration of Trastuzumab in HER2-positive Early Breast Cancer

- Results from the PHARE trial suggest that 12 months of trastuzumab is preferred over 6 months.
- Results from the HERA trial suggest that 1 year of trastuzumab is as beneficial as 2 years of treatment.
- Trastuzumab given for 1 year or longer reduces the risk of relapse and death by at least 24%, based on HERA data.
- Cardiotoxicity was generally increased with longer durations of treatment in each trial, but in HERA, the rate of severe heart failure and cardiac death was < 1%.

Trastuzumab as Standard of Care in HER2 Positive MBC

1L MBC Trastuzumab + Docetaxel : M77001 trial



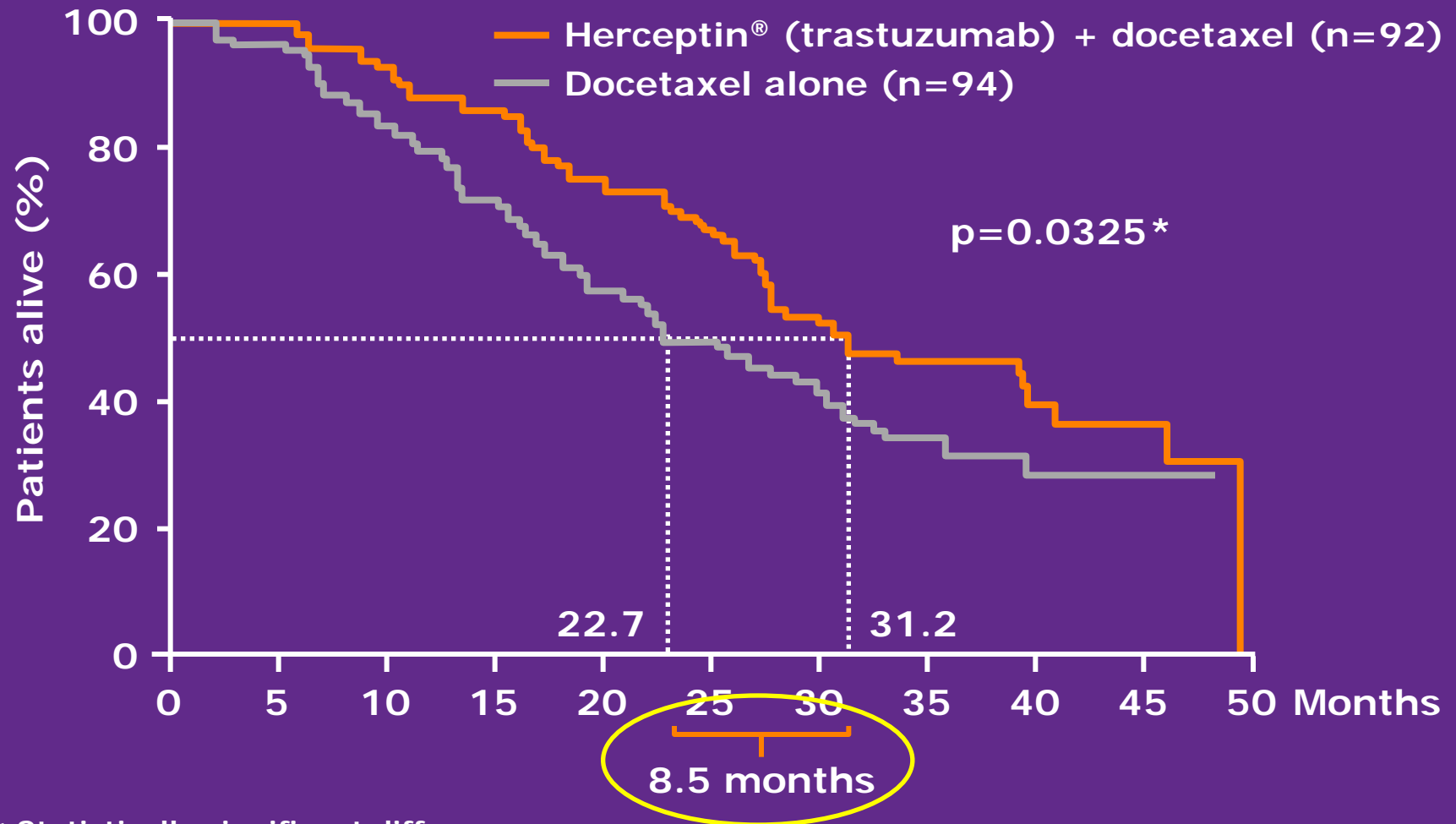
*2 patients did not receive study medication.

†Additional cycles of docetaxel administered at investigator's discretion.

Patients progressing on docetaxel alone could cross over to receive Herceptin® (trastuzumab); FISH, fluorescence *in situ* hybridisation; LVEF, left ventricular ejection fraction; PD, progressive disease

Marty et al 2005

M77001: overall survival (IHC 3+/FISH-positive)



* Statistically significant difference

Take Home Messages

- Status of HER-2 in Breast Cancer Patients will define the treatment for patients.
- Trastuzumab remains the standard of care for HER2-Positive Breast Cancer.
- **1-year Adjuvant Trastuzumab** is the optimal duration for Early Breast Cancer.

-Thank You-