# National Cancer Institute's Rare Tumors Initiative

## Clinical Trials for Desmoid Tumors

**Shivaani Kummar, MD**
Head, Early Clinical Trials Dev
Office of the Director
Division of Cancer Treatment and Diagnosis
National Cancer Institute

**Abby B. Sandler, Ph.D.**
Special Assistant to the Director, Rare Tumors Initiative
Center for Cancer Research
National Cancer Institute

# NCI Rare Tumor Initiative

- **Goal: To leverage existing NCI expertise in basic and clinical science studies of rare tumors to more effectively translate potential new therapies**

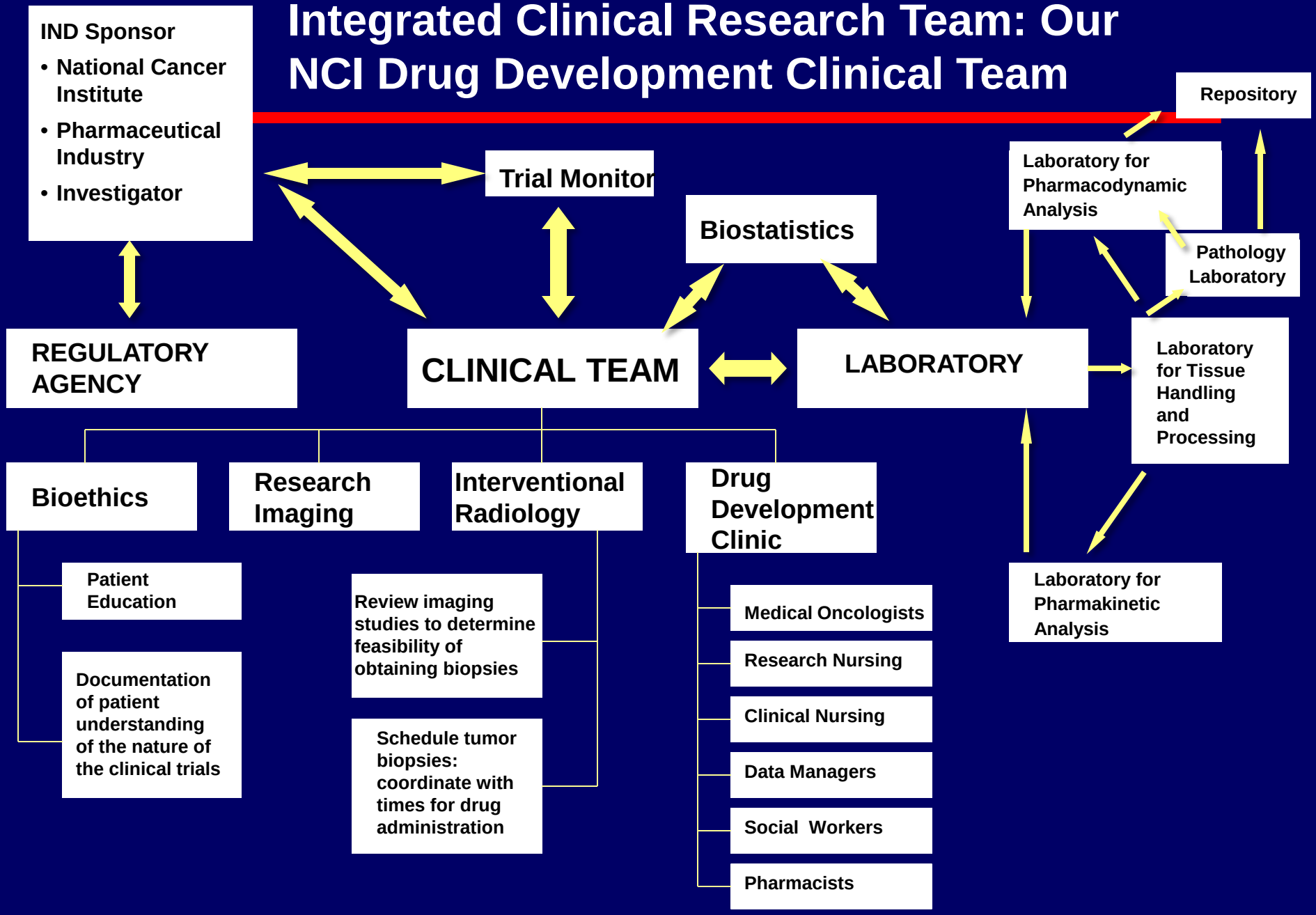
- **Logistics:**
  - **Pilot phase focused on a small number of tumor types**
    - **Ras-related (MPNSTs and plexiform neurofibromas)**
    - **Non-Ras (desmoid tumors)**

# National Institutes of Health Clinical Center, Bethesda, MD

# Developmental Therapeutics Clinic, NCI

- DTC was created to capitalize on the clinical research and the drug development expertise of NCI
- DTC is engaged in the evaluation of novel agents to treat a variety of tumors with the goal to identify new effective therapies for these tumor types and expedite their development.
- DTC works collaboratively with a number of labs to study drug effect on tumors as well as to identify additional drug targets.
- DTC has a number of ongoing clinical trials (15-17/year) and enrolls over 150 patients a year on these trials.

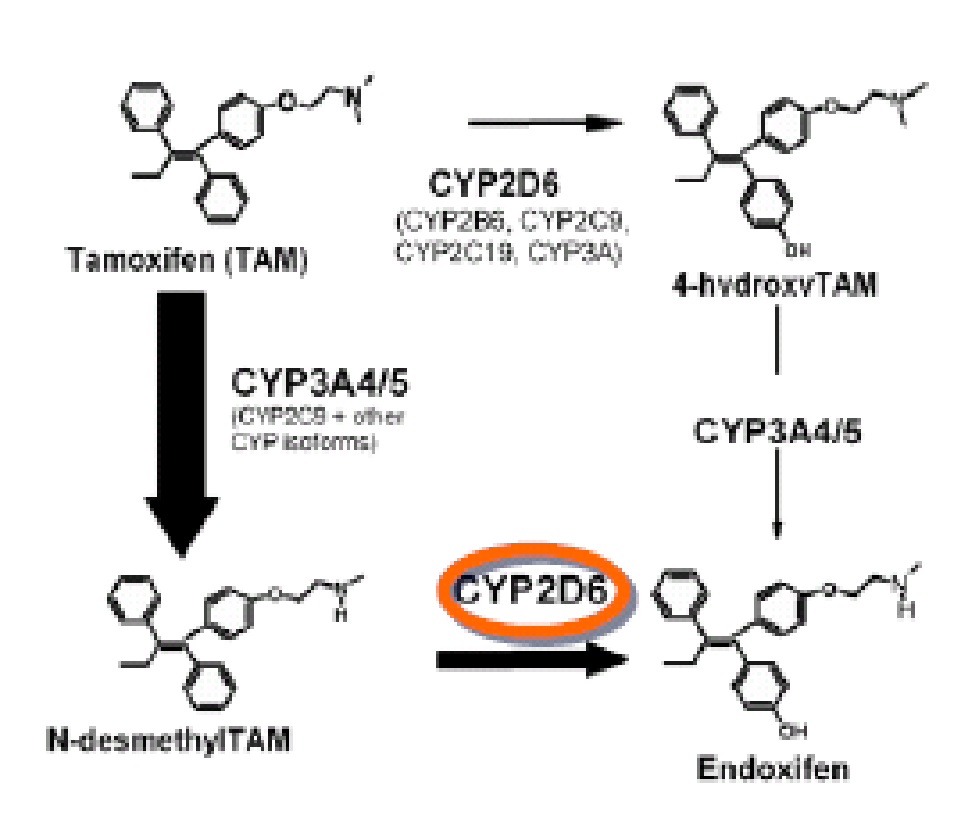
# Integrated Clinical Research Team: Our NCI Drug Development Clinical Team



# Clinical Trials for Desmoid Tumors

- **Ongoing Trial:**
  - **Phase I Trial of Z-Endoxifen in Adults With Refractory Hormone Receptor–Positive Breast Cancer, Desmoid Tumors, Gynecologic Tumors, or Other Hormone Receptor–Positive Solid Tumors**
- **Upcoming Trial:**
  - **Phase II Trial of the γ-secretase Inhibitor PF-03084014 in Adults with Desmoid Tumors/Aggressive Fibromatosis**

# Phase I Trial of Z-Endoxifen in Adults With Desmoid and ER + Solid Tumors

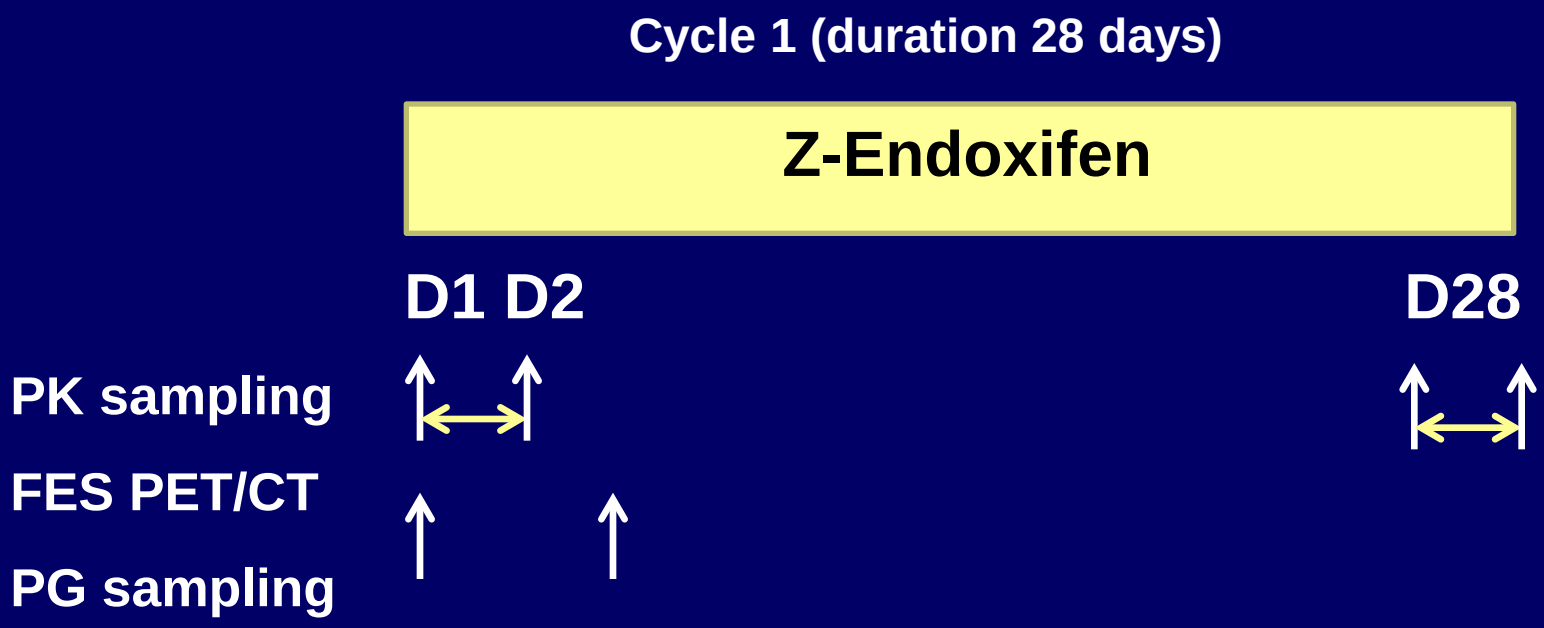



Pathway for tamoxifen metabolism

- Tamoxifen 120 mg with sulindac 300 mg daily resulted in responses in patients with FAP associated desmoids.
- Patients with CYP 2D6 polymorphisms or on antidepressants have lower levels of active metabolites of tamoxifen
- Endoxifen is the active metabolite that results in the activity of tamoxifen

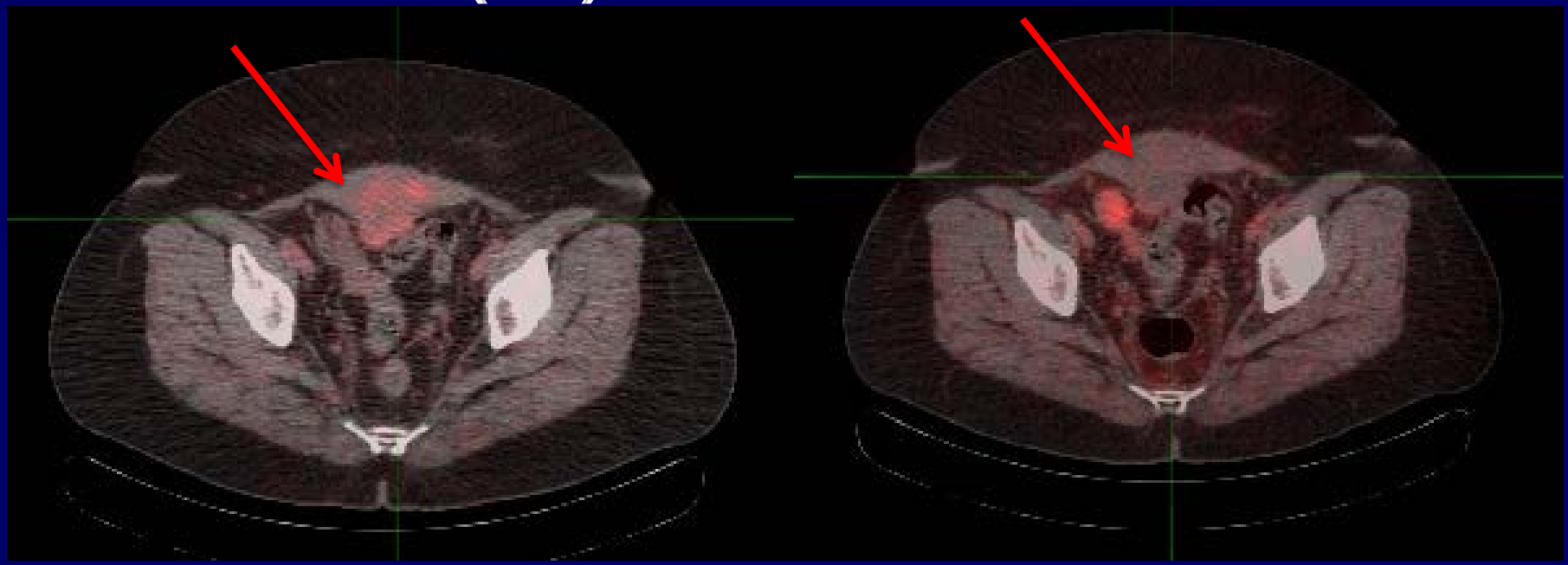
# Phase I Trial of Z-Endoxifen in Adults With Desmoid and ER + Solid Tumors

**Endoxifen is given once a day; 28 day cycles**



# ER+ (>80% by IHC) Endometrial Cancer

## ($^{18}$F)FES-PET Scan



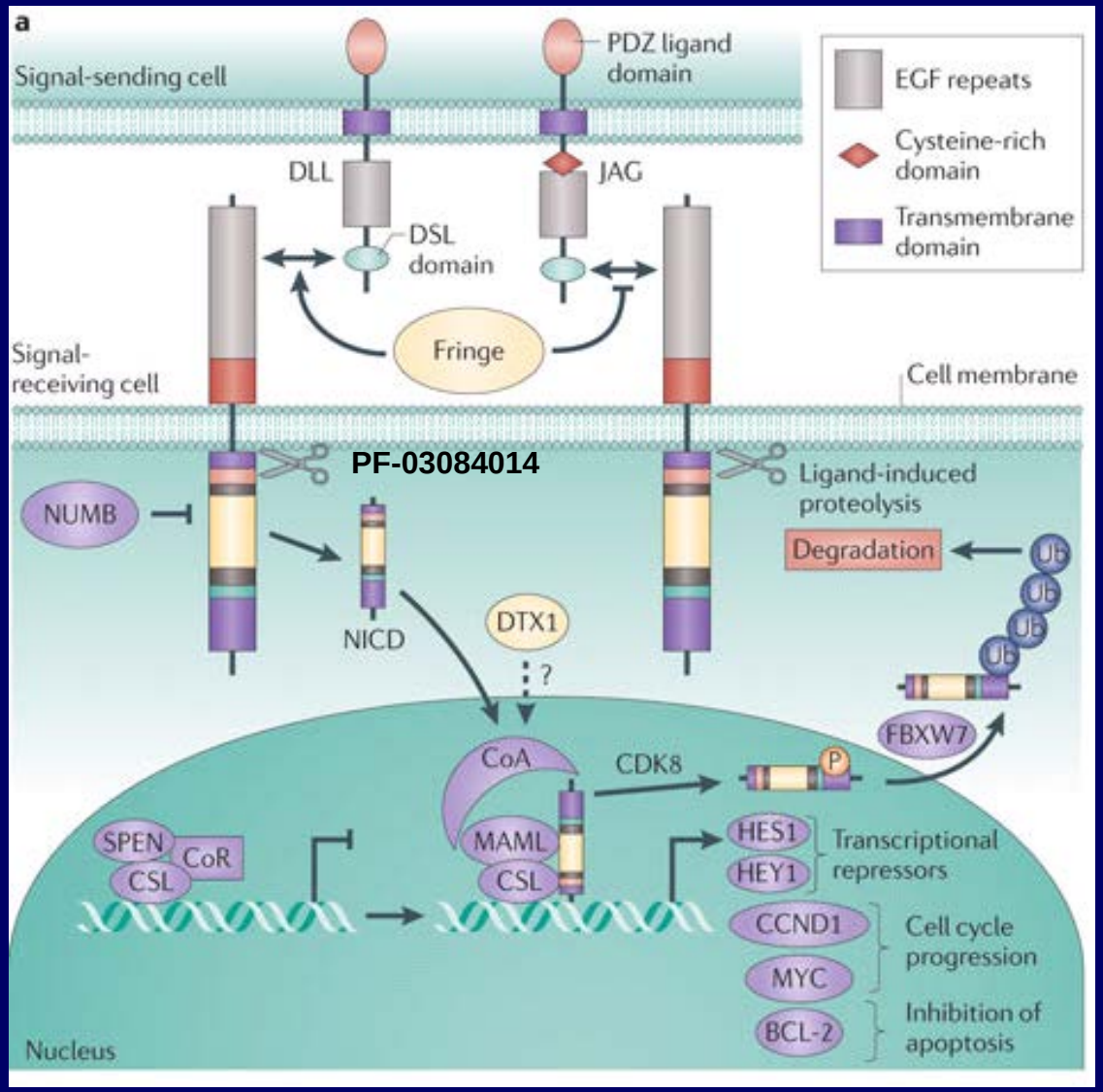
Prior to Z-Endoxifen

Day 3 of Z-Endoxifen

# Phase I Trial of Z-Endoxifen in Adults With Desmoid and ER + Solid Tumors

- Trial is currently accruing patients
- High levels of active drug in blood; well tolerated
- Preliminary evidence of activity in breast and gyn malignancies expressing ER on the surface
- FES-PET showing initial uptake and then modulation following administration of endoxifen
- Need to evaluate activity in patients with desmoid tumors

# **Notch Signaling:** PF-03084014 is a gamma-secretase inhibitor

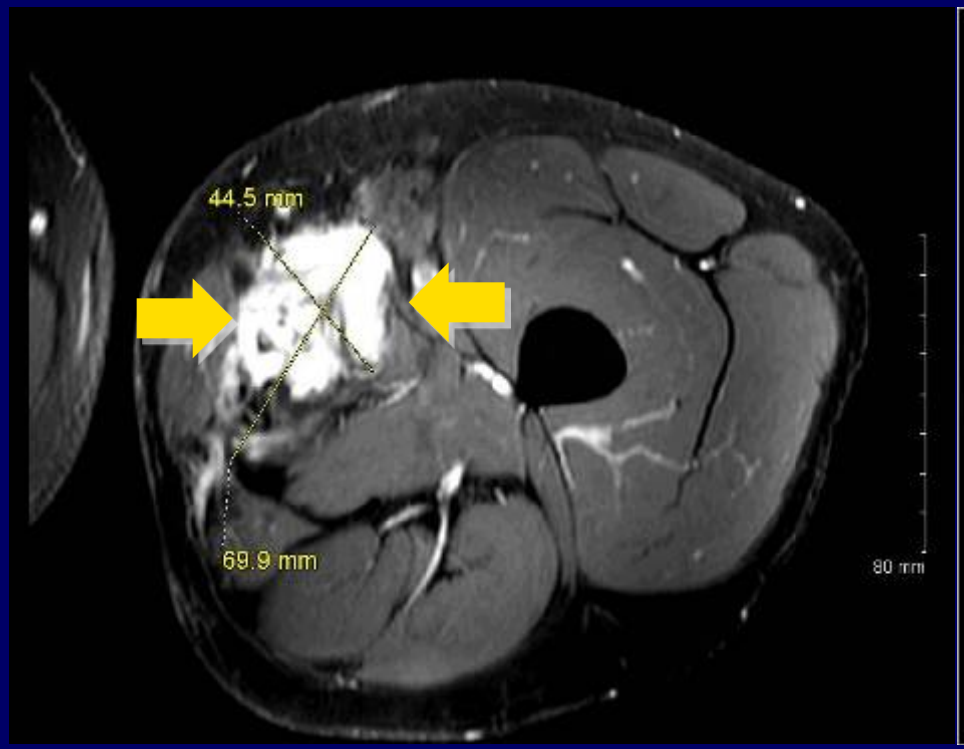


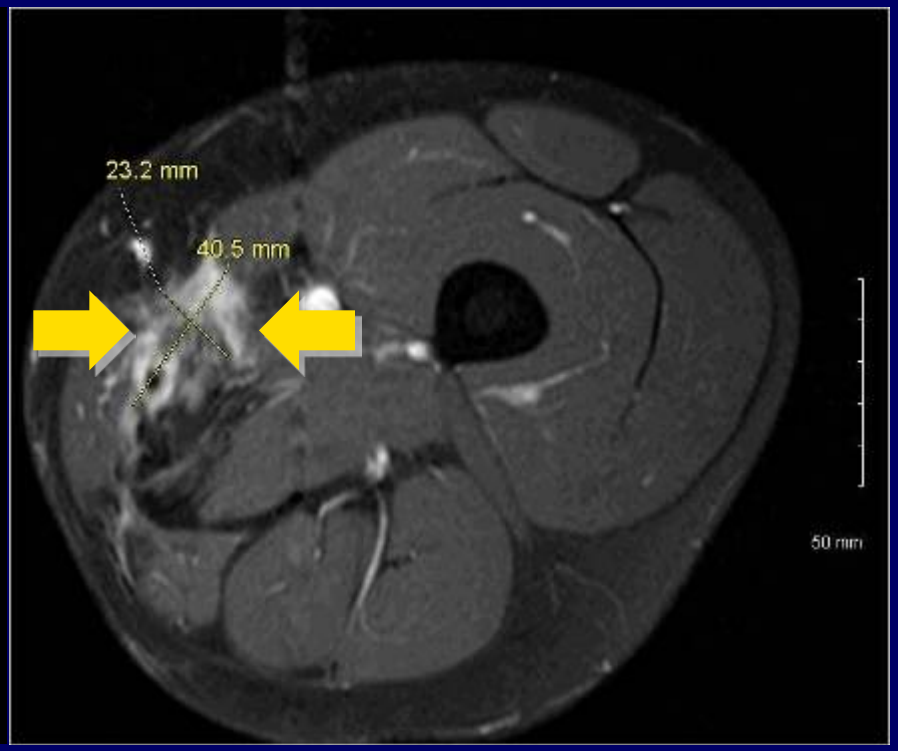

Nature Reviews Cancer 2011

- Notch signaling directs cell fate decisions that promote tumor proliferation and survival
- Inhibition of Notch signaling redirects cell fate decisions that inhibit tumor proliferation and survival

# Partial Responses Seen in Patients with Desmoid Tumors on PF-03084014

**28 Year Old M with Right, Inner Thigh Desmoid Initially Responded to 150 mg BID by Cycle 3, with PR (-26%); Decreased Again Cycle 5 to (-45%)**



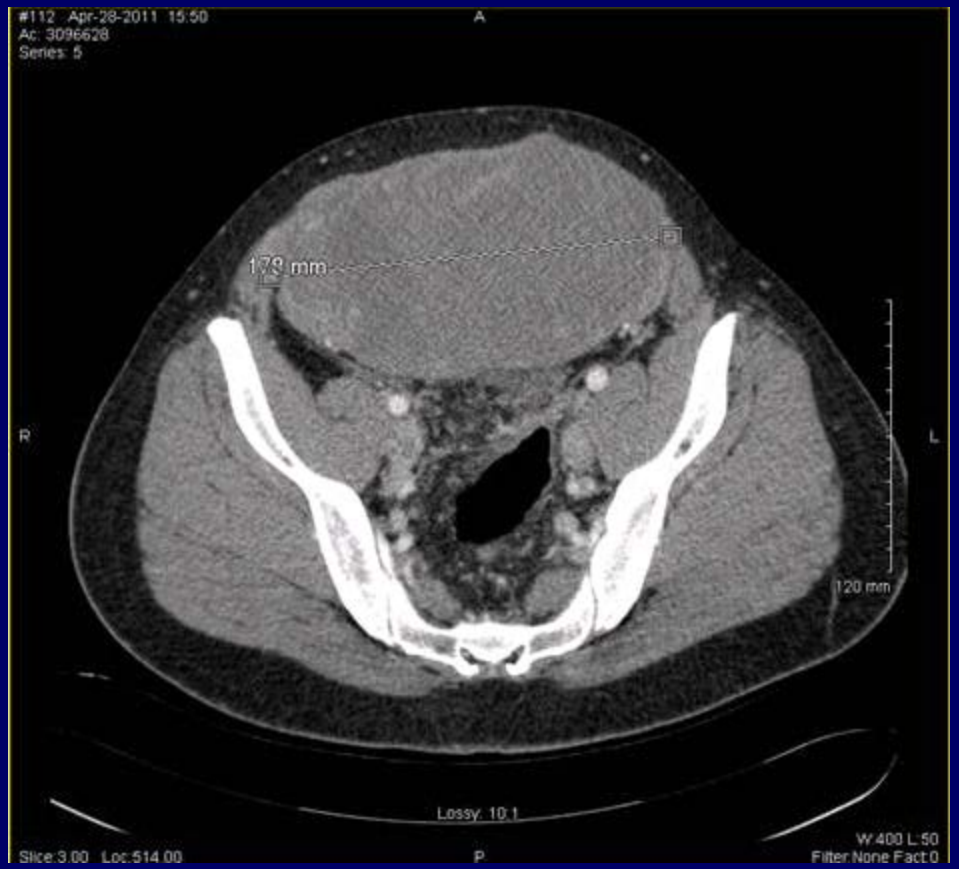

**Baseline MRI of Thigh Desmoid: 44.5 mm x 69.9 mm**

**150 mg BID x 3 cycles**

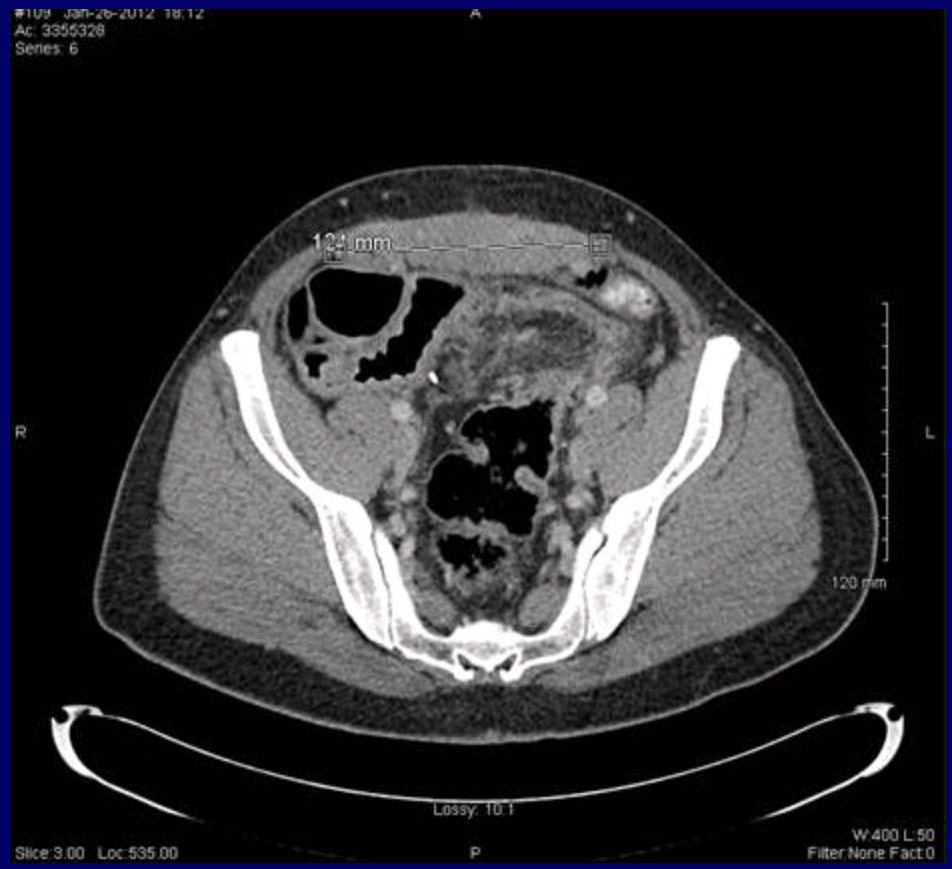
**Cycle 3 MRI of Thigh Desmoid: 23.2 mm x 40.5 mm**

# PF-03084014 has completed phase 1 testing and shown activity in patients with desmoid tumors

Patient with Intra-abdominal desmoid on PF-03084014




**Baseline**




**s/p cycle 13**

# Phase II Trial of PF-03084014 in Adults with Desmoid Tumors

- PF-03084014 will be administered orally at 150 mg twice a day in 21-day cycles
- Assess response of desmoid to study treatment using MRI with diffusion weighting
- Assess symptom measures at baseline and on study
- Perform genotyping for germline and somatic mutations in *APC* and *CTNNB1* genes
- Depending on availability of tissue study the underlying biology of desmoids

# Contact Information

- **Principle Investigators**
  - Dr. Shivaani Kummar
  - Dr. James H. Doroshow
    - Email: kummars@mail.nih.gov, Phone: 301-435-0517
- **Research Coordinators**
  - Janelle Bingham
    - Email: jbingham@mail.nih.gov, Phone: 301-435-2715
  - Lemual Clayborn
    - Email: claybornl@mail.nih.gov, Phone: 301-451-0992
- **Research RNs**
  - Ramya Parthasarathy
    - Email: parthasarathyr@mail.nih.gov, Phone: 301-594-4949
  - Jennifer Zlott
    - Email: zlottjh@mail.nih.gov, Phone: 301-435-5664

# Our DTC Clinical Team