SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Ferrara

università di ferrara
DA SEICENTO ANNI GUARDIAMO AVANTI.

Recenti acquisizioni nel trattamento del carcinoma mammario

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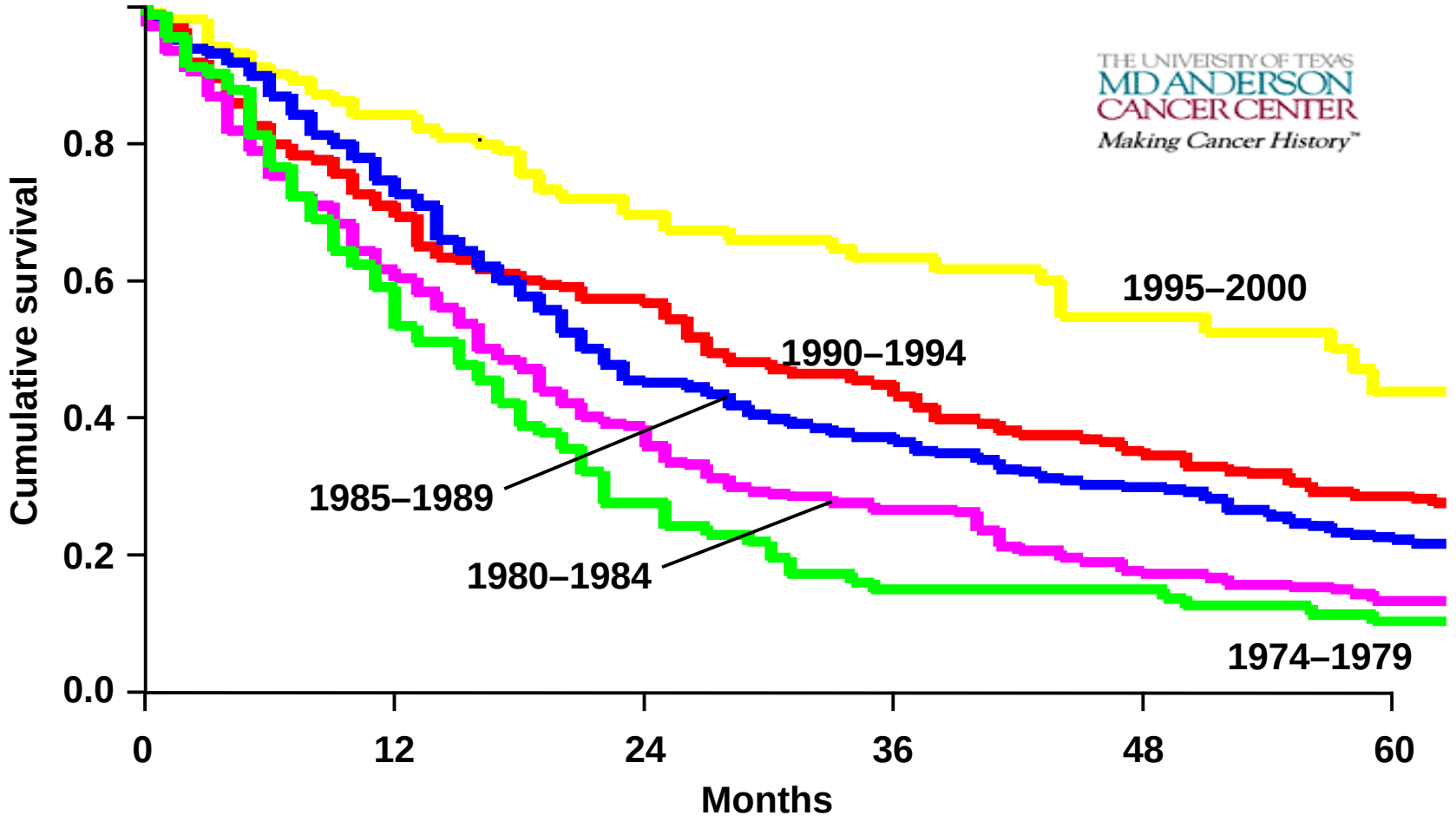
Ferrara

Riunione Società Medico Chirurgica di Ferrara
16 aprile 2011

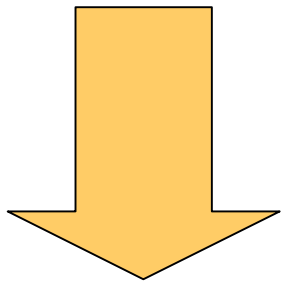
Miglioramenti della sopravvivenza nel carcinoma mammario metastatico



Giordano et al. Cancer 2004;100:44–52

Nuovo paradigma nel trattamento locale del tumore mammario

Dalla massima terapia tollerabile



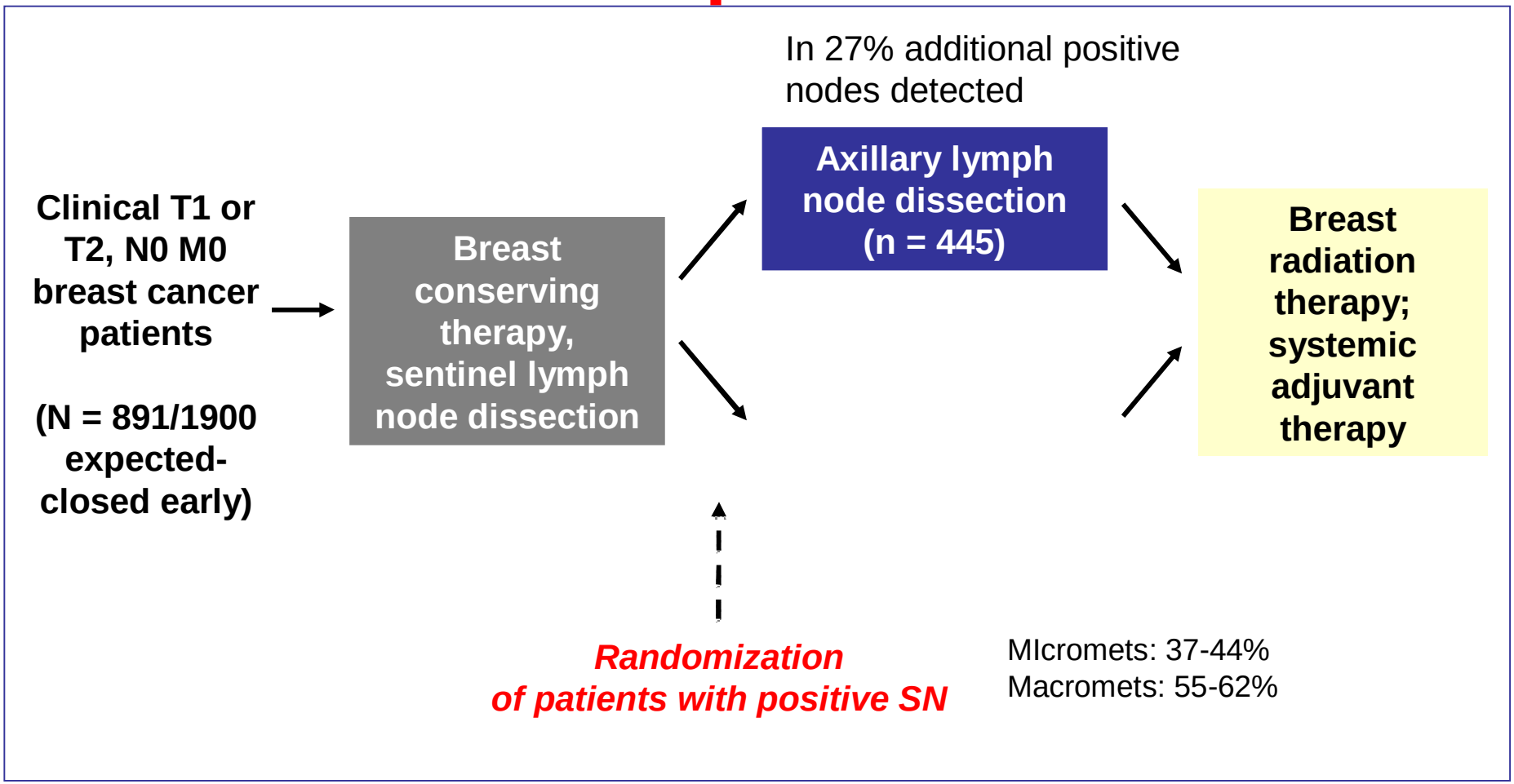
Alla minima terapia efficace

Dal massimo tollerabile al minimo efficace

- **Chirurgia**
  - Mastectomia radicale sec Halsted
  - Mastectomia radicale modificata
  - Quadrantectomia
  - Chirurgia oncoplastica

  - Svuotamento ascellare
  - Biopsia linfonodo sentinella

E’ necessario svuotare l’ascella se il LNS è positivo?



Median T-size: 1,6 cm; about 70% T1; 30% grade III; adjuvant therapy 97%
Overall survival as primary endpoint (non-inferiority)

Giuliano AE, et al. ASCO 2010. Abstract CRA506.

E’ necessario svuotare l’ascella se il LNS è positivo?

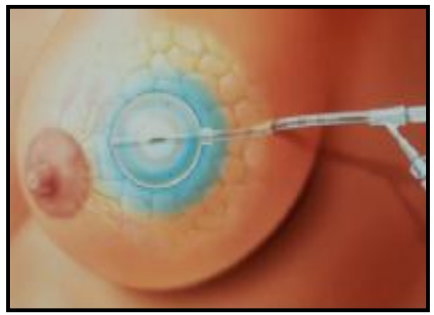
- Nessun beneficio in sopravvivenze o in minori recidive dallo svuotamento ascellare
- I fattori che influenzano la sopravvivenza non sono correlati con il tipo di intervento
  - Eta’, grado istolgico, stato recettori ormoanli, uso di terapia adiuvante

Giuliano AE, et al. ASCO 2010. Abstract CRA506.

Irradiazione parziale della mammella

- Brachiterapia interstiziale:
  - Basse dosi
  - Alte dosi
- Terapia Intracavitaria:
  - Fotoni Ortovoltaggio (Intrabeam)
  - Elettroni Intraoperatori
  - Brachitherapia (Mammosite)



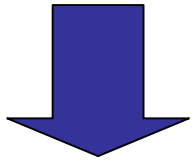



Vantaggi

- **Alta conformabilità**
- **Minor esposizione dei tessuti non target**

Nuovo paradigma nel trattamento medico sistemico del tumore mammario

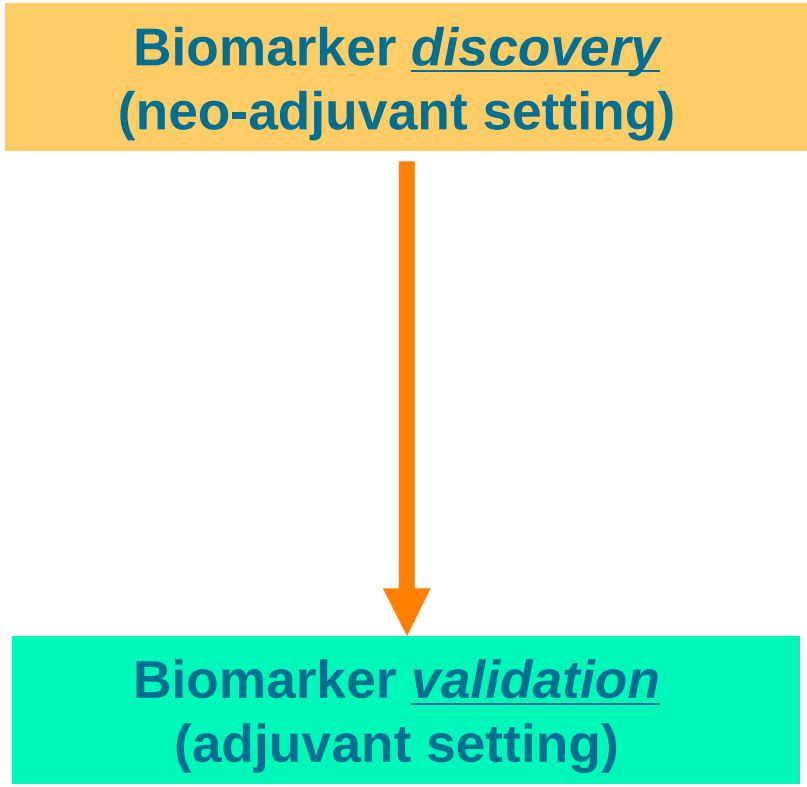
- Da **terapia uguale per tutte** le pazienti



- A **terapia individualizzata**
  - Predizione del rischio
  - Probabilità di effetto dei farmaci

Ruolo della terapia sistemica primaria

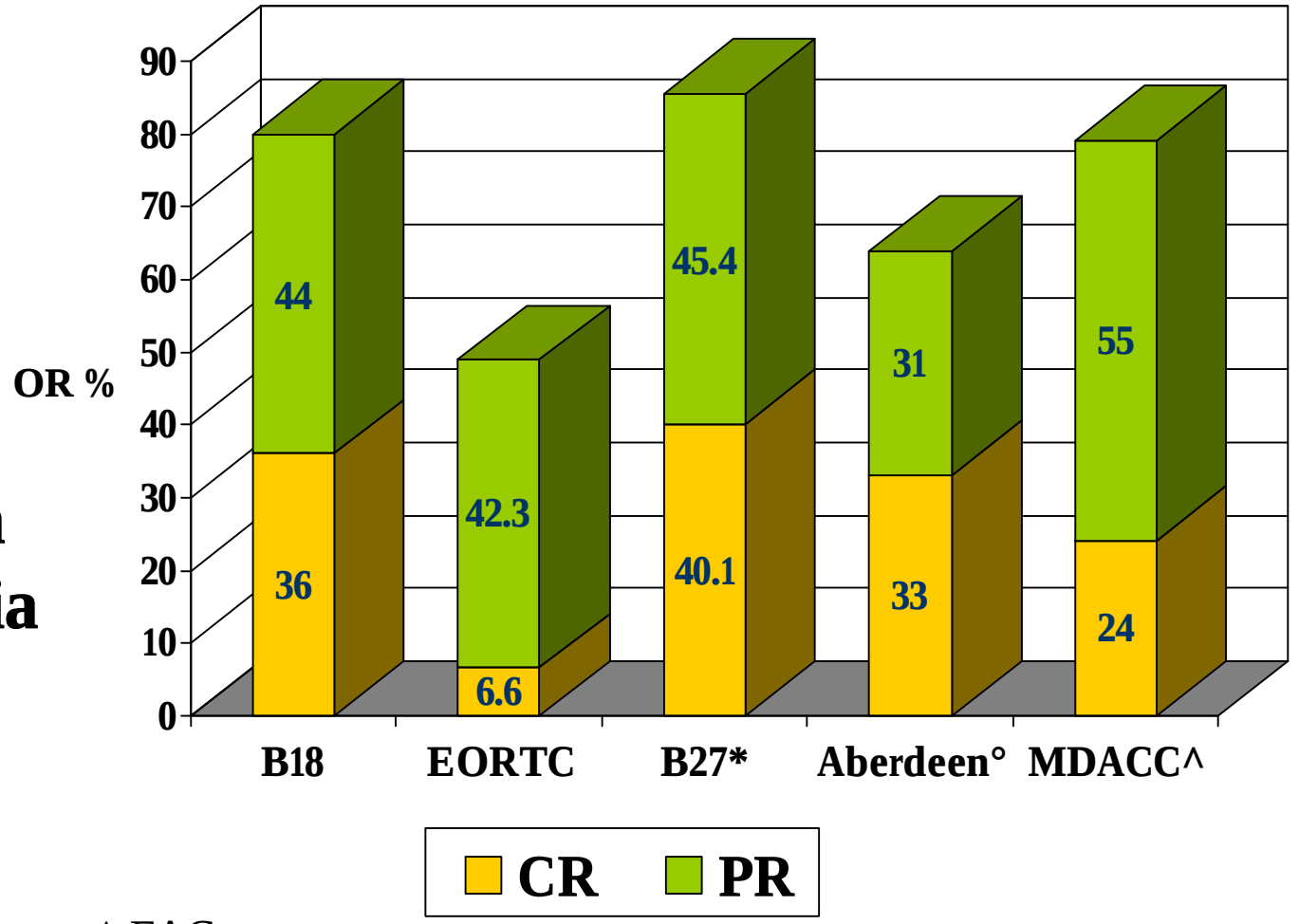
- **Aumentare il tasso di chirurgia conservativa**
- **Eradicare il tumore**
- **Aumentare l'efficacia**
- **Identificare nuovi marcatori di beneficio clicnico**



L. Gianni, 2009

LA chemioterapia primaria riduce il volume del tumore

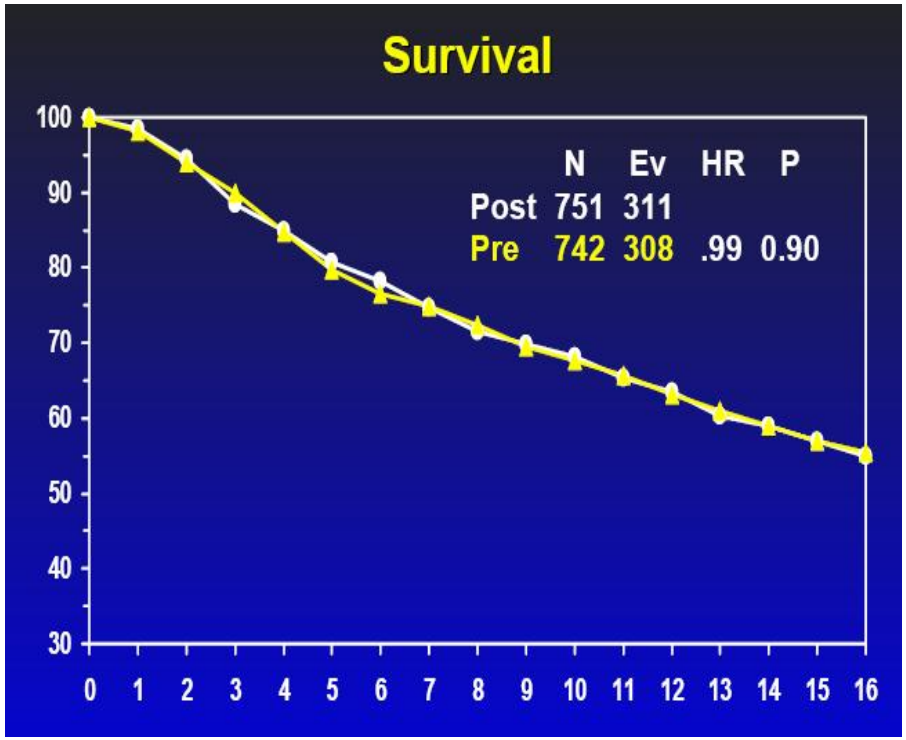
Risposte cliniche con chemioterapia primaria



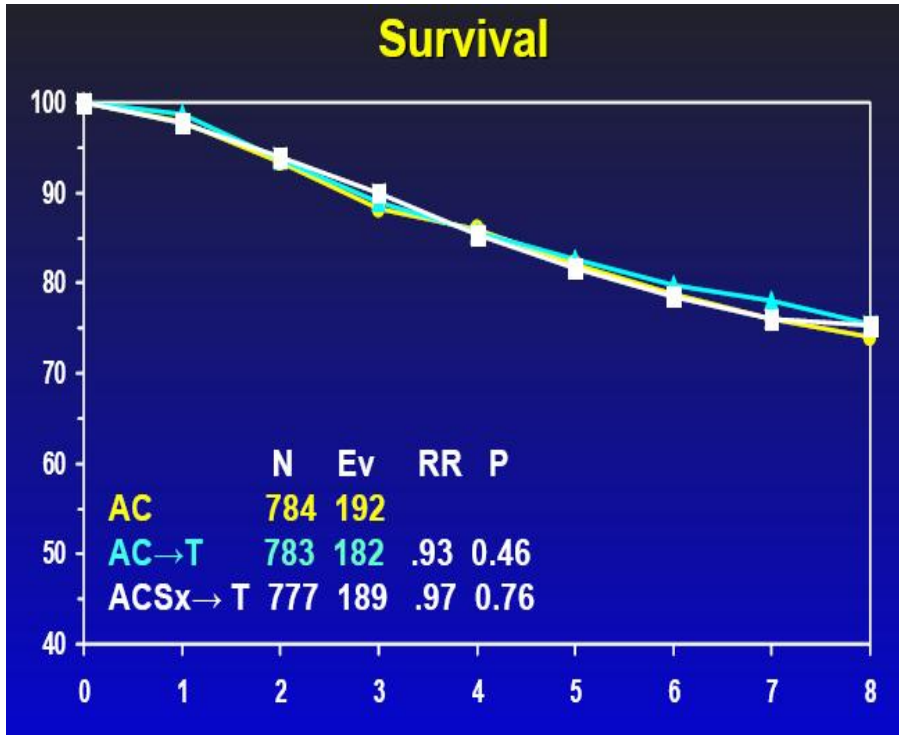
* AC arm; ° CVAP arm; ^ FAC arm.

Non vi sono svantaggi in sopravvivenza quando di impiega chemioterapia primaria

B-18

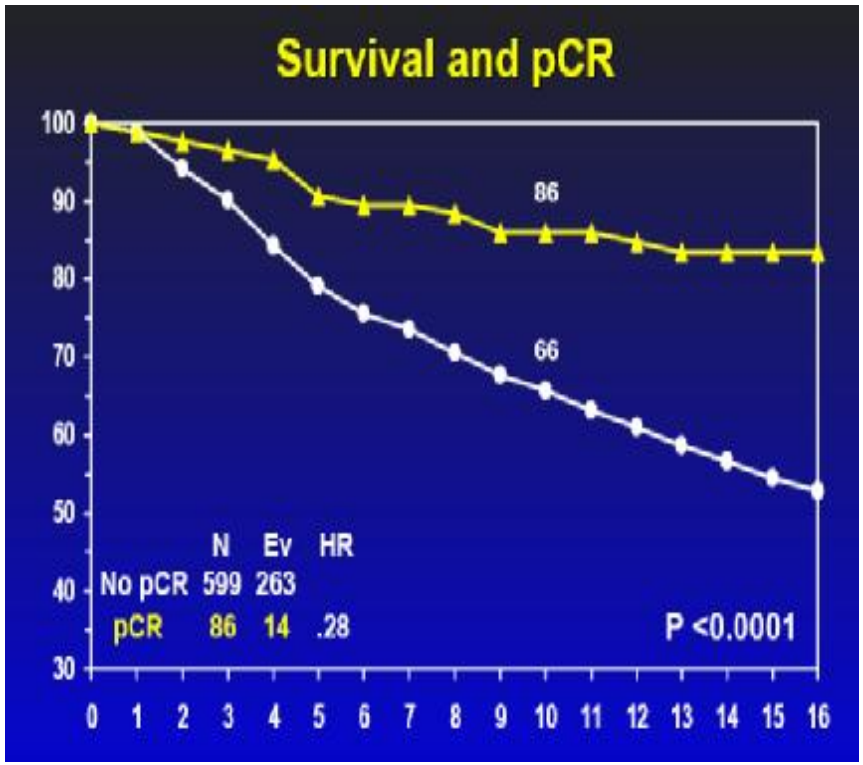


B-27



Vantaggi in sopravvivenza per le pazienti che ottengono una pCR

B-18



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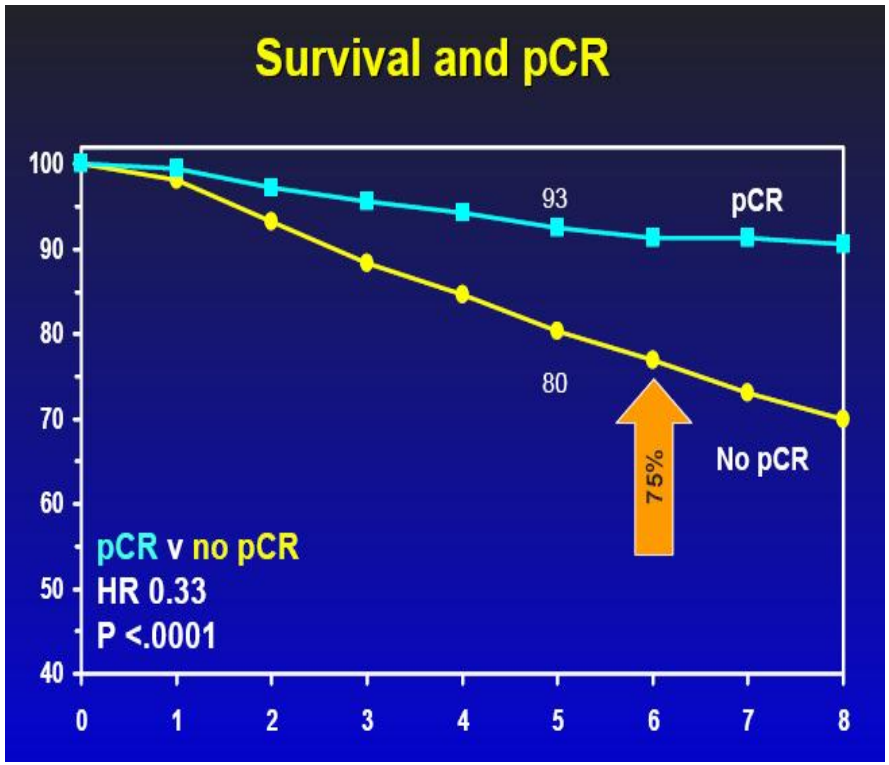
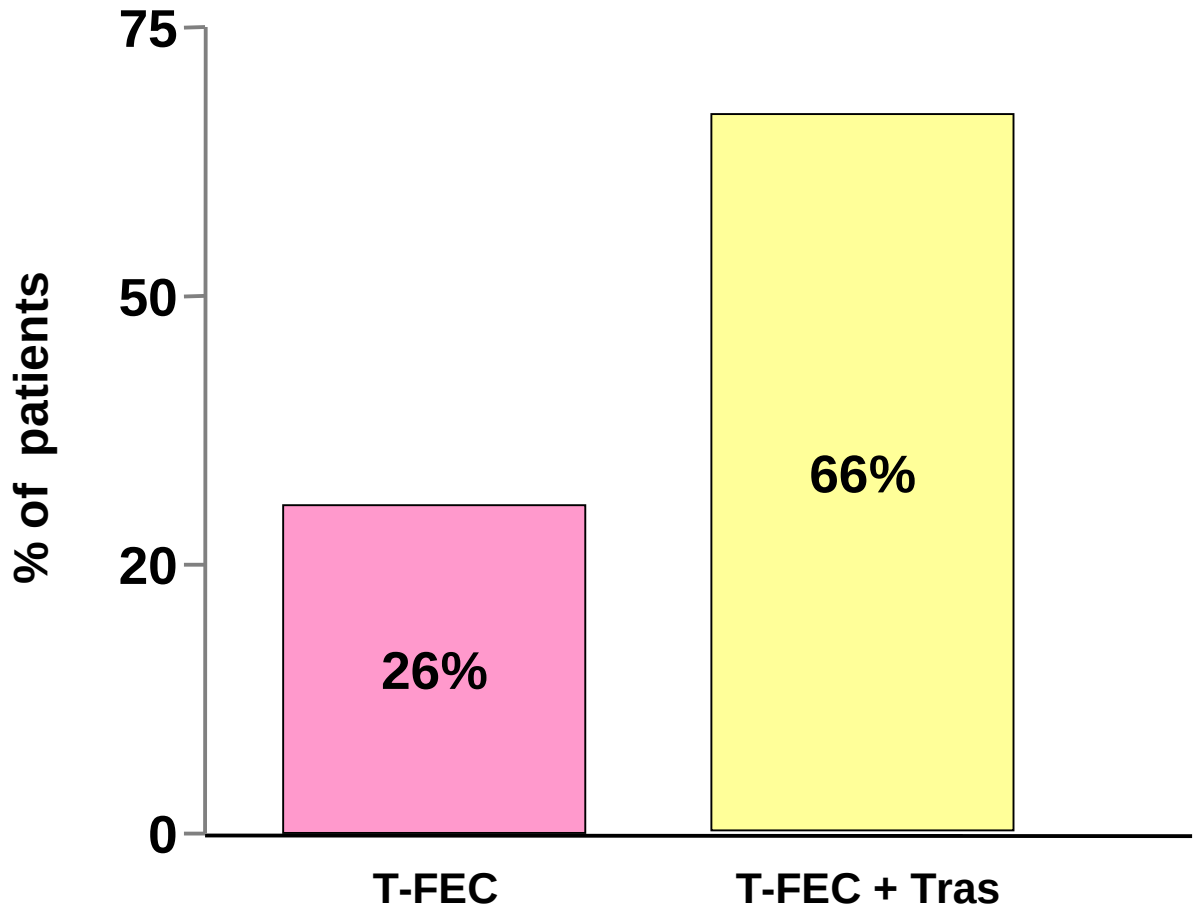
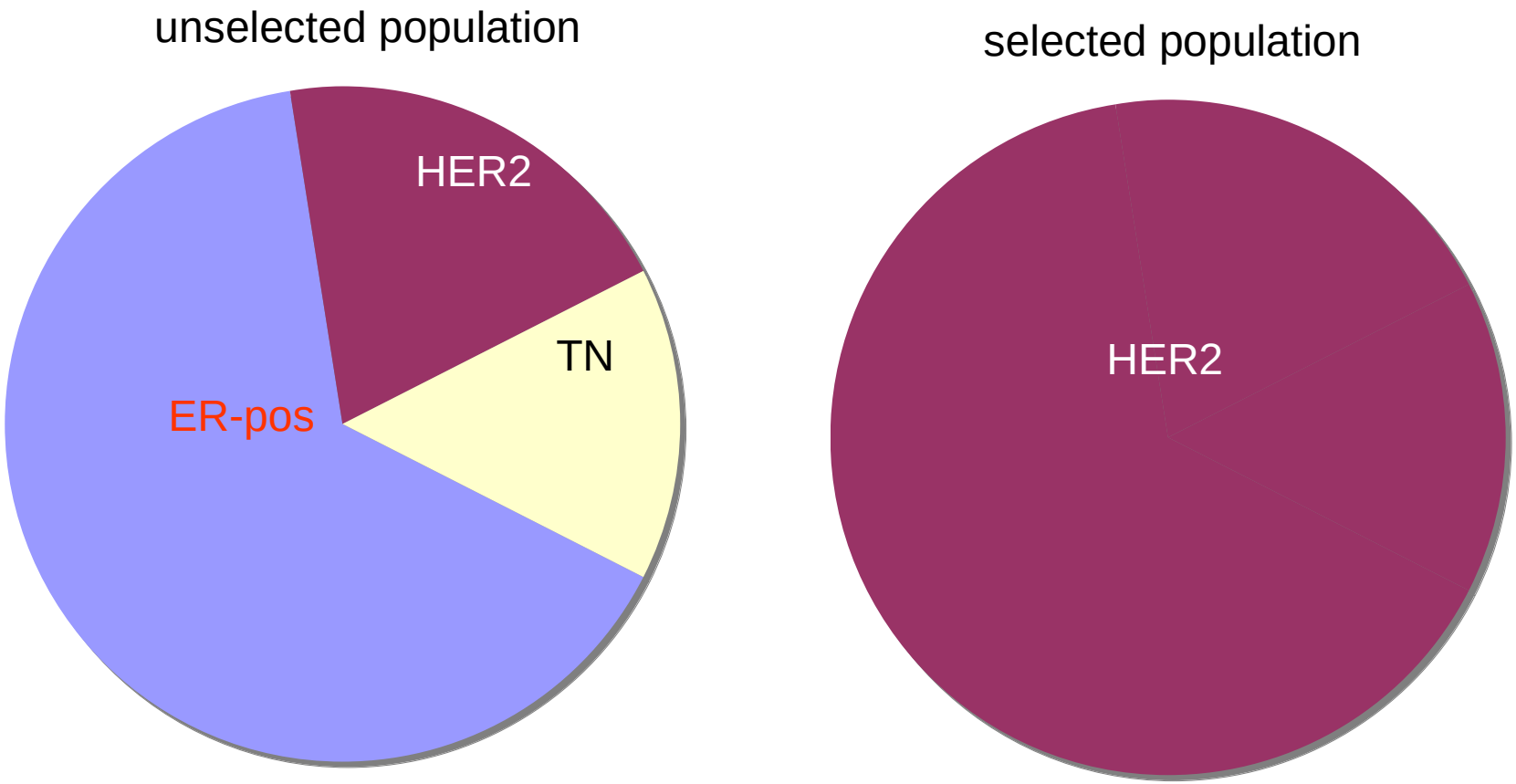


pCR con CT ± Trastuzumab

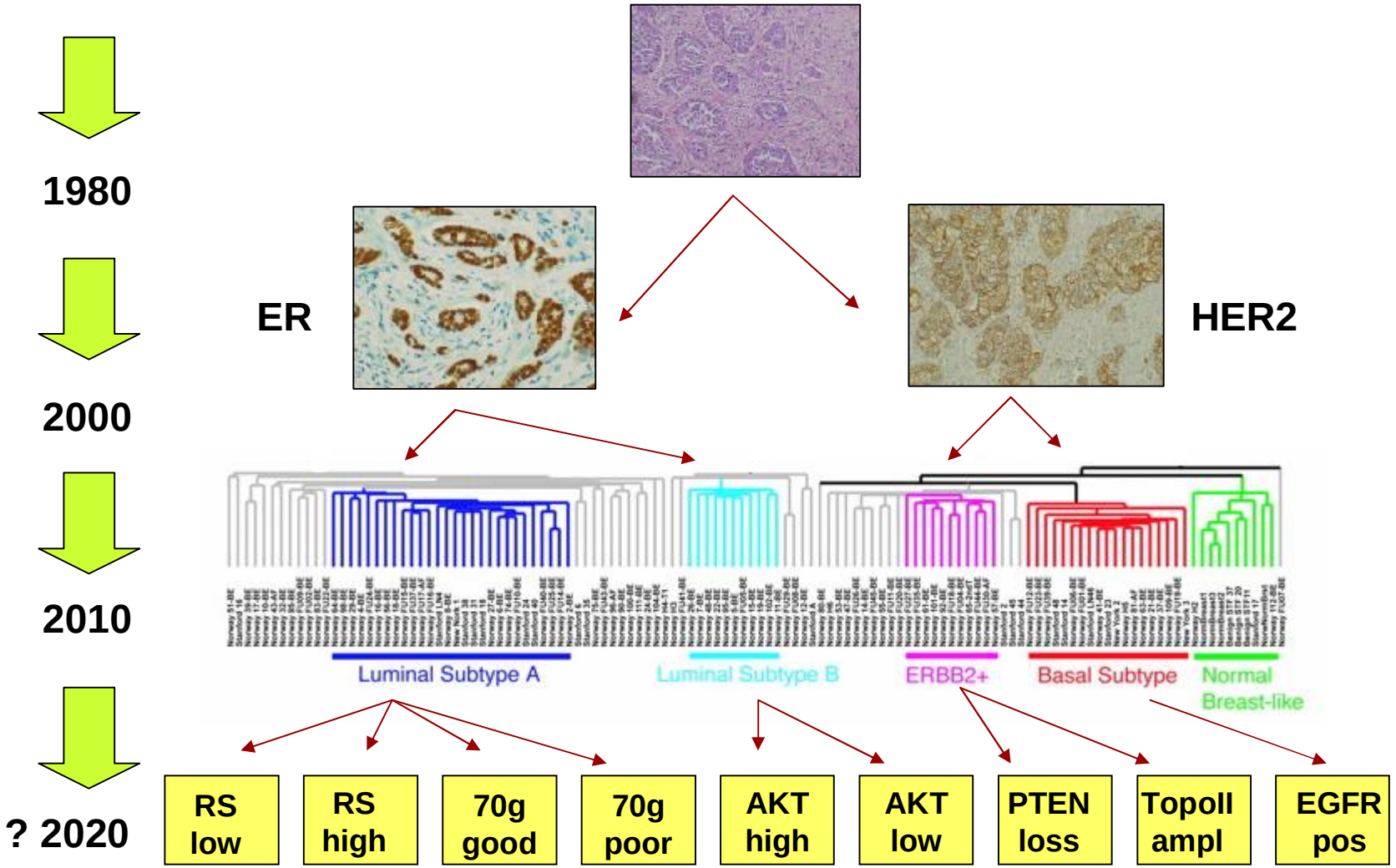


Buzdar A et al, JCO 2005

Selezionare il tupo di tumore incrementa la probabilità di effetto della terapia specifica



Tumore mammario – quanti sono?

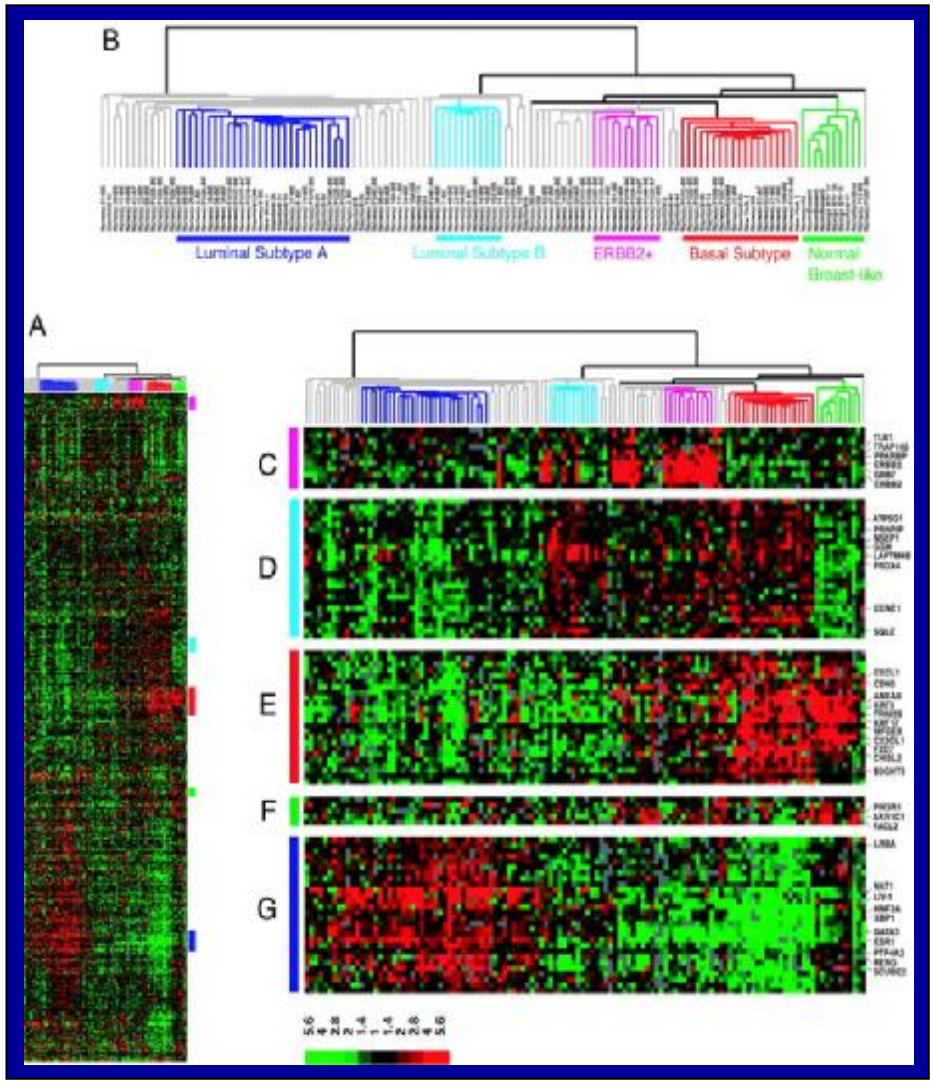


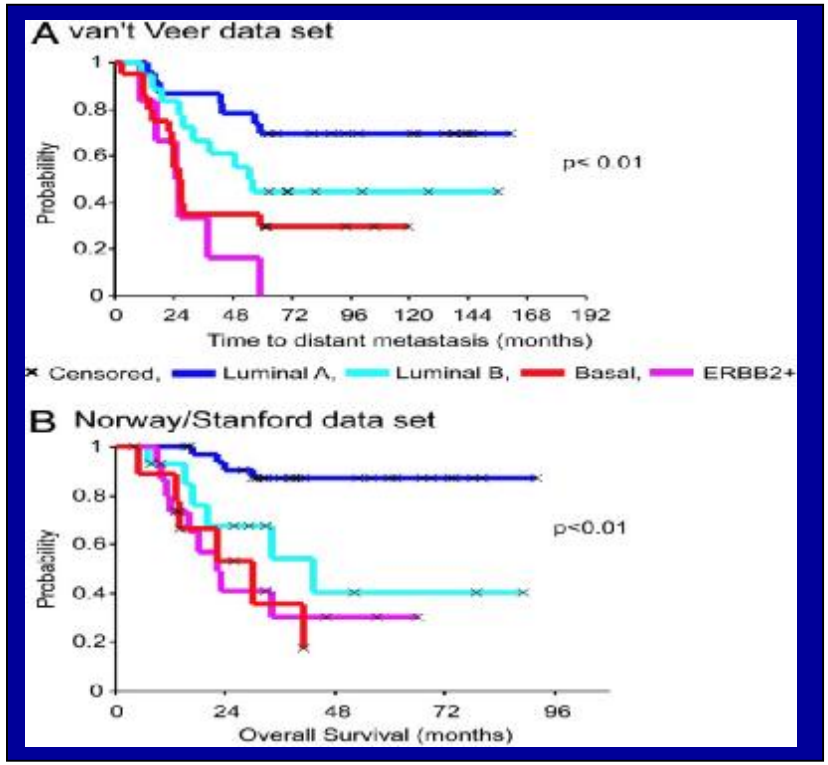
Classificazione Predittiva

St. Gallen 2007

Highly Endocrine responsive	Non endocrine responsive	Incompletely endocrine responsive
• High ER & PgR *and* • No HER2 overexpr *and* • Low Ki-67	• ER & PgR both absent	•Low ER & PgR *or* • PgR absent *or* • HER2 overexpr *or* • High Ki-67

Classificazione genomica





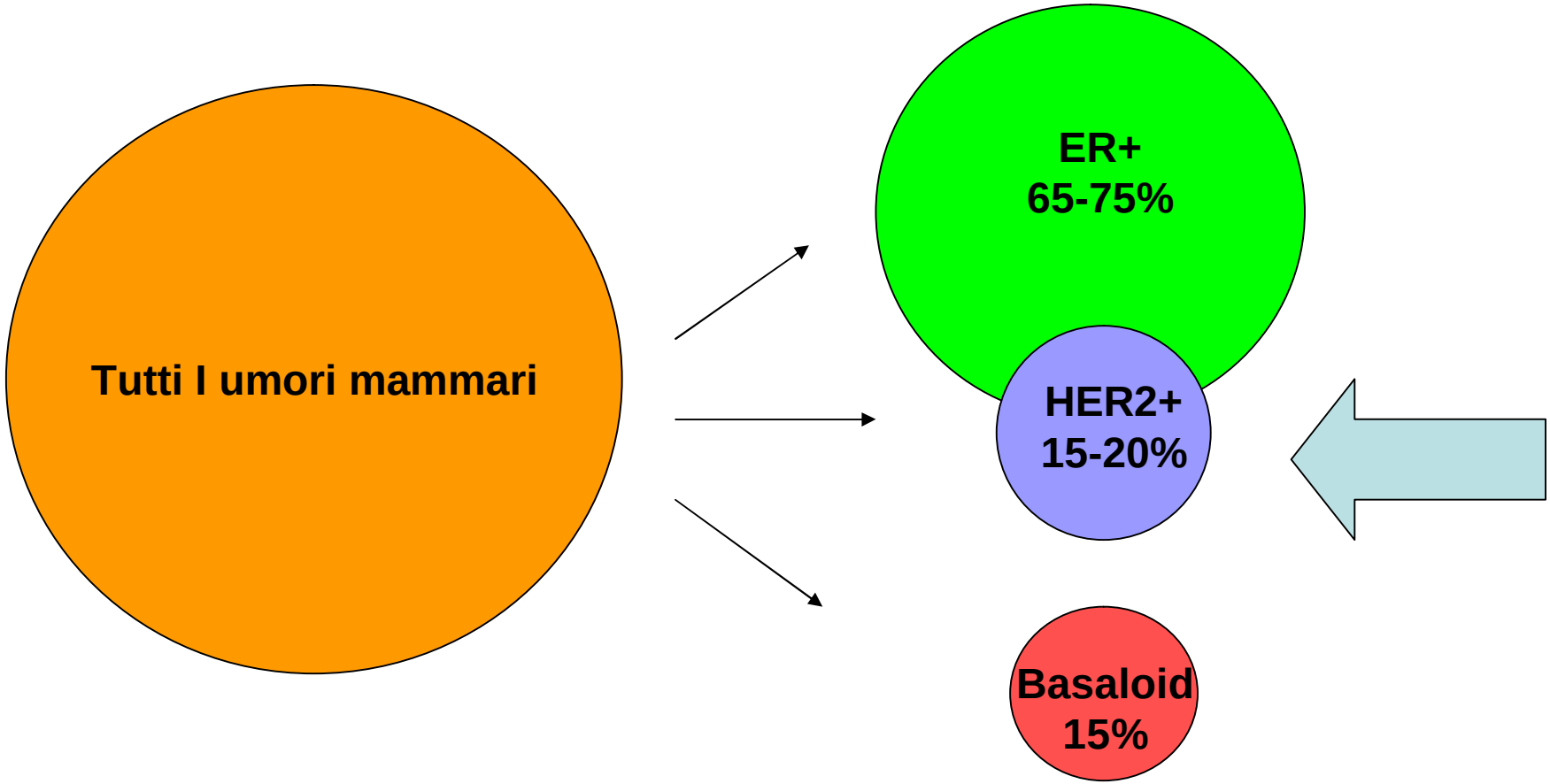
Perou, Nature 2000; Sorlie, PNAS 2003

Reis-Filho, J Clin Path 2006

Clasificazione genomica in base a ER ed HER2

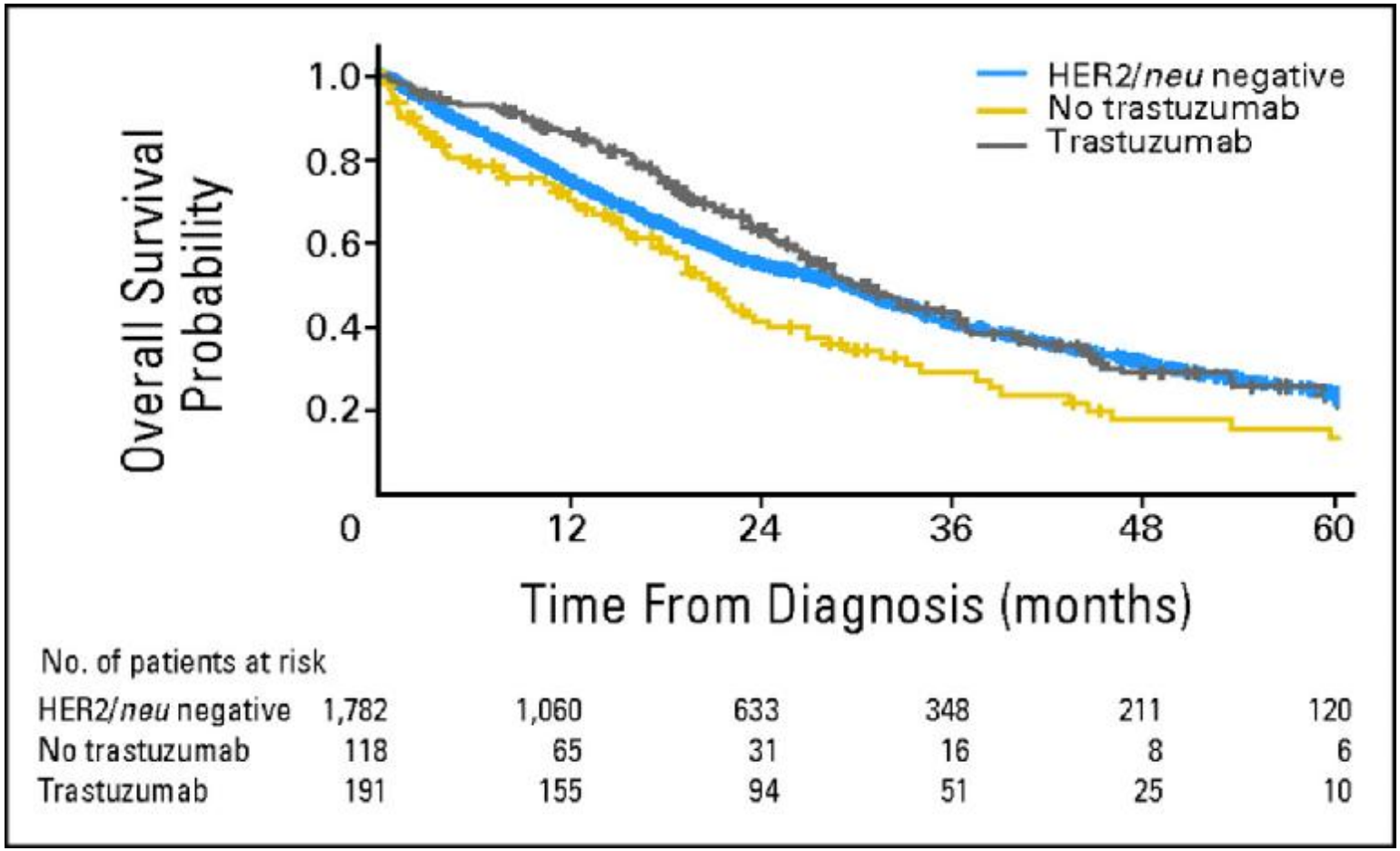
- **ER+ e/o PR+/HER2-, basso Ki-67**: Larga coincidenza con **Luminal A**
- **ER+ e/o PR+/HER2+, e/o alto Ki-67**: prevalenti tumori **Luminal B**
- **ER-/PR-/HER2+**: sottotipo **HER2+**
- **ER-/PR-/HER2-**: Larga coincidenza con sottotipo **basaloide (o Triplo negativo)**

Frequenza dei diversi sottotipi



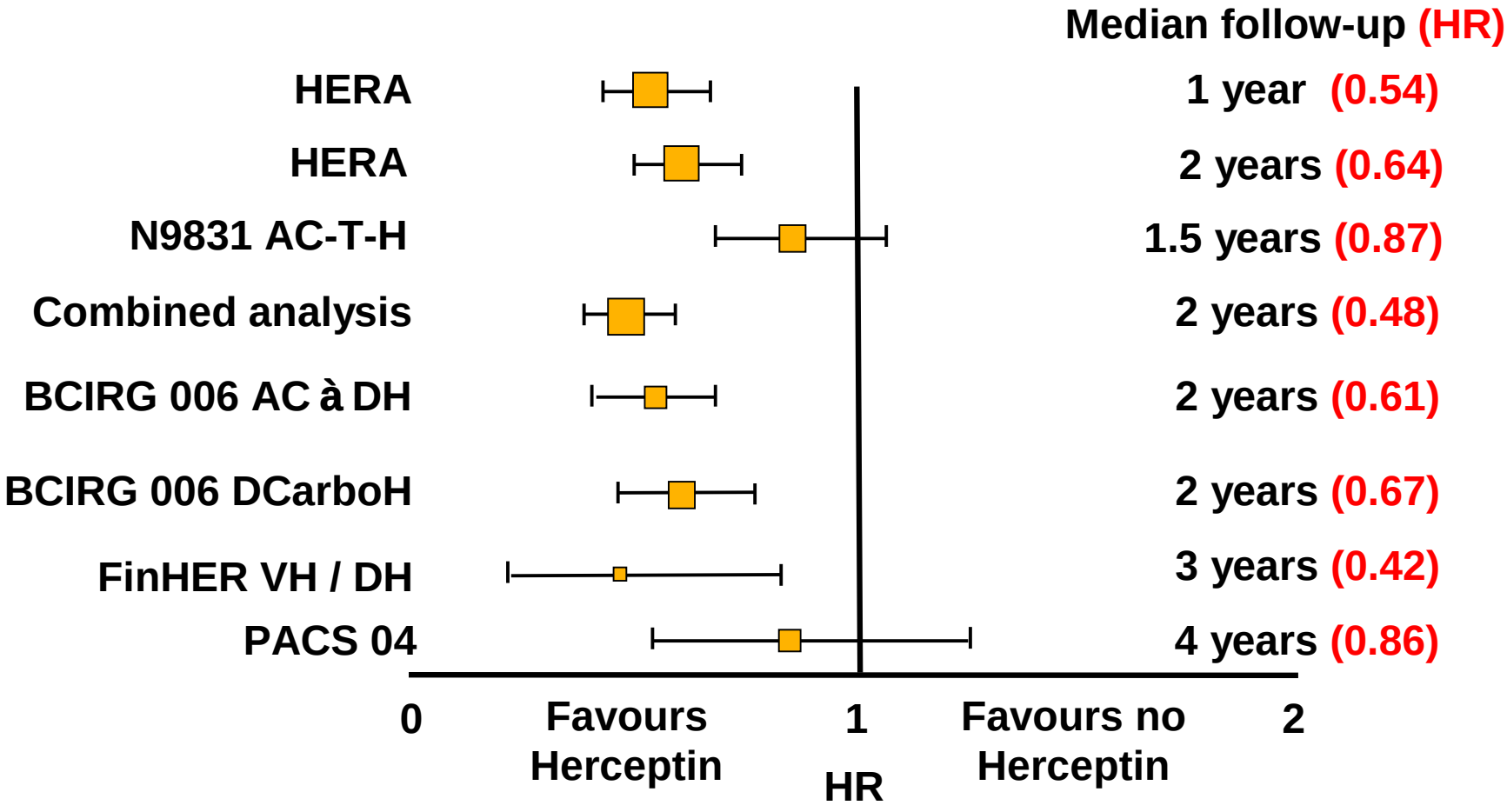
H Burstein and A Goldhirsch St Gallen 2007

Sopravvivenza globale in rapporto alla terapia con trastuzumab in HER2+



Dawood, S. et al. J Clin Oncol; 28:92-98 2010

Efficacia del Trastuzumab nella terapia adiuvante della malattia in fase precoce

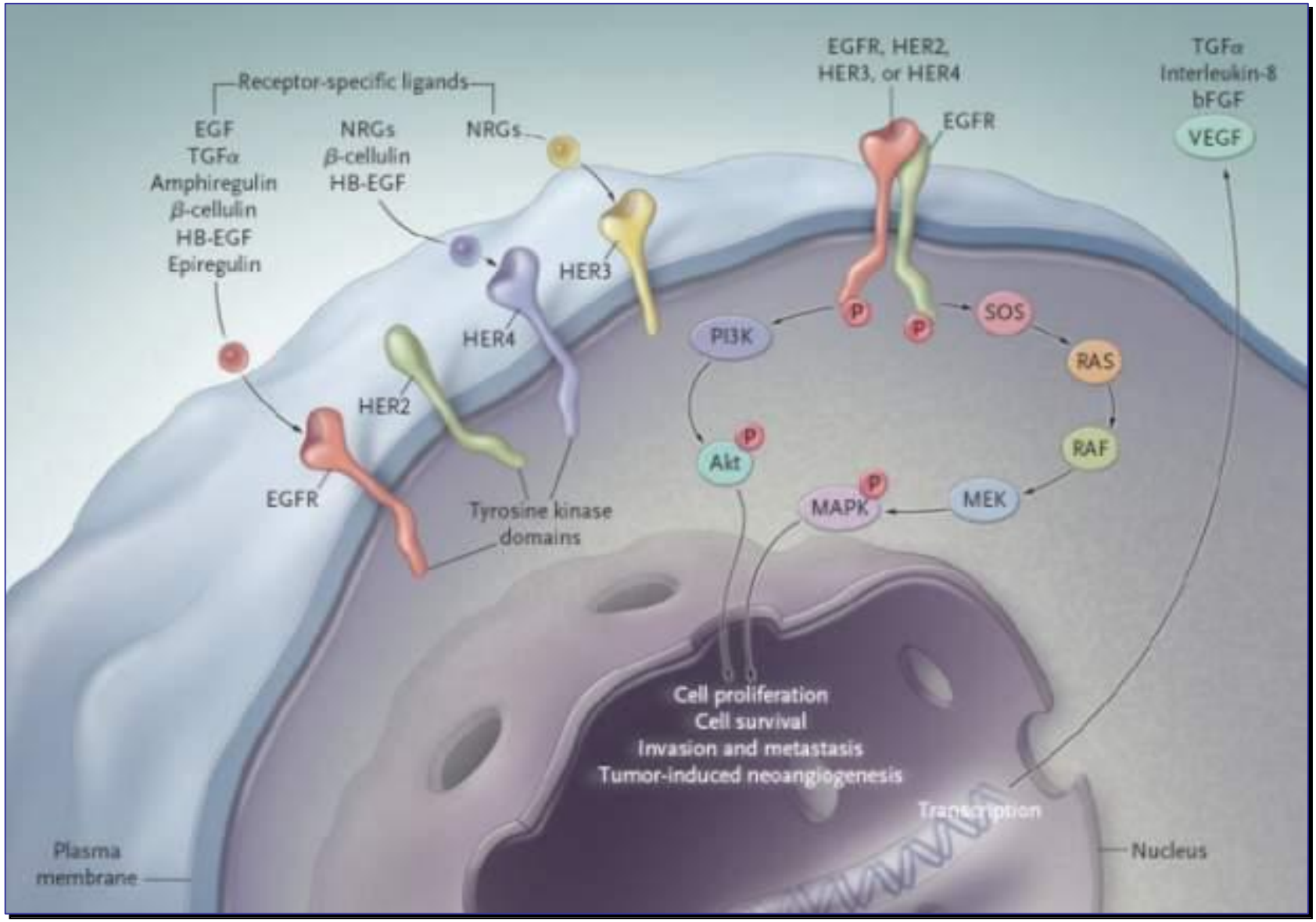


Piccart-Gebhart NEJM 2005; Romond NEJM 2005;
Slamon SABCS 2006; Smith, Lancet 2007; Perez ASCO 2005

Studi in corso con una durata di trattamento adiuvante con trastuzumab < ad 1 anno

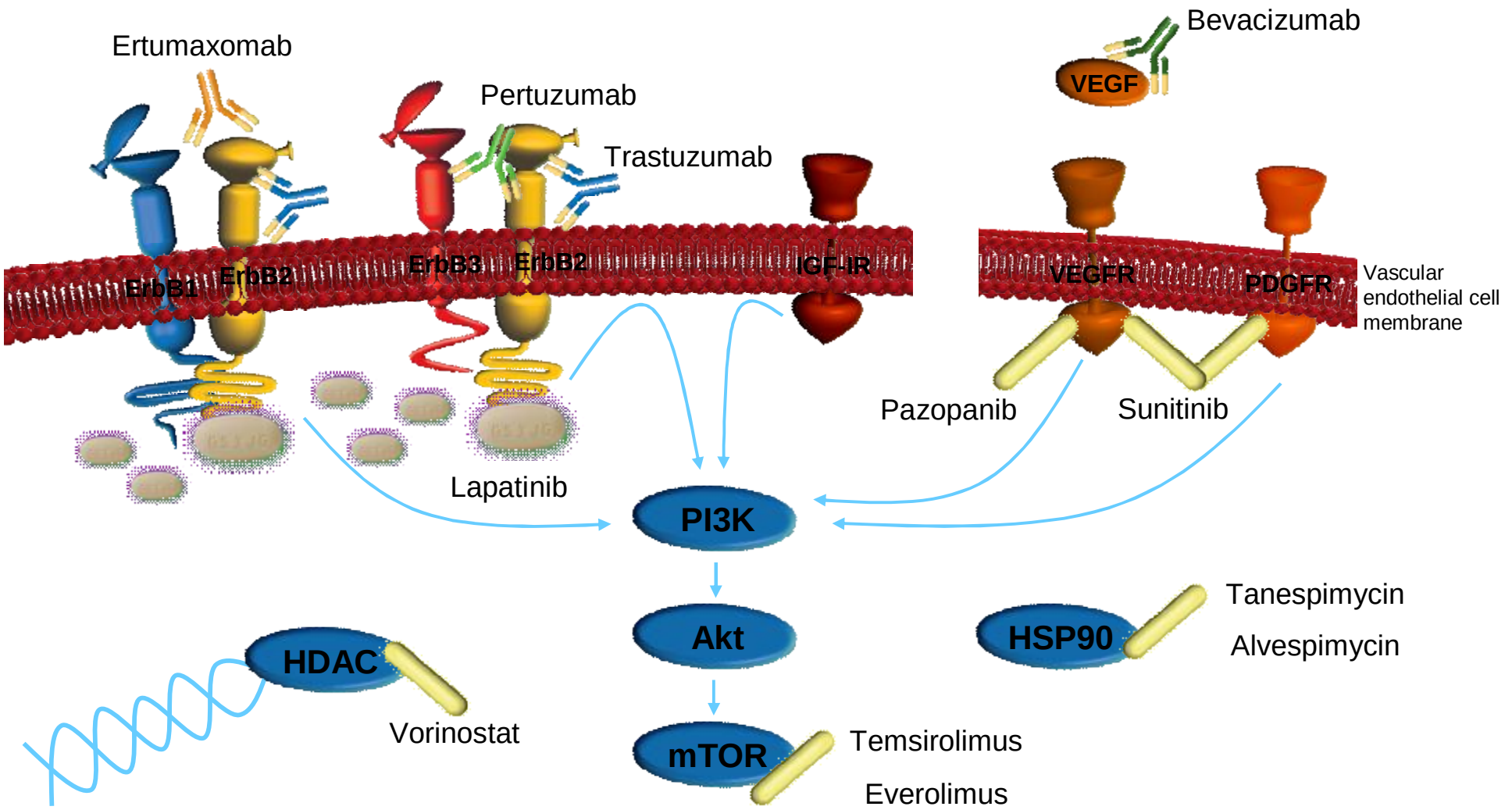
Trial	Sponsor	Durata in mesi	Tipo di CT	No. of paz
PHARE	INCAN, Paris	6 vs. 12	Center's choice	3,400
PERSEPHONE	U. Warwick,	6 vs. 12	Center's choice	4,000
SHORTER	U. Modena	2 vs.12	A+T vs. T+FEC	2,500
SOLD	Finnish BCG	2 vs 12	T+FEC	3,000

La resistenza al trattamento con trastuzumab



Ciardiello and Tortora, NEJM, 2008

Bersagli e pallottole nel carcinoma mammario HER2+



HDAC=histone deacetylase

Lapatinib plus capecitabine: efficacy°

(EGF100151, independent assessment)

Outcome	*Tyverb* + capecitabine (n=198)	Capecitabine (n=201)	Hazard ratio (95% CI)	Odds ratio (95% CI)	p value
TTP (median, wks [mos])	27.1 (6.2)	18.6 (4.3)	0.57 (0.43- 0.77)	–	0.00013
OS (median, wks [mos])	67.7 (15.6)	66.6 (15.3)	0.78 (0.55- 1.12)	–	0.177
ORR (%)	23.7	13.9	–	1.9 (1.1- 3.4)	0.017
CB* (%)	29.3	17.4	–	2.0 (1.2- 3.3)	0.008

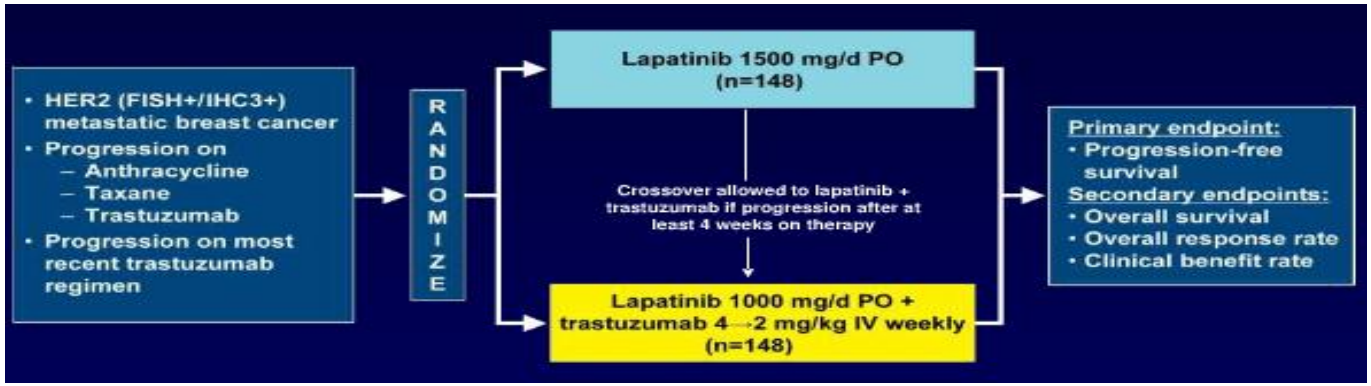
*CR + PR + SD≥6months

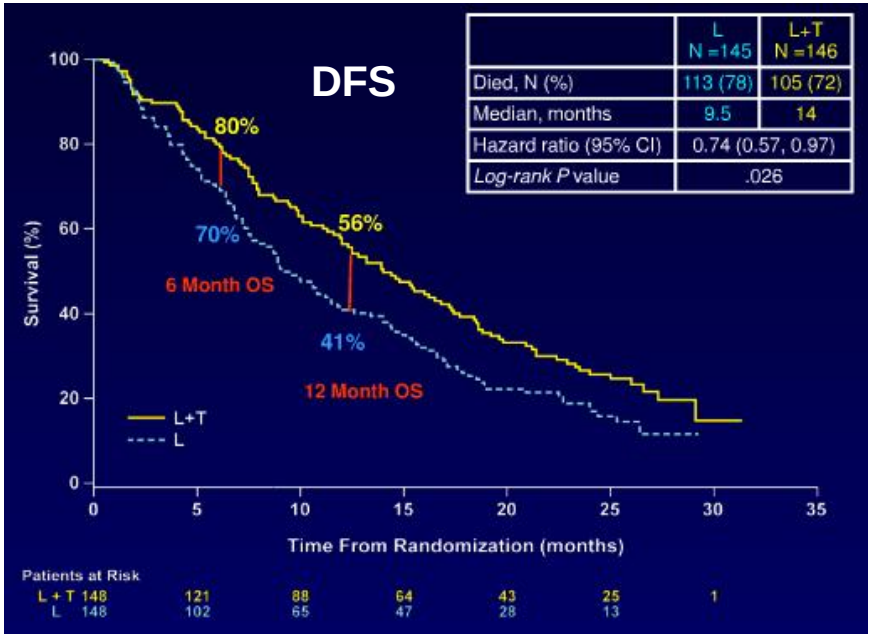
° pts progressing after Trastuzumab, Taxane and Anthra

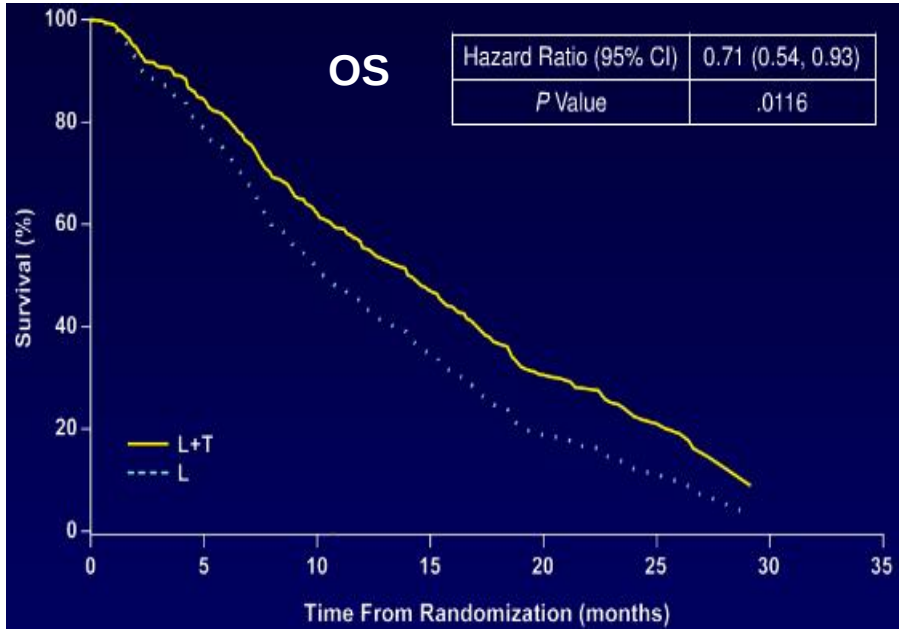
Cameron et al. Breast Cancer Res Treat 2008

Lapatinib + trastuzumab

Phase III
EGF104900

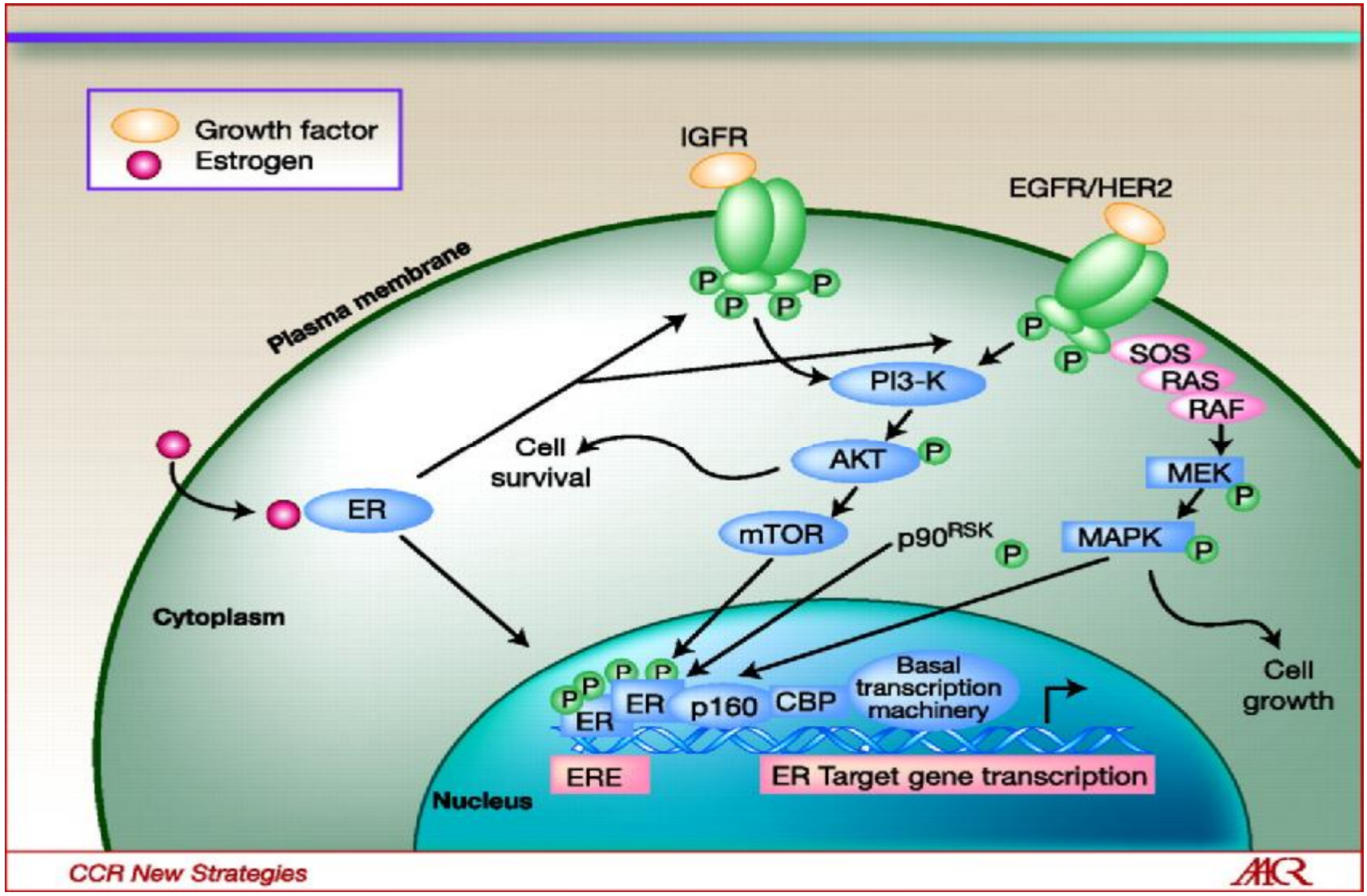




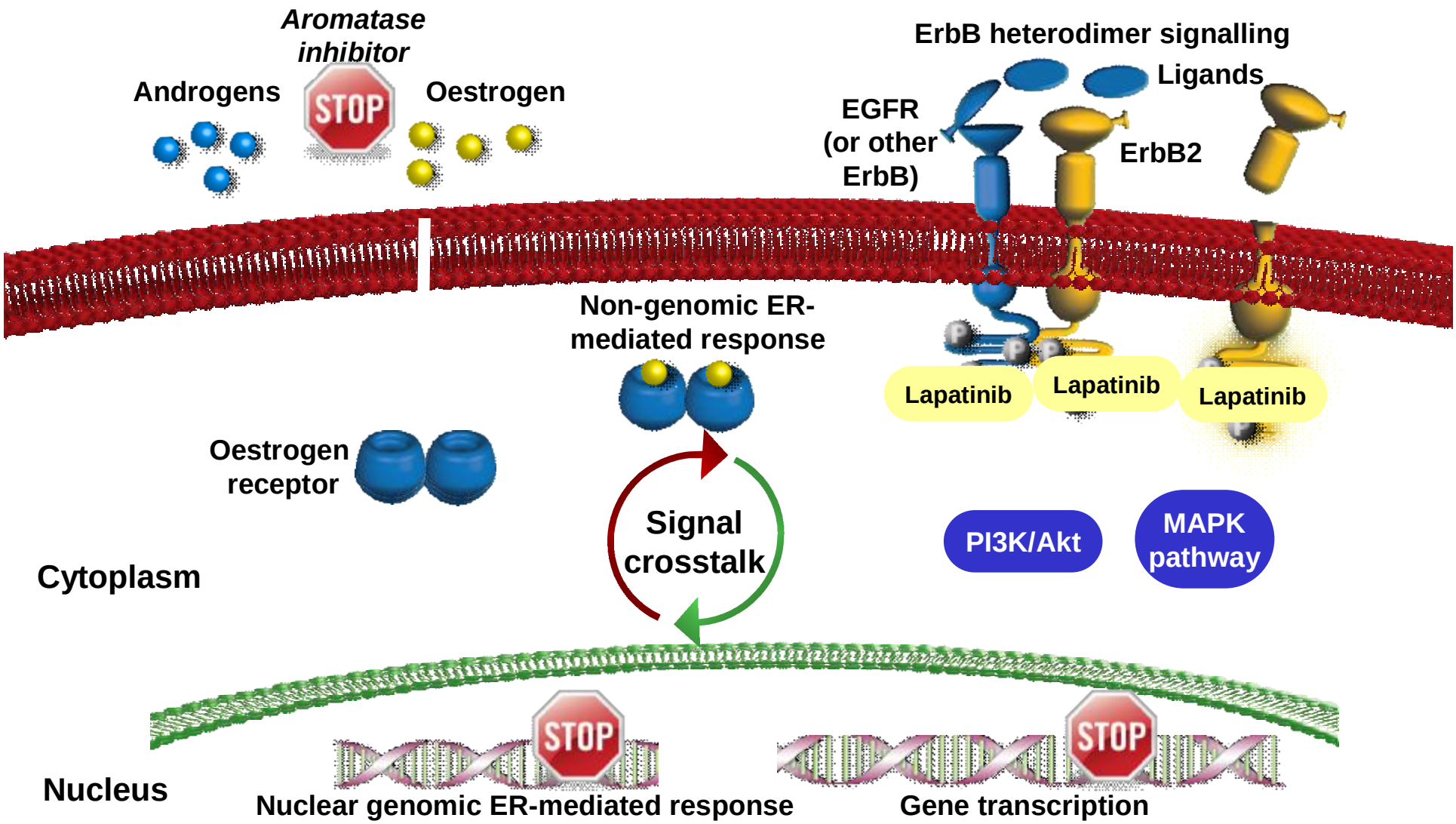


Blackwell, SABCS 2009, JCO 2010

HER2+ / ER+ BC: relazioni fra le vie di trasduzione del segnale e possibili modalità di intervento

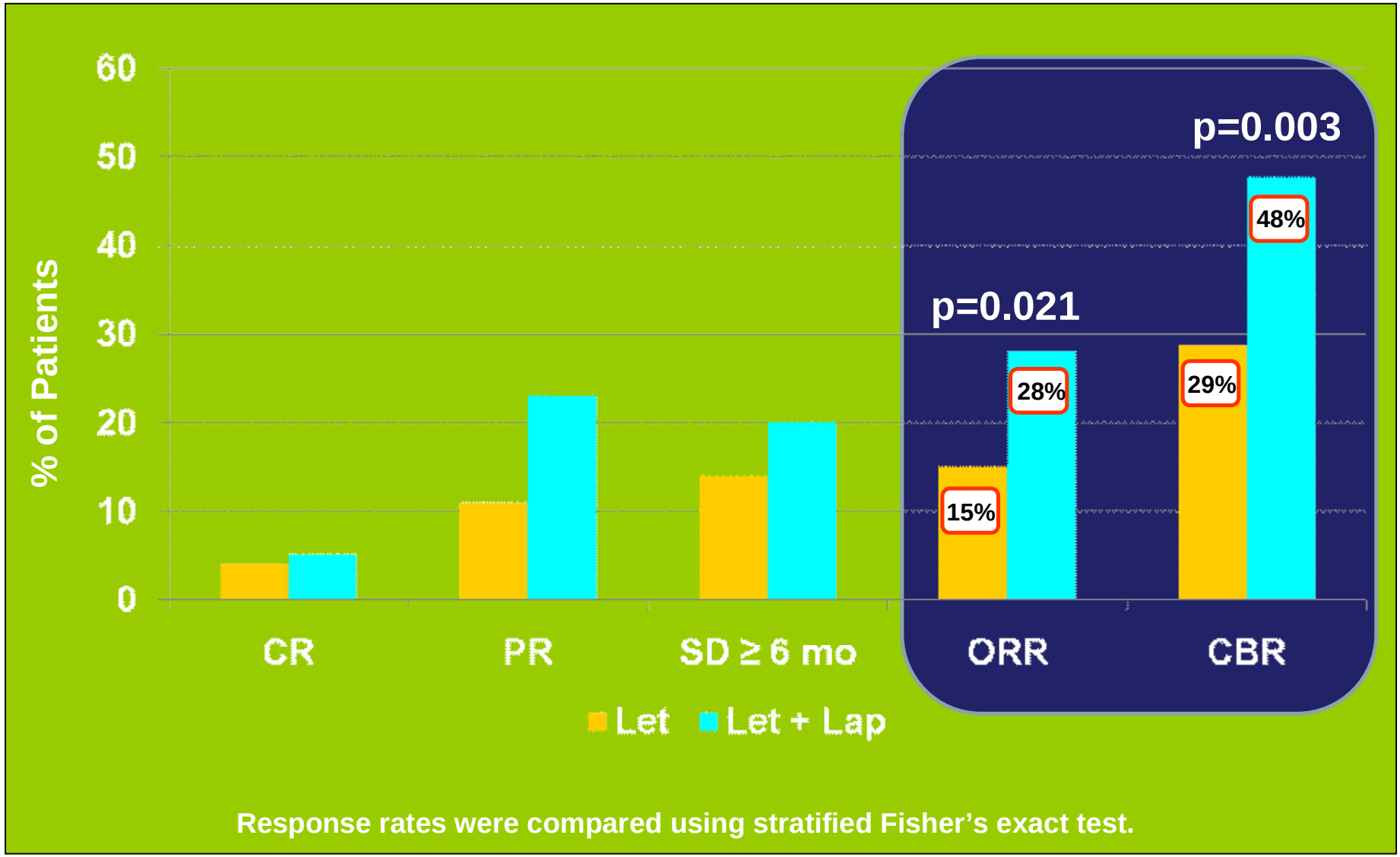


Superamento della resistenza nei tumori mammari ErbB2+/HR+



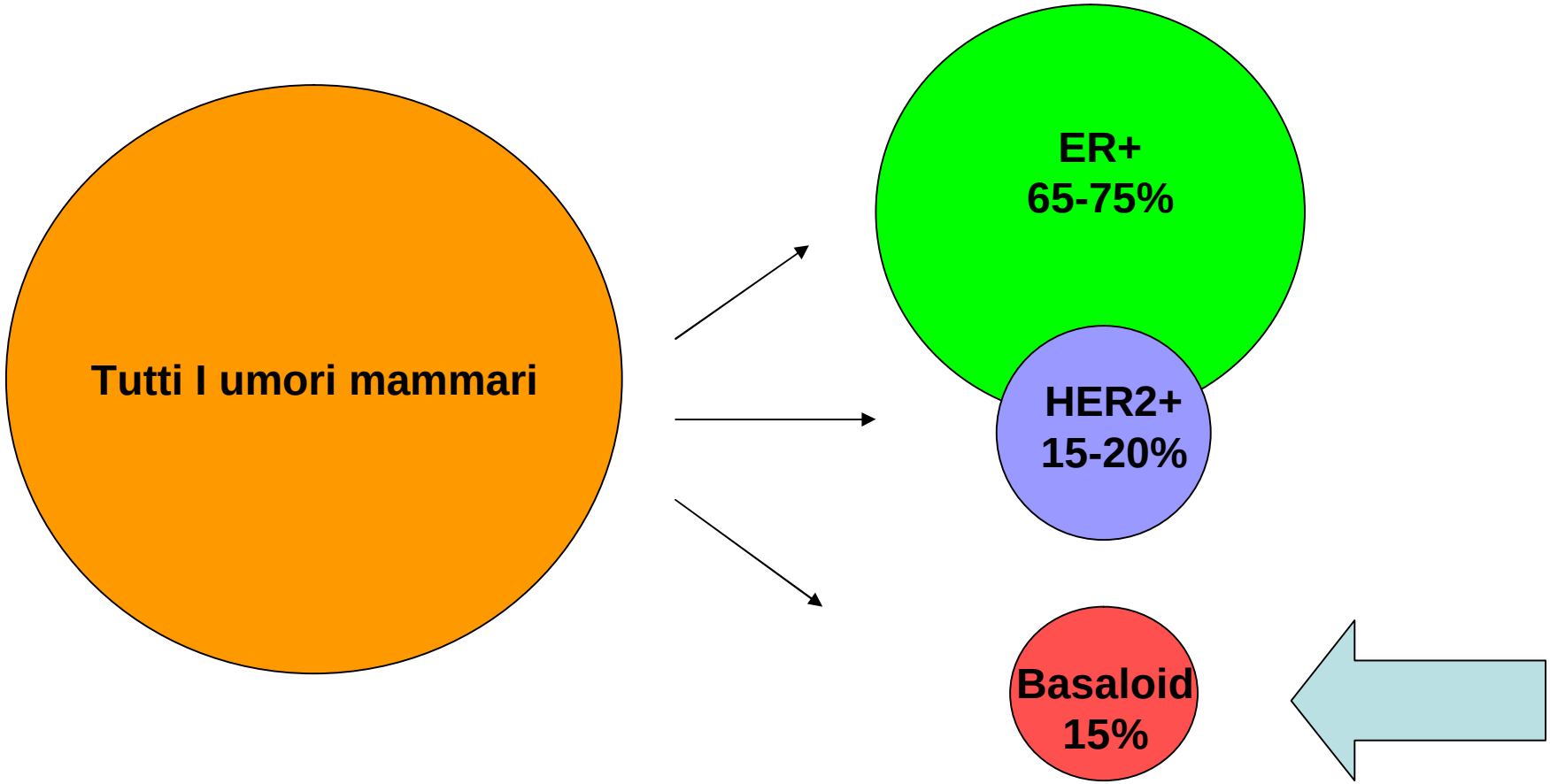
Adapted from Prat and Baselga. Nat Clin Pract Oncol 2008; **5**: 531–42

Risposte alla terapia con Lapatinib + letrozolo in tumori HER2+/ER+ (N=219)



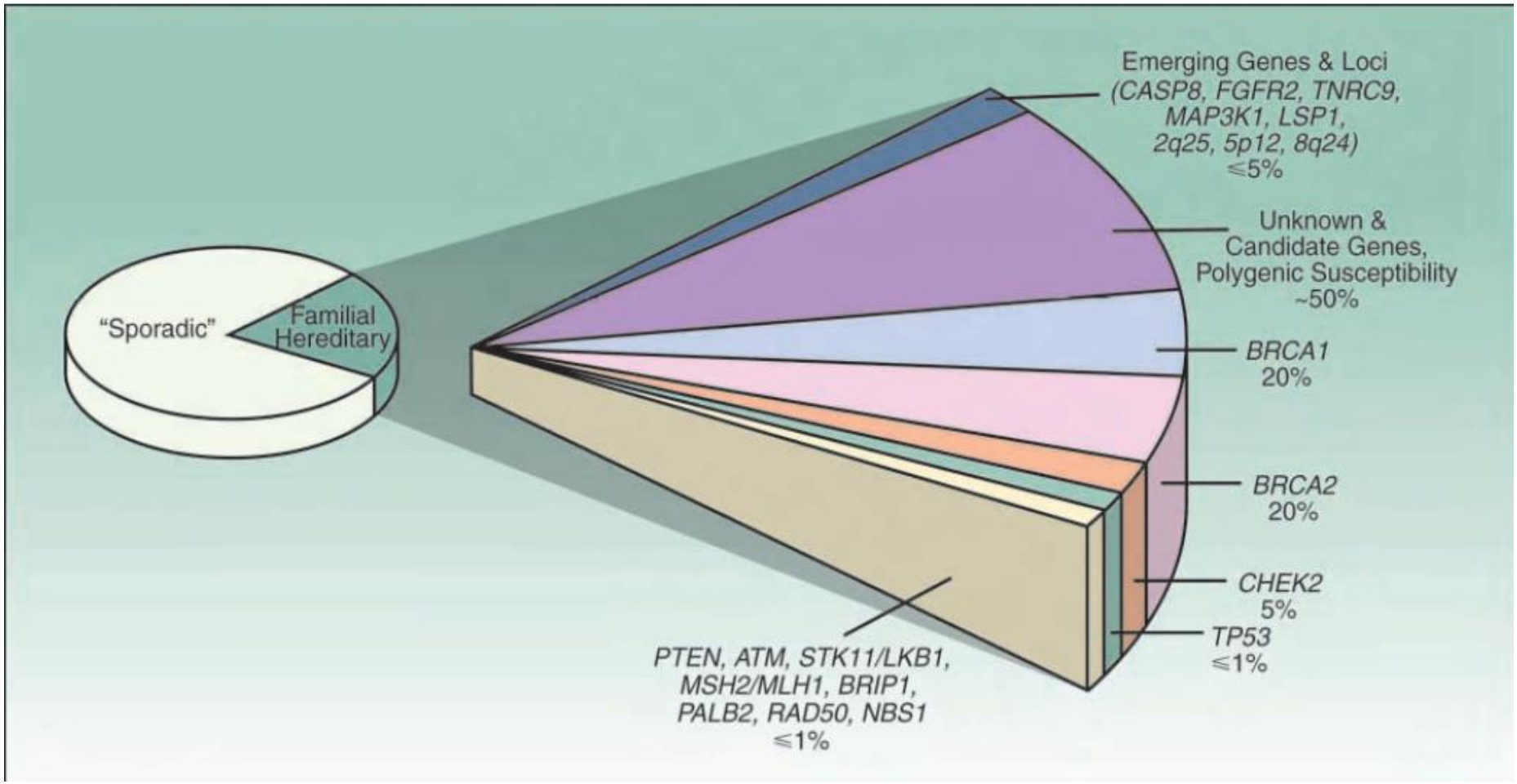
Response rates were compared using stratified Fisher's exact test.

Frequenza dei diversi sottotipi

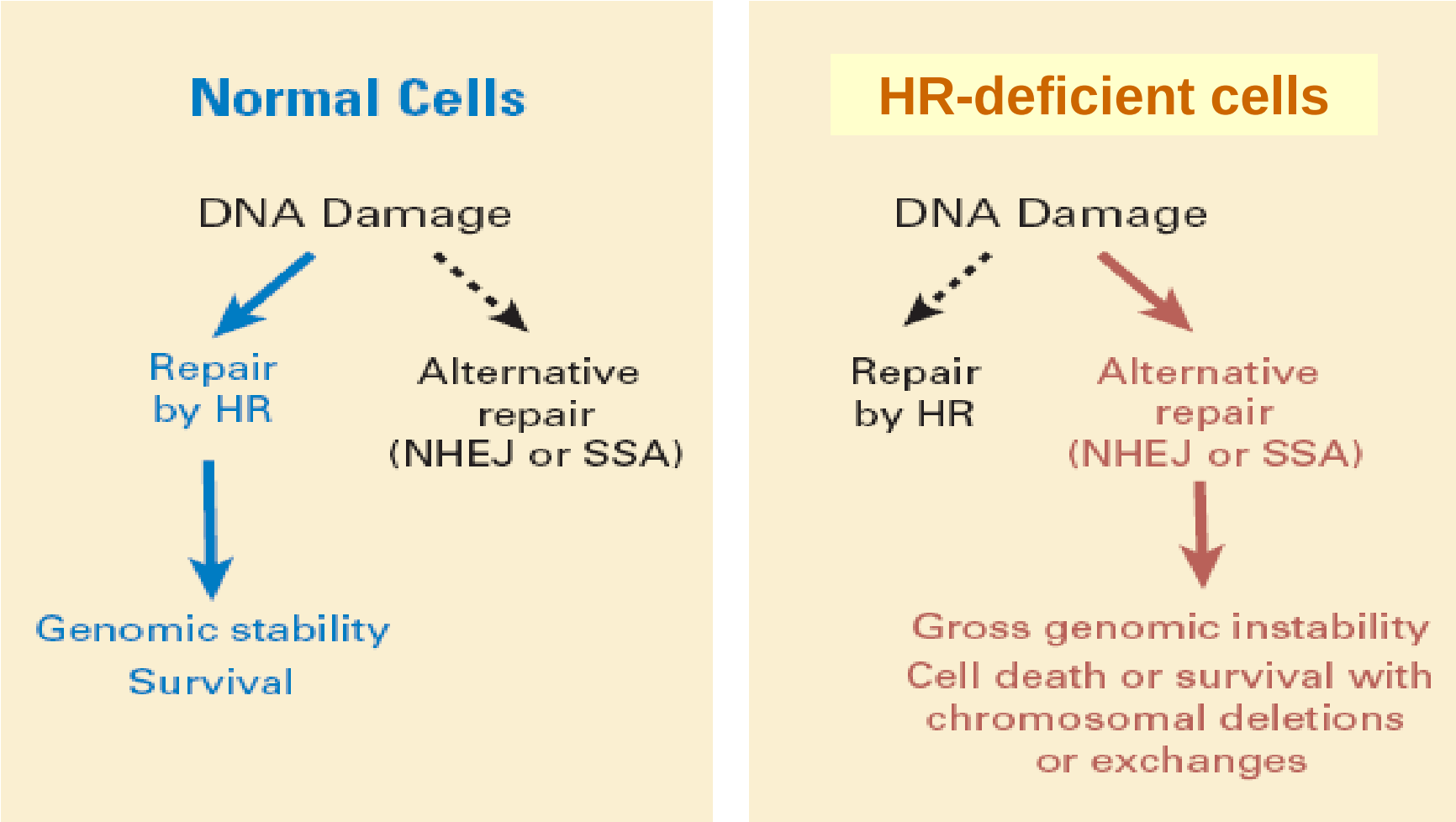


H Burstein and A Goldhirsch St Gallen 2007

Tumore mammario ereditario

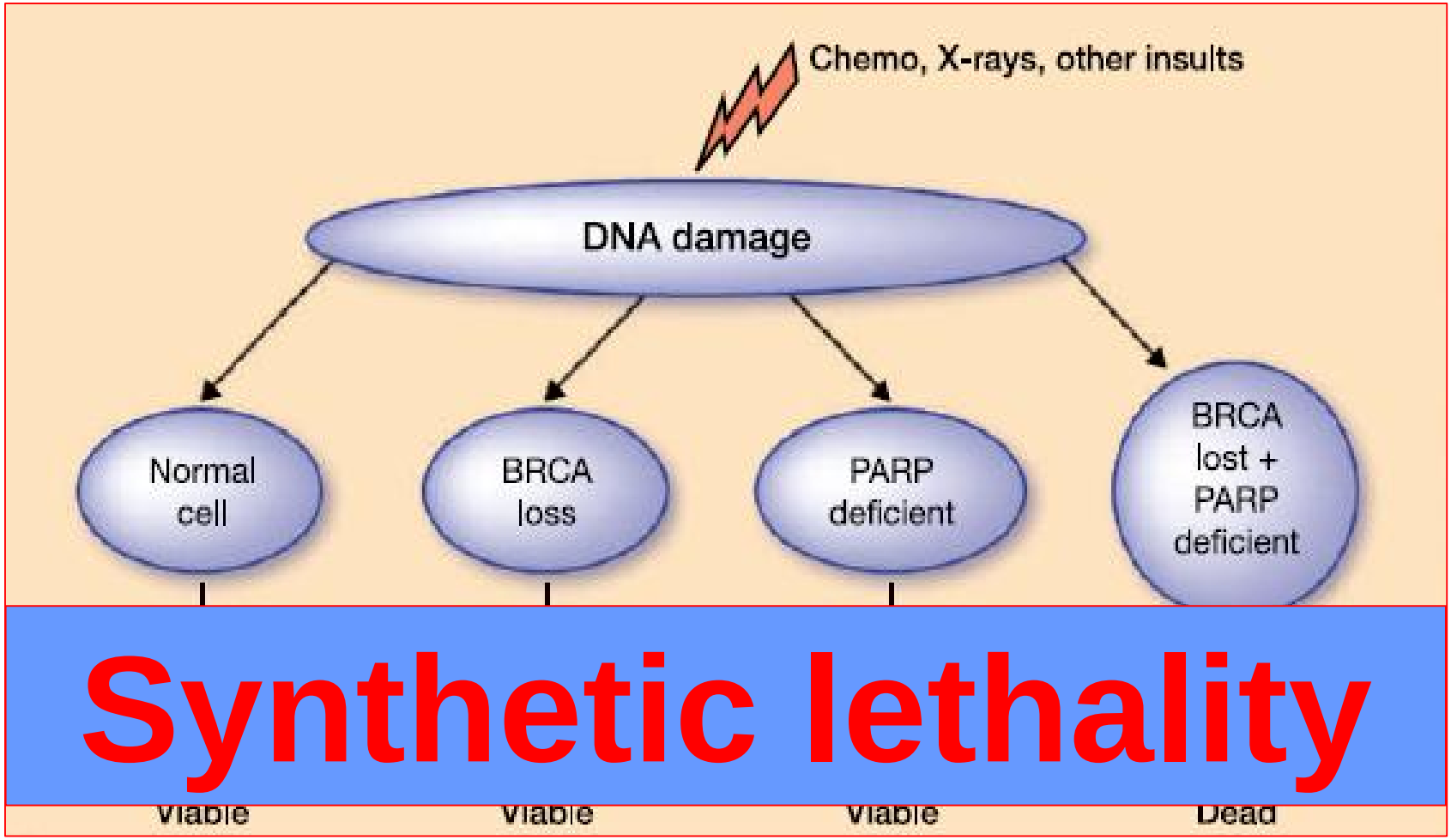


Sistemi di riparo del DNA: un nuovo bersaglio



Turner, Nat Rev Cancer 2004;
Carey, Clin Canc Rev 2010

Nuovi bersagli nel carcinoma mammario



Anders, Clin Cancer Res 2010

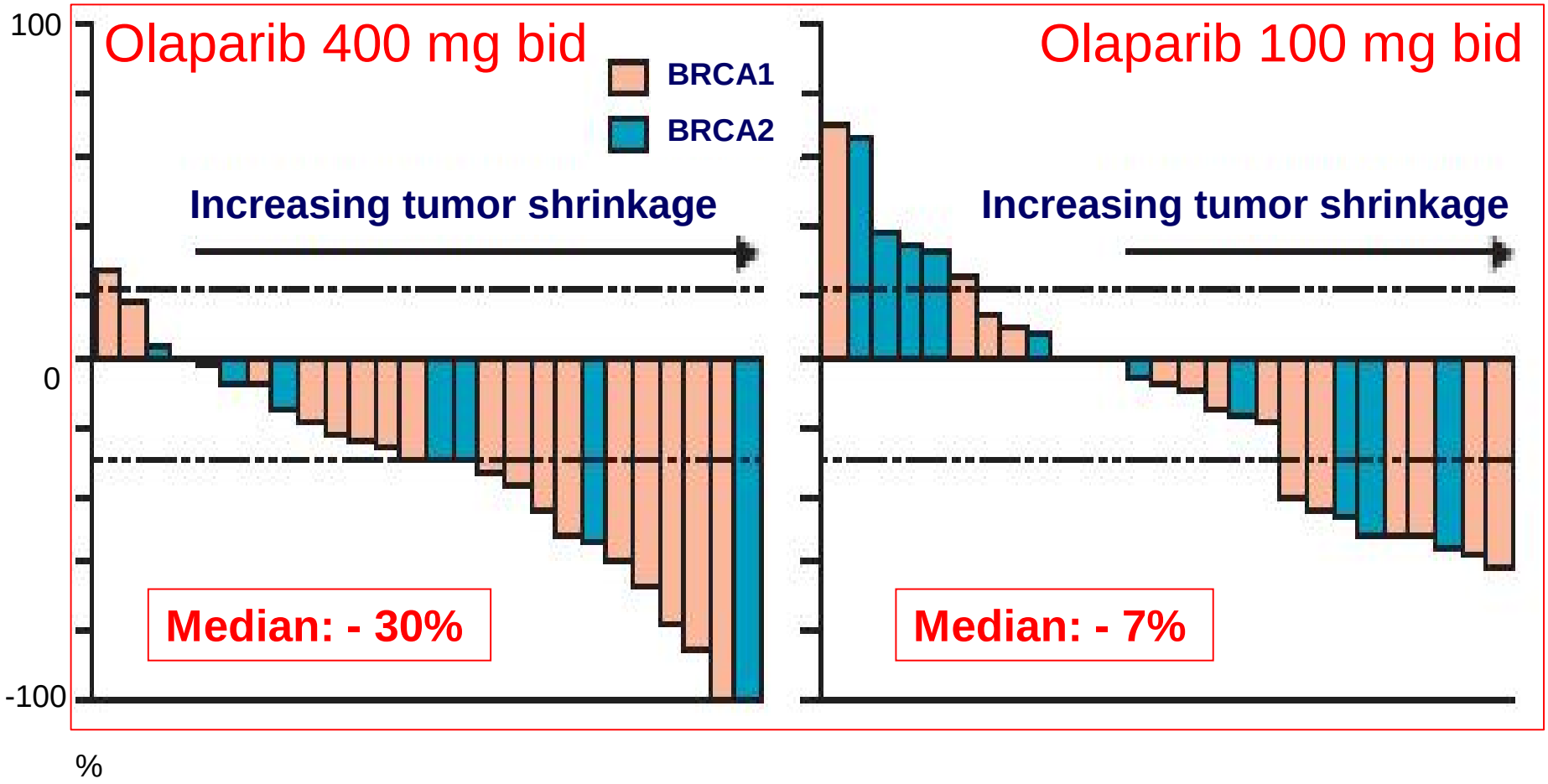
Risultati del trattamento con inibitori di PARP (blocco di BER)

	Olaparib 400 mg twice daily	**Olaparib 100 mg twice daily**
	N=27	N=27
Objective response	11° (41%)	6 (22%)
CR	1 (4%)	0
PR	10 (37%)	6 (22%)
Stable disease	12 (44%)	12 (44%)
Progressive disease	4 (15%)	9 (33%)

* Intention to treat; ° all but 1 within first 4 courses

Tutt, Lancet 2010

Modifiche del volume tumorale



Tutt, Lancet 2010

Alcuni tumori sporadici sono fenocopie dei tumori con deficit di BRCA1 o BRCA2, senza avere mutazioni germinali

The *"BRCAness"* tumors

- High grade
- ER- and HER2-negative
- C-myc amplified
- Medullary
- Pushing margins
- DCIS less common
- Lymphocytic infiltrate
- TP53 mutations
- Basal phenotype
- EGFR expression

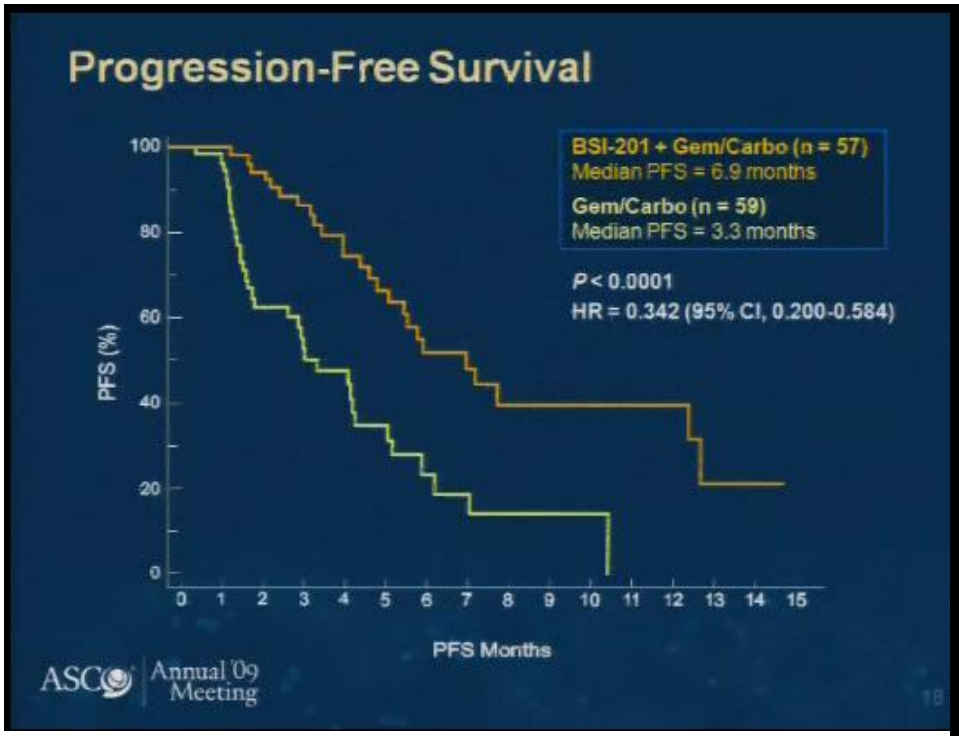
PARP1 is Upregulated in TNBC

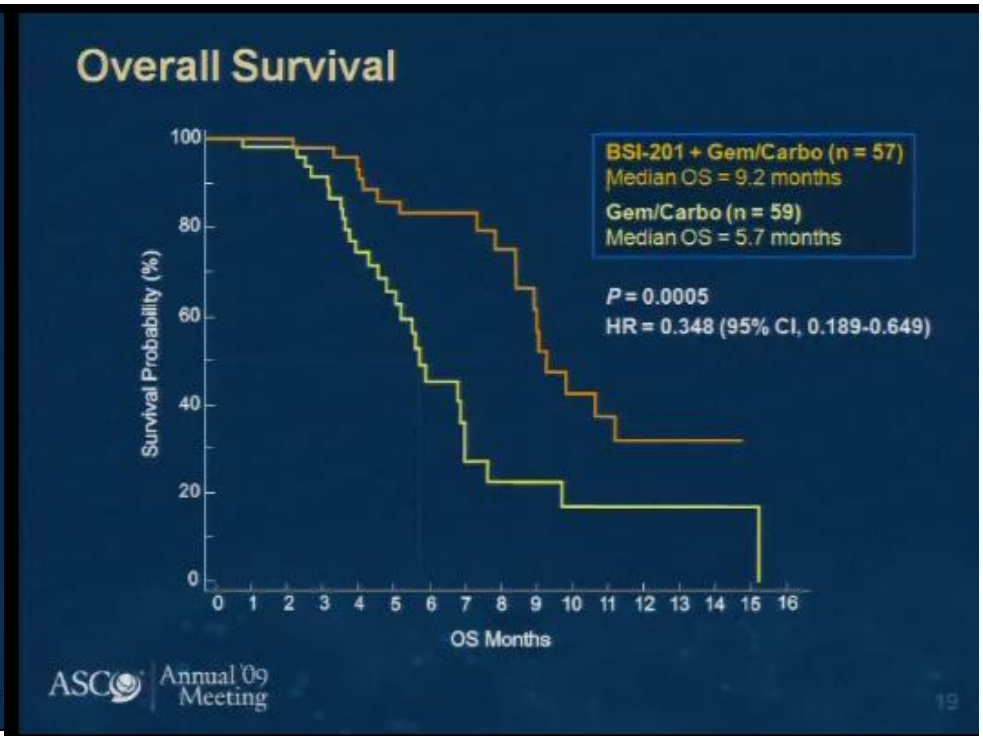
Gene expression profiling showed that *PARP1* was significantly upregulated in the majority of triple negative breast cancers (n = 50)

***PARP1* mRNA**
(Red Fluorescence Units Normalized to β-Glucoronidase)

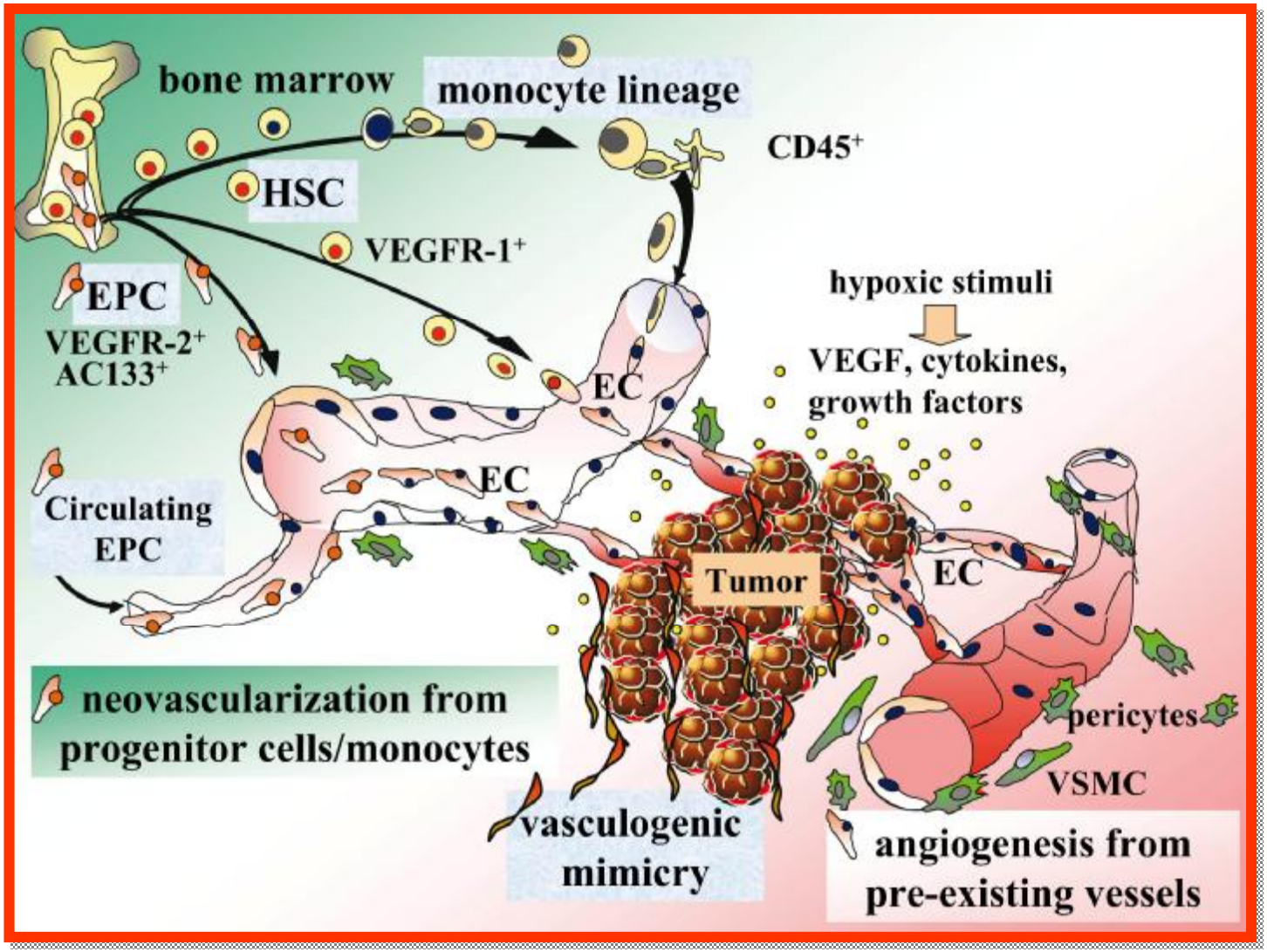
Risultati con inibitori di PARP in TNBC

Risposte cliniche nel 48% dei casi (verso il 16& dei controlli), in paz molto pretrattati



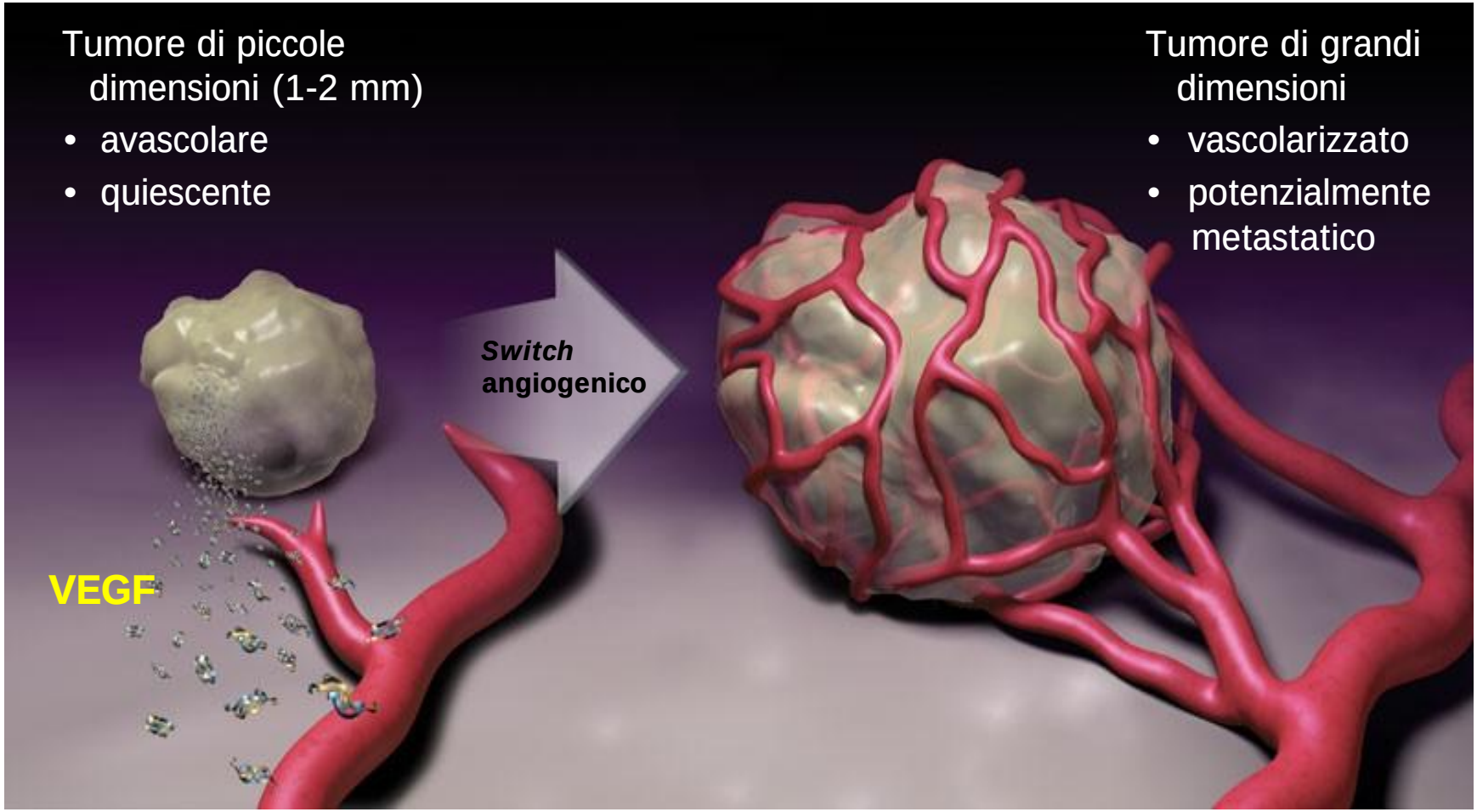


Il ruolo del microambiente – la neoangiogensi



Furuya M, Vascular Health and Risk Management 2005

Switch angiogenico e sviluppo tumorale



Bergers G, et al. Nat Rev Cancer 2002; 3: 401-10

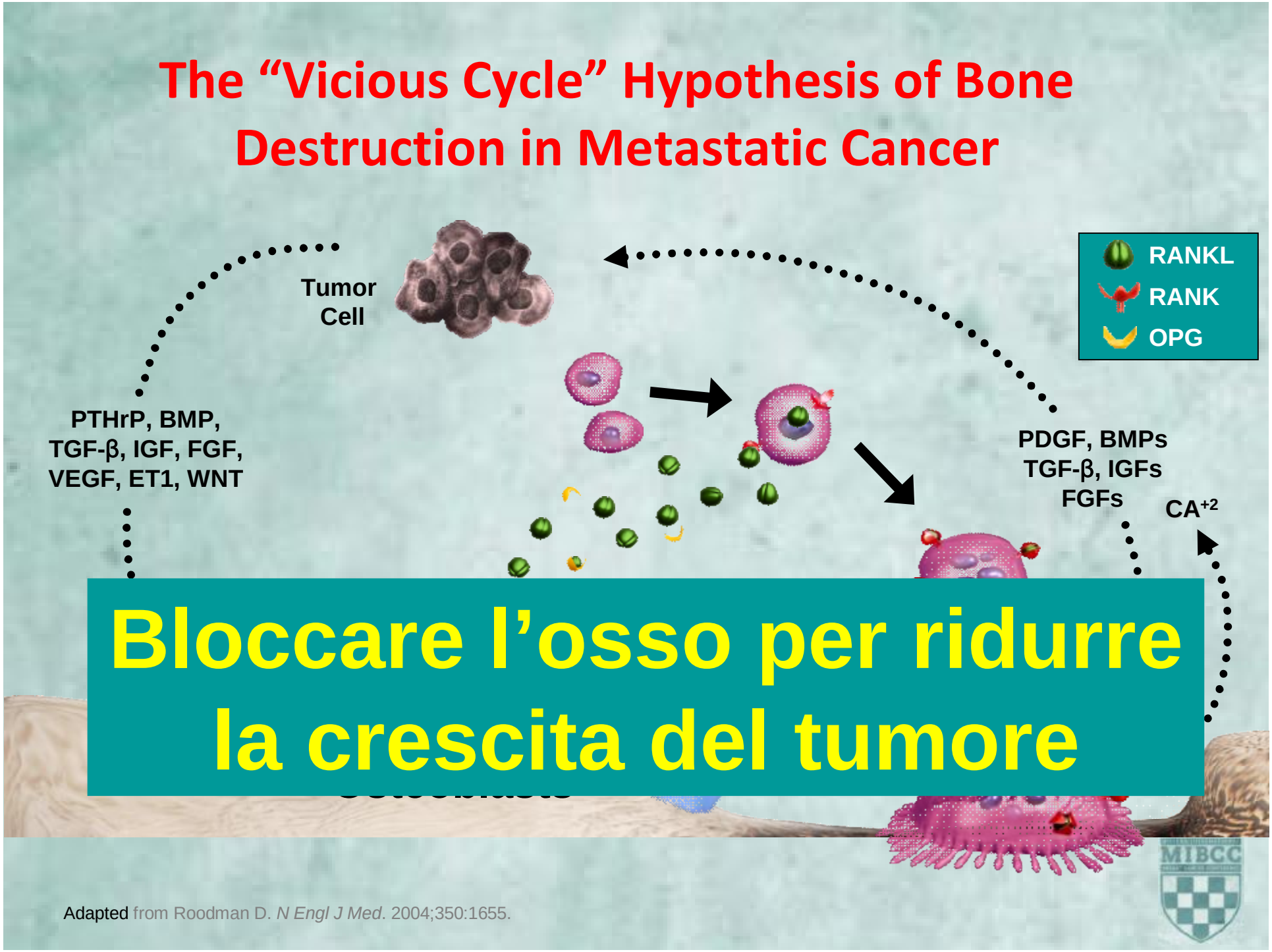
Randomized phase III trials with Bevacizumab in MBC

	E2100°		AVADO°°		RIBBON-1°°°			
Study design	1° line		1° line		1° line			
Pts #	673		736		615		622	
Comparator	**Paclitaxel q7**		**Docetaxel q21**		**Capecitabine**		**Anthra/taxane**	
	Rx	**Rx+B**	**Rx**	**Rx+B (7.5/15)**	**Rx**	**Rx+B**	**Rx**	**Rx+B**
Median PFS (mos)	**5.8**	**11.3**	**8.1**	**9.0/10.0**	**5.7**	**8.6**	**8.0**	**9.2**
HR	**0.48**		**0.80/0.67**		**0.69**		**0.64**	
ORR %	**22.0**	**50.0**	**46.4**	**52.2/ 64.1**	**23.6**	**35.4**	**37.9**	**51.3**
OS (mos)	**24.8**	**26.5**	**31.9***	**30.8*/ 30.2**	**21.2**	**29**	**23.8**	**25.2**

°Miller, NEJM 2007; Gray, JCO 2009. °° Miles, SABCS 2009; °°°Robert, ASCO 2009, SABCS 2009

* Cross-over allowed

The "Vicious Cycle" Hypothesis of Bone Destruction in Metastatic Cancer



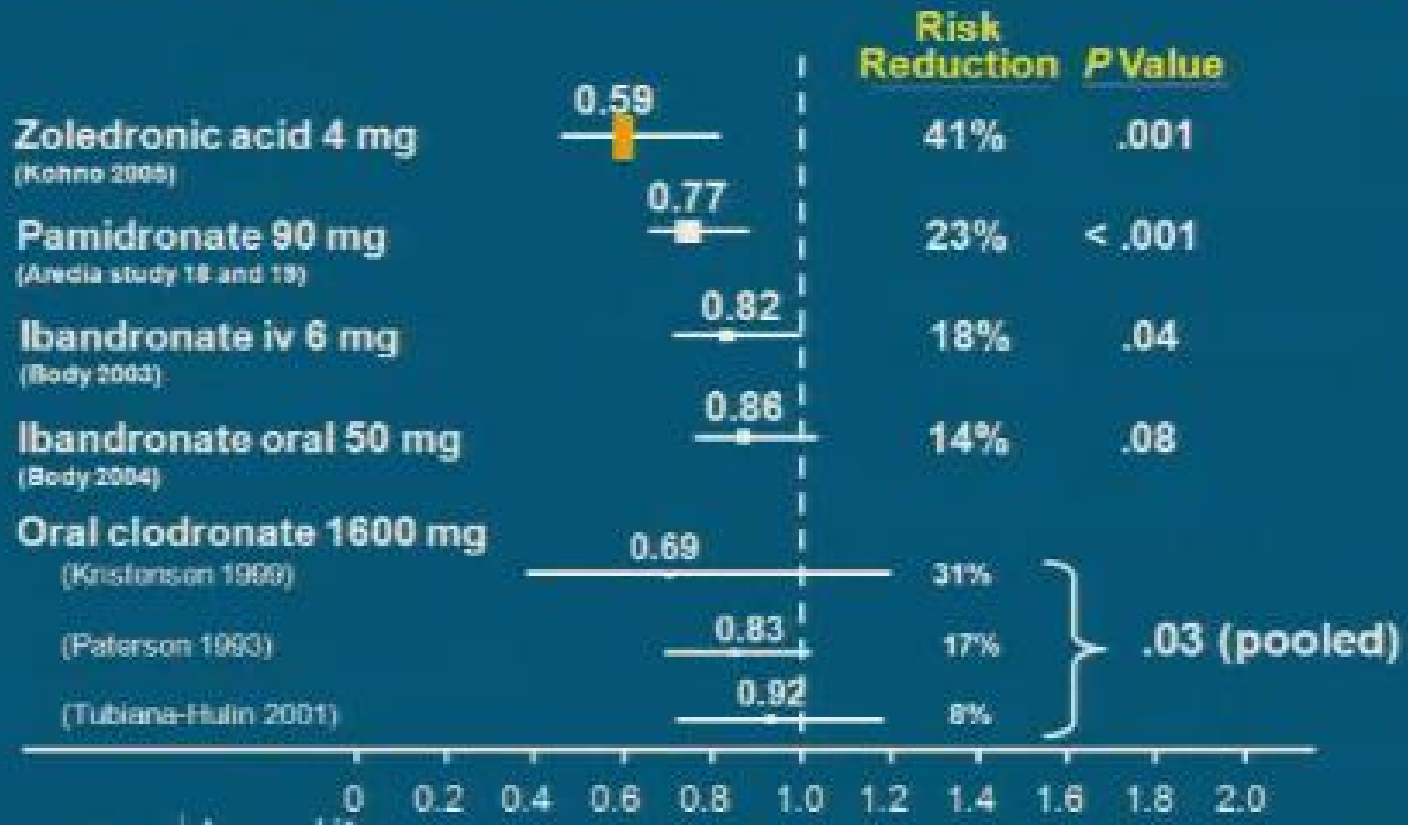
Bloccare l'osso per ridurre la crescita del tumore

Adapted from Roodman D. *N Engl J Med*. 2004;350:1655.

Meta-analysis: SRE Risk Reduction in MBC With Bone Mets BPs vs Placebo

Over 2600 patients

Cochrane Database Comparing Placebo-Controlled Trials in Breast Cancer Setting



Adapted from Pavlakis N, et al. Cochrane Database Syst Rev. 2005;CD003474.

ASCO Annual '10 Meeting

MIBCC

Hortobagyi, ASCO 2010

Osteonecrosi della mandibola (ONJ)

- **Clinical features of suspected ONJ**
  - Exposed bone in maxillofacial area that occurs in association with dental surgery or occurs spontaneously, with no evidence of healing
- **Working diagnosis of ONJ**
  - No evidence of healing after 6 wks of appropriate evaluation and dental care
  - No evidence of metastatic disease in the jaw or osteoradionecrosis

Risk factors

- **oral infections**
- **surgical trauma of the jaw**
- **concomitant cancer treatments**
- **comorbidities (diabetes)**
- **BP potency, schedule and duration**

Weitzman R, et al. Crit Rev Oncol Hematol. 2007;62:148-152.

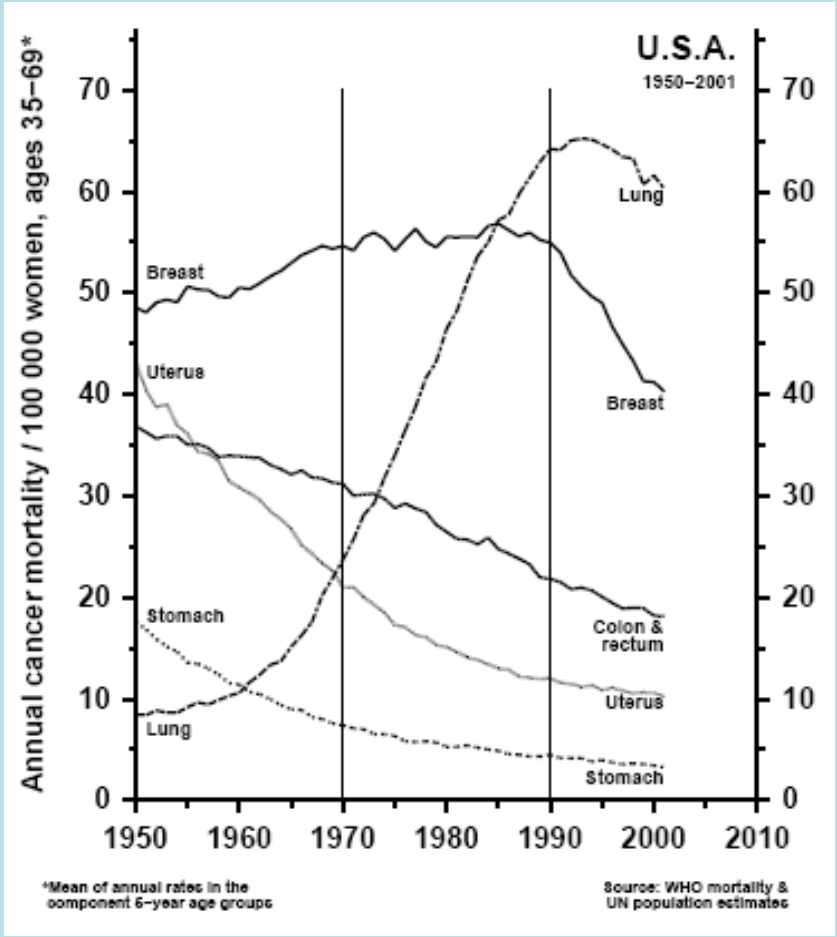
Evidenze cliniche di un effetto antitumorale dei bifosfonati

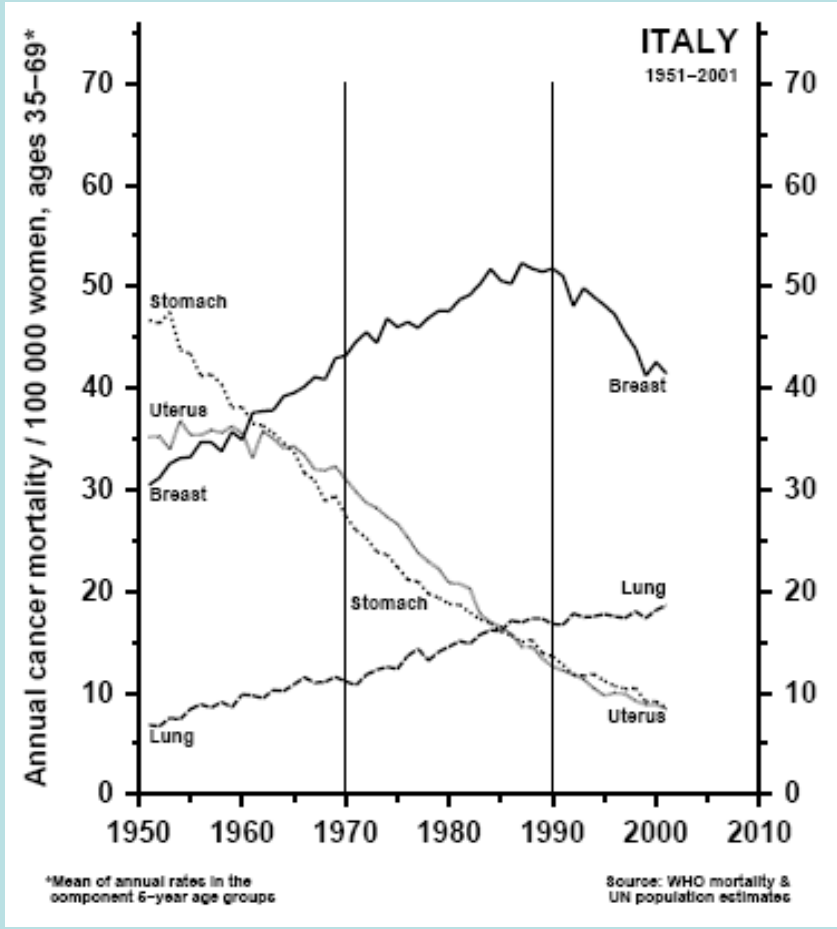
Trial	Treatment	Pts #	End point	HR	p
Diel	Clodronate *(oral)*	290	B.Mets rate	23.6 vs 26.2%	0.77
Powles	Clodronate *(oral)*	1069	BMFS (primary)	**0.69** (0.48-0.99)	0.043
ABGCSG12	Zol vs Pl + LhRh and Ana or Tam	1803	DFS (primary)	**0.64** (0.46-0.91)	0.01
ZO-FAST	Zol immed. vs delayed + Letro	1065	DFS (secondary)	**0.59** (0.36-0.96)	0.0314
neoAZURE	Zol vs pl	205	pCR	**6.9 vs 11.7%**	0.146
WHI-OS	BP vs not for osteoporosis	154,768	BC risk	**0.68** (0.52-0.88)	<0.01
BCINIS	BP vs not for osteoporosis	4039	BC risk	Odds ratio **0.72** (0.57-0.90)	n.r.

Benefici delle terapie adiuvanti

- E’ stimato che
  - Una terapia **endocrina** ottimale può ridurre il rischio di recidiva annuale di circa il 60%-70%
  - Una **chemioterapia** ottimale può ridurre il rischio di recidiva annuale di circa 50%-60%
  - **Il Trastuzumab** può ridurre il rischio di recidiva annuale del 45%-55%
  - **Lo Zoledronato** può ridurre il rischio di recidiva annuale di **circa il** 36%

Riduzione della mortalità per tumore mammario





EBCTCG, Lancet 2005