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High *p62* and *ALDH1A3* Reduce the Effectiveness of Endocrine Therapy in Luminal B Breast Cancer

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Abstract

Background/Aim: High expression of *p62* and *ALDH1A3* indicates a poor clinical outcome in luminal B breast cancer, and p62 is involved in the progression of ALDH1-positive luminal B breast cancer stem cells. However, the association between endocrine therapy and high *p62* and *ALDH1A3* expression, in luminal B breast cancer remains unclear.

Materials and Methods: Two datasets with gene expression and clinical data for patients with primary breast cancer (METABRIC, n=2,509; The Cancer Genome Atlas, n=1,084) were downloaded and statistically analyzed. To evaluate the association between the *p62* and *ALDH1A3* expression levels and endocrine therapy, including tamoxifen and aromatase inhibitor, in patients with luminal B breast cancer, disease-specific survival was examined using Kaplan-Meier and multivariate Cox regression analyses.

Results: Patients with *p62*^{high} *ALDH1A3*^{high} luminal B breast cancer treated with endocrine therapy exhibited a poor prognosis. Moreover, patients with *p62*^{high} *ALDH1A3*^{high} luminal B breast cancer treated with tamoxifen showed a trend towards a poor prognosis, but those treated with aromatase inhibitors showed a significantly poor prognosis. These results suggest that endocrine therapy, especially aromatase inhibitors, exhibits a reduced effectiveness against *p62*^{high} *ALDH1A3*^{high} luminal B tumors.

Conclusion: p62 and *ALDH1A3* could be used together as a prognostic biomarker for predicting the efficacy of endocrine therapy for luminal B breast cancer.

Keywords: *p62*, *ALDH1A3*, endocrine therapy, breast cancer, luminal B.

[*]These Authors contributed equally to this study.

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Introduction

Breast cancer has the highest incidence rate and is the leading cause of cancer-related death among women worldwide (1). Among the breast cancer subtypes, luminal A and luminal B express estrogen receptor (ER) and/or progesterone receptor, and certain luminal B tumors express HER2 and highly express the proliferation marker Ki-67 (*MKI67*) (2, 3). Additionally, luminal B breast cancer has a poorer prognosis among the breast cancer subtypes (2-10). The main treatments for luminal B breast cancer entail surgery, radiotherapy and drug therapy, which include endocrine therapy, HER2-targeted therapy, and chemotherapy (2, 3, 11). However, since the luminal B subtype still exhibits a poorer prognosis, further stratification and the development of prognostic markers and therapeutic targets are required for improving the quality of life of patients. It is also important to identify effective prognostic biomarkers to assess the effectiveness of treatments for luminal B breast cancer.

Cancer stem cells (CSCs) have stem-like properties such as self-renewal, multi-differentiation and tumorigenicity (12, 13). Since CSCs are resistant to conventional drug therapy and radiotherapy, the development of targeted therapies against CSCs is necessary to improve the clinical outcomes of patients (12-15). Aldehyde dehydrogenase 1 (ALDH1) is a detoxifying enzyme that converts aldehydes into carboxylic acids and is known as a CSC marker (16). Among the *ALDH1* genes*, ALDH1A3* is known to be a CSC marker in several cancer types (17, 18). *ALDH1A3* expression is correlated with tumor grade, metastasis and the clinical outcome of breast cancer (19-21), and it is a significant contributory factor to ALDH1 activity in this disease (20, 22). *ALDH1A3* expression is also associated with chemoresistance and radioresistance in several cancer types (17, 22, 23). However, the association between *ALDH1A3* expression and the effectiveness of endocrine therapy in luminal B breast cancer remains to be elucidated.

p62 is a multifunctional scaffold protein that is involved in various biological and cellular activities, including the NF-κB signaling pathway, antioxidant response and autophagy (24-34). p62 is highly expressed in a number of cancer types (35-45), and high p62 expression is corelated with a poor clinical outcome in several cancer types (38, 41, 43, 46-49). The p62 gene and protein are also highly expressed in breast cancer (50-52), and high p62 expression is corelated with a poor clinical outcome (51-55). Furthermore, high expression of *p62* and *ALDH1A3* indicates a poor clinical outcome in luminal B breast cancer, and p62 is involved in the cancerous progression of ALDH1-positive luminal B breast CSCs (55). Moreover, co-expression of *p62* and *ALDH1A3* in luminal B breast cancer reduces the effectiveness of radiotherapy (56). However, the association between endocrine therapy and high *p62* and *ALDH1A3* expression, in luminal B breast cancer remains unclear.

The results of the present study revealed that *p62*^{high} *ALDH1A3*^{high} luminal B tumors are associated with a reduced effectiveness of endocrine therapy, especially aromatase inhibitor therapy.

Materials and Methods

Datasets. The Molecular Taxonomy of Breast Cancer International Consortium (METABRIC; n=2,509) (57, 58) and The Cancer Genome Atlas (TCGA; n=1,084) (59) datasets were downloaded from cBioportal (60, 61) on August 1, 2024. The details of the data are shown in Figure 1 and have also been reported previously (62).

Statistical analysis. The details of the statistical analyses have been reported previously (62). The optimal cutoff determined by the Youden's index following receiver operating characteristic analysis was used to divide each group into the *p62* or/and *ALDH1A3* high and low gene expression groups for disease-specific survival (DSS) analysis (Table I). Kaplan-Meier curves for DSS were plotted and then compared using the log-rank (Cochran-Mantel-Haenszel) test. Multiplicity was adjusted using the Holm test as a post hoc test. A multivariate Cox regression analysis for DSS was performed to evaluate the influence

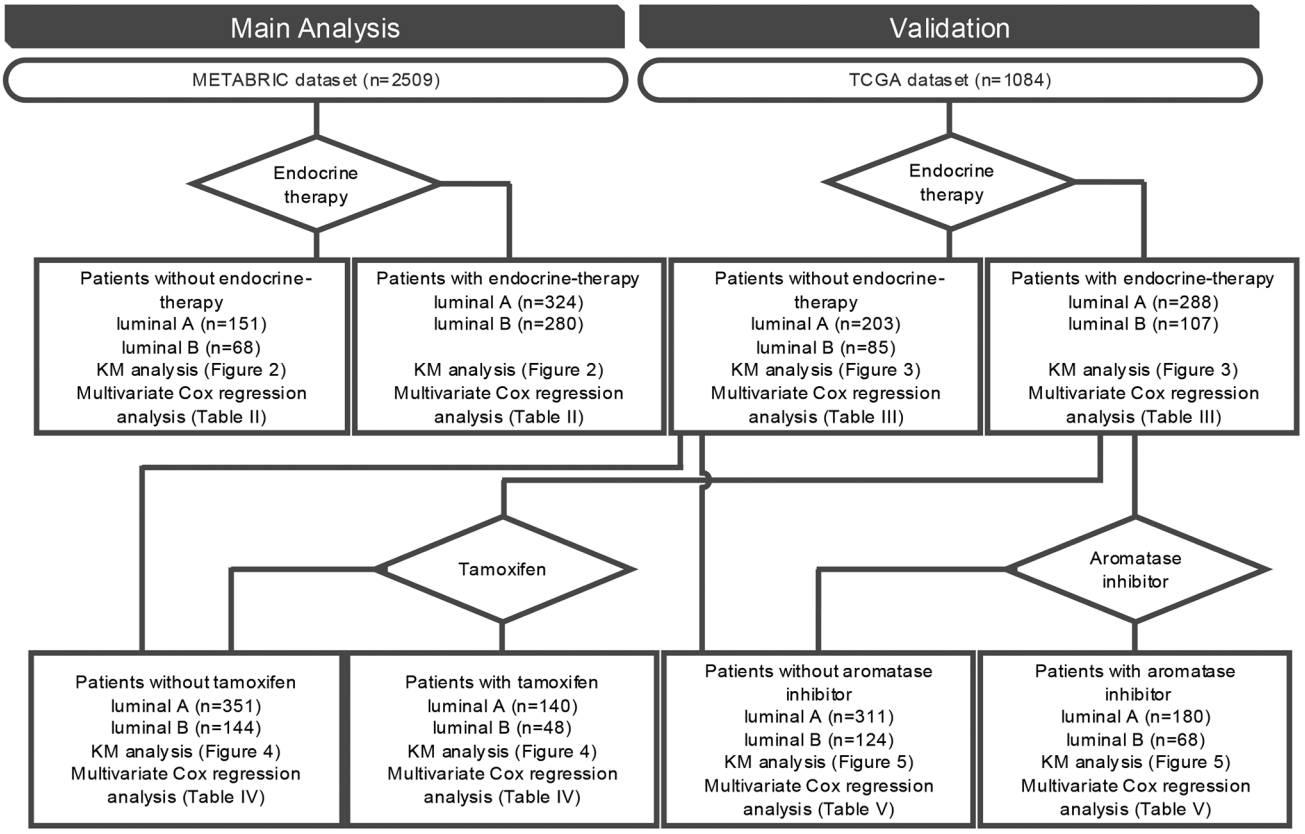


Figure 1. *The overall workflow and design of the present study.*

of gene expression and to estimate the adjusted hazard ratios (HRs) with the age at diagnosis as a confounding factor in Table II, Table III, Table IV and Table V. In Table II, chemotherapy and radiotherapy were also included as additional confounding factors. Two-sided $p<0.05$ was considered to indicate a statistically significant difference. All statistical analyses were conducted using R software (version 4.3.0) and BellCurve for Excel (version 4.05; Social Survey Research Information Co., Ltd., Tokyo, Japan).

Results

Endocrine therapy is insufficient for treating p62^{high} luminal A breast cancer but sufficient for p62^{high} luminal B breast cancer in the METABRIC dataset. High *p62* expression is associated with poorer clinical outcomes in luminal A and luminal B breast cancer (55). However, the association between endocrine therapy and high *p62* expression in the luminal A and luminal B breast cancer subtypes remains unclear. Therefore, to examine the clinical outcome of patients with *p62*^{high} luminal A and luminal B breast cancer treated with endocrine therapy, Kaplan-Meier and multivariate analyses for DSS were performed. The overall workflow of the present study is shown in Figure 1. We first analyzed the gene expression data from patients with breast cancer in the METABRIC dataset. We performed Kaplan-Meier analysis to compare the DSS of patients with *p62*^{high} or *p62*^{low} luminal A and luminal B breast cancer who did or did not receive endocrine therapy. Patients with *p62*^{high} luminal A breast cancer who did not receive endocrine therapy exhibited a good prognosis and those who received endocrine therapy displayed a poorer

Table I. *Youden's index calculated by ROC analysis of each group from the METABRIC and TCGA datasets.*

Dataset	Gene	Patient group		Cutoff threshold
METABRIC	*p62*	Luminal A	Without endocrine-therapy	10.4525
			With endocrine-therapy	11.0546
		Luminal B	Without endocrine-therapy	10.5908
			With endocrine-therapy	10.0867
	ALDH1A3	Luminal A	Without endocrine-therapy	7.8129
			With endocrine-therapy	7.7156
		Luminal B	Without endocrine-therapy	7.5717
			With endocrine-therapy	6.3074
TCGA	*p62*	Luminal A	Without endocrine-therapy	–0.2057
			With endocrine-therapy	–0.2864
			Without Tamoxifen	–0.2057
			With Tamoxifen	–0.6765
			Without Aromatase inhibitor	–0.2057
			With Aromatase inhibitor	–0.2864
		Luminal B	Without endocrine-therapy	–1.2247
			With endocrine-therapy	0.4611
			Without Tamoxifen	0.5312
			With Tamoxifen	–0.8610
			Without Aromatase inhibitor	–0.4941
			With Aromatase inhibitor	0.4611
	ALDH1A3	Luminal A	Without endocrine-therapy	–0.6529
			With endocrine-therapy	–0.1829
			Without Tamoxifen	0.3004
			With Tamoxifen	–0.1077
			Without Aromatase inhibitor	0.0483
			With Aromatase inhibitor	–0.1829
		Luminal B	Without endocrine-therapy	–0.7934
			With endocrine-therapy	–1.1410
			Without Tamoxifen	–0.7934
			With Tamoxifen	–0.9330
			Without Aromatase inhibitor	–0.6501
			With Aromatase inhibitor	–0.2114

ROC: Receiver operating characteristic; METABRIC: Molecular Taxonomy of Breast Cancer International Consortium; TCGA: The Cancer Genome Atlas; ALDH1A3: aldehyde dehydrogenase 1 family member A3.

prognosis (p=0.0035) (Figure 2A). Although patients with *p62*^{high} luminal B breast cancer who did not receive endocrine therapy exhibited a poorer prognosis (p<0.001), those who did receive endocrine therapy showed an improved prognosis (Figure 2B).

Next, multivariate Cox regression analysis of DSS was performed with age, chemotherapy and radiotherapy as confounding factors. As with the Kaplan-Meier analysis, patients with *p62*^{high} luminal A breast cancer who received endocrine therapy exhibited poorer clinical outcomes [without endocrine therapy: hazard ratio (HR)=1.66, 95% confidence interval (CI)=0.85-3.25, p=0.142; with endocrine therapy: HR=1.57, 95%CI=1.06-2.33, p=0.024] (Table II). Patients with *p62*^{high} luminal B breast cancer who did not receive endocrine therapy exhibited poorer clinical outcomes (HR=3.84, 95%CI=1.64-8.99, p=0.002) and those who received endocrine therapy exhibited improved clinical outcomes (HR=1.41, 95%CI=0.90-2.19, p=0.132) (Table II). These results suggest that endocrine therapy may be insufficient for treating *p62*^{high} luminal A breast cancer.

Endocrine therapy is insufficient for treating p62^{high}ALDH1A3^{high} luminal B breast cancer in the METABRIC dataset. We have

Table II. *Multivariate Cox regression analyses for DSS among the p62^{high}ALDH1A3^{high}, p62^{high}ALDH1A3^{low}, p62^{low}ALDH1A3^{high} and p62^{low}ALDH1A3^{low} groups of patients with the luminal breast cancer subtypes treated with or without endocrine therapy in the METABRIC dataset.*

METABRIC dataset		Hazard ratio	95% Confidence interval		*p*-Value
p62^{high} *vs. p62*^{low}					
Without endocrine-therapy					
Luminal A		1.657	0.845	3.251	0.142
Luminal B		3.844	1.644	8.987	**0.002**
With endocrine-therapy					
Luminal A		1.573	1.062	2.330	**0.024**
Luminal B		1.405	0.903	2.186	0.132
ALDH1A3^{high} *vs. ALDH1A3*^{low}					
Without endocrine-therapy					
Luminal A		1.362	0.747	2.486	0.313
Luminal B		0.462	0.185	1.154	0.098
With endocrine-therapy					
Luminal A		0.728	0.486	1.090	0.123
Luminal B		1.746	0.988	3.088	0.055
p62^{high} *ALDH1A3*^{high} *vs.* others					
Without endocrine-therapy					
Luminal A		1.342	0.720	2.501	0.355
Luminal B		1.539	0.540	4.389	0.420
With endocrine-therapy					
Luminal A		1.194	0.678	2.103	0.540
Luminal B		1.517	1.045	2.202	**0.028**
p62^{high} *ALDH1A3*^{high} *vs.*					
Without endocrine-therapy					
Luminal A	*p62*^{high} *ALDH1A3*^{low}	0.975	0.476	1.998	0.946
	p62^{low} *ALDH1A3*^{high}	1.087	0.429	2.751	0.860
	p62^{low} *ALDH1A3*^{low}	2.489	0.881	7.031	0.085
Luminal B	*p62*^{high} *ALDH1A3*^{low}	0.968	0.334	2.809	0.953
	p62^{low} *ALDH1A3*^{high}	4.682	0.802	27.345	0.086
	p62^{low} *ALDH1A3*^{low}	1.933	0.424	8.816	0.394
With endocrine-therapy					
Luminal A	*p62*^{high} *ALDH1A3*^{low}	0.629	0.309	1.279	0.201
	p62^{low} *ALDH1A3*^{high}	1.739	0.865	3.494	0.120
	p62^{low} *ALDH1A3*^{low}	1.182	0.645	2.165	0.588
Luminal B	*p62*^{high} *ALDH1A3*^{low}	1.567	0.882	2.784	0.125
	p62^{low} *ALDH1A3*^{high}	1.312	0.840	2.050	0.233
	p62^{low} *ALDH1A3*^{low}	N.D.	N.D.	N.D.	N.D.

N.D.: Not determined; METABRIC: Molecular Taxonomy of Breast Cancer International Consortium; DSS: disease-specific survival; *ALDH1A3*: aldehyde dehydrogenase 1 family member A3. The hazard ratio of the *p62*^{high}*ALDH1A3*^{high} group relative to the *p62*^{high} *ALDH1A3*^{low}, *p62*^{low}*ALDH1A3*^{high} and *p62*^{low}*ALDH1A3*^{low} groups was adjusted using age, chemotherapy and radiotherapy as confounding factors, as estimated using the Cox proportional hazard model. Significant differences are shown in bold.

previously shown that high *p62* and *ALDH1A3* expression is associated with poorer clinical outcomes in luminal B breast cancer (55). Moreover, the effectiveness of radiotherapy is reduced in luminal B breast cancer with *p62* and *ALDH1A3* co-expression (56). However, the association between endocrine therapy and high *p62* and *ALDH1A3* expression, in luminal B breast cancer remains unclear. Therefore, we next performed Kaplan-Meier analysis for patients with *p62*^{high}*ALDH1A3*^{high} luminal A and luminal B breast cancer who did or did not receive endocrine therapy.

Table III. *Multivariate Cox regression analyses for DSS among the p62^{high}ALDH1A3^{high}, p62^{high}ALDH1A3^{low}, p62^{low}ALDH1A3^{high} and p62^{low}ALDH1A3^{low} groups of patients with luminal breast cancer subtypes treated with or without endocrine therapy in TCGA dataset.*

TCGA dataset		Hazard ratio	95% Confidence interval		*p*-Value
p62^{high} *vs. p62*^{low}					
Without endocrine-therapy					
Luminal A		0.422	0.158	1.130	0.086
Luminal B		0.114	0.011	1.149	0.065
With endocrine-therapy					
Luminal A		0.466	0.101	2.154	0.328
Luminal B		7.177	1.638	31.448	**0.009**
ALDH1A3^{high} *vs. ALDH1A3*^{low}					
Without endocrine-therapy					
Luminal A		0.603	0.216	1.686	0.335
Luminal B		0.169	0.032	0.890	**0.036**
With endocrine-therapy					
Luminal A		N.D.	N.D.	N.D.	N.D.
Luminal B		N.D.	N.D.	N.D.	N.D.
p62^{high} *ALDH1A3*^{high} *vs.* others					
Without endocrine-therapy					
Luminal A		0.467	0.165	1.321	0.151
Luminal B		0.170	0.032	0.899	**0.037**
With endocrine-therapy					
Luminal A		1.349	0.301	6.038	0.695
Luminal B		9.863	2.219	43.847	**0.003**
p62^{high} *ALDH1A3*^{high} *vs.*					
Without endocrine-therapy					
Luminal A	*p62*^{high} *ALDH1A3*^{low}	1.115	0.127	9.793	0.921
	p62^{low} *ALDH1A3*^{high}	0.540	0.176	1.653	0.280
	p62^{low} *ALDH1A3*^{low}	0.278	0.070	1.100	0.068
Luminal B	*p62*^{high} *ALDH1A3*^{low}	0.199	0.036	1.114	0.066
	p62^{low} *ALDH1A3*^{high}	N.D.	N.D.	N.D.	N.D.
	p62^{low} *ALDH1A3*^{low}	N.D.	N.D.	N.D.	N.D.
With endocrine-therapy					
Luminal A	*p62*^{high} *ALDH1A3*^{low}	N.D.	N.D.	N.D.	N.D.
	p62^{low} *ALDH1A3*^{high}	0.638	0.139	2.938	0.565
	p62^{low} *ALDH1A3*^{low}	N.D.	N.D.	N.D.	N.D.
Luminal B	*p62*^{high} *ALDH1A3*^{low}	N.D.	N.D.	N.D.	N.D.
	p62^{low} *ALDH1A3*^{high}	6.065	1.312	28.039	**0.021**
	p62^{low} *ALDH1A3*^{low}	N.D.	N.D.	N.D.	N.D.

N.D.: Not determined; TCGA: The Cancer Genome Atlas; DSS: disease-specific survival; *ALDH1A3*: aldehyde dehydrogenase 1 family member A3. The hazard ratio of the *p62*^{high}*ALDH1A3*^{high} group relative to the *p62*^{high}*ALDH1A3*^{low}, *p62*^{low}*ALDH1A3*^{high} and *p62*^{low}*ALDH1A3*^{low} groups was adjusted using age as a confounding factor, as estimated using the Cox proportional hazard model. Significant differences are shown in bold.

First, the effect of high *ALDH1A3* expression in luminal A and luminal B breast cancer was examined. Kaplan-Meier analyses showed that patients with *ALDH1A3*^{high} luminal A and luminal B breast cancer treated without endocrine therapy did not have poor clinical outcomes compared with *ALDH1A3*^{low} patients (Figure 2C and D). Additionally, multivariate Cox regression analysis showed that patients with *ALDH1A3*^{high} luminal A and luminal B breast cancer treated without endocrine therapy did not have poorer clinical outcomes compared with *ALDH1A3*^{low} patients (Table II). However, *ALDH1A3*^{high} luminal B breast cancer treated with endocrine therapy was predictive of poorer

Table IV. *Multivariate Cox regression analyses for DSS among the p62^{high}ALDH1A3^{high}, p62^{high}ALDH1A3^{low}, p62^{low}ALDH1A3^{high} and p62^{low}ALDH1A3^{low} groups of patients with luminal breast cancer subtypes treated with or without tamoxifen in TCGA dataset.*

TCGA dataset		Hazard ratio	95% Confidence interval		*p*-Value
p62^{high} *vs. p62*^{low}					
Without Tamoxifen					
Luminal A		0.328	0.126	0.856	**0.023**
Luminal B		5.788	1.477	22.682	**0.012**
With Tamoxifen					
Luminal A		N.D.	N.D.	N.D.	N.D.
Luminal B		N.D.	N.D.	N.D.	N.D.
ALDH1A3^{high} *vs. ALDH1A3*^{low}					
Without Tamoxifen					
Luminal A		1.212	0.512	2.866	0.662
Luminal B		0.313	0.076	1.297	0.109
With Tamoxifen					
Luminal A		N.D.	N.D.	N.D.	N.D.
Luminal B		N.D.	N.D.	N.D.	N.D.
p62^{high} *ALDH1A3*^{high} *vs.* others					
Without Tamoxifen					
Luminal A		0.850	0.309	2.335	0.752
Luminal B		1.803	0.455	7.146	0.402
With Tamoxifen					
Luminal A		N.D.	N.D.	N.D.	N.D.
Luminal B		N.D.	N.D.	N.D.	N.D.
p62^{high} *ALDH1A3*^{high} *vs.*					
Without Tamoxifen					
Luminal A	*p62*^{high} *ALDH1A3*^{low}	4.918	0.535	45.185	0.159
	p62^{low} *ALDH1A3*^{high}	0.558	0.156	1.991	0.368
	p62^{low} *ALDH1A3*^{low}	0.537	0.181	1.592	0.262
Luminal B	*p62*^{high} *ALDH1A3*^{low}	0.378	0.064	2.217	0.281
	p62^{low} *ALDH1A3*^{high}	8.646	0.718	104.156	0.089
	p62^{low} *ALDH1A3*^{low}	1.341	0.181	9.956	0.774
With Tamoxifen					
Luminal A	*p62*^{high} *ALDH1A3*^{low}	N.D.	N.D.	N.D.	N.D.
	p62^{low} *ALDH1A3*^{high}	N.D.	N.D.	N.D.	N.D.
	p62^{low} *ALDH1A3*^{low}	N.D.	N.D.	N.D.	N.D.
Luminal B	*p62*^{high} *ALDH1A3*^{low}	N.D.	N.D.	N.D.	N.D.
	p62^{low} *ALDH1A3*^{high}	N.D.	N.D.	N.D.	N.D.
	p62^{low} *ALDH1A3*^{low}	N.D.	N.D.	N.D.	N.D.

N.D.: Not determined; TCGA: The Cancer Genome Atlas; DSS: disease-specific survival; *ALDH1A3*: aldehyde dehydrogenase 1 family member A3. The hazard ratio of the *p62*^{high}*ALDH1A3*^{high} group relative to the *p62*^{high}*ALDH1A3*^{low}, *p62*^{low}*ALDH1A3*^{high} and *p62*^{low}*ALDH1A3*^{low} groups was adjusted using age as a confounding factor, as estimated using the Cox proportional hazard model. Significant differences are shown in bold.

clinical outcomes in Kaplan-Meier analysis (p=0.032) and poorer tendency in multivariate Cox regression analysis (HR=1.75, 95%CI=0.99-3.09, p=0.055) compared with *ALDH1A3*^{low} (Figure 2C and D and Table II).

Next, Kaplan-Meier analyses showed that patients with *p62*^{high} *ALDH1A3*^{high} luminal A and luminal B breast cancer treated without endocrine therapy did not have poorer clinical outcomes than the other patient groups (*p62*^{high} *ALDH1A3*^{low}, *p62*^{low} *ALDH1A3*^{high} and *p62*^{low} *ALDH1A3*^{low}) with the luminal A and luminal B subtypes (Figure 2E and F). Notably, in patients treated with endocrine therapy, there was a significant difference between the survival

Table V. *Multivariate Cox regression analyses for DSS among the p62^{high} ALDH1A3^{high}, p62^{high}ALDH1A3^{low}, p62^{low}ALDH1A3^{high} and p62^{low}ALDH1A3^{low} groups of patients with luminal breast cancer subtypes treated with or without aromatase inhibitor in TCGA dataset.*

TCGA dataset		Hazard ratio	95% Confidence interval		*p*-Value
p62^{high} *vs. p62*^{low}					
Without aromatase inhibitor					
Luminal A		0.469	0.186	1.181	0.108
Luminal B		0.205	0.054	0.772	**0.019**
With aromatase inhibitor					
Luminal A		0.326	0.053	2.004	0.227
Luminal B		N.D.	N.D.	N.D.	N.D.
ALDH1A3^{high} *vs. ALDH1A3*^{low}					
Without aromatase inhibitor					
Luminal A		1.596	0.631	4.037	0.324
Luminal B		0.391	0.127	1.209	0.103
With Aromatase inhibitor					
Luminal A		N.D.	N.D.	N.D.	N.D.
Luminal B		4.263	0.377	48.225	0.241
p62^{high} *ALDH1A3*^{high} *vs.* others					
Without aromatase inhibitor					
Luminal A		0.945	0.365	2.448	0.907
Luminal B		0.344	0.103	1.150	0.083
With aromatase inhibitor					
Luminal A		0.906	0.150	5.470	0.914
Luminal B		N.D.	N.D.	N.D.	N.D.
p62^{high} *ALDH1A3*^{high} *vs.*					
Without aromatase inhibitor					
Luminal A	*p62*^{high} *ALDH1A3*^{low}	5.872	0.648	53.206	0.115
	p62^{low} *ALDH1A3*^{high}	0.641	0.217	1.897	0.422
	p62^{low} *ALDH1A3*^{low}	0.786	0.247	2.505	0.684
Luminal B	*p62*^{high} *ALDH1A3*^{low}	0.567	0.139	2.314	0.429
	p62^{low} *ALDH1A3*^{high}	0.473	0.042	5.306	0.544
	p62^{low} *ALDH1A3*^{low}	0.157	0.032	0.764	**0.022**
With aromatase inhibitor					
Luminal A	*p62*^{high} *ALDH1A3*^{low}	N.D.	N.D.	N.D.	N.D.
	p62^{low} *ALDH1A3*^{high}	0.450	0.074	2.722	0.385
	p62^{low} *ALDH1A3*^{low}	N.D.	N.D.	N.D.	N.D.
Luminal B	*p62*^{high} *ALDH1A3*^{low}	N.D.	N.D.	N.D.	N.D.
	p62^{low} *ALDH1A3*^{high}	N.D.	N.D.	N.D.	N.D.
	p62^{low} *ALDH1A3*^{low}	N.D.	N.D.	N.D.	N.D.

N.D.: Not determined; TCGA: The Cancer Genome Atlas; DSS: disease-specific survival; *ALDH1A3*: aldehyde dehydrogenase 1 family member A3. The hazard ratio of the *p62*^{high}*ALDH1A3*^{high} group relative to the *p62*^{high} *ALDH1A3*^{low}, *p62*^{low}*ALDH1A3*^{high} and *p62*^{low}*ALDH1A3*^{low} groups was adjusted using age as a confounding factor, as estimated using the Cox proportional hazard model. Significant differences are shown in bold.

rates of those with *p62*^{high} *ALDH1A3*^{high} luminal B breast cancer and the other patients with the luminal B subtype (p=0.030) (Figure 2F). The comparison among the four groups indicated that *p62*^{high} *ALDH1A3*^{high} did not have the poorest survival of the four groups of patients with the luminal A breast cancer subtype, whereas *p62*^{high} *ALDH1A3*^{high} had the poorest survival among the four groups of patients with the luminal B breast cancer subtype (p=0.067) (Figure 2G and H). Next, a multivariate Cox regression analysis for DSS was performed with age at diagnosis as a confounding factor (Table II). Multivariate Cox regression analysis also showed that *p62*^{high}

ALDH1A3^{high} was not predictive of poorer clinical outcomes of patients with luminal A breast cancer treated without endocrine therapy compared with the other patient groups (*p62*^{high} *ALDH1A3*^{low}, *p62*^{low} *ALDH1A3*^{high} and *p62*^{low} *ALDH1A3*^{low}) with the luminal A subtype (Table II). However, *p62*^{high} *ALDH1A3*^{high} was predictive of poorer clinical outcomes of patients with luminal B breast cancer treated with endocrine therapy compared with other patient groups with the luminal B subtype (HR=1.52, 95%CI=1.05-2.20, p=0.028) (Table II). These results suggest that p62 may be involved in cancer progression and contribute to the poor prognosis of patients with ALDH1A3-positive CSC-enriched luminal B breast cancer. These results also suggest that endocrine therapy may be insufficient for treating *p62*^{high} *ALDH1A3*^{high} luminal B breast cancer.

Endocrine therapy is insufficient for treating p62^{high} ALDH1A3^{high} luminal B breast cancer in TCGA dataset. To confirm the above results from the METABRIC dataset analysis, we next examined TCGA dataset as another cohort. Of the *p62*^{high} groups of patients with luminal A and luminal B breast cancer who did or did not receive endocrine therapy, those with the luminal B subtype treated with endocrine therapy showed a poor prognosis (p=0.0021) (Figure 3A and B). The *ALDH1A3*^{high} groups of patients with luminal A and luminal B breast cancer who did or did not receive endocrine therapy did not show a poor prognosis (Figure 3C and D). Next, Kaplan-Meier analyses showed that patients with *p62*^{high} *ALDH1A3*^{high} luminal A and luminal B breast cancer treated without endocrine therapy did not have poorer clinical outcomes than the other patient groups (*p62*^{high} *ALDH1A3*^{low}, *p62*^{low} *ALDH1A3*^{high} and *p62*^{low} *ALDH1A3*^{low}) with the luminal A and luminal B subtypes (Figure 3E and F). For patients treated with endocrine therapy, there was a significant difference between the survival rates of those with *p62*^{high} *ALDH1A3*^{high} luminal B breast cancer and the other patient groups with the luminal B subtype (luminal B: p<0.001) (Figure 3F). The comparison among the four groups indicated that the *p62*^{high} *ALDH1A3*^{high} group did not have the poorest survival of the four groups of patients with the luminal A subtype (Figure 3G), whereas the *p62*^{high} *ALDH1A3*^{high} group had the poorest survival of the four groups of patients with the luminal B subtype (p=0.0013) (Figure 3H). Subsequently, multivariate Cox regression analysis for DSS was performed with age as a confounding factor, and similar results were obtained as those in the Kaplan-Meier analysis (Table III). These results also suggest that endocrine therapy may be an insufficient treatment option for patients with *p62*^{high} *ALDH1A3*^{high} luminal B breast cancer.

Tamoxifen is sufficient for treating p62^{high} luminal A and luminal B breast cancer in TCGA dataset. Next, the endocrine therapy group was divided into two groups, those treated with tamoxifen and those treated with aromatase inhibitors, to examine in more detail the relationship between high *p62* and *ALDH1A3* expression, and endocrine therapy. Of the *p62*^{high} groups of patients with luminal A and luminal B breast cancer who did or did not receive tamoxifen treatment as endocrine therapy, those with the luminal B subtype treated without tamoxifen showed a poor prognosis (p=0.0045) (Figure 4A, B and Table IV). The *ALDH1A3*^{high} groups of patients with luminal A and luminal B breast cancer who did or did not receive tamoxifen treatment as endocrine therapy did not show a significant difference (Figure 4C, D and Table IV).

Tamoxifen is insufficient for treating p62^{high} ALDH1A3^{high} luminal A breast cancer in TCGA dataset. In patients treated with tamoxifen, there was a significant difference between the survival rates of those with *p62*^{high} *ALDH1A3*^{high} luminal A breast cancer and the other patient groups with the luminal A subtype, and patients with *p62*^{high} *ALDH1A3*^{high} luminal B breast cancer treated with tamoxifen tended to have a poor outcome (luminal A with tamoxifen: p=0.013; luminal B with tamoxifen therapy: p=0.054) (Figure 4E and F). The comparison among the four groups showed that the *p62*^{high} *ALDH1A3*^{high} group had the poorest survival of the four

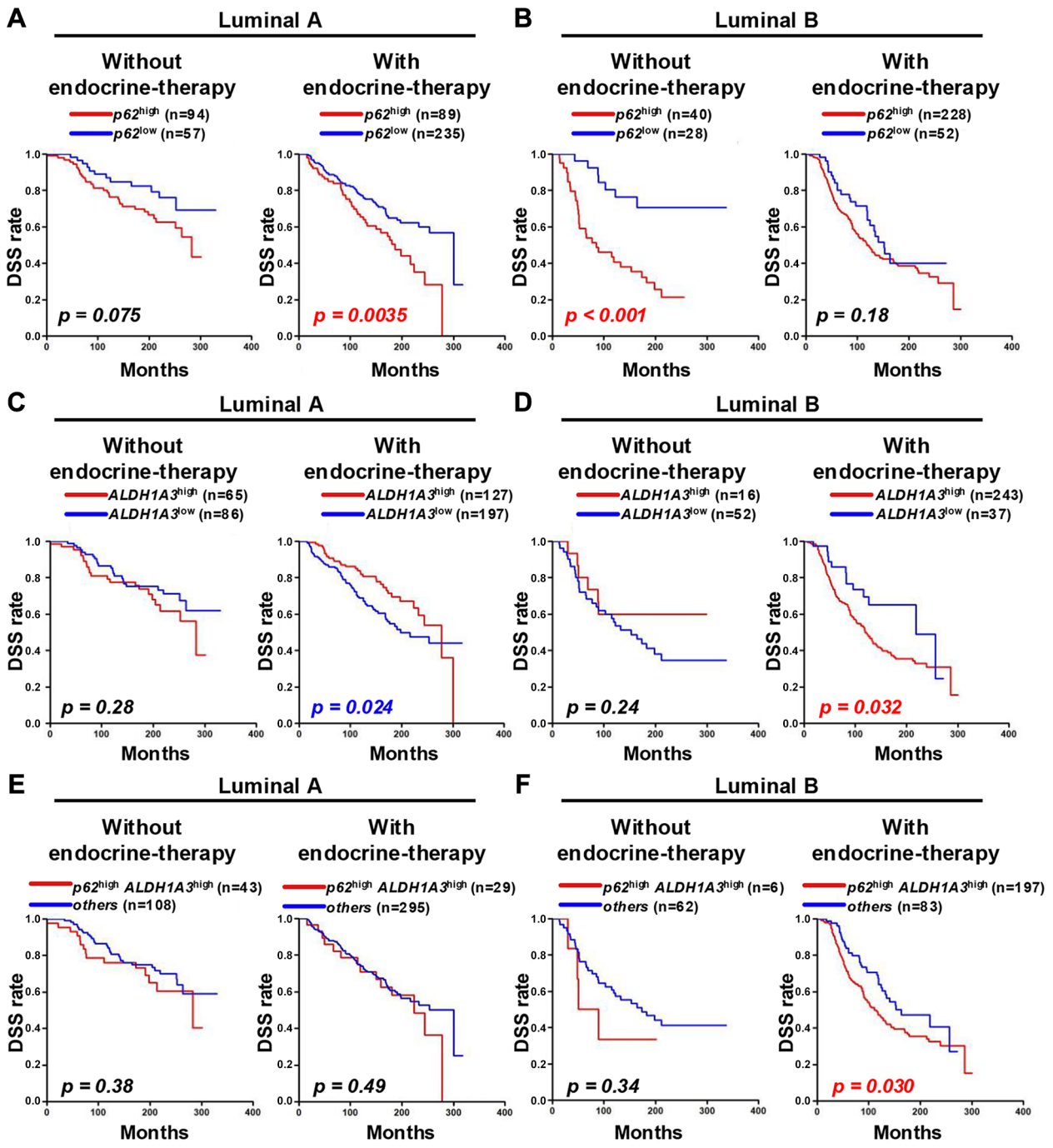
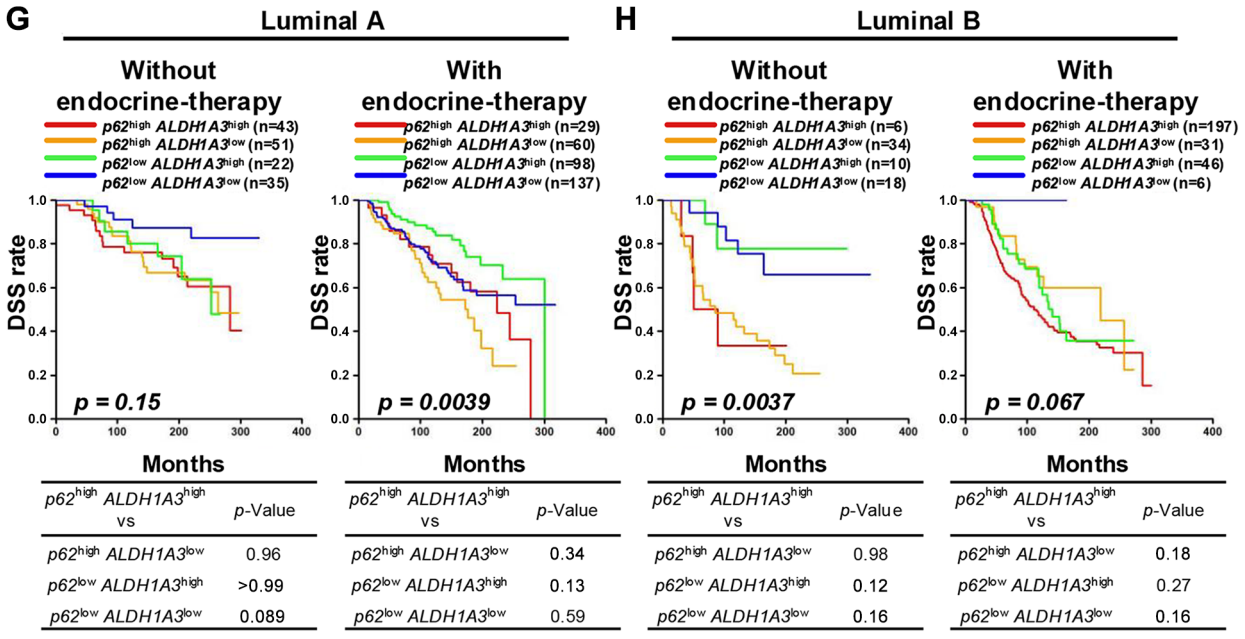


Figure 2. *Continued*

groups of patients with the luminal A and luminal B subtypes, although there was not a significant difference (Figure 4G and H).

Aromatase inhibitor therapy is insufficient for treating p62^{high} luminal B breast cancer in TCGA dataset. Of the *p62*^{high} groups of patients with luminal A and luminal B



$p62^{high}$ $ALDH1A3^{high}$ vs	*p*-Value	$p62^{high}$ $ALDH1A3^{high}$ vs	*p*-Value	$p62^{high}$ $ALDH1A3^{high}$ vs	*p*-Value	$p62^{high}$ $ALDH1A3^{high}$ vs	*p*-Value
$p62^{high}$ $ALDH1A3^{low}$	0.96	$p62^{high}$ $ALDH1A3^{low}$	0.34	$p62^{high}$ $ALDH1A3^{low}$	0.98	$p62^{high}$ $ALDH1A3^{low}$	0.18
$p62^{low}$ $ALDH1A3^{high}$	>0.99	$p62^{low}$ $ALDH1A3^{high}$	0.13	$p62^{low}$ $ALDH1A3^{high}$	0.12	$p62^{low}$ $ALDH1A3^{high}$	0.27
$p62^{low}$ $ALDH1A3^{low}$	0.089	$p62^{low}$ $ALDH1A3^{low}$	0.59	$p62^{low}$ $ALDH1A3^{low}$	0.16	$p62^{low}$ $ALDH1A3^{low}$	0.16

Figure 2. *Kaplan-Meier analyses for DSS according to p62 and ALDH1A3 expression, the luminal subtypes whether treated with or without endocrine therapy in the METABRIC dataset. (A-H) The METABRIC dataset was downloaded from cBioPortal. (A and B) Kaplan-Meier analyses comparing the DSS between $p62^{high}$ and $p62^{low}$ luminal A and luminal B breast cancer treated with or without endocrine therapy. (C and D) Kaplan-Meier analyses comparing the DSS between $ALDH1A3^{high}$ and $ALDH1A3^{low}$ luminal A and luminal B breast cancer treated with or without endocrine therapy. (E and F) Kaplan-Meier analyses comparing the DSS between $p62^{high}$ $ALDH1A3^{high}$ patients and others ($p62^{high}ALDH1A3^{low}$, $p62^{low}ALDH1A3^{high}$ and $p62^{low}ALDH1A3^{low}$) with the luminal A and luminal B breast cancer subtypes treated with or without endocrine therapy. (G and H) Kaplan-Meier survival curves for DSS for $p62^{high}$ $ALDH1A3^{high}$, $p62^{high}$ $ALDH1A3^{low}$, $p62^{low}$ $ALDH1A3^{high}$ and $p62^{low}$ $ALDH1A3^{low}$ patients with luminal A and luminal B breast cancer treated with or without endocrine therapy. p-values were calculated using the Cochran-Mantel-Haenszel generalized log-rank test. Multiplicity was adjusted using the Holm test as a post hoc test. METABRIC: Molecular Taxonomy of Breast Cancer International Consortium; DSS: disease-specific survival; ALDH1A3: aldehyde dehydrogenase 1 family member A3.*

breast cancer who did or did not receive aromatase inhibitor treatment as endocrine therapy, those with the luminal B subtype showed a poor prognosis (p<0.001) (Figure 5A and B). The *ALDH1A3*^{high} groups of patients with luminal A and luminal B breast cancer who did or did not receive aromatase inhibitor treatment as endocrine therapy did not show a poor prognosis (Figure 5C and D).

Aromatase inhibitor therapy is insufficient for treating $p62^{high}$ $ALDH1A3^{high}$ luminal B breast cancer in TCGA dataset. For patients treated with aromatase inhibitors, there was no significant difference between the survival rates of those with *p62*^{high} *ALDH1A3*^{high} luminal A breast cancer and other patients with the luminal A subtype (Figure 5E). However, patients with *p62*^{high} *ALDH1A3*^{high} luminal B breast cancer treated with aromatase inhibitors had a poor clinical outcome (p<0.001) (Figure 5F). The comparison among the four expression groups showed that *p62*^{high} *ALDH1A3*^{high} luminal A breast cancer did not show a poor prognosis (Figure 5G), but *p62*^{high} *ALDH1A3*^{high} indicated a poorer prognosis among the four groups of patients with the luminal B subtype (p<0.001) (Figure 5H). These results also suggest that aromatase inhibitor as endocrine therapy may be an insufficient treatment option for patients with *p62*^{high} *ALDH1A3*^{high} luminal B breast cancer.

Discussion

The present study demonstrated that the *p62*^{high} *ALDH1A3*^{high} luminal B subtype tumors treated with

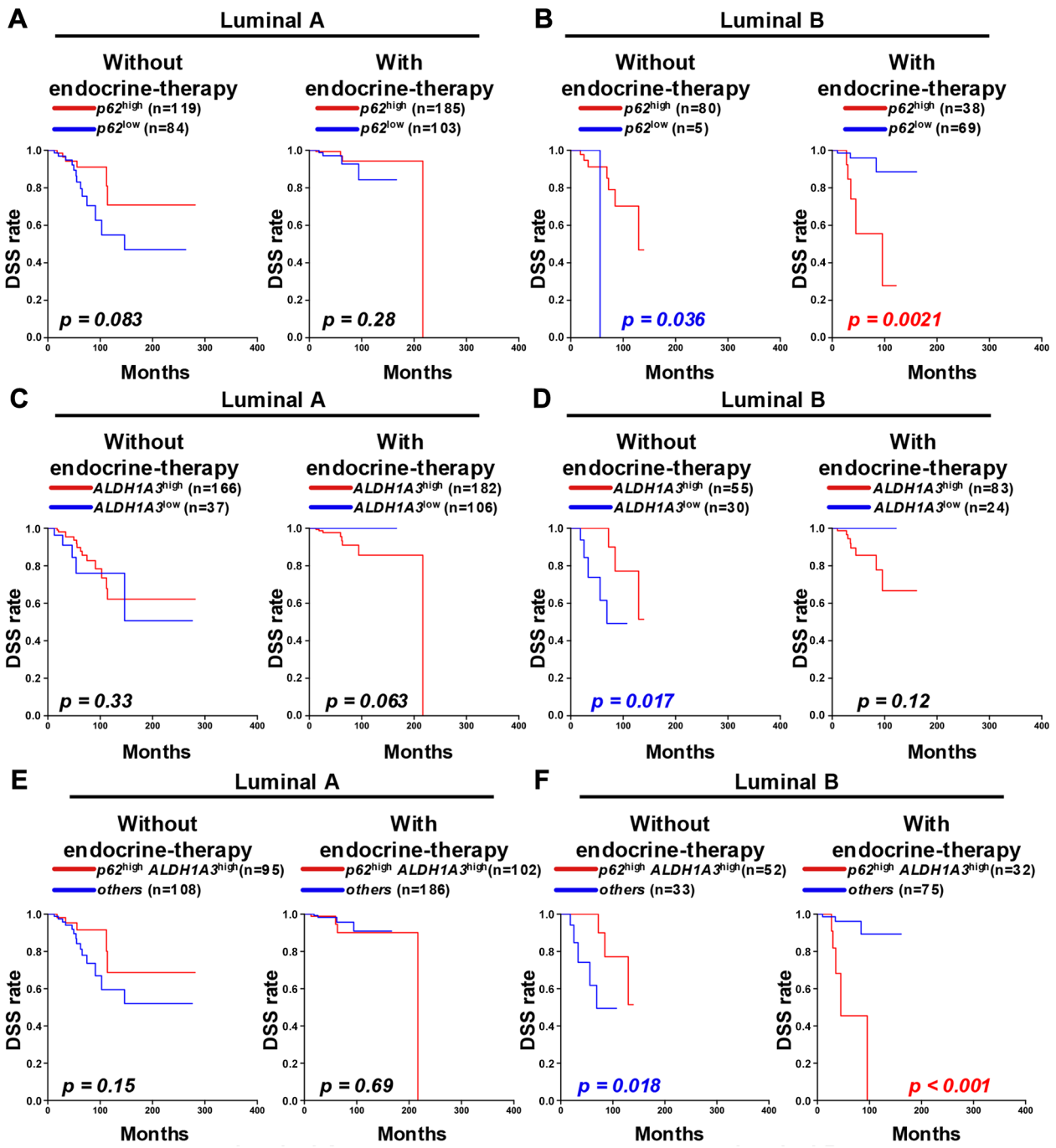
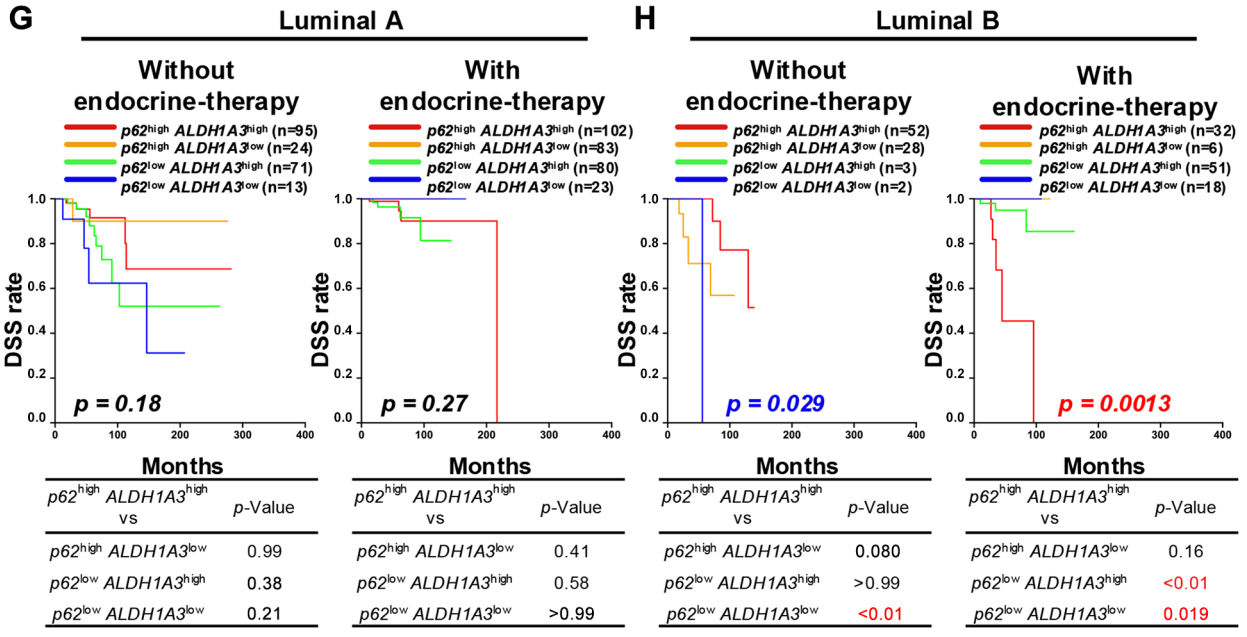


Figure 3. *Continued*

endocrine therapy, especially those treated with aromatase inhibitors, exhibited poor clinical outcomes. High p62 expression in cancer tissue at the gene and protein level contributes to cancer progression and metastasis (52, 63-68) and is associated with a poor clinical outcome in patients with breast cancer, including the luminal B subtype (55).



p62high ALDH1A3high vs	p-Value	p62high ALDH1A3high vs	p-Value	p62high ALDH1A3high vs	p-Value	p62high ALDH1A3high vs	p-Value
p62high ALDH1A3low	0.99	p62high ALDH1A3low	0.41	p62high ALDH1A3low	0.080	p62high ALDH1A3low	0.16
p62low ALDH1A3high	0.38	p62low ALDH1A3high	0.58	p62low ALDH1A3high	>0.99	p62low ALDH1A3high	<0.01
p62low ALDH1A3low	0.21	p62low ALDH1A3low	>0.99	p62low ALDH1A3low	<0.01	p62low ALDH1A3low	0.019

Figure 3. *Kaplan-Meier analyses for DSS according to p62 and ALDH1A3 expression, the luminal subtype and whether treated with or without endocrine therapy in TCGA Pan-Cancer. (A-H) TCGA Pan-Cancer dataset was downloaded from cBioPortal. (A and B) Kaplan-Meier analyses comparing the DSS between p62^{high} and p62^{low} luminal A and luminal B breast cancer treated with or without endocrine therapy. (C and D) Kaplan-Meier analyses comparing the DSS between ALDH1A3^{high} and ALDH1A3^{low} luminal A and luminal B breast cancer treated with or without endocrine therapy. (E and F) Kaplan-Meier analyses comparing the DSS between p62^{high} ALDH1A3^{high} patients and others (p62^{high} ALDH1A3^{low}, p62^{low} ALDH1A3^{high} and p62^{low} ALDH1A3^{low}) with luminal A and luminal B breast cancer treated with or without endocrine therapy. (G and H) Kaplan-Meier survival curves for DSS for p62^{high} ALDH1A3^{high}, p62^{high} ALDH1A3^{low}, p62^{low} ALDH1A3^{high} and p62^{low}ALDH1A3^{low} patients with luminal A and luminal B breast cancer treated with or without endocrine therapy. p-values were calculated using the Cochran-Mantel-Haenszel generalized log-rank test. Multiplicity was adjusted using the Holm test as a post hoc test.*

Therefore, p62 is expected to predict prognosis after medical treatment for several cancer types. A series of experiments at the cellular level have shown that p62 is also involved in cell proliferation, survival, antioxidant response, autophagy and tumor formation (24, 26, 31, 55, 69). In addition, p62 is involved in chemoresistance and radioresistance in cancer cells by enhancing the level of NF-κB signaling, mTOR signaling and autophagy flux (70, 71). In breast cancer cell lines, p62 binds to vimentin and induces invasion and metastasis (52). In endometrial cancer cell lines, 17β-estradiol induces p62 phosphorylation and ERα expression *via* the PI3K/Akt/mTOR signaling pathway, and p62 phosphorylation releases ERα from the p62-KEAP1-ERα complex (72). Endocrine therapy activates the integrated stress response through NF-κB signaling in a subpopulation of ER-positive breast cancer cells (73). However, the mechanism linking high p62 expression to cancer progression and to the reduced effectiveness of endocrine therapy in luminal B breast cancer is unclear. Because aromatase inhibitors block estrogen production in postmenopausal adipose tissue, the estrogen-independent and p62-dependent signaling pathways that remain active in luminal B breast cancer cells may be responsible for the reduced therapeutic efficacy of aromatase inhibitors. This is supported by the results of the present study in which tamoxifen, which acts directly on the ER, showed a tendency towards a reduced effectiveness in *p62*^{high} *ALDH1A3*^{high} luminal B breast cancer (Figure 4). Thus, it will be important to clarify the detailed molecular mechanism in the future.

The luminal B breast cancer subtype expresses HER2 and is treated with HER2-targeted therapy (2, 3). Therefore, we investigated the prognosis (DSS) of patients with *p62*^{high}

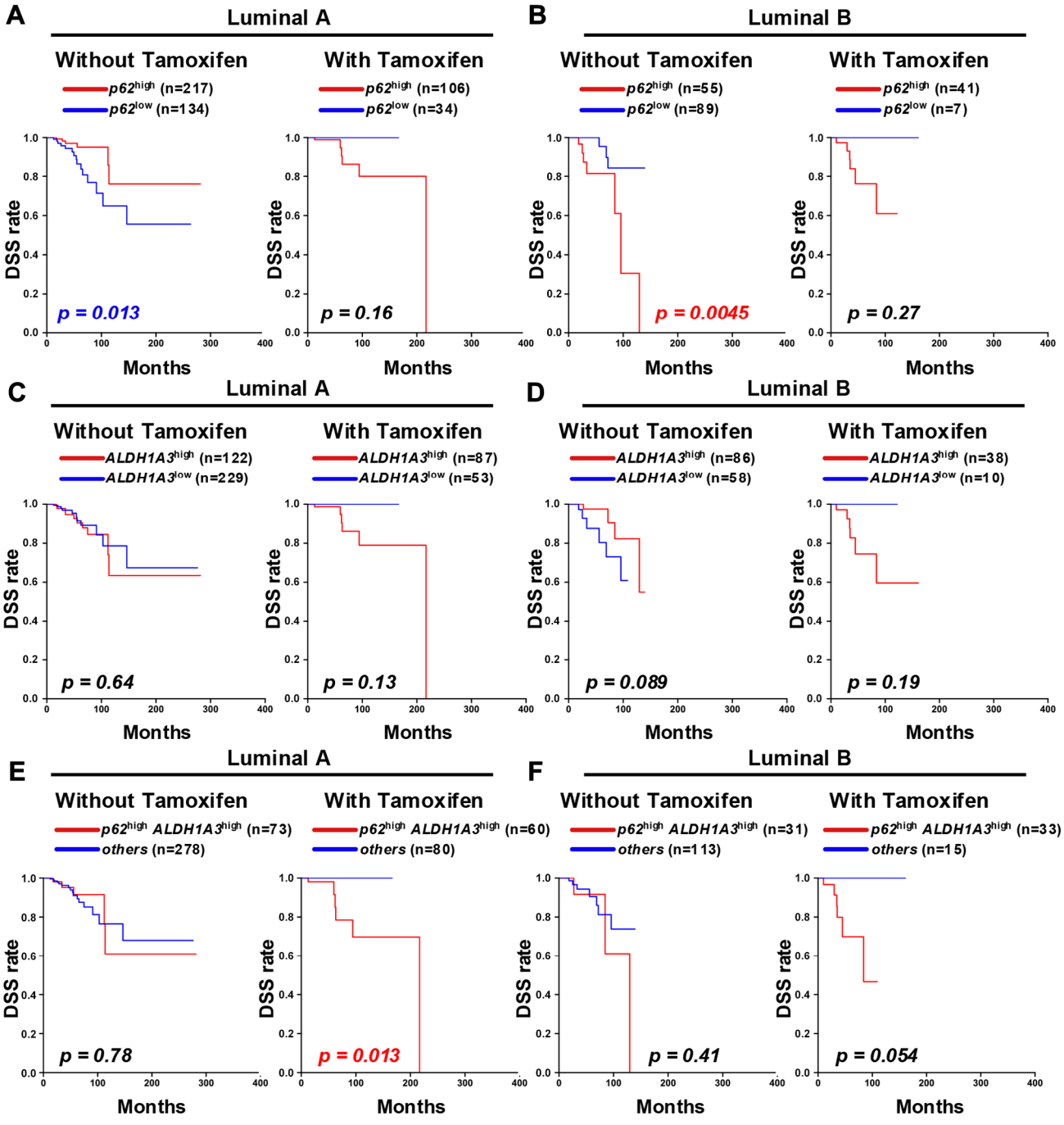
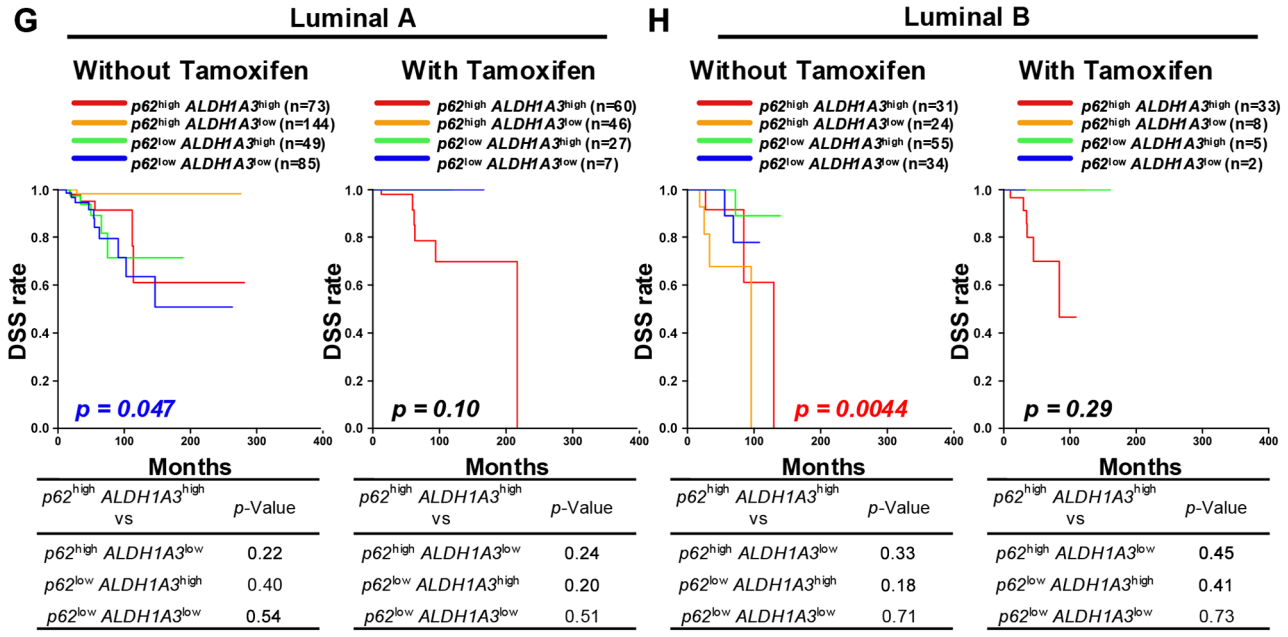


Figure 4. *Continued*

luminal B breast cancer who received HER2-targeted therapy, but we were unable to perform a prognostic analysis as no patients who received HER2 targeted therapy died in the dataset. Additionally, since the luminal B type has a high proliferation rate, chemotherapy is usually also performed. It is important to examine the effects of



$p62^{high}$ $ALDH1A3^{high}$ vs	*p*-Value	$p62^{high}$ $ALDH1A3^{high}$ vs	*p*-Value	$p62^{high}$ $ALDH1A3^{high}$ vs	*p*-Value	$p62^{high}$ $ALDH1A3^{high}$ vs	*p*-Value
$p62^{high}$ $ALDH1A3^{low}$	0.22	$p62^{high}$ $ALDH1A3^{low}$	0.24	$p62^{high}$ $ALDH1A3^{low}$	0.33	$p62^{high}$ $ALDH1A3^{low}$	0.45
$p62^{low}$ $ALDH1A3^{high}$	0.40	$p62^{low}$ $ALDH1A3^{high}$	0.20	$p62^{low}$ $ALDH1A3^{high}$	0.18	$p62^{low}$ $ALDH1A3^{high}$	0.41
$p62^{low}$ $ALDH1A3^{low}$	0.54	$p62^{low}$ $ALDH1A3^{low}$	0.51	$p62^{low}$ $ALDH1A3^{low}$	0.71	$p62^{low}$ $ALDH1A3^{low}$	0.73

Figure 4. *Kaplan-Meier analyses for DSS according to p62 and ALDH1A3 expression, the luminal subtype and tamoxifen treatment in TCGA Pan-Cancer. (A and B) Kaplan-Meier analyses comparing the DSS between $p62^{high}$ and $p62^{low}$ luminal A and luminal B breast cancer treated with or without tamoxifen. (C and D) Kaplan-Meier analyses comparing the DSS between $ALDH1A3^{high}$ and $ALDH1A3^{low}$ luminal A and luminal B breast cancer treated with or without tamoxifen. (E and F) Kaplan-Meier analyses comparing the DSS between $p62^{high}$ $ALDH1A3^{high}$ patients and others ($p62^{high}$ $ALDH1A3^{low}$, $p62^{low}$ $ALDH1A3^{high}$ and $p62^{low}$ $ALDH1A3^{low}$) with luminal A and luminal B breast cancer treated with or without tamoxifen. (G and H) Kaplan-Meier survival curves for DSS for $p62^{high}$ $ALDH1A3^{high}$, $p62^{high}$ $ALDH1A3^{low}$, $p62^{low}$ $ALDH1A3^{high}$ and $p62^{low}$ $ALDH1A3^{low}$ patients with luminal A and luminal B breast cancer treated with or without tamoxifen. p-Values were calculated by the Cochran-Mantel-Haenszel generalized log-rank test. Multiplicity was adjusted using the Holm test as a post hoc test.*

HER2-targeted therapy and chemotherapy in patients with high p62 expression in luminal B subtype in the future.

p62 is involved in the maintenance of cancer stem-like properties by stabilizing MYC mRNA and NRF2 activation (51, 74) in several cancer types. p62 is also involved in the stem-like properties of ALDH1-positive luminal B breast CSCs (55). Furthermore, $p62^{high}$ $ALDH1A3^{high}$ luminal B breast cancer exhibits reduced response to radiotherapy, and X-ray irradiation suppresses the tumor formation of p62-deficient, ALDH1-positive luminal B breast CSCs (56). These findings raise the possibility that the reduced effectiveness of endocrine therapy in $p62^{high}$ $ALDH1A3^{high}$ luminal B breast cancer results from the stem-like properties of ALDH1A3-positive luminal B breast CSCs. Therefore, it is necessary to reveal the mechanism by which p62 is involved in these properties. p62 binds to atypical protein kinase C such as PKCζ and PKCλ/ι *via* a PB1-PB1 domain interaction (25). $PKC\zeta^{high}$ and $PKC\zeta^{high}$ $ALDH1A3^{high}$ luminal B breast cancers exhibit reduced response to endocrine therapy and aromatase inhibitor treatment (62, 75). Thus, p62 and PKCζ may be cooperatively involved in the reduced effectiveness of endocrine therapy in ALDH1A3-positive luminal B breast cancer.

Conclusion

The present study revealed that endocrine therapy, especially aromatase inhibitor therapy, exhibits reduced effectiveness in $p62^{high}$ $ALDH1A3^{high}$ luminal B subtype tumors for. Therefore, $p62^{high}$ and $ALDH1A3^{high}$ may be used as a prognostic biomarker for predicting the efficacy of endocrine therapy for luminal B breast cancer.

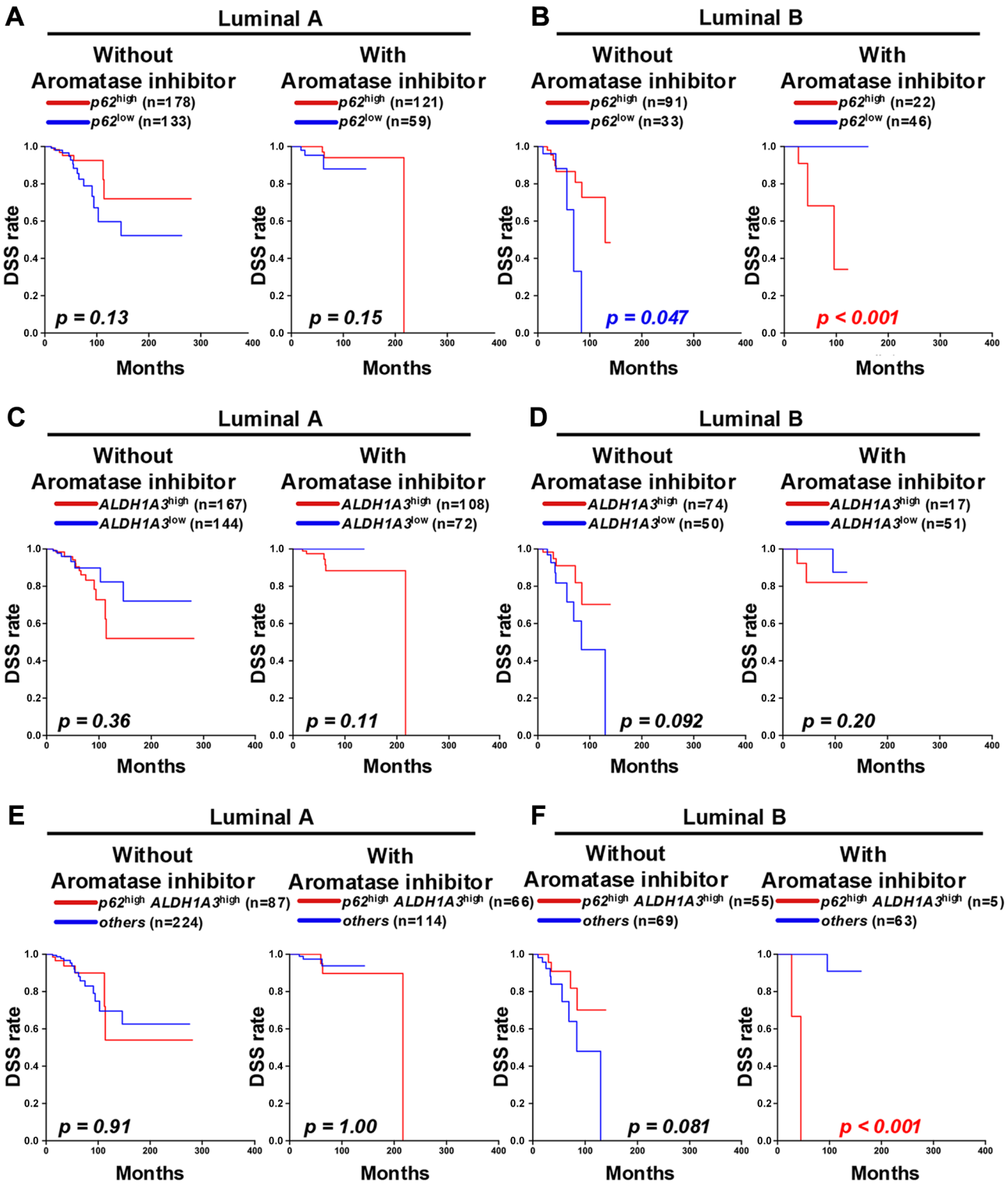
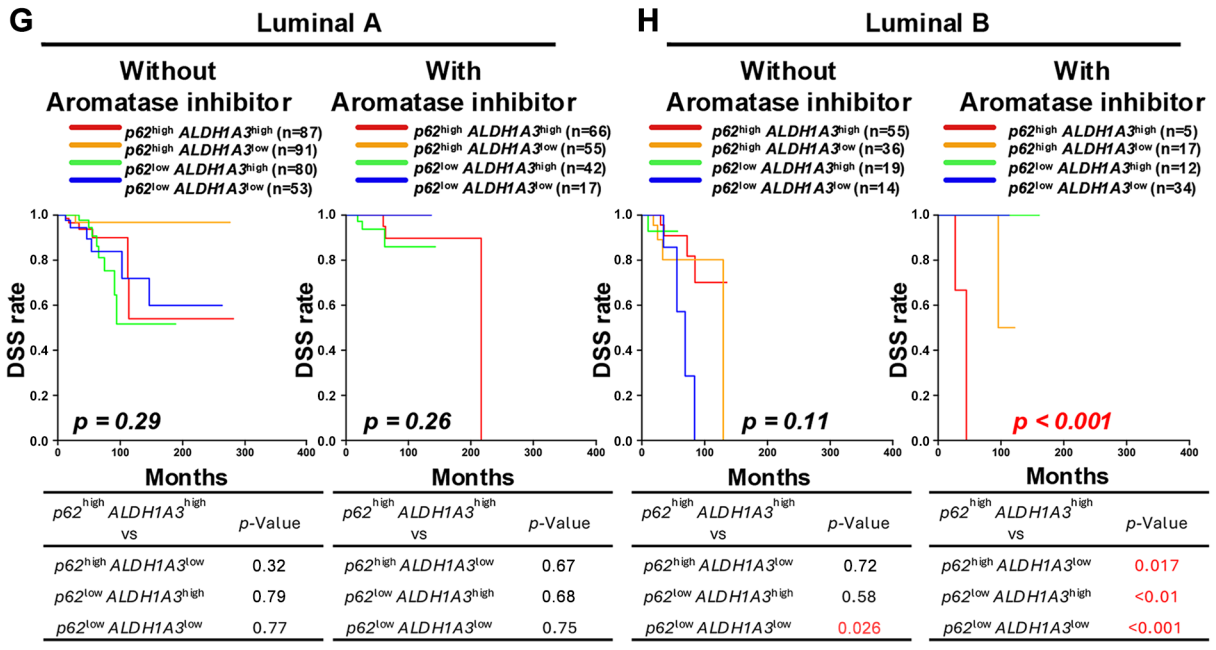


Figure 5. *Continued*



p62high ALDH1A3high vs	p-Value	p62high ALDH1A3high vs	p-Value
p62high ALDH1A3low	0.32	p62high ALDH1A3low	0.67
p62low ALDH1A3high	0.79	p62low ALDH1A3high	0.68
p62low ALDH1A3low	0.77	p62low ALDH1A3low	0.75

p62high ALDH1A3high vs	p-Value	p62high ALDH1A3high vs	p-Value
p62high ALDH1A3low	0.72	p62high ALDH1A3low	0.017
p62low ALDH1A3high	0.58	p62low ALDH1A3high	<0.01
p62low ALDH1A3low	0.026	p62low ALDH1A3low	<0.001

Figure 5. *Kaplan-Meier analyses for disease-specific survival (DSS) according to p62 and ALDH1A3 expression, the luminal subtype and aromatase inhibitor treatment in TCGA Pan-Cancer. (A and B) Kaplan-Meier analyses comparing the DSS between $p62^{high}$ and $p62^{low}$ luminal A and luminal B breast cancer treated with or without aromatase inhibitor. (C and D) Kaplan-Meier analyses comparing the DSS between $ALDH1A3^{high}$ and $ALDH1A3^{low}$ luminal A and luminal B breast cancer treated with or without aromatase inhibitor. (E and F) Kaplan-Meier analyses comparing the DSS between $p62^{high}$ $ALDH1A3^{high}$ patients and others ($p62^{high}$ $ALDH1A3^{low}$, $p62^{low}$ $ALDH1A3^{high}$ and $p62^{low}$ $ALDH1A3^{low}$) with luminal A and luminal B breast cancer treated with or without aromatase inhibitor. (G and H) Kaplan-Meier survival curves for DSS for $p62^{high}$ $ALDH1A3^{high}$, $p62^{high}$ $ALDH1A3^{low}$, $p62^{low}$ $ALDH1A3^{high}$ and $p62^{low}ALDH1A3^{low}$ patients with luminal A and luminal B breast cancer treated with or without aromatase inhibitor. p-values were calculated using the Cochran-Mantel-Haenszel generalized log-rank test. Multiplicity was adjusted using the Holm test as a post hoc test.*

Conflicts of Interest

The Authors declare that they have no competing interests in relation to this study.

Authors' Contributions

Conceptualization: YM, AO, KA; Formal analysis: YM, AO, RC, KN; Founding Acquisition: AO, RC, ST, SO, KS, KA; Investigation: YM, AO, RC, ME, KN, KS, KA; Methodology: YM, AO, KN, KA; Project Administration: KA; Supervision: KA; Validation: RC, ME, YT, HI, KN, TK, RO, YH, ST, KS; Visualization: YM, AO, ME; Writing – Original Draft Preparation: YM, AO, YN, HI, KA; Writing – Review & Editing: YM, AO, RC, ME, YT, YN, HI, KN, TK, RO, YH, ST, SO, KS, KA.

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Artificial Intelligence (AI) Disclosure

No artificial intelligence (AI) tools, including large language models or machine learning software, were used in the preparation, analysis, or presentation of this manuscript.

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