32ND ANNUAL

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AN UPDATE OF KEY PRESENTATIONS

CTRC–AACR SAN ANTONIO BREAST CANCER SYMPOSIUM®

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Sunnybrook Odette Cancer Centre, Toronto, CANADA

I. BREAST CANCER EPIDEMIOLOGY

Lifestyle Factors and Breast Cancer Risk

Breast Cancer Prevention

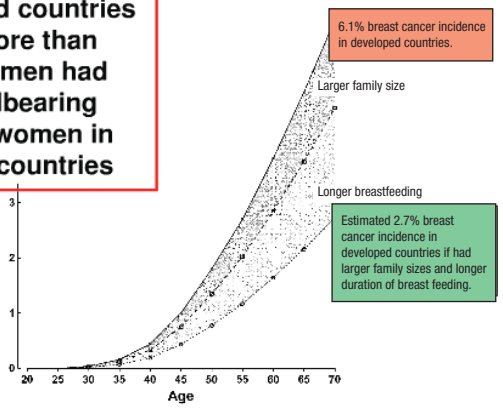
A Global and Historical Perspective (Plenary Session)

V Bear, University of Oxford.

- In the 18th and 19th centuries, breast cancer was thought to be an occupational disease of nuns *(Collaborative Group on Human Factors in Breast Cancer. Lancet. 2002.)* The incidence was **2.7% versus 0.4%** in the general population; mortality was also 7 times higher *(Rigona-Stern, 1842)* and this was thought to be reflective of childbearing practices.
- Incidence of breast cancer in developed countries: **6.1% vs. 1%** in rural Asia and Africa *(WHO/IARC 2002).* If developed nations had similar childbearing and breastfeeding practices, breast cancer incidence estimated to be halved to 3%.
- **As childbearing practices are impractical to target, could focus on developing interventions (such as an adult vaccine or hormonal therapies) to mimic the hormonal changes of pregnancy/lactation. Controversial.**
- Other risk factors for breast cancer in developed nations are earlier age of menarche, increased height and BMI, and increased alcohol consumption. These factors are independent of polygenetic risk modelling.

Impact of Childbearing

Breast cancer incidence in developed countries would be more than halved if women had similar childbearing patterns to women in developing countries



Collaborative Group on Hormonal Factors in Breast Cancer, Lancet. 2002.

Alcohol Consumption and Breast Cancer Prognosis and Survival in the LACE Study

A Prospective Cohort of Breast Cancer Survivors.

ML Kwan, California.

- Increased alcohol (>6g/day, or 0.5 drinks/day or 3-4 drinks/week) independently increases breast cancer recurrence risk, **HR 1.34** (p=0.05). Adjusted for age at diagnosis, BMI, disease stage, hormone receptor and lymph node status, tamoxifen use, and overall treatment status. Association highest in postmenopausal and obese women.
- >6g/day of alcohol increases risk of breast cancer death HR of 1.51 (p=0.05).
- Total mortality in this cohort NOT affected by alcohol; likely offset by protective effect of moderate alcohol use on cardiovascular health.

Alcohol and Breast Cancer Death

	n (%)	HR	95% CI	P-value
Alcohol g/day				
None	939 (49)	Ref	---	---
< 6.0 g/day	480 (26)	1.11	0.74-1.69	0.61
≥ 6.0 g/day	478 (25)	1.51	1.00-2.28	0.05
p for trend			0.05	
Wine (svg/wk)				
None	1030 (54)	Ref	---	---
≤ 1 svg	473 (25)	1.11	0.74-1.67	0.61
≥ 2 svg	390 (21)	1.37	0.88-2.13	0.17
p for trend			0.18	

* Adjusted for age at diagnosis, pre-diagnosis BMI, total folate intake, stage of disease, hormone receptor status, tamoxifen use, treatment, and lymph node status

Effect of Obesity on Prognosis after Early Breast Cancer

M Ewertz, Denmark, on behalf of Danish Breast Cancer Cooperative Group

- Study aim: to determine if obesity is an independent risk factor for breast cancer recurrence or death, or for poorer response to adjuvant treatment.
- Adjusting for other prognostic variables, patients with BMI >25 had a statistically significant 42-46% increase in developing distant metastases within 10 years, and 26-38% risk of dying from breast cancer 10 or more years after diagnosis.

EPIDEMIOLOGY TAKE HOME MESSAGE

- Breast cancer risk is increased by **lifestyle patterns in developed countries** (such as lower rates of childbearing, increased alcohol consumption, and obesity.)
- Adoption of similar lifestyle habits in **developing countries** is leading to a **rising** breast cancer incidence in these areas.
- Need to develop **novel strategies** to decrease the incidence of breast cancer.
- Breast cancer **prognosis and mortality** independently affected by **alcohol and obesity**.
- In addition to standard breast cancer treatment, we should regularly advocate lifestyle changes in patients, including **decreased alcohol consumption, weight loss, and exercise.**

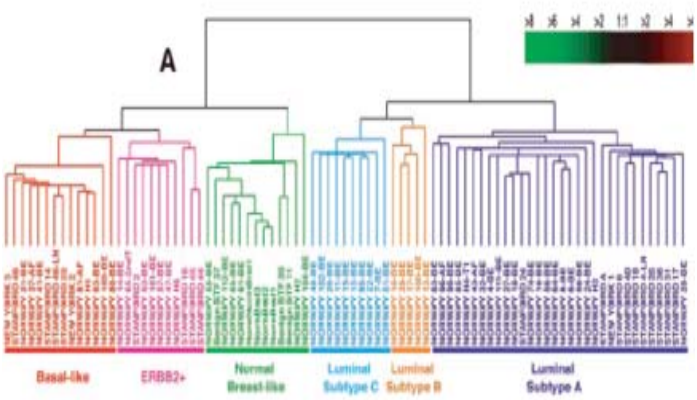
II. BREAST TUMOUR BIOLOGY

Therapeutic Implications of the Molecular Portraits of Breast Cancer

CM Perou, North Carolina.

Reviewed the heterogeneity of breast tumours based on molecular biology and histopathology. **Breast cancer prognosis is impacted greatly by these subtypes.**

Sorlie T et al, PNAS.2001

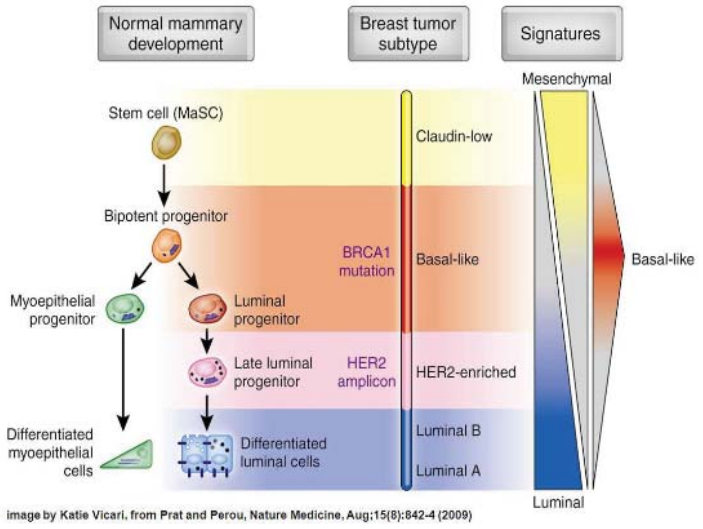


HER-2 IN BREAST CANCER

- Approximately 20% of breast carcinomas are "clinically" HER-2 positive (by standard histopathologic techniques.)
- Introduced new concept of HER-2 over-expression: HER-2 enriched ➔ at molecular level. Represents 10-15% of all breast tumours. Not all are clinically HER-2 positive (example: triple negative). Conversely, 1/2 to 2/3 of all clinically HER-2 positive tumours are also HER-2 enriched. The rest are Luminal B, Luminal A, and Basal-like.
- Baseline prognosis is still poor. Trastuzumab and chemotherapy benefit remains high in clinically Her-2 positive patients, and remains to be studied in the molecular Her-2 enriched subtype.

TRIPLE NEGATIVE (TN) BREAST CANCER

- Understanding of this tumour subtype continues to develop.
- 75% of TN tumours are truly basal-like.
- Basal-like tumours represent 10-15% of breast tumours overall.
- 75% of basal like tumours are also TN. Show distinct cell of origin or developmental stage of arrest. More than 50% have p53 mutations. Highly proliferative, highly aneuploid, and associated with BRCA-1 mutations.
- Baseline prognosis poor, high chemotherapy benefit, ?PARP-inhibitor benefit.
- The TN classification misses 25% of true basal like tumours and includes 25% of tumours that are NOT basal-like.
- **New subtype introduced: Claudin-low.** 5-10% of tumours, typically TN, low expression of cell junction proteins, lymphocytic infiltrates, and predominantly stem cell features.



Prat, Perou et al. Nat Med. 2009.

TUMOUR BIOLOGY TAKE HOME MESSAGE

- Each breast tumour biologic subtype corresponds with cell cycle arrest at a unique phase of mammary development. The earlier the arrest stage, the more triple negative and/or basal like features the tumour is likely to have. Latter stages of arrest are likely to create tumours with more differentiated, luminal features.
- Our understanding of tumour biology and its implications on tumour behaviour, prognosis, and therapeutic implications continues to grow. Molecular and histopathologic features of tumours need to be considered in concert.

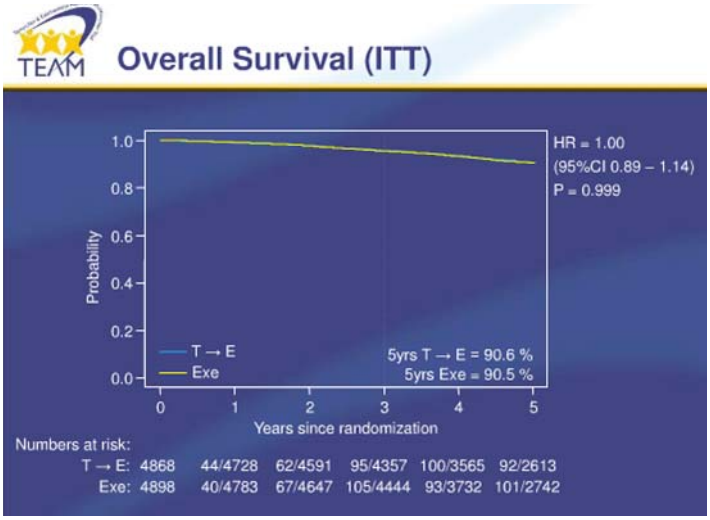
III. ENDOCRINE THERAPY

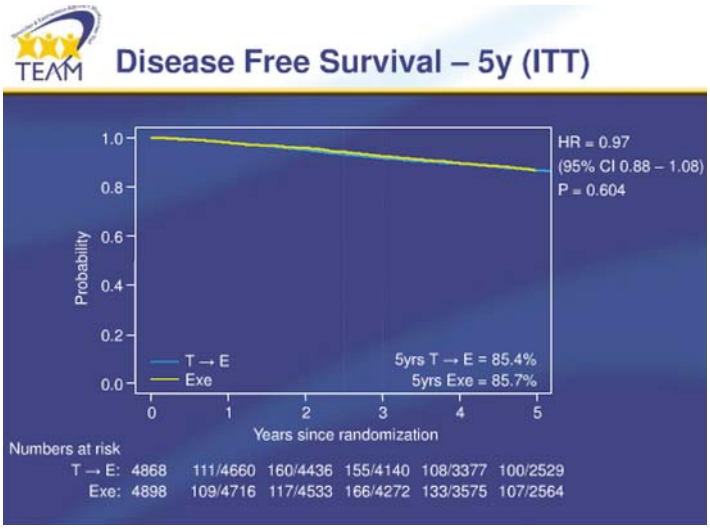
Five Years of Exemestane as Initial Therapy Compared to Tamoxifen Followed by Exemestane for Five Years

The TEAM Trial . A prospective, randomized, phase III trial in post-menopausal women with hormone-sensitive early breast cancer.

D Rea, University of Birmingham, United Kingdom, on behalf of TEAM collaboration.

- **Exemestane versus tamoxifen sequenced to Exemestane at 2-3 years. Results of planned analysis:** Median follow up 5.1 years. 60% of patients completed 5 year follow up. Largest AI study to date, comparing two of most common treatment strategies. All patients were HR+, and baseline characteristics were well-balanced.
- **No difference in T → E versus E upfront in DFS or OS in ITT population.** Nodal status did not influence outcome. There were more DVTs with tamoxifen, and more osteoporosis and fractures with exemestane.
- **Significant discontinuation rate which may have impacted results:** 29% of patients discontinued tamoxifen and 18.9% discontinued exemestane in the first 2.75 years. It is unclear what happened to these patients, and final publication will need to be reviewed.
- 5 years may be too short a follow up period, particularly for lymph node negative patients.



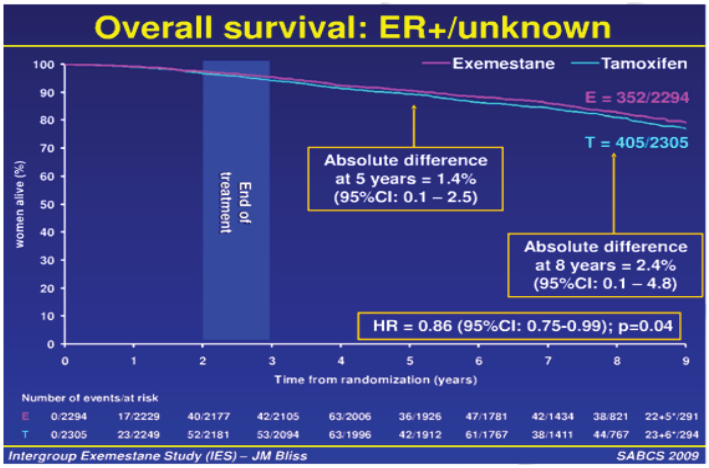


Disease Related Outcome with Long Term Follow up

An updated analysis of the Intergroup Exemestane Study (IES)

JM Bliss, United Kingdom, on behalf of IES Steering Committee.

- Compared tamoxifen for 5 years versus tamoxifen for 2-3 years with switch to exemestane to complete 5 years. Median follow up 91 months. 85% HR +, half were lymph node +.
- **Improvement in OS with T→E: absolute difference at 5 years 1.4%. Absolute difference at 8 years 2.4 % HR 0.85 p=0.04.**
- **Confirmed that risk of recurrence persists beyond 5 years.**
- **Other findings:** decreased bone only metastases in exemestane group (75 events versus 109 with tamoxifen), no difference in visceral metastases. Also less non-endometrial secondary cancers were found with exemestane. This is unexplained, and should be studied in a meta-analysis of AI trials.



ENDOCRINE TREATMENT TAKE HOME MESSAGE

- It is important to integrate AI therapy in the treatment of post-menopausal HR +ve breast cancer. Benefit is modest and different strategies may have minimal differences in outcome.
- There is a persistent risk of disease relapse beyond five years, despite integrating tamoxifen and AI therapy. In addition, we need to better understand what type of distant events are prevented by each strategy.
- Adherence to endocrine therapy continues to be a great concern; we need to better understand and address patient adherence issues.

IV. CHEMOTHERAPY

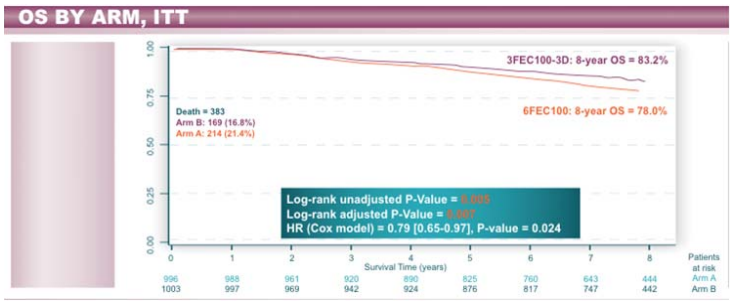
PACS 01 Updated Analysis

B Coudert, France, on behalf of FNCLCC

- Compared **FEC-100** chemotherapy (5FU 500mg/m2, epirubicin 100mg/m2, cyclophosphamide 500mg/m2, all on day 1) every 21 days x 6 cycles, to **FEC-100 for 3 cycles, followed by docetaxel** (100mg/m2) every 21 days x 3 cycles (FEC-D). **Updated 8 year analysis.**
- At 5 year analysis, DFS and OS were improved with FEC-D (DFS-78.3% vs. 73.5%, OS-90.7% vs. 88.7%).
- **At 8 years, continued benefit with FEC-D:**

DFS **FEC-D: 70.2%** **FEC: 65.8%** (HR 0.85 p=0.035)

OS **FEC-D: 83.2%** **FEC: 78%** (HR 0.79 p=0.024)



CHEMOTHERAPY TAKE HOME MESSAGE

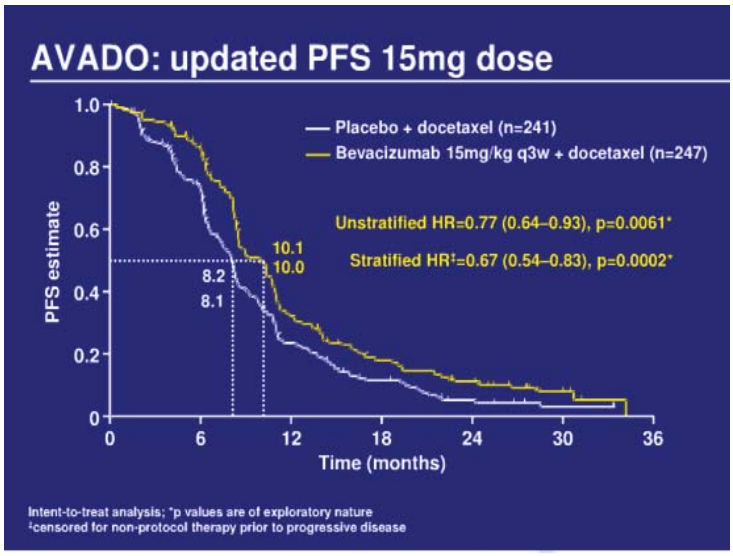
- The DFS and OS benefit of a widely used adjuvant chemotherapy regimen incorporating anthracyclines and taxanes (FEC100-Docetaxel), remains after 8 years of follow up. The absolute OS benefit is even greater at 8 years (close to 5%).

V. TARGETED ANTI-ANGIOGENIC THERAPY (HER-2 NORMAL)

Final overall survival results from the randomized, 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.

DW Miles, United Kingdom, on behalf of the BO17708 study group.

- Previous untreated metastatic breast or locally relapsed breast cancer patients were randomized to either docetaxel (100mg/m2) with placebo, or combined with either bevacizumab at 7.5mg/kg or 15mg/kg, every 3 weeks, until diseases progression. Were allowed to get bevacizumab with second line chemotherapy on progression.
- **Final OS data:** Median follow up of 25 months. **Docetaxel + bevacizumab (15mg/kg) improved PFS compared to docetaxel + placebo (10.1 vs. 8.2 months, HR 0.77, p=0.0061).** Stratification factors were time to relapse/prior taxane use, HR status, measurable disease, and region. Stratified HR was 0.67, p=0.0002. **OS at 1 year was also improved (84% vs. 76% p=0.02). Improved Overall response rate (ORR) with 15mg dose of bevacizumab (64.1% vs 46.4%, p=0.0003).**



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

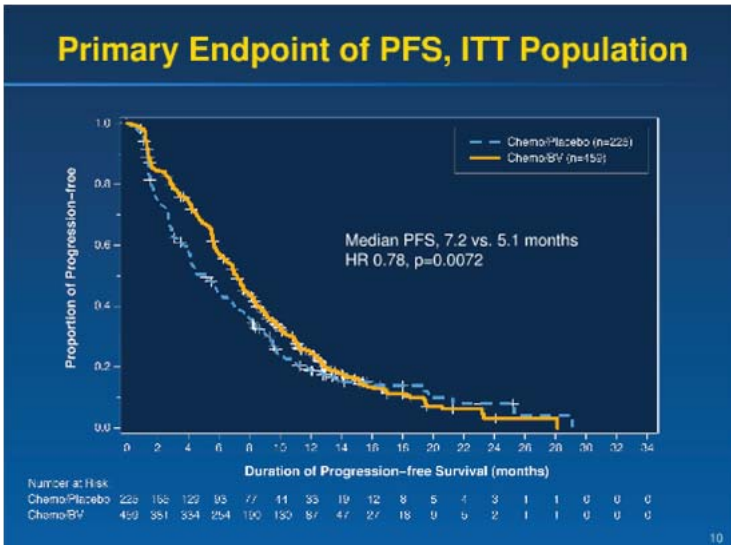
*mg/kg q3w
‡p values are of exploratory nature

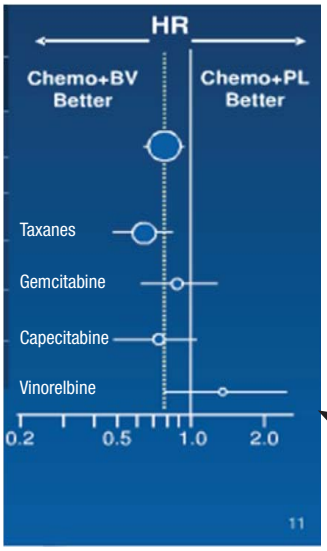
Important points: There was significant crossover, with patients allowed to receive bevacizumab with second line chemotherapy; this may have diluted the OS results at 2 years. Regardless, one year survival may be an important endpoint in metastatic breast cancer therapy. Finally, the combination of docetaxel and bevacizumab at 15mg/kg may be a useful combination for those patients requiring an immediate response from therapy, given the ORR data.

RIBBON-II: a randomized, double-blind, placebo-controlled, phase III trial evaluating the efficacy and safety of bevacizumab in combination with chemotherapy for the second line treatment of HER-2 negative metastatic breast cancer.

A Brufksy, University of Pittsburgh, on behalf of coauthors.

- Previously treated metastatic breast cancer patients stratified by hormone status, choice of second line chemotherapy, and interval to progressive disease on first line treatment. Assigned to second line chemotherapy (investigator choice): 45% received taxanes, 21% received gemcitabine, 21% received capecitabine, 13% received vinorelbine. Randomized 2:1 to receive bevacizumab (15mg/m2 q 3weekly or 10mg/m2 q2weekly), or placebo in combination with second line chemotherapy. Treated until progression.





Addition of bevacizumab to second line chemotherapy improved PFS (7.2 vs. 5.1 months, HR 0.78, p=0.0072). OS not improved (but interim analysis with only 57% of events.) Benefit was independent of chemotherapy (except perhaps vinorelbine).

SOLTI-0701- Multinational, double blind, randomized, placebo-controlled phase IIb study

J Baselga, Spain, on behalf of coauthors.

- Locally advanced or metastatic breast cancer patients (with one or less prior treatments) randomized to **capecitabine (1000mg/m2 po bid, 14 days on in 21 day cycle), plus either placebo or sorafenib 400mg po bid**. 60% of patients had prior taxane therapy.
- **Improved PFS with combination of capecitabine + sorafenib compared to capecitabine alone (6.4 vs. 4.1 mos, HR 0.58 p=0.0006).**

Adverse Event Rates*

Overall incidence > 10% and Grade 3/4 ≥ 2% in either treatment arm

	Sorafenib + Capecitabine (N=112)			Placebo + Capecitabine (N=112)		
	All (%)	Grade 3 (%)	Grade 4 (%)	All (%)	Grade 3 (%)	Grade 4 (%)
HFSR / HFS	89	45	-	63	13	-
Diarrhea	53	5	0	30	5	0
Mucosal inflammation	32	1	0	19	3	1
Asthenia	24	0	0	27	2	0
Rash	22	3	0	8	0	0
Hypertension	17	1	0	12	2	0
Fatigue	14	2	0	13	1	0
Musculoskeletal pain	12	2	0	6	0	0
Dyspnea	12	5	0	12	3	1
Neutropenia	11	4	1	4	2	1

*Treatment-emergent

- **However, hand foot syndrome was significantly increased with the combination (89% vs. 63%) and 45% of these in the combination arm were grade 3 events.**
- **The decision is to now study this combination in a Phase III trial.**

ANTI-ANGIOGENIC THERAPY TAKE HOME MESSAGE

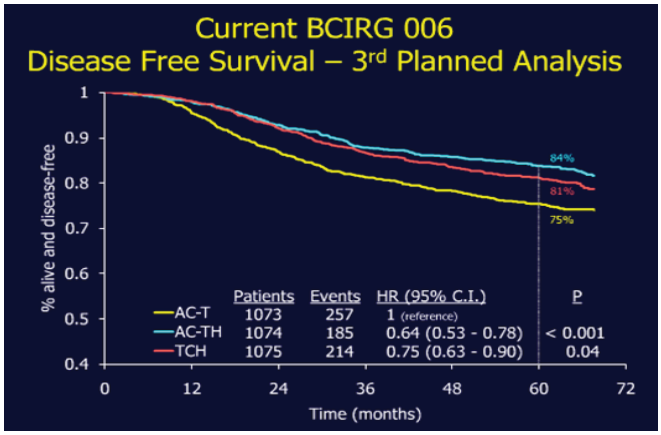
- Modest benefit of adding an anti-angiogenic to chemotherapy for metastatic disease. The benefit is most striking in first line, but it is also seen in the second line setting.
- Anti-angiogenics (including multi-targeted TKIs) alone have limited activity in breast cancer.
- The lack of an OS benefit still limits the use of these drugs in Canada.
- One may consider the combination of chemotherapy and an anti-angiogenic (such as bevacizumab) for patients who will benefit from a higher response rate.
- Need to develop predictive biomarkers for the use of these agents.

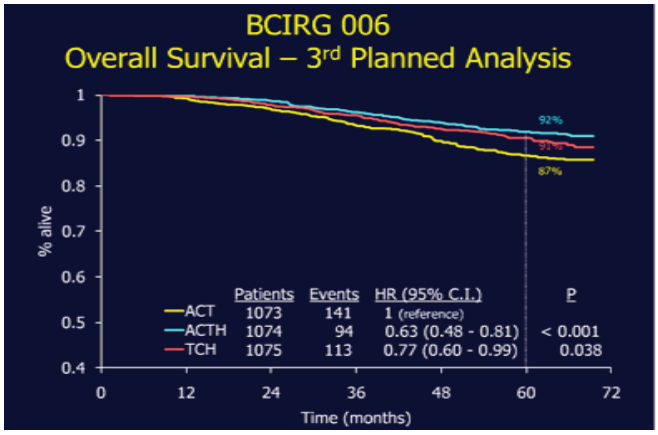
VI. TARGETED ANTI-HER-2 THERAPY (HER-2 POSITIVE)

Phase III randomized trial comparing doxorubicin and cyclophosphamide followed by docetaxel with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab with docetaxel, carboplatin and trastuzumab in Her2neu positive early breast cancer patients: BCIRG 006 Study.

D Slamon, UCLA California, on behalf of BCIRG006 Investigators.

- Adjuvant trastuzumab (Herceptin®) trial. **AC-T** (adriamycin, cyclophosphamide chemotherapy x 4, followed by docetaxel x 4) versus **AC-TH** (AC followed by docetaxel + Herceptin®), versus **TCH** (docetaxel, carboplatin, Herceptin®). Herceptin® continued for one year. **65 month update:**





Improved DFS with both Herceptin® containing arms, compared to AC-T chemotherapy alone. Independent of lymph node status (high/low risk).

DFS (primary endpoint)
AC-TH: 84% (HR 0.64, p<0.001)
TCH: 81% (HR 0.75, p=0.04)
AC-T: 75%

Number of DFS events slightly higher in TCH arm compared to AC-TH (214 vs. 185). Metastatic event also higher (144 vs. 124).

Improved OS with both Herceptin containing arms, compared to AC-T chemotherapy alone. Independent of lymph node status (high/low risk).

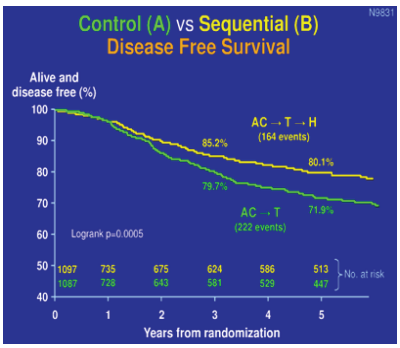
OS
AC-TH: 92% (HR 0.63, p<0.001)
TCH: 91% (HR 0.77, p=0.038)
AC-T: 87%

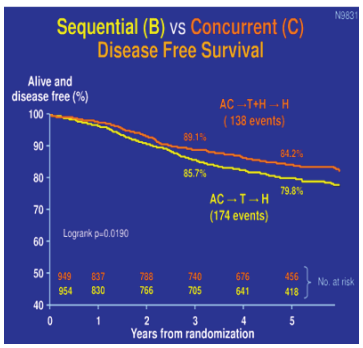
Number of OS events slightly higher in TCH arm compared to AC-TH (113 vs. 94). Breast cancer death events also higher (97 vs. 83).

- Analysis of topoisomerase 2a tumour status suggested that Herceptin® benefit was limited to **topoisomerase 2a non co-amplified** tumours. This remains controversial.
- Grade 3/4 congestive heart failure events remained higher in AC-TH arm compared to TCH (21 versus 4). Leukemia events also higher in both AC containing arms versus TCH (7 versus 0).

Results of chemotherapy alone, with sequential or concurrent addition of 52 weeks of trastuzumab in the NCCTG N9831 HER2-positive adjuvant breast cancer trial

EA Perez, Mayo Clinic Florida, on behalf of NCCTG/NSABP co-trialists.





- Randomized HER-2 positive patients to either **A: AC-T** (adriamycin, cyclophosphamide x 4 followed by paclitaxel x 12) or **B: AC-T-H** (AC x 4, followed by P x 12, followed by Herceptin® x 52) or **C: AC-TH-H** (AC x 4, followed by P concurrent with H x 12, followed by H for another 40.) **5 year update**:

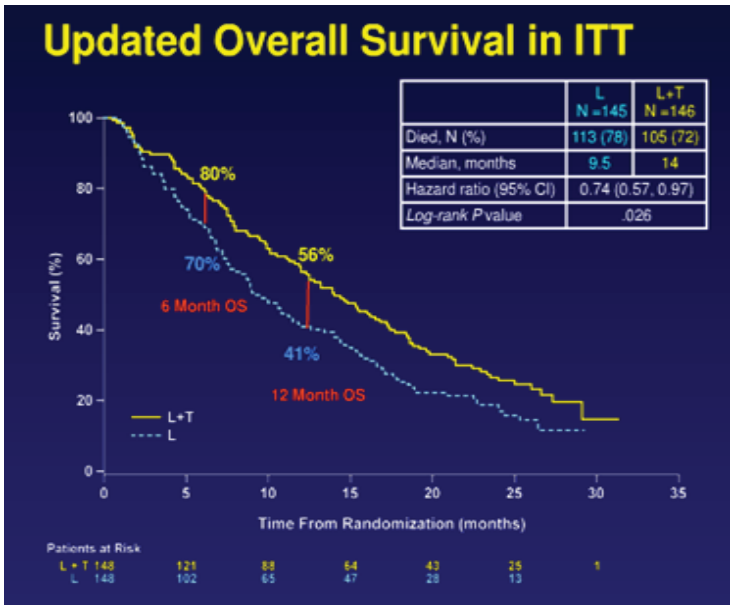
5 years DFS improved by Herceptin arms.
AC-T: 71.9%
AC-T-H: 80.1%

Concurrent H had better DFS vs. Sequential:
AC-TH-H: 84.2%
AC-T-H: 79.8%

EGF 104900

Updated survival analysis of a randomized study of lapatinib alone or in combination with trastuzumab in women with HER-2 positive metastatic breast cancer progressing on trastuzumab therapy.

KL Blackwell, Duke University, Durham. On behalf of EGF 104900 group.



- HER-2 positive metastatic breast cancer patients with progression on: anthracyclines, taxanes and progression on most recent trastuzumab regimen, randomized to: **lapatanib 1500mg po od** or **lapatanib 1000mg po od + trastuzumab (4mg/kg → 2mg/kg) weekly.**

- **2008 analysis: improved PFS (primary endpoint) in combination arm and 2.9 months improvement in OS.**
- **Current updated analysis: improved median OS in lapatanib + trastuzumab arm, compared to lapatanib alone (14 vs. 9.5 mos, HR 0.74, p=0.026).**
- **Benefit seen despite 52% crossover. Heavily pre-treated (on average 3 prior trastuzumab regimens).**
- **Well tolerated (8% grade 3/4 events compared to 7% lapatanib alone).**

TARGETED HER-2 THERAPY TAKE HOME MESSAGE

Adjuvant

- Trastuzumab given concurrently with chemotherapy (taxane portion of treatment or with non-anthracyline regimen) appears to be more effective than initiating trastuzumab after chemotherapy.
- A non-anthracycline approach (TCH), while efficacious, may not be as effective as using a regimen with an anthracycline and trastuzumab in the HER-2 positive population overall.
- Need to validate use of Topo-2a as a marker for therapy, and develop trials for those who are Topo-2a co-amplified.

Metastatic

- The combination of trastuzumab and lapatinib appears to be synergistic, even in patients who have been heavily pre-treated with trastuzumab therapy.
- We need to validate the use of trastuzumab beyond progression.
- We have limited data for using the combination of trastuzumab and lapatanib (HER-2 dual targeted approach), in combination with chemotherapy.
- Further trials are required to compare the HER-2 dual targeted approach with standard metastatic regimens containing chemotherapy and a HER-2 targeted agent.

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