Latest Advances in Breast Cancers

October 30, 2012

Key Facts and New Therapies

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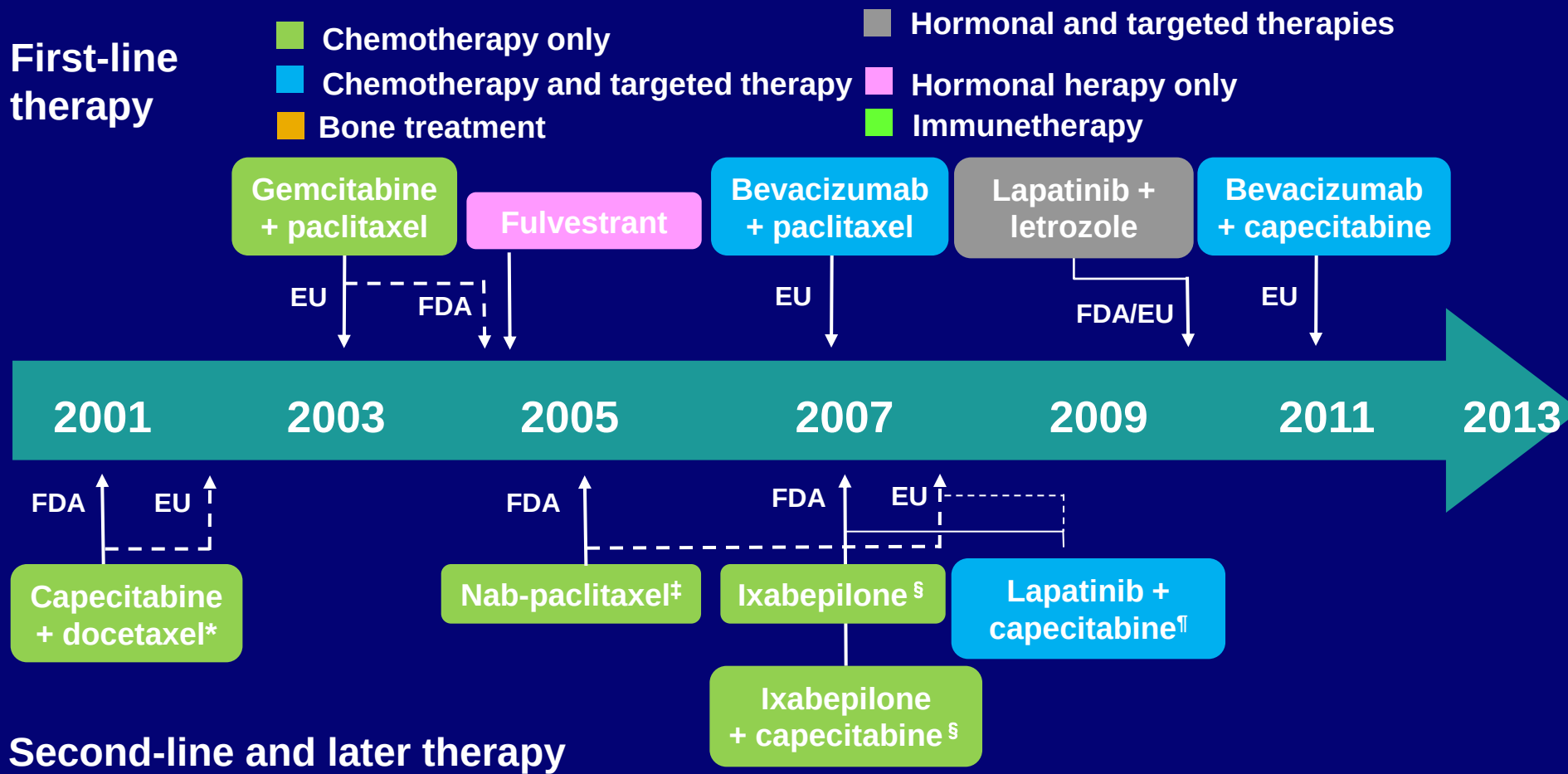
AUSTRIAN BREAST & COLORECTAL CANCER STUDY GROUP

bgz BRUST GESUNDHEITS ZENTRUM
MedUni Wien | AKH Wien

Regulatory approvals in mBC over the past decade



*In the US, approved for use after failure of anthracycline-containing therapy, so could be given in first line
‡Can be given first-line in patients with disease progression <6 months after adjuvant therapy
§ Marketing application withdrawn in EU
¶ Approved for use after failure of anthracycline- and taxane-containing therapies, so could be given first line

Tumor charakteristics & choice of therapy

Advanced Breast Cancer

HER2$^{+++/FISH+}$ (15-20%)

ER+ and/or PgR+ (30-70 %)

HER2^{negativ} & HR^{negativ} (10 - 15%)

HER2 pos ER/PgR pos

Trastuzumab
Lapatinib

± Chemotherapy
(± Hormonal Tx)

Hormonal Tx

Chemotherapy
(± Bevacizumab)

Chemotherapy
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Tumor charakteristics & choice of therapy

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Chemotherapy
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HERMINE – Study

OS for patients who continued Herceptin after 1st progession vs Patients who stopped Herceptin. OS from start of 1st line treatment (A) or OS from first Progression (B)

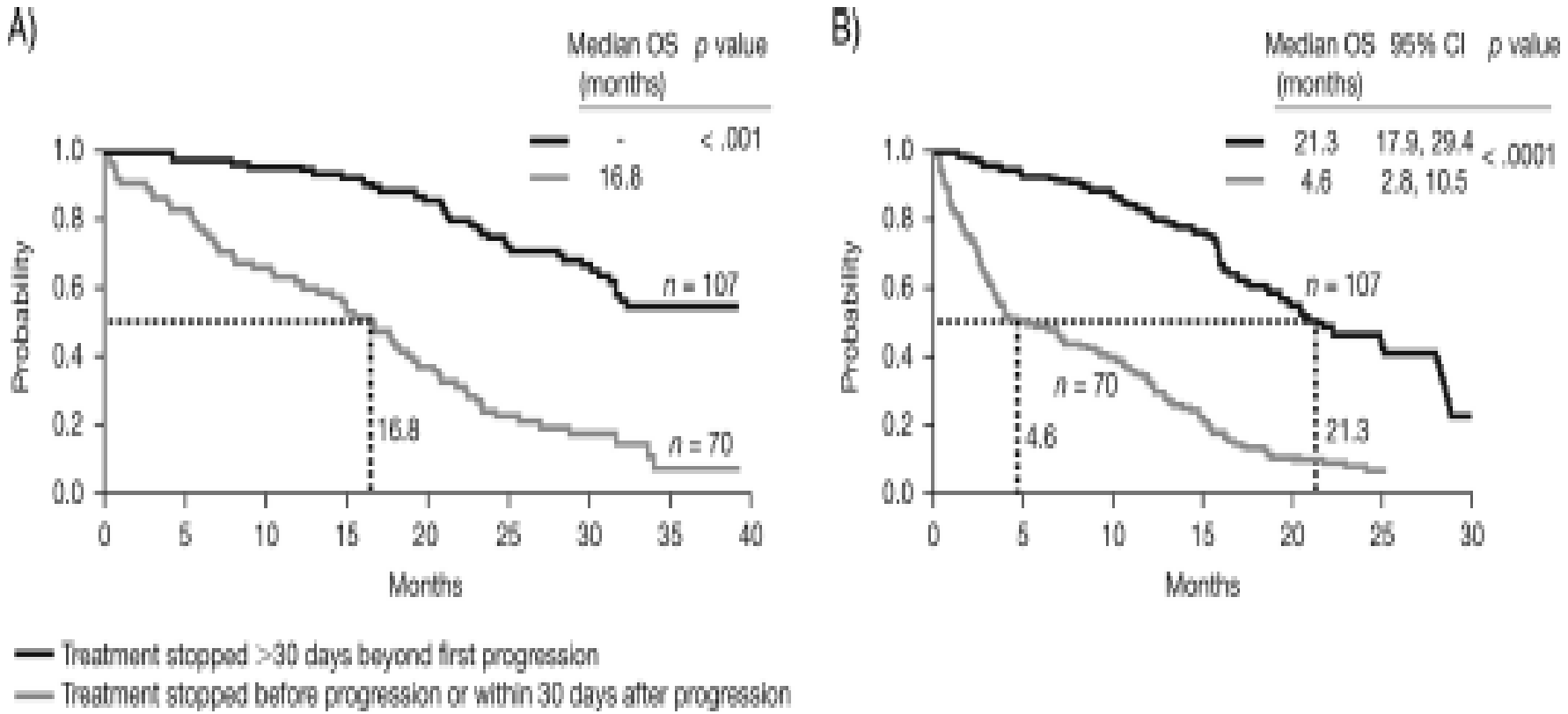
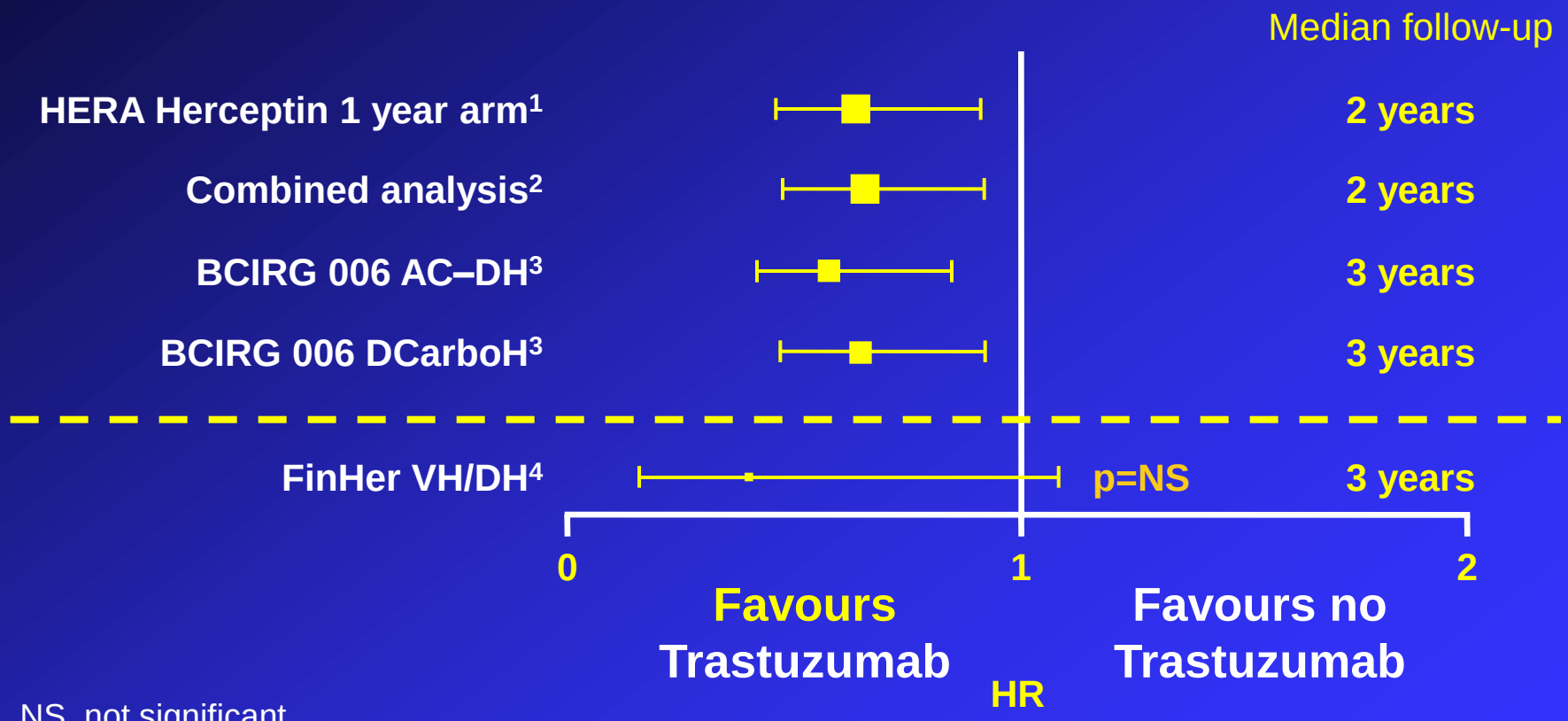


Figure 3. Kaplan–Meier plot comparing OS data from patients who continued trastuzumab beyond progression with that of patients who stopped trastuzumab treatment at or prior to progression from initiation of trastuzumab (A) and date of progression (B).

EXTRA et al, The Oncologist 2010;15:799-809

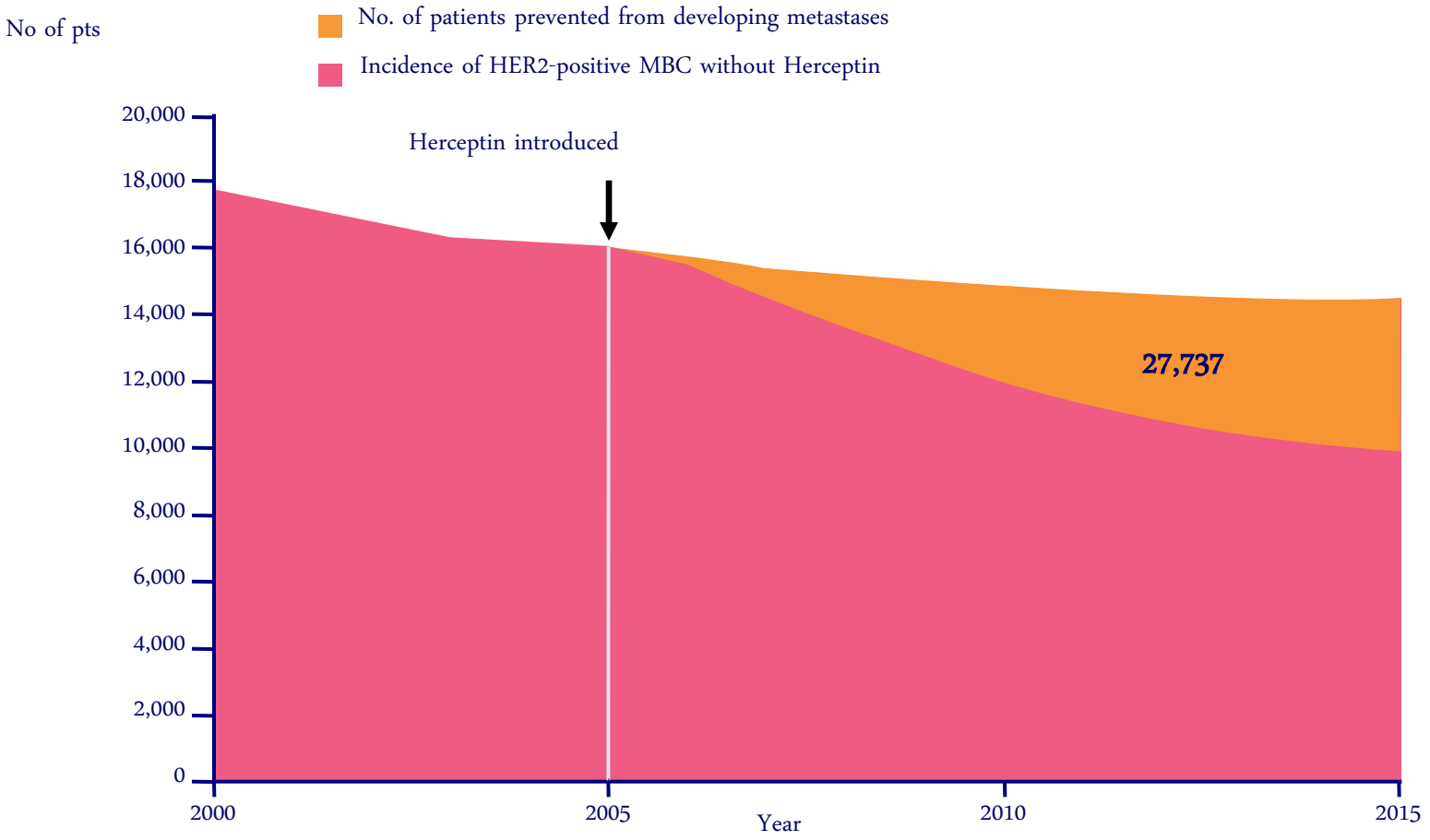
Adjuvant trastuzumab trials:
summary of OS data



NS, not significant

1. Smith I et al. Lancet 2007;369:29–36; 2. Romond EH et al. N Engl J Med 2005;353(16):1673–84;
3. Slamon D et al. SABCS 2006;Abstract 52; 4. Joensuu H et al. N Engl J Med. 2006;354:809-20

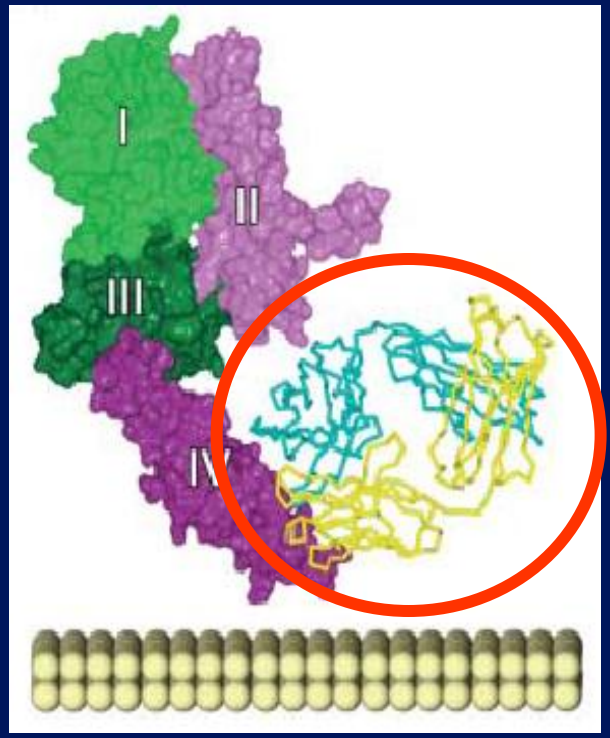
Adjuvant trastuzumab predicted to prevent recurrence in almost 28,000 patients over a 10-year period in the 5 major EU countries



Weisgerber-Kriegl et al 2008

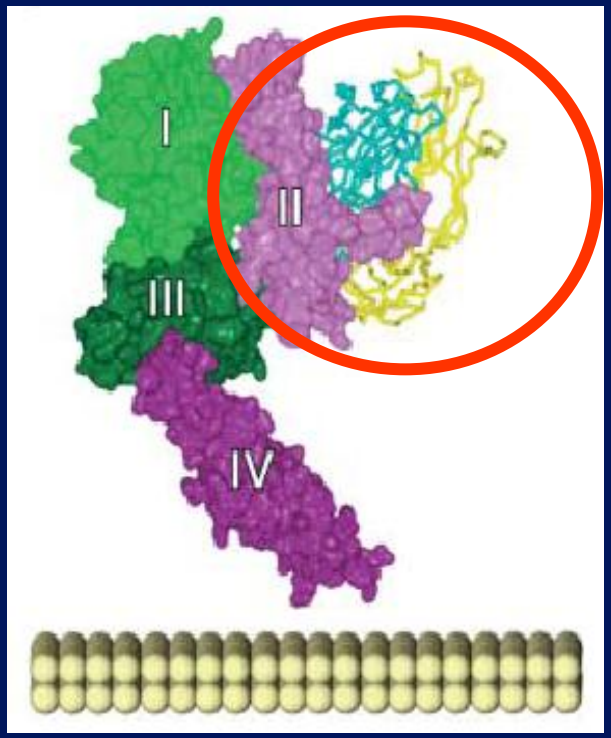
Trastuzumab and Pertuzumab bind to distinct epitopes on HER2 extracellular domain

Trastuzumab



- Activates antibody-dependent cellular cytotoxicity
- Inhibits HER2-mediated signalling
- Inhibits shedding and, thus, formation of new p95
- Inhibits HER2-related angiogenesis

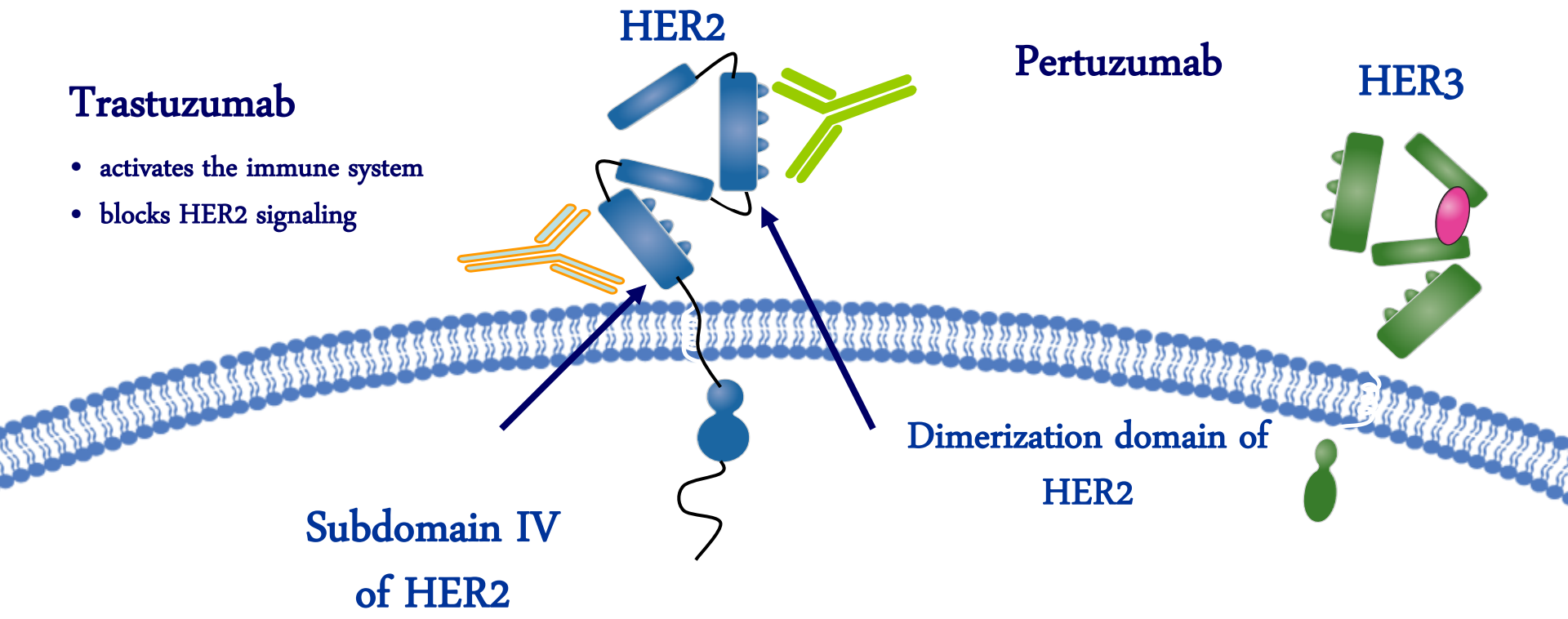
Pertuzumab



- Activates antibody-dependent cellular cytotoxicity
- **Prevents receptor dimerisation**
- Potent inhibitor of HER2/HER2- and HER2/HER3-mediated signalling pathways

Hubbard 2005

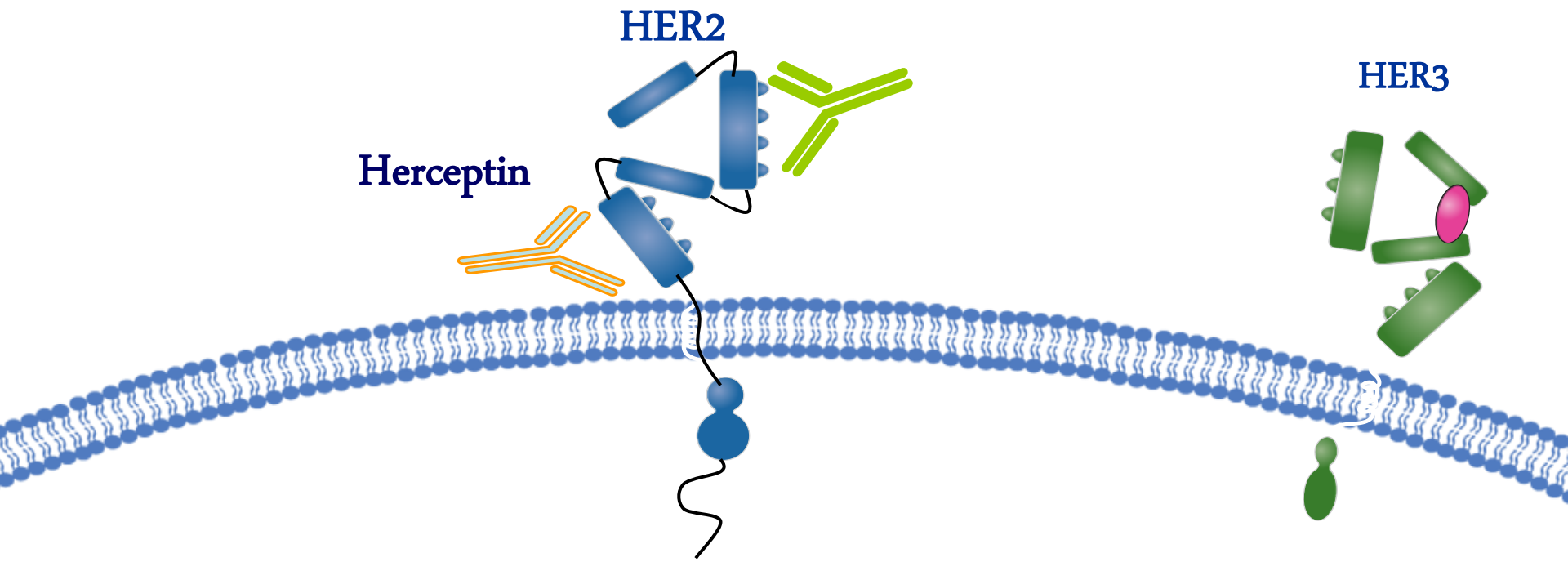
Pertuzumab and Herceptin bind to different regions on HER2 and have synergistic activity



Pertuzumab and Herceptin bind to different regions on HER2 and have synergistic activity

Pertuzumab

- Inhibits HER2/HER3 dimerization



Trastuzumab-Emtansine (T-DM1)

First-in-class antibody–drug conjugate (ADC)

Target expression: HER2

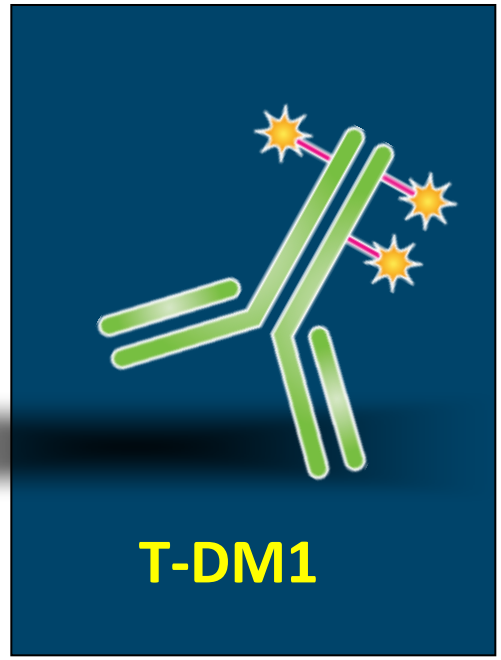
Monoclonal antibody: trastuzumab

Cytotoxic agent: DM1

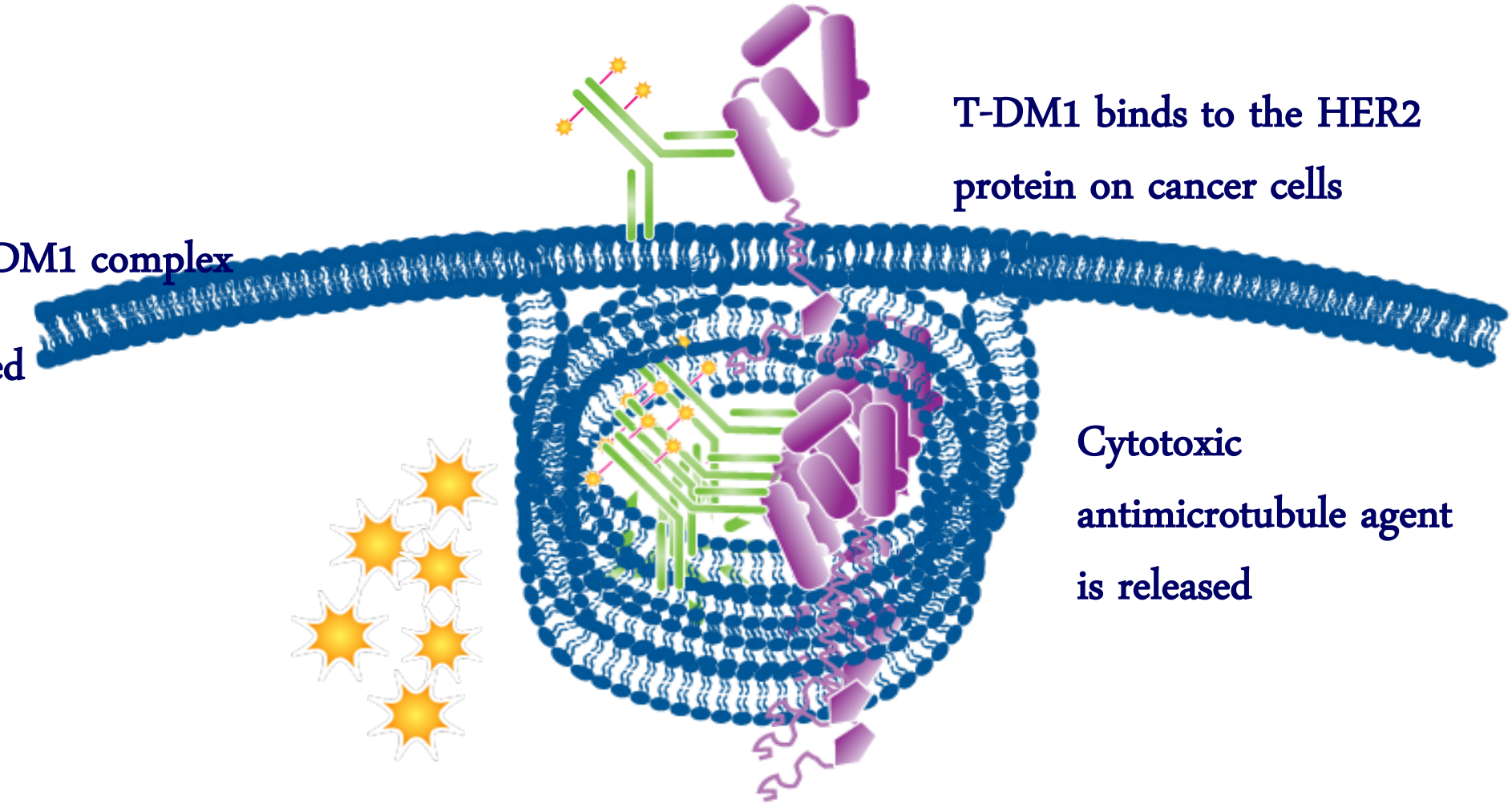
Highly potent chemotherapy
(maytansine derivative)

Linker

Systemically stable
Breaks down in target cancer cell



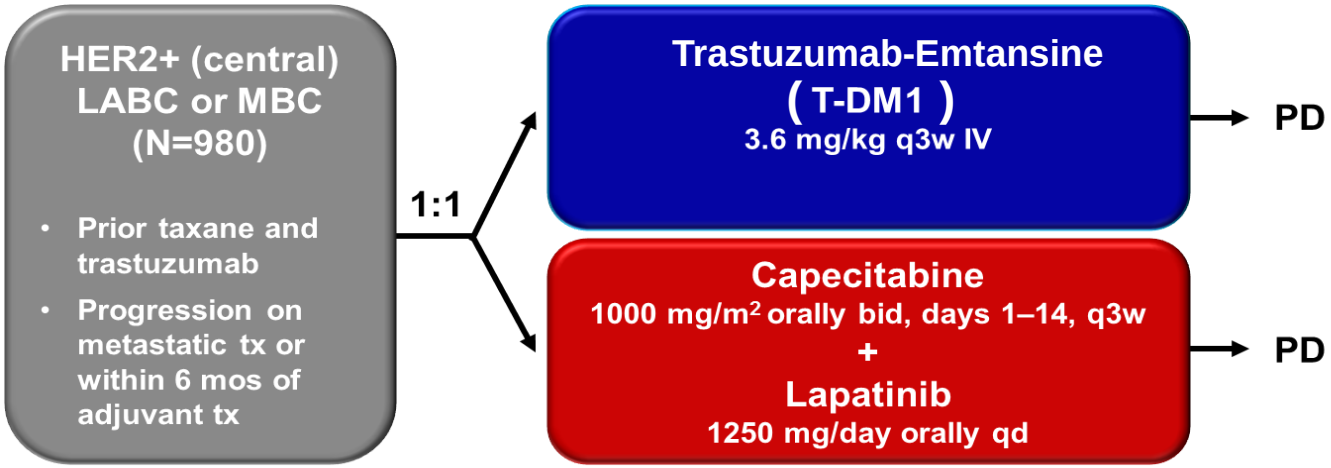
T-DM1 selectively delivers a highly toxic payload to HER2-positive tumour cells



Primary Results From EMILIA, a Phase 3 Study of Trastuzumab Emtansine (T-DM1) vs Capecitabine and Lapatinib in HER2-Positive Locally Advanced or Metastatic Breast Cancer Previously Treated With Trastuzumab and a Taxane

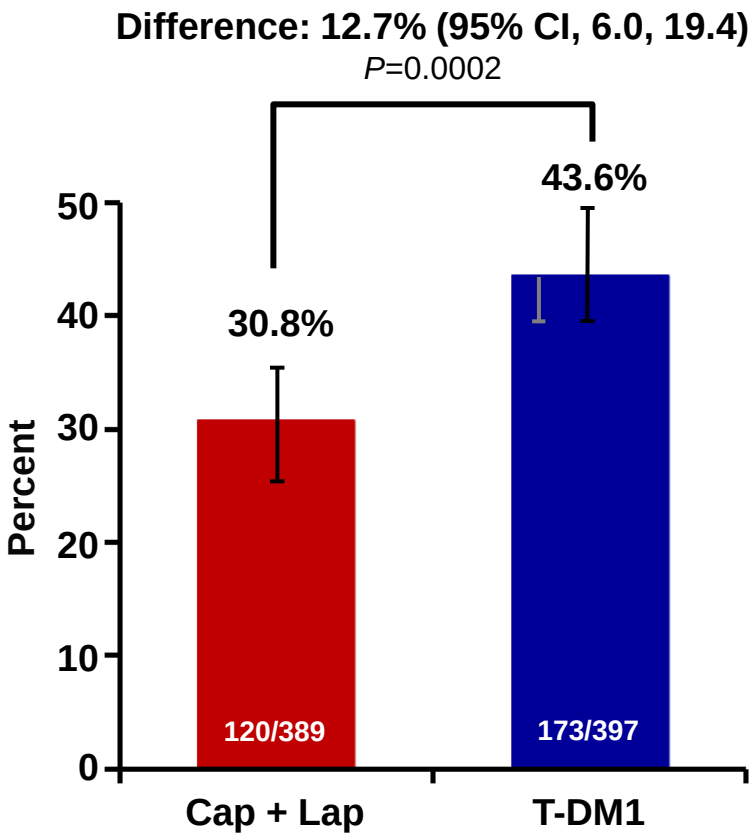
K Blackwell,[1] D Miles,[2] L Gianni,[3] IE Krop,[4] M Welslau,[5] J Baselga,[6] M Pegram,[7] D-Y Oh,[8] V Diéras,[9] S Olsen,[10] L Fang,[10], MW Lu,[10] E Guardino,[10] S Verma[11]

EMILIA Study Design



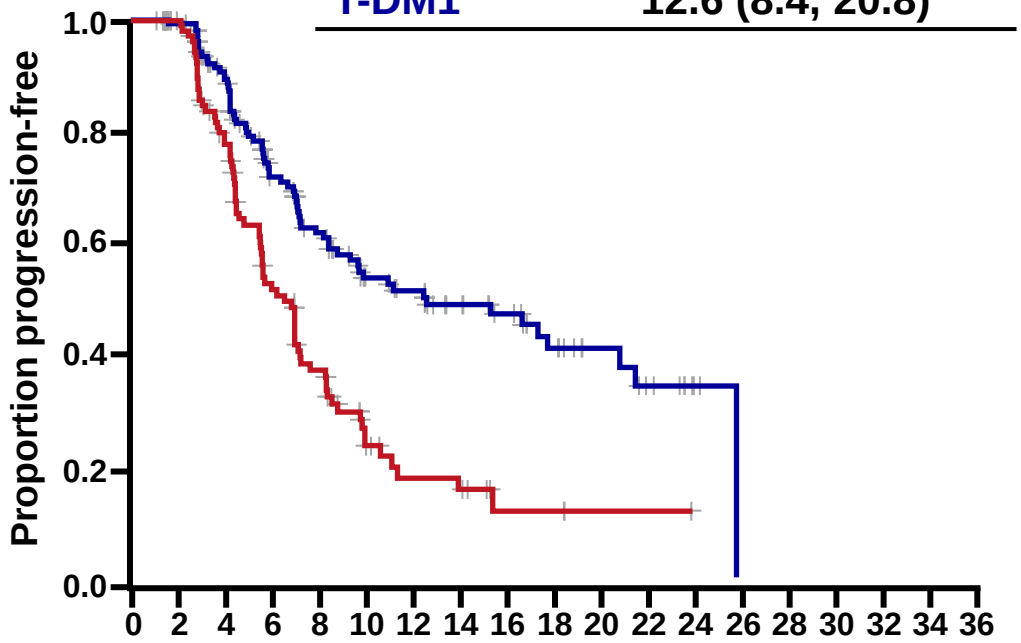
Objective Response Rate (ORR) and Duration of Response (DOR) in Patients with Measurable Disease

ORR



DOR

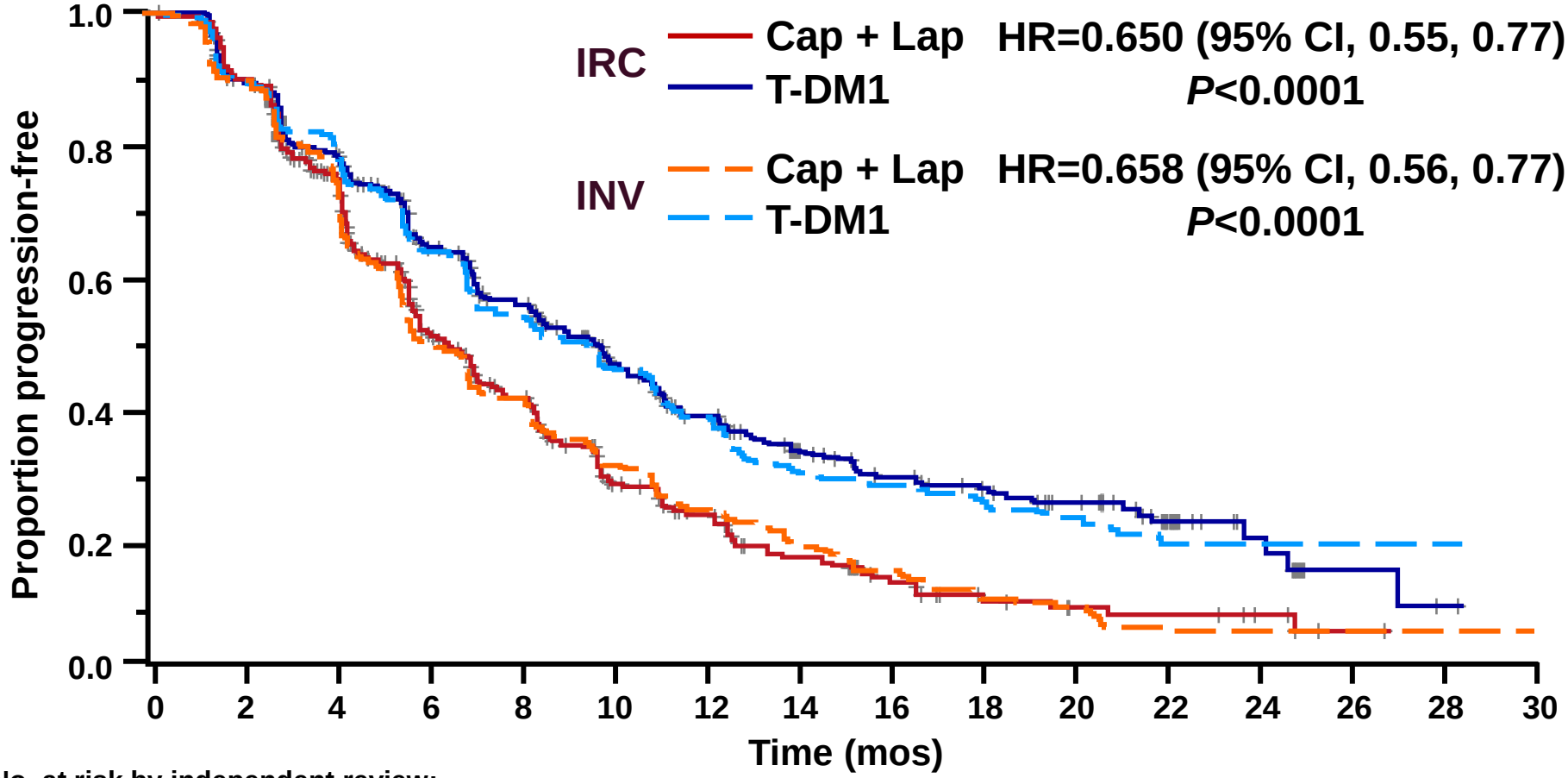
	Median, mos (95% CI)
Cap + Lap	6.5 (5.5, 7.2)
T-DM1	12.6 (8.4, 20.8)



No. at risk

Cap + Lap	120	105	77	48	32	14	9	8	3	3	1	1	0	0	0	0	0	0	0
T-DM1	173	159	126	84	65	47	42	33	27	19	12	8	2	0	0	0	0	0	0

Progression-Free Survival by Independent (IRC) and Investigator (INV) Review

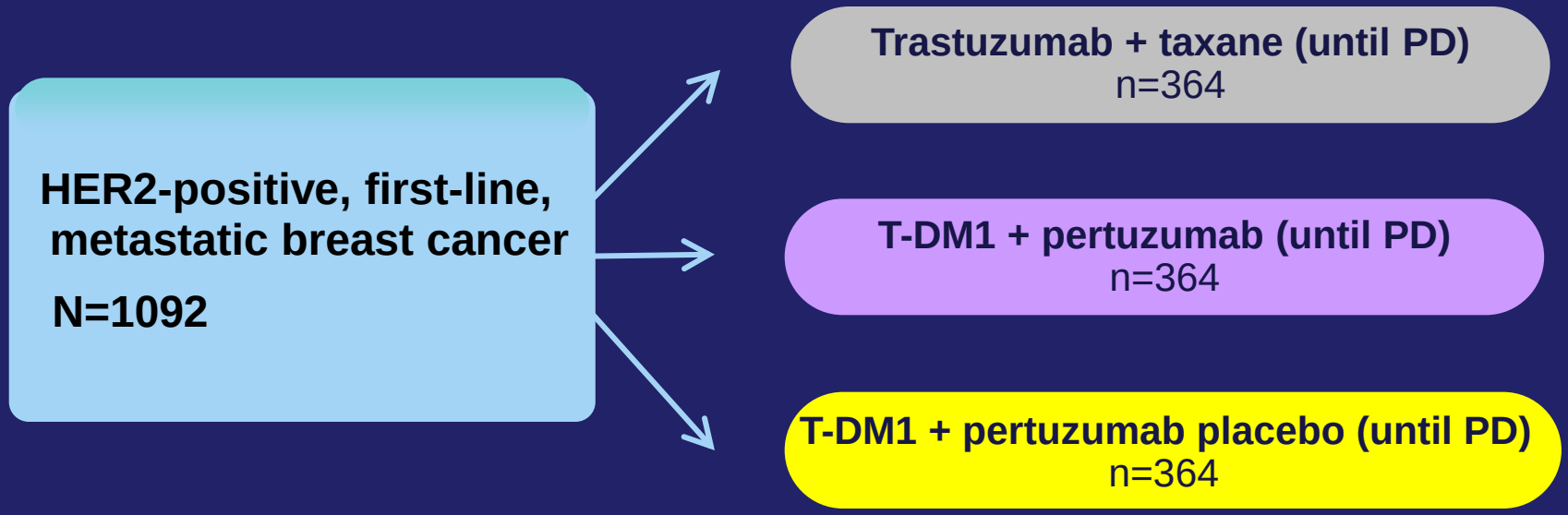


No. at risk by independent review:

Cap + Lap	496	404	310	176	129	73	53	35	25	14	9	8	5	1	0	0
T-DM1	495	419	341	236	183	130	101	72	54	44	30	18	9	3	1	0

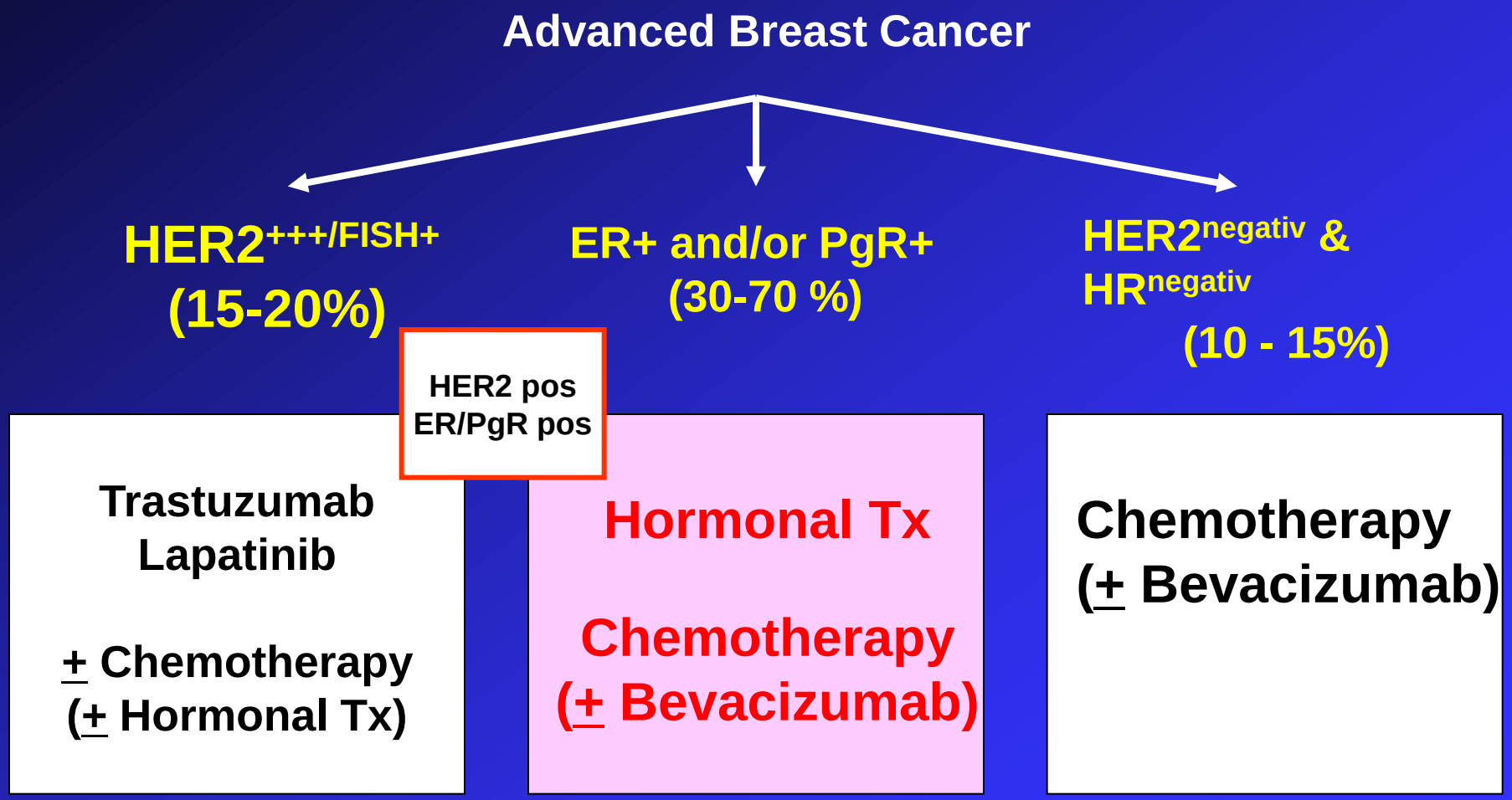
Unstratified HR by independent review=0.66 (*P*<0.0001).

1st Line mBC Phase III MARIANNE Study: BO22589/TDM4788g

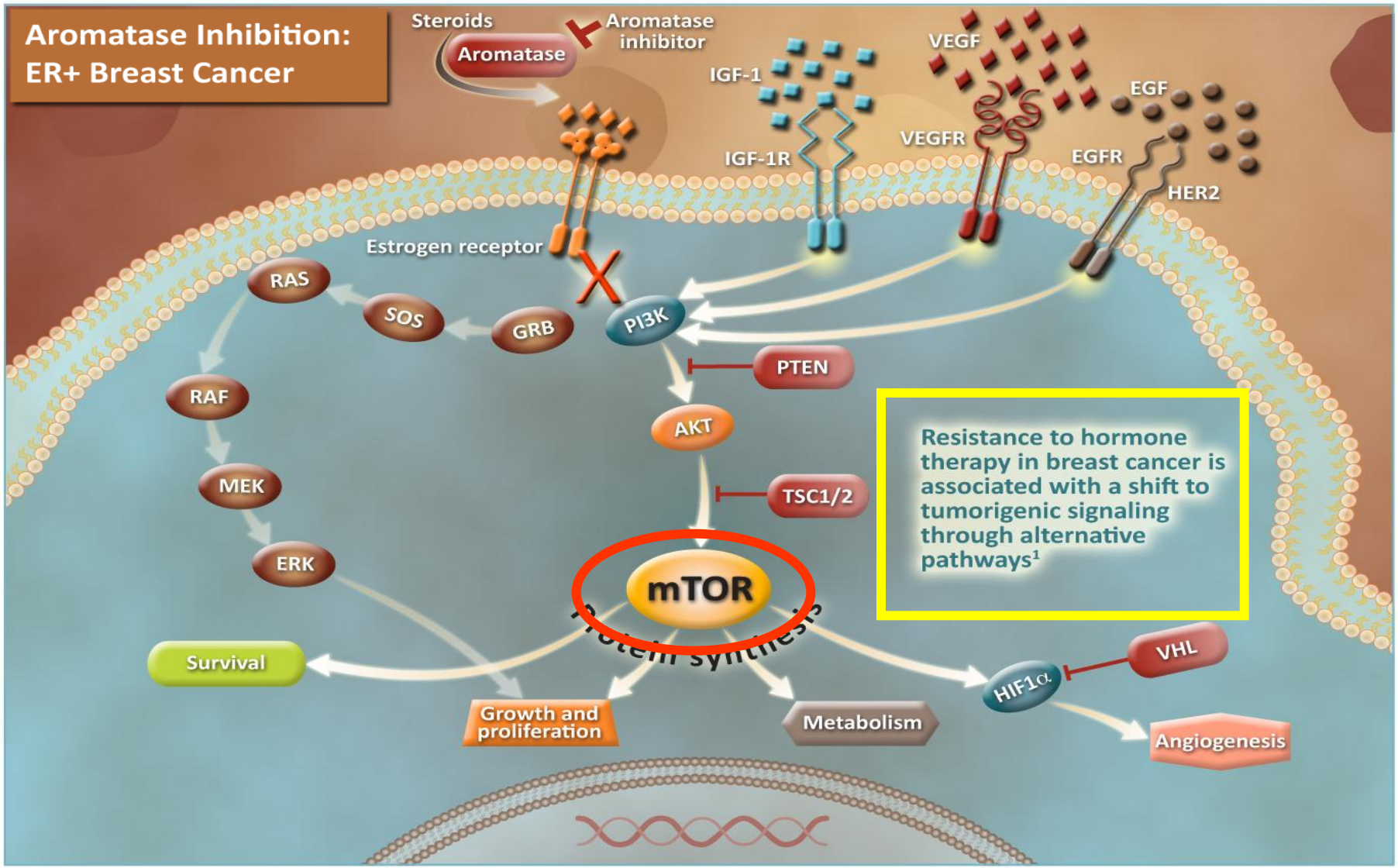


- **Primary endpoints:** PFS as assessed by IRF; Safety
- **Secondary endpoints:** OS; PFS by investigator; patient reported outcomes analysis; biomarkers

Tumor charakteristics & choice of therapy

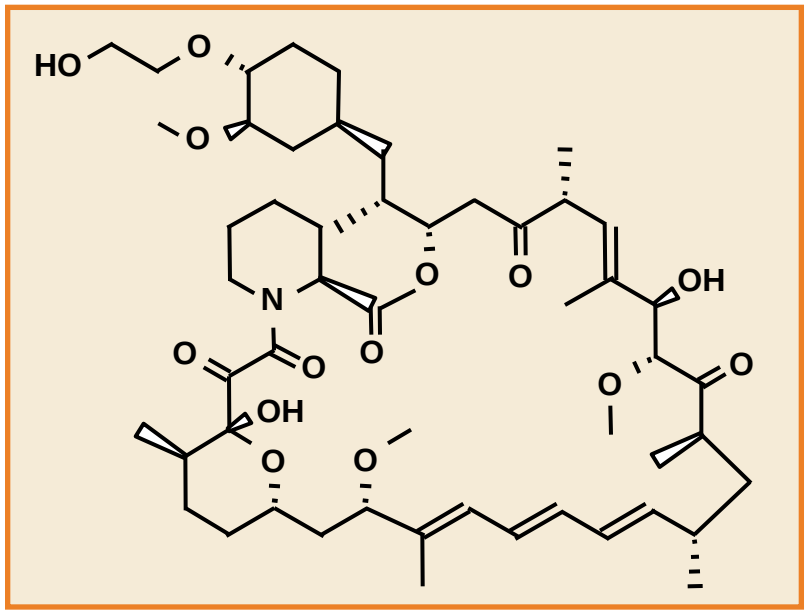


Aromatase Inhibition: ER+ Breast Cancer



1. Moy B et al. *Clin Cancer Res*. 2006;12:4790-4793

EVEROLIMUS/RAD001: Oral mTOR Inhibitor

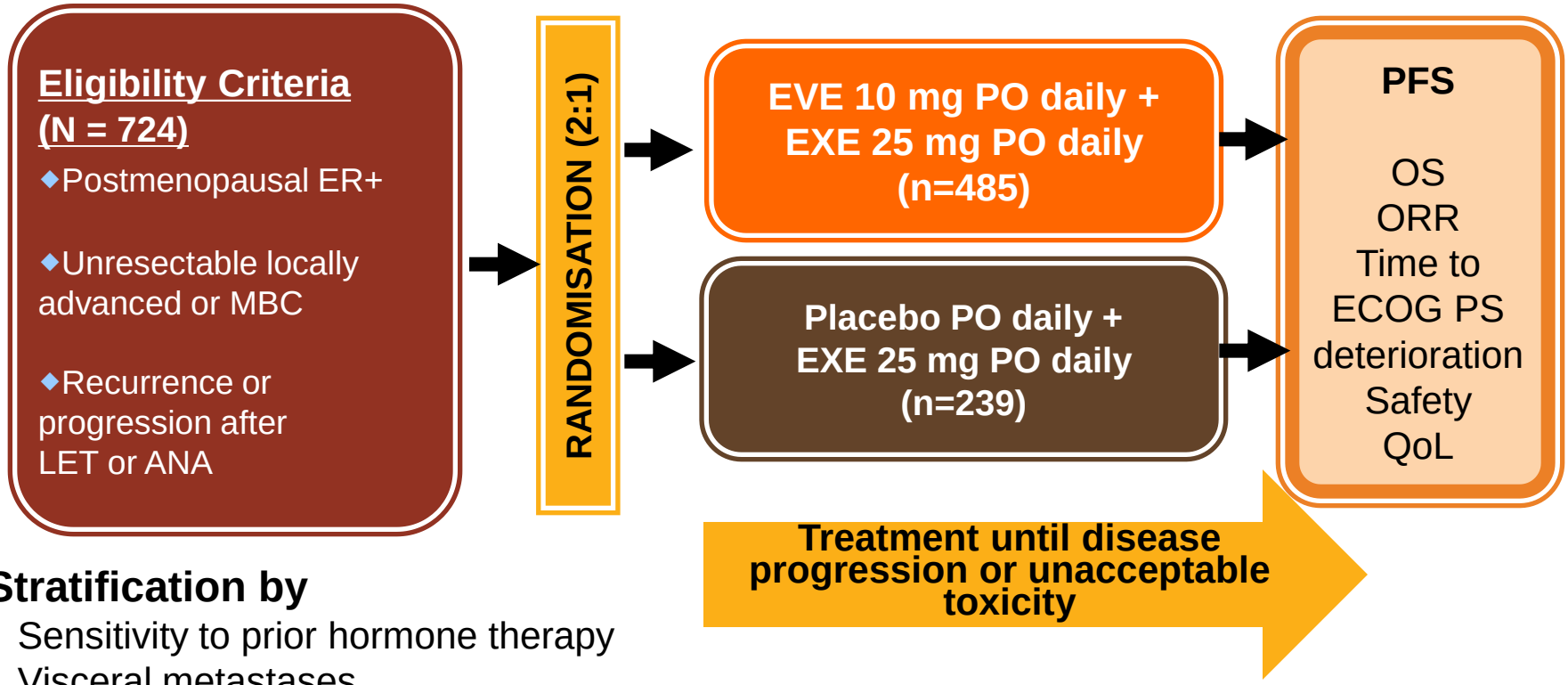


RAD001 (Everolimus)

- Active rapamycin derivative
- Orally bioavailable; $T_{1/2}$ ~ 30 hours; CYP3A4 metabolism
- Sustained inhibition of mTOR via daily administration[1,2]
- Crosses blood-brain barrier[3]
- Broad antitumor activity
  - Inhibits cell growth and angiogenesis
  - Potential synergy with chemotherapy, radiation, and other targeted agents
  - Demonstrated single-agent efficacy and safety in several pivotal phase 3 trials
- Investigated in over 4,000 cancer patients

1. O'Donnell et al. *J Clin Oncol*. 2008;26:1588-1595; 2. Tabernero et al. *J Clin Oncol*. 2008;26:1603-11610; 3. Data on file;

Phase III: Everolimus + Exemestane in mBC



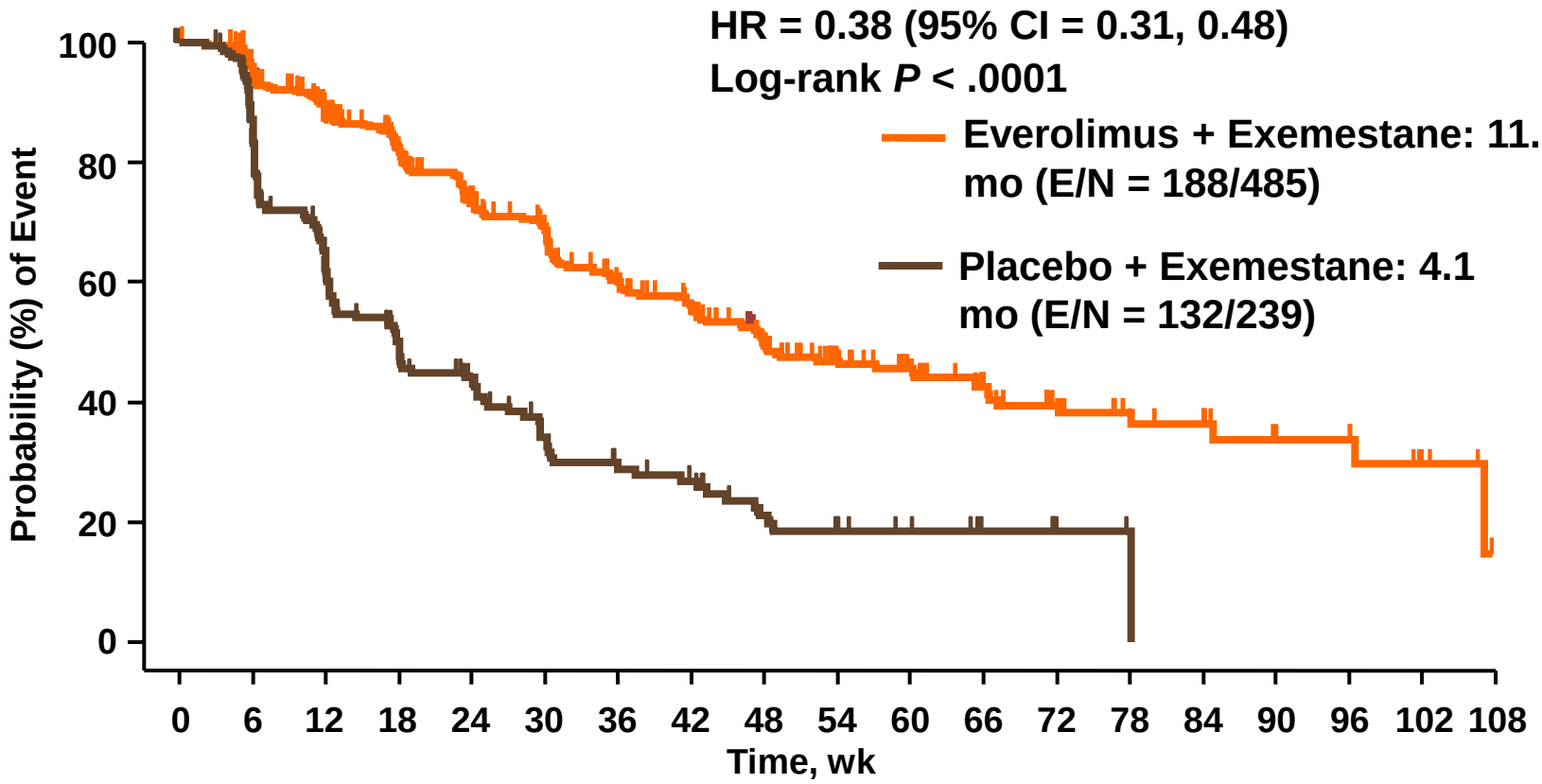
Stratification by

- Sensitivity to prior hormone therapy
- Visceral metastases

PO = orally; ECOG PS = Eastern Cooperative Oncology Group performance status; LET = letrozole; ANA = anastrozole; EVE = everolimus; EXE = exemestane

Baselga et al. *N Engl J Med*. 2012 Feb 9;366(6):520-9.

BOLERO-2: Primary Endpoint, PFS (Central Assessment)

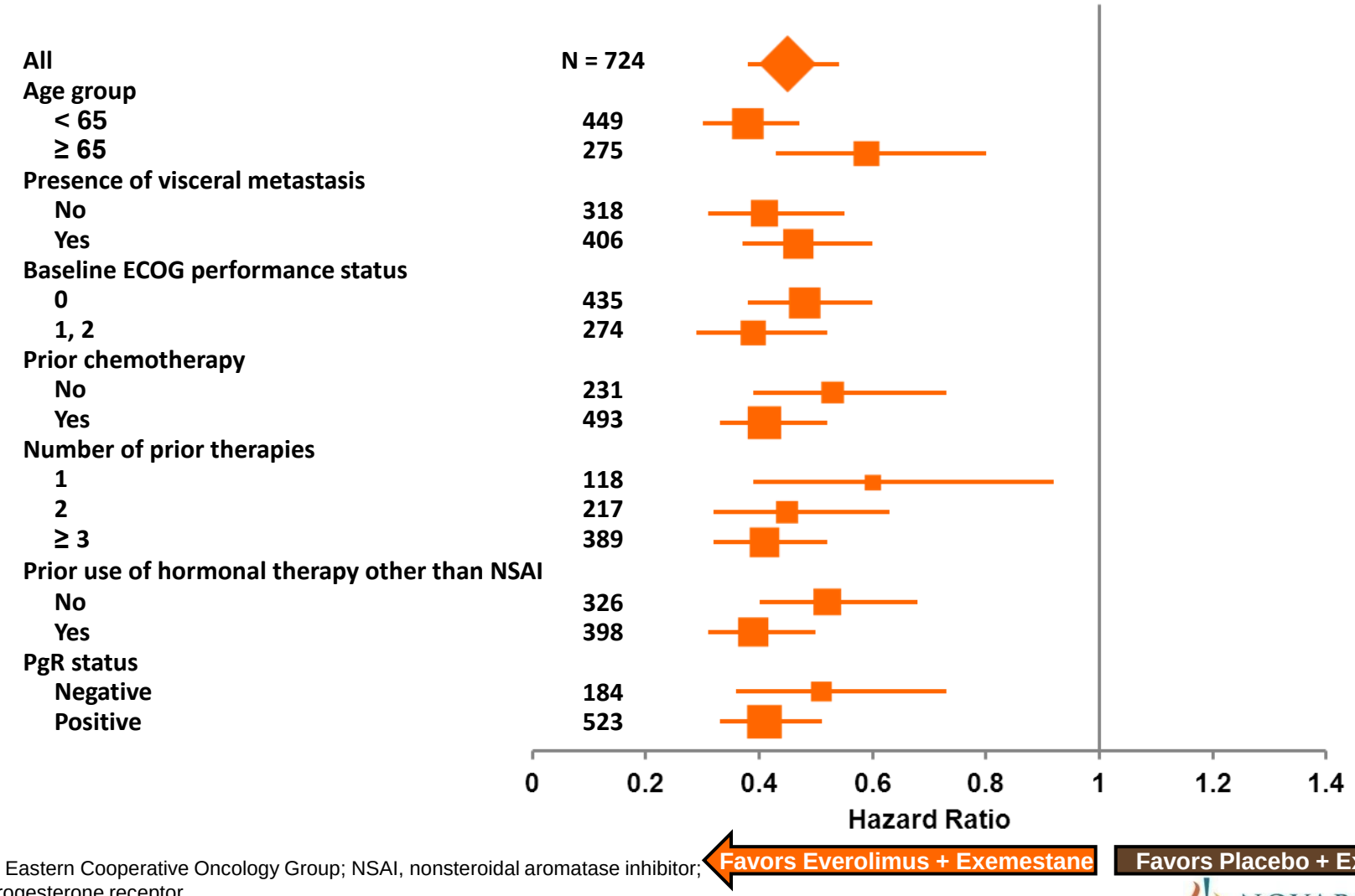


Number of patients still at risk

Everolimus	485	427	359	292	239	211	166	140	108	77	62	48	32	21	18	11	10	5	0
Placebo	239	179	114	76	56	39	31	27	16	13	9	6	4	1	0	0	0	0	0

CI, confidence interval; E/N, patients with events/total patients; HR, hazard ratio; PFS, progression-free survival.
Piccart-Gebhart M, et al. *J Clin Oncol.* 2012;30(suppl; abstr 559)(poster).

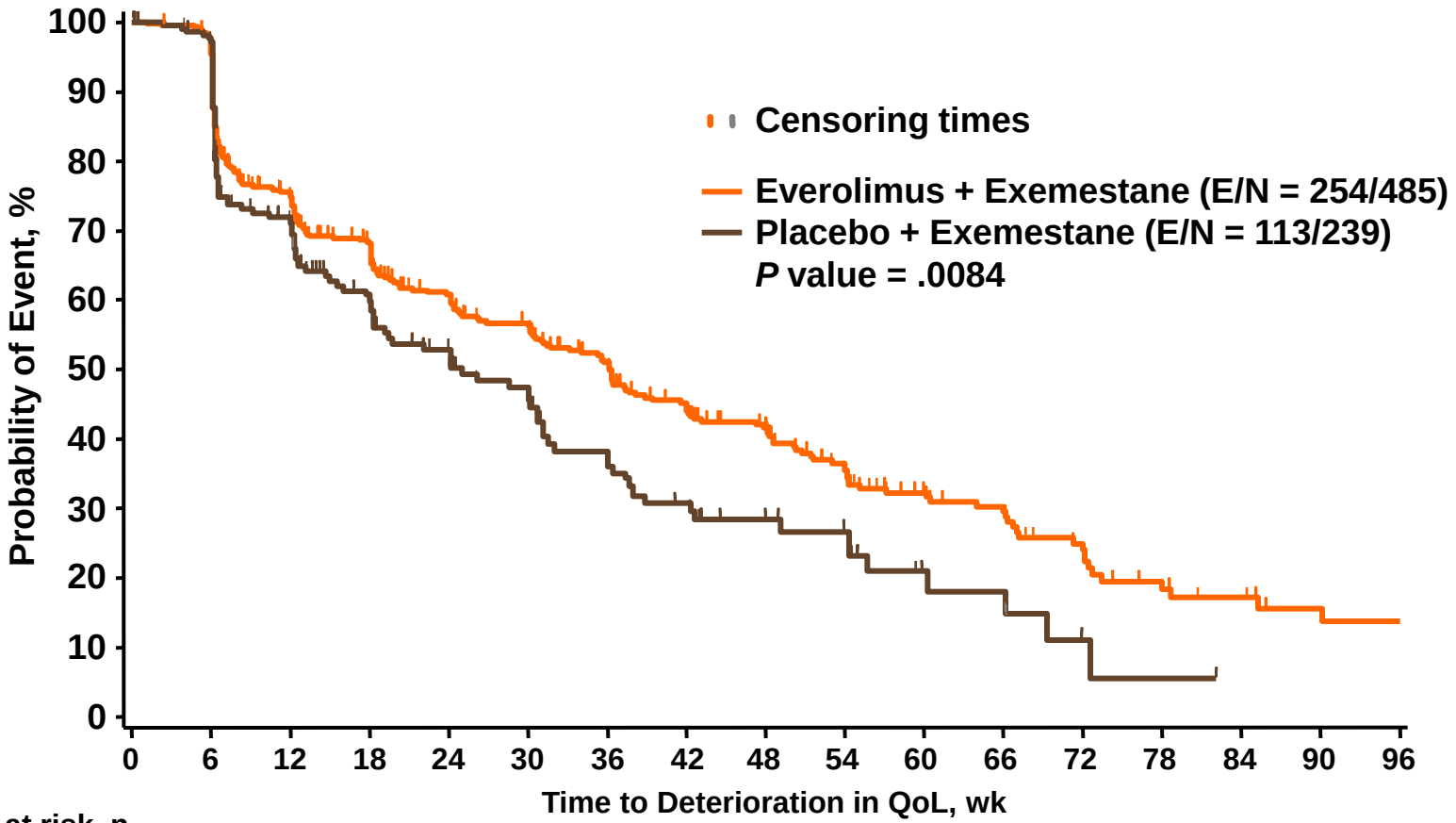
BOLERO-2: PFS in Prespecified Subgroups



ECOG, Eastern Cooperative Oncology Group; NSAI, nonsteroidal aromatase inhibitor; PgR, progesterone receptor.

Piccart-Gebhart M, et al. *J Clin Oncol.* 2012;30(suppl; abstr 559)(poster).

BOLERO-2: Quality of Life (EORTC QLQ-C30 Global Health Score, Time to Deterioration MID=5%)



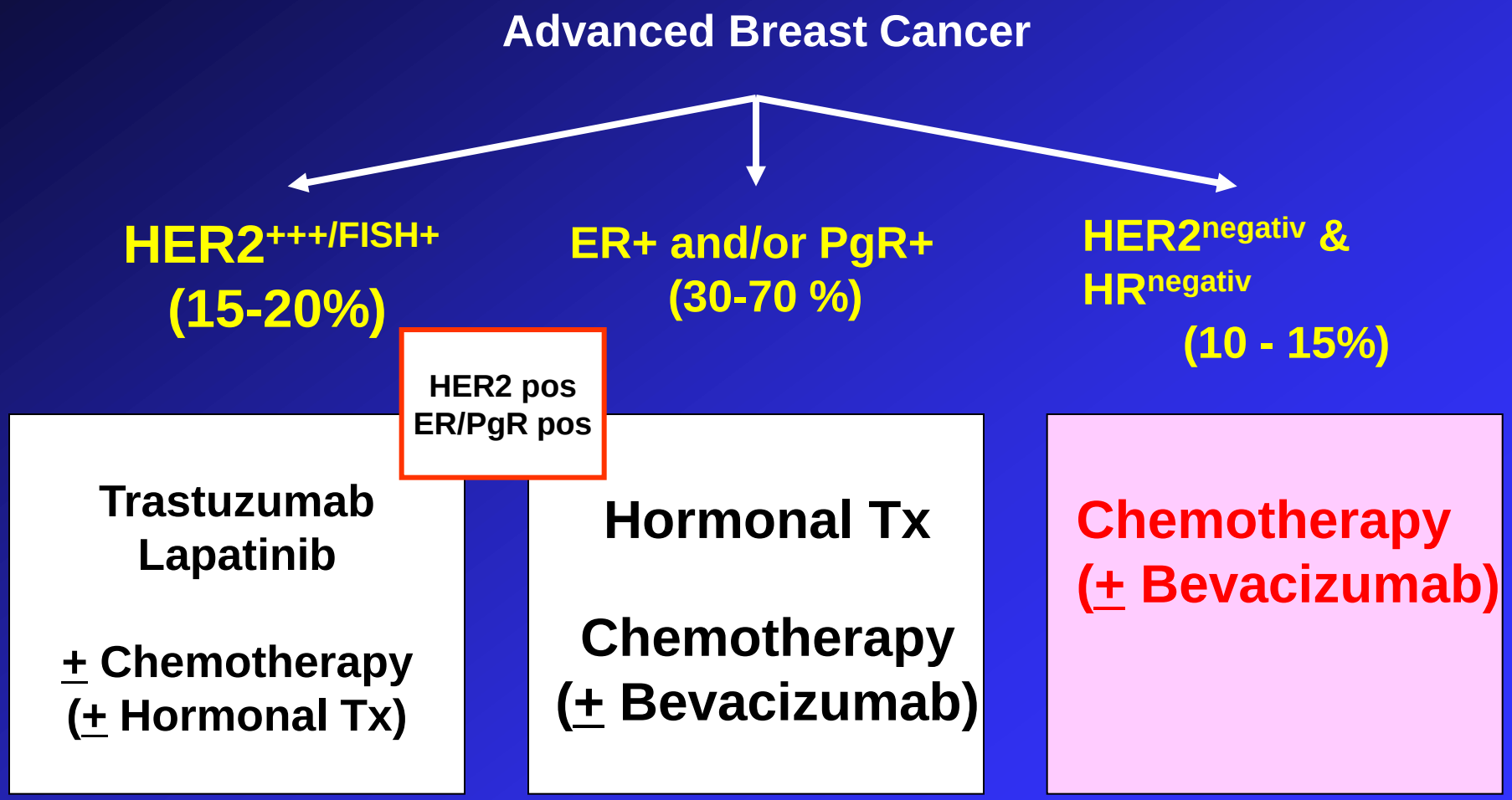
Patients still at risk, n

Eve+ Exe	485	427	305	245	198	176	145	119	99	71	52	43	29	18	13	9	8
Placebo + Exe	239	201	116	83	62	49	36	27	19	16	7	6	3	1	0	0	0

EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Core Cancer Quality of Life Questionnaire; E/N, patients with events/total patients; MID, minimal important difference; QoL, quality of life.

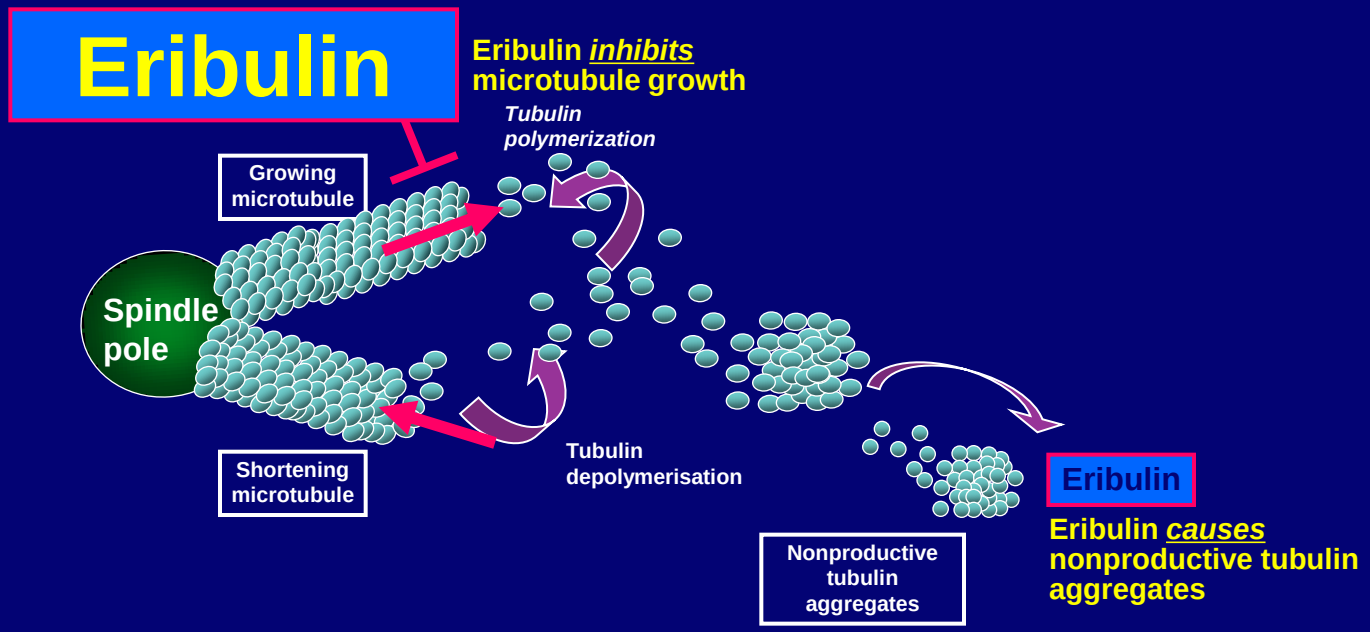
Beck JT, et al. *J Clin Oncol.* 2012;30(suppl; abstr 539)(poster).

Tumor charakteristics & choice of therapy



New Chemotherapy: Eribulin

- Eribulin: non-taxane microtubule dynamics inhibitor

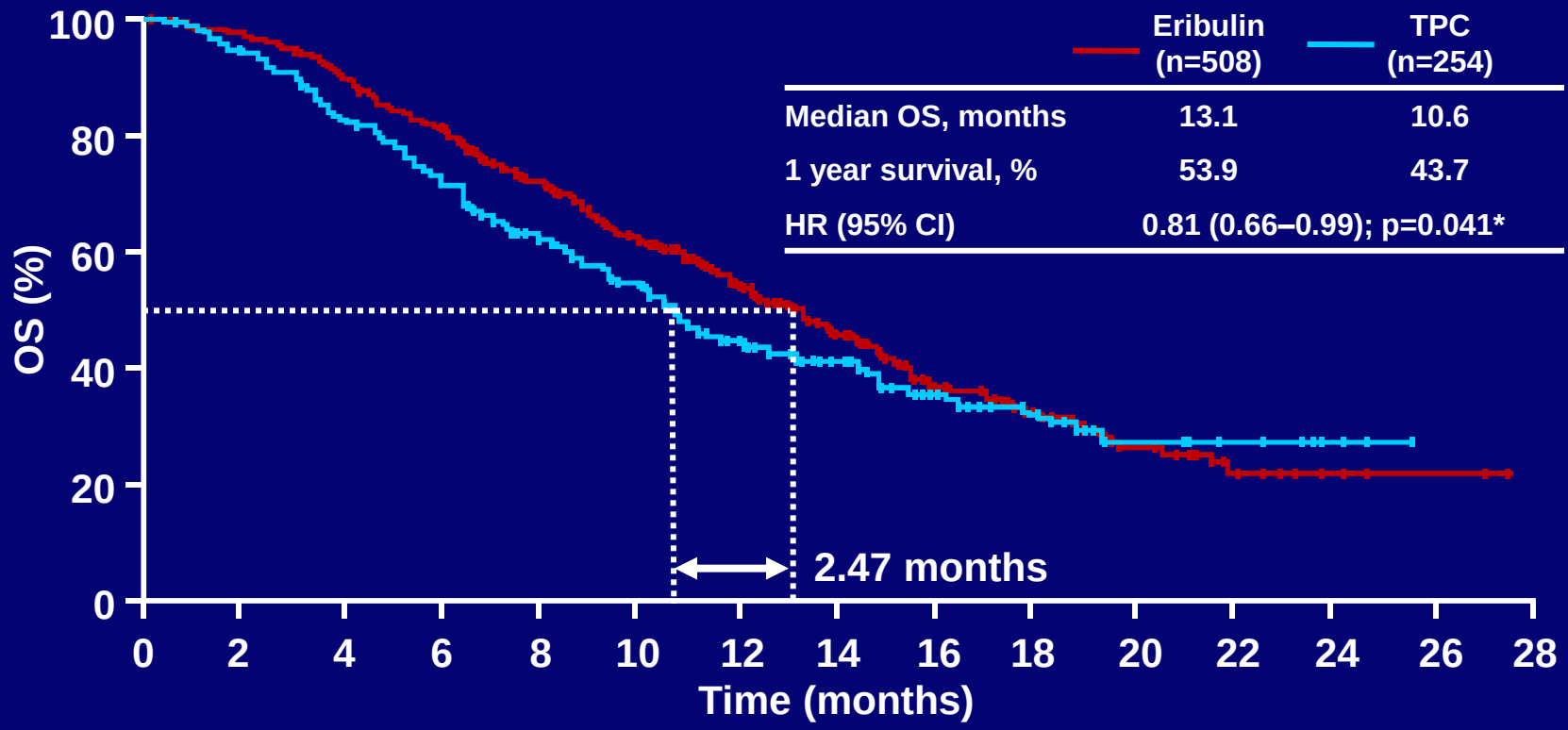


- Inhibition of microtubule formation → irreversible block of cell division and apoptosis
- May be effective against cancer that is resistant to taxanes

Adapted from Jordan, et al. Nat Rev Cancer 2004

Eribulin significantly improved OS versus standard therapy (EMBRACE)

Phase III trial of eribulin compared with TPC in patients with heavily pretreated locally recurrent or mBC



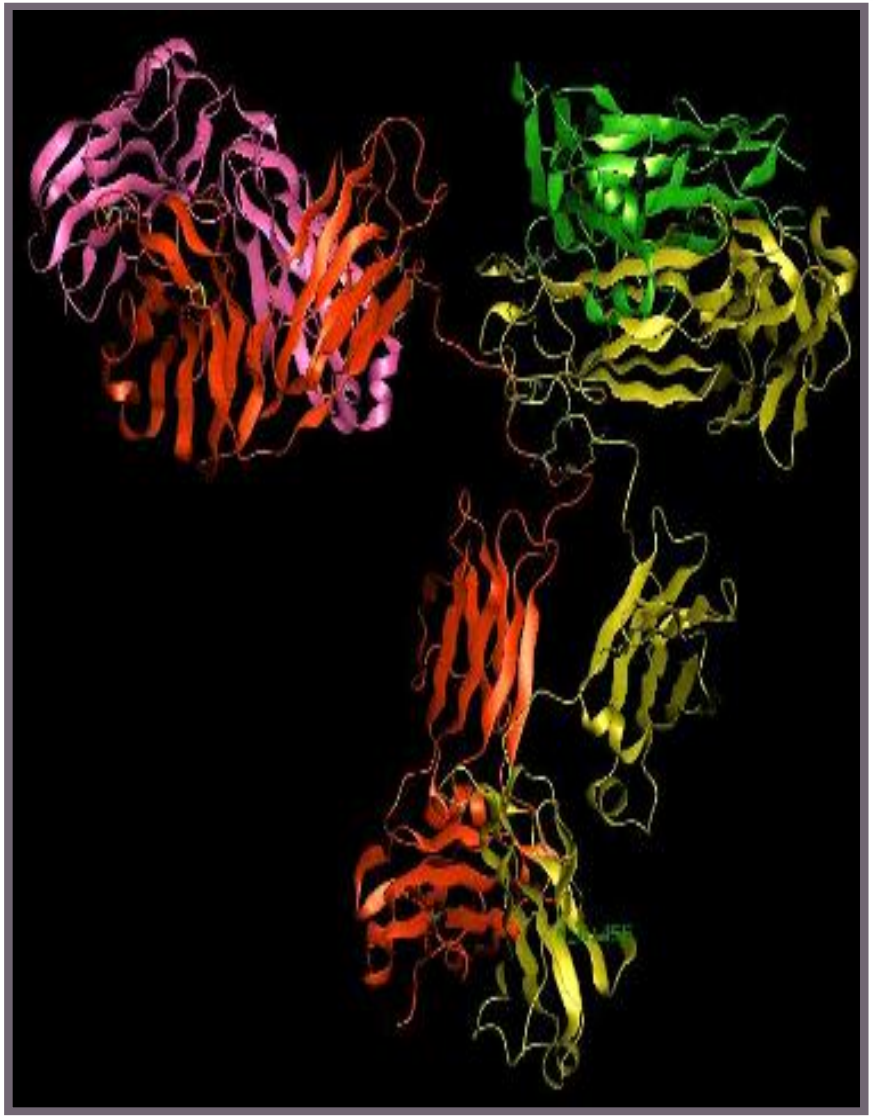
- **Eribulin approved by FDA and EMEA**

*Stratified log-rank test
TPC = treatment of physician's choice

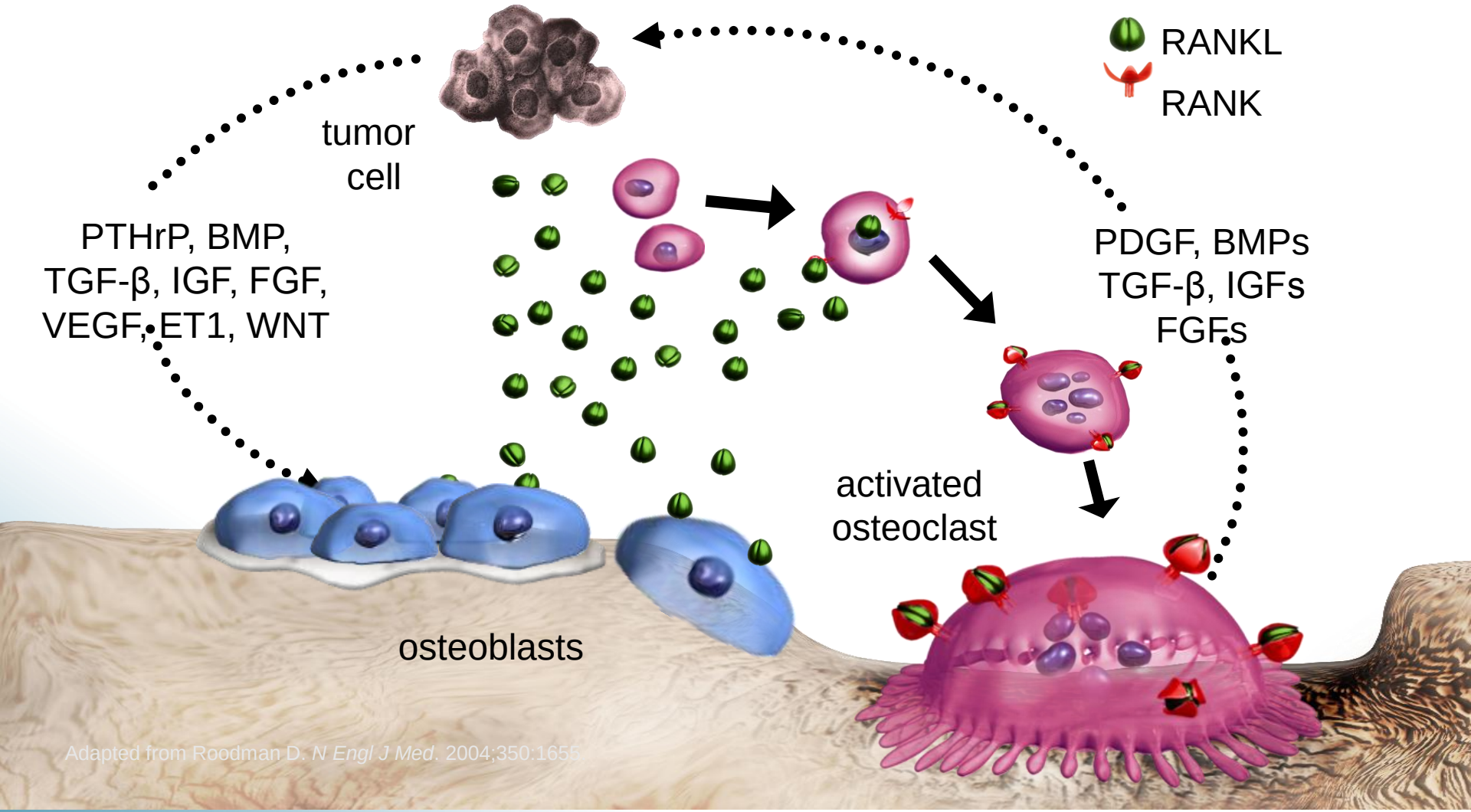
Cortes, et al. Lancet 2011

Denosumab

- fully human monoclonal antibody- IgG_2 Isotyp
- High affinity tohuman RANK Ligand
- High specificity for RANK Ligand
  - no binding to TNF-α, TNF-β, TRAIL or CD40L
- no neutralizing antibodies detectable

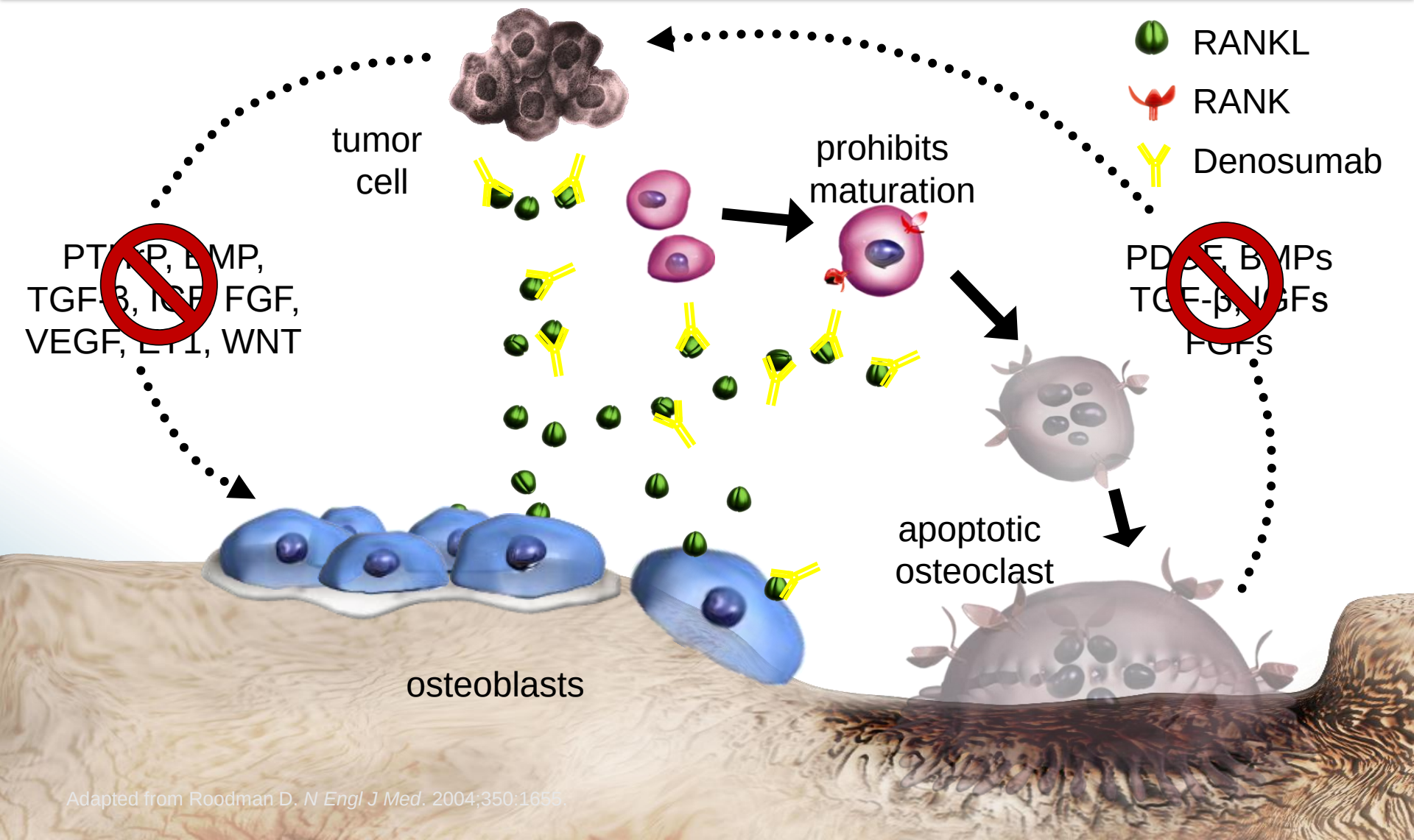


RANK-L: central role in the "vicious circle" of bone decay in bone metastases



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

Denosumab
Disruption of the "vicious circle" of bone decay



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

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Denosumab Compared With Zoledronic Acid for the Treatment of Bone Metastases in Patients With Advanced Breast Cancer: A Randomized, Double-Blind Study

Alison T. Stopeck, Allan Lipton, Jean-Jacques Body, Guenther G. Steger, Katia Tonkin, Richard H. de Boer, Mikhail Lichinitser, Yasuhiro Fujiwara, Denise A. Yardley, María Viniegra, Michelle Fan, Qi Jiang, Roger Dansey, Susie Jun, and Ada Braun

See accompanying editorial doi: 10.1200/JCO.2010.31.0128

From the University of Arizona, Arizona Cancer Center, Tucson, AZ; Penn State Milton S. Hershey Medical Center, Hershey, PA; Centre Hospitalier Universitaire Brugmann, Université Libre de Bruxelles, Brussels, Belgium; Medical University of Vienna, Vienna, Austria; Cross Cancer Institute, Edmonton, Alberta, Canada; Western and Royal Melbourne Hospitals, Melbourne, Victoria, Australia; Blokhin Cancer Research Center, Moscow, Russia; National Cancer Center Hospital, Tokyo, Japan; Sarah Cannon Research Institute, Nashville, TN; Corporacion Medica de General San Martin, San Martin, Argentina; and Amgen, Thousand Oaks, CA.

Submitted April 7, 2010; accepted June 22, 2010; published online ahead of print at www.jco.org on November 8, 2010.

Written on behalf of the 20050136

ABSTRACT

Purpose

This randomized study compared denosumab, a fully human monoclonal antibody against receptor activator of nuclear factor κ B (RANK) ligand, with zoledronic acid in delaying or preventing skeletal-related events (SREs) in patients with breast cancer with bone metastases.

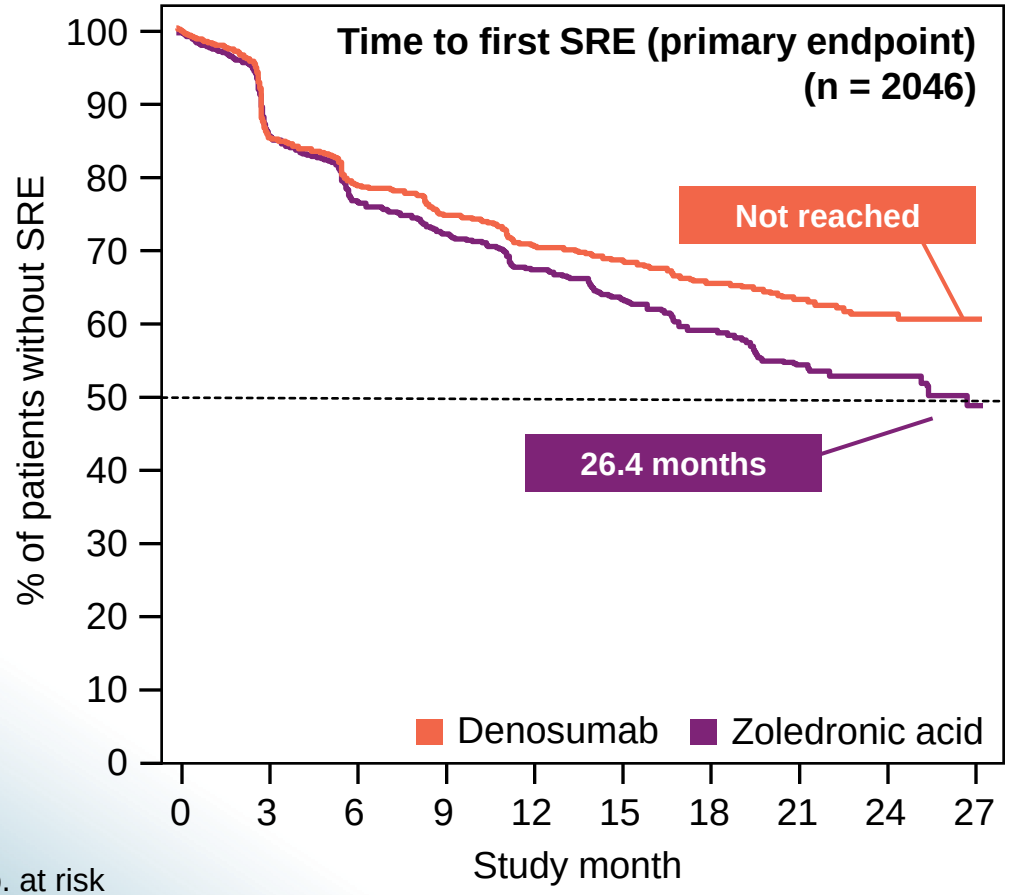
Patients and Methods

Patients were randomly assigned to receive either subcutaneous denosumab 120 mg and intravenous placebo (n = 1,026) or intravenous zoledronic acid 4 mg adjusted for creatinine clearance and subcutaneous placebo (n = 1,020) every 4 weeks. All patients were strongly recommended to take daily calcium and vitamin D supplements. The primary end point was time to first on-study SRE (defined as pathologic fracture, radiation or surgery to bone, or spinal cord compression).

Results

Denosumab was superior to zoledronic acid in delaying time to first on-study SRE (hazard ratio, 0.82; 95% CI, 0.71 to 0.95; $P = .01$ superiority) and time to first and subsequent (multiple) on-study SREs (rate ratio, 0.77; 95% CI, 0.66 to 0.89; $P = .001$). Reduction in bone turnover markers was greater with denosumab. Overall survival, disease progression, and rates of adverse events (AEs) and serious AEs were similar between groups. An excess of renal AEs and

Significantly longer time without an SRE with denosumab vs zoledronic acid



No. at risk										
Zoledronic acid	1020	829	676	584	498	427	296	191	94	29
Denosumab	1026	839	697	602	514	437	306	189	99	26

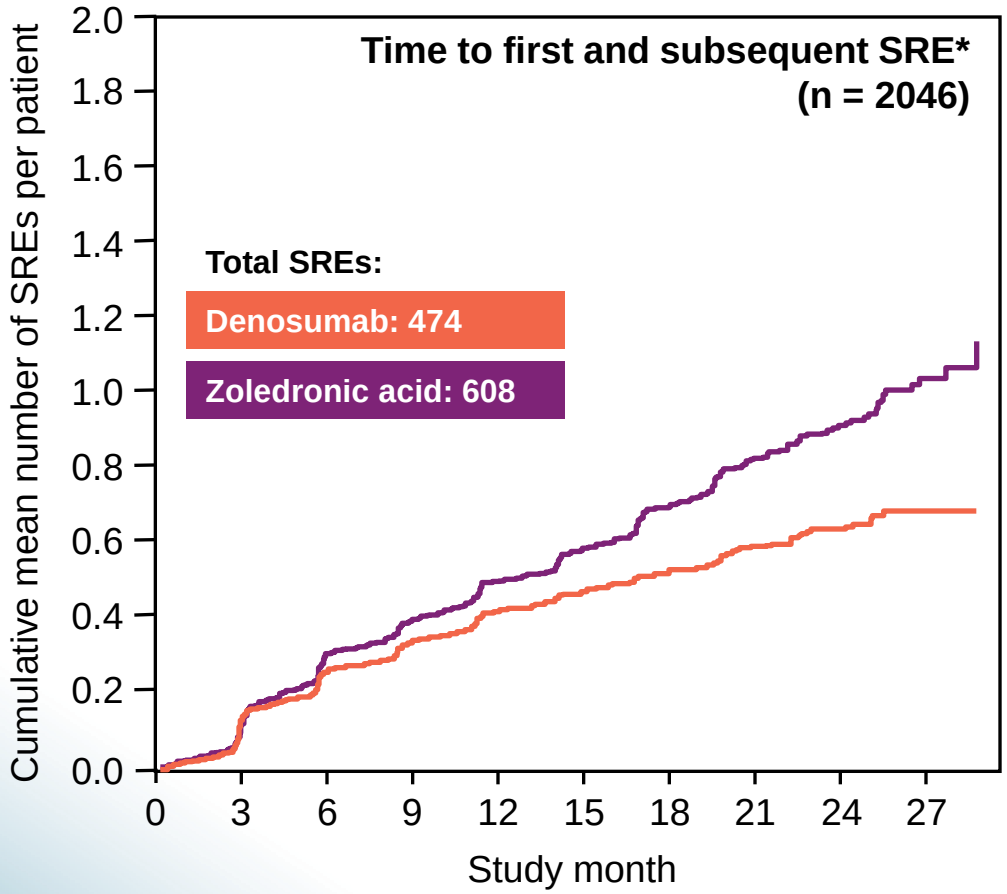
HR = 0.82 (95% CI, 0.71–0.95)
***P* = 0.0001 (non-inferiority)**
***P* = 0.01 (superiority)**

18% Risk Reduction

Stopeck AT et al. J Clin Oncol 2010;28:5132–9.

HR, hazard ratio

Significantly fewer SREs with denosumab vs zoledronic acid



RR = 0.77 (95% CI, 0.66–0.89)
***P* = 0.001 (superiority)**

23% Risk Reduction

*Events occurring at least 21 days apart (multiple event analysis)
RR, rate ratio

Stopeck AT et al. J Clin Oncol 2010;28:5132–9.

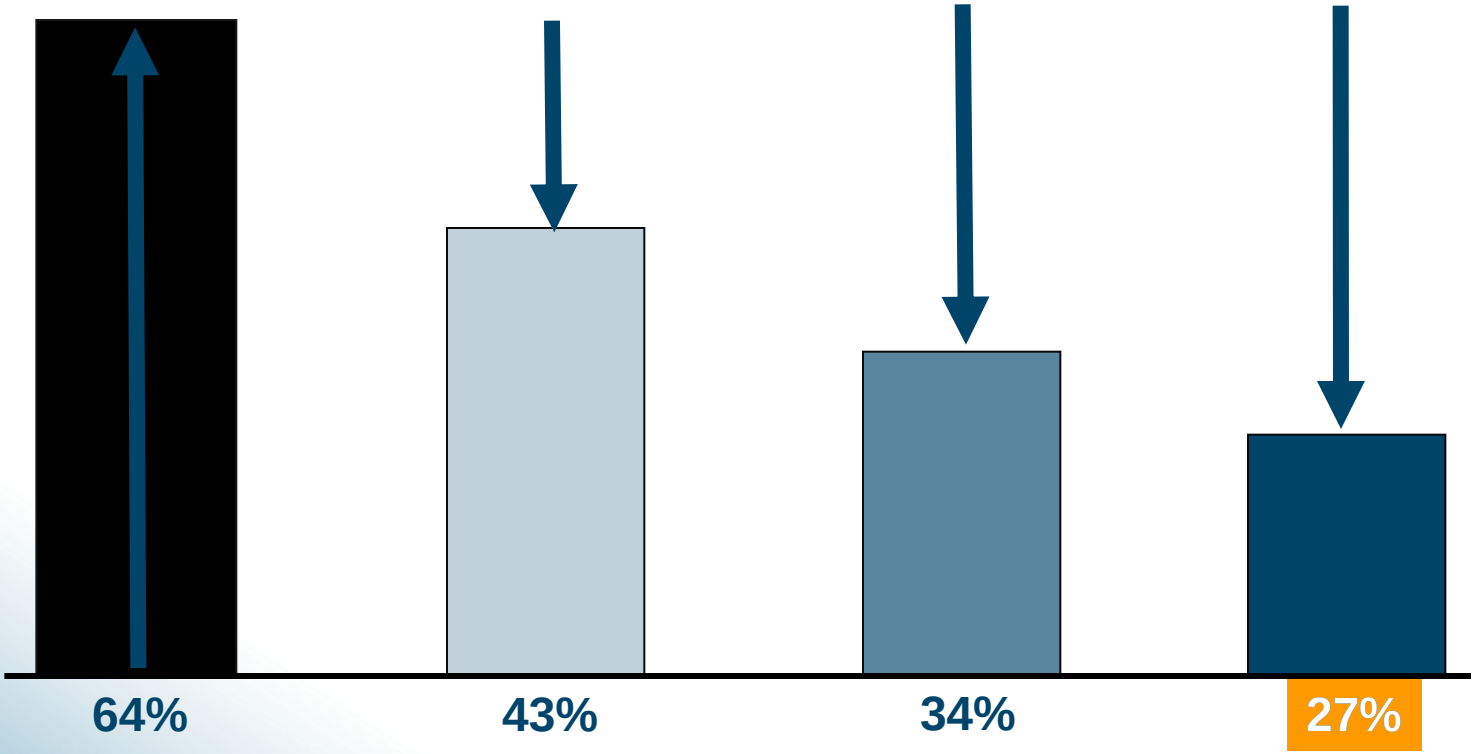
Placebo vs. Bisphosphonate vs. Denosumab

64% risk of SRE without **bisphosphonates**

~ **33%** risk reduction with **pamidronat**

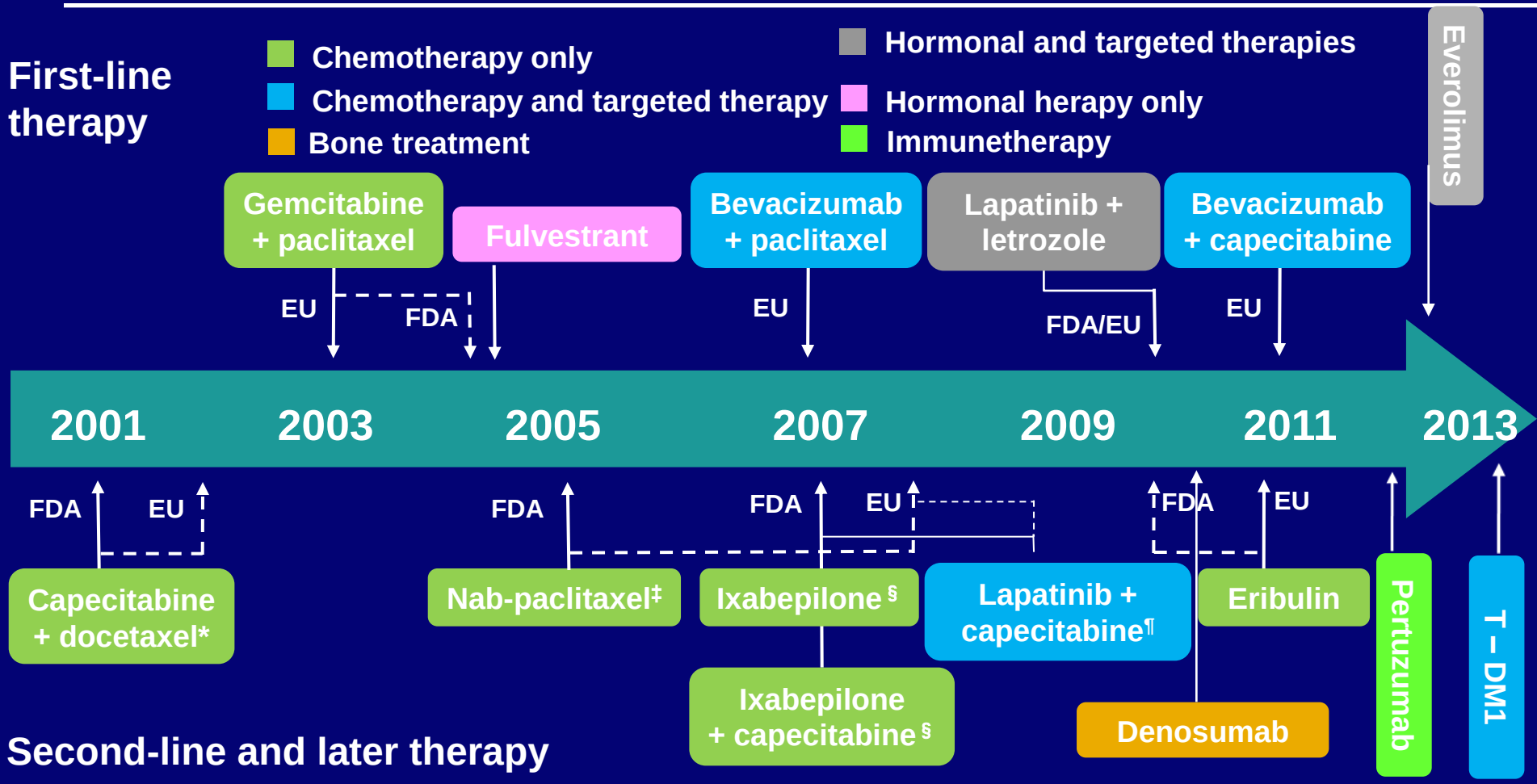
additional **20%** risk reduction with **zoledronat**

additional **18%** risk reduction with **denosumab**



Lipton A, et al. Cancer. 2000;88:3033-3037. Rosen LS, et al. Cancer. 2003;100:36-43.
Stopeck A, et al. JCO Dec. 10, 2010:5132-5139

Regulatory approvals in mBC over the past decade



*In the US, approved for use after failure of anthracycline-containing therapy, so could be given in first line
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