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

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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

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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**

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Concurrent RT-targeted treatments

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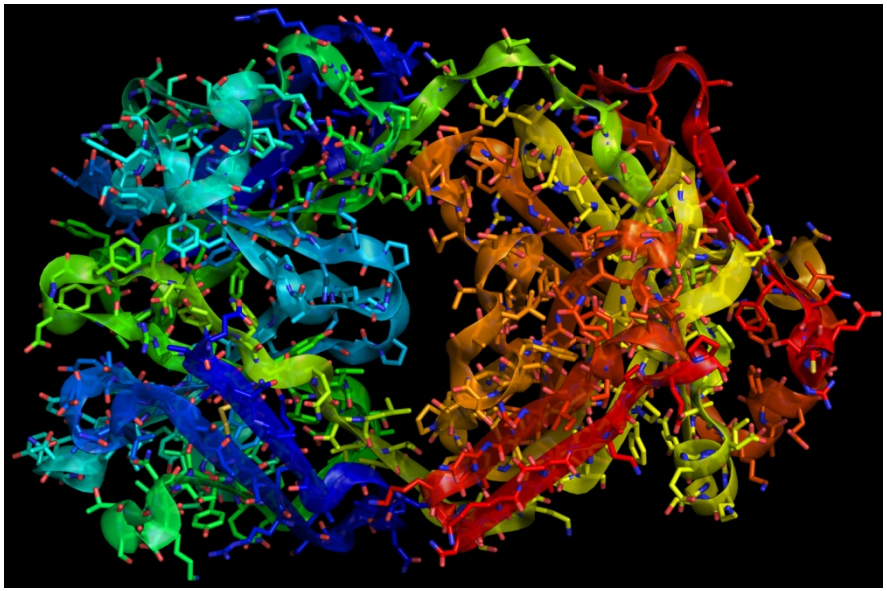
Trastuzumab-RT



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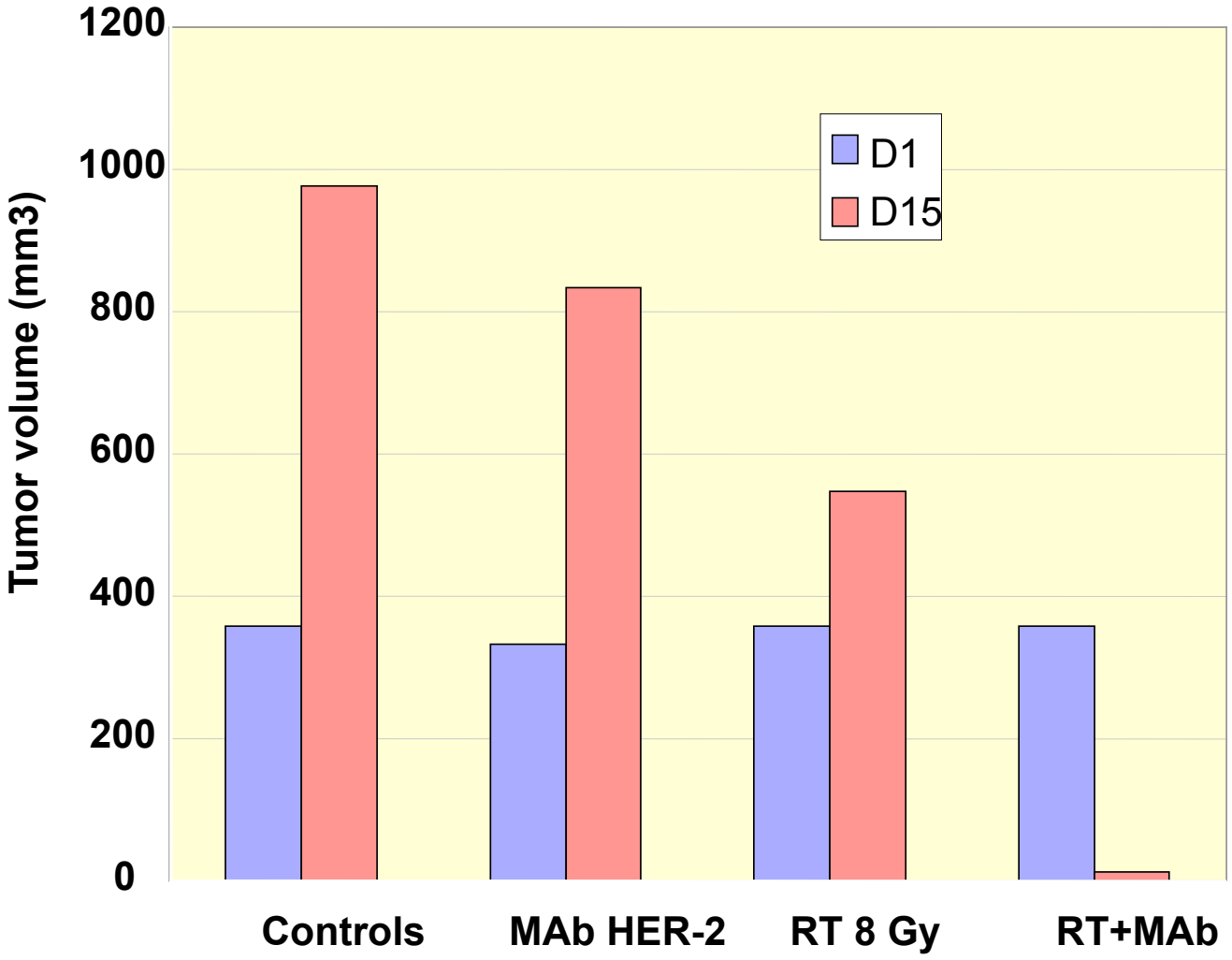
MCF7 surexpression of HER2 (murine model)
RT + Ac anti HER2



Pietras RJ et al. Cancer Res 59: 1347-1355, 1999

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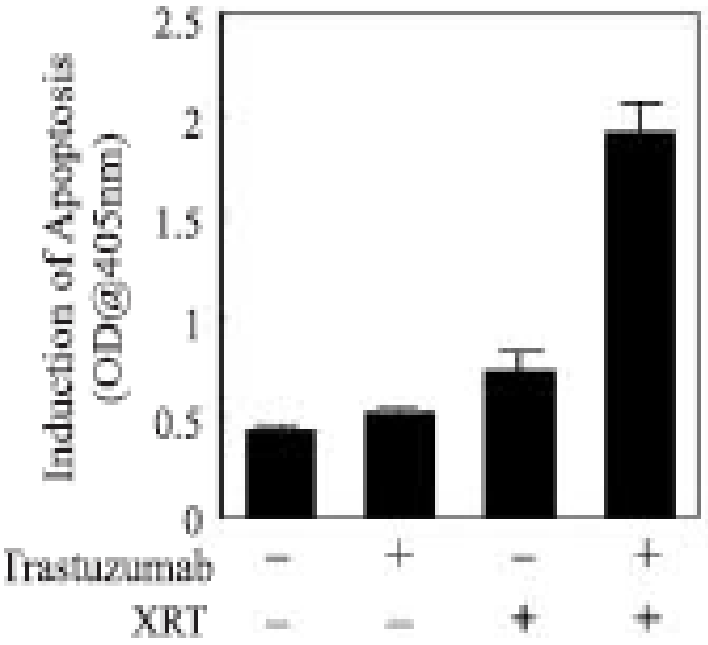
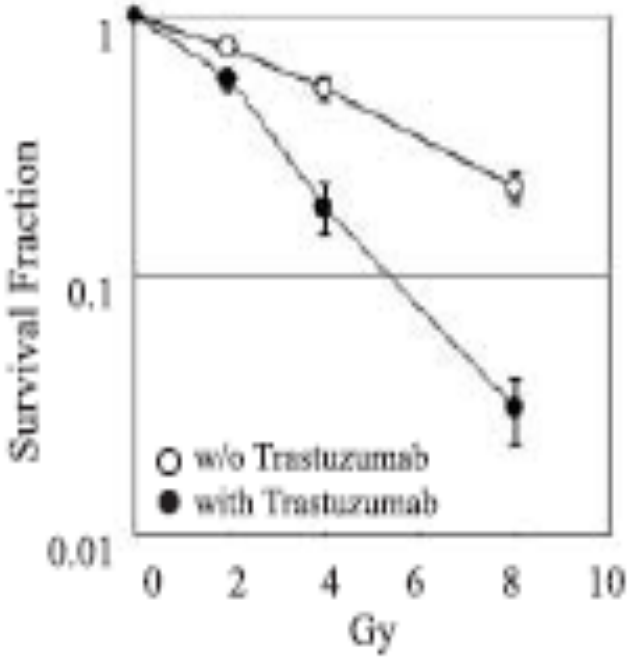
MCF7 cells transfected with HER2

From Liang K et al. *Mol Cancer Ther* 2003





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RT +Trastuzumab. Efficacy

9 pts with LABC (T4 or N2 or M1)

Chimiotherapy followed by RT : 50 Gy breast and LN

Concurrent Trastuzumab (2mg/m^2 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

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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

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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

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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

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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

leucopoenia (p=0.02) ↑ with H

Halyard, Pisansky et al. JCO 2009

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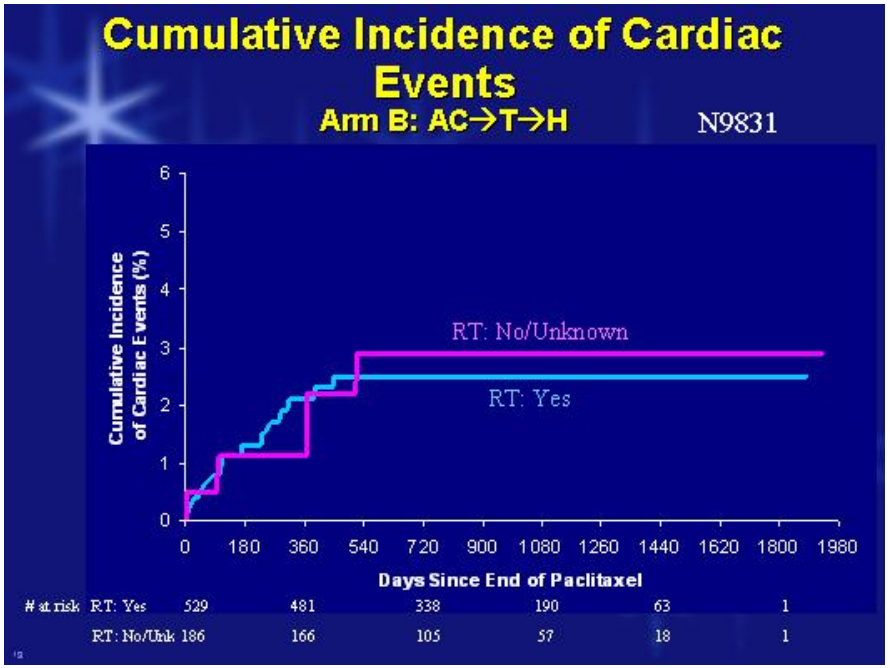
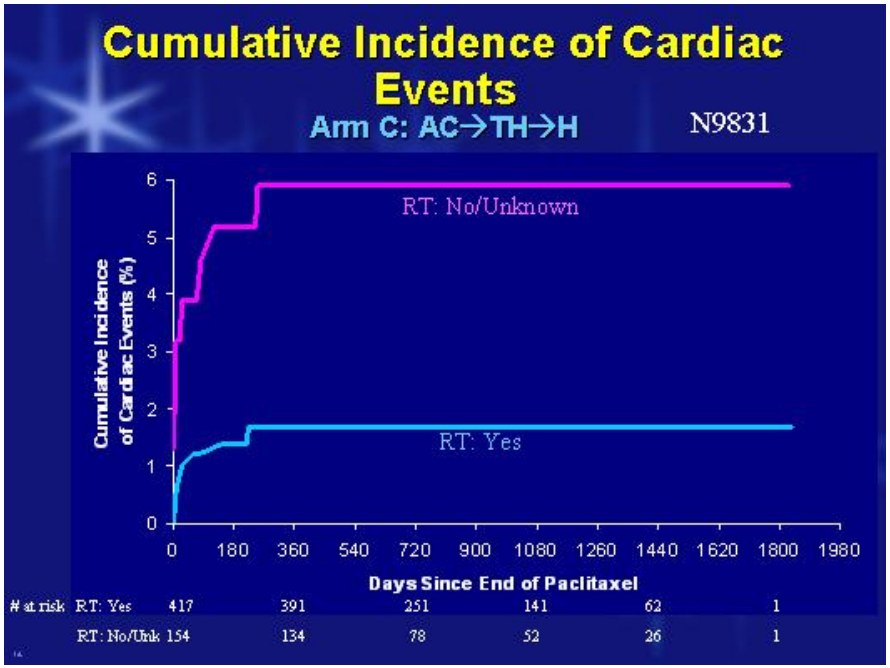
RT + Trastuzumab. Toxicity





Halyard, Pisansky et al. JCO 2009

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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

41 p

Halyard, Pisansky et al. JCO 2009

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2010

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

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 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,*]

n=106

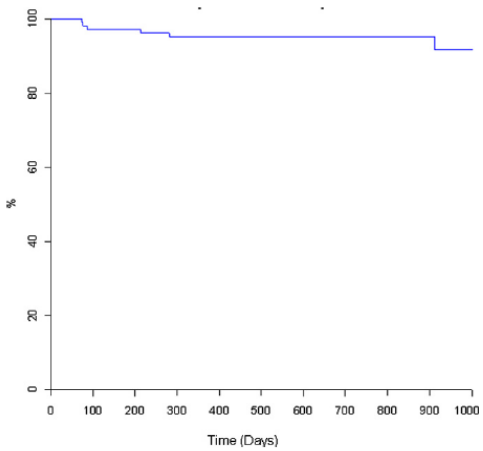

Fig. 1 – Cardiac toxicity free interval in the 106 patients treated with concurrent trastuzumab and radiotherapy.

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Caussa et al., 2011

Early toxicity

	N	%	Median dose at apparition of the maximum toxicity Gy [min–max]
Dermatitis			
Grade 1	87	82	38 [6–66]
Grade 2	14	13	38 [14–50]
Grade 3	2	2	50
Missing data	3	3	
Oesophagitis	13	12	36 [24–50]
Grade 1	9	9	36 [24–50]
Grade 2	3	3	32 [30–50]
Grade 3[a]	1	1	14
Interruption[b]	2	2	
Total RT time			
All patients time in days: median (min–max)			40 (32–71)
Breast RT time in days: median (min–max)			48 (35–71)
Chest-wall RT time in days: median (min–max)			37 (32–61)

Dysfunction VG grade ≥ 2 in 6 patients

Late toxicity

Pain	All patients (106)	
	N	%
Missing data	5	5
No toxicity	79	75
Minor	19	18
Moderate	3	3
Fibrosis		
Missing data	5	4
No toxicity	85	80
Minor	16	16
Telangiectasia		
Missing data	5	4
No toxicity	96	90
Minor[a]	5	6
Lymphoedema		
Missing data	5	4
No toxicity	93	88
Minor	6	6
Moderate[b]	1	1
Late toxicity		
Total	4	4
Assessed	87	82
Missing data	19	18
No toxicity	83	78
Cardiac ischemia[c]	1	1
Dyspnoea	1	1
Dysphagia	1	1
Paresia	1	1

2010

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journal homepage: www.ejconline.com

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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.

New actualisation in 2013 ECCO Amsterdam

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Institut Curie experience

Jacob et al, 2013, ECCO

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)

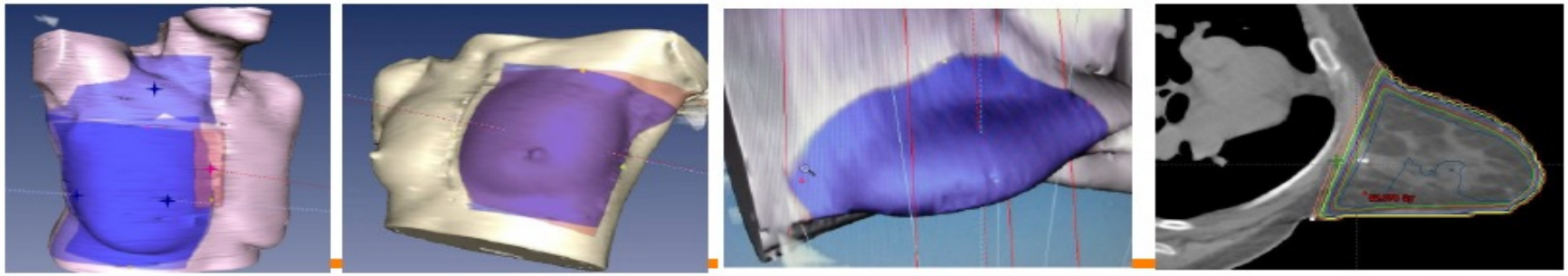
Exclusion criteria:

Bilateral breast cancer

Hypofractinated radiotherapy

Recurrences of breast cancer

Normofractionated radiotherapy
Breast: 50 Gy
LN: 46 Gy
Boost: 16 Gy
Different techniques



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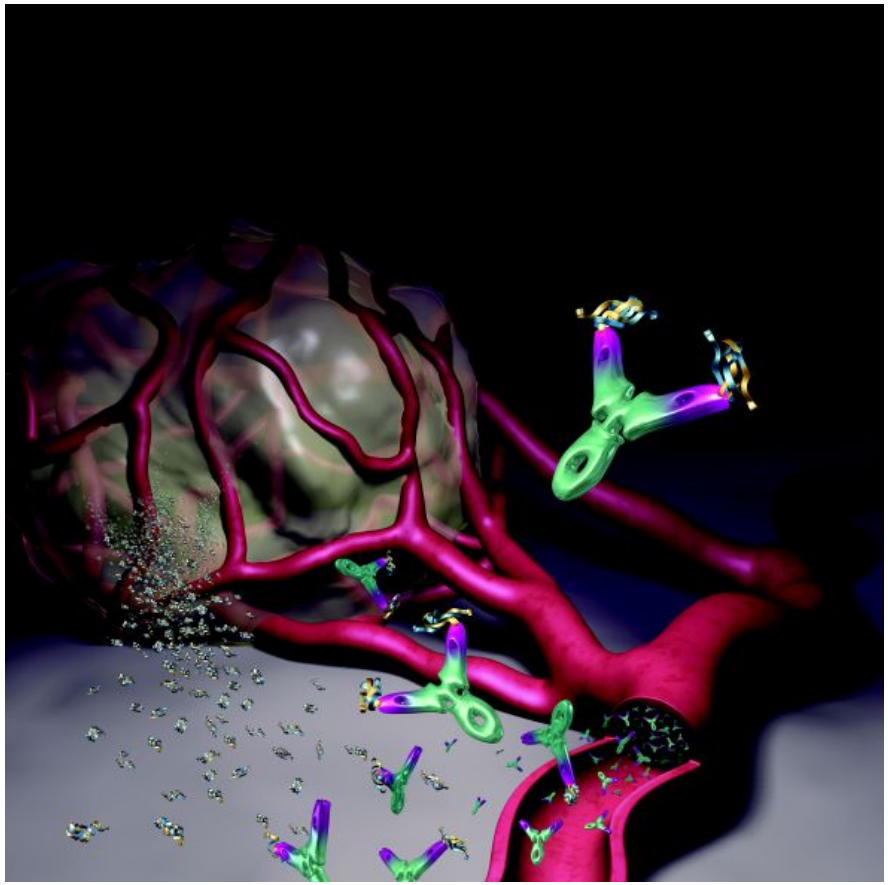
Anti-Angiogenic treatment + RT



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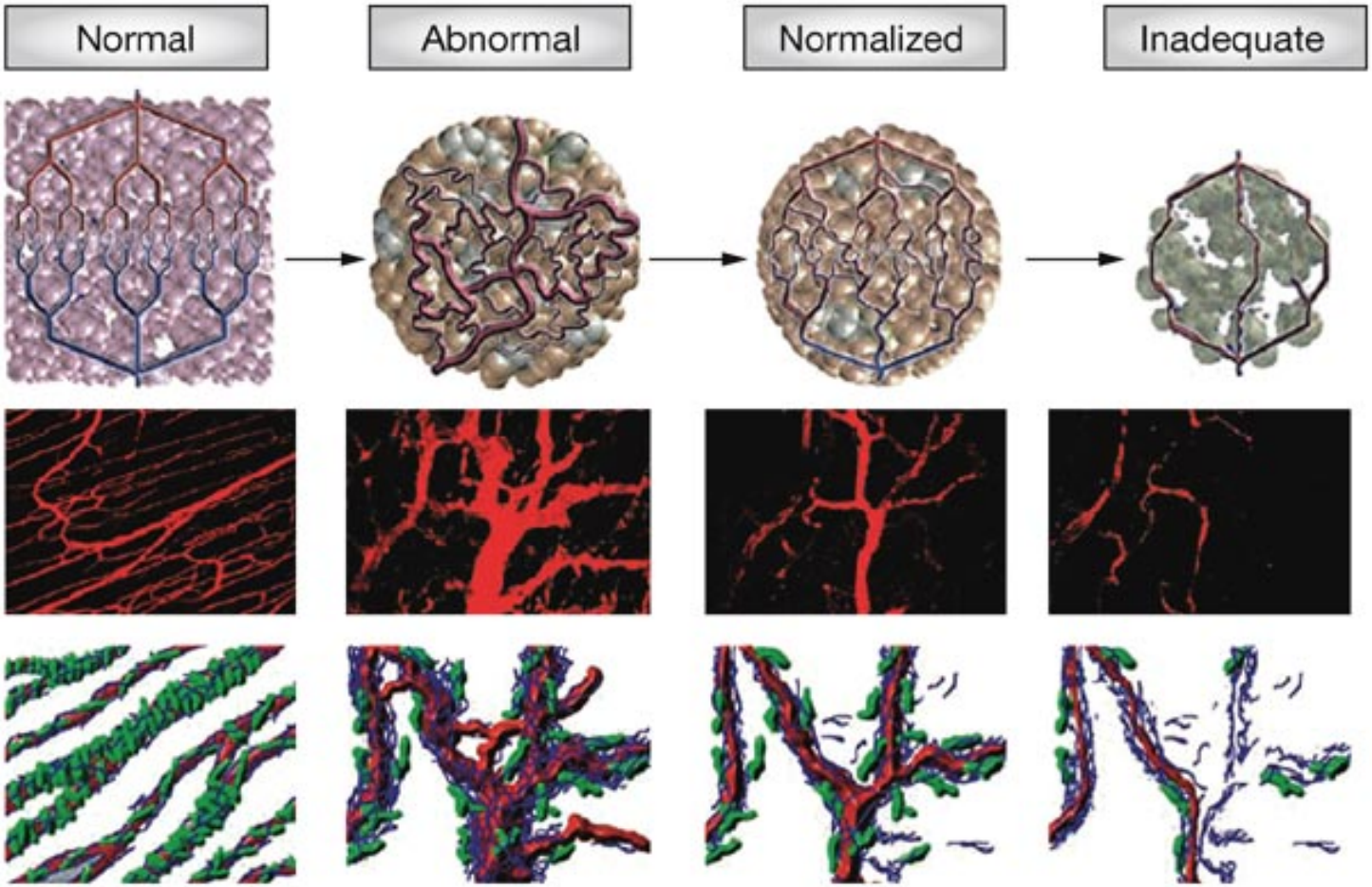
Bevacizumab and vascular normalization



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Bevacizumab in the neo-adjuvant treatment of BC: *phase 2 studies*

Studies	IHC	Traitement néo-adjuvant	n	Clinical CR	Pathological CR
Balduzzi et al	HER2-neg	Epirubicine, cisplatine, 5-FU → paclitaxel + bevacizumab	30	3	33
Rastogi et al	HER2-neg	Doxorubicine, cyclophosphamide + bevacizumab → docetaxel + capecitabine + bevacizumab	45	31	9
Ryan et al	Triple-neg	Cisplatin + bevacizumab	46	26	15
Makhoul et al	All types	Docetaxel, cyclophosphamide + bevacizumab	40	_	33
Greil et al	All types	Capecitabine, docetaxel + bevacizumab	18	_	22
Yardley et al	HER2+++	Paclitaxel, carboplatin, trastuzumab + bevacizumab	29	_	69
Smith et al	HER2+++	Epirubicine, cyclophosphamide + bevacizumab → docetaxel + bevacizumab + trastuzumab	75	_	63
Pierga et al	HER2+++	Epirubicine, cyclophosphamide + bevacizumab → docetaxel + bevacizumab + trastuzumab	52	_	63,5

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Bevacizumab in the adjuvant treatment of BC: *Running phase 3 studies*

Trial Sponsor/Number	Official Title	Phase
HER2-Positive		
NSABP B-44-I	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	III
HER2-Negative		
ECOG 5103	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	III
NSABP B-46-I	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	III
Dana Farber 09-134	ABCDE: A Phase III Randomized Study of Adjuvant Bevacizumab, Metronomic Chemotherapy (CM), Diet and Exercise After Preoperative Chemotherapy for Breast Cancer	III
Triple-Negative Tumors		
Hoffmann-La Roche BO20289	An Open Label 2-arm Study to Evaluate the Impact of Adjuvant Bevacizumab on Invasive Disease Free Survival in Triple Negative Breast Cancer	III

Derleth and Mayer, 2010

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Bevazumab+ RT

Locoregional toxicity	Bevacizumab + RT		RT alone	
	Grade 1–2 *n* affected (total)	Grade 3–5 *n* affected (total)	Grade 1–2 *n* affected (total)	Grade 3–5 *n* affected (total)
Nausea	1 (14)	0 (14)	0 (14)	0 (14)
Fatigue	13 (14)	0 (14)	14 (14)	0 (14)
Pneumonitis	1 (14)	0 (14)	0 (14)	0 (14)
Radiation Dermatitis	14 (14)	0 (14)	11 (14)	3 (14)
Radiation fibrosis	0 (14)	0 (14)	0 (14)	0 (14)
Lymphedema	0 (14)	0 (14)	0 (14)	0 (14)

n=14

Goyal et al, IJROBP 2011

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Bevazumab+ RT: French experience

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

V. Pernin [a], L. Belin [b], P. Cottu [c], P. Bontemps [d], C. Lemanski [e], B. De La Lande [f], P. Baumann [g], F. Missohou [h], C. Levy [i], K. Peignaux [j], P. Bougnoux [k], F. Denis [l], A. Gobillion [b], M. Bollet [a], R. Dendale [a], F. Campana [a], A. Fourquet [a] and V. M. Kirova [a]

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.

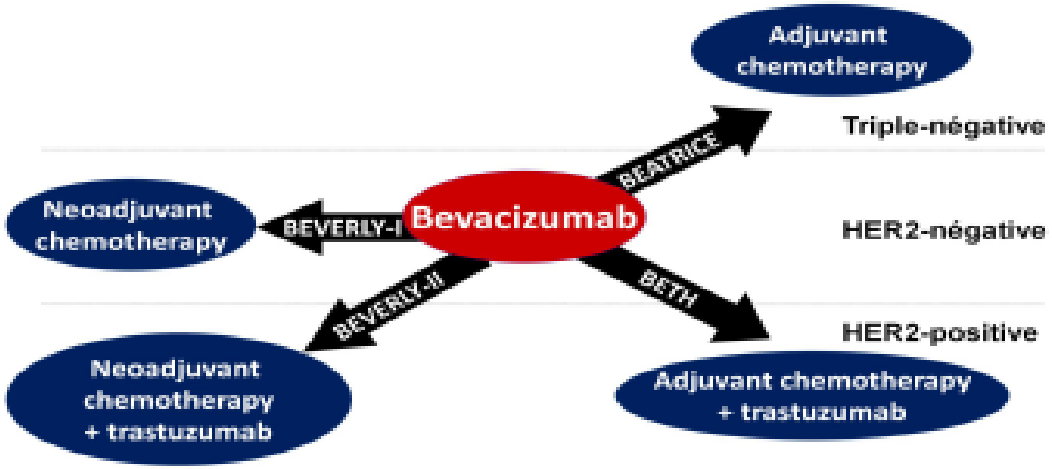


Figure 1: clinical trials with bevacizumab in combination with radiotherapy in whom patients were included

Median FU: 21.5 months

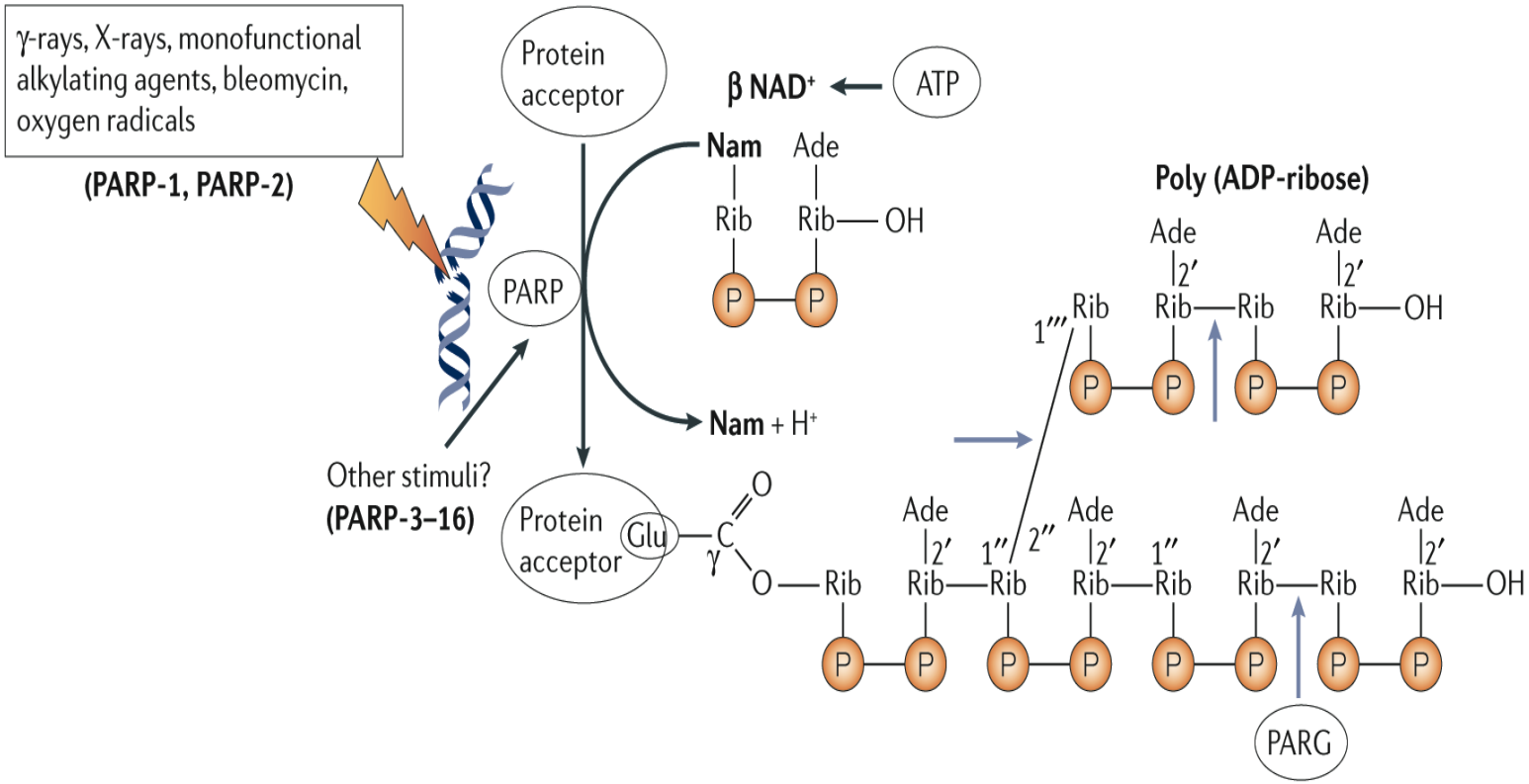
At 12 months: evaluation available in 63 cases

Mean age 51 years

In our multicenter prospective and descriptive study, we analyzed toxicities of adjuvant radiotherapy in patients with non-metastatic BC receiving concurrent bevacizumab in trials evaluating bevacizumab in a neoadjuvant strategy or in an adjuvant strategy (figure 1). Early and late toxicities were assessed with the Common Terminology Criteria for Adverse Events (v3.0). Evaluation was done during RT and 12 months after the end of radiotherapy. All patients provided written informed consent before enrollment.

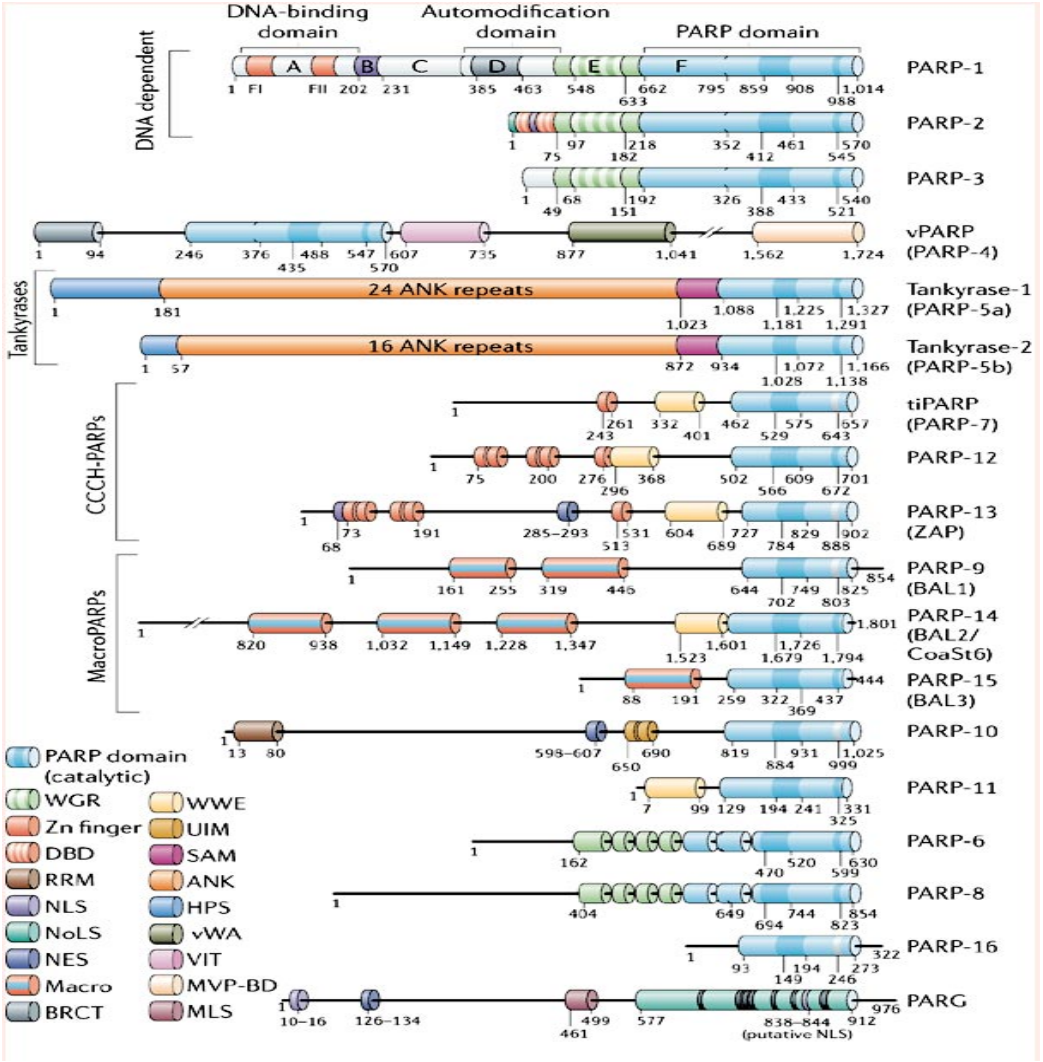
Pernin et al, ECCO 2013

PARP inhibitors and RT



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



Schreiber et al. Nature Reviews Molecular Cell Biology ***7****, 517–528 (July 2006)*

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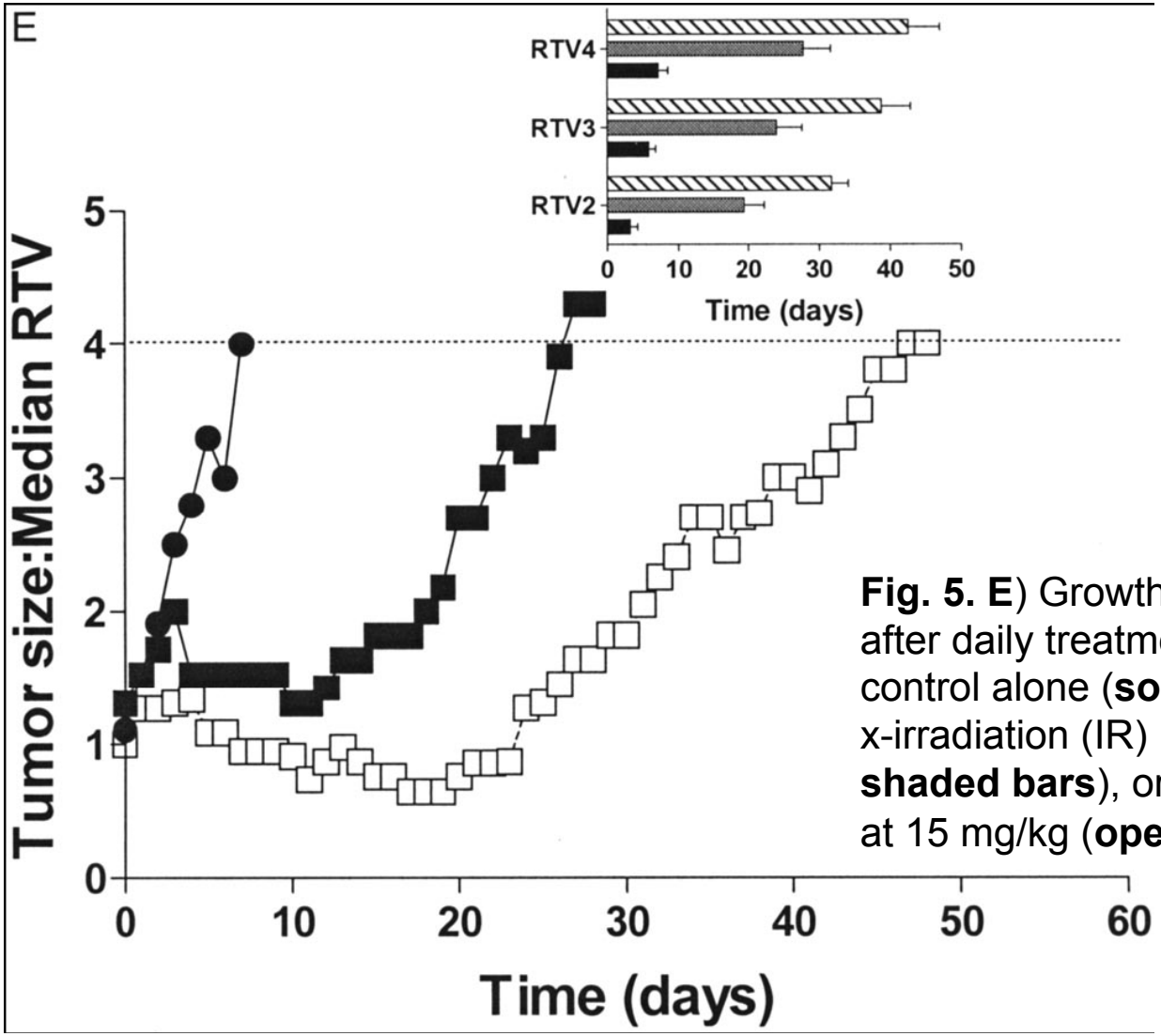
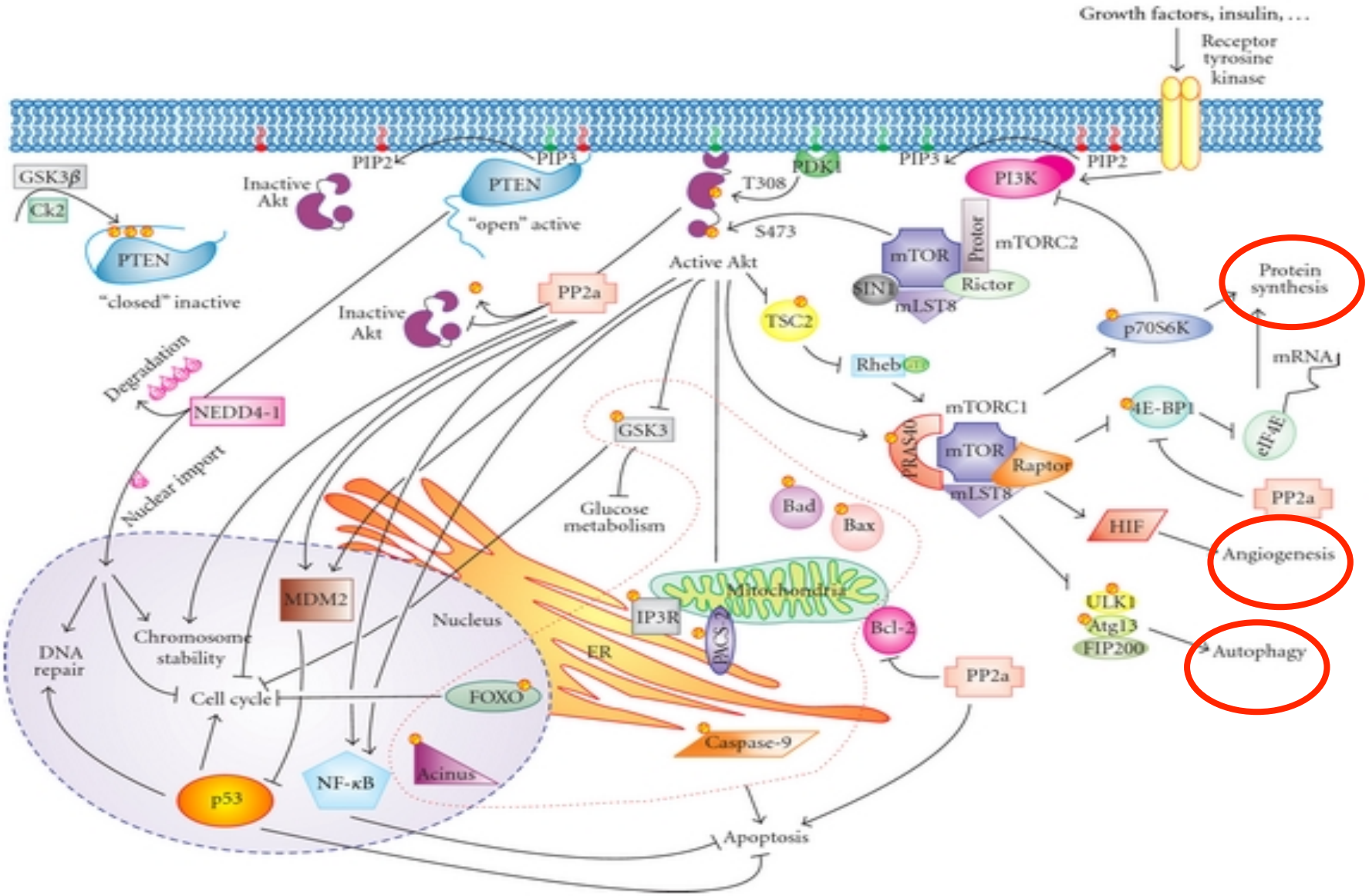


Fig. 5. E) Growth of SW620 tumor xenografts after daily treatment for 5 days with vehicle control alone (**solid circles, solid bars**), 2 Gy of x-irradiation (IR) vehicle (**solid squares, shaded bars**), or 2 Gy of x-irradiation AG14361 at 15 mg/kg (**open squares, hatched bars**).

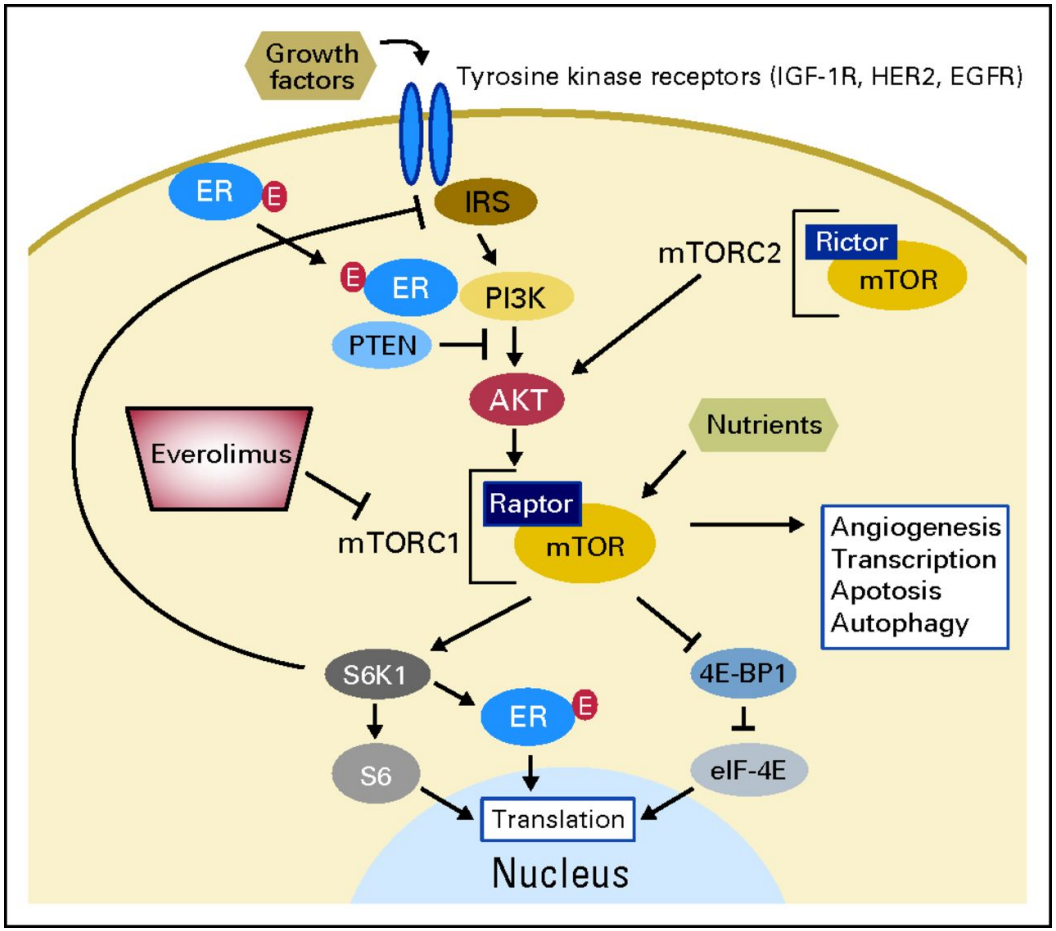
PARP inhibitors combined with radiation will also increase the formation of DSBs and increase cell killing, particularly in a background of reduced levels of DSB repair proteins.

Currently: phase I study in breast inflammatory cancer and in brain metastases

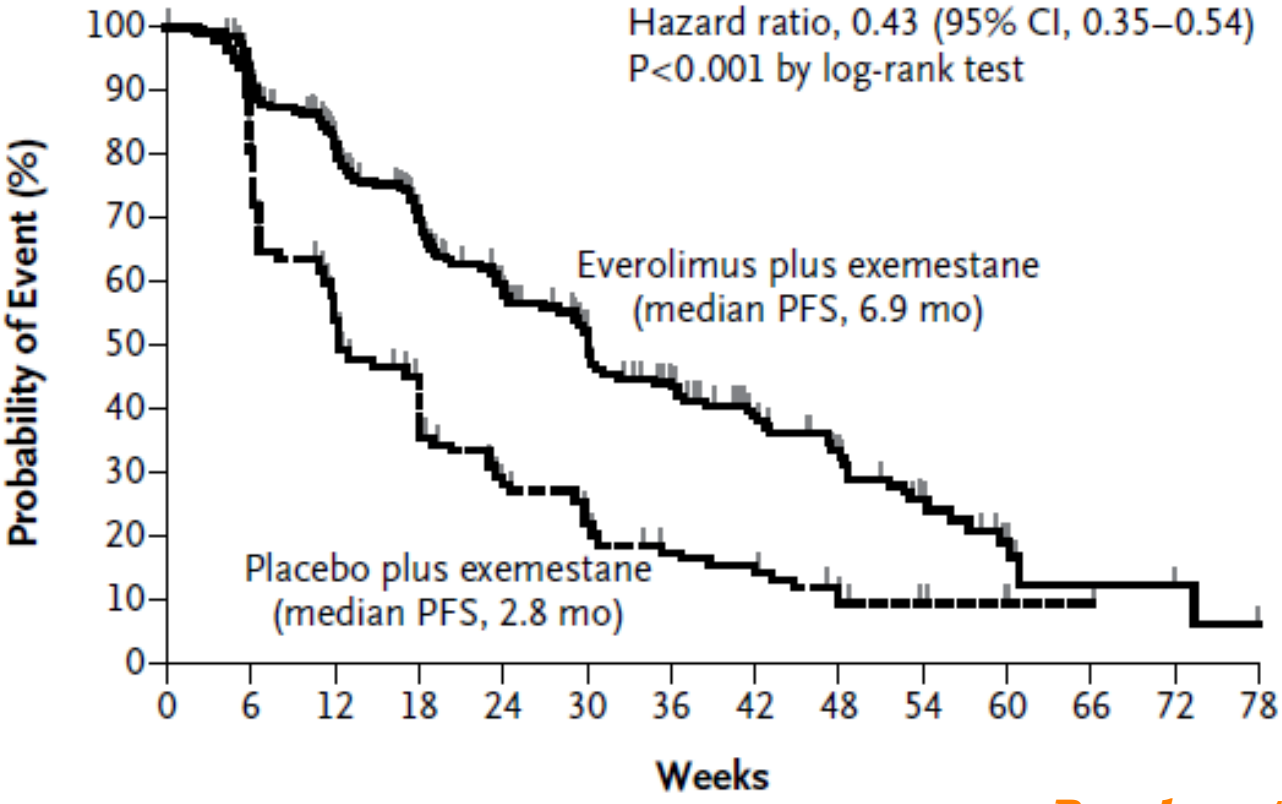
PI3K/AKT/mTor inhibitors



Inhibition of mTor and restauration of the hormonal sensibility



Everolimus & exemesthane: BOLERO-2 Study



Baselga et al., NEJM, 2012

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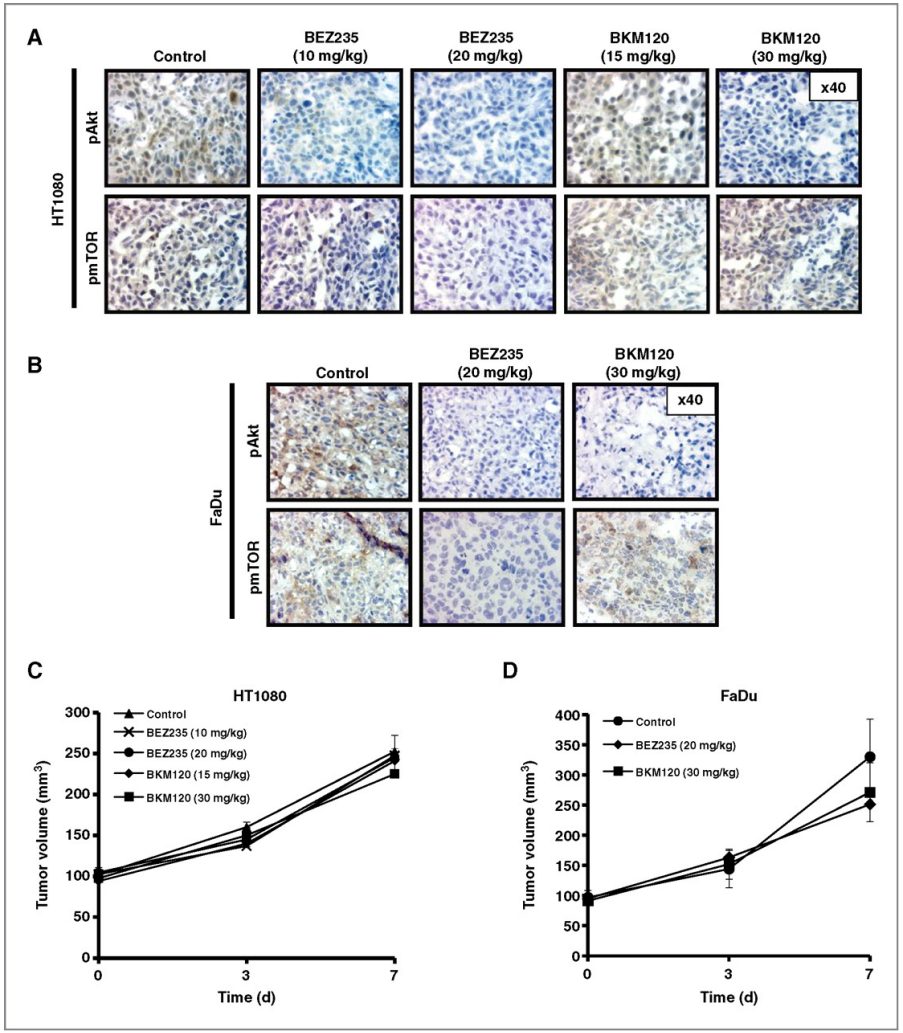
Immunohistochemical analysis of HT1080 and FaDu tumors from mice treated with signaling inhibitors.



Immunohistochemical analysis of HT1080 and FaDu tumors from mice treated with signaling inhibitors.

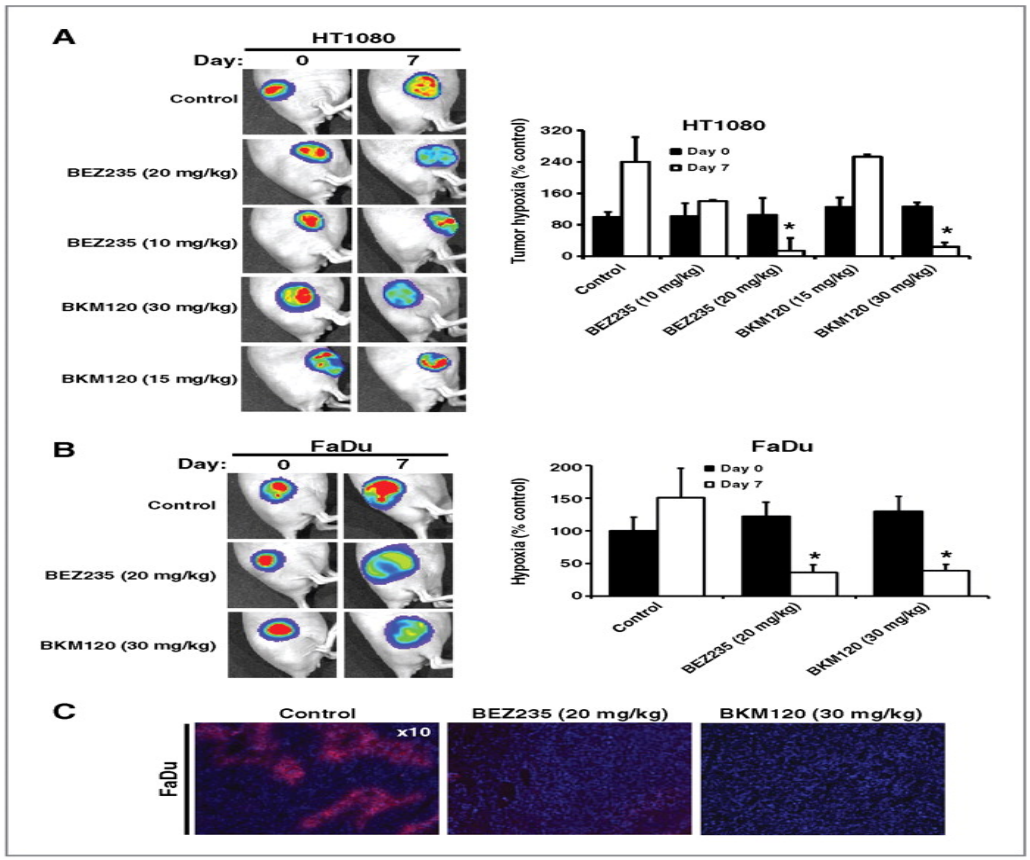
Evaluation of the effects of BKM120 and BEZ235 on p-Akt and p-mTOR in (A) HT1080 and (B) FaDu tumors.

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.

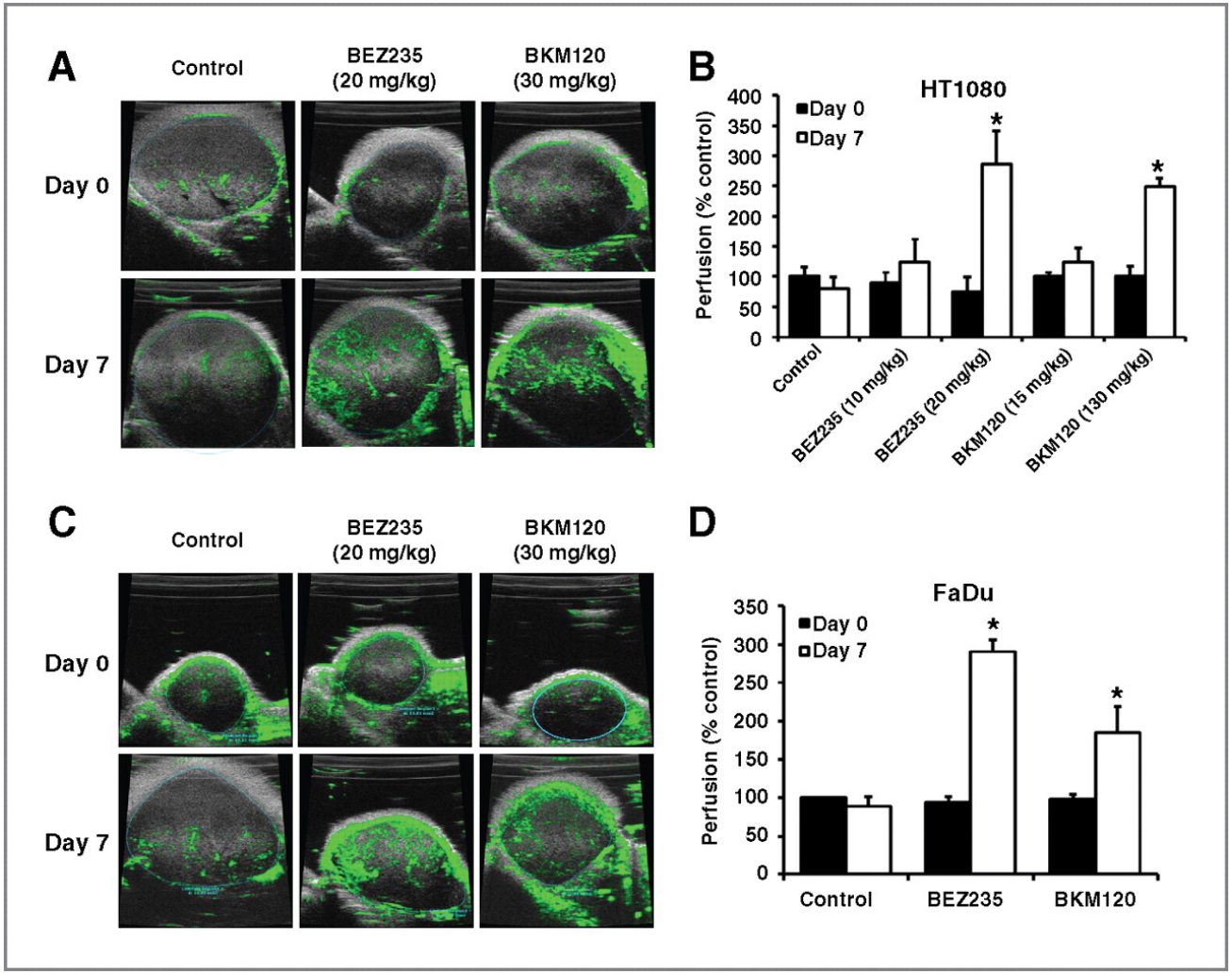
Fokas E et al. Cancer Res 2012;72:239-248

BEZ235 and BKM120 reduce hypoxia in vivo.



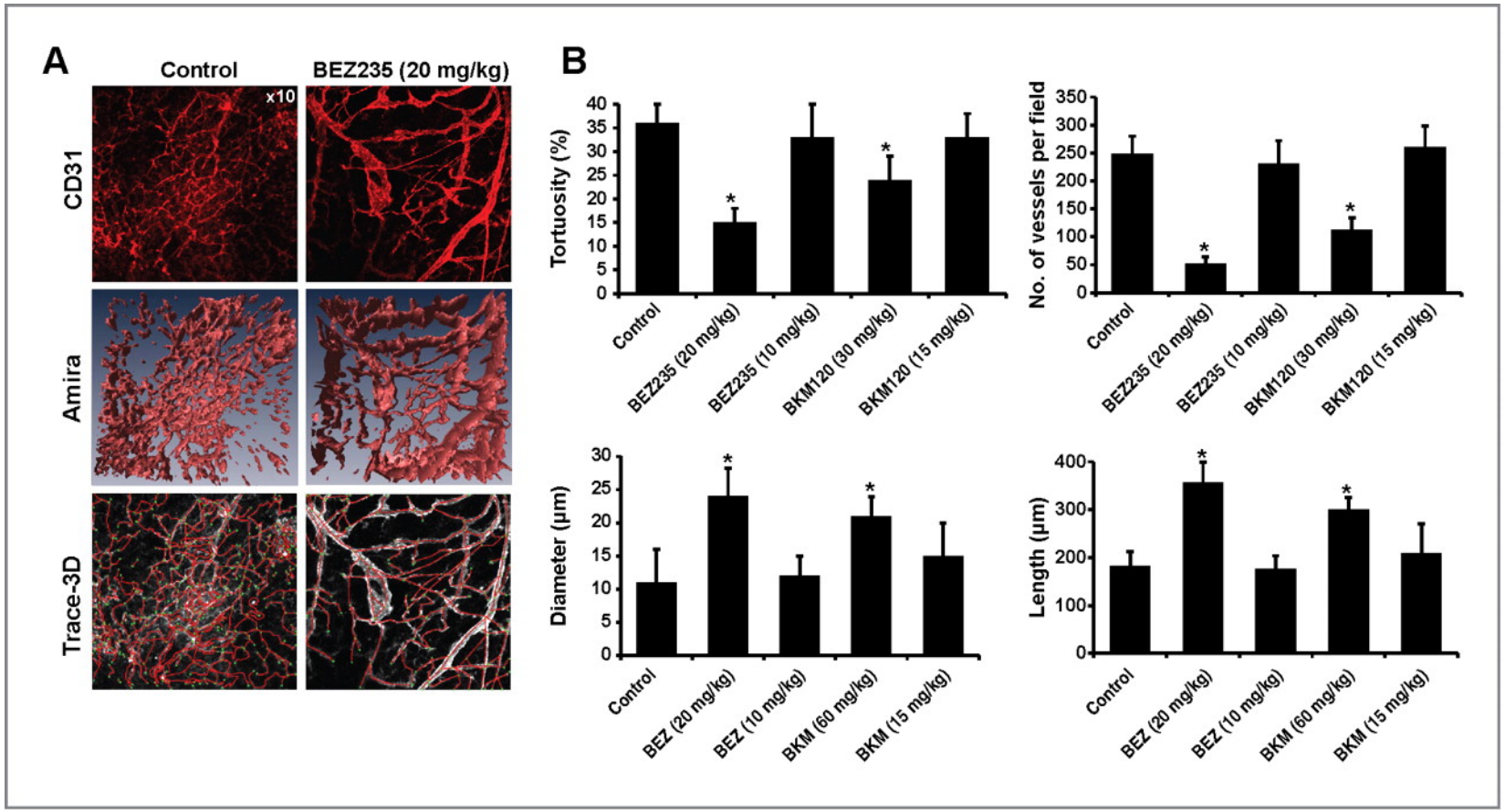
Fokas E et al. Cancer Res 2012;72:239-248

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



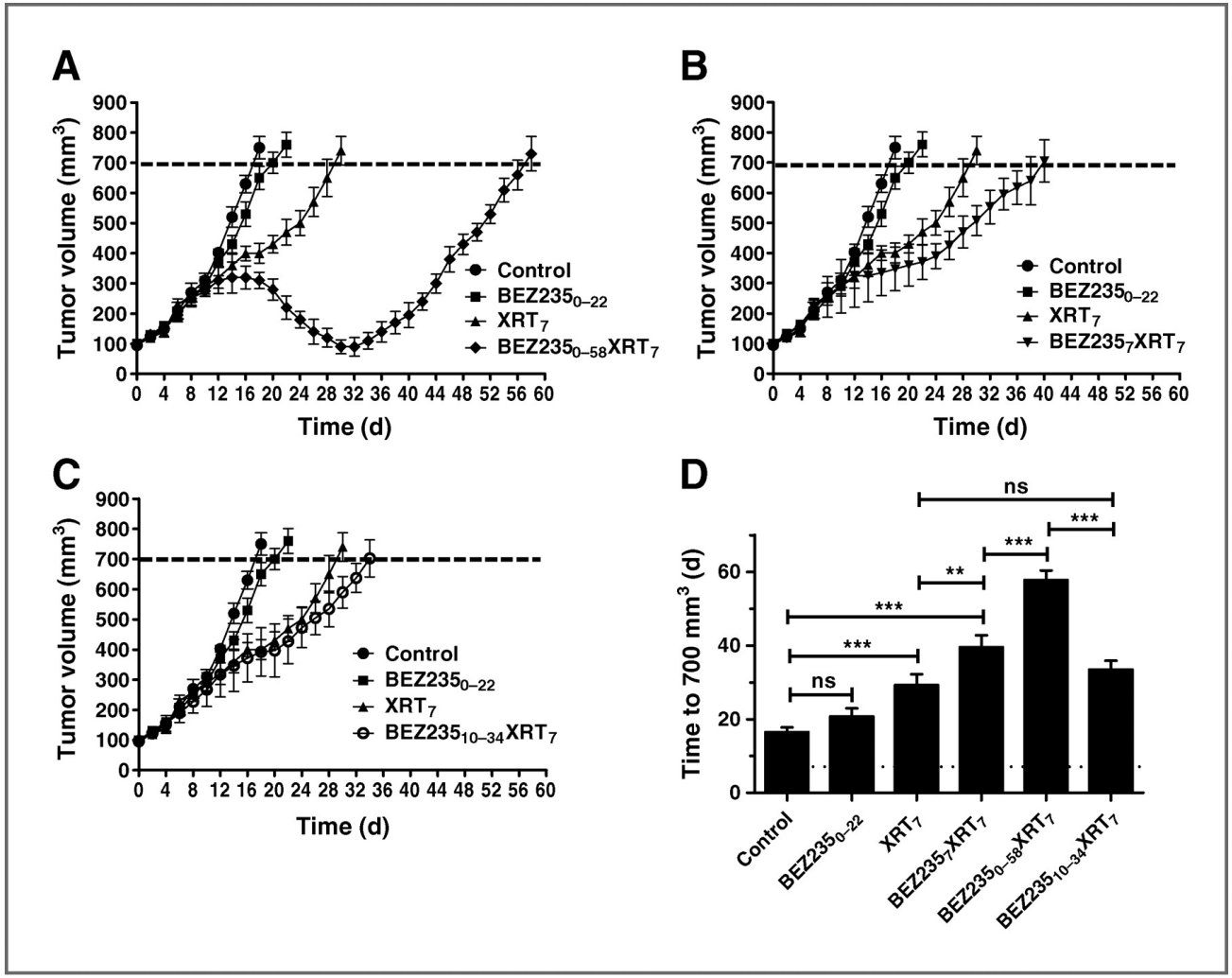
Fokas E et al. Cancer Res 2012;72:239-248

BEZ235- and BKM120-induced vascular remodeling and normalization.



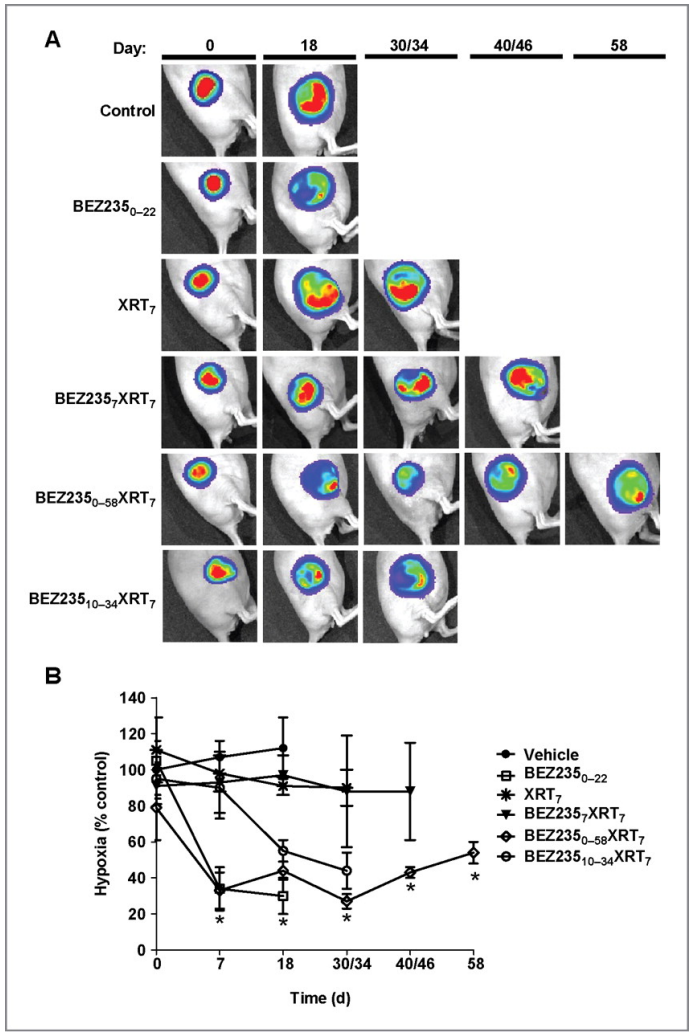
Fokas E et al. Cancer Res 2012;72:239-248

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



Fokas E et al. Cancer Res 2012;72:239-248

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



Fokas E et al. Cancer Res 2012;72:239-248

Conclusions

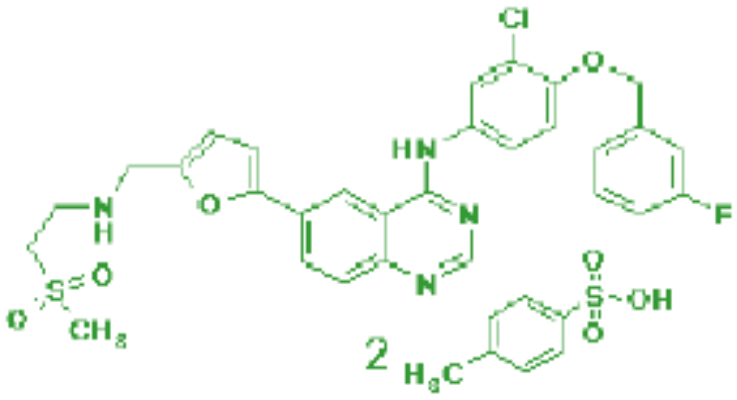
The results of this study provide evidence that inhibition of the PI3K/mTOR signaling displays significant effects on tumour growth by remodeling blood vessels and enhancing tumor perfusion and oxygenation.

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

Fokas E et al. Cancer Res 2012;72:239-248

LAPATINIB & RT



Lapatinib

N-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-
[5-({[2(methylsulfonyl)ethyl]amino}methyl)-2-furyl]-
4-quinazolinamine

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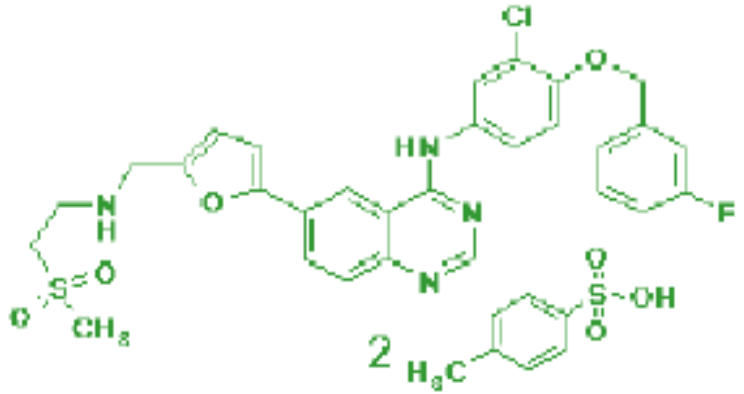
Lapatinib is a novel oral dual-tyrosine kinase inhibitor with specificity for the ErbB-1 and ErbB-2 receptors

- Belongs to the 4-anilinoquinazoline class of tyrosine kinase inhibitors
- Binds reversibly to the cytoplasmic ATP-binding site of the kinase, thereby preventing receptor phosphorylation and activation



Lapatinib

N-(3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-{{[2(methylsulfonyl)ethyl]amino}methyl)-2-furyl]-4-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.

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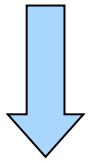
In vitro studies of Lapatinib

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

Conclusion:
amplification du gène HER-2
surexpression de HER-2



Better sensibility of lapatinib *in vitro* .

Cell line	IC 50 vmol/L	HER2 ng/mg	EGFR ng/mg
UACC812	↑0.010	↑436	25
SUM190	0.018	↑396	↑3.1
BT474	↑0.022	↑530	↑7.3
SK-BR-3	↑0.037	↑913	↑38
SUM225	↑0.083	↑1,161	↑51
UACC893	0.433	577	↑14
MDA-MB-361	0.989	211	↑6.6
EFM192A	↑1.1	115	↑1.0
T47D	↑1.9	11	↑31
MDA-MB-453	3.9	108	↑1.3
EFM19	4.6	22	↑0.8
MDA-MB-468	4.7	0.1	↑908
KPL1	5.4	8.4	↑3.2
MDA-MB-157	6.3	4.3	↑59
MCF-7	↑7.7	4.7	↑2.7
CAMA1	↑8.3	↑18	↑3.2
MDA-MB-435	↑8.5	↑2.2	↑4.4
BT20	9.8	↑36	↑295
ZR-75-1	9.9	40	↑8.3
MDA-MB-231	↑18.6	5.2	↑58

Cancer Res 2006; 66: (3). February 1, 2006

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J Natl Cancer Inst 2008;100:1092–1103

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

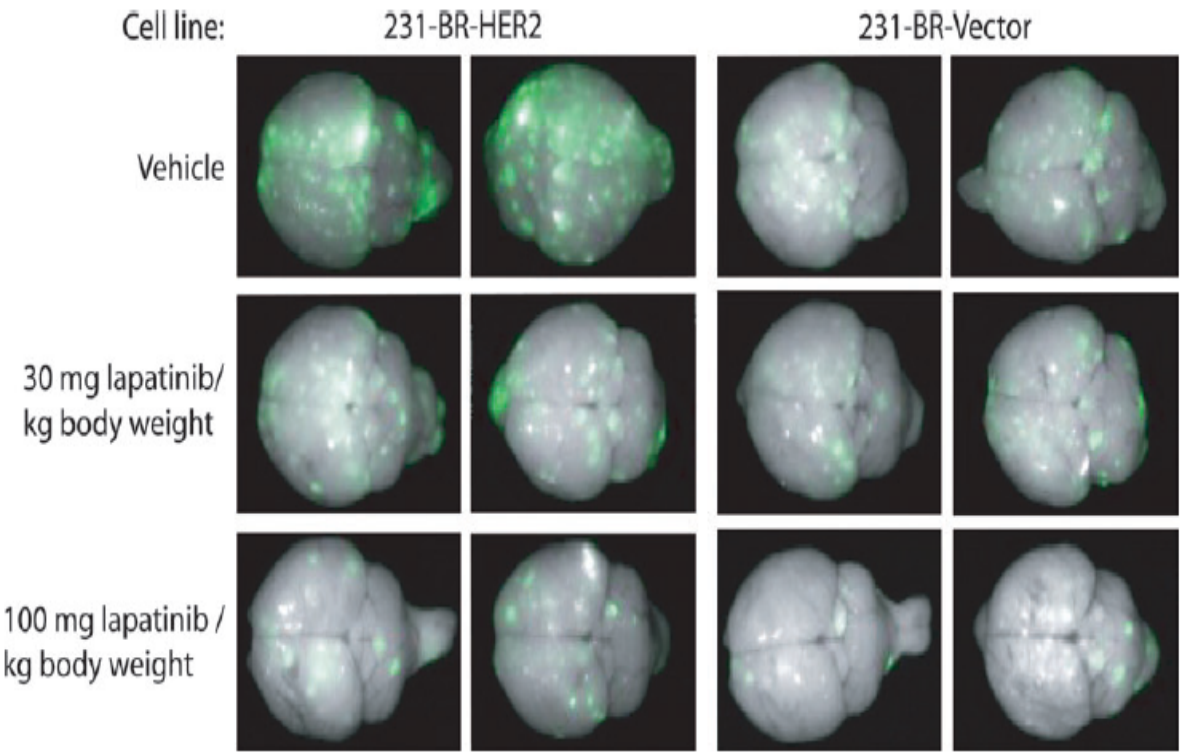

Figure 3. Lapatinib inhibition of metastatic colonization of mouse brain by 231-BR breast carcinoma cells. 231-BR-HER2 cells or 231-BR-vector cells, both of which were transduced with a retrovirus that expressed enhanced green fluorescent protein (EGFP), were injected into the left cardiac ventricle 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.

J Natl Cancer Inst 2008;100:1092–1103

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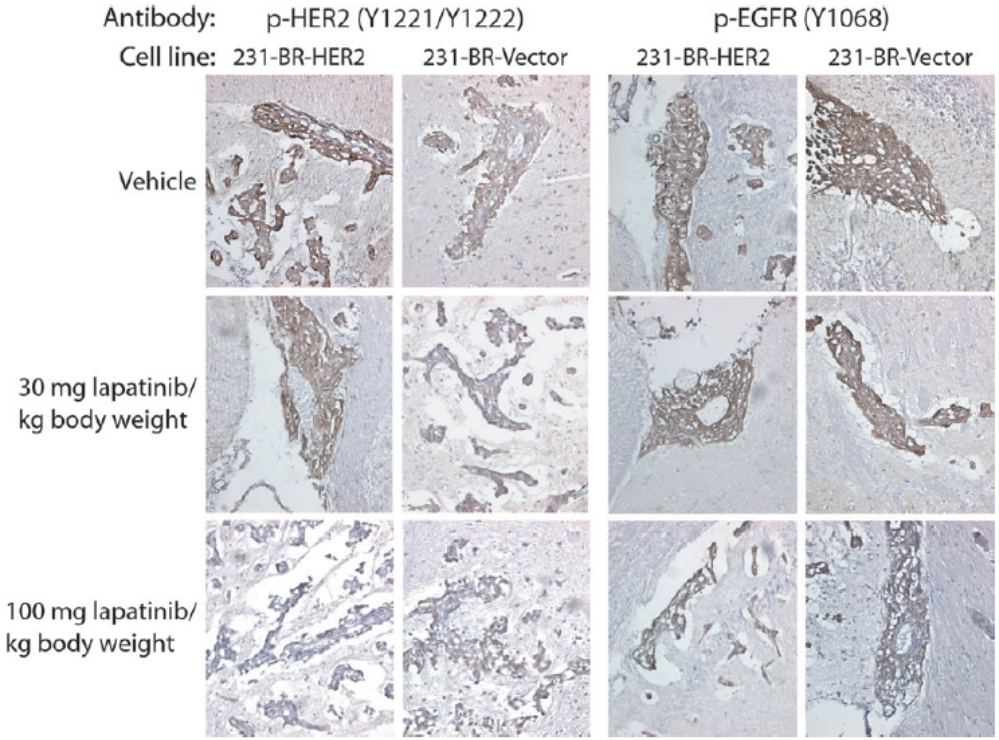

Figure 4. Immunohistochemical evaluation of HER2 and epidermal growth factor receptor (EGFR) activation in vivo in response to lapatinib treatment. Frozen sections (5 μm thick) of brains from mice injected with 231-BR-vector or 231-BR-HER2 cells and treated with lapatinib (30 or 100 mg/kg body weight) 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 (ie, >50 μm^2) 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 1st 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^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 ≥ 1CTC, 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.

IJROBP 2010

And Tyverb-RT?

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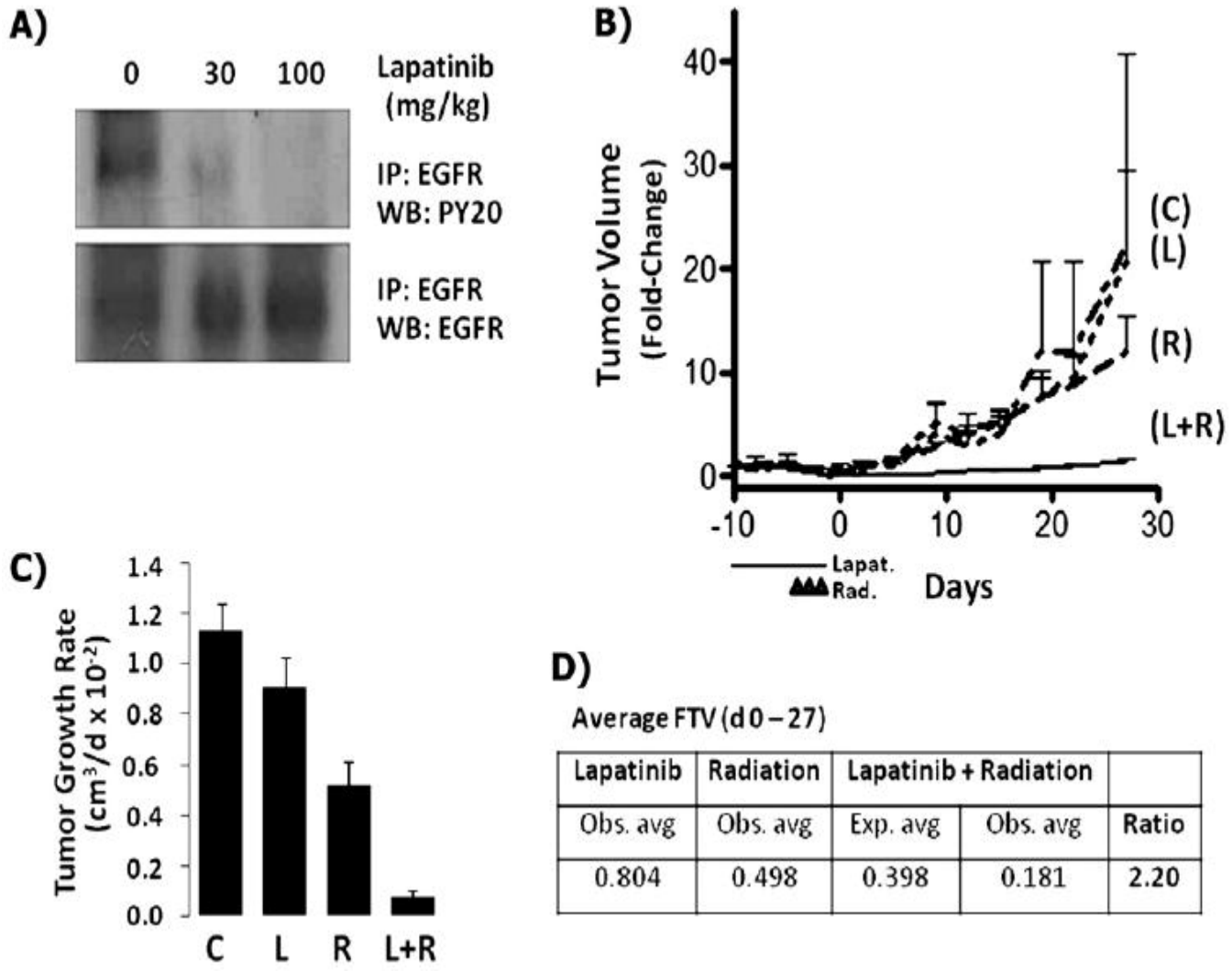

D)

Average FTV (d 0 – 27)

Lapatinib	Radiation	Lapatinib + Radiation		
Obs. avg	Obs. avg	Exp. avg	Obs. avg	Ratio
0.804	0.498	0.398	0.181	2.20

Sambade et al, IJROBP 2010: Lapatinib-mediated radiosensitization of SUM149 basal-like/epidermal growth factor receptor-positive (EGFR+) breast cancer xenografts.

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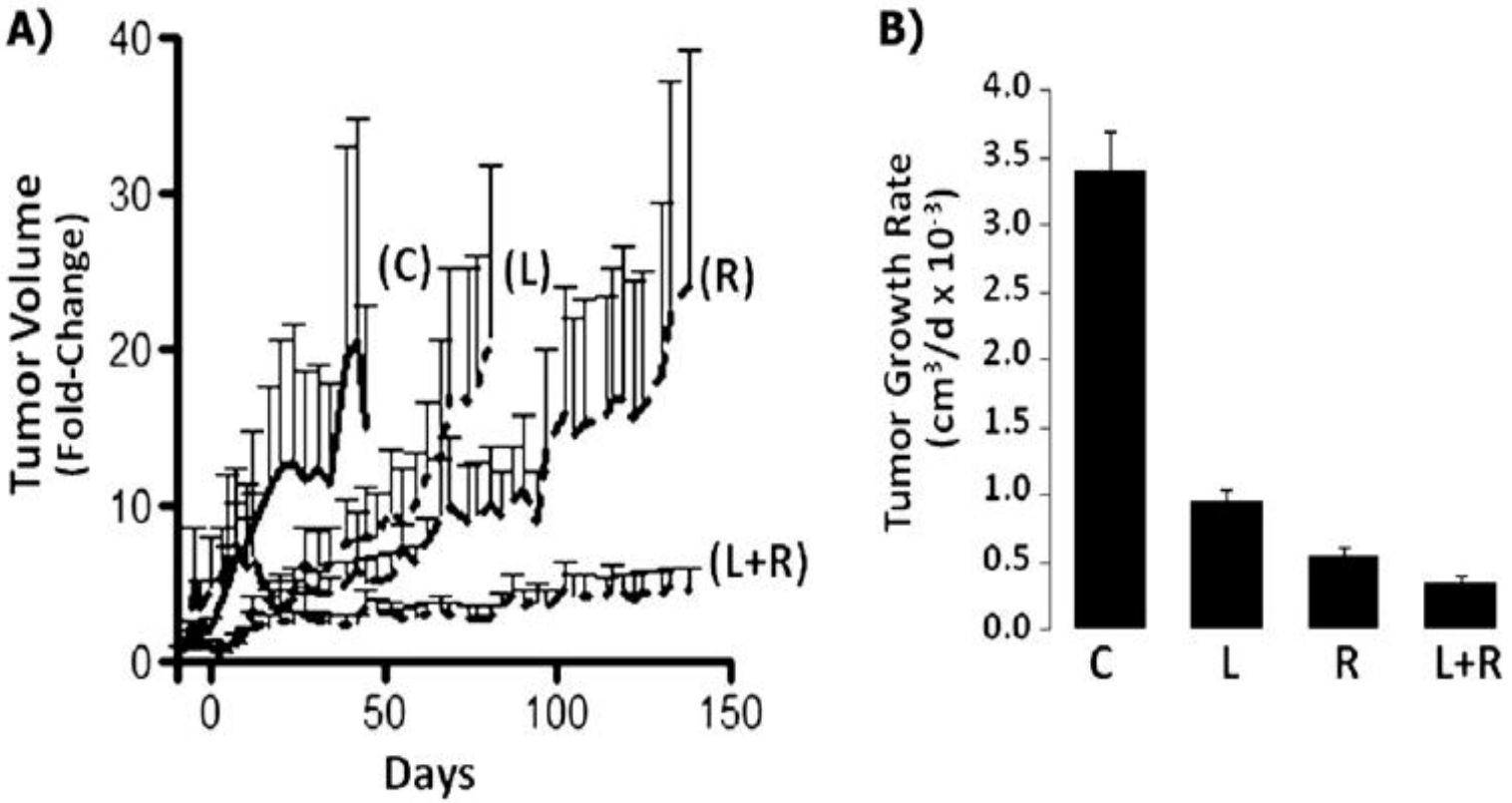

Sambade et al, IJROBP 2010
Lapatinib-mediated radiosensitization of SUM225 HER2+ breast cancer xenografts

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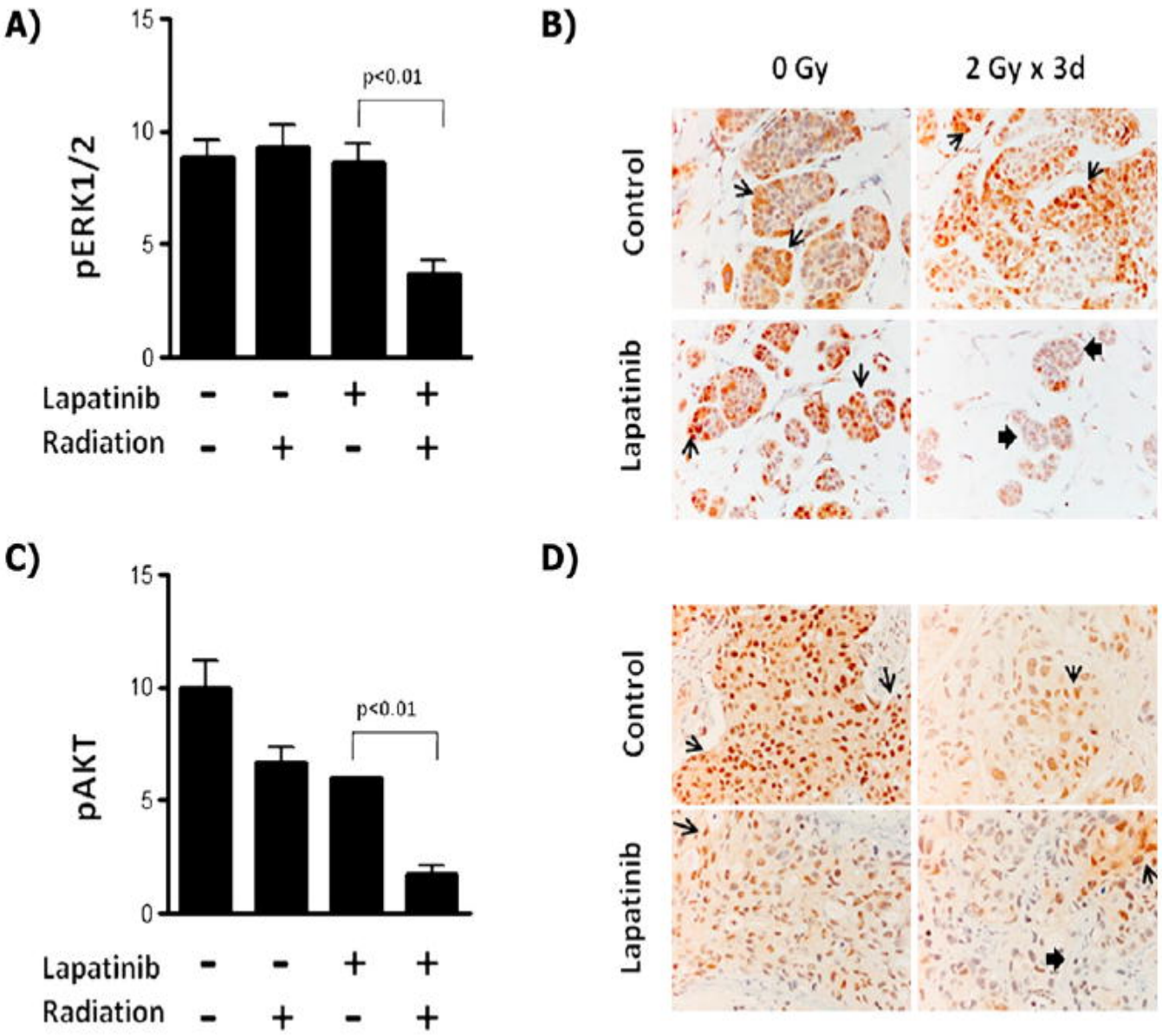

(A) Tumors from basal-like/EGFR+ SUM149 xenografts were processed for immunohistochemistry with phosphorylated ERK1/2 antiserum and quantified from mice treated with lapatinib, radiotherapy, lapatinib plus radiotherapy, or vehicle control.

(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

(C) quantified.

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

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.

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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.

Sambade et al, IJROBP 2010

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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!**

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Thank you for your attention

Questions?

youlia.kirova@curie.fr

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