Poster Discussion session
Breast cancer, metastatic

Poster 322, 323, 325 & LBA14

Thomas Bachelot,
Centre Léon Bérad, Lyon

Disclosure

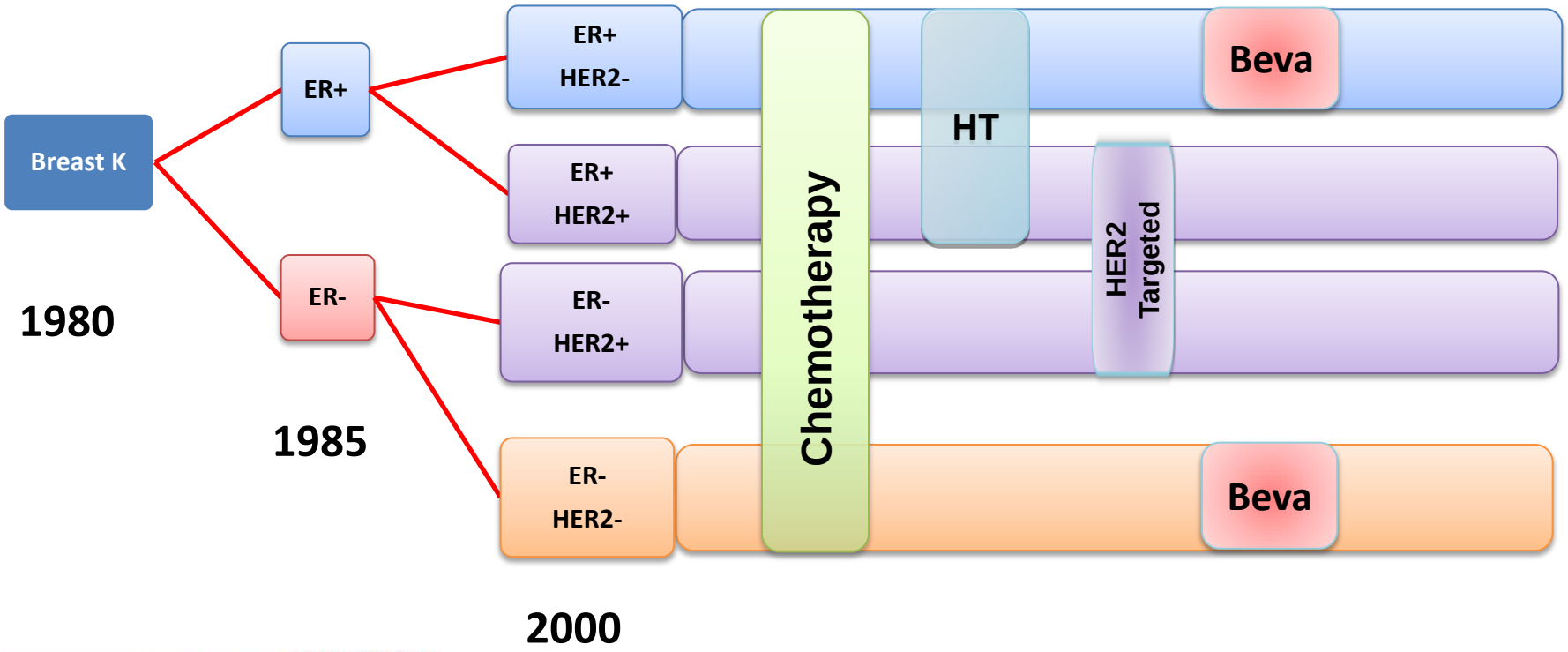
Board and reserach funding:

- Roche
- Novartis
- GSK

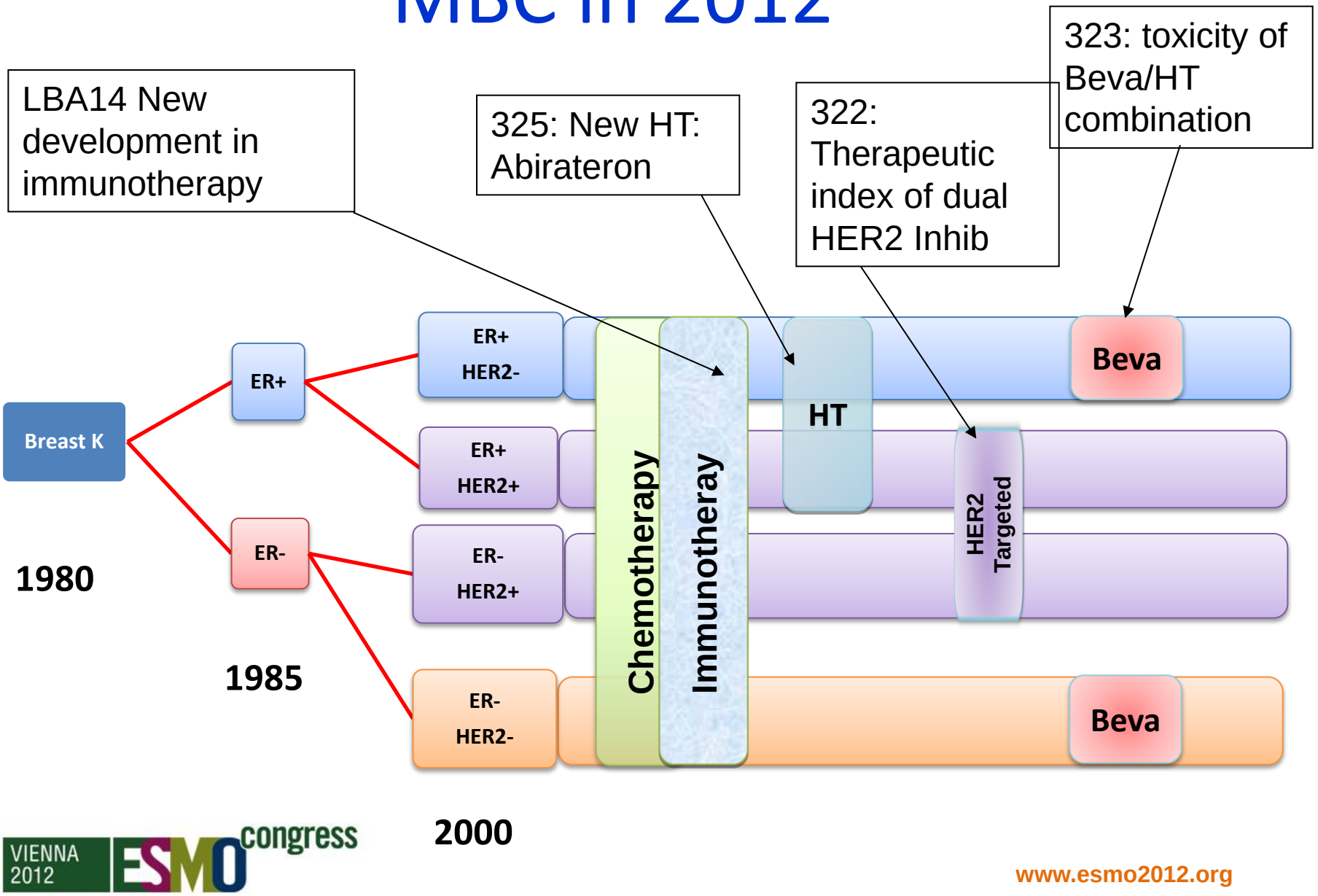
MBC in 2012

Multiple disease

Multiple treatment



MBC in 2012


LBA14 New development in immunotherapy
325: New HT: Abirateron
322: Therapeutic index of dual HER2 Inhib
323: toxicity of Beva/HT combination
Breast K
ER+
ER-
ER+ HER2-
ER+ HER2+
ER- HER2+
ER- HER2-
Chemotherapy
Immunotheray
HT
HER2 Targeted
Beva
Beva
1980
1985
2000

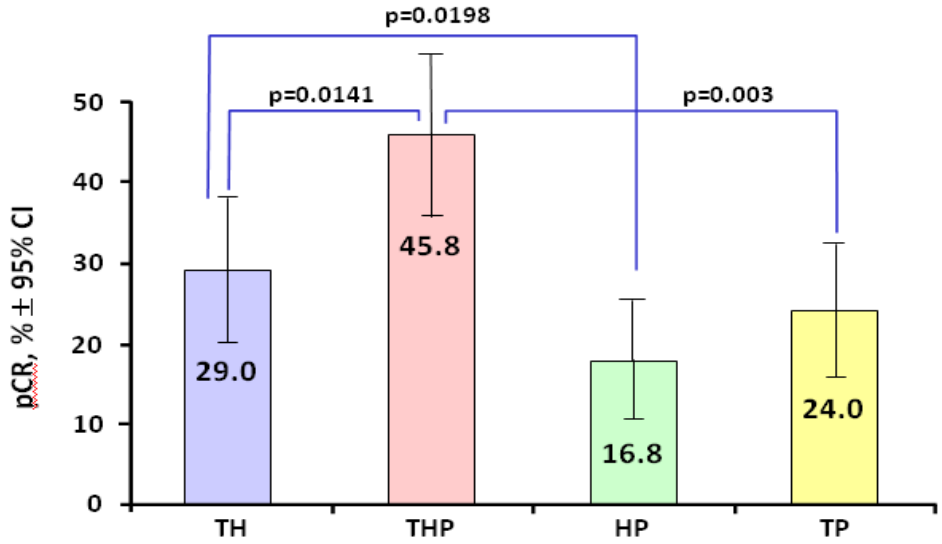
322PD

A TREATMENT-INTERACTION ANALYSIS BALANCING PATHOLOGICAL COMPLETE RESPONSES (PCR) AND CARDIOTOXICITY OF SINGLE-(S)/DUAL-(D) HER2 INHIBITION AND NEOADJUVANT CHEMOTHERAPY (CT) BACKBONE IN OPERABLE/LOCALLY ADVANCED BREAST CANCER (O/LABC) PATIENTS.

Emilio Bria et Col, Verona, ITALY

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

NeoSphere: Primary endpoint – pathologic complete response (ITT population)



H, trastuzumab; P, pertuzumab; T, docetaxel
p values from Cochran-Mantel-Haenszel test and adjusted for multiplicity

Gianni L, et al. Lancet Oncol 2011 DOI:10.1016/S1470-2045(11)70336-9

322PD

A TREATMENT-INTERACTION ANALYSIS BALANCING PATHOLOGICAL COMPLETE RESPONSES (PCR) AND CARDIOTOXICITY OF SINGLE-(S)/DUAL-(D) HER2 INHIBITION AND NEOADJUVANT CHEMOTHERAPY (CT) BACKBONE IN OPERABLE/LOCALLY ADVANCED BREAST CANCER (O/LABC) PATIENTS.

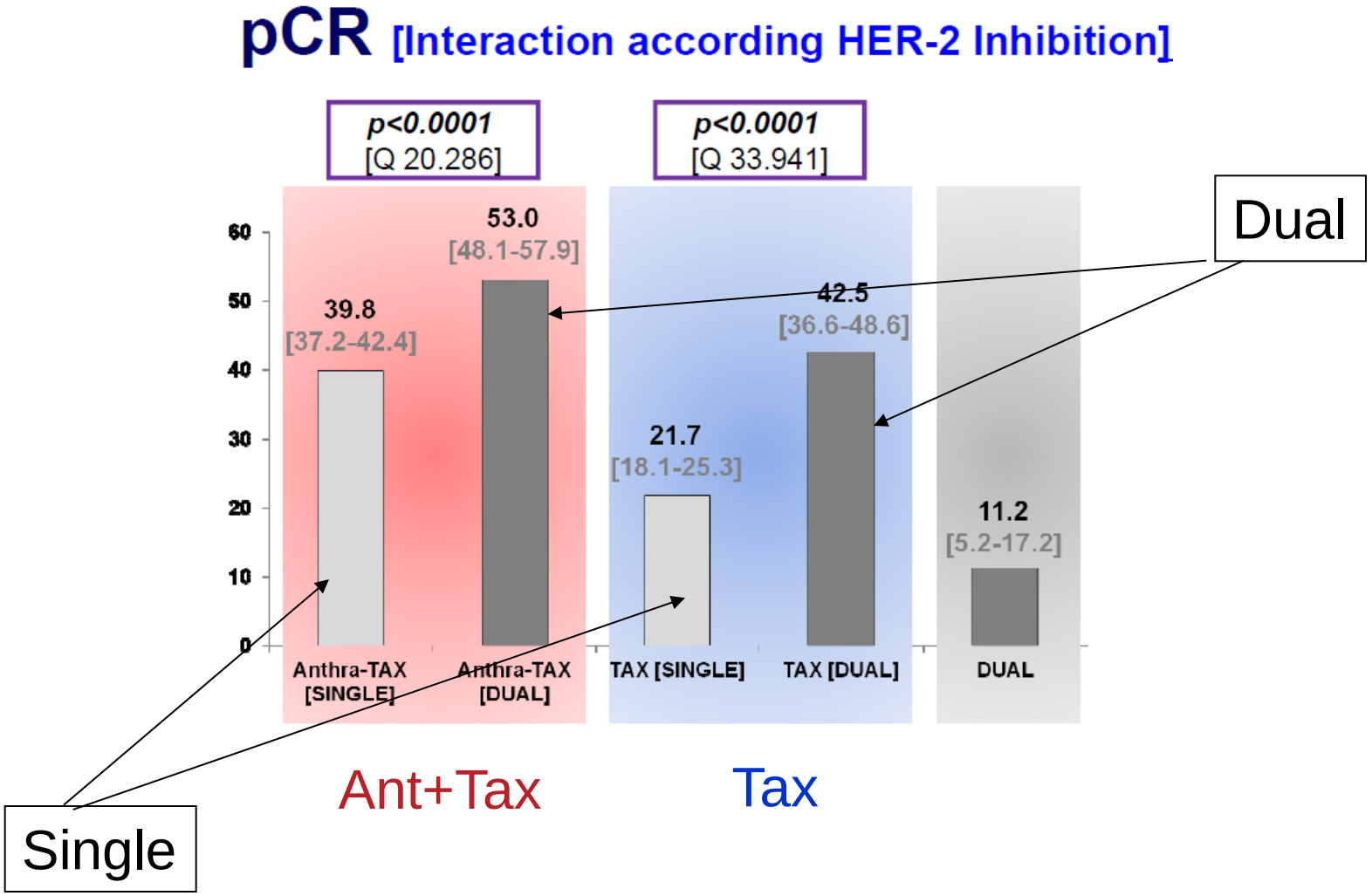
Emilio Bria et Col, Verona, ITALY

- With the intent **to weigh the relative impact upon pCR and clinically meaningful toxicities of both DUAL HER-2 inhibition and the addition of Anthra**, a **treatment interaction analysis** of the available Randomized CTs was accomplished.
- pCR , BCS, Grade 3-4 Neutro, Cardio and FN events were extracted, with a **literature-based meta-analysis approach**.

10 RCTs (2,627 pts), Phase IIR [5 RCTs, 888 pts], Phase III [5 RCTs, 1,739 pts]

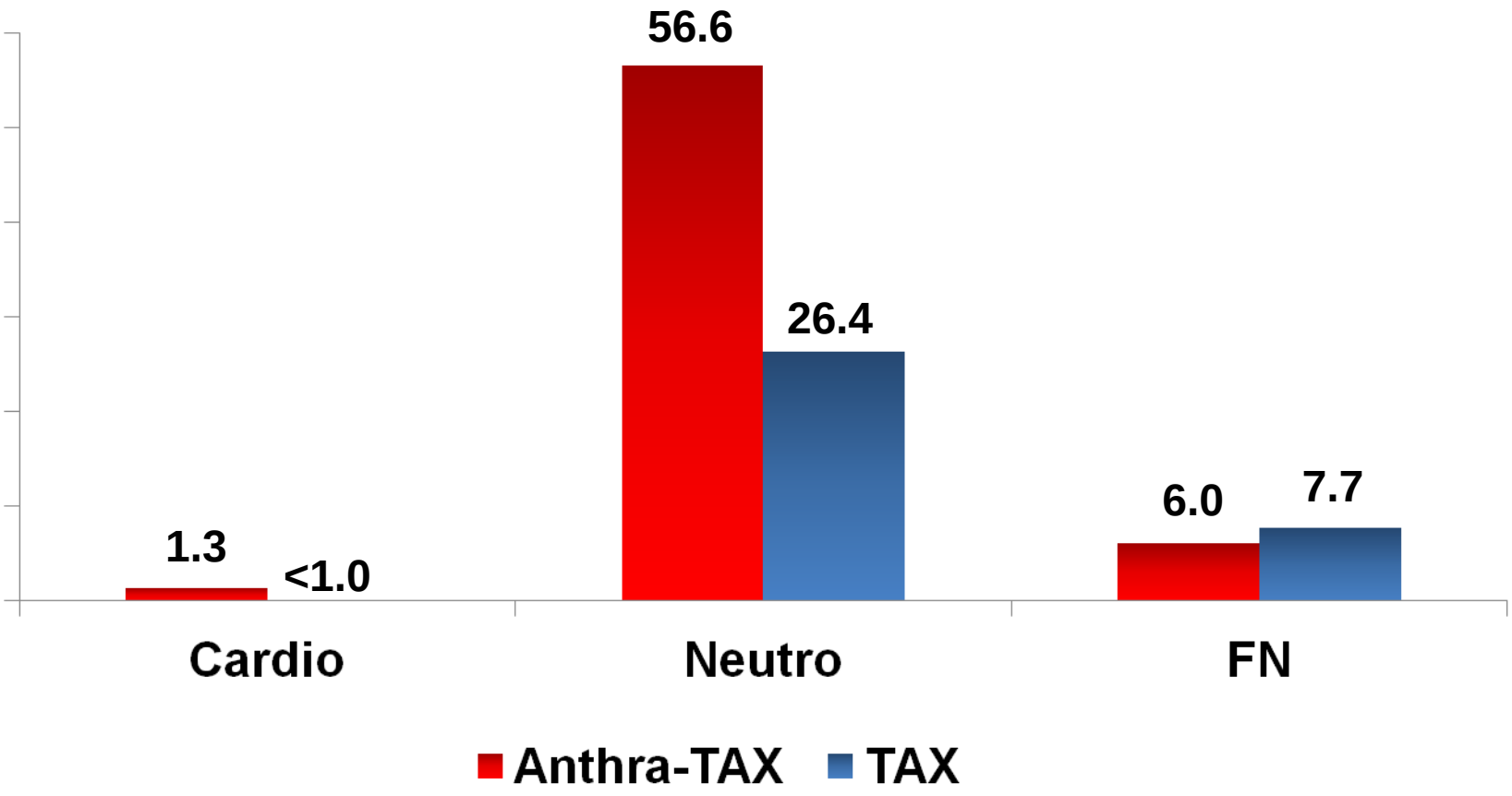
  - A sensitivity analysis was accomplished, according to:
    - **SINGLE/DUAL HER-2 inhibition,**
    - **Hormonal Receptors (HRs),**
    - **Administered CT**

pCR according to HER2 inhibition and Chemo: 2>1 !!



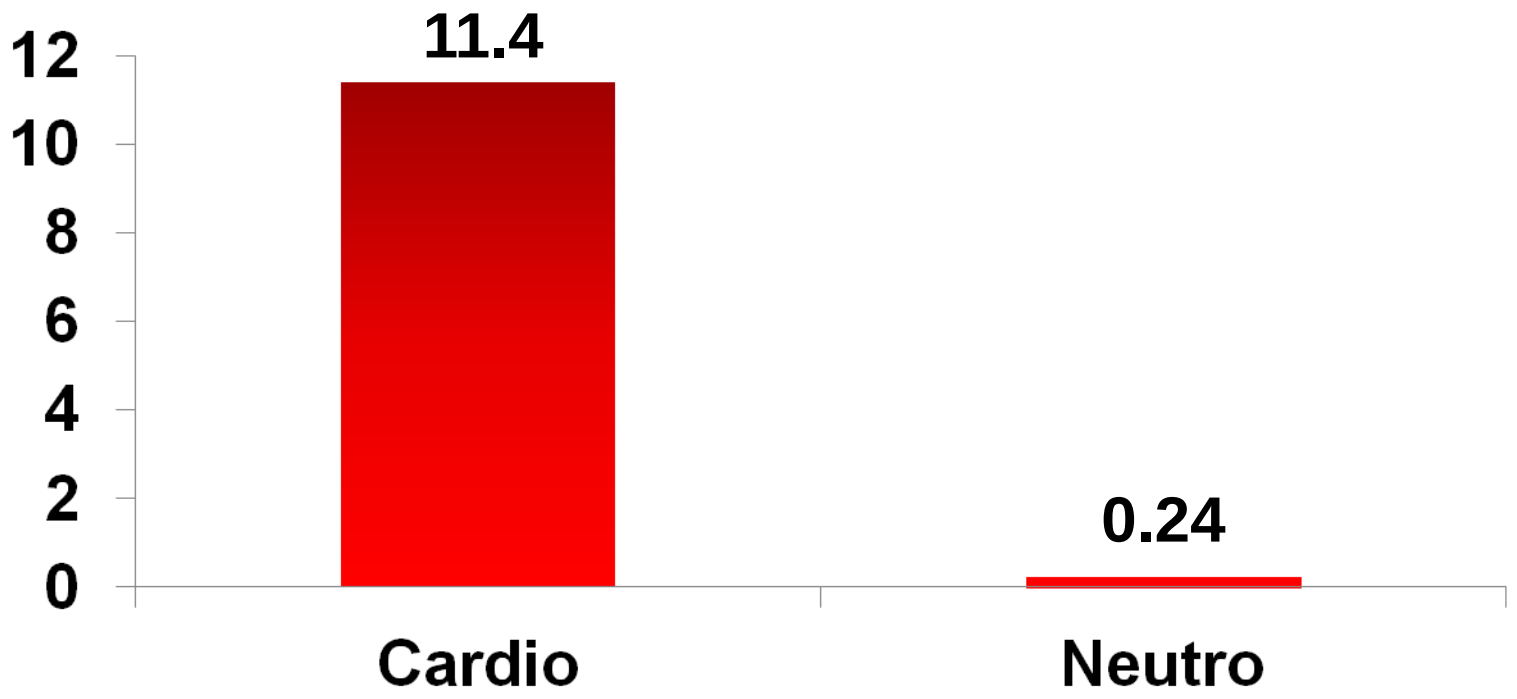
Toxicity [Interaction according to Chemo]

p=0.006 [Q 7.534]	***p<0.0001*** [Q 84.202]	***p=0.769*** [Q 0.0.86]



LHH [Weighted with the NNT of pCR]

i.e. how much is more likely to achieve a pCR than to be harmed when adding Anthra to TAX



Legend: LHH: likelyhood of bieng helped and/or harmed; pCR: pathological complete response rate; NNH: number needed to harm; NNT: number needed to treat; Cardio: grade 3-4 cardiotoxicity; Neutro: grade 3-4 neutropenia; FN; febrile neutropenia

- Patients receiving a **Anti-HER-2 treatment** **significantly benefit from the addition of Anthra to TAX** , in terms of pCR and BCS, **regardless of the inhibition (SINGLE or DUAL).**
- Grade 3-4 cardiotoxicity accounts for an additional 1.2% overall risk against Anthra plus TAX (1.3%) in comparison to TAX alone (0.1%).
- Patients receiving Anthra in addition to TAX are >**11 times more likely to achieve a pCR than to be harmed** in terms of clinically meaningful cardiotoxicity.

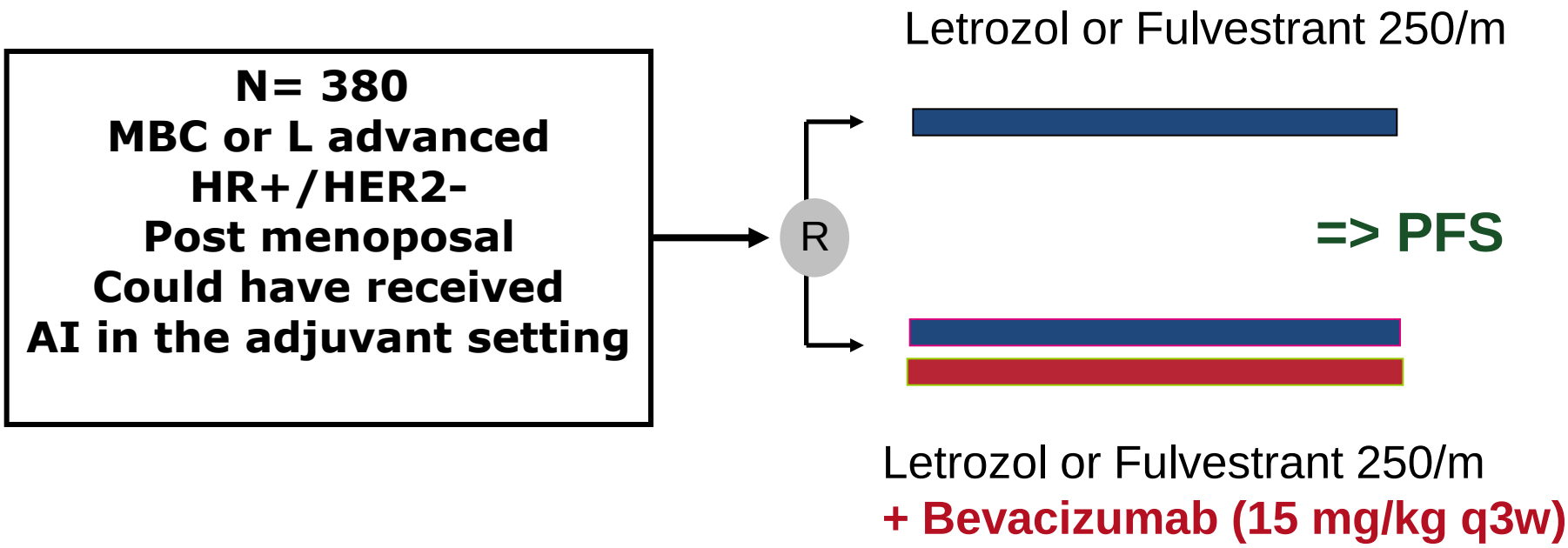
Ok for Adjuvant/neoAdjuvant, but for MBC ??

- Patients receiving a **Anti-HER-2 treatment significantly benefit from the addition of Anthra to TAX** , in terms of pCR and BCS, **regardless of the inhibition (SINGLE or DUAL).**
- Grade 3-4 cardiotoxicity accounts for an additional 1.2% overall risk against Anthra plus TAX (1.3%) in comparison to TAX alone (0.1%).
- Patients receiving Anthra in addition to TAX are >**11 times more likely to achieve a pCR than to be harmed** in terms of clinically meaningful cardiotoxicity.

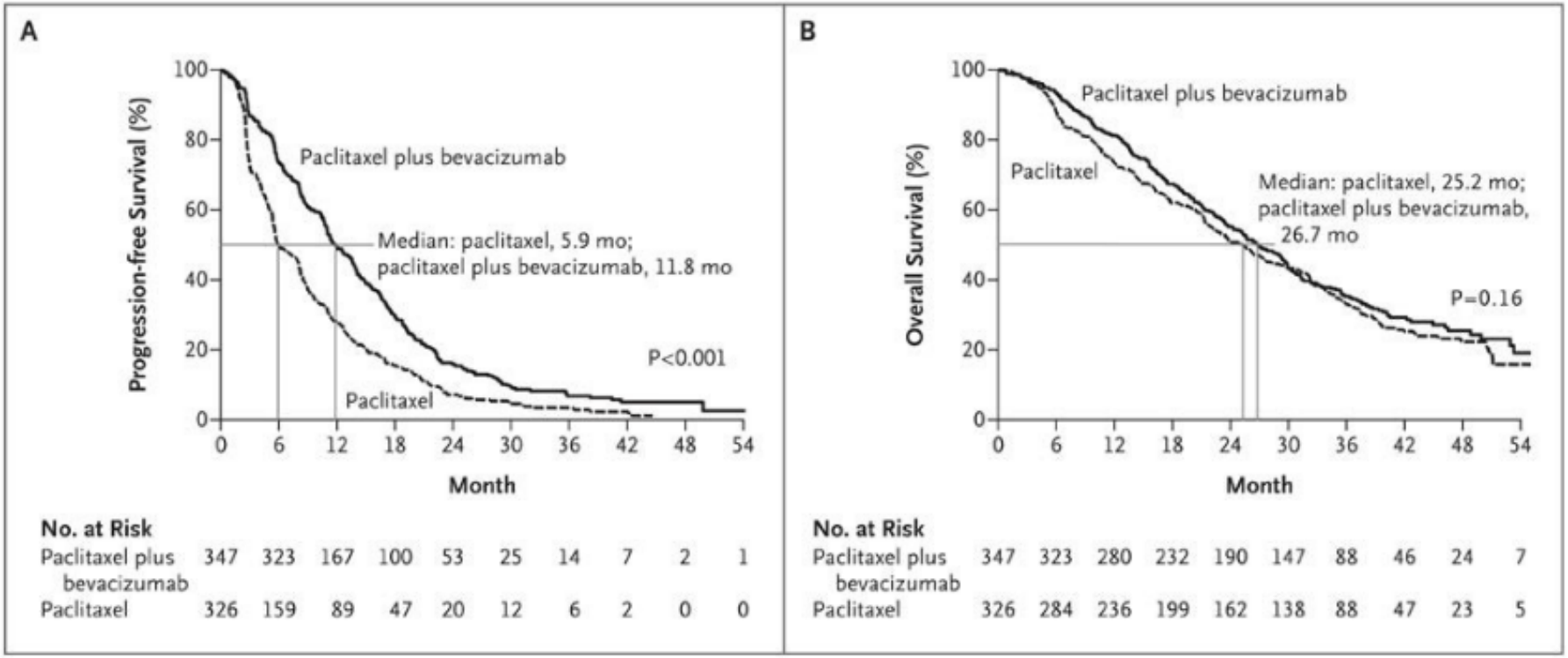
Is it worth it ? We will have to wait for TTP and survival results

323 PD: Phase III trial evaluating the addition of bevacizumab to endocrine therapy as first-line treatment for advanced breast cancer: the GEICAM/GBG LEA study. Safety Analysis

Sibylle Loibl et col., German Breast Group & GEICAM



Bevacizumab and MBC: its utility is still controversial



Miller, N ENGL J MED 2007; 357:2666-2676;

Bevacizumab and MBC: its utility is still controversial

Treatment-Related Mortality With Bevacizumab in Cancer Patients

A Meta-analysis

Vishal Ranpura, MD
Sanjaykumar Hapani, MD
Shenhong Wu, MD, PhD

Context Fatal adverse events (FAEs) have been reported in cancer patients treated with the widely used angiogenesis inhibitor bevacizumab in combination with chemotherapy. Currently, the role of bevacizumab in treatment-related mortality is not clear.

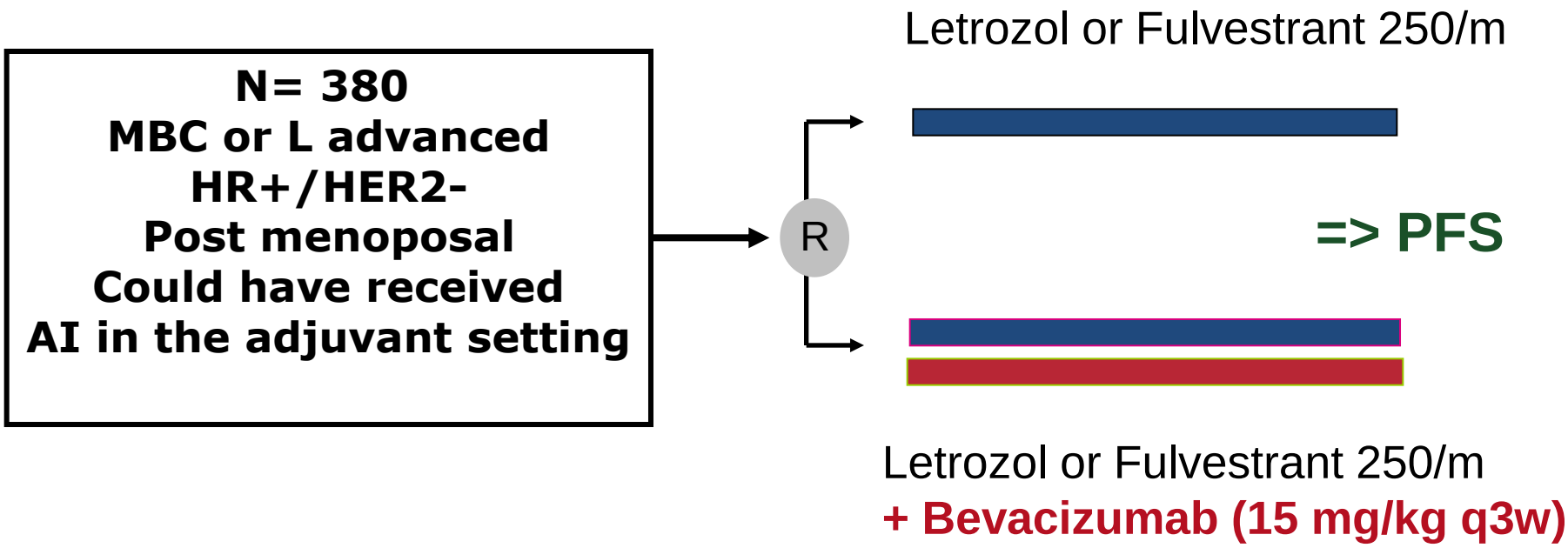
Conclusion In a meta-analysis of RCTs, bevacizumab in combination with chemotherapy or biological therapy, compared with chemotherapy alone, was associated with increased treatment-related mortality.

JAMA. 2011;305(5):487-494

www.jama.com

323 PD: Phase III trial evaluating the addition of bevacizumab to endocrine therapy as first-line treatment for advanced breast cancer: the GEICAM/GBG LEA study. Safety Analysis

Sibylle Loibl et col., German Breast Group & GEICAM



Significant different Non-haematological AEs grade 1-4

	ET n(%)	ET-B n(%)	P-value
Creatinine elevation	14 (8.0)	32 (17.1)	0.011
Diarrhoea	10 (5.7)	23 (12.2)	0.03
Fatigue	51 (29.0)	95 (50.5)	<0.001
Fever w/on neutropenia	6 (3.4)	17 (9.0)	0.031
Haemorrhage	3 (1.7)	35 (18.6)	<0.001
Hyperbilirubinaemia	7 (4.0)	19 (10.2)	0.026
Hypertension grade 3-4	4 (2.3)	24 (12.8)	<0.001
Liver Dysfunction	0	6 (3.2)	0.03
Liver enzymes elevation (ASAT)	49 (28.0)	87 (46.5)	<0.001
Proteinuria grade 3-4	0	11 (5.9)	0.001
Pain	83 (47.2)	128 (68.1)	<0.001
Vomiting	6 (3.4)	22 (11.7)	0.003

Deaths on Study: 7, all in the Bevacizumab arm

	Age at death	Co-morbidity at baseline	ET	ET-B
Pulmonary Embolism	**75**	**Hypertension, osteoporosis, immobility (1 month on treat.)**		**1**
Acute myocardial infarction	**82**	**Hypertension, hypercholesterolemia, obesity**		**1**
Heart Failure	**74**	**Hypertension, TIA, obesity**		**1**
Sudden Death	**73**	**Hypertension, hypercholesterolemia**		**1**
Cerebellum infarction	**53**	**None**		**1**
Liver Decompensation	**79**	**Hepatitis C, alcoholism**		**1**
Acute myocardial infarction	**53**	**None**		**1**

It's toxic: Patient selection is important

Deaths on Study: 7, all in the Bevacizumab arm

	Age at death	Co-morbidity at baseline	ET	ET-B
Pulmonary Embolism	**75**	**Hypertension, osteoporosis, immobility (1 month on treat.)**		**1**
Acute myocardial infarction	**82**	**Hypertension, hypercholesterolemia, obesity**		**1**
Heart Failure	**74**	**Hypertension, TIA, obesity**		**1**
Sudden Death	**73**	**Hypertension, hypercholesterolemia**		**1**
Cerebellum infarction	**53**	**None**		**1**
Liver Decompensation	**79**	**Hepatitis C, alcoholism**		**1**
Acute myocardial infarction	**53**	**None**		**1**

Waiting for efficacy results !

325PD

Phase I/II trial of Abiraterone Acetate (AA) in estrogen receptor (ER) or androgen receptor (AR) positive metastatic breast cancer (MBC); Chau Ng et col, Royal Marsden Hospital, UK.

Phase I/II trial of AA with hydrocortisone

Two patient population:

- **ERα+/AR+ : 32pts,** all previously received HT
- **ERα-/AR+ : 6pts** all previously received CT

=> Role of Androgen receptor in BC biology

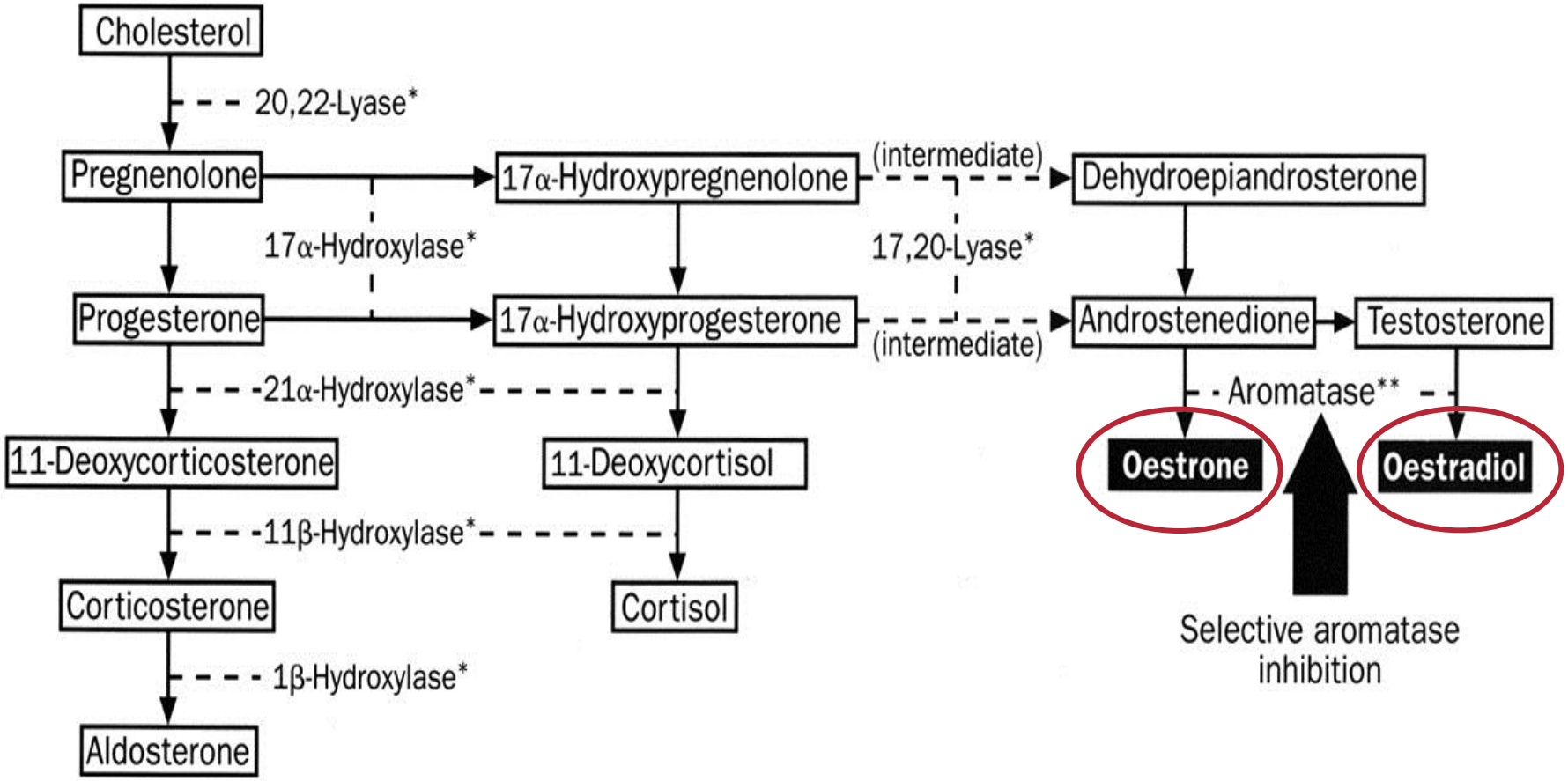
=> Possible therapeutic potential

Role of AR in BC ??

- **Most frequent HR on BC cells !**
- **Mostly a good prognosis factor**
- **In vitro, Its inhibition may inhibits or activate BC proliferation, depending on the model !!**
- **Some interest in TNBC as it is expressed in 10-35% of cases**

Peters, Cancer Res 2009; 69: 6131-40; Garay, Am J Cancer Res 2012;2(4):434-445

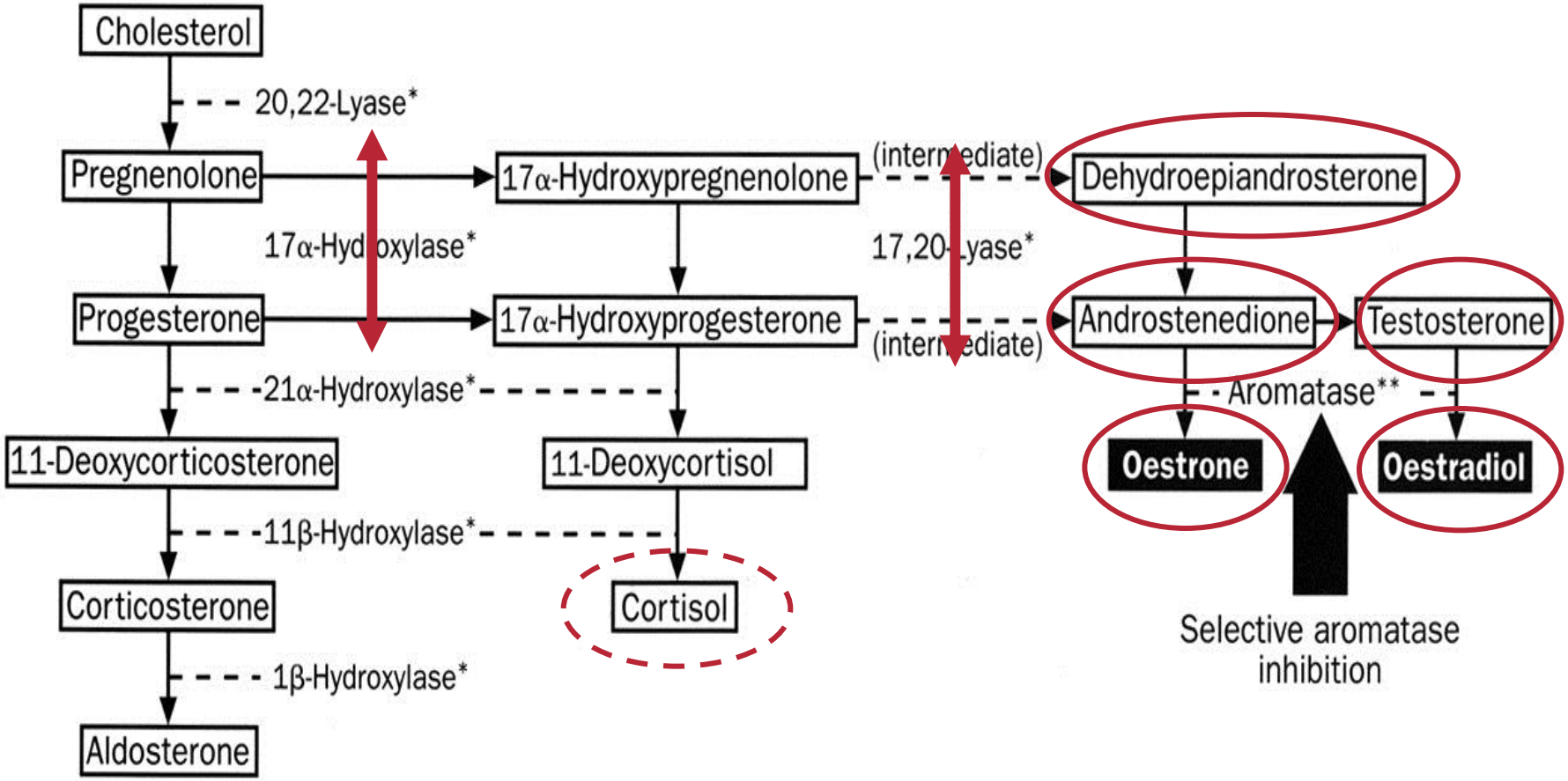
Estrogen synthesis from cholesterol
AI biological action



Biosynthesis of oestrogens: different targets of selective** and non-selective* aromatase inhibitors.

Abiraterone is a CYP17 inhibitor

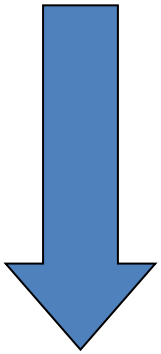
=> Decrease both androgen and estrogen



Biosynsthesis of oestrogens: different targets of selective** and non-selective* aromatase inhibitors.

Abiraterone is a CYP17 inhibitor

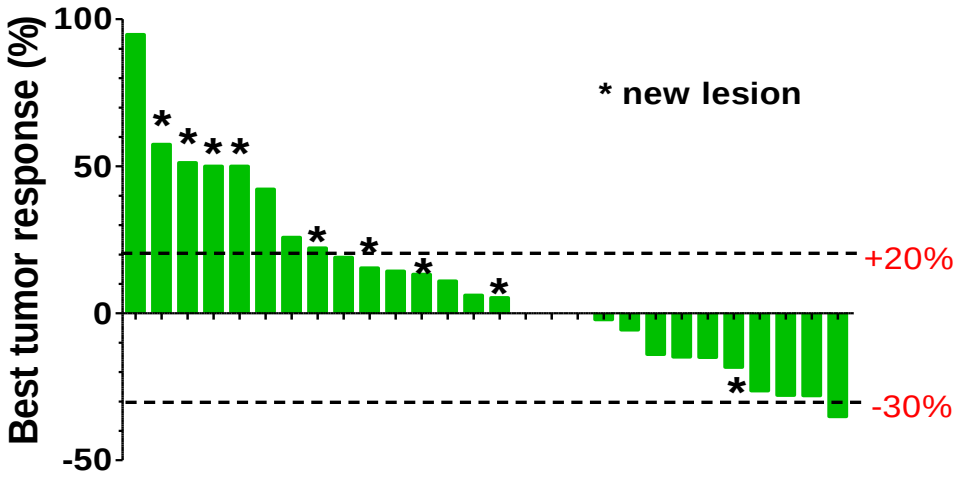
=> Decrease both androgen and estrogen



Which one is responsible for clinical efficacy ?

Phase I/II trial of Abiraterone Acetate (AA) in estrogen receptor (ER) or androgen receptor (AR) positive metastatic breast cancer (MBC)

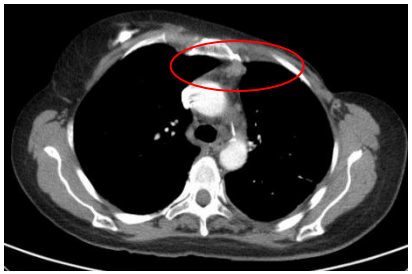
ERα+/AR+



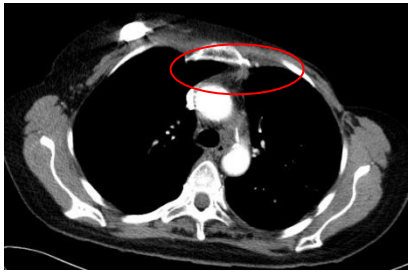
Size of target tumor lesions c/w baseline.

In ERα+/AR+ pts
RR: 4%; CBR: 22%

ERα-/AR+



November 2011



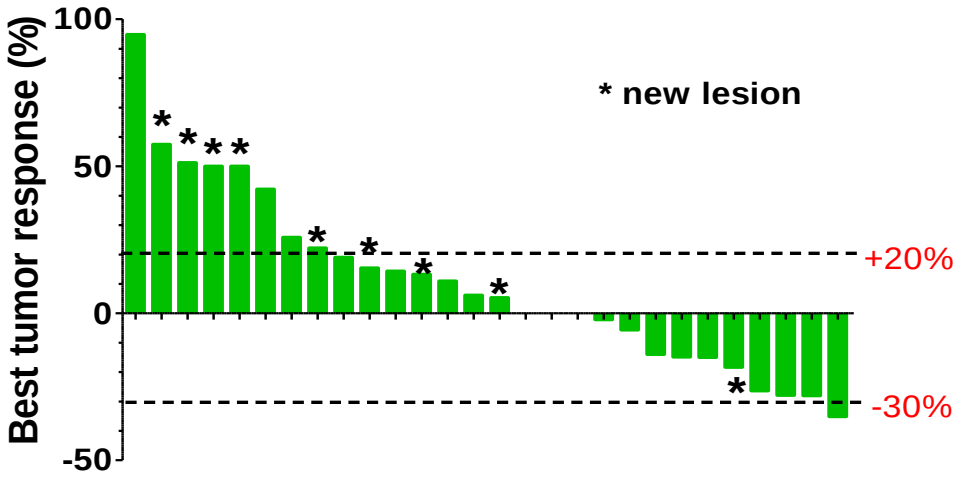
March 2012

Tumour reduction not achieving confirmed PR in internal mammary node and pleural nodule

In ER-/AR+ pts:
1 minor response (7 m)
CBR: 1/6

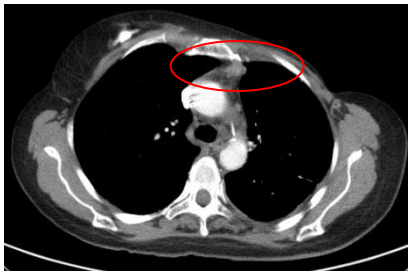
Phase I/II trial of Abiraterone Acetate (AA) in estrogen receptor (ER) or androgen receptor (AR) positive metastatic breast cancer (MBC)

ERα+/AR+

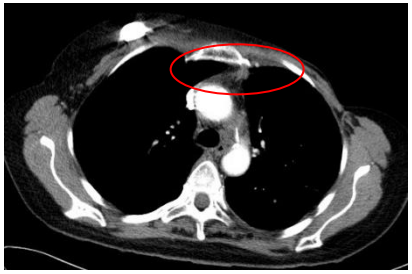


Size of target tumor lesions c/w baseline.

ERα-/AR+



November 2011



March 2012

Tumour reduction not achieving confirmed PR in internal mammary node and pleural nodule

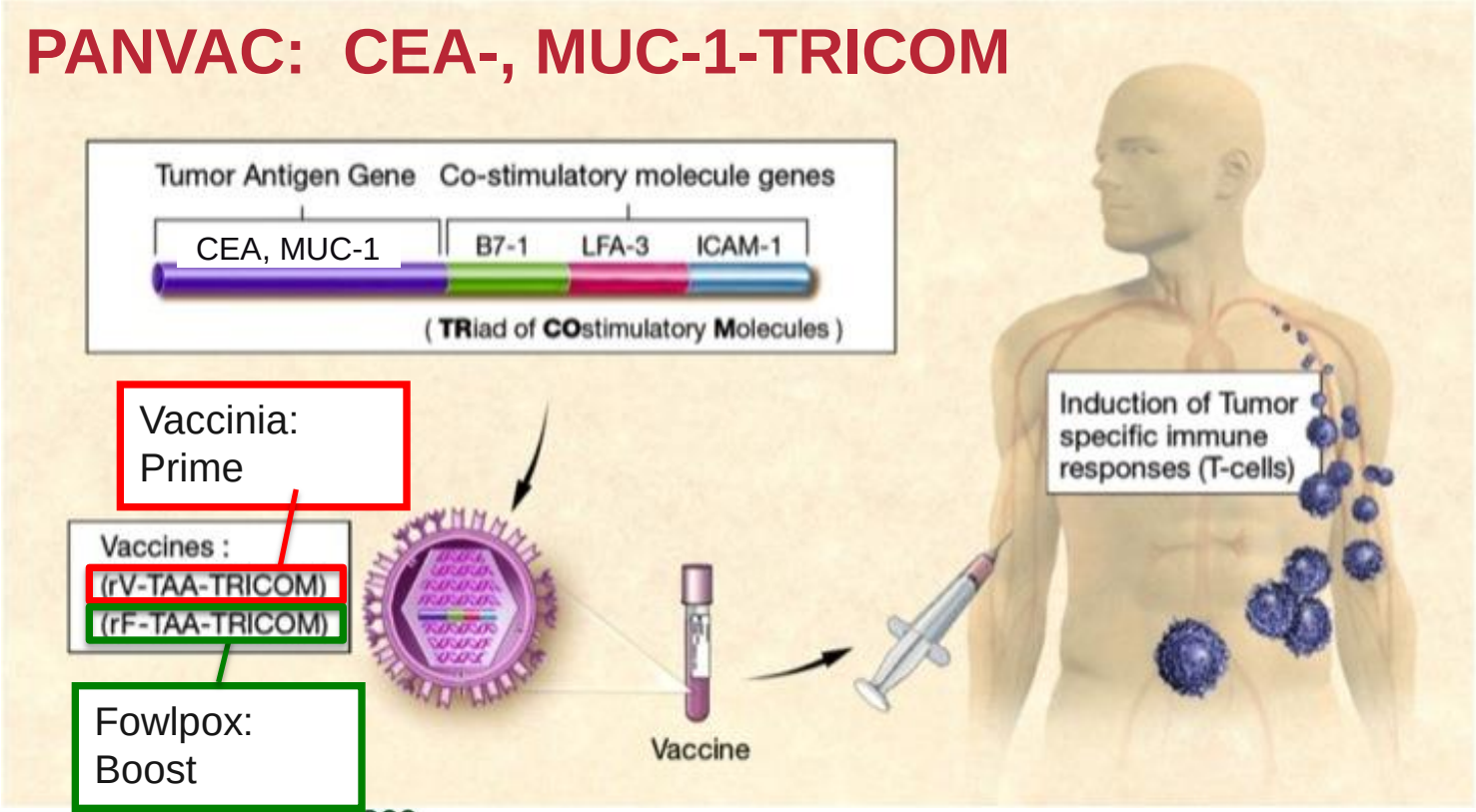
Potential New hormonal therapy

=> Need predictive factor

=> Need more knowledge of AR role in breast carcinogenesis

LBA14

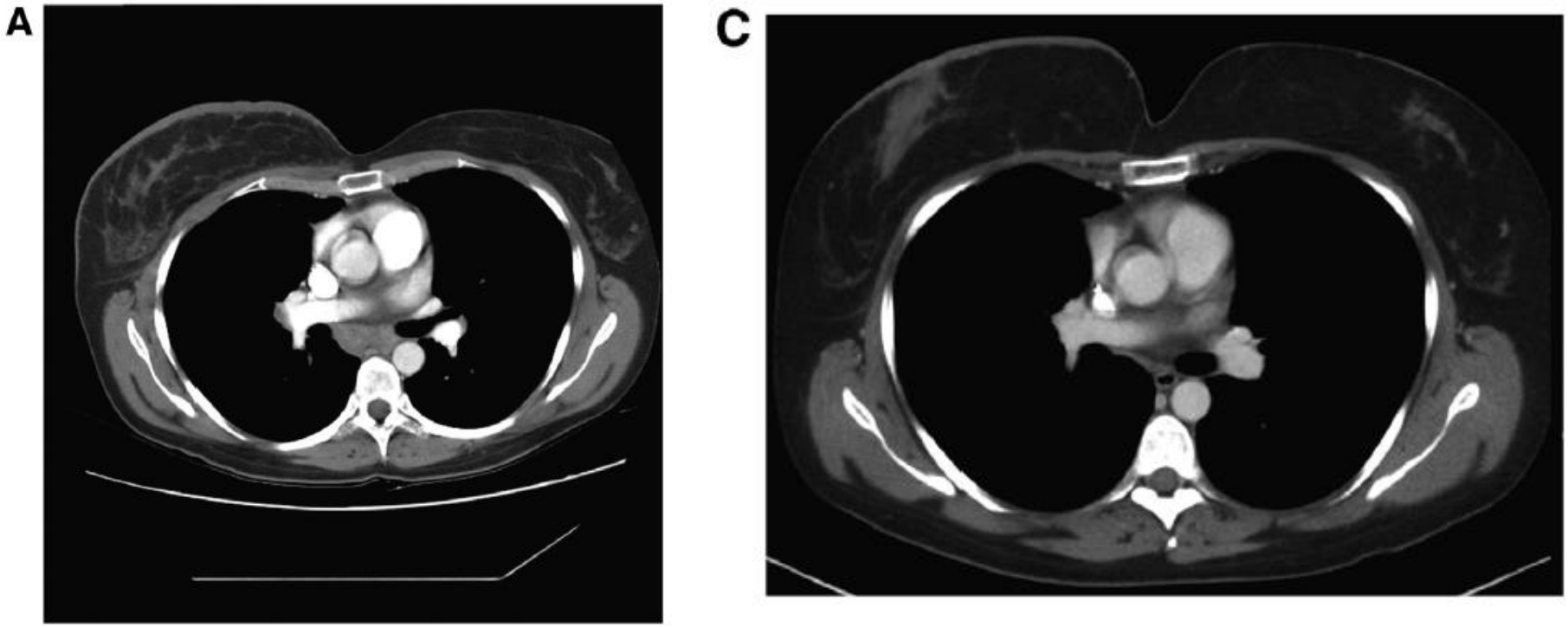
A phase 2 randomized trial of docetaxel alone or in combination with therapeutic cancer vaccine, CEA-, MUC-1-TRICOM Christopher R. Heery et al., NCI



Pilot Study of MUC-1/CEA/TRICOM Poxviral-Based Vaccine (PANVAC) on 26 breast and ovarian cancer

For the 12 MBC, median time to progression was 2.5 months (1–37+) and median overall survival was 13.7 months. Four patients had stable disease

On patient was in PR after 10 months of vaccine and in CR after 18 months (C). It lasted at least 3 years

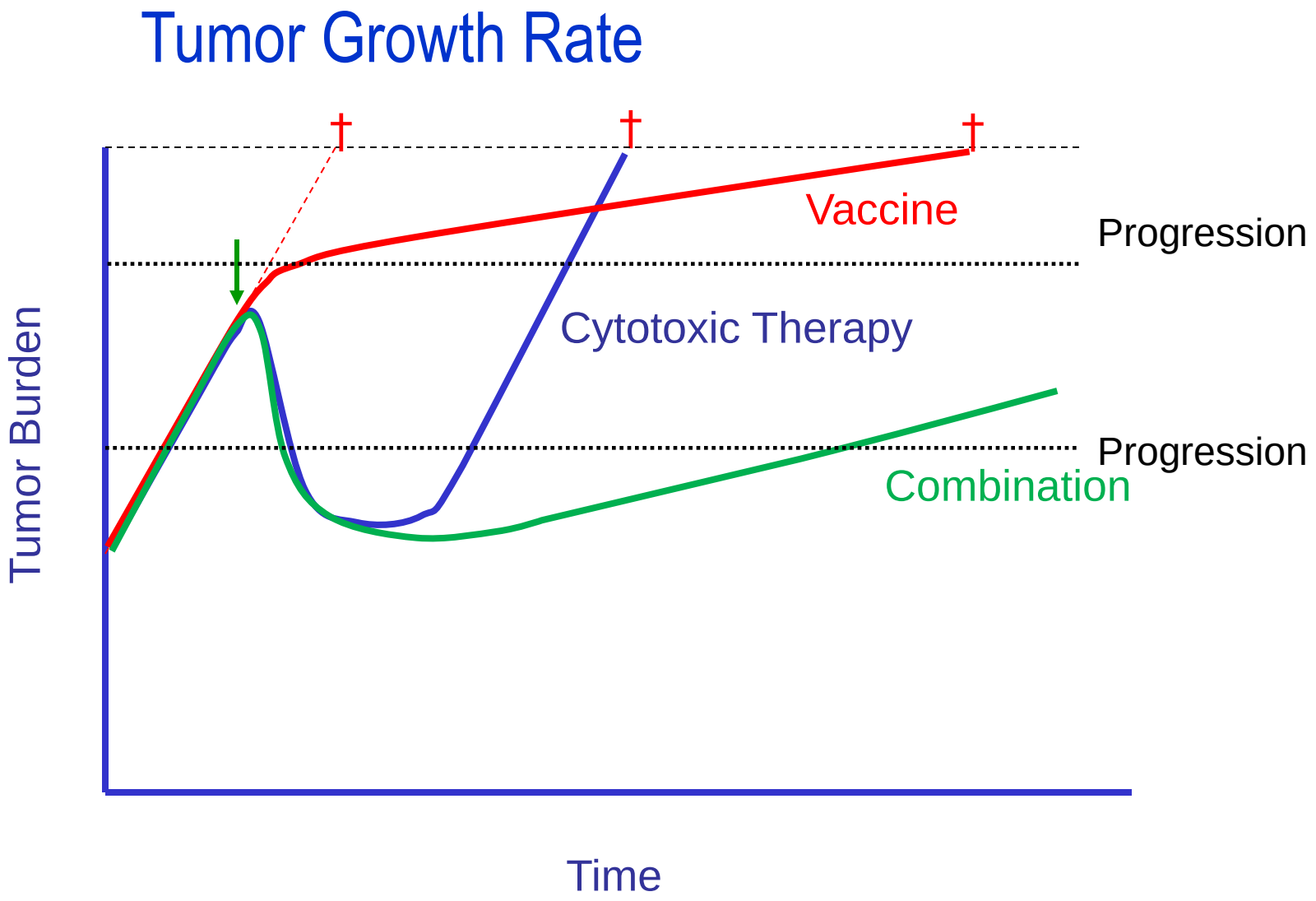


Mohebtash M et al. Clin Cancer Res 2011;17:7164-7173

Rational for combination of PANVAC and chemotherapy

- Docetaxel, may allow time for immune response to occur. If vaccine slows growth rate, time to progression on combination arm should improve.
- Docetaxel enhances expression of MHC class I and tumor associated antigens (TAAs), which leads greater cytolytic T-cell (CTL) killing (Hodge 2008)
- “Danger Signals” are created by chemotherapy induced tumor cell lysis, which may increase the immune response (Matzinger 1994)
- Chemotherapy-induced lysis of cells, may expose an activated immune response to new TAAs for CTL to target (Zitvogel, Kroemer)

Rational for combination of PANVAC and chemotherapy

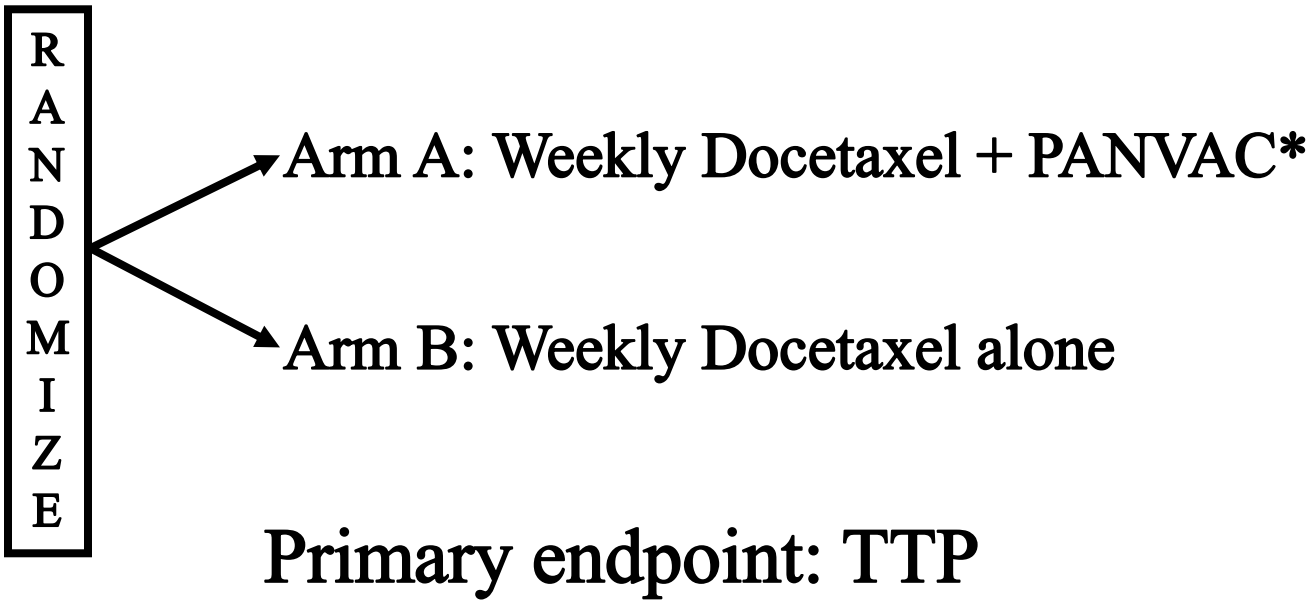


Stein W, Gulley JL, et al. *Clin Ca Res*, 2011

National Cancer Institute

Study Schema

Patient Population: Metastatic Breast Cancer (Docetaxel Naïve) n=48



*PANVAC given day 1, 15, 29, then every 4 weeks

NCI 6977: PI, Gulley; M. D. Anderson (Ibrahim)

Started : 5/23/2006
Completed accrual 2/28/2012

National Cancer Institute

Statistical Design

- Phase 2.5 design: employs one-tailed alpha = 0.10, aiming for a P = 0.10 to indicate a strong trend toward benefit
- Used this design for small trial, goal to guide statistics for a larger phase 3 only
- Based on 80% power to detect a difference between docetaxel alone arm (assumed 4.2 month median PFS) and combination (assumed 8 month median PFS)

National Cancer Institute

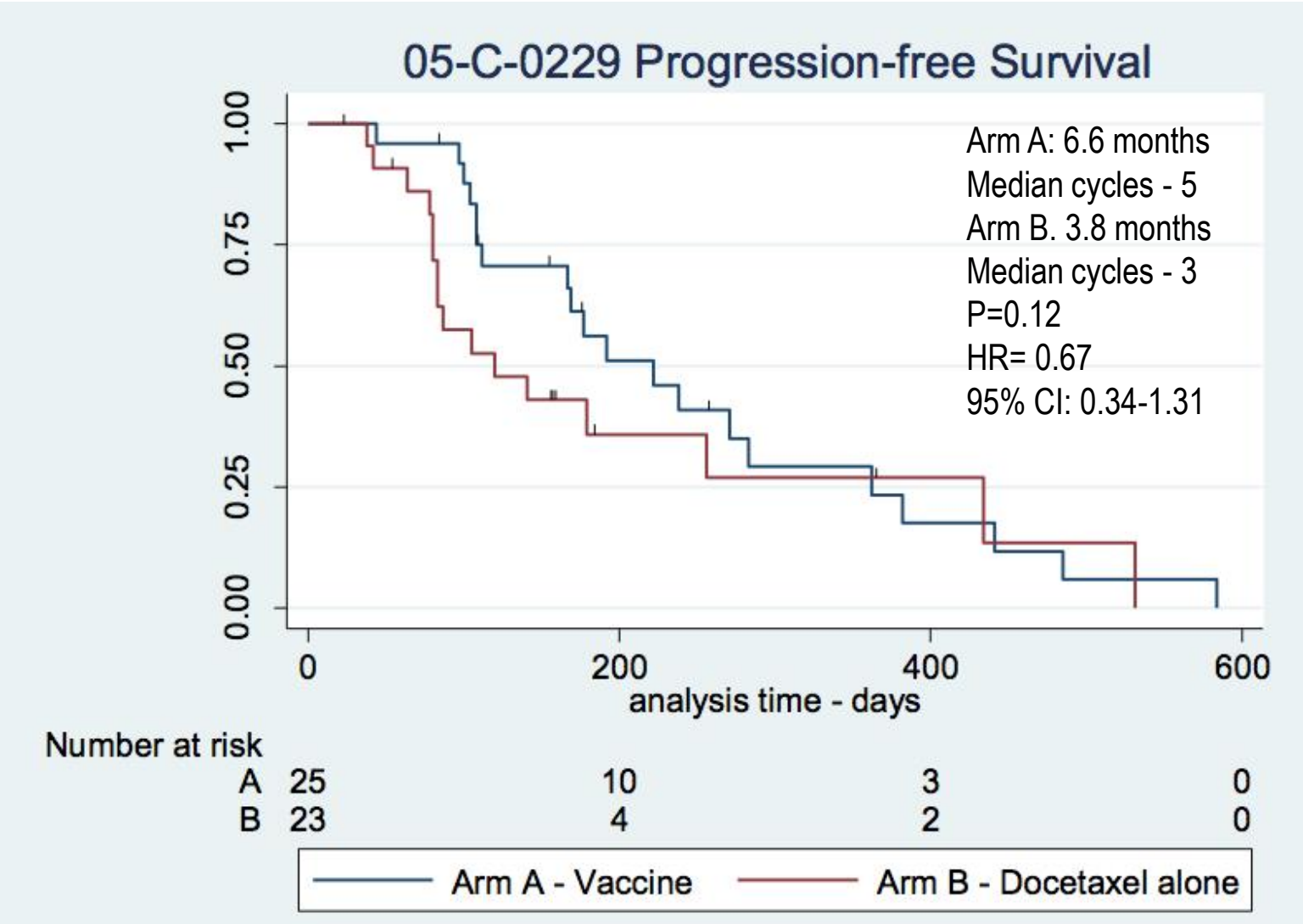
Baseline Characteristics

	Arm A (n=25)	Arm B (n=23)
Age		
On Study	55 (33-73)	51 (34-76)
At Diagnosis	48 (31-60)	43 (26-73)
Hormone negative	7	7
Her 2 +	3	4
Dx with Mets	2	3
Days since diagnosis	1910 (377-6839)	1834 (279-6,236)
Days from Dx to Metastasis	992 (0-6063)	1133 (0-4916)
# prior chemo	2 (1-7)	3 (0-8))
Days since prior chemotherapy	68 (19-1583)	45 (10-2760)

TNBC = Triple Negative Breast Cancer
HR neg = hormone receptor negative
Dx = diagnosis

National Cancer Institute

Progression Free Survival



National Cancer Institute

Adverse Events

- Adverse events occurring in this trial, with the exception of injection site reactions in the combination arm, were consistent with docetaxel alone treatment.
- No obvious difference between the groups was observed.
- Statistical analysis of the Arm A versus Arm B demonstrated a difference in the incidence of edema (36 v 13% grade 1 and 8 vs 0% grade 2, P = 0.018) and injection site reactions (8 v 0% grade 1 and 56 v 0% grade 2, P = <0.0001).

PANVAC: CEA-, MUC-1-TRICOM

Conclusion

First randomized trial of vaccine therapy for MBC

Important but preliminary results: Will survival be affected ?

Needs more patients selection ?