Jean PERRIN Comprehensive Cancer Centre of'Auvergne

Clermont-Ferrand, FRANCE

« Modern Management of Breast Cancer »

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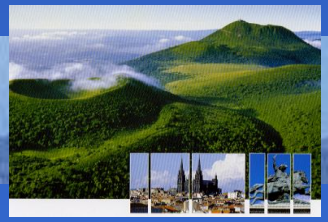
Fédération Nationale DES CENTRES DE LUTTE CONTRE LE CANCER

Centre JEAN PERRIN

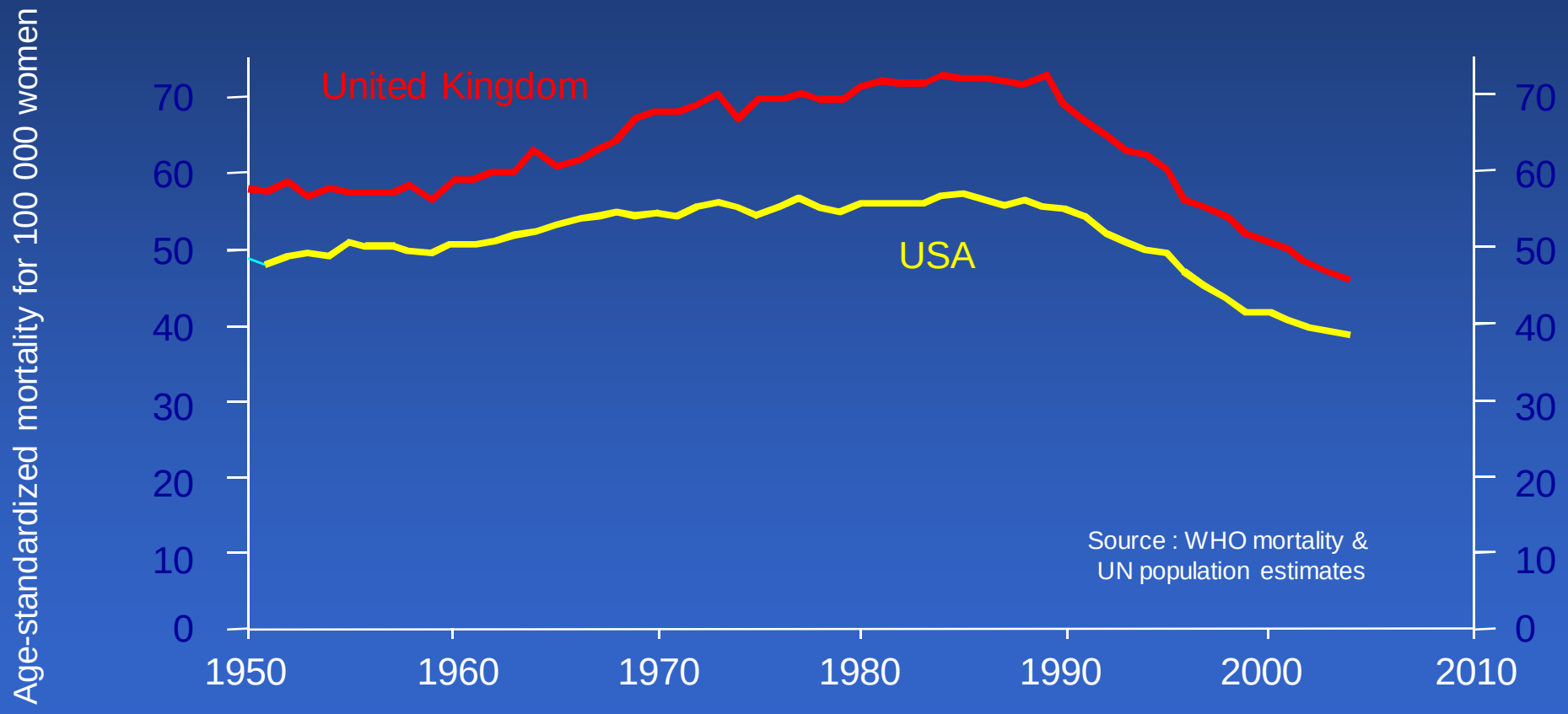


Breast Cancer

- Worldwide :
  - 1,390,000 new cases/year
  - > 450,000 deaths/year
- Early disease: Curable
  - Cure rates
    - Stable from 1930 until 1990
    - Improvement in the 1990's (Screening, Adjuvant therapy)
    - Ageing population in Europe: Absolute No of deaths still rising (2004: 130,000 / 2006: 132,000)
- Metastatic disease: Non Curable
    - Concept of chronic disease

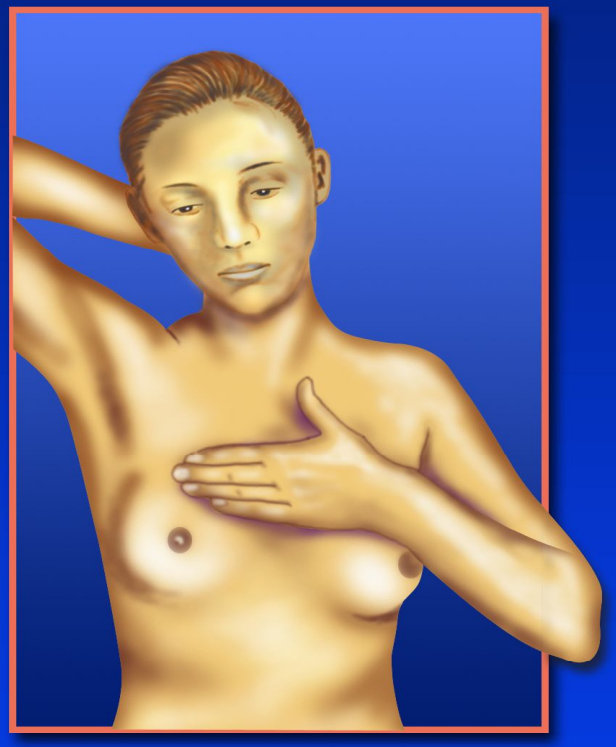
Epidemiology

Recent reduction of mortality (ages : 35-69 years)
United Kingdom and USA 1950 - 2004



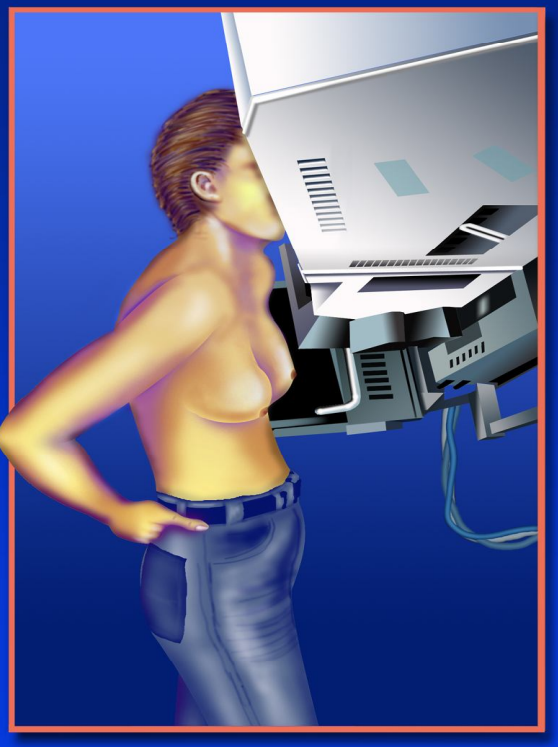
SABCS 2007 – according to Peto R et al., Key note lecture 1.

Breast Cancer Screening



Self-Examination

Examination by Physician

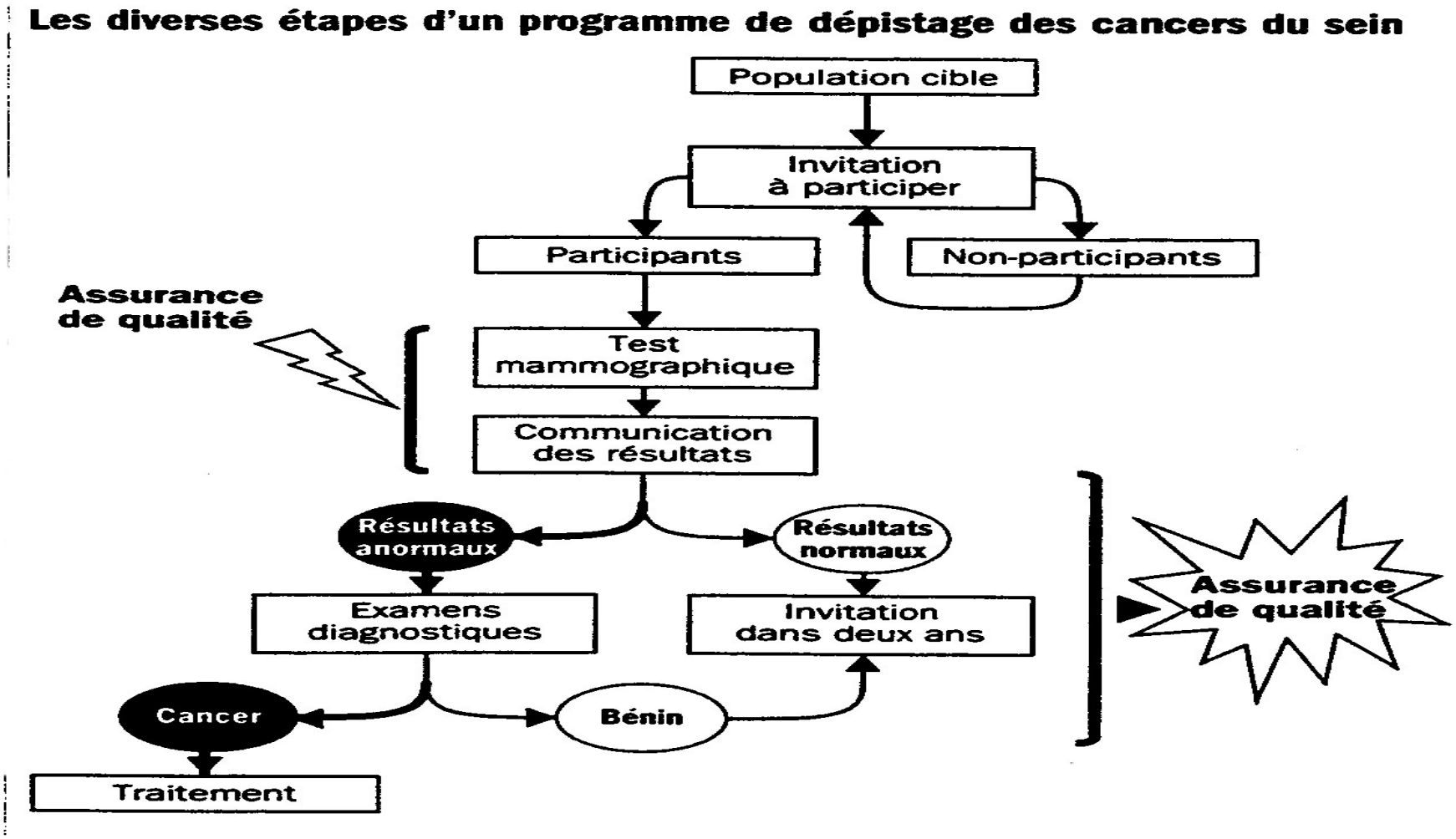


Mammography/Ultrasound

Screening

- Main reason for improved survival, proportional to increased incidence
- Survival benefit around 30%
- Recognised method : mammography + clinical examination
- Organized screening: 1 mammography/2 years from 50 to 74 years
- Problems : dense breasts, women <50 ans
- Extension to all territory difficult

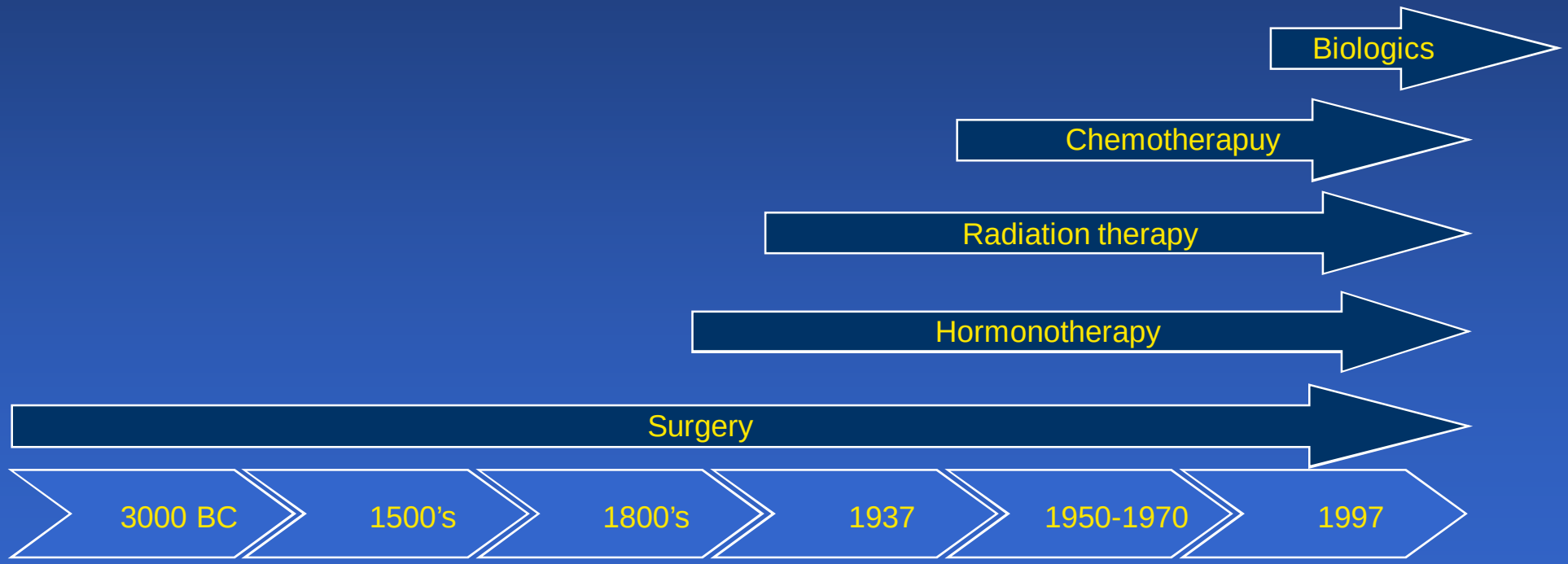
Steps of screening



Breast Cancer Therapies

- Local:
  - Surgery
  - Radiation Therapy
- Systemic:
  - Chemotherapy
  - Hormone therapy
  - Biologic modifiers

Breast Cancer Therapies



Rayter & Mansi. Medical Therapy of Breast Cancer 2003

Rationale for Breast Cancer Therapy

From Prognostic to predictive Approaches

Classical Prognostic Factors

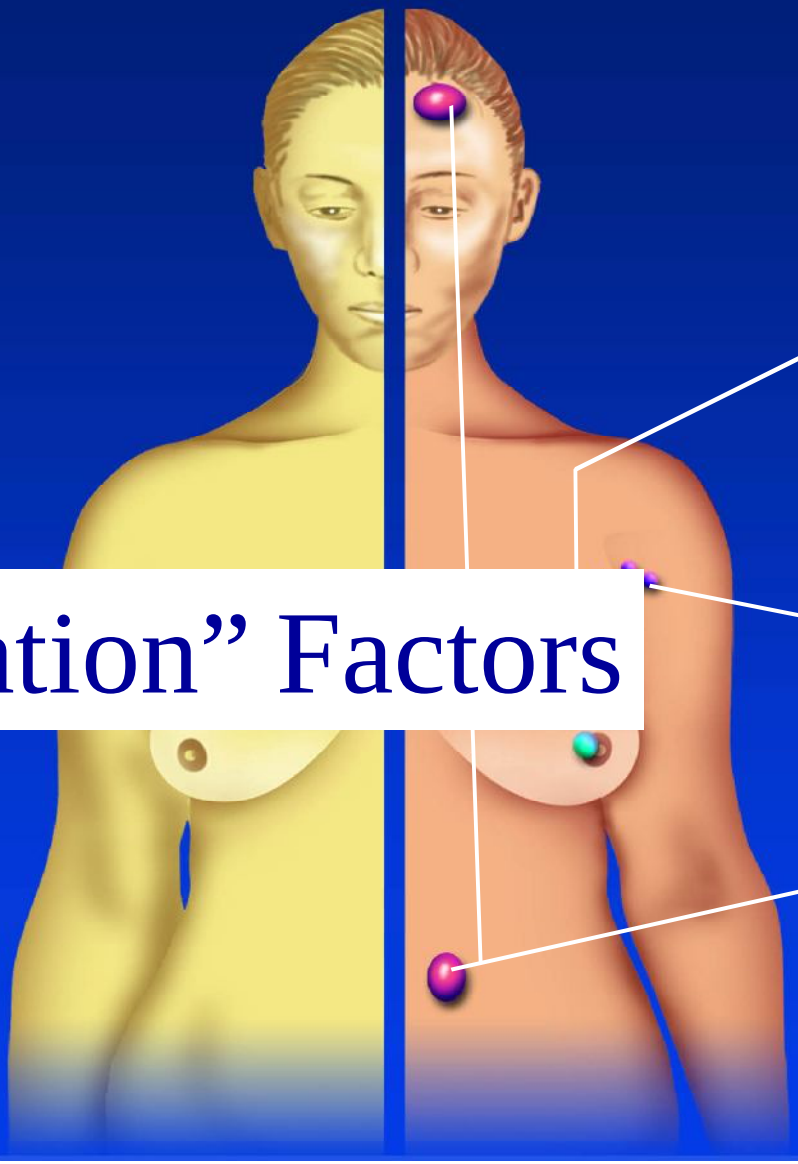
TNM Classification

Age

Histo Type
Histo Grade

Hormonal Receptors

"First Generation" Factors



Tumor

Nodes (ADP)

Metastasis

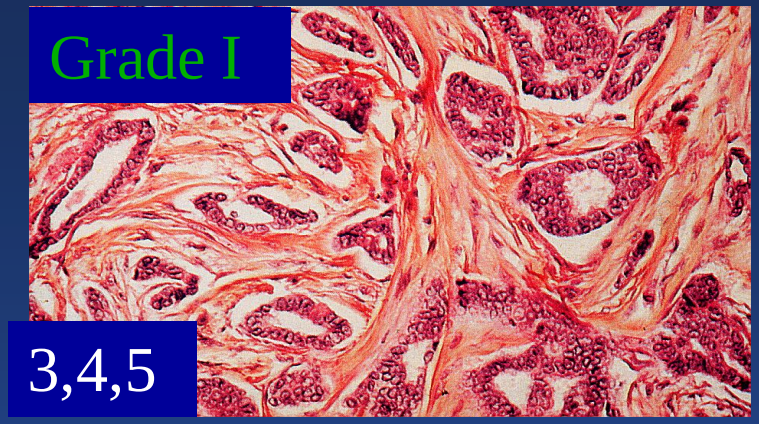
First Generation Factors

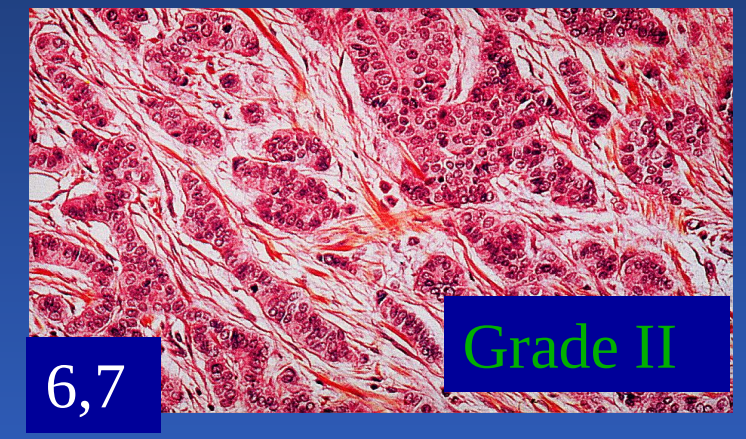
- Used in Consensus Conferences for therapeutic decisions.
- Tumor size with threshold of 1 cm (NCI) or 2 cm (St Gallen) for adjuvant chemotherapy decision
- Number of positive nodes [0 ; 1-3 ; 4-9 et $\geq$ 10]
- Age, histologic type, histoprognostic grade (American college of pathologists)
- Hormonal receptors

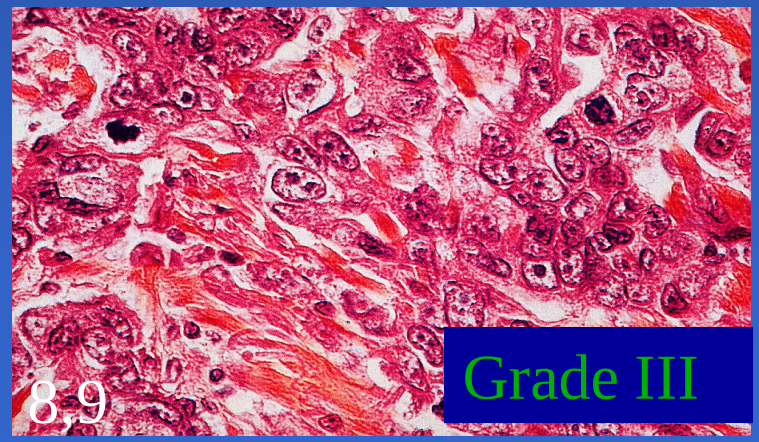
• Grade SBR

- Prognostic index based upon
  - Glandular differentiation
  - Cellular abnormalities
  - Mitosis

- Used for therapeutic decision (chemotherapy / hormonetherapy)

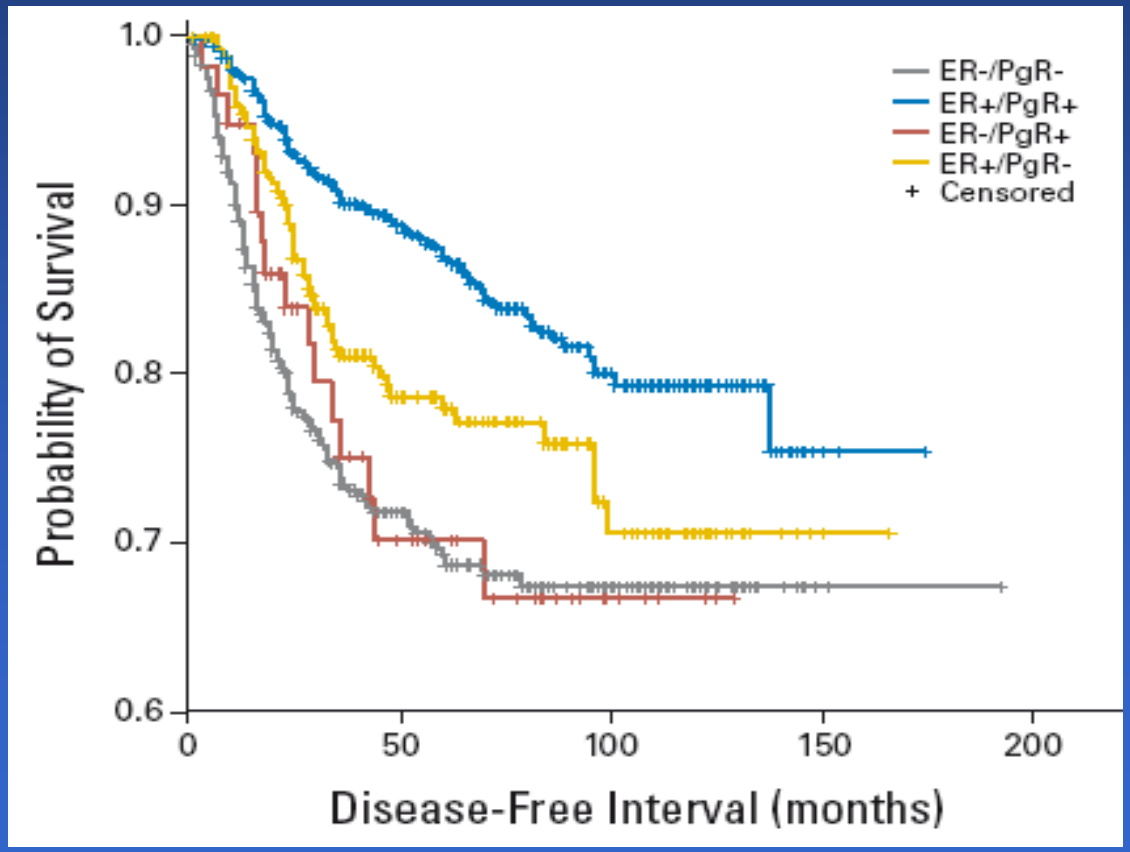






ER+ MBC: Anti-endocrine or cytotoxic therapy ? Hints for hormone sensitivity

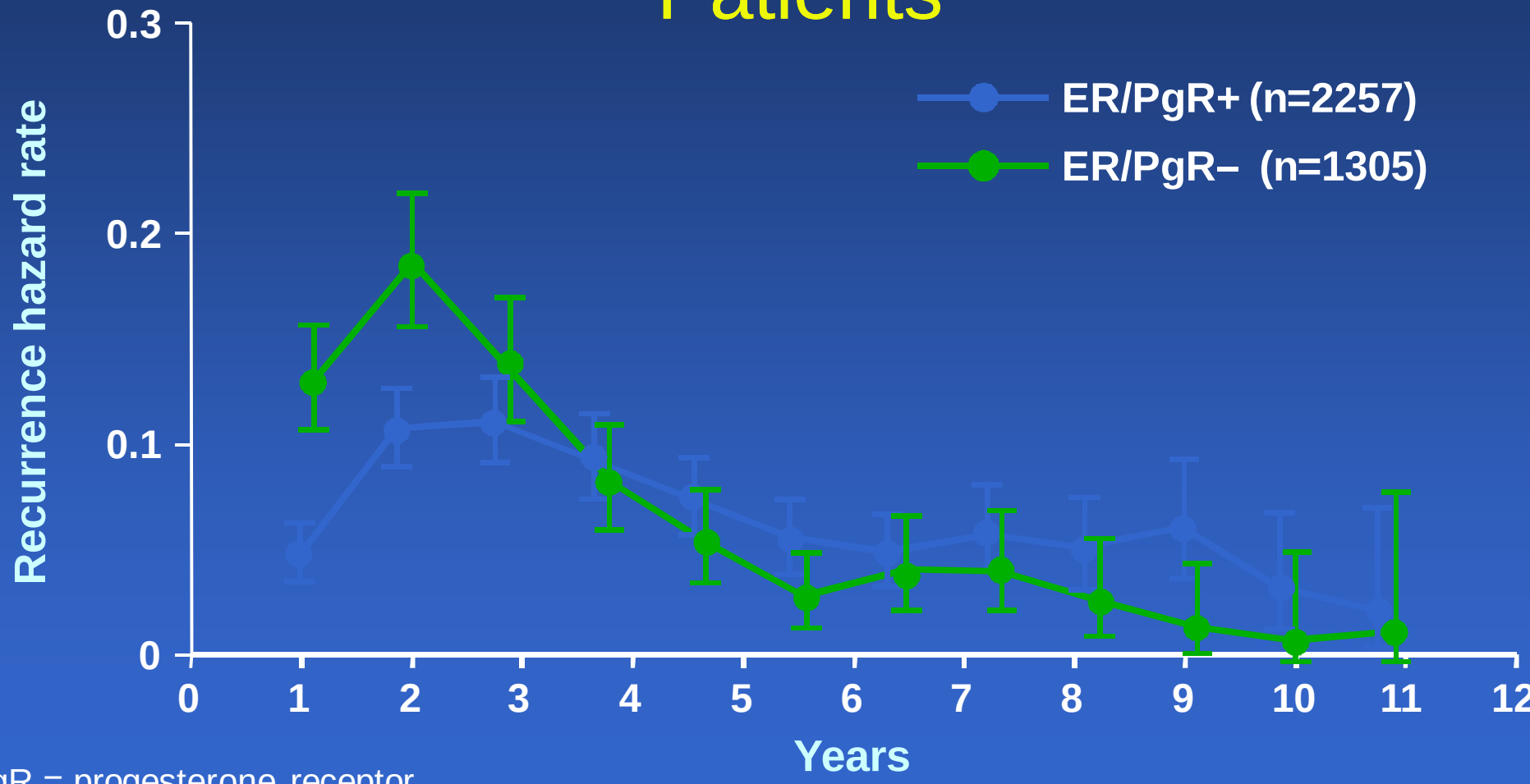
- **<u>HR-status</u> (ER+PR+, ER+,PR-, ER-,PR+)**



Receptor status	Patients
ER + PR +	n = 963 (55.3%)
ER + PR -	n = 272 (15.6%)
ER - PR +	n = 60 (3.4%)
ER - PR -	n = 448 (25.7%)

Rakha ED J Clin Oncol 25 (2007)

Long-Term Risk of Breast Cancer Recurrence Remains High in ER/PR+ Patients



PgR = progesterone receptor.

Saphner et al. *J Clin Oncol*. 1996;14:2738.

2005 Meta-analysis - Adjuvant Therapy Improved Survival

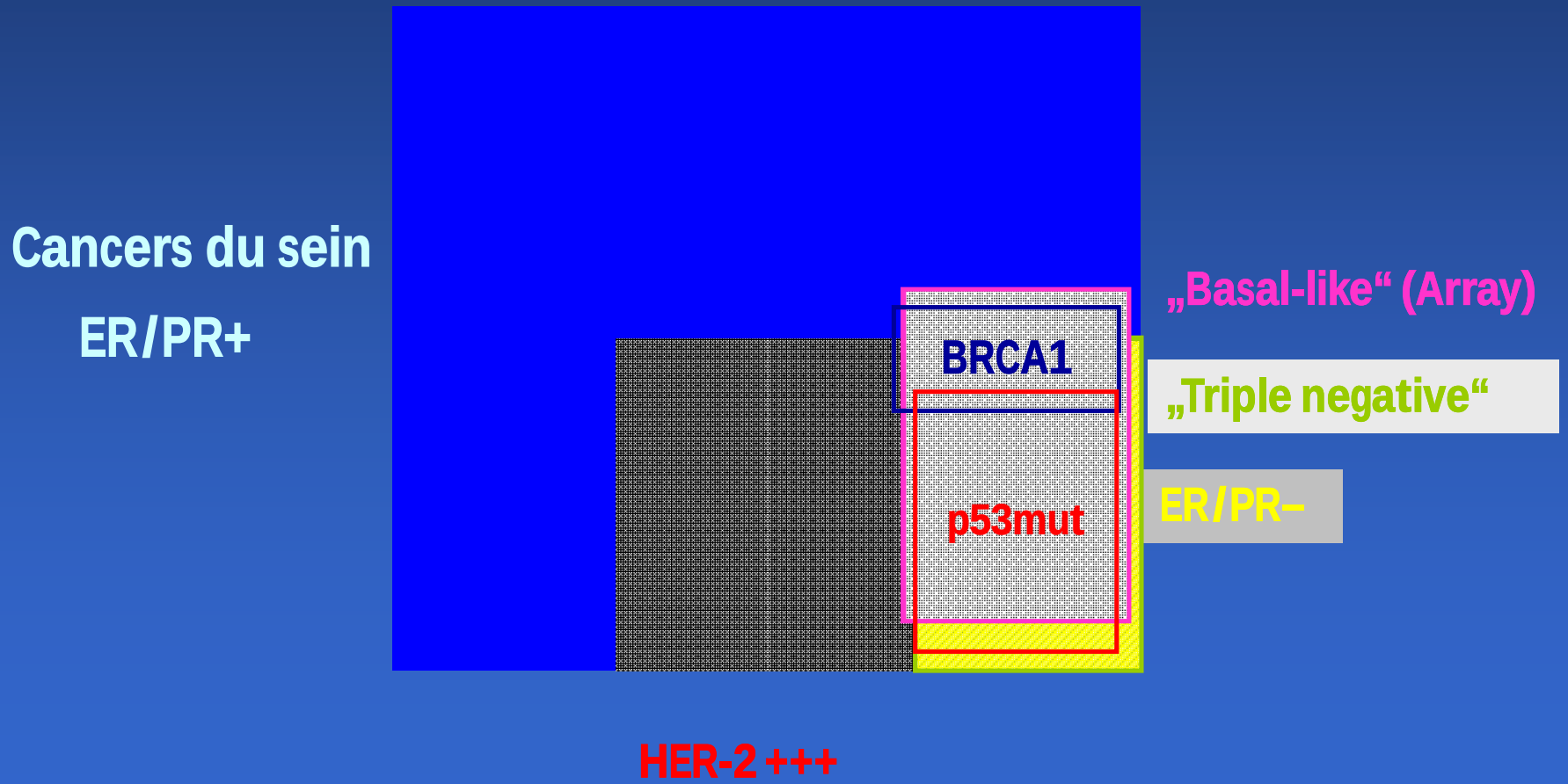
	Hormono	Chimio	Combined
<50 ans			
ER+	25%	25%	45%
ER-	0%	35%	---
> 50 ans			
ER+	25%	10%	35%
ER-	0%	20%	---

First Generation Factors

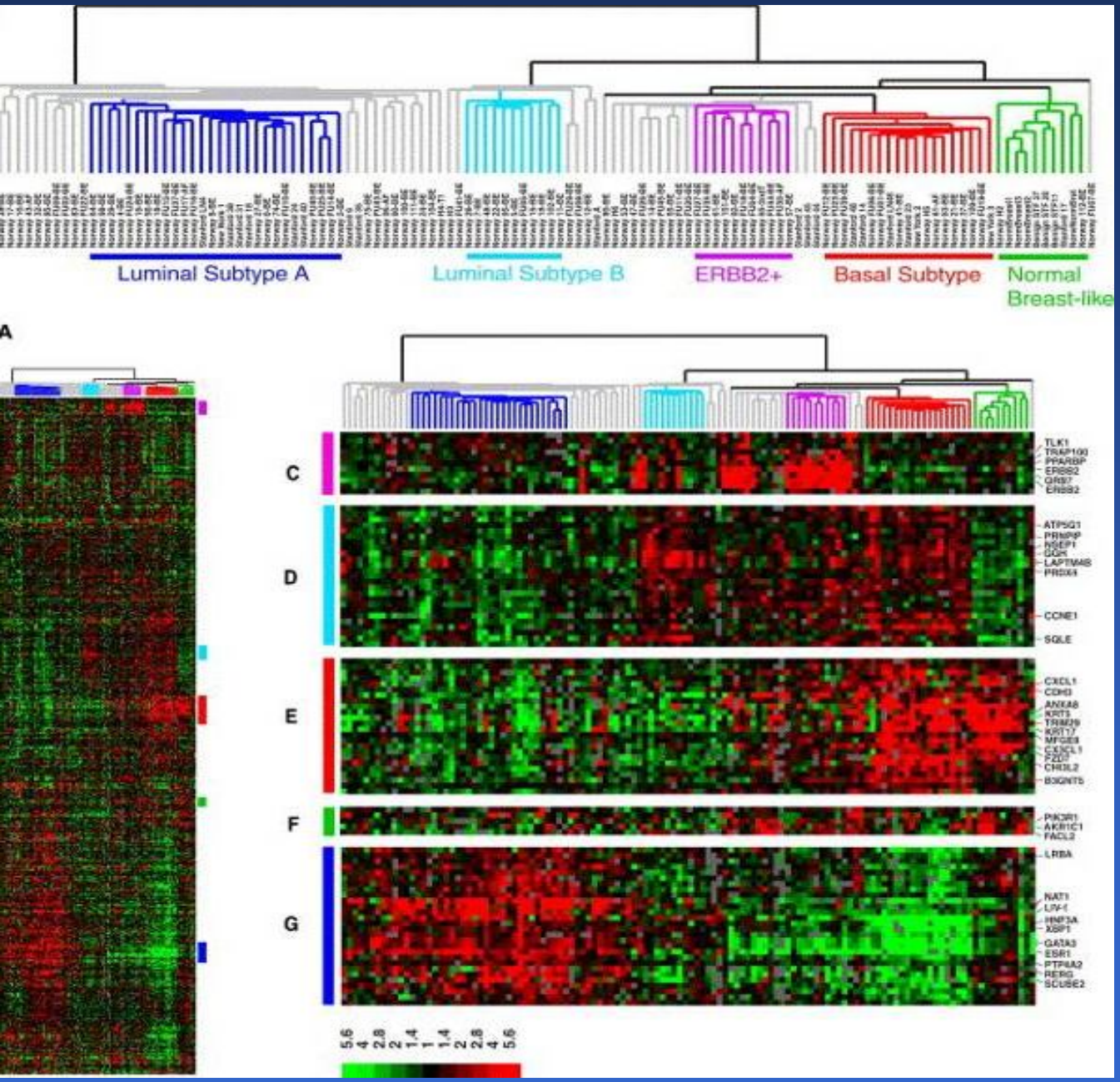
- Frequent problems
  - High risk patients with long survival
  - Low risk patients relapsing quickly…

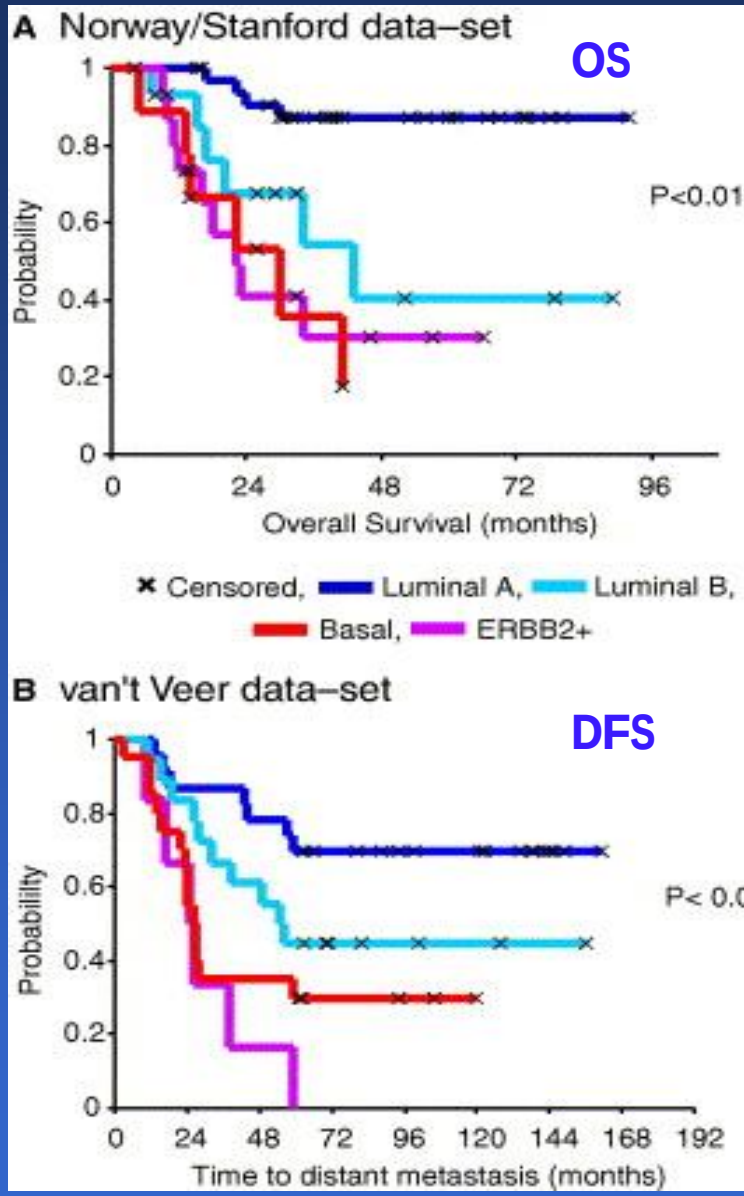
Need for new prognostic factors => Better knowledge of tumor biology

Breast Cancer Subtypes



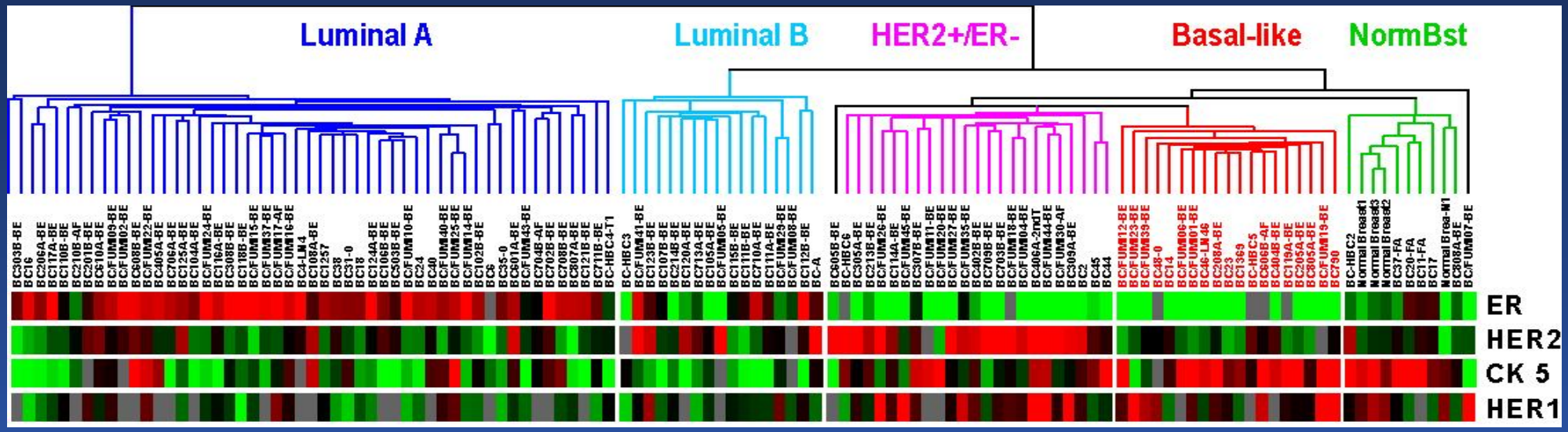
Breast Cancer is an Heterogeneous Group of Diseases





Sorlie, T et al: PNAS 2001; 98:10869-10874

IHC intrinsic subtype surrogates



Luminal A= ER+, HER2-, KI67 low (<15%)
Luminal B= ER+, HER2-, KI67 high (>15%)
HER2+ = ER- and HER2+ (IHC 3+ or FISH+)
Basal-like = ER-, HER2-, CK5/6+ and/or HER1+
Unclassified = negative for all 4 markers

T.O. Nielsen *et al.*,
Clinical Cancer Research 10, 5367-74 (2004).

Intrinsic Classification of Breast Cancer: ER + Tumors

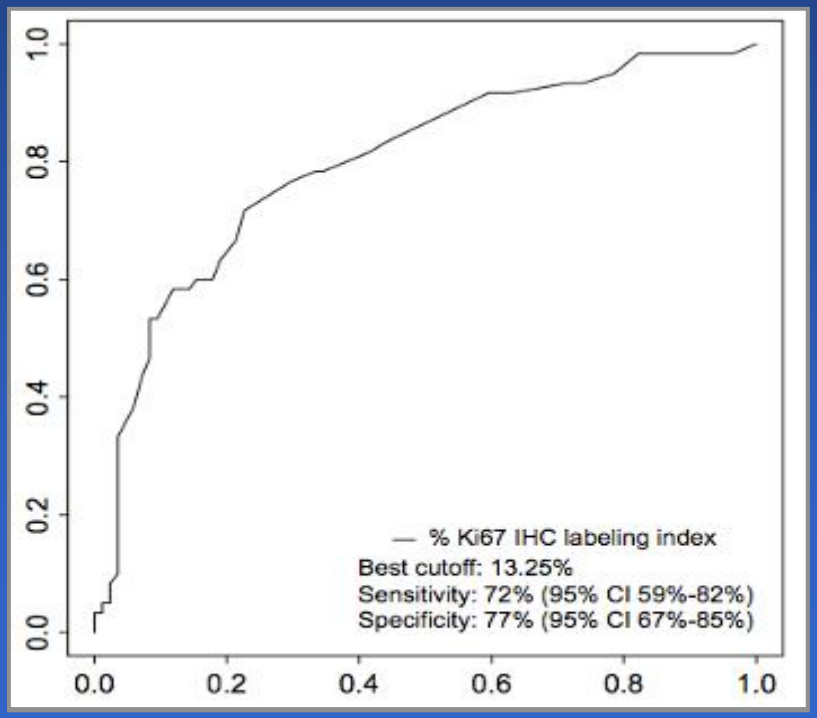
Luminal A	Luminal B
60% Breast Cancers	20% Breast Cancers
High expression ER	Lower expression ER
High expression of genes regulated byER (Gata-3, FOX A1...)	Lower expression of genes regulated byER (Gata-3, FOX A1...)
Low proliferation	High proliferation
Mutated P53: 13%	Mutated P53: 66%

ARTICLE

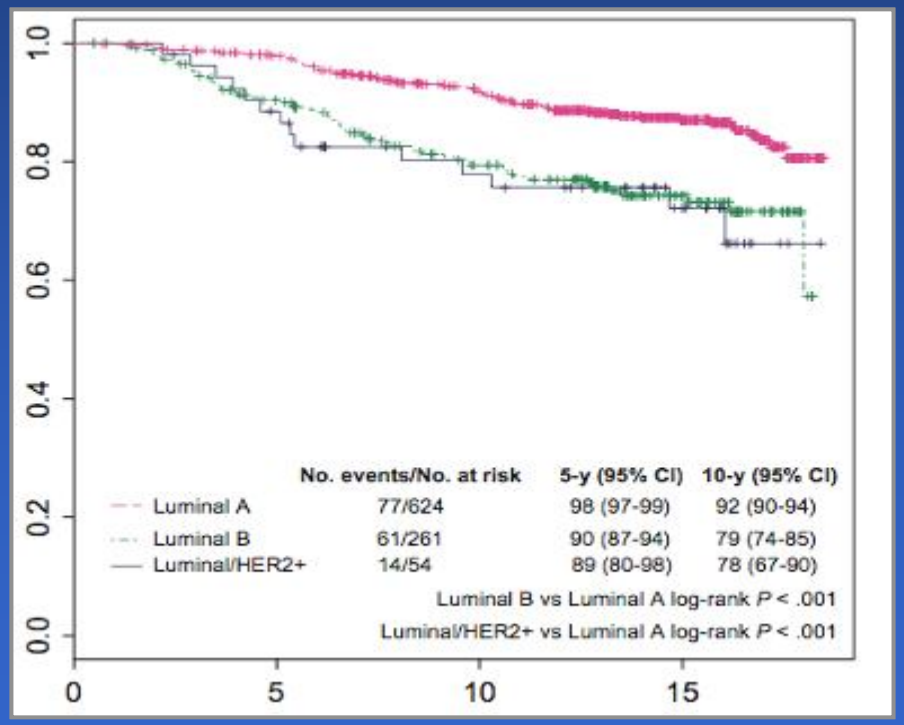
Ki67 Index, HER2 Status, and Prognosis of Patients With Luminal B Breast Cancer

Maggie C. U. Cheang, Stephen K. Chia, David Voduc, Dongxia Gao, Samuel Leung, Jacqueline Snider, Mark Watson, Sherri Davies, Philip S. Bernard, Joel S. Parker, Charles M. Perou, Matthew J. Ellis, Torsten O. Nielsen

Ki67 predicts Luminal B



Clinical Outcome



J Natl Cancer Inst. 2009 May 20;101(10):736-50

HER2+/ER- Tumors

1. 15-25% of tumors
2. prognostic/predictive
3. two types (ER -/+)

HER2

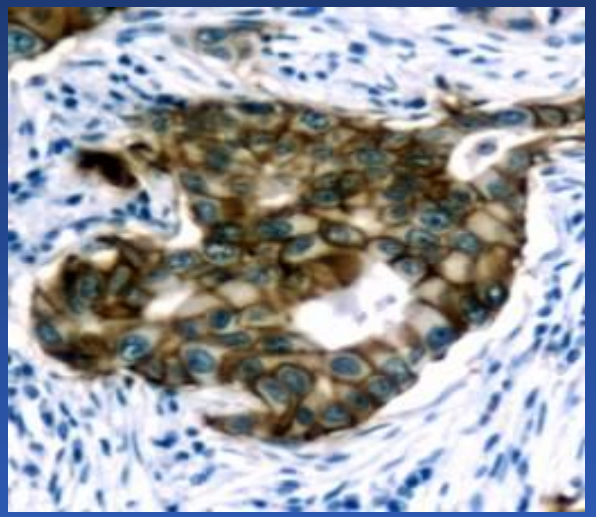
Basal

Luminal

roliferation

HER2
GRB7

17q11-12 amplification



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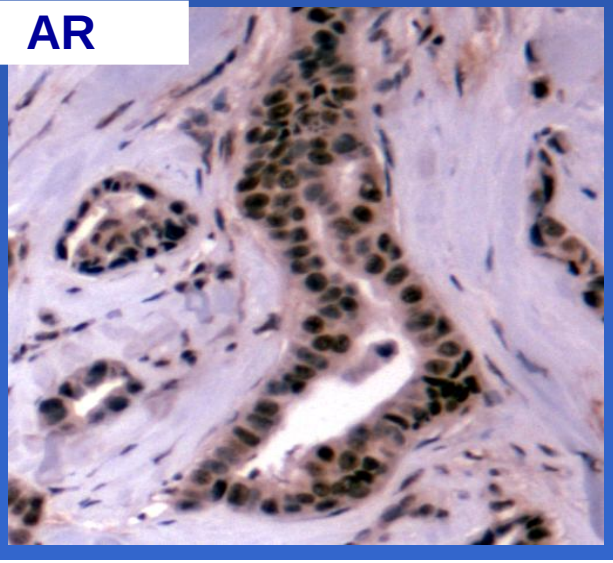
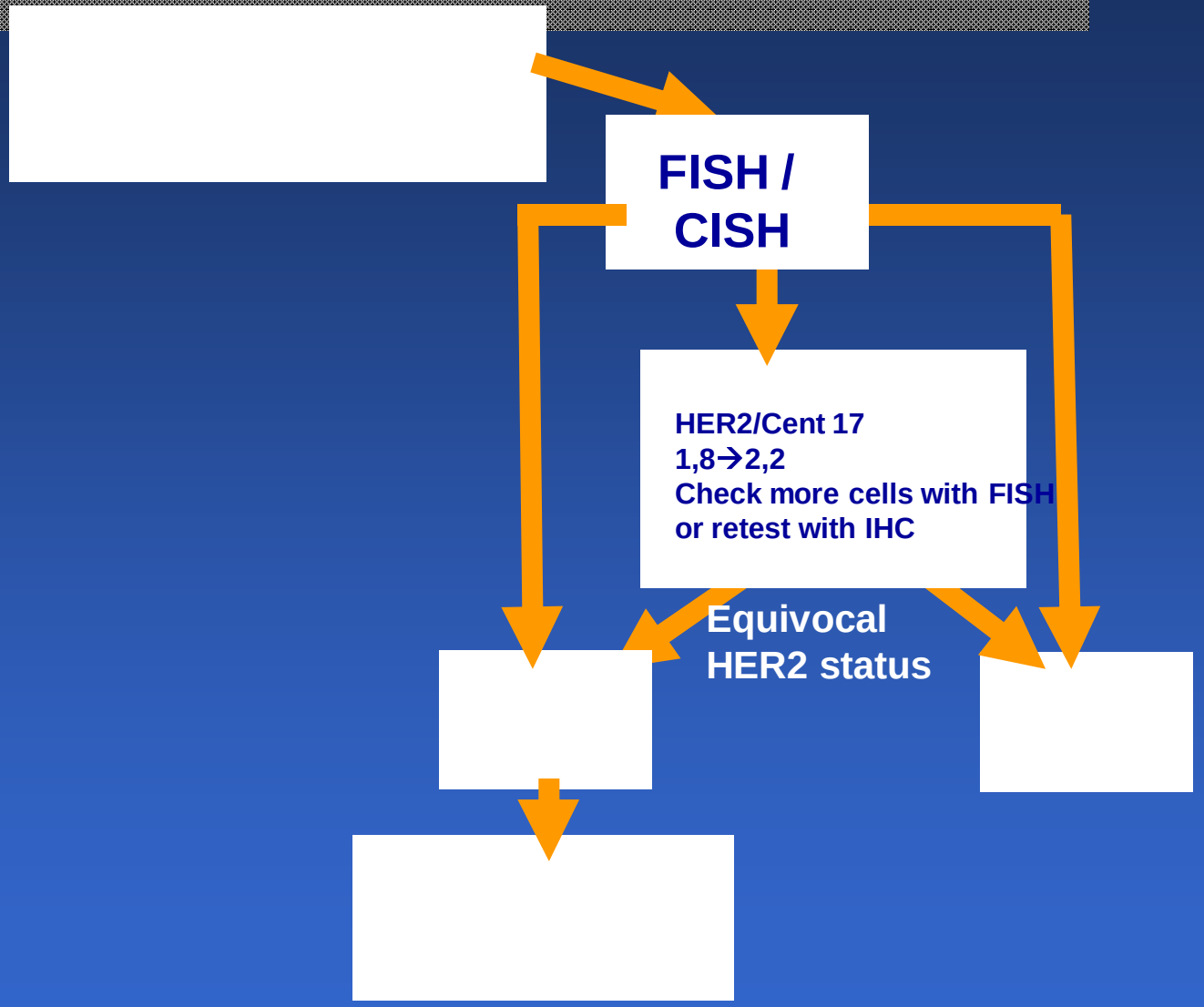


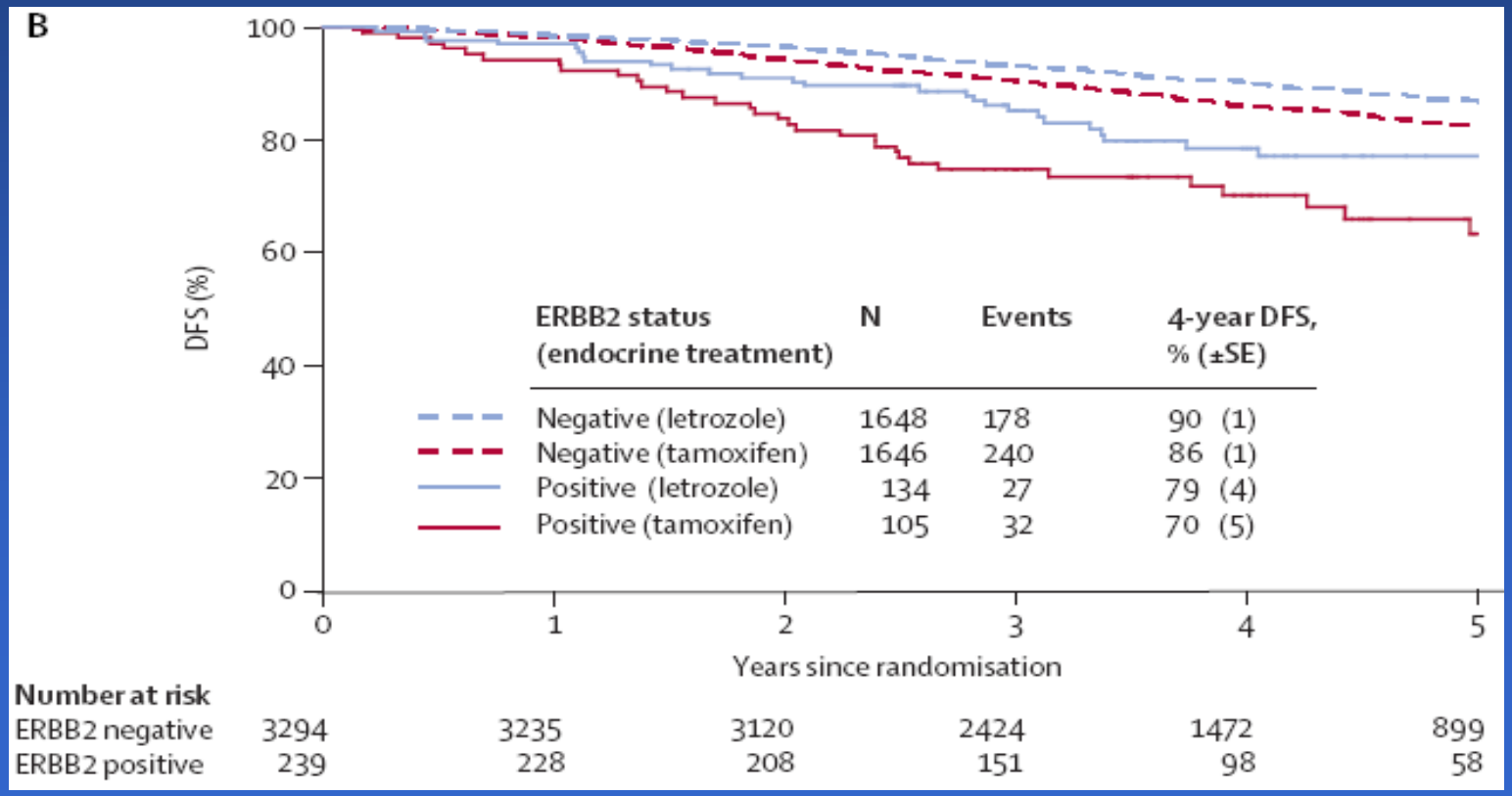
General Algorythm to test HER2



Réf. : HERA, BCIRG, NSABP B31, FIN HER

ER+ MBC: Anti-endocrine or cytotoxic therapy ? Hints for hormone sensitivity

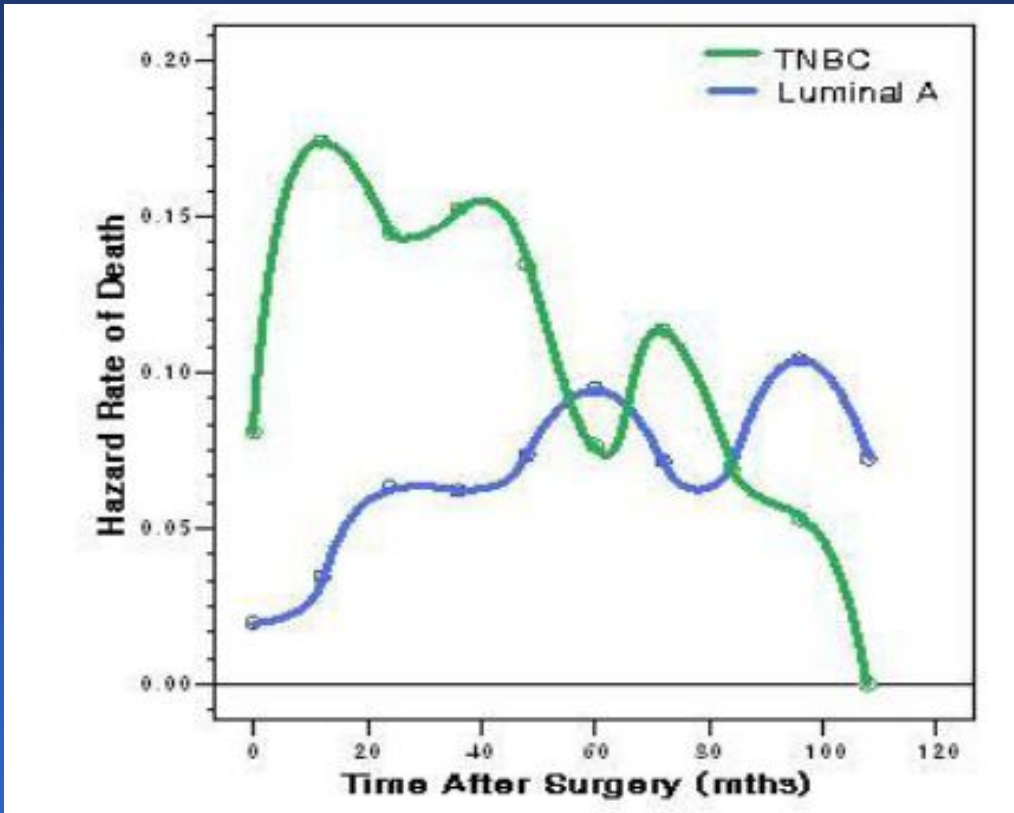
- **HER2 status**



Rasmussen Lancet Oncol 2008; 9: 23–28

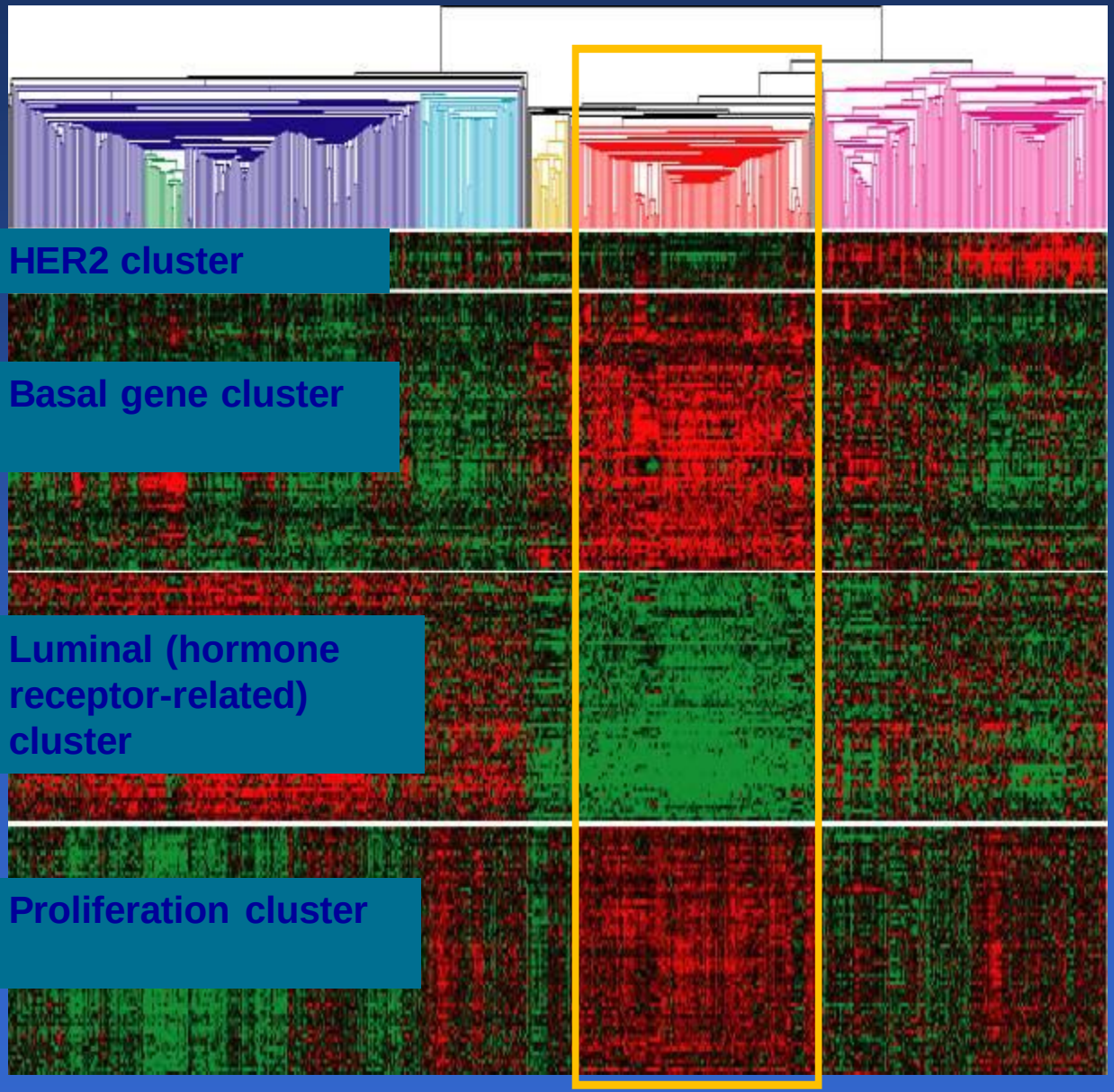
TNBC clinical characteristics

- Young age
- More prevalent in
  - African-American (>30%)
  - Hispanic (>30%)
  - North African women (>30%)
- >75% of BRCA1 carriers
- Relapse :
  - High risk of relapse
  - Early (<2 years)
  - Atypical (lung 40% and brain 30%)



Foulkes WD et al, New England J Med 2010

The Picture of Basal-like Breast Cancer



- Low ER (and related genes) expression
- Low HER2 cluster expression

  → usually "triple negative"
- High basal cluster
  - basal cytokeratins
  - EGFR
  - c-kit
  - others…
- Very proliferative
- Often p53 mutant
- Evidence of genomic instability

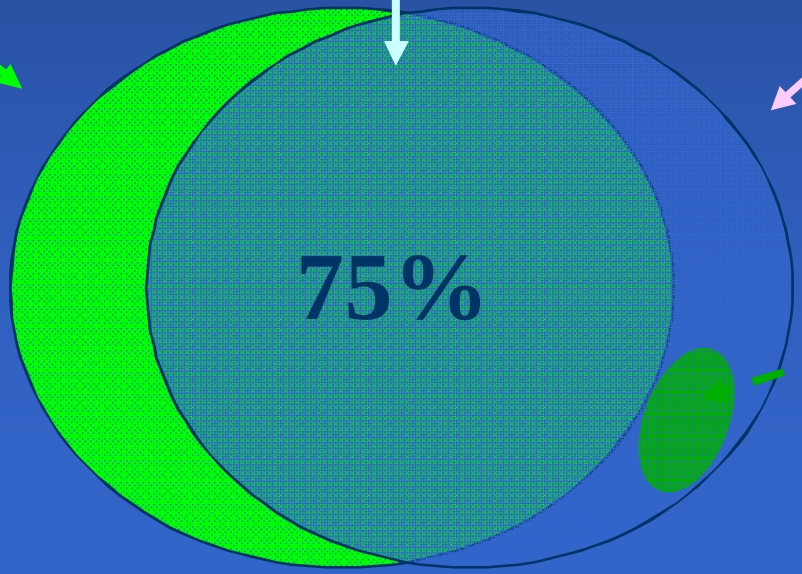
Heterogeneity of “triple negative” B.C.

Triple-negative and basal

show a 65% pCR rate to neoadj. CTX

Basal non triple negative

Basal, non triple – have a 50% pCR to neoadj. CTX



Triple-negative non-basal

Show a 20% pCR to neoadj. CTX

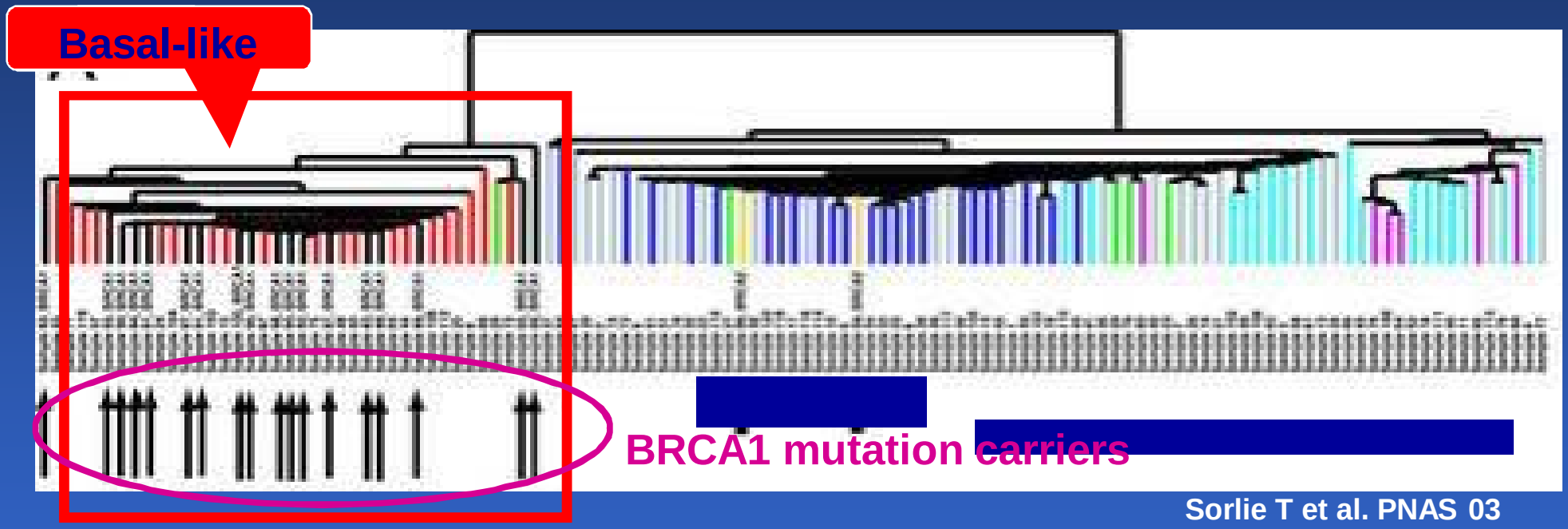
« Claudin-low »

- ***Low-expression of cell-cell junction proteins***
- ***Sometimes metaplastic features***
- ***Stem cell features***
- ***Does it exist ?***

C. Perou, SABCS 2009

Association between BRCA1 mutations and basal-like cancers

Intrinsic gene list applied to Van't Veer dataset (Nature 2002)



Sorlie T et al. PNAS 03

- Most cancers in BRCA1 mutation carriers are basal-like
- Most basal-like breast cancers are <u>not</u> in BRCA1 carriers

Clinical implications

- Luminal A breast cancer could be treated by hormonal treatment only ?
- Luminal B breast cancer could benefit from adjuvant chemotherapy ?

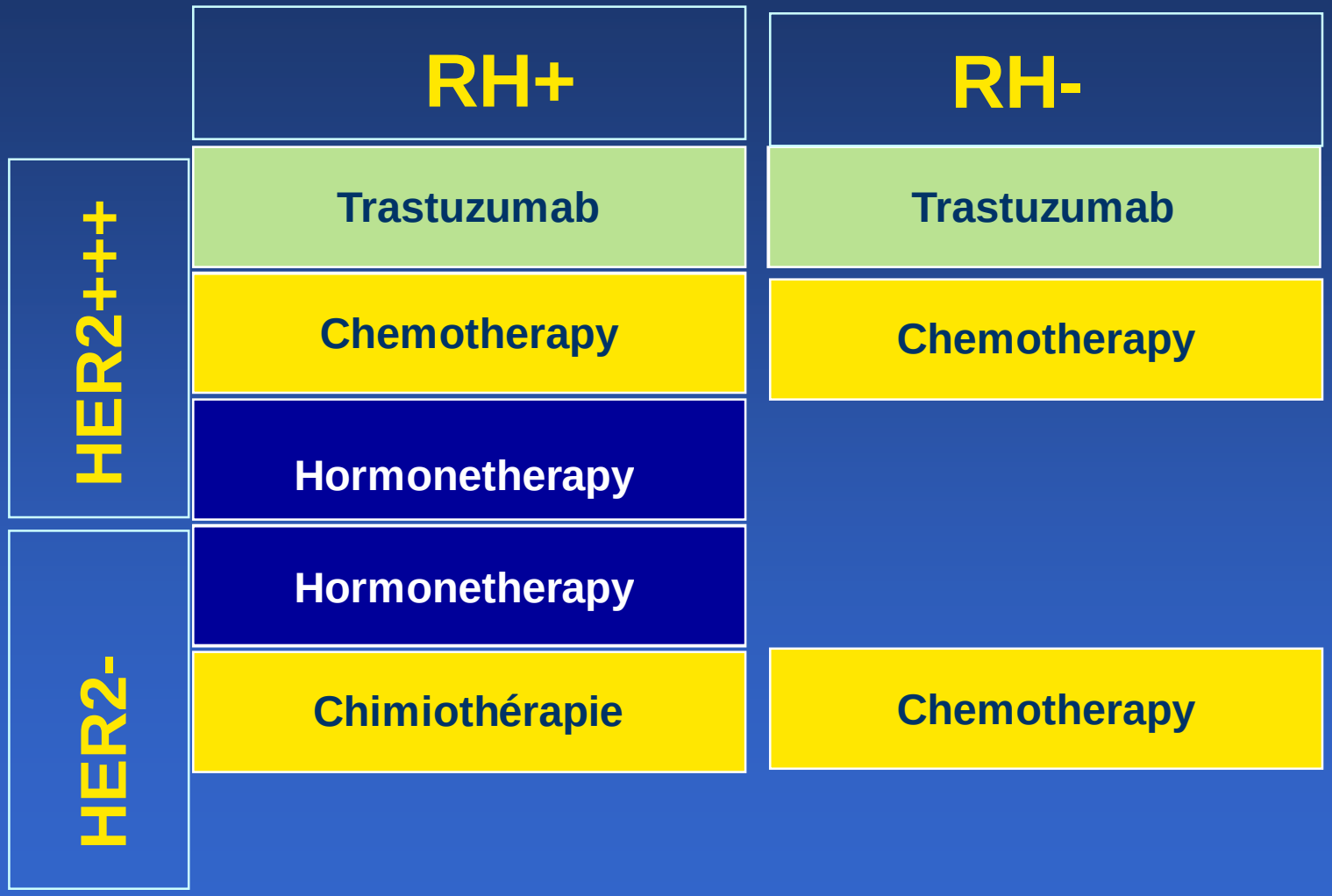
Clinical implications

- Poor prognosis of HER2+
- Traztuzumab treatment ++++
- HER2+, ER+: choice of hormonal treatment is important (ER deprivation, castration,LH-RH analogs, anti aromatase)

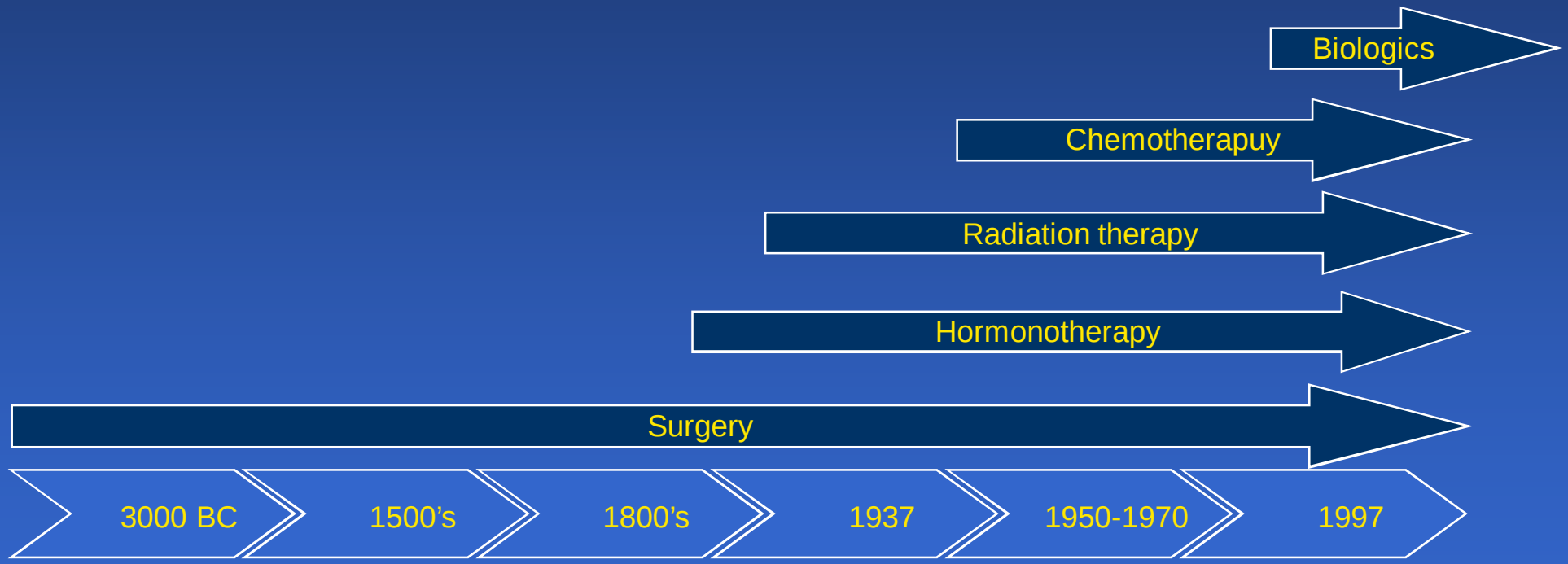
Clinical implications

- Triple negative BC
  - Heterogeneity ++++
  - Chemotherapy only…

Predictive Factors



Breast Cancer Therapies



Rayter & Mansi. Medical Therapy of Breast Cancer 2003

Surgery

Towards less…

Surgery

- Halsted
- Mastectomy
- Conservative surgery
- Sentinel node biopsy…

Chirurgie axillaire et Récidives axillaires

Avant l'ère du GS (Ganglion Sentinelle Node)

Étude (année)	Patientes	pT1 (%)	pN+ (si curage)	Suivi	Curage et récidive axil.	Pas de curage Récidive axil.
Guy I (1987)	232	17	24%	60-120	0,9%	18,8%
Guy II (1987)	258	38	-	60-120	1,4%	12,5%
NSABP B04	727	39	39	120	1,4%	18,4%

- En l'absence de toute chirurgie axillaire
  - Le risque de récidive axillaire
    - Dépend de la taille de la tumeur
      - Si 40% de pT1: risque de 5 à 10 ans de **20%**

Avant l'ère du GS

Étude (année)	Patientes	pT1 (%)	pN+ (si curage)	Suivi	Curage et récidive axil.	Pas de curage Récidive axil.
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NSABP B04	727	39	39	120	1,4%	18,4%

- En cas de curage axillaire
  - Le risque de récidive axillaire
    - Dépend de la taille de la tumeur
      - Si 40% de pT1: risque de 5 à 10 ans de **1,4%**

Avant l'ère du GS

- **Pas de curage axillaire**

  - **Essai AXIL 95**
    - Schéma de l'étude (1995-2005):
      - Patientes >50 ans, carcinome infiltrant <10mm, N0
      - Groupe n°1:
        - » 297 patientes: pas de curage
      - Groupe n°2:
        - » 310 patientes: curage (pN+=14%)
    - Résultats
      - Récidive axillaire
        - » Groupe n°1: **2%** (6 patientes)
        - » Groupe n°2: **0%** (0 patientes),

Avril A et al, EJSO 2010

A l'ère du GS

- **GS et curage axillaire**

  - **Essai NSABP B32**
    - Schéma de l'étude:
      - Groupe n°1:
        - » 2619 patientes: GS+curage
      - Groupe n°2:
        - » 2697patientes: GS +/- curage
      - Suivi moyen 95 mois
    - Résultats
      - Récidive axillaire
        - » Groupe n°1: **0,3%** (8 patientes)
        - » Groupe n°2: **0,5%** (14 patientes), [p=0,22]

Krag D et al, Lancet Oncol 2010

A l'ère du GS

- **GS pN- <u>sans</u> curage axillaire**

Auteur (année)	Patientes	T1 (%) ou T médian	Suivi	Récidives axillaires
Veronesi (2009)	3548	84%	48 mois	0,9%
Bergvist (2008)	2246	14mm	37mois	1,2%
Christiansen 2008)	3717	71%	20 mois	0,5%
Naik (2004)	2340	89%	31 mois	0,1%

- Résultats
  - Récidive axillaire (suivi de 20 à 48 mois)
    - » **0,1%** à **1,2%**

A l'ère du GS

- **GS pN+ <u>sans</u> curage axillaire**

  - **<u>Cohortes</u>**
    - National cancer data base
      - **1981** patientes
        - » GS micro-métastase: 530
        - » GS macro-métastase: 1458
    - Résultats
      - Suivi 64 mois
      - Taux de récidive axillaire
        - » GS micro-métastase: **0,6%**
        - » GS macro-métastase: **1,2%**

Bilimoria et al, JCO 2009

A l'ère du GS

- **GS pN+ <u>sans</u> curage axillaire**

  - **<u>Essai Randomisé</u>**
    - American College of Surgeon Oncology Group Z0011
      - Patientes T1-T2, tumorectomie, GS pN+ (pré sélectionnées / Z0010)
        - » GS seul: 445 (44% micro-métastase)
        - » GS et curage: 446 (37% micro-métastase)
    - Résultats
      - Suivi 6,3 ans
      - Taux de récidive axillaire
        - » GS seul: **0,9%**
        - » GS et curage: **0,5%**

Giuliano et al, Ann Surg 2010

Radiation Therapy

Critical for local control

May be more…

Chemotherapy

Towards less…?

Development of Chemotherapy Breast Cancer

1970s

- **Before anthracyclines**
  - CMF, CMFVP

1980s

- **With anthracyclines**
  - Combinations: AC, FAC, AVCMF, FEC, CEF
  - Sequence and Alternating (Milan A & B)
  - Dose intensity,dose density, HDCT

1990s

- **Taxanes (Paclitaxel/Docetaxel)**
  - **Sequential:** A⇒ T⇒ C or AC⇒ T
  - **Combinations**: TA, TAC

2000s

- **Biologic Modifiers (Herceptin)**
  - Integration in chemotherapy strategies

Adjuvant Chemotherapy

EBCTCG Metaanalysis

Therapy	Reduction of Annual Odds, %		Absolute Improvement, %
	Relapse	Death	Death
PolyCT vs. no CT (1995)	23.5 (*P* < .00001)	15 (*P* < .00001)	3.0% (*P* < .00001)
Anthracyclines vs. CMF (2000)	10.8 (*P* < .0005)	15.7 (*P* < .00001)	4.3% (*P* < .00001)

Chimiothérapies
1ère ligne Cancer du Sein

Agent	Année de publication	CR + PR (%)
Taxotere (75-100mg/m²)	1993 - 95	48 - 68
Taxol (175 - 250 mg/m² : 3-24hr)	1991 - 95	29 - 63
Doxorubicin (60-75mg/m²)	1974 - 94	43 - 54
Navelbine	1992 - 94	30 - 41
Capecitabine	1995 - 98	30-41
Gemcitabine	1995-97	25-37
Cisplatin	1978 -88	9 - 50
Cyclophosphamide	1959 - 68	36
Fluorouracil	1961 - 81	28
Methotrexate	1952 - 81	26
Mitomycin C	1976 - 85	32

Vogel CL, Nabholtz Oncologist 1999; 4: 17-33.
Nabholtz et al. Exp. Opin Pharmacother 2000; 1: 187-206.

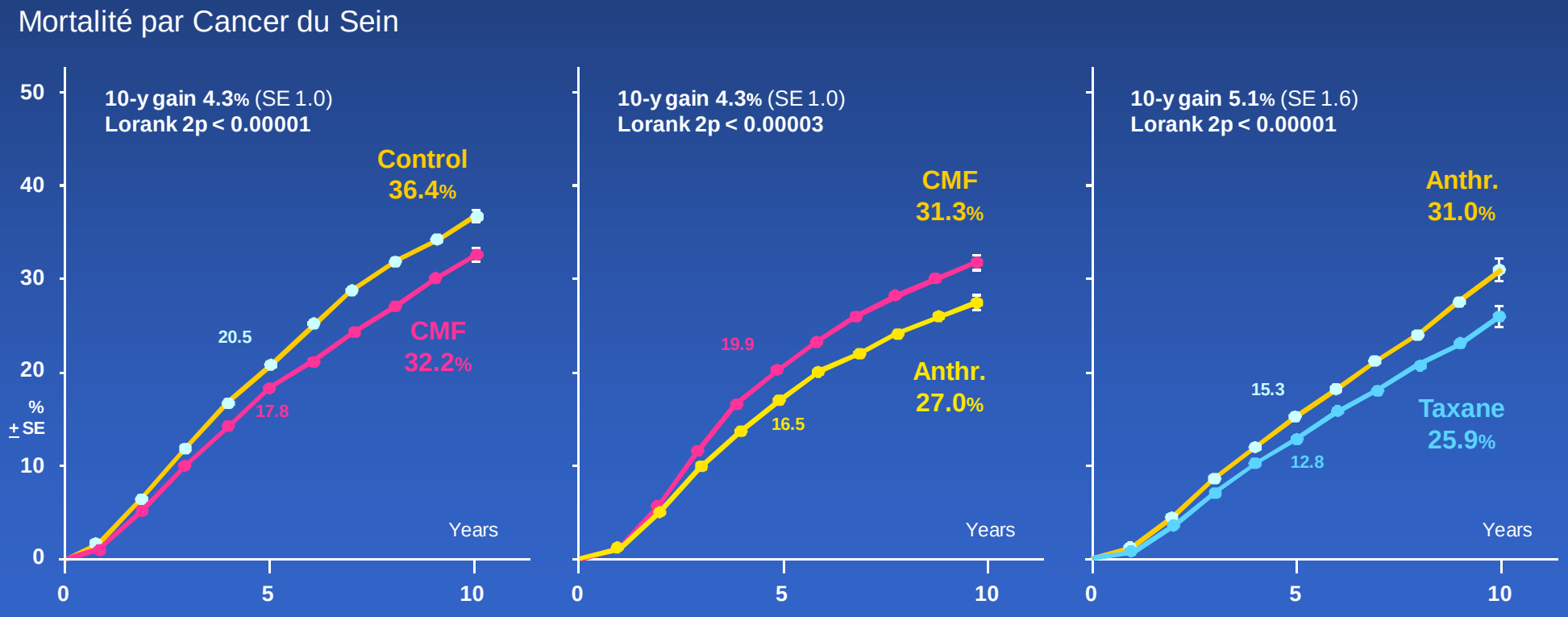
Adjuvant Chemotherapy

Taxanes vs Anthracyclines

Therapy	Risk reduction %		Absolute Benefit, %
	Relapse	Death	Death
Anthra vs. CT -Paclitaxel	18 (*P* < .001)	15 (*P* < .01)	3.0% (*P* < .01)
Anthra vs. CT-Docetaxel	27 (*P* < .001)	21 (*P* < .005)	5.1% (*P* < .00001)

Benefits of Adjuvant Chemotherapy
BC Mortality at 10 Years

Taxanes > anthra > CMF > No Chemotherapy



Death rates (% / year: total – rate in women without recurrence) & logrank analyses

Peto et al, SABCS 2007

Hormonetherapy

Changes in dogmas…

Efficacy of Endocrine Agents in Women With Advanced Breast Cancer

Response data from comprehensive reviews

Therapy		Response Rate (%)
Ablative	Oophorectomy	33
	Adrenalectomy	32
	Hypophysectomy	36
	Radiationtherapy	32
Inhibitive	Aminoglutethimide + HC	31
Additive	Estrogens	26
	Progestins	29
	Androgens	21
	Glucocorticoids	25
Competitive	Tamoxifen	32

Rose C, et al. Acta Oncol 1998; 27: 721-8

Tamoxifen

was

Gold Standard in Adjuvant Breast Cancer.

Aromatase Inhibitors

- Nonselective
  - Aminoglutethimide (competitive)
- Selective: Discovery Late 80's
  - Competitive (nonsteroidal)
    - Anastrozole
    - Letrozole
    - Vorozole
    - Fadrozole
  - Noncompetitive (steroidal)
    - Exemestane
    - Formestane

Efficacy of Endocrine Agents in Women With Advanced Breast Cancer

Response data from comprehensive reviews

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	Adrenalectomy, Hypophysectomy	32
	Radiation therapy	32
Additive	Estrogens	26
	Progestins	29
	Androgens	21
	Glucocorticoids	25
Competitive	Tamoxifen	32
Inhibitive	Aminoglutethimide + HC	31
	AI 3rd generation	40-45

Third Generation Aromatase Inhibitors

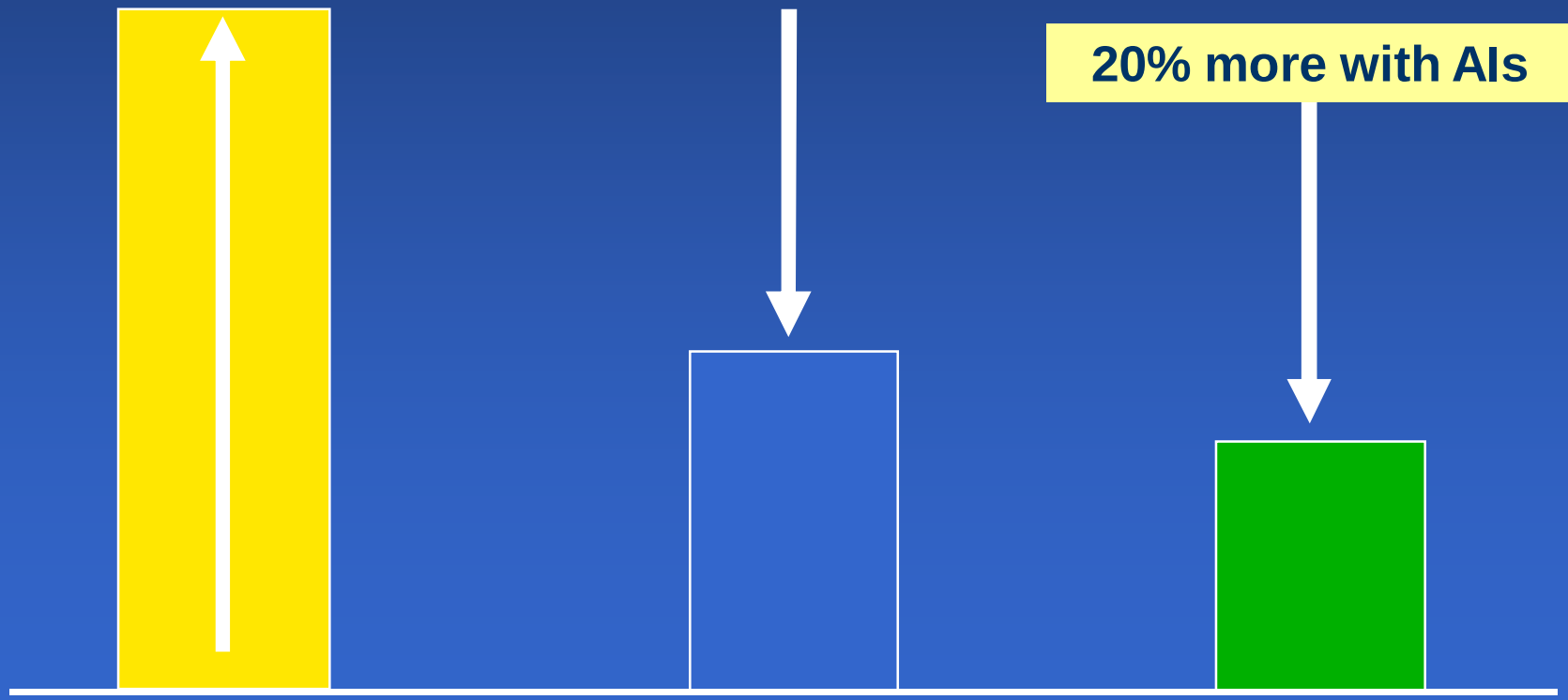
Adjuvant Breast Cancer

ADDITIONAL EFFECTS OF AROMATASE INHIBITORS IN EARLY BREAST CANCER

38% relapse rates without adjuvant Tt (EBCTCG)

50% risk decrease with tamoxifen

20% more with AIs



Efficacy of Endocrine Agents in Women With Advanced Breast Cancer

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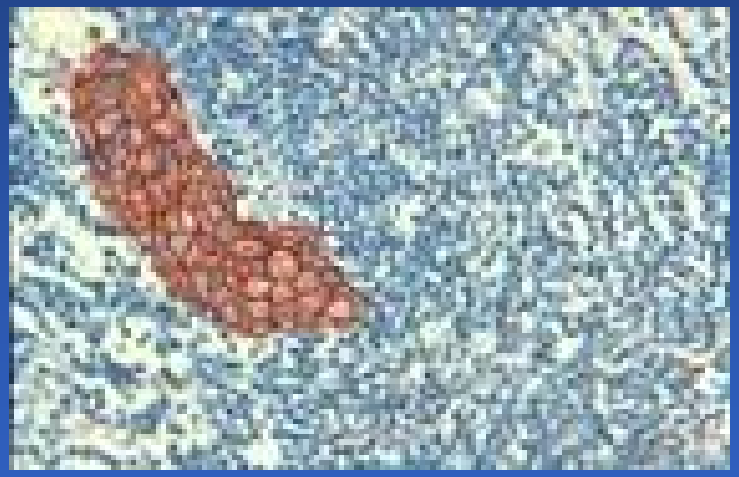
Competitive	Tamoxifen	32
Inhibitive	Aminoglutethimide + HC	31
	AI 3rd generation	40-45
ER down Regulators	Fulvestrant	45-50

Antibody anti HER-2

Herceptin

HER-2 and Breast Cancer

Amplification of
HER-2 Oncogène



SOverexpression of Her-2 Oncoprotein

Decreased survival

Median survival

HER-2 altérations	**3 years**
HER-2 normal	**6 - 7 years**

Slamon et al, 1987

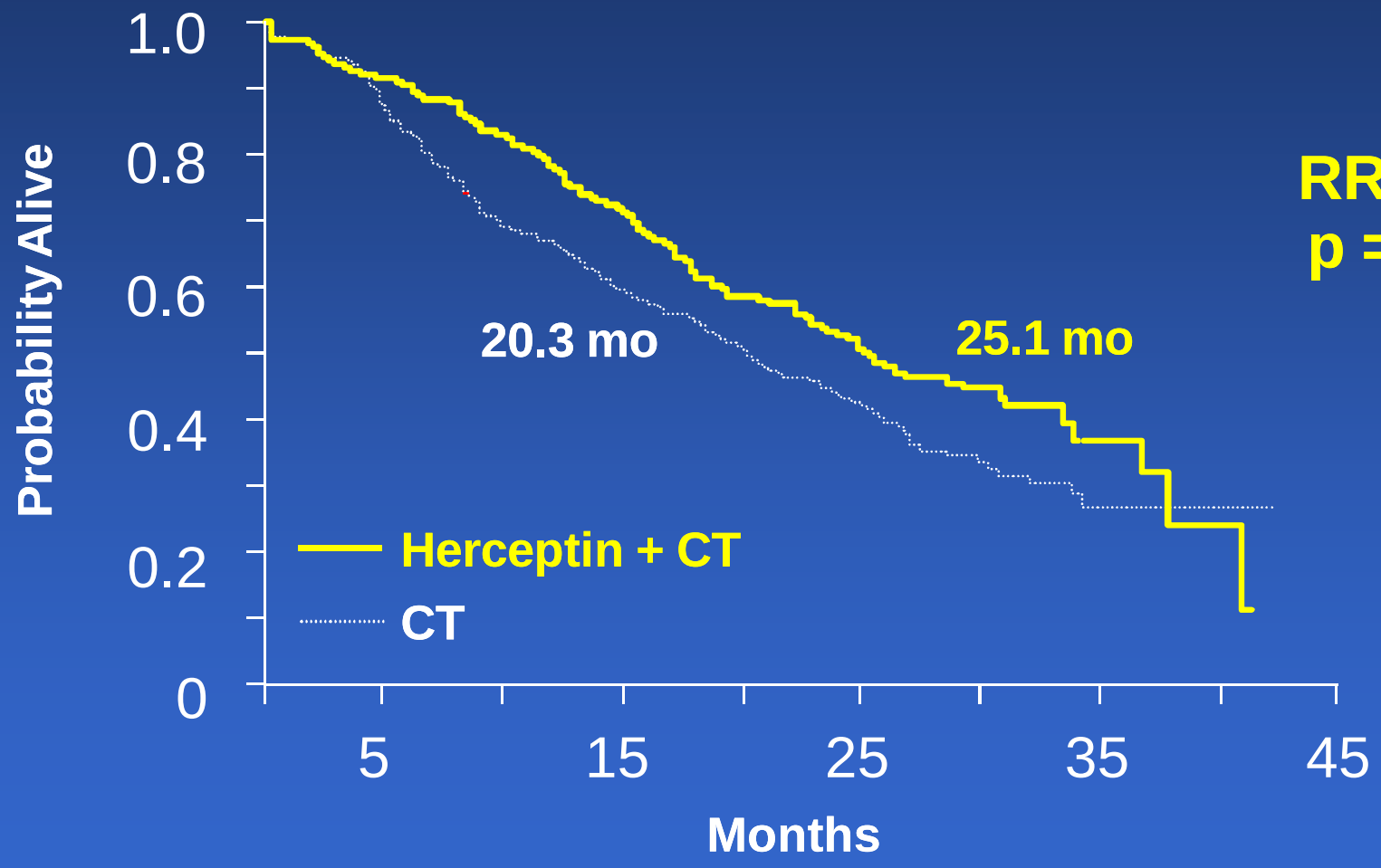
Chimetherapy ± Herceptin:1st line Therapy MBC Registration Trial (H0648g): Results

	H + CT (n = 235)	CT (n = 234)	*Valeur P*
PFS Median, mo	7.4	4.6	.0001
Response rates, %	50	32	.0001
Duration of response Median,mo	9.1	6.1	.0001
TTF Median, mo	6.6	4.5	.0001

Slamon et al. N Eng J Med, 2001.

Comparative Study H0648g

Overall Survival

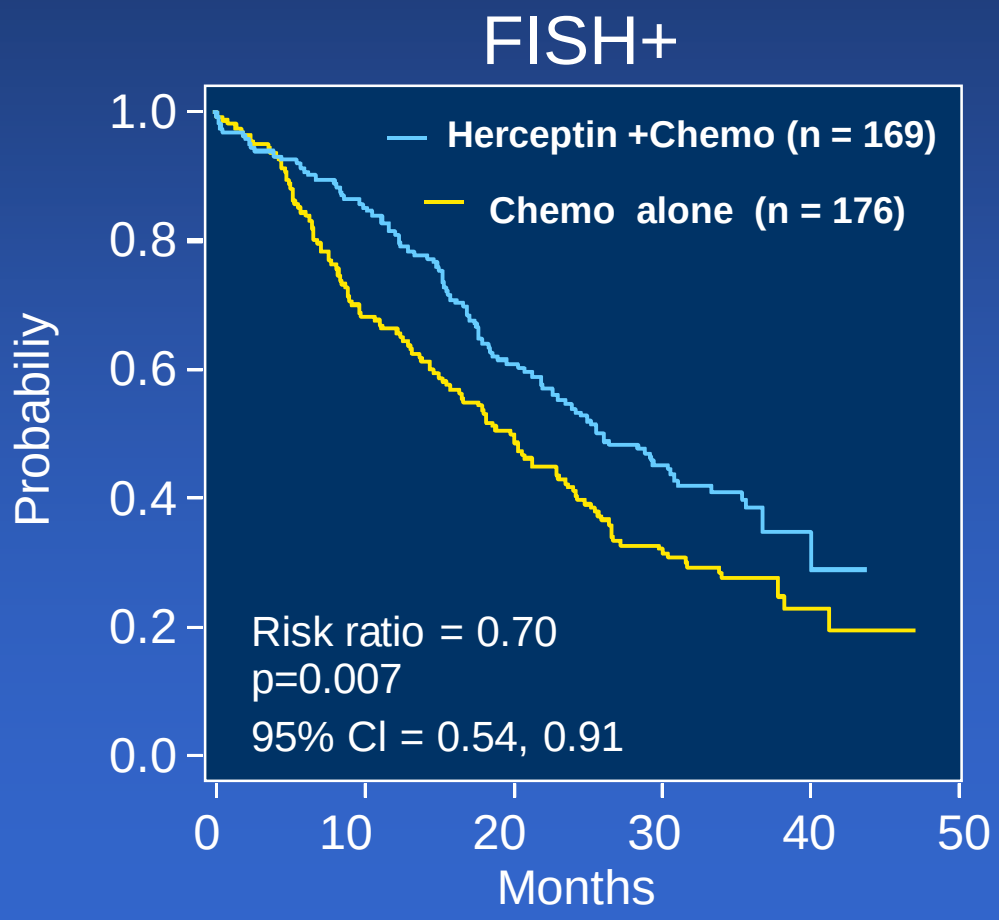


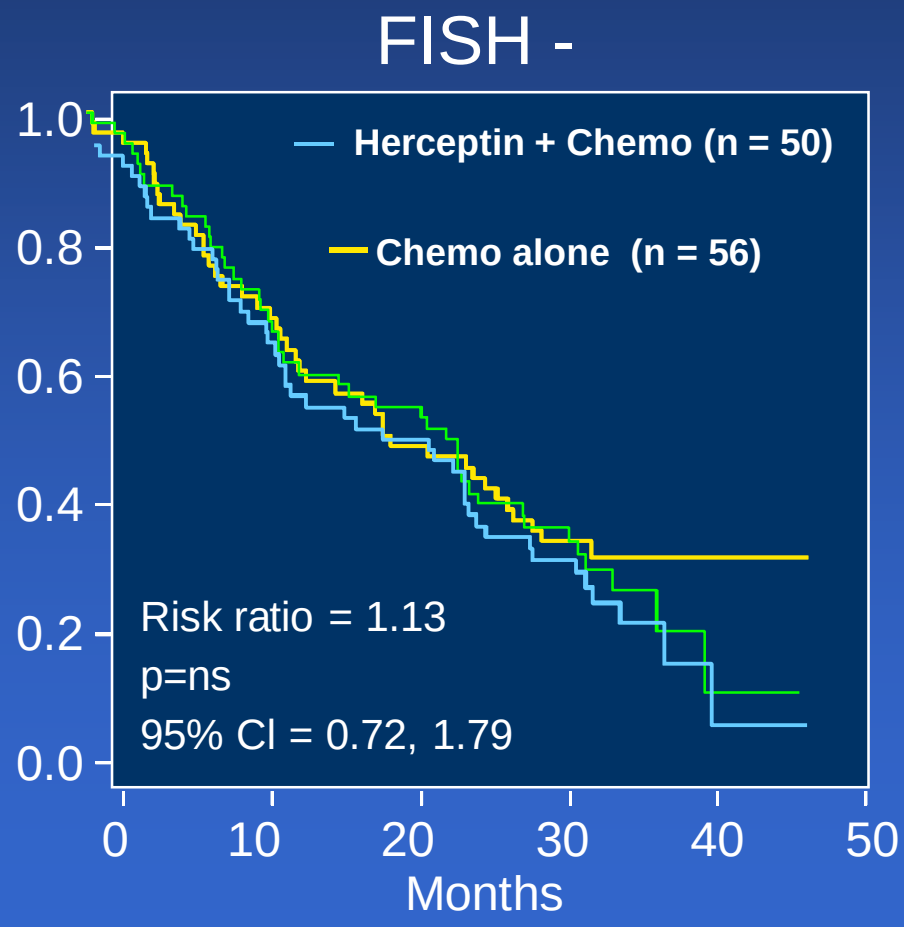
RR = .80
p = .046

65 % of CT group crossed over to Herceptin

FISH/Overall Survival H0648g

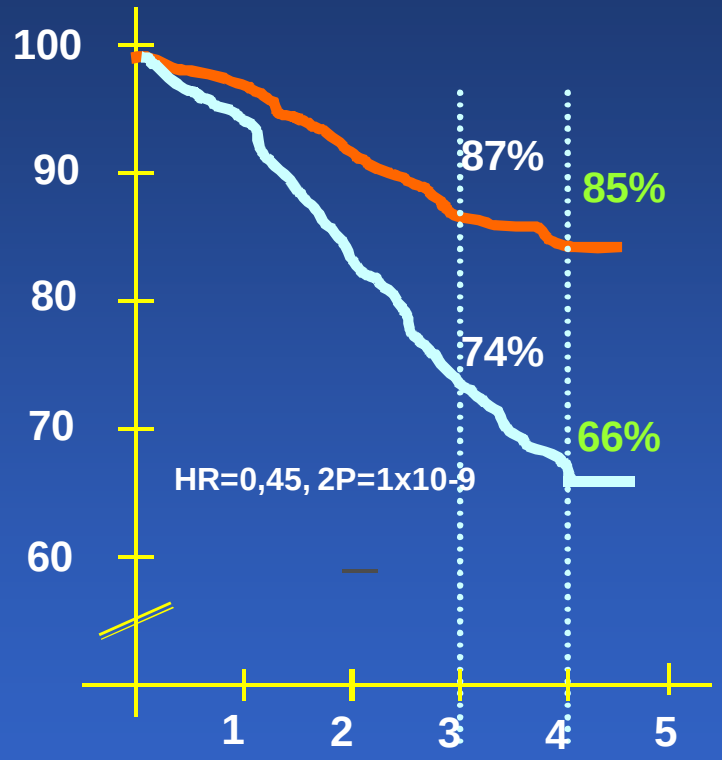
Chemotherapy +/- Herceptin, 1st Line





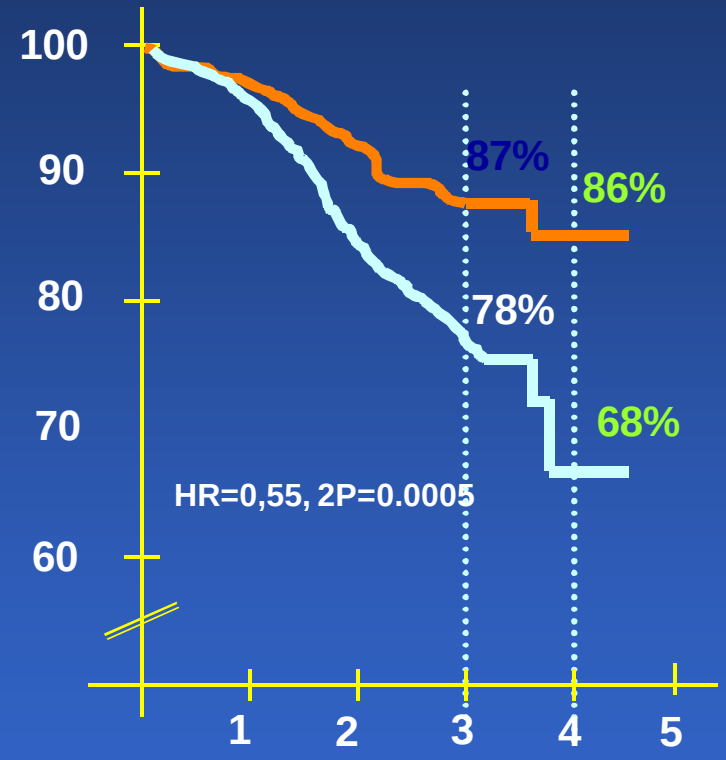
Adjuvant Trastuzumab Disease-Free Survival

•B-31



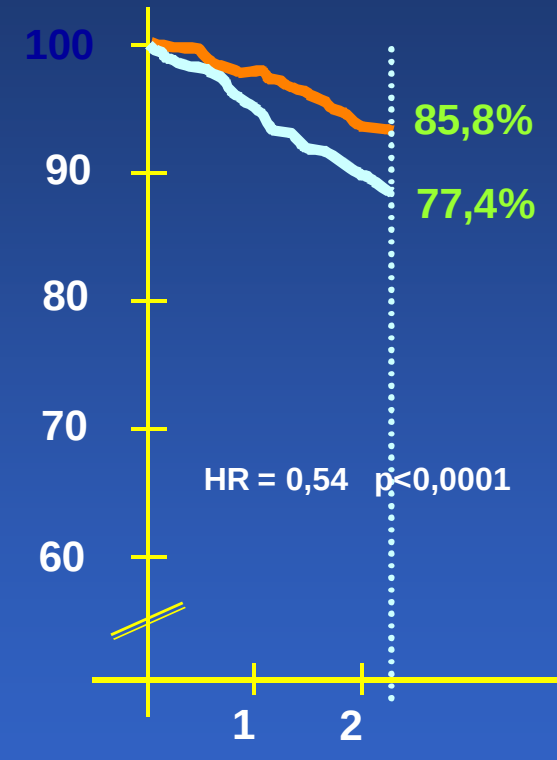
	N	Events
AC -> T	872	171
AC -> TH	864	83

•N9831



	N	Events
AC -> T	807	90
AC -> TH	808	51

•HERA

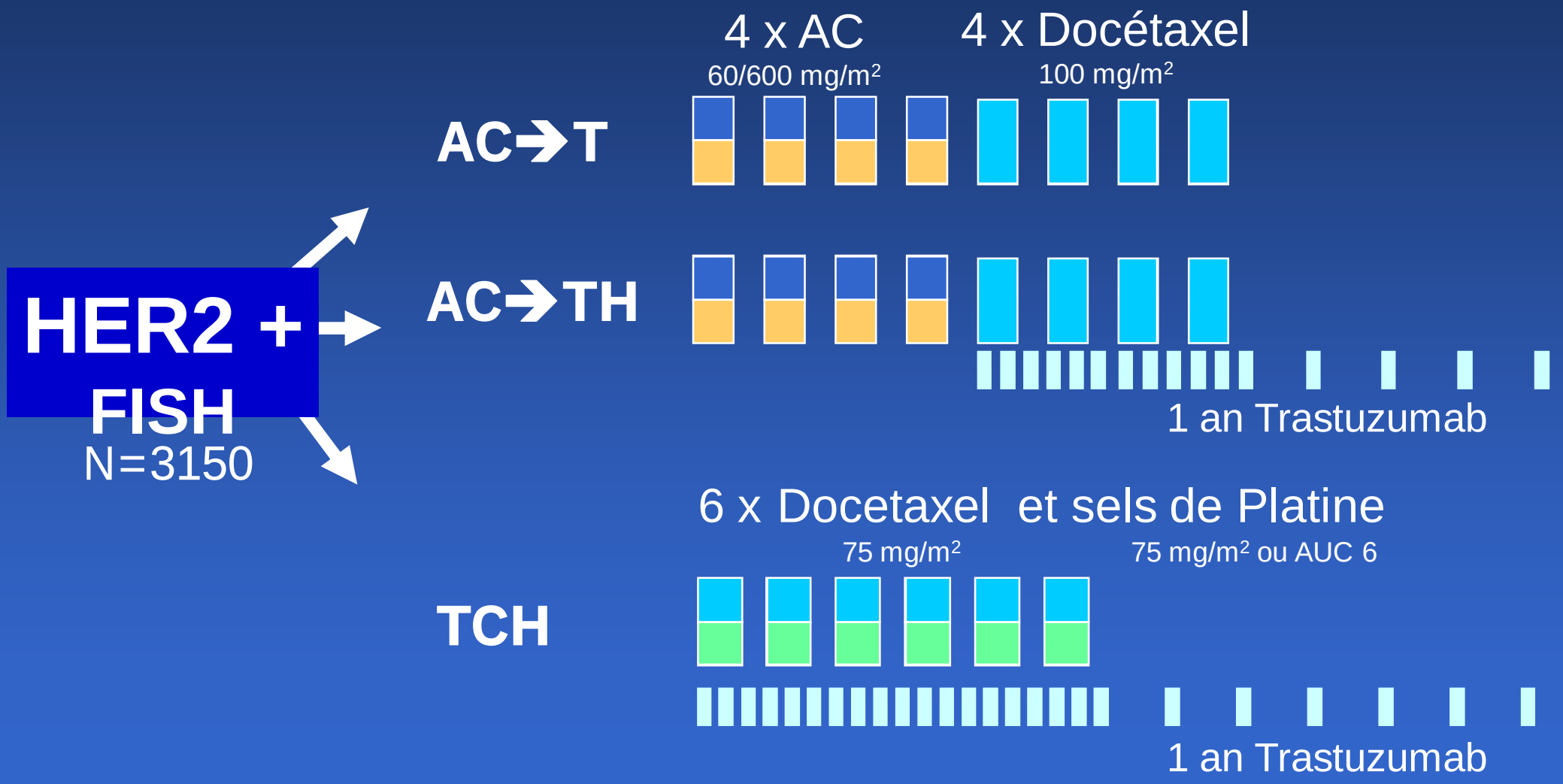


	N	Events
Chimio	1694	127
Chimio -> H	1693	220

ASCO 2005

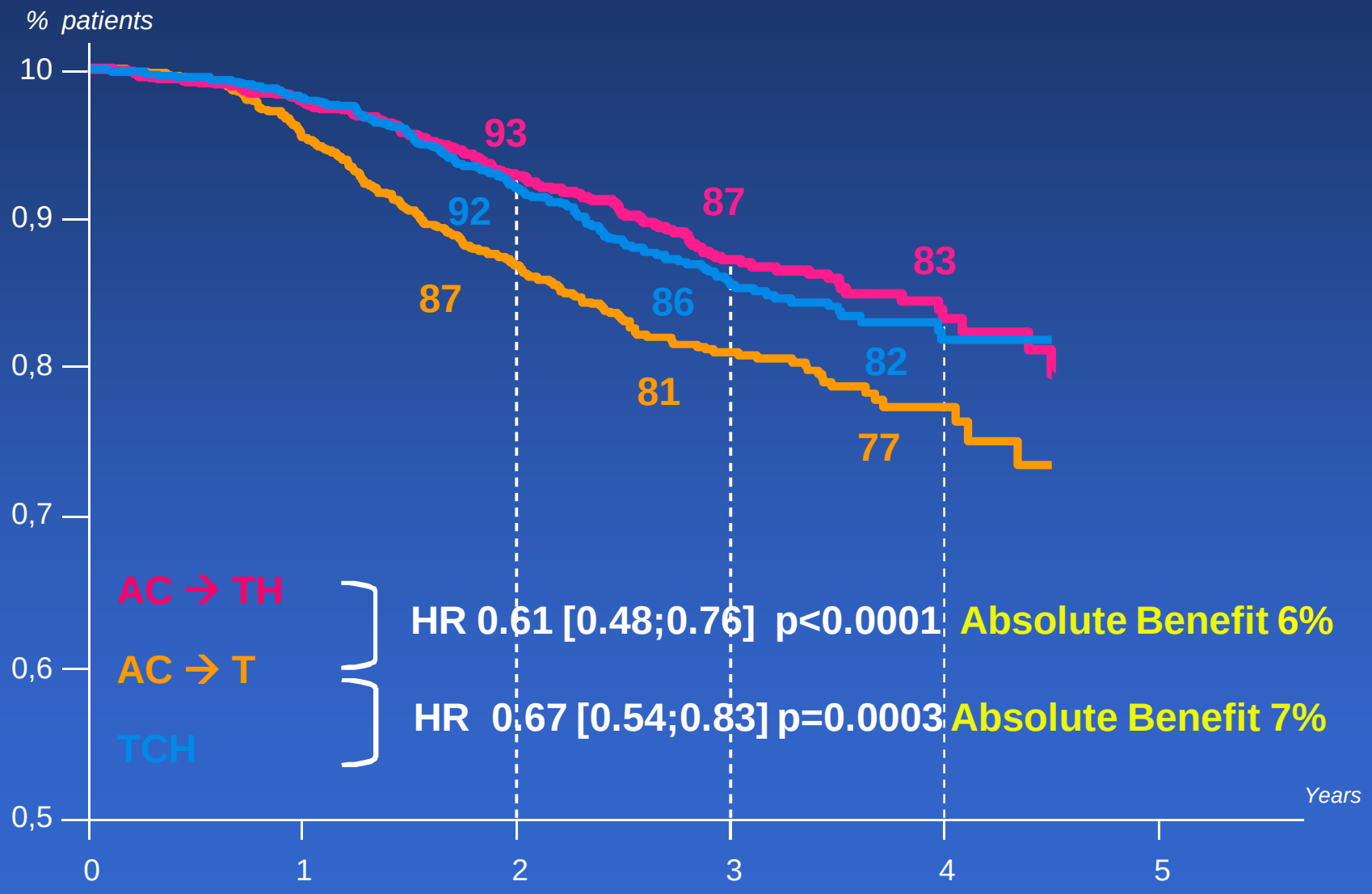
BCIRG 006

Breast Cancer Adjuvant HER-2 Positive by FISH



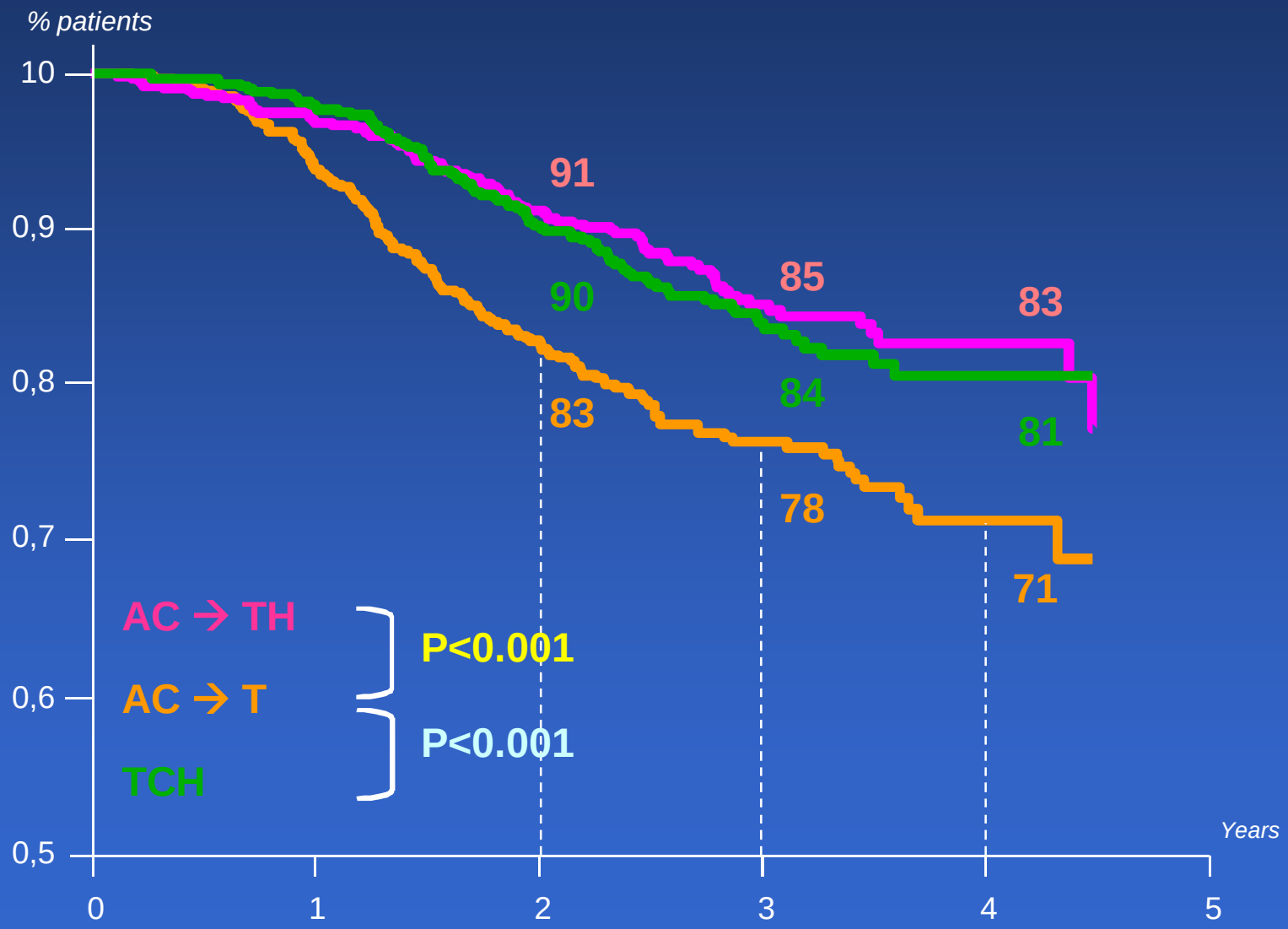
Nabholtz JM, Slamon D et al

BCIRG 006:DFS



D. Slamon et al., SABCS 2007, abst. 13

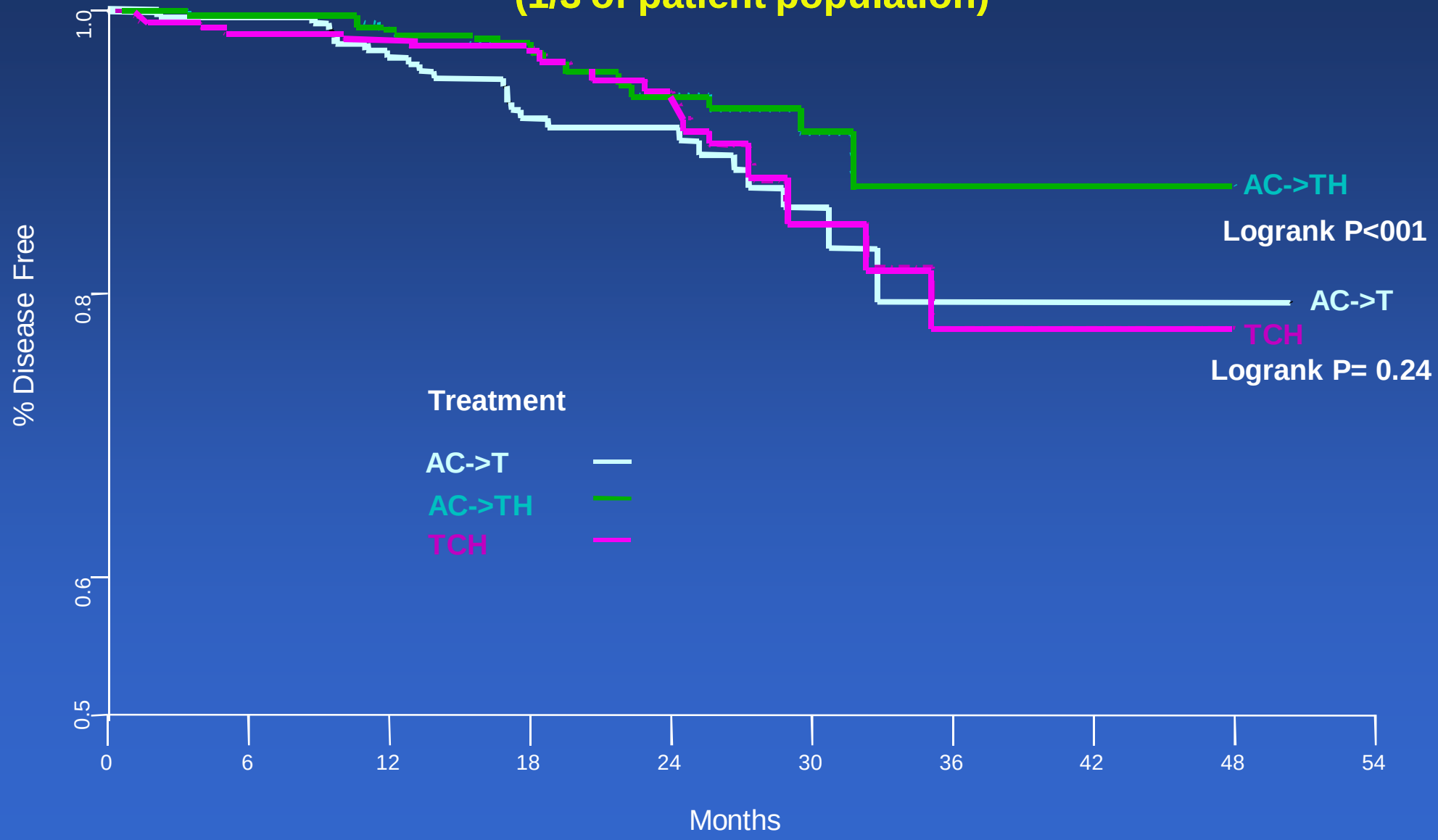
BCIRG 006: DFS no Co-Amplification Gene Topo IIa
(2/3 of patient population)



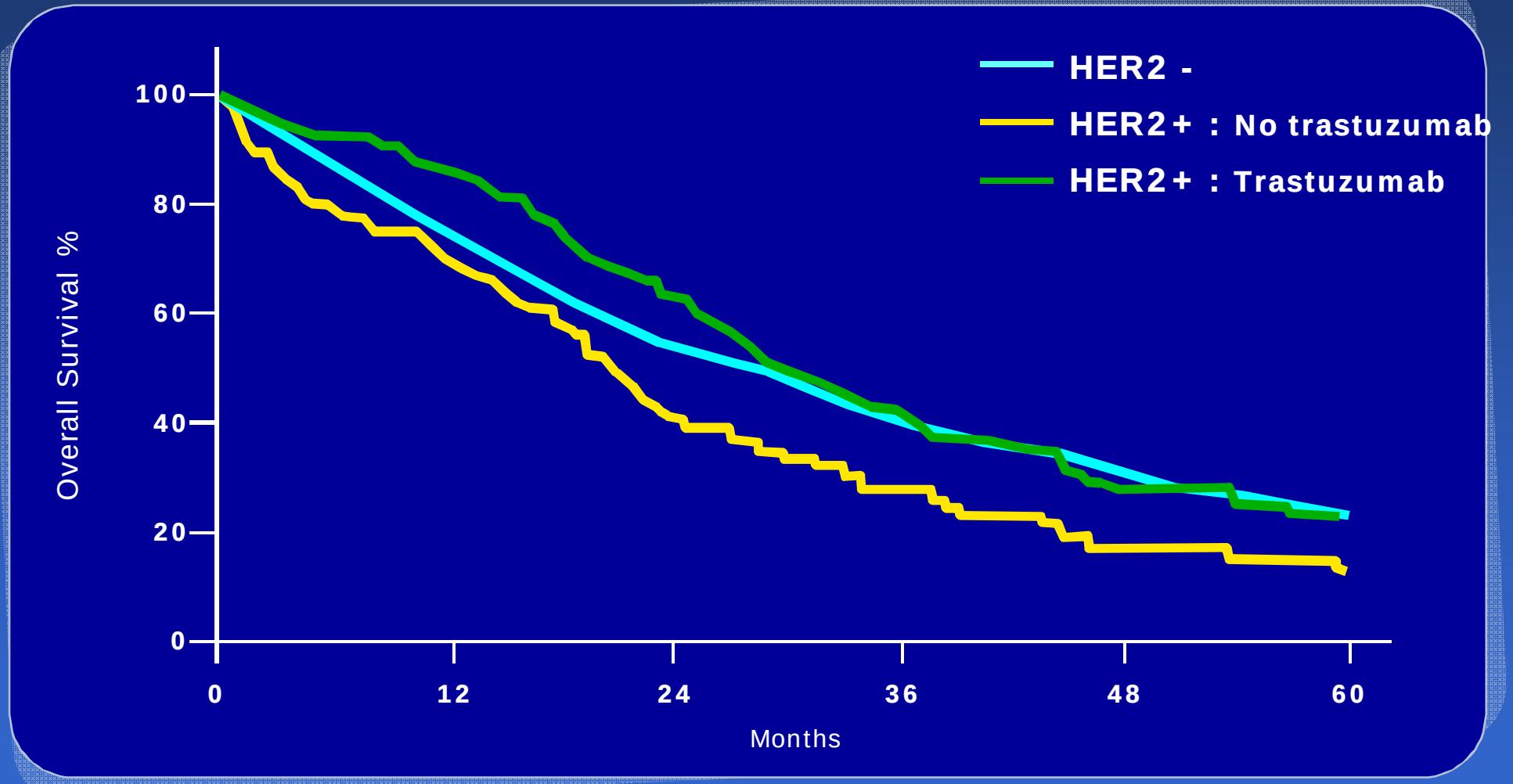
D. Slamon et al., SABCS 2007, abst. 13

BCIRG 006: DFS Co-Amplified Gene Topo IIa

(1/3 of patient population)



Overall Survival According to HER status and Herceptin treatment



S.S. Dawood et al. ASCO 2008. Abstract 1018

Change in Paradigm: towards Translational approaches

"From humans to the lab, back to humans" instead of "from the lab to humans"

- Identification of abnormalities in humans: Prognostic value
- Confirmation of relevance in human cancers (Xenografts)
- Identification of a therapy targeting the anomalies
- Development of tests for targeting patient subpopulations: Confirmation of predictive value
- Pivotal clinical development (Phase II,III) in selected population of patients

Role of Neoadjuvant Strategies in Breast Cancer Therapeutics

Two generations so far

Neoadjuvant strategies
First generation (1990s)

Question: What is the role of Neoadjuvant (systemic treatment before surgery) versus Adjuvant strategies (systemic therapy after surgery)?

Neoadjuvant strategies
First generation

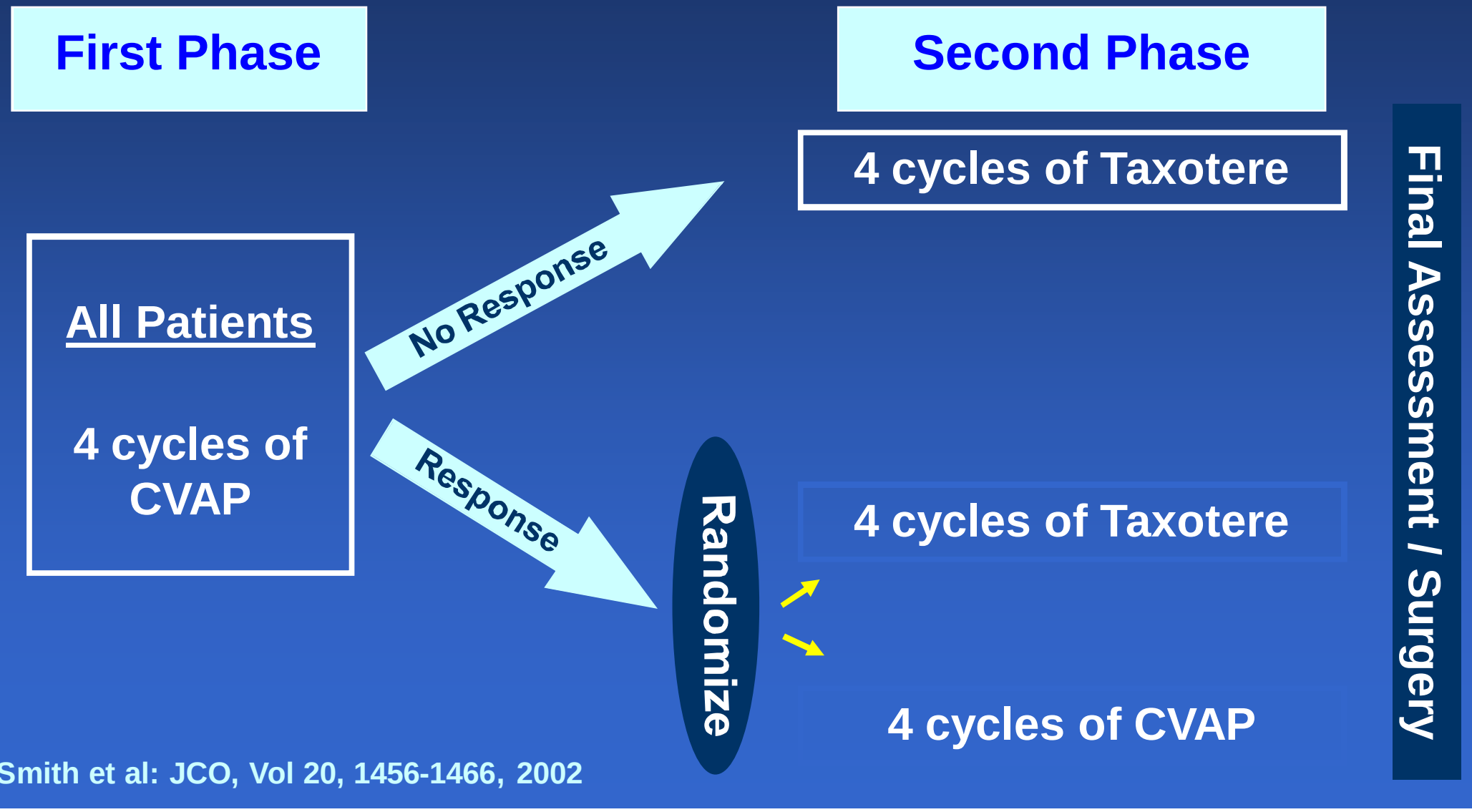
Answers:

1. Neoadjuvant similar to adjuvant (Survival)
2. Increase rates of conservative surgery
3. pCR correlated with survival

Neoadjuvant strategies
Second generation

The Quest for Pathologic Complete Response (pCR)

Single Agent Neoadjuvant Taxotere After 4 Cycles CVAP



Smith et al: JCO, Vol 20, 1456-1466, 2002

Objective Response after Eight Cycles of Chemotherapy

	4CVAP (162)	No response → 4Docetaxel (N=55)	Randomized to 4 CVAP (N= 52)	Randomized to 4Docetaxel (N=52)
cCR+cPR	56%	47%	64%	85%
Clinical complete response	14%	11%	33%	56%
PCR: In breast and Axilla.		**2%**	**15%**	**31%**

Breast conserving surgery: CVAP=48% Docetaxel = 67% P=0.01

Higher Five yr DFS 90% vs 72% P=0.04

Smith et al: JCO, Vol 20, 1456-1466, 2002

Neoadjuvant strategies
Second generation

Answers:

1. Neoadjuvant allows to select “in vivo sub-populations” of patients based upon their sensitivity to therapy…
2. Potential model for predictivity of efficacy or non efficacy of therapy.
3. Potential human model for biologic developments

Neoadjuvant strategies Second generation

1. No information for optimization of adjuvant therapy, based upon biologic modifications induced by exposition to therapy in neoadjuvant setting (individualized therapy)
2. Limited biologic data from neoadjuvant trials...

Neoadjuvant strategies Third Generation (2010s)

From Neoadjuvant to adaptative Adjuvant therapies

Neoadjuvant strategies Third Generation (2010s)

"From humans to the lab, back to humans" instead of "from the lab to humans"

- Identification of abnormalities in biologically defined sub-populations: Prognostic value with confirmation of relevance in human cancers (Xenografts).
- Exposition to new therapies targeting the abnormalities.
- Development of tests for targeting patient subpopulations: Confirmation of potential predictive value.
- Study of mechanisms of resistance to therapy: predictive tests
- Prerequisite to pivotal clinical development (Phase II,III) in selected sub- populations.
  - Towards the concept of adaptative adjuvant strategies instead of "blind adjuvant approaches"

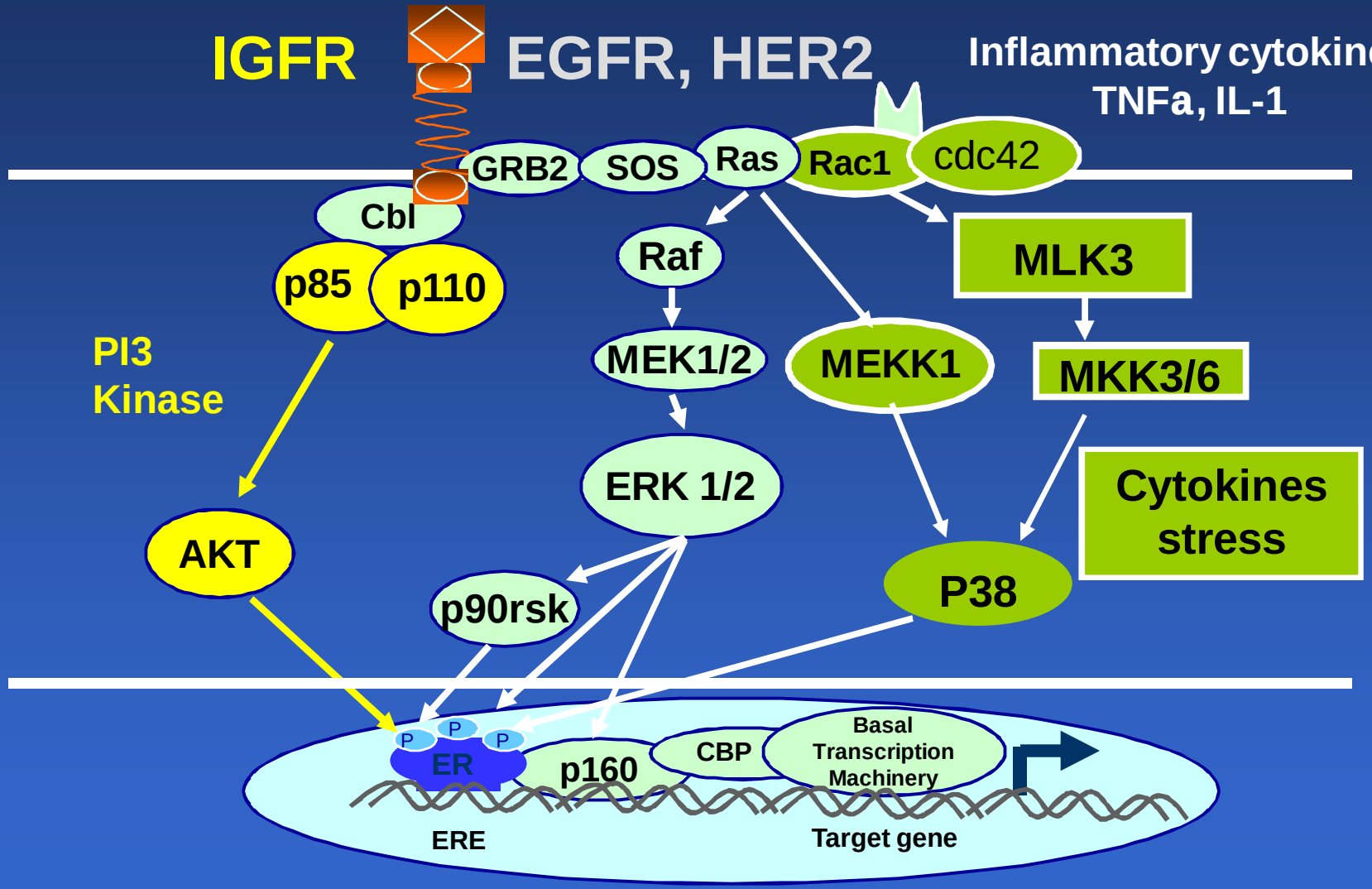
The future?

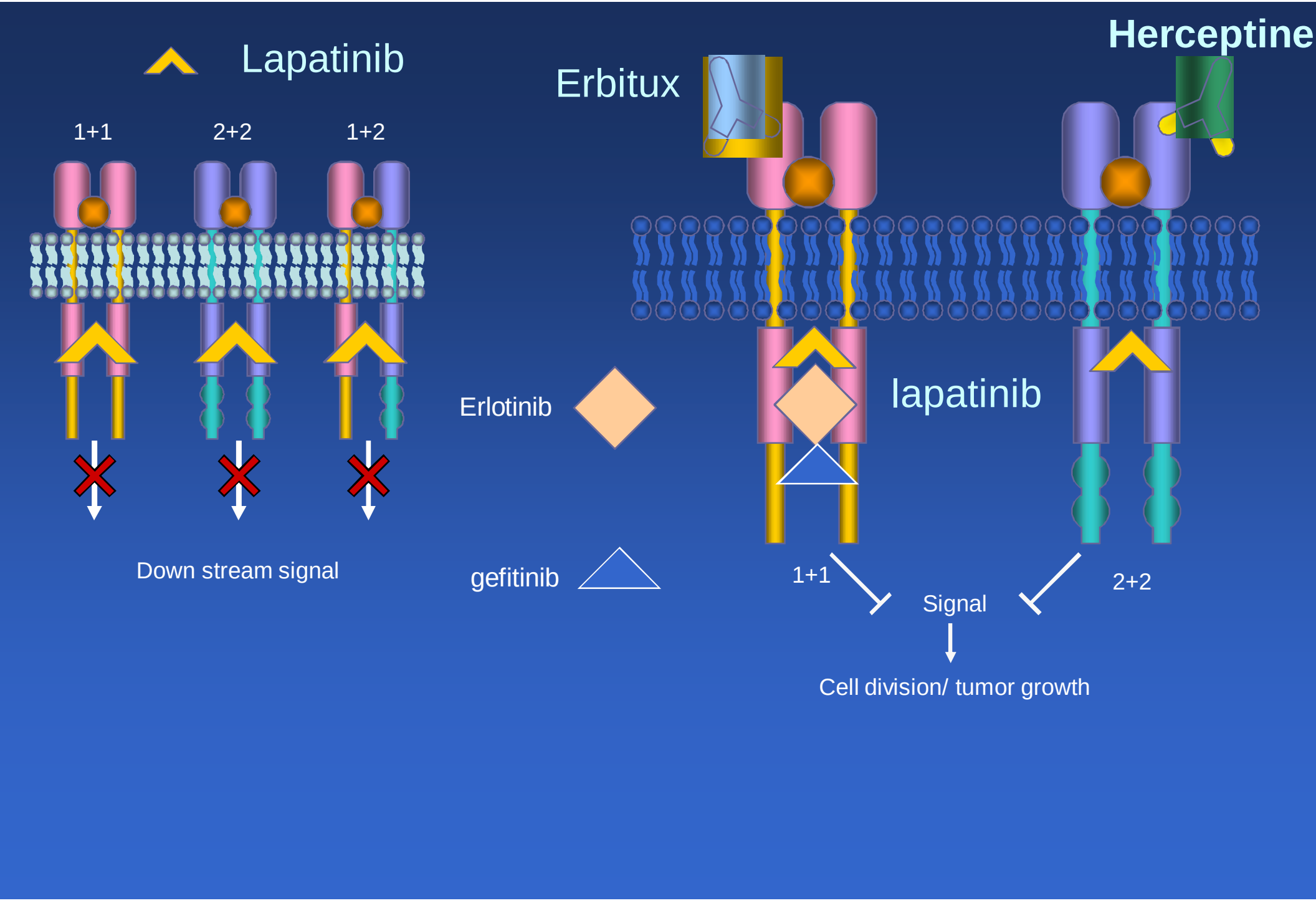
Already Present..

Biologic revolution

Targeting HER-2, Her-1 (EGFR), IGRF…

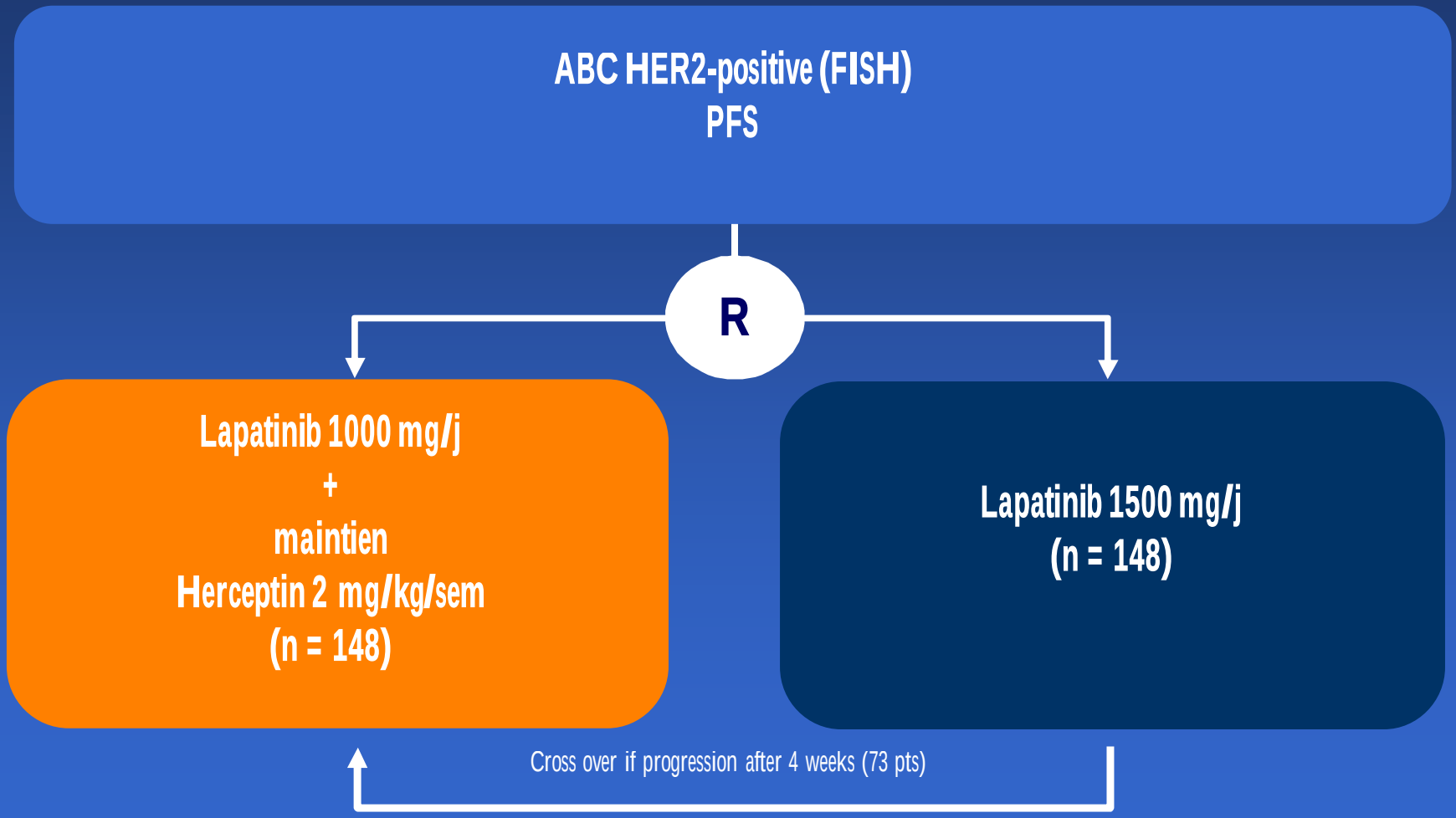
Multiple signaling pathways in breast cancer cells: Multiple targets




Lapatinib
1+1
2+2
1+2
Down stream signal
Erbitux
Herceptine
Erlotinib
gefitinib
lapatinib
1+1
2+2
Signal
Cell division/ tumor growth

Herceptin + Lapatinib *vs* Lapatinib (Etude EGF104900)

Phase III Randomized trial

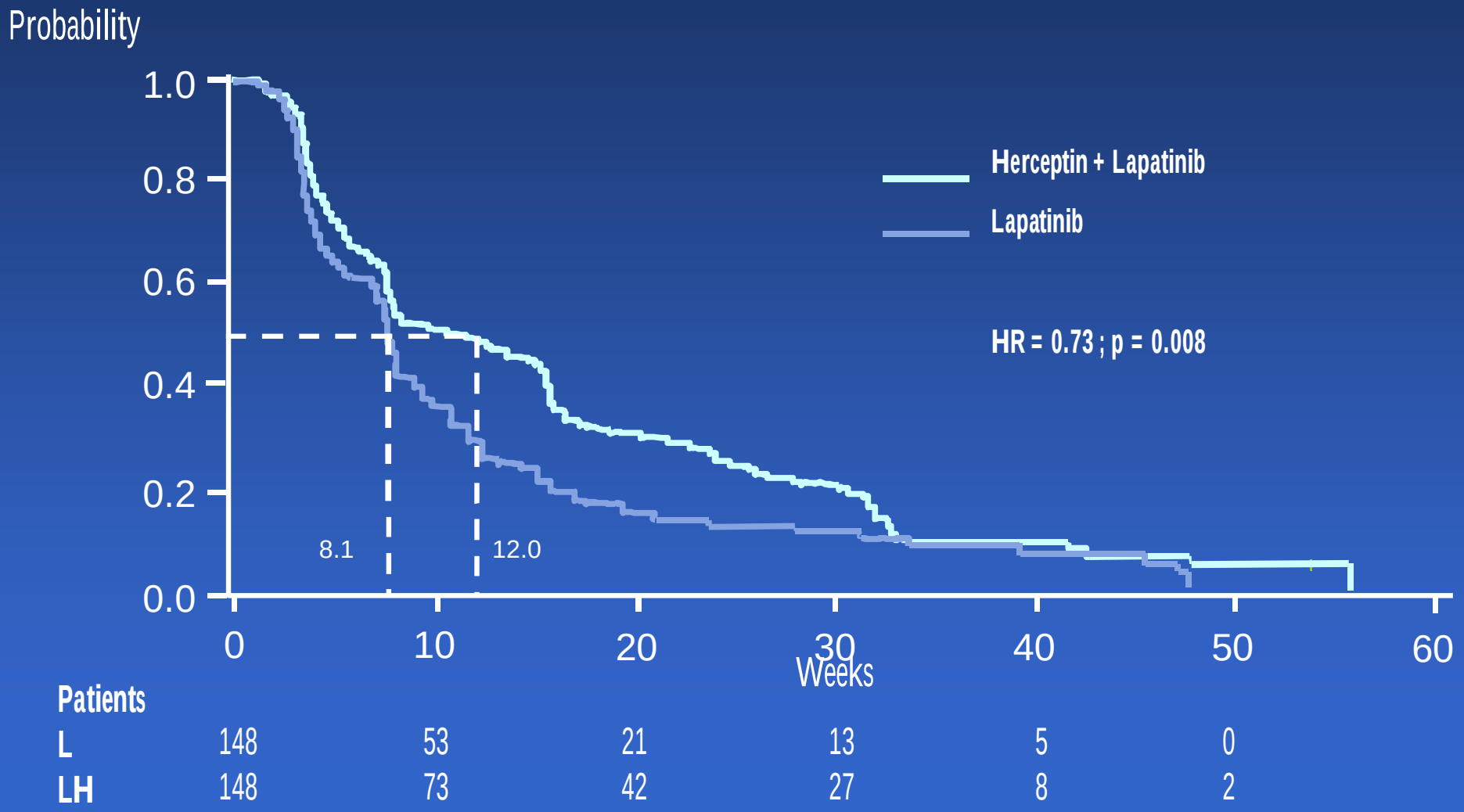


Primary Endpoint : PFS

O'Shaughnessy et al. ASCO 2008

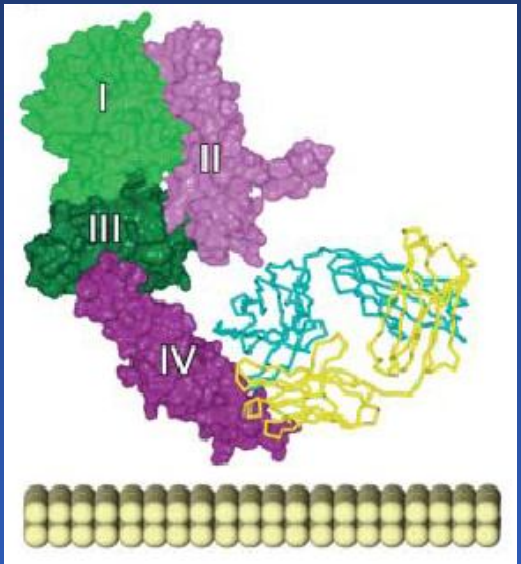
Herceptin + Lapatinib *vs* Lapatinib

Progression-free Survival



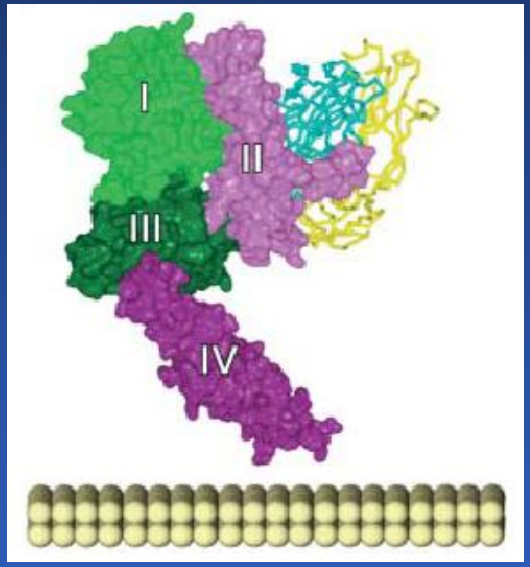
O'Shaughnessy et al. ASCO 2008

Herceptin and Pertuzumab target 2 distinct epitopes of the HER2 extracellular domain



Herceptin

- Activate cellular antibody-dependent oytotoxicity
- Inhibit HER2 Clivage and formation of p95 fragments
- Inhibit HER2 signaling pathway

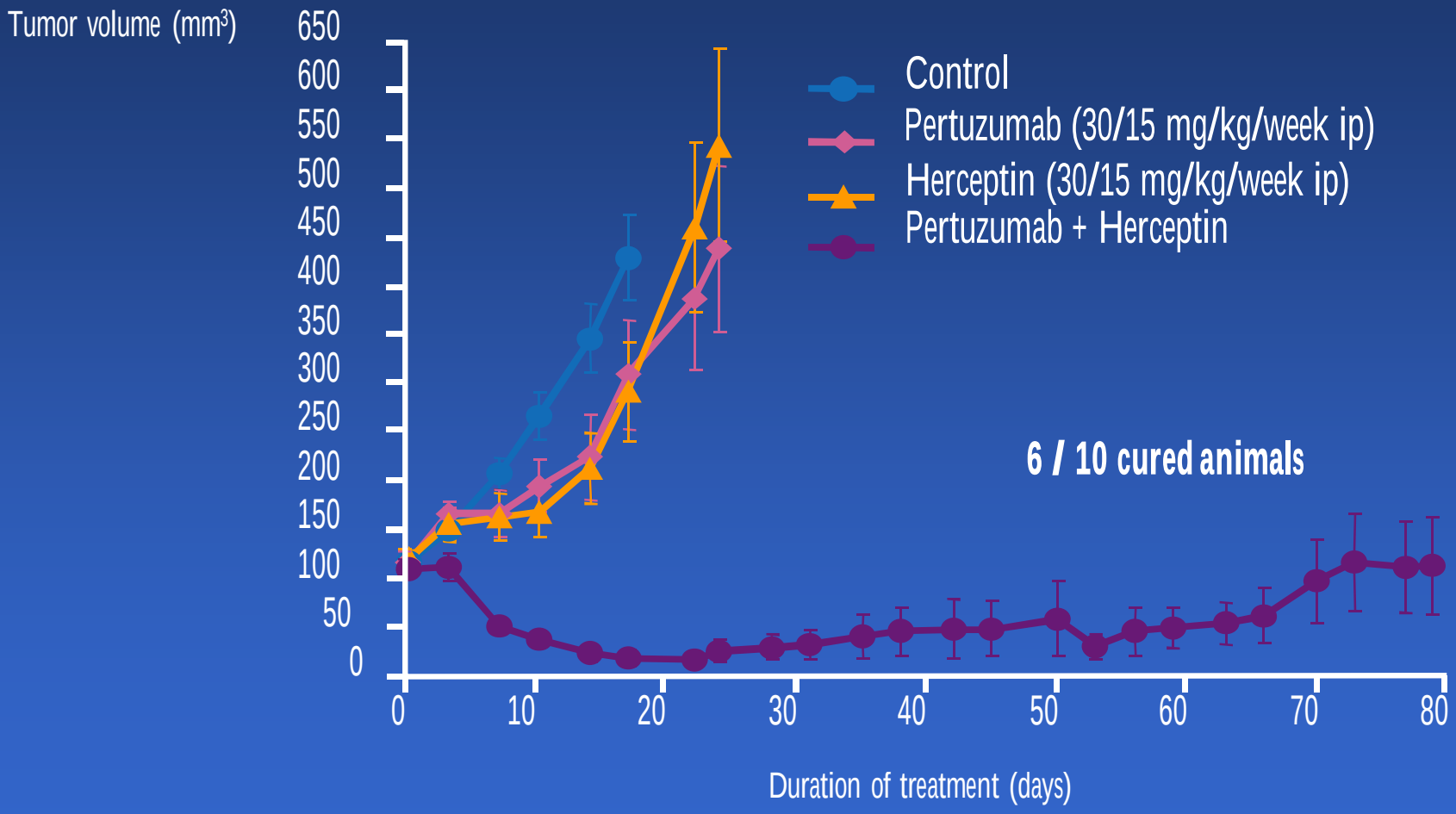


Pertuzumab

- Block receptor dimerazation
- Strong inhibition of HER2 signaling pathway
- Activate cellular antibody-dependent oytotoxicity

Hubbard 2005

Combination Herceptin + Pertuzumab : Breast cancer Xemografts



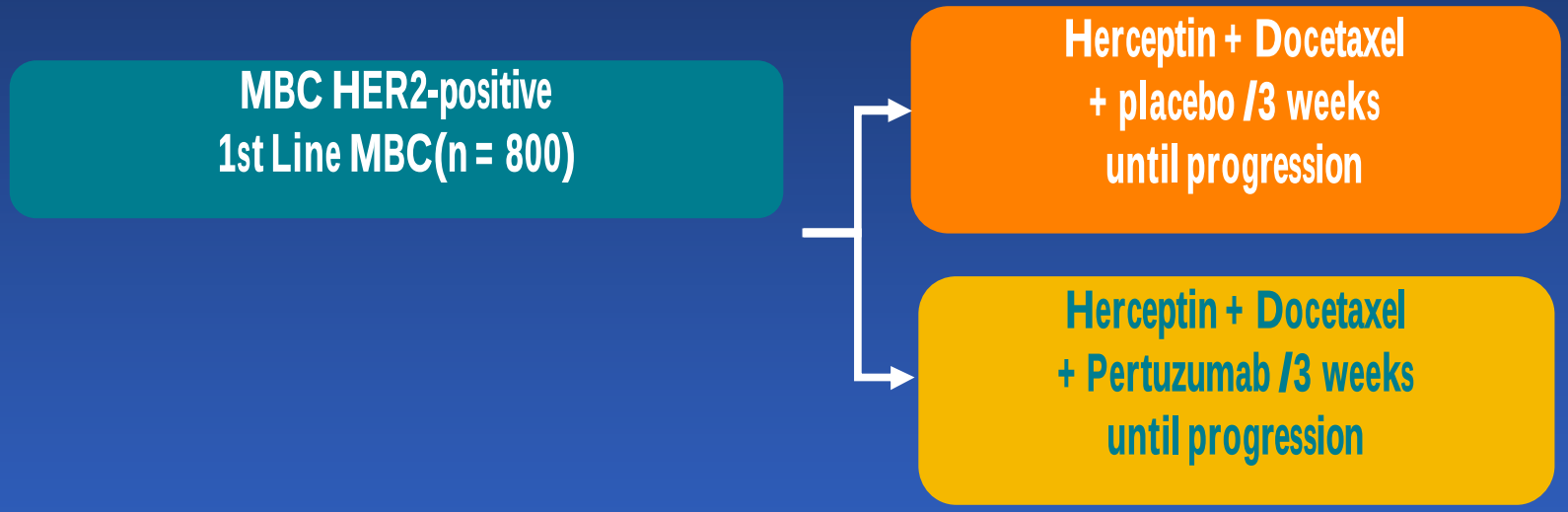
Friess et al. ESMO 2006

Herceptin + Pertuzumab after progression on herceptin (phase II)

Response	n (%) n = 66
Complete response	5 (7,6 %)
Partial response	11 (16,7 %)
Global response	16 (24,2 %)
Stabilisation (≥ 6 months) (≥ cycle 8)	17 (25,8 %)
Clinical benefit	33 (50,0 %)
Progression	33 (50,0 %)

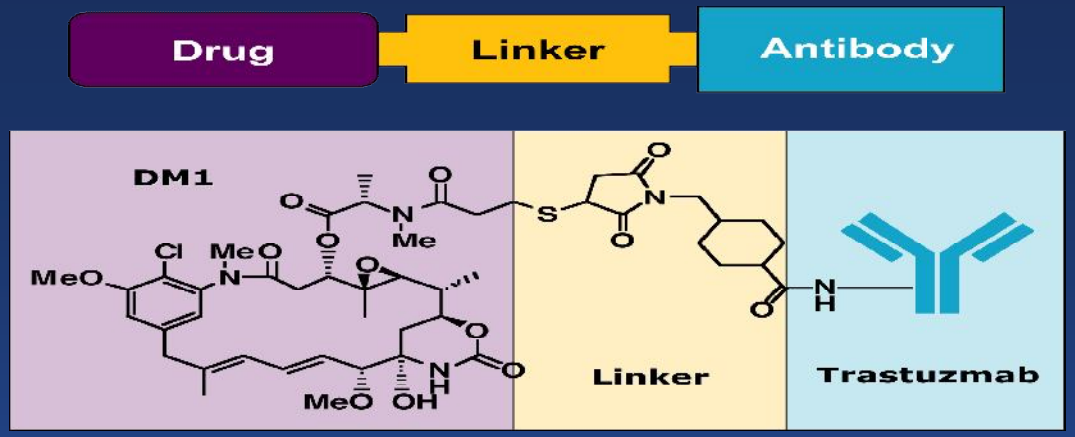
Gelmon et al. ASCO 2008

Herceptin + Docetaxel ± Pertuzumab En 1ère ligne du MBC (phase III, CLEOPATRA)



- Primay endpoint : PFS
- Secondary endpoints : OS, RR, toxicity quality of life.
- International study

T-DM1 : Targeted Chemotherapy



Target expression: HER2

Monoclonal antibody: Trastuzumab

Cytotoxic agent: DM1

Highly potent cytotoxic agent

Linker: MCC

Systemically stable

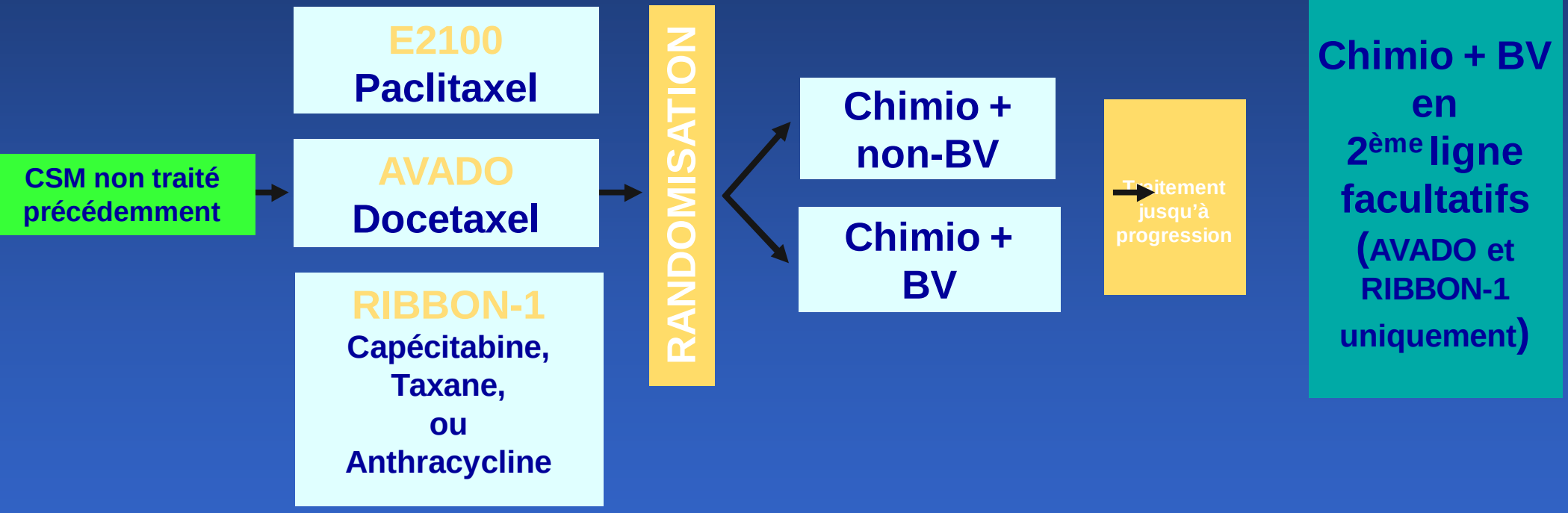
T-DM1

Average drug:
antibody ratio ≅3.5:1

Targeting the Angiogenesis…

Bevacizumab (Avastin) = Anti-VEGF Antibody

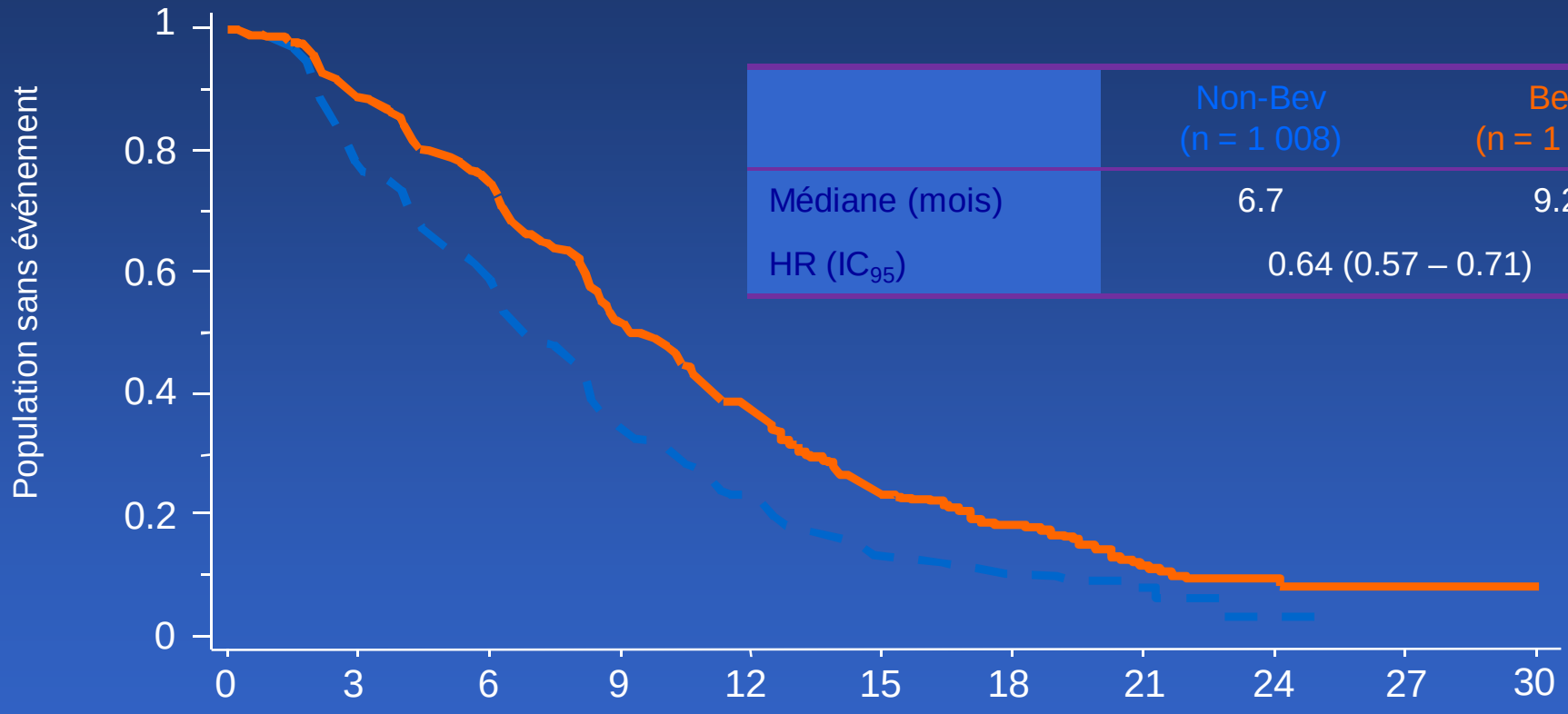
Méta-analyse E2100, AVADO et Ribbon-1
Design des études



O'Shaughnessy J. et al. ASCO 2010

Méta-analyse E2100, AVADO et Ribbon-1

Survie sans progression, population poolée



	Non-Bev (n = 1 008)	Bev (n = 1 439)
Médiane (mois)	6.7	9.2
HR (IC_{95})	0.64 (0.57 – 0.71)	

Patientes à risque (n)

Non-Bev	1 008	680	464	210	111	38	18	9	1	0	0
Bev	1 439	1 157	885	491	292	134	67	22	8	2	1

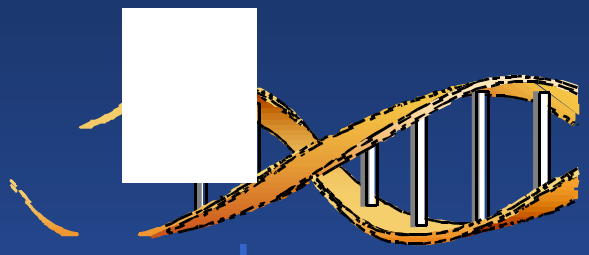
O'Shaughnessy J. et al. ASCO 2010

Triple negative BC

Inhibitors of PARP

Mechanisms of DNA Repair

DNA DAMAGE



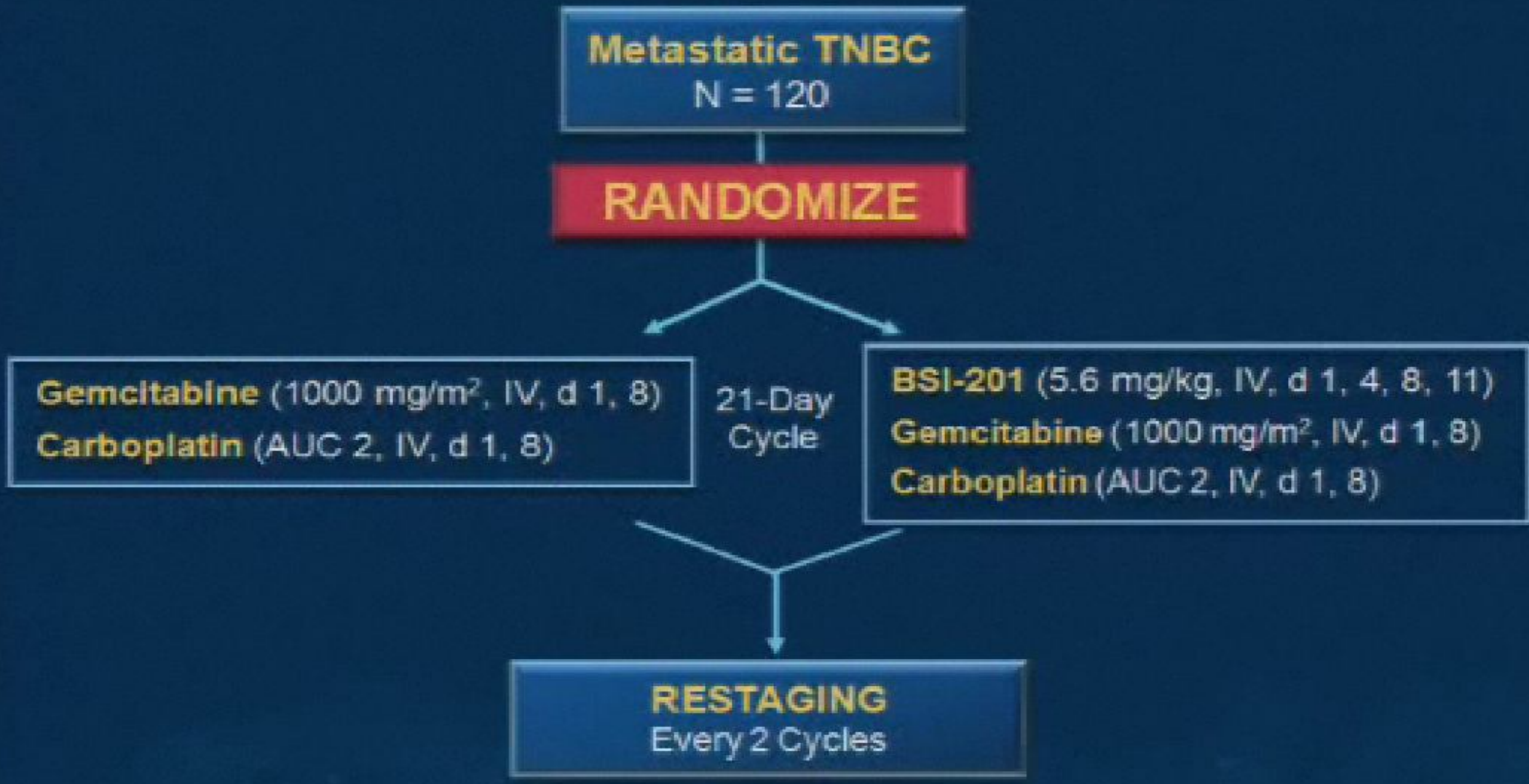
Cell Death

MAJOR DNA REPAIR PATHWAYS

Replication Lesions
- Base excision repair
  - PARP1

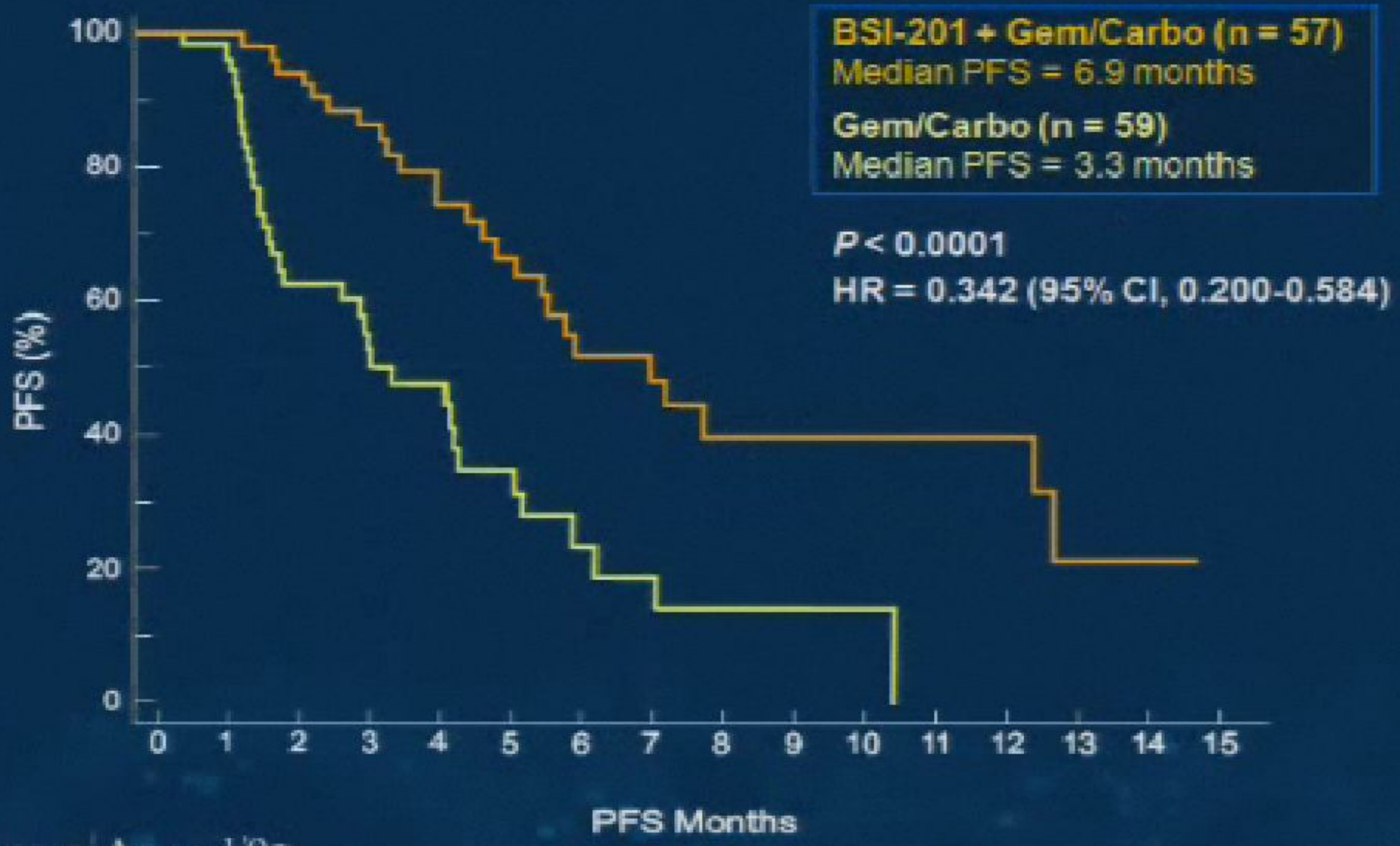
DNA Adducts/Base Damage
- Alkyltransferases
- Nucleotide excision repair
- Base excision repair
  - PARP1

Phase II TNBC Study: Treatment Schema

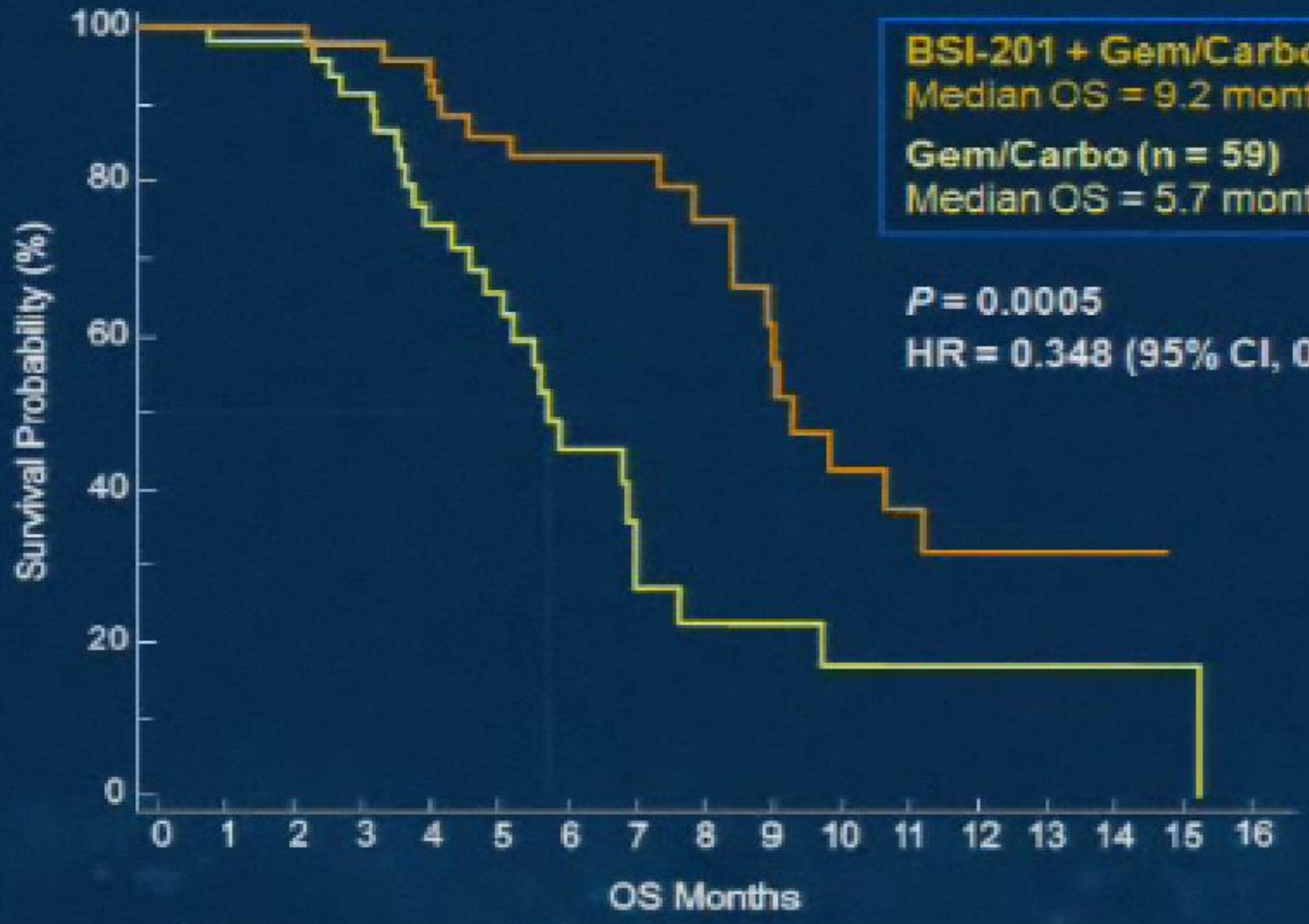


* Patients randomized to gem/carbo alone could crossover to receive gem/carbo + BSI-201 at disease progression

Progression-Free Survival



Overall Survival



BSI-201 + Gem/Carbo (n = 57)
Median OS = 9.2 months

Gem/Carbo (n = 59)
Median OS = 5.7 months

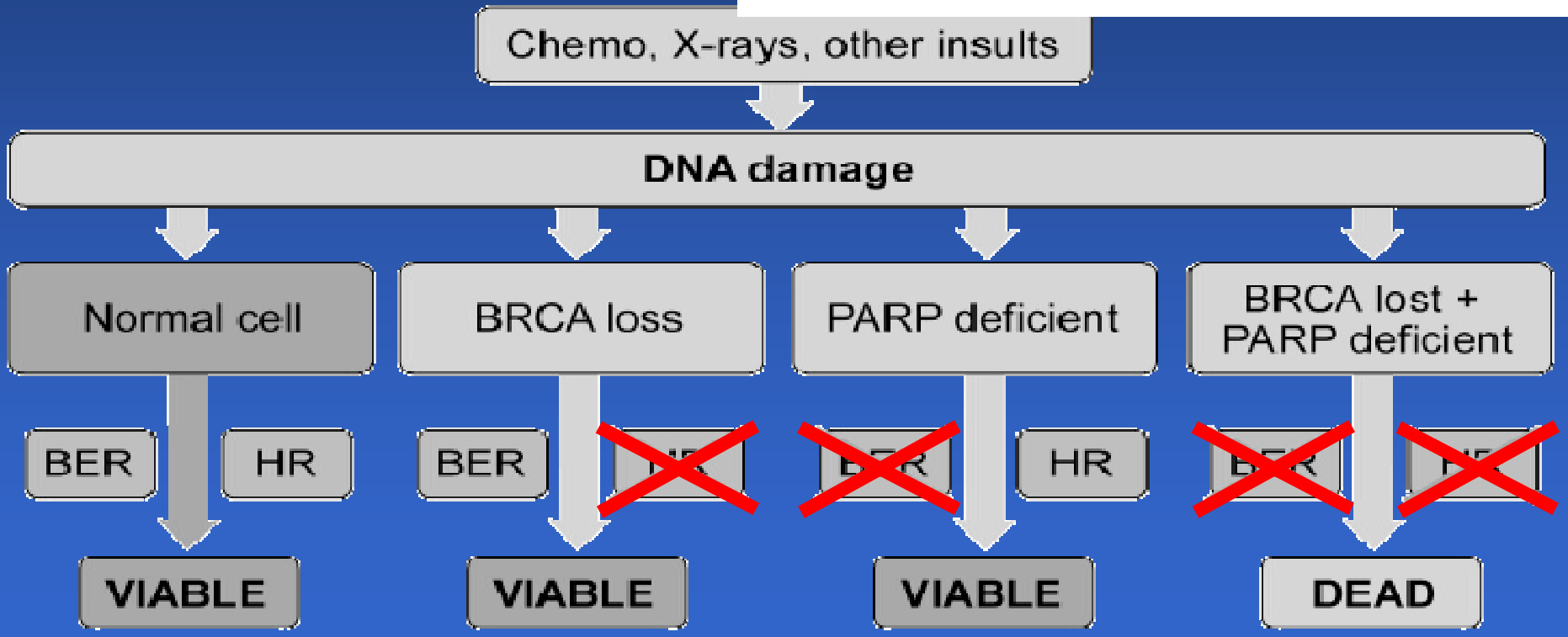
P = 0.0005
HR = 0.348 (95% CI, 0.189-0.649)

BRCA1 and PARP Abnormalities Synergize to Kill Cells

"SYNTHETIC LETHALITY"

Cell death by dual targeting of pathways that in isolation are not lethal

HR= homologous recombi
BER=base excision re

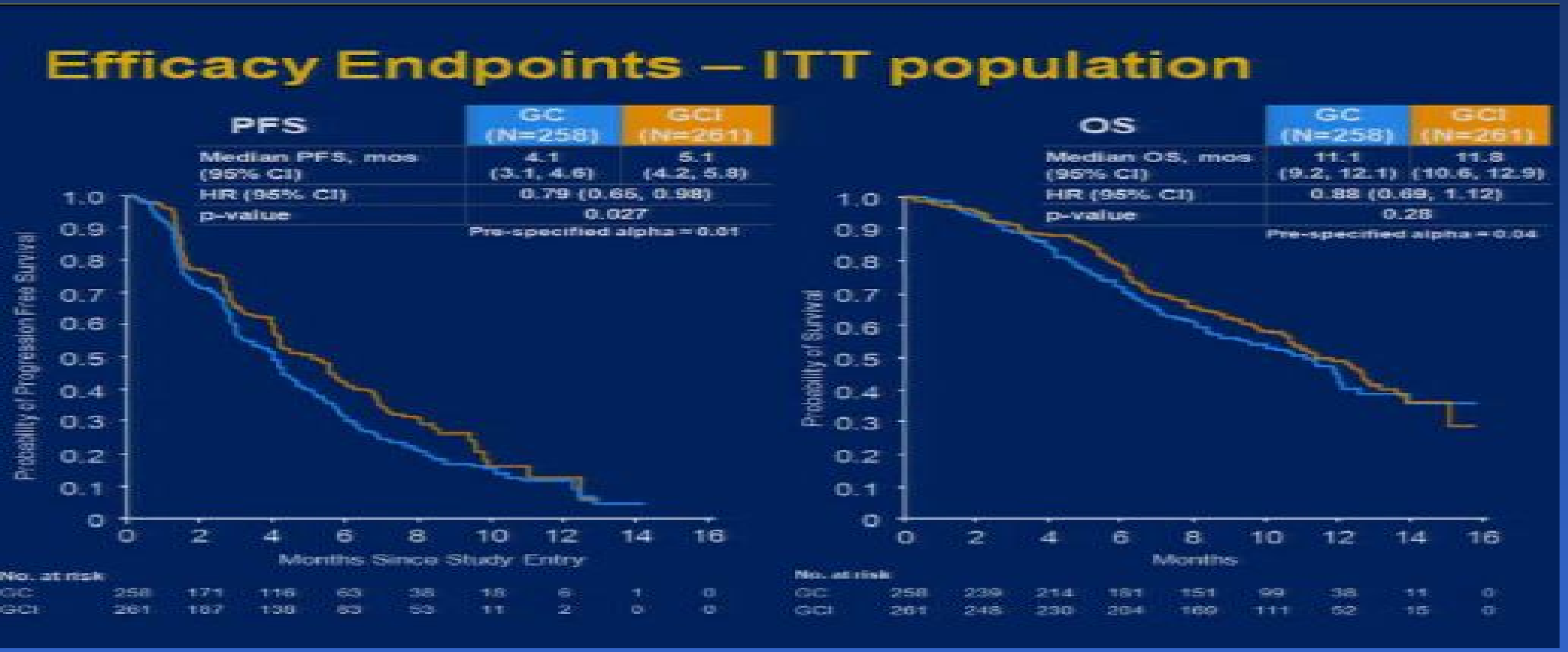


PARP Inhibitors in Development

Drug	Route	Phase*
ABT-888	Oral	II
AG-014699	IV	II
Olaparib (AZD2281)	Oral	II
Iniparib (BSI-201)	IV	III
INO-1001	IV	II
GPI 15427	Oral	I
MK4827	Oral	I/II
CEP-9722	Oral	II

***Highly heterogeneous regarding tumor types and combinations/single agents**

Chemotherapyimiothérapies et Thérapies ciblées des HER2- and anti_PARP Triple negative BC…

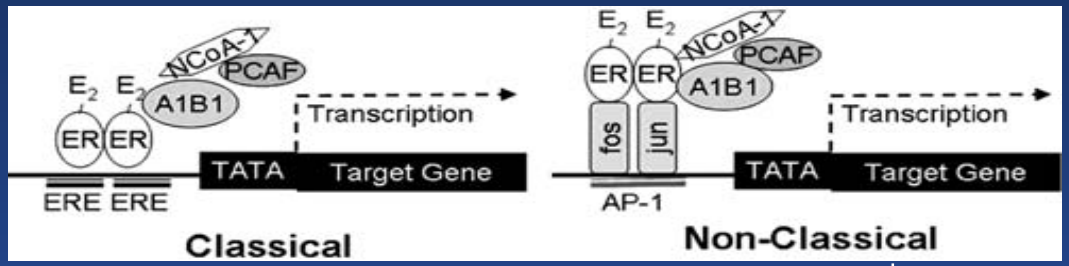


O’Shaughnessy, ASCO 2011

Combination of Hormonotherapy with biologic modifiers

Estrogen Receptors

Nuclear level

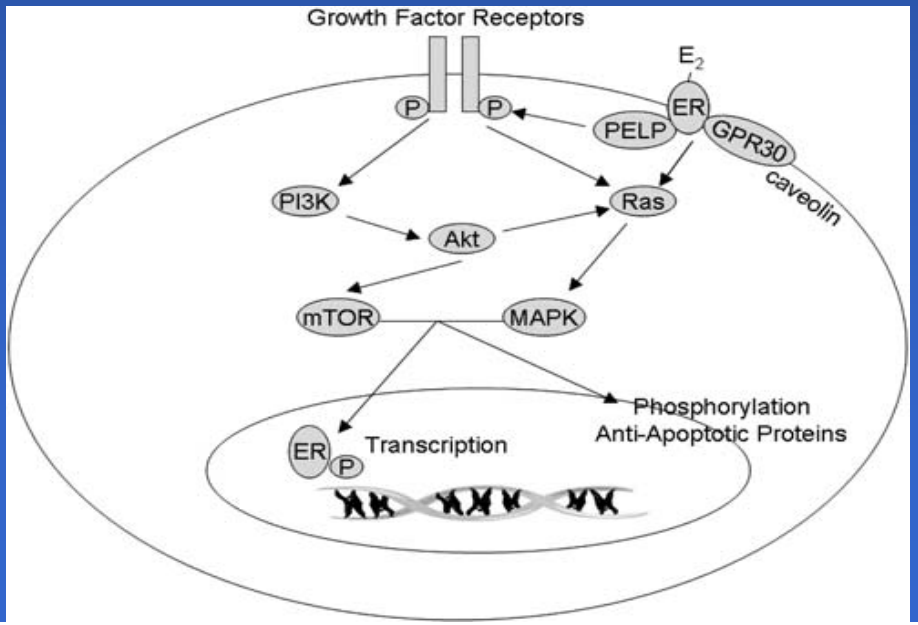


Genes involved in proliferation, inhibition of apoptosis, angiogenesis and invasion metastasis

Co-activators involved in the expression of different genes such as proliferation, metastasis (IGF-1, myc, cycline D1, Bcl-2, collagenase)

Cytoplasmic and membrane levels

« Cross-talks » with type 1 tyrosine kinase GPR30 et calveline receptors . Activation of ER-E2 complex with activation of membrane growth factor receptors such as IGF-1R, ErbB2/HER-2, and ErbB1/EGFR, with activation of ER at the nuclear level via Akt and MAPK ….



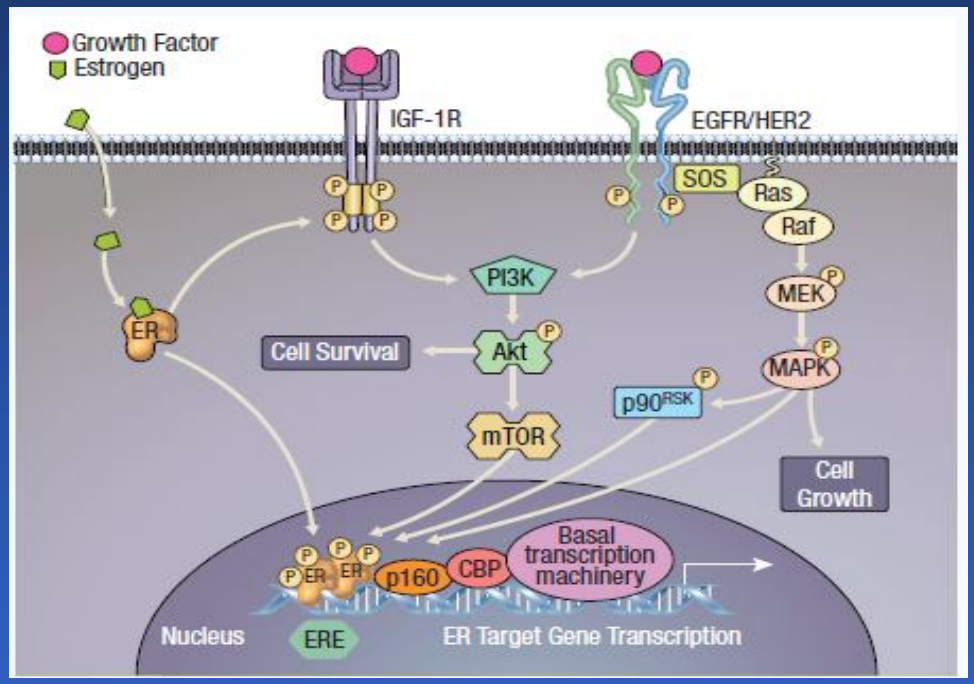
Resistance to hormonotherapy

❖40 à 50% of tumors will not express ER at time of progression on hormonetherapy

➢ Epigenetic « silencing » epigénetique of ER via methylation of CpGin the promoting region of ERα gene (DNA methylation inhibitors →reexpression de ER)

➢Suppression of ER expression by activation of signal transduction pathways (EGFR – HER2) via MAPK which suppress the expression of ERα.

10 patients with advanced BC ER- /HER2+ treated with herceptine 2 -6 mois → new expression of ER in 3 patients (Munzone 2006)



➢ hypersensibility to low levels of œstradiol

➢ « crosstalks » between signal transduction growth factors(EGFR, HER2, IGFR) and activation of ER-dependant transcription genes ER via phosphorylation of ER and/or its association to coactivators of transcription such as AIB1

Cross-talk and endocrine resistance

- Increased EGFR and HER2 signalling is associated with the development of resistance to endocrine agents
- Targeting growth factor signalling pathways may delay the onset of endocrine-resistant disease

EGFR, epidermal growth factor receptor
HER2, human EGFR 2 (also known as c-erbB-2 / neu)

Conclusions

- Significant improvement of breast cancer prognosis
  - Screening programs
  - Better and more adapted therapies with less toxicity
- Evolution towards individualized strategies based upon the tumor biology and the patient
- Future:
  - Less chemotherapy
  - Explosion of biology understanding and biologic therapies ….Concept of "Biologic cocktails"