Possible interactions between radiotherapy and new targeted agents

Possibili interazioni tra RT e nuovi farmaci a bersaglio molecolare

Youlia M. Kirova, MD
Department of Radiation Oncology

youlia.kirova@curie.fr
Introduction

Widespread use of systemic treatments in breast cancer

- Hormone therapy
- Chemotherapy
- Targeted therapy (trastuzumab, lapatinib, Avastin, Afinitor)

All these treatments have an impact on local control and survival

In the adjuvant setting, they are usually delivered sequentially

Few studies have evaluated the delivery of concurrent radiotherapy and systemic treatments
Concurrent radiotherapy and systemic treatments

Theoretical benefit:

Reduction of delay of initiation of each modality

« Supra-additive » effect on tumor control

Theoretical risk

Toxicity and sequelae

Decreased radiosensitivity
Concurrent RT-targeted treatments
Trastuzumab-RT
MCF7 surexpression of HER2 (murine model)
RT + Ac anti HER2

MCF7 cells transfected with HER2
From Liang K et al. Mol Cancer Ther 2003
RT + Trastuzumab. Efficacy

9 pts with LABC (T4 or N2 or M1)
Chimiotherapy followed by RT : 50 Gy breast and LN
Concurrent Trastuzumab (2mg/m² hebdo.)
Median FU: 23 months
No cardiac toxicity
3/9 mastectomies
No LR recurrence in the 6 patients treated without surgery

Sartor C et al. SABCS, 2003
RT + Trastuzumab. Tolerance

Halyard, Pisansky et al. JCO 2009

Belkacémi, Gligorov Annals of Oncology 2008

Shaffer, Tyldesley et al. Radiother Oncol 2009

Kirova, Bollet et al, Cancer Radiother 2008

Caussa, Kirova et al. Eur J Cancer 2010

Jacob, Belin et al, ASTRO 2013, ECCO 2013
RT + Trastuzumab. Toxicity

59 pts treated in 2005

• 44 RT of them 18 with IMN (17 partial wide tangent)
  40–42.5 Gy/16# in 25 pts (57%);
  45–50 Gy/25–28# in 17 pts (38%);
  36 Gy/10# in 2 pts (5%).
Central Heart Distance : 0.8 cm (0-2.8)

• 15 without RT

Median FU 12 months

Median decrease of the FEV after RT was 4%

Shaffer, Tyldesley et al. Radiother Oncol 2009
RT + Trastuzumab. Toxicity

9 French centres, study design July 2005, median F-U 16 months (4–30)

146 pts stade II-III
Median age was 46 years.
23% weekly and 77% 3-week schedule
A median dose of 50 Gy. Internal mammary chain (IMC) was irradiated in 71%.

Acute side effects evaluation 135 pts
Grade ≥ 2 dermatitis: in 51%
Grade ≥ 2 esophagitis in 12%
Grade ≥2 of left ventricular ejection fraction (LVEF) decrease: 10% (6% HERA)

Risk Factors
Dermatitis: menopause P=0.002
Esophagitis: dose of T ≥ 1600 mg and RT including IMC P = 0.05).
LVEF: menopause, age, weekly T schedule

Belkacémi, Gligorov Annals of Oncology 2008
RT + Trastuzumab. Toxicity

NCCTG N9831 trial (1.5 yrs median FU)

AC → T

vs AC → T → H

vs AC → T+H →H

RT breast

supraclavicular (+/- chest wall) si N+ > 3

No IMN RT!

1460 pts analysed with RT

1286 pts analysed for cardiac events with H

No significant difference between arms with and without RT

leucopenia (p=0.02) ↑ with H

Halyard, Pisansky et al. JCO 2009
RT + Trastuzumab. Toxicity

Halyard, Pisansky et al. JCO 2009
RT + Trastuzumab.

Cardiac Events (CE)

Analysed in 1286 pts (908 RT+ et 378 RT-)

Bras AC->T->H, incidence of CE was 2.2% chez pts RT+ versus 2.9% chez pts RT-

Bras AC->TH->H, , incidence of CE was 1.5% chez pts RT+ versus 6.3% chez pts RT-

No difference of CE in pts + RT of breast R vs L ∀ bras H

Halyard, Pisansky et al. JCO 2009
The acute skin and heart toxicity of a concurrent association of trastuzumab and locoregional breast radiotherapy including internal mammary chain: A single-institution study

Institut Curie experience
Lucas Gaussa a, Youlia M. Kirova a, Nathalie Gault b, Jean-Yves Pierga c, Alexia Savignoni b, François Campana a, Rémi Dendale a, Alain Fourquet a, Marc A. Bollet a,*

n=106

Fig. 1 – Cardiac toxicity free interval in the 106 patients treated with concurrent trastuzumab and radiotherapy.
Caussa et al., 2011

**Early toxicity**

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>%</th>
<th>Median dose at apparition of the maximum toxicity Gy [min-max]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dermatitis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>87</td>
<td>82</td>
<td>38 [6-66]</td>
</tr>
<tr>
<td>Grade 2</td>
<td>14</td>
<td>13</td>
<td>38 [14-50]</td>
</tr>
<tr>
<td>Grade 3</td>
<td>2</td>
<td>2</td>
<td>50</td>
</tr>
<tr>
<td>Missing data</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td><strong>Oesophagitis</strong></td>
<td>13</td>
<td>12</td>
<td>36 [24-50]</td>
</tr>
<tr>
<td>Grade 1</td>
<td>9</td>
<td>9</td>
<td>36 [24-50]</td>
</tr>
<tr>
<td>Grade 2</td>
<td>3</td>
<td>3</td>
<td>32 [30-50]</td>
</tr>
<tr>
<td>Grade 3</td>
<td>1</td>
<td>1</td>
<td>14</td>
</tr>
<tr>
<td>Interruption</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

**Late toxicity**

<table>
<thead>
<tr>
<th>Pain</th>
<th>All patients (106)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Missing data</td>
<td>5</td>
</tr>
<tr>
<td>No toxicity</td>
<td>79</td>
</tr>
<tr>
<td>Minor</td>
<td>19</td>
</tr>
<tr>
<td>Moderate</td>
<td>3</td>
</tr>
<tr>
<td>Fibrosis</td>
<td>5</td>
</tr>
<tr>
<td>Missing data</td>
<td>5</td>
</tr>
<tr>
<td>No toxicity</td>
<td>85</td>
</tr>
<tr>
<td>Minor</td>
<td>16</td>
</tr>
<tr>
<td>Telangectasia</td>
<td>5</td>
</tr>
<tr>
<td>Missing data</td>
<td>5</td>
</tr>
<tr>
<td>No toxicity</td>
<td>96</td>
</tr>
<tr>
<td>Minor</td>
<td>16</td>
</tr>
<tr>
<td>Lymphoedema</td>
<td>5</td>
</tr>
<tr>
<td>Missing data</td>
<td>5</td>
</tr>
<tr>
<td>No toxicity</td>
<td>93</td>
</tr>
<tr>
<td>Minor</td>
<td>6</td>
</tr>
<tr>
<td>Moderate</td>
<td>1</td>
</tr>
</tbody>
</table>

**Late toxicity**

<table>
<thead>
<tr>
<th>Late toxicity</th>
<th>All patients (106)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Total</td>
<td>4</td>
</tr>
<tr>
<td>Assessed</td>
<td>87</td>
</tr>
<tr>
<td>Missing data</td>
<td>19</td>
</tr>
<tr>
<td>No toxicity</td>
<td>83</td>
</tr>
<tr>
<td>Cardiac ischemia</td>
<td>1</td>
</tr>
<tr>
<td>Dyspnœa</td>
<td>1</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>1</td>
</tr>
<tr>
<td>Paresia</td>
<td>1</td>
</tr>
</tbody>
</table>

Dysfunction VG grade ≥ 2 in 6 patients
The acute skin and heart toxicity of a concurrent association of trastuzumab and locoregional breast radiotherapy including internal mammary chain: A single-institution study

Lucas Caussa a, Youlia M. Kirova a, Nathalie Gault b, Jean-Yves Pierga c, Alexia Savignoni b, François Campana a, Rémi Dendale a, Alain Fourquet a, Marc A. Bollet a,*

In conclusion, with a median follow-up of 28 months, the treatment by concomitant trastuzumab and radiotherapy with, in most cases, anthracycline-based chemotherapy and adapted internal mammary chain irradiation, seems to be well tolerated by breast cancer patients both in terms of acute skin toxicity and early cardiac function, as long as measures are taken to ensure that the heart is successfully spared irradiation. Longer follow-up is however essential, bearing in mind the potential late occurrence of radiation-induced toxicities, especially cardiac toxicity.
A single institution study prospective study 2000-2009

**Inclusion criteria:**
Non metastatic HER2+++ breast cancer treated by radiotherapy and concurrent trastuzumab (8 mg/kg (then 6 mg/kg every 3 wks after anthracycline based and associated to TXT CT, trastuzumab during 1 year)

**Exclusion criteria:**
Bilateral breast cancer
Hypofractinated radiotherapy
Recurrences of breast cancer

Normofractionated radiotherapy
   Breast: 50 Gy
   LN: 46 Gy
   Boost: 16 Gy
   Different techniques
Anti-Angiogenic treatment + RT
Bevacizumab and vascular normalization
## Bevacizumab in the neo-adjuvant treatment of BC: phase 2 studies

<table>
<thead>
<tr>
<th>Studies</th>
<th>IHC</th>
<th>Traitement néo-adjuvant</th>
<th>n</th>
<th>Clinical CR</th>
<th>Pathological CR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Balduzzi et al</td>
<td>HER2-neg</td>
<td>Epirubicine, cisplatine, 5-FU → paclitaxel + bevacizumab</td>
<td>30</td>
<td>3</td>
<td>33</td>
</tr>
<tr>
<td>Rastogi et al</td>
<td>HER2-neg</td>
<td>Doxorubicine, cyclophosphamide + bevacizumab → docetaxel + capecitabine + bevacizumab</td>
<td>45</td>
<td>31</td>
<td>9</td>
</tr>
<tr>
<td>Ryan et al</td>
<td>Triple-neg</td>
<td>Cisplatin + bevacizumab</td>
<td>46</td>
<td>26</td>
<td>15</td>
</tr>
<tr>
<td>Makhoul et al</td>
<td>All types</td>
<td>Docetaxel, cyclophosphamide + bevacizumab</td>
<td>40</td>
<td>_</td>
<td>33</td>
</tr>
<tr>
<td>Greil et al</td>
<td>All types</td>
<td>Capecitabine, docetaxel + bevacizumab</td>
<td>18</td>
<td>_</td>
<td>22</td>
</tr>
<tr>
<td>Yardley et al</td>
<td>HER2+++</td>
<td>Paclitaxel, carboplatin, trastuzumab + bevacizumab</td>
<td>29</td>
<td>_</td>
<td>69</td>
</tr>
<tr>
<td>Smith et al</td>
<td>HER2+++</td>
<td>Epirubicine, cyclophosphamide + bevacizumab → docetaxel + bevacizumab + trastuzumab</td>
<td>75</td>
<td>_</td>
<td>63</td>
</tr>
<tr>
<td>Pierga et al</td>
<td>HER2+++</td>
<td>Epirubicine, cyclophosphamide + bevacizumab → docetaxel + bevacizumab + trastuzumab</td>
<td>52</td>
<td>_</td>
<td>63,5</td>
</tr>
</tbody>
</table>
# Bevacizumab in the adjuvant treatment of BC: Running phase 3 studies

<table>
<thead>
<tr>
<th>Trial Sponsor/Number</th>
<th>Official Title</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HER2-Positive</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSABP B-44-I</td>
<td>BETH Study: A Multicenter Phase III Randomized Trial of Adjuvant Therapy for Patients With HER2-Positive Node-Positive or High Risk Node-Negative Breast Cancer Comparing Chemotherapy Plus Trastuzumab With Chemotherapy Plus Trastuzumab Plus Bevacizumab</td>
<td>III</td>
</tr>
<tr>
<td><strong>HER2-Negative</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECOG 5103</td>
<td>A Double-Blind Phase III Trial of Doxorubicin and Cyclophosphamide Followed by Paclitaxel With Bevacizumab or Placebo in Patients With Lymph Node Positive and High Risk Lymph Node Negative Breast Cancer</td>
<td>III</td>
</tr>
<tr>
<td>NSABP B-46-I</td>
<td>A Phase III Clinical Trial Comparing the Combination of TC Plus Bevacizumab to TC Alone and to TAC for Women With Node-Positive or High-Risk Node-Negative, HER2-Negative Breast Cancer</td>
<td>III</td>
</tr>
<tr>
<td>Dana Farber 09-134</td>
<td>ABCDE: A Phase III Randomized Study of Adjuvant Bevacizumab, Metronomic Chemotherapy (CM), Diet and Exercise After Preoperative Chemotherapy for Breast Cancer</td>
<td>III</td>
</tr>
<tr>
<td><strong>Triple-Negative Tumors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hoffmann-La Roche BO20289</td>
<td>An Open Label 2-arm Study to Evaluate the Impact of Adjuvant Bevacizumab on Invasive Disease Free Survival in Triple Negative Breast Cancer</td>
<td>III</td>
</tr>
</tbody>
</table>

Derleth and Mayer, 2010
### Bevazumab + RT

<table>
<thead>
<tr>
<th>Locoregional toxicity</th>
<th>Bevacizumab + RT</th>
<th>RT alone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1–2</td>
<td>Grade 3–5</td>
</tr>
<tr>
<td>Nausea</td>
<td>n affected</td>
<td>n affected</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1 (14)</td>
<td>0 (14)</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>1 (14)</td>
<td>0 (14)</td>
</tr>
<tr>
<td>Radiation Dermatitis</td>
<td>14 (14)</td>
<td>0 (14)</td>
</tr>
<tr>
<td>Radiation fibrosis</td>
<td>0 (14)</td>
<td>0 (14)</td>
</tr>
<tr>
<td>Lymphedema</td>
<td>0 (14)</td>
<td>0 (14)</td>
</tr>
</tbody>
</table>

n=14

Goyal et al, IJROBP 2011
Bevazumab+ RT: French experience

Early and late toxicities of adjuvant radiotherapy associated with concurrent bevacizumab in patients with breast cancer: Tolerab study


Purpose/objectives

Few data are available regarding the safety of the concurrent combination of bevacizumab with adjuvant radiotherapy in breast cancer, especially in terms of late toxicity. The aim of this study was to determine early and late loco-regional toxicity among patients with non-metastatic BC treated with this combination in several clinical trials.

Median FU: 21.5 months

At 12 months: evaluation available in 63 cases

Mean age 51 years

Pernin et al, ECCO 2013
PARP inhibitors and RT

γ-rays, X-rays, monofunctional alkylating agents, bleomycin, oxygen radicals

(PARP-1, PARP-2)

Other stimuli? (PARP-3–16)

β NAD⁺ → ATP

Poly (ADP-ribose)

Nam + H⁺ → PARP

Protein acceptor

Protein acceptor

Glu

PARP

(PAR)
PARPs: poly(ADP-ribose) polymerases

- Superfamily of 16 members.
- 6 have poly(ADP-ribosyl)ating activity
- PARP-1 accounts for more than 90% of this activity.
- Share a common catalytic site
- Inhibitors are often analogues of its substrate NAD> will inhibit many PARPs

Fig. 5. E) Growth of SW620 tumor xenografts after daily treatment for 5 days with vehicle control alone (solid circles, solid bars), 2 Gy of x-irradiation (IR) vehicle (solid squares, shaded bars), or 2 Gy of x-irradiation AG14361 at 15 mg/kg (open squares, hatched bars).
PARP inhibitors combined with radiation will also increase the formation of DSBs and increase cell killing, particularly in a background of reduced levels of DSB repair proteins.

Currently: phase I study in breast inflammatory cancer and in brain metastases
PI3K/AKT/mTor inhibitors
Inhibition of mTor and restauration of the hormonal sensibility
Everolimus & exemesthane: BOLERO-2 Study

- Hazard ratio, 0.43 (95% CI, 0.35–0.54)
- P<0.001 by log-rank test

Baselga et al., NEJM, 2012
Immunohistochemical analysis of HT1080 and FaDu tumors from mice treated with signaling inhibitors.

Evaluation of the effects of BKM120 and BEZ235 on p-Akt and p-mTOR in (A) HT1080 and (B) FaDu tumors.

Sections were stained with the indicated antibodies.

Magnification (×40). C, HT1080 and D, FaDu tumor growth after treatment with the signaling inhibitors. Points, mean; bars, SD.

BEZ235 and BKM120 reduce hypoxia in vivo.

Ultrasound analysis of the effects of PI3K/Akt/mTOR inhibition on tumor blood flow.

BEZ235- and BKM120-induced vascular remodeling and normalization.

Therapeutic efficacy of BEZ235 (20 mg/kg) and radiation in FaDu-HRE-luc xenograft model.

Monitoring of hypoxia in irradiated FaDu-HRE-luc xenograft model.

Conclusions

The results of this study provide evidence that inhibition of the PI3K/mTOR signaling displays significant effects on tumour growth by remodeling blood vessels and enhancing tumor perfusion and oxygenation.

BEZ235-induced changes promoted a substantial response to radiotherapy and showed a supra-additive effect in delaying tumor regrowth, as compared with other drug–radiation combinations.

Modulation of oncogenic signaling could be potentially used as a therapeutic approach for cancer therapy

LAPATINIB & RT

\[
\text{Lapatinib}
\]

\[
N^1\text{-[3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl]-6-}
\{5-[(2\text{(methylsulfanyl)ethyl}l\text{amino)methyl}-2\text{-furyl}]-
4\text{-quinazolinamine}
\]
RATIONALE:
Lapatinib may stop the growth of tumor cells by blocking some of the enzymes needed for cell growth.

Radiation therapy uses high-energy x-rays to kill tumor cells.

Giving lapatinib together with radiation therapy may kill more tumor cells.
In vitro studies of Lapatinib

Rationale:
HER-2 gene amplification
EGFR overexpression
Low HER-2 and EGFR expression

<table>
<thead>
<tr>
<th>Cell line</th>
<th>IC 50 vmol/L</th>
<th>HER2 ng/mg</th>
<th>EGFR ng/mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>UACC812</td>
<td>0.010</td>
<td>1436</td>
<td>25</td>
</tr>
<tr>
<td>SUM190</td>
<td>0.018</td>
<td>396</td>
<td>3.1</td>
</tr>
<tr>
<td>BT474</td>
<td>0.022</td>
<td>530</td>
<td>7.3</td>
</tr>
<tr>
<td>SK-BR-3</td>
<td>0.037</td>
<td>1913</td>
<td>3.8</td>
</tr>
<tr>
<td>SUM225</td>
<td>0.083</td>
<td>1,161</td>
<td>51</td>
</tr>
<tr>
<td>UACC893</td>
<td>0.433</td>
<td>577</td>
<td>14</td>
</tr>
<tr>
<td>MDA-MB-361</td>
<td>0.989</td>
<td>211</td>
<td>6.6</td>
</tr>
<tr>
<td>EFM192A</td>
<td>1.1</td>
<td>115</td>
<td>1.0</td>
</tr>
<tr>
<td>T47D</td>
<td>1.9</td>
<td>11</td>
<td>31</td>
</tr>
<tr>
<td>MDA-MB-453</td>
<td>3.9</td>
<td>108</td>
<td>1.3</td>
</tr>
<tr>
<td>EFM19</td>
<td>4.6</td>
<td>22</td>
<td>0.8</td>
</tr>
<tr>
<td>MDA-MB-468</td>
<td>4.7</td>
<td>0.1</td>
<td>908</td>
</tr>
<tr>
<td>KPL1</td>
<td>5.4</td>
<td>8.4</td>
<td>3.2</td>
</tr>
<tr>
<td>MDA-MB-157</td>
<td>6.3</td>
<td>4.3</td>
<td>59</td>
</tr>
<tr>
<td>MCF-7</td>
<td>7.7</td>
<td>4.7</td>
<td>2.7</td>
</tr>
<tr>
<td>CAMA1</td>
<td>8.3</td>
<td>18</td>
<td>3.2</td>
</tr>
<tr>
<td>MDA-MB-435</td>
<td>18.5</td>
<td>2.2</td>
<td>4.4</td>
</tr>
<tr>
<td>BT20</td>
<td>9.8</td>
<td>36</td>
<td>295</td>
</tr>
<tr>
<td>ZR-75-1</td>
<td>9.9</td>
<td>40</td>
<td>8.3</td>
</tr>
<tr>
<td>MDA-MB-231</td>
<td>18.6</td>
<td>5.2</td>
<td>58</td>
</tr>
</tbody>
</table>

Conclusion:
Better sensibility of lapatinib in vitro.

Cancer Res 2006; 66: (3). February 1, 2006
Effect of Lapatinib on the Outgrowth of Metastatic Breast Cancer Cells to the Brain

Brunilde Gril, Diane Palmieri, Julie L. Bronder, Jeanne M. Herring, Eleazar Vega-Valle, Lionel Feigenbaum, David J. Liewehr, Seth M. Steinberg, Maria J. Merino, Stephen D. Rubin, Patricia S. Steeg

Figure 3. Lapatinib inhibition of metastatic colonization of mouse brain by 231-BR breast carcinoma cells. 231-BR-HER2 cells or 231-BR-vector cells, both of which were transduced with a retrovirus that expressed enhanced green fluorescent protein (EGFP), were injected into the left cardiac ventricle of BALB/c nude mice. Five days after injection, lapatinib (30 or 100 mg/kg body weight) or vehicle (0.5% hydroxypropylmethylcellulose with 0.1% Tween 80 in water) was administered by twice-daily oral gavage for 24 days (n = 22-26 mice per treatment group). Brains dissected at necropsy were imaged using a Maestro 420 Spectral Imaging System to detect the presence of EGFP expressing metastases derived from the injected 231-BR cells (metastatic foci on a green to white [greater intensity] fluorescent intensity spectrum). Representative dorsal whole-brain images from two mice in each treatment group are shown.
Effect of Lapatinib on the Outgrowth of Metastatic Breast Cancer Cells to the Brain

Brunilde Gril, Diane Palmieri, Julie L. Bronder, Jeanne M. Herring, Eleazar Vega-Valle, Lionel Feigenbaum, David J. Liewehr, Seth M. Steinberg, Maria J. Merino, Stephen D. Rubin, Patricia S. Steeg

Figure 4. Immunohistochemical evaluation of HER2 and epidermal growth factor receptor (EGFR) activation in vivo in response to lapatinib treatment. Frozen sections (5 μm thick) of brains from mice injected with 231-BR-vector or 231-BR-HER2 cells and treated with lapatinib (30 or 100 mg/kg body weight) or vehicle (n = 5 mice per group) were stained with antibodies specific for phosphorylated HER2 (p-HER2; tyrosines 1221 and 1222) or phosphorylated EGFR (p-EGFR; tyrosine 1068). The staining of all large metastases (i.e., >50 μm²) and 125 micrometastases per treatment group was scored on a 0–3+ intensity scale by two investigators who were blinded to the treatment group assignment. Representative images of large metastases for each group are shown (×200 magnification). The presence of p-HER2 or p-EGFR antigen is indicated by brown staining; nuclei were counterstained purple with hematoxylin.

Conclusions
Lapatinib is the first HER2-directed drug to be validated in a preclinical model for activity against brain metastases of breast cancer.
LANDSCAPE: An FNCLCC phase II study with lapatinib (L) and capecitabine (C) in patients with brain metastases (BM) from HER2-positive (+) metastatic breast cancer (MBC) before whole-brain radiotherapy (WBR).

ASCO 2011

Background and purpose: A clinical interest of this combination as 1\textsuperscript{st} line treatment for BM in HER2+ MBC patients (pts) with the aim to avoid or to delay WBR.

Methods: Eligible pts had HER2+ MBC with BM not previously treated with WBR, C or L. Pts received L1250 mg/day and C2000 mg/m\textsuperscript{2}/day, days 1-14, every 21 days. The primary endpoint was a centrally assessed CNS objective response.

Results: 45 pts were enrolled. Median age was 56 (range 35 to 79), 37 pts had multiple metastatic sites, PS was 0 (17 pts), 1 (25 pts) or 2 (2 pts); 36 pts had two or more BM and 42 had previously received trastuzumab. 41 pts received at least 2 cycles of study treatment. 43 pts were evaluable for efficacy endpoints, with a median follow-up of 10 months (range 2.9-16.5). The CNS-OR rate was 67% (95%CI 51-81), with a median time from inclusion to response of 1.8 month. Median TTP was 5.5 months (95% CI 3.9-5.9) and median time to WBR was 8.3 months (95% CI 5.1-11.7). At baseline, 21/42 pts had \( \geq 1 \) CTC, vs 7/39 at day 21, \( p<0.01 \) (correlation study ongoing). 20 patients (44\%) experienced grade 3 or 4 treatment related toxicity, treatment was discontinued due to toxicity in 3 pts. At the time of analysis, 21 pts had received WBR and 10 pts had died.

Conclusions: With a high response rate, L + C is an active treatment option and a viable alternative to immediate WBR for HER2+ MBC pts with newly diagnosed BM.
PRELIMINARY RESULTS OF WHOLE BRAIN RADIOTHERAPY WITH CONCURRENT TRASTUZUMAB FOR TREATMENT OF BRAIN METASTASES IN BREAST CANCER PATIENTS

Cyrus Chargari, M.D.,* Hind Riahi Idrissi, M.D.,* Jean-Yves Pierga, M.D., Ph.D.,† Marc A. Bollet, M.D.,* Véronique Diéras, M.D.,† François Campana, M.D.,* Paul Cottu, M.D.,† Alain Fourquet, M.D.,* and Youlia M. Kirova, M.D.*

Departments of *Radiation Oncology and †Medical Oncology, Institut Curie, Paris, France

Purpose: To assess the use of trastuzumab concurrently with whole brain radiotherapy (WBRT) for patients with brain metastases from human epidermal growth factor receptor-2–positive breast cancer.

Methods and Materials: Between April 2001 and April 2007, 31 patients with brain metastases from human epidermal growth factor receptor-2–positive breast cancer were referred for WBRT with concurrent trastuzumab. At brain progression, the median age was 55 years (range, 38–73), and all patients had a performance status of 0–2. The patients received trastuzumab 2 mg/kg weekly (n = 17) or 6 mg/kg repeated every 21 days (n = 14). In 26 patients, concurrent WBRT delivered 30 Gy in 10 daily fractions. In 6 patients, other fractionations were chosen because of either poor performance status or patient convenience.

Results: After WBRT, radiologic responses were observed in 23 patients (74.2%), including 6 (19.4%) with a complete radiologic response and 17 (54.8%) with a partial radiologic response. Clinical responses were observed in 27 patients (87.1%). The median survival time from the start of WBRT was 18 months (range, 2–65). The median interval to brain progression was 10.5 months (range, 2–27). No Grade 2 or greater acute toxicity was observed.

Conclusion: The low toxicity of trastuzumab concurrently with WBRT should probably not justify delays. Although promising, these preliminary data warrant additional validation of trastuzumab as a potential radiosensitizer for WBRT in brain metastases from breast cancer in the setting of a clinical trial. © 2010 Elsevier Inc.
Sambade et al, IJROBP 2010: Lapatinib-mediated radiosensitization of SUM149 basal-like/epidermal growth factor receptor-positive (EGFR+) breast cancer xenografts.
Lapatinib-mediated radiosensitization of SUM225 HER2+ breast cancer xenografts
Sambade et al, IJROBP 2010; Radiosensitization by lapatinib correlates with inhibition of ERK1/2 in EGFR+/basal-like cells and with AKT in HER2+ breast cancer cells.

(A) Tumors from basal-like/EGFR+ SUM149 xenografts were processed for immunohistochemistry with phosphorylated ERK1/2 antiserum and quantified from mice treated with lapatinib, radiotherapy, lapatinib plus radiotherapy, or vehicle control.

(B) Sample immunohistochemistry staining of SUM149 tumors with phosphorylated ERK1/2 serum at 400×. Similarly, tumors from HER2+ SUM225 xenografts were processed for immunohistochemistry with phosphorylated AKT antiserum and quantified.

(C) Sample immunohistochemistry of SUM225 tumors with phosphorylated AKT serum at 400×. Open arrows indicate areas of increased staining; solid arrows, areas of reduced staining.
Conclusions

Although EGFR and HER2 activate common downstream signaling pathways, our studies have shown that fundamental differences exist between EGFR and HER2 response to RT, providing insight into the divergent consequences of EGFR and HER2 signaling and inhibition.

A model based on the present study correlates lapatinib-mediated radiosensitization of EGFR+ cells with ERK1/2 inhibition in basal-like/EGFR+ cells and with AKT inhibition in HER2+ cells. Importantly, our results suggest that although EGFR+ breast cancers appear unresponsive to lapatinib monotherapy, the combination of lapatinib plus RT might provide a therapeutic option for patients with basal-like/EGFR+ breast cancers, who currently have few therapeutic options.

In addition, HER2+ breast cancer patients who are candidates for adjuvant RT could experience better outcomes with longer response durations with combined RT and lapatinib.
Lapatinib and Radiation Therapy in Treating Patients With Locally Recurrent or Chemotherapy-Refractory Locally Advanced or Metastatic Breast Cancer

This study is ongoing, but not recruiting participants.

First Received on September 20, 2006. Last Updated on June 6, 2011  History of Changes

| Sponsor: | UNC Lineberger Comprehensive Cancer Center |
| Collaborator: | National Cancer Institute (NCI) |
| Information provided by: | UNC Lineberger Comprehensive Cancer Center |
| ClinicalTrials.gov Identifier: | NCT00379509 |

Purpose

RATIONALE: Lapatinib may stop the growth of tumor cells by blocking some of the enzymes needed for cell growth. Radiation therapy uses high-energy x-rays to kill tumor cells. Giving lapatinib together with radiation therapy may kill more tumor cells.

PURPOSE: This phase I trial is studying the side effects and best dose of lapatinib when given together with radiation therapy in treating patients with locally recurrent or chemotherapy-refractory locally advanced or metastatic breast cancer.
Conclusions

1. Concurrent radiotherapy with Herceptin is probably safe

2. No officially available information of Lapatinib-RT (impossible before the publication of ALTTO Study)

3. Limited clinical data on radiotherapy and mTOR inhibitors

4. Concomitant radiotherapy with current chemotherapy protocols should be evaluated in trials

5. There is an urgent need to evaluate the concurrent use of new targeted therapy and radiotherapy in breast cancer!
Thank you for your attention

Questions?