

EBCC 2010 Review

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Objectives

- To discuss key research findings from the 2010 EBCC meeting
- To discuss the implications of this research on our clinical practice
- To review some key ongoing trials that are expected to report in the next year



Outline

- Adjuvant Chemotherapy
- Adjuvant Targeted Therapy
- Bisphosphonates in EBC
- Pregnancy post breast cancer treatment
- Metastatic Chemotherapy
- Metastatic Targeted Therapy



Outline

- **Adjuvant Chemotherapy**
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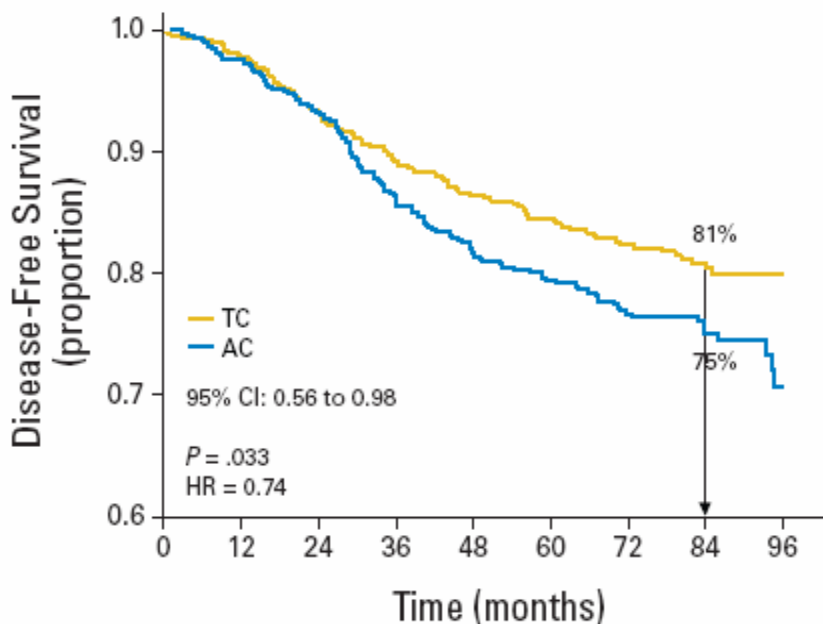


Is 4 cycles of chemotherapy enough?

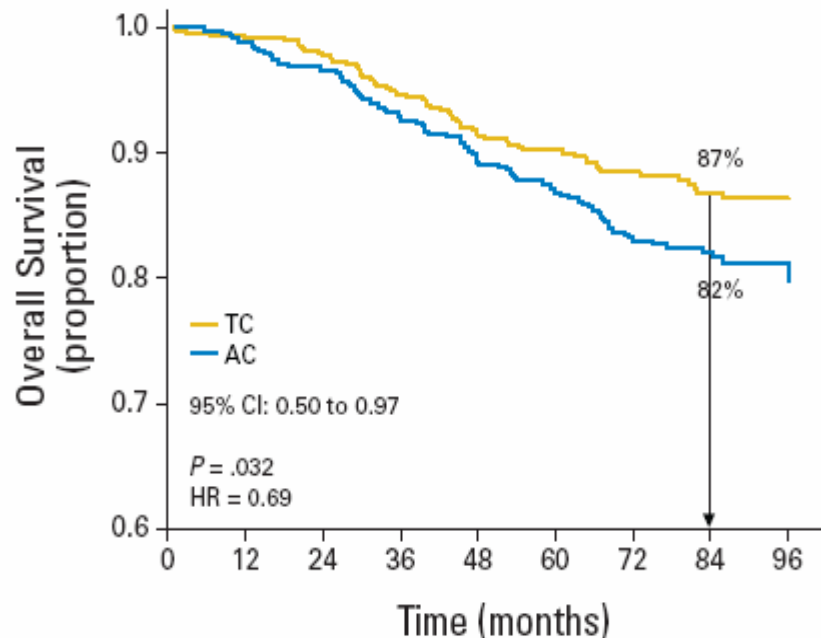
- We continue to personalize our treatment approach for patients with ESBC?
 - What is the risk of recurrence?
 - Do they need chemotherapy?
 - Do they need anthracyclines?
 - How many cycles of chemotherapy?
- Most of our protocols have anywhere from 4-8 cycles of treatment



US Oncology 9735: TC vs AC 7-Year Results



No. at risk	0	12	24	36	48	60	72	84	96
TC	506	481	442	410	378	349	320	195	
AC	510	483	449	405	372	343	303	194	



No. at risk	0	12	24	36	48	60	72	84	96
TC	506	487	461	434	398	371	344	207	
AC	510	488	464	438	407	375	327	210	

BCIRG 005: Study Design

HER2 normal
(FISH)
N= 3298

Stratification:

- Nodes:
1-3
4+
- HR+/-
- Center

Endpoints:

- Primary: DFS
- Secondary: OS, safety



4 x AC

60/600 mg/m²



4 x Docetaxel

100 mg/m²



6 x TAC

75 / 50 / 500 mg/m²



Dexamethasone premedication, 8 mg bid, 3 days
Prophylactic ciprofloxacin 500 mg bid, day 5-14

Eiermann et al. Submitted to JCO 2010.

NSABP B-30

Median follow-up: 73 mo

Eligibility

- Node positive
- Known HR status

Stratification

- Number of positive nodes
- Tamoxifen (Y/N)
- Surgery and radiotherapy

N=5351



4 x AC → 4 x T q3w

Doxorubicin

(60 mg/m²)

Cyclophosphamide

(600 mg/m²)

Taxotere®

(100 mg/m²)

4 x AT q3w

Doxorubicin

(50 mg/m²)

Taxotere®

(75 mg/m²)

4 x TAC q3w

Taxotere®

(75 mg/m²)

Doxorubicin

(50 mg/m²)

Cyclophosphamide

(500 mg/m²)

- Tamoxifen x 5 yr if ER/PR +

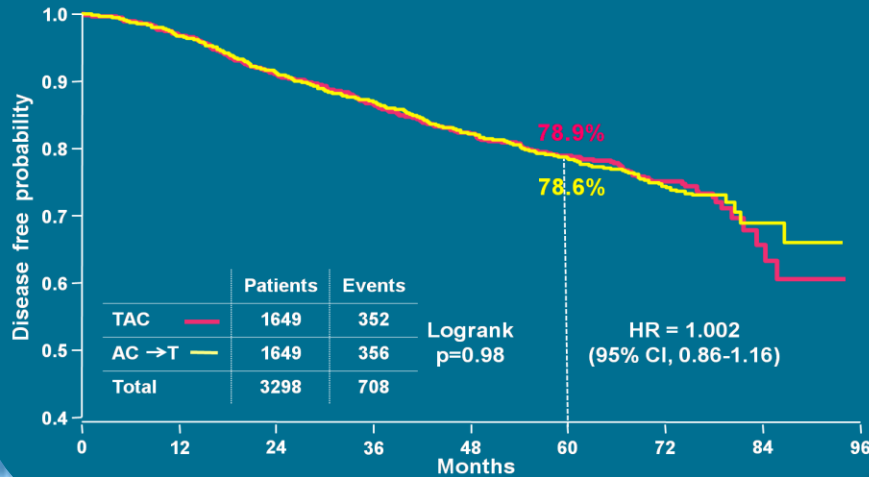
Primary endpoints: DFS, OS

Secondary endpoints: Toxicity, QOL, amenorrhea incidence and relationship to symptoms, QOL, and efficacy.

Swain et al. Submitted to NEJM. 2010.

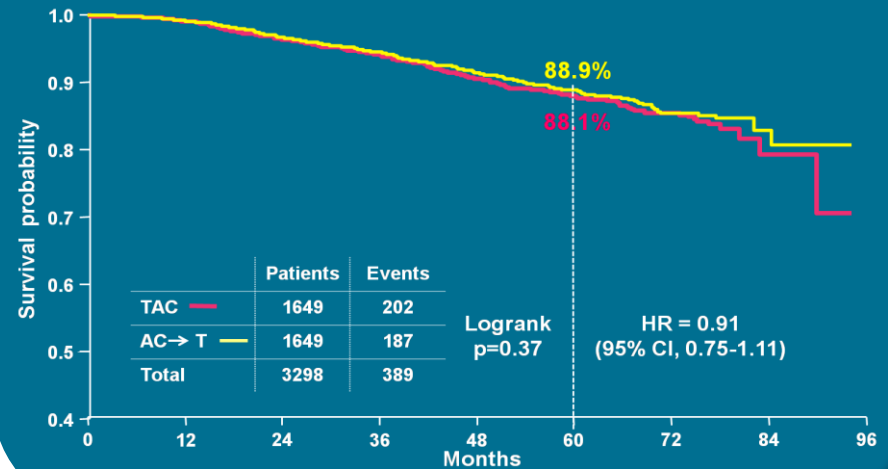
BCIRG 005

Disease-free Survival – Primary Analysis



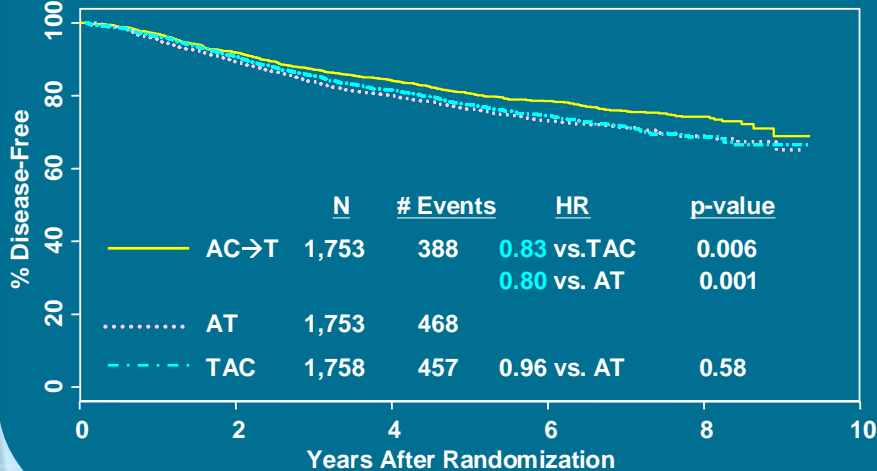
BCIRG 005

Overall Survival – Primary Analysis



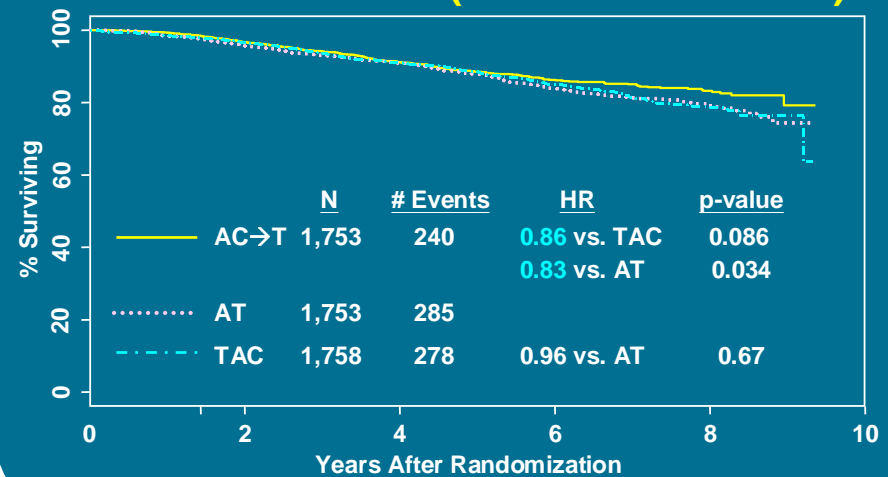
NSABP B-30

Disease-Free Survival (Intention-To-Treat)



NSABP B-30

Overall Survival (Intention-To-Treat)





EBCC 2010 Update

Duration of Chemotherapy

- Kim et. al South Korea
- Phase III neoadjuvant chemotherapy for patients with Stage II and III Breast Cancer
- Randomized (n=176 pts)
 - 4 cycles of Epi (75mg/m²) + Doce (75 mg/m²) or
 - 6 cycles of Epi (75mg/m²) + Doce (75 mg/m²)
- Primary endpoint
 - Pathologic complete response



Results

	4 cycles	6 cycles	
pCR	11%	24%	p=0.047
BCS	47%	58%	



Summary

- While TC x 4 cycles is superior to 4 cycles of AC chemotherapy, there is now strong evidence that suggests that 4 cycles of chemo may not be sufficient
- We do need to tailor our approach based on patient and tumor factors
- If one is considering a non-anthracycline based approach, then six cycles of TC should be considered
 - TC x 4 cycles should be offered to only selected individuals



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- Bisphosphonates in EBC
- Pregnancy post breast cancer treatment
- Role of surgery in MBC
- Metastatic Chemotherapy
- Metastatic Targeted Therapy



Herceptin in the adjuvant setting

- We have incorporated Herceptin in the adjuvant setting since August 2005
- Data is now quite suggestive that concurrent approach is superior and that an anthracycline-taxane backbone with herceptin provides the best efficacy (c/w TCH)
- There still is ongoing controversy on duration of therapy



EBCC 2010

Why patients don't receive Herceptin?

- Maria S et.al Glasgow, United Kingdom
- Evaluated 3,424 patients at six centers with ESBC
 - 14% (n=478) were Her 2 positive
- Only 61.7% of patients received Herceptin
 - Range – 56.7% – 63.9%



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Why patients don't receive Herceptin?

Reasons for not receiving Herceptin

Tumor size <1cm, node neg	35.8%
Small node neg (1-2cm)	10.8%
Age	18.2%
Comorbidities	13.5%
Patient refusal	12.8%
Other	8.8%



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Outcome of Her 2 positive patients

- Chia, S British Columbia, Canada
- Population based analysis of patients receiving adjuvant Herceptin
 - July 2004-December 2006
 - 704 Her 2 positive patients
 - 68% received Herceptin
 - All with chemotherapy
 - 71% - concurrent
 - 29% - sequential



EBCC 2010

Outcome of Her 2 positive patients

- Results

- Median f/up of 2.1 years

Received H

2yr RFS 95.9%

2 yr OS 99.3%

- In those patients who didn't receive H

2 yr RFS node neg 90.7%

2 yr RFS node pos 75.5%



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FEC followed by Docetaxel + Herceptin

Jacquemin L. et al. Belgium

- FEC followed by Docetaxel is one of the most common regimens used in the adjuvant setting
- There is no prospective evidence for this regimen in combination with Herceptin
- The study authors conducted a retrospective cardiac safety review of patients receiving this regimen with Herceptin



EBCC 2010

FEC followed by Docetaxel + Herceptin

- 37 patients identified
- 94% completed their one year course of herceptin
- Asymptomatic decline in EF of 7.7%
 - Previous evidence for herceptin post anthracyclines have reported asymptomatic declines in > 10%



Summary

Adjuvant Trastuzumab

- Adjuvant Trastuzumab is associated with significant benefit for Her 2 positive EBC patients
- Only about 60-70% of Her2 positive patients in the early stage setting are actually receiving this treatment
- We need to better individualize our approach for early stage Her 2 positive patients to select the right treatment approach
- FEC followed by Docetaxel and Herceptin appears to be safe, however we need to continue to study the long term safety and efficacy data for this regimen



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Breast Cancer: Adjuvant Clodronate Trials Second Analysis

	Diel/Jaschke^{1,2}	Powles³	Saarto⁴	Paterson⁵
No. of patients	290	1,069	299	173
Selection	BM^a	Stage I-III	LN⁺	BM⁺
Treatment length, yr	2	2	3	3
Follow-up time, yr	8.5	5/10	10	3
Skeletal effect	NS	+	NS	+
Extraskelatal effect	NS	NS	-	NS
Disease-free survival	NS	NS	- (ER⁻)	NS
Overall survival	+	+	NS	NS

BM, bone metastases; LN, lymph node; NS, not significant; ER, estrogen receptor; +, better than competitor; -, worse than competitor.

^a Patients with primary breast cancer (T1 to T4 and N0 to N2) with micrometastases in the bone marrow.

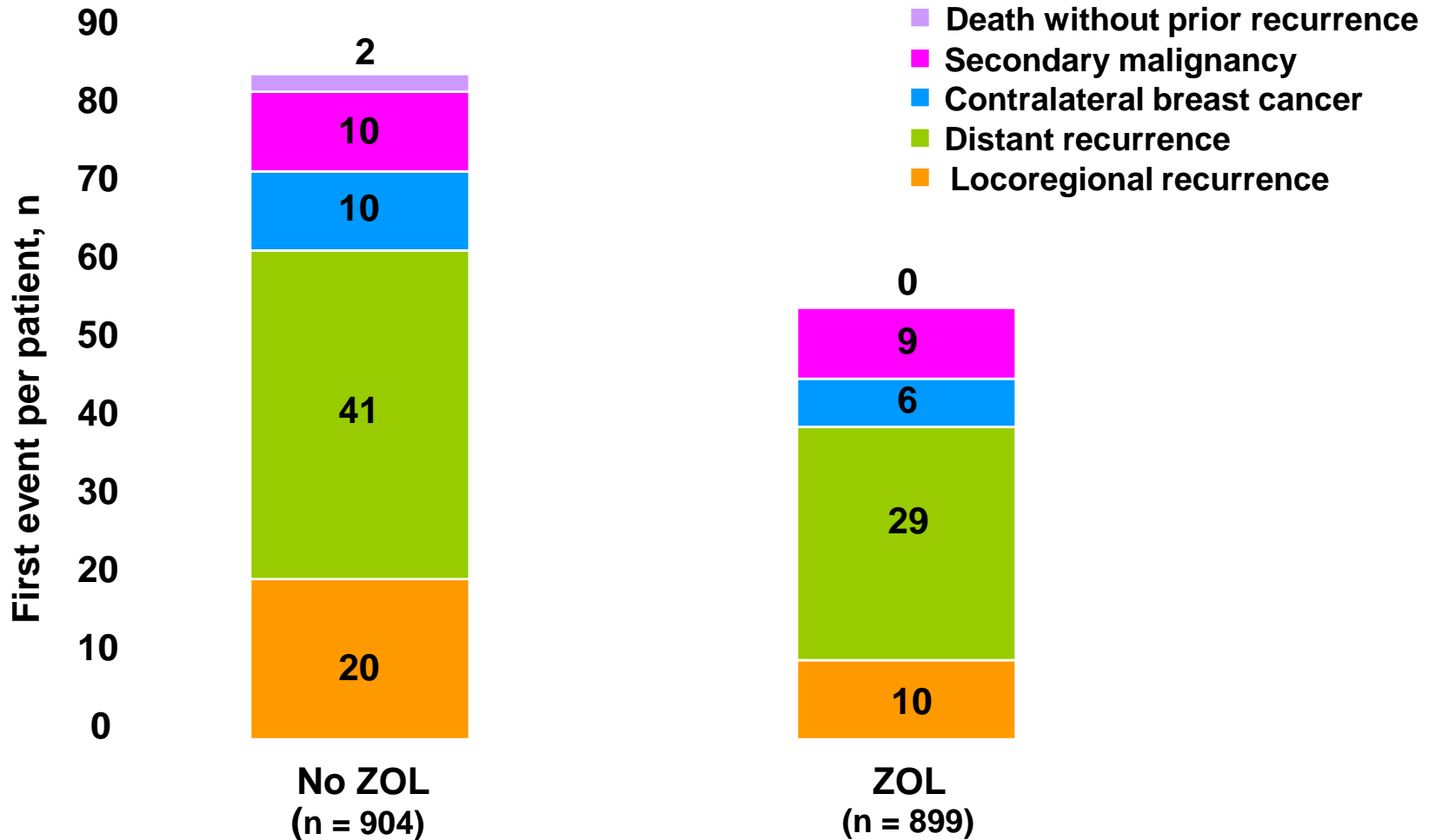
1. Diel IJ, et al. *N Engl J Med.* 1998;339(6):357-363; 2. Jaschke A, et al. *Proc Am Soc Clin Oncol.* 2004;22:9. Abstract 529;

3. Powles TJ, et al. *Breast Cancer Res.* 2006;8(2):R13; 4. Saarto T, et al. *Acta Oncol.* 2004;43(7):650-656;

5. Paterson AHG, et al. *J Clin Oncol.* 1993;11(1):59-65.



First DFS Events (ITT Population): ZOL vs No ZOL



DFS, disease-free survival; ITT, intent-to-treat; ZOL, zoledronic acid.

Gnant M, et al. *N Engl J Med.* 2009;360(7):679-691.



Overview of Other Bisphosphonate Trials in Early Breast Cancer

Targeted total accrual > 20,000 patients with MM and breast, prostate, and lung cancer.

Name	Patients	Treatment arms	Primary endpoint
SUCCESS	3,754 BC pts (Stage I, II, III)	FEC + DOC then endocrine therapy + ZOL 3 or 5 yr; FEC + DOC + GEM then endocrine therapy + ZOL 3 or 5 yr	DFS at 5 years
SWOG 0307	4,500 BC pts (Stage I, II, III)	ZOL (4 mg q1m; q3m); CLO (1,600 mg qd); IBN (50 mg qd)	DFS at 3 years
NATAN	654 BC pts (Stage II, III)	Standard therapy ± ZOL (4 mg q1m; q3m; q6m)	EFS at 5 years
GAIN	3,024 BC pts	EPI + PAC+ CYC ± IBN; EPI + CYC + TAX + CAP ± IBN	DFS at 2 years
ICE	1,500 BC pts (Stage II, III)	CAP ± IBN (50 mg qd or 6 mg IV q4w)	Relapse at 2 years
ABCSG-18	2,800 BC pts	Placebo ± denosumab (60 mg SC q6m)	Time to first clinical fracture

MM, multiple myeloma; BC, breast cancer; FEC, fluorouracil (5FU), epirubicin, and cyclophosphamide; DOC, docetaxel; ZOL, zoledronic acid; GEM, gemcitabine; DFS, disease-free survival; CLO, clodronate; IBN, ibandronate; EFS, event-free survival; EPI, epirubicin; PAC, paclitaxel; CYC, cyclophosphamide; TAX, taxol; CAP, capecitabine; SC, subcutaneous.



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NATAN Study – Safety Update

Von Minckwitz et.al Germany

- P who had residual invasive tumor after a min of 4 cycles of NAC were randomized
 - Zol 4 mg IV monthly x 6 then q 3mon x 2yrs and then q 6 mon x 2.5 yrs
 - observation



EBCC 2010

NATAN Study – Safety Update

Safety Update

- 693 patients enrolled
- 2 years of f/up
- No unexpected toxicity seen yet
- No cases of ONJ seen yet

Efficacy analysis expected in 2011



Summary – Adjuvant Bisphosphonates

- Adjuvant Bisphosphonates appear to have anti-cancer effect
- One of the limitations of their use may be the occurrence of ONJ in this curable setting
- So far there doesn't appear to be significant ONJ risk associated with these agents in this setting
 - We do need some more long term data and careful vigilance



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- **Pregnancy post breast cancer treatment**
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Background Pregnancy in BC

- The first age of pregnancy in the Western world is now around 30-31 yrs
- We are seeing an increasing no. of patients who are being diagnosed with breast cancer who haven't started their family yet
- There remains ongoing controversy on the effect of pregnancy on the risk of breast cancer recurrence



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Safety of pregnancy in breast cancer – A Meta Analysis

Azim et. al Belgium and Italy

Methods

- 14 trials published between 1970 and 2009 met the inclusion criteria (1417 pregnancy and 18059 controls)

Results

- Patients who got pregnant following BC diagnosis had significantly better survival compared to women who did not get pregnant
 - **HR 0.58; CI: 0.49–0.68**

Conclusion by authors

- On the contrary of what is perceived; pregnancy in BC survivors is not detrimental on survival but seems to be **associated with a protective value**
- Several immunological and endocrinal theories could explain this finding.



Summary

Is Pregnancy safe after the diagnosis of breast cancer?

- This meta-analysis is provocative but by no means conclusive.
 - All the studies done on this subject are biased by the ‘healthy mother’ effect
- While clearly pregnancy has a protective role in the onset of breast cancer, there is limited biologic rationale to explain why it will be protective after someone has been diagnosed with breast cancer
- This remains a very interesting and relevant area of interest for patients and clinicians alike. Well thought out clinical studies need to be initiated to help guide our approach for patients considering to become pregnant after being diagnosed with breast cancer.

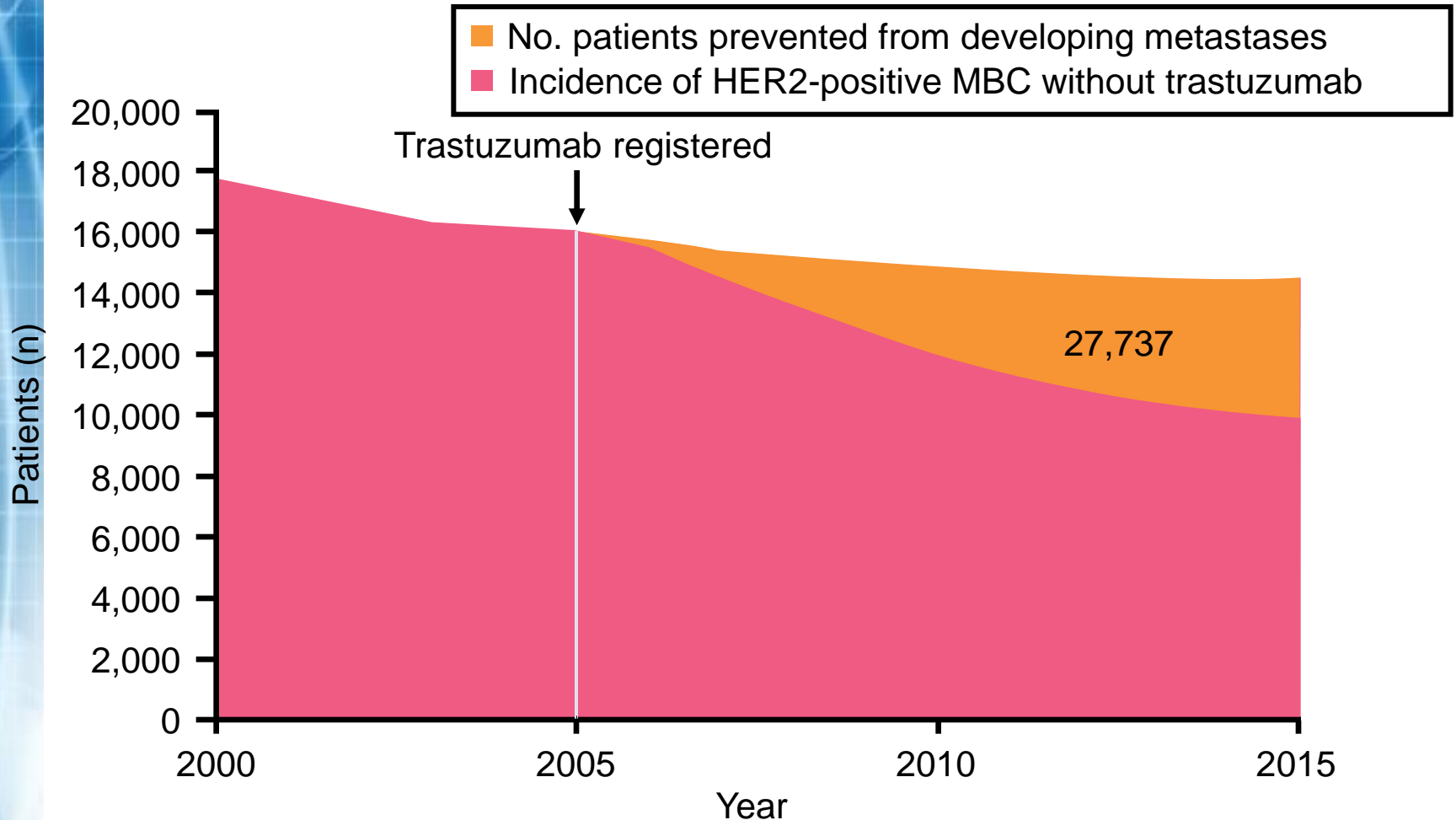


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Adjuvant trastuzumab is predicted to prevent recurrence in almost 28,000 patients over a 10-year period in the 5 major EU countries



MBC, metastatic breast cancer

Weisgerber-Kriegel U et al, ASCO 2008; Poster 6589.



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Taxane + Herceptin vs. Vin + Herceptin

- Andersson et. al Netherlands
- Randomized 284 Her2 positive patients to
 - Docetaxel 100 mg/m², or
 - Vinorelbine 30-35mg/m² day 1 + d8With Herceptin q 3 weeks until progression or toxicity
- Well balanced
- Adjuvant chemotherapy <1-2% taxane use



EBCC 2010

Taxane + Herceptin vs. Vin + Herceptin

Results:

Median f/up of 34 months

	Doc + H	Vino + H	
No. of cycles	8	10	
Grade $\frac{3}{4}$ toxicity	81%	51%	
TTF	6.3 m	8.4m	p<0.0001
TTP	12.5m	13.6m	p=NS
OS	36.1m	39.1m	p=NS



Summary

- Vinorelbine + Herceptin is an effective regimen and one should now consider this regimen in the first line setting
- This is especially important for those who have progressed after adjuvant taxanes and Herceptin
- There continues to be strong data for considering an anti-Her2 approach post progression on herceptin



A comparison of physician and patient perceptions of clinically important endpoints in the treatment of Metastatic Breast Cancer

A. Sheik-Yousouf¹, S. Gandhi², S. Dukhovny¹, S. Verma².



Background and Method

- To examine and compare, clinical trial endpoints physicians and patients consider important in MBC treatment.
- 28 breast oncologists responded to a secure, anonymous, and self-administered online survey.
- 52 Patients with MBC were also surveyed through a self-administered paper survey.
- Results were assessed using descriptive statistics.



Results

Physician Results

- 52% believed OS was the most important endpoint considered in choosing a specific therapy.
 - 48% thought that a minimum meaningful incremental improvement in OS from a 1st MBC therapy was 4-6 months.
 - 44% believed 2-4 months was meaningful.
- 48% believed PFS was the most important.
- 60% of oncologist thought patients considered improvement in OS to be the most important endpoint
- 36% believed that overall QOL is the second most important factor to patients with MBC.



Results

PHYSICIAN RESULTS

- 52% believed OS was the most important endpoint considered in choosing a specific therapy.
 - 48% thought that a minimum meaningful incremental improvement in OS from a 1st MBC therapy was 4-6 months.
 - 44% believed 2-4 months was meaningful.
- 48% believed PFS was the most important.
- 60% of oncologist thought patients considered improvement in OS to be the most important endpoint
- 36% believed that overall QOL is the second most important factor to patients with MBC.

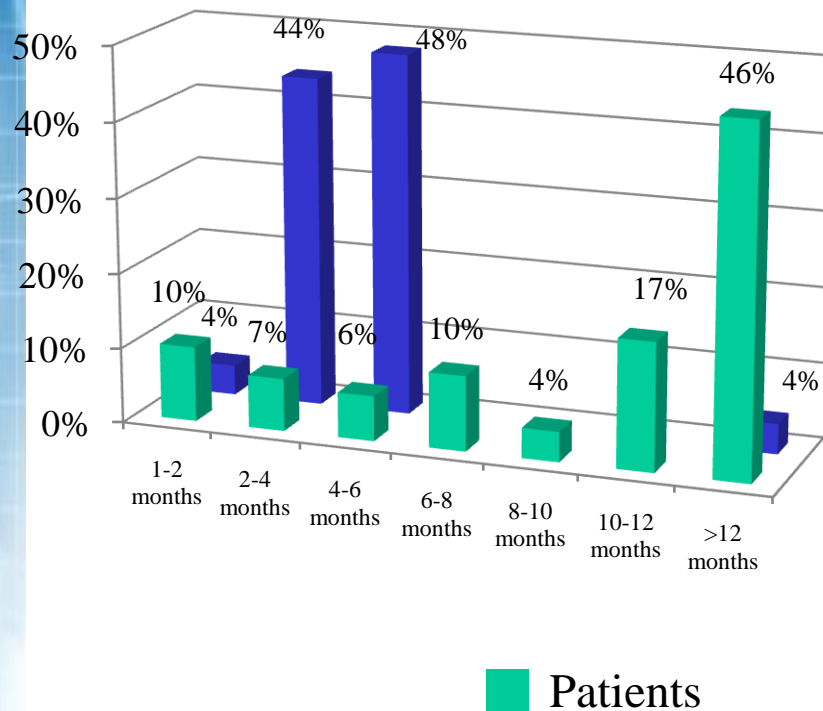
PATIENT RESULTS

- **54%** believed prolonging survival the most important endpoint in accepting MBC therapy.
 - **46%** of patients thought **>12 months** the minimum improvement in OS considered as making treatment worthwhile.
 - **17%** thought **10-12 months** was acceptable.
- 17% thought shrinking tumour size was the most important.
- 10% only thought 1-2 months was an acceptable improvement in OS.

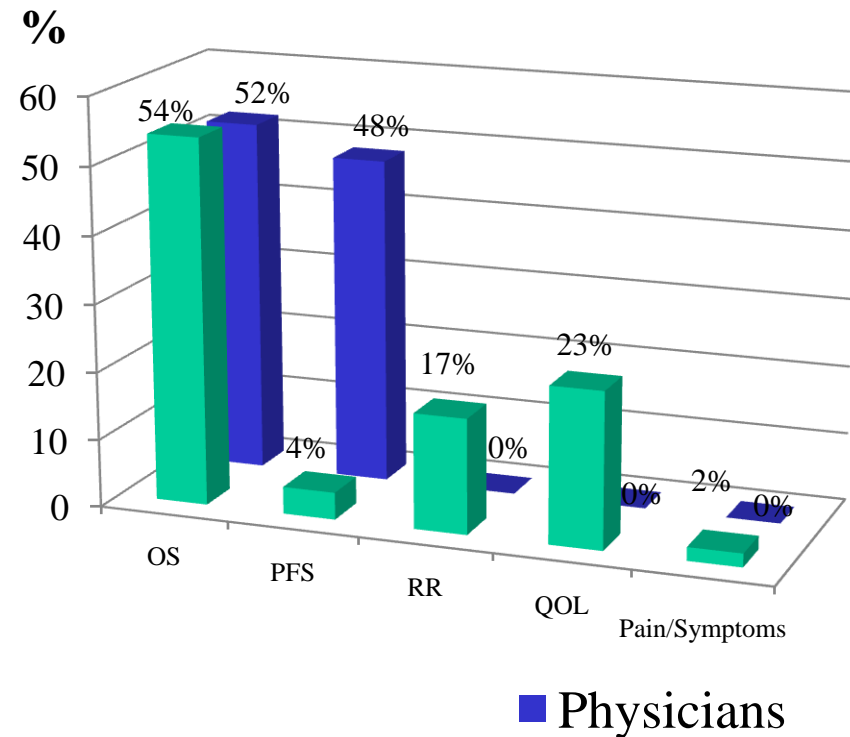


Physician / Patient Comparison

Minimal improvement in OS



Clinically important end points in treatment of MBC





Study Limitations

- This study is limited by
 - Small response numbers
 - Patient's interpretation of the questions
 - Only two centers involved
 - Survey done at one time point
 - Focused just on two specific groups, what about
 - Funding Bodies
 - Regulatory Agencies
 - Industry
 - General Public



Discussion and Conclusions

- The data highlights disparities between oncologists and patients in the relative ranking of defined therapeutic endpoints, and in MBC treatment expectations.
- It thus emphasizes the ongoing need for thorough discussion of treatment goals with patients and for clinical trials to bring about meaningful results to both patients and physicians alike



Other relevant MBC trials

- Anti-Angiogenics (Abstracts 480,487,489, 496)
 - The effect of bevacizumab is seen across all tumor profiles
 - TN patients have similar benefit as non-TN
 - No increase in tumor malignant potential following treatment of MBC with BV and Doc
 - PFS in AVADO was longer after discontinuation of BV than after discontinuation of PL
 - The proportion of BV patients with new metastatic lesions at PD was lower than that of PL patients



PARP Inhibitors

- Clinical Science Symposium
 - Presentation by Dr. Andrew Tutt
- PARP Inhibitors
 - Effective as single agents in the BRCA popn.
 - Effective in combination with Platinums in TN pts
 - Will they be effective in a patient population beyond TN
 - Hypermethylation of BRCA genes
- Questions
 - Should the control arm be Cis instead of Carbo?
 - Are platinumums are a poor man's PARP-I?
 - Potential tumorigenicity associated with this class?



Conclusion - I

- The data is now strong to suggest that six cycles of adjuvant chemotherapy should be considered for patients
- We really need to be come up with a personalized approach for our Her 2 positive EBC patients to offer them the right treatment
- Bisphosphonates appear to be promising and safe for patients with EBC



Conclusion - II

- Vinorelbine in combination with Herceptin appears to be an acceptable regimen, especially for those who have progressed on taxanes and herceptin in the adjuvant setting
- We have to discuss the magnitude of benefit from our metastatic treatment with our patients to guide our treatment decision



Thank You