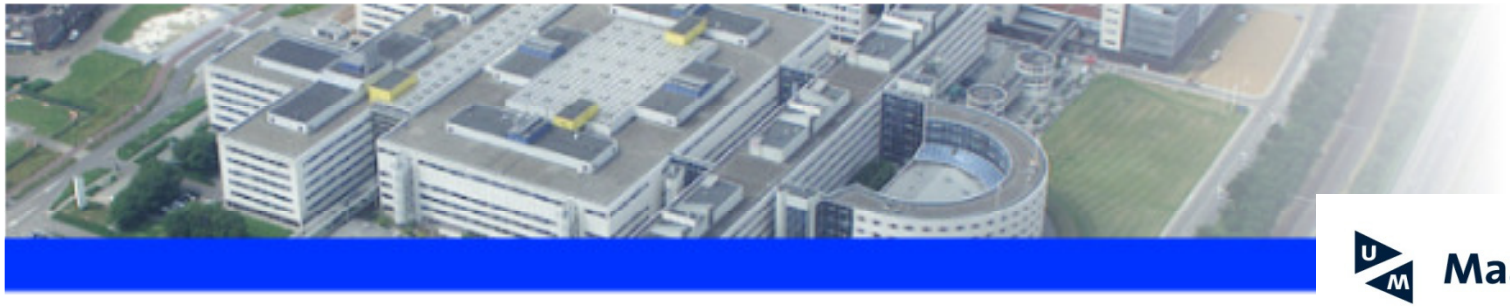


azM

Maastricht University

Berichten uit San Antonio

CTRC-AACR
SAN ANTONIO BREAST CANCER SYMPOSIUM **2012**

Birgit Vriens
Medisch oncoloog
MUMC, Maastricht

3e Mammacongres Harderwijk
27 januari 2012

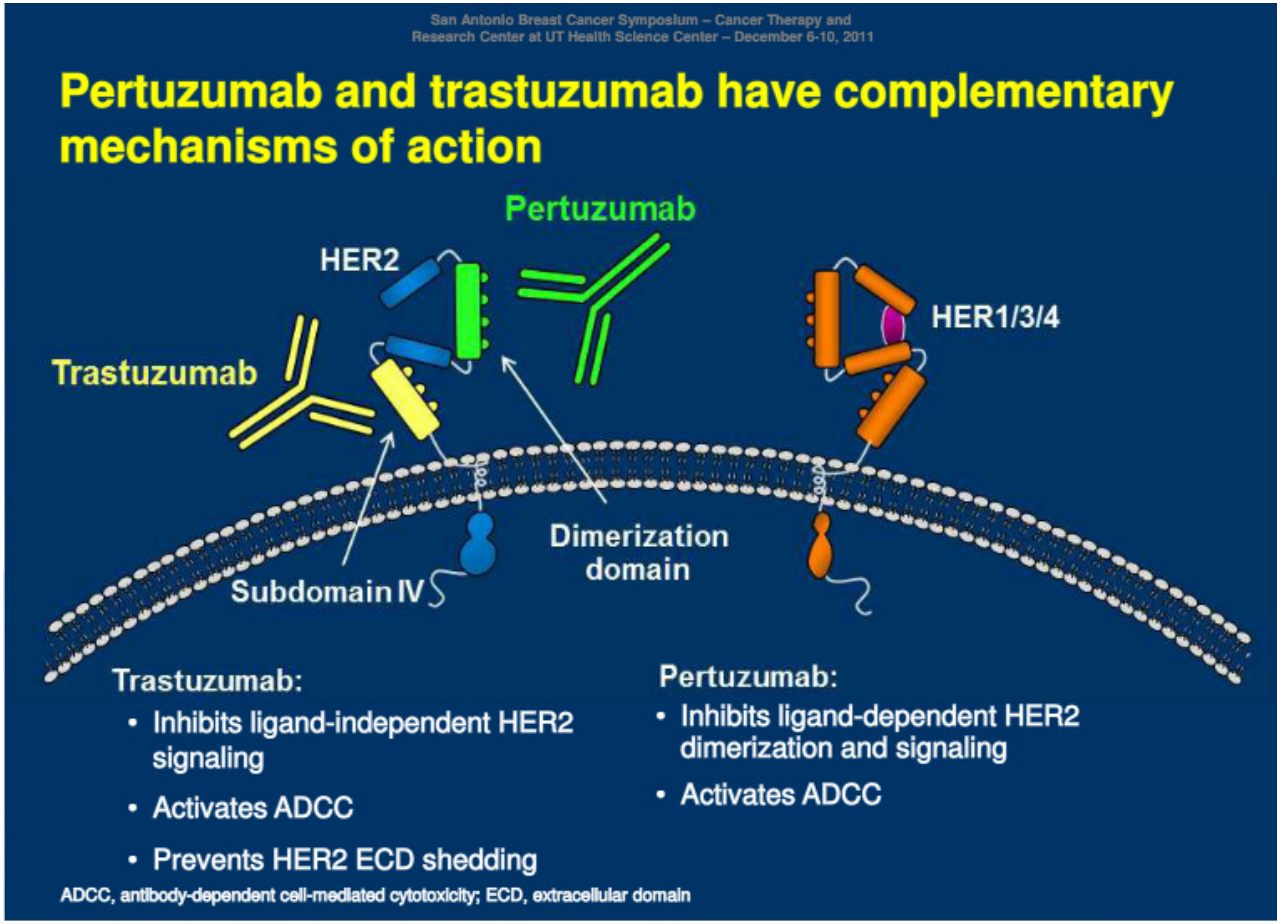
- **Targeted therapy (pertuzumab)**
  - Gemetastaseerde setting: Cleopatra
  - Neo-adjuvant: Thryphaena

- **Endocriene therapie en MTOR-remmer**
  - Bolero-2 trial

- **Bisfosfonaten**
  - Hormonale therapie, pre-menopauzale patient (ABCSG-12)
  - Chemotherapie (GAIN-trial, NSABP-B34)

Pertuzumab

- Pertuzumab en trastuzumab beiden een anti HER2 monoklonale antistof
- Pertuzumab heeft door de belemmering van de receptordimerisatie een complementaire werking op trastuzumab.



San Antonio Breast Cancer Symposium – Cancer Therapy and
Research Center at UT Health Science Center – December 6-10, 2011

A Phase III, Randomized, Double-Blind, Placebo-Controlled Registration Trial to Evaluate the Efficacy and Safety of Placebo + Trastuzumab + Docetaxel vs. Pertuzumab + Trastuzumab + Docetaxel in Patients with Previously Untreated HER2-Positive Metastatic Breast Cancer (CLEOPATRA)

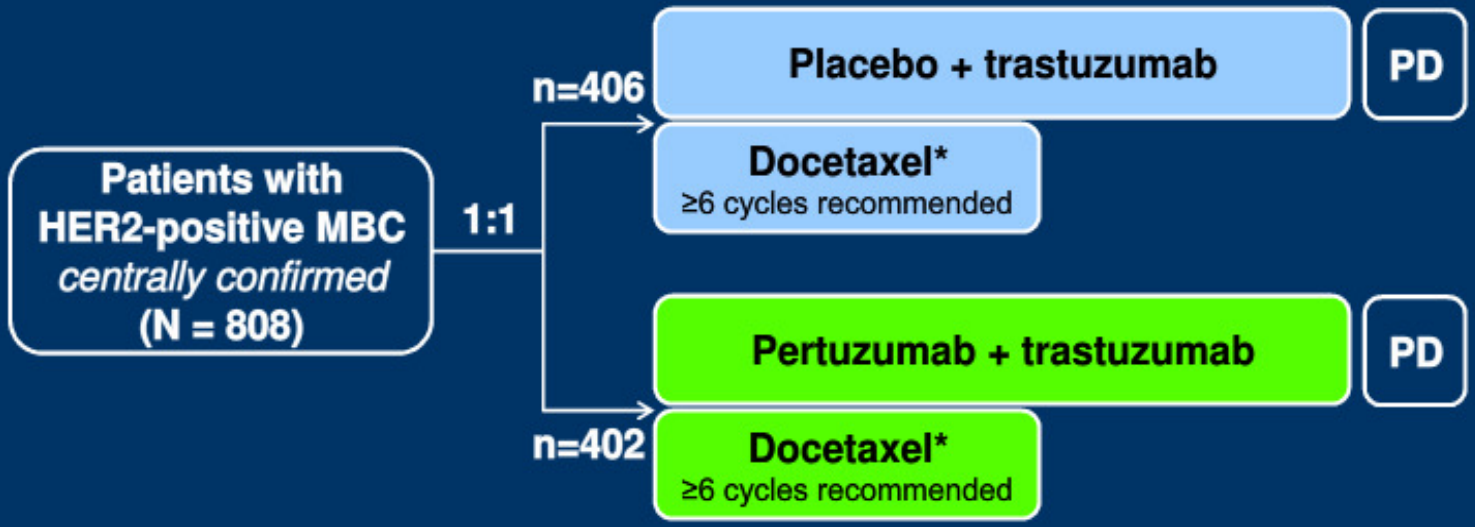
J Baselga,[1] S-B Kim,[2] S-A Im,[3] R Hegg,[4] Y-H Im,[5] L Roman,[6]
J L Pedrini,[7] J Cortés,[8] A Knott,[9] E Clark,[9] G Ross[9] and S M Swain[10]

[1]Massachusetts General Hospital Cancer Center, Boston, MA, USA; [2]Department of Oncology, Asan Medical Center, University of Ulsan, College of Medicine, Seoul, Korea; [3]Division of Hematology and Medical Oncology, Department of Internal Medicine, Seoul National University College of Medicine, Seoul, Korea; [4]Hospital Pérola Byington, São Paulo, Brazil; [5]Division of Hematology and Medical Oncology, Department of Internal Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; [6]Leningrad Regional Oncology Dispensary, St Petersburg, Russian Federation; [7]CPMEC-Mastology Unit of Conceição Hospital, Porto Alegre, Brazil; [8]Department of Oncology, Vall d'Hebron University Hospital, Barcelona, Spain; [9]Roche Products Limited, Welwyn, UK; [10]Washington Cancer Institute, Washington Hospital Center, Washington D.C., USA

Design

San Antonio Breast Cancer Symposium – Cancer Therapy and Research Center at UT Health Science Center – December 6-10, 2011

Study design



- Randomization was stratified by geographic region and prior treatment status (neo/adjuvant chemotherapy received or not)
- Study dosing q3w:
  - Pertuzumab/Placebo: 840 mg loading dose, 420 mg maintenance
  - Trastuzumab: 8 mg/kg loading dose, 6 mg/kg maintenance
  - Docetaxel: 75 mg/m^2, escalating to 100 mg/m^2 if tolerated

* <6 cycles allowed for unacceptable toxicity or PD; >6 cycles allowed at investigator discretion

MBC, metastatic breast cancer; PD, progressive disease

Eerdere (neo) adjuvante therapie

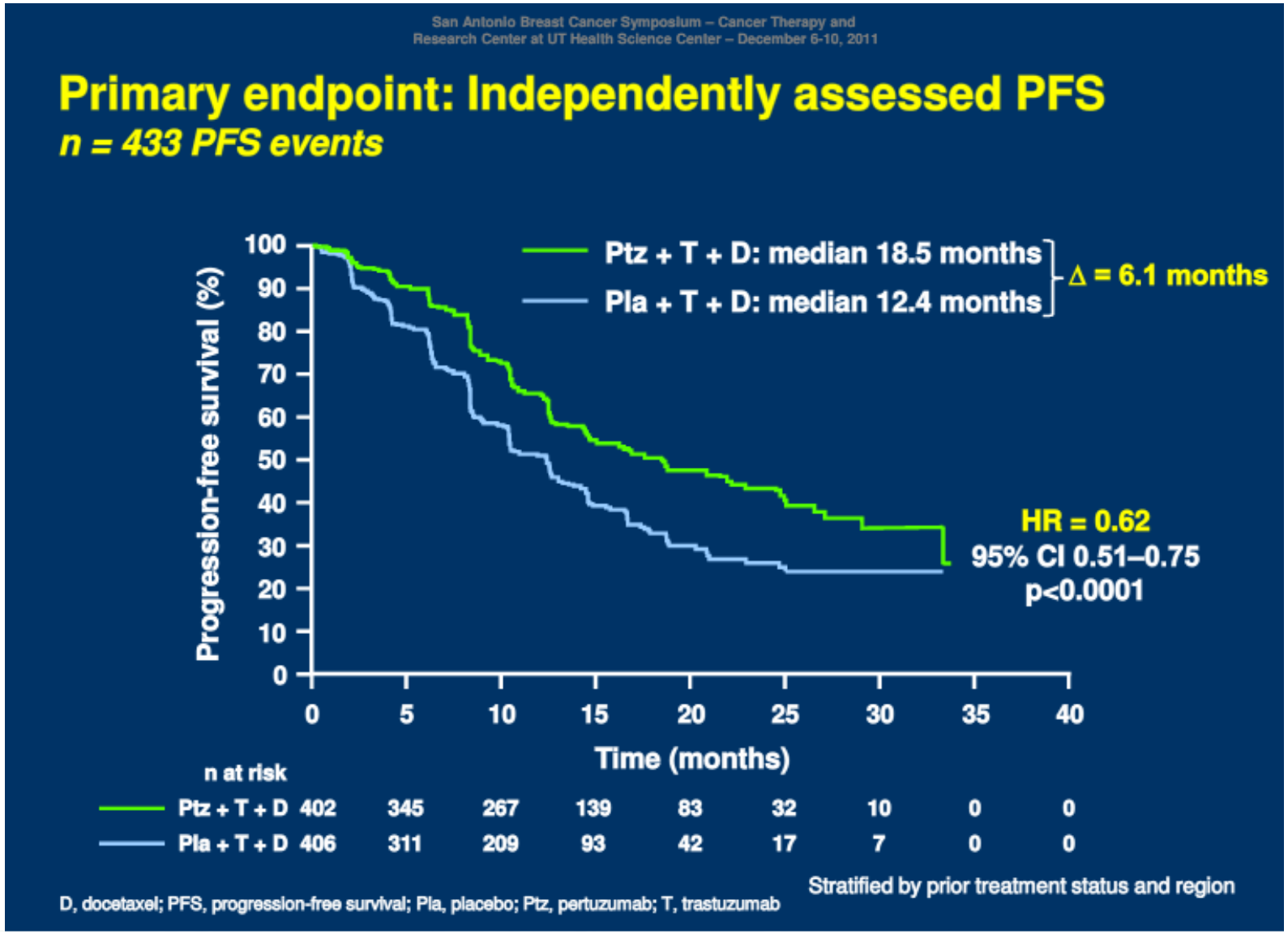
San Antonio Breast Cancer Symposium – Cancer Therapy and Research Center at UT Health Science Center – December 6-10, 2011

Prior therapy for breast cancer

	Placebo + trastuzumab + docetaxel (n = 406)	Pertuzumab + trastuzumab + docetaxel (n = 402)
Prior (neo)adjuvant chemotherapy, n (%)		
Yes	192 (47.3)	184 (45.8)
No	214 (52.7)	218 (54.2)
Components of (neo)adjuvant therapy*, n (%)		
Anthracycline	164 (40.4)	150 (37.3)
Hormones	97 (23.9)	106 (26.4)
Taxane	94 (23.2)	91 (22.6)
Trastuzumab	41 (10.1)	47 (11.7)

* Numbers add up to more than 100% because patients could have received more than one therapy

Progressie vrije overleving (PFS) (primair eindpunt)



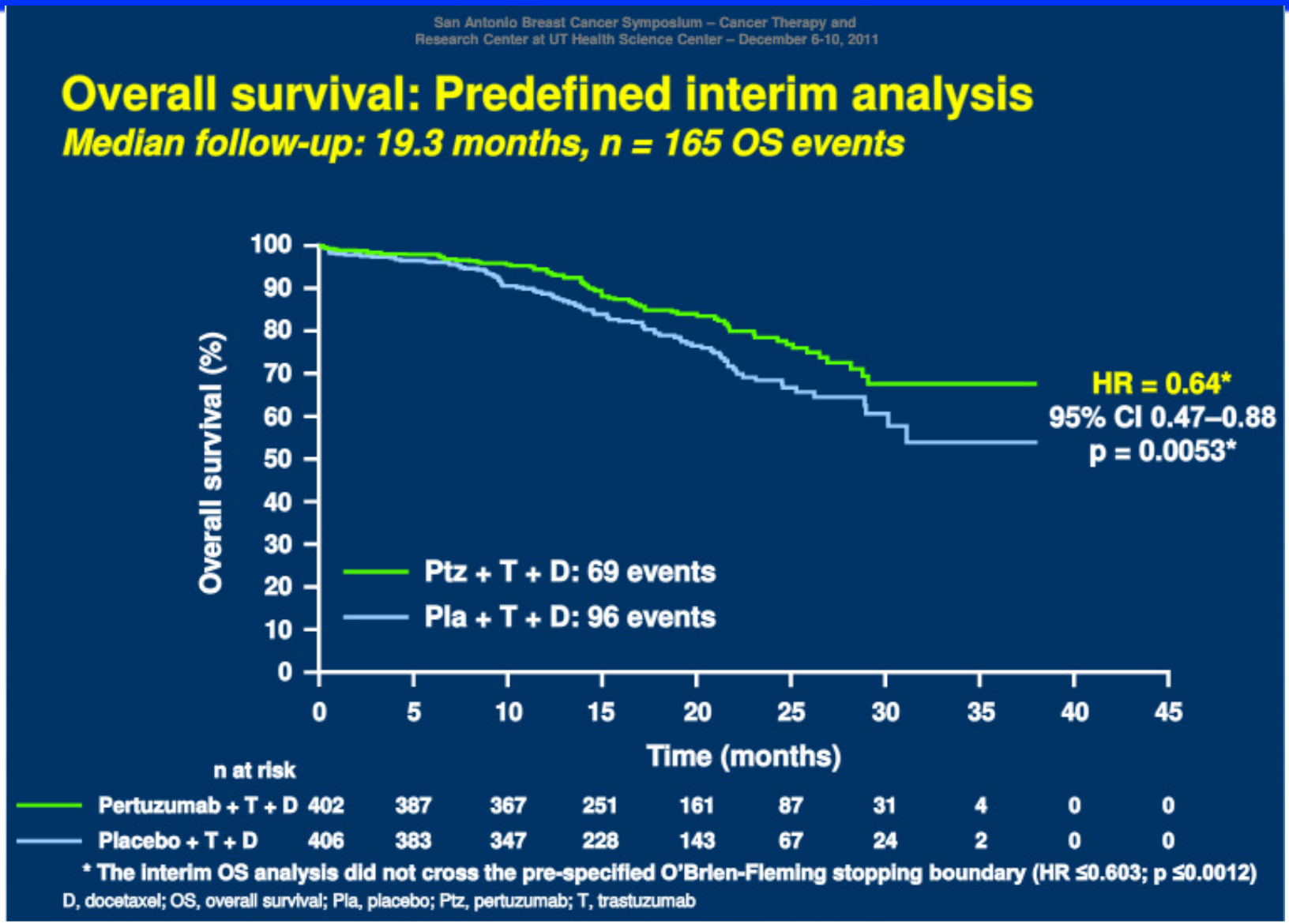
PFS wel/niet eerder trastuzumab

San Antonio Breast Cancer Symposium – Cancer Therapy and Research Center at UT Health Science Center – December 6-10, 2011

Independently assessed PFS by prior trastuzumab therapy in patients with (neo)adjuvant therapy

	Placebo + trastuzumab + docetaxel Median PFS, months	Pertuzumab + trastuzumab + docetaxel Median PFS, months	Hazard ratio (CI)
Prior (neo)adjuvant trastuzumab treatment (n = 88)	10.4	16.9	0.62 (0.35–1.07)
No prior (neo)adjuvant trastuzumab treatment (n = 288)	12.6	21.6	0.60 (0.43–0.83)

Overall survival (secundair eindpunt)



Toxiciteit

San Antonio Breast Cancer Symposium – Cancer Therapy and Research Center at UT Health Science Center – December 6-10, 2011

Adverse events (all grades) ≥25% incidence or ≥5% difference between arms

Adverse event, n (%)	Placebo + trastuzumab + docetaxel (n = 397)	Pertuzumab + trastuzumab + docetaxel (n = 407)
Diarrhea	184 (46.3)	272 (66.8)
Alopecia	240 (60.5)	248 (60.9)
Neutropenia	197 (49.6)	215 (52.8)
Nausea	165 (41.6)	172 (42.3)
Fatigue	146 (36.8)	153 (37.6)
Rash	96 (24.2)	137 (33.7)
Decreased appetite	105 (26.4)	119 (29.2)
Mucosal inflammation	79 (19.9)	113 (27.8)
Asthenia	120 (30.2)	106 (26.0)
Peripheral edema	119 (30.0)	94 (23.1)
Constipation	99 (24.9)	61 (15.0)
Febrile neutropenia	30 (7.6)	56 (13.8)
Dry skin	17 (4.3)	43 (10.6)

Conclusie

San Antonio Breast Cancer Symposium – Cancer Therapy and Research Center at UT Health Science Center – December 6-10, 2011

Summary and conclusions

- CLEOPATRA met its primary endpoint and demonstrated a statistically significant and clinically meaningful improvement in PFS (HR = 0.62) in patients with HER2-positive MBC
  - Median PFS increased by 6.1 months from 12.4 to 18.5 months
  - The PFS improvement was consistent across subgroups and supported by the secondary endpoints of ORR and OS (immature)
- The combination of pertuzumab and trastuzumab plus docetaxel increased rates of diarrhea, rash, mucosal inflammation, febrile neutropenia, and dry skin
  - These adverse events were primarily grades 1–2, manageable, and occurred during docetaxel therapy
  - There was no increase in cardiac adverse events or LVSD
- This new regimen may be practice-changing in HER2-positive first-line MBC

San Antonio Breast Cancer Symposium – Cancer Therapy and Research Center at UT Health Science Center – December 6–10, 2011

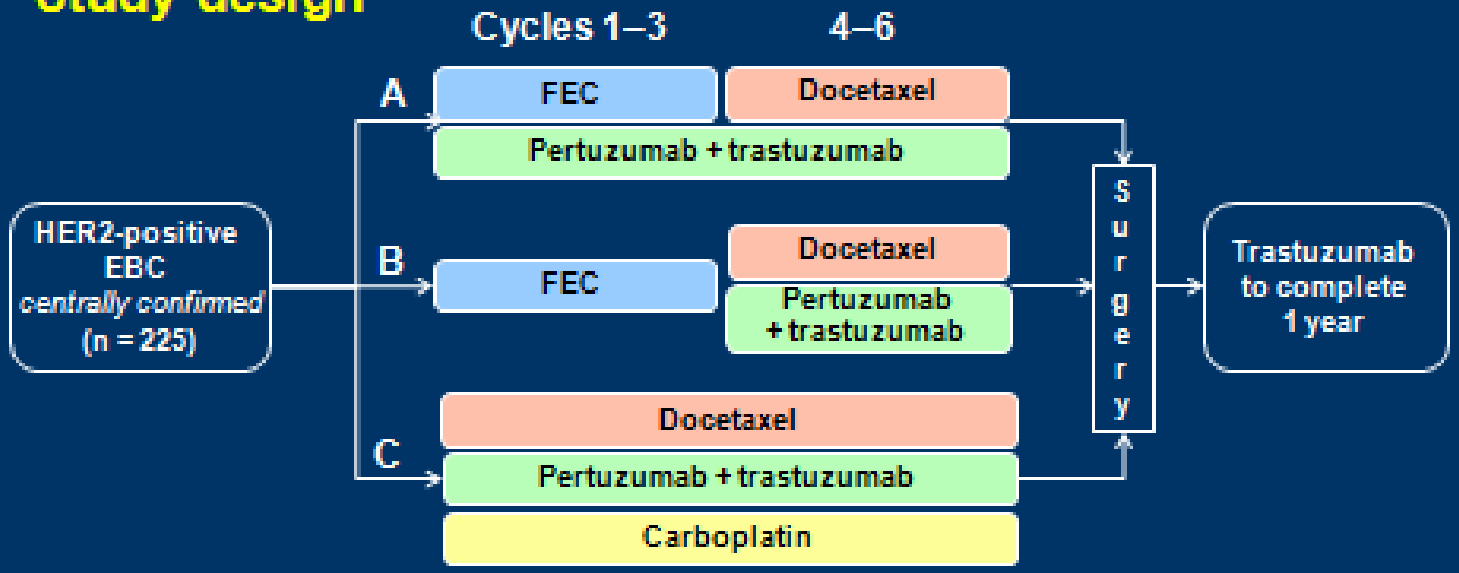
Neoadjuvant Pertuzumab and Trastuzumab Concurrent or Sequential with an Anthracycline-Containing or Concurrent with an Anthracycline-Free Standard Regimen: A Randomized Phase II Study (TRYPHAENA)

A Schneeweiss,[1] S Chia,[2] T Hickish,[3] V Harvey,[4] A Eniu,[5] R Hegg,[6] C Tausch,[7] J-H Seo,[8] Y-F Tsai,[9] A Ackrill,[10] G Ross,[10] J Cortés[11]

[1]*National Center for Tumor Diseases, University Hospital, Heidelberg, Germany;* [2]*British Columbia Cancer Agency – Vancouver Centre, University of British Columbia, Vancouver, Canada;* [3]*Royal Bournemouth Hospital, Bournemouth University, Bournemouth, UK;* [4]*Regional Cancer and Blood Centre, Auckland City Hospital, Auckland, New Zealand;* [5]*Cancer Institute "I Chiricuta", Cluj-Napoca, Romania;* [6]*Hospital Pérola Byington, São Paulo, Brazil;* [7]*Breast Center, Zürich, Switzerland;* [8]*Department of Internal Medicine, Korea University Guro Hospital, Korea;* [9]*Taipei-Veterans General Hospital, Taipei, Taiwan;* [10]*Roche Products Limited, Welwyn, United Kingdom;* [11]*Vall d'Hebron University Hospital, Barcelona, Spain*

Design

Study design



- All 3 arms were experimental
- Study dosing q3w:
  - FEC: 500 mg/m², 100 mg/m², 600 mg/m²
  - Carboplatin: AUC 6
  - Trastuzumab: 8 mg/kg loading dose, 6 mg/kg maintenance
  - Pertuzumab: 840 mg loading dose, 420 mg maintenance
  - Docetaxel: 75 mg/m² (escalating to 100 mg/m² if tolerated, in Arms A and B only)

AUC, area under the plasma concentration-time curve; EBC, early breast cancer; FEC, 5fluorouracil, epirubicin, cyclophosphamide

Eindpunten

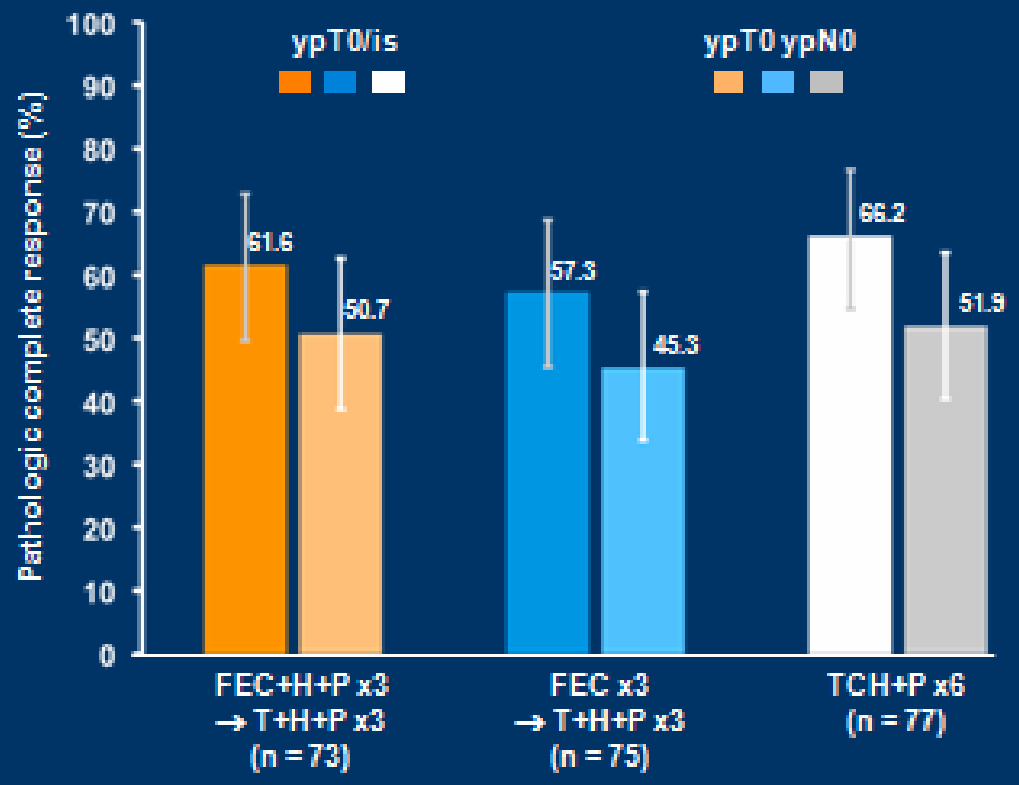
Study endpoints

- Primary endpoint:
  - Cardiac safety
    - Symptomatic LVSD (grade ≥3)
    - LVEF declines (≥10 percentage points and below 50%)
- Secondary endpoints:
  - Toxicity
  - pCR (defined as the absence of invasive tumor residues in the breast at surgery; remaining *in situ* lesions allowed; ypT0/is)
    - Study was not powered for formal comparison between arms
  - Clinical response rate
  - Rate of breast-conserving surgery
  - Disease-free survival and overall survival
  - Biomarker evaluation

LVEF, left ventricular ejection fraction; LVSD, left ventricular systolic dysfunction; pCR, pathologic complete response

Pathologisch complete respons (pCR) (secundair eindpunt)

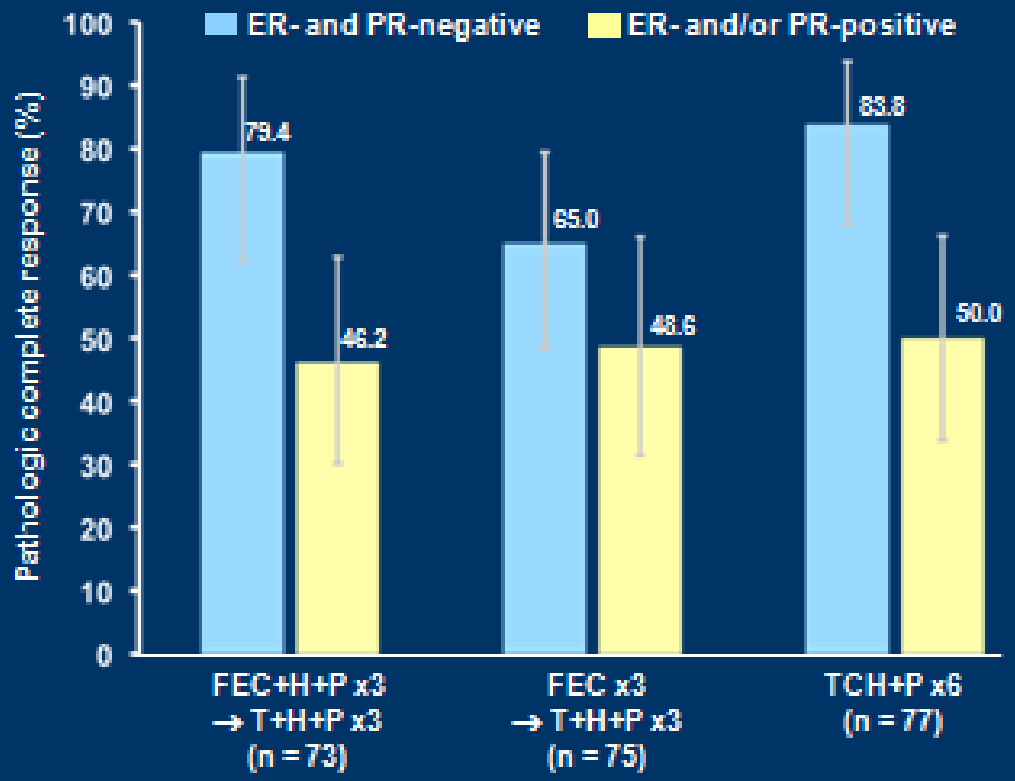
Pathologic complete response



FEC, 5-fluorouracil, epirubicin, cyclophosphamide; H, trastuzumab; P, pertuzumab; T, docetaxel; TCH, docetaxel/carboplatin/trastuzumab

pCR
Hormoonreceptor negatief/positief

Pathologic complete response by hormone receptor status



ER, estrogen receptor; FEC, 5fluorouracil, epirubicin, cyclophosphamide; H, trastuzumab; P, pertuzumab; PR, progesterone receptor; T, docetaxel; TCH, docetaxel/carboplatin/trastuzumab

Conclusie

Summary and conclusions

- Results from TRYPHAENA indicate a low incidence of symptomatic and asymptomatic LVSD across all arms
  - Concurrent administration of pertuzumab plus trastuzumab with epirubicin resulted in similar cardiac tolerability compared with sequential administration or the anthracycline-free regimen
- Neutropenia, febrile neutropenia, leukopenia, and diarrhea were most frequently reported adverse events (grade ≥3) across all arms
- Regardless of chemotherapy chosen, the combination of pertuzumab with trastuzumab in the neoadjuvant setting resulted in high pCR rates (57–66%)
- TRYPHAENA supports the ongoing APHINITY study, a Phase III trial to evaluate pertuzumab and trastuzumab plus standard chemotherapy in the adjuvant setting (poster: OT1-02-04) (NCT01358877)

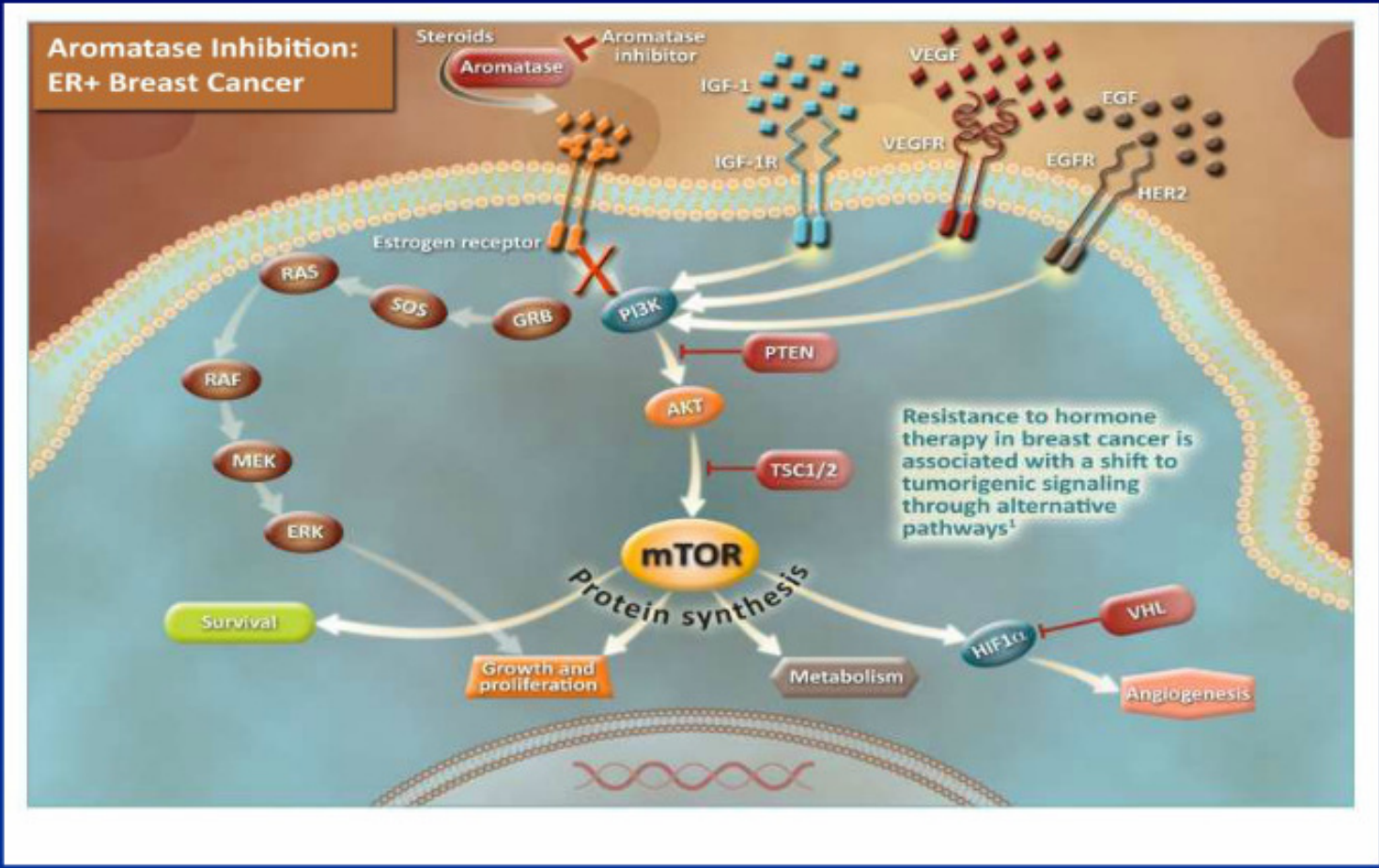
Everolimus for postmenopausal women with advanced breast cancer: updated results of the BOLERO-2 trial

G. N. Hortobagyi, M. Piccart, H. Rugo, H. Burris, M. Campone, S. Noguchi, M. Gnant, K. I. Pritchard, L. Vittori, P. Mukhopadhyay, T. Sahmoud, D. Lebwohl, J. Baselga

On behalf of the BOLERO-2 Investigators

Endocriene resistentie en mTOR

Aromatase Inhibition: ER+ Breast Cancer

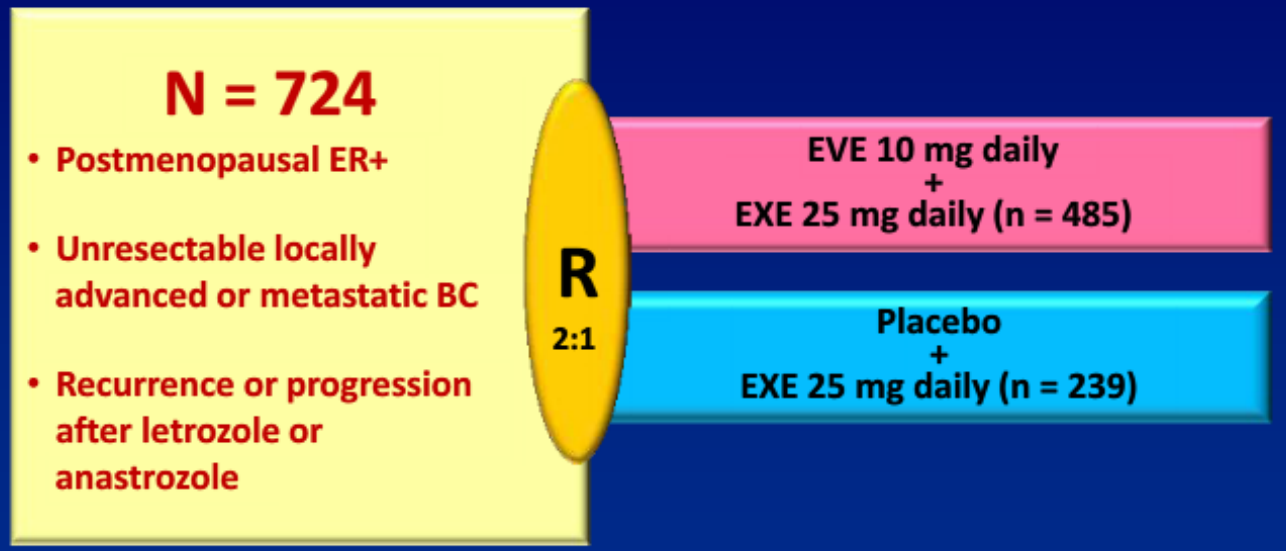


ER+ = estrogen receptor-positive.

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

Design

BOLERO-2 (Ph III): Everolimus in Advanced BC



Stratification: Sensitivity to prior hormone therapy and presence of visceral metastases

Endpoints

- **Primary:** PFS (local assessment)
- **Secondary:** OS, ORR, QOL, safety, bone markers, PK

BC = breast cancer; ER+ = estrogen receptor-positive; EVE = everolimus; EXE = exemestane; ORR, overall response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetics; QOL = quality of life.
Hortobagyi G et al. SABCS 2011 (Abstract #S3-7)

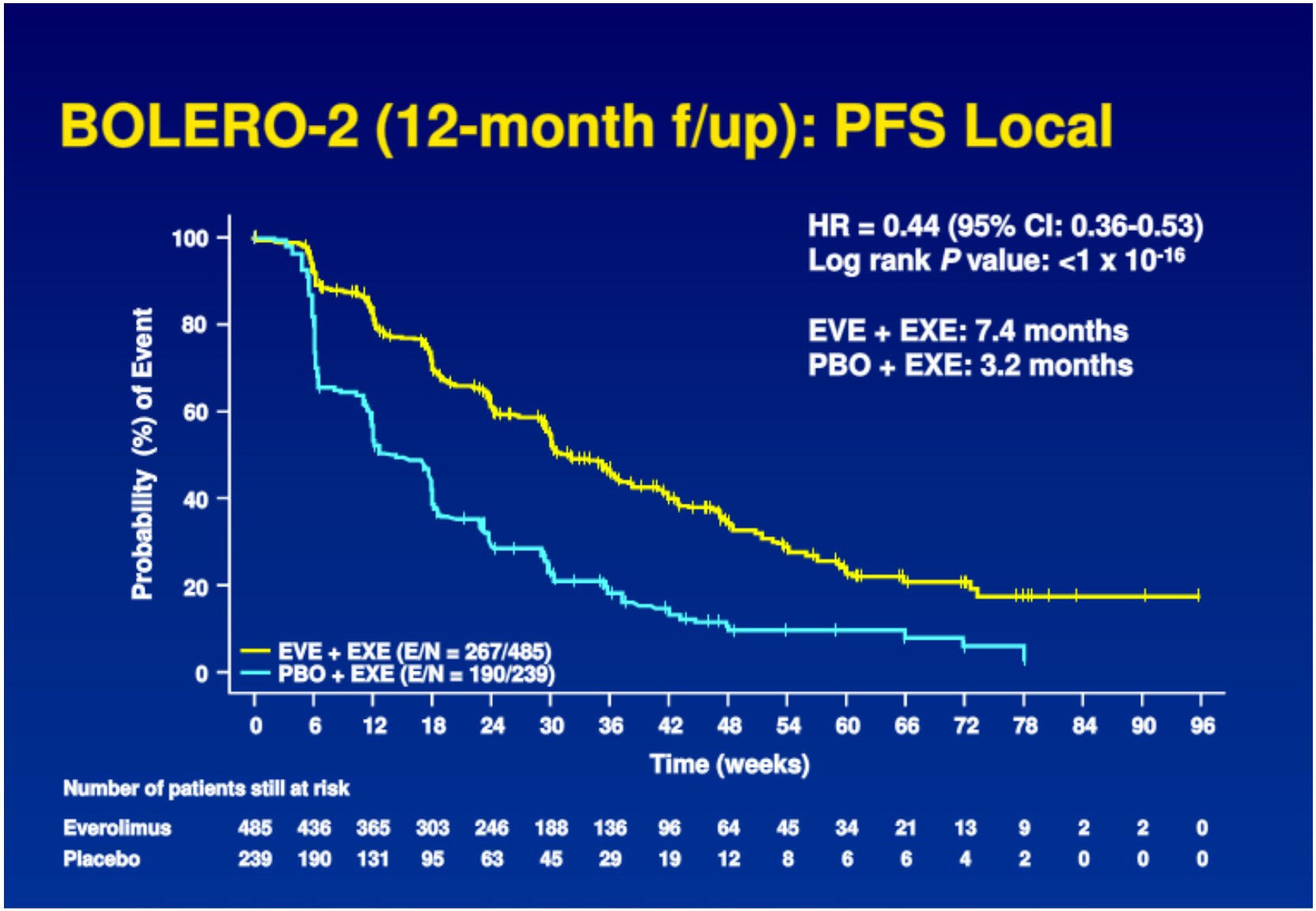
Eerdere therapie

BOLERO-2: Prior Therapy

	Everolimus + Exemestane (n = 485), %	Placebo + Exemestane (n = 239), %
Sensitivity to prior hormonal therapy	84	84
Last treatment: LET/ ANA	74	75
Last treatment		
Adjuvant	21	15
Metastatic	79	85
Prior tamoxifen	47	50
Prior fulvestrant	17	16
Prior chemotherapy for metastatic BC	26	26
Number of prior therapies: ≥3	54	53

ANA = anastrozole; BC = breast cancer; LET = letrozole.
Hortobagyi G et al. SABCS 2011 (Abstract #S3-7)

Progresie vrije overleving (primair eindpunt)



Toxiciteit

BOLERO-2 (12 mo f/up): Most Common Adverse Events

	Everolimus + Exemestane (n = 482), %			Placebo + Exemestane (n = 238), %		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Stomatitis	59	8	0	11	<1	0
Rash	39	1	0	6	0	0
Fatigue	36	4	<1	27	1	0
Diarrhea	33	2	<1	19	<1	0
Appetite decreased	30	1	0	12	<1	0
Nausea	29	<1	<1	28	1	0
Non-infectious Pneumonitis*	15	3	0	0	0	0
Hyperglycemia*	14	5	<1	2	<1	0

*Adverse Events of clinical interest
Hortobegyi G et al. SABCS 2011 (Abstract #S3-7)

BOLERO-2 (12 mo f/up): Conclusion

- Everolimus is the first agent to significantly enhance the efficacy of hormonal therapy in patients with ER+, HER2- breast cancer
- The addition of everolimus in advanced breast cancer could represent a paradigm shift in the management of this patient population

azM

- Winst in PFS in uitgebreid voorbehandelde patientenpopulatie
- Toxiciteit…
- Plaatsbepaling praktijk?

Abstract S1-2: Gnant M, Mlineritsch B, Luschin-Ebengreuth G, Stoeger H, Dubsky P, Jakesz R, Singer C, Eidtmann H, Fesl C, Eiermann W, Marth C, Greil R, on behalf of the ABCSG

Long-Term Follow-Up in ABCSG-12: Significantly Improved Overall Survival With Adjuvant Zoledronic Acid in Premenopausal Patients With Hormone-Receptor-Positive Early Breast Cancer

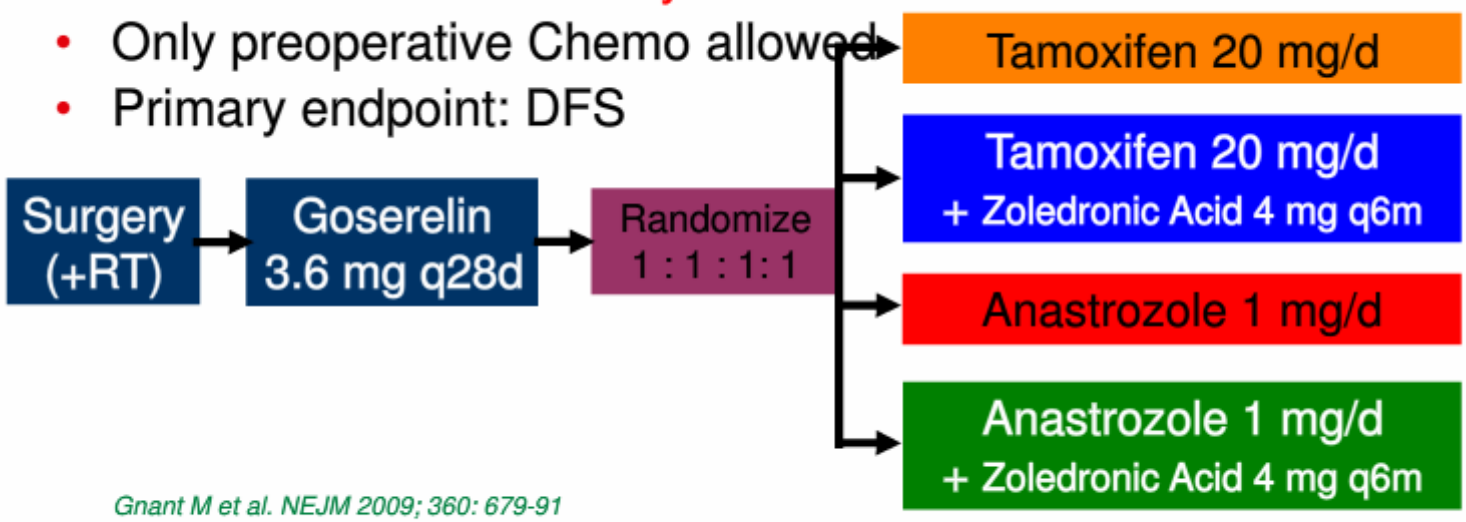
Michael Gnant

Professor of Surgery, Medical University of Vienna
Austrian Breast & Colorectal Cancer Study Group

Design

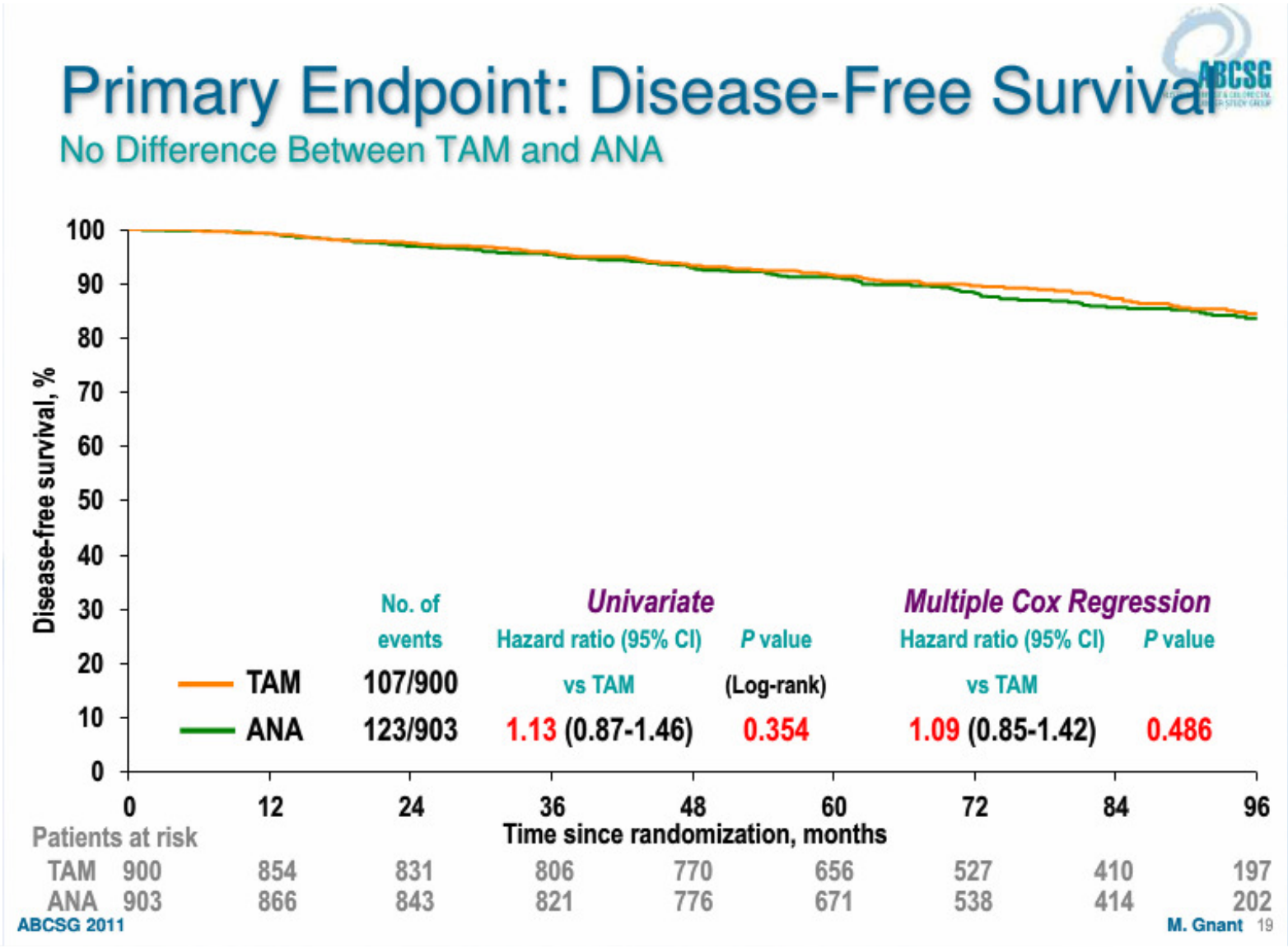
ABCSG-12 Trial Design

- Recruitment 1999-2006
- 1,803 premenopausal patients
- Stage I&II, ER+ and/or PgR+
- Duration of treatment: 3 years
- Only preoperative Chemo allowed
- Primary endpoint: DFS

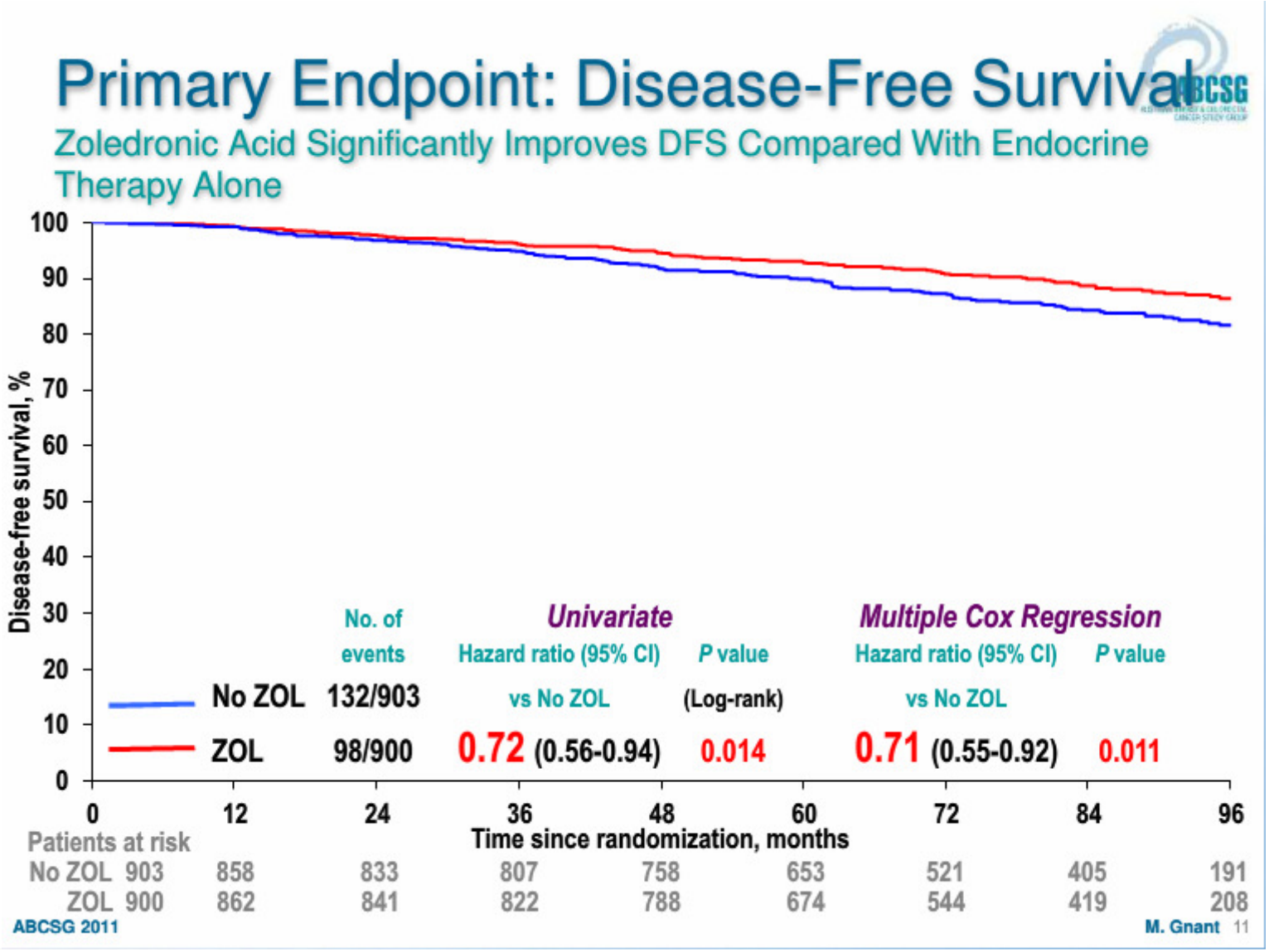


Gnant M et al. NEJM 2009; 360: 679-91
Gnant M et al. Lancet Oncol 2008; 9: 840-9
Gnant M et al. ASCO 2010 Proceedings; abs #533
Gnant M et al. Lancet Oncol 2011; 12: 631-41
Gnant M et al. ASCO 2011 Proceedings; abs #520

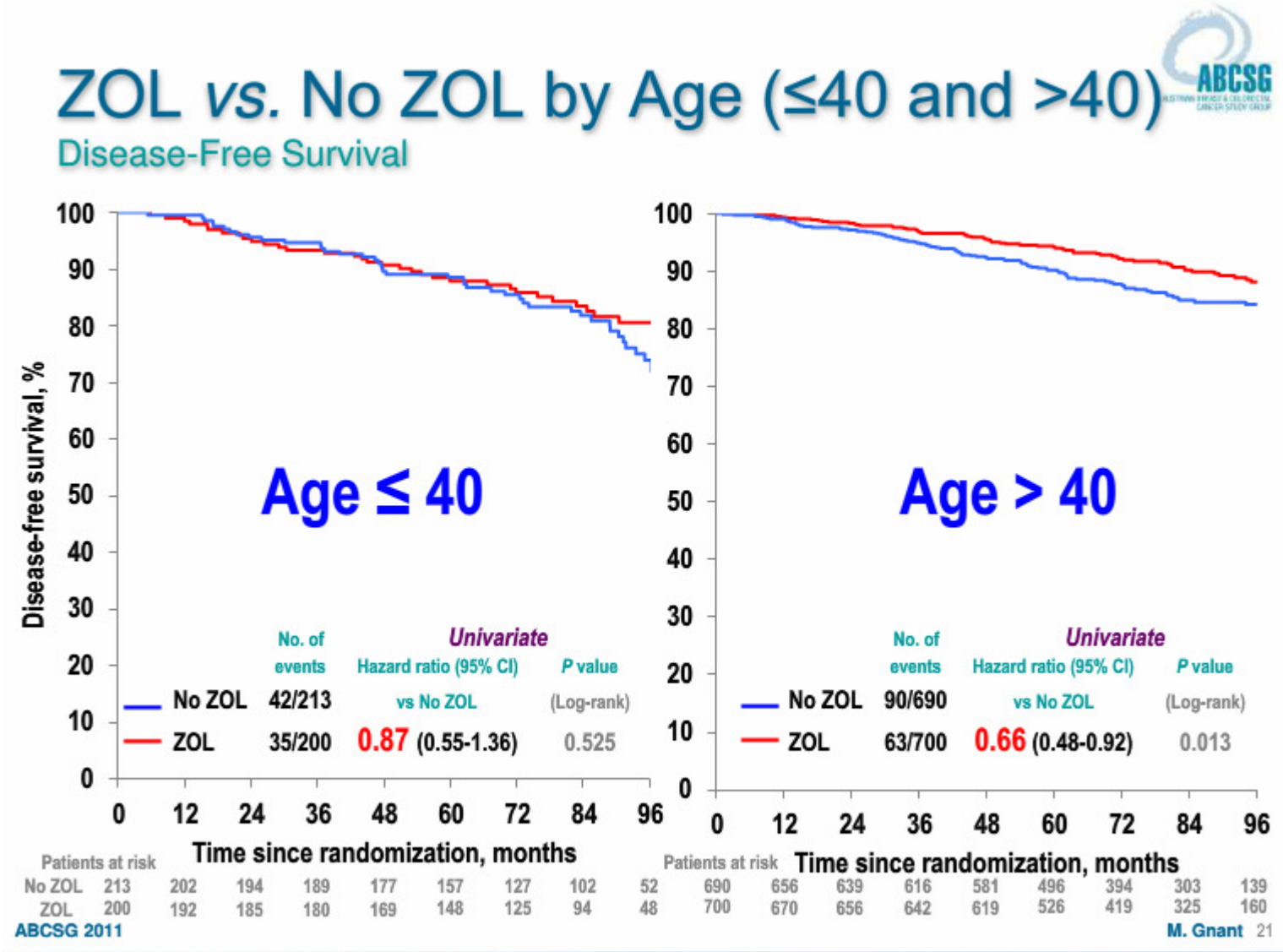
Ziekte vrije overleving TAM vs ANA (primair eindpunt)



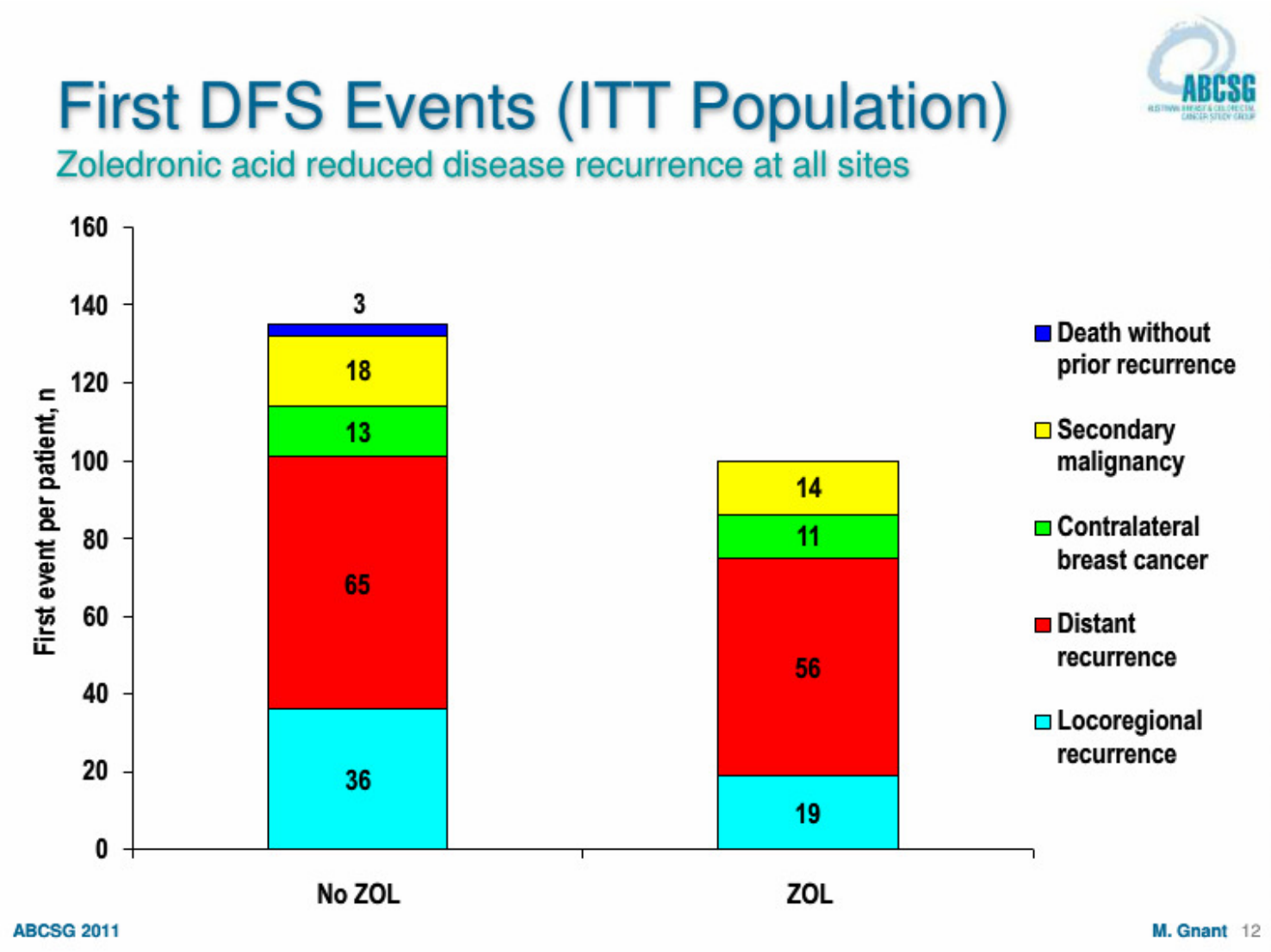
Ziekte vrije overleving ZOL vs no-ZOL (primair eindpunt)



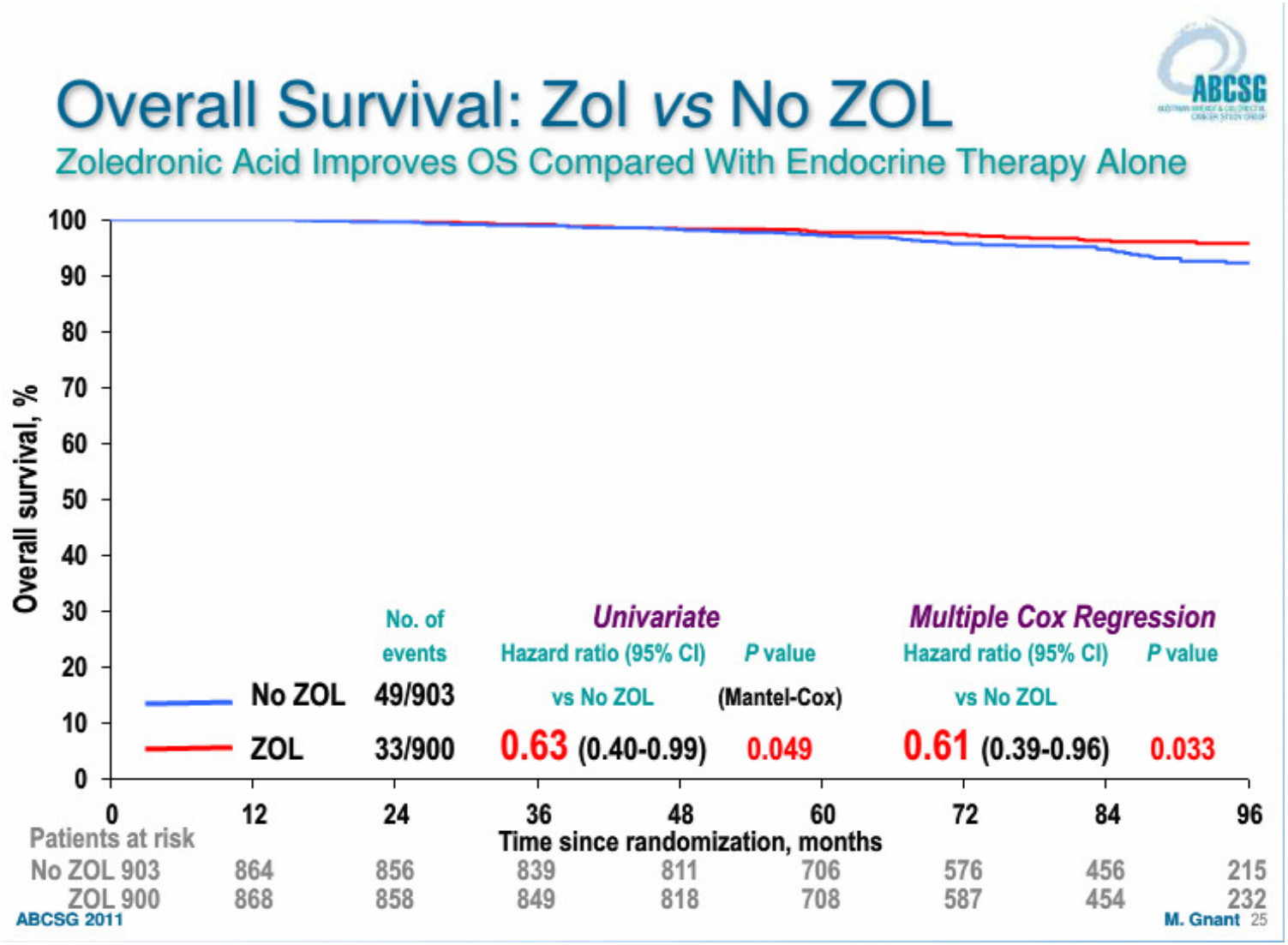
DFS ZOL vs no-ZOL
Leeftijd 40 en jonger vs 40+



Eerste DFS event



Overall survival Zol vs No Zol
Secundair eindpunt



Conclusie

Lange termijn follow-up ABSCG-12

- Significante winst DFS en OS bij pre-menopauzale patienten (hormonale therapie)
  - Patienten leeftijd 40+
- OS na 7,5 jaar follow-up = 95% (ook N+) zonder adjuvante chemotherapie!
- Geen verschil lokatie recidief met/zonder ZOL

GAIN STUDY: A PHASE III TRIAL TO COMPARE ETC VS. EC-TX AND IBANDRONATE VS. OBSERVATION IN PATIENTS WITH NODE-POSITIVE PRIMARY BREAST CANCER – 1ST INTERIM EFFICACY ANALYSIS

Möbus V, Diel IJ, Elling D, Harbeck N, Jackisch C, Thomssen C, Untch M, Conrad B, Schneeweiss A, Kreienberg R, Huober J, Müller V, Lück HJ, Bauerfeind I, Loibl S, Nekljudova V, von Minckwitz G

for the AGO-B/GBG/NOGGO study groups

Design

San Antonio Breast Cancer Symposium - Cancer Therapy and Research Center at UT Health Science Center – December 6-10, 2011

GAIN
GERMAN ADJUVANT INTERGROUP NODE-POSITIVE STUDY

Trial Design

Arm A1:

Epirubicin
150 mg/m²
q 2w

Paclitaxel
225 mg/m²
q 2w

Cyclophosphamide
2000 mg/m²
q 2w

Pegfilgrastim

Darbepoetin alfa or Epoetin beta

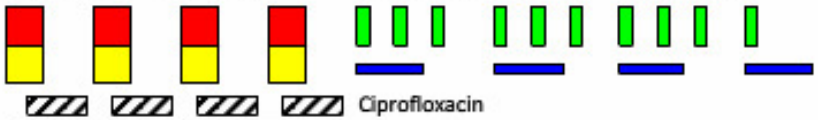
Arm B1:

Ibandronate
50 mg daily p.o.
2 yrs.

Arm A2:

Epirubicin
112.5 mg/m²
Cyclophosphamide
600 mg/m² q 2w

Paclitaxel
67.5 mg/m² weekly
Capecitabine
2000 mg/m² d1 – d14 q3w



Pegfilgrastim

Darbepoetin alfa or Epoetin beta

Arm B2:

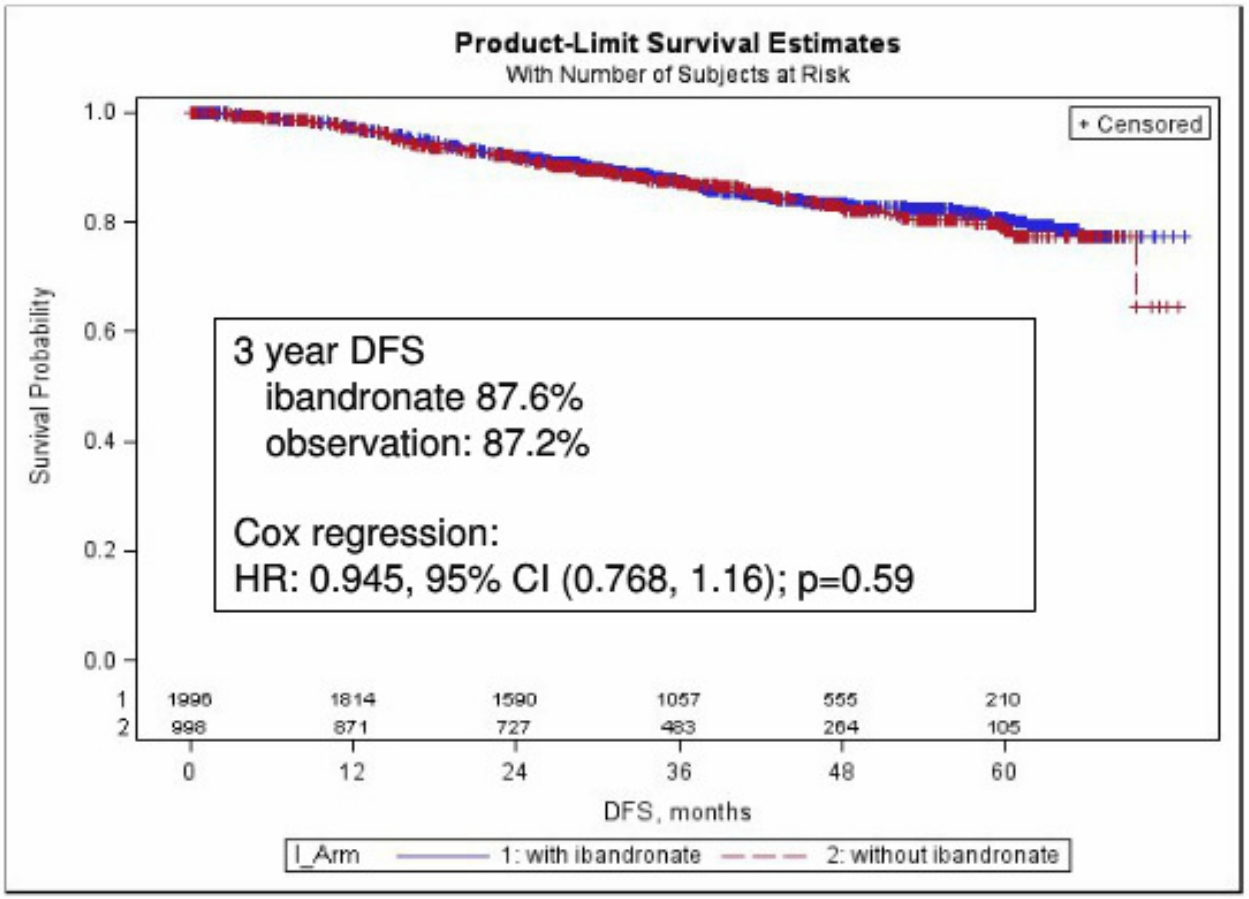
Observation

Ziekte vrije overleving (primair eindpunt)

San Antonio Breast Cancer Symposium - Cancer Therapy and Research Center at UT Health Science Center – December 6-10, 2011

GAIN
GERMAN ADJUVANT INTERGROUP NODE-POSITIVE STUDY

DFS Ibandronate vs. Observation

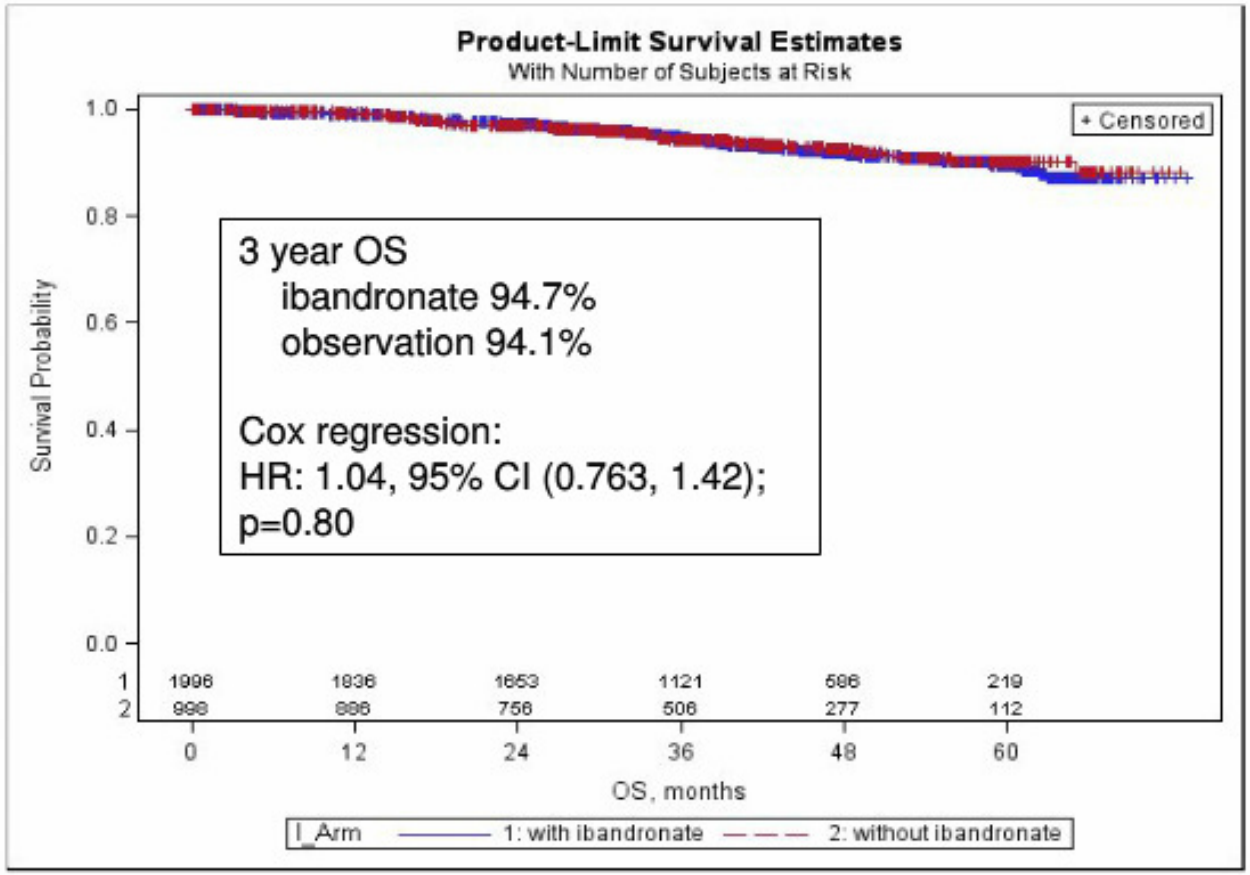


Overall survival (secundair eindpunt)

San Antonio Breast Cancer Symposium - Cancer Therapy and Research Center at UT Health Science Center – December 6-10, 2011

GAIN GERMAN ADJUVANT INTERGROUP NODE-POSITIVE STUDY

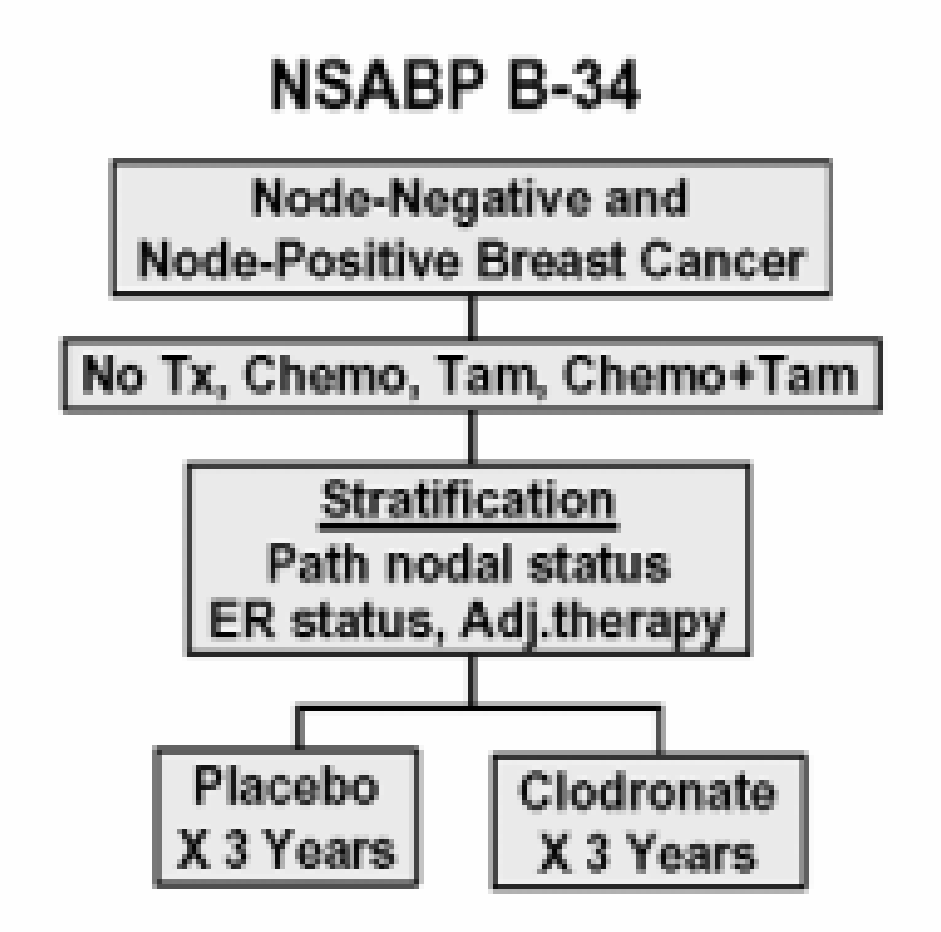
OS Ibandronate vs. Observation



Conclusie GAIN

- Nog geen resultaten data chemotherapie
- Geen verschil DFS en OS
- Geen verschil subgroep analyse

Design NSABP B-34



Conclusie NSABP B-34

- Clodronaat goed verdragen
- Probleem met compliantie
- Relatief weinig events beide groepen
- Geen verschil DFS, mogelijk positief effect 50+

- *Zijn adjuvant bisfofonaten zinvol bij adjuvante behandeling met **chemotherapie** in mammacarcinoom?*

Neen, mogelijk wel klein voordeel bij postmenopauzale vrouwen, maar voorlopig geen standaard therapie gezien tegenstrijdige studieresultaten.

Advies: deelname TEAM IIb

Dank voor uw aandacht