



# Hormonal Aspects of Breast Cancer

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# Hormonal Aspects of Breast Cancer

## Division of Cancer Treatment and Diagnosis Research Portfolio FY01 Grants

- ◆ \$85M 241 grants breast cancer
  - \$6.5 M (7.6%) 26 breast cancer and hormones
  - \$5.8 M (6.8%) 22 breast cancer and imaging
  - \$8.3 M (9.8%) 30 breast cancer and radiation
- ◆ Clinical Trials in U10 Cooperative Groups and other sites in US and internationally
- ◆ Drug Development with NCI on site and contract resources

# Current Clinical Trials

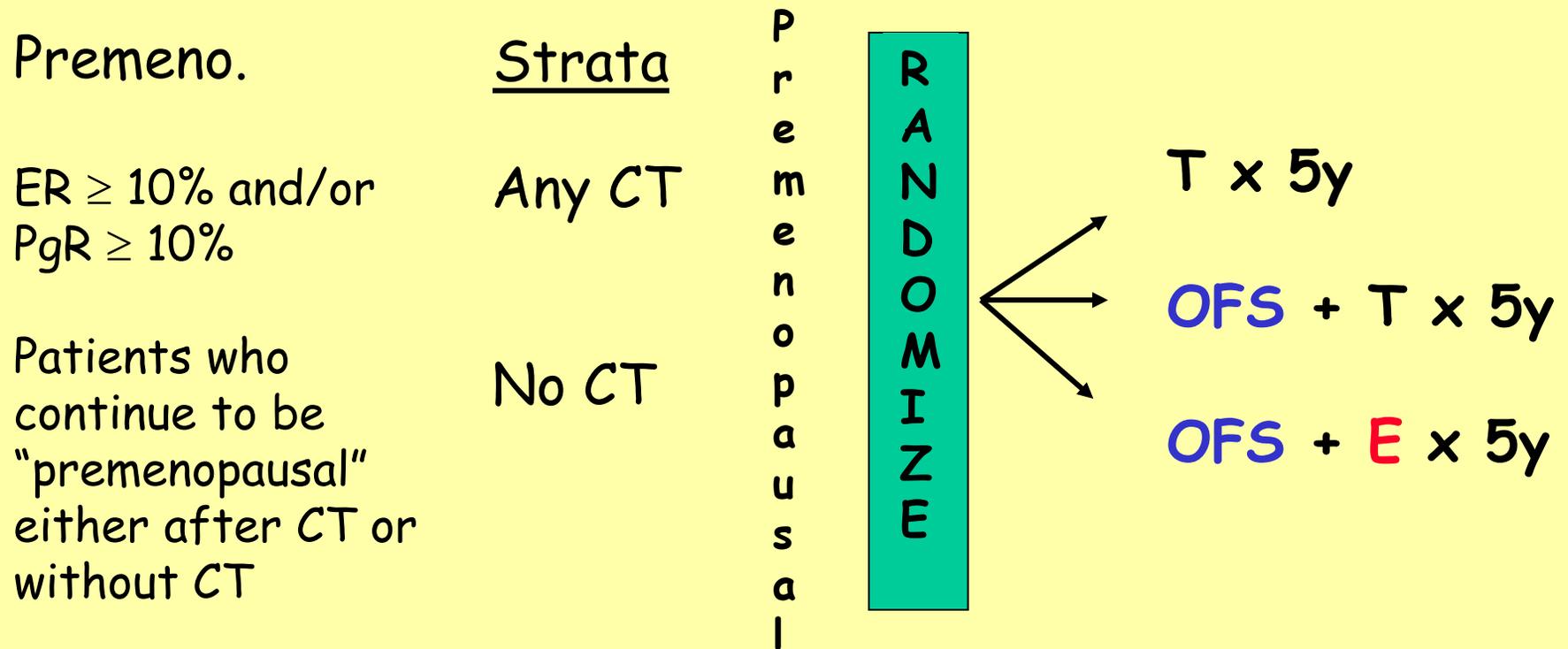
## Breast Cancer and Hormones

- ◆ North American Intergroup and Breast International Group

Anticipated Activation: Fall 2002

- Does the addition of ovarian suppression improve survival in premenopausal women receiving tamoxifen?
- Can an aromatase inhibitor substitute for tamoxifen when ovarian suppression is used in premenopausal women?

# IBCSG 24-02: SOFT (suppression of ovarian function trial)



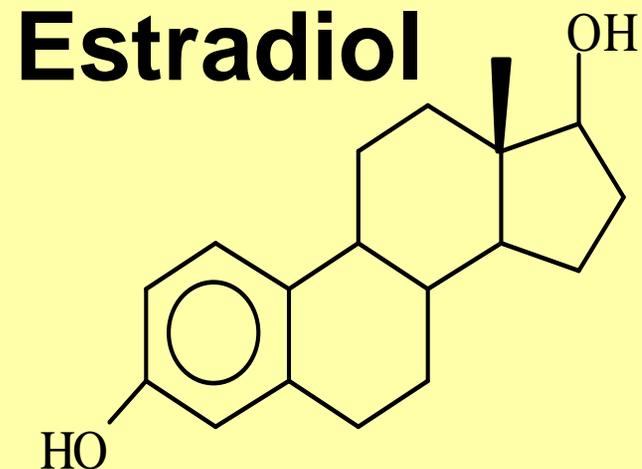
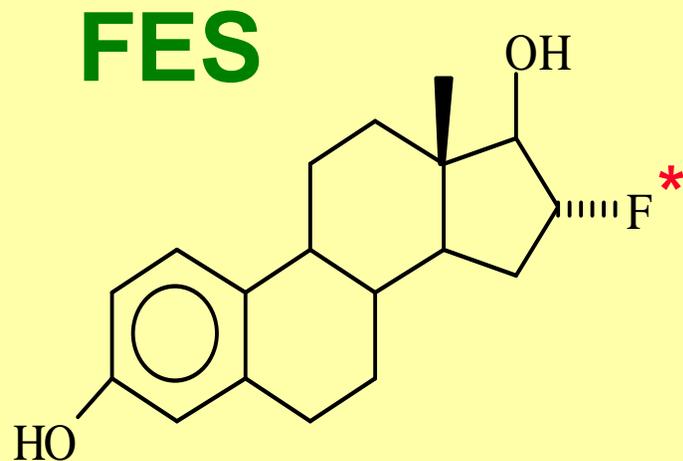
CT=chemotherapy; T=tamoxifen; E=exemestane;  
OFS=ovarian function suppression using GnRH analogue x 5 years or bilateral oophorectomy or radiation

# Role of Aromatase Inhibitors

- ◆ MA.17 – adjuvant letrozole after 5 yrs of adjuvant tamoxifen in stage 1 and 2 breast cancer
- ◆ B-33 – adjuvant exemestane after 5 years of adjuvant tamoxifen in stage 1 and 2 breast cancer
- ◆ B-35 – exemestane vs. tamoxifen in post-menopausal DCIS
- ◆ NCIC Intergroup Trial– 2 x 2 factorial: exemestane vs anastrozole and celecoxib vs. placebo in stage 1 and 2 breast cancer

# Imaging and Breast Cancer

[F-18]-Fluoroestradiol (FES):  
A Tracer for Estrogen Receptor  
Imaging



# [F-18] FES Measures the ER Status of Breast Cancer

(thick sagittal planes)

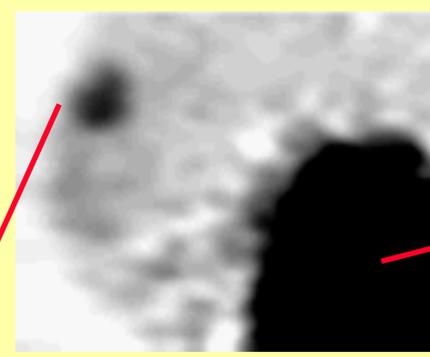
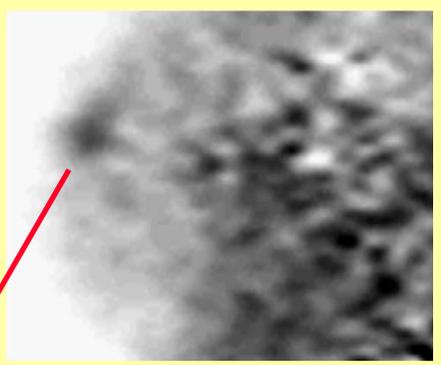
**FDG**

**FES**

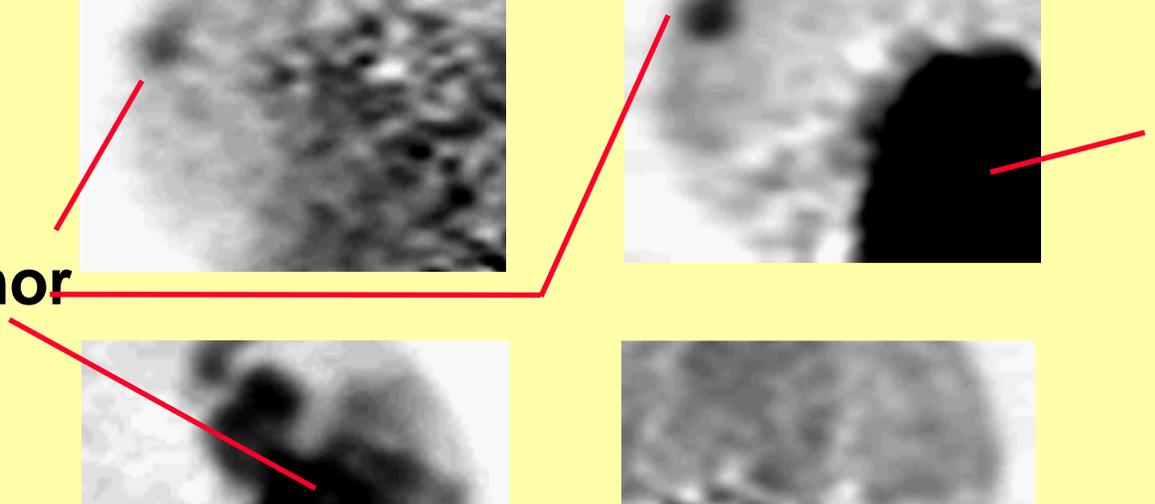
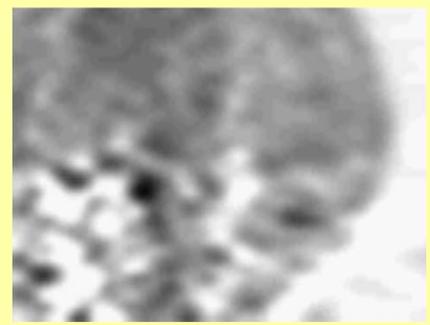
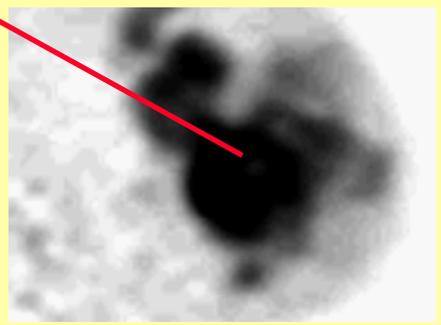
**ER+**

**Breast Tumor**

**ER-**



**Liver**



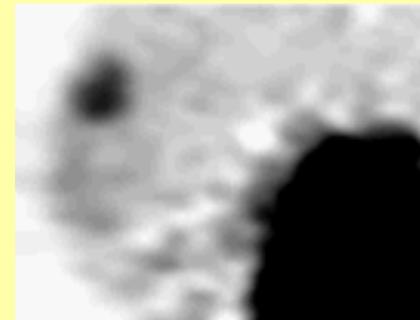
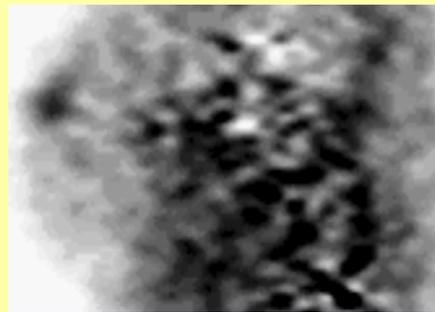
# FES Imaging Measures Estrogen Binding Antagonism by Tamoxifen

(thick sagittal planes)

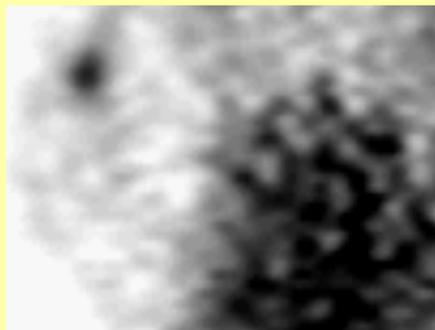
**FDG**

**FES**

**Baseline**



**2 months  
Tamoxifen**



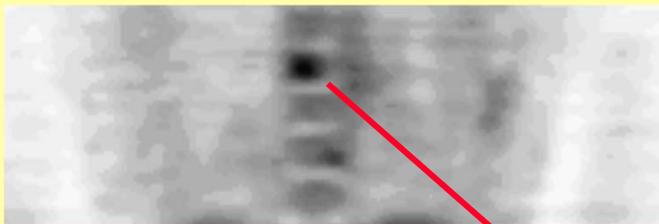
# FES Measures the Heterogeneity of ER Expression in Breast Cancer

Pt with advanced axillary disease, ER+ on biopsy

**FDG**

Primary Tumor Expresses ER Heterogenously

**FES**

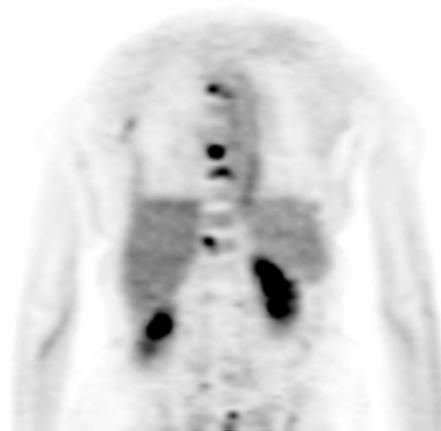


(coronal slices)

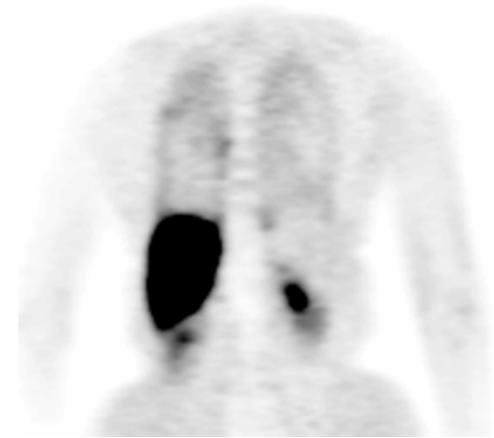
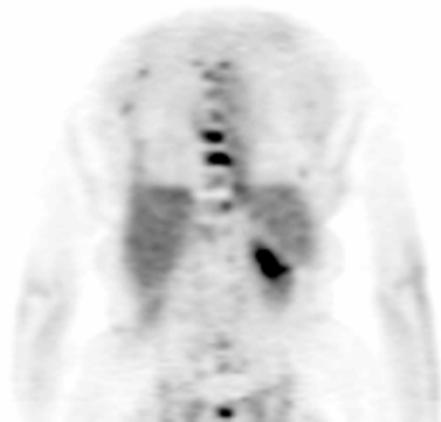
Bone Met Does Not Express ER

# Heterogeneous ER Expression in Breast Cancer: Progression of Disease That Has Lost ER Expression

## FDG PET



## FES PET



**-Multiple bone  
mets on FDG  
PET**

**-no uptake on  
FES PET**

(coronal slices)

# Drug Development and Breast Cancer

## Anti-HER2 Immunoliposomes

- ◆ Investigators are Drs. John Park and James Marks of UCSF
- ◆ For targeted delivery of drug (initially doxorubicin) to cancer cells expressing HER2/neu
- ◆ Developmental Therapeutics Program is providing:
  - GMP-grade fermentation of the liposome
  - GMP production of the anti-HER2 monoclonal antibody construct
- ◆ Sponsoring organization will perform conjugation of the final product

# Anti-HER2 Immunoliposomes

- ◆ Anti-HER2 immunoliposomes bind to and internalize in HER2-overexpressing cells in vitro, resulting in intracellular drug delivery
- ◆ Produced marked therapeutic results in four relevant xenograft models and superior antitumor efficacy over liposomal doxorubicin
- ◆ Anti-HER2 Immunoliposomes: Enhanced Efficacy Attributable to Targeted Delivery.

Clin Can Res Vol 8, April 2002, 1172-1181

# Aryl Hydrocarbon Receptor (AHR) Modulator

- ◆ Small molecule
- ◆ Potent inhibitor of carcinogen-induced breast tumor growth
- ◆ Active against ER-negative tumors
- ◆ Exhibits synergistic activity with tamoxifen
- ◆ DTP is providing:
  - Xenograft studies in relevant breast tumors
  - Early Formulation and Pharmacology

## LY353381-HCl (Lilly)

### Selective estrogen receptor modulator

- ◆ Potential for use as a preventive and as a therapeutic agent.
- ◆ Possible activity in tamoxifen-refractory patients.
- ◆ NCI will conduct clinical trials.

# 17 AAG (Kaken in Japan)

## Binds to the cellular chaperone protein hsp90

- ◆ Screened in NCI's drug screen, developed formulation, and manufactured clinical dose form Hsp90 of importance to hormonally dependent cancers:
  - Causes degradation of tyrosine kinases by the proteasome system and steroid hormone receptors.
  - Linked to maintaining the stability of a number of important targets to cancer cell biology
- ◆ Potential to down regulate signaling by hormone receptor and growth factor modulated signaling
- ◆ NCI sponsors clinical trials in US and in collaboration with CR-UK in the UK

# Molecular Target Drug Discovery Grant – Selective Inhibitors of SRC Family Kinases

SRC kinases couple the EGF receptor and HER2/Neu to Stat activation in breast cancer and interact with BCR-Abl in CML.

- ◆ Dr. Thomas Smithgall, University of Pittsburgh  
Funded FY 2001
- ◆ Activities: to develop a fluorescent SH2-substrate capture assay for SRC tyrosine kinase activity; to develop a high-content cell-based screen for SRC-dependent signaling .
- ◆ Goal – to identify novel inhibitors that target specific SRC kinase isoforms and oncogenic signaling pathways.

# Diagnosics and Breast Cancer

- ◆ An alternate transcript of the Her-2 gene encodes Herstatin, a molecule consisting of the extracellular domain of the Her-2 protein and a novel C-terminus
- ◆ Herstatin is a secreted protein that interacts with the receptor for epidermal growth factor (EGF) and acts as a natural autoinhibitor of signaling by both Her-2 and EGF

Doherty et al. (1999) Proc. Natl. Acad. Sci. USA 96:10869  
Justman and Clinton (2002) J. Biol. Chem. 277:20618

# Diagnosics and Breast Cancer

- ◆ Current immunohistochemical assays for Her-2 measure the quantity of protein present in a tumor
- ◆ Assays that measure protein function, such as phosphorylation, may be more informative

Thor et al. (1999) J. Clinical Oncol. 18:3230

- ◆ A somatic mutation in the estrogen receptor (ER) gene that increases the responsiveness of ER to estrogen is common in premalignant breast lesions
- ◆ This mutation may promote or accelerate the development of cancer

Fuqua et al. (2000) Cancer Research 60:4026

- ◆ Acquired resistance to tamoxifen is associated with increased AP-1 binding to DNA and increased activity of c-Jun NH2-terminal kinase in breast tumor cells. These observations suggest strategies to predict and overcome tamoxifen-resistance

Johnston et al. (1999) Clin. Cancer Res. 5:251