A Pilot, Single-Arm, Phase II Trial of Tamoxifen plus Pegylated Liposomal Doxorubicin in Patients with Metastatic Triple Negative Breast Cancer

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BACKGROUND

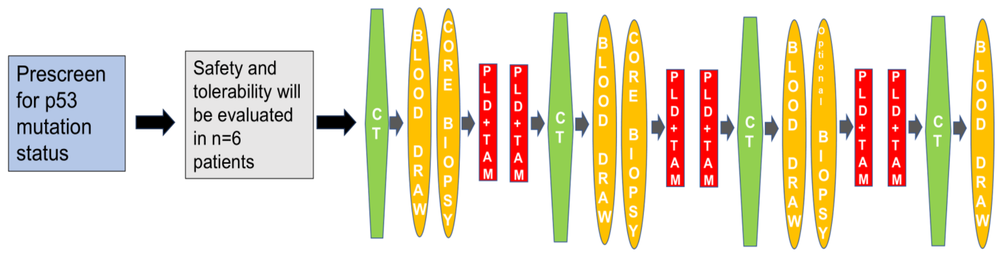
- **TNBC causes disproportionate mortality** due to **aggressive biology**, **early visceral/brain metastases**, and the **absence of targeted therapies**; despite being ERα-negative, **~80% of tumors express ERβ**, and a similar proportion harbor **TP53 mutations**.
- **ERβ directly interacts with p53**, exerting **tumor-suppressive effects in mutant-p53 (mut-p53)** TNBC but potential oncogenic effects with **wild-type p53** (Mukhopadhyay et al., *JNCI*, 2019).
- **Tamoxifen (Tam) stabilizes ERβ**, enhances **ERβ–mut-p53 binding**, **sequesters mut-p53 away from TP73**, and **restores TP73-mediated tumor suppression**; Tam shows **synergistic cytotoxicity with doxorubicin** in ERβ/mut-p53+ TNBC models, with **superior tumor regression** in xenografts.
- **Clinical proof-of-concept** was demonstrated in a patient with **metastatic ERβ/mut-p53 TNBC** who experienced **marked tumor regression with Tam** (Scarpetti et al., *The Oncologist*, 2023), supporting clinical translation of **Tam-based combinations**

METHODS

•**Eligibility:** Enrolling pts ≥18 years with mTNBC, defined by **ERα-low (≤10%)** expression and **progression on ≥2 prior systemic therapies**.

•**Treatment:** Pts receive **Tamoxifen 20 mg orally once daily** plus **Pegylated Liposomal Doxorubicin 50 mg/m² intravenously every 28 days**.

Single Arm, Phase II Trial of Tamoxifen (Tam) plus Pegylated Liposomal Doxorubicin (PLD) in Patients with Stage IV Metastatic TNBC



Eligible patients must have p53 mutant tumor at metastatic site by RPCI OPA assay
CT at baseline, and after every two cycles of therapy
Blood draw at baseline, and after every two cycles of therapy
Core biopsy (if historical sample is not available) at baseline and after one cycle of therapy. An optional additional biopsy at progression.
Tamoxifen: 20mg PO, daily
PLD: 50mg/m^2 (every 28 days)

ENDPOINTS

Primary Endpoint
- Overall Response Rate (RECIST v1.1)

Secondary Endpoints
- Progression-Free Survival (PFS)
- Overall Survival (OS)
- Duration of Response (DOR)
- Safety/tolerability (CTCAE v5.0)

Exploratory Endpoints
- ctDNA dynamics
- ERβ–mut-p53 interaction (PLA)
- Differential gene expression analysis by RNA-seq
- Immune deconvolution (CIBERSORT)
- Cytokine/flow cytometry immune profiling
- Spatial tumor microenvironment profiling using CyCIF to evaluate ERβ, mutant-p53, and immune architecture

CONTACTS

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STATUS

The study is currently open to enrollment (planned accrual: 27 patients).
NCT06434064

SIGNIFICANCE

- If effective, this study could establish a novel, **mechanism-driven option for pretreated mTNBC**, with correlative analyses identifying molecular and immune predictors of response.