CYP450 2D6 and Tamoxifen Metabolism
Morphology of breast cancer associated with *BRCA1* mutations.
The tumor (to the right of the picture) shows pushing margins (broad, smooth edge to the tumor) and a prominent lymphocytic infiltrate (small blue nuclei).
Tamoxifen Therapy

- **Tamoxifen** (Nolvadex®) interferes with the activity of estrogen (a hormone).
  - Tamoxifen has been used for more than 20 years to treat patients with advanced breast cancer.
  - It is used as adjuvant, or additional, therapy following primary treatment for early stage breast cancer.
  - In women at high risk of developing breast cancer, Tamoxifen reduces the chance of developing the disease.¹
  - Tamoxifen is only given for a maximum of 5 years.
  - 3.4 million prescriptions (2002)

Tamoxifen is metabolized to its active metabolite, Endoxifen primarily via the pathways indicated by the bold arrows shown below.

Endoxifen concentrations are typically 5-10X higher than 4-OH TAM.

2D6 Tamoxifen

• FDA Pharmaceutical Advisory Sub-Committee
  – Click here to access the FDA website.
    • October 18-19, 2006 Clinical Pharmacology Subcommittee Meeting
  – Executive Summary
    • Click here to access the FDA website.
  – Meeting On Oct. 18th, 2006
    – Quote from the executive summary:

  “…at the Annual ASCO Meeting in June 2006 showed that the 3-year relapse-free survival was 68% in patients who are poor metabolizers of CYP2D6 and patients on strong inhibitors of CYP2D6 compared to 98% in patients who are extensive metabolizers of CYP2D6.”
Meeting Summary
Advisory Committee Pharmaceutical Science

• Does the clinical evidence demonstrate that postmenopausal women with ER-positive breast cancer who are CYP2D6 poor metabolizer (by genotype or drug interaction) are at increased risk for breast cancer recurrence?

– The consensus of the subcommittee is:
"the label should be updated to reflect the increased risk for breast cancer along with the mechanistic data presented."¹

¹ http://www.fda.gov/ohrms/dockets/ac/06/minutes/2006-4248m1.pdf
Some CYP450 2D6 variants may impact the metabolism of tamoxifen to its active metabolite, endoxifen.


- Heterozygous or homozygous
  - Significantly Reduced Plasma Endoxifen Concentrations[^1]
    - Allele Frequency
      - 2D6 *4 18.0%
      - 2D6 *5 2.3%

Many 2D6 variants may have an impact on Tamoxifen metabolism

- CYP450 2D6 Variant Activity:
  - Alleles with **NO** enzymatic activity
  - Alleles with **Reduced** enzymatic activity
  - Alleles with **Multiple** copies (**High** activity)
    » 2D6 *1, *2, *35, *41

INFINITI™ 2D6 – Tamoxifen*

- INFINITI 2D6 Tamoxifen Variants Detected:

* INFINITI™ 2D6 Assay is “For Research Use Only” (RUO)
“It follows that an improved understanding of factors that influence CYP2D6 activity in breast cancer patients and its consequences on endoxifen formation is important to the rational optimization of tamoxifen therapy.”

2D6 Genotypes and Tamoxifen With 2D6 Inhibitors

• “Among subjects who carried a homozygous wild type genotype, the mean plasma endoxifen concentration for those who were using CYP2D6 inhibitors was 58% lower than that for those who were not.”\(^1\)

  – SSRI Strong 2D6 Inhibitors
    • Paroxetine
    • Fluoxetine

Tamoxifen is widely used to treat estrogen receptor positive breast cancer

- 2D6 Variants Reduce Tamoxifen’s Active Metabolite (Endoxifen)
- Reduced Endoxifen, Increases Chances of Breast Cancer Relapse
Take Home Messages

• 2 Strong 2D6 Inhibitors, Reduce Endoxifen Levels
  – Paroxetine
  – Fluoxetine

• INFINITI™ 2D6 Assay Reagents* Can Be Easily Utilized On The INFINITI Analyzer

* INFINITI™ 2D6 Assay is “For Research Use Only” (RUO)