Breast Cancer: the interplay of biology, drugs, radiation

Prof. L. Livi
Università degli Studi di Firenze

Brescia, October 3rd – 4th, 2013

BACKGROUND (1)

The complex interactions between tumor-specific signaling and radiation response provide a rationale for targeting multiple-signaling pathways.

This may be achieved by agents that have the capacity to target multiple oncoproteins or through the combination of multiple single-target agents.

BACKGROUND (2)

1. BIOLOGICAL RESEARCH

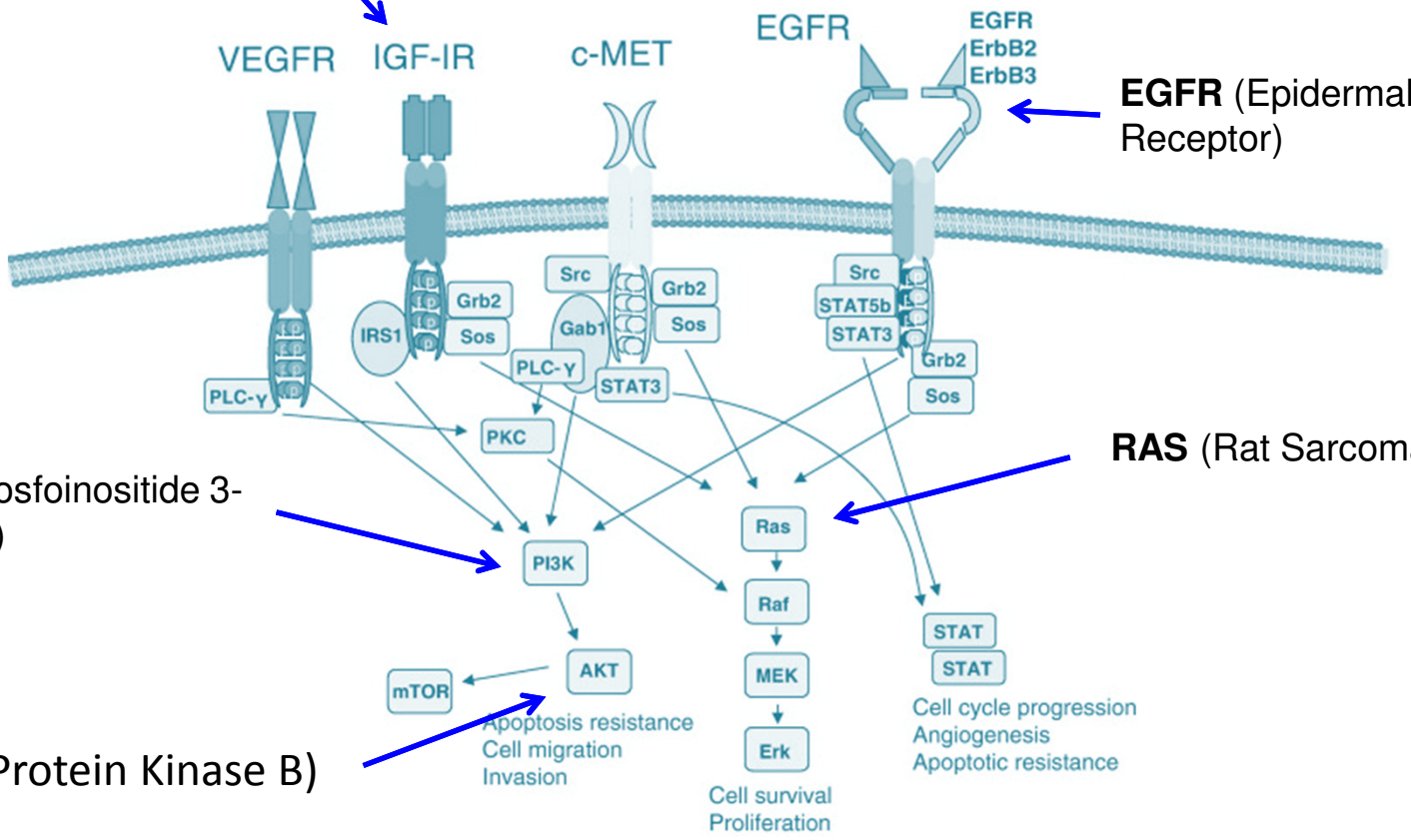
2. PRE-CLINICAL RESEARCH

3. ROUTINE AND CLINICAL RESEARCH

BACKGROUND (3)

The most straightforward approach is to target a specific molecule involved in proliferation, tumor-cell survival, differentiation responses, resistance to radiation and chemotherapy (EGFR, IGF-1R, Ras, PI3K, AKT).

IGF-1R (Insulin-like growth factor-1 Receptor)



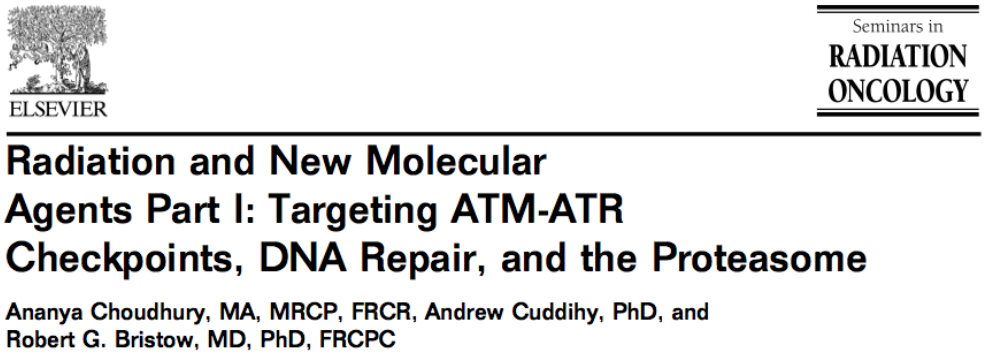
EGFR (Epidermal Growth Factor Receptor)

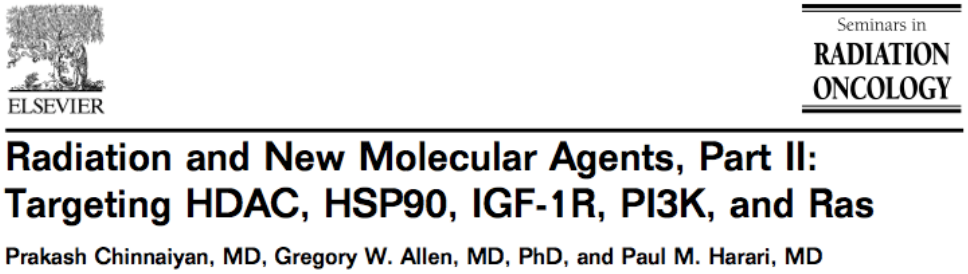
RAS (Rat Sarcoma protein)

PI3K (fosfoinositide 3-chinasi)

AKT (Protein Kinase B)

BIOLOGICAL RESEARCH





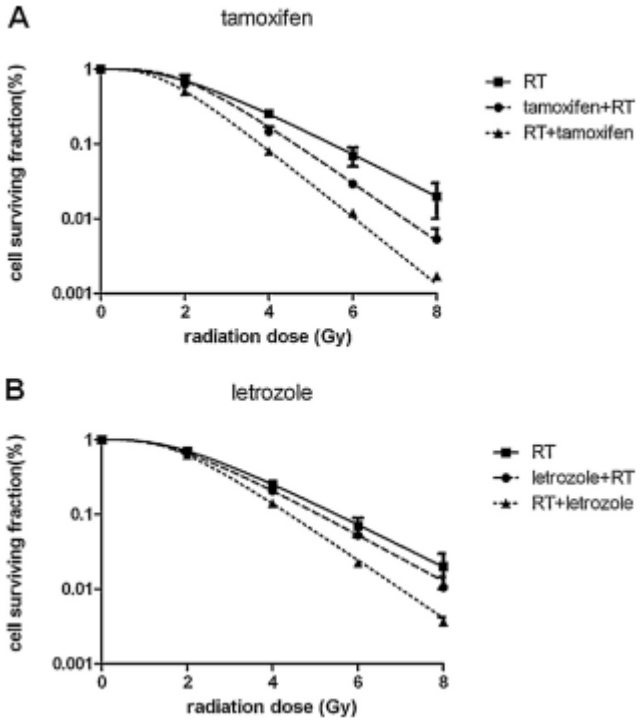
- ✓ Although exciting in concept, clinical trial data for many of these agents in combination with radiotherapy is still lacking.
- ✓ The relative sensitization in vitro may not predict the sensitization achieved in vivo because of microenvironmental factors or altered pharmacodynamics.

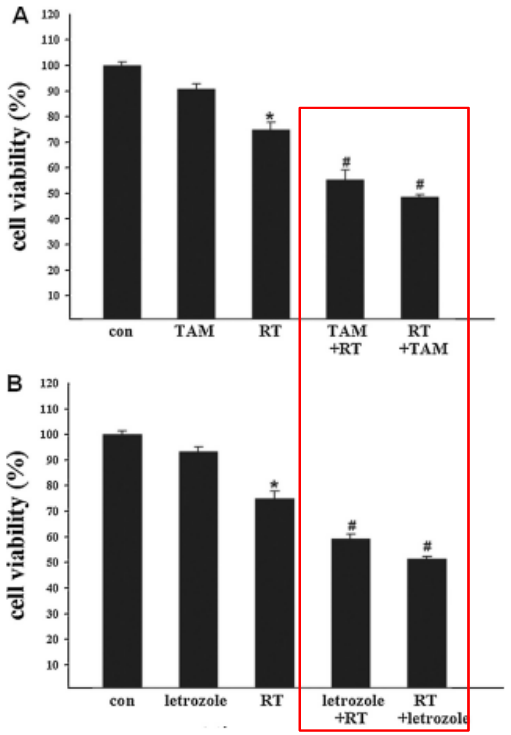
ENDOCRINE DRUGS AND RADIATION

Optimal combination of radiotherapy and endocrine drugs in breast cancer treatment

Z.J. Zeng[a], J.H. Li[b], Y.J. Zhang[c], S.T. Zhao[b,*]

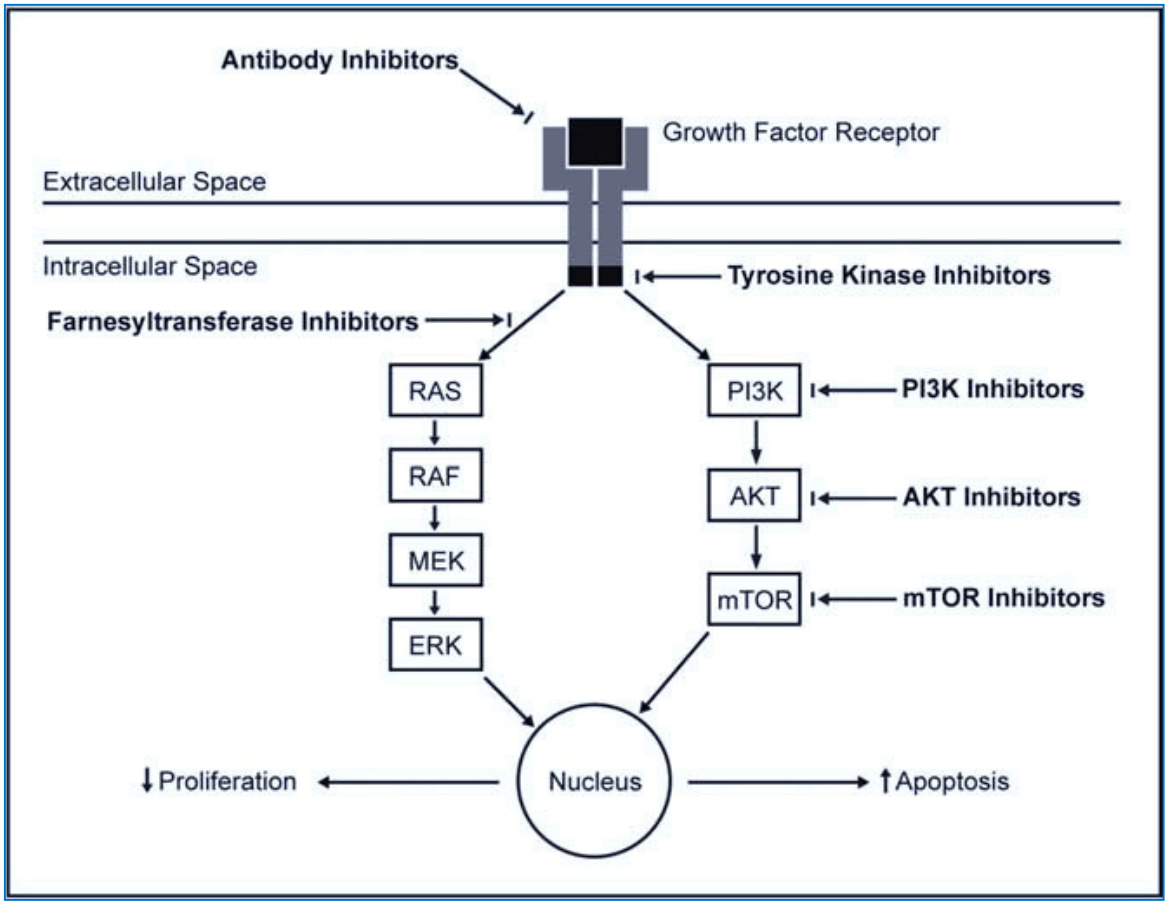
Cancer/Radiothérapie 17 (2013) 208–214





TARGET THERAPY AND BREAST CANCER

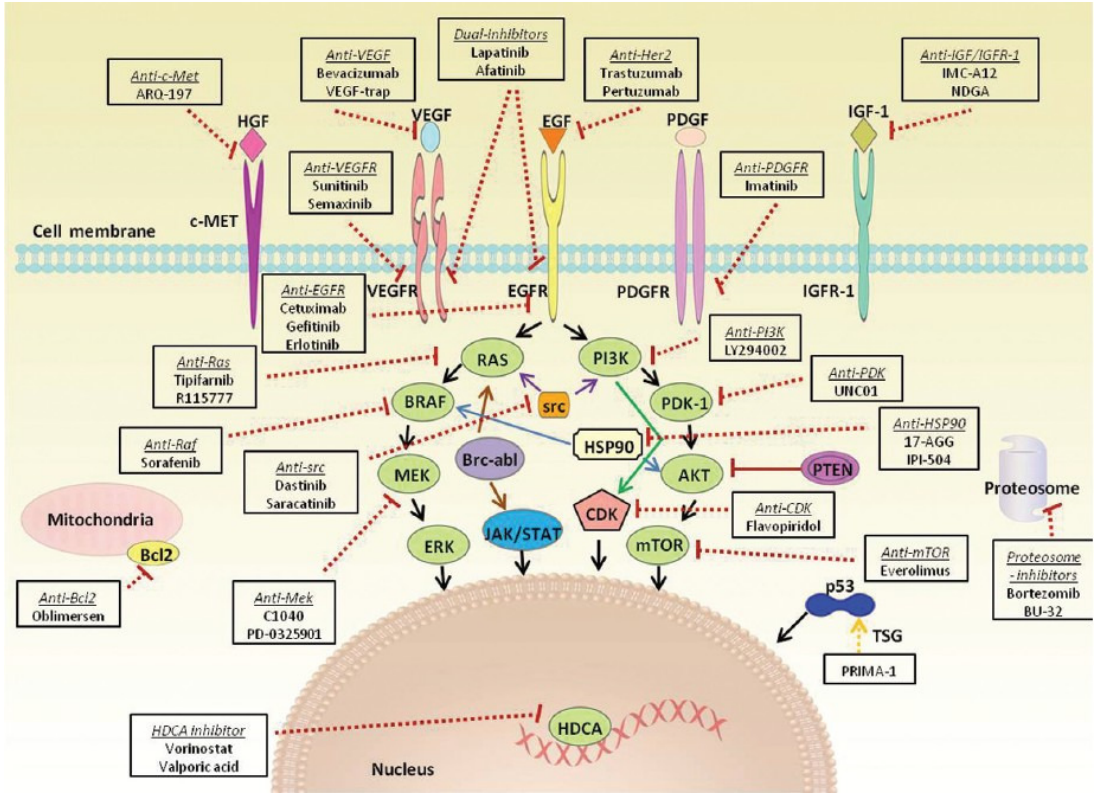
Pathways and molecular sites of targeted therapies



Chinnaiyan et al. Sem Rad Oncol 2005

TARGET THERAPY AND BREAST CANCER

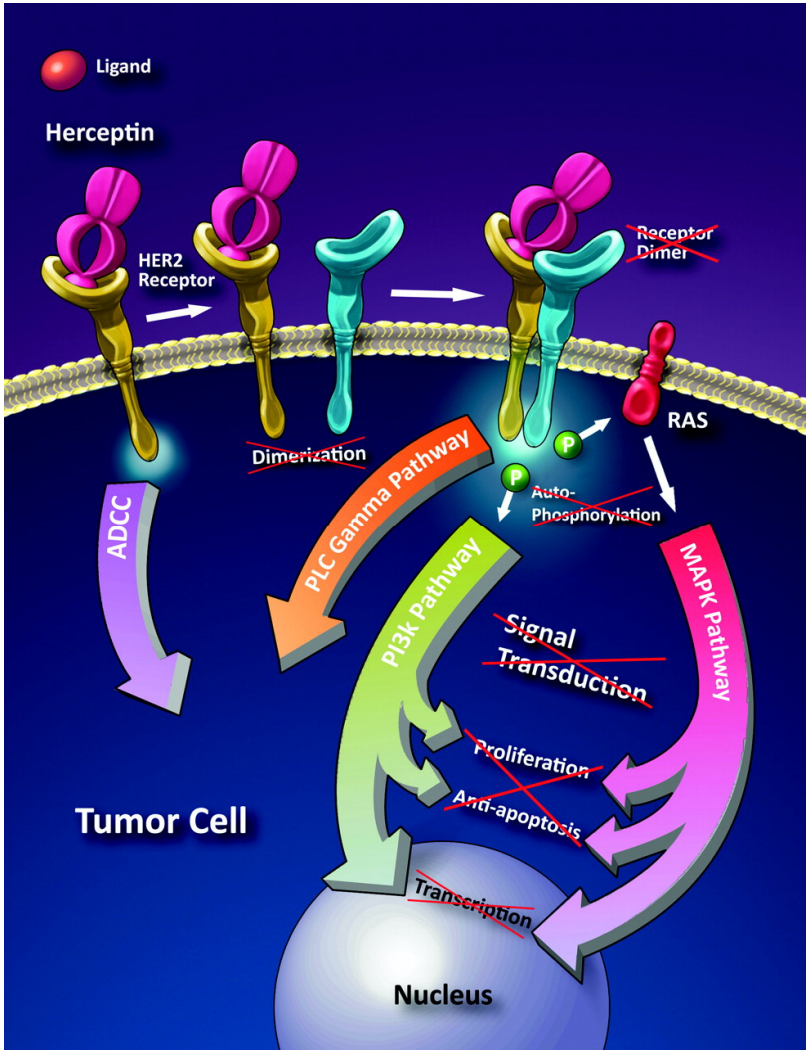
- *Trastuzumab*
- *Lapatinib*
- *Everolimus*
- *Bevacizumab*
- *Pertuzumab*
- *Novel targeted therapies*



TRASTUZUMAB AND RADIATION (1)

Trastuzumab blocks her2-activated cell signalling reducing cell proliferation restoring ability to undergo apoptosis by inhibiting the phosphatidylinositol 3 kinase/Akt pathway

increases cellular sensitivity to chemotherapy and radiotherapy



TRASTUZUMAB AND RADIATION (2)

TRASTUZUMAB AND CARDIAC TOXICITY:

1. the incidence of cardiac dysfunction in the trastuzumab arm (**HERA Trial**) at a median follow-up time of 1 year was 0.6% for severe CHF and 7.0% for left ventricular (LV) dysfunction

2. approximately **10 %** had a substantial decrease in the left ventricular ejection fraction (LVEF)

3. the risk of cardiac dysfunction with trastuzumab treatment increases with the use of anthracyclines.

TRASTUZUMAB AND RADIATION (3)

TRASTUZUMAB AND CARDIAC TOXICITY:

The ErbB2 receptor is expressed on **cardiomyocytes**, in addition to tumor tissue, where it exerts a protective effect on cardiac function:

- maintenance of normal cardiac contractility
- dependence on HER2 for myocyte survival

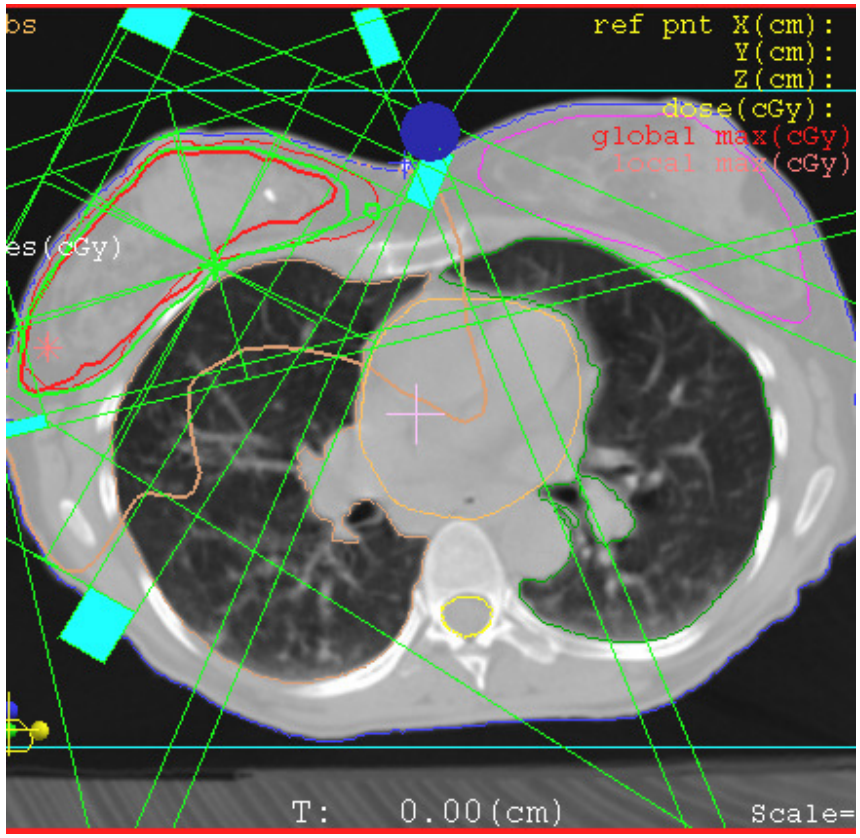
Interference with ErbB2-signaling (Trastuzumab) may block this protective effect

Procter M, JCO 2009
Perez EA, Clin Breast Cancer 2008
Doyen J. Cancer Radiother. 2010

TRASTUZUMAB AND RADIATION (4)

Radiation-associated cardiac damage occurs by both **microvascular** (fibrotic) and **macrovascular** (coronary atherosclerosis) damage occurring after a longer latency period.

Modern irradiation techniques seem to be associated with **a limited risk** of heart complication.



TRASTUZUMAB AND RADIATION (5)

Cardiac toxicity

Acute cardiot
internal mam

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Radiotherapy

The acute skin and heart toxicity of a concurrent association of trastuzumab and locoregional breast radiotherapy including internal mammary chain: A single-institution study

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ABSTRACT

Background: To evaluate the skin and heart toxicity of a concurrent adjuvant trastuzumab-radiotherapy for breast cancer (BC), especially in the case of internal mammary chain (IMC) irradiation.

Material and methods: Prospective study of 106 patients treated between 06/2003 and 03/2007 by concurrent trastuzumab-radiotherapy for non-metastatic BC. Left ventricular ejection fractions (LVEF) was assessed at baseline, before and after radiotherapy and then every 4–6 months. All toxicities were evaluated using CTCAEV3.

Results: Median age was 52 years (25–76). Chemotherapy with anthracycline was administered in 92% of patients. All patients received trastuzumab every three weeks (8 mg/kg followed by 6 mg/kg) for a median duration of 12 months (3-40). The IMC was irradiated in 83% of patients. There were: 87 grade 1, 14 grade 2 and 2 grade 3 skin reactions. There were 13 oesophagitis: 9 grade 1; 3 grade 2, and 1 grade 3. Out of 101 patients with assessments after 6 months, late telangiectasia grade 1 occurred in 5 patients, local pain grade 1 in 19 patients and grade 2 in 3 patients, fibrosis grade 1 in 16 patients. A reversible grade $\geqslant 2$ left ventricular systolic dysfunction occurred in 6 patients.

Conclusion: In this prospective study of breast cancer patients treated with trastuzumab-radiotherapy with, in most cases, anthracycline-based chemotherapy and IMC irradiation, both the rate of abnormal LVEF after concurrent trastuzumab-radiotherapy and the skin toxicity were deemed acceptable. Further follow-up is needed.

TRASTUZUMAB AND RADIATION (6)

VOLUME 27 · NUMBER 16 · JUNE 1 2009

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Radiotherapy and Adjuvant Trastuzumab in Operable Breast Cancer: Tolerability and Adverse Event Data From the NCCTG Phase III Trial N9831

Michele Y. Halyard, Thomas M. Pisansky, Amylou C. Dueck, Vera Suman, Lori Pierce, Larry Solin, Larry Marks, Nancy Davidson, Silvana Martino, Peter Kaufman, Leila Kutteh, Shaker R. Dakhil, and Edith A. Perez

From the Mayo Clinic Scottsdale, Scottsdale, AZ; Mayo Clinic and Mayo Foundation, Rochester, MN; Southwest Oncology Group Operations Office, San Antonio, TX; Eastern Cooperative Oncology Group Data Management Office, Brookline, MA; Cancer and Leukemia Group B Data Management Center, Durham, NC; Cedar Rapids Oncology Project, Community Clinical Oncology Program, Cedar Rapids, IA; Wichita Community Clinical Oncology Program, Wichita, KS; and Mayo Clinic Jacksonville, Jacksonville, FL.

Submitted May 28, 2008; accepted December 9, 2008; published online ahead of print at www.jco.org on April 6, 2009.

Supported in part by Public Health Service Grants No. CA-25224, CA-37404, CA-15083, CA-63826, CA-52352, CA-63849, CA-35195, CA-35272, CA-60276, CA-35269, CA-37417, CA-63848, CA-35101, CA-35415, and CA-35103.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Clinical Trials repository link available on

A B S T R A C T

Purpose
To assess whether trastuzumab (H) with radiotherapy (RT) increases adverse events (AEs) after breast-conserving surgery or mastectomy.

Patients and Methods
Patients with early-stage resected human epidermal growth factor receptor 2 (HER-2) –positive breast cancer (BC) were randomly assigned to doxorubicin (A) and cyclophosphamide (C), followed by weekly paclitaxel (T; AC-T-H or AC-TH-H). RT criteria (with or without nodal RT) were postlumpectomy breast or (optional) postmastectomy chest wall. RT of internal mammary nodes was prohibited. RT commenced within 5 weeks after T, concurrently with H. Analysis included 1,503 irradiated patients for RT-associated AEs across treatment arms. Rates of cardiac events (CEs) with and without RT were compared within arms.

Results
No significant differences among arms were found in incidence of acute skin reaction, pneumonitis, dyspnea, cough, dysphagia, or neutropenia. A significant difference occurred in incidence of leukopenia, with higher rates for AC-T-H versus AC-T (odds ratio = 1.89; 95% CI, 1.25 to 2.88). At a median follow-up of 3.7 years (range, 0 to 6.5 years), RT with H did not increase relative frequency of CEs regardless of treatment side. The cumulative incidence of CEs with AC-T-H was 2.7% with or without RT. With AC-TH-H, the cumulative incidence was 1.7% *v* 5.9% with or without RT, respectively.

Conclusion
Concurrent adjuvant RT and H for early-stage BC was not associated with increased acute AEs. Further follow-up is required to assess late AEs.

J Clin Oncol 27:2638-2644. © 2009 by American Society of Clinical Oncology

No significant differences among arms were found in incidence of acute skin reaction, pneumonitis, dyspnea, cough, dysphagia, or neutropenia

TRASTUZUMAB AND RADIATION (7)

ELSEVIER

Int. J. Radiation Oncology Biol. Phys., Vol. 81, No. 3, pp. 631–636, 2011

0360-3016/$–see front matter

doi:10.1016/j.ijrobp.2010.06.057

CLINICAL INVESTIGATION **Brain**

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.*

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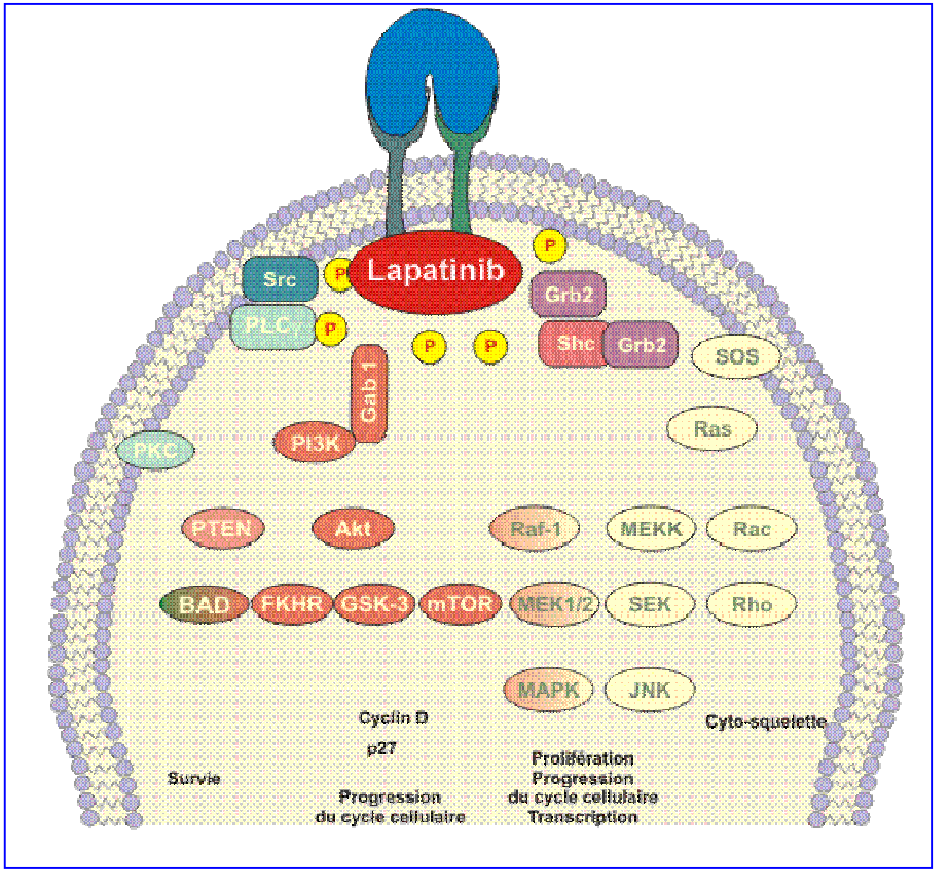
- 31 pz
- 74,2% radiologic response
- 87,1% clinical response
- No G2 or greater acute toxicity

Promising results but further studied are needed

LAPATINIB AND RADIATION (1)

Lapatinib is an oral dual tyrosine kinase inhibitor that targets epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor-2 (HER2)



Geyer et al N Engl J Med 2006

LAPATINIB AND RADIATION (2)

Radiation biology

Mechanism of lapatinib-mediated radiosensitization of breast cancer cells is primarily by inhibition of the Raf > MEK > ERK mitogen-activated protein kinase cascade and radiosensitization of lapatinib-resistant cells restored by direct inhibition of MEK

Maria J. Sambade [a,c], J. Terese Camp [a,c], Randall J. Kimple [a,c], Carolyn I. Sartor [a,c], Janiel M. Shields [a,b,c,*]

- Breast tumor cell lines of the basal-subtype, which express elevated levels of EGFR and normal levels of HER2, are growth impaired and radiosensitized by treatment with lapatinib
- EGFR expression correlates with radioresistance
- EGFR can signal to a variety of downstream signaling pathways including MEK > ERK, PI3K > AKT, STAT, p38 and JNK.

Radiosensitization by lapatinib is mediated largely through inhibition of MEK/ERK . Direct inhibition of this pathway may provide an additional avenue of radiosensitization in EGFR+ or HER2+ breast cancers

LAPATINIB AND RADIATION (3)

BIOLOGY CONTRIBUTION

LAPATINIB IN COMBINATION WITH RADIATION DIMINISHES TUMOR REGROWTH IN HER2+ AND BASAL-LIKE/EGFR+ BREAST TUMOR XENOGRAFTS

MARIA J. SAMBADE, PH.D.,*† RANDALL J. KIMPLE, M.D., PH.D.,*† J. TERESE CAMP, B.S.,*† ELDON PETERS, B.S.,*† CHAD A. LIVASY, M.D.,†‡ CAROLYN I. SARTOR, M.D.,*† AND JANIEL M. SHIELDS, PH.D.*†§

- Tumors from basal-like/EGFR+ cells were insensitive to lapatinib monotherapy treatment but were radiosensitized when lapatinib was combined with RT.

- Tumors from HER2+ cells were highly sensitive to lapatinib monotherapy alone and showed an enhanced therapeutic response when lapatinib was combined with RT.

In mouse xenograft models **lapatinib can radiosensitize both HER2+ and basal-like/EGFR+** breast cancer cell lines

LAPATINIB AND RADIATION (4)

The Oncologist®

Breast Cancer

Phase I Study and Biomarker Analysis of Lapatinib and Concurrent Radiation for Locally Advanced Breast Cancer

RANDALL J. KIMPLE,[a] JANET K. HORTON,[b] CHAD A. LIVASY,[c,d] JANIEL M. SHIELDS,[d,e] JULIA A. LAWRENCE,[f] WINGKEUNG M. CHIU,[d] ANASTASIA IVANOVA,[d,g] DAVID W. OLLILA,[d,h] LISA A. CAREY,[d,i] JAN S. HALLE,[d,e] CAROLYN I. SARTOR,[d,e] E. CLAIRE DEES[d,i]

This phase I study assessed the toxicity and safety of combining daily lapatinib with RT.

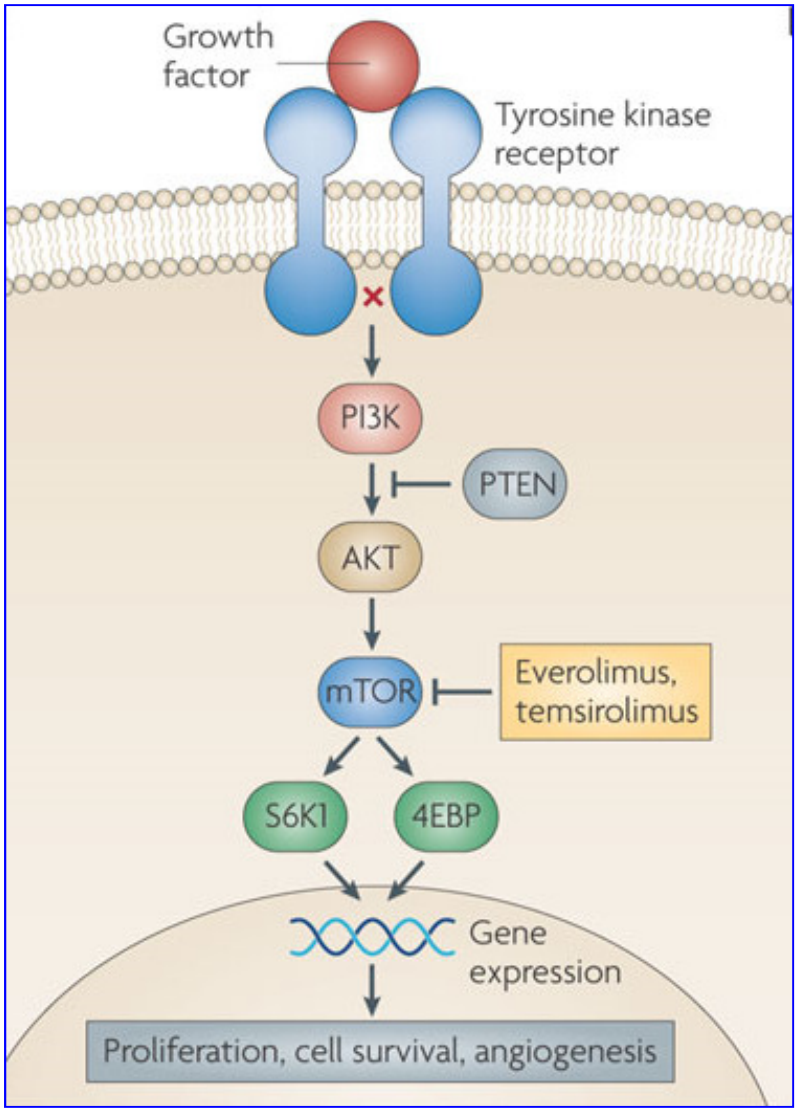
Sequential tumor biopsies were obtained to evaluate changes in biomarkers, such as EGFR and HER2 signaling pathways.

The combination of lapatinib and RT was **well tolerated**. Overall local response rates were comparable to those reported in other studies.
In biopsies inhibition of HER2 and down-stream signaling pathways was identified, although **no strong correlation** with response was seen.

EVEROLIMUS AND RADIATION (1)

Everolimus acts as a selective inhibitor of mTOR, a serine/threonine protein kinase that regulates cell growth, cell proliferation, cell motility, cell survival, protein synthesis, and transcription.

- Concomitant Radiotherapy is not recommended
- Novartis suggests to wait at least 30 days
- Nothing from the literature



EVEROLIMUS AND RADIATION (2)

Ann Oncol. 2011 Feb;22(2):485-6. doi: 10.1093/annonc/mdq741.

Total recall of radiotherapy with mTOR inhibitors: a novel and potentially frequent side-effect?

Bourgier C, Massard C, Moldovan C, Soria JC, Deutsch E.

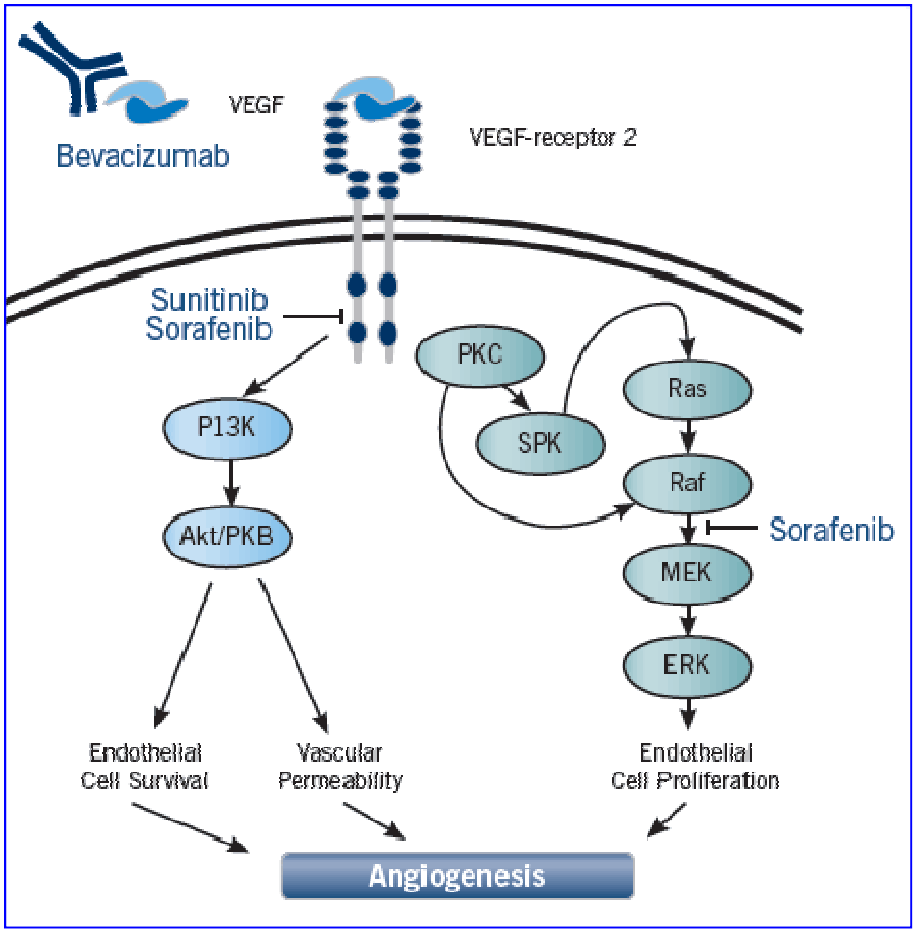
- 67-year-old woman with left breast
- Bone metastases → palliative RT to bone metastases (D12- L3) in January 2008.
- In March 2008 Paclitaxel, trastuzumab, and everolimus (10 mg daily) combination was initiated for metastatic progression
- Sixteen weeks after the initiation of everolimus, **grade 3 gastric hemorrhage and grade 2 anemia** occurred.
- Comparison of endoscopic findings and radiotherapy portals were consistent with '**in-radiation-field**' mucosal reaction as well as gastritis histological characteristics.

Radiation Recall Syndrome (RRS): an inflammatory reaction within a previously irradiated volume after chemotherapy administration

BEVACIZUMAB AND RADIATION (1)

Bevacizumab is a humanized monoclonal antibody that inhibits vascular endothelial growth factor A (VEGF-A), a chemical signal that stimulates angiogenesis

On October 2011 the FDA announced that the agency is revoking the approval of the breast cancer indication for bevacizumab after concluding that the drug has not been shown to be safe and effective for that use



BEVACIZUMAB AND RADIATION (2)

CLINICAL INVESTIGATION **Breast**

EVALUATION OF ACUTE LOCOREGIONAL TOXICITY IN PATIENTS WITH BREAST CANCER TREATED WITH ADJUVANT RADIOTHERAPY IN COMBINATION WITH BEVACIZUMAB

SHARAD GOYAL, M.D., MALAY S. RAO, PHARM.D., ATIF KHAN, M.D., LIEN HUZZY, R.N., CAMILLE GREEN, M.D., AND BRUCE G. HAFFTY, M.D.

Department of Radiation Oncology, The Cancer Institute of New Jersey, UMDNJ/Robert Wood Johnson Medical School, New Brunswick, NJ

- 14 patients have received bevacizumab plus RT
- no RT treatment breaks
- No Grade 3 toxicity
- no difference in fatigue, radiation fibrosis, pneumonitis, or lymphedema between the two groups.

Concurrent bevacizumab and RT did **not increase acute locoregional toxicity**. The addition of concurrent RT when treating the intact breast, chest wall, and associated nodal regions in breast cancer seems to be safe and well tolerated

PERTUZUMAB AND RADIATION

Pertuzumab is a humanized monoclonal antibody that binds to the extracellular domain II of HER2.
Its mechanism of action is complementary to trastuzumab, inhibiting ligand- dependent HER2–HER3 dimerization and reducing signaling via intracellular pathways such as phosphatidylinositol 3-kinase (PI3K/Akt).

reviews

Annals of Oncology 24: 273–282, 2013
doi:10.1093/annonc/mds328
Published online 21 August 2012

Pertuzumab: new hope for patients with HER2-positive breast cancer

M. Capelan[1,2], L. Pugliano[1,3], E. De Azambuja[1,2], I. Bozovic[1,2], K. S. Saini[1,3], C. Sotiriou[1,4], S. Loi[3,4] & M. J. Piccart-Gebhart[1,3]*

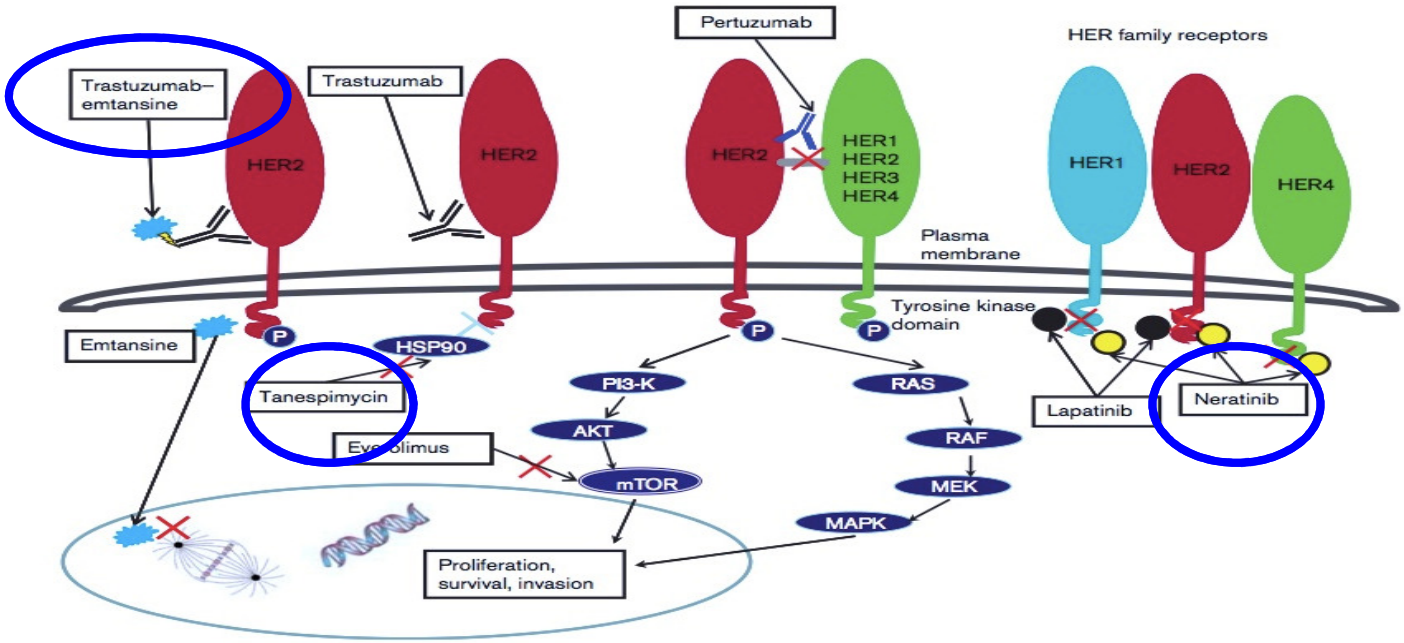
[1]*Department of Medicine, Institute Jules Bordet, L'Université Libre de Bruxelles, Brussels;* [2]*BrEAST Data Center, Institute Jules Bordet, l'Université Libre de Bruxelles, Brussels;* [3]*Breast International Group (BIG), Brussels;* [4]*Breast Cancer Translational Research Laboratory (BCTL) JC Heuson, Institut Jules Bordet, Brussels, Belgium*

Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial

Luca Gianni, Tadeusz Pienkowski, Young-Hyuck Im, Laslo Roman, Ling-Ming Tseng, Mei-Ching Liu, Ana Lluch, Elżbieta Staroslawska, Juan de la Haba-Rodriguez, Seock-Ah Im, Jose Luiz Pedrini, Brigitte Poirier, Paolo Morandi, Vladimir Semiglazov, Vichien Srimuninnimit, Giulia Bianchi, Tania Szado, Jayantha Ratnayake, Graham Ross, Pinuccia Valagussa

No data about pertuzumab AND radiotherapy

NOVEL TARGETED THERAPIES AND BREAST CANCER



TRASTUZUMAB–EMTANSINE: trastuzumab bound by a stable thioether linkage to a derivative of maytansine, a microtubule-binding chemotherapeutic agent.

TANESPIMYCIN: is an inhibitor of heat shock protein 90 (HSP90), which is responsible for conformational stabilization of HER2; inhibitio of HSP90 leads to proteasomal degradation of the HER2 protein.

NERATINIB: is an oral irreversible small molecule tyrosine kinase inhibitor of HER1, HER2, and HER4.

No data about this novel agents AND radiotherapy

CONCLUSIONS

- Promising new preclinical data show potential therapeutic benefit for combining molecularly targeted agents with radiation.

- The long-term outcome of trastuzumab-related heart failure is unknown so it is important to spare the heart volume during RT, but trastuzumab given postoperatively is well tolerated and produced optimal clinical results.

- The data on combining targeted therapies with radiation in breast cancer are still scarce and do not allow for meaningful conclusions.