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# *PKCζ*, *CTNNBIP1* and *ALDH1A3* Expression in Luminal B Breast Cancer Indicates Decreased Hormone Therapy Effectiveness

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## Abstract

*Background/Aim:* The role of catenin β interacting protein 1 (*CTNNBIP1*), a negative regulator of the canonical Wnt/β-catenin signaling pathway, in luminal A and B breast cancer stem cells treated with hormone therapy is unknown. This study investigated the relationship between *CTNNBIP1* and aldehyde dehydrogenase 1 family member A3 (*ALDH1A3*) expression and its impact on disease-specific survival in luminal A and B breast cancer. Given that high protein kinase ζ (*PKCζ*) expression, together with elevated *CTNNBIP1* or *ALDH1A3*, is linked to poor prognosis in luminal B tumors, we also examined their combined influence.

*Materials and Methods:* Gene expression and clinical data from the Molecular Taxonomy of Breast Cancer International Consortium (METABRIC; n=2,509) were analyzed using Kaplan-Meier and Cox proportional hazards models. Findings were validated with The Cancer Genome Atlas Pan-Cancer Atlas (TCGA; n=1,084).

*Results:* *CTNNBIP1*$^{high}$*ALDH1A3*$^{high}$ indicated a poor prognosis in patients with luminal B breast cancer treated with hormone therapy in the METABRIC dataset and aromatase inhibitors as hormone therapy in the TCGA data set, suggesting that high *CTNNBIP1* and *ALDH1A3* expression contributed to decreased effectiveness of hormone therapy in patients with luminal B breast cancer. *PKCζ*$^{high}$*CTNNBIP1*$^{high}$*ALDH1A3*$^{high}$ was associated with a poor prognosis in patients with luminal B breast cancer treated with hormone therapy and aromatase inhibitors, suggesting that high *PKCζ, CTNNBIP1* and *ALDH1A3* expression contributed to decreased effectiveness of hormone therapy in patients with luminal B breast cancer.

*continued*

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*Conclusion: PKCζ* and *CTNNBIP1* may be involved in the progression of ALDH1A3-positive luminal B breast cancer. In luminal B breast cancer, *PKCζ, CTNNBIP1* and *ALDH1A3* could serve as molecular drug targets and prognostic biomarkers to predict the effectiveness of hormone therapy.

**Keywords:** *ALDH1A3*, *CTNNBIP1*, *PKCζ*, hormone therapy, luminal B breast cancer.

## Introduction

Breast cancer has the highest incidence rate and is the leading cause of cancer- related death among women worldwide (1). Breast cancer is classified into subtypes such as luminal A, luminal B, HER2 and triple-negative breast cancer based on immunohistochemical classification and as normal-like, luminal A, luminal B, HER2-enriched, claudin-low and basal-like based on gene expression patterns of the PAM50 signature (2-8). Among these subtypes, the luminal A and B subtypes are estrogen receptor (ER)-positive and account for 70-80% of breast cancer cases (9). Numerous luminal B types highly express HER2 and Ki67 (10, 11). The current standard drug care for luminal A and B breast cancer is hormone therapy, while luminal B type breast cancer is also treated with HER2-targeted drugs and chemotherapy drugs. Patients with the luminal B subtype have a poorer prognosis than those with the luminal A subtype (10-16). Therefore, it is necessary to identify target molecules for novel therapeutic drugs and biomarkers to predict the efficacy of drug treatment in luminal B breast cancer.

Cancer stem cells (CSCs) have stem cell properties, including self-renewal, multipotency and tumorigenicity (17, 18). CSCs are also resistant to drug therapy and radiotherapy. Thus, the development of molecular targeted therapies against CSCs is necessary to improve clinical outcomes of patients with cancer (17-20). Aldehyde dehydrogenase 1 family member A3 (ALDH1A3) is a member of the ALDH1A family, an enzyme converting aldehydes into carboxylic acids, and is a CSC marker in several cancer types (21-23). ALDH1A3 contributes to ALDH1 activity in breast cancer (24, 25). ALDH1A3 expression is associated with tumor grade, metastasis and poor clinical outcomes in breast cancer (24, 26, 27). The canonical Wnt/β-catenin signaling pathway is involved in CSC stemness characteristics such as cell proliferation, metastasis and metabolism (28). Several Wnt/β-catenin signaling pathway-related genes are associated with resistance to hormone therapy in ER-positive breast cancer (29). Wnt3a also induces the expression of ALDH1A1, another isotype of ALDH1A3 and CSC marker, in MCF7 breast cancer cells (30). However, the association between ALDH1A3 and Wnt/β-catenin signaling is unclear. Catenin β interacting protein 1 (*CTNNBIP1*) has an inhibitory effect on the Wnt/β-catenin signaling pathway *via* inhibitory interactions with β-catenin and T-cell transcription factor family members, and *CTNNBIP1* mutations are detected in breast cancer (31, 32). Furthermore, in the luminal B subtype, high *CTNNBIP1* expression is associated with low efficacy of hormone therapy (33). However, the relationship between *CTNNBIP1* and *ALDH1A3* expression and the efficacy of hormone therapy in luminal B breast cancer remains to be determined.

Atypical protein kinase C (aPKC) is a PKC subfamily and is insensitive to $Ca^{2+}$ and diacyl glycerol (34-36). aPKC is composed of two isoforms, PKCζ and PKCλ/ι (34-36), and activated by lipids such as phosphatidylinositol (3,4,5)-trisphosphate and ceramide (37-40), and by the Par-6-Cdc42/Rac1 complex *via* PB1-PB1 domain interaction (35, 41, 42). PKCζ is involved in several biological properties such as cell polarity (35) and cell survival (43-45), and is also involved in cancer cell proliferation and invasion (46-48). Experimental studies using animal models and cell lines have reported that PKCζ contributes to endocrine therapy resistance, particularly to tamoxifen, as well as to chemoresistance to taxane, cisplatin and doxorubicin, and radioresistance in cancer cell lines (49-53). Furthermore, in

patients with the luminal B subtype treated with hormone therapy, especially aromatase inhibitors, high *PKCζ* expression or high *PKCζ* and *CTNNBIP1* expression is associated with a poor clinical outcome (33). In addition, in patients with luminal B breast cancer treated with hormone therapy, especially aromatase inhibitors, high *PKCζ* and *ALDH1A3* expression is also associated with a poor clinical outcome (54). However, the relationship between *PKCζ*, *CTNNBIP1* and *ALDH1A3* expression and the efficacy of hormone therapy in the luminal B subtype remains to be determined.

The present study examined the effectiveness of hormone therapy based on *PKCζ*, *CTNNBIP1* and *ALDH1A3* expression in the luminal B subtype. The results demonstrated that patients with *PKCζ*$^{high}$*CTNNBIP1*$^{high}$*ALDH1A3*$^{high}$ luminal B breast cancer treated with hormone therapy, especially aromatase inhibitors, had a poor prognosis. The results suggested that high expression levels of *PKCζ, CTNNBIP1* and *ALDH1A3* contributed to decreased effectiveness of hormone therapy in luminal B breast cancer.

## Materials and Methods

*Datasets.* The Molecular Taxonomy of Breast Cancer International Consortium (METABRIC) dataset (n=2,509) (55, 56) and The Cancer Genome Atlas (TCGA) dataset (n=1,084) (57) were downloaded from cBioPortal (58, 59) on August 13, 2024. The details of the data have been reported previously (33, 54).

*Statistical analysis of cancer genomics data.* Statistical analysis of the disease-specific survival (DSS) using the Kaplan-Meier method and multivariate Cox regression analysis, using age at diagnosis, chemotherapy, and radiotherapy as a confounding factor, was performed as previously described (33, 54). Briefly, patients were divided into high and low *PKCζ, CTNNBIP1* and *ALDH1A3* expression groups, receiver operating characteristic curves were plotted using the DSS data, and the Youden index was utilized as the optimal cut-off. Two-sided $p<0.05$ was considered to indicate a statistically significant difference. Three dimensional scatterplots were generated, and Kaplan-Meier analyses for patients with high and low *PKCζ, CTNNBIP1* and *ALDH1A3* expression were performed using R software version 4.4.1 (R Core Team, R Foundation for Statistical Computing, Vienna, Austria).

## Results

*Patients with CTNNBIP1$^{high}$ALDH1A3$^{high}$ luminal B breast cancer treated with hormone therapy have a poor clinical outcome in the METABRIC dataset.* Our previous study demonstrated that the efficacy of hormone therapy was low in patients with *CTNNBIP1*$^{high}$ and *PKCζ*$^{high}$*CTNNBIP1*$^{high}$ luminal B breast cancer (33). However, the relationship between cancer stemness and high *CTNNBIP1* expression in luminal B breast cancer is unclear. Our previous studies have also demonstrated that patients with *PKCζ*$^{high}$*CTNNBIP1*$^{high}$ or *PKCζ*$^{high}$*ALDH1A3*$^{high}$ breast cancer had poor clinical outcomes among patients with the luminal B subtype (33, 54). Therefore, to examine the association between *ALDH1A3* expression and the effect of hormone therapy in patients with luminal B breast cancer with high *CTNNBIP1* expression, the association between *CTNNBIP1* and *ALDH1A3* expression and the effect of hormone therapy was analyzed in patients with luminal B breast cancer, and in patients with luminal A breast cancer, using the METABRIC dataset. The results indicated that patients with high expression of both *CTNNBIP1* and *ALDH1A3* with luminal A and luminal B subtypes treated without hormone therapy did not exhibit poor clinical outcomes (Figure 1A and B). High expression of both *CTNNBIP1* and *ALDH1A3* in patients with the luminal A subtype treated with hormone therapy also was not associated with poor clinical outcomes (Figure 1C). However, patients with *CTNNBIP1*$^{high}$*ALDH1A3*$^{high}$ luminal B breast cancer treated with hormone therapy had a poor prognosis ($p$=0.017; log-rank test) (Figure 1D). Multivariate analysis also showed that patients with *CTNNBIP1*$^{high}$*ALDH1A3*$^{high}$ luminal B breast cancer treated with hormone therapy had a poor prognosis compared with *CTNNBIP1*$^{low}$*ALDH1A3*$^{low}$ patients (hazard ratio=2.08; 95%CI=1.04-4.16; $p$=0.04), while patients with *CTNNBIP1*$^{high}$*ALDH1A3*$^{high}$ luminal A

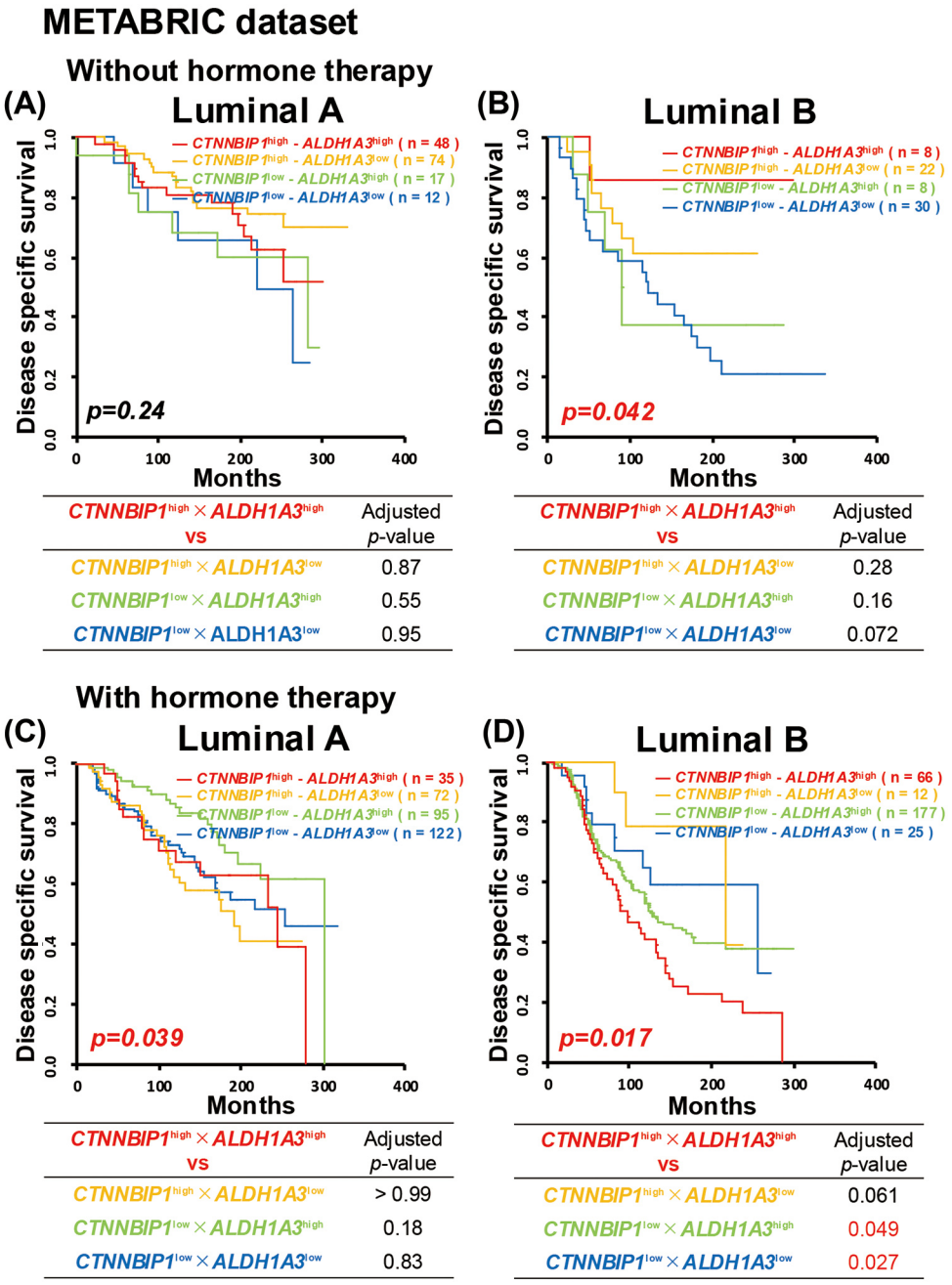



Figure 1. *Continued*

breast cancer treated with hormone therapy did not (Table I). These results suggested that hormone therapy was not effective for luminal B breast cancer with high *CTNNBIP1* and *ALDH1A3* expression.

*Patients with CTNNBIP1$^{high}$ALDH1A3$^{high}$ luminal B breast cancer treated with aromatase inhibitors as hormone therapy have poor clinical outcomes based on the dataset from TCGA.* To validate the results in the METABRIC

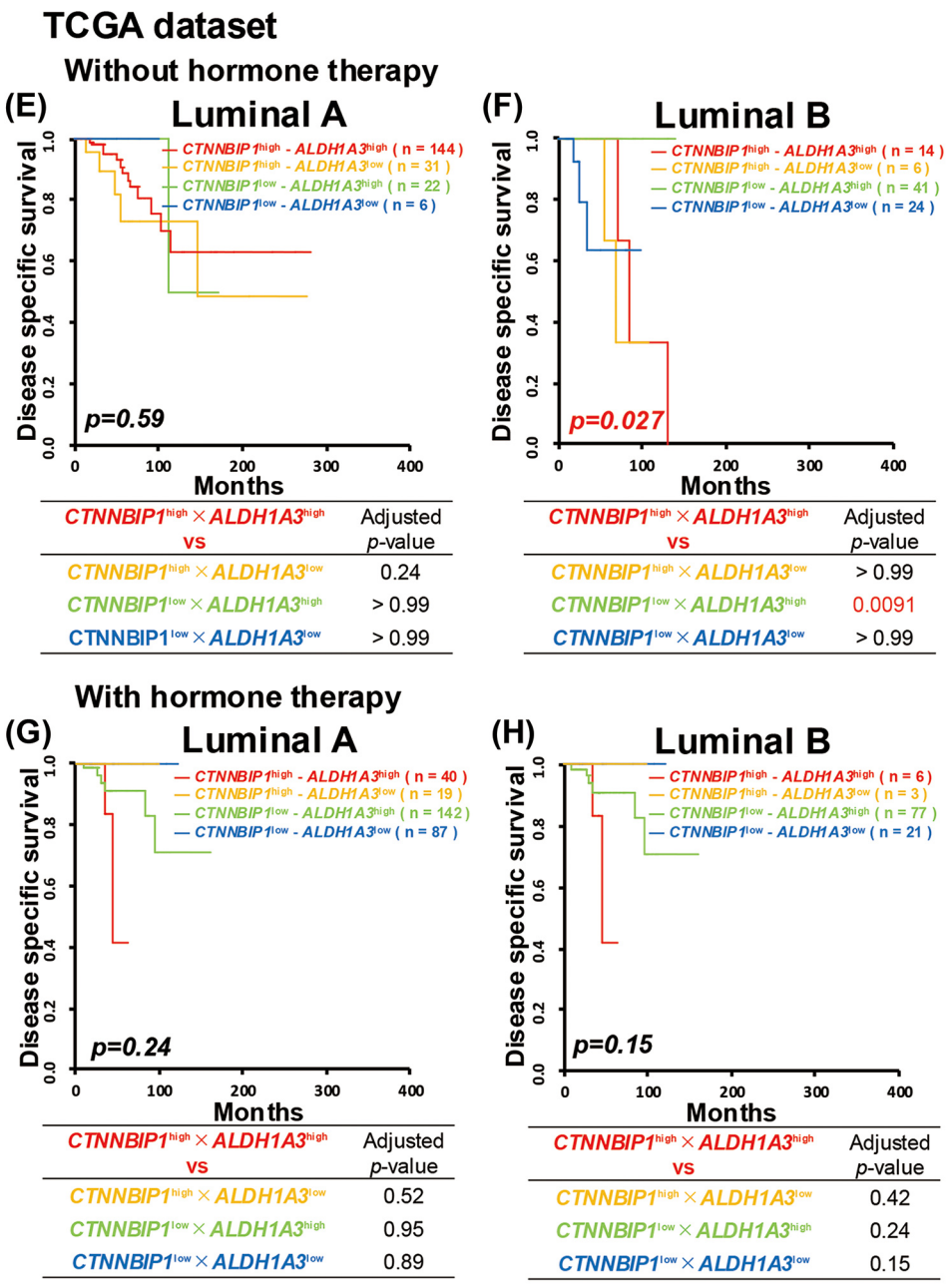



Figure 1. *Disease-specific survival Kaplan-Meier analyses of patients with luminal breast cancer according to CTNNBIP1 and ALDH1A3 expression and hormone therapy. (A-D) Molecular Taxonomy of Breast Cancer International Consortium data were downloaded from cBioPortal. (A) Patients with luminal A breast cancer and (B) patients with luminal B breast cancer who were treated without hormone therapy. (C) Patients with luminal A breast cancer and (D) patients with luminal B breast cancer who were treated with hormone therapy. (E-H) The Cancer Genome Atlas Pan-Cancer Atlas data was downloaded from cBioPortal. (E) Patients with luminal A breast cancer and (F) patients with luminal B breast cancer who were treated without hormone therapy. (G) Patients with luminal A breast cancer and (H) patients with luminal B breast cancer who were treated with hormone therapy. Comparison of the CTNNBIP1$^{high}$ALDH1A3$^{high}$ vs. CTNNBIP1$^{high}$ALDH1A3$^{low}$ vs. CTNNBIP1$^{low}$ALDH1A3$^{high}$ vs. CTNNBIP1$^{low}$ALDH1A3$^{low}$ groups of patients. p-values were calculated using the Cochran-Mantel-Haenszel generalized log-rank test. The adjusted p-values for the CTNNBIP1$^{high}$ALDH1A3$^{high}$ group vs. CTNNBIP1$^{high}$ALDH1A3$^{low}$, CTNNBIP1$^{low}$ALDH1A3$^{high}$ and CTNNBIP1$^{low}$ALDH1A3$^{low}$ groups were determined using the Holm method. CTNNBIP1: Catenin β interacting protein 1; ALDH1A3: aldehyde dehydrogenase 1 family member A3.*

Table I. *Disease-specific survival multivariate Cox regression analyses according to CTNNBIP1 and ALDH1A3 expression in patients with different luminal subtypes of breast cancer treated with hormone therapy in the Molecular Taxonomy of Breast Cancer International Consortium dataset.*

| Patient group | Hazard ratio[a] | 95% confidence interval | *p*-Value[b] |
|---|---|---|---|
| A, Without hormone therapy | | | |
| Luminal A (*CTNNBIP1*$^{high}$*ALDH1A3*$^{high}$ *vs.*) | | | |
| *CTNNBIP1*$^{high}$*ALDH1A3*$^{low}$ | 1.61 | 0.78-3.31 | 0.19 |
| *CTNNBIP1*$^{low}$*ALDH1A3*$^{high}$ | 0.83 | 0.32-2.12 | 0.70 |
| *CTNNBIP1*$^{low}$*ALDH1A3*$^{low}$ | 0.62 | 0.22-1.75 | 0.37 |
| Luminal B (*CTNNBIP1*$^{high}$*ALDH1A3*$^{high}$ *vs.*) | | | |
| *CTNNBIP1*$^{high}$*ALDH1A3*$^{low}$ | 0.31 | 0.04-2.63 | 0.29 |
| *CTNNBIP1*$^{low}$*ALDH1A3*$^{high}$ | 0.09 | 0.00-2.45 | 0.15 |
| *CTNNBIP1*$^{low}$*ALDH1A3*$^{low}$ | 0.14 | 0.02-1.03 | **0.05** |
| B, With hormone therapy | | | |
| Luminal A (*CTNNBIP1*$^{high}$*ALDH1A3*$^{high}$ *vs.*) | | | |
| *CTNNBIP1*$^{high}$*ALDH1A3*$^{low}$ | 0.98 | 0.50-1.90 | 0.95 |
| *CTNNBIP1*$^{low}$*ALDH1A3*$^{high}$ | 1.77 | 0.88-3.55 | 0.11 |
| *CTNNBIP1*$^{low}$*ALDH1A3*$^{low}$ | 1.08 | 0.58-2.00 | 0.81 |
| Luminal B (*CTNNBIP1*$^{high}$*ALDH1A3*$^{high}$ *vs.*) | | | |
| *CTNNBIP1*$^{high}$*ALDH1A3*$^{low}$ | 3.23 | 1.00-10.48 | **0.05** |
| *CTNNBIP1*$^{low}$*ALDH1A3*$^{high}$ | 1.42 | 0.99-2.04 | **0.05** |
| *CTNNBIP1*$^{low}$*ALDH1A3*$^{low}$ | 2.08 | 1.04-4.16 | **0.04** |

[a]Hazard ratios of the *CTNNBIP1*$^{high}$*ALDH1A3*$^{high}$ group *vs.* *CTNNBIP1*$^{high}$*ALDH1A3*$^{low}$, *CTNNBIP1*$^{low}$*ALDH1A3*$^{high}$ and *CTNNBIP1*$^{low}$*ALDH1A3*$^{low}$ groups were adjusted using age, chemotherapy, and radiotherapy as the confounding factor, as estimated using the Cox proportional hazard model. [b]Significant differences are shown in bold. *CTNNBIP1*: Catenin β interacting protein 1; *ALDH1A3*: aldehyde dehydrogenase 1 family member A3.

dataset, another breast cancer cohort, TCGA Pan-Cancer Atlas, was analyzed. TCGA Pan-Cancer Atlas dataset was used to examine the effects of hormone therapy in luminal A and B breast cancer with high *CTNNBIP1* and *ALDH1A3* expression. As shown in Figure 1E-H, unlike in the METABRIC dataset, patients classified as *CTNNBIP1*$^{high}$ *ALDH1A3*$^{high}$ and treated with hormone therapy did not exhibit a poor prognosis in the luminal A and luminal B subtypes, although patients classified as *CTNNBIP1*$^{high}$ *ALDH1A3*$^{high}$ and treated with hormone therapy had the worst prognosis. Multivariate Cox regression analyses similarly showed no significant differences or were not analytically feasible (data not shown). The discrepancy in the results between the two cohorts may be due to the smaller number of patients, shorter observation period and more censoring in the dataset from TCGA compared with the METABRIC dataset. However, for hormone therapy in the luminal A and B subtypes, the dataset from TCGA included data on drugs with two different methods of action, including tamoxifen and aromatase inhibitors. As shown in Figure 2, patients with *CTNNBIP1*$^{high}$*ALDH1A3*$^{high}$ luminal B breast cancer treated with tamoxifen did not exhibit a poor clinical outcome. However, patients with *CTNNBIP1*$^{high}$*ALDH1A3*$^{high}$ luminal B breast cancer treated with aromatase inhibitors exhibited a poor prognosis ($p$=0.047; log-rank test) (Figure 2). These results suggested that the decreased effectiveness of hormone therapy in patients with *CTNNBIP1*$^{high}$*ALDH1A3*$^{high}$ luminal B breast cancer in the METABRIC dataset was due to the decreased effectiveness of aromatase inhibitors, as shown by the dataset from TCGA. Thus, patients with *CTNNBIP1*$^{high}$ *ALDH1A3*$^{high}$ luminal B breast cancer treated with aromatase inhibitors exhibited a poor prognosis.

*Patients with PKCζ*$^{high}$*CTNNBIP1*$^{high}$*ALDH1A3*$^{high}$ *luminal B breast cancer treated with aromatase inhibitors exhibit poor clinical outcomes.* Our recent study demonstrated that patients with *PKCζ*$^{high}$ and *CTNNBIP1*$^{high}$luminal B breast cancer treated with aromatase inhibitors exhibited poorer clinical outcomes among luminal B breast cancers (33).

Patients with *PKCζ*$^{high}$ and *ALDH1A3*$^{high}$ luminal B breast cancer treated with aromatase inhibitors also have poor clinical outcomes (54). Therefore, the present study examined the population of patients with the luminal B subtype with the *PKCζ*$^{high}$*CTNNBIP1*$^{high}$*ALDH1A3*$^{high}$ expression profile. As shown in Figure 3A and B, the proportions of patients with the *PKCζ*$^{high}$*CTNNBIP1*$^{high}$ *ALDH1A3*$^{high}$ expression profile among patients with luminal B breast cancer were as follows: METABRIC dataset, 12.9% (45/348); TCGA dataset, 4.2% (8/192). In the METABRIC dataset, patients with *PKCζ*$^{high}$*CTNNBIP1*$^{high}$*ALDH1A3*$^{high}$ luminal B breast cancer treated with hormone therapy exhibited a poor prognosis compared with others ($p$<0.001; log-rank test) (Figure 3). Furthermore, in the dataset from TCGA, although the number of patients with *PKCζ*$^{high}$*CTNNBIP1*$^{high}$*ALDH1A3*$^{high}$ luminal B breast cancer treated with aromatase inhibitors was small, patients with *PKCζ*$^{high}$*CTNNBIP1*$^{high}$*ALDH1A3*$^{high}$ luminal B breast cancer treated with aromatase inhibitors also exhibited a poor prognosis compared with others ($p$<0.001; log-rank test) (Figure 3). The results suggested that *PKCζ* and *CTNNBIP1* cooperatively contribute to disease progression in ALDH1A3-positive luminal B breast cancer, possibly by enhancing the stemness of cancer stem cells. Furthermore, for patients with *PKCζ*$^{high}$*CTNNBIP1*$^{high}$ *ALDH1A3*$^{high}$ luminal B breast cancer, tamoxifen treatment may be more effective than aromatase inhibitor treatment.

## Discussion

The present study demonstrated that high *PKCζ, CTNNBIP1* and *ALDH1A3* expression contributed to the decreased effectiveness of hormone therapy and aromatase inhibitor treatment in patients with the luminal B subtype. These results suggested that *PKCζ* and *CTNNBIP1* are involved in progression of the ALDH1A3-positive luminal B cancer subtype and contribute to the decreased effectiveness of hormone therapy for the luminal B subtype.

The present study revealed that high expression of both *CTNNBIP1* and *ALDH1A3* contributed to the decreased effectiveness of hormone therapy in patients with the luminal B subtype in the METABRIC dataset (Figure 1 and Table I). Consistently, high expression of both *CTNNBIP1* and *ALDH1A3* was associated with decreased effectiveness of aromatase inhibitor therapy in patients with the luminal B subtype in TCGA Pan-Cancer Atlas dataset (Figure 2). Our recent study demonstrated that patients with high expression of *CTNNBIP1* and *PKCζ* had poor clinical outcomes among patients with the luminal B subtype treated with hormone therapy, especially aromatase inhibitors (33). High expression of both *PKCζ* and *ALDH1A3* is also associated with poor clinical outcomes in patients with luminal B breast cancer treated with hormone therapy, especially aromatase inhibitors (54). Thus, PKCζ and CTNNBIP1 appear to cooperate to reduce the effectiveness of aromatase inhibitors in the ALDH1A3-positive luminal B subtype. However, the molecular mechanism of the relationship between PKCζ and CTNNBIP1 and poor effectiveness of aromatase inhibitors in ALDH1A3-positive luminal B breast cancer remains unclear. PKCζ interacts with scaffold protein p62 (48, 60-62). Patients with the luminal B subtype highly expressing *p62* exhibit a poor prognosis, and p62 deficiency in luminal B cell lines suppresses tumor-sphere formation (63, 64). Furthermore, high expression of *p62* and *ALDH1A3* reduced the effectiveness of hormone therapy and aromatase inhibitor (65). Thus, the interaction between PKCζ and p62 may be involved in the PKCζ-mediated decreased effectiveness of hormone therapy and aromatase inhibitors in ALDH1A3-positive luminal B breast cancer. In addition to high ER expression, the luminal B subtype often expresses HER2 (10, 11). Thus, the present study aimed to examine the effect of the *PKCζ*$^{high}$*CTNNBIP1*$^{high}$*ALDH1A3*$^{high}$ expression profile on HER2-targeted therapy in the luminal B subtype using the dataset from TCGA, which included information on HER2-targeted therapy. However, the prognostic analysis was impossible as no deaths occurred among the patients who received HER2-targeted therapy in the dataset from TCGA. Furthermore, because luminal B is highly proliferative, chemotherapy is usually administered. Therefore, the

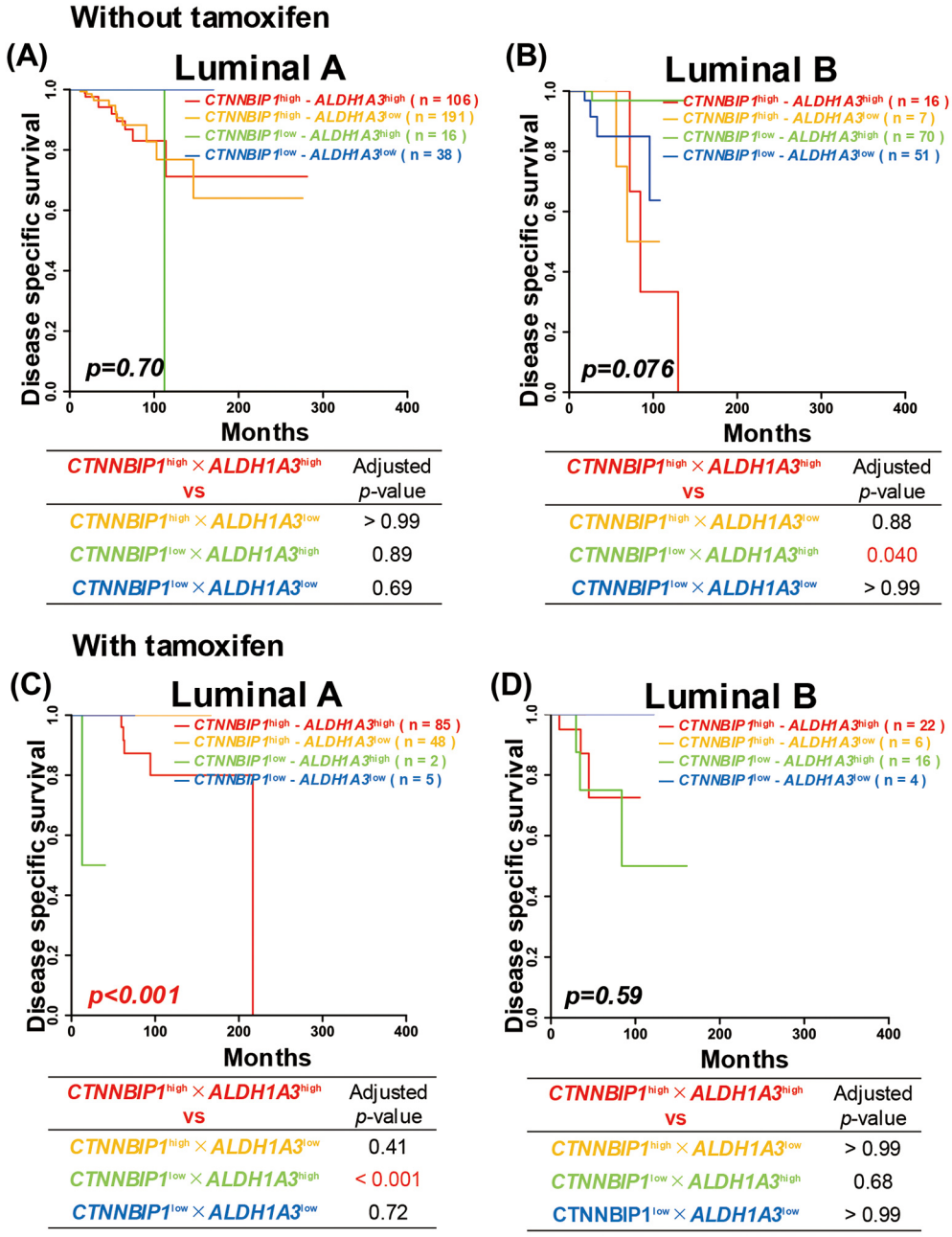
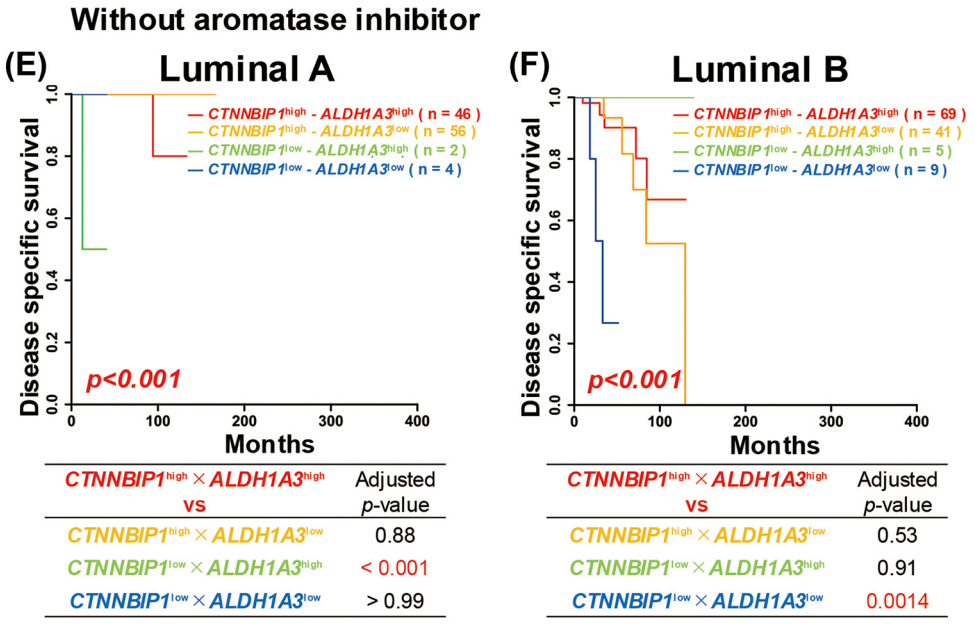



Figure 2. *Continued*

effectiveness of HER2-targeted therapy and chemotherapy in *PKCζ*$^{high}$*CTNNBIP1*$^{high}$*ALDH1A3*$^{high}$ luminal B breast cancer remains to be determined.

Another aPKC subtype, PKCλ, regulates the stem-like properties of ALDH1A3-positive CSCs such as tumor formation, cell survival, cell mortality and asymmetric cell division (66-68). It is also important to analyze the differences in the functions of PKCζ and PKCλ in the resistance to hormone therapy in luminal B breast cancer.




| CTNNBIP1high × ALDH1A3high vs | Adjusted *p*-value |
|---|---|
| CTNNBIP1high × ALDH1A3low | 0.88 |
| CTNNBIP1low × ALDH1A3high | < 0.001 |
| CTNNBIP1low × ALDH1A3low | > 0.99 |

| CTNNBIP1high × ALDH1A3high vs | Adjusted *p*-value |
|---|---|
| CTNNBIP1high × ALDH1A3low | 0.53 |
| CTNNBIP1low × ALDH1A3high | 0.91 |
| CTNNBIP1low × ALDH1A3low | 0.0014 |

| CTNNBIP1high × ALDH1A3high vs | Adjusted *p*-value |
|---|---|
| CTNNBIP1high × ALDH1A3low | 0.54 |
| CTNNBIP1low × ALDH1A3high | 0.32 |
| CTNNBIP1low × ALDH1A3low | 0.24 |

| CTNNBIP1high × ALDH1A3high vs | Adjusted *p*-value |
|---|---|
| CTNNBIP1high × ALDH1A3low | 0.81 |
| CTNNBIP1low × ALDH1A3high | > 0.99 |
| CTNNBIP1low × ALDH1A3low | 0.0056 |

Figure 2. *Disease-specific survival Kaplan-Meier analyses of patients with luminal breast cancer grouped according to CTNNBIP1 and ALDH1A3 expression and treated with tamoxifen or aromatase inhibitors. (A-H) The Cancer Genome Atlas Pan-Cancer Atlas data was downloaded from cBioPortal. (A) Patients with luminal A breast cancer and (B) patients with luminal B breast cancer who were treated without tamoxifen. (C) Patients with luminal A breast cancer and (D) patients with luminal B breast cancer who were treated with tamoxifen. (E) Patients with luminal A breast cancer and (F) patients with luminal B breast cancer who were treated without aromatase inhibitors. (G) Patients with luminal A breast cancer and (H) patients with luminal B breast cancer who were treated with aromatase inhibitors. Comparison of the CTNNBIP1$^{high}$ALDH1A3$^{high}$ vs. CTNNBIP1$^{high}$ALDH1A3$^{low}$ vs. CTNNBIP1$^{low}$ALDH1A3$^{high}$ vs. CTNNBIP1$^{low}$ALDH1A3$^{low}$ groups of patients. p-Values were calculated using the Cochran-Mantel-Haenszel generalized log-rank test. The adjusted p-values for the CTNNBIP1$^{high}$ALDH1A3$^{high}$ group vs. CTNNBIP1$^{high}$ALDH1A3$^{low}$, CTNNBIP1$^{low}$ALDH1A3$^{high}$ and CTNNBIP1$^{low}$ALDH1A3$^{low}$ groups were determined using the Holm method. CTNNBIP1: Catenin β interacting protein 1; ALDH1A3: aldehyde dehydrogenase 1 family member A3.*

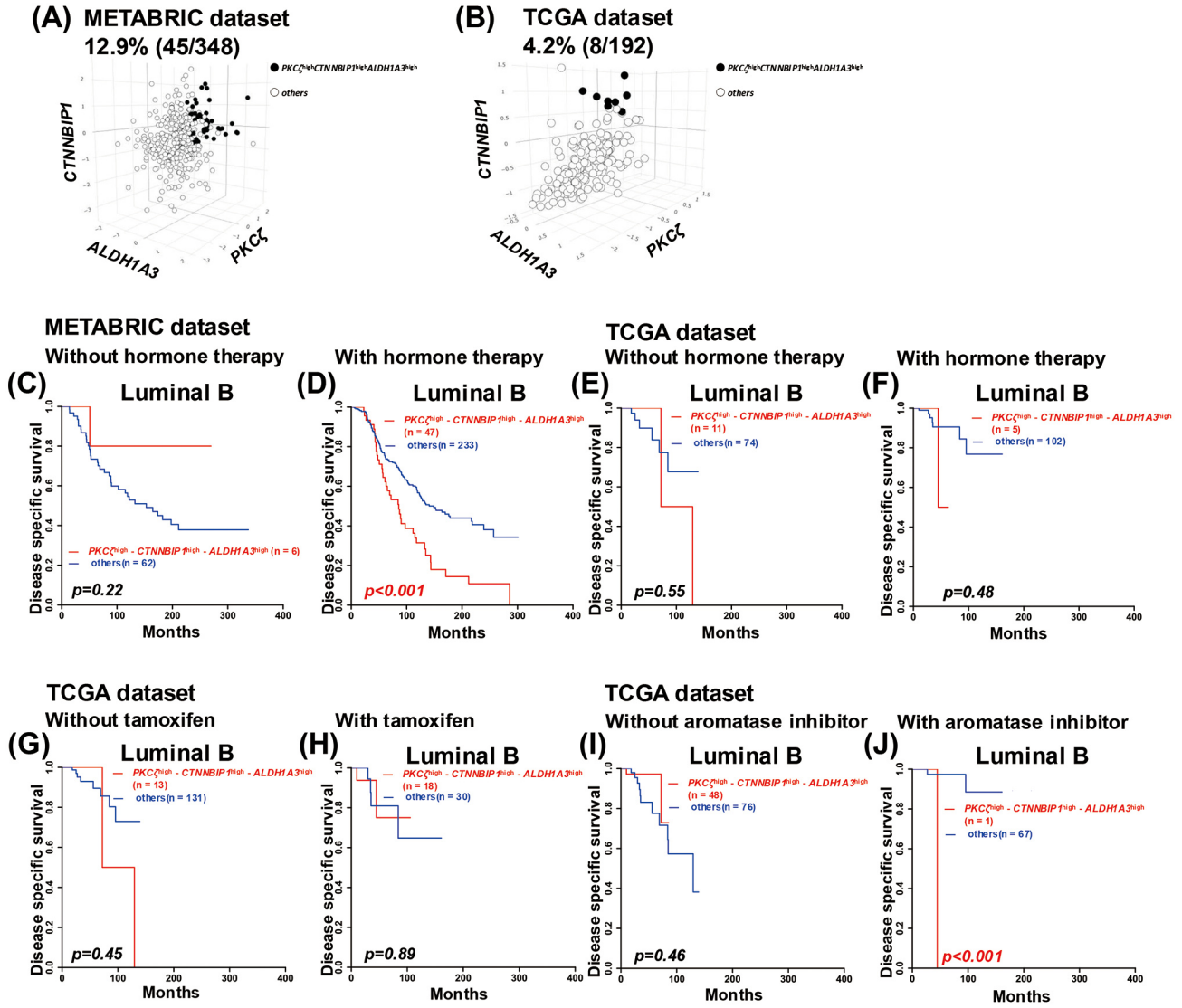



Figure 3. *Disease-specific survival Kaplan-Meier analyses of patients with luminal B breast cancer according to PKCζ, CTNNBIP1 and ALDH1A3 expression in patients treated with tamoxifen or aromatase inhibitors. (A and B) Three dimensional scatterplots of PKCζ, CTNNBIP1 and ALDH1A3 in luminal B breast cancer. Each graph is shown as a three dimensional scatterplot representing PKCζ, CTNNBIP1 and ALDH1A3 gene expression. • represents patients with PKCζ$^{high}$, CTNNBIP1$^{high}$ and ALDH1A3$^{high}$ profiles, whilst ○ represents patients with other PKCζ, CTNNBIP1 and ALDH1A3 profiles. The number indicates the ratio of patients classified as PKCζ$^{high}$, CTNNBIP1$^{high}$ and ALDH1A3$^{high}$. Comparison of PKCζ, CTNNBIP1 and ALDH1A3 in luminal B breast cancer according to the (A) METABRIC data and (B) TCGA Pan-Cancer Atlas data. METABRIC data was downloaded from cBioPortal. (C-J) Kaplan-Meier analyses of PKCζ, CTNNBIP1 and ALDH1A3 in luminal B breast cancer. (C) Patients with luminal B breast cancer who were treated without hormone therapy and (D) patients with luminal B breast cancer who were treated with hormone therapy. TCGA Pan-Cancer Atlas data was downloaded from cBioPortal. (E) Patients with luminal B breast cancer who were treated without hormone therapy and (F) patients with luminal B breast cancer who were treated with hormone therapy. (G) Patients with luminal B breast cancer who were treated without tamoxifen and (H) patients with luminal B breast cancer who were treated with tamoxifen. (I) Patients with luminal B breast cancer who were treated without aromatase inhibitors and (J) patients with luminal B breast cancer who were treated with aromatase inhibitors. Comparison of PKCζ$^{high}$CTNNBIP1$^{high}$ALDH1A3$^{high}$ vs. others (PKCζ$^{high}$CTNNBIP1$^{high}$ALDH1A3$^{low}$, PKCζ$^{high}$CTNNBIP1$^{low}$ALDH1A3$^{high}$, PKCζ$^{low}$CTNNBIP1$^{high}$ALDH1A3$^{high}$, PKCζ$^{low}$CTNNBIP1$^{high}$ALDH1A3$^{low}$, PKCζ$^{low}$CTNNBIP1$^{low}$ALDH1A3$^{high}$ and PKCζ$^{low}$CTNNBIP1$^{low}$ALDH1A3$^{low}$ groups of patients). p-Values were calculated using the Cochran-Mantel-Haenszel generalized log-rank test. METABRIC: Molecular Taxonomy of Breast Cancer International Consortium; TCGA: The Cancer Genome Atlas; CTNNBIP1: catenin β interacting protein 1; ALDH1A3: aldehyde dehydrogenase 1 family member A3; PKCζ: protein kinase Cζ.*

## Conclusion

The present study demonstrated that *PKCζ* and *CTNNBIP1* are involved in ALDH1A3-positive luminal B cancer subtype progression, and contribute to the decreased effectiveness of hormone therapy, especially aromatase inhibitors in patients with luminal B breast cancer. Therefore, it was concluded that, in luminal B breast cancer, *PKCζ*, *CTNNBIP1* and *ALDH1A3* could serve as molecular drug targets for treatment and prognostic biomarkers to predict the effectiveness of hormone therapy.

## Conflicts of Interest

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

## Authors' Contributions

Conceptualization: KN, ME and KA; formal analysis: KN, ME and AI; funding acquisition: YN, ST, SO, KS, and KA; investigation: KN, ME, AI and KA; methodology: KN, ME, AI, YN and KA; project administration: KA; supervision: KA; validation: YN, RO, TK, ST, YH and KS; visualization: KN, ME, AI and RO; writing – original draft preparation: KN, ME and KA; writing – review & editing: AI, YN, RO, TK, ST, YH, SO, KS and KA.

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## Artificial Intelligence (AI) Disclosure

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

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