Evaluation of steroid hormone receptor expression and clinical outcomes in ER-positive breast cancer bone metastases

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SAN ANTONIO BREAST CANCER SYMPOSIUM

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ABSTRACT

Background: Estrogen receptor-positive (ER+) breast cancer (BC) has a high affinity for progression in bone, which is often the initial metastatic site. ER+ BC treatment responses may depend on the expression of additional steroid hormone receptors (SHRs), such as progesterone receptors (PR) or androgen receptors (AR). However, the predictive value of these SHRs in determining ER+ BC bone metastases (BMET) outcomes remains largely unexplored. The possible functional impact of PR and AR targeting on bone-specific ER+ BC progression is also not known. To address this knowledge gap, we evaluated the predictive associations of AR and PR expression with clinical outcomes for ER+ BMET. **Results**: SHR expression was common in ER+ BMET, with 87.1% AR+ and 59.3% PR+. "Triple positive" (AR+/PR+/ER+) BMET were the largest group (53.7%), followed by PR-null AR+/ER+ BMET (33.2%). AR-null ER+ BMET were much less common, with 5.6% or 7.3% PR+ or PR-, respectively. Only 9.4% of PR+/ER+ BMET were AR-, while 38.2% of AR+/ER+ BMET were PR-. AR positivity was associated with the longest OS for ER+ BMET. A similar trend for improved OS was observed in AR-expressing ER- BMET (n=305), though not statistically significant. When stratifying ER+ BMET by the proportion of AR+ cells stained by IHC, having a higher proportion (≥ median) was associated with longer OS only for PR+/ER+ BMET (Cox proportional hazards ratio (HR)=0.70, p=0.003 for high vs low AR % cells stained). There was no significant difference in CDKi TOT across groups. However, OS was significantly and uniquely longer for AR+ (not AR-) ER+ BMET patients (pts) who received CDKi, which was highest when PR was co-expressed (HR=0.62, p<0.0001 for pts with vs without CDKi), as compared to PR- (HR=0.73, p=0.012). ESR1mut prevalence was similar in AR+ (17.0%) vs AR- (10.7%) ER+ BMET, with OS reduced in ESR1mut (vs wildtype, wt) AR+/ER+ BMET (HR=1.92, p<0.0001). PIK3CAmut were more prevalent in AR+ (51.5%) vs AR- (27.3%) ER+ BMET. However, there was no difference in OS between PIK3CAmut vs wt for any SHR ER+ BMET subtype. While not SHR-regulated, RNA expression of the SHR pioneer factor FOXA1 positively correlated with that of AR, PGR (PR), and ESR1 (ER) in ER+ BMET across all SHR subtypes. Several known AR-regulated genes were among the most highly expressed genes in AR+ vs AR- BMET, consistent with functional AR signaling. Notably, expression of PIP, HMGCS2, and CYP4Z1 was significantly higher in AR+ vs AR- BMET, regardless of ER status. **Conclusions:** Our findings suggest that AR expression may have utility as a predictive biomarker of improved survival and response to CKD4/6 inhibitors in those with HER2-/ER+ BMET, particularly when co-expressed with PR, with evidence of functional AR signaling in both ER+ and ER- AR-expressing BC BMET. Whether AR in this context is a biomarker or mediator of improved survival cannot be determined. Therapeutic consequences of AR targeting to reduce AR+ BC progression in bone, also an AR-regulated tissue, may hold promise, although whether with an agonist or antagonist remains an intriguing and yet unanswered question.

INTRODUCTION

- Estrogen receptor-positive (**ER+)** breast cancer (**BC**) has a high affinity for progression in bone, which is often the initial metastatic site.
- ER+ BC treatment responses may depend on the expression of additional steroid hormone receptors (SHRs), such as progesterone (**PR**) or androgen receptors (**AR**).
- However, the predictive value of these SHRs in determining ER+ BC bone metastases (**BMET**) outcomes and the possible functional impact of AR or PR targeting remains unclear.[1,2]

OBJECTIVE

- To evaluate predictive associations of AR +/- PR expression with ER+ BMET clinical outcomes.

METHODS

- A retrospective analysis was conducted using BC BMET samples profiled at Caris Life Sciences, with survival outcomes inferred from insurance claims.
- HER2-/ER+ BC BMET specimens (n=1677; see **Table 1**) were identified and then further stratified for AR and PR staining using immunohistochemistry (IHC):
  - HER2-: ≤1+ intensity or ≤10% cells stained, or 2+ & >10% with CISH-null reflex test;
  - ER+: ≥1+ & ≥1%;[5] and then: AR+: ≥1+ & ≥10%[6] and/or PR+: ≥1+ & ≥1%.[5]
- Associations between AR ± PR expression and 1) overall survival (OS, inferred from biopsy to last contact), including CDK4/6 inhibitor time-on-therapy (CDKi TOT); 2) pathogenic gene mutations (mut) known to alter BC survival (*ESR1mut* or *PIK3CAmut*); or 3) AR-regulated gene expression[3,4] via whole-transcriptome RNA-seq (WTS) were examined.
- Correlations were determined using Spearman's Rho (ρ).

RESULTS

FIG 1. BMET SAMPLE CHARACTERISTICS

Table 1. HER2-/ER+ BMET Demographics

Category	Characteristic	All ER+BMETs	ER+/PR+/AR+	ER+/PR-/AR+	ER+/PR+/AR-	ER+/PR-/AR-
Cohort Size	n	1677	902	558	94	123
Median (range)	Age	63.0 (25-90)	63.0 (25-90)	64.0 (28-90)	62.5 (27-86)	60.0 (31-90)
Specimen Site	Bone	1677 (100.0%)	902 (100.0%)	558 (100.0%)	94 (100.0%)	123 (100.0%)
Gender	Female	1646.0 (98.2%)	882.0 (97.8%)	550.0 (98.6%)	91.0 (96.8%)	123.0(100.0%)
	Male	31.0 (1.8%)	20.0 (2.2%)	8.0 (1.4%)	3.0 (3.2%)	0 (0%)
Race	White	1073 (64.0%)	590 (65.4%)	361 (64.7%)	46 (48.9%)	76 (61.8%)
	Unknown/Other	385 (23.0%)	205 (22.7%)	118 (21.1%)	31 (33.0%)	31 (25.2%)
	Black or African American	179 (10.7%)	88 (9.8%)	63 (11.3%)	16 (17.0%)	12 (9.8%)
	Asian or Pacific Islander	40 (2.4%)	19 (2.1%)	16 (2.9%)	1 (1.1%)	4 (3.3%)
Ethnicity	Not Hispanic or Latino	1217 (72.6%)	658 (72.9%)	418 (74.9%)	59 (62.8%)	82 (66.7%)
	Unknown/Other	327 (19.5%)	172 (19.1%)	98 (17.6%)	24 (25.5%)	33 (26.8%)
	Hispanic or Latino	133 (7.9%)	72 (8.0%)	42 (7.5%)	11 (11.7%)	8 (6.5%)
ESR1	*ESR1wt*	866 (82.2%)	461 (77.6%)	299 (88.5%)	45 (83.3%)	61 (89.7%)
	*ESR1mut**	171 (16.2%)	126 (21.2%)	32 (9.5%)	9 (16.7%)	4 (5.9%)
PIK3CA	*PIK3CAwt*	534 (50.9%)	279 (46.9%)	167 (50.0%)	39 (73.6%)	49 (72.1%)
	*PIK3CAmut**	511 (48.7%)	311 (52.3%)	167 (50.0%)	15 (28.3%)	18 (26.5%)
Treatment of Interest	Tamoxifen	362 (21.6%)	185 (20.5%)	123 (22.0%)	26 (27.7%)	28 (22.8%)
	Anastrozole	573 (34.2%)	283 (31.4%)	209 (37.5%)	29 (30.9%)	52 (42.3%)
	Exemestane	353 (21.0%)	175 (19.4%)	132 (23.7%)	19 (20.2%)	27 (22.0%)
	Letrozole	741 (44.2%)	408 (45.2%)	239 (42.8%)	41 (43.6%)	53 (43.1%)
	Fulvestrant	819 (48.8%)	423 (46.9%)	293 (52.5%)	38 (40.4%)	65 (52.8%)
	Abemaciclib	250 (14.9%)	129 (14.3%)	95 (17.0%)	17 (18.1%)	9 (7.3%)
	Palbociclib	680 (40.5%)	361 (40.0%)	228 (40.9%)	47 (50.0%)	44 (35.8%)
	Ribociclib	136 (8.1%)	77 (8.5%)	48 (8.6%)	5 (5.3%)	6 (4.9%)

*mut = any pathogenic or likely pathogenic (P/LP) mutation

FIG 2. AR+ BMET ASSOCIATED WITH SIGNIFICANTLY LONGER OS

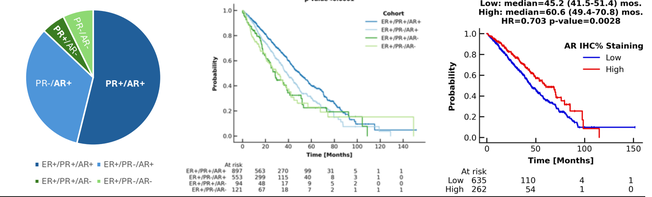


Fig 2. A. The majority (87%) of HER2-/ER+ BMET are AR+. "Triple positive" (ER+/PR+/AR+) BMET comprise the largest SHR subtype. **B.** OS was longest among patients with AR+ BMET, with a similar trend seen for AR-expressing ER- BMET (not shown). **C.** Having a higher proportion of cells staining for AR by IHC (divided at the cohort-specific median % cells stained for AR by IHC, at any intensity; low, ≤ 90%; high, >90%) was associated with longer OS only for "triple positive" BMET.

FIG 3. CDKi OUTCOMES BY HER2-/ER+BMET SHR SUBTYPE

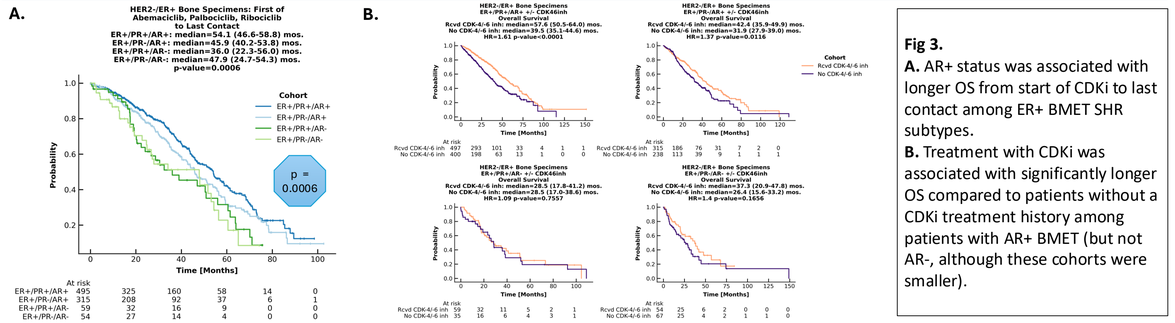


Fig 3.
A. AR+ status was associated with longer OS from start of CDKi to last contact among ER+ BMET SHR subtypes.
B. Treatment with CDKi was associated with significantly longer OS compared to patients without a CDKi treatment history among patients with AR+ BMET (but not AR-, although these cohorts were smaller).

FIG 4. *ESR1* AND *PIK3CA* MUTATIONS ARE MORE PREVALENT IN AR+ BMET

Fig 4.
A. Prevalence of pathogenic or likely pathogenic *ESR1* or *PI3KCA* mutations was higher in AR+ (vs AR-) BMET.
B. *ESR1* mutations were associated with shorter OS in AR+ BMET with or without PR (AR+/PR+ shown here).
C. OS did not vary by *PIK3CA* mutational status in AR+ BMET with or without PR (AR+/PR+ shown here).

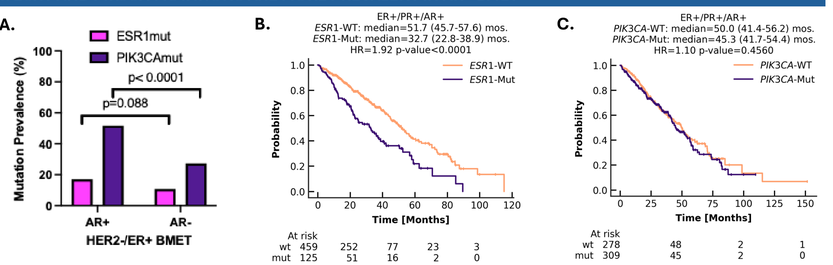


FIG 5. GENE EXPRESSION OF FOXA1, A SHR PIONEER FACTOR, CORRELATED WITH SHR

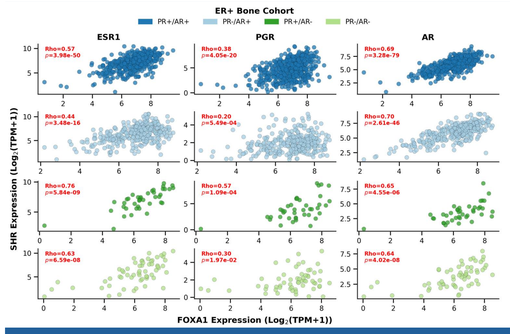


Fig 5. WTS analysis of ER+ BMETs demonstrated a positive correlation between gene expression of FOXA1, a SHR pioneer factor facilitating SHR gene transcription,[7] and SHR gene expression across all SHRs and SHR subtypes. *Rows/color, SHR subtype; columns, SHR gene; y-axis, SHR gene expression; x-axis, FOXA1 gene expression*

FIG 6. EXPRESSION OF AR-REGULATED GENES BY BMET SHR SUBTYPE

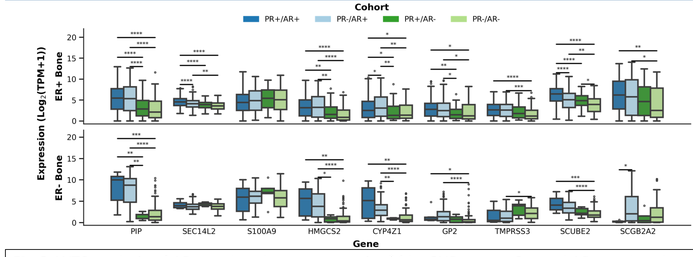


Fig 6. WTS analysis of AR-regulated gene expression[3,4] by SHR status. Several AR-regulated genes were more highly expressed in AR+ (vs AR-) BMET regardless of ER status, consistent with functional AR signaling activity.

CONCLUSIONS

- Our findings suggest that AR expression may have utility as a predictive biomarker of improved survival in those with HER2-/ER+ BMET, particularly when co-expressed with PR.
- Co-expression of SHR pioneer factor FOXA1 with AR in BMET,[7] combined with evidence of higher expression of AR-regulated genes in AR+ (vs AR-) BMET, is consistent with active AR signaling in AR+ BMET.
- However, whether AR in this context is a biomarker or mediator of improved survival cannot be determined from data presented here.
- Targeting AR to reduce AR+ BC progression in bone, an AR-regulated tissue, may hold therapeutic promise, although whether to use an agonist or antagonist remains an intriguing and yet unanswered question.

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