Molecular landscape of patients with metastatic breast cancer who progressed on second line (2L) selective estrogen receptor degraders (SERDs)

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INTRODUCTION

SERDs are a common 2L treatment for patients with HR+ metastatic breast cancer following progression on CDK4/6 inhibitors + endocrine therapy. However, many patients do not benefit from SERDs, and even among those who benefit, the majority of responders progress in < 6 months. Here, we analyzed genomic and transcriptomic differences between patients who progressed on 2L SERDS in < 6 months vs > 6 months to elucidate biological mechanisms contributing to a durable benefit from SERDs.

METHODS

We retrospectively identified patients with metastatic breast cancer from the de-identified Tempus multi-modal database (HR+, HR+/HER2-, or HER2-) who underwent Tempus xF or xT/xR next-generation DNA and RNA sequencing. Patients were filtered to those that received 1L palbociclib, abemaciclib, or ribociclib mono- or combination therapy, followed by 2L elacestrant or fulvestrant mono- or combination therapy (commercially approved SERDs), whose sample was collected < 6 months pre- or post- 2L therapy initiation. Patients were stratified based on timing of progression on 2L therapy into early vs late progressors. P-values and significance ($p<0.05$) in all reported results were computed via either Pearson's Chi-squared test, Fisher's exact test, or Wilcoxon rank sum test, as applicable, and corrected for multiple testing using false discovery rate.

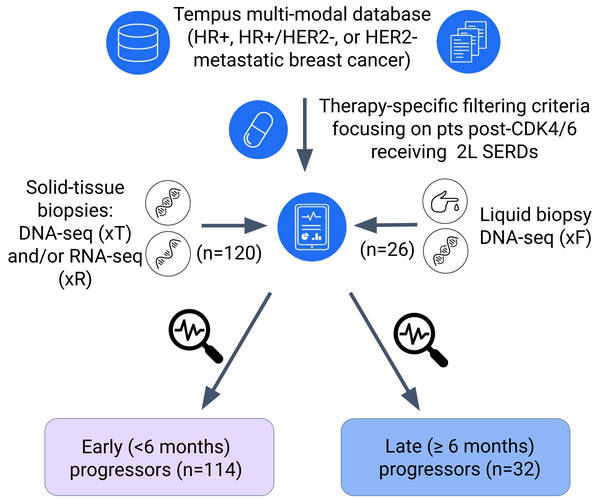

Figure 1. Graphical display of cohort inclusion / exclusion criteria based on retrospective analysis of the Tempus multi-modal database.

SUMMARY

- Higher expression of *ESR1*, *PGR*, and *BAG1* was observed in patients post CDK4/6 who had durable clinical benefit for at least 6 months on second-line SERDs.
- Further validation of these findings should focus on determining whether increased expression of these genes contributes to an improved duration of response to second-line SERDs.

RESULTS

Table 1: Patient Demographics and Clinical Characteristics

	Age at primary diagnosis	Sex	Race				Ethnicity	Subtype				HR status			Menopausal status at sample collection based on age	
	Median (Q1, Q3)	Female	White	Black or African American	Other Race	Asian	Hispanic/ Latino	Invasive Breast Carcinoma, NOS	Breast Invasive Ductal Carcinoma	Breast Invasive Lobular Carcinoma	Invasive Ductal and Invasive Lobular Breast Carcinoma	HR+, HER2-	HR+	HER2-	Premenopausal	Postmenopausal
Overall N=146	58 (50, 64)	145 (99%)	95 (65%)	11 (7.5%)	9 (6.2%)	3 (2.1%)	2 (1.4%)	100 (68%)	30 (21%)	15 (10%)	1 (0.7%)	117 (80%)	24 (16%)	5 (3.4%)	12 (8.2%)	125 (86%)
Early Progressors N=114	57 (49, 64)	113 (99%)	73 (64%)	7 (6.1%)	6 (5.3%)	2 (1.8%)	1 (0.9%)	80 (70%)	22 (19%)	11 (9.6%)	1 (0.9%)	93 (82%)	17 (15%)	4 (3.5%)	11 (9.6%)	97 (85%)
Late Progressors N=32	60 (50, 69)	32 (100%)	22 (69%)	4 (13%)	3 (9.4%)	1 (3.1%)	1 (3%)	20 (63%)	8 (25%)	4 (13%)	0 (0%)	24 (75%)	7 (22%)	1 (3.1%)	1 (3.1%)	28 (88%)

*No significant differences were observed for any of these comparisons ($p>0.1$).

Table 2: 1L and 2L Treatment Details

	Year of 1L therapy start		Year of 2L therapy start		Sample relative to 1L therapy		Sample relative to 2L therapy		Months from 1L therapy start to sample collection	Months from 2L therapy start to sample collection	Fulvestrant in 1L	Fulvestrant in 2L	Elacestrant in 2L
	Prior to 2018	2018 and later	Prior to 2018	2018 and later	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	Median (Q1, Q3)	Median (Q1, Q3)			
Overall N = 146	29 (20%)	116 (80%)	2 (1.4%)	144 (99%)	22 (15%)	122 (85%)	67 (46%)	79 (54%)	19 (7, 30)	0 (-1, 3)	27 (18%)	145 (99%)	1 (0.7%)
Early Progressors N = 114	22 (19%)	91 (81%)	2 (1.8%)	112 (98%)	13 (12%)	100 (88%)	41 (36%)	73 (64%)	19 (10, 30)	2 (-1, 4)	18 (16%)	113 (99%)	1 (0.9%)
Late Progressors N = 32	7 (22%)	25 (78%)	0 (0%)	32 (100%)	9 (29%)	22 (71%)	26 (81%)	6 (19%)	20 (0, 30)	-1 (-4, 0)	9 (28%)	32 (100%)	0 (0%)
p-value	0.8		> 0.9		0.024		< 0.001		0.7	< 0.001	0.11	> 0.9	> 0.9

Treatment journeys between 1L and 2L for eligible patients

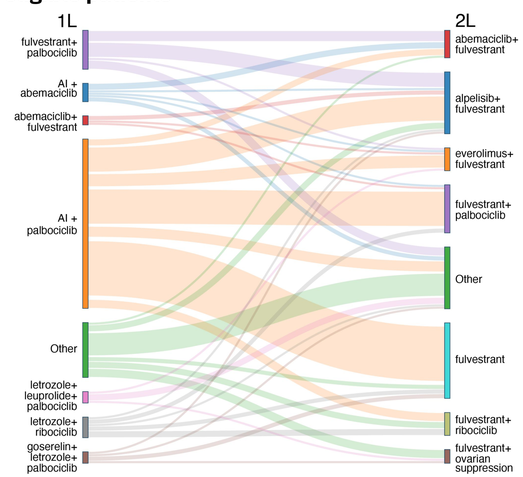

Figure 2. The top 8 most frequent 1L and 2L therapies are explicitly graphed. Less frequent treatments are grouped into the "Other" category.

Somatic mutation prevalence in early and late progressors

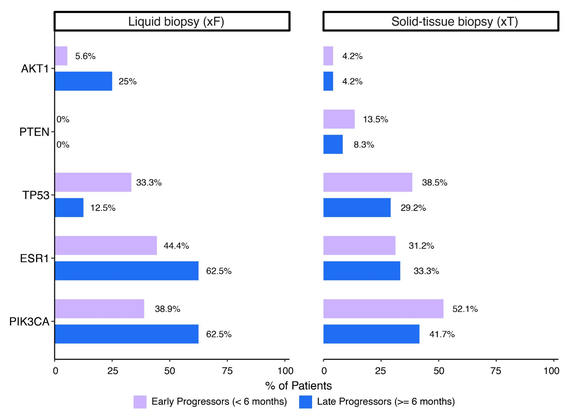

Figure 3. Frequency of mutations in selected genes, assessed using blood- and tissue-based sequencing (Tempus xF and Tempus xT, respectively). There were no genes mutated at statistically different frequencies after correction for multiple testing.

Comparison of select RNA expression levels between early and late progressors

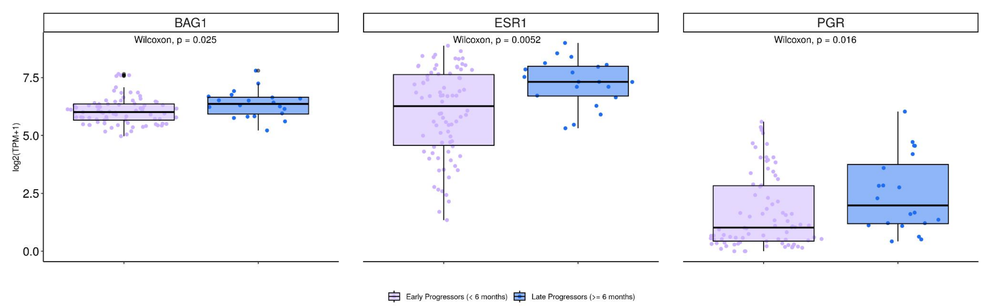

Figure 4. Analysis was restricted to patients that had xT testing and RNA-seq (n=102). N=82 for early progressors and n=20 for late progressors.

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