

HER2-Amplified Early Breast Cancer: Choosing the Most Effective Adjuvant Therapy

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Main Characteristics of the Case

- **Small tumor mass: 1-cm tumor in the breast and negative sentinel node**
- **Aggressive tumor: high grade, amplification of HER2, moderately hormone sensitive**

Prognosis of HER2-Positive Tumors 1 cm or Smaller

- T1 a , T1b, N–, HER2 positive (6% to 10%)
- n = 965 (MDACC) + 350 (others)

- HER2 positive vs negative :

Recurrence-free survival (RFS):

HR: 2.7 (1.4-5) $P = .002$

Distant recurrence-free survival (DRFS):

HR: 5.3 (2.2-12.6) $P = .0002$

- The 5-year recurrence rate of HER2-positive patients with tumors 1 cm or less was 23%



Other Data Regarding HER2-Positive Small Invasive Breast Cancer

- If screen-detected, 90% overall survival (OS) at 10 years w/o therapy
- 15% to 20% event rate at 5 years (5% to 8% distant!)
- HER2+ ER+ do better than HER2+ ER- (75% vs 61% 10-year RFS)

Poor Prognosis Characteristics

An adjuvant treatment should be considered.

Endocrine Therapy Alone?

- **Poor hormone sensitivity (ER 40%, PR 20%)**
- **Grade III, highly proliferative**
- **HER2 positive**
- **Endocrine therapy should not be given alone but should follow chemotherapy**

Chemotherapy Followed by Endocrine Therapy?

- Since the tumor is HER2 positive, it is mandatory to propose trastuzumab together with and after chemotherapy or only after chemotherapy

Trastuzumab + Endocrine Therapy

- To our knowledge, no **adjuvant** clinical trial has shown the benefit of such a treatment
- Furthermore, the hormone sensitivity of the tumor is poor

Trastuzumab + Chemotherapy + Endocrine Therapy

- Association to be proposed
- The duration of trastuzumab treatment is an open question
- Even if the hormone sensitivity is poor, endocrine therapy can decrease the risk of relapse and should be given after chemotherapy

Which Chemotherapy Regimen ?

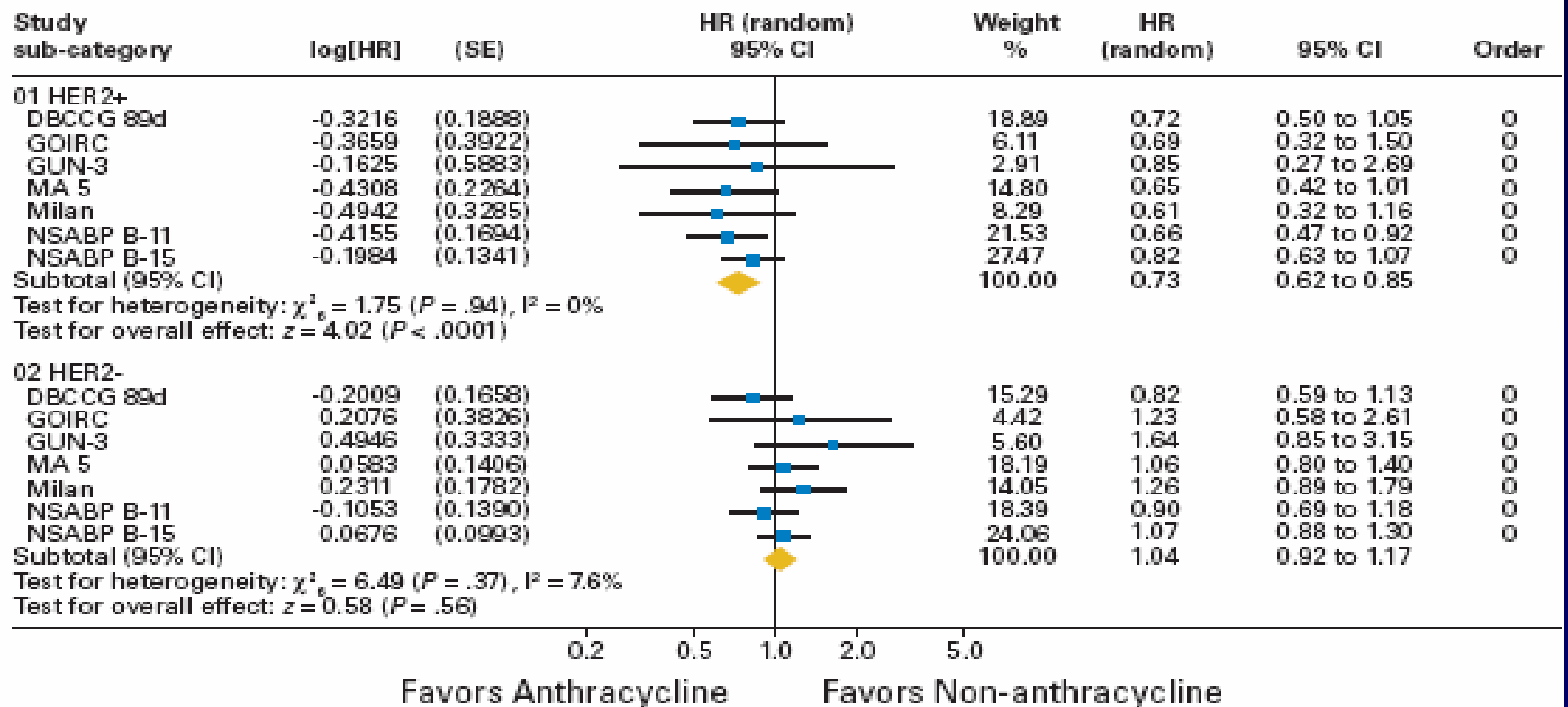
- Anthracyclines alone?
- Anthracyclines and taxanes?
- Non-anthracycline–containing regimen?
- Trastuzumab together with taxanes or after chemotherapy?

Adjuvant Anthracyclines - Risk of Death (EBCTCG 2005)

- Patients < 50 years: OR: .62 ($P < .00001$)
- Patients 50 – 69 years: OR: .80 ($P < .00001$)

HER2 and Sensitivity to Anthracyclines: Risk of Death

B



IS IT USEFUL TO GIVE TAXANES TOGETHER WITH ANTHRACYCLINES ?

Taxane-Based Combinations As Adjuvant Chemotherapy of EBC: A Meta-Analysis of Randomized Trials for Overall Survival

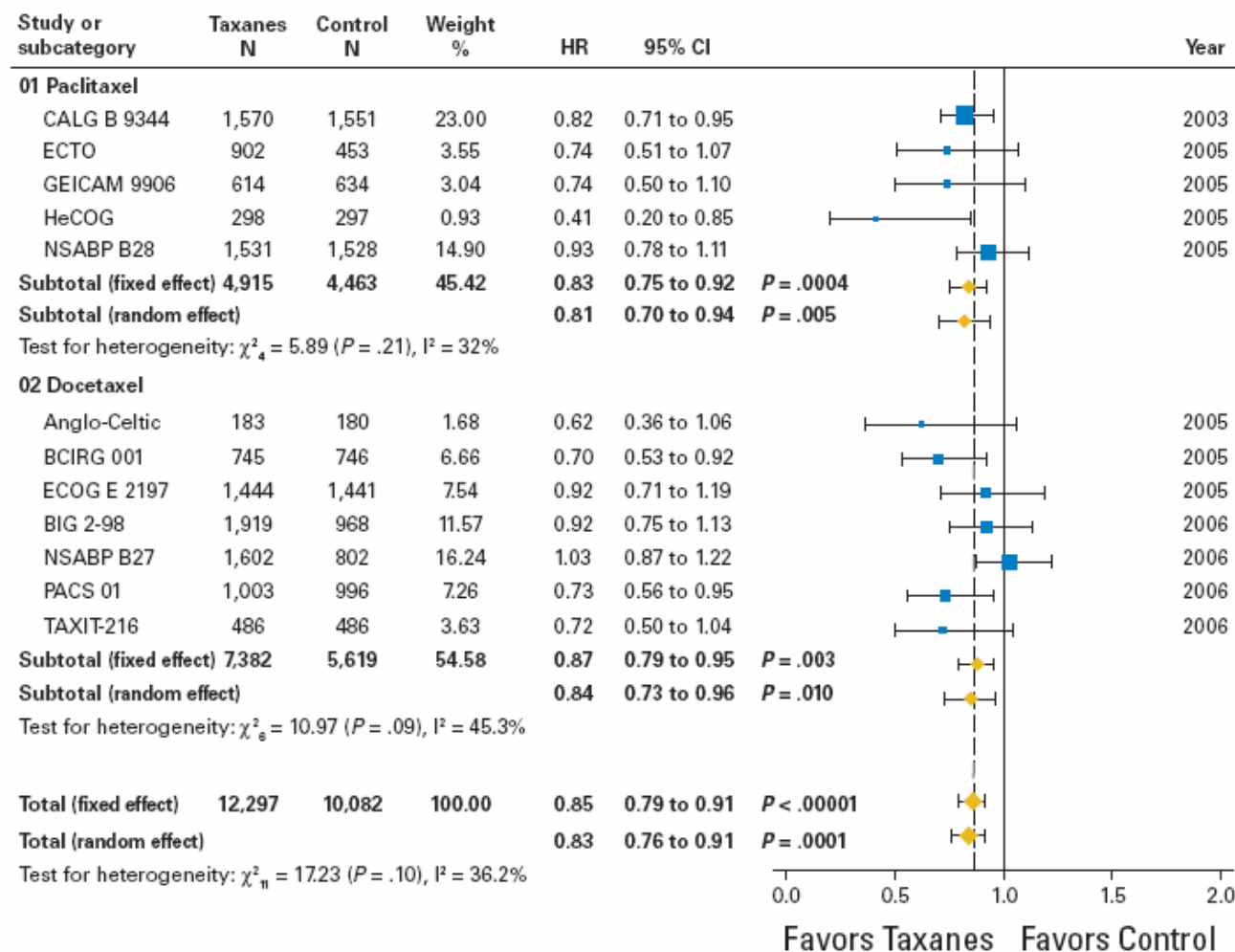


Fig 2. Meta-analysis of overall (OS). Studies are grouped based on the type of taxane used. Within each group, trials are ordered by year of reporting and by alphabetical order; squares on the hazard ratio plot are proportional to the weight of each study; weighting is based on the inverse variance method.

4 AC vs 4 AT in Patients N+ 1-3

- No difference in DFS or OS
- More toxicity with AT

WHICH REGIMEN IS THE BEST?

BCIRG 005

- 6 TAC vs 4 AC → 4 T
- DFS and OS: NS
- Febrile neutropenia : 17.9% after TAC and 8.3% after AC → T ($P < .0001$)

NSABP 30

- 4 AC → 4T vs 4 AT vs 4 TAC
- DFS: 4 AC → 4T > 4 TAC ($P = .006$)
> 4 AT ($P = .001$)
- OS: 4 AC → 4T > 4 AT ($P = .03$)
4 AC → 4T vs TAC ($P = .08$)

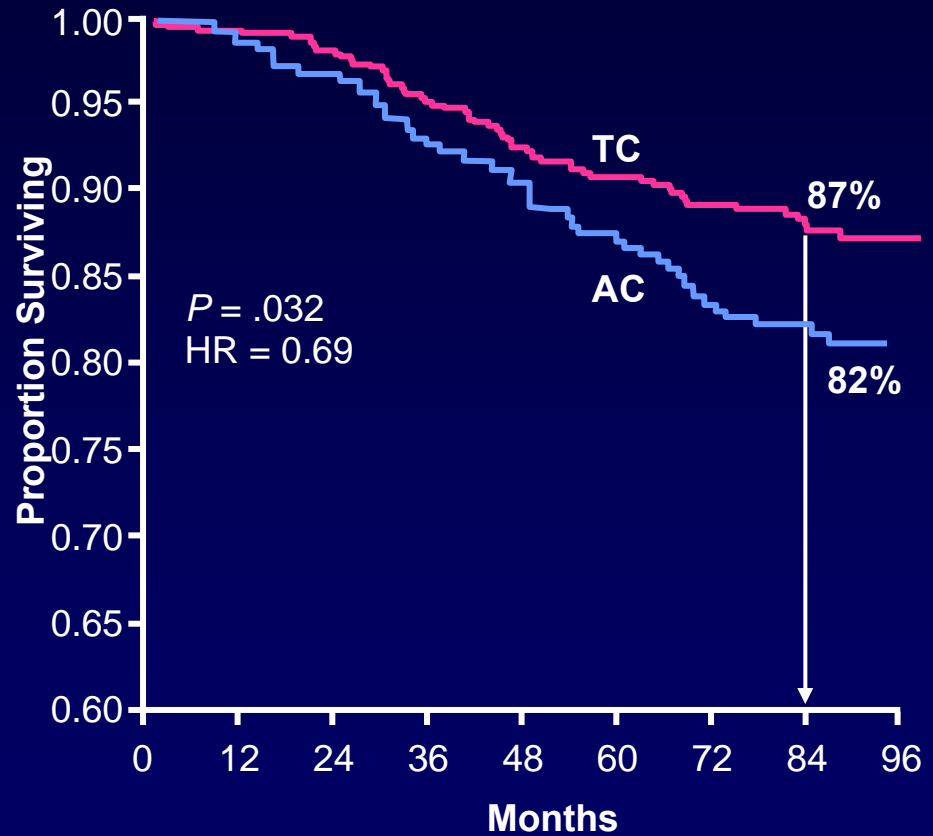
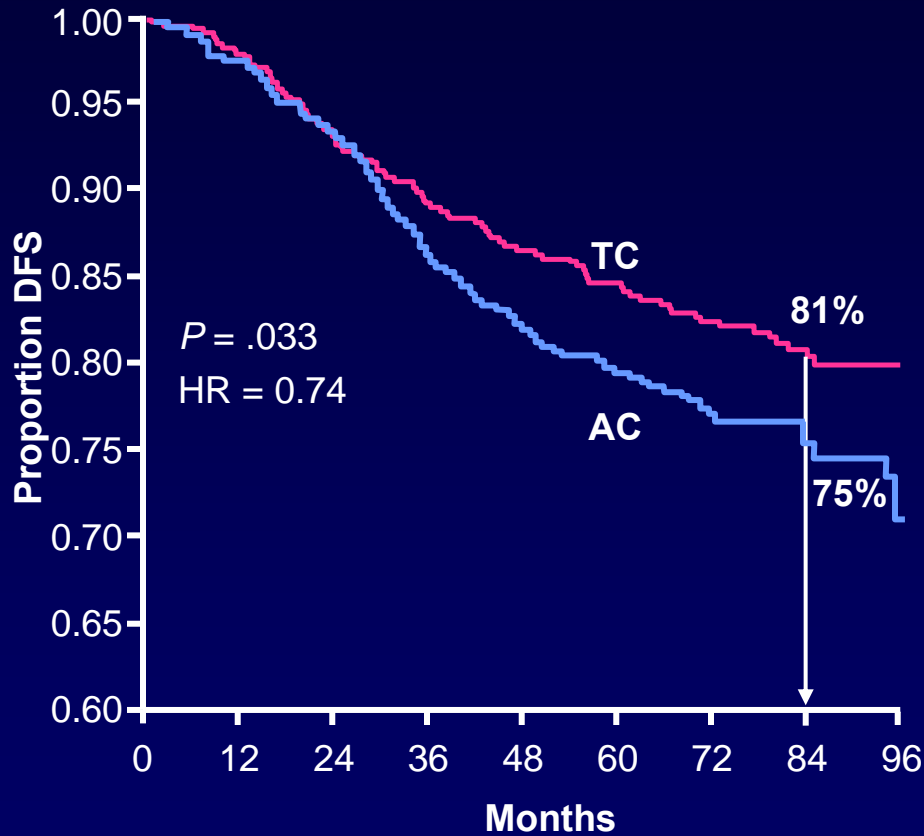
West German Study

- **4 EC → 4T vs 6 FEC100**
- **EFS: 4 EC → 4 T > 6 FEC100 ($P = .009$)**
(74 vs 84 events in 2011 patients)
- **OS: 4 EC → 4T > 6 FEC100 ($P = .04$)**
(36 vs 42 deaths in 2011 patients)

IS IT POSSIBLE TO AVOID ANTHRACYCLINES?

USON 9735: 4 AC vs 4 TC

DFS and OS by Treatment (7-year Follow-Up)



Jones SE, et al. *J Clin Oncol*. 2006;24(34):5381-5387.

Jones SE, et al. *Breast Cancer Res Treat*. 2007;106(suppl 1): Abstract 12.

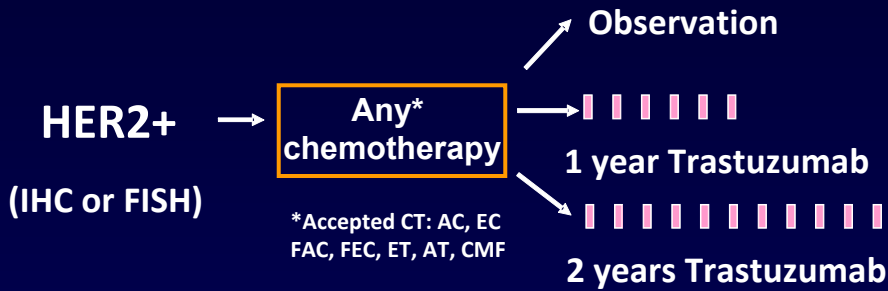
Which Chemotherapy Regimen?

- **A regimen with anthracyclines and taxanes should be preferred in high-risk patients**
- **The particular type of anthracycline/taxane should be discussed according to the benefit:risk ratio of each of agent/regimen**

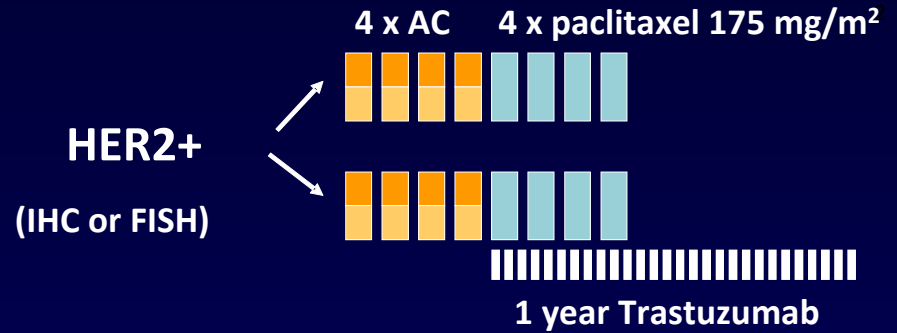
TRASTUZUMAB

Large Adjuvant Trastuzumab Trials

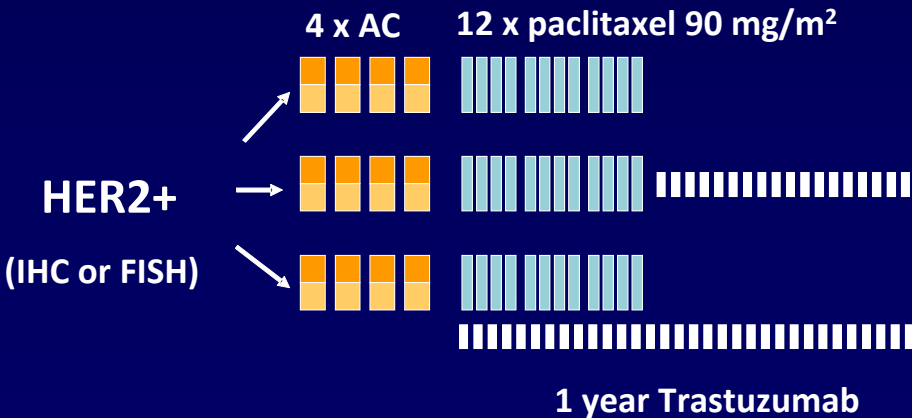
HERA



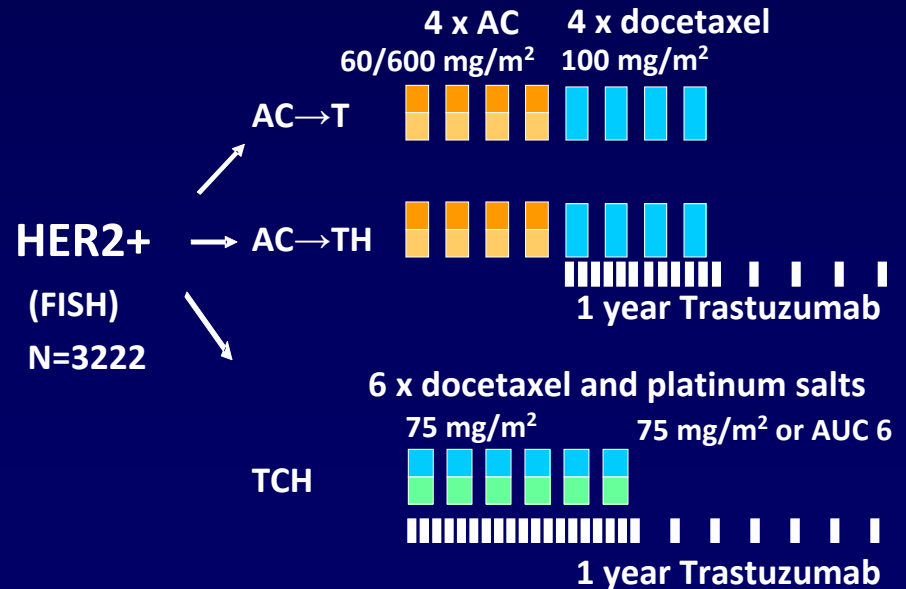
NSABP B-31



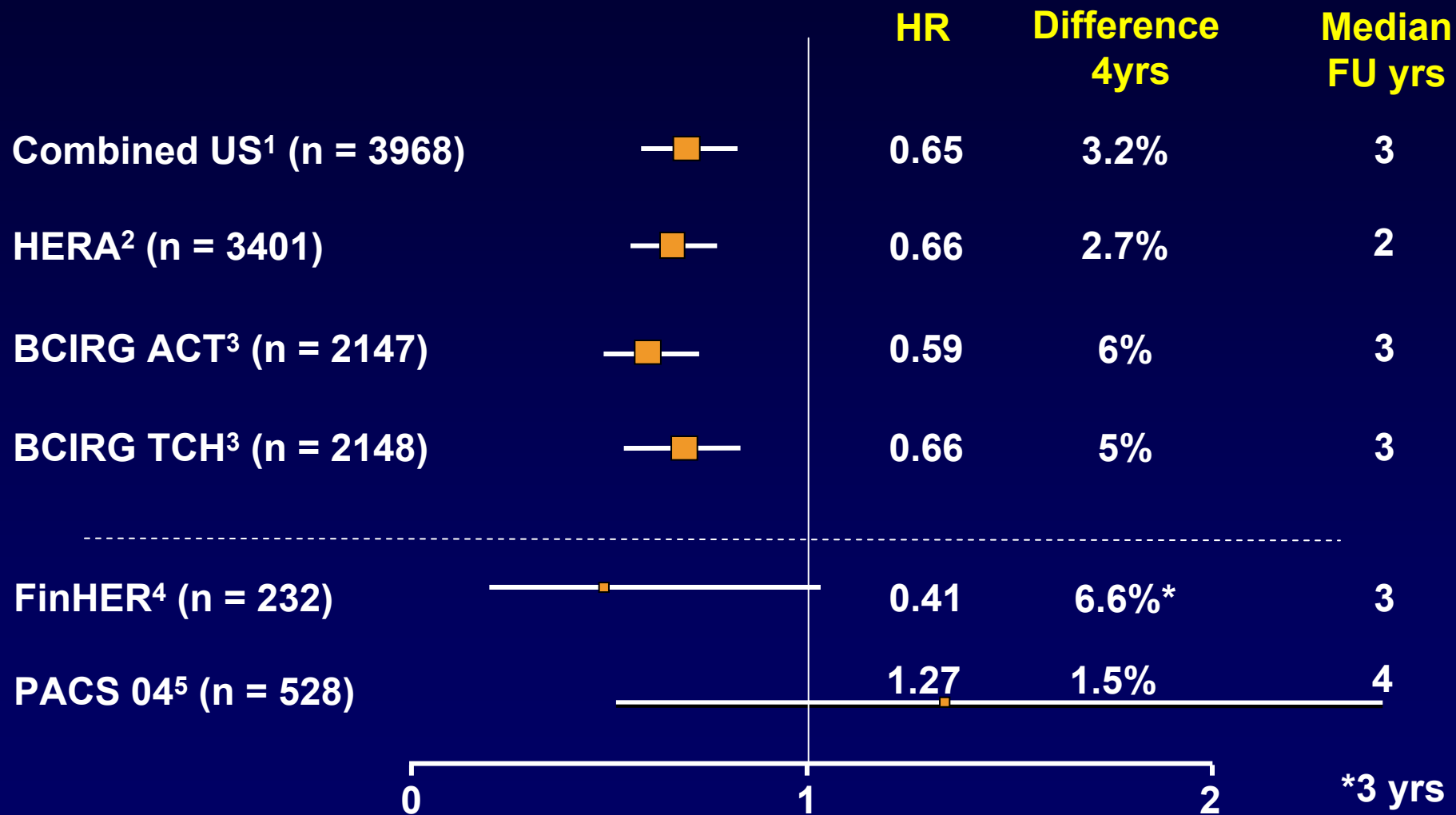
NCCTG N9831



BCIRG 006



Adjuvant Trastuzumab Trials: OS

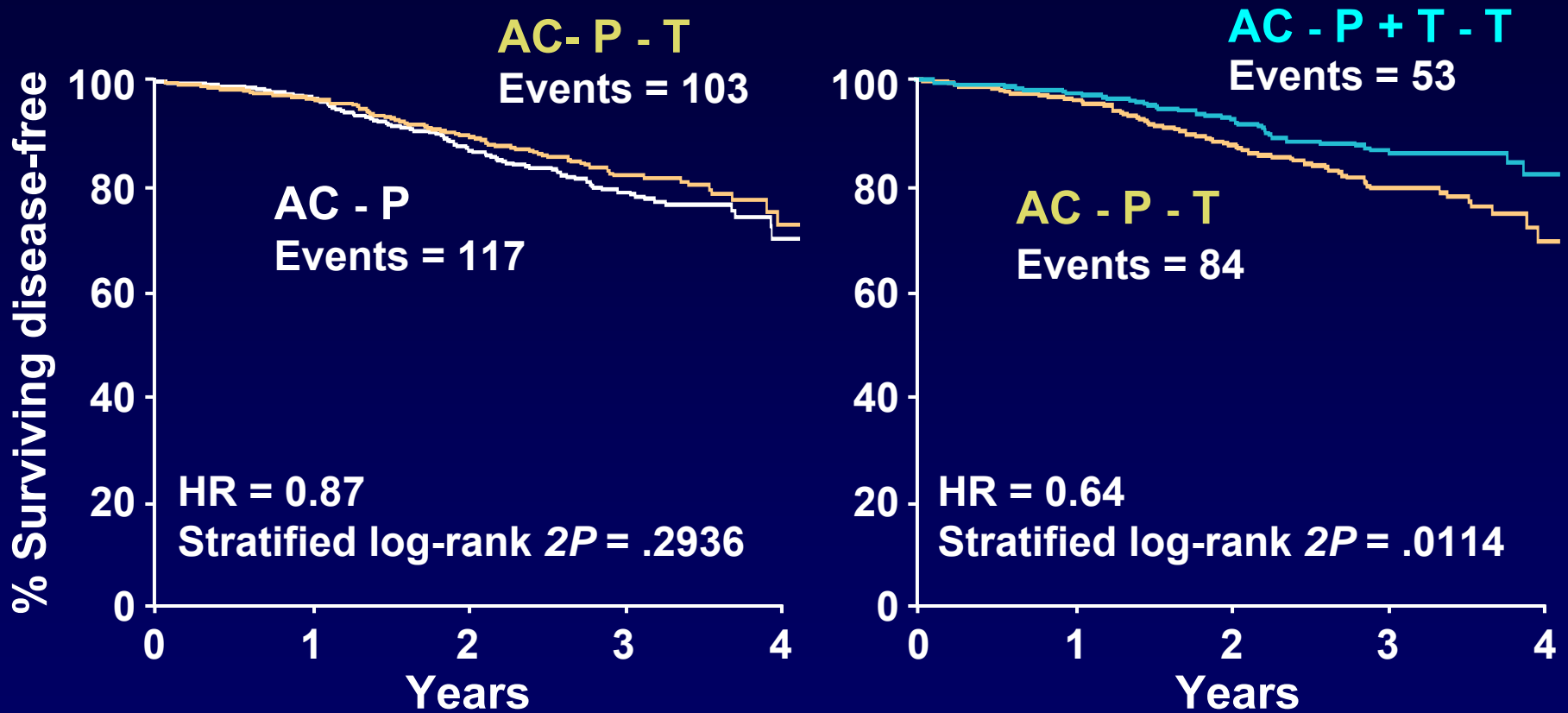


1. Perez EA, et al. *J Clin Oncol.* 2007;25(18S part I) Abstract 512. 2. Smith I, et al. *Lancet.* 2007;369(9555):29-36. 3. Slamon SD, et al. *Breast Cancer Res Treat.* 2006;100(suppl 1): Abstract 52. 4. Joensuu H, et al. *N Engl J Med.* 2006;354(8):809-20. 5. Spielmann M, et al. *Breast Cancer Res Treat.* 2007;106(suppl 1): Abstract 72.

Adjuvant Trastuzumab Trials

- Patients with N0 and tumors less than 1 cm were not eligible in most of the trials

N9831: Impact of Concurrent vs Sequential Trastuzumab on DFS



Trastuzumab

- **Trastuzumab should be given together with taxanes or after chemotherapy for one year – outside of a clinical trial**

Endocrine Therapy

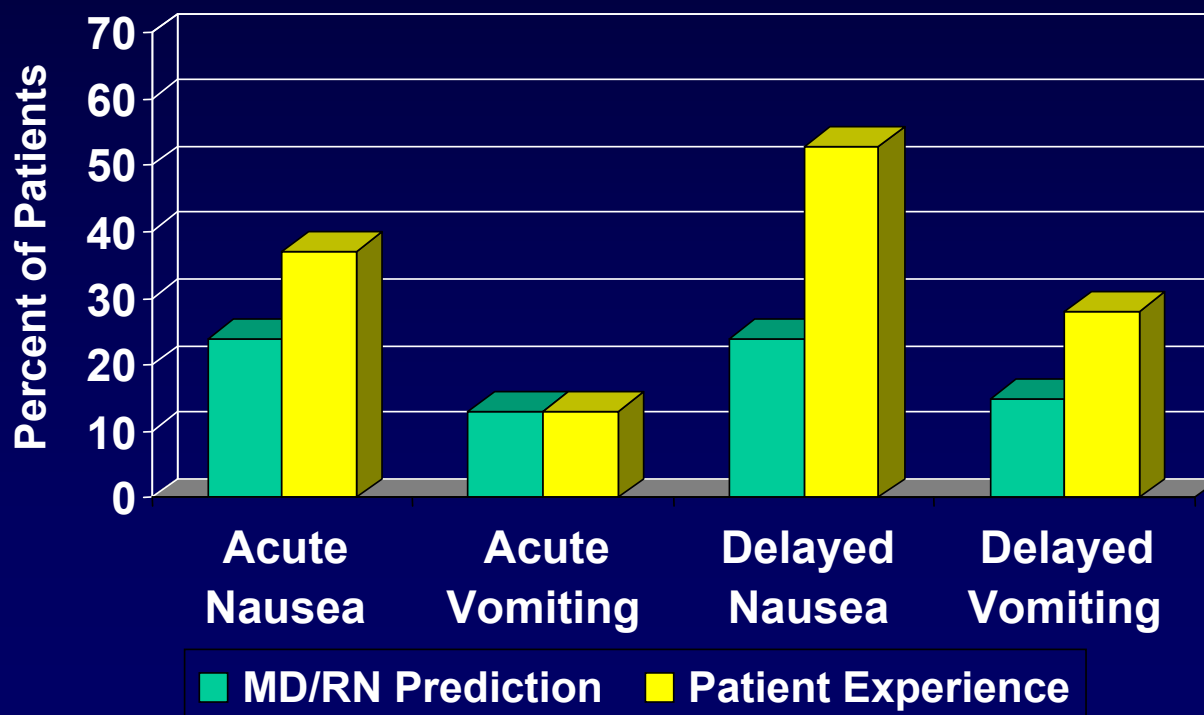
- **An aromatase inhibitor (AI) should be preferred to tamoxifen in this postmenopausal patient**
 - **Improved DFS with AI regardless of HER2 status**
(centrally assessed HER2 status in BIG 1-98¹ and TransATAC² trials)
- **Outside of a clinical trial, the treatment duration should be 5 years**

Antiemetic Regimen

- **Anti 5 HT3: ondansetron, granisetron, dolasetron, tropisetron, palonosetron**
- **Anti NK1: aprepitant, casopitant**
- **Glucocorticoids**

Perception vs Reality

Moderately Emetogenic Chemotherapy (MEC)



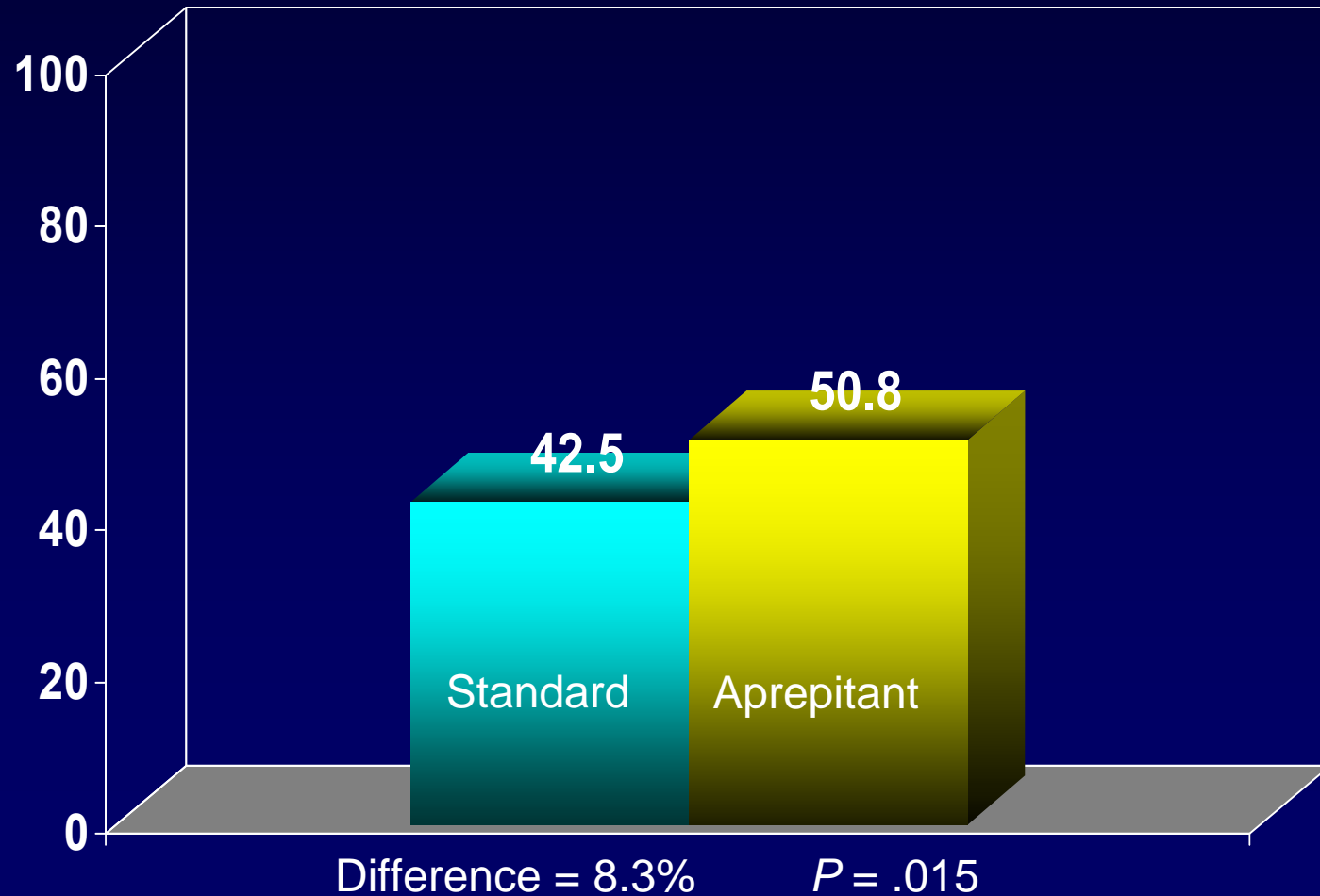
CINV is still the most feared side effect of chemotherapy

Antiemetic Regimen

Palonosetron vs Other Anti-5HT₃

- Longer duration of the half life: 40 hours vs 4-8 hours
- Higher binding affinity to the receptor
- Better control of acute and delayed emesis if used without NK1 inhibitors

Aprepitant: Complete Response 5 Days Post Chemotherapy

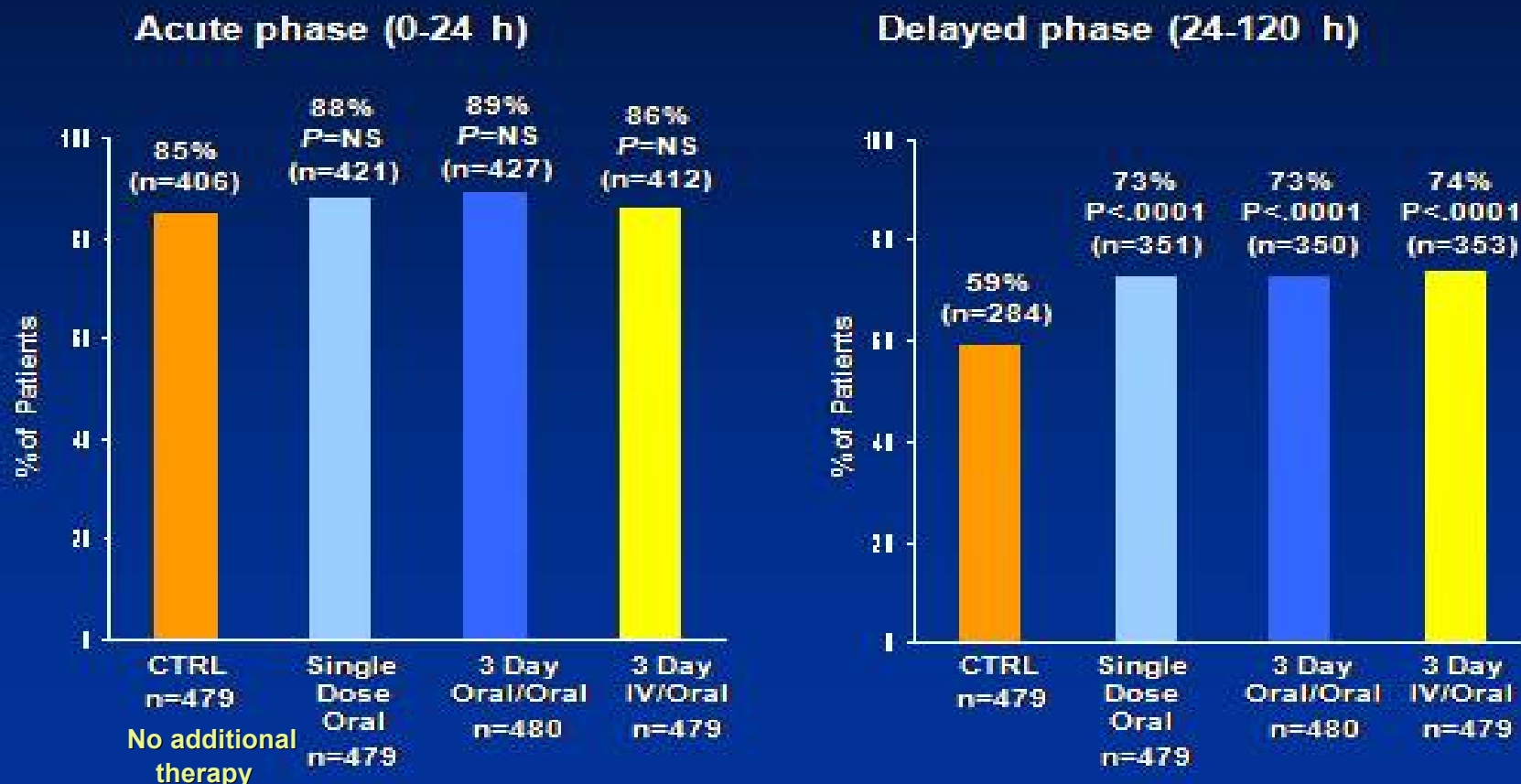


Casopitant + Anti 5HT3 and DEX

- **OND/DEX vs OND/DEX/casopitant**
- **N = 1993 patients receiving MEC**
- **Comparison of no additional therapy vs a single oral dose (150 mg po D1) or a 3-day oral or 3-day iv/oral dose (150 mg D1 or 90 mg iv D1 + 50 mg po D2-3) of casopitant**
- **Increase of the complete response rate (no emesis, no retching, no rescue) more frequent in the casopitant arms for the 4 courses**

Phase III Trial of NK1 Receptor Antagonist Casopitant: Single Oral and 3-Day Oral Dosing Regimens for CINV in Patients Receiving MEC

RESULTS: Complete Response in CYCLE 1



Antiemetic Regimen

- 5HT3 inhibitor +
- NK1 inhibitor +
- Corticosteroids