CYP2D6 Genotype and the Use of Tamoxifen in Breast Cancer

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ER+ breast cancer: brief review of the benefit of endocrine therapy

Tamoxifen metabolism: Does variation in the hydroxylated metabolites matter?
  - Tamoxifen pk/pg
  - The effects of tamoxifen and metabolites on estrogen-induced proliferation and ER transcription
    - Clinical: CYP2D6 metabolism and Ki-67
    - Clinical: association between CYP2D6 genotype and recurrence: Reasons for discrepancy

Steps forward for standardization
Breast Cancer
Endocrine Therapy

**Therapeutic Strategies**

- Block ER – Tamoxifen
- Block estrogen synthesis – aromatase inhibitors
- Target the ER for degradation (Fulvestrant)
Tamoxifen Mechanism of Action

Membrane

- ER
- PI3K
- EGFR/HER2
- Ras
- Raf
- MAPK

Nucleus

- ER
- Co A
- mTOR
- Co R
- mRNA
- Protein
  - Cell growth
  - Metastasis
  - Angiogenesis

TAM

- MISS
- NISS

Osborne JNCI 2003
Tamoxifen and Aromatase Inhibitors: Adjuvant Treatment of Postmenopausal ER+ Breast Cancer

Tamoxifen vs Control

Al's vs Tamoxifen

Summary

- Adjuvant hormonal therapy results in substantial improvements in recurrence and survival in women with ER+ breast cancer
- What are the accepted molecular markers which drive endocrine response?
- Does genetic variation in drug metabolism contribute to endocrine resistance?
Breast Cancer Molecular Subtypes

Importance of ER in Tamoxifen-treated Breast Cancer

Time to Recurrence in ATAC according to HER2 status

Dowsett M et al. JCO 2008;26:1059-1065
21 Gene Recurrence Score: Distant Recurrence in NSABP B14

The difference among the three recurrence score (RS) groups is significant (P<0.001)

SOFT: Estrogen Suppression in Addition to Tamoxifen: Overall and Age < 35

Francis et al. NEJM 2014
Endocrine Resistance

- Partial List of genes/pathways associated with primary endocrine resistance
  - Low or absent ER
  - ER+/HER2+ (luminal HER2) (effects abrogated in the setting of trastuzumab)
  - Luminal B (heterogeneous)
    - Activation of Growth Factor Pathways (e.g. EGFR1)
    - Activation of proliferation genes
  - Gene expression assays encompass many of these genes/pathways (Oncotype Dx)
  - Host “estrogen” levels
  - ? Does tamoxifen metabolism provide independent “prediction” of treatment benefit?
Tamoxifen Biotransformation

Tamoxifen Biotransformation

Tamoxifen

- CYP3A4
- CYP3A5
- CYP2D6
- CYP2B6
- CYP2C9
- CYP2C19
- CYP1A2

4-hydroxytamoxifen

- CYP2D6
- SULT1A1
- UGTs

N-desmethyltamoxifen

- CYP2D6

4-hydroxy-N-desmethyltamoxifen (Endoxifen)

<table>
<thead>
<tr>
<th>Drug and metabolite</th>
<th>EMs</th>
<th>IMs</th>
<th>PMs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tamoxifen</td>
<td>383 nM</td>
<td>413 nM</td>
<td>459 nM</td>
</tr>
<tr>
<td>NDMTAM</td>
<td>358 nM</td>
<td>776 nM</td>
<td>952 nM</td>
</tr>
<tr>
<td>4-OHT</td>
<td>6.3 nM</td>
<td>5.3 nM</td>
<td>5.1 nM</td>
</tr>
<tr>
<td>Endoxifen</td>
<td>35.6 nM</td>
<td>24.7 nM</td>
<td>9.0 nM</td>
</tr>
</tbody>
</table>

5-10 nM (average ~ 7 nM)

5-60 nM (average ~ 30 nM)
## Endoxifen Concentrations and CYP2D6 Genotype


<table>
<thead>
<tr>
<th>*Genotype</th>
<th>SNPs detected by xTAG CYP2D6 v3 Kit</th>
<th>Frequency in the U.S. Caucasian population</th>
<th>Frequency in the African American population</th>
<th>Predicted Enzyme Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>*1</td>
<td>None</td>
<td>37 to 40%</td>
<td>29 to 35%</td>
<td>Normal</td>
</tr>
<tr>
<td>*2</td>
<td>-1584A&gt;G, 1661G&gt;C, 2850C&gt;T, 4180G&gt;C</td>
<td>26 to 53%</td>
<td>18 to 27%</td>
<td>Normal</td>
</tr>
<tr>
<td>*3</td>
<td>2549A&gt;del</td>
<td>1%</td>
<td>0.2 to 0.5%</td>
<td>None</td>
</tr>
<tr>
<td>*4</td>
<td>100C&gt;T, 1661G&gt;C, 1840G&gt;A, 4180G&gt;C,2850C&gt;T</td>
<td>18 to 20%</td>
<td>6 to 9%</td>
<td>None</td>
</tr>
<tr>
<td>*5</td>
<td>deletion</td>
<td>2 to 4%</td>
<td>6 to 7%</td>
<td>None</td>
</tr>
<tr>
<td>*6</td>
<td>1707T&gt;del, 4180G&gt;C</td>
<td>1%</td>
<td>0.50%</td>
<td>None</td>
</tr>
<tr>
<td>*7</td>
<td>2935A&gt;C</td>
<td>Not known</td>
<td>Not known</td>
<td>None</td>
</tr>
<tr>
<td>*8</td>
<td>1661G&gt;C, 1758G&gt;T, 2850C&gt;T, 4180G&gt;C</td>
<td>Not known</td>
<td>Not known</td>
<td>None</td>
</tr>
<tr>
<td>*9</td>
<td>2813delAGA</td>
<td>Not known</td>
<td>Not known</td>
<td>None</td>
</tr>
<tr>
<td>*10</td>
<td>100C&gt;T, 1661G&gt;C, 4180G&gt;C</td>
<td>Not known</td>
<td>Not known</td>
<td>None</td>
</tr>
<tr>
<td>*11</td>
<td>883G&gt;C, 1661G&gt;C, 2850C&gt;T, 4180G&gt;C</td>
<td>Not known</td>
<td>Not known</td>
<td>None</td>
</tr>
<tr>
<td>*15</td>
<td>1288ntT</td>
<td>Not known</td>
<td>Not known</td>
<td>None</td>
</tr>
<tr>
<td>*17</td>
<td>1023C&gt;T, 1661G&gt;C, 2850C&gt;T, 4180G&gt;C</td>
<td>2 to 8%</td>
<td>0.50%</td>
<td>None</td>
</tr>
<tr>
<td>*29</td>
<td>1659G&gt;A, 1661G&gt;C, 2850C&gt;T, 3183G&gt;A, 4180G&gt;C</td>
<td>Not known</td>
<td>Not known</td>
<td>None</td>
</tr>
<tr>
<td>*35</td>
<td>-1584A&gt;G, 31G&gt;A, 1661G&gt;C, 2850C&gt;T, 4180G&gt;C</td>
<td>0.2 to 0.3%</td>
<td>15 to 26%</td>
<td>Reduced</td>
</tr>
<tr>
<td>*41</td>
<td>1661G&gt;C, 2850C&gt;T, 2985G&gt;A, 4180G&gt;C</td>
<td>Not known</td>
<td>Not known</td>
<td>Reduced</td>
</tr>
</tbody>
</table>

*IC₉₀(ER) vs CYP2D6 genotype*

- PM/PM
- PM/IM
- IM/IM
- PM/EM
- IM/EM
- EM/EM
- UM

DUP duplication
Summary

- Extensive variability in the concentration of tamoxifen and its metabolites
- CYP2D6 is responsible for the hydroxylation of N-desmethyl tamoxifen
- *CYP2D6* genetic variation accounts for approximately 30-50% of the variation in endoxifen concentrations in tamoxifen treated patients
- Does variability in the concentrations of tamoxifen and its metabolites affect estrogen induced stimulation/transcription?
Effects of tamoxifen and metabolites on ER stimulated proliferation and transcription

[Graph showing relative fold change from vehicle for MCF7 cells with different treatments]
Effects of “pre-menopausal” estrogen levels on ER-stimulated proliferation in the presence of tamoxifen and metabolites

Maximov et al. JNCI 2014
Endoxifen and Letrozole in MCF7/AC1 Xenografts

Letrozole vs Endoxifen in MCF7/AC1 Xenograft Model

Goetz et al.
Effects of SERMs on AKT on letrozole sensitive and resistant MCF7 cells in vivo and in vitro (1 hour)

Letrozole sensitive treated with AND

LR –treated with tamoxifen

Letrozole resistant (LR)

LR treated with Endoxifen

P-AKT (Ser473)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Protein Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>No trt</td>
<td>P-Akt</td>
</tr>
<tr>
<td>ETOH</td>
<td>P-Akt</td>
</tr>
<tr>
<td>1 nM AND</td>
<td>P-Akt</td>
</tr>
<tr>
<td>1 µM LET</td>
<td>P-Akt</td>
</tr>
<tr>
<td>1 nM AND + 1 µM LET</td>
<td>P-Akt</td>
</tr>
<tr>
<td>100 nM TAM</td>
<td>P-Akt</td>
</tr>
<tr>
<td>5 uM TAM</td>
<td>P-Akt</td>
</tr>
<tr>
<td>100 nM 4HT</td>
<td>P-Akt</td>
</tr>
<tr>
<td>5 uM 4HT</td>
<td>P-Akt</td>
</tr>
<tr>
<td>100 nM END</td>
<td>P-Akt</td>
</tr>
<tr>
<td>5 uM END</td>
<td>P-Akt</td>
</tr>
</tbody>
</table>

Letrozole resistant MCF7: effects of SERMs on AKT

Goetz et al.
Endoxifen is a critical metabolite that is necessary for full inhibition of proliferation and ER transcription in ER+ cells. The pre-clinical effects of endoxifen may vary depending on the amount of estrogen present and the endocrine sensitivity of the tumor cells. The importance of endoxifen (and thus CYP2D6 genotype) in tamoxifen treated women may greatest in the premenopausal setting.
Outline

• ER+ breast cancer: brief review of the benefit of endocrine therapy
• Tamoxifen metabolism: Does variation in the hydroxylated metabolites matter?
  • Tamoxifen pk/pg
  • The effects of tamoxifen and metabolites on estrogen-induced proliferation and ER transcription
    • Clinical: CYP2D6 metabolism and Ki-67
    • Clinical: association between CYP2D6 genotype and recurrence: Reasons for discrepancy
• Steps forward for standardization
Higher Ki-67 expression after 2 weeks of endocrine therapy was significantly associated with lower recurrence-free survival ($P=0.004$).

Ki-67 is a surrogate marker for the response to tamoxifen therapy.
C-GENT study
- Prospective Clinical Study to Clarify the Relationship between CYP2D6 Genotype and the Therapeutic Effects of Preoperative Tamoxifen Therapy

ER (+)
Her2 (-)
any T, any N, M0

Neoadjuvant Tamoxifen Therapy
For 2-4 weeks

Radical Operation

Ki-67 Labeling index
Core needle biopsy sample

Ki-67 Labeling index
Surgically resected breast cancer tissue

Primary Endpoint: Change in Ki-67 Labeling index (LI)
Secondary Endpoint: Tumor reduction (US)
Histological response
Breast conservative operation

Association Study

CYP2D6 genotype
C-GENT collaborative study group (17 sites)

- Sapporo Medical University
- Sapporo Breast Surgical Clinic
- Higashi-Sapporo Hospital
- Kotoni Breast Clinic
- Saitama Cancer Center
- Nippon Medical School
- Showa University
- Tokyo Medical University
- Nakagami Hospital
- Sagara Hospital
- Koiki Monbetsu Hospital
- Hirosaki Municipal Hospital
- St Marianna University
- Yokohama City University Medical Center
- Yokohama City Minato Red Cross Hospital
- Singapore: National University of Singapore
- Tan Tock Seng Hospital
Ki-67 change after neoadjuvant tamoxifen therapy

<table>
<thead>
<tr>
<th>Ki-67 (%)</th>
<th>Ki-67 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pre-TAM</td>
<td>post-TAM</td>
</tr>
<tr>
<td>0-10</td>
<td>0-10</td>
</tr>
<tr>
<td>10-20</td>
<td>10-20</td>
</tr>
<tr>
<td>20-30</td>
<td>20-30</td>
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<tr>
<td>30-40</td>
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<td>40-50</td>
<td>40-50</td>
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<td>50-60</td>
<td>50-60</td>
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<tr>
<td>60-70</td>
<td>60-70</td>
</tr>
<tr>
<td>70-80</td>
<td>70-80</td>
</tr>
<tr>
<td>80-90</td>
<td>80-90</td>
</tr>
</tbody>
</table>

\[ P = 2.4 \times 10^{-10} \]

Reduction rate 52%

N=273
Primary Endpoint
(CYP2D6 genotype and Ki-67 LI change after tamoxifen therapy)

N=272

*V/*V vs Wt/Wt : P=0.0029
*V/*V vs Wt/Wt+Wt/*V : P=0.000014
*V/*V vs Wt/*V vs Wt/Wt : P=0.023

P=1.43 x 10^-5
Summary

• Level 1 data that.....

• CYP2D6 genetic variation is associated with endoxifen concentrations

• CYP2D6 genotype affects Ki-67 response in a 2-week window study

• What is the level of evidence for the use of CYP2D6 genotyping for patients with ER+ breast cancer?
• ER+ breast cancer: brief review of the benefit of endocrine therapy

• Tamoxifen metabolism: Does variation in the hydroxylated metabolites matter?
  • Tamoxifen pk/pg
  • The effects of tamoxifen and metabolites on estrogen-induced proliferation and ER transcription
  • Clinical: CYP2D6 metabolism and Ki-67
  • Clinical: association between CYP2D6 genotype and recurrence

• Steps forward for standardization
Simon/Hayes/Paik Criteria for Biomarker Studies

- **Category A**: Prospective Clinical Trial (PCT) designed to address tumor biomarker
- **Category B**: PCT not designed to address biomarker, but design accommodates tumor marker utility
- **Category C**: Prospective Observational Registry, treatment and follow-up not dictated
- **Category D**: No prospective aspect to study

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

Number of patients: 1325

Time-To-Recurrence

Event-Free-Survival

Follow-up (years)

Proportion of patients

EM
46%
hetEM/IM
48%
PM
6%

P < 0.001

P = 0.0029

Schroth, Goetz et al., JAMA 2009
ITPC: Pooled Analysis of Category C Studies

- International Tamoxifen Pharmacogenomics Consortium. 4,973 tamoxifen-treated patients
- Using clinical trial eligibility (Criterion 1: \( n=1,996 \)) (postmenopausal ER+-positive, 20 mg/day tamoxifen for 5 years, standard follow-up), CYP2D6 PM associated with IDFS and BCFI: HR 1.25; (1.06, 1.47; \( p = 0.009 \)).

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Meta-estimates</th>
<th>IDFS</th>
<th>Meta-estimates</th>
<th>BCFI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( \text{HR} )</td>
<td>95% CI</td>
<td>( \text{P value} )</td>
<td>( \text{HR} )</td>
</tr>
<tr>
<td>Criterion 1</td>
<td>1.25</td>
<td>(1.06,1.47)</td>
<td>0.899</td>
<td>0.009</td>
</tr>
<tr>
<td>Criterion 2</td>
<td>1.17</td>
<td>(0.90,1.52)</td>
<td>0.055</td>
<td>0.249</td>
</tr>
<tr>
<td>Criterion 3</td>
<td>1.07</td>
<td>(0.92,1.26)</td>
<td>0.099</td>
<td>0.382</td>
</tr>
</tbody>
</table>

BCFI: breast cancer-free interval; Homog, homogeneity; HR: hazard ratio; IDFS, invasive disease-free survival; ITPC, International Tamoxifen Pharmacogenomics Consortium.

\( ^a \) The homogeneity \( P \) value tests the hypothesis that the individual ITPC site estimates meet the statistical random-effects modeling assumptions of the meta-analysis. A significant value indicates that there is significant heterogeneity among the sites, which casts doubt on the "combinability" of the studies for that parameter and on the validity of the corresponding association test. \( ^b \) The association \( P \) value tests the hypothesis that the combined meta-analysis estimate of the HR is significantly different from the null hypothesis value of HR = 1.

Simon/Hayes/Paik Criteria

• Category A: Prospective Clinical Trial (PCT) designed to address tumor biomarker

• Category B: PCT not designed to address biomarker, but design accommodates tumor marker utility

• Category C: Prospective Observational Registry, treatment and follow-up not dictated

• Category D: No prospective aspect to study

• Secondary analysis of a phase III trial\(^1\)
  - "prospective-retrospective" designs using archived specimens
  - adequate amounts of archived tissue must be available for statistical power
  - patients studied must be representative of patients in the trial
  - test should be analytically and pre-analytically validated for use with archived tissue

• Did ATAC, BIG 1-98, and ABCSG8 fulfill each of these criteria?

Prospective 5 year Tamoxifen Trials in Postmenopausal Women Evaluating CYP2D6

• Adjuvant treatment of invasive ER+ breast ca
  • ATAC: Tam or anastrozole for 5 years (Rae et al JNCI 2012)
  • BIG 1-98 Tam or letrozole for 5 years  (Regan, Leyland-Jones: JNCI 2012
  • ABCSG 8:  Tam for 5 yrs or Tam for 2 yrs followed by anastrozole for 3 yrs (Goetz: Clin Canc Research 2013)
Postmenopausal Women with ER+ Breast Cancer:

• **BIG 1-98**: Tam or letrozole (5 yrs) *(Negative Study)*
  • DNA derived from FFPE Tumor Cores

• **ATAC**: Tam or anastrozole (5 yrs) *(Negative Study)*
  • DNA derived from FFPE Tumor Cores
  • Analyzed less than 20% of the patients

• **ABCSG 8**: Tam (5 yrs) or Tam (2 yrs) followed by anastrozole (3 yrs) *(Positive Study)*
  • DNA derived from FFPE enriched for normal tissue

2. Rae et al J National Canc Institute 2012
Controversy: CYP2D6 and Tamoxifen

- The first two studies:
  - BIG 1-98 and ATAC demonstrated no association between CYP2D6 genotype and outcomes in either study
  - CYP2D6 Genotyping has “no value in practice:

- Editorial:
  - “the fact that these two studies confirm each other suggests that this matter has likely been laid to rest. Why has such a good hypothesis gone wrong?”

Kelly, CM Pritchard K JNCI 2012
**BIG 1-98: Observed vs Expected CYP2D6 Alleles---excess homozygotes and deficiency of heterozygotes**

<table>
<thead>
<tr>
<th>CYP2D6 Phenotype</th>
<th>N</th>
<th>Observed (%)</th>
<th>Expected (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor (PM)</td>
<td>236</td>
<td>9</td>
<td>5-7</td>
</tr>
<tr>
<td>Intermediate (IM)</td>
<td>716</td>
<td>27</td>
<td>55-65</td>
</tr>
<tr>
<td>Extensive (EM)</td>
<td>1585</td>
<td>59</td>
<td>30-35</td>
</tr>
</tbody>
</table>

***Hardy Weinberg equilibrium:***
- CYP2D6 *4: X^2 test P value = 1 x 10^{-92}*
- CYP2D6*41: X^2 test P value = 2 x 10^{-174};

Stanton V Jr: J Natl Cancer Inst 104:1265-1266; author reply
Pharoah PD, Abraham J, Caldas C: J Natl Cancer Inst 104:1263-1264; author
ARTICLE
Loss of Heterozygosity at the CYP2D6 Locus in Breast Cancer: Implications for Germline Pharmacogenetic Studies


Department of Oncology (MPG, MMA, JNI), Department of Health Sciences Research (VJS, KRK), and Department
• TCGA: Loss of Heterozygosity (LOH) at the CYP2D6 Locus (chromosome 22q13.1) > 40% of ER+ BC

• Heterozygotes mislabeled as homozygotes

• Comparing purified ER+ tumor DNA (FFPE tumor cores) vs germline (buccal cells), CYP2D6*4 genotype discordant in 6/31 (19.4%)

• Conclusion: Tumor DNA should not be used to determine germline CYP2D6 genotype without sensitive techniques to detect low frequency alleles and quality control procedures appropriate for somatic DNA.

Primary therapy:
- Anastrozole (3 years)
- Tamoxifen (2 years)
- Tamoxifen (3 years)
- Anastrozole (3 years)

Primary endpoint: event-free survival

CYP2D6: OR: 2.54
CYP2D6*4; within HWE

CYP3A4/5: OR: 0.28

P = 0.04
P = 0.46

Summary

• Three (Category B) studies have been reported regarding CYP2D6 and tamoxifen.

• Only ABCSG 8 CYP2D6 analysis demonstrated a positive association.

• Significant methodology issues in BIG -98 and ATAC preclude their use in formulating guidelines.

• When should patients be tested for CYP2D6? ASCO and NCCN Guidelines reference BIG 1-98 and ATAC and recommend against CYP2D6 genotyping.
CPIC Tamoxifen Guidelines

- Focusing only on studies evaluating the use of tamoxifen in the adjuvant setting for ER+ breast cancer
- Excluded studies which focused on single CYP2D6 allele (e.g. *10 or *4)
- Nearly 50 studies extensively curated for all clinical and PG phenotypes
- Group of experts have classified the literature findings regarding the effects of CYP2D6 genotype on PK, PD, side-effects, recurrence, DFS, and OS
• Strong consensus that CYP2D6 genotype consistently alters endoxifen concentrations and pharmacodynamic effects (e.g. Ki-67)

• Moderate consensus that the literature demonstrates evidence for an effect of CYP2D6 genotype on recurrence and event free survival

• Next steps:
  • Crafting of clinical recommendations for each CYP2D6 phenotype (AS)
  • Publication

CPIC Tamoxifen Guidelines (Summary)
Ways to overcome CYP2D6 metabolism in Tamoxifen treated patients

• Substitute AI for tamoxifen\(^1\)
• Increase the dose of tamoxifen (40-60 mg/day)\(^2-4\)
• Substitute another SERM (toremifene)
• Directly administer endoxifen

1. Schroth, Goetz et al., JAMA 2009

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; John R. Hawse; Tufia Haddad; Charles Erlichman; Matthew M. Ames; and James N. Ingle

Mayo Clinic, Rochester, MN and Scottsdale, AZ; NCI

Goetz SABC 2015 and submitted 2017
• 40 and 80 mg/day: $C_{\text{min}}$: 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 and submitted 2017
AI Refractory Breast Cancer: Endoxifen Responses according to progression on Tamoxifen (A) and Fulvestrant (B)

Change in tumor size from pre-treatment, %

Goetz SABC 2015 and submitted 2017
Endoxifen Responses according to Prior Tamoxifen

Expected median PFS of 60-90 days:

Goetz SABC 2015 and submitted 2017
Endoxifen activity in tamoxifen, AI, fulvestrant and Everolimus refractory breast cancer

Goetz SABC 2015
Metastastic ER+ breast cancer and progression on a nonsteroidal AI

Tumor biopsy to confirm ER status and to obtain tissue for ER mutations

Randomize

Tamoxifen 20 mg daily

Endoxifen 80 mg daily

Randomize

Endoxifen 80 mg daily

Stratify: endocrine resistance (primary/secondary) and prior everolimus/palbociclib (yes/no)
Genetic Variation in tamoxifen metabolism alters
• Endoxifen concentrations
• The effects of tamoxifen metabolism on clinical outcomes is controversial
• A substantial proportion of the unresolved controversy can be explained by poorly conducted studies.

Recommendations:
• Prospective Clinical Trials are key
• Secondary analyses of prospective clinical trials are still forthcoming (SOFT/TEXT)