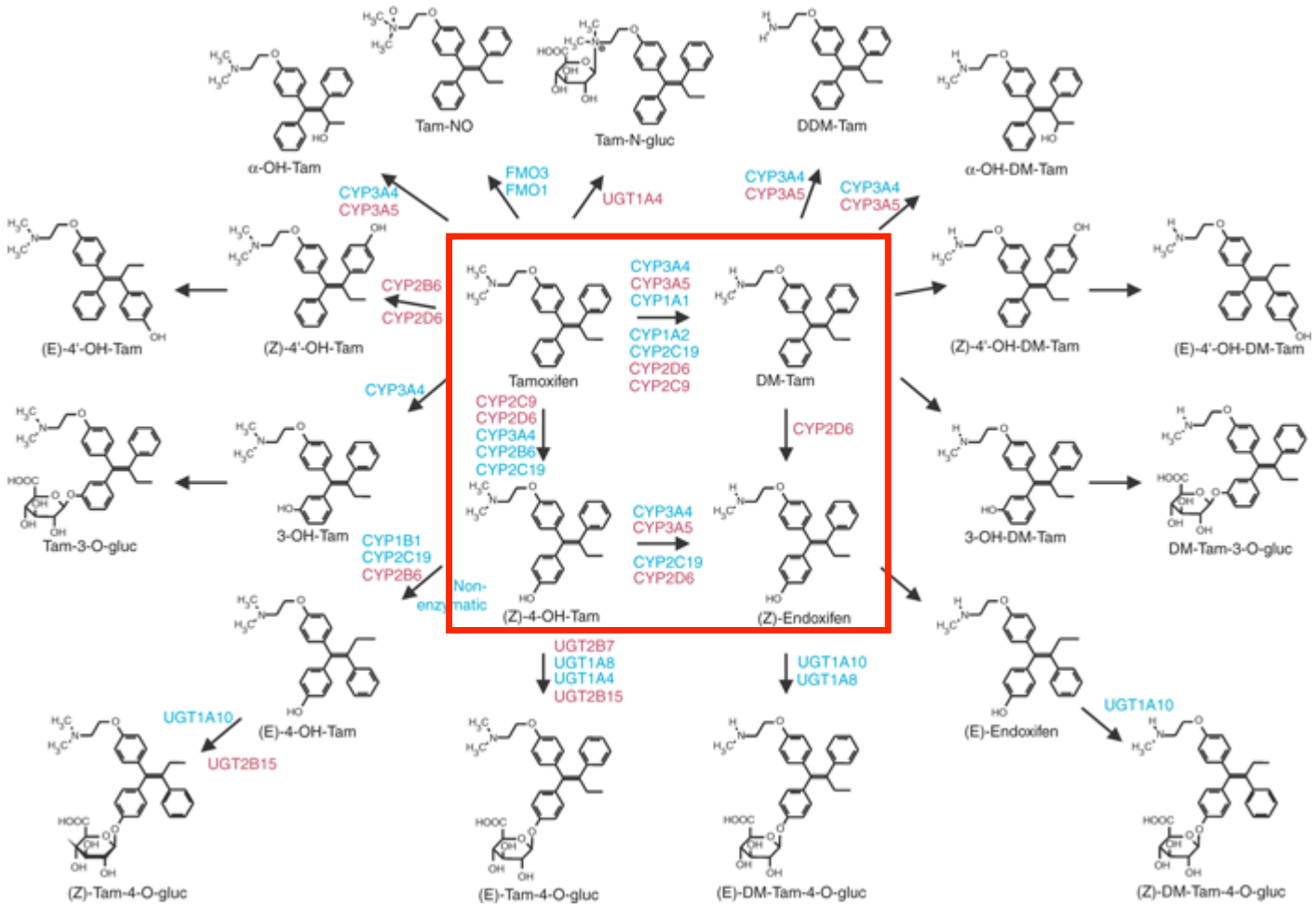
A011203: A Randomized Phase II Trial of Tamoxifen and Z-endoxifen in Postmenopausal Women with Metastatic ER+, HER2- Breast Cancer

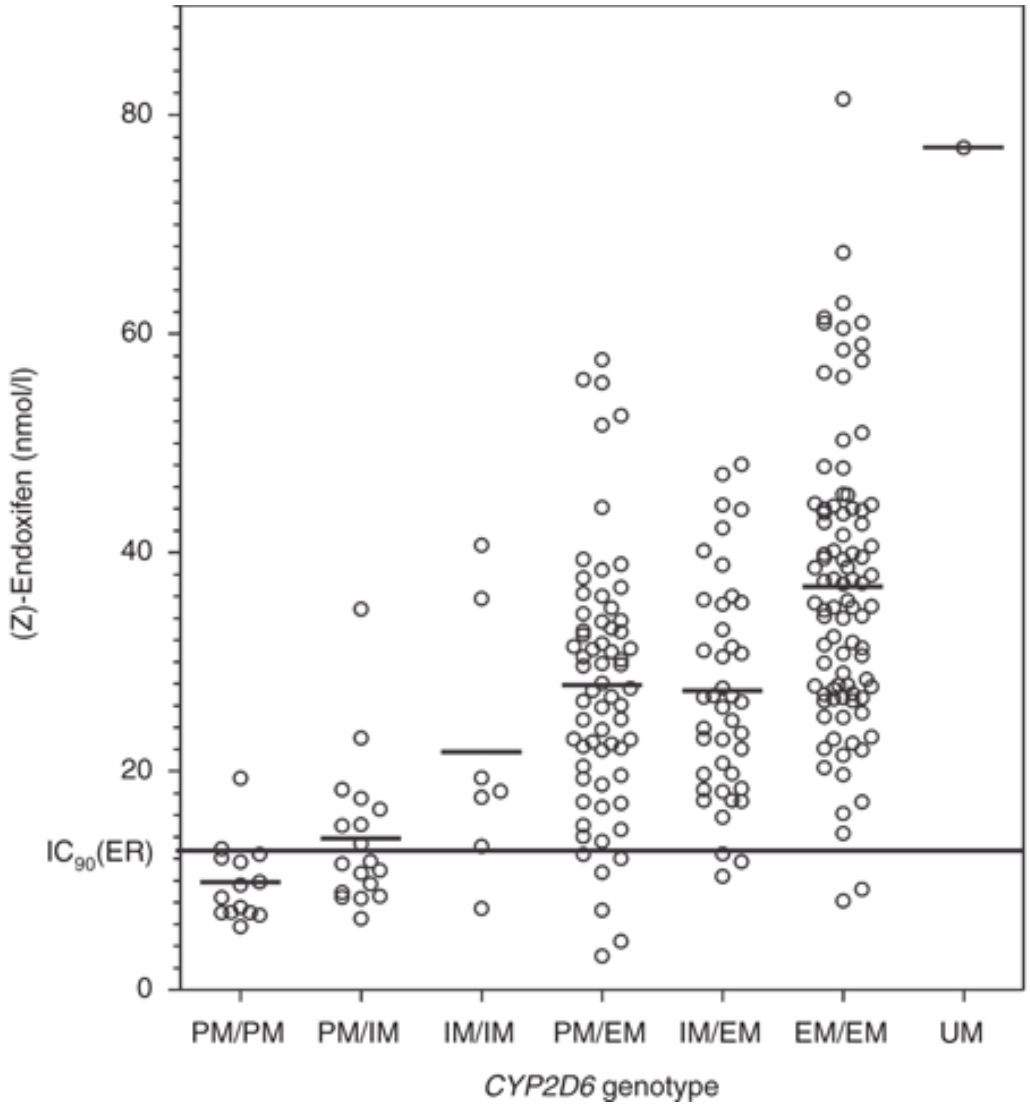
Matthew P. Goetz, MD

Tamoxifen Biotransformation



Murdter et al. Clin Phar Ther 2011

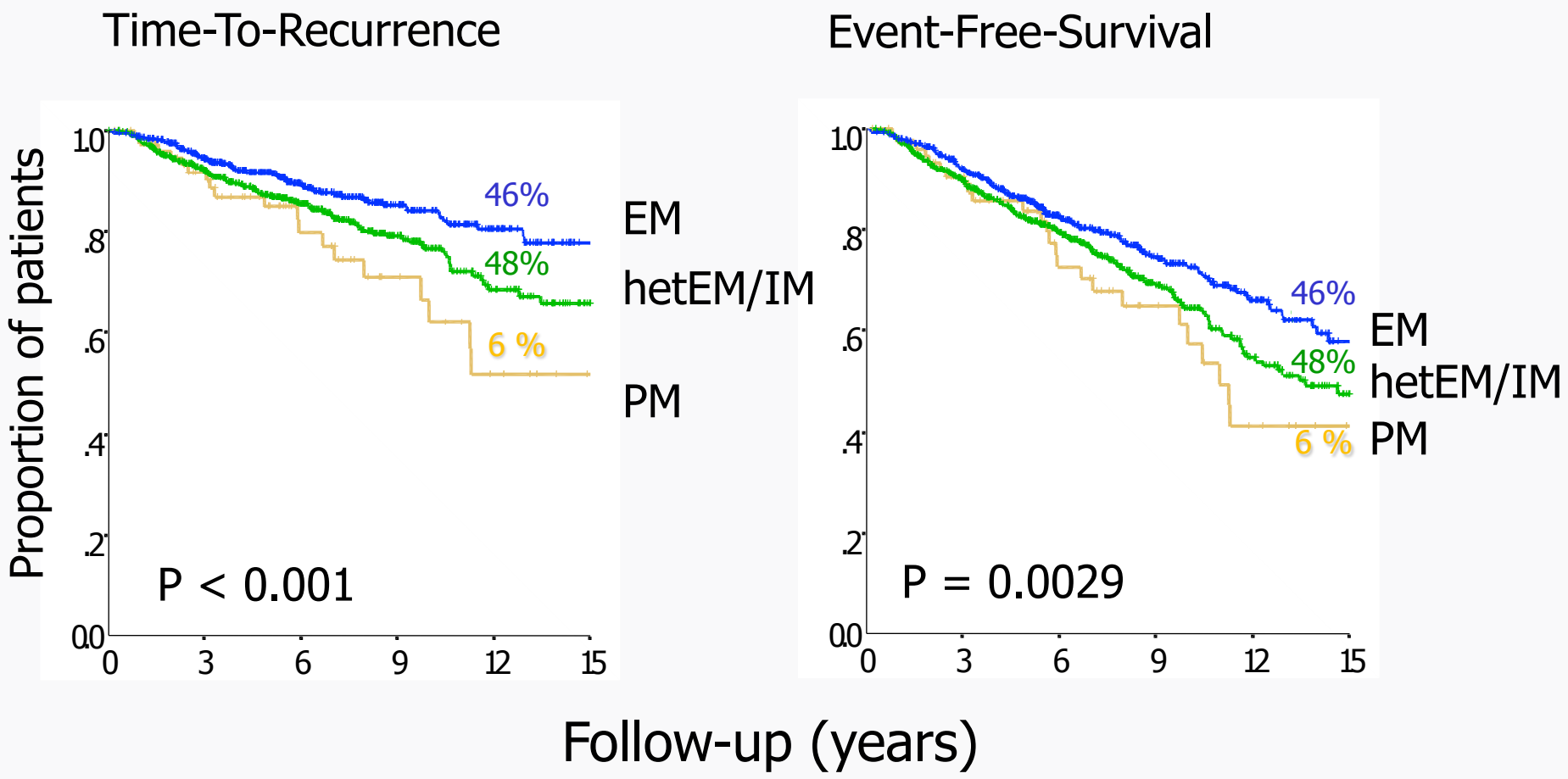
Endoxifen Concentrations and *CYP2D6* Genotype



Murdter et al. Clin Phar Ther 2011

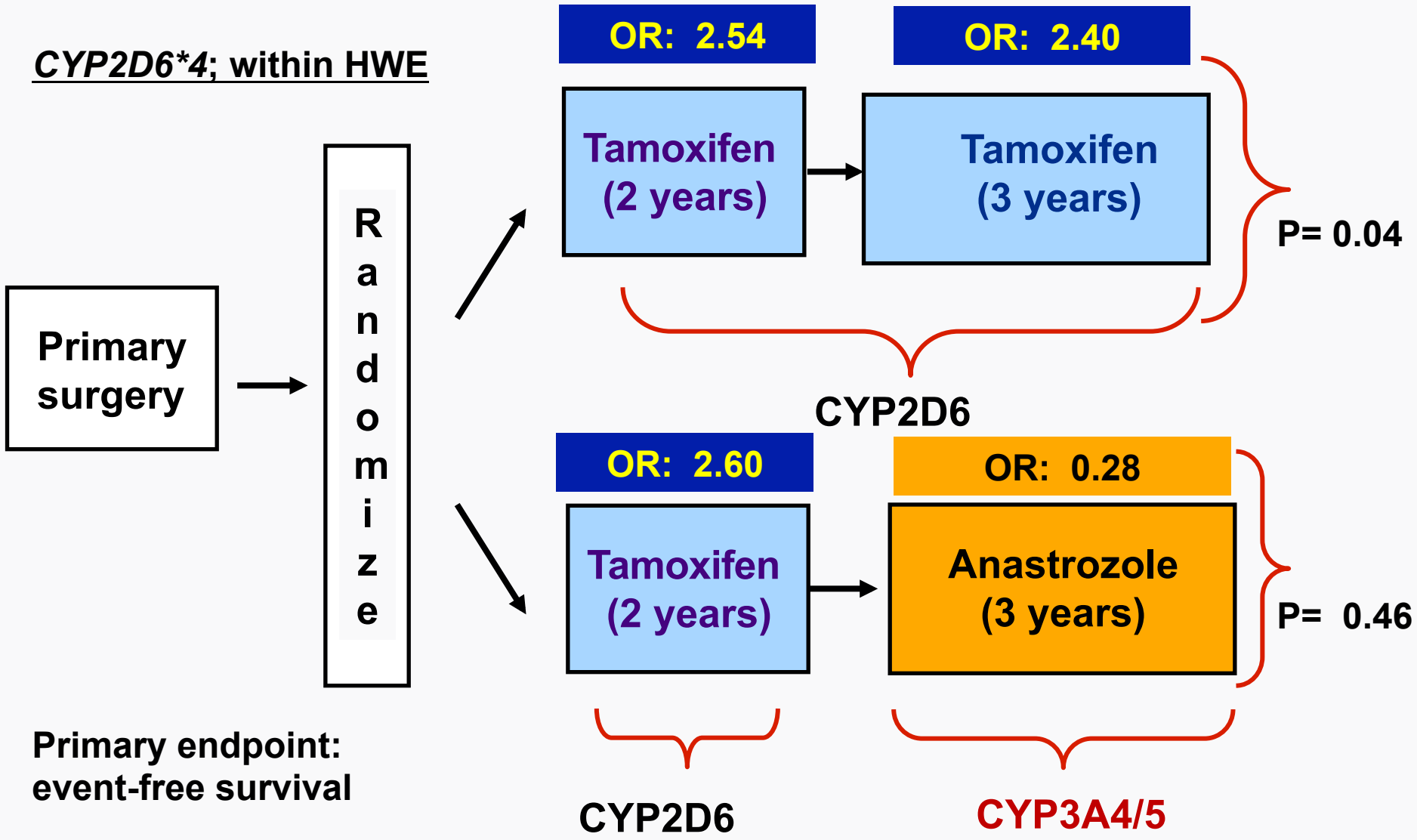
CYP2D6 Polymorphism is a Determinant of Tamoxifen Response in Early Breast Cancer

Number of patients: 1325



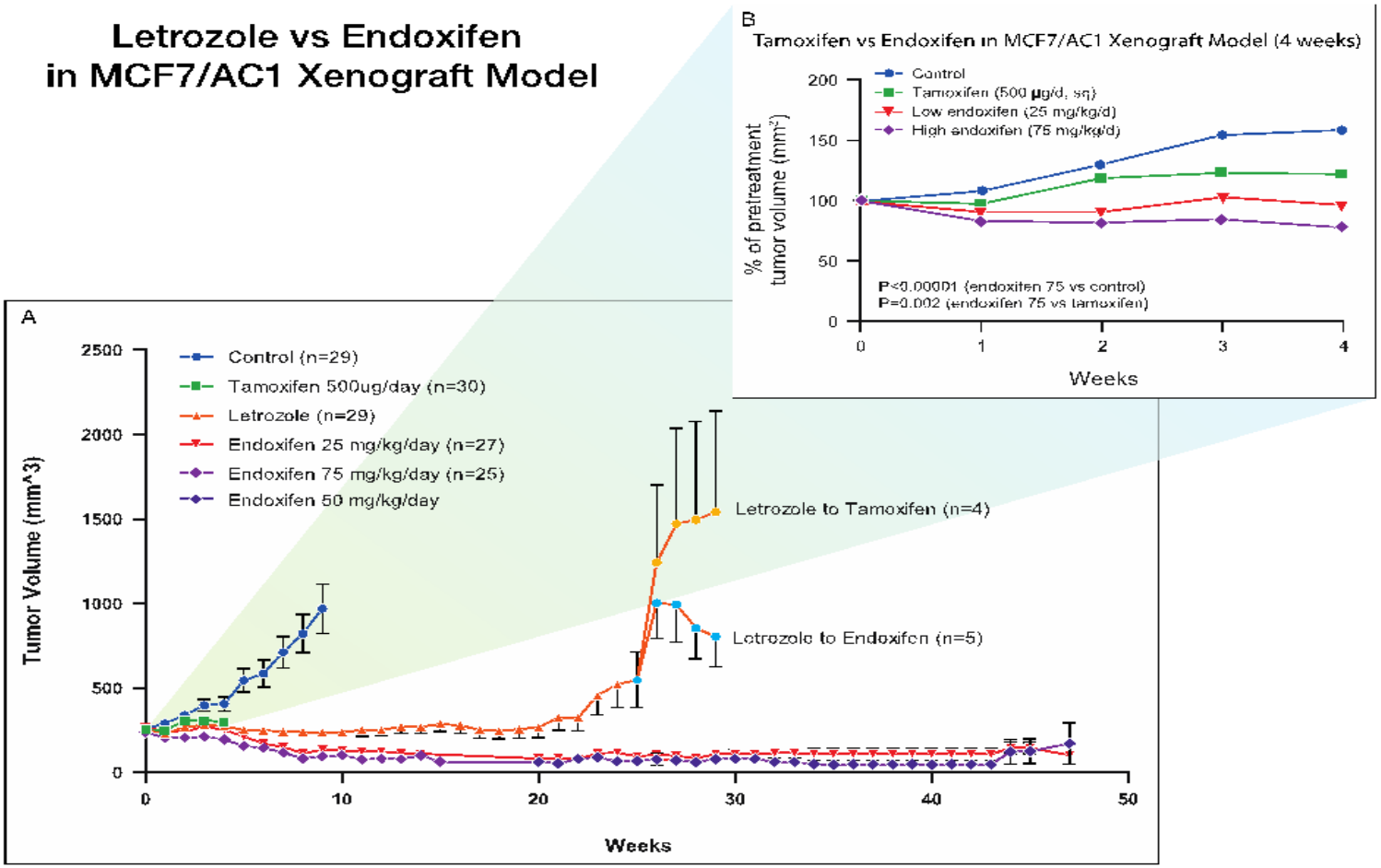
Schroth, Goetz *et al.*, JAMA 2009

ABCSG Trial 8: CYP2D6 PM/PM vs EM/EM



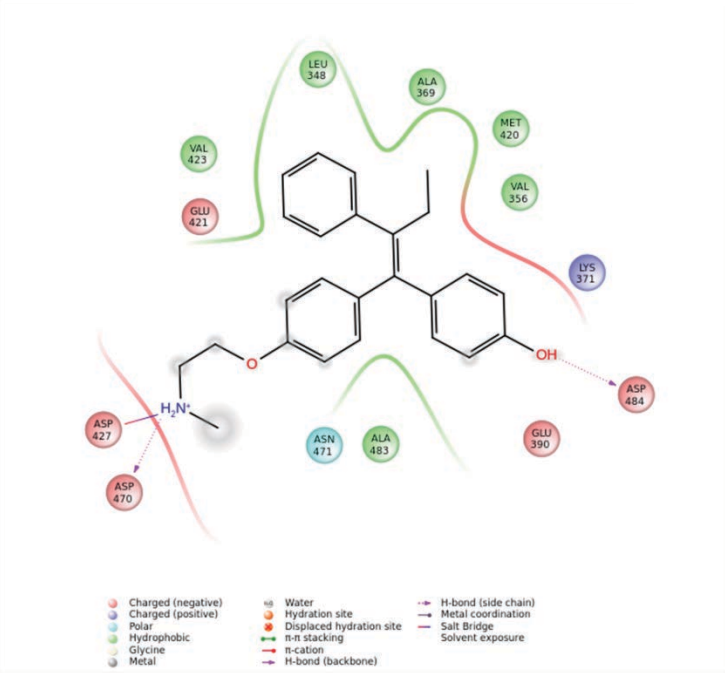
Goetz, M. P. et al. (2013). Clinical cancer research : **19**(2): 500-507.

Endoxifen and Letrozole in MCF7/AC1 Xenografts

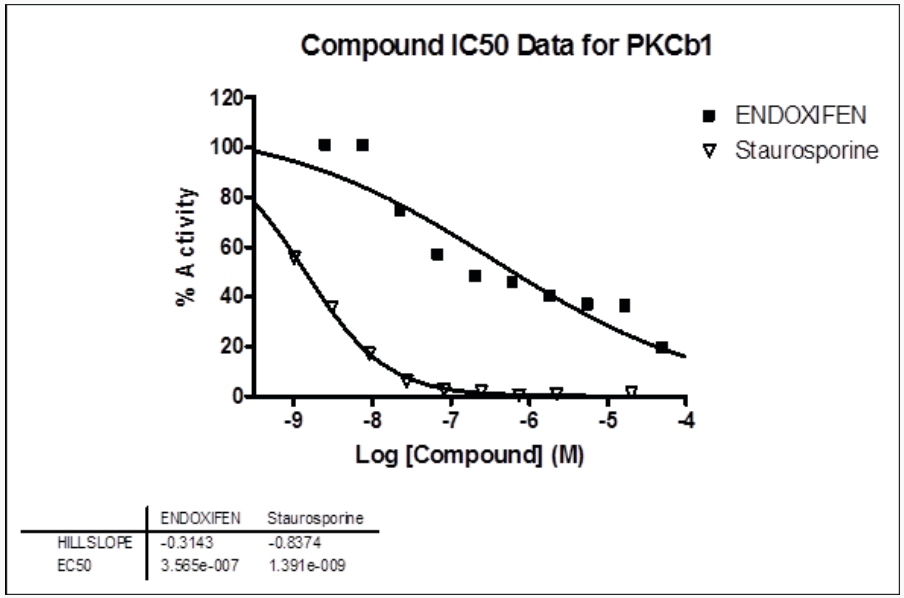


Goetz et al.

Endoxifen Docking, Binding and Effects on PKCβ1 Kinase Activity



Docking model of PKC beta with endoxifen. Several H-Bonds formed between endoxifen and Asp427, Asp470 and Asp484 of PKC beta at the ATP binding pocket. Endoxifen also formed hydrophobic interactions with PKC beta with Val356, Met420, Ala369 and Leu348.



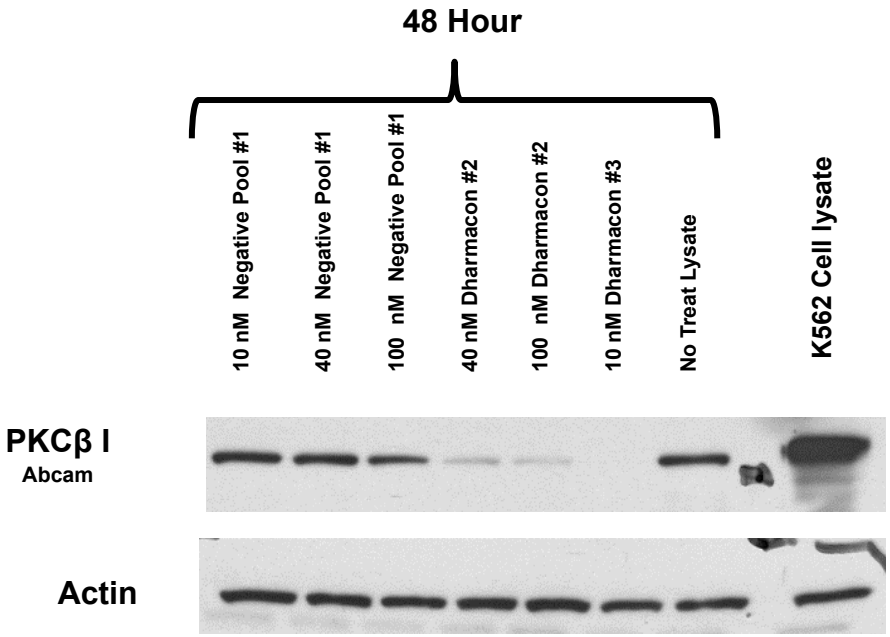
	ENDOXIFEN	Staurosporine
HILLSLOPE	-0.3143	-0.8374
EC50	3.565e-007	1.391e-009

Enzyme screen (IC50) demonstrates endoxifen inhibits PKCβ1 (350 nM) (tamoxifen 5 micromolar).

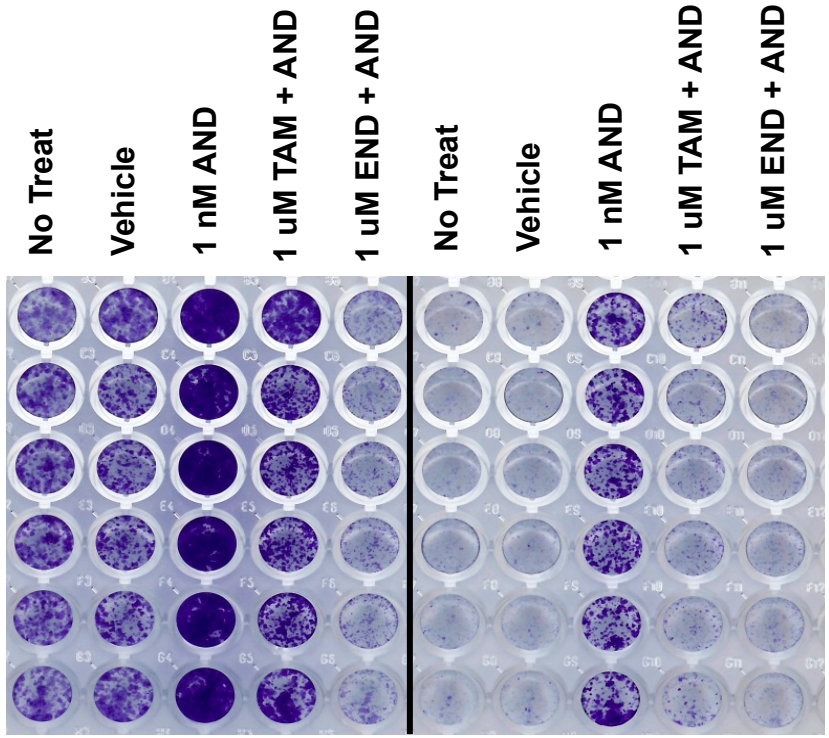
	Endoxifen	Tamoxifen	N-Desmethyl	4-Hydroxytam
PKC Beta 1	0.1 uM	2.06 uM	7.29 uM	2.078 uM

Goetz et al.

Anti-proliferative effects of PKCβ1 Knockdown and SERMS in MCF7 ER+ cell line:



Proliferation



Endoxifen Pre-Clinical Summary

- **Endoxifen results in greater antitumor activity compared to tamoxifen and letrozole both *in vitro* and *in vivo***
- **Endoxifen inhibits PKCβ1 with an IC50 of 350 nM (compared to 5 micromolar of tamoxifen)**
- **Knockdown of PKCβ1 inhibits proliferation, both in the absence/presence of estrogen and SERMs**
- **Is the activity of Endoxifen in MBC associated with it's effects on PKCβ1???**

San Antonio Breast Cancer Symposium, December 8-12, 2015

Final results of a First-in-human Phase I Study of the Tamoxifen (TAM) Metabolite, Z-Endoxifen Hydrochloride (Z-Endx) in Women with Aromatase Inhibitor (AI) Refractory Metastatic Breast Cancer (MBC) (NCT01327781)

Matthew P. Goetz; Vera J Suman; Joel M. Reid; Don W. Northfelt; Michael A. Mahr; Travis Dockter; Mary Kuffel; Andrew T. Ralya; Sarah Burhow; Stephanie Safgren; Renee McGovern; Jerry Collins; Howard Streicher; Zachary R. Chalmers; Garrett Frampton; John R. Hawse; Tufia Haddad; Charles Erlichman; Matthew M. Ames; and James N. Ingle

Mayo Clinic, Rochester, MN and Scottsdale, AZ; Foundation Medicine, Cambridge, MA

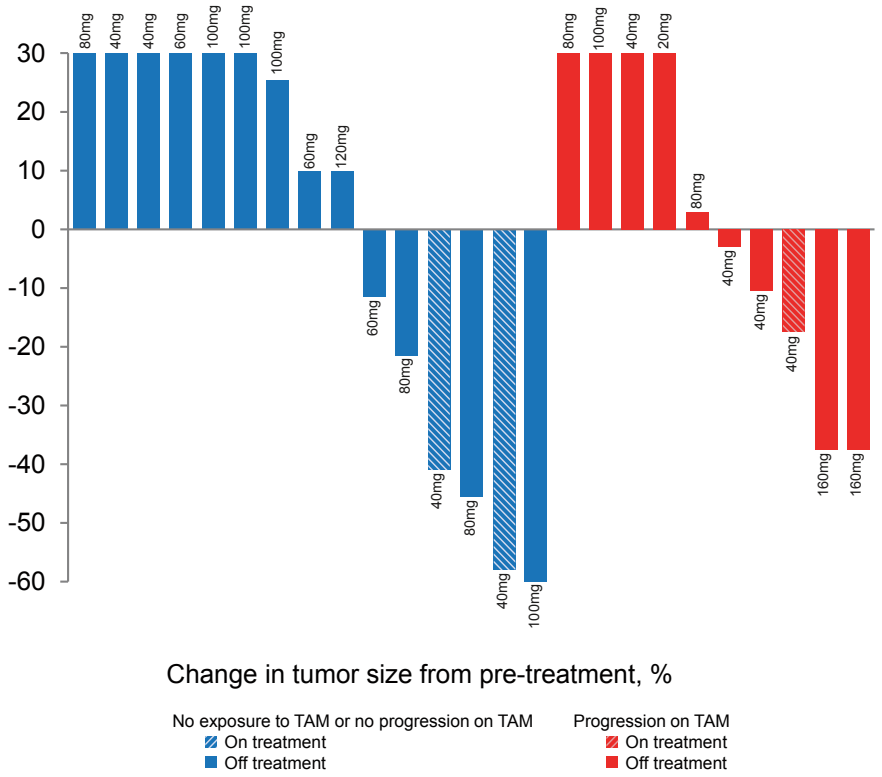
Goetz SABC 2015

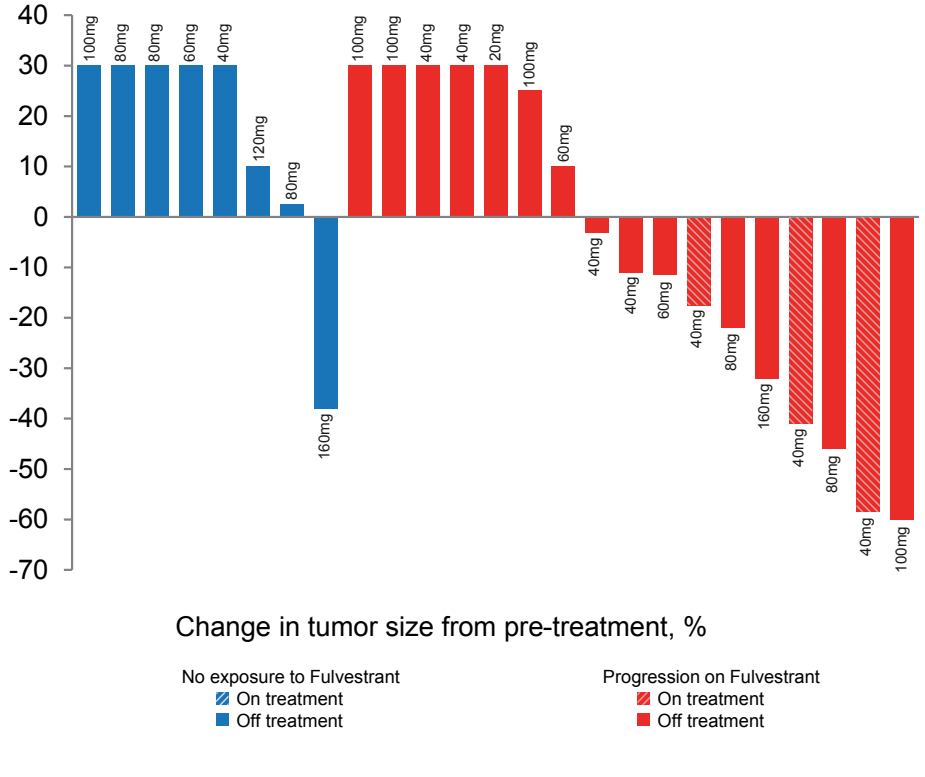
Endoxifen PK Summary

- 40 and 80 mg/day: C_{min}: 248 and 602 ng/ml respectively
- Compare to tamoxifen 20 mg/day: endoxifen conc: range 2-25 ng/ml
- $T_{1/2}$ of 50 hours
- 3 fold accumulation over 28 days, but no further accumulation at 2 and 6 months

Goetz SABC 2015

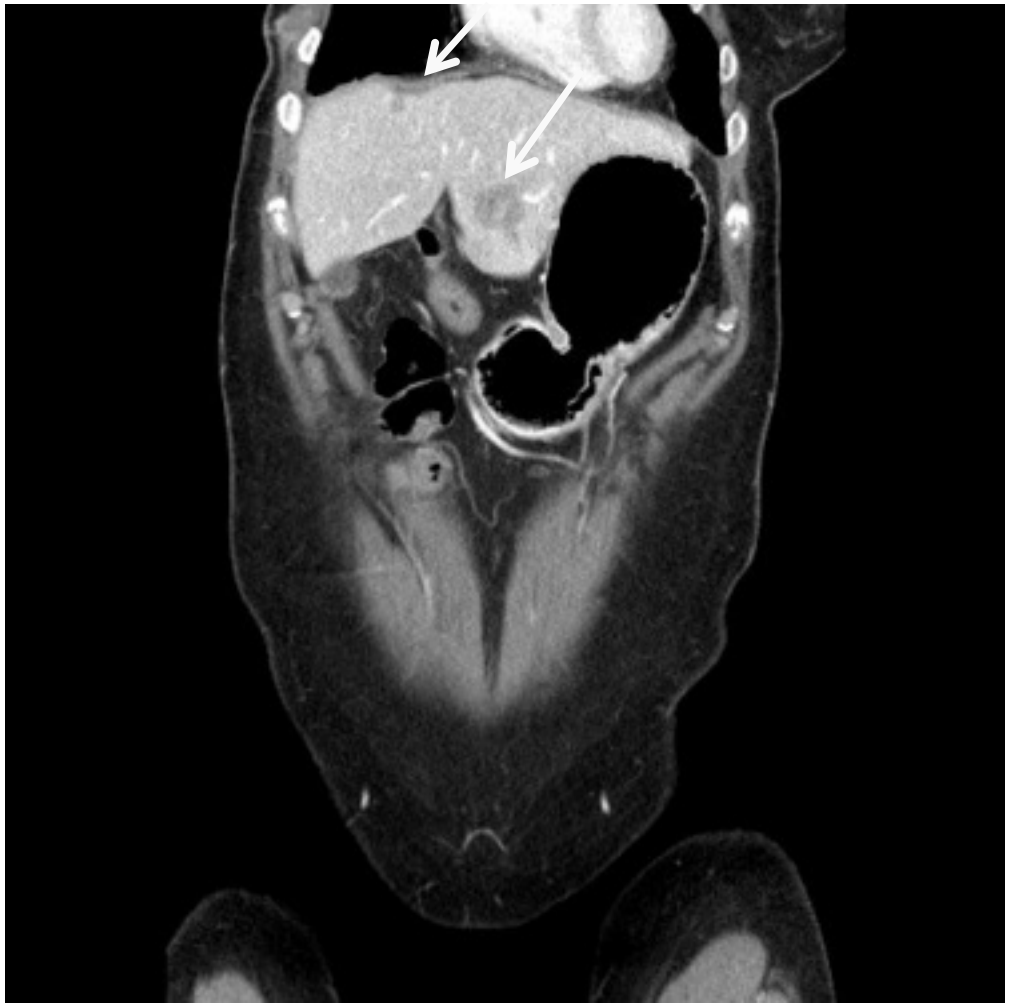
AI Refractory Breast Cancer: Endoxifen Responses according to progression on Tamoxifen (A) and Fulvestrant (B)

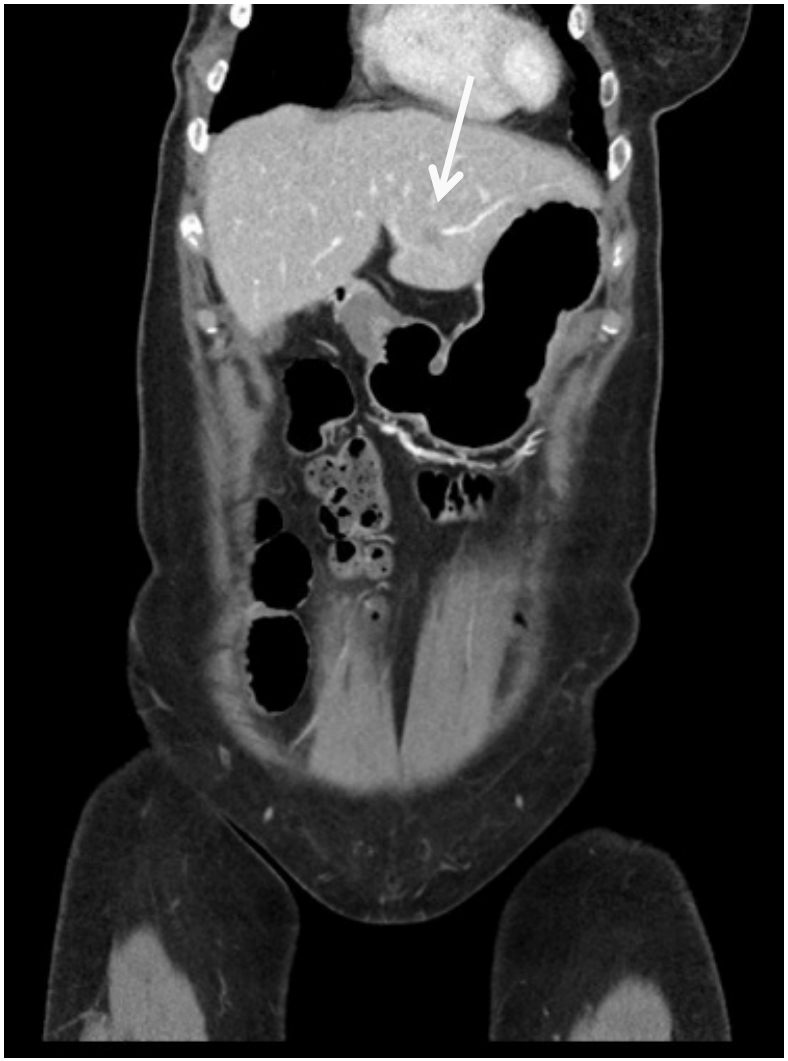




Goetz SABC 2015

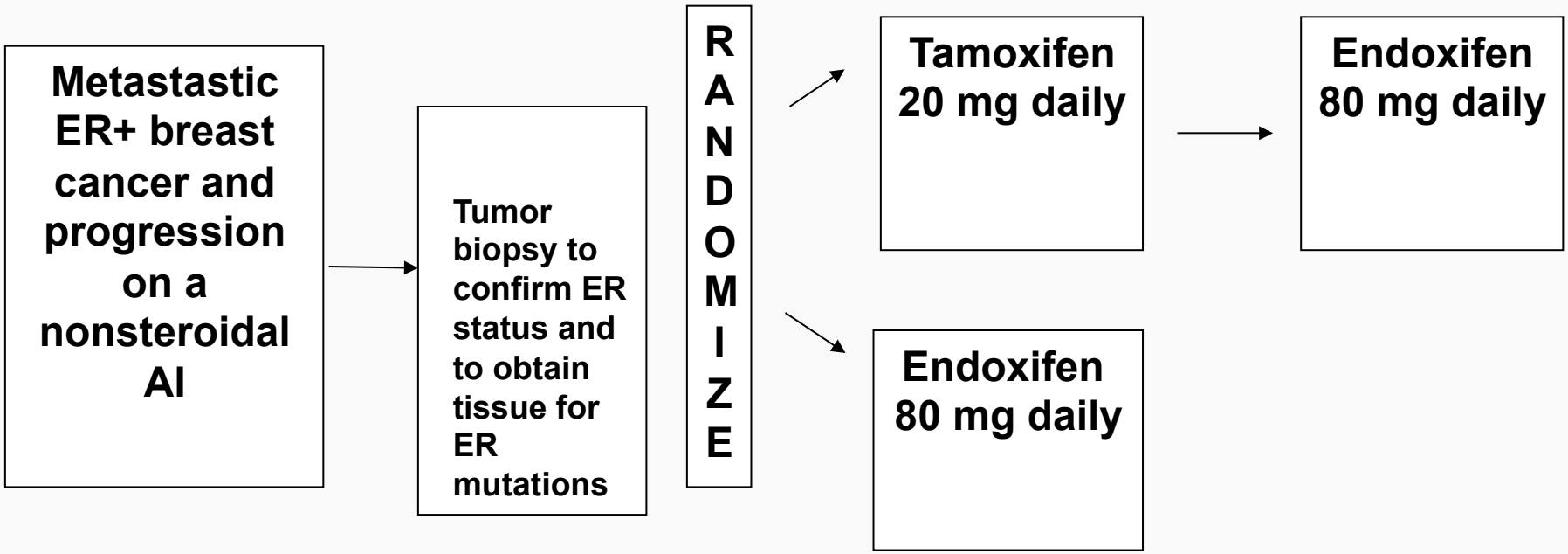
Endoxifen activity in tamoxifen, AI, fulvestrant and Everolimus refractory breast cancer (on study for 9 months)





Goetz SABC 2015

A11023 (activated)



Stratify: endocrine resistance (primary/secondary) and prior everolimus/palbociclib (yes/no)

Key Eligibility Requirements

- ER+ (≥10%), HER2- (as documented by on study biopsy)
- Prior treatment with an AI either in the adjuvant or metastatic setting required. Prior tamoxifen (adjuvant setting only) allowed, but relapse could not have occurred within 1 year of stopping tamoxifen.
- Apart from tamoxifen, unlimited endocrine regimens in the metastatic setting, including everolimus and palbociclib containing regimens
- At most two prior chemotherapies in the metastatic setting

Translational Studies:

- Tumor biopsy to confirm ER+, HER2- breast cancer mandatory (standard of care)
- Evaluation of biomarkers [(germline, somatic, and circulating somatic (CTC and DNA)] that may be prognostic and/or predictive of drug effect (e.g. activating ER mutations)
- Pharmacology: Limited PK sampling of parent drugs and metabolites
- Bone biomarker studies

Pre-Reg Biopsy: Is it necessary?

- 45 patients pre-registered and 31 patients eligible and registered.
- 14 patients screen failures:
  - 3 patients: tumor not breast in origin
  - 5 patients: TumorER negative or HER2 positive
  - 5 patients: malignant tissue not present on core
-

Amendment highlights

- Patients with bone only disease with either no tumor or insufficient tumor on biopsy eligible to participate
- Allow prior biopsy up to 90 days prior to pre-registration if no anticancer therapy administered during that window
- Patients with both non-measurable and bone only disease eligible
- Prior CDK 4/6 and/or everolimus based therapy allowed
- Frequency of lipid monitoring minimized

Common Questions

- PK samples:
  - Q: Do they have to be sent out the day they are drawn/processed/frozen, or can they be shipped the following day. I'm concerned about cycle 1 day 1 sample that is drawn 4-6 hours after dose of medication . Our last FED-EX pick up is ~ 3:30 PM which may lead to a time constraint.
  - A: If they are frozen they can be sent the next day.

Common Questions

- Section 3.2.2: Primary vs secondary resistance Definition:
  - **Primary: Recurrence during the first 2 years of AI therapy or within first 6 months of initiating first line endocrine therapy (either fulvestrant or AI)**
  - **Secondary: recurrence after year 2 while receiving adjuvant AI therapy or within 12 months of completing aduvant AI therapy or progression occruing 6 or months after initiating the first endocrine therapy for metastatic disease (either fulvestrant or AI**
  -

Common Questions

Question: Would endocrine resistance include patients who stopped taking endocrine therapy due to toxicities or who stopped taking endocrine therapy on their own accord

Answer: The goal of this study is to evaluate endoxifen and tamoxifen in women with prior progression on prior endocrine therapy. If a patient went off endocrine therapy for toxicity or other reason, and now has metastatic disease and has not received prior endocrine therapy for metastatic disease, she would not have “resistance’ and is not eligible. The patient who went off for toxicity, had a recurrence, and then went onto AI based therapy and then progressed would be eligible. This latter patient would be defined as having either primary or secondary resistance based on how fast the disease progressed on first line endocrine therapy therapy in the metastatic setting.

Common Questions

- Q: Per protocol section 3.2.3 patients must have measurable disease as by the RECIST criteria. Do patients have to have MEASURABLE disease or can they have NON-MEASURABLE disease only (ie: bone only disease)?
- A: The patient is eligible regardless of measurable disease or bone only disease.
- **Note: Some patients have bone disease plus other non-measurable disease (e.g. pleural effusion or small lymph nodes). These pts are are eligible**

Common Questions

- Q: Would a patient be eligible for A011203 with stable scans but rising tumor marker?
- **A: If the treating physician believes the patient has progression (either radiographic or clinically) and there is tumor to biopsy, and the results of the biopsy show ER positive and HER2 negative breast cancer, then the patient should be eligible.**

Common Questions

- Q: I have a potential subject with recent treatment for brain mets? I see known brain mets is an exclusion. What if the area has been treated with radiation?
- **A: Eligibility criterion 3.2.5 states "<u>No history of</u> visceral crisis, lymphangitic spread or <u>known brain metastases</u>."**
- Q: Does bone mets to the spine exclude the patient?
- **A: No**

Common Questions

- Does a history of cataract surgery (Grade 3) exclude the patient?
- **No. She is eligible as long as the patient does not have current symptomatic untreated cataracts.**

Common Questions

- Q: One criteria regarding prior treatments is “No more than two prior chemotherapy regimens in metastatic setting.” What is the definition of a treatment? If a patient started a treatment but then stopped due to toxicities would we count that as a treatment?
- **A: If the patient started a chemotherapy regimen and stopped for toxicity (but not progression) this would not count as a “regimen”.**

Common Questions

- Q: When patients have PET CT‘s do we also have to do the bone scan at those timepoints as well.
- **Section 11.2 of the protocol states the following:**
- **A: For patients with non-measurable bone only disease, follow-up imaging (either with PET/CT or bone scan) should be performed at the time of tumor assessment. The method of assessment used at baseline must be used consistently**

Common Questions

- This patient meets "secondary clinical resistance, after 6 + months of ETx for metastatic disease”. Does the progression need to be confirmed using RECIST or can it be at the discretion/judgement of the treating MD?
- **Prior progression can be at the judgment of the physician.**

Common Questions

- A patient is ready to start on A011203. She originally consented to the optional blood draws, but no longer wishes to do the PKs (substudy A011203-PP1). She would like to do the other additional blood samples (ST2 and ST3) if possible. Since the consent bundles the blood studies into one optional consent, would it still be possible for the patient to participate in ST2 and ST3?
- **Question #2 in the model consent form includes all of the companion blood studies ST2, ST3 and PP1. So if a patient says "no" to question 2 she is saying no to all of the companion blood studies.**