



SERVIZIO SANITARIO REGIONALE  
EMILIA-ROMAGNA

AZIENDA OSPEDALIERO-UNIVERSITARIA DI FERRARA

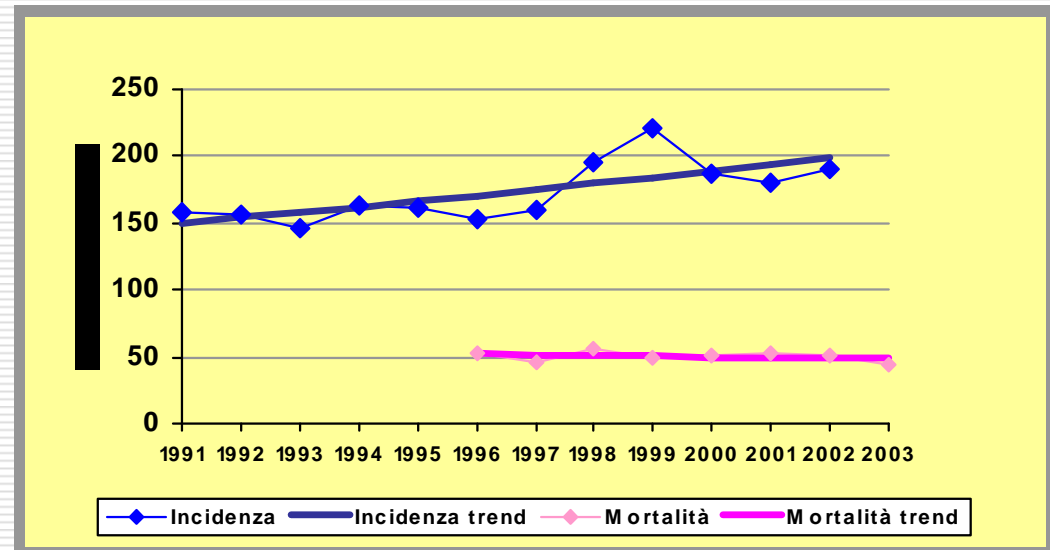
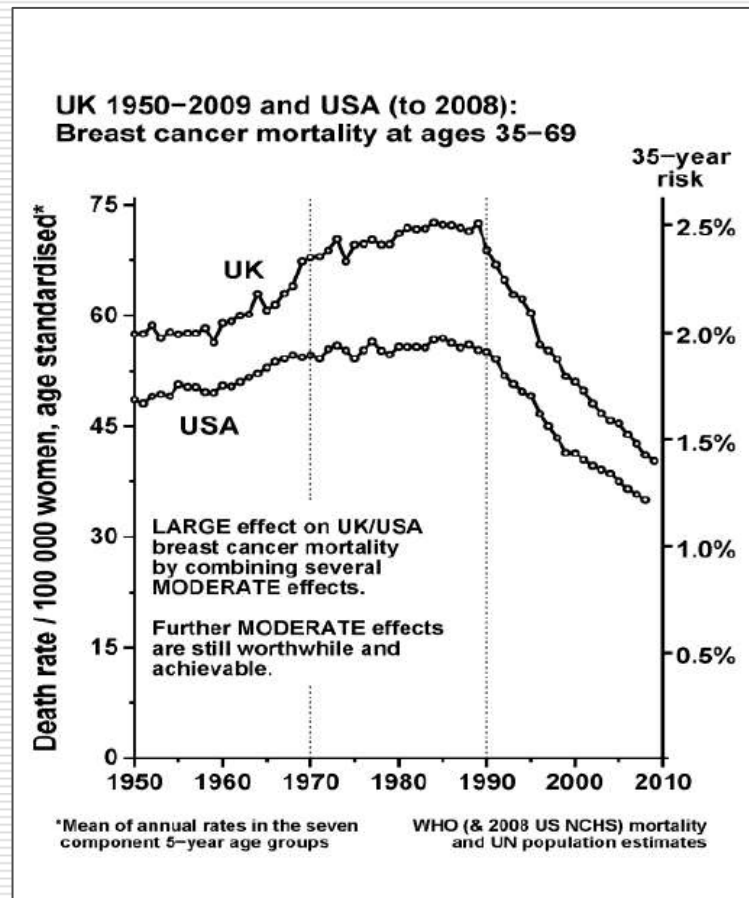
# I nuovi farmaci hanno modificato la storia naturale della malattia?

**Monica Indelli**

U.O. Oncologia Clinica  
Ferrara 8 giugno 2013



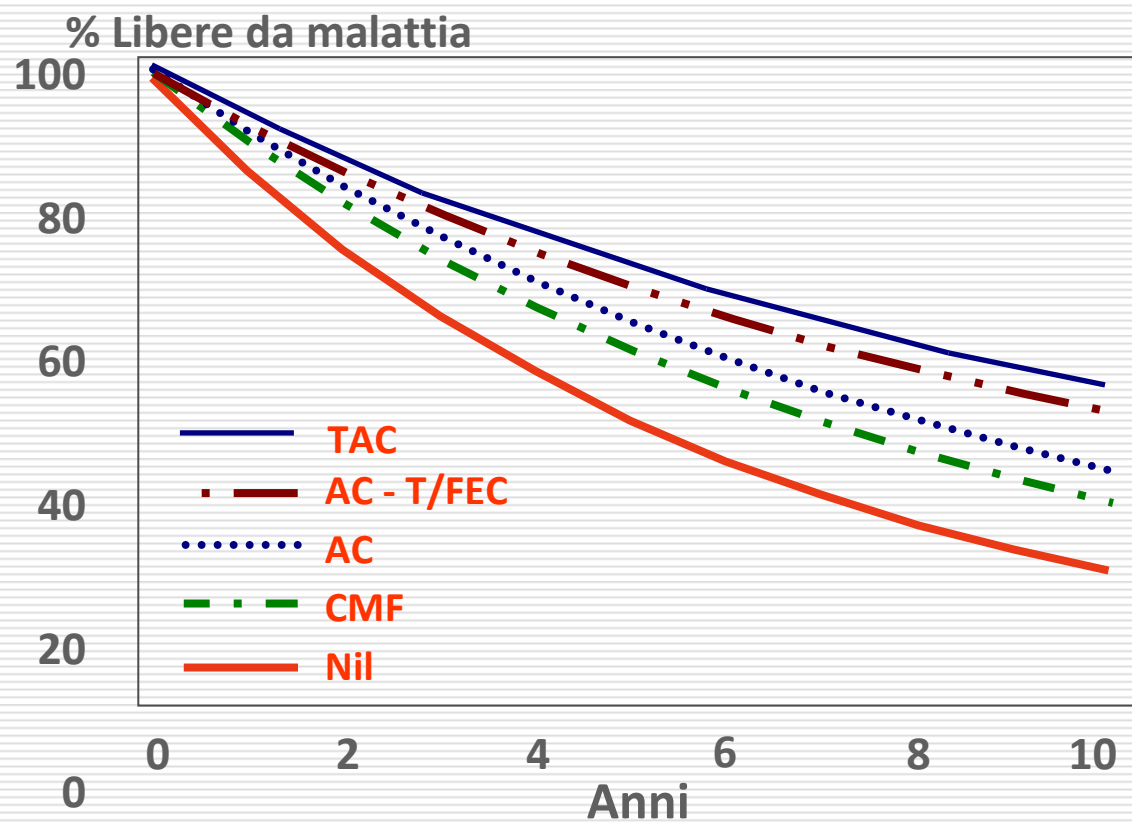
# La storia naturale negli ultimi anni



Registro tumori della provincia di Ferrara

# Una crescita lenta e continua...

Ca mammario N+: evoluzione dei risultati della chemioterapia



Rischio ricaduta/anno

TAC<sup>4</sup> = 6,5 % (-32%)

AC - T<sup>3</sup>  
FEC<sup>2</sup> } ~ 8 % (-17%)

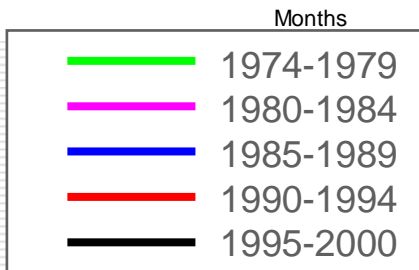
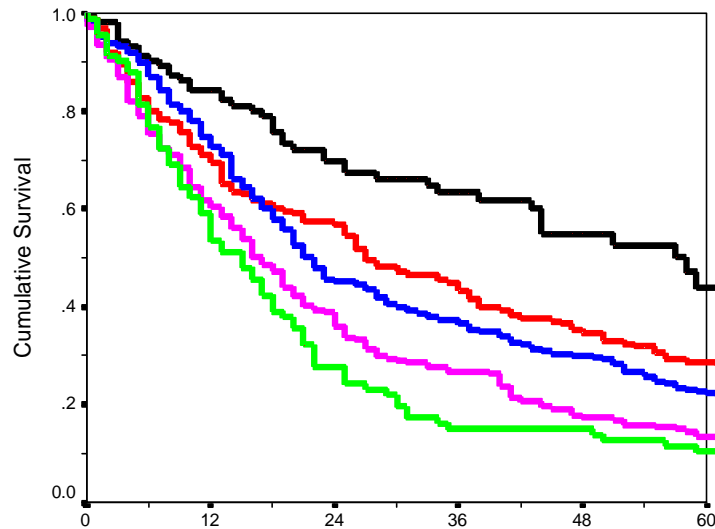
AC<sup>1</sup> = 10,0 % (-11%)

CMF<sup>1</sup> = 11,4 % (-24%)

Nil<sup>1</sup> = 15,0 %

<sup>1</sup> EBCTCG 2000 <sup>2</sup> Levine, JCO 1998; FASG, JCO 2001 <sup>3</sup> Henderson, JCO 2003 <sup>4</sup> Martin, NEJM 2005

# Una crescita lenta e continua...



## Five Year Relative Survival Rates for Breast Cancer: 1973 - 2004

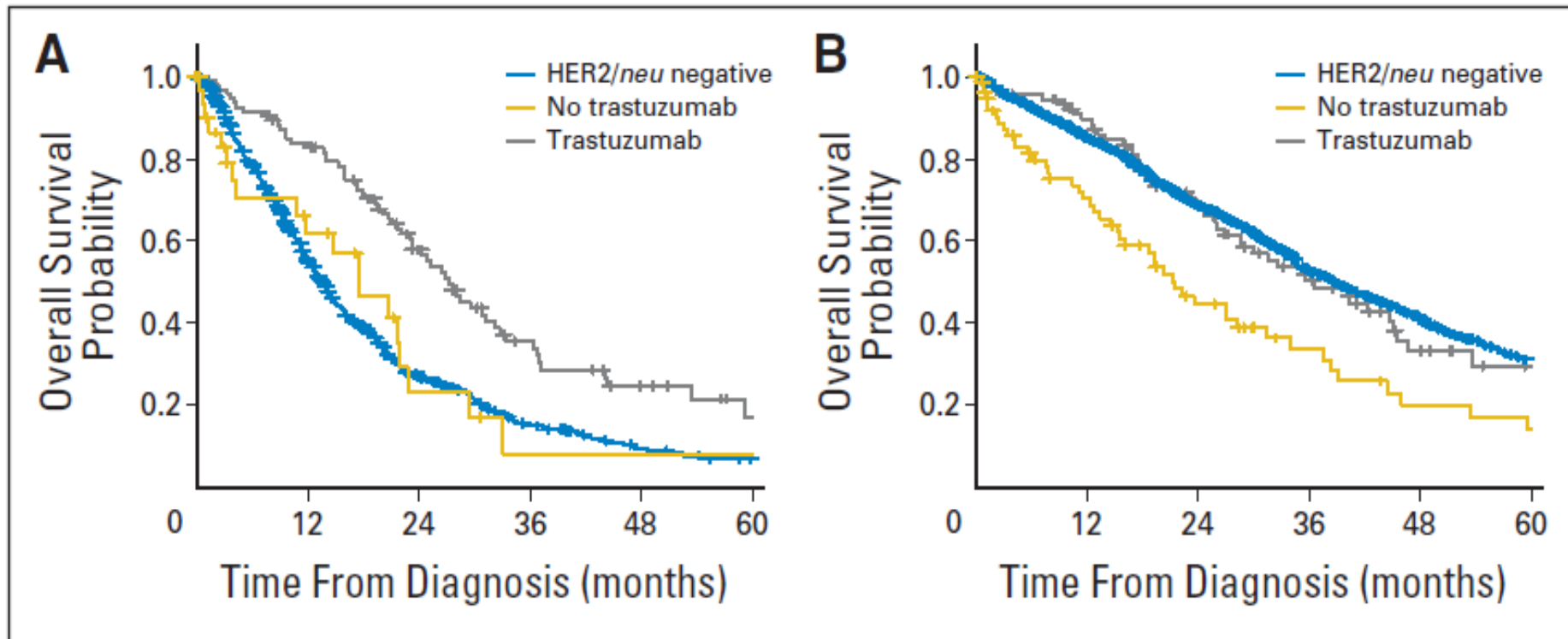
	Localized	Regional	Distant
1973	85	53	<10
<b>2004</b>	<b>98</b>	<b>84</b>	<b>27</b>

Cancer survivors increased from 3 M to 11 M in the same period

*CA, Jan 1978 and Jan 2009*

Sopravvivenza dopo diagnosi di ricaduta

# La "rivoluzione" dei biologici



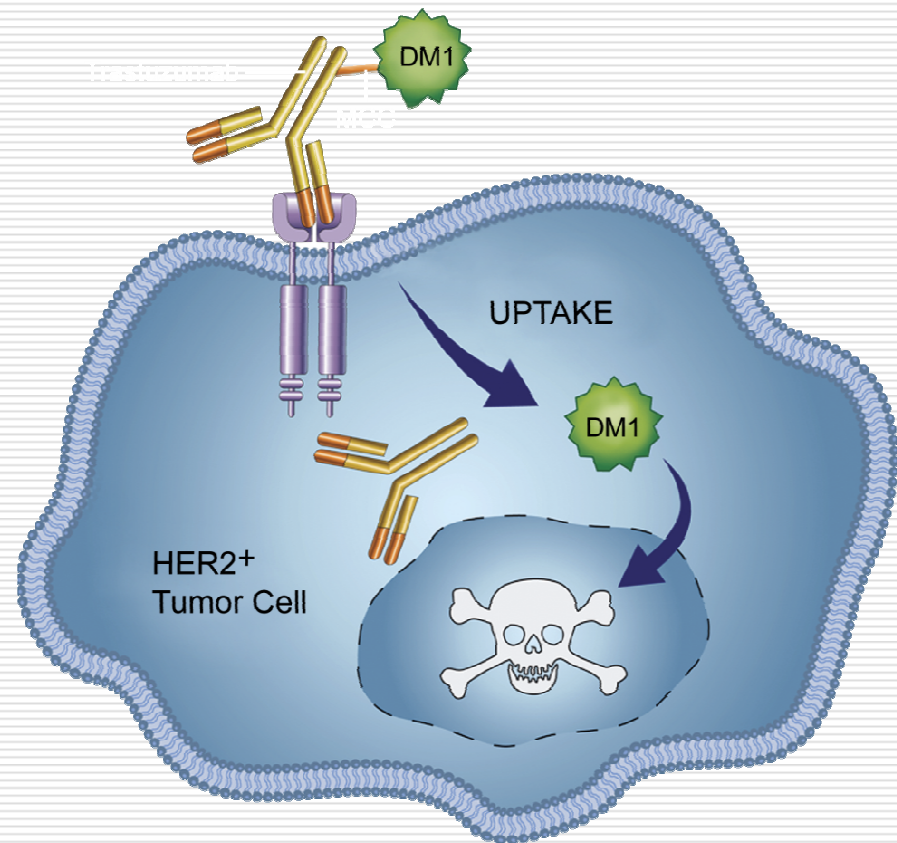
Recettori ormonali negativi

Recettori ormonali positivi

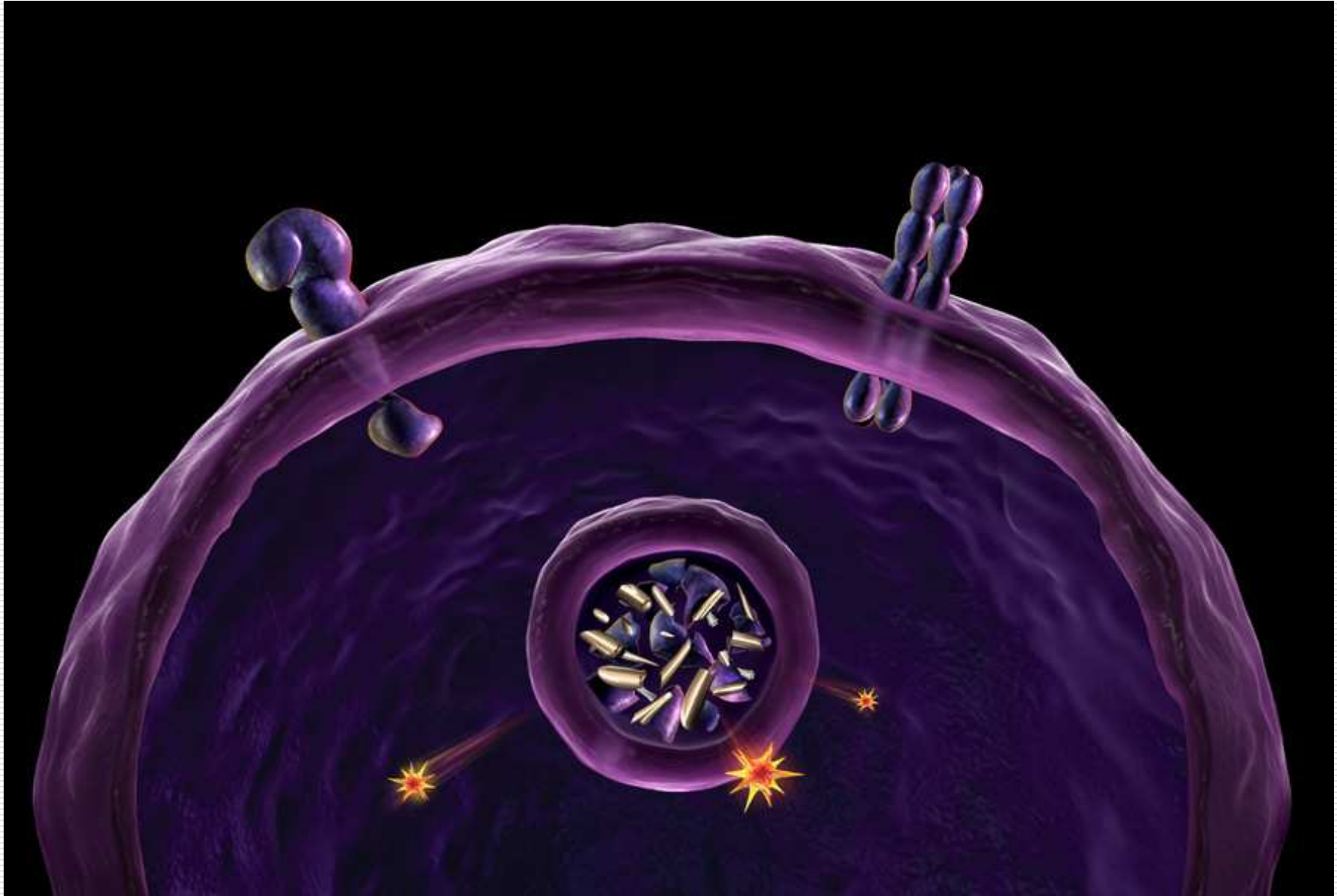
# Trastuzumab-DM1

## Attività citotossica Target-Dipendente

- DM1-Derivato dalla maytansina
  - Antibiotico antitumorale di origine naturale
  - Attività preclinica significativa, ma alta tossicità come farmaco libero
- Trastuzumab-DM1 è stato disegnato per rilasciare DM1 nelle cellule tumorali Her2+
  - Aumenta l'indice terapeutico di DM1
  - Mantiene l'effetto biologico del trastuzumab



# Meccanismo d'azione



# Trastuzumab-DM1

## Attività citotossica Target-Dipendente

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*The NEW ENGLAND JOURNAL of MEDICINE*

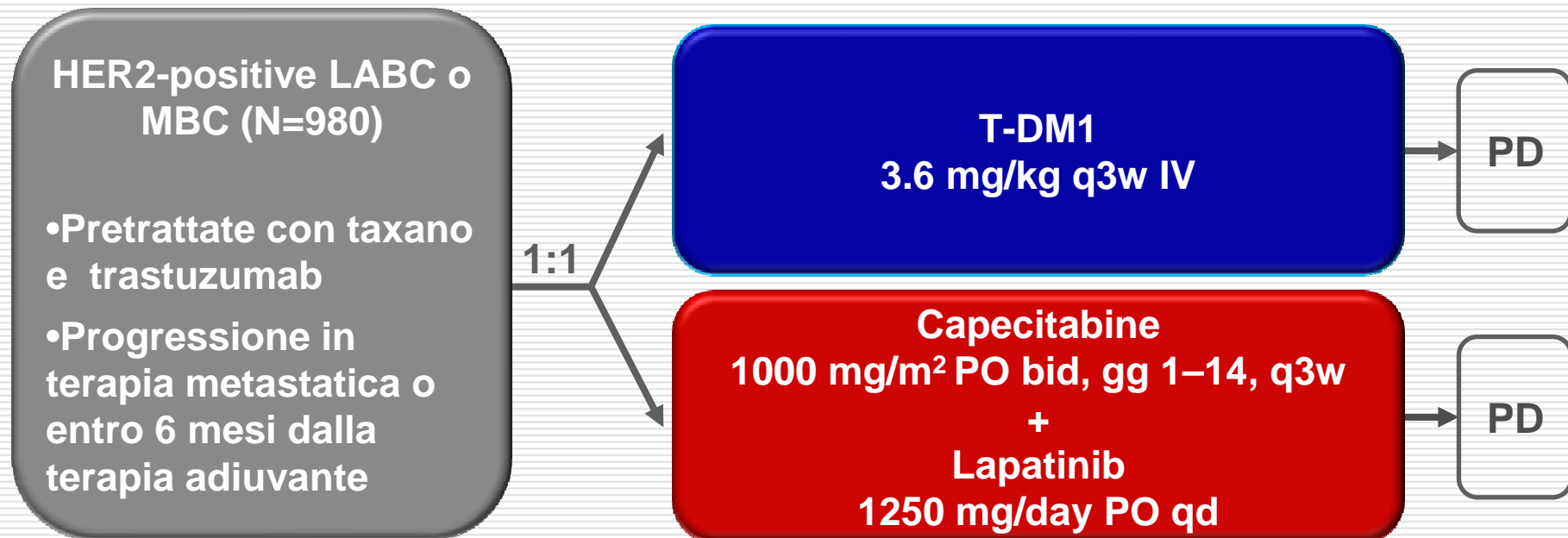
ORIGINAL ARTICLE

### Trastuzumab Emtansine for HER2-Positive Advanced Breast Cancer

Sunil Verma, M.D., David Miles, M.D., Luca Gianni, M.D., Ian E. Krop, M.D., Ph.D.,  
Manfred Welslau, M.D., José Baselga, M.D., Ph.D., Mark Pegram, M.D.,  
Do-Youn Oh, M.D., Ph.D., Véronique Diéras, M.D., Ellie Guardino, M.D., Ph.D.,  
Liang Fang, Ph.D., Michael W. Lu, Pharm.D., Steven Olsen, M.D., Ph.D.,  
and Kim Blackwell, M.D., for the EMILIA Study Group

# Trastuzumab-DM1

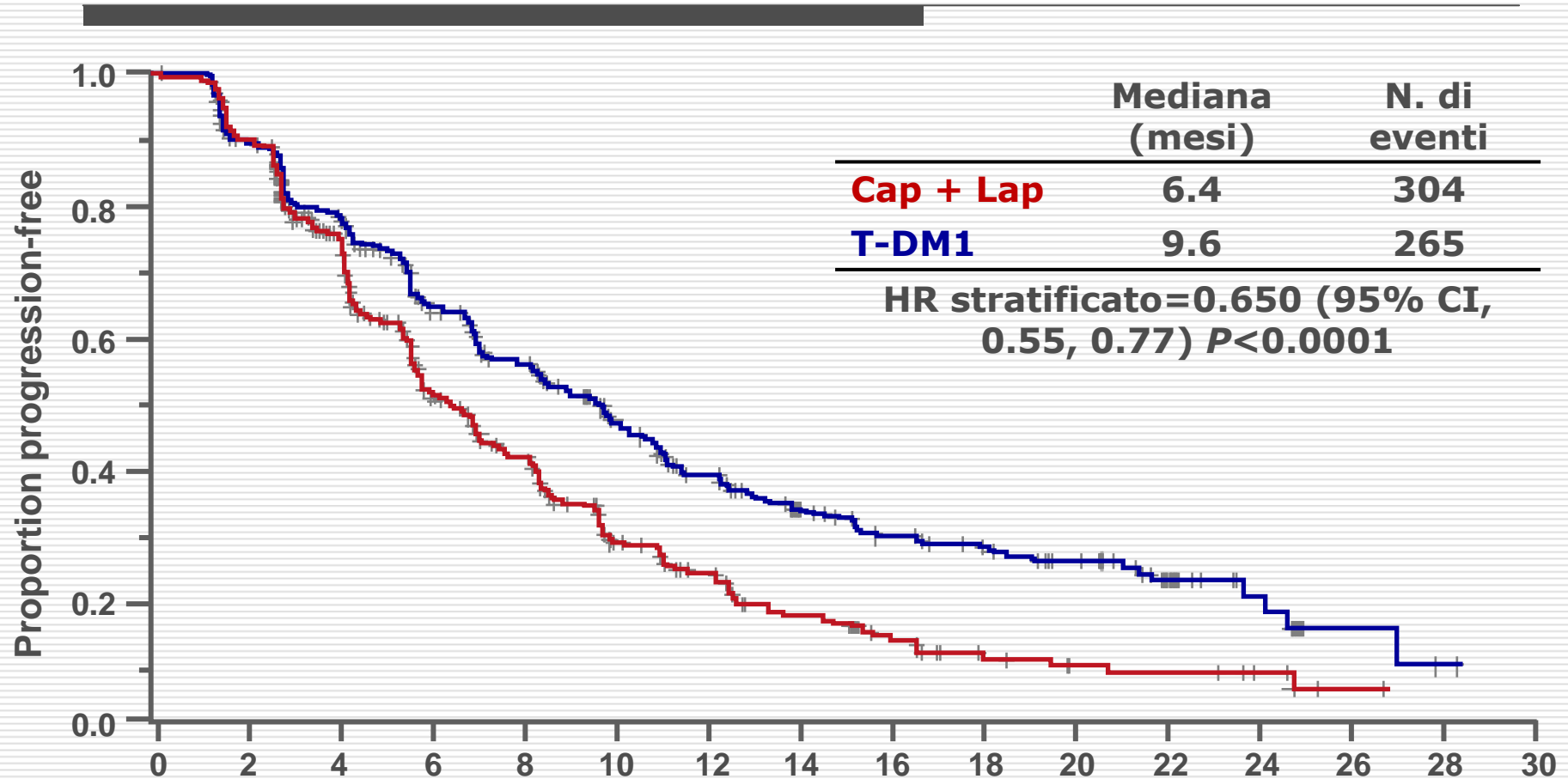
## EMILIA: disegno dello studio



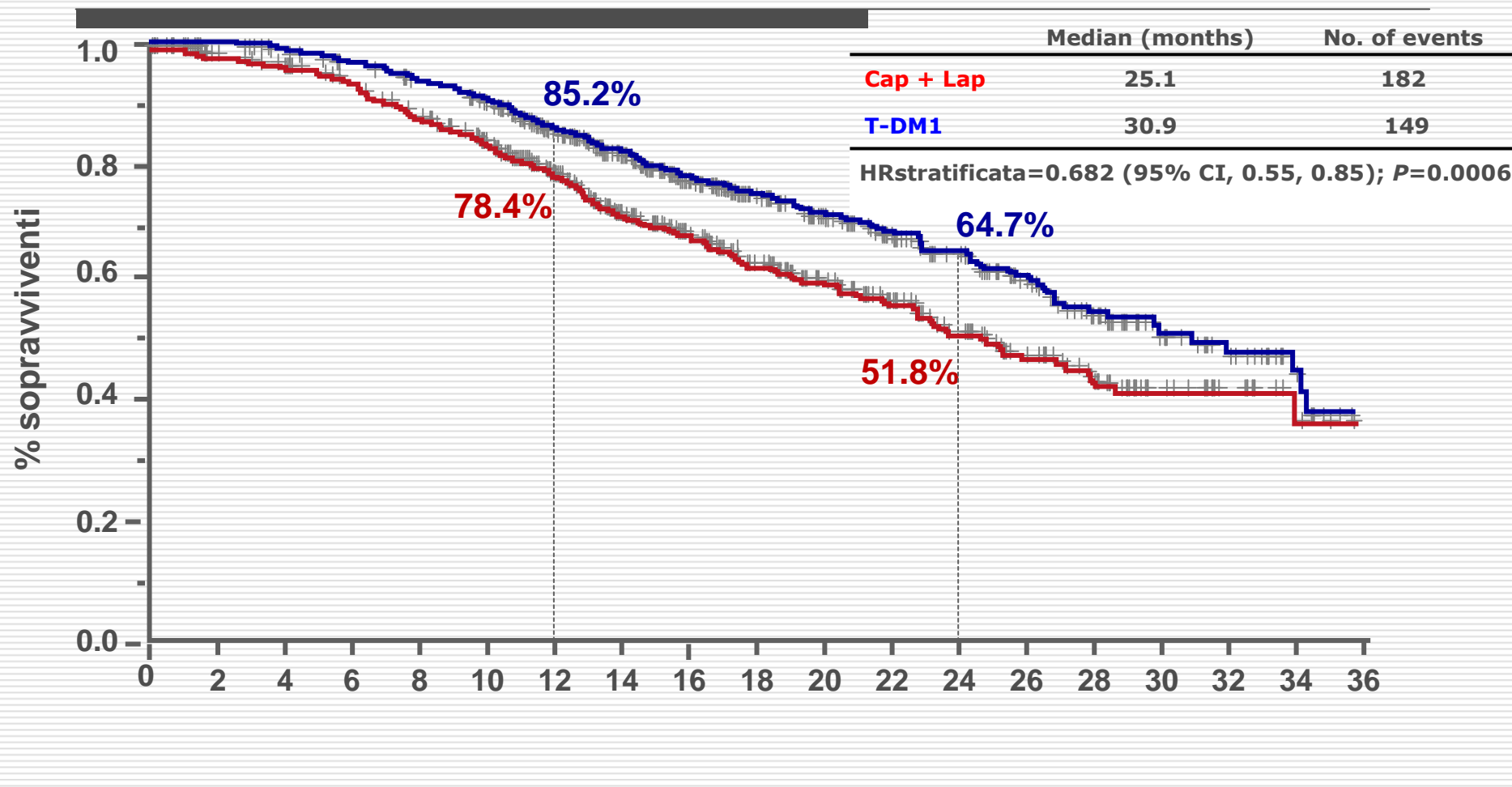
- **Primary endpoints:** PFS (review indipendente), OS, e tossicità
- **Key secondary endpoints:** PFS (investigatori), ORR, DOR

# Trastuzumab-DM1

## PFS: Review indipendente

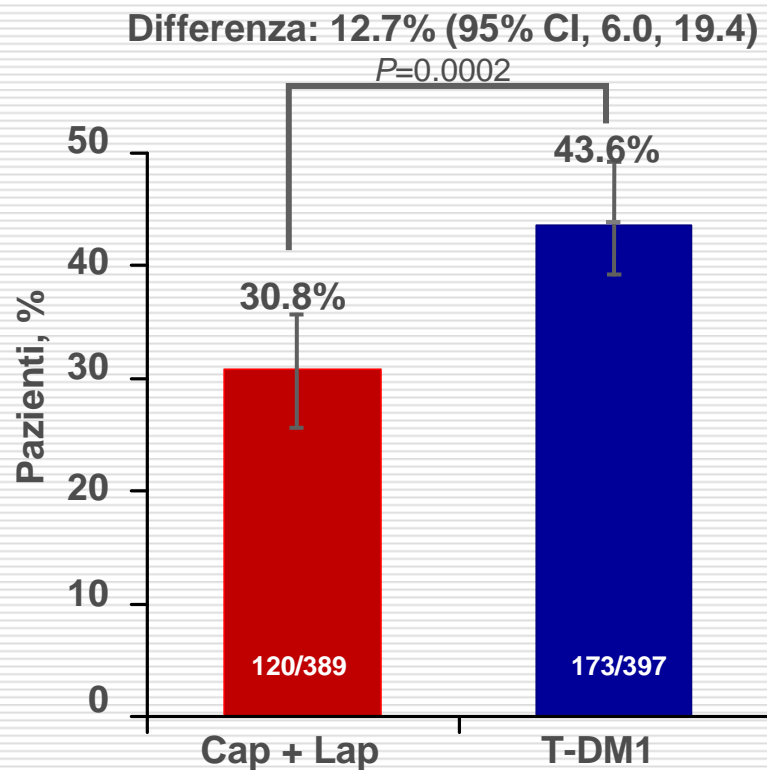


# Trastuzumab-DM1 OS

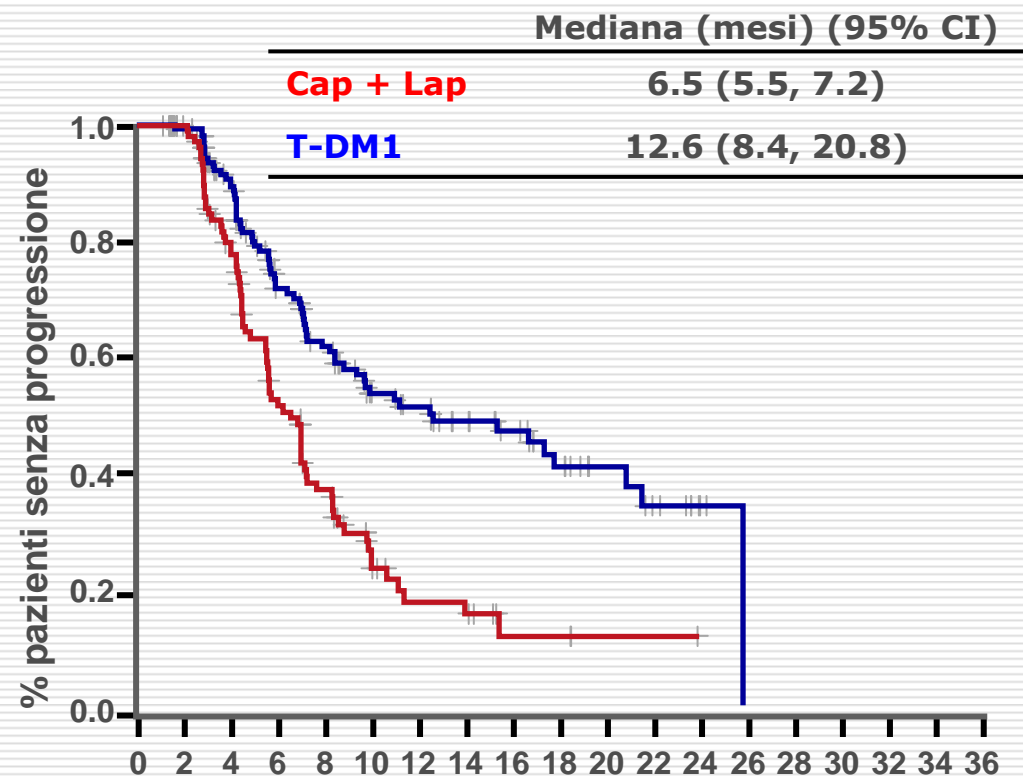


# Trastuzumab-DM1

## Risposta oggettiva



## Durata della risposta (DOR)

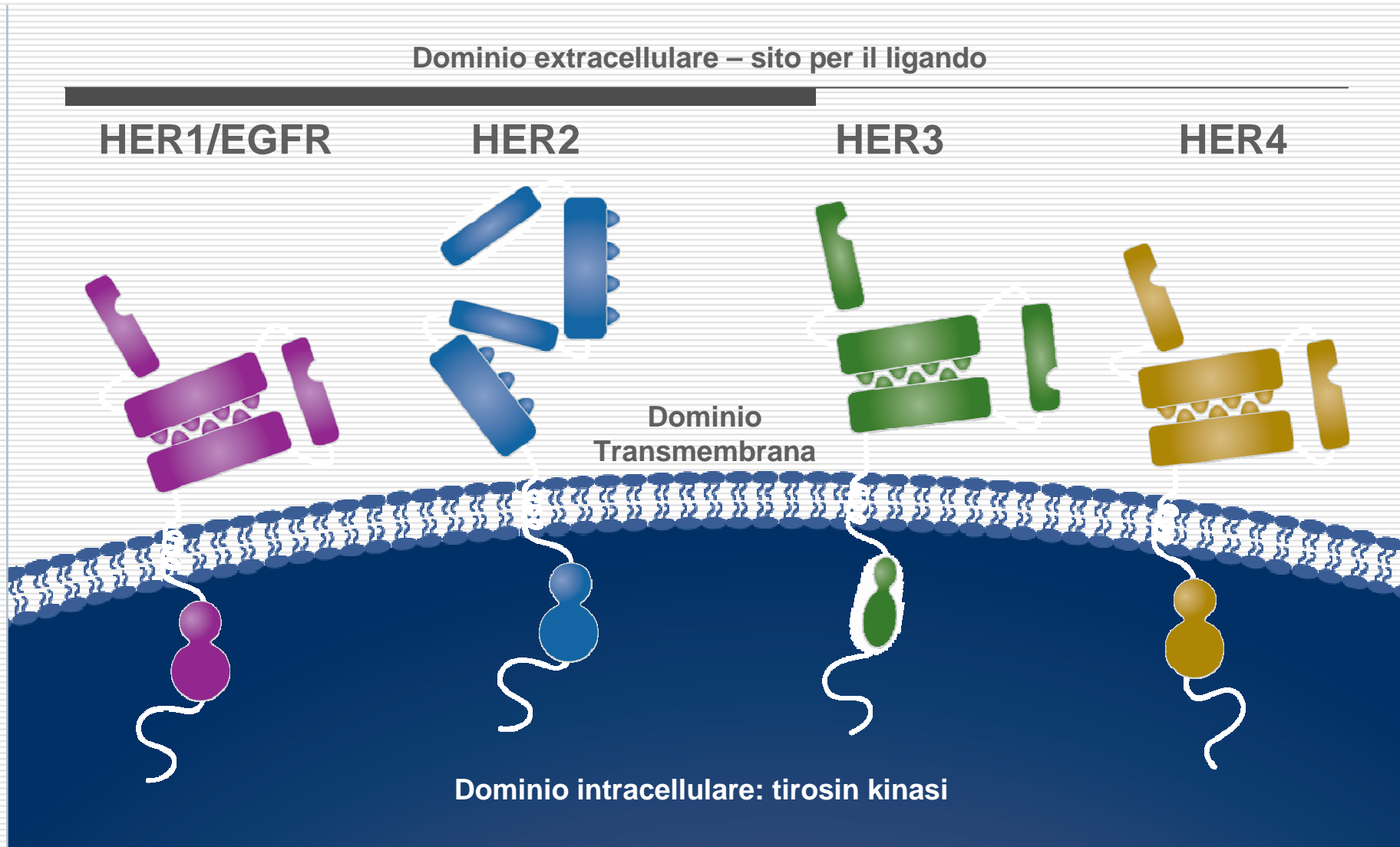


# Trastuzumab-DM1

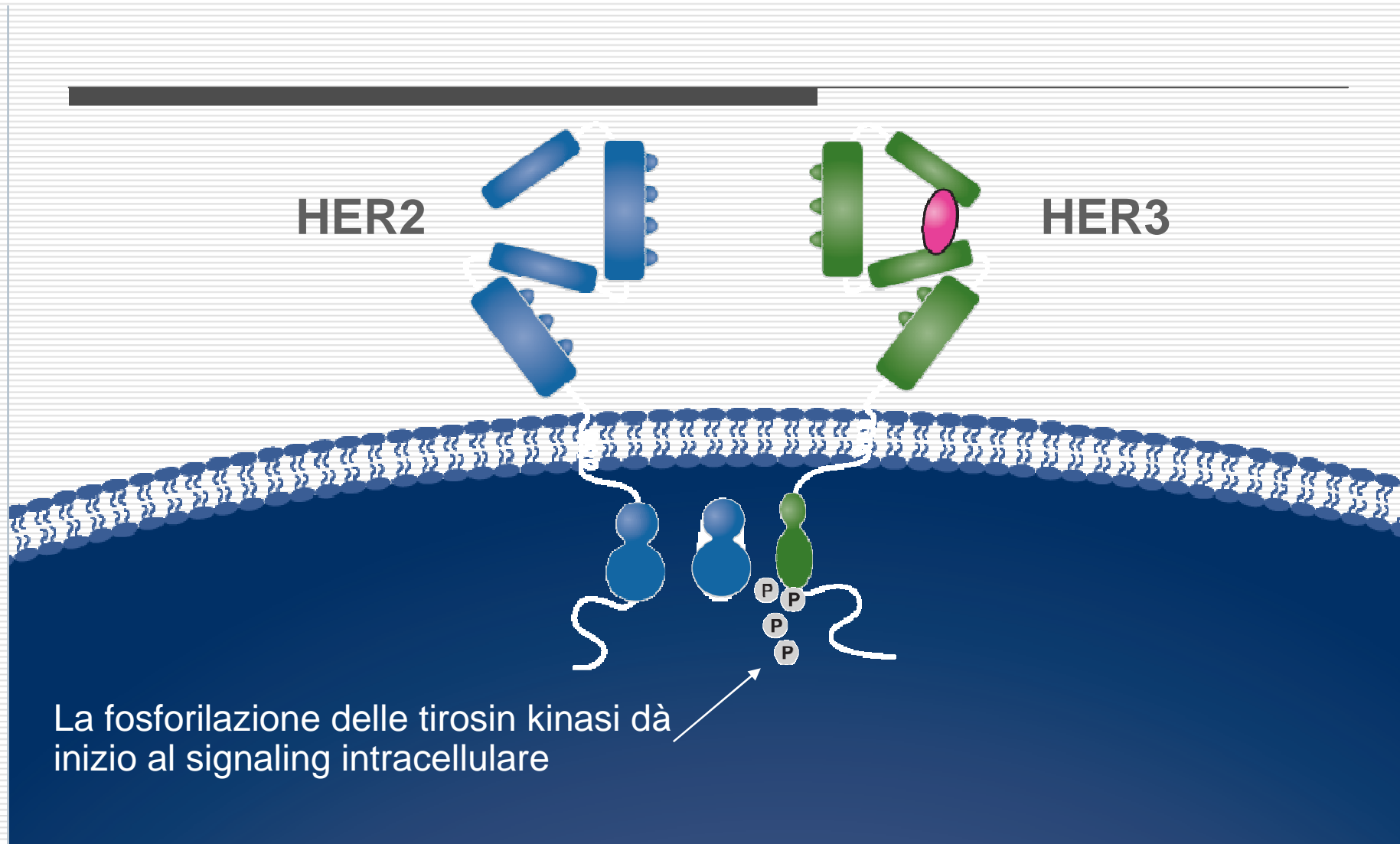
## Effetti collaterali

Evento avverso	Cap + Lap (n=488)		T-DM1 (n=490)	
	All Grades, %	Grade ≥3, %	All Grades, %	Grade ≥3, %
Diarrea	79.7	<b>20.7</b>	23.3	1.6
Hand-foot syndrome	58.0	<b>16.4</b>	1.2	0.0
Vomito	29.3	<b>4.5</b>	19.0	0.8
Neutropenia	8.6	<b>4.3</b>	5.9	2.0
Ipokaliemia	8.6	<b>4.1</b>	8.6	2.2
Fatigue	27.9	<b>3.5</b>	35.1	2.4
Nausea	44.7	<b>2.5</b>	39.2	0.8
Mucosite	19.1	<b>2.3</b>	6.7	0.2
Trombocitopenia	2.5	0.2	28.0	<b>12.9</b>
Aumento AST	9.4	0.8	22.4	<b>4.3</b>
Aumento ALT	8.8	1.4	16.9	<b>2.9</b>
Anemia	8.0	1.6	10.4	<b>2.7</b>

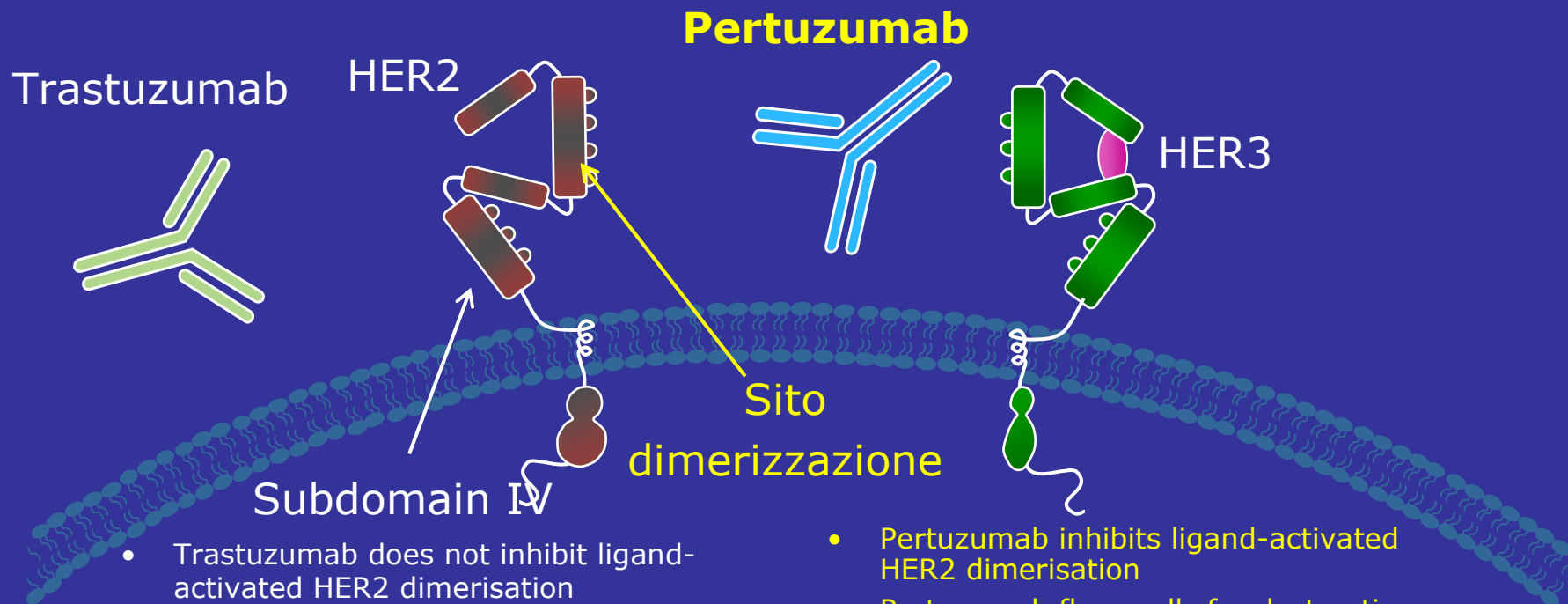
# La famiglia degli EGFR



# Il dimero HER2 – HER3



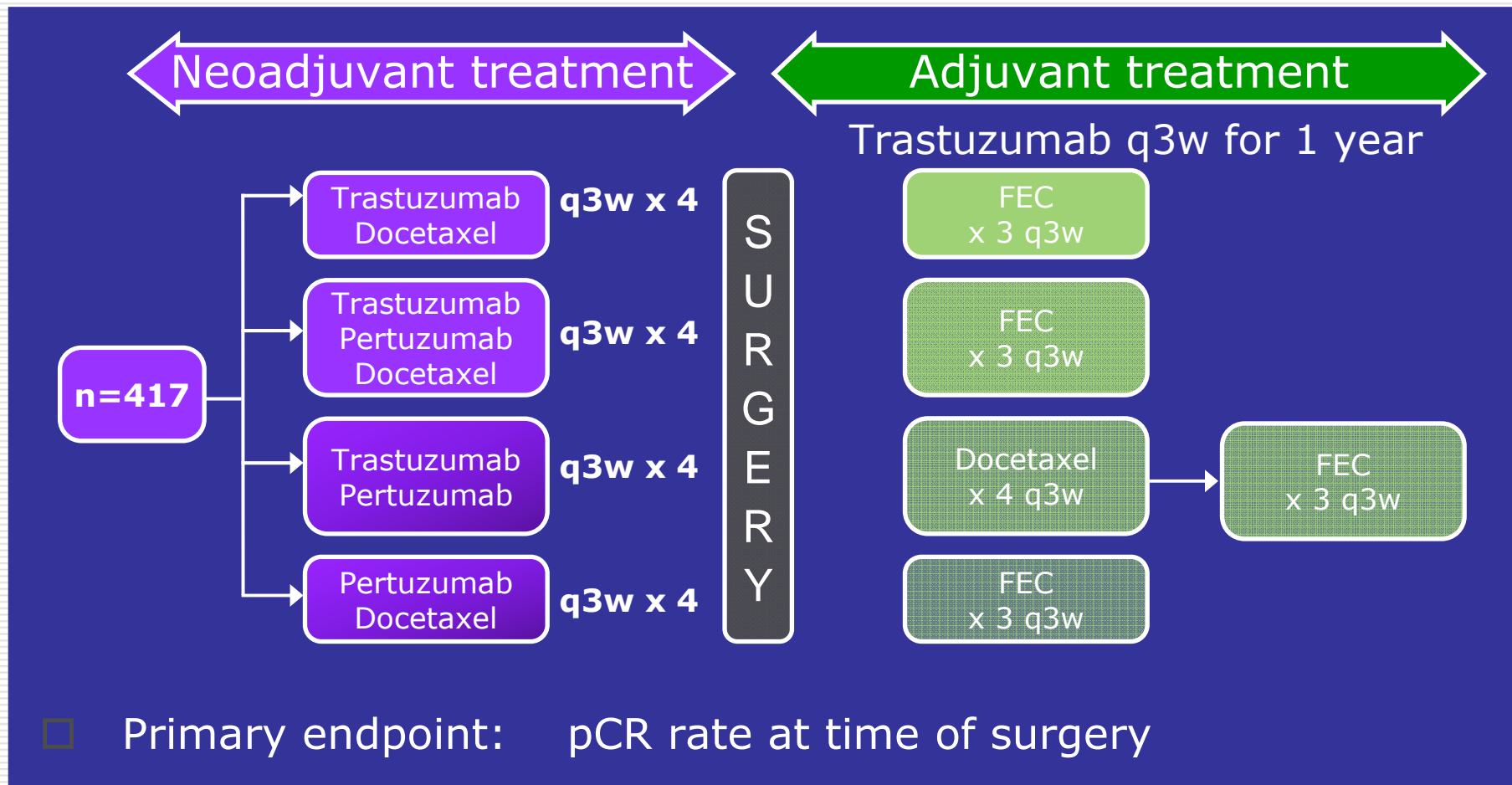
# Pertuzumab: meccanismo di azione



- Trastuzumab does not inhibit ligand-activated HER2 dimerisation
- Trastuzumab prevents HER2 activation by extracellular domain shedding
- Trastuzumab inhibits ligand-independent HER2 signalling and flags cells for destruction by the immune system

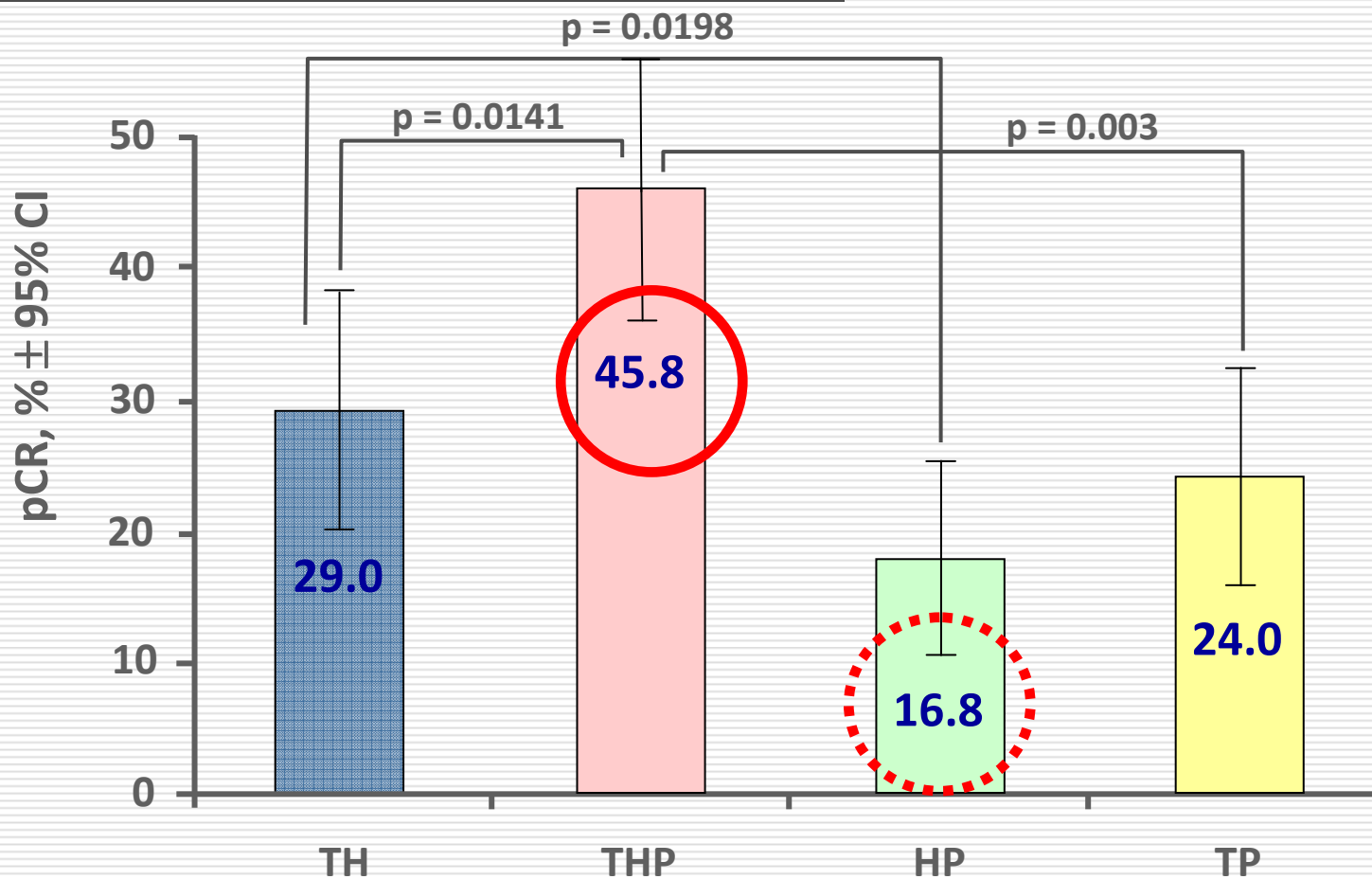
- Pertuzumab inhibits ligand-activated HER2 dimerisation
- Pertuzumab flags cells for destruction by the immune system
- Pertuzumab suppresses multiple HER signalling pathways, leading to a more comprehensive blockade of HER2-driven signalling

# Trastuzumab + Pertuzumab Terapia neoadiuvante



EBC = early-stage breast cancer; FEC = 5-fluorouracil, epirubicin, cyclophosphamide;  
pCR = pathological complete response; q3w = every 3 weeks

# Trastuzumab + Pertuzumab Terapia neoadiuvante



# Trastuzumab + Pertuzumab

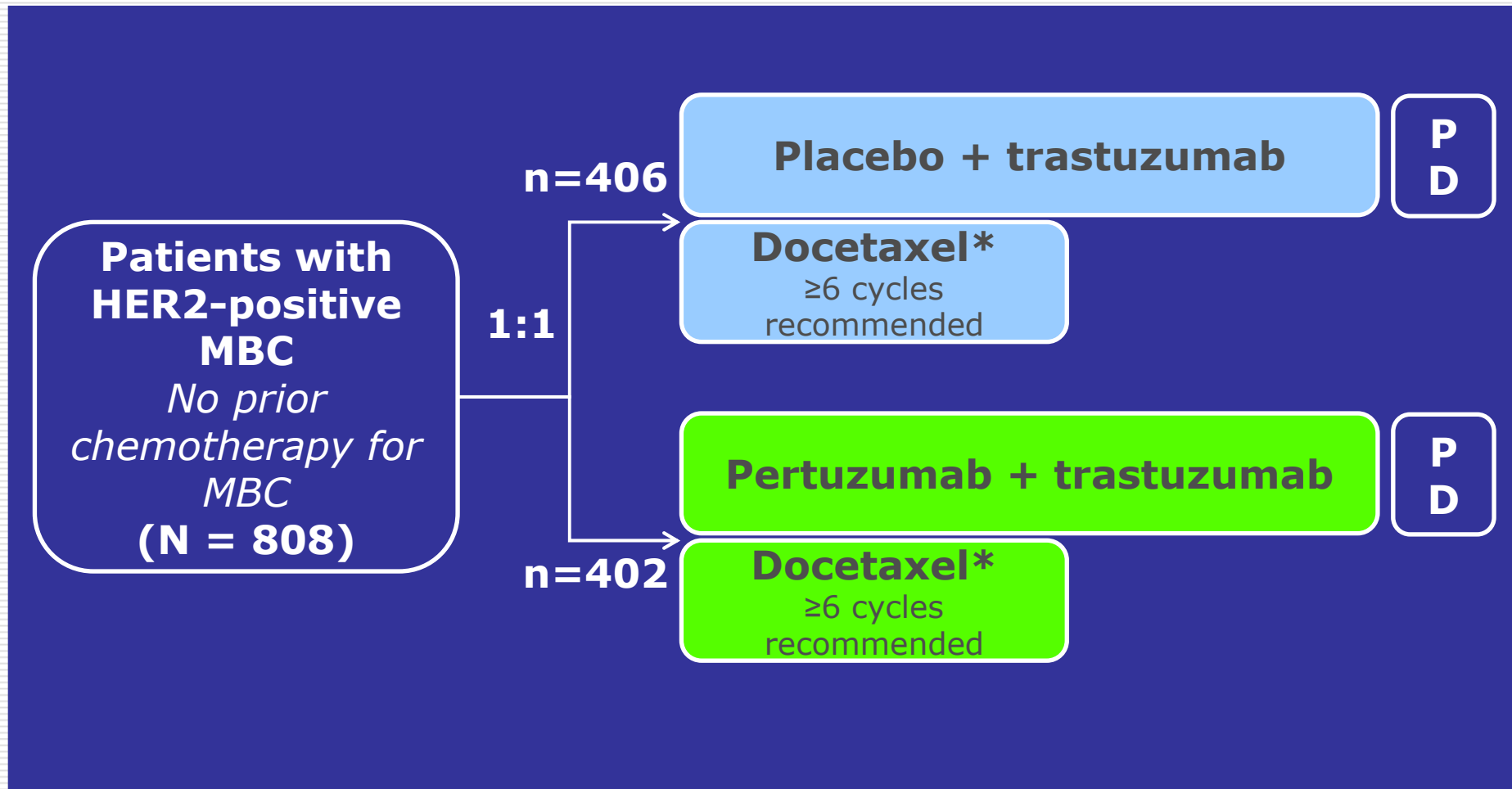
## NEOSPHERE: effetti collaterali

	Patients, %			
	TH (n=107)	THP (n=107)	HP (n=108)	TP (n=94)
<b>Neutropenia</b>	<b>57.0</b>	<b>44.9</b>	<b>0.9</b>	<b>55.3</b>
<b>Neutropenia febbrile</b>	<b>7.5</b>	<b>8.4</b>	<b>0.0</b>	<b>7.4</b>
<b>Leucopenia</b>	<b>12.1</b>	<b>4.7</b>	<b>0.0</b>	<b>7.4</b>
<b>Diarrea</b>	<b>3.7</b>	<b>5.6</b>	<b>0.0</b>	<b>4.3</b>
<b>Astenia</b>	<b>0.0</b>	<b>1.9</b>	<b>0.0</b>	<b>2.1</b>
<b>Granulocitopenia</b>	<b>0.9</b>	<b>0.9</b>	<b>0.0</b>	<b>2.1</b>
<b>Rash</b>	<b>1.9</b>	<b>1.9</b>	<b>0.0</b>	<b>1.1</b>
<b>Irregolarità mestruali</b>	<b>0.9</b>	<b>0.9</b>	<b>0.0</b>	<b>4.3</b>
<b>Reaz ipersensibilità</b>	<b>0.0</b>	<b>0.9</b>	<b>1.9</b>	<b>0.0</b>
<b>Aumento ALT</b>	<b>2.8</b>	<b>0</b>	<b>0</b>	<b>1.1</b>

AE, adverse event; ALT, alanine aminotransferase  
 H, trastuzumab; P, pertuzumab; T, docetaxel

# Trastuzumab + Pertuzumab

## CLEOPATRA: disegno dello studio



# Trastuzumab + Pertuzumab CLEOPATRA: PFS

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JOURNAL of MEDICINE

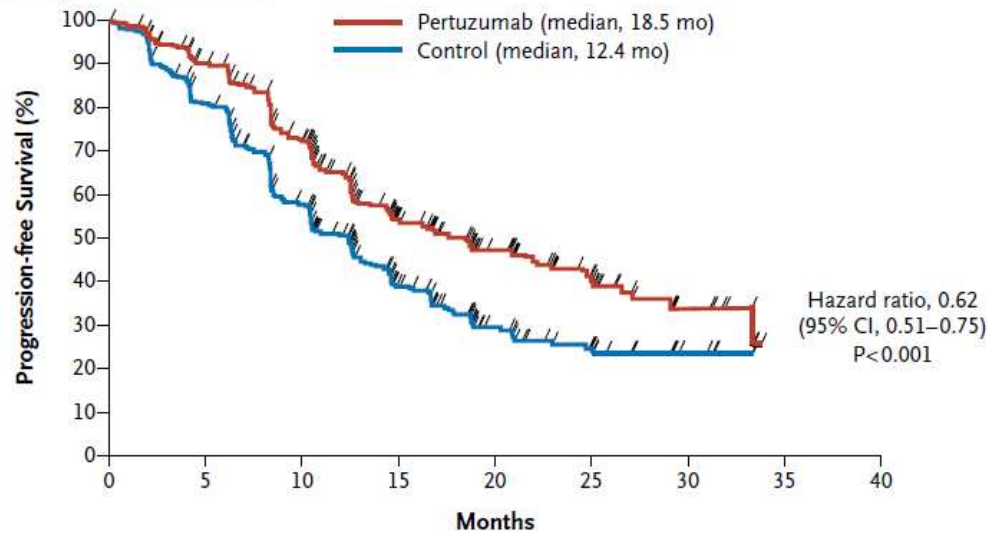
ESTABLISHED IN 1812

JANUARY 12, 2012

VOL. 366 NO. 2

Pertuzumab plus Trastuzumab plus Docetaxel  
for Metastatic Breast Cancer

Independently Assessed Progression-free Survival



No. at Risk

Pertuzumab	402	345	267	139	83	32	10	0	0
Control	406	311	209	93	42	17	7	0	0

In prima linea

# Trastuzumab + Pertuzumab

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**Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA study): overall survival results from a randomised, double-blind, placebo-controlled, phase 3 study**



*Sandra M Swain, Sung-Bae Kim, Javier Cortés, Jungsil Ro, Vladimir Semiglazov, Mario Campone, Eva Ciruelos, Jean-Marc Ferrero, Andreas Schneeweiss, Adam Knott, Emma Clark, Graham Ross, Mark C Benyunes, José Baselga*

[www.thelancet.com/oncology](http://www.thelancet.com/oncology) Vol 14 May 2013

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# Trastuzumab + Pertuzumab

## CLEOPATRA: OS

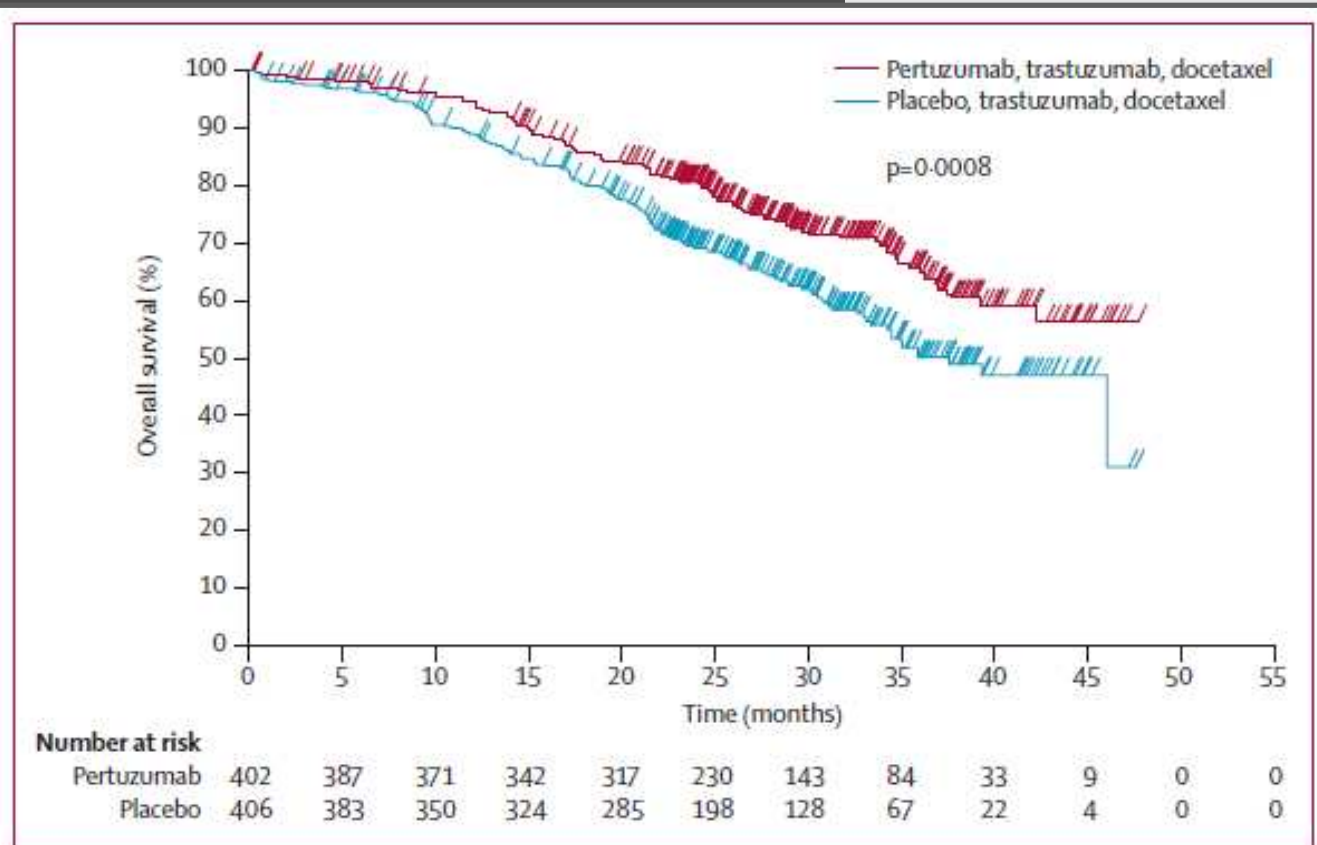
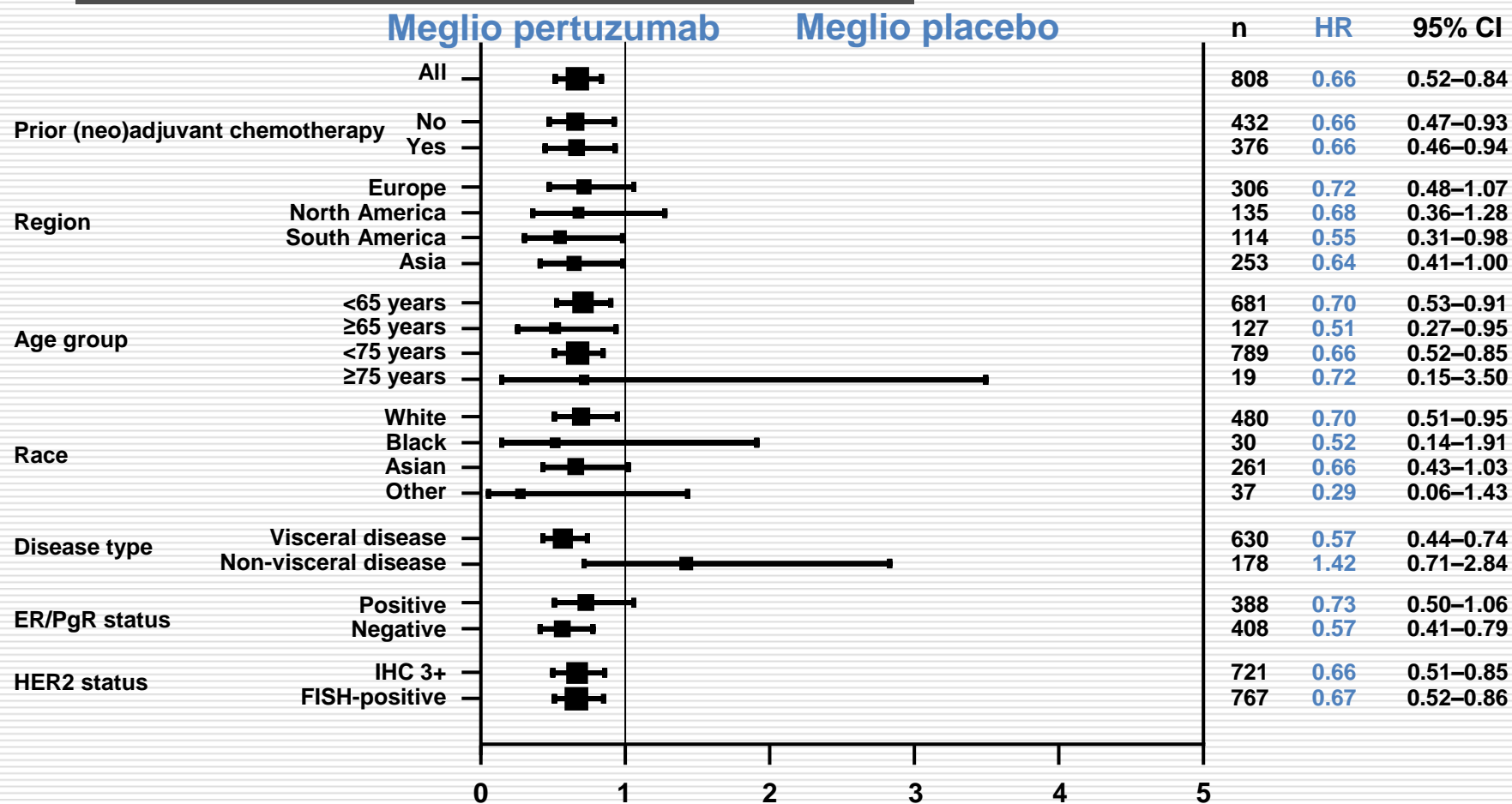


Figure 2: Kaplan-Meier estimates of overall survival (intention-to-treat population)

Patients are stratified by previous treatment status and region. Tick marks indicate censoring events.

# Trastuzumab + Pertuzumab

## CLEOPATRA: OS



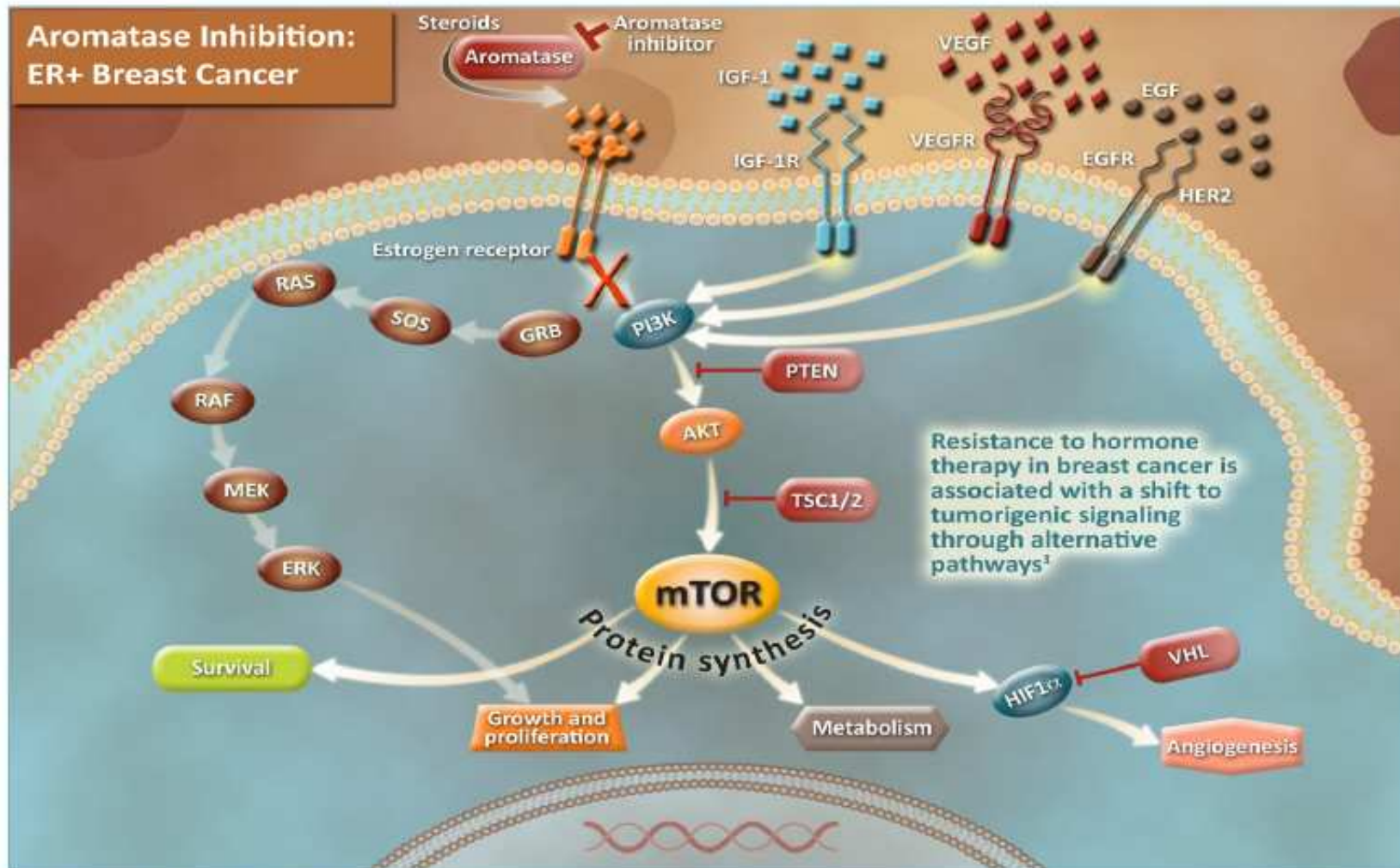
ER, estrogen receptor; FISH, fluorescence *in situ* hybridization; IHC, immunohistochemistry; PgR, progesterone receptor

# Trastuzumab + Pertuzumab

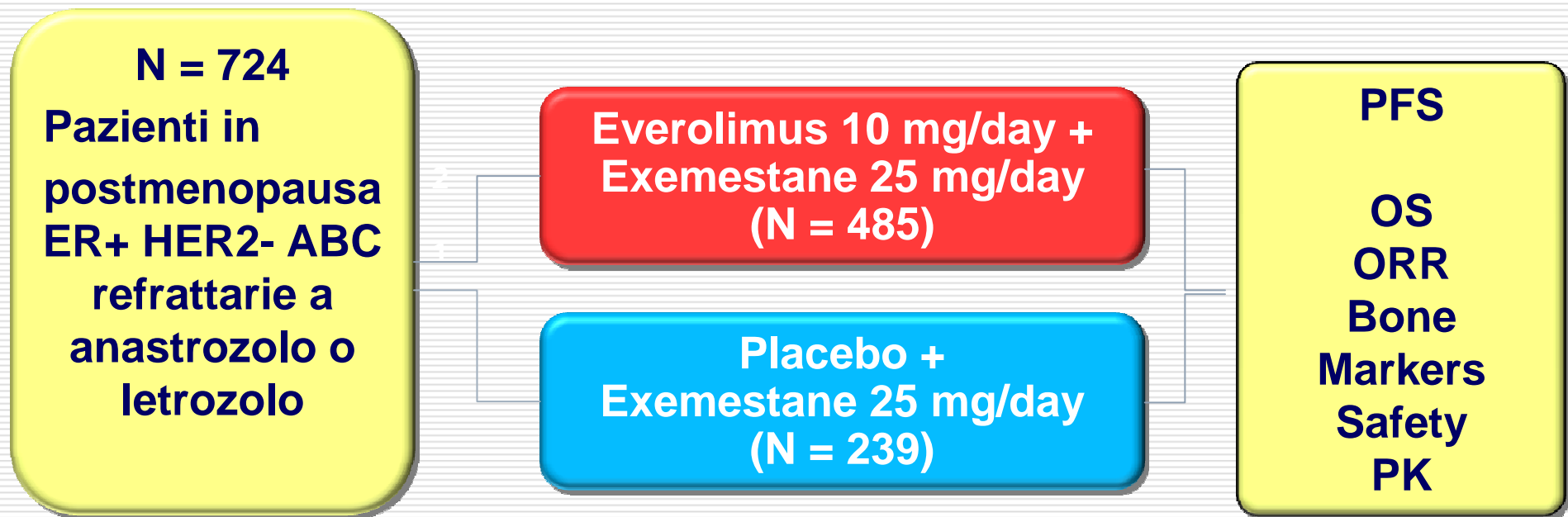
CLEOPATRA: effetti collaterali (>25% tot o con differenze >5%)

n (%)	Placebo + trastuzumab + docetaxel (n=396)	Pertuzumab + trastuzumab + docetaxel (n=408)
Diarrea	191 (48.2)	278 (68.1)
Alopecia	240 (60.6)	248 (60.8)
Neutropenia	197 (49.7)	216 (52.9)
Nausea	168 (42.4)	179 (43.9)
Fatigue	148 (37.4)	155 (38.0)
Rash	95 (24.0)	149 (36.5)
Iporessia	105 (26.5)	121 (29.7)
Mucosite	79 (19.9)	112 (27.5)
Astenia	121 (30.6)	110 (27.0)
Vomito	97 (24.5)	104 (25.5)
Edemi periferici	122 (30.8)	101 (24.8)
Prurito	40 (10.1)	68 (16.7)
Stipsi	101 (25.5)	63 (15.4)
Neutropenia febbrile	30 (7.6)	56 (13.7)
Secchezza cutanea	23 (5.8)	44 (10.8)

# Inibitori mTOR



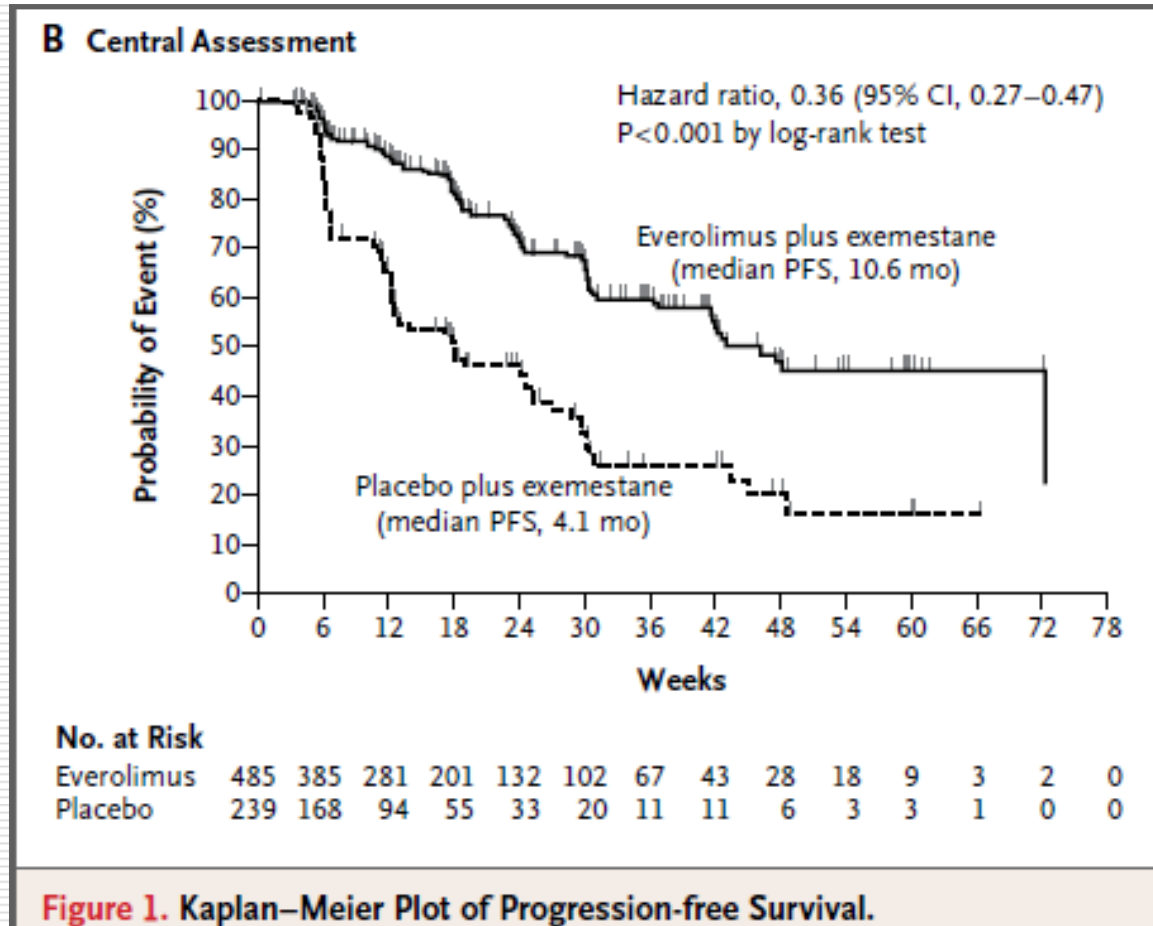
# BOLERO-2: Studio di fase III



- Stratificazione:
  1. Risposta alla precedente terapia ormonale
  2. Presenza di malattia viscerale
- No cross-over

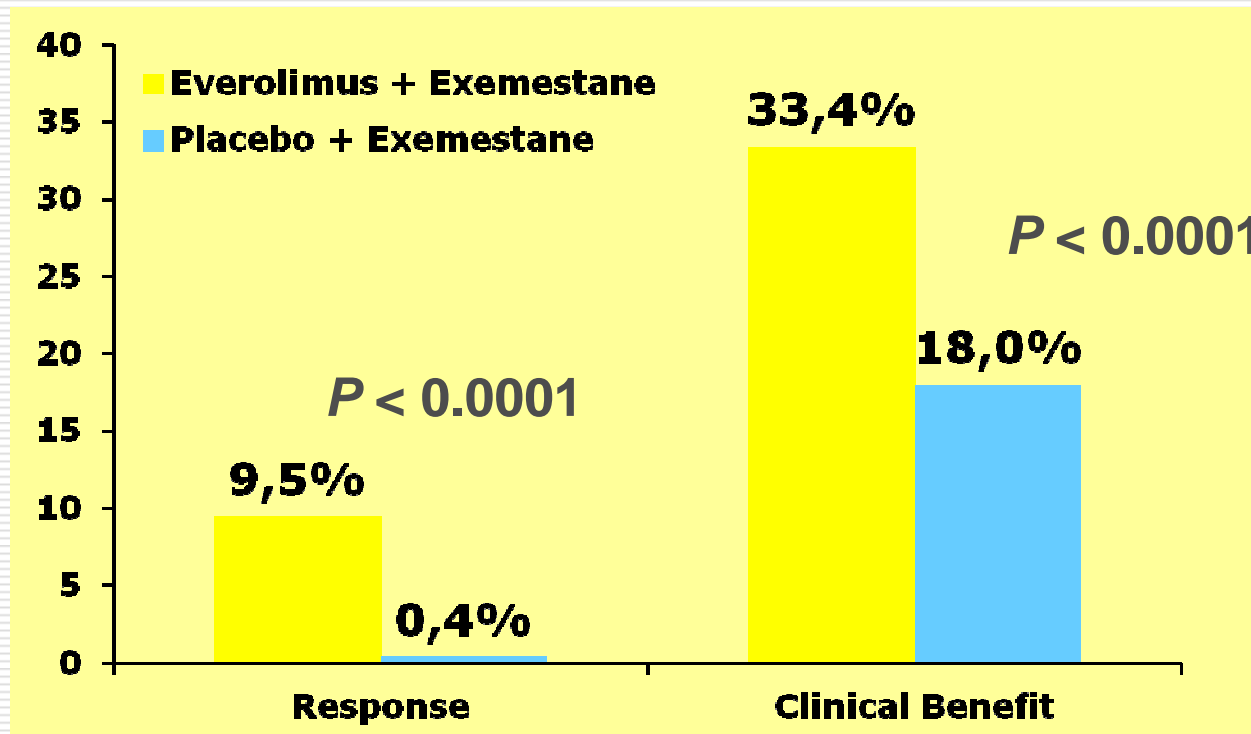
# BOLERO-2: Studio di fase III

Endpoint primario: PFS



# BOLERO-2: Studio di fase III

ORR e Clinical Benefit valutati localmente



Central assessment:

- Response rate: 7.0% vs 0.4%
- Clinical benefit rate: 30.9% vs 15.1%

# BOLERO-2: Studio di fase III

## Principali effetti collaterali

Evento avverso	Eve + Exe (n=482)		Plac + Exe (n=238)	
	All Grades, %	Grade 3, %	All Grades, %	Grade ≥3, %
Stomatite	56	8	11	1
Rash	36	1	6	0
Fatigue	33	3	26	1
Diarrea	30	2	16	1
Tosse	22	1	11	1
Disgeusia	21	<1	5	0
Epistassi	15	0	1	0
Polmonite	12	3	0	0
Anemia	16	5	4	<1
Iperglicemia	13	4	2	1
Trombocitopenia	12	2	<1	0
Aumento AST/ALT	13/11	3/3	6/3	1/2

# BOLERO-2: Studio di fase III

## Qualità della vita

