ESMO 2102. Controversy Session

Can neo-Adjuvant breast cancer data be used to accelerate drug approval?

THE PRO VIEW

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Physician in Chief

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MEMORIAL SLOAN-KETTERING CANCER CENTER · ESTABLISHED 1884 ·

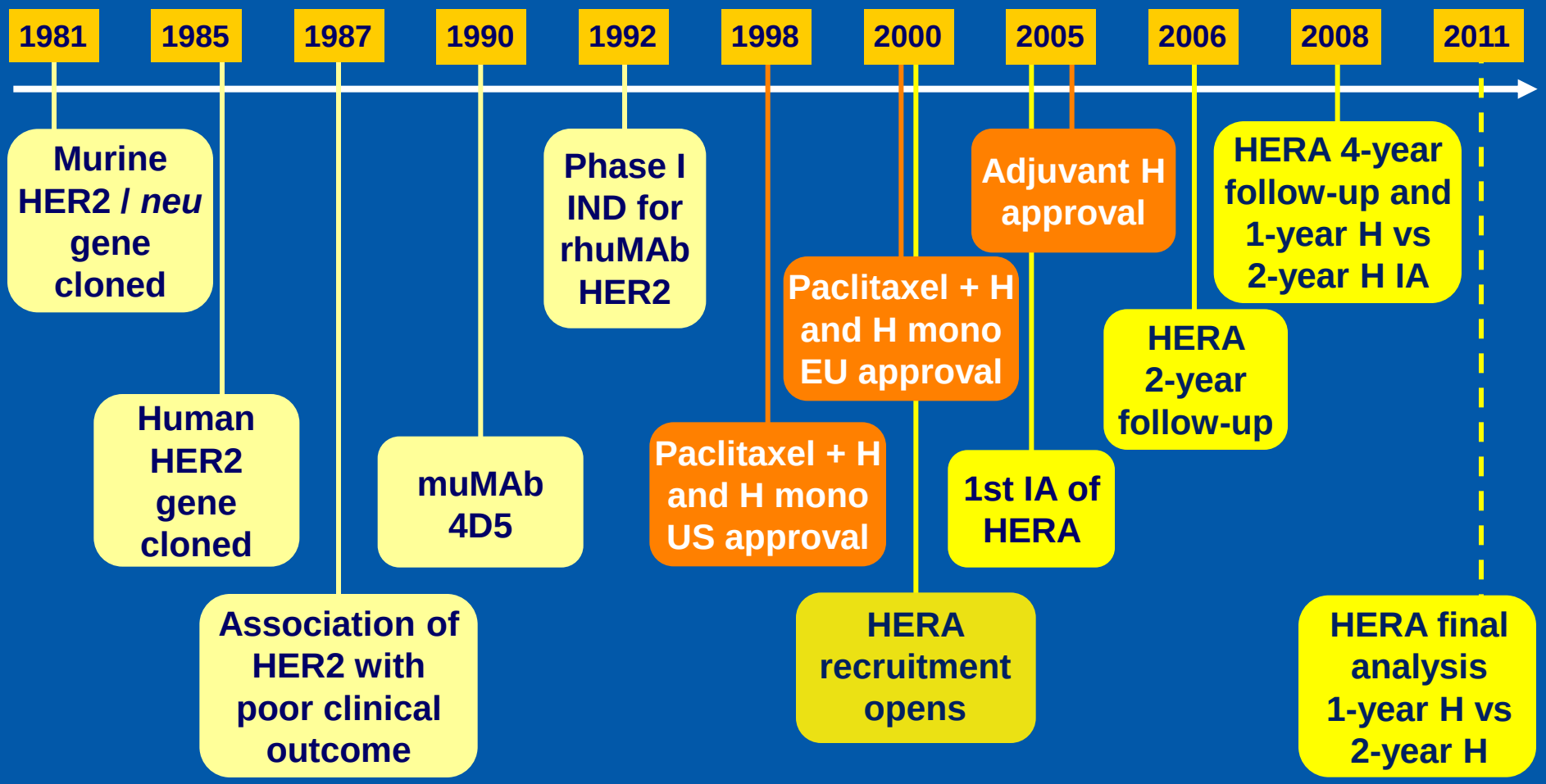
Neo-Adjuvant studies for Drug Approval THE PRO VIEW

- **What Ian Tannock is going to tell you:**
  - **Only survival benefit from randomized phase III adjuvant trials should be used as an endpoint for approval of a new agent.**
  - **Safety is critical in patients with curable disease**
  - **Neoadjuvant trials**
    - **Are too small, too short follow up**
    - **pCR is not a validated endpoint**
    - **ER + tumors do not even achieve a pCR**
  - **He will imply that we stick to the same old approach that the field has championed over many decades**

Neo-Adjuvant studies for Drug Approval THE PRO VIEW

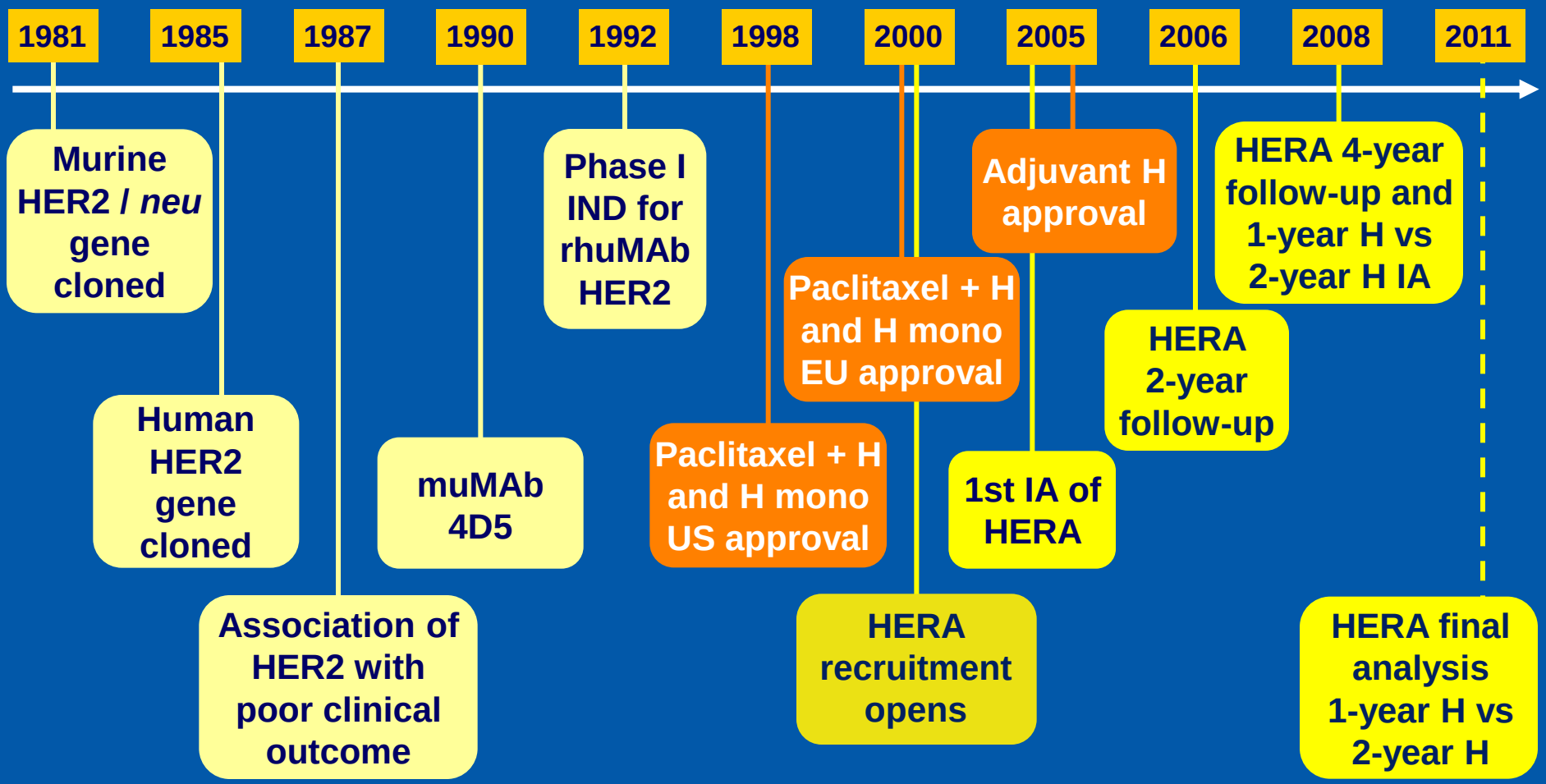
- **What Ian Tannock is going to tell you:**
  - **Only survival benefit from randomized phase III adjuvant trials should be used as an endpoint for approval of a new agent. WRONG**
  - **Safety is critical in patients with curable disease. WE AGREE, NEOADJUVANT TRIALS DO THIS**
  - **Neoadjuvant trials**
    - **Are too small, too short follow up. WRONG**
    - **pCR is not a validated endpoint. WRONG**
    - **ER + tumors with hormone Rx do not even achieve a pCR. WRONG AGAIN. WE DO NOT measure pCR in ER+ DISEASE**

~~The fascinating~~ history of Trastuzumab



HER2, human epidermal growth factor receptor 2; H, Herceptin; IA, interim analysis

The SLOW history of Trastuzumab



HER2, human epidermal growth factor receptor 2; H, Herceptin; IA, interim analysis

What Have We Learned?

Targeted therapies require new types of clinical trials

To realize the full benefits of targeted cancer therapies we need . . .

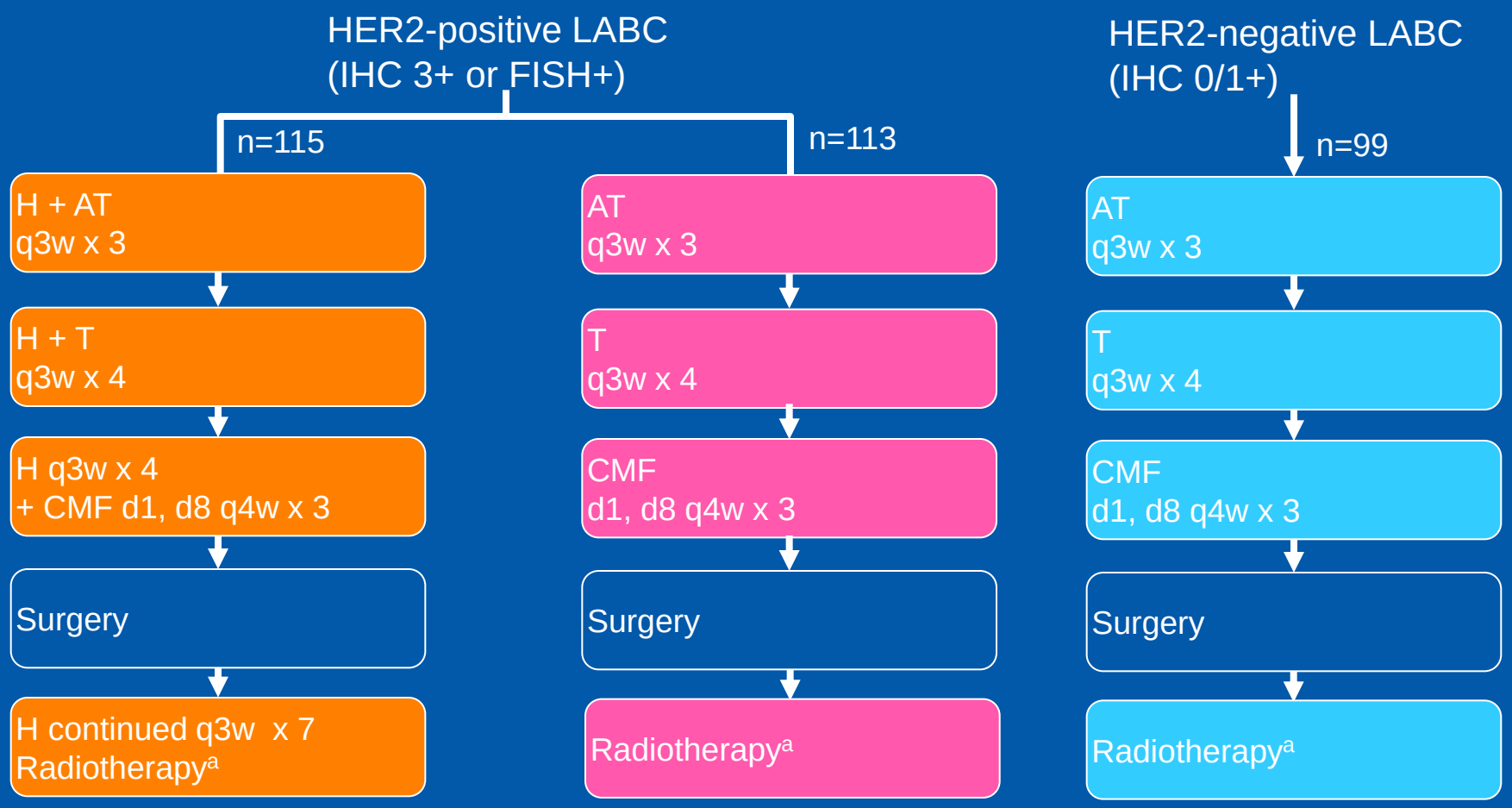
- **Early clinical trials--enrolling some patients at diagnosis**
- **Smaller clinical trials**
- **Combinatorial (multi-drug) trials**

Neoadjuvant (Primary) Therapy in Breast Ca.

Advantages

- **Improves rate of breast-conservation therapy for localized breast cancer.**
- **Allows assessment of tumor response to systemic therapy.**
- **Facilitates identification of predictive biomarkers.**
- **Provides an efficient trial design for assessment of efficacy of novel therapies utilizing pCR (pathological complete remission) as a surrogate marker for disease free-survival and overall survival.**
    - **Faster**
    - **Smaller sample size**
    - **Reduced cost**

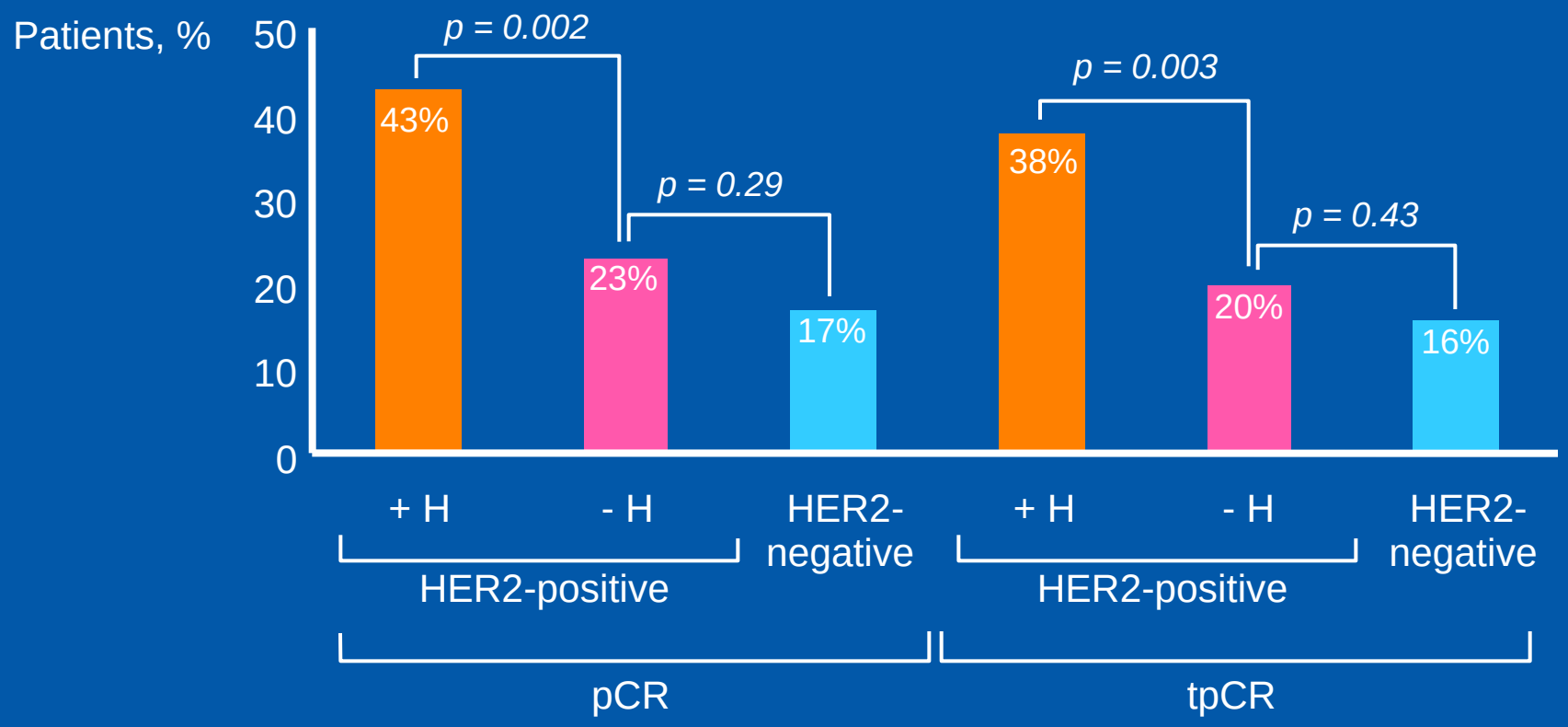
Neoadjuvant Trastuzumab (NOAH)



LABC, locally advanced breast cancer; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; FISH, fluorescence *in situ* hybridisation; A, doxorubicin (60 mg/m^2); H, Herceptin (8 mg/kg loading, then 6 mg/kg); T, paclitaxel (150 mg/m^2); CMF, cyclophosphamide (600 mg/m^2)/methotrexate (40 mg/m^2)/5-fluorouracil (600 mg/m^2);
[a]Hormone receptor-positive patients receive adjuvant tamoxifen

Gianni, …Baselga. Lancet. 2010

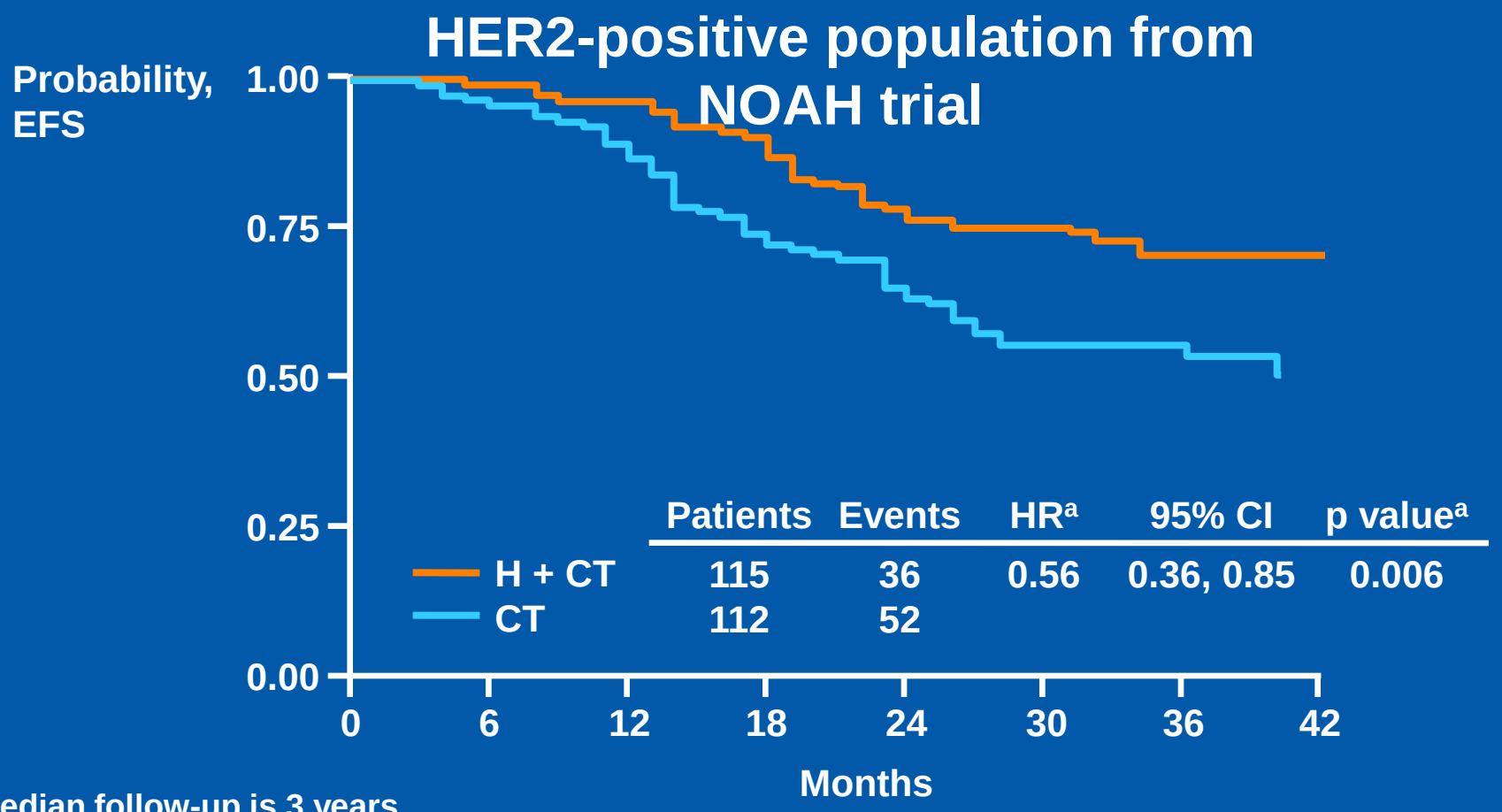
NOAH: tumor response



pCR, pathological complete response; tpCR, total pathological complete response in breast and nodes

Gianni,…Baselga. Lancet. 2010

Neoadjuvant Trastuzumab (NOAH): Event-Free Survival



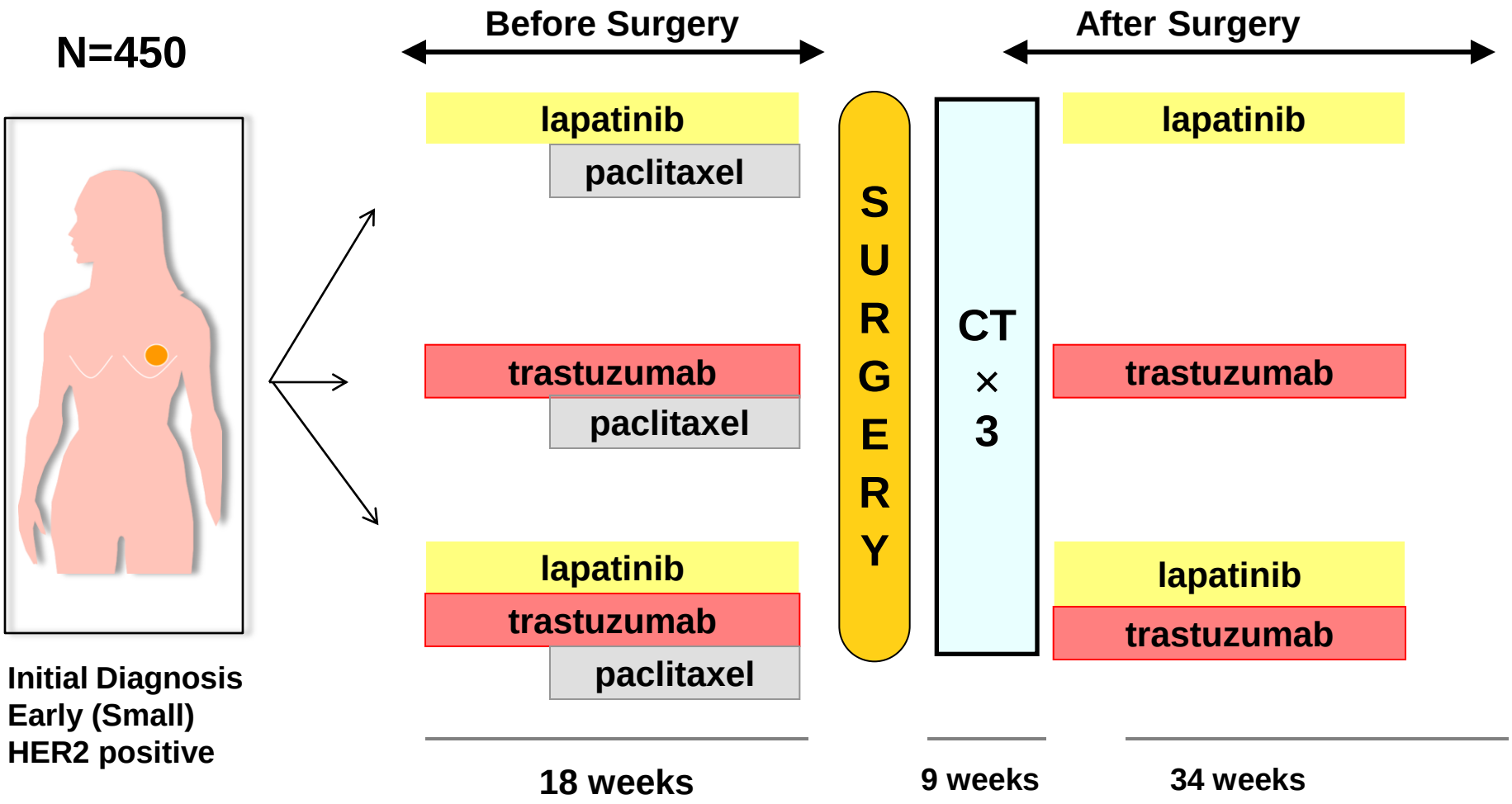
Median follow-up is 3 years

[a]Unadjusted for stratification variables: adjusted HR=0.55, p=0.0062

HER2, human epidermal growth factor receptor 2; EFS, event-free survival; H, Herceptin; CT, chemotherapy; HR, hazard ratio; CI, confidence interval

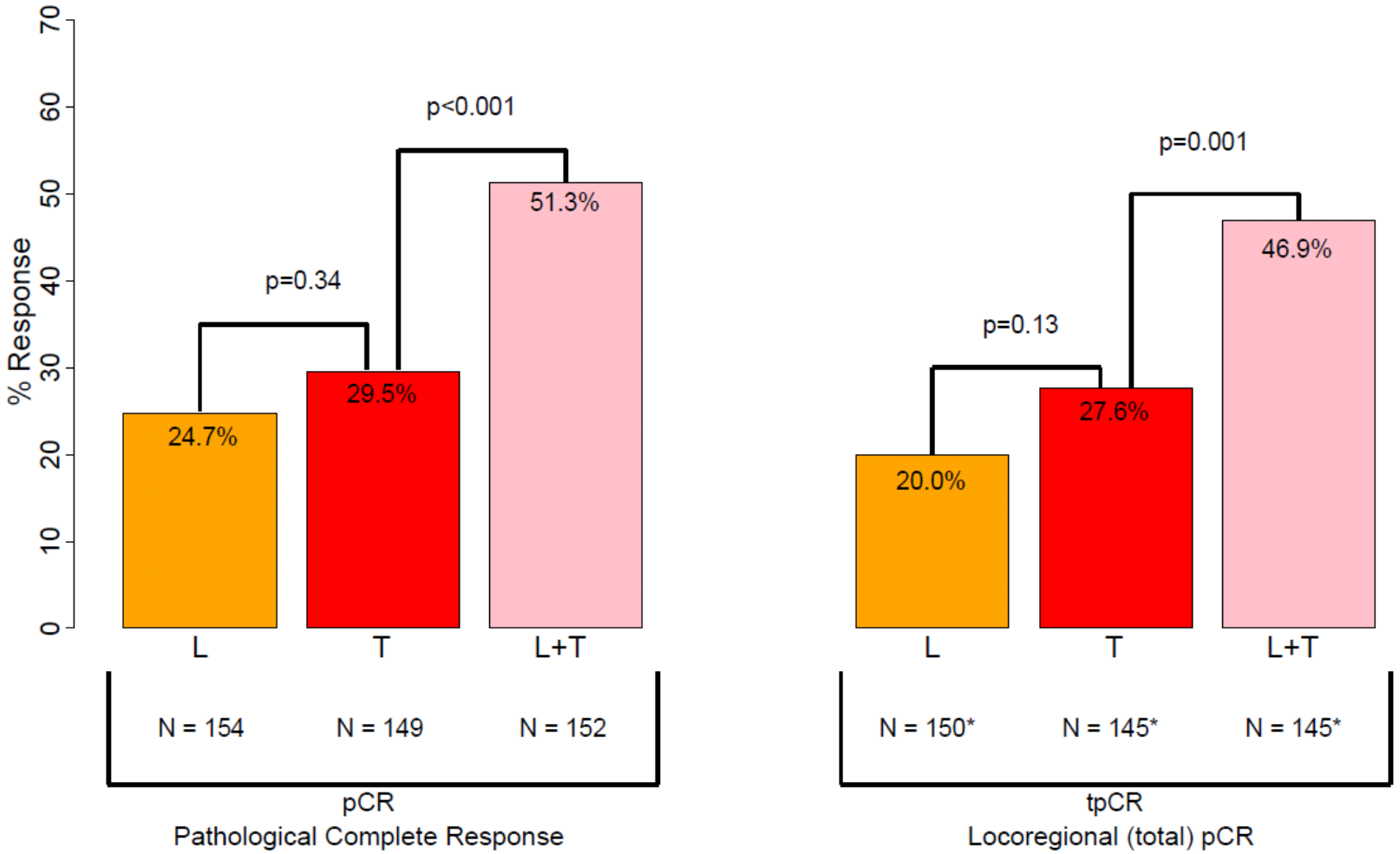
Gianni,…Baselga. Lancet 2010

Apply Novel Therapies Earlier in Disease: Neoadjuvant Studies in Breast Cancer



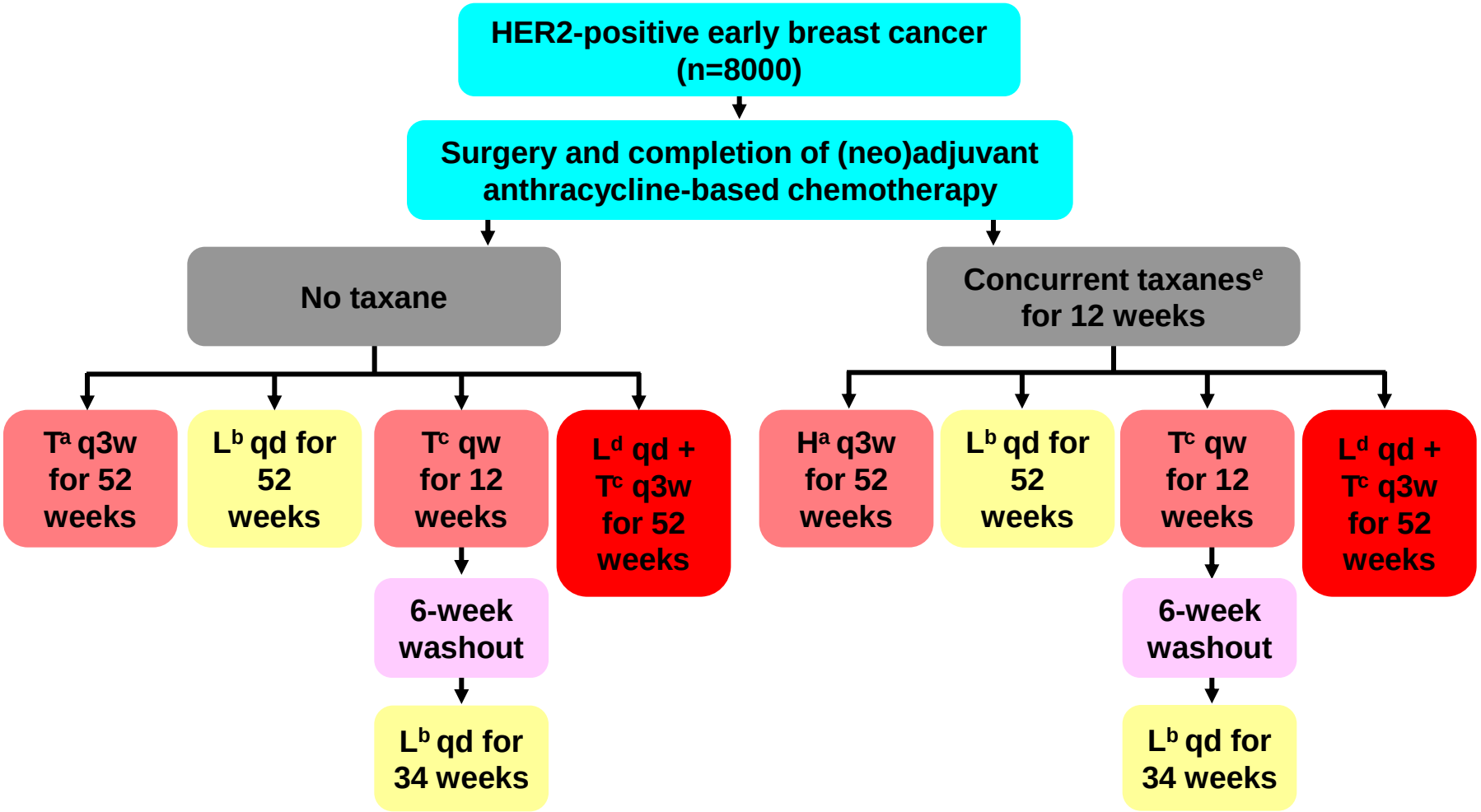
Baselga *et al*. Lancet 2010. Jan 16

Neo-ALTTO
Efficacy- pCR and tpCR



Baselga et al. Lancet 2012

ALTTO: Phase III randomised open-label trial comparing adjuvant Lapatinib +/– Trastuzumab



[a] Trastuzumab 8 mg/kg iv loading dose followed by 6 mg/kg q3w; [b]Lapatinib 1500 mg; [c]Trastuzumab 4 mg/kg iv loading dose followed by 2 mg/kg qw; [d]Lapatinib 1000 mg; [e]Paclitaxel 80 mg/m^2 qw or docetaxel q3w

Metanalysis of Neoadjuvant trials

- **To conduct a systematic review of published neoadjuvant chemotherapy studies to comprehensively evaluate:**
  - **Overall association between pCR with subsequent disease free survival (DFS) and overall survival (OS).**
  - **Association between pCR with DFS and OS in HR+, HER-2+ & triple negative (TN) breast cancer.**

Bardia,…., Baselga. AACR Breast 2011

Study Results

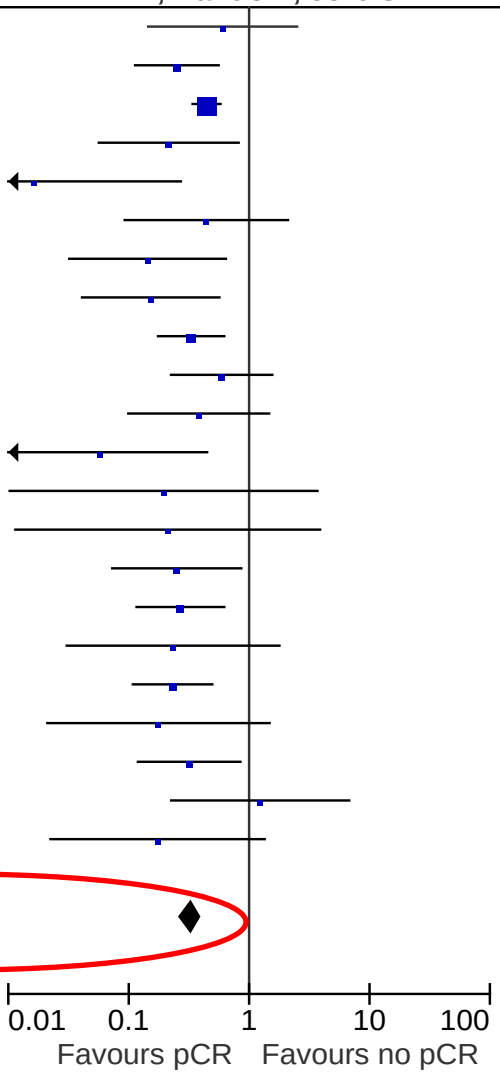
- **Total eligible studies = 30 (till July 2011)**
- **Overall sample size = 11,206 patients**
- **Overall pCR% = 22% (range: 10%-68%)**
    - **HR+ = 13% (range: 3%-27%)**
    - **HER-2+ = 34% (range: 11%-68%)**
    - **TN = 31% (range: 17%-62%)**

pCR is associated with improved disease free survival

Study or Subgroup	pCR Events	pCR Total	No pCR Events	No pCR Total	Weight	Odds Ratio M-H, Random, 95% CI
Al-Tweigeri 2010	3	14	14	45	2.3%	0.60 [0.15, 2.51]
Andre 2008	7	100	100	434	6.8%	0.25 [0.11, 0.56]
Bear NSABP B 27 2006	76	410	644	1899	35.2%	0.44 [0.34, 0.58]
Chang 2010	3	19	27	58	2.6%	0.22 [0.06, 0.82]
Chen 2010	0	28	102	197	0.6%	0.02 [0.00, 0.27]
Eralp 2009	2	23	14	79	1.9%	0.44 [0.09, 2.11]
Ezzat 2004	2	29	32	94	2.1%	0.14 [0.03, 0.64]
Frasci 2009	5	46	8	18	2.7%	0.15 [0.04, 0.57]
Giani 2010	16	76	71	159	10.2%	0.33 [0.18, 0.62]
Guiu 2010	8	44	15	55	4.8%	0.59 [0.22, 1.56]
Hankoop 1998	5	23	8	19	2.5%	0.38 [0.10, 1.47]
Huang 2009	1	22	42	93	1.1%	0.06 [0.01, 0.45]
Hurley 2008	0	8	9	40	0.5%	0.20 [0.01, 3.70]
Jung 2010	0	10	10	56	0.6%	0.21 [0.01, 3.89]
Kim 2010	3	26	79	231	3.0%	0.25 [0.07, 0.86]
Kuerer 1999	7	43	138	329	6.2%	0.27 [0.12, 0.62]
Min 2011	1	33	25	212	1.1%	0.23 [0.03, 1.79]
Precht 2010	8	81	123	383	7.4%	0.23 [0.11, 0.50]
Robidoux 2010	1	19	11	46	1.0%	0.18 [0.02, 1.48]
Shimizu 2009	6	43	27	80	4.7%	0.32 [0.12, 0.85]
Sikov 2009	3	24	3	29	1.6%	1.24 [0.23, 6.78]
Toi 2008	1	47	16	144	1.1%	0.17 [0.02, 1.35]
Total (95% CI)		**1168**		**4700**	**100.0%**	**0.33 [0.27, 0.41]**
Total events	158		1518			

Heterogeneity: Tau² = 0.02; Chi² = 22.37, df = 21 (P = 0.38); I² = 6%

Test for overall effect: Z = 9.95 (P < 0.00001)



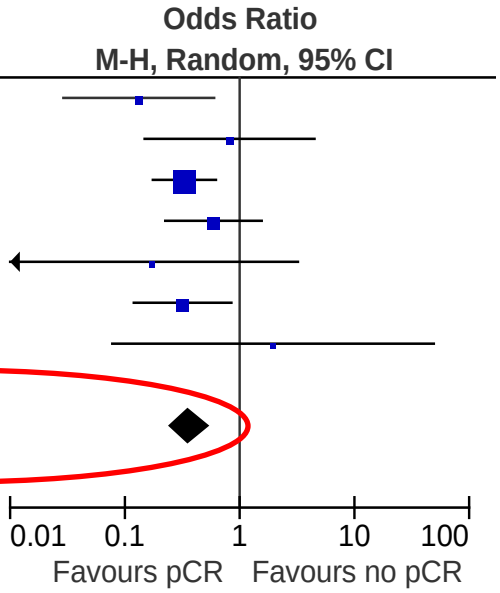
pCR is associated with improved disease free survival

HER-2+ Tumors

Study or Subgroup	pCR Events	pCR Total	No pCR Events	No pCR Total	Weight	Odds Ratio M-H, Random, 95% CI
Andre 2008	2	35	22	70	7.8%	0.13 [0.03, 0.60]
Coudert 2005	3	14	4	16	6.1%	0.82 [0.15, 4.51]
Giani 2010	16	76	71	159	44.5%	0.33 [0.18, 0.62]
Guiu 2010	8	44	15	55	19.1%	0.59 [0.22, 1.56]
Hurley 2008	0	8	10	40	2.1%	0.17 [0.01, 3.22]
Shimizu 2009	6	43	27	80	18.7%	0.32 [0.12, 0.85]
Sikov 2009	2	13	0	4	1.7%	1.96 [0.08, 49.26]
Total (95% CI)		**233**		**424**	**100.0%**	**0.37 [0.24, 0.56]**
Total events	37		149			

Heterogeneity: Tau² = 0.00; Chi² = 5.06, df = 6 (P = 0.54); I² = 0%

Test for overall effect: Z = 4.64 (P < 0.00001)



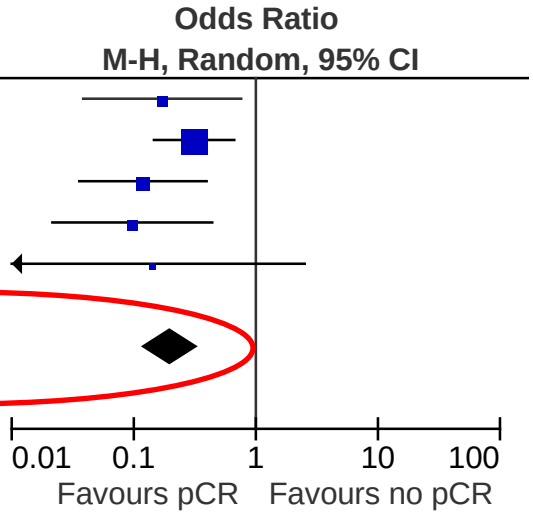
pCR is associated with improved disease free survival

Triple Negative Tumors

Study or Subgroup	pCR Events	pCR Total	No pCR Events	No pCR Total	Weight	Odds Ratio M-H, Random, 95% CI
Fischer 2011	2	26	41	125	13.1%	0.17 [0.04, 0.76]
Guarneri 2006	8	135	71	423	50.5%	0.31 [0.15, 0.67]
Leidkte 2008	3	57	63	198	20.2%	0.12 [0.04, 0.40]
Ring 2006	2	24	42	87	12.8%	0.10 [0.02, 0.44]
Sikov 2009	1	8	2	4	3.5%	0.14 [0.01, 2.52]
Total (95% CI)		**250**		**837**	**100.0%**	**0.20 [0.12, 0.34]**
Total events	16		219			

Heterogeneity: Tau² = 0.00; Chi² = 3.03, df = 4 (P = 0.55); I² = 0%

Test for overall effect: Z = 5.87 (P < 0.00001)

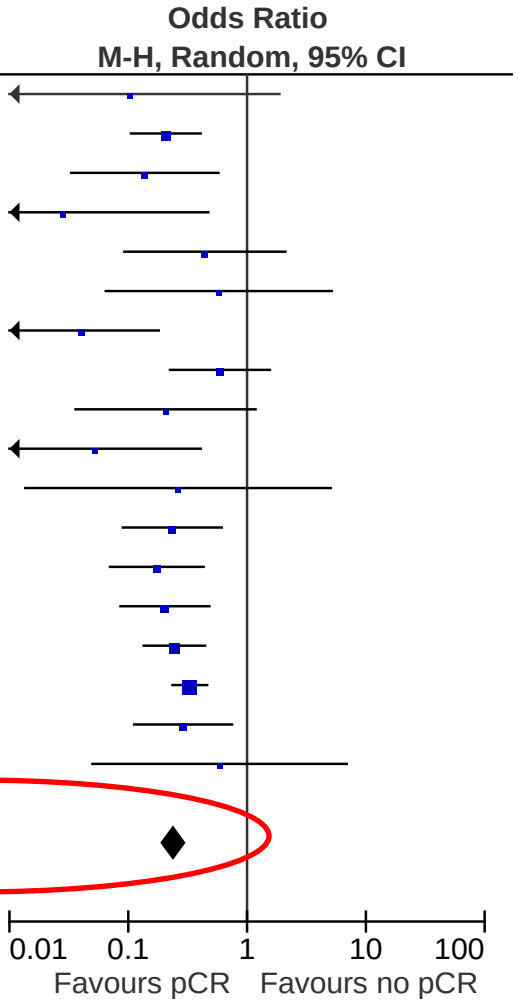


pCR is associated with improved overall survival

Study or Subgroup	pCR Events	pCR Total	No pCR Events	No pCR Total	Weight	Odds Ratio M-H, Random, 95% CI
Al-Tweigeri 2010	0	14	11	45	0.8%	0.10 [0.01, 1.87]
Amat 2005	10	92	229	618	11.1%	0.21 [0.11, 0.41]
Andre 2008	2	100	56	434	3.2%	0.14 [0.03, 0.57]
Chen 2010	0	28	75	197	0.9%	0.03 [0.00, 0.47]
Eralp 2009	2	23	14	79	2.7%	0.44 [0.09, 2.11]
Ezzat 2004	1	29	5	86	1.4%	0.58 [0.06, 5.17]
Fischer 2011	2	26	84	125	2.9%	0.04 [0.01, 0.18]
Guiu 2010	8	44	15	55	6.3%	0.59 [0.22, 1.56]
Hankoop 1998	2	23	6	19	2.2%	0.21 [0.04, 1.18]
Huang 2009	1	22	46	97	1.6%	0.05 [0.01, 0.41]
Hurley 2008	0	8	7	40	0.8%	0.26 [0.01, 5.07]
Kuerer 1999	5	43	118	329	6.4%	0.24 [0.09, 0.61]
Leidkte 2008	5	155	155	963	7.0%	0.17 [0.07, 0.43]
Precht 2010	6	81	108	383	7.6%	0.20 [0.09, 0.48]
Rastogi B 18 2008	14	86	265	599	13.2%	0.25 [0.14, 0.44]
Rastogi B 27 2008	42	397	490	1857	24.3%	0.33 [0.24, 0.46]
Ring 2006	5	52	103	383	6.5%	0.29 [0.11, 0.75]
Sikov 2009	1	24	2	29	1.1%	0.59 [0.05, 6.90]
Total (95% CI)		**1247**		**6338**	**100.0%**	**0.24 [0.19, 0.32]**
Total events	106		1789			

Heterogeneity: Tau² = 0.05; Chi² = 20.12, df = 17 (P = 0.27); I² = 16%

Test for overall effect: Z = 10.48 (P < 0.00001)



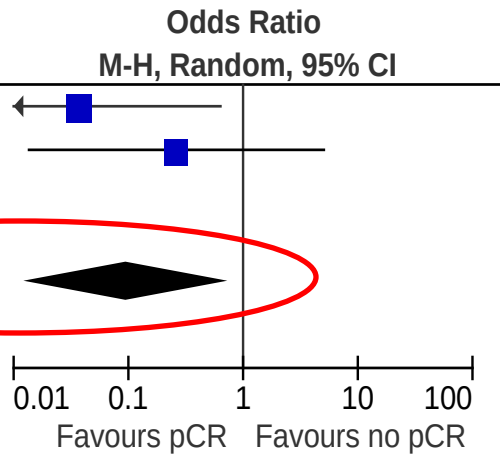
pCR is associated with improved overall survival

HER-2+ Tumors

Study or Subgroup	pCR Events	pCR Total	No pCR Events	No pCR Total	Weight	Odds Ratio M-H, Random, 95% CI
Andre 2008	0	35	19	70	52.1%	0.04 [0.00, 0.64]
Hurley 2008	0	8	7	40	47.9%	0.26 [0.01, 5.07]
Sikov 2009	0	13	0	4		Not estimable
Total (95% CI)		**56**		**114**	**100.0%**	**0.09 [0.01, 0.74]**
Total events	0		26			

Heterogeneity: Tau² = 0.00; Chi² = 0.93, df = 1 (P = 0.34); I² = 0%

Test for overall effect: Z = 2.25 (P = 0.02)



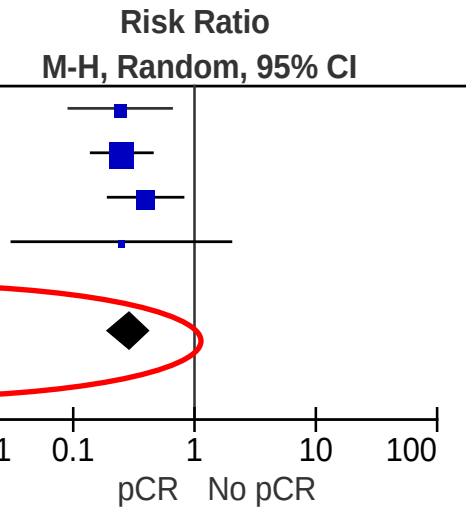
pCR is associated with improved overall survival

Triple Negative Tumors

Study or Subgroup	pCR Events	pCR Total	No pCR Events	No pCR Total	Weight	Risk Ratio M-H, Random, 95% CI
Frasci 2009	5	46	8	18	16.9%	0.24 [0.09, 0.65]
Guarneri 2006	11	132	140	423	47.5%	0.25 [0.14, 0.45]
Ring 2006	6	24	55	87	31.8%	0.40 [0.19, 0.81]
Sikov 2009	1	8	2	4	3.7%	0.25 [0.03, 2.00]
Total (95% CI)		**210**		**532**	**100.0%**	**0.29 [0.19, 0.43]**
Total events	23		205			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.10$, df = 3 (P = 0.78); $I^2 = 0\%$

Test for overall effect: Z = 6.06 (P < 0.00001)



German Breast Cancer Group Experience N= 6377 patients in 7 Neoadjuvant Trials

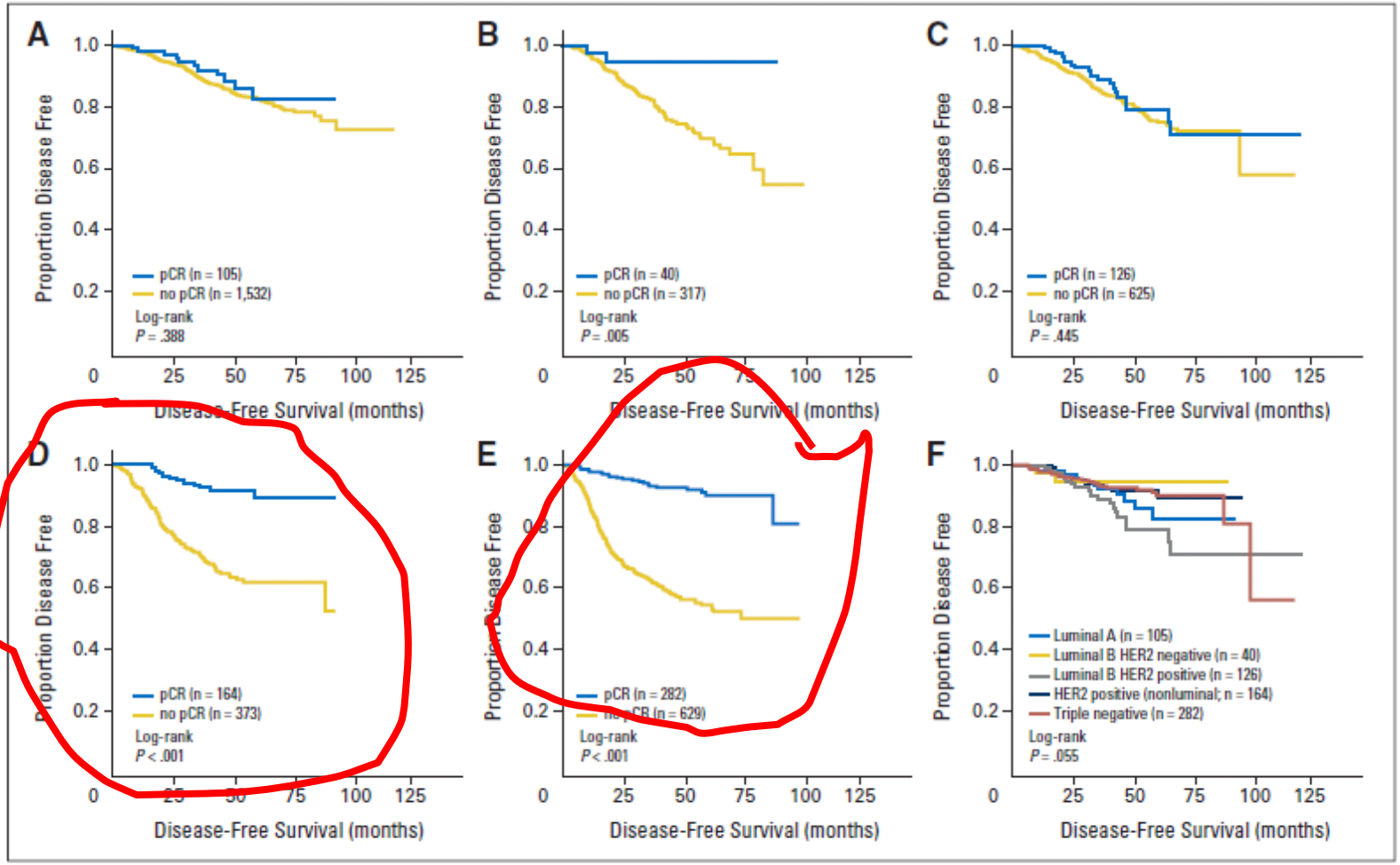


Fig 2. Prognostic impact of pathologic complete response (pCR) on disease-free survival (DFS) in 4,193 patients according to breast cancer intrinsic subtype. (A) Patients with luminal A–like tumors, (B) luminal B/human epidermal growth factor receptor 2 (HER20 –negative–like tumors, (C) luminal B/HER2-positive–like tumors, (D) HER2-positive (nonluminal) –like tumors, and (E) triple-negative tumors; (F) comparison of DFS in 717 patients achieving pCR according to breast cancer intrinsic subtype.

Von Minckwitz et al. J Clin Oncol 2012

Conclusions

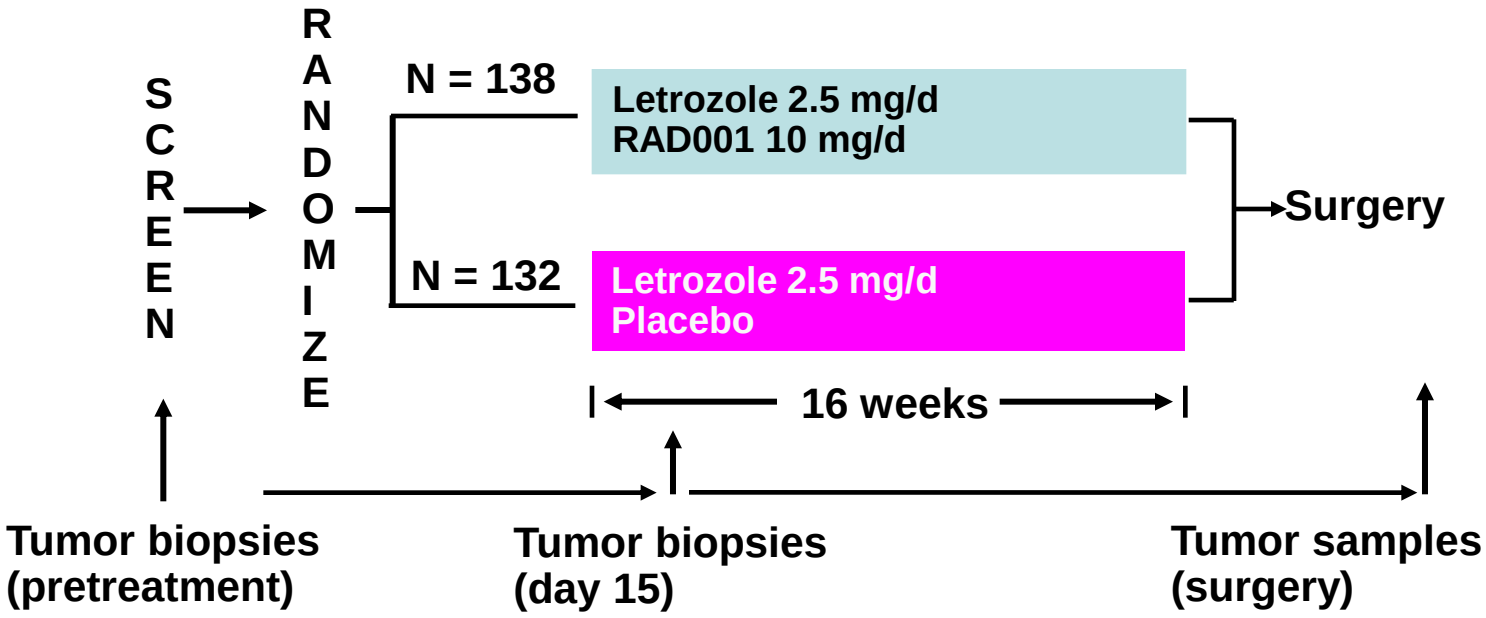
- **pCR after neoadjuvant chemotherapy is associated with significantly improved DFS and OS, particularly for HER-2+ and triple negative breast cancer.**

- **pCR could be considered as a surrogate marker for survival outcomes as new therapies are evaluated in the neoadjuvant setting.**

Bardia,…., Baselga. AACR Breast 2011, Von Minckwitz et al. J Clin Oncol 2012

Phase II neoadjuvant everolimus (RAD001) breast cancer study

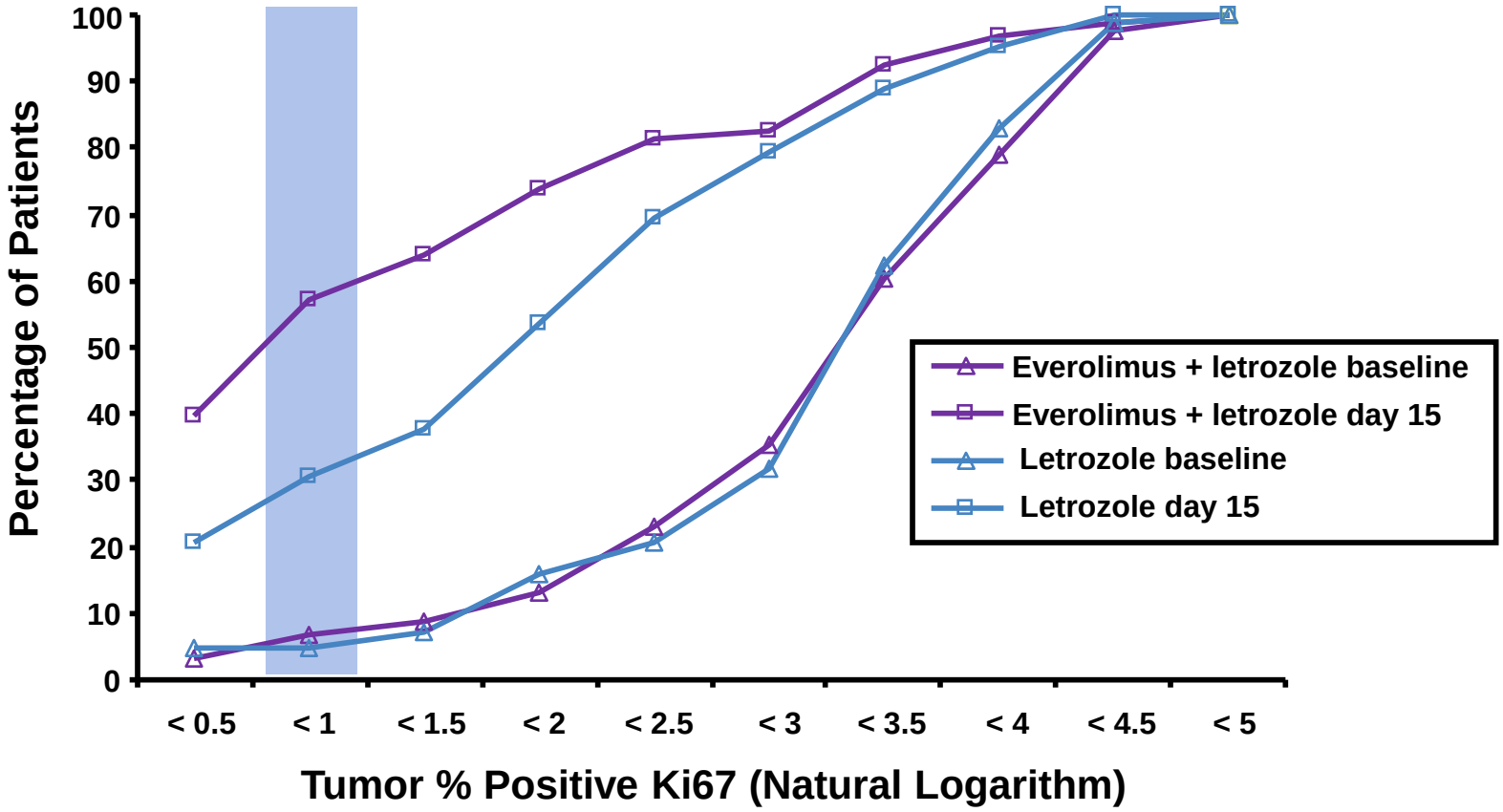
- Newly diagnosed, untreated patients with ER^+ localized breast cancer likely to benefit from hormonal therapy
- Palpable tumor: > 2 cm diameter



Baselga *et al*. J Clin Oncol. 2009

Phase II neoadjuvant everolimus (RAD001) breast cancer study – Change in Ki67

- At day 15, a large difference in Ki67 values is seen between the everolimus + letrozole and the placebo + letrozole arms, which was not seen at baseline



The Food and Drugs Administration DIXIT:

“Regular approval of a new drug requires adequate, well-controlled trials demonstrating clinical benefit, which is generally defined in early-stage breast cancer as an improvement in disease-free or overall survival”

Alternatively, the Food and Drug Administration (FDA) may grant accelerated approval on the basis of a surrogate end point that is “reasonably likely to predict clinical benefit.” **For neoadjuvant breast-cancer treatment, we propose that the rate of pathological complete response be used as this surrogate.**

Prowell T. Food and Drug Administration. Draft Guidance for Industry. Pathologic complete response in neoadjuvant treatment of high-risk early-stage breast cancer: use as an endpoint to support accelerated approval **(http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM305501.pdf).**

Neo-Adjuvant studies for Drug Approval THE PRO VIEW

- Our mission is to save lives.
  - Neoadjuvant and adjuvant therapies save lives
- Yet,…we can not afford to waste years (and resources we do not have) waiting for results of adjuvant trials, that we know are going to be positive.
  - The day that ALTTO is positive, we are going to feel good but also very bad. Because we knew that trastuzumab and lapatinib was superior to trastuzumab. How many lives have we lost? Was this necessary?
  - There is not a single well conducted neoadjuvant trial that has not been confirmed in the adjuvant setting
- It is time to move forward
  - The same old approach does simply not work any longer.

Neo-Adjuvant studies for Drug Approval
THE PRO VIEW

- Science has spoken

  Massive data from single studies as well as from meta-analysis in favor of neodjuvant studies

  - pCR in TNBC and HER2 correlates with clinical outcome
  - PEPI score and Ki 67 in ER positive correlates with clinical outcome
- Major academic groups embrace the concept
- Pharma has embraced it too
- Regulatory agencies have also embraced it

Neo-Adjuvant studies for Drug Approval
THE PRO VIEW

- **Let us move forward, we should never go back…..**
- **Stop 10,000-patient adjuvant trials**

Go Neo-Adjuvant!