Low dose (Z)-endoxifen treatment in the ISPY 2 Endocrine Optimization Pilot EOP

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BACKGROUND

- (Z)-endoxifen, an **oral selective estrogen receptor modulator**, is the most abundant active tamoxifen metabolite. It is a 100-fold more potent ER-antagonist than tamoxifen.
- (Z)-endoxifen has **dual mechanisms of action**:
  1) potent ER antagonism (5-10 ng/ml) achieved with doses below 10 mg/day and
  2) inhibition of ERα and protein kinase Cβ1 (> 500 ng/ml).
- It is active in the endocrine resistant metastatic setting at a dose of 80 mg/day (Goetz, JCO 2017). **However, the optimal dose in an endocrine naïve population is not defined**.
- We explored low dose neoadjuvant (Z)-endoxifen (10 mg once daily) in the EOP platform study.

ELIGIBILITY

Screening included pts screened for the main I-SPY2 trial with Stage II/III HR+ HER2- breast cancer. Pts with low risk MammaPrint (MP) were eligible; high MP scores were eligible if clinically node-negative.

I-SPY2.2 TRIAL DESIGN

- Pts received (Z)-endoxifen 10 mg orally once daily for 6 cycles (cycle = 28 days). Premenopausal pts started ovarian function suppression on cycle 2, day 1. (Z)-endoxifen was continued until the day prior to surgery. **The primary study endpoint was feasibility, defined as ≥75% of pts completing ≥75% of study therapy**.
- Baseline (T0), 3-wk (T1) biopsies, and the surgical specimens (T3) were assessed centrally for Ki-67. Rates of modified preoperative endocrine prognostic index (mPEPI) 0 were reported, defined as pT1-2 pN0, Ki67< 2.7%, or pathologic complete response. A genomic index for sensitivity to endocrine therapy (SET) index was done at BL. Breast MRI measurement of functional tumor volume (FTV) was performed at T0, T1, 12 weeks (T2), and pre-operatively (T3).
- Blood was collected for tumor informed ctDNA at T0, T1, T2, T3 and for pharmacokinetic (PK) steady state concentrations (Css) at T1. Safety data using CTCAE V5 is reported.

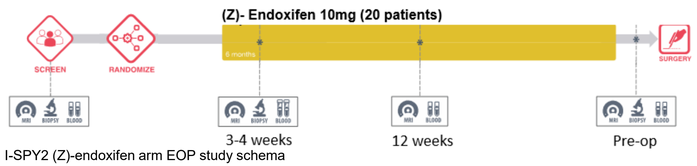


Fig 1. I-SPY2 (Z)-endoxifen arm EOP study schema

DEMOGRAPHICS

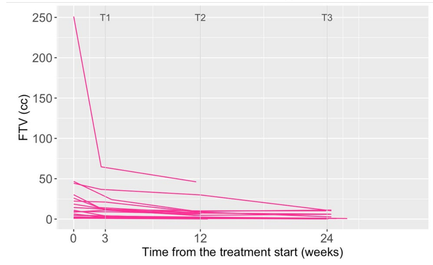
	(Z)-Endoxifen
# of pts	N = 20
Age at screening	
Median [Min, Max]	52.5 [32.0-73.0]
Race	
White	12 (60%)
Asian	3 (15%)
Not reported/Missing	5 25%)
Menopausal status	
Premenopausal	13 (65%)
Postmenopausal	7 (35%)

T Stage at Screening	
T1/T2	12 (60%)
T3/T4	7 (35%)
Tx	1 (5%)
N stage at Screening	
Node negative	9 (45%)
Node positive	11 (55%)
Grade	
I	4 (20%)
II	12 (60%)
III	1 (5 %)
Missing	3 (15%)

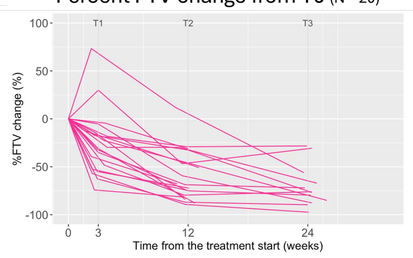
MammaPrint Risk	
High Risk	3 (15%)
Low Risk	17 (85%)
BluePrint Subtype	
Luminal	20 (100%)
SET Status	
High	16 (80.0%)
Low	4 (20.0%)

MRI FTV SHIFTS

2A Absolute FTV change (N = 20)



2B Percent FTV change from T0 (N = 20)

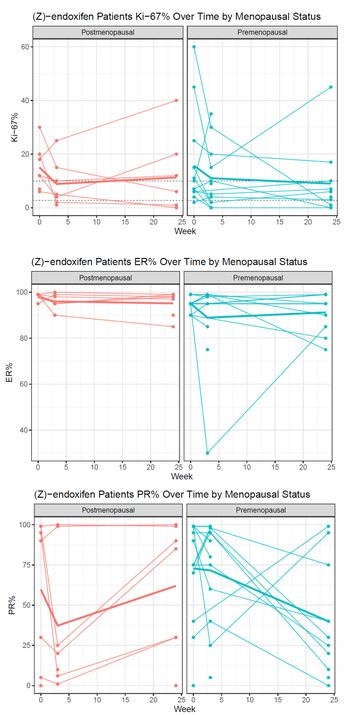


The median T0 FTV was 8.9 ccs (range 0.9 to 251.1). The median T3 FTV was 1.3 ccs (range 0 to 11.2). The median change in FTV from T0 to T3 was -72.0% (range -88.5% to -61.6%).

A reduction in tumor FTV was observed in all patients.

CHANGES IN KI-67, ER, and PR DURING (Z)-ENDOXIFEN THERAPY

	Post menopausal	Pre menopausal	Overall
# of pts	N = 7	N = 13	N = 20
KI-67			
Baseline Ki-67			
Median [Min, Max]	12.0 [6.0, 30.0]	7.0 [2.0, 60.0]	10.5 [2.0, 60.0]
Week 3 Ki-67			
Median [Min, max]	5.0 [1.0, 25.0]	7.0 [0, 35.0]	5.1 [0, 35.0]
Missing	0	1 (7.7%)	1 (5.0%)
Surgical Ki-67			
Median [Min, max]	6.0 [0, 40.0]	9.0 [0, 45.0]	6.0 [0, 45.0]
Missing	0	2 (15.4%)	2 (10.0%)
ER			
Baseline ER%			
Median [Min, Max]	99.0 [95.0, 99.0]	95.0 [90.0, 99.0]	95.0 [90.0, 99.0]
Week 3 ER%			
Median [Min, max]	95.0 [95.0, 99.0]	96.5 [30.0,99.0]	95.0 [30.0, 99.0]
Missing	0	1 (7.7%)	1 (5.0%)
Surgical ER%			
Median [Min, max]	98.0 [85.0, 99.0]	95.0 [75.0, 99.0]	95.0 [75.0, 99.0]
Missing	0	3 (23.1%)	3 (15.0%)
PR			
Baseline PR%			
Median [Min, Max]	90.0 [0, 99.0]	75.0 [0, 99.0]	82.5 [0, 99.0]
Week 3 PR%			
Median [Min, max]	20.0 [1.0, 100]	85.0 [5.0, 99.0]	75.0 [1.0, 99.0]
Missing	0	1 (7.7%)	1 (5.0%)
Surgical PR%			
Median [Min, max]	85.0 [0, 100]	27.5 [0, 99.0]	30.0 [0, 100]
Missing	0	3 (23.1%)	3 (15.0%)



Ki-67:

• 13/19 (68.5%) of pts had a 3-wk Ki-67 of ≤10%.

• Premenopausal pts (n=12): 3-wk Ki-67 ≤10% was observed in 66.7% of pts (all prior to OFS initiation).

• Baseline Ki-67 >10% (n=11): 3-wk Ki-67 ≤10% was observed in 36.4% of pts.

ER/PR:

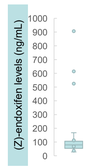
• No clear fluctuations in ER-were observed. Decreases in PR-expression were noted in both pre and postmenopausal pts.

mPEPI:

• mPEPI-0 was observed in 1 pt (5%).

Css:

• Right: Median (Z)-endoxifen Css was 79.3 ng/mL (range 73.6 - 906.4 ng /mL).



CTDNA DYNAMICS DURING THERAPY

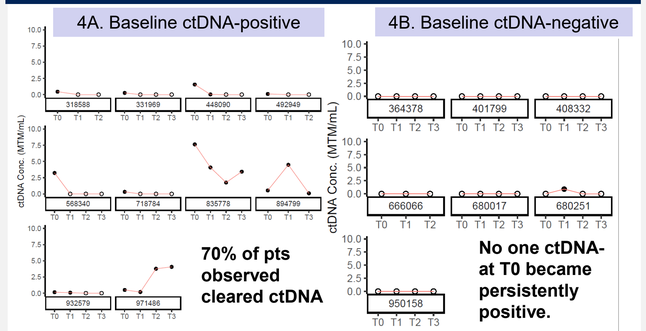


Fig 4. Serial assessments of tumor informed ctDNA using the Signatera WES platform are displayed by those with baseline ctDNA status.

SAFETY / TOLERABILITY

(Z)-endoxifen at 10 mg was well tolerated with no G3/G4 AEs. 19/20 pts received ≥ 75% of treatment with the current median duration of therapy of 168 days (range 82 to 182 days).

Table 3: Term	Grade 1	Grade 2	Grade ≥ 3	Any grade
Hot flush	12 (60%)	0	0	12 (60%)
Nausea	8 (40%)	0	0	8 (40%)
Fatigue	7 (35%)	3 (15%)	0	10 (50%)
Insomnia	7 (35%)	0	0	7 (35%)
Dizziness	5 (25%)	0	0	5 (25%)
Headache	5 (25%)	0	0	5 (25%)
Breast Pain	4 (20%)	0	0	4 (20%)
Cough	4 (20%)	0	0	4 (20%)
Myalgia	4 (20%)	0	0	4 (20%)
Night Sweats	3 (15%)	1 (5%)	0	4 (20%)

CONCLUSIONS

- **(Z)-endoxifen at 10 mg once daily met the primary endpoint** with 19/20 (95%) receiving ≥ 75 % of planned treatment.
- **Low dose (Z)-endoxifen was well tolerated and additionally demonstrated sustained reductions Ki-67, in MRI FTV and ctDNA.**

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