Maastricht University

azM

Berichten uit San Antonio
SABCS 2009

Birgit Vriens
Medisch oncoloog,
MUMC, Maastricht

1e Mammacongres Harderwijk
28 januari 2010

- **Adjuvante therapie**
  - **Endocriene therapie**
    - Intergroup Exemestane Trial
    - BIG 1-98
    - Team trial
  - **Chemotherapie en targeted therapie**
    - NCCTG N9831 trial
    - BCIRG 006 trial
- **Gemetastaseerde setting**
    - Denosumab
    - Avado study

IES-Trial

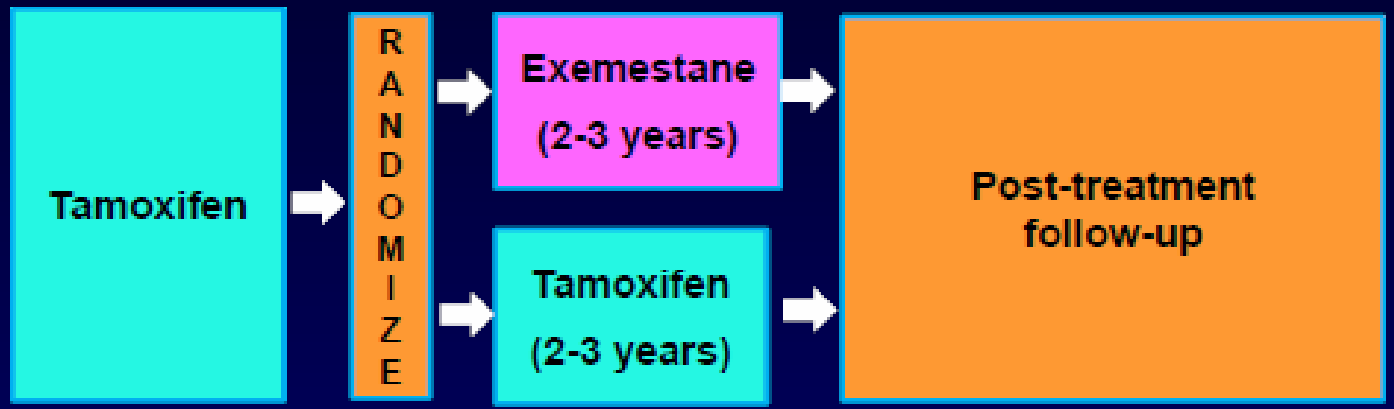
Disease related outcome with long term follow-up: an updated analysis of the intergroup exemestane study (IES)

Bliss JM et al

Design IES

Postmenopausal women with ER+/unknown primary breast cancer

Intergroup Exemestane Study: Trial Design



Total follow-up available from randomization at June 2009 analysis = 32296 women years

Coombes RC et al, *Eur J Cancer Suppl.* 2009;7(2): Abstract 5010.

Results: Efficacy

Median follow-up: 91 months

	T N=2305	T→E N=2294	HR	P-value
OS	405/2305 82.4%	352/2294 84.7 %	0.86	0.04
DFS	622/2305 73.0 %	530/2294 76.9 %	0.82	0.0009
BCFS	508/2305 78.0 %	425/2294 81.5 %	0.81	0.001

BCFS Breast Cancer Free Survival

- Tam 5y vs Tam→Exemestane
  - Persisterend voordeel Switch (DFS & OS)

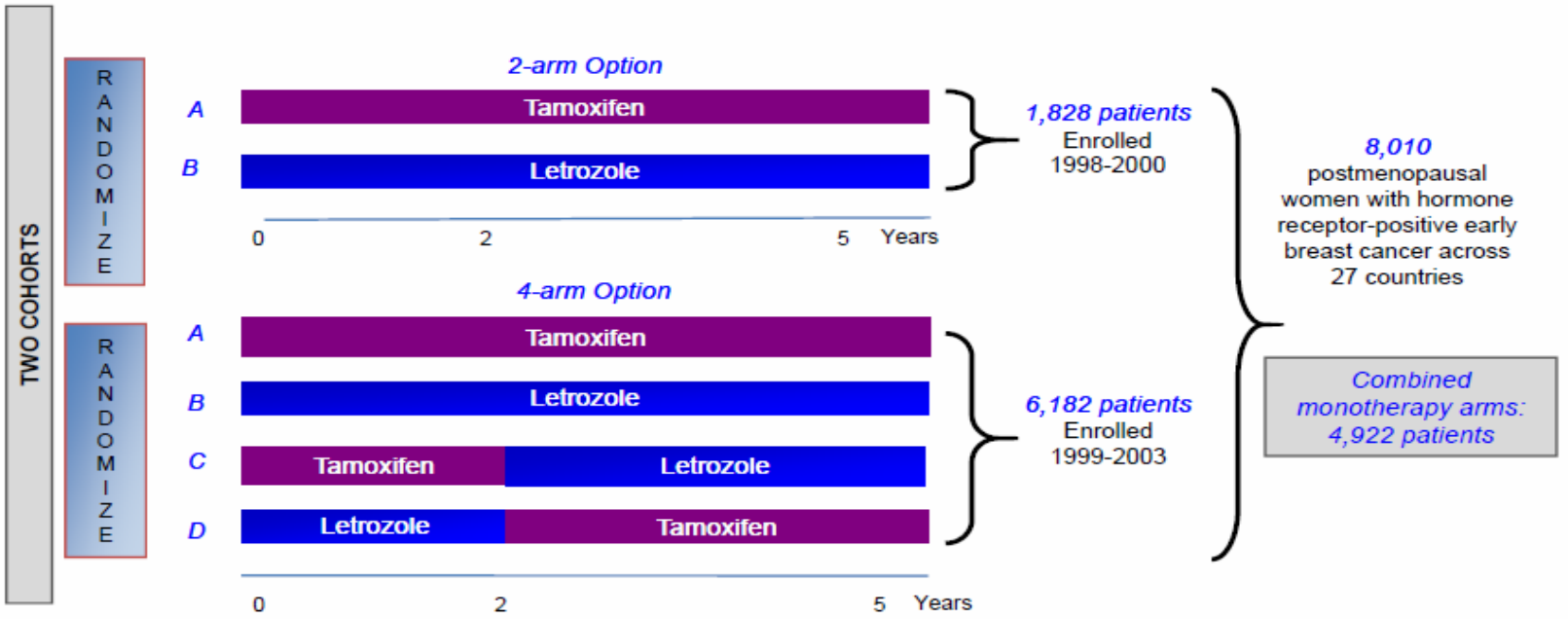
BIG 1-98

Adjusting for selective crossover in analyses of Letrozole versus Tamoxifen in the BIG 1-98 trial

Regan MM et al

BIG 1-98 design

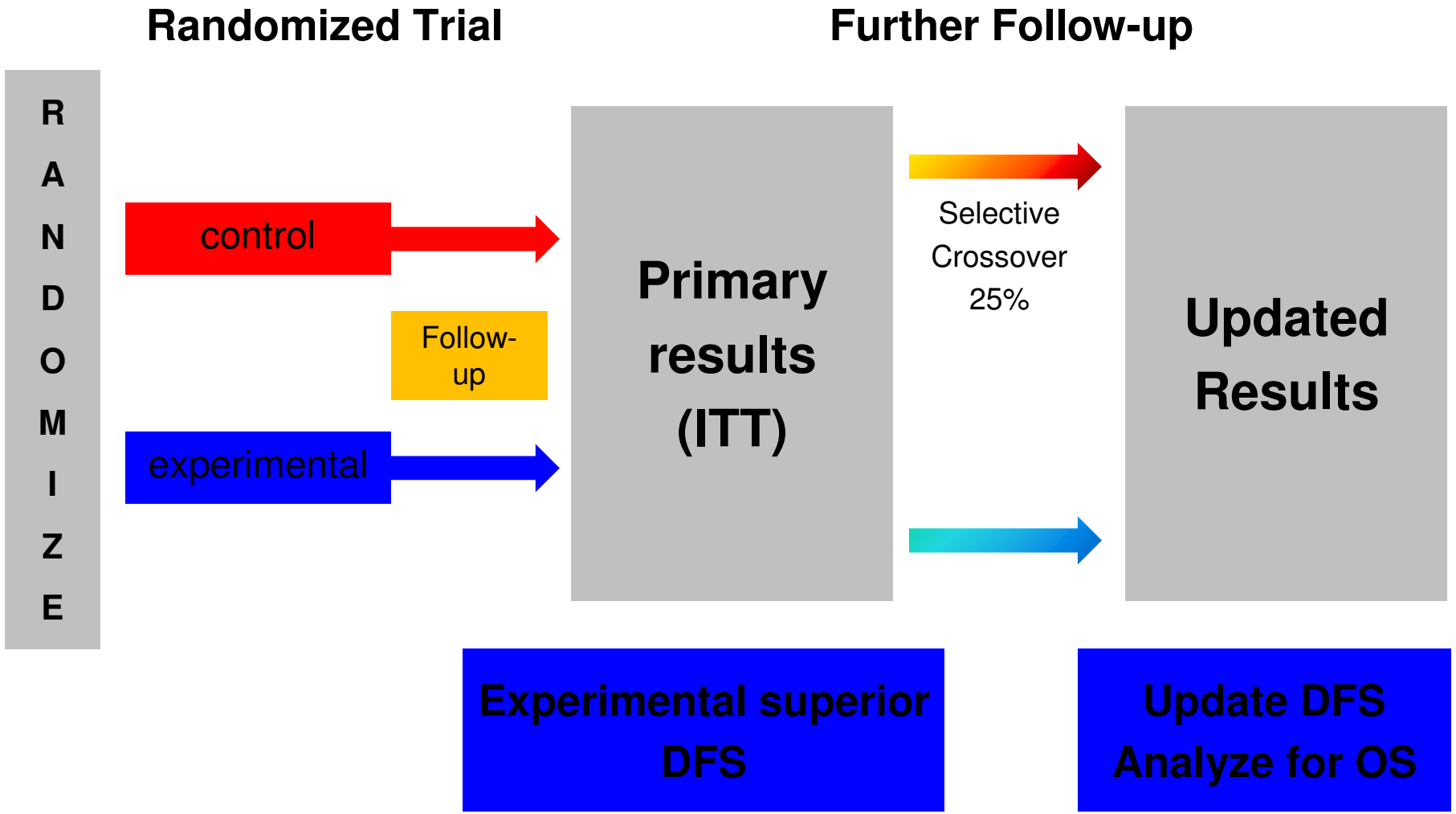
H. Mouridsen



Previous analysis showed superiority of 5y letrozole vs 5y tamoxifen in terms of

- Disease free survival
- Time to distant recurrence

Big 1-98


Randomized Trial
Further Follow-up
RANDOMIZE
control
experimental
Follow-up
Primary results (ITT)
Selective Crossover 25%
Updated Results
Experimental superior DFS
Update DFS Analyze for OS

Monotherapy tamoxifen vs letrozole
Median Follow up 76 mths

ITT (SABCS 2008)	P-value	HR (95% CI)	
DFS	P=0.03	0.88 (0.78 – 0.99)	Favours letrozole
OS	P=0.08	0.87 (0.75 – 1.02)	
Time to dist recurrence	P=0.05	0.85 (0.72 – 1.00)	Favours letrozole

Censored analysis	HR (95% CI)	
DFS	0.84 (0.74 – 0.95)	Favours letrozole
OS	0.81 (0.69 – 0.94)	Favours letrozole
Time to dist recurrence	0.81 (0.68 – 0.96)	Favours letrozole

IPCW (Inverse probability of weighted analysis)	HR (95% CI)	
DFS	0.85 (0.76 – 0.96)	Favours letrozole
OS	0.83 (0.71 – 0.97)	Favours letrozole
Time to dist recurrence	0.81 (0.69 – 0.96)	Favours letrozole

Conclusie BIG 1-98

- Selectieve cross over beinvloedt de ITT resultaten van de BIG 1-98 monotherapie vergelijking

- Na aanpassing voor selective cross over middels IPCW analyse: 5 jr AI beter dan 5 jaar Tamoxifen
  - Significante verbetering DFS
  - Significante verbetering OS

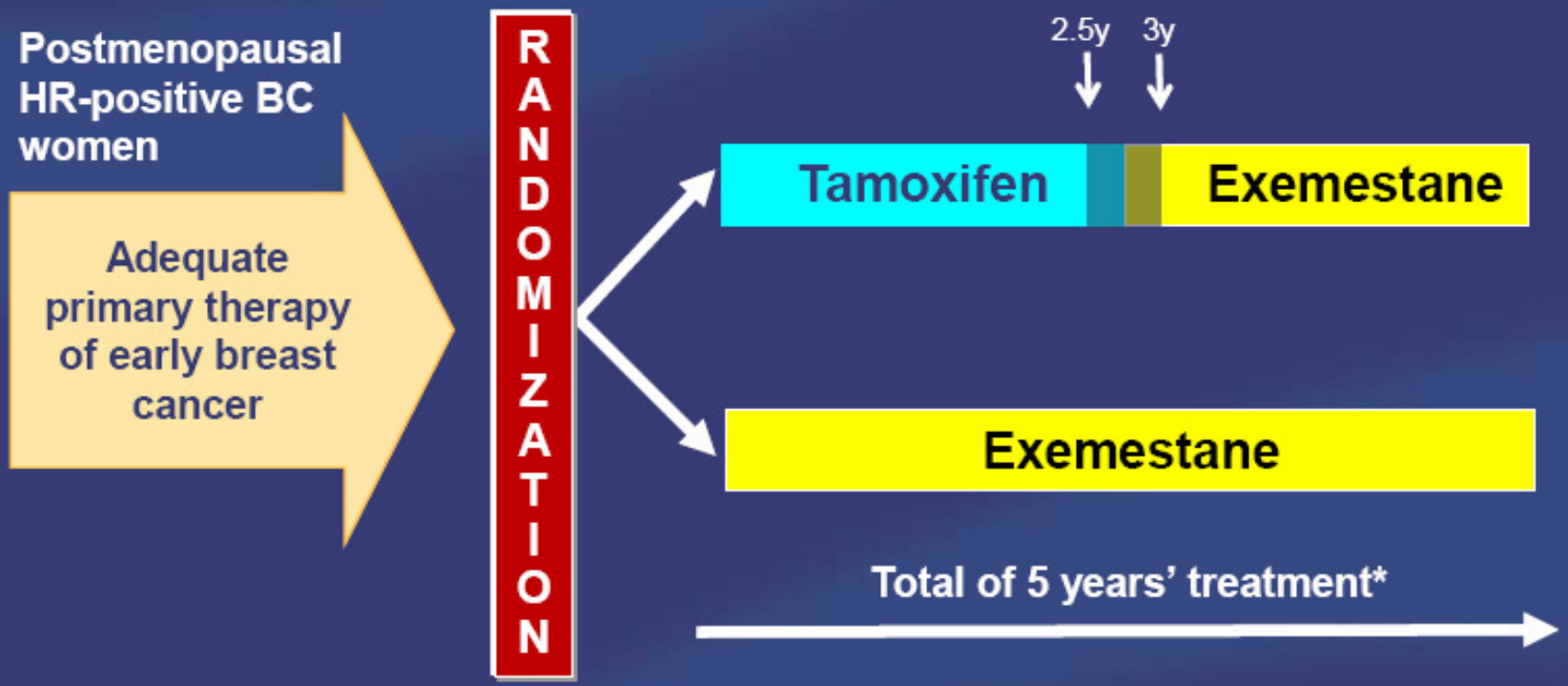
Team trial

Five Years of Exemestane as Initial Therapy Compared to Tamoxifen Followed by Exemestane for Five years: The TEAM Trial, a Prospective, Randomized, Phase III Trial in postmenopausal women with Hormone-Sensitive early Breast Cancer

D. Rea[1], A. Hasenburg[2], C. Seynaeve[3], S.E. Jones[4] J.M. Vannetzel[5], R. Paridaens[6], C. Markopoulos[7], Y. Hozumi[8], H. Putter[9], E. Hille[9], L. Asmar [4], R. Urbanski[10], C.J.H. van de Velde[9] , J.M.S. Bartlett[11], J. Smeets[10], D. Kieback[12]

[1]The University of Birmingham, Birmingham, United Kingdom; [2]University Hospital Freiburg, Freiburg, Germany, [3]Erasmus MC Daniel Den Hoed, Rotterdam, the Netherlands [4]US Oncology Research, Houston, TX, USA, [5]Institut du Sein Henri Hartmann (ISHH), Neuilly sur Seine, France; [6]U. Z. Gasthuisberg, Leuven, Belgium; [7]Athens University Medical School, Greece; [8]Jichi Medical University, Shimotsuke, Japan; [9]Leiden University Medical Center, Leiden, The Netherlands; [10]Pfizer, New York, USA,[11]Endocrine Cancer Group, Edinburgh University, Scotland [12]Diakonie-Krankenhaus Bremen, Germany;

Design Team trial



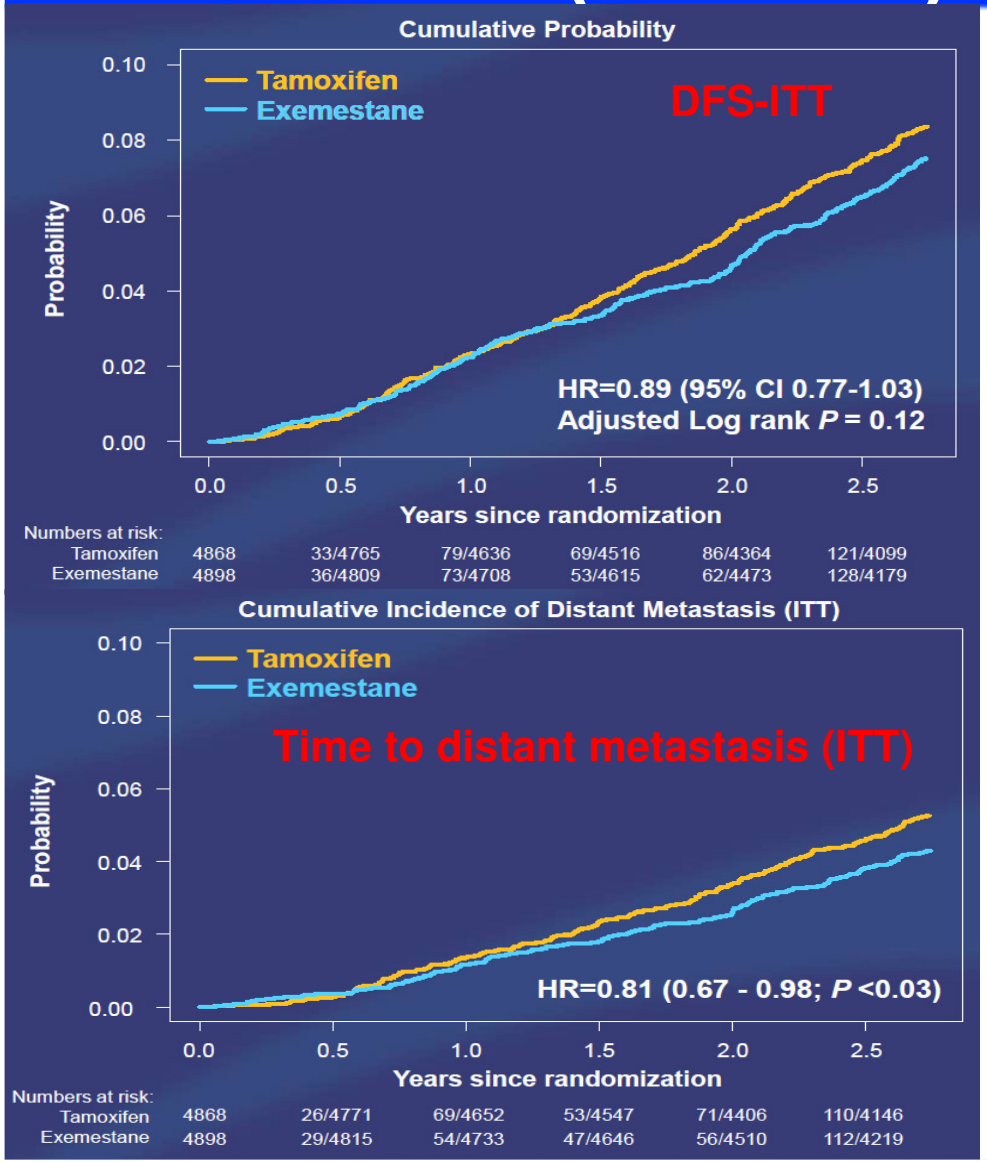
N = 9779 accrued

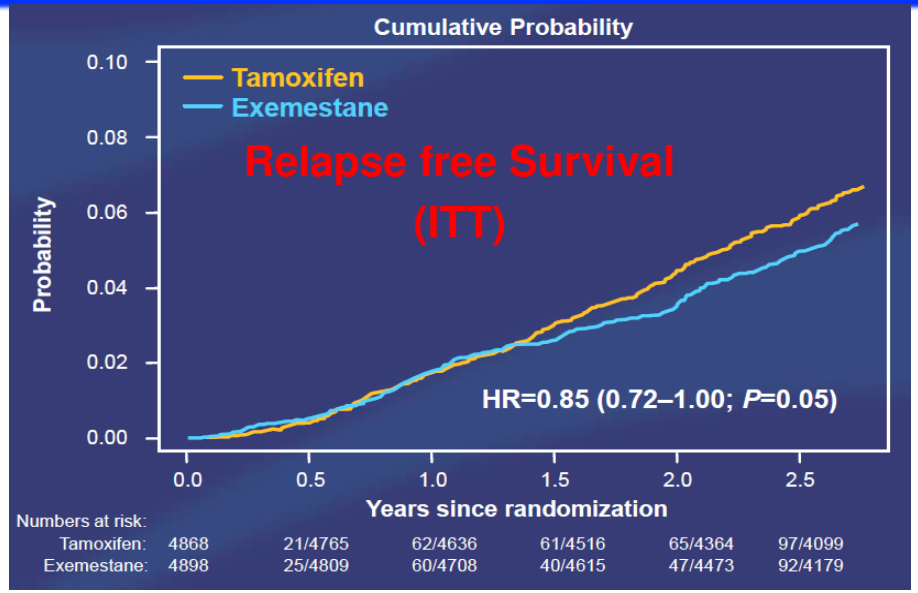
Co-primary endpoints

DFS at 2.75 years
DFS at 5 years

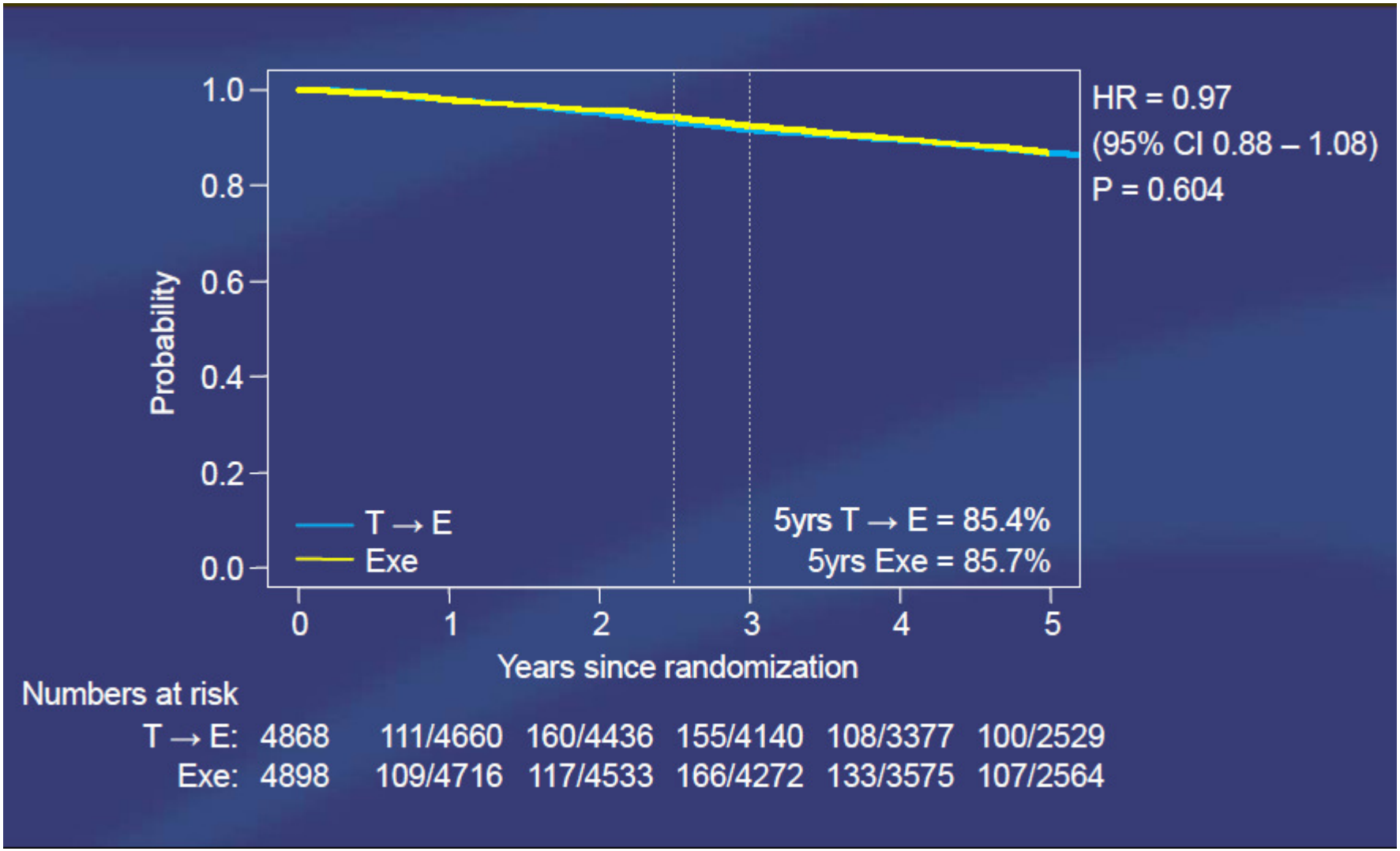
* Therapy provided on open label basis

Exemestane vs Tamoxifen (FU=2.75)

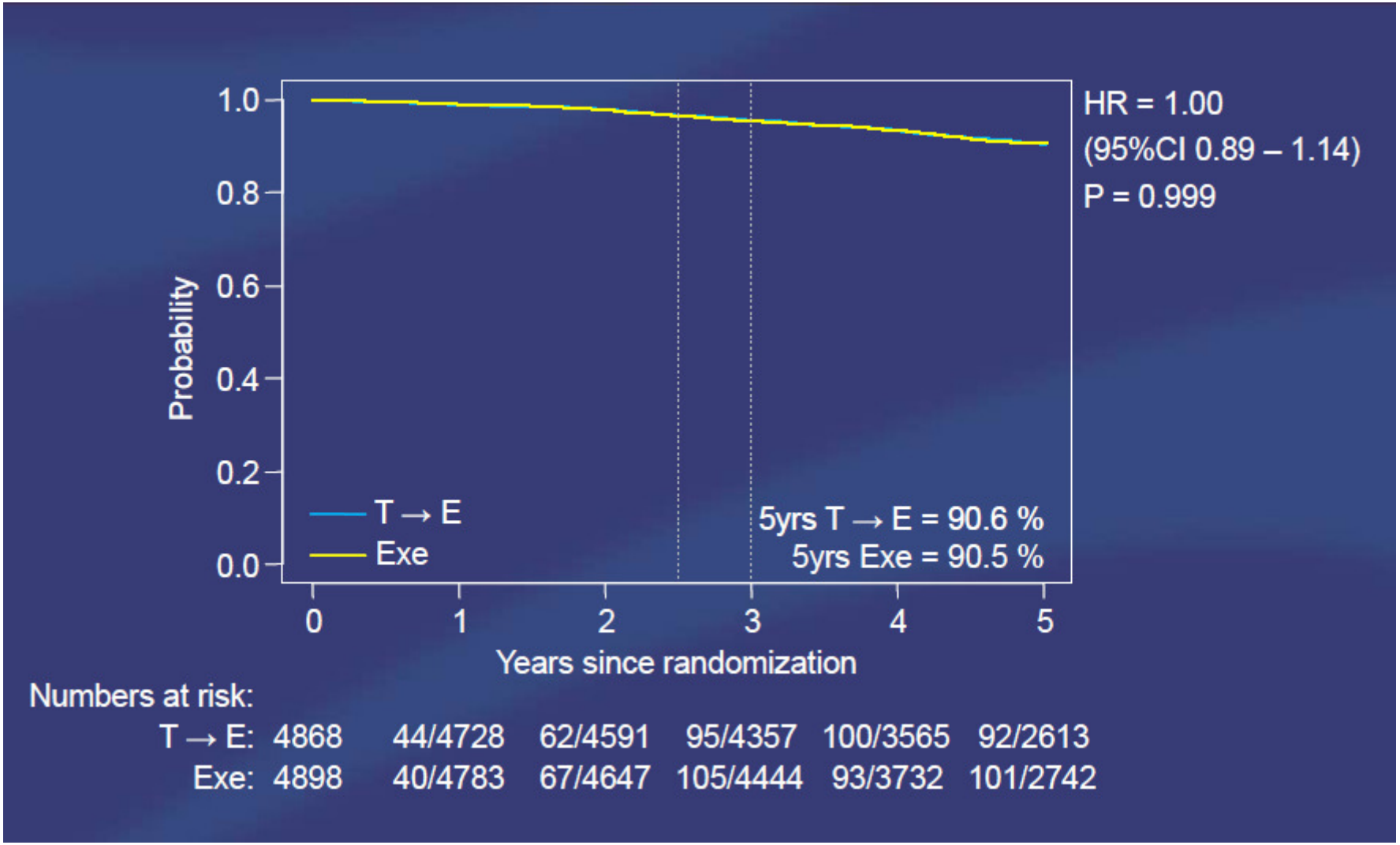




Results: DFS


1.0
0.8
0.6
0.4
0.2
0.0
Probability
T → E
Exe
5yrs T → E = 85.4%
5yrs Exe = 85.7%
HR = 0.97
(95% CI 0.88 – 1.08)
P = 0.604
0
1
2
3
4
5
Years since randomization
Numbers at risk
T → E: 4868 111/4660 160/4436 155/4140 108/3377 100/2529
Exe: 4898 109/4716 117/4533 166/4272 133/3575 107/2564

Results: OS


1.0
0.8
0.6
0.4
0.2
0.0
Probability
T → E
Exe
5yrs T → E = 90.6 %
5yrs Exe = 90.5 %
HR = 1.00
(95%CI 0.89 – 1.14)
P = 0.999
0
1
2
3
4
5
Years since randomization
Numbers at risk:
T → E: 4868 44/4728 62/4591 95/4357 100/3565 92/2613
Exe: 4898 40/4783 67/4647 105/4444 93/3732 101/2742

Discussie TEAM

- Geen verschil effectiviteit 5y upfront behandeling exemestaan vs Tam→ exemestaan
  - DFS (ITT), Time to recurrence (ITT),OS (ITT)
  - Bij postmenopausale patiënten, hormoongevoelig, beiden goede behandeling
- Veiligheid consistent met bekende bijwerkingen van exemestaan en tamoxifen
- Translationeel onderzoek naar welke behandelarm voor welke patiënt het meest geschikt is

NCCTG N9831

N9831

Results of Chemotherapy Alone, with Sequential or Concurrent Addition of 52 Weeks of Trastuzumab in the NCCTG N9831 HER2-Positive Adjuvant Breast Cancer Trial

Perez EA[1], Suman VJ[2] Davidson NE[3], Gralow J[4], Kaufman PA[5], Ingle JN[2], Dakhil SR[6], Zujewski JA[7], Pisansky TM[2], Jenkins RB[2]

[1]Mayo Clinic, Jacksonville, FL; [2]Mayo Clinic, Rochester, MN; [3]University of Pittsburgh, Pittsburgh, PA; [4]Seattle Cancer Center Alliance, Seattle, WA ; [5]Dartmouth Hitchcock Medical Center, Lebanon, NH; [6]Cancer Center of Kansas, Wichita, KS; [7]National Cancer Institute, Bethesda, MD

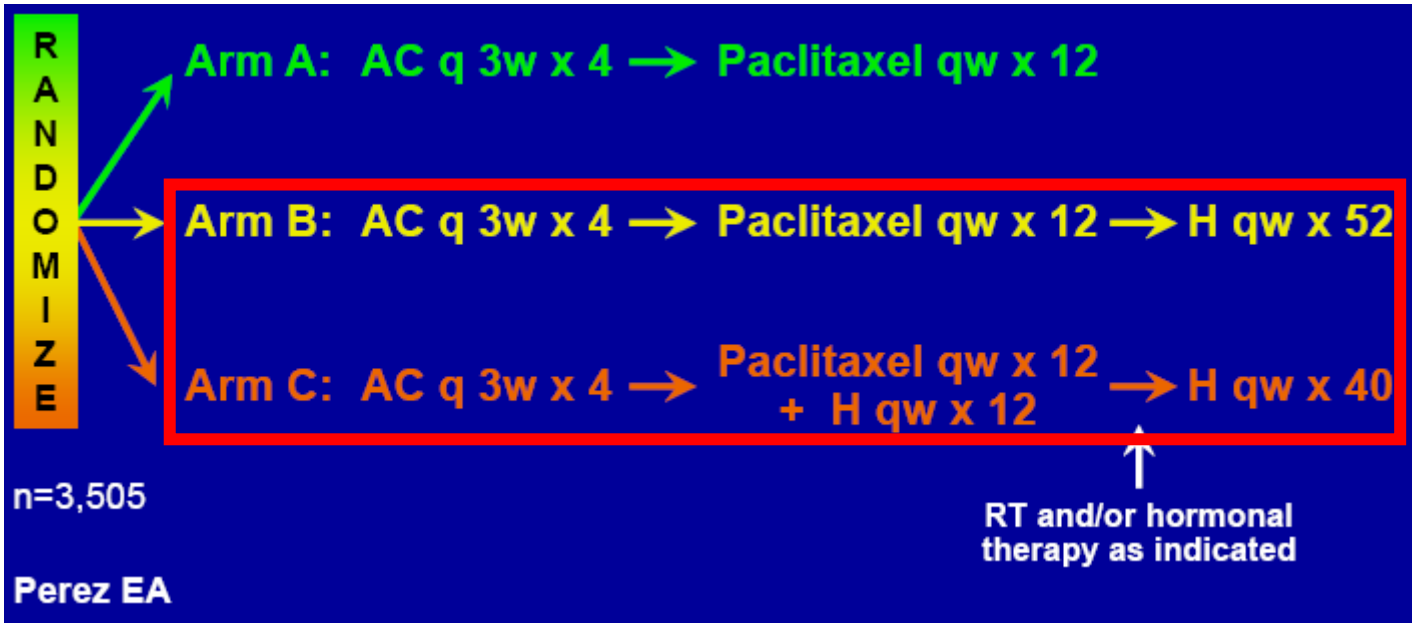
MAYO CLINIC

NCCTG, ECOG, CALGB, SWOG

SABCS 2009

3025495-2

Design N9831

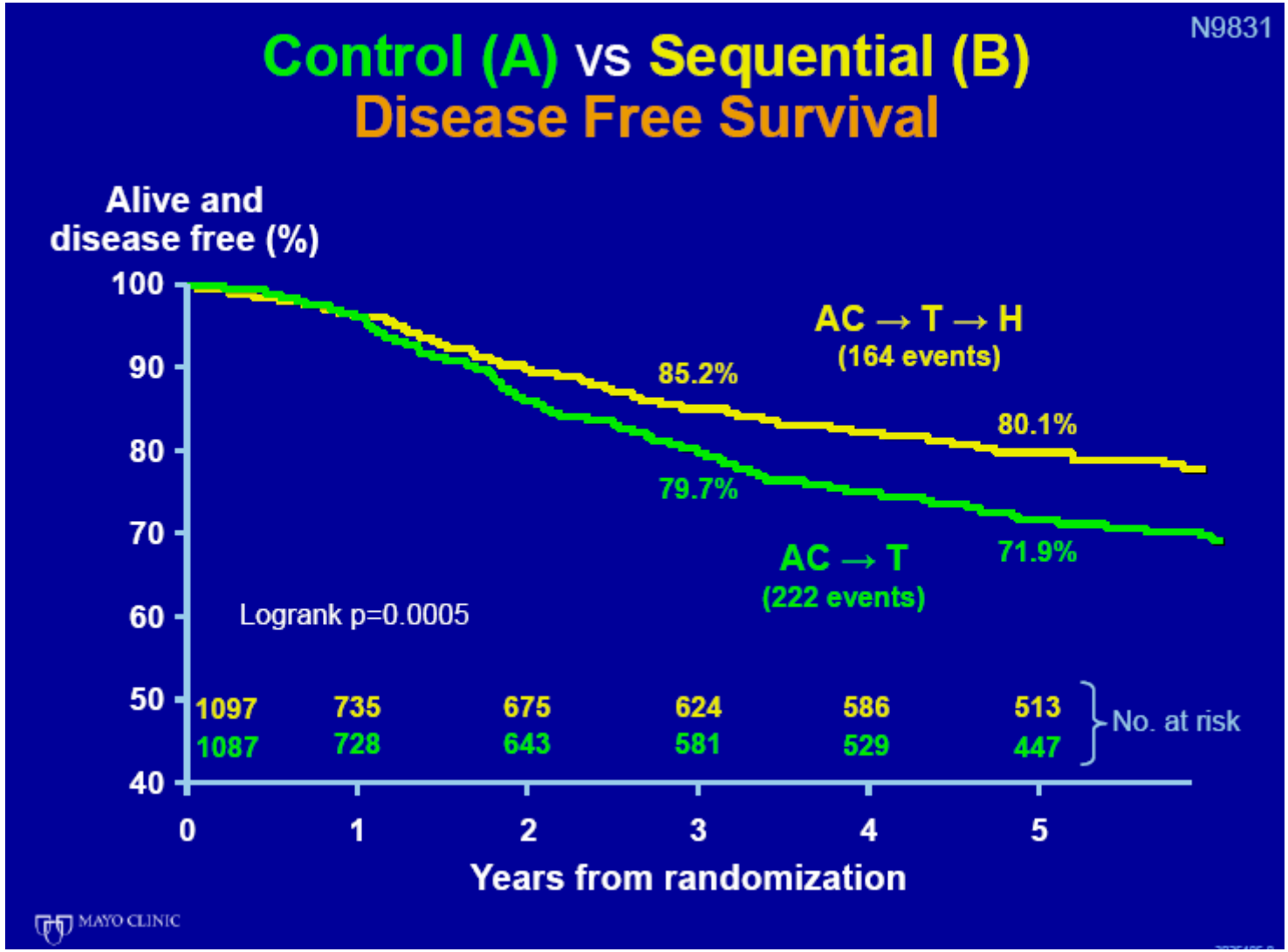


H=trastuzumab (4 mg/kg loading dose, followed by 2 mg/kg); A=doxorubicin dose 60 mg/m^2; C=cyclophosphamide, 600 mg/m^2; paclitaxel, 80 mg/m^2; q 3w=every 3 weeks; qw=weekly

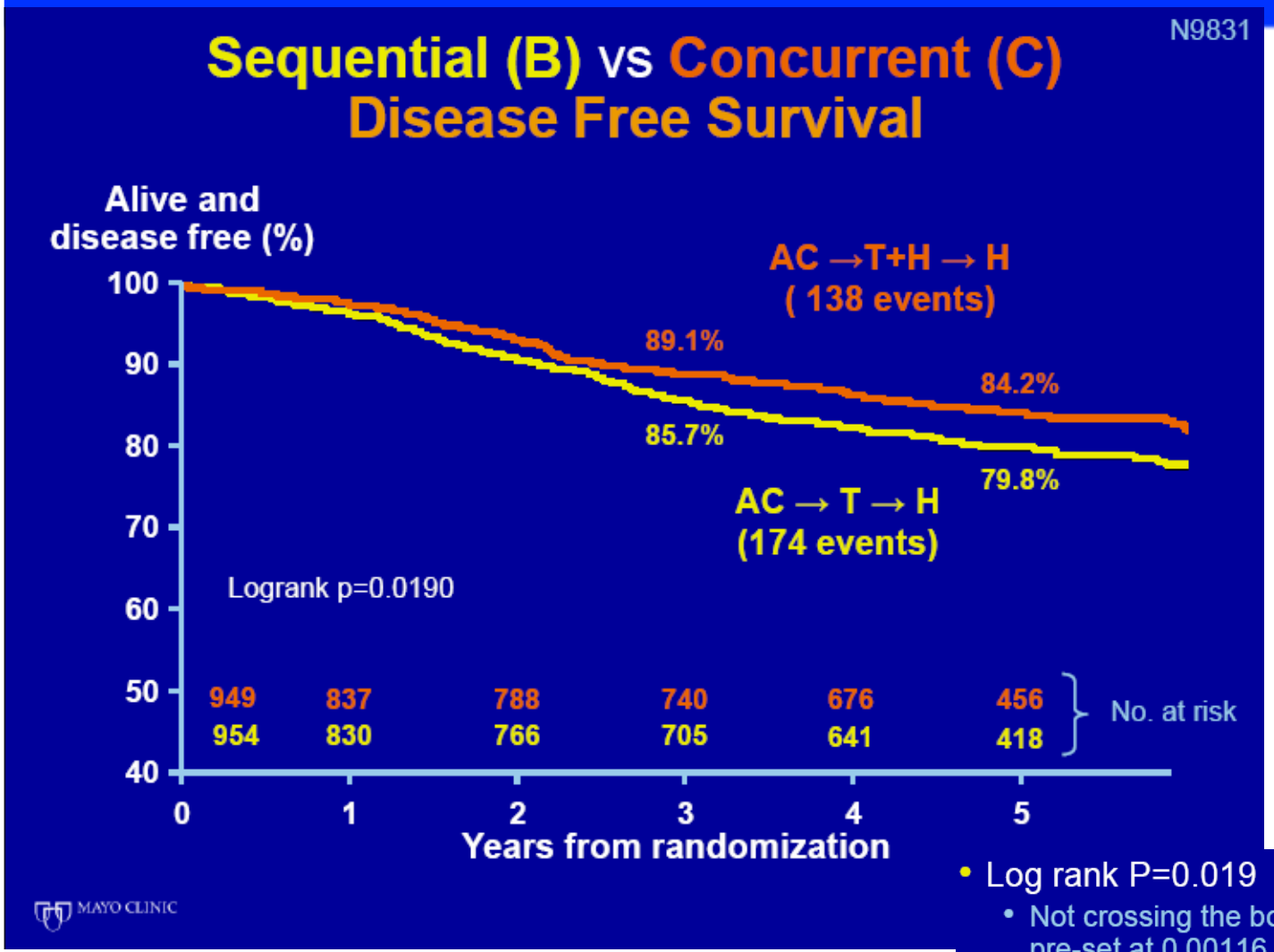
2009

- IDMC data release based on 2nd Interim Analysis of **A** vs **B**
- Events for 1st Interim Analysis of **B** vs **C** reached afterwards

DFS +/- trastuzumab



DFS seq/concurrent trastuzumab



- Log rank P=0.019
  - Not crossing the boundary for statistical significance, pre-set at 0.00116
- Estimated hazard ratio: 0.77
  - 95% CI: 0.61- 0.96

Discussie N9831

- **Significante verbetering DFS na toevoegen trastuzumab aan AC→ T na 5 jaar follow up**
- **33% risico reductie trastuzumab sequentieel aan AC→T**
  - **5y DFS 72 vs 80%**
- **Trend risico reductie door trastuzumab concurrent vs sequentieel**
  - **5yr DFS 80 vs 84%**

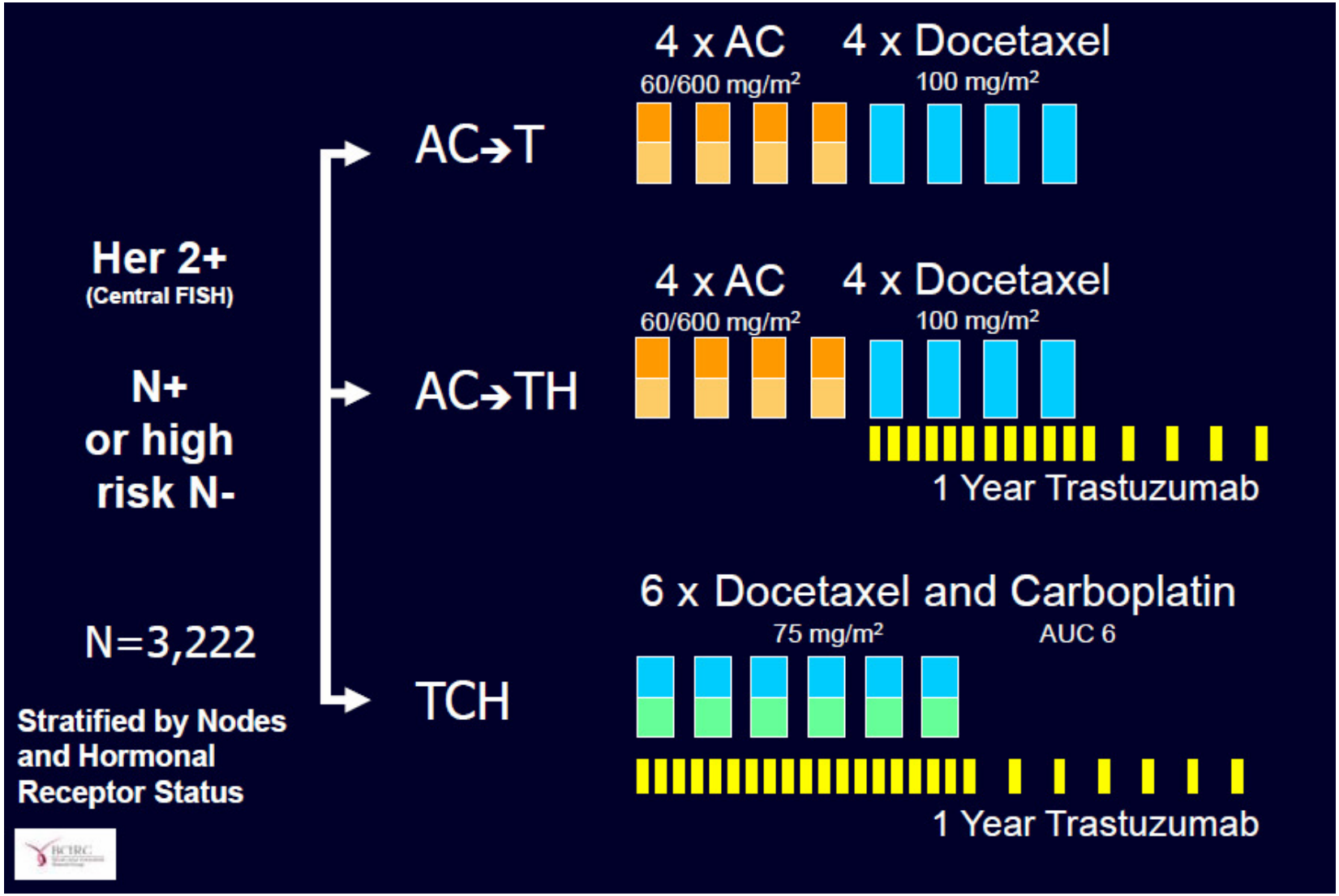
BCIRG 006
Phase III Trial Comparing AC→T with AC→TH and with TCH in the Adjuvant Treatment of HER2-Amplified Early Breast Cancer Patients:

Third Planned Efficacy Analysis

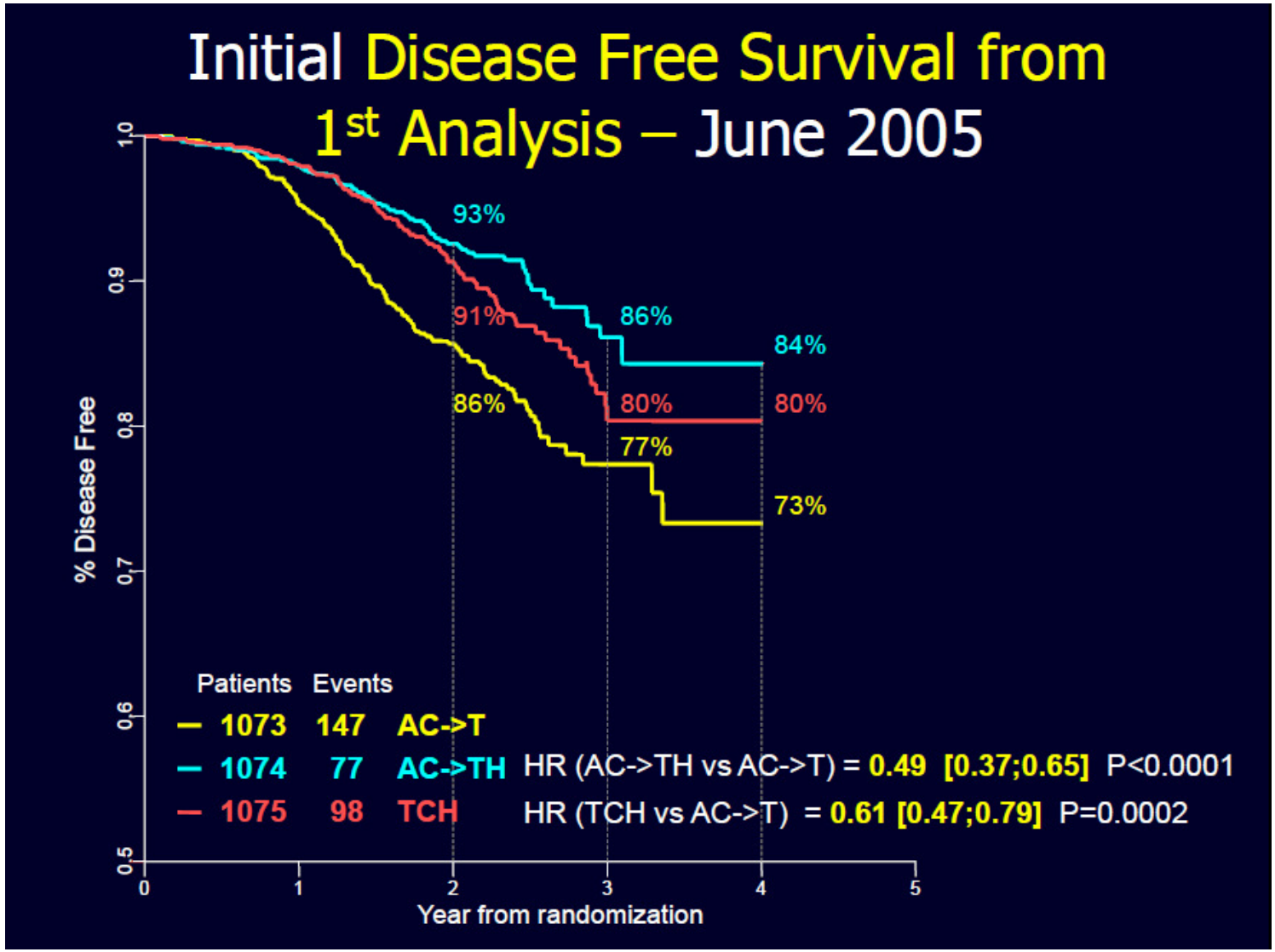
Slamon D, Eiermann W, Robert N, Pienkowski T, Martin M, Rolski J, Chan A, Mackey J, Liu M, , Pinter T, Valero V, Falkson C, Fornander T, Shiftan T, Olsen S, Buyse M, Kiskartalyi T, Landreau V, Wilson V, Press M, Crown J, on behalf of the BCIRG 006 Investigators.

Study sponsored by sanofi-aventis
Support from Genentech

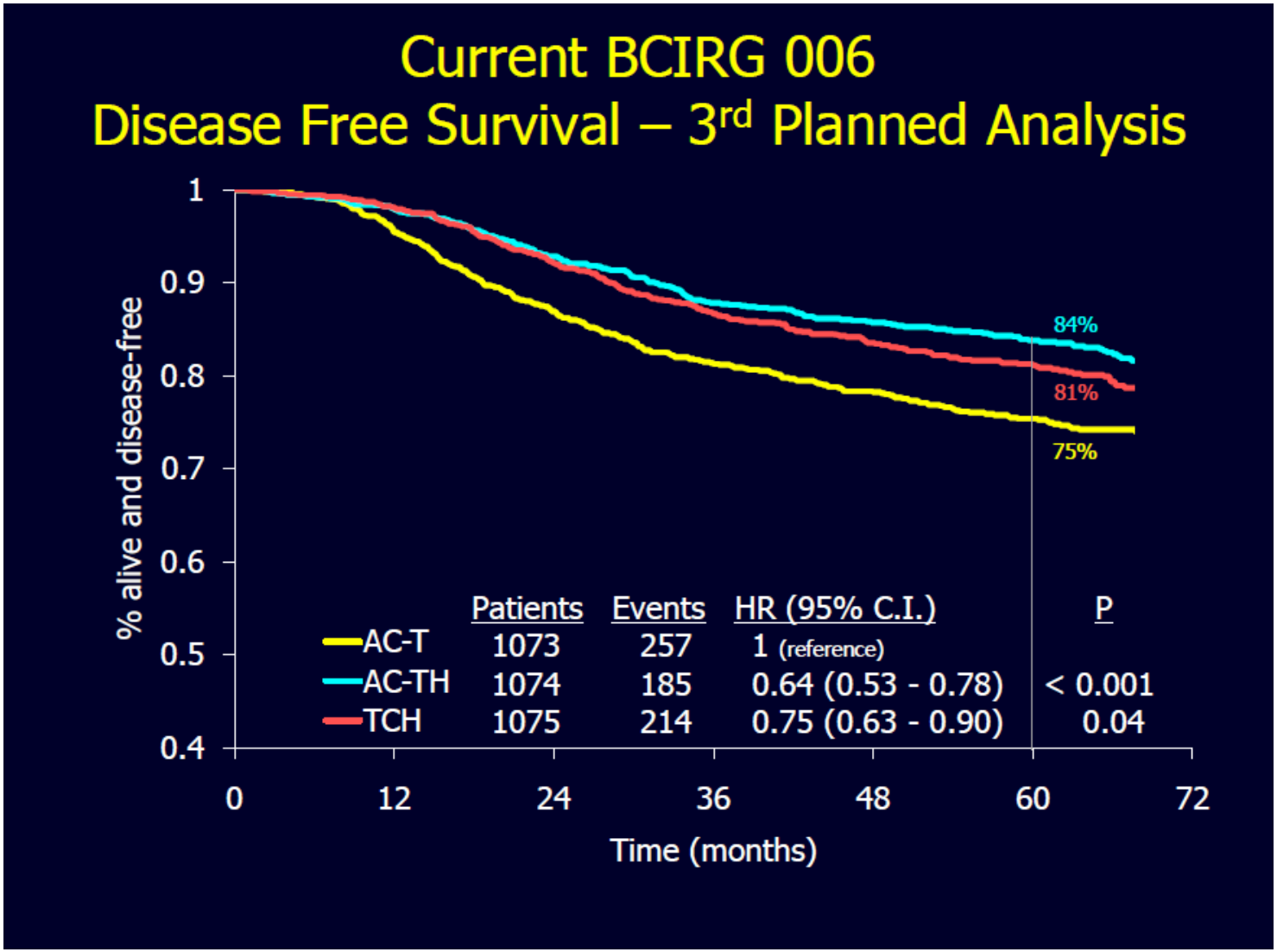
Design BCIRG 006



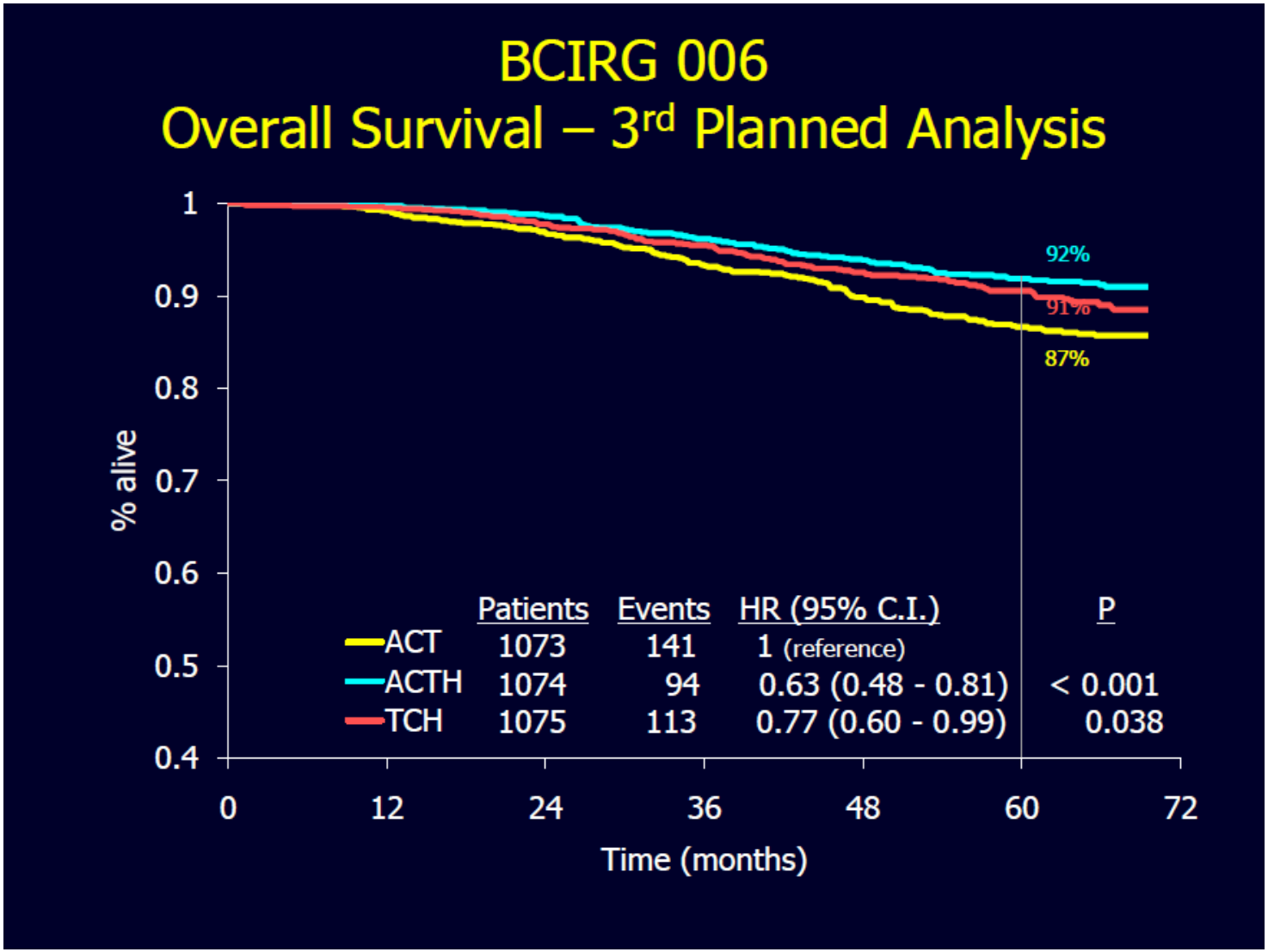
DFS after 36 mths



DFS after 65 mths



OS after 65 mths



Discussie BCIRG 006

- **Toevoegen van trastuzumab significant voordeel OS & DFS aan antracycline wel/niet bevattende therapie**
  - Voordeel bij hoog en laagrisico patiënten
- **Toxiciteit TCH vs ACTH lager**
- **Geen statistisch voordeel ACTH boven TCH in DFS**
  - 29 minder DFS events in ACTH groep
  - 21 vs 4 hartfalen events en 8* leukemie in ACTH groep
- **Topo IIa amplificatie, bij 25-35% van Her+ tumoren (+/- 8% van totaal aantal tumoren)**
  - Topo IIa amplificatie is een voorspeller voor effectiviteit van anthracyclines
  - Gezien de lange termijn toxiciteit is bij 92% van alle ptn met borstkanker – dus: zonder Topo IIa amplificatie – mogelijk in de toekomst een ander beleid dan anthracyclines aangewezen

Denosumab

A Comparison of Denosumab Versus Zoledronic Acid for the Prevention of Skeletal Related Events in Breast Cancer Patients With Bone Metastases

Alison Stopeck[1], Richard de Boer,[2]
Yasuhiro Fujiwara[3], Mikhail Lichinitser[4],
Katia Tonkin[5], Denise Yardley[6], Michelle Fan[7],
Qi Jiang[7], Susie Jun[7], Roger Dansey,[7] Ada Braun[7]

[1]University of Arizona, Arizona Cancer Center, Tucson, AZ, USA
[2]Western and Royal Melbourne Hospitals, Victoria, Australia
[3]National Cancer Center Hospital, Tokyo, Japan
[4]Blokhin Cancer Research Center, Moscow, Russia
[5]Cross Cancer Institute, Edmonton, AB, Canada
[6]Sarah Cannon Research Institute, Nashville, TN, USA
[7]Amgen Inc, Thousand Oaks, CA, USA

Study design

Study Design: International, Randomized, Double-Blind, Active-Controlled Study

Key Inclusion

- Adults with advanced breast cancer and confirmed bone metastases

Key Exclusion

- Current or prior intravenous bisphosphonate administration

Denosumab 120 mg SC and
Placebo IV* every 4 weeks (N = 1026)

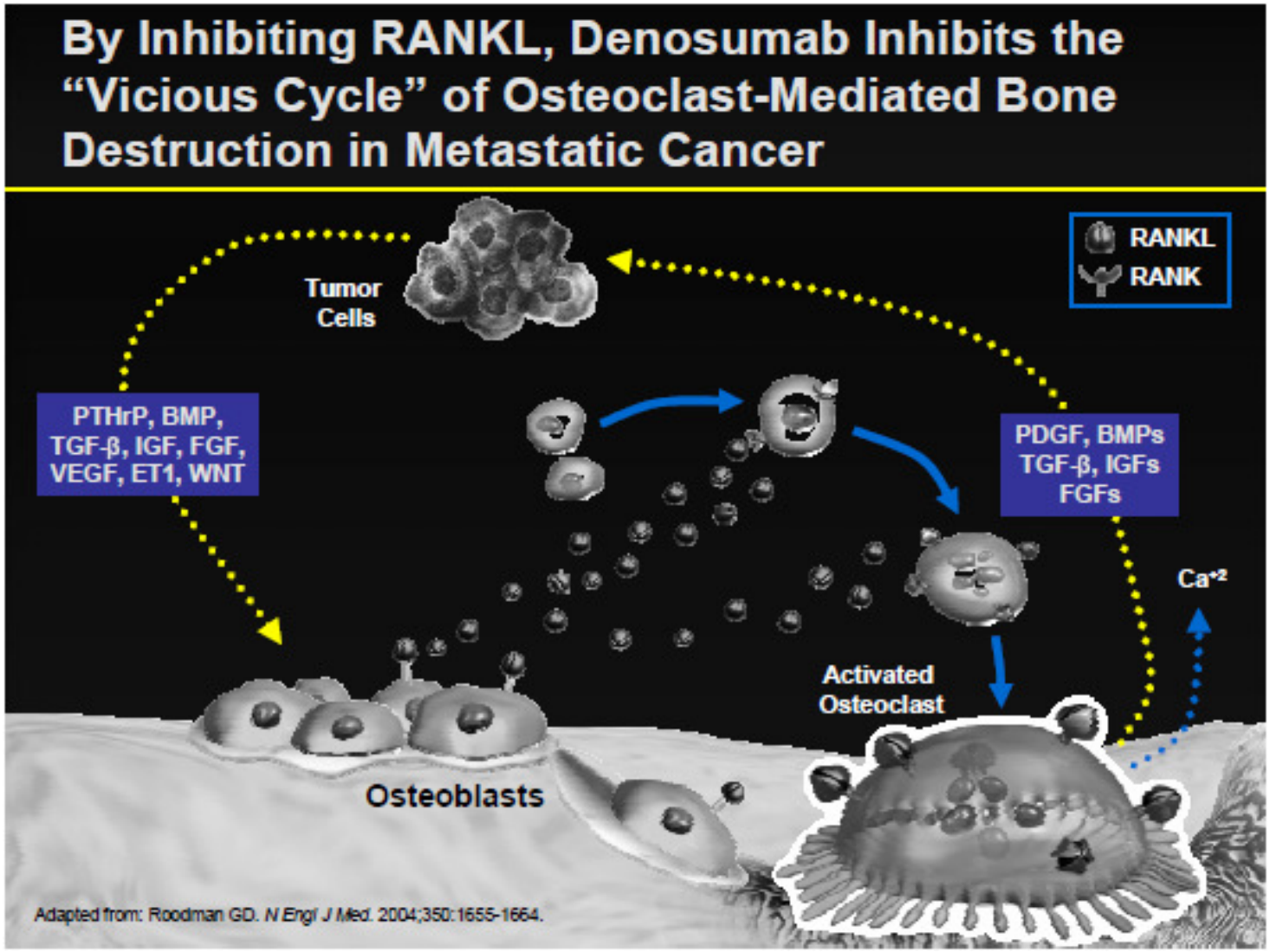
Supplemental Calcium and Vitamin D

Placebo SC every 4 weeks and
Zoledronic acid 4 mg IV* (N = 1020)

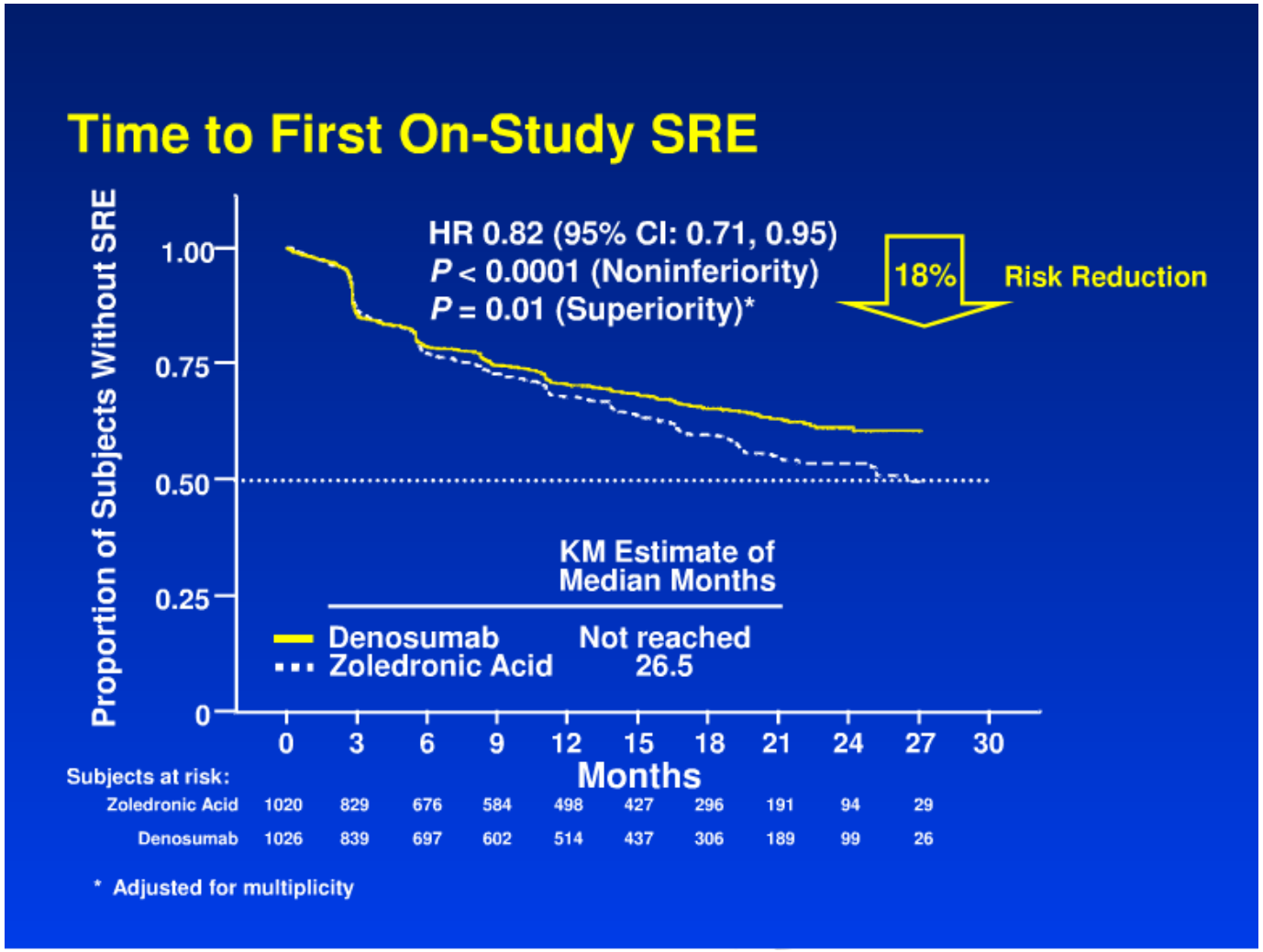
1 Endpoint	• Time to first on-study SRE (non-inferiority)
2 Endpoints	• Time to first on-study SRE (superiority) • Time to first and subsequent on-study SRE (superiority)

*IV product dose adjusted for baseline creatinine clearance and subsequent dose intervals determined by serum creatinine (per Zometa® label).

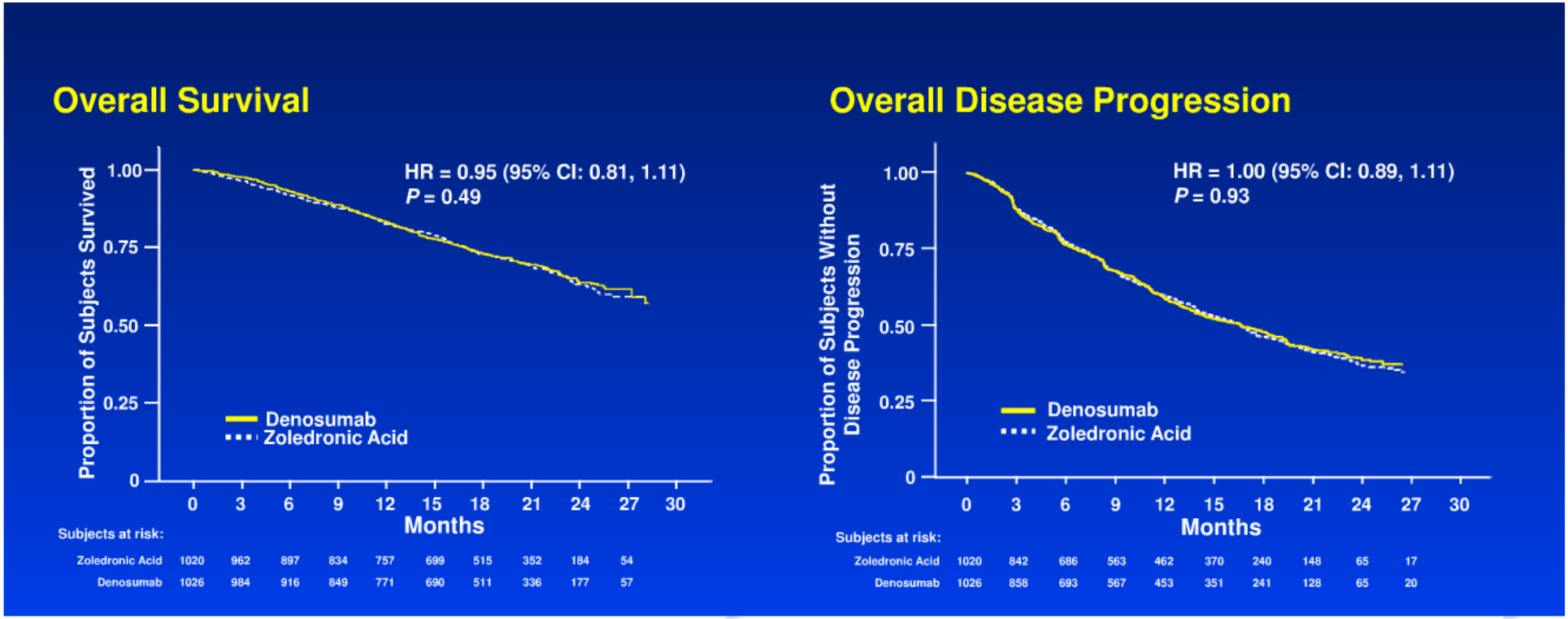
Inhibition RANKL



Skeletel related event



OS & DFS Denosumab



No difference OS and DFS between treatment arms

Discussie Denosumab

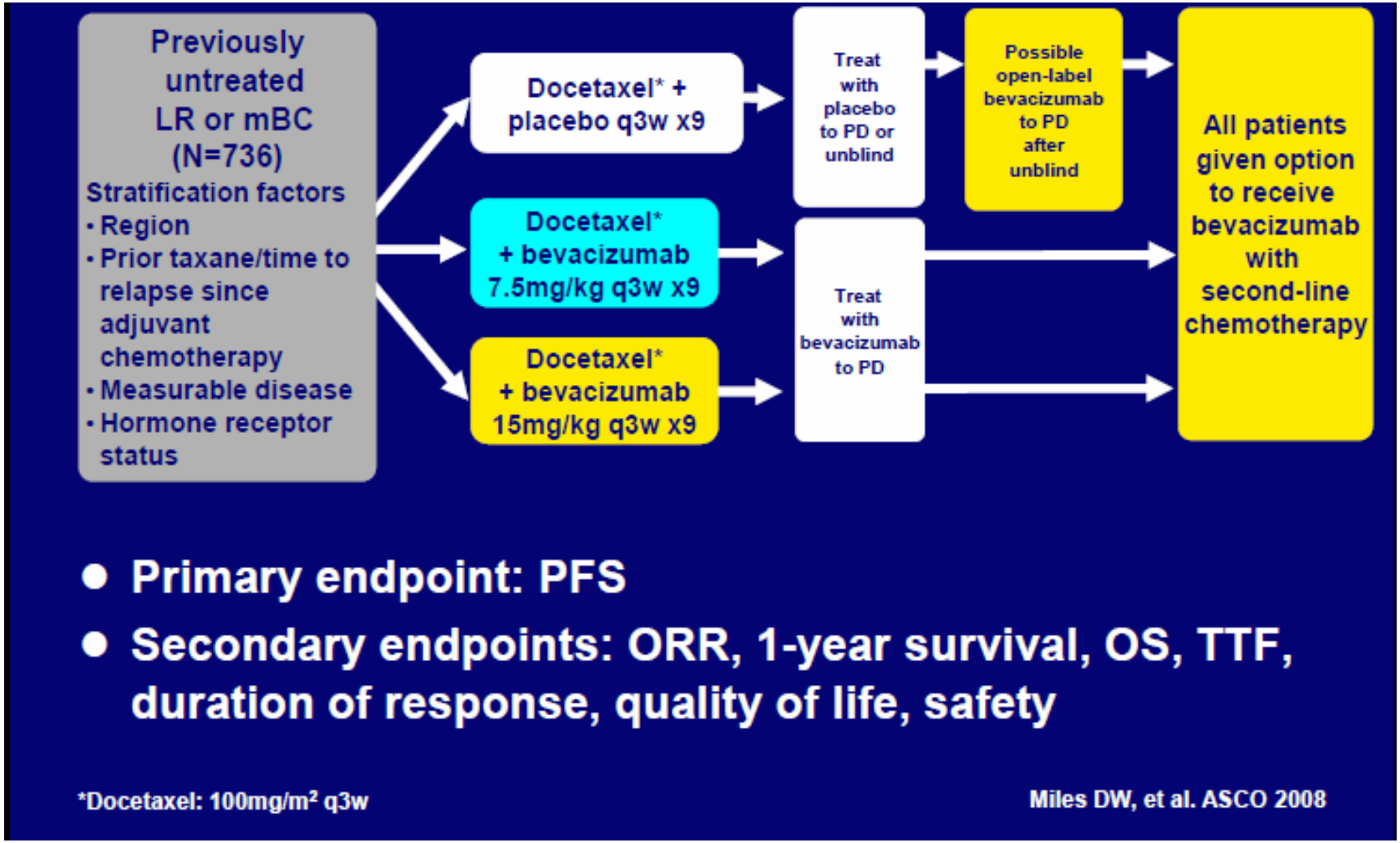
- **Denosumab effectiever dan Zolendronaat**
  - **Vertragen/preventie van skelet-gerelateerde events**
  - **Minder hypercalciëmie**
  - **Later optreden en/of verminderde intensiteit pijn**
- **Zolendronaat**
  - **Toename nierfunctieproblemen**
- **Denosumab**
  - **Toename hypocalciëmie**
- **Kaaknecrose is gelijk beide behandelarmen**

Avado study

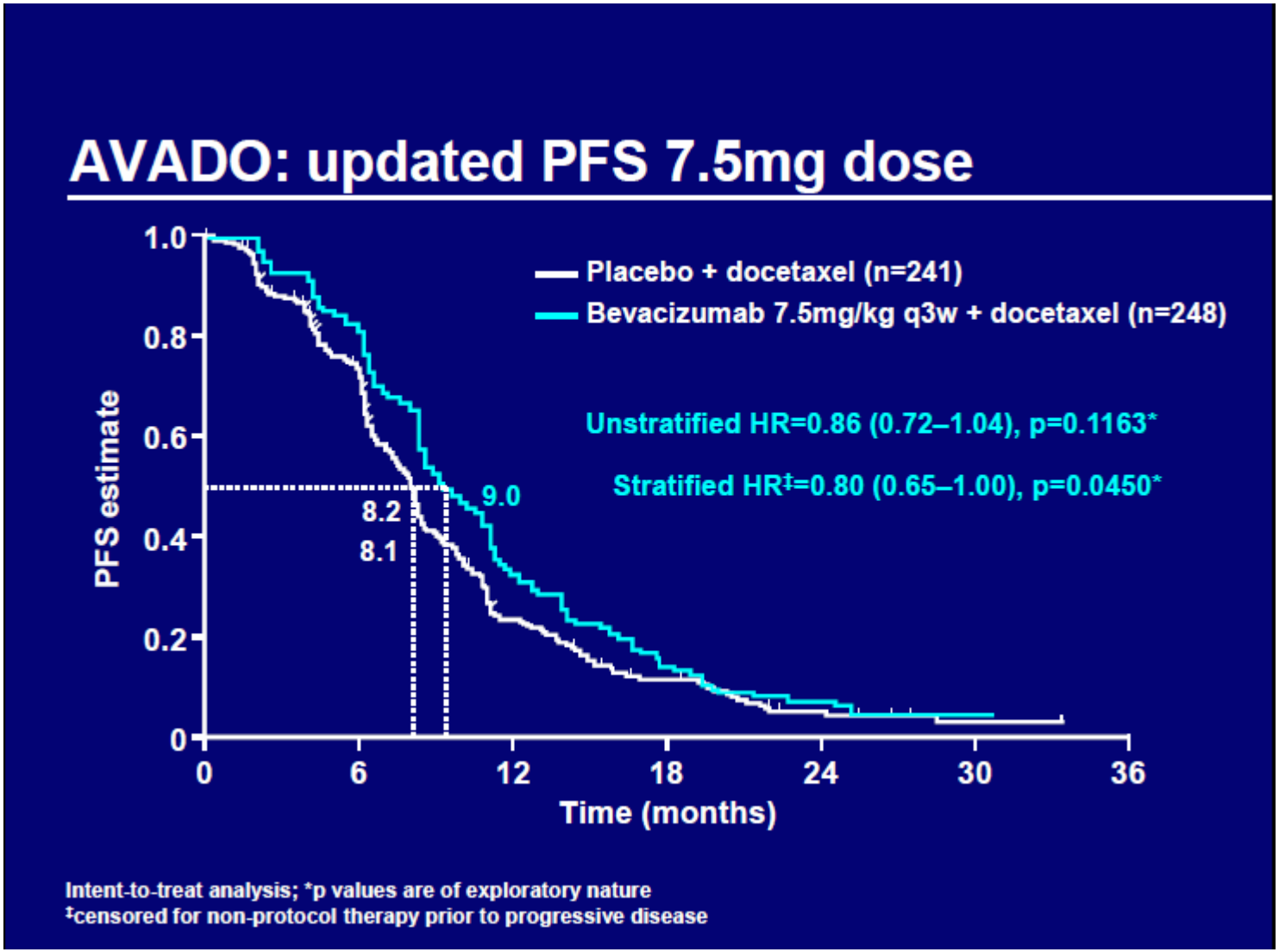
Final overall survival results from the randomised, double-blind, placebo-controlled, phase III AVADO study of bevacizumab plus docetaxel compared with placebo plus docetaxel for the first-line treatment of locally recurrent or metastatic breast cancer

Miles DW, Chan A, Romieu G, Dirix LY, Cortés J, Pivot X, Tomczak P, Juozaityte E, Harbeck N, Steger GG
on behalf of the BO17708 study group

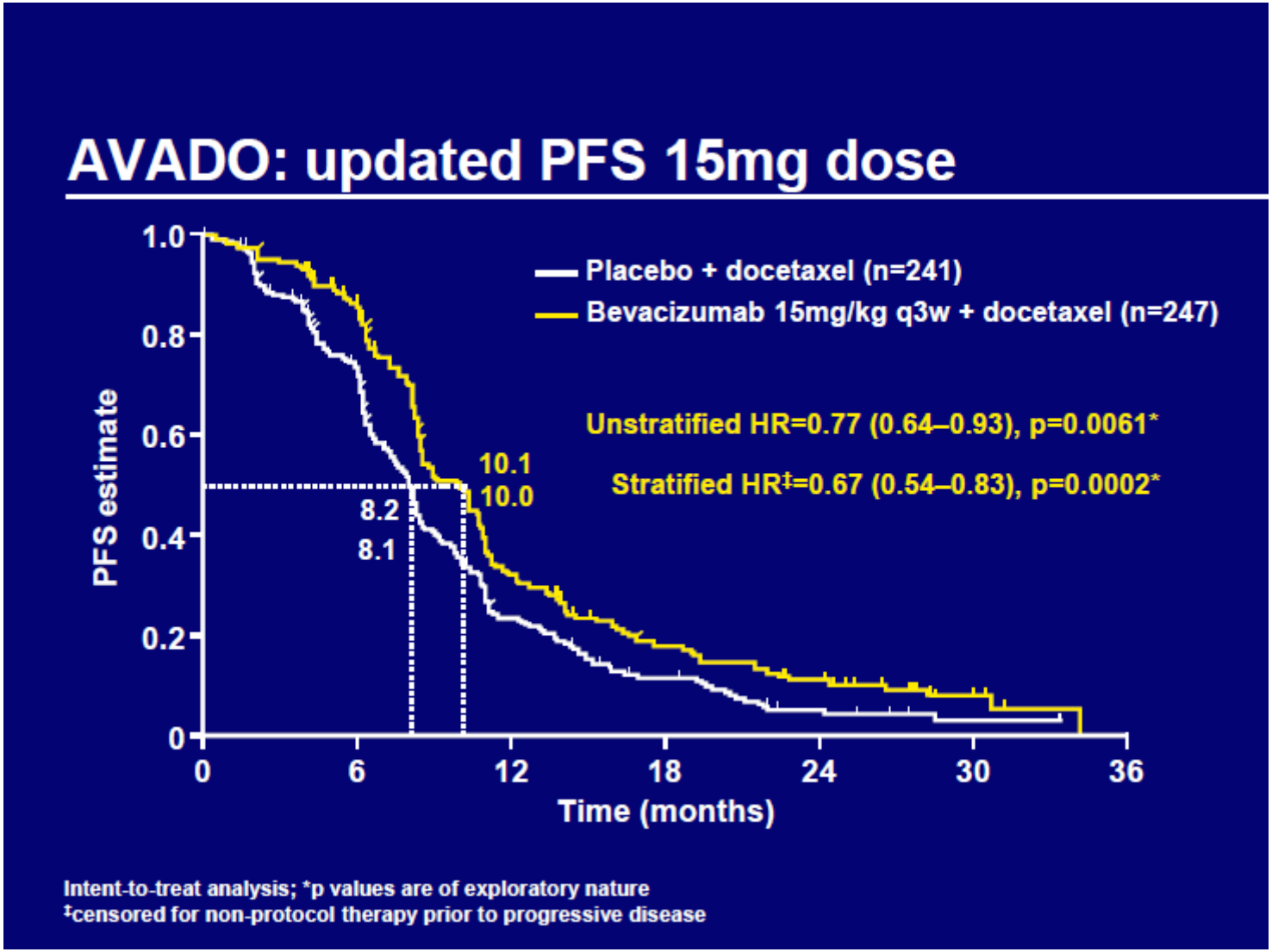
Avado: double blind, placebo-controlled trial



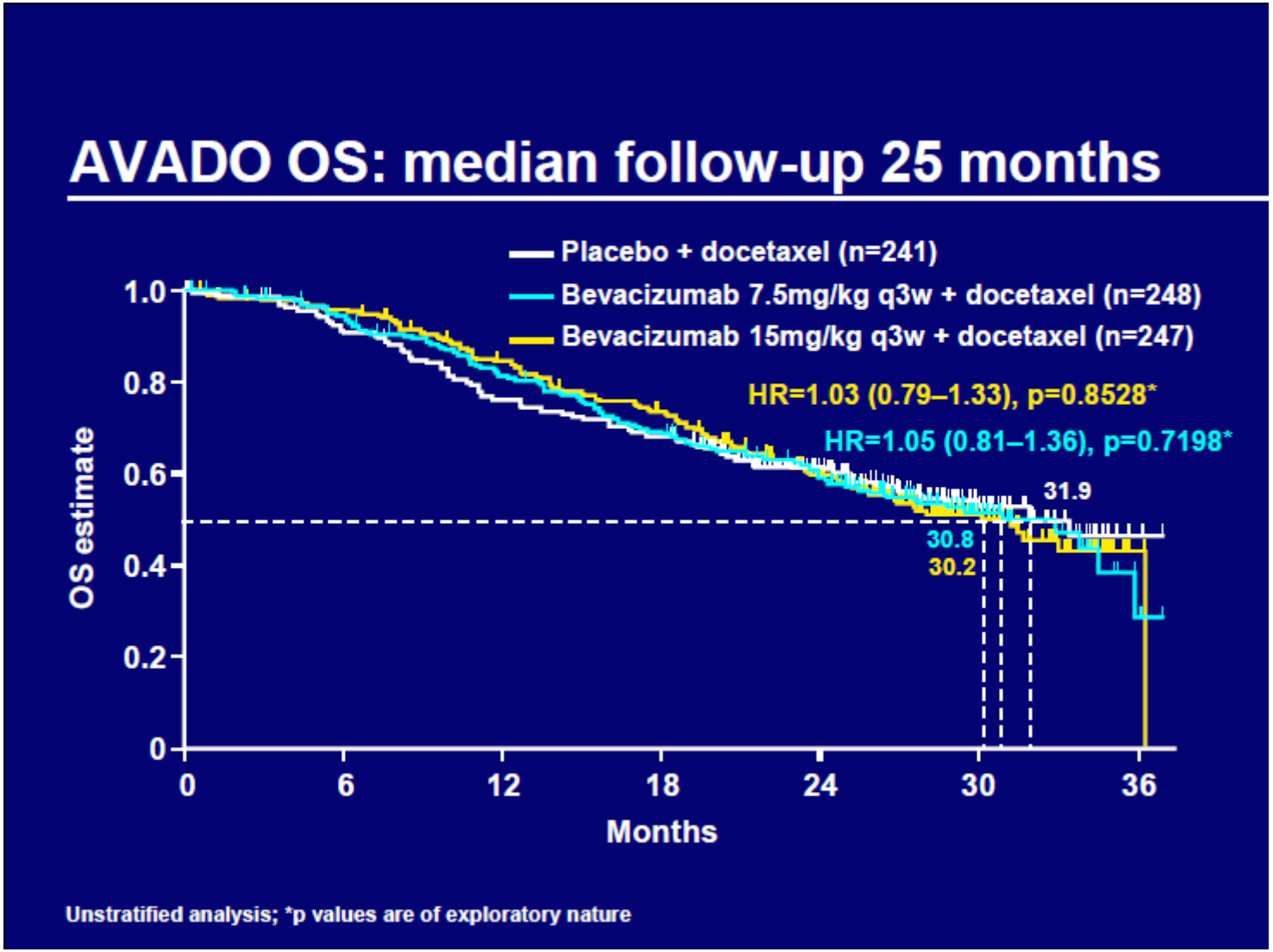
Results PFS (7.5 mg)



Results PFS (15mg)



Results OS


AVADO OS: median follow-up 25 months
Placebo + docetaxel (n=241)
Bevacizumab 7.5mg/kg q3w + docetaxel (n=248)
Bevacizumab 15mg/kg q3w + docetaxel (n=247)
HR=1.03 (0.79–1.33), p=0.8528*
HR=1.05 (0.81–1.36), p=0.7198*
31.9
30.8
30.2
OS estimate
1.0
0.8
0.6
0.4
0.2
0
0
6
12
18
24
30
36
Months
Unstratified analysis; *p values are of exploratory nature

Results ORR

AVADO: updated efficacy ORR and 1-year survival

	Placebo + docetaxel	Bev 7.5* + docetaxel	Bev 15* + docetaxel
Patients with measurable disease at baseline	n=207	n=201	n=206
ORR, %	46.4	55.2	64.1
Difference vs placebo		8.8	17.7
p value vs placebo		0.0739‡	0.0003‡
ITT population	n=241	n=248	n=247
1-year survival rate, %	76	81	84
Difference vs placebo		4.9	8.5
p value vs placebo		0.198‡	0.02‡
Patients still at risk, n	178	195	201

*mg/kg q3w

‡p values are of exploratory nature

Discussie Avado

- **Toevoegen van bevacizumab 15mg/kg q3w aan docetaxel 1e lijn MBC**
  - **Verbetering PFS (8.1 vs 10 months)**
  - **Verbetering ORR (46.4 vs 64.1%)**
- **Geen verschil in OS tussen studie armen**
- **Toxiciteit is acceptabel**

Eindconclusies

- AR tov Tam mono: DFS maar ook OS benefit (IES, BIG 1-98)
- AR implementeren indien postmenopauzaal: upfront of sequentieel. Geen verschil DFS & OS (TEAM trial)
- Toxiciteitsprofiel kan keuze upfront/sequentie mee bepalen
- Toevoegen van trastuzumab (adjuvant) significant voordeel OS & DFS (NCCTG N9831, BCIRG 006)
- Trend risico reductie door trastuzumab concurrent vs sequentieel (NCCTG N9831)
- Denosumab effectiever dan Zolendronaat SRE, hypercalciemie, optreden/intensiteit van pijn
- Toevoegen van bevacizumab 15mg/kg q3w aan docetaxel 1^{e} lijn MBC verbetering PFS & ORR, NIET OS (AVADO)