Response of Persistent Metastatic ER+/Her2- Breast Cancer Treated with Fulvestrant plus Enzalutamide

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Abstract

Background: While androgen receptor (AR) protein is expressed in over 90% of estrogen receptor alpha (ER) positive breast cancers[1], clinical implications of the androgen receptor (AR), particularly in the context of aromatase inhibitor (AI) refractory metastatic breast cancer (MBC) remain unclear. While AR is associated with more indolent primary tumors, high AR relative to ER in primary breast cancer is associated with endocrine resistance, and in the absence of estradiol (low or blocked ER), AR can exert a pro-survival signal[2-6]. Following extensive preclinical studies and a brief phase I to demonstrate a lack of significant PK interaction[7], in this phase II trial of Fulvestrant (Fulv) plus Enzalutamide (Enza) in ER+/Her2- MBC (NCT02953860), we analyze serial biopsies pre- and post-treatment.

Methods: Eligible patients were women with ECOG 0-2, ER+/Her2- MBC. Fulv 500 mg IM days 1, 15, 29 and every 4 weeks thereafter and Enza at 160 mg PO daily on a continual basis were administered. Biopsies were required at study entry and at ~4 weeks on therapy. 32 patients were eligible, median age was 61 years (46-87), and 90.6 % had visceral disease. They had a median of 4 prior non-hormonal therapies and 3 prior hormonal agents (including 37.5% with prior Fulv). The clinical benefit rate at 24 weeks (CBR24) was the primary endpoint for efficacy. Baseline biopsies were analyzed for mutations[8] in *ESR1* exon 8, as well as 67 other gene hotspots frequently altered in cancer using a modified Archer VariantPlex Solid Tumor Assay in the CMOCO Laboratory (Department of Pathology, University of Colorado, Aurora, CO). We examined estrogen, progesterone, androgen, and glucocorticoid receptors, multiplex analysis of immune cells and PD-L1, and performed reverse phase protein array (RPPA) based protein pathway activation analysis of over 150 proteins/phosphoprotein drug targets from LCM-enriched tumor in baseline and post-treatment metastatic biopsies. Comparisons of long progression free survival (PFS) equal to or longer than 24 weeks versus short (PFS shorter than or equal to 60 days) were performed using moderated t-tests on log2 transformed data.

Results: A total of 38 patients were consented, of whom 32 were eligible. TEAEs >20% included fatigue, nausea/vomiting, constipation, headache, anorexia, although most were low grade. There were no G4 or G5 toxicities. CBR24 was 22 (95% CI: 8.3 to 41.0) percent. The median time to progression was 57 (95% CI: 56 to 143) days and 7 (21.9%) participants had PFS longer than 24 weeks. Approximately half of patients who had prior Fulv received benefit from the combined Fulv plus Enza. *ESR1* mutant metastases had significantly higher levels of ER and PR than those with wild type *ESR1* (p<0.05). Biopsies with *ESR1* mutations had significantly more T helper cells, T regulatory cells, and macrophages than those with wild type *ESR1,* while those with *TP53* or *PIK3CA* mutations had increased CD8+ T cells, but also higher T regulatory cell infiltration. PD-L1 positive macrophages were significantly higher in *ESR1* mutated versus wild type biopsies (p<0.02). Overall, PD-L1 increased significantly following Fulv plus Enza treatment (paired t test P<0.002). RPPA analysis indicated that activation of mTOR pathway proteins was associated with short PFS, and patients with *PIK3CA* and or *PTEN* mutated disease had a shorter PFS.

Hypothesis

ER+ metastatic breast cancer resistant to traditional endocrine therapy may benefit from blocking both ER and AR by using an estrogen degrader combined with an AR antagonist.

Study Design

Single arm, non-randomized, open-label treatment:

- Fulvestrant 500 mg IM given days 1, 15, 28, then every 4 weeks as per standard of care (SOC).
- Prior Fulvestrant was allowed. Enzalutamide 160 mg po daily.
- If pre- or perimenopausal, patients will also receive goserelin 3.6 mg sq every 4 wks as per SOC.

Statistical Design:

- CBR at 24 weeks was primary endpoint. Assuming an undesirable rate of 10% and desirable rate of 30%, a sample size of 24 provides 89% power to detect this difference with a one-sided alpha of 0.085.

Inclusion & Exclusion Criteria

- ER+ Her2- metastatic breast cancer
- Female, at least 18 years of age
- Candidate for fulvestrant therapy – patients who have started fulvestrant may enter this trial if within 3 months of starting fulvestrant.
- Measurable or Evaluable by RECIST 1.1
- ECOG PS 0-2
- Able to swallow study drug and comply with study requirements
- Two biopsies – pretreatment just prior to starting fulvestrant plus enzalutamide, and during treatment at 5 weeks.
- No CNS metastases or history of seizures

Clinical benefit rate and progression free survival

Clinical Benefit Rate*	Eligible for Efficacy (N)***	Stable Disease (N)	Partial Response (N)	CBR (95% CI)
CBR16**	28	8	1	32.1% (15.9%, 52.4%)
CBR24**	28	6	0	21.4% (8.3%, 41.0%)

CBR, clinical benefit rate defined as complete response, partial response, or stable disease; CBR 16, CBR at 16 weeks; CBR 24, CBR at 24 weeks; CI, confidence interval; enza, enzalutamide; RECIST, Response Evaluation Criteria in Solid Tumors version 1.1.

*The assessment of the target lesion and the non-target lesion were combined

**The week 17 assessment was used for CBR16 and the week 25 assessment was used for CBR24

***28 patients had evaluable disease, had taken Enz for at least 4 weeks, and had at least one post-baseline tumor assessment

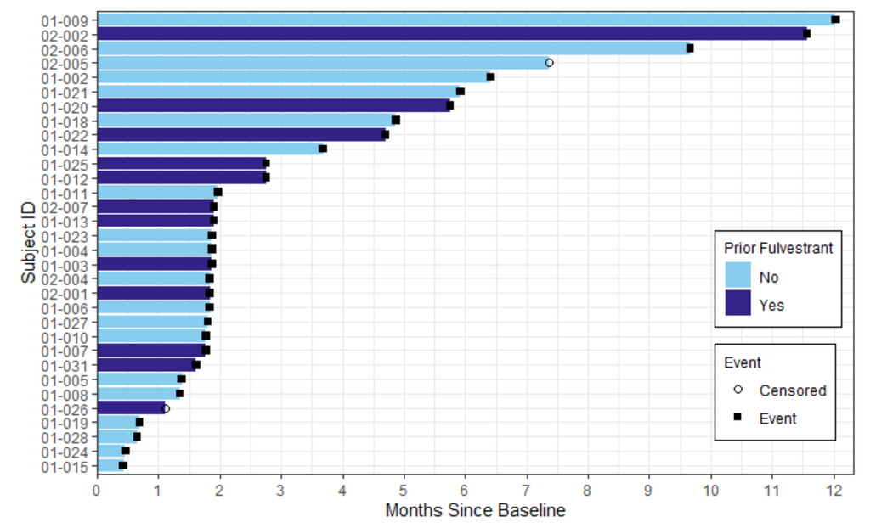
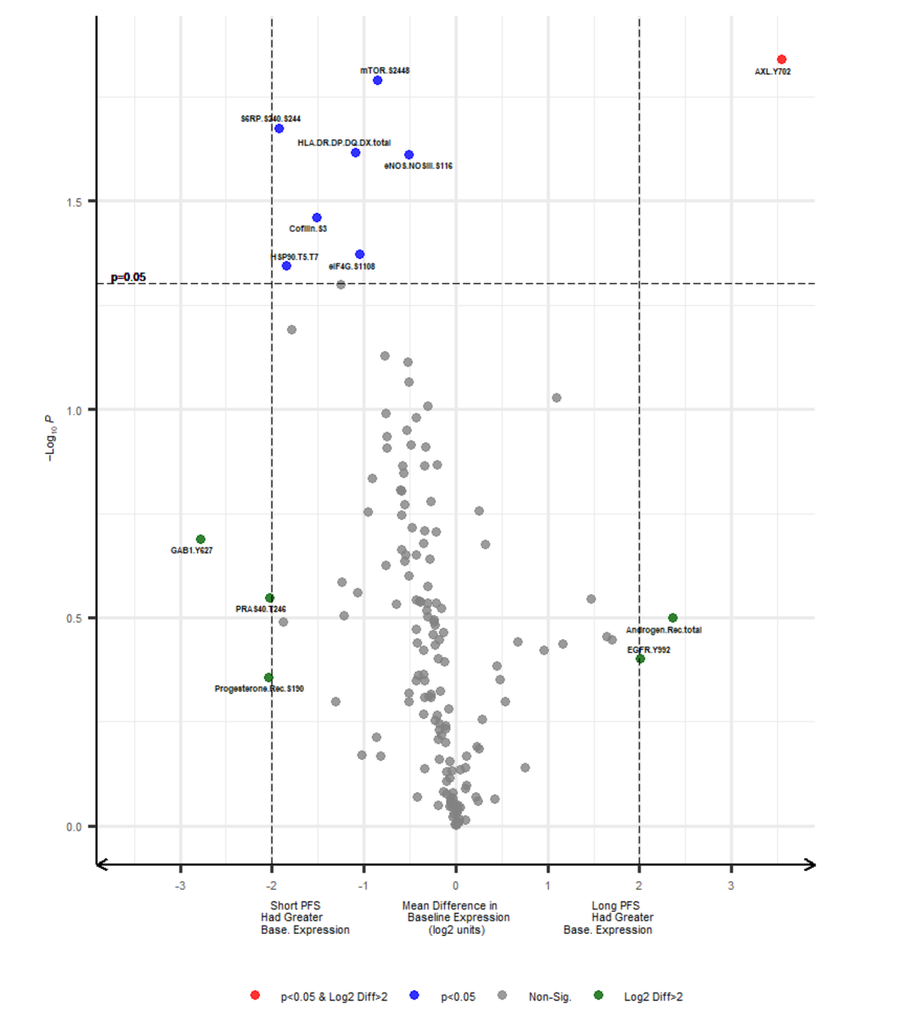


***Figure 1.* Progression Free Survival Analysis shows some patients with prior Fulvestrant appear to have benefited from Fulvestrant plus Enzalutamide** *Clinical benefit rate after 16 weeks (CBR16) or 24 weeks (CBR24) of enzalutamide plus fulvestrant treatment (left). Swimmer plot of each subject in the study stratified by prior fulvestrant status (right) is shown with prior fulvestrant represented with purple and no prior fulvestrant in blue. Censored end times are marked with an open circle, and participants who experienced an event are marked with black squares.*

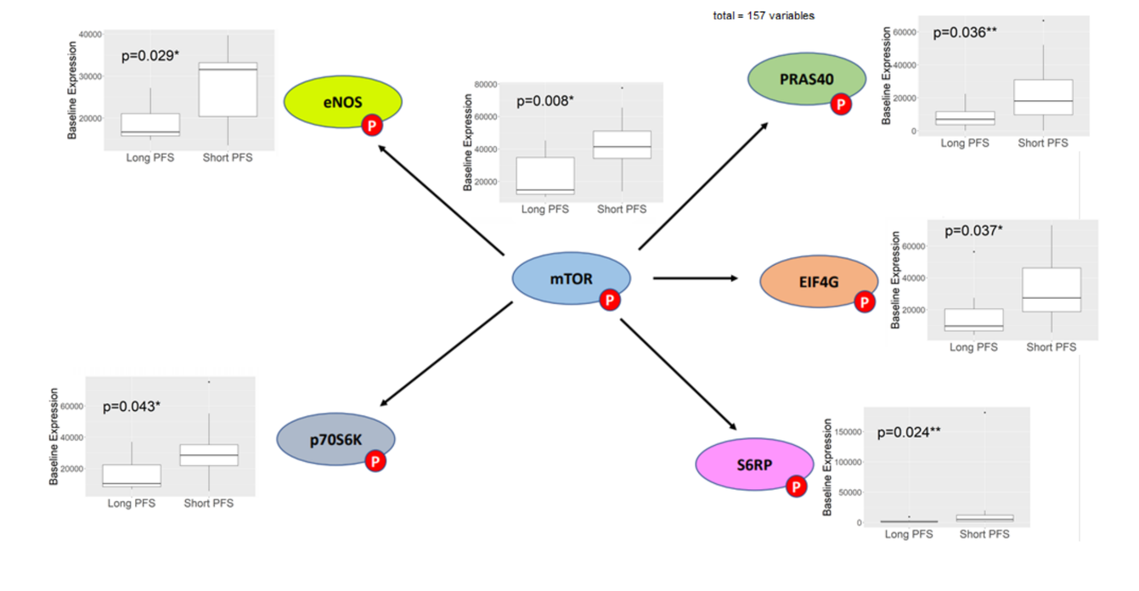
RPPA indicated that the mTOR pathway was significantly active at baseline in tumor biopsies from patients with short versus long PFS



Protein	Log₂ Moderated t-test: Long PFS Mean (SD)[b]	Short PFS Mean (SD)[b]	Mean Diff[a]	p-value	Wilcoxon Rank Sum: Long PFS Med [Min, Max][b]	Short PFS Med [Min, Max][b]	p-value
AXL.Y702	3.55 (5.27)	0 (0)	3.55	0.014	0 [0,12810]	0 [0,0]	0.019
mTOR.S2448	14.43 (0.95)	15.29 (0.61)	-0.86	0.016	21515 [10332,46630]	39340 [13975,77653]	0.076
S6RP.S240.S244	10.5 (1.36)	12.43 (2)	-1.93	0.021	1080 [642,9219]	4854 [985,181680]	0.013
HLA.DR.DP.DQ.DX.total	11.57 (0.16)	12.67 (1.28)	-1.10	0.024	2990 [2620,3583]	6213 [2502,46630]	0.116
eNOS.NOSIII.S116	14.23 (0.34)	14.74 (0.51)	-0.51	0.024	17809 [14765,27174]	31888 [13507,39735]	0.024
Cofilin.S3	13.11 (1.58)	14.63 (1.54)	-1.52	0.035	6647 [3124,80017]	25591 [2271,126754]	0.029
eIF4G.S1108	13.61 (1.23)	14.66 (1.06)	-1.05	0.043	11396 [4036,56387]	25591 [5682,73130]	0.056
HSP90.T5.T7	11.61 (1.47)	13.46 (2.26)	-1.85	0.045	3940 [486,9576]	9745 [726,113550]	0.059
MET.Y1234.Y1235	11.68 (1.24)	12.93 (1.48)	-1.25	0.05	3605 [582,9721]	8296 [884,82454]	0.029
PAK1.S199.S204.PAK2.S192.S197	11.83 (0.31)	12.34 (0.76)	-0.51	0.086	3707 [2631,5177]	5586 [2002,16731]	0.042
NRF2.total	14.74 (0.15)	15.05 (0.45)	-0.31	0.098	28001 [21375,30333]	31730 [20910,64861]	0.029
YAP.S127	14.03 (0.31)	14.36 (0.48)	-0.33	0.123	16301 [12772,22248]	22584 [9557,31571]	0.034
FOXM1.T600	12.48 (0.55)	13.07 (0.99)	-0.59	0.136	6266 [2928,9164]	9629 [1893,20723]	0.042
PRAS40.T246	11.41 (4.81)	13.44 (3.99)	-2.03	0.283	8770 [0,22471]	22505 [0,66836]	0.04
HER2.Y1248	14.17 (0.84)	12.7 (3.84)	1.47	0.285	17579 [7586,57526]	10668 [0,169397]	0.042

[a]Difference is defined as the mean baseline expression amongst the Long PFS group minus the mean baseline expression amongst Short PFS group. A positive difference indicates that the Long PFS group had a larger mean baseline expression than the Short PFS group. A negative difference indicates that the Short PFS group had a larger mean baseline expression than the Long PFS group. The corresponding p-values indicate whether this difference in baseline expression was statistically significant.

[b]Means and SDs are reported in log2 units. Medians, minimums and maximums are reported in original units.



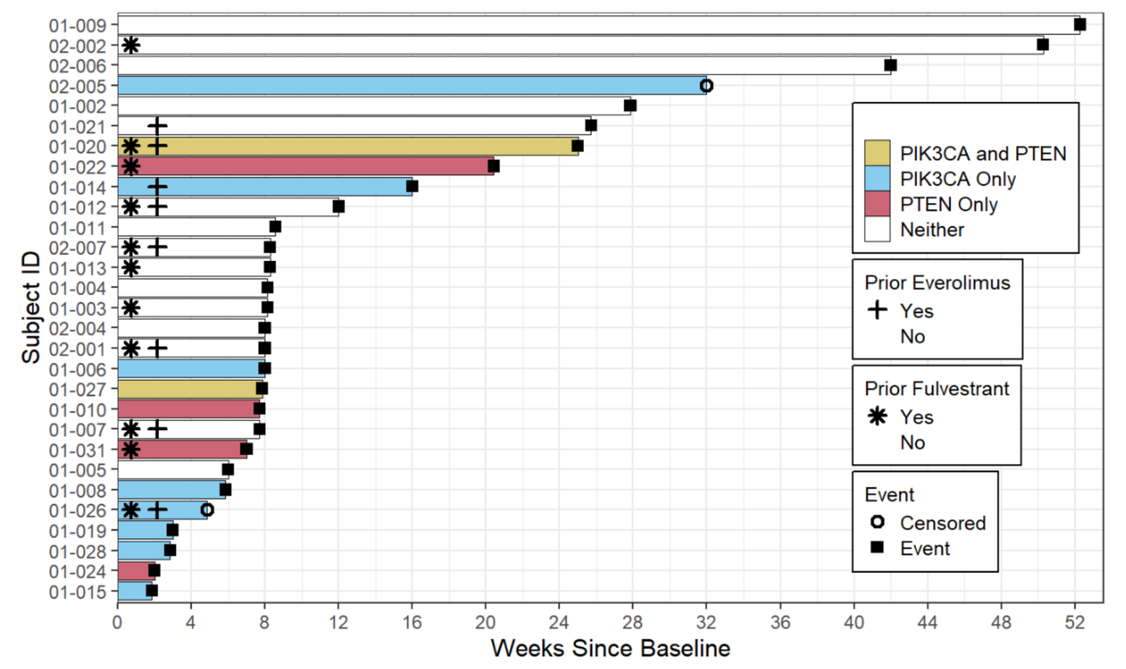
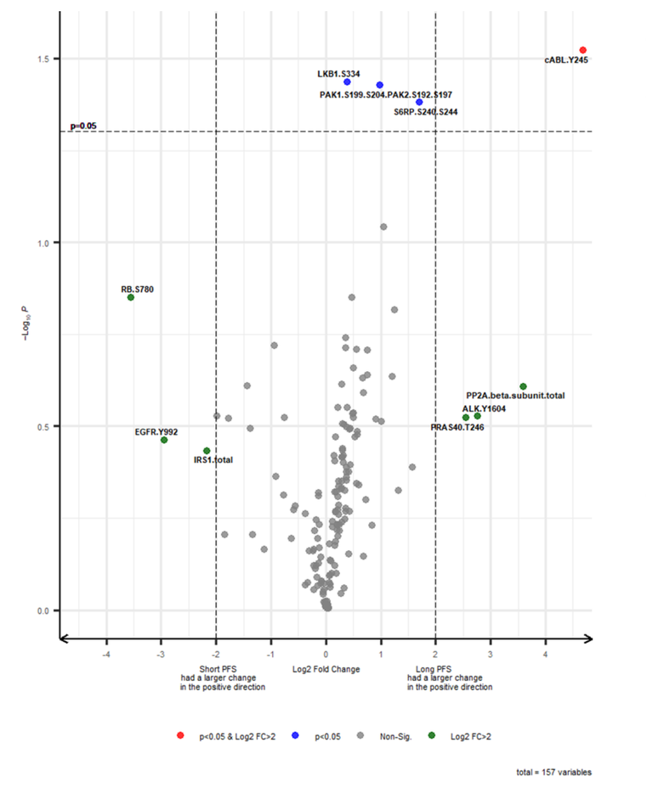


Figure 2. Phosphorylated proteins in the mTOR pathway are significantly higher in patients with short versus long Progression Free Survival at baseline and are associated with mutations in the PIK3CA pathway. *Volcano plot (top left) shows proteins differentially expressed in patients with short versus longer PFS by either the Wilcoxon Rank Sum Test or Log2 Moderated t-test, based on the Clinical 24 Week PFS Definition (table on top right). Phospho-proteins in the mTOR pathway significantly higher in short PFS (less than 60 days) are depicted in box and whiskers plots (bottom left). Swimmer plot shows PFS with PIK3CA and or PTEN mutations and prior Everolimus or Fulvestrant indicated (bottom right).*

Phospho-proteins differentially changed with treatment in metastases from patients with short versus long PFS



Protein	Log₂ Moderated t-test: Long PFS Mean Change (SD)*	Short PFS Mean Change (SD)*	LogFC	p-value	Wilcoxon Rank Sum: Long PFS Med Change [Min, Max]*	Short PFS Med Change [Min, Max]*	p-value
cABL.Y245	1.57 (3.9)	-3.1 (4.69)	4.68	0.03	0 [-6031,3503]	-42 [-101318,5795]	0.552
LKB1.S334	0.35 (0.3)	-0.03 (0.28)	0.38	0.037	4166 [-2011,16247]	-271 [-11742,11612]	0.019
PAK1.S199.S204.PAK2.S192.S197	0.42 (0.59)	-0.56 (1.08)	0.98	0.037	1269 [-1253,5052]	-331 [-13898,1599]	0.03
S6RP.S240.S244	1.48 (1.69)	-0.21 (1.72)	1.69	0.042	1547 [345,22949]	-278 [-65836,43607]	0.157
eIF4G.S1108	0.76 (1.26)	-0.29 (1.3)	1.05	0.091	3804 [-30017,27676]	75 [-52386,31166]	0.536
EGFR.total	0.35 (0.53)	-0.12 (0.69)	0.47	0.141	360 [-1219,10365]	-202 [-8718,7287]	0.211
RB.S780	-1.25 (5.06)	2.31 (5.21)	-3.56	0.141	1153 [-16613,13880]	2639 [-19641,31194]	0.938
S6RP.S235.S236	1.21 (1.83)	-0.04 (1.86)	1.25	0.152	528 [45,11777]	-81 [-78367,54924]	0.275
cKIT.Y719	0.27 (0.29)	-0.08 (0.59)	0.35	0.182	3319 [-1712,11830]	-1146 [-47581,16248]	0.115
TROP2.total	-0.72 (2.1)	0.23 (1.16)	-0.95	0.19	-1161 [-52212,16909]	774 [-49825,46361]	0.311
ATP.Citrate.Lyase.S454	0.34 (0.56)	-0.02 (0.53)	0.36	0.193	178 [-159,2590]	-7 [-1843,4214]	0.241
mTOR.S2448	0.41 (1.14)	-0.14 (0.71)	0.55	0.195	6282 [-6523,33815]	-5769 [-42761,53006]	0.157
STAT1.Y701	0.37 (0.68)	-0.39 (1.42)	0.75	0.196	48 [-1086,3679]	-409 [-20436,3376]	0.311
SRC.Family.Y416	0.21 (0.7)	-0.29 (1.14)	0.50	0.298	1365 [-2821,6044]	-561 [-63627,7800]	0.183
FOXO3a.S253	0.13 (0.21)	-0.01 (0.29)	0.14	0.379	3596 [-3244,11496]	-852 [-13736,16252]	0.183
ATM.S1981	0.26 (0.43)	0.05 (1.1)	0.21	0.627	865 [-1874,7377]	-367 [-7100,7181]	0.183
AKT.T308	-1.96 (4.81)	-0.83 (6.62)	-1.13	0.684	0 [-8631,19558]	8442 [-140808,68004]	0.097

*Change is defined as the difference between baseline and week5 of treatment. A positive change indicates a greater expression at baseline than at week 5. A negative change indicates a greater expression at baseline than at week5

Figure 3. C-ABL pY245 significantly increased with treatment in biopsies from those with longer PFS. *Volcano plot (left) and table (right) show phospho-proteins changing with treatment in patients with short versus long PFS according to either the Wilcoxon Rank Sum Test or the Log2 Moderated t-test. Fold change was calculated as the log_2-transformed ratio of expression at week 5 to expression at baseline is on the y-axis. Positive fold change indicates an increase in expression between baseline and week 5 while a negative fold change indicates a decrease in expression between baseline and week 5. P-values are reported as the minimum of the Wilcoxon Rank Sum Test and the Log_2 Moderated t-test.*

At baseline, ER and PR were significantly higher in *ESR1* mutant versus WT biopsies

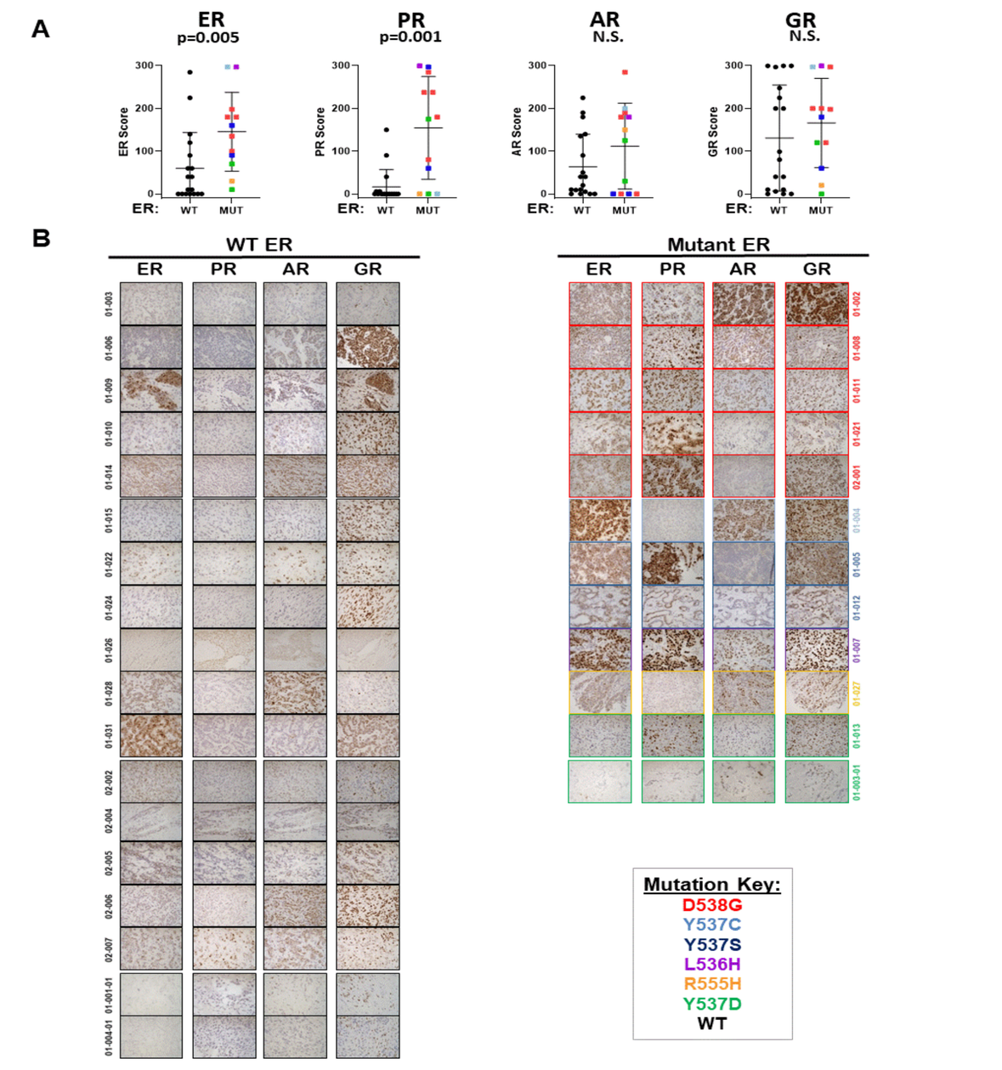


Figure 4. Steroid hormone receptor expression in biopsies of metastatic breast cancer with wild type or mutant ESR1. A. *FFPE sections of core needle biopsies (N=18 ESR1 WT, N=12 mutant ESR1) were stained by IHC for ER, PR, AR and GR. Depicted are the mean scores (intensity x percent cells staining) ± SEM. Mann-Whitney tests were performed. Mutations in ESR1 exon 8 were detected using a modified Archer VariantPlex Solid Tumor Assay through the CMOCO Laboratory (University of Colorado Department of Pathology).* ***B.*** *Representative images for all WT ER metastases (left) and all mutant ER metastases (right) stained for ER, PR, and AR are shown at 400X.*

Immune infiltrate differs in *ESR1* mutant versus WT biopsies

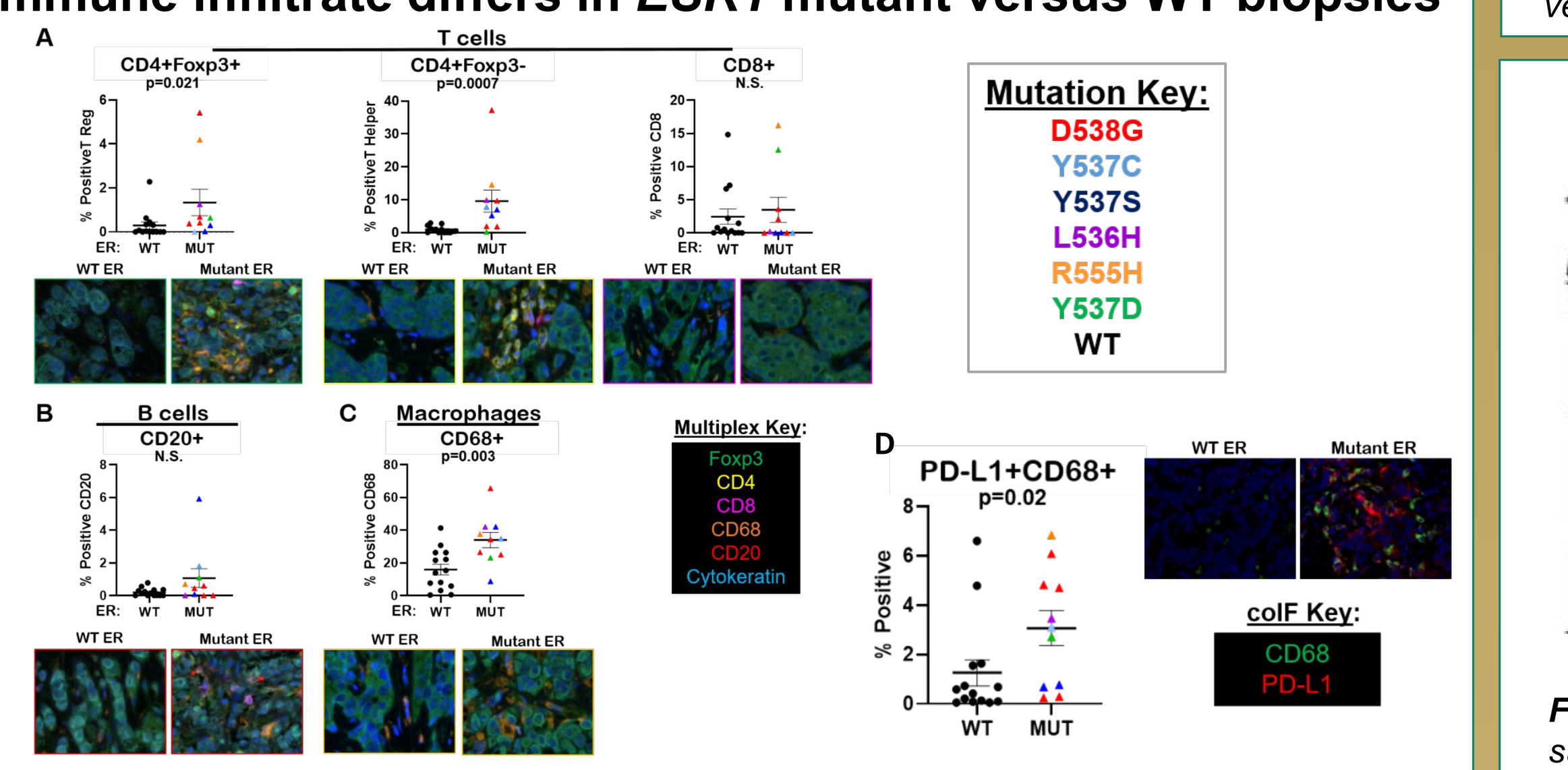


Figure 5. T Regulatory cells, T Helper cells, and macrophages are significantly higher in ESR1 mutant versus WT biopsies at baseline. PD-L1 positive macrophages were also higher in ESR1 mutant biopsies compared to WT. *Biopsies from patients with metastatic breast cancer (n=14 ER WT, n=10 ER mutation) were stained for CD4, Foxp3, CD8, CD68, CD20 and cytokeratin or PD-L1 and CD68 using Opal™ TSA technology (Akoya Biosciences) and slides were scanned using Vectra 3 Automated Quantitative Pathology Imaging System (Perkin Elmer) and 3 to 5 representative fields/tumor analyzed for percent positive cells. Error Bars = Mean with SEM, Mann-Whitney test.*

Immune infiltrates differ in biopsies with *TP53* or *PIK3CA* mutations

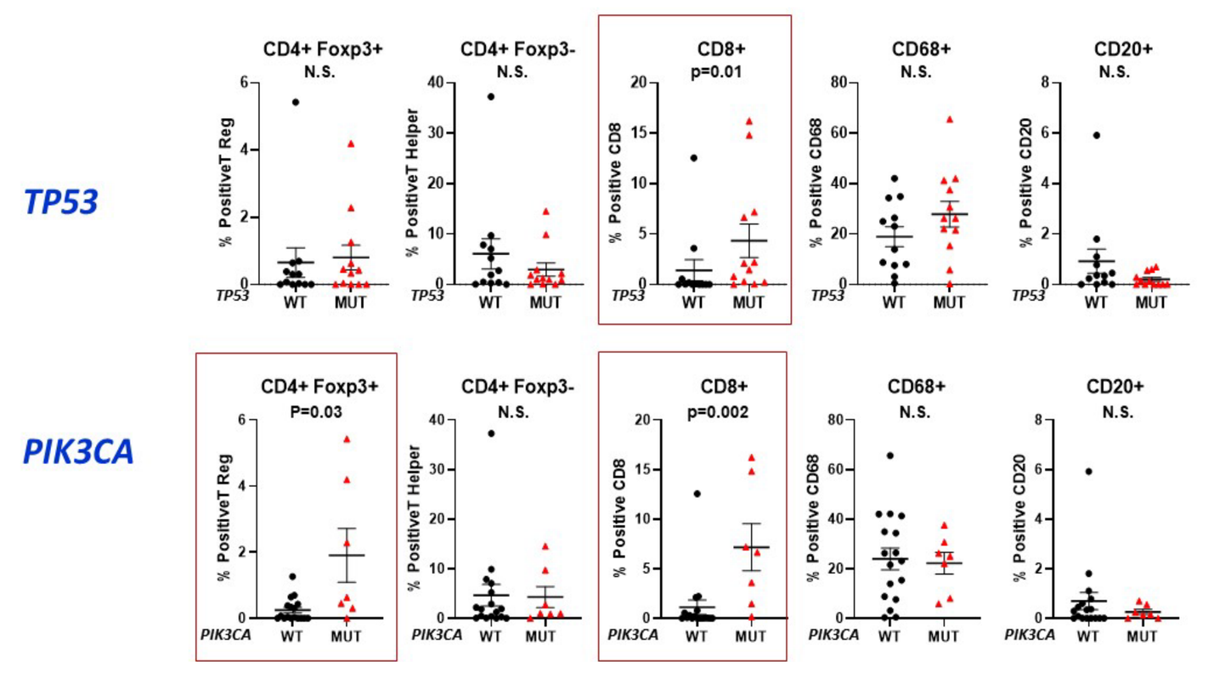


Figure 6. Cytotoxic T cells and T regulatory cells are elevated in TP53 and PIK3CA mutant biopsies compared to wildtype. *Using the same methods as above, biopsies were parsed by TP53 or PIK3CA mutation status and immune cell infiltration. Error Bars = Mean with SEM, Mann-Whitney test.*

PD-L1 significantly increases with Fulvestrant plus Enzalutamide

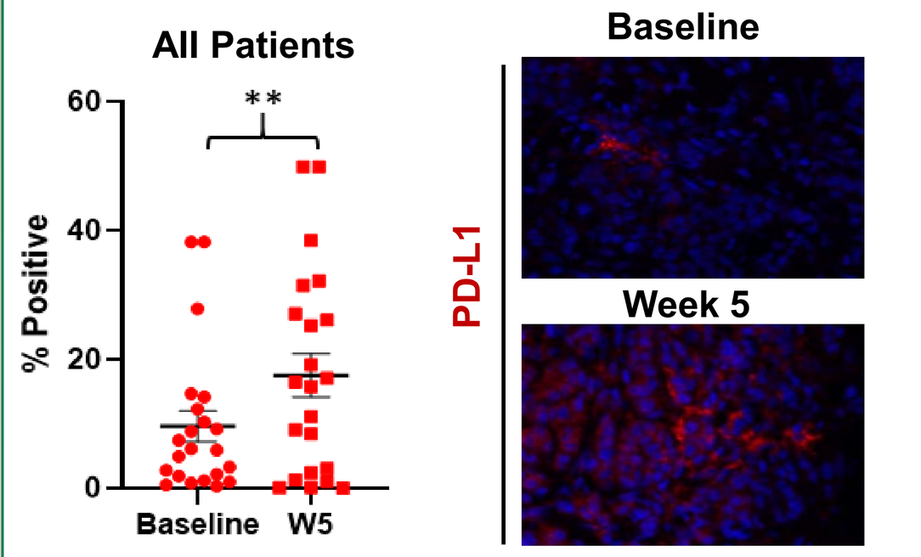


Figure 7. Total PD-L1 expression increased after 5 weeks of Fulvestrant plus Enzalutamide treatment in both ESR1 mutant and wild type biopsies. *Core needle biopsies of metastatic breast cancer were stained for PD-L1 (Abcam SP142) and results show a significant increase in PD-L1 after 5 weeks of treatment by paired t test, **p<0.002. Error bars = SEM. Representative images are shown (right).*

ER and Ki67 decreased significantly with treatment

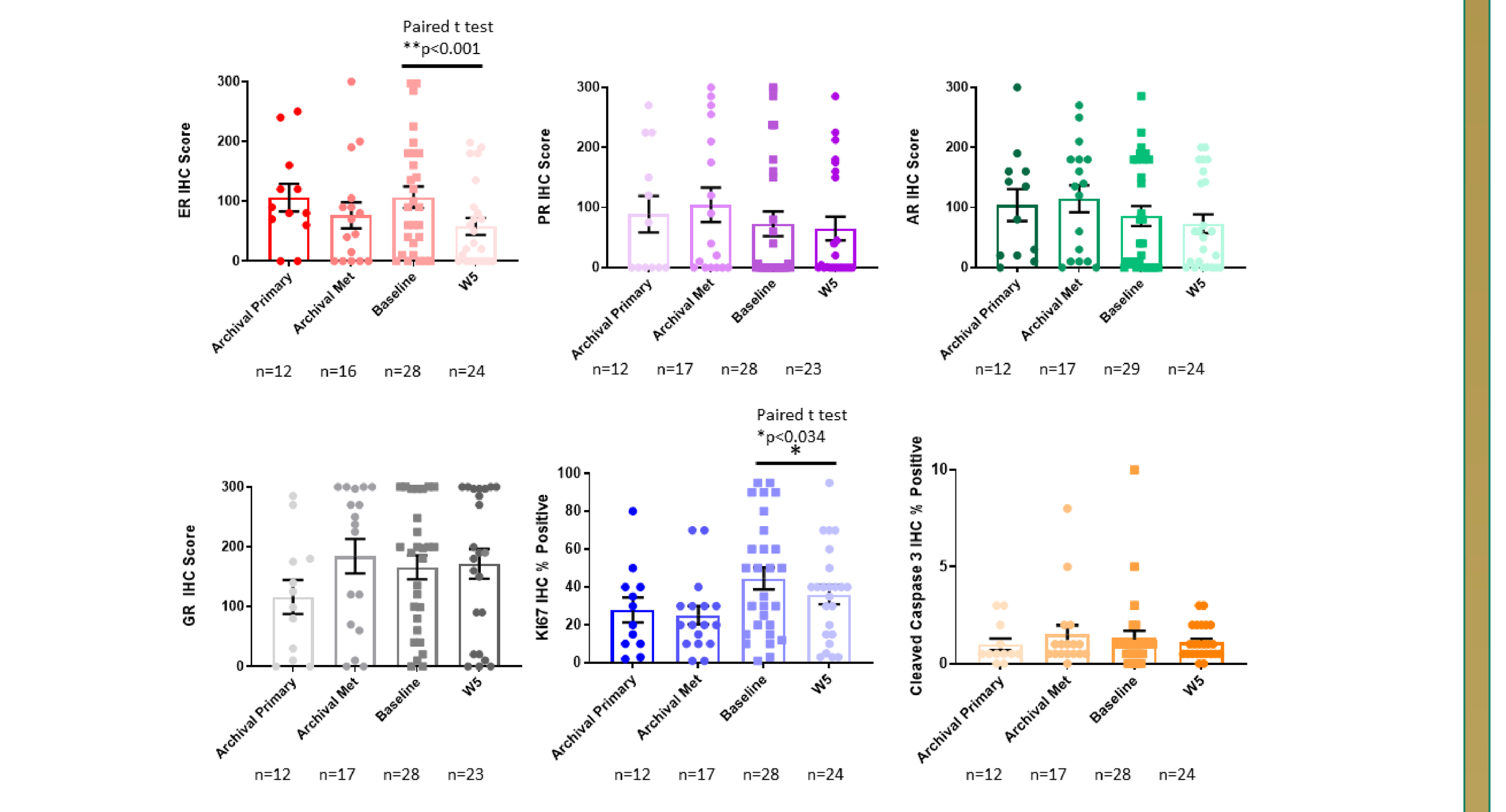


Figure 8. ER and Ki67 significantly decreased with Fulvestrant plus Enzalutamide treatment.. *ER, PR, AR, GR, Ki67, and cleaved caspase 3 were examined by IHC in biopsies at baseline before going on treatment and 5 wks post-treatment and scored by a pathologist. Paired student's t test pre-versus post-treatment were performed.*

Univariate analysis

Predictors	Time to Disease Progression: Hazard Ratio	CI	p
AR<10% Positive	2.28	0.93 – 5.62	**0.073**
ER<10% Positive	4.32	1.46 – 12.83	**0.008**
AR and ER <10% Positive	2.35	0.99 – 5.58	**0.052**
PR<10% Positive	0.73	0.32 – 1.67	0.452
ESR1 Mutation	1.10	0.52 – 2.34	0.797
PTEN and/or PIK3CA	1.99	0.88 – 4.50	**0.096**
Baseline Ki67 (10%)*	1.10	0.97-1.25	**0.133**

Baseline Ki67 was parameterized in terms of 10% increments, such that each 10% increase in baseline Ki67 was associated with a 10.3% increase (95% CI: 3.0% decrease to 25.3% increase) in the hazard of progression (p=0.133). The association between progression and the change in Ki67 between baseline and week 5 was non-significant (p=0.664).

The reference level for "AR and ER <10% Positive" are participants with AR≥10% positive and/or ER≥10% positive. The reference level for "PTEN and/or PIK3CA" was patients with neither loss.

The hazard of disease progression for participants with AR<10% positive was 2.28 (95% CI: 0.93 to 5.62; p=0.073) times the hazard for participants with AR≥10 % positive and the hazard of disease progression for participants with ER<10% positive was 4.32 (95% CI: 1.46 to 12.83) times the hazard for participants with ER ≥ 10 % positive (p=0.008). The hazard of disease progression for participants with AR and/or ER <10% positive was 2.35 (95% CI: 0.99 to 5.58; p=0.052) times the hazard for participants with AR and/or ER≥10% positive. The hazard of disease progression for patients with PTEN and/or PIK3CA was 1.99 (95% CI: 0.88 to 4.50; p=0.096) times the hazard for participants with neither PTEN and/or PIK3CA.All other univariate associations of interest were non-significant predictors of progression, with p-values greater than 0.2.

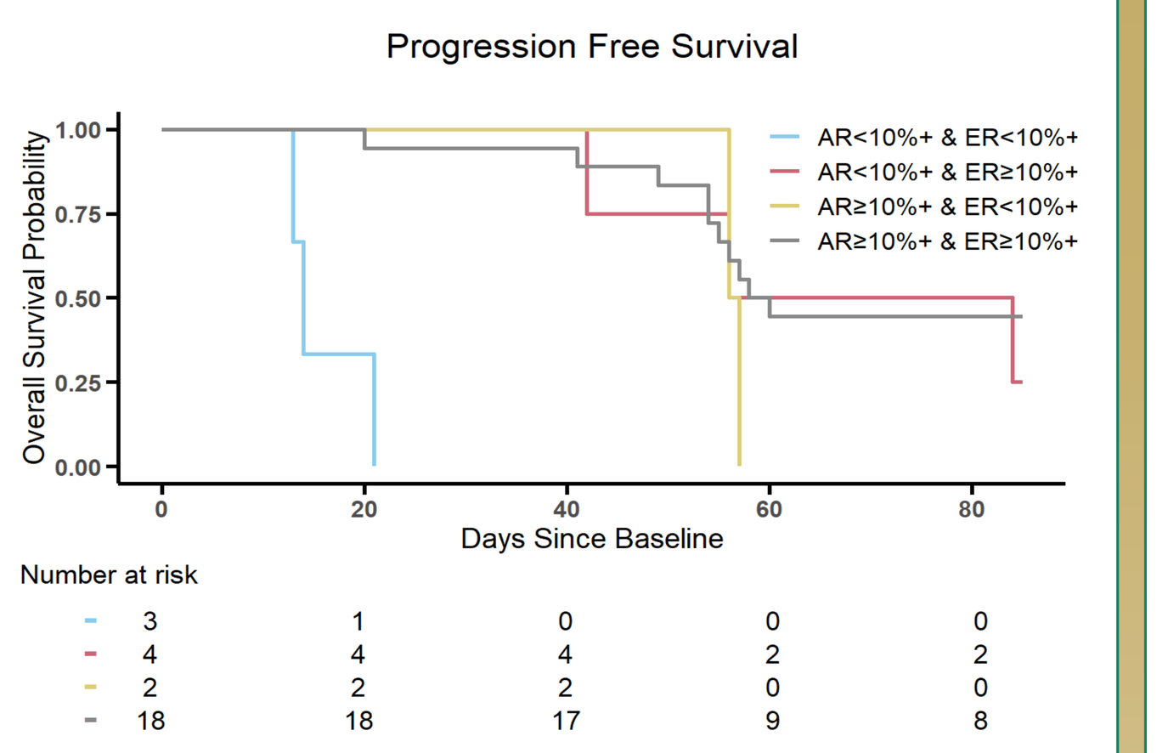


Figure 9. Univariate analysis and survival probability after treatment (censored at 12 weeks) stratified by percent ER and AR status. *A univariate analysis was performed to assess predictors to disease progression (top). Progression free survival was assessed for study subjects stratified by ER and AR status (bottom). Median time to progression for patients with ER ≥ 10 % positive was 59 (95% CI: 56 to Inf[1]) days, while those with ER <10 % positive was 21 days (95% CI: 14 to Inf). Median time to progression for patients with AR ≥ 10 % positive was 57.5 (95% CI: 56 to Inf[1]) days versus AR <10 % positive of 42 days (95% CI: 14 to Inf[1]). Stratified by both AR and ER, median time to progression was 59 (95% CI: 55 to Inf) days when both were high and 14 days (95% CI: 13 to Inf) days when both were low.*

Conclusions

- Fulv plus Enza achieved a CBR at 24 weeks of ~22% in a heavily pretreated population of women with persistent metastatic ER+ BC. Toxicity of the treatment was low grade.
- **Some patients treated with prior Fulv had disease that responded to combined Fulv plus Enza.** This activity may be clinically important and warrants further trials to identify the biologic characteristics of tumors that may benefit from this new combination.
- Univariate analysis indicated that ER and AR protein expression and mutation status affect disease progression.
- RPPA indicated that tumors from patients with short PFS with Fulvestrant plus Enzalutamide **have activated mTOR pathway**.
- 47.6% of metastatic breast cancer biopsies (primarily from liver) harbored mutant *ESR1.*
- Mutant *ESR1* biopsies had significantly higher ER/PR protein expression than those with wild type ESR1. Both mutant and wild type often retain AR and GR.
- Mutant *ESR1* biopsies had significantly higher tumor associated macrophages, CD4 helper T cells, T regulatory cells, and PD-L1 positive macrophages, while *TP53* and *PIK3CA* mutant biopsies had higher cytotoxic T cells.
- **PD-L1 significantly increased with Fulv plus Enza treatment**, suggesting that this new combined endocrine therapy could sensitize ER+ metastatic breast cancers to checkpoint inhibitor therapy. This will need to be investigated and validated.

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