TRIPLE NEGATIVE BREAST CANCER

Finding the Positives in Triple-Negative Breast Cancer: A Three-Part Live CME Webcast Series

Seminar III: Tuesday, March 16, 2010, 8:00 PM - 9:00 PM EST

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Disclosures for Moderator Neil Love, MD

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Agenda

Module 5 — Dr Miller

- New pathways and novel agents in TNBC
- Met activation and amplification: Trials evaluating Met inhibitors
- Nm23-H1 metastases suppressor gene; trials of medroxyprogesterone acetate (MPA) to stimulate production

Module 6 — Dr Rugo

- Neoadjuvant and adjuvant therapy
- Systemic therapy for metastatic disease
  - Ixabepilone
  - Bevacizumab and other anti-angiogenic strategies
  - Platinum agents

Submit a Challenging Case or Question

- Use the text box at the bottom-left of the screen to type in a case or question. You may also submit a case or question by phone at (866) 447-3623.
- You may include your full name, city and state of practice or you may choose to remain anonymous.
- Select entries will be discussed and reviewed by our esteemed faculty during the hour-long segment.

Seminar Overview

- This is the third of three unique online, integrated educational courses.
- An archive of these webcasts will also be available on **www.ResearchToPractice.com** within three days of the broadcast.
- Please remember to complete your CME evaluation. A link will be provided at the conclusion of each seminar.

Outside of a clinical trial, what is your treatment regimen for triple negative breast cancer (TNBC) in the:

a. Neoadjuvant setting

b. Adjuvant setting

— Atif Hussein, MD

A 44-year-old woman presenting with a 4.5-cm triple-negative right breast invasive ductal carcinoma, palpable nodes. No inflammatory component. PET-CT showed no metastases. She wishes for neoadjuvant chemotherapy in hopes of better post-surgical cosmesis. What is your take on using neoadjuvant single-agent cisplatin in such a situation?

— Jess F Armor, MD, Oklahoma City, Oklahoma

Is adjuvant therapy recommended for an 83-year-old woman (without any major medical problems x HBP) with 2-cm, LN-neg TNBC?

— Anonymous

A 52-year-old woman with TNBC...three treatments of AC and then five treatments of paclitaxel. Surgery: Bilateral mastectomy, 37 nodes removed, 35 positive...now what?

— Anonymous

De novo metastatic TNBC, off trial, community setting, suggested first-line therapy and sequencing?

— Anonymous

A 38-year-old with BRCA-negative TNBC with axillary metastases received neoadjuvant chemotherapy and at surgery did not have a complete response. Within six months she has metastatic disease to the bone only. Would you consider a PARP inhibitor for first-line therapy?

— AKC, Portland, Oregon

When a patient with ER-positive/HER2-negative disease converts to triple negativity in her metastatic lesion, is this phenotype to be treated like an original triple-negative?

— Michael Messer, MD

What is the status of the development of PARP inhibitors aside from BSI-201 and olaparib, such as ABT-888, AG 014699, MK4827 and INO-1001?

— Karen Tedesco, MD

BSI-201: Any use in hormone receptor-positive or HER2-positive? Any use in other cancer types?

— Helmy Guidis, MD

Please respond to whether we can obtain a PARP inhibitor through compassionate use.

— New Mexico

CASE PRESENTATION #1
Dr Miller

- 56-year-old presented with large (15 cm) mass in left breast with associated inflammatory changes and palpable axillary adenopathy
  - Biopsy Grade III IDC, ER-/PR-/HER2- (confirmed by FISH and IHC)
  - Staging negative for metastatic disease

CASE PRESENTATION #1
Dr Miller

- Enrolled in phase II clinical trial of docetaxel + capecitabine + bevacizumab
  - Resolution of inflammatory changes with modest decrease in mass after cycle 1 but with profound diarrhea (>10/day) and GCP fever
  - Admit to hospital with GCP fever and bilateral peri-rectal abscess after cycle 2
- During recovery, deleterious mutation of BRCA1 identified

CASE PRESENTATION #1
Dr Miller

- Began cisplatin 75 mg/m^2 q3 weeks x 4
  - All palpable disease resolved after cycle 2
  - Imaging negative after cycle 4
- Bilateral mastectomy – pCR
- Proceeding to RT

TRIPLE NEGATIVE BREAST CANCER

New Pathways and Novel Agents in TNBC

Kathy D Miller, MD
Sheila D Ward Scholar of Medicine
Associate Professor of Medicine
The Indiana University Melvin and Bren Simon Cancer Center
Indianapolis, Indiana

Disclosures for Kathy D Miller, MD

Research Support/PI	N/A
Employee	N/A
Consultant	Bristol-Myers Squibb Company
Major Stockholder	N/A
Speakers' Bureau	Genentech BioOncology, Roche Laboratories Inc
Scientific Advisory Board	N/A

N/A = Not Applicable

Introduction

- Identifying novel pathways
- C-MET activation
- Metastasis suppressor genes

Finding the Positive

- Goal – identify genes that are consistently overexpressed when amplified
  - 56 by CGH, 24 by genome-wide expression
- 78% with at least one amplification
  - 40 genes identified
  - No individual amplification at high frequency

Turner N et al. *Oncogene* 2010;[Epub ahead of print].

Finding the Positive (continued)

- Known oncogenes identified
  - FGFR2, BUB3, RAB20, PKN1, NOTCH3
- FGFR2 activation in 2 TBC cell lines
  - Sensitive to FGFR2 inhibition
- Independent series – relevance?
  - FGFR2 amplification in 4% (6/165) of TNBC and none (0/214) in other subtypes

Turner N et al. *Oncogene* 2010;[Epub ahead of print].

Tyrosine Kinase Receptor Pathways Activated

- Gain of function common in TNBC
  - Angiopoietin
  - HGF (ligand for c-MET)
  - FAK
  - FGF
  - VEGF
  - IGF-1
- Specific genes identified varied

Turner N et al. *Oncogene* 2010;[Epub ahead of print].

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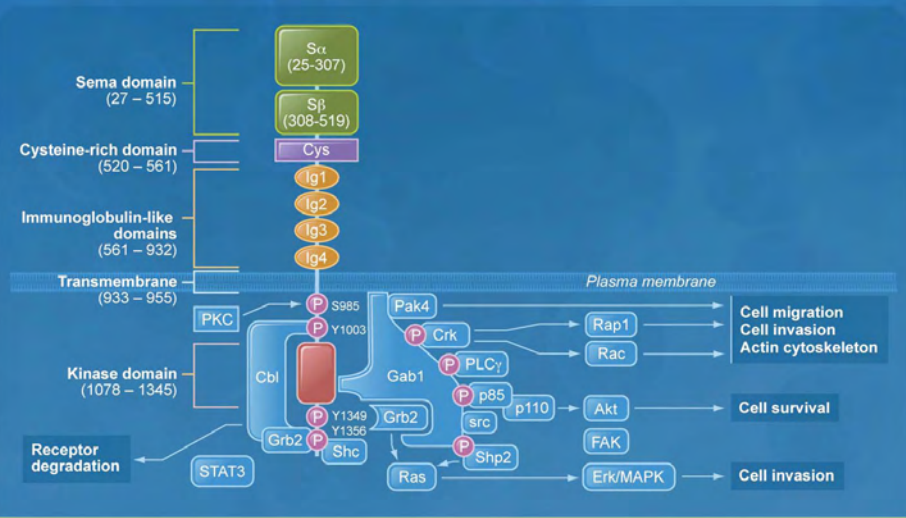
Gene Expression Meta-analysis

- High expression in TNBC
  - GGI (proliferation), IGF1, MYC, RAS/MAPK, PI3K/AKT/mTOR gene sets
- High expression of immune-related genes is consistently associated with better prognosis in TNBC
  - Strategies to enhance immune response?

Ignatiadis M et al. San Antonio Breast Cancer Symposium 2009;Abstract 106.

MET



Adapted from Lai et al. *Trends Cell Biol* 2009;19(10):542-51.

MET in Breast Cancer

	Overexpression	Mutation or Amplification	Significance
Breast (NOS)	LN neg – 15-20% LN pos – 30-80% Increased HGF - 65%	Not reported	Decreased OS with MET: 8 mos vs. 53 mos. Resistance to EGFR inhibition and trastuzumab
Basal	65-95%	Not reported	

Summary of several references.
Full list available at http://www.vai.org/met/

Learning from Mice

- Transgenic mouse models with activating MET mutations
  - Develop breast cancers with a variety of histologies with basal characteristics by gene expression and IHC
  - Correlates with EGFR, keratin-5, markers of EMT (vimentin, snail)
  - Inversely correlated with ER and PR

Ponzo MG et al. *PNAS* 2009;106(31):12903-8
Graveel CR et al. *PNAS* 2009;106(31):12909-14.

MET Inhibitors

	MET		VEGFR			Other Targets			
	RON	MET	VEGFR 1	VEGFR 2	VEGFR 3	Tie2	PDGFRß	FLT3	RET
MGCD265	X	X	X	X	X	X			
XL880	X	X		X		X	X	X	
XL184		X		X					X
ARQ-197		?							
PF-04217903	X								
AMG 102, MetMab	X								
AMG 386						X			

Metastasis Suppressor Genes

- Unique from classical tumor suppressors
  - Inhibit development and growth at distant sites
  - Little or no impact on primary tumor growth
- Expression frequently lost in aggressive tumors
- Hypothesis – increased expression of MSGs may decrease growth of mets

Medroxyprogesterone Acetate

- Low doses: Birth control, HRT
- High doses: Used for advanced breast cancer until Tam
- Increases Nm23-H1 expression *in vitro*
- In hormone receptor-negative BC, Nm23-H1 acts via **glucocorticoid receptor**
- Inhibits angiogenesis
  - Upregulates thrombospondin and PAI-1

Inhibition of Vascular Tube Formation by MPA

Preclinical Data

- MDA-MB-231T *in vivo* model
  - Mets in 100% of control mice vs 64-73% of MPA-treated mice
  - Mean number of mets:

	Mean number of mets	Percent change
Control	32-33	–
MPA 2.0 mg	14.5	57% decrease
MPA 1.0 mg	12.6	62% decrease
MPA 0.5 mg	23.8	34% decrease

- Nm23 increased in lung mets and skin biopsies
- Trough PK clinically achievable but bioavailability highly variable

Palmieri D et al. *J Natl Cancer Inst* 2005;97(9):632-42.

TBCRC 007: MPA Alone or with Metronomic Chemotherapy

- Post-menopausal, ER-/PR-
- Primary objective – identify clinical benefit rate ≥ 20%
  - Requires 2 CBR in first 15 patients
- MPA 1000-1500 mg daily
  - Intra-patient dose escalation based on PK data
  - Goal ≥ 50 ng/ml

TBCRC 007: Cohort 1, MPA Monotherapy

- N = 15, heavily pre-treated
- Median PFS = 55 days
  - 3 patients with SD for 63, 111, 504 days
- PAI-1 antigen increased at 4 wks
  - 16.74 ng/ml vs 21.78 ng/ml, *P*=0.0467
  - No changes in PAI-1 activity or TSP

Miller K, unpublished data

Conclusions

- Genomic profiling has identified many potential therapeutic targets in TNBC
  - Heterogeneity greater than expected
  - Expression alone may not be sufficient
  - Transgenic models may be more compelling

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CASE PRESENTATION #1
Dr Rugo

29-year-old Hispanic woman
- 4.5-cm right high grade, node-neg TNBC + DCIS
- AC → T

8/2008 (seven months after adjuvant chemo completed)
- Chest wall & arm pain, pleuritic-like sternal pain, SOB
- Biopsy-confirmed TNBC lower right lung
- Stains: TTF, chromogranin, synaptophysin, CK 7 & 20, BRST2
- Paclitaxel/anti-angiogenic: excellent response
- Seizures, brain mets

9/2009
- RT → phase III BSI-201 clinical trial

TNBC | TRIPLE NEGATIVE BREAST CANCER

Emerging Treatment Strategies for Triple-Negative Breast Cancer

Hope S Rugo, MD
Clinical Professor of Medicine
Director, Breast Oncology and Clinical Trials Education, University of California, San Francisco, Helen Diller Family Comprehensive Cancer Center
San Francisco, California

Disclosures for Hope S Rugo, MD

Research Support/PI	N/A
Employee	N/A
Consultant	N/A
Major Stockholder	N/A
Speakers' Bureau	AstraZeneca Pharmaceuticals LP
Scientific Advisory Board	N/A

N/A = Not Applicable

TRIPLE NEGATIVE BREAST CANCER

Response to Neoadjuvant Therapy and Long-Term Survival in Patients with Triple-Negative Breast Cancer

Liedtke C et al.

***J Clin Oncol* 2008;26(8):1275-81.**

Method

Cases selected from Breast Medical Oncology Database of MD Anderson Cancer Center from patients diagnosed with nonmetastatic breast cancer between 1985-2004 who had received neoadjuvant chemotherapy.

Patients included: 1,118
TNBC patients: 255 (23%)
Non-TNBC patients: 863 (77%)

Results: pCR Rates as a Function of Triple-Negative Status and Chemotherapy Regimens

	pCR Rates			
Regimens	All Patients	TNBC	Non-TNBC	*p*-value
FAC/FEC/AC (n=308)	8%	20%	5%	0.0001
TFAC/TFEC (n=588)	19%	28%	17%	0.0072
Single-agent taxane (n=58)	5%	12%	2%	0.82
Other (n=164)	9%	14%	7%	0.33
Total (n=1,118)	15%	22%	11%	0.034

Liedtke C et al. *J Clin Oncol* 2008;26(8):1275-81.

Conclusions

- Patients with TNBC have increased pCR rates compared to patients with non-TNBC.
  - pCR rates: 22% vs 11% (p=0.034)
- Patients who achieved pCR had excellent survival regardless of receptor status (data not shown).

Liedtke C et al. *J Clin Oncol* 2008;26(8):1275-81.

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TRIPLE NEGATIVE BREAST CANCER

Breast Cancer Molecular Profiles Predict Tumor Response of Neoadjuvant Doxorubicin and Paclitaxel, the I-SPY TRIAL (CALGB 150007/150012, ACRIN 6657)

Esserman LJ et al.

ASCO 2009; Abstract LBA515.

I-SPY TRIAL: pCR in Context of IHC and Select Molecular Subtypes

IHC	pCR (n=190)	*p*-value
HR-positive, HER2-negative (n=91)	10%	NR
HR-positive, HER2-positive (n=23)	32%	
HR-negative, HER2-positive (n=23)	50%	
HR-negative, HER2-negative (n=53)	33%	
Gene Profile Intrinsic Subtypes	**pCR (n=144)**	***p*-value**
Luminal A or B (n=72)	17%	<0.0001
HER2-enriched (n=22)	52%	
Basal (n=48)	34%	

Esserman LJ et al. ASCO 2009; Abstract LBA515.

Conclusions

- In low-risk subsets, low pCR rates are observed, but patients have good outcomes (<5 yrs).
- In high-risk subsets, high pCR rates are highly predictive of improved early outcome.

Esserman LJ et al. ASCO 2009; Abstract LBA515.

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Comparison of Subgroup Analyses of PFS from Three Phase III Studies of Bevacizumab in Combination with Chemotherapy in Patients with HER2-Negative Metastatic Breast Cancer

O'Shaughnessy et al.

SABCS 2009; Abstract 207. (Poster)

Method

- Assess activity of bevacizumab (B) in patients with triple negative breast cancer (ER-, PR-, HER2-) by comparing progression-free survival (PFS) in clinically important subgroups across three studies:
  - E2100: paclitaxel + B 15 mg/kg
  - AVADO: docetaxel + B 7.5 or 15 mg/kg or placebo (P)
  - RIBBON-1: capecitabine, taxane or anthracycline + B or P

O'Shaughnessy J et al. SABCS 2009; Abstract 207.

Results: Improvement in PFS with Addition of B in E2100, AVADO and RIBBON-1

Improvement in PFS (mos)	E2100 (n=722)	AVADO* (n = 736)	RIBBON-1** (n=1,237)
Overall (Hazard Ratio, HR)	5.5 (0.48)	0.8 (0.70); 0.9 (0.61)	2.9 (0.69); 1.2 (0.64)
Triple-negative (HR)	5.3 (0.49)	0.8 (0.69); 2.8 (0.53)	1.9 (0.72); 0.3 (0.78)
Neoadjuvant/adjuvant taxane (HR)	7.3 (0.33)	4.2 (0.62); 1.9 (0.43)	4.5 (0.62); 2.4 (0.65)
Age ≥ 65 (HR)	4.3 (0.67)	0.8 (0.76); 0.8 (0.68)	2.9 (0.69); 1.6 (0.83)

*B 7.5 mg/kg; 15 mg/kg; ** Capecitabine/B; Taxane/anthracycline/B

O'Shaughnessy J et al. SABCS 2009; Abstract 207.

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Conclusions

- The addition of B led to an increase in median PFS for patients with triple-negative tumors, patients > 65 yr and patients who had received prior adjuvant taxane chemotherapy
- The addition of B consistently improved PFS across a number of clinically relevant subsets, regardless of the chemotherapy backbone used

O'Shaughnessy J et al. SABCS 2009; Abstract 207.

TNBC | TRIPLE NEGATIVE BREAST CANCER

First-Line Bevacizumab Combination Therapy in Triple-Negative Locally Recurrent (LR)/Metastatic Breast Cancer (mBC): Subpopulation Analysis of Study MO19391 (ATHENA) in >2000 Patients

Thomssen C et al.

SABCS 2009; Abstract 6093. (Poster)

MO19391 (ATHENA) Trial Design (n = 2,251)

Eligibility
HER2-negative
No prior chemotherapy, or concomitant endocrine therapy

→ Bevacizumab + chemotherapy

- **Bevacizumab** = 10 mg/kg q2wks or 15 mg/kg q3wks
- **Chemotherapy** = taxane alone or in combination (clinician's choice) or standard chemotherapy if taxane not considered standard of care

Thomssen C et al. SABCS 2009; Abstract 6093.

Results: Efficacy (median follow-up 12.7 months)

	TNBC (n = 577)	Non-TNBC (n = 1,593)
Median time to progression (TTP)*	7.2 mos	10.4 mos
Overall response rate	47%	53%
Overall Survival		
Deaths, n (%)	216 (37%)	398 (25%)
BC deaths, n (%)	199 (34%)	339 (21%)

* One patient in whom TTP was recorded before treatment start is not included in the TTP analysis.

Thomssen C et al. SABCS 2009; Abstract 6093.

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Conclusions

The median TTP reported in this analysis for patients with TNBC is within the range reported for median progression free survival in subpopulations of patients with TNBC treated with bev in randomized trials (SABCS 2009; Abstract 207).

Thomssen C et al. SABCS 2009; Abstract 6093.

TNBC TRIPLE NEGATIVE BREAST CANCER

Pathologic Complete Response Rates in Young Women With *BRCA1*-Positive Breast Cancers After Neoadjuvant Chemotherapy

Byrski T et al.

J Clin Oncol 2010;28(3):375-79.

Method

- Cases selected from patients diagnosed with early-onset incident breast cancer at 18 hospitals in Poland between 1996 and 2008 that received neoadjuvant chemotherapy.
- Patients screened for the three founding BRCA1 mutations occurring in Polish families.
- 102 patients identified with a BRCA1 mutation, the majority of which had triple negative breast cancer.

Byrski T et al. *J Clin Oncol* 2010;28(3):375-79.

Results: Treatment and Response to Different Chemotherapy Regimens

Regimen	No. Patients Treated	No. of pCRs	% pCRs
CMF	14	1	7
AC	23	5	22
FAC	28	6	21
AT	25	2	8
Cisplatin	12	10	83

CMF = cyclophosphamide/methotrexate/fluorouracil
AC = doxorubicin/cyclophosphamide
FAC = fluorouracil/doxorubicin/cyclophosphamide
AT = doxorubicin/docetaxel

Byrski T et al. *J Clin Oncol* 2010;28(3):375-79.

Conclusions

- Early data suggest that chemotherapy containing doxorubicin and cyclophosphamide or platinum may have the most potential to be beneficial to patients with breast cancer that carry BRCA1 mutations.
- Study limited by small sample size, lack of random assignment or standardization of treatment protocols and its observational nature.

Byrski T et al. *J Clin Oncol* 2010;28(3):375-79.

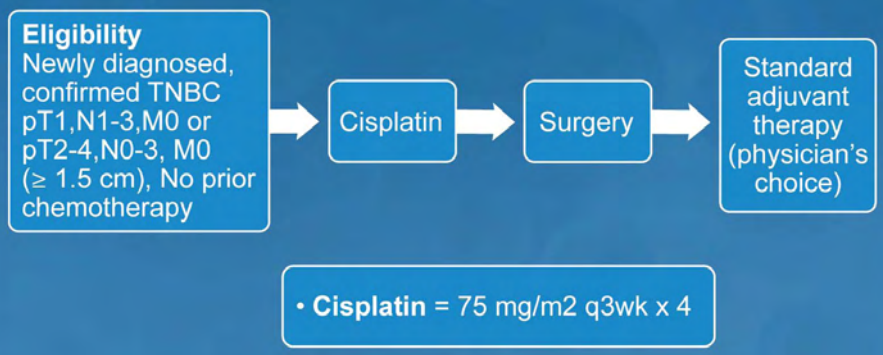
TNBC | TRIPLE NEGATIVE BREAST CANCER

Efficacy of Neoadjuvant Cisplatin in Triple-Negative Breast Cancer

Silver DP et al.

***J Clin Oncol* 2010; Jan 25 [epub ahead of print].**

Trial Design (n = 28): Neoadjuvant Cisplatin



Silver DP et al. *J Clin Oncol* 2010; Jan 25 [epub ahead of print].

Results: Response to Cisplatin Neoadjuvant Treatment

	n (%) (n=28)	95% Conditional CI
Clinical response	18 (64)	44% - 81%
Complete response	4* (14)	—
Partial response	14 (50)	—
Good pathologic response (Miller-Payne 3, 4, and 5)	14 (50)	31% - 70%
Pathologic complete response	6* (21)	9% - 43%
Pathologic partial response	8 (29)	—
Disease progression	4 (14)	—

* Includes 2 patients with *BRCA1* germline mutations.

Silver DP et al. *J Clin Oncol* 2010; Jan 25 [epub ahead of print].

Conclusions

- Neoadjuvant cisplatin demonstrated activity in a subset of patients with TNBC:
  - Miller-Payne grade 3, 4 or 5 pathologic response achieved by 50% of patients.
- Multivariate analysis demonstrated several biomarkers, including low BRCA1 mRNA expression, may predict cisplatin response (data not shown).

Silver DP et al. *J Clin Oncol* 2010; Jan 25 [epub ahead of print].

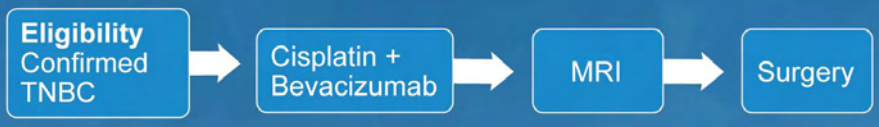
TNBC TRIPLE NEGATIVE BREAST CANCER

Neoadjuvant Cisplatin and Bevacizumab in Triple Negative Breast Cancer (TNBC): Safety and Efficacy

Ryan PD et al.

ASCO 2009; Abstract 551. (Poster)

Trial Design (n = 51): Neoadjuvant Cisplatin Plus Bevacizumab



- **Cisplatin** = 75 mg/m2 q3wk x 4
- **Bevacizumab** = 15 mg/kg q3wk x 3

Ryan PD et al. ASCO 2009; Abstract 551.

Results: Response to Neoadjuvant Therapy

Characteristic	n (%)
Pathologic Response (n=45)	
Miller-Payne grade 5 (no tumor left)	8 (16)
Miller-Payne grade 4 (> 90% decrease)	11 (21)
Progressive Disease	1 (2)
Nonresponders	6 (12)
Clinical Response (n=51)	
Complete response	14 (27)
Partial response	27 (53)

Ryan PD et al. ASCO 2009; Abstract 551.

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Conclusions

- Neoadjuvant cisplatin plus bevacizumab demonstrated activity in patients with TNBC:
  - Miller-Payne grade 4 or 5 pathologic response achieved by 37% of patients.
  - Proportion of evaluable patients that achieved a clinical response was 80%.

Ryan PD et al. ASCO 2009; Abstract 551.

TNBC | TRIPLE NEGATIVE BREAST CANCER

Ixabepilone plus Capecitabine vs. Capecitabine in Patients with Triple Negative Tumors: A Pooled Analysis of Patients from Two Large Phase III Clinical Studies

Rugo HS et al.

SABCS 2008; Abstract 3057 (Poster).

Study Design for CA 163-046 and CA 163-048*

Eligibility

Locally advanced or metastatic breast cancer (MBC)

Pretreated or resistant to taxanes and anthracyclines

R

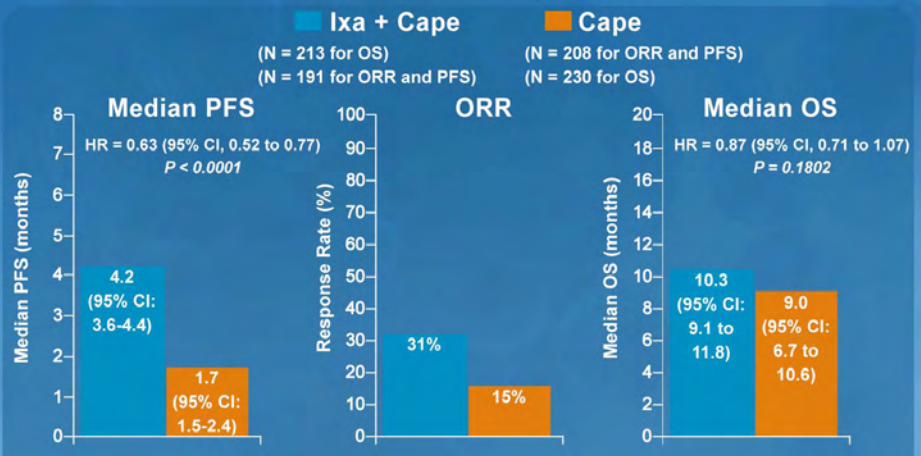
Ixabepilone (Ixa)
40mg/m^2 IV over 3 hr d1 q3wk +
Capecitabine 1,000 mg/m^2 BID 14 days q3wk

Capecitabine (Cape)
1,250 mg/m^2 BID 14 days q3wk

*Phase III trials with similar design. Data pooled (n=443)

Rugo HS et al. SABCS 2008; Abstract 3057.

Results: Pooled Analysis of Patients with Triple Negative MBC



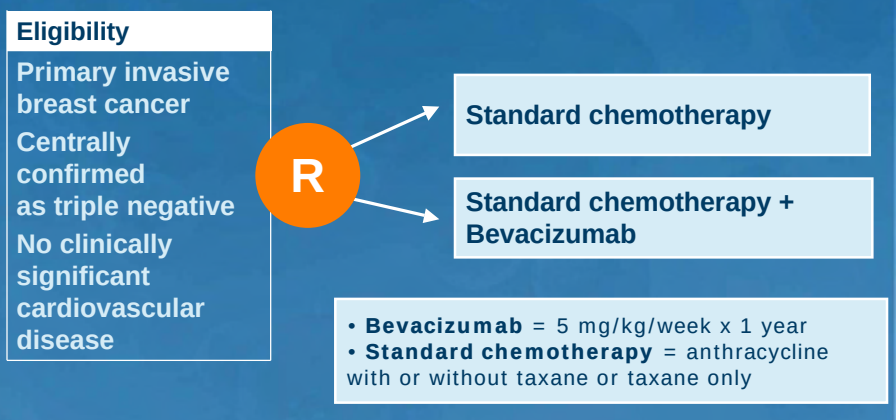
Rugo HS et al. SABCS 2008; Abstract 3057.

Conclusions

- In the largest clinical data set recorded, Ixa plus Cape in patients with triple negative MBC (TN MBC) resulted in:
  - Prolonged PFS by 2.5 months
  - Doubling of ORR
- Ixa plus Cape did not increase OS compared to Cape alone.
- Cape alone offers little benefit for patients with TN MBC previously treated with an anthracycline and taxane.

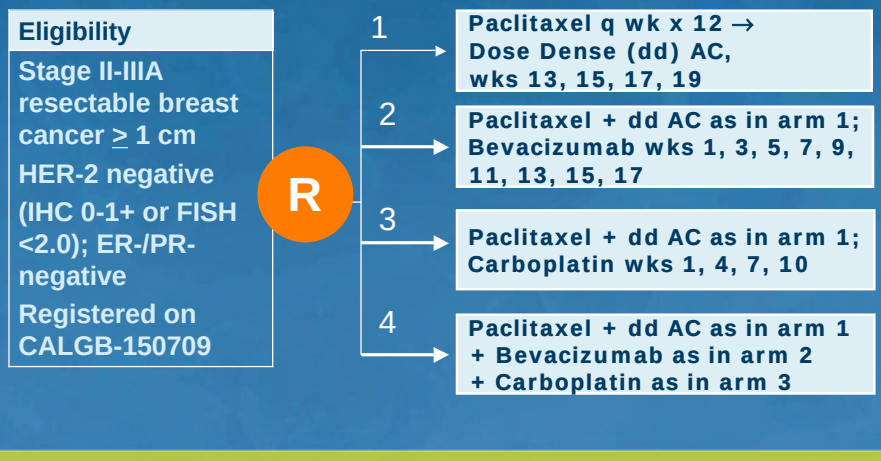
Rugo HS et al. SABCS 2008; Abstract 3057.

BEATRICE Trial: Estimated enrollment = 2,530 (closed)



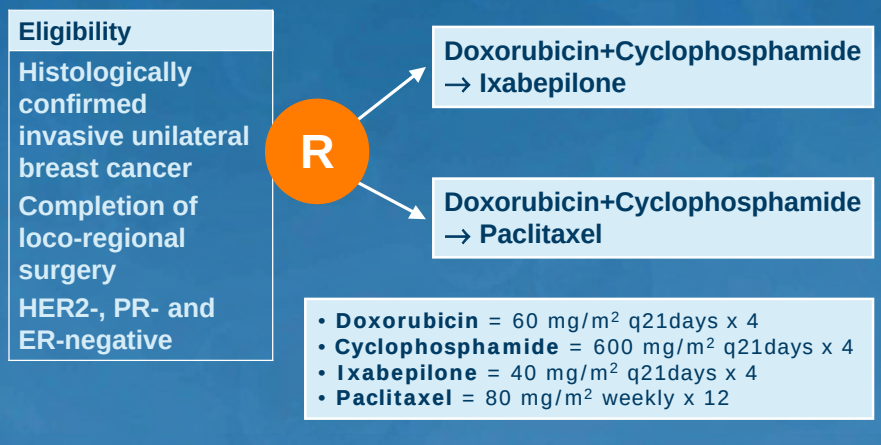
NCI Physician Data Query, February 2010

CALGB 40603 Neoadjuvant Trial Design: Target accrual = 362



NCI Physician Data Query, February 2010

TITAN Trial Design: Estimated enrollment = 1,800 (open)



www.ClinicalTrials.gov, February 2010

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