Optimal management of Breast CA

- How to clinical application about the IHD-based cancer classification?

  Evidence publication and clinical trial

- Are the ten markers enough? Identify more biomarkers-

  Understand the drug resistance mechanism

→Preclinical testing of clinically applicable strategies for overcoming drugs resistance: focus on erbB2 overexpressing tumors

From Bench to Bed side:

Novel mechanisms of taxol- & Herceptin-resistance of ErbB2 overexpressing breast cancers

Clinical Significance

- ErbB2 plays a crucial role in breast cancer progression, metastasis, and therapeutic resistance. In order to combat ErbB2 mediated chemotherapeutic resistance, it is necessary to understand the precise mechanism of action. This would then allow for intervention opportunities in the pathway.
- Designing new therapeutic strategies to disrupt this pathway and , therefore, sensitize previously resistant ErbB2 over-expressing breast cancer cells to Taxol and other agents targeting mitotic phase of the cell cycle.

Trastuzumab (Herceptin) resistance

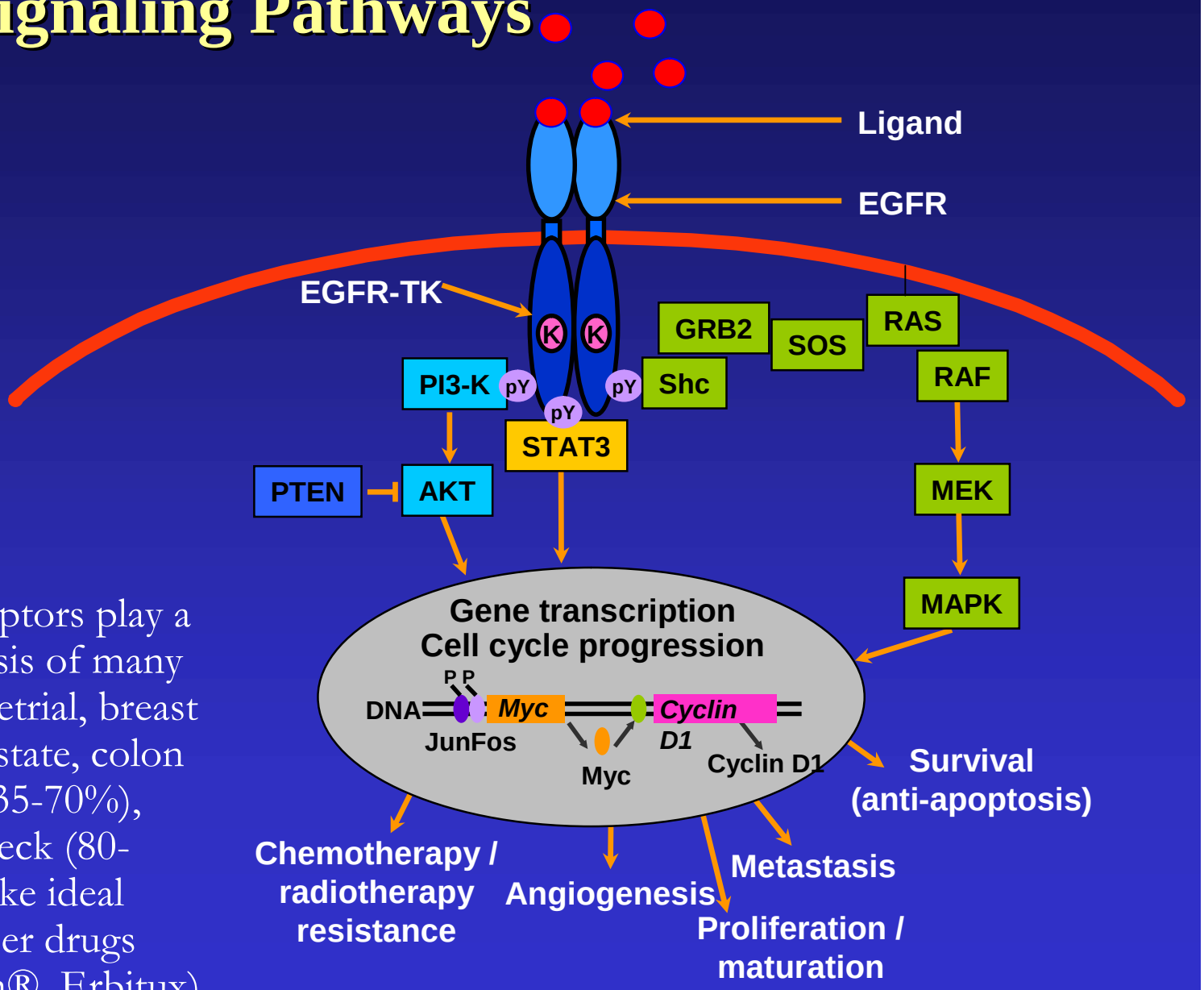
< 35% of patients with ErbB2-overexpressing metastatic breast cancer respond to trastuzumab as a single agent

~5% patients suffer from severe side effects (e.g., cardiac dysfunction)

40% patients experience other adverse effects from trastuzumab treatment

Need to identify patients who do not respond to trastuzumab
Spare them the side effects and unnecessary cost.
Factors conferring trastuzumab resistance may serve as molecular targets for overcoming trastuzumab resistance.

HER Family Proliferation and Survival Signaling Pathways

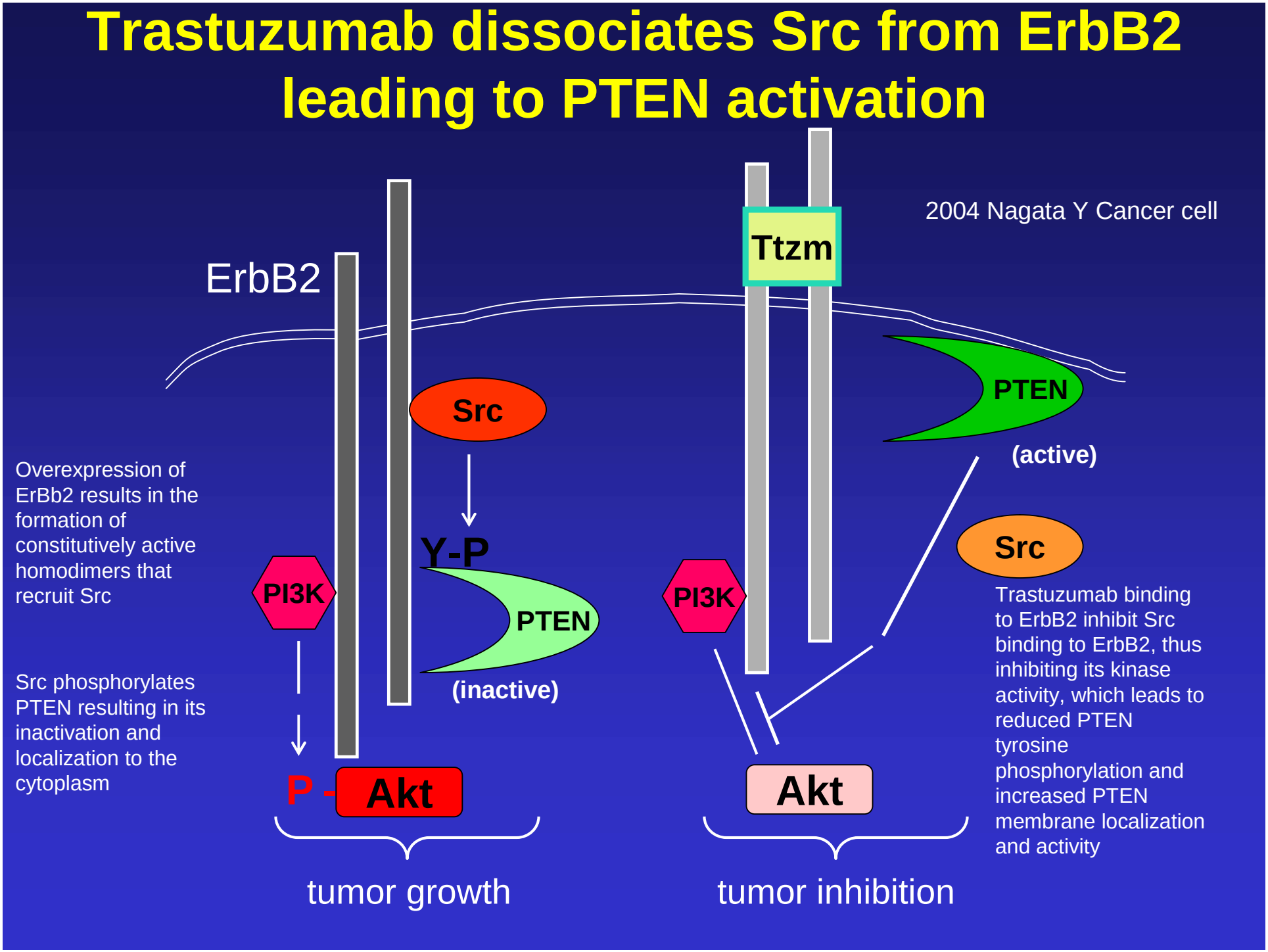


ErbB family of receptors play a key role in the genesis of many tumors (like endometrial, breast (14-91%), lung, prostate, colon (25-77%), ovarian (35-70%), bladder, head and neck (80-100%)) and also make ideal targets for anti-cancer drugs (Iressa™, Herceptin®, Erbitux)

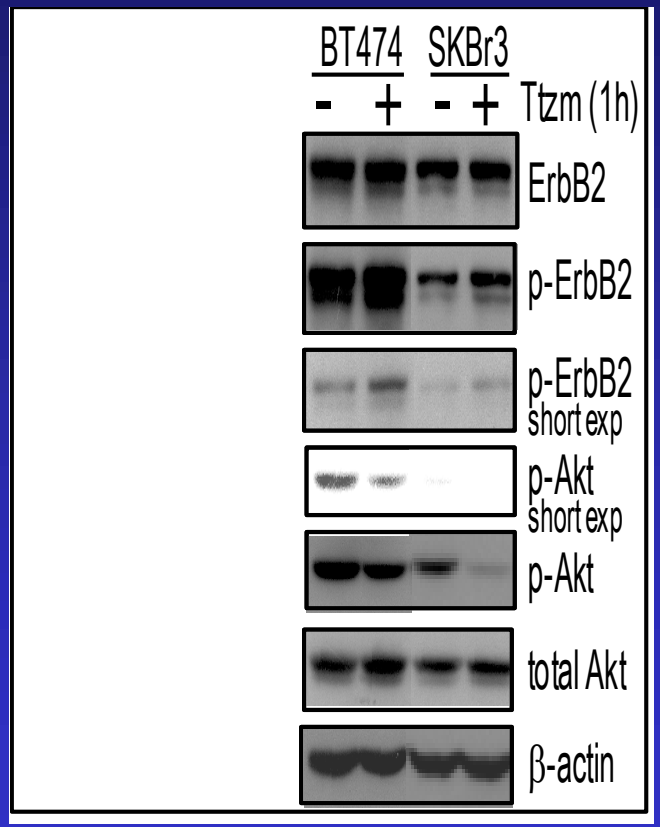
Several challenges remain concerning ErbB-targeted therapies for breast caner

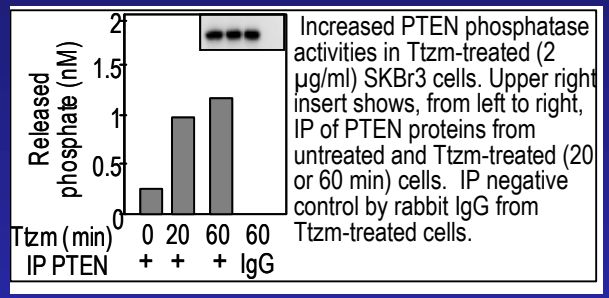
- Resistance to the only currently approved ErbB-targeted agent for beast cancer, trastuzumab (Herceptin), has been well characterized; however, the exact mechanisms for this resistance are still being explored.
- Hormone therapy resistance that develops as a result of ErbB receptor cross-talk with other signaling pathways.
- Increasing incidence of brain metastasis in patients with ErbB2-overexpressing tumors.
- Trastuzumab therapy appears to be associated with an increased incidence of cardiotoxicity.

Trastuzumab dissociates Src from ErbB2 leading to PTEN activation



PTEN activation contributes to tumor inhibition by trastuzumab, and loss of PTEN predicts trastuzumab resistance in patients





Increased PTEN phosphatase activities in Ttzm-treated (2 μg/ml) SKBr3 cells. Upper right insert shows, from left to right, IP of PTEN proteins from untreated and Ttzm-treated (20 or 60 min) cells. IP negative control by rabbit IgG from Ttzm-treated cells.

PI3K activity is the same
PTEN activity is increased

trastuzumab induces PTEN activation by increasing the translocation of PTEN from the cytoplasm to the membrane through reduction in the inhibitory tyrosine phosphorylation of PTEN

Akt activity decreases after 1h treatment before ErbB2 is downregulated

2004 Nagata Y, Dihua yu et al. Cancer cell;6:117-27

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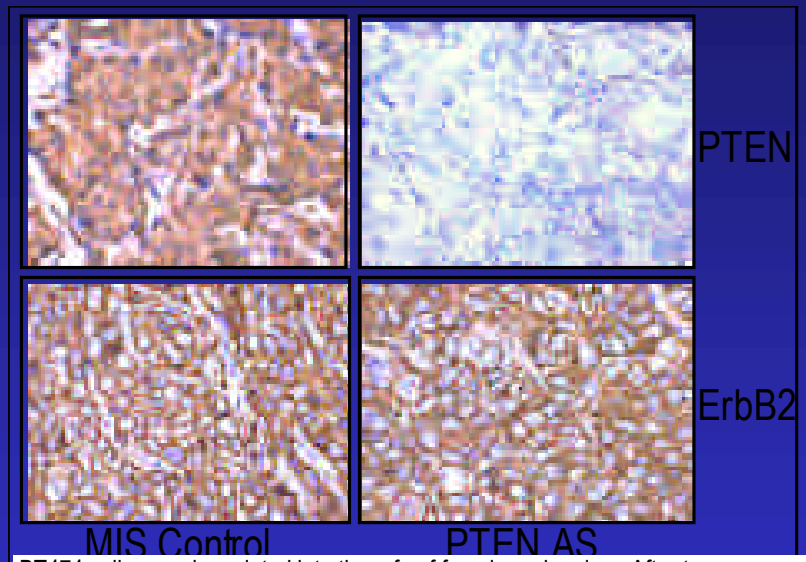
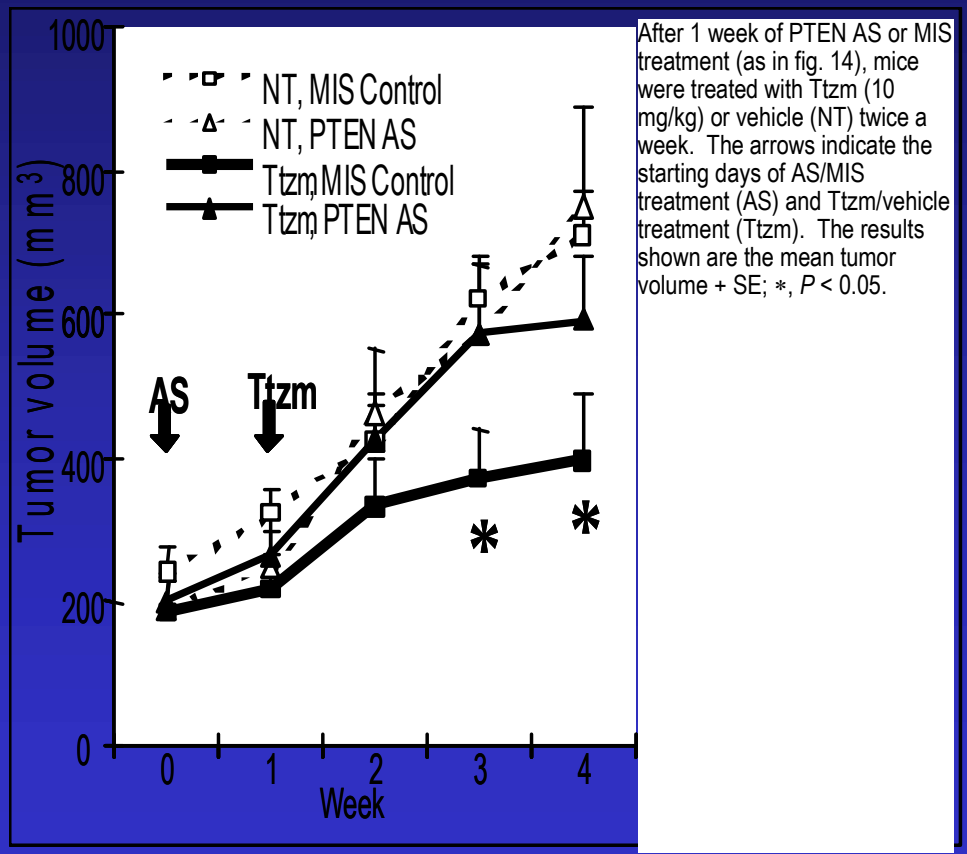


BT474 cells were inoculated into the mfp of female nude mice. After tumors reached 150mm^3, MIS or PTEN AS were injected intra-tumor (15 µg/injection, twice a week) for 1 week. Then, tumors were removed from 5 animals and stained with antibodies to PTEN and ErbB2.



After 1 week of PTEN AS or MIS treatment (as in fig. 14), mice were treated with Ttzm (10 mg/kg) or vehicle (NT) twice a week. The arrows indicate the starting days of AS/MIS treatment (AS) and Ttzm/vehicle treatment (Ttzm). The results shown are the mean tumor volume + SE; ∗, $P < 0.05$.

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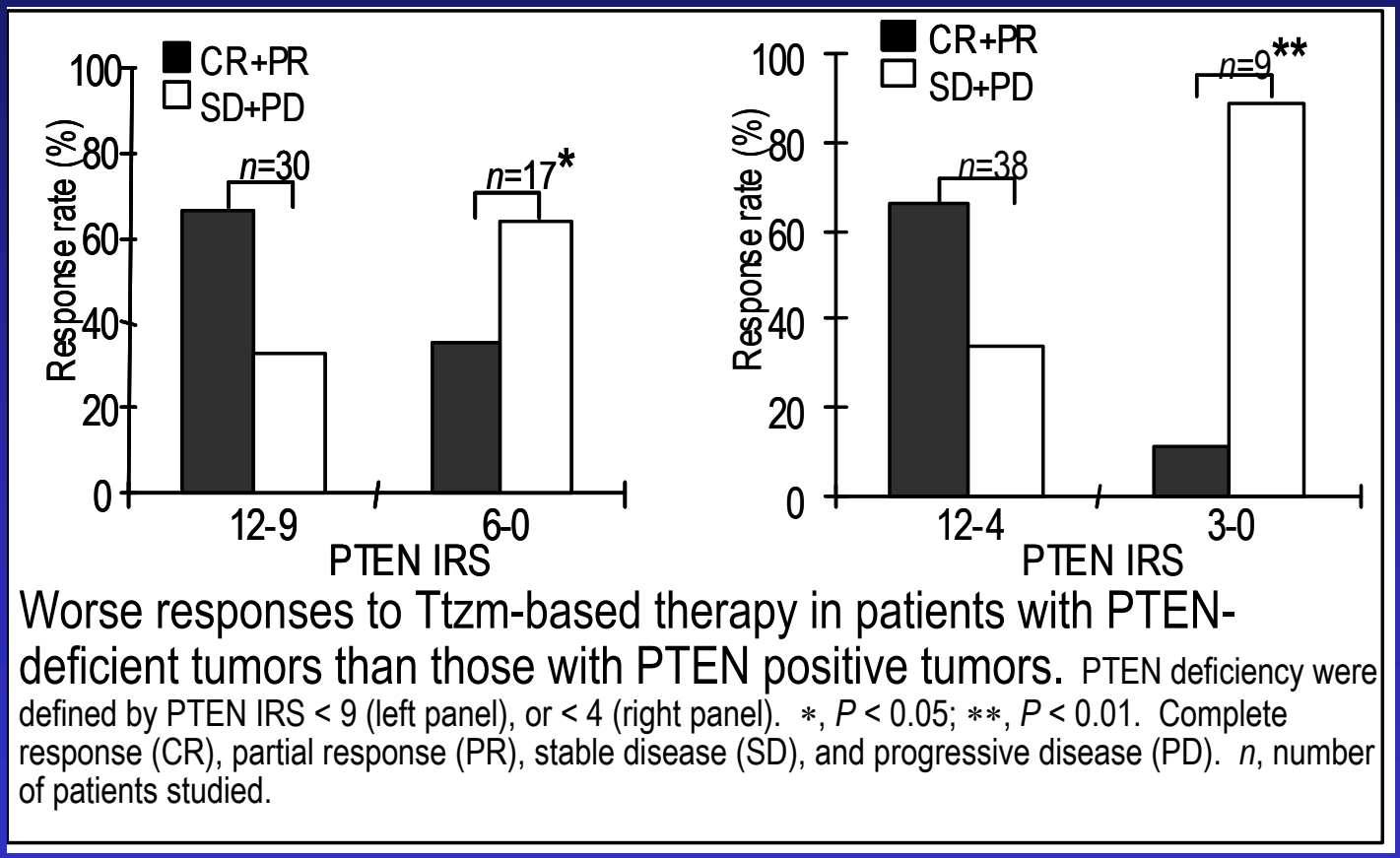

Worse responses to Ttzm-based therapy in patients with PTEN-deficient tumors than those with PTEN positive tumors. PTEN deficiency were defined by PTEN IRS < 9 (left panel), or < 4 (right panel). ∗, $P < 0.05$; ∗∗, $P < 0.01$. Complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). *n*, number of patients studied.

IRS: immunoreactive score,percentage of PTEN+cell(scored 0-4) with the PTEN staining intensity (1 to 3)

Same thing if ErbB2 levels are assessed by FISH as by IHC

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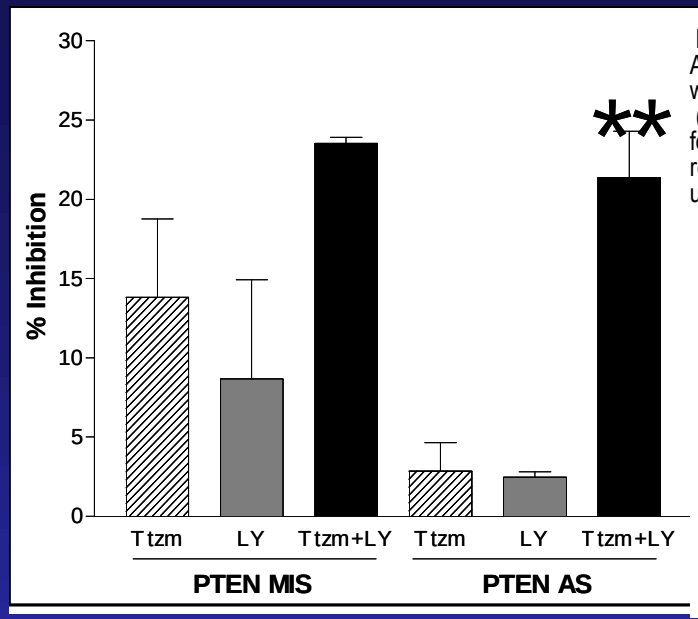
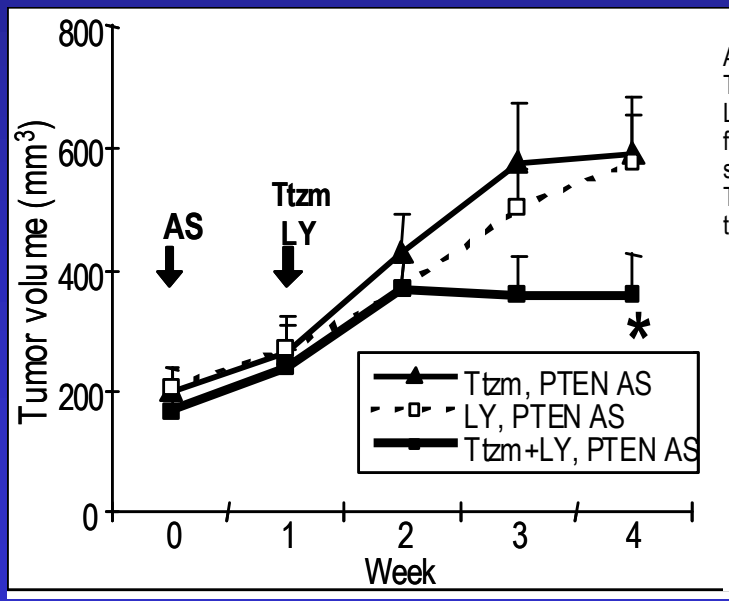


BT474 cells were treated with MIS or PTEN AS oligonucleotides . Cells were then treated with Ttzm (2 μg/ml), LY294002 (0.8 μM), or Ttzm plus LY294002 (Ttzm + LY) for 3 days. Percent (%) inhibition is % growth reduction under each treatment relative to untreated cells. **, $P < 0.01$.

PTEN activation contributes to tumor inhibition by trastuzumab, and loss of PTEN predicts trastuzumab resistance in patients



BT474 xenografts were treated with PTEN AS as in Fig. 16. Mice were treated with Ttzm (10 mg/kg) twice a week or/and LY294002 (LY, 100mg/kg) 3 times a week for 3 weeks. The arrows indicate the starting days of AS treatment (AS) and Ttzm and/or LY treatment. The results are the mean tumor volume + SE. *, $P < 0.05$.

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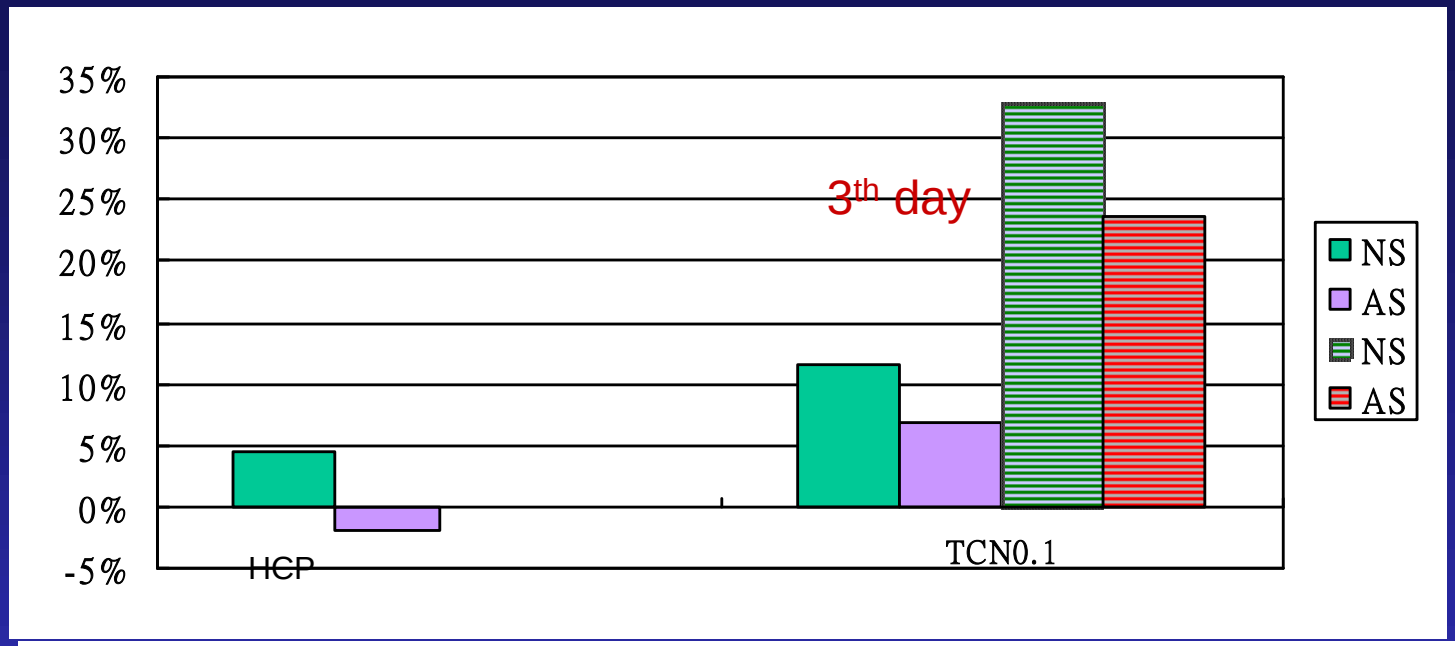
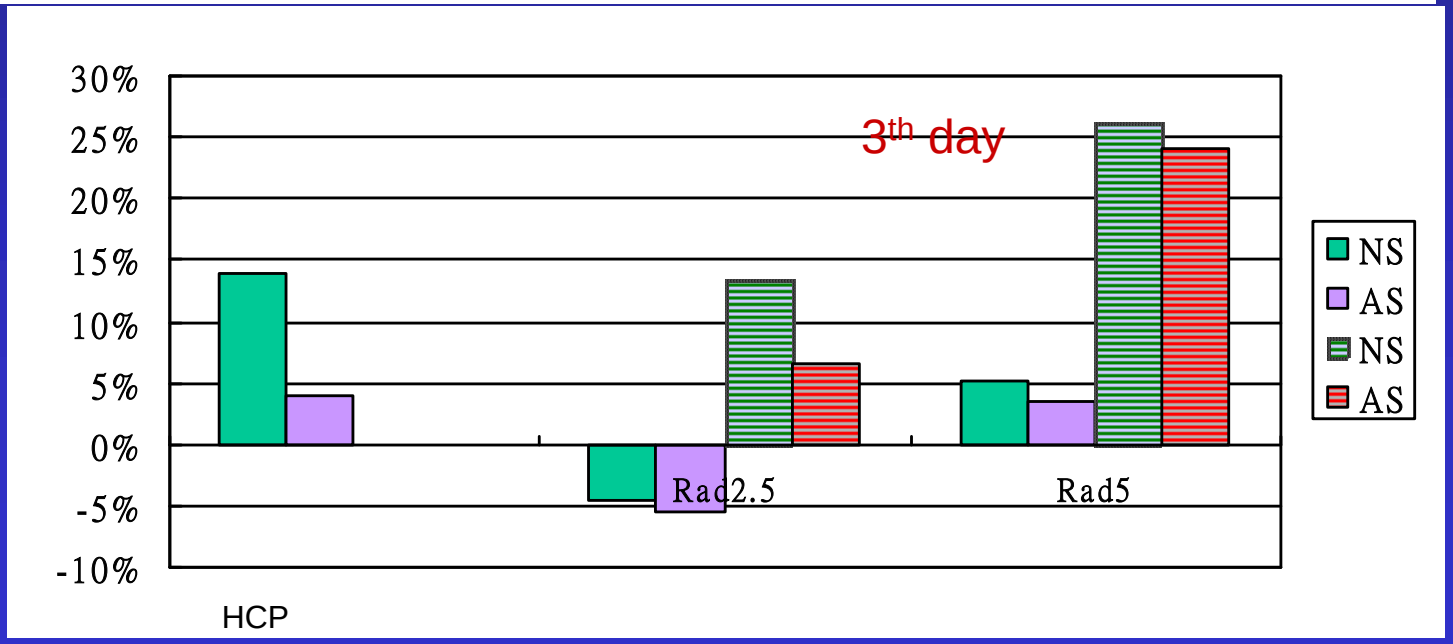
Combating Herceptin Resistance with Combination therapies of Herceptin+ TCN&RAD in SKBR3-



single

combination

%growth inhibition



Lapatinib activity in trastuzumab resistance breast cancer

- HER2+ breast cancer cell lines resistant to trastuzumab are sensitive to lapatinib[1]
- Clinical activity has been demonstrated in HER2+ breast cancer patients which refractory to trastuzumab treatment[2]

[1] Konecny et al. Cancer Res.2006;66:1630-39

[2] C.E. Geyer, EGF100151, 2006

Lapatinib monotherapy is clinically active in heavy pre-treated IBC pts (EGF103009, a phase II trial): Clinical activity and biologic predictors of response

34 patients with relapsed/refractory IBC were assigned to Cohort A (ErbB2 overexpressors: 2/3+ IHC/FISH+) or B (ErbB1 +/ErbB2 non-overexpressors)

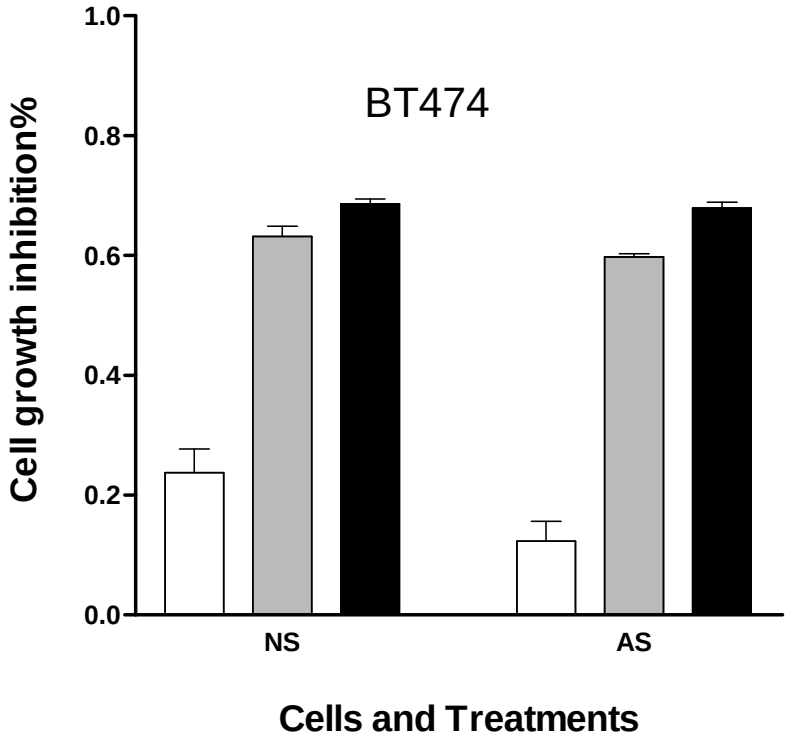
Tumor expression of ErbB2, p-ErbB2, ErbB1, p-ErbB3, IGF-IR, PTEN, ER/PR, E-cadherin, β-catenin, and Rho B/C was analyzed by quantitative IHC from a fresh, pre-treatment biopsy.

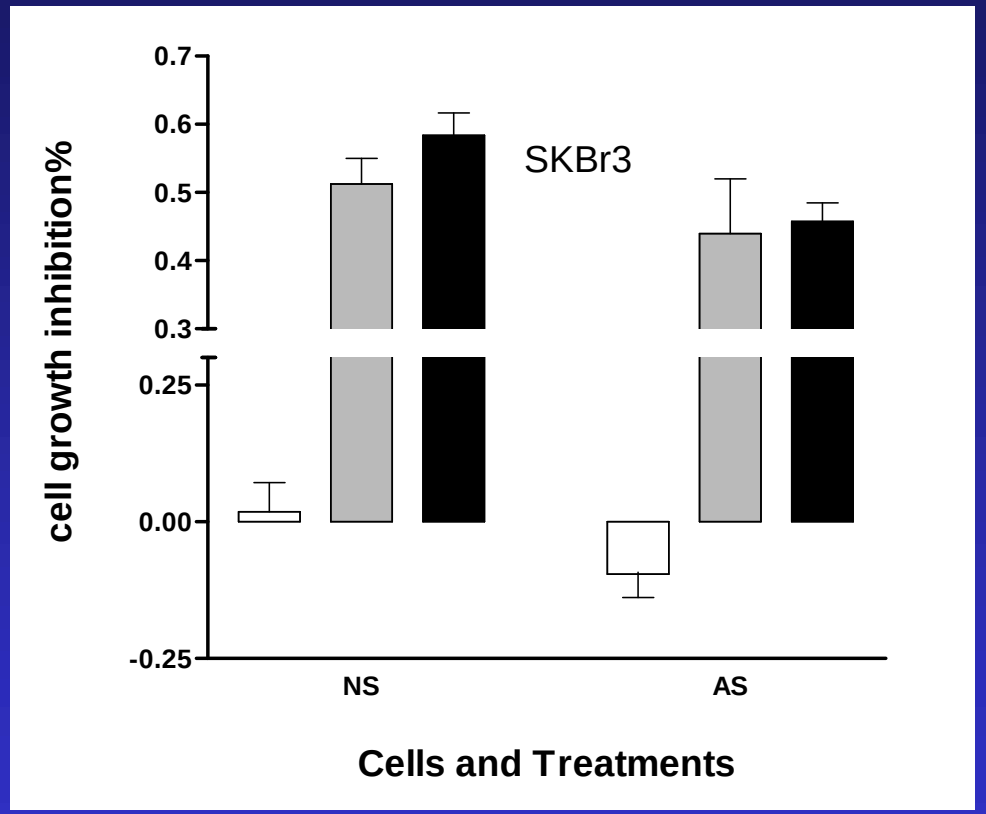
ErbB2 overexpression but not ErbB1 expression alone, predicts for sensitivity to lapatinib in IBC. High ErbB2, p-ErbB2 and IGF-IR co-expression predict for clinical response to lapatinib monotherapy

PTEN status did not affect response to lapatinib.

Spector et al. **2006 ASCO Abstract No:502**

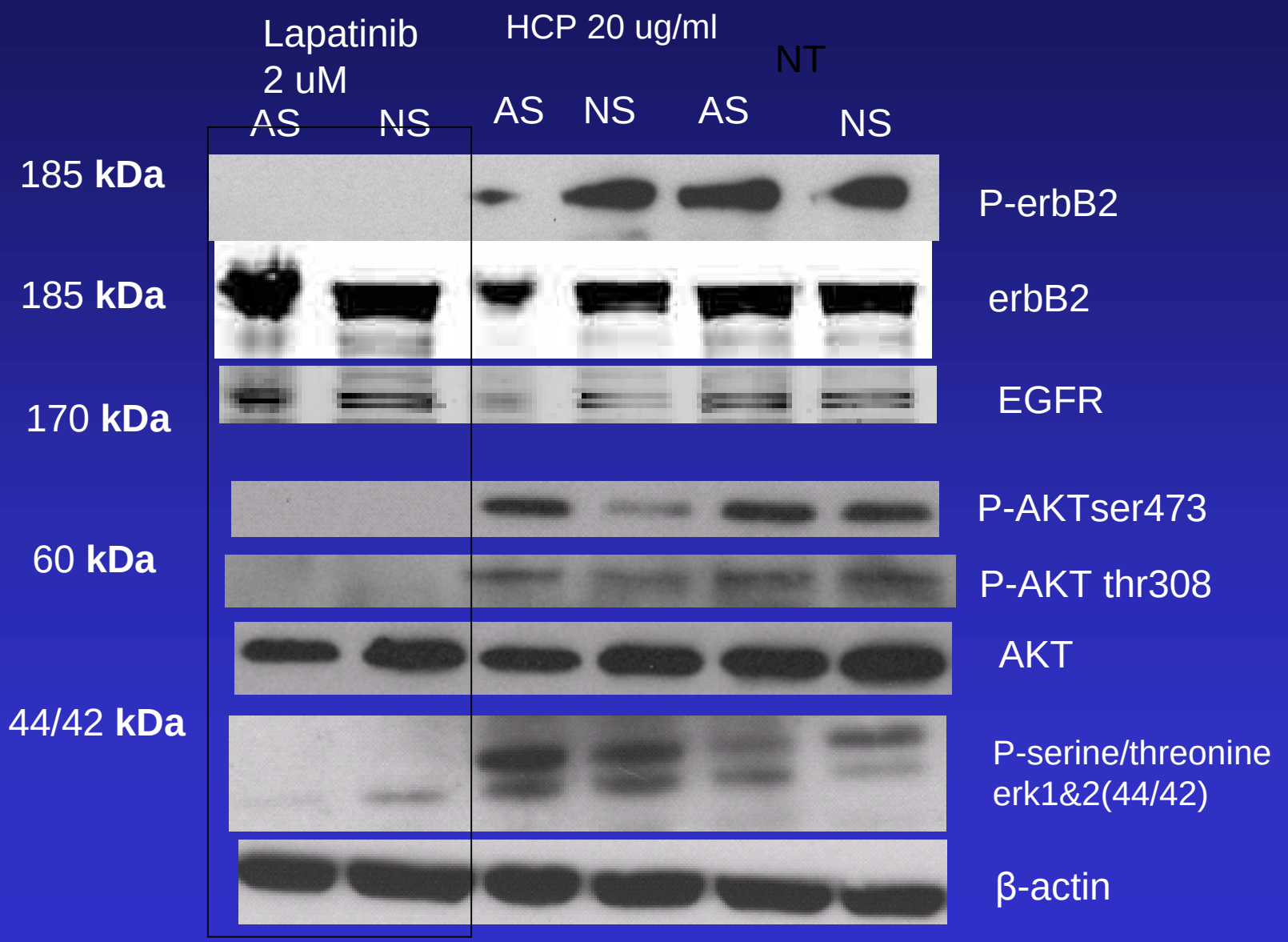
Lapatinib effectively inhibited both PTEN-normal and PTEN-deficient breast cancer cell (BT474,SKBR3)





s/p Tx 3 days

Activity of Lapatinib on EGFR,ErbB2, ERK phosphorylation (compare PTEN NS vs AS)



Areas for Future Clinical Research Using ErbB Inhibition

- Determine causes of trastuzumab resistance
- Investigate ErbB-targeted agents alone or in combination with chemotherapy
- Test the ability of small-molecule ErbB inhibitors to penetrate the CNS and to treat brain metastases
- Evaluate ErbB inhibitors in combination with endocrine agents
- Combine HER-2 targeting agents with other biologic therapies
  - Anti-HER-2 + Anti-VEGF (E2100)
- "Upstream-downstream" targeting of HER-2 pathway
  - MAb plus RTKI
  - MAb plus mTOR, MEK, AKT, Raf, etc.
- Identify accurate biomarkers predicting clinical response