Poster Discussion session
Breast cancer, metastatic

Poster 322, 323, 325 & LBA14

Thomas Bachelot,
Centre Léon Bérad, Lyon
Disclosure

Board and research funding:

• Roche
• Novartis
• GSK
MBC in 2012

Multiple disease

Breast K

1980

ER+

ER-

1985

ER+

HER2-

ER+

HER2+

ER-

HER2+

Chemotherapy

HT

HER2 Targeted

2000

ER-

HER2-

Beva

Beva

www.esmo2012.org
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

1980

1985

2000

Breast K

ER+

ER-

ER+ HER2-

ER+ HER2+

ER- HER2+

ER- HER2-

Chemotherapy

Immunotherapy

HT

HER2 Targeted

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323: toxicity of Beva/HT combination

2000
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
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 IIIR [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 !!

pCR [Interaction according HER-2 Inhibition]
Toxicity [Interaction according to Chemo]

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

Bar chart showing:
- Cardio: Anthra-TAX 1.3, TAX <1.0
- Neutro: Anthra-TAX 56.6, TAX 26.4
- FN: Anthra-TAX 6.0, TAX 7.7

Legend: red = Anthra-TAX, blue = TAX
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: likelihood of being 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 an 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

N= 380
MBC or L advanced HR+/HER2-
Post menoposral
Could have received AI in the adjuvant setting

Letrozol or Fulvestrant 250/m
=> PFS
Letrozol or Fulvestrant 250/m
+ Bevacizumab (15 mg/kg q3w)
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
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

N= 380 MBC or L advanced HR+/HER2-
Post menoposal
Could have received AI in the adjuvant setting

Letrozol or Fulvestrant 250/m

R

Letrozol or Fulvestrant 250/m + Bevacizumab (15 mg/kg q3w)

=> PFS
## Significant different Non-haematological AEs grade 1-4

<table>
<thead>
<tr>
<th>Condition</th>
<th>ET n(%)</th>
<th>ET-B n(%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine elevation</td>
<td>14 (8.0)</td>
<td>32 (17.1)</td>
<td>0.011</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>10 (5.7)</td>
<td>23 (12.2)</td>
<td>0.03</td>
</tr>
<tr>
<td>Fatigue</td>
<td>51 (29.0)</td>
<td>95 (50.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fever w/on neutropenia</td>
<td>6 (3.4)</td>
<td>17 (9.0)</td>
<td>0.031</td>
</tr>
<tr>
<td>Haemorrhage</td>
<td>3 (1.7)</td>
<td>35 (18.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hyperbilirubinaemia</td>
<td>7 (4.0)</td>
<td>19 (10.2)</td>
<td>0.026</td>
</tr>
<tr>
<td>Hypertension grade 3-4</td>
<td>4 (2.3)</td>
<td>24 (12.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Liver Dysfunction</td>
<td>0</td>
<td>6 (3.2)</td>
<td>0.03</td>
</tr>
<tr>
<td>Liver enzymes elevation (ASAT)</td>
<td>49 (28.0)</td>
<td>87 (46.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Proteinuria grade 3-4</td>
<td>0</td>
<td>11 (5.9)</td>
<td>0.001</td>
</tr>
<tr>
<td>Pain</td>
<td>83 (47.2)</td>
<td>128 (68.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6 (3.4)</td>
<td>22 (11.7)</td>
<td>0.003</td>
</tr>
</tbody>
</table>
Deaths on Study: 7, all in the Bevacizumab arm

<table>
<thead>
<tr>
<th>Condition</th>
<th>Age at death</th>
<th>Co-morbidity at baseline</th>
<th>ET</th>
<th>ET-B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary Embolism</td>
<td>75</td>
<td>Hypertension, osteoporosis, immobility (1 month on treat.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>82</td>
<td>Hypertension, hypercholesterolemia, obesity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart Failure</td>
<td>74</td>
<td>Hypertension, TIA, obesity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sudden Death</td>
<td>73</td>
<td>Hypertension, hypercholesterolemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebellum infarction</td>
<td>53</td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver Decompensation</td>
<td>79</td>
<td>Hepatitis C, alcoholism</td>
<td></td>
<td></td>
</tr>
<tr>
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<td>53</td>
<td>None</td>
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*It’s toxic: Patient selection is important*
Deaths on Study: 7, all in the Bevacizumab arm

<table>
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<th>Death Diagnosis</th>
<th>Age at death</th>
<th>Co-morbidity at baseline</th>
<th>ET</th>
<th>ET-B</th>
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<tr>
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<td>1</td>
<td></td>
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*Waiting for efficacy results!*. 

www.esmo2012.org
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

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

Biosynthesis 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)

**In ERα+/AR+ pts:**
- RR: 4%; CBR: 22%
- 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

**Diagram:**
- Bar chart showing best tumor response (%)
- ERα+/AR+ and ERα-/AR+
- New lesion marker
- Size of target tumor lesions c/w baseline

**Images:**
- November 2011
- March 2012

**Chart notes:**
- * new lesion
- +20%
- -30%
Phase I/II trial of Abiraterone Acetate (AA) in estrogen receptor (ER) or androgen receptor (AR) positive metastatic breast cancer (MBC)

**Potential New hormonal therapy**

- Need predictive factor
- Need more knowledge of AR role in breast carcinogenesis

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**ERα+/AR+**

Size of target tumor lesions c/w baseline.

**ERα-/AR+**

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

- November 2011
- March 2012

---

[Image of tumor response chart]

* new lesion

+20%

-30%
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

PANVAC: CEA-, MUC-1-TRICOM

Vaccinia: Prime

Fowlpox: Boost
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

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

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

**Primary endpoint**: TTP

**Randomize**

- Arm A: Weekly Docetaxel + PANVAC*
- Arm B: Weekly Docetaxel alone

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

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

*Completed accrual*: 2/28/2012
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).
## Baseline Characteristics

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

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

Arm A: 6.6 months
Median cycles - 5

Arm B: 3.8 months
Median cycles - 3

P=0.12
HR= 0.67
95% CI: 0.34-1.31
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).
Conclusion

First randomized trial of vaccine therapy for MBC

Important but preliminary results: Will survival be affected?

Needs more patients selection?