Clinical Research on Tubulin Inhibition and Anti-angiogenic Agents in TNBC

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Disclosures for Edith A Perez, MD

Paid Research to Mayo Clinic	Genentech BioOncology, GlaxoSmithKline, Roche Laboratories Inc, sanofi-aventis

Key Topics Discussed

- Anti-tubulin agents and TNBC: Taxanes and ixabepilone
- Angiogenesis inhibitors and TNBC: Bevacizumab

CALGB-40603: The Triple-Negative Neoadjuvant Trial (TNNT)

Target accrual = 362

Eligibility

- **Stage II-IIIA resectable breast cancer ≥ 1 cm**
- **HER2-negative (IHC 0-1+ or FISH <2.0); ER-/PR-poor**
- **Registered on CALGB-150709 correlative tissue study**

1 → **Paclitaxel** 80 mg/m^2 x 12 → Dose Dense (dd) AC x 4

2 → **Paclitaxel** + dd AC as in arm 1; **Bevacizumab** 10 mg/kg q2wk x 9

3 → **Paclitaxel** + dd AC as in arm 1; **Carboplatin** AUC 6 q3wk x 4

4 → **Paclitaxel** + dd AC as in arm 1 + **Bevacizumab** as in arm 2 + **Carboplatin** as in arm 3

Courtesy of Clifford A Hudis.

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.**

pCR Rates to Neoadjuvant Chemotherapy as a Function of Triple-Negative Status

Regimens	pCR Rates			*p*-value
	All Patients	TNBC	Non-TNBC	
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

Patients with TNBC have a higher incidence of pCR to taxane-based regimens

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

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.

Proc ASCO **2009;Abstract LBA515.**

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

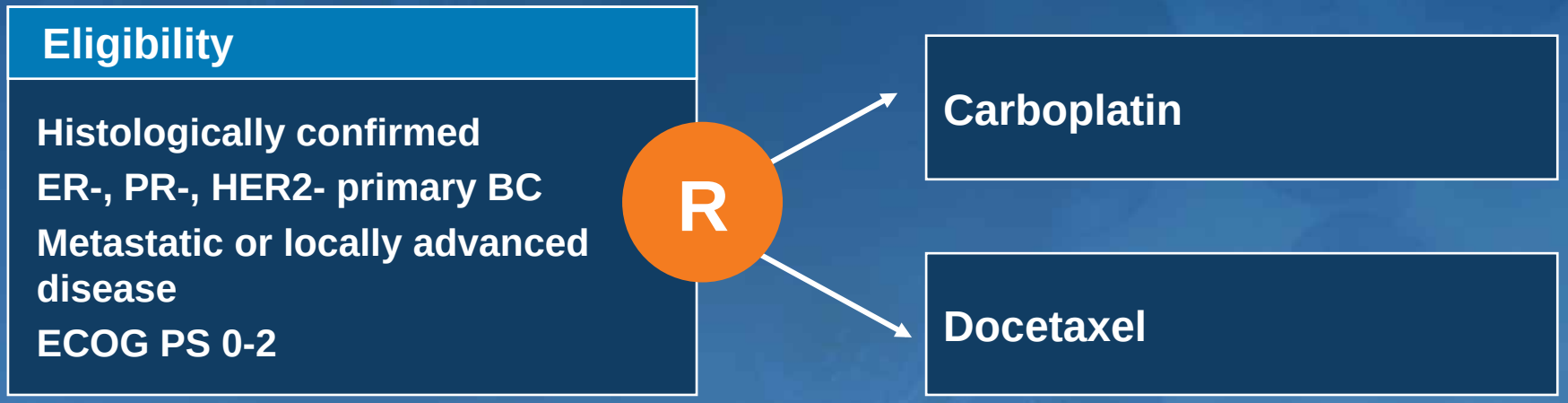
IHC	pCR (n = 190)	*p*-value
HR-positive, HER2-negative (n = 91)	10%	NR
HR-positive, HER2-positive (n = 23)	32%	
HR-negative, HER2-positive (n = 23)	50%	
HR-negative, HER2-negative (n = 53)	33%	
Gene Profile Intrinsic Subtypes	**pCR (n = 144)**	***p*-value**
Luminal A or B (n = 72)	17%	NR
HER2-enriched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

Patients with TNBC are responsive to neoadjuvant paclitaxel/doxorubicin x 4.

Esserman LJ et al. *Proc ASCO* 2009;Abstract LBA515.

TNT Trial: A Phase III Trial of Carboplatin versus Docetaxel for Metastatic or Recurrent Locally Advanced TNBC

Target accrual = 400 (open)



- Carboplatin = AUC 6 every 3 weeks for six cycles
- Docetaxel = 100 mg/m^2 every 3 weeks for six cycles

www.ClinicalTrials.gov, December 2010.

CALGB-40502/NCCTG N063H: A Phase III Trial of Bevacizumab with Paclitaxel, *Nab* Paclitaxel or Ixabepilone in Patients with Stage IIIC-IV Breast Cancer

Target accrual = 900 (open)

Eligibility

- **Stage IIIC-IV measurable disease ≥ 1 cm by CT scan, or ≥ 2 cm by conventional techniques**
- **Known ER, PR and HER2 status**
- **No prior chemotherapy for metastatic disease**

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1 → **Paclitaxel** 90 mg/m^2 IV d1, 8 and 15 → **Bevacizumab** d1 and 15 q28 days

2 → ***Nab* paclitaxel** 150 mg/m^2 IV d1, 8 and 15 **Bevacizumab** d1 and 15 q28 days

3 → **Ixabepilone** 16 mg/m^2 IV d1, 8 and 15 → **Bevacizumab** d1 and 15 q28 days

www.ClinicalTrials.gov, December 2010.

Phase II Genomics Study of Ixabepilone as Neoadjuvant Treatment for Breast Cancer

Baselga J et al.

J Clin Oncol **2009;27(4):526-34.**

pCR_{Breast} Rates to Neoadjuvant Ixabepilone by Hormone and HER2 Receptor Status

Patient Subgroup	Total Patients	Patients w/ Response	%
All treated patients	161	29	18
ER-negative	72	21	29
ER/PR-negative	61	20	33
ER/PR/HER2-negative	42	11	26

Neoadjuvant ixabepilone is active in various breast cancer subtypes including TNBC

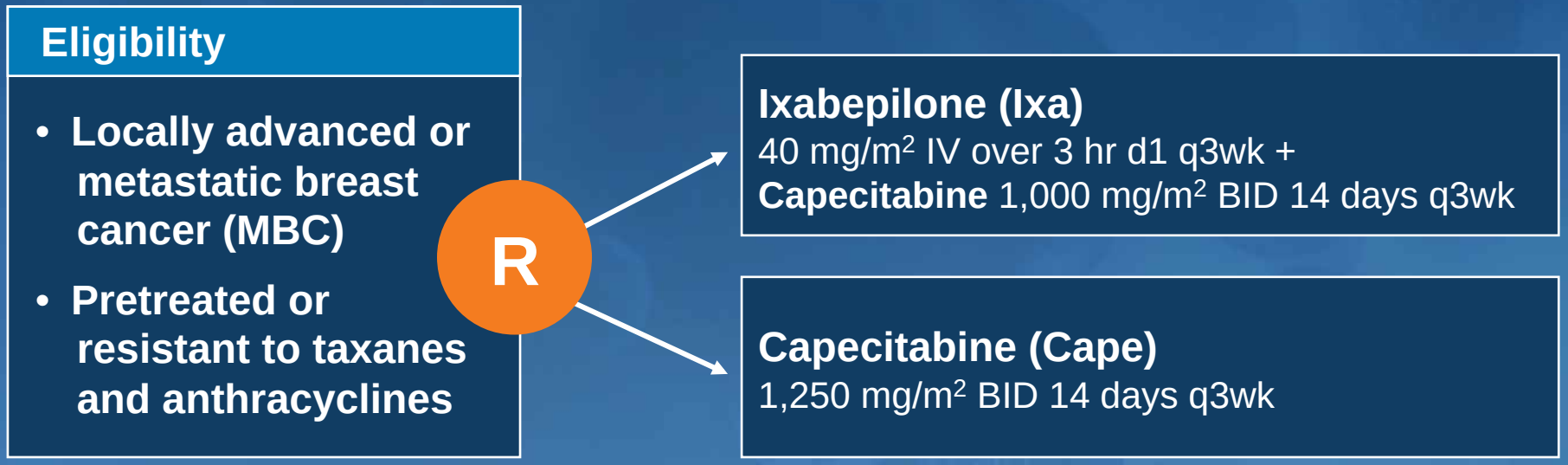
Baselga J et al. *J Clin Oncol* 2009;27(4):526-34.

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.

Proc SABCS **2008;Abstract 3057.**

Capecitabine +/- Ixabepilone: Study Design for CA 163-046 and CA 163-048*

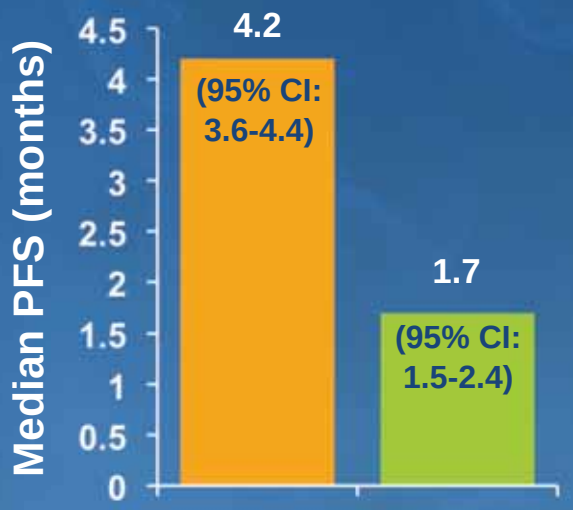


* Phase III trials with similar design. Data pooled (n = 443)

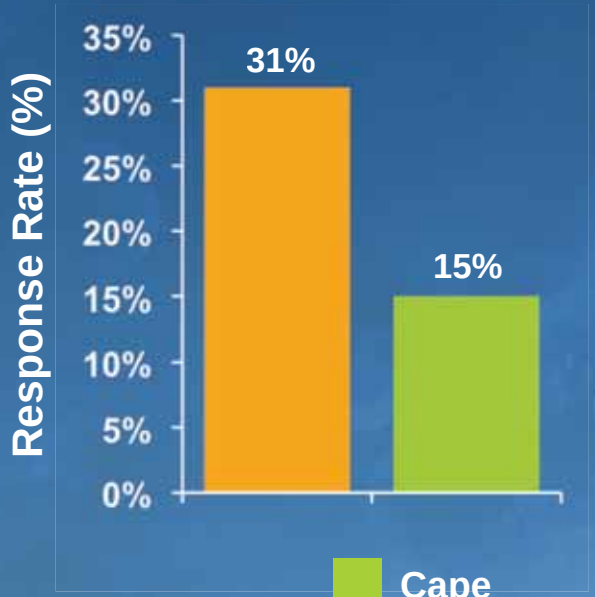
Rugo HS et al. *Proc SABCS* 2008;Abstract 3057.

Results: Pooled Analysis of Patients with Metastatic TNBC

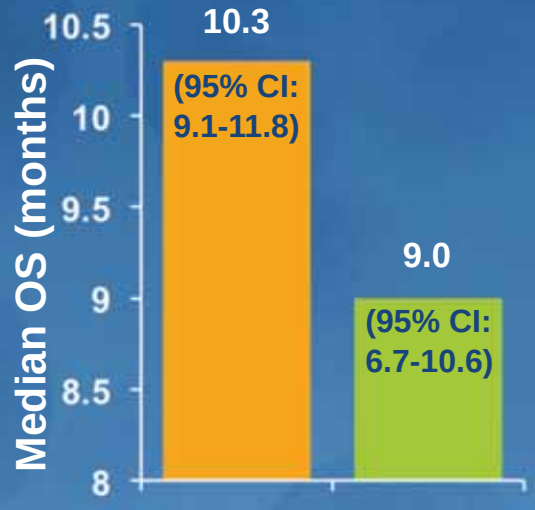
Median PFS
HR = 0.63 (95% CI, 0.52 to 0.77)
p < 0.0001



ORR



Median OS
HR = 0.87 (95% CI, 0.71 to 1.07)
p = 0.1802



Ixa + Cape
(N = 213 for OS)
(N = 191 for ORR and PFS)

Cape
(N = 230 for OS)
(N = 208 for ORR and PFS)

Rugo HS et al. *Proc SABCS* 2008;Abstract 3057. (Poster)

Conclusions Related to Ixabepilone in Metastatic TNBC

- In the largest clinical data set recorded, Ixa plus Cape in patients with metastatic TNBC 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 a taxane

Rugo HS et al. *Proc SABCS* 2008;Abstract 3057.

TITAN Phase III Trial Design

Target accrual = 1,800 (open)

Eligibility

- **Histologically confirmed invasive unilateral breast cancer**
- **Completion of locoregional surgery**
- **HER2-, PR- and ER-negative**

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Doxorubicin + Cyclophosphamide → Ixabepilone

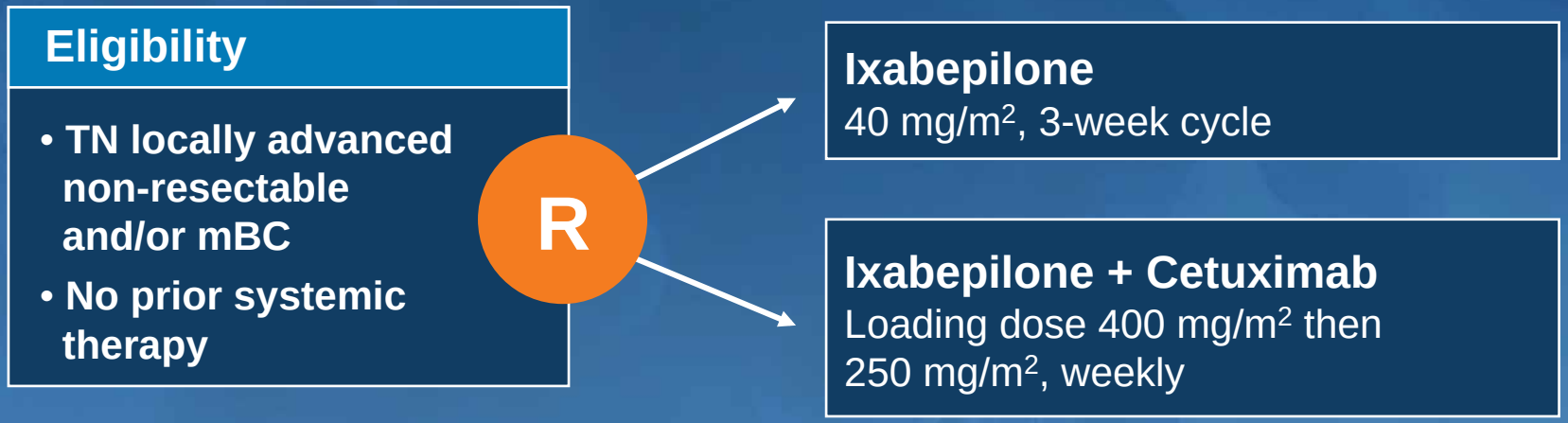
Doxorubicin + Cyclophosphamide → Paclitaxel

- Doxorubicin = 60 mg/m^2 q21days x 4
- Cyclophosphamide = 600 mg/m^2 q21days x 4
- Ixabepilone = 40 mg/m^2 q21days x 4
- Paclitaxel = 80 mg/m^2 weekly x 12

www.ClinicalTrials.gov, December 2010.

CA163-139 Phase II Trial Design

Target accrual = 80 (closed)

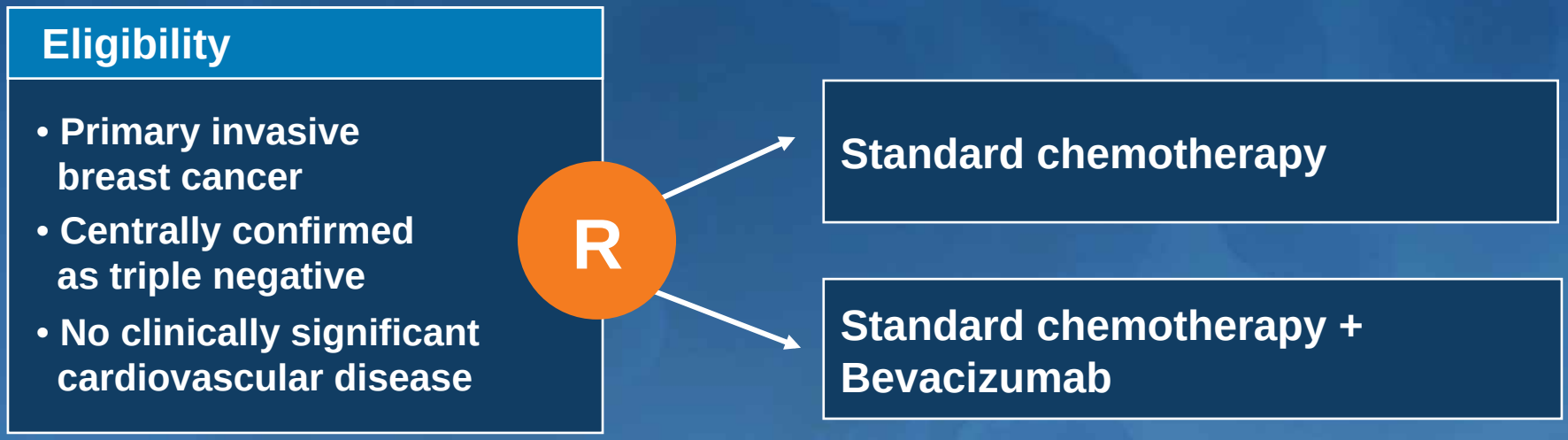


- Study will be completed once all subjects have progressed or 15 months after the Last Patient First Visit, which ever comes first

www.ClinicalTrials.gov, December 2010.

BEATRICE Phase III Trial Design

Target accrual = 2,530 (open)



- **Bevacizumab** = 5 mg/kg/week x 1 year
- **Standard chemotherapy** = anthracycline with or without taxane or taxane only
- **Primary endpoint:** DFS

www.ClinicalTrials.gov, December 2010.

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 J et al.

Proc SABCS **2009;Abstract 207. (Poster)**

Improvement in PFS with Addition of Bevacizumab (B) in E2100, AVADO and RIBBON-1

Patient Subgroup	Improvement in PFS, months (HR)		
	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 (doses were also used in the other two trials);
† Capecitabine/B; Taxane/anthracycline/B

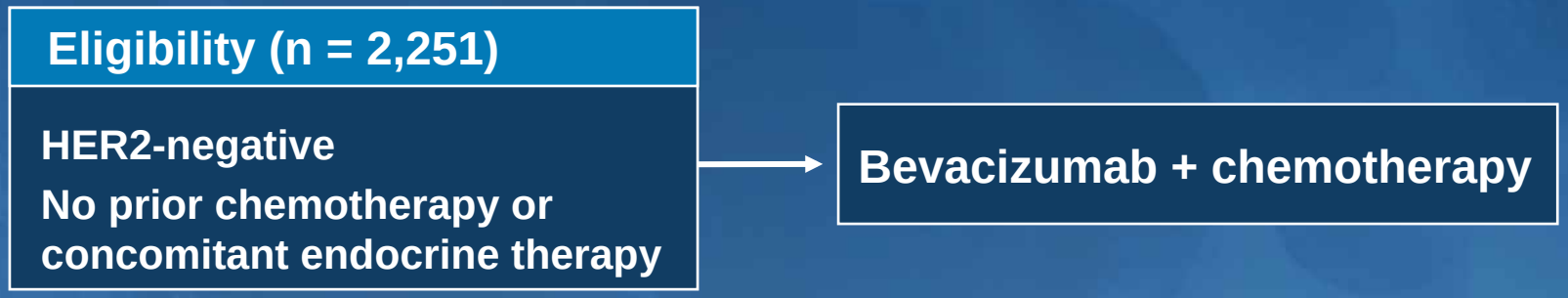
O'Shaughnessy J et al. *Proc SABCS* 2009;Abstract 207. (Poster)

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.

Proc SABCS **2009;Abstract 6093.**

MO19391 (ATHENA) Trial Design



- **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. *Proc SABCS* 2009;Abstract 6093.

ATHENA 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 (%) BC deaths, n (%)	 216 (37%) 199 (34%)	 398 (25%) 339 (21%)

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

Thomssen C et al. *Proc SABCS* 2009;Abstract 6093.

Brostallicin – A Novel Cytotoxic Agent

- Brostallicin is a new synthetic α-bromoacrylic derivative that belongs to the DNA minor groove binding anticancer agents.
- By binding to the DNA minor groove, brostallicin interferes with cell division and leads to apoptosis.
- Active in cancer cells with deficient double-stranded DNA break repair mechanisms and cells with mismatch repair deficiency
- Preclinical and clinical studies indicate that tumors with BRCA1 dysfunction are sensitive to agents that cause DNA damage such as cisplatin and brostallicin.

N0937: A Phase II Trial of Brostallicin and Cisplatin in Patients with Metastatic Triple-Negative Breast Cancer

Target accrual = 46

Eligibility

- Metastatic TNBC
- 0-4 prior therapies for metastatic TNBC
- Prior cisplatin therapy allowed
- No uncontrolled CNS metastases

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- Cisplatin 50 mg/m^2 IV d1
- Brostallicin 10 mg/m^2 IV d2
- GCSF or pegylated GCSF from d3

- **Primary endpoint: PFS at 3 months**
- **Secondary endpoints: RR, 6-mo PFS, OS, tolerability**

www.ClinicalTrials.gov, December 2010.