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Neoadjuvant chemotherapy response in androgen receptor-positive triple-negative breast cancer: potential predictive biomarkers and genetic alterations

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Abstract

Background The aim of the present study was to investigate whether the androgen receptor (AR) status affects the efficacy of neoadjuvant chemotherapy (NACT) in triple negative breast cancer (TNBC) patients, and to elucidate the predictive biomarkers and mutations associated with pathological complete response (pCR) in AR-positive TNBC patients.

Methods The current retrospective cohort included 226 TNBC patients who underwent NACT. AR and FOXC1 were assessed by immunohistochemistry on pretreatment biopsy specimens of 226 TNBC patients from 2018 to 2022. The clinicopathological features of AR-negative, AR < 10%, and AR ≥ 10% TNBC patients were analyzed to confirm the appropriate threshold. The response was evaluated in terms of pCR and Miller-Payne (MP) grade in the subsequent mastectomy or breast conservation samples. Next-generation sequencing (NGS) was utilized to further investigate the molecular characteristics of 44 AR-positive TNBC patients.

Results Among the 226 TNBC patients, compared with AR-negative and AR < 10% tumors (68.58%, 155/226), AR ≥ 10% TNBC patients (31.41%, 71/226) exhibited distinct clinicopathological features, while no significant difference was detected between those with AR-negative tumors and those with AR < 10% tumors. Thus, tumors with AR ≥ 10% expression were defined as having AR positive expression. The pCR rate of AR-positive TNBCs was lower than that of AR-negative TNBC patients (12.68% vs. 34.19%, $p < 0.001$). In TNBC, multivariate analysis demonstrated that FOXC1 was an independent predictor of pCR ($p = 0.042$), whereas AR was not. The pCR rate was higher in FOXC1 positive patients than in FOXC1 negative patients (34.44% vs. 3.13%, $p < 0.001$). In the AR-positive TNBC subgroup, patients with FOXC1 expression had lower AR expression, higher Ki-67 expression, and higher histological grade. Compared with AR-positive TNBC patients who achieved pCR, the non-pCR patients had a greater percentage of mutations in genes involved in the PI3K/AKT/mTOR pathway.

Conclusions The current study indicated that the AR-positive TNBC is correlated with lower rates of pCR after NACT. The expression of FOXC1 in TNBC patients and AR-positive TNBC patients could be utilized as a predictive marker for

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the efficacy of NACT. The present study provides a rationale for treating these non-pCR AR-positive TNBC tumors with PI3K/AKT/mTOR inhibitors.

Keywords Androgen receptor, Neoadjuvant chemotherapy, Predictive biomarkers, Genetic alterations

Introduction

Triple-negative breast cancer (TNBC), which is defined by the absence of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) expression, is a molecularly diverse disease including a collection of heterogeneous tumors with variable clinical outcomes [1]. Gene expression-based analysis has been widely applied for TNBC subtyping to better identify molecular-based therapies. Lehmann et al. initially classified TNBC into six subtypes based on gene expression analysis, including two basal-like subtypes (BL1 and BL2), an immunomodulatory subtype (IM), a mesenchymal subtype (M), a mesenchymal stem-like subtype (MSL), and a luminal androgen receptor (LAR) subtype [2, 3] The LAR subtype, characterized by androgen receptor (AR) signaling, has also been confirmed in refined versions of the TNBC molecular classification system and is more common in the Chinese population compared to that in Caucasian patients [4, 5]. The prognosis of LAR subtype patients varies across previous studies. The majority of previous studies have reported that the LAR subtype patients are less aggressive. However, it has also been reported that patients with the LAR subtype tend to have worse clinical outcomes than patients with the non-LAR subtype [6].

Recently, surrogate immunohistochemistry (IHC)-based classification for TNBC subtyping has been developed. Based on IHC, the LAR subtype is defined as TNBC patients with positive AR expression [7]. Previous studies reported that AR is positive in 10 to 75% of TNBCs [8, 9]. Compared with AR-negative TNBC patients, AR-positive TNBC patients show larger tumors, older ages, and lower Ki-67 indices [10, 11]. Additionally, AR is more likely to be expressed in Invasive breast cancer with apocrine differentiation. However, the clinical significance of AR in TNBC remains controversial due to the absence of a clearly defined cutoff value of positive AR expression [12]. The cutoff points for AR positivity used in different studies vary, and the most widely used cutoff values are 1% [7] and 10% [13]. Therefore, confirming an appropriate AR cutoff value is crucial for identifying the AR positive expression and evaluating its clinicopathological role in TNBC.

Neoadjuvant chemotherapy (NACT) is an important therapeutic strategy for TNBC. Pathological complete response (pCR) is defined as the absence of Invasive cancer cells in the breast and axillary lymph nodes of the surgical specimen. Studies have demonstrated that patients who achieve pCR after NACT have better long-term outcomes [14, 15]. Triple-negative breast cancers typically respond well to NACT, with a pCR rate up to 40%. However, it has been reported the AR-positive TNBC/LAR subtype has less chemotherapy responsiveness and a lower pCR rate after NACT compared to other TNBC subtypes [16]. AR protein expression has also been reported to be predictive of the potential response to NACT in TNBC patients [17]. Owing to the limited number of LAR patients in previous studies, whether AR expression and the LAR subtype can serve as independent predictors of the NACT response in TNBC patients remains to be further investigated. Therefore, there is an unmet clinical need to explore potential predictive biomarkers and genomic changes associated with the NACT response and to optimize therapeutic strategies for the neoadjuvant treatment of AR-positive TNBCs.

FOXC1 is a basal-like specific marker in breast cancer and one of the IHC markers for surrogate TNBC subtyping [7, 13]. High *FOXC1* mRNA levels have been reported to be significantly related to increased pathologic response regardless of breast cancer subtype [18]. Whether FOXC1 protein expression is associated with pCR in the TNBC and AR-positive TNBC patients has not been reported. In addition, genomic and transcriptomic analyses may characterize the peculiar genomic drivers and identify potential therapeutic targets for patients who do not achieve pCR.

The aims of the present analysis were (i) to identify an appropriate cutoff value for AR-positive expression: (ii) to explore potential biomarkers associated with the NACT response in TNBC and AR-positive TNBC patients; and (iii) to investigate the landscape of genomic alterations associated with the NACT response in AR-positive TNBC patients.

Methods

Patients

The present study enrolled 226 TNBC patients who underwent NACT and surgery at Fudan University Shanghai Cancer Center (Shanghai, China) between 2018 and 2022. All patients were diagnosed via core needle biopsy (CNB) with ER, PR, HER2, and AR immunohistochemical (IHC) staining. The present study was approved by the Institutional Review Board of the Fudan University Shanghai Cancer Center, and informed consent was obtained from all subjects. Information regarding the clinicopathological characteristics, treatments, and NACT response was retrieved from the medical records. The hematoxylin-eosin (HE) stained slides of CNBs and

resection specimens were collected and reviewed. The stromal tumor-infiltrating lymphocytes(TILs) were evaluated according to the International TILs Working Group 2014 [19].

Immunohistochemistry (IHC)

The details of the IHC antibodies used are shown in Table S1. All staining was performed with a Ventana BenchMark Ultra Autostainer (Ventana Medical System Inc., Roche, Tucson, AZ, USA) according to the manufacturer's instructions.

AR and FOXC1 expression were evaluated in core biopsy samples before neoadjuvant chemotherapy. AR is reported as both the percentage and intensity of positively stained nuclei in tumor cells. Nuclear FOXC1 staining in ≥1% of cells was defined as FOXC1 positive. The response to neoadjuvant chemotherapy was evaluated according to the Miller-Payne (MP) grading system and pCR rate criteria.

Comprehensive genomic profiling

FUSCC NGS panel sequencing detected somatic and germline mutations in 484 breast cancer-specific genes [20] in 44 pretreatment AR-positive TNBC samples.

Statistical analysis

The clinicopathological parameters were compared among the different subgroups using chi-square analysis. Statistical analyses were performed using SPSS 20.0 (SPSS, Chicago, IL, USA) or GraphPad Prism 8.0 (GraphPad Software, La Jolla, CA, USA). A value of $p < 0.05$ was considered to indicate statistical significance.

Results

Clinicopathological characteristics of TNBC patients

A total of 226 patients with TNBC were included in this study. Prior to NACT, most patients presented with positive lymph nodes (68.14%, 154/226), a high histological grade (grade 3, 78.32%, 177/226), a large tumor size (81.86%,185/226 with a tumor > 2 cm), and high Ki-67 index (87.61%, 198/226, Table 1). Among these 226 TNBC patients, 200 patients (88.50%) were invasive breast carcinoma of no special type (IBC-NST), and 26 patients were special histological types, including lobular (3 patients, 1.33%), metaplastic (13 patients, 5.75%), and apocrine (10 patients, 4.42%). All patients received NACT. Specifically, 123 patients (54.42%) received anthracycline-taxane-based NACT, and 103 patients received other regimens enrolled in clinical trials, including platinum-containing therapy, PD-1 blockade-containing therapy and others (Table 1).

Establishing a threshold for AR-positive expression

Considering that the most commonly adopted cutoff value for AR positivity in previous studies was 1% or 10%, clinicopathological characteristics were compared among AR-negative, AR < 10%, and AR ≥ 10% TNBCs. Among the 226 TNBC patients, 31.42% (71/226) had AR ≥ 10% tumors, 7.08% (16/226) had AR < 10% tumors, and 61.50% (139/226) had AR-negative tumors according to IHC (Table 1). There was no statistically significant difference in treatment regimens among the three groups ($p > 0.05$).

Compared with 155 patients with AR-negative tumors and AR < 10% tumors, those with AR ≥ 10% tumors showed significantly older age ($p < 0.001$), lower histological grade ($p < 0.001$), and lower Ki-67 index($p < 0.001$). FOXC1 expression was more likely to be negative in AR ≥ 10% tumors ($p < 0.001$). Patients with histological types of invasive lobular carcinoma and invasive carcinoma with apocrine differentiation were more likely to have AR expression ≥ 10%, while patients with invasive metaplastic carcinoma were more likely to be with AR-negative or AR < 10% expression ($p < 0.001$). In addition, patients with AR ≥ 10% tumors achieved a significantly lower pCR rate ($p < 0.001$) and had more posttherapy lymph node metastasis ($p < 0.001$) than patients with AR-negative and AR < 10% tumors. Furthermore, compared to patients with AR < 10% tumors, those with AR ≥ 10% tumors had more negative FOXC1 expression ($p = 0.02$) and a lower histological grade ($p = 0.018$). However, the clinicopathological characteristics of AR < 10% tumors were not significantly different from that of patients with AR-negative tumors.

Overall, patients with AR ≥ 10% tumors demonstrated distinct clinical and pathological features compared with those with AR-negative and AR < 10% tumors, whereas no significant difference was observed between patients with AR-negative tumors and those with AR < 10% tumors. On the basis of these results, the threshold for AR-positivity was defined as ≥ 10% AR-positivity.

Associations of clinicopathological variables with response to NACT in TNBC patients

Total pCR was achieved in 27.43% (62/226) of patients in the entire cohort (Table 1). According to the defined cutoff value for AR positivity, 31.42% (71/226) of the patients were in the AR-positive TNBC subgroup. In AR-positive TNBC subgroup, pCR was achieved in 12.68% (9/71) of the patients, while the pCR rate in patients with AR-negative tumors was 34.19% (53/155), which indicated that patients with the AR-positive TNBC subgroup were less likely to experience a pCR ($p < 0.001$, Fig. 1A) compared to patients with other TNBCs (Supplemental Fig. 1A). Similar findings were observed when AR expression was compared across MP scores ($p = 0.016$, Fig. 1B).

Table 1 Comparison of clinicopathological characteristics among patients with AR-negative, AR < 10%, and AR ≥ 10% TNBCs

			AR negative		AR < 10%		AR ≥ 10%		*p* AR ≥ 10% vs. others (including AR < 10% and AR negative)	*p* AR ≥ 10% vs. AR < 10%	*p* AR < 10% vs. AR negative
	n	%	*n*	%	*n*	%	*n*	%			
	226		**139**	**61.50**	**16**	**7.08**	**71**	**31.42**			
Age									**< 0.001**	0.148	0.466
< 50	126	55.75	91	65.47	9	56.25	26	36.62			
≥ 50	100	44.25	48	34.53	7	43.75	45	63.38			
Histologic subtype	0								**< 0.001**	0.216	> 0.999
Invasive breast carcinoma of no special type	200	88.50	128	92.09	15	93.75	57	80.28			
Invasive lobular carcinoma	3	1.33	0	0.00	0	0.00	3	4.23			
Invasive metaplastic carcinoma	13	5.75	11	7.91	1	6.25	1	1.41			
Invasive carcinoma with apocrine differentiation	10	4.42	0	0.00	0	0.00	10	14.08			
Pretherapy histological grade									**< 0.001**	**0.018**	0.699
1,2	46	20.35	20	14.39	1	6.25	25	35.21			
3	177	78.32	118	84.89	15	93.75	44	61.97			
Unavailable	3	1.33	1	0.72	0	0.00	2	2.82			
Ki-67									**< 0.001**	0.174	> 0.999
≤ 20	28	12.39	10	7.19	1	6.25	17	23.94			
> 20	198	87.61	129	92.81	15	93.75	54	76.06			
Pretherapy tumor size, cm									0.112	0.104	0.097
cT1	26	11.50	19	13.67	4	25.00	3	4.23			
cT2	126	55.75	77	55.40	5	31.25	44	61.97			
cT3	59	26.11	33	23.74	7	43.75	19	26.76			
Unavailable	15	6.64	10	7.19	0	0.00	5	7.04			
Pretherapy lymph node status									0.783	0.46	0.279
Core biopsy positive	154	68.14	93	66.91	11	68.75	50	70.42			
Core biopsy negative	31	13.72	17	12.23	4	25.00	10	14.08			
Unavailable	41	18.14	29	20.86	1	6.25	11	15.49			
NACT regimen									0.854	0.48	0.347
Anthracycline-taxane based	123	54.42	78	56.12	7	43.75	38	53.52			
others[a]	103	45.58	61	43.88	9	56.25	33	46.48			
FOXC1									**< 0.001**	**0.02**	0.197
Negative	32	14.16	6	4.32	2	12.50	24	33.80			
Positive	151	66.81	114	82.01	12	75.00	25	35.21			
Unavailable	43	19.03	19	13.67	2	12.50	22	30.99			
Pathological response									**0.001**	0.688	0.169
non-pCR	164	72.57	89	64.03	13	81.25	62	87.32			
pCR	62	27.43	50	35.97	3	18.75	9	12.68			
Post-therapy lymph node status									**< 0.001**	0.264	0.568
N0	121	53.54	86	61.87	9	56.25	26	36.62			
N1	54	23.89	22	15.83	3	18.75	29	40.85			
N2	27	11.95	18	12.95	1	6.25	8	11.27			
N3	24	10.62	13	9.35	3	18.75	8	11.27			

a: others(including platinum-containing, PD-1 blockade containing therapy, and others)

The patients with apocrine differentiation exclusively belonged to the AR positive TNBC subgroup, and had a pCR rate of 10% (1/10).

Univariate analysis of 183 TNBC patients in which FOXC1 was evaluated revealed that AR, FOXC1, histological grade, histological subtype, Ki-67, and NACT regimen types were significantly associated with pCR (Table 2). However, multivariate analysis revealed that only FOXC1 expression and NACT regimen types were independent factors associated with pCR in TNBC patients (Table 2). Five out of 62 patients (8.1%) who achieved pCR experienced relapse (distant metastasis). Among the 164 patients who did not achieve pCR, 33 patients (20.12%) relapsed. Of those, 10 patients experienced locoregional relapse, and 27 had distant metastases. TNBC patients who achieved pCR after NACT had

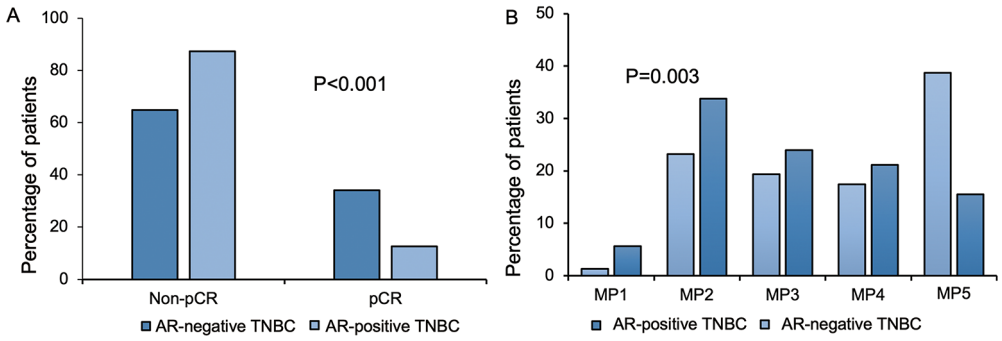

Fig. 1 TNBC subtypes and response to neoadjuvant therapy. **A** pCR rates in TNBC patients with and without AR expression. **B** MP response in TNBC patients with and without AR expression

Table 2 Univariate and multivariate analyses of clinicopathologic variables and biomarkers associated with the NACT response in TNBC patients

	Pathological response					Univariate analysis	Multivariate analysis		
	n	pCR	%	Non-pCR	%	p	OR	95% CI	p
	226	**62**	**27.43**	**164**	**72.57**				
AR						**< 0.001**	0.429	0.159–1.154	0.094
Negative	155	53	34.19	102	65.81				
Positive	71	9	12.68	62	87.32				
Pretherapy tumor size, cm						0.104			
≤ 2 cm	26	11	42.31	15	57.69				
> 2 cm	186	50	26.88	136	73.12				
Histologic subtype						**0.016**	0.154	0.597–9.622	0.084
Invasive breast carcinoma of no special type	200	60	30.00	140	70.00				
Others	26	2	7.69	24	92.31				
Pretherapy histological grade						**0.004**	2.396	0.597–9.622	0.218
3	177	57	32.20	120	67.80				
1,2	46	5	10.87	41	89.13				
Age						0.183			
< 50	126	39	30.95	87	69.05				
≥ 50	100	23	23.00	77	77.00				
Pretherapy lymph node status						0.201			
Core biopsy positive	31	12	38.71	19	61.29				
Core biopsy negative	154	42	27.27	112	72.73				
ki-67						**0.034**	3.924	0.428–35.944	0.226
≤ 20%	28	3	10.71	25	89.29				
> 20%	198	59	29.80	139	70.20				
FOXC1						**< 0.001**	**8.627**	**1.054–70.606**	**0.045**
Negative	32	1	3.13	31	96.88				
Positive	151	52	34.44	99	65.56				
NACT regimen						**0.001**			
Anthracycline-taxane based	123	24	19.51	99	80.49				
PD-1 blockade containing therapy	37	19	51.35	18	48.65		**0.234**	**0.097–0.563**	**0.001**
Others(including platinum-containing, and others)	66	19	28.79	47	71.21		0.573	0.270–1.217	0.148

better disease-free survival (DFS) (Fig. 2A). In the AR-positive TNBC subgroup, although the difference was not statistically significant, the DFS was better in patients who achieved pCR than in non-pCR patients (Fig. 2B). Overall survival (OS) was not significantly different between pCR and non-pCR patients in TNBCs (Fig. 2C) and AR-positive TNBCs (Fig. 2D) for short follow-up times. In addition, the DFS and OS were not significantly different between AR-positive TNBCs and AR-negative TNBCs (Supplemental Fig. 1B-C).

FOXC1 is negatively correlated with AR expression. pCR was achieved in 34.44% (52/151) of patients with FOXC1-positive tumors, which was significantly higher than that in patients with FOXC1-negative tumors

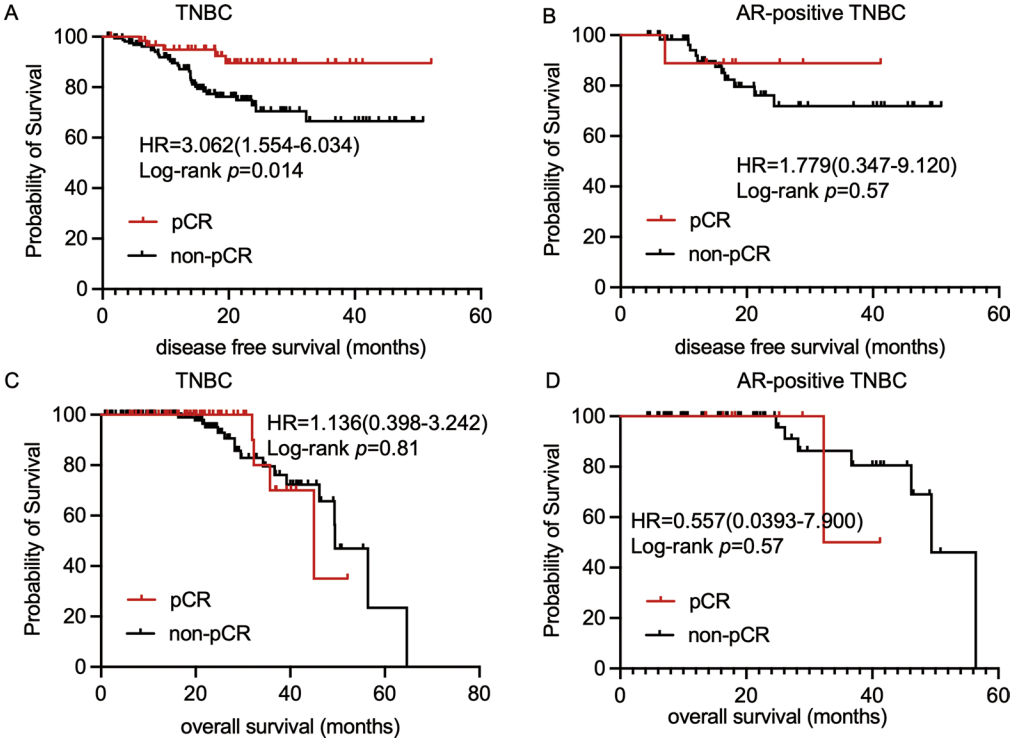

Fig. 2 Kaplan–Meier analysis of the prognosis of TNBC patients with and without AR expression. **A**-**B** Disease-free survival and overall survival in TNBC patients who achieved a pCR and who did not achieve pCR. **C**-**D** Disease-free survival and overall survival in AR-positive TNBC patients who achieved a pCR and who did not achieve pCR

(3.13%, 1/32, $p < 0.001$; Fig. 3A). Tumors with FOXC1 expression showed a significantly higher Miller response rate than those without FOXC1 expression (Supplemental Fig. 2A).

In general, AR-positive TNBCs were less likely to experience a pCR compared to than AR-negative TNBCs. In addition, FOXC1 was found to be an independent predictor of NACT response in TNBC patients.

Associations of FOXC1 expression with clinical variables and response to NACT in AR-positive TNBC patients

Among the 71 AR-positive TNBC patients, FOXC1 IHC was detected in 49 patients. 51.02% (25/49) of the AR-positive TNBC patients showed FOXC1 expression (Table 3; Fig. 3D). To investigate the clinical significance of FOXC1 expression in the AR-positive TNBCs, AR and FOXC1 expression patterns were investigated and correlated with pathologic response and clinicopathological characteristics.

In the AR-positive TNBC subgroup, patients without FOXC1 expression had increased AR expression ($p < 0.001$, Fig. 3B), lower histological grade ($p < 0.001$), and lower Ki-67 expression ($p = 0.011$, Table 3). In addition, patients with special histological subtypes of ILC and Invasive carcinoma with apocrine differentiation were more likely to have negative FOXC1 expression ($p = 0.003$). Tumors with FOXC1 expression had a significantly higher pCR rate (28.00% vs. 0.00%, $p = 0.01$; Fig. 3C) than in patients with FOXC1-negative tumors (Table 3). Similar findings were observed when FOXC1 expression was compared across MP scores ($p = 0.001$, Supplemental Fig. 2B).

Moreover, the pCR rate was not significantly different between FOXC1-positive/AR-positive patients (7/25, 28.00%) and AR-negative TNBC patients (46/134, 34.33%), and the pCR rate of FOXC1-positive/AR-positive patients was slightly higher than that of FOXC1-negative/AR-negative patients (12.50%, $p = 0.643$) but slightly lower than that of FOXC1-positive/AR-negative patients (35.71%, $p = 0.458$; Table 3). However, the pCR rate of FOXC1-negative/AR-positive patients (0/24, 0.00%) was significantly lower than that of FOXC1-positive/AR-negative patients ($p < 0.001$) but not significantly different from that of FOXC1-negative/AR-negative patients ($p = 0.25$, Table 3).

In terms of the AR-positive TNBC subgroup, univariate analysis demonstrated that FOXC1 expression, low AR expression, and NACT regimen type were significantly associated with higher pCR rates (Table 4). Among the seven pCR patients, all exhibited FOXC1 expression and were treated with platinum containing therapy and six patients exhibited weak AR expression (scores ≤ 20%); thus, multivariable analysis was not performed. In addition, Two of the 7 cases who achieved pCR showed

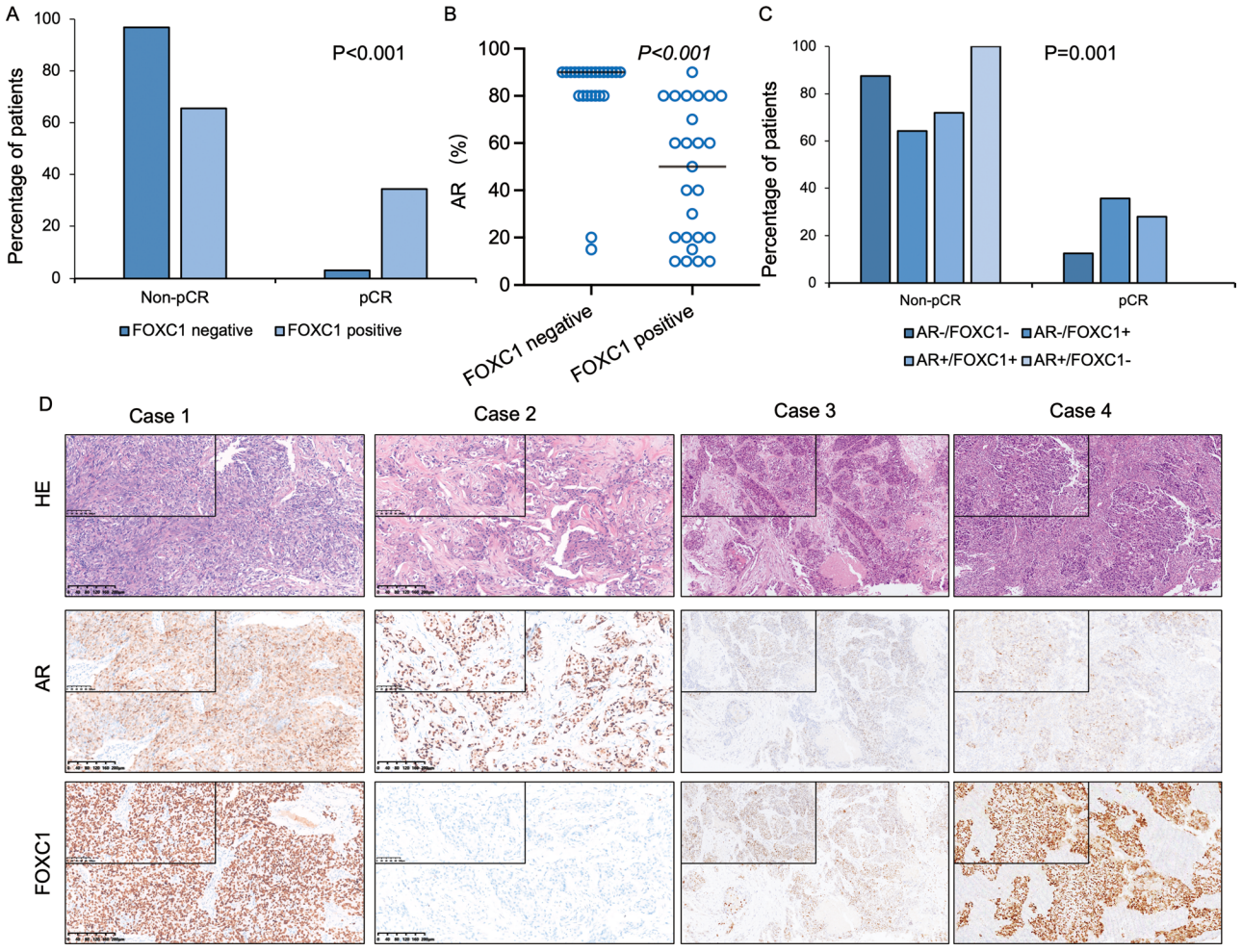

Fig. 3 TNBC subtype and response to neoadjuvant therapy. A pCR rates in FOXC1-positive and FOXC1-negative TNBC patients. B AR expression levels in FOXC1-positive and FOXC1-negative/AR-positive TNBC patients. C pCR rates in FOXC1-positive and FOXC1-negative patients with and without AR expression. D Representative images of AR and FOXC1 staining in AR-positive TNBC patients

high stromal TILs (≥ 50%). The pCR rate of cases with high stromal TILs (2/8, 25.00%) was slightly higher than that of patients with low and intermediate stromal TILs (5/41,12.19%, $p = 0.737$).

Taken together, these results suggest that in AR-positive TNBC patients, FOXC1 expression and low AR expression are associated with a potential NACT response.

Genomic landscape of the AR-positive TNBC subgroup and association with NACT response

To compare the genomic landscape of AR-positive TNBC patients who achieved pCR and non-pCR, targeted sequencing was performed on pretreatment tumor biospecimens from 44 AR-positive TNBC samples, of which 9 cases were MP5 (6 patients achieved pCR and 3 patients did not achieve pCR), 6 were MP4, and 29 were MP2-3(Fig. 4A). *TP53* (65.91%), *PIK3CA* (29.55%), *PTEN* (11.36%), and *KMT2D* (11.36%) were the most frequently mutated genes in these AR-positive TNBCs. Importantly, MP5 patients exhibited a low frequency of mutations affecting *PIK3CA* (11.11%, 1/9), which were frequently found in MP4 and MP2-3 patients (34.29%, 12/35). Moreover, mutations affecting *PTEN*, *KMT2D*, *ANKRD11*, *FOXA1*, *PIK3R1*, and *ARID1A* were more frequently observed in MP2-3 cases but undetected in MP4-5 cases. *MYC* amplification and mutations affecting *ATRX*, *AKT1*, *FAM47C*, *HK2*, and *TSC2* were not detected in pCR patients, while *COL2A1* and *MAP1A* mutations were more frequently observed in pCR patients. In 21 cases with alterations affecting the PI3K/AKT/mTOR pathway (loss or mutation of *PTEN* or mutations in *PIK3CA*, *PIK3R1*, *TSC2*, or *AKT1*), the pCR rate was 4.76% (1/21), which was lower than that in cases without alterations affecting this pathway (21.74%, 5/23, $p = 0.188$). In addition, fewer cases achieved MP4-5 (5/21,23.80%) than did those without alterations affecting this pathway (43.48%,10/23, $p = 0.169$).

Table 3 Comparison of clinicopathological characteristics among the FOXC1 positive and FOXC1 negative TNBC patients with or without AR expression

		FOXC1- /AR-		FOXC1- /AR+		FOXC1+ /AR-		FOXC1+ /AR+		FOXC1- /AR+ vs.			FOXC1+ /AR+ vs.		FOXC1- /AR- vs.
	n	n	%	n	%	n	%	n	%	FOXC1- /AR-	FOXC1+ /AR-	FOXC1+ /AR+	FOXC1- /AR-	FOXC1+ /AR-	FOXC1+ /AR-
	183	8	4.37	24	13.11	126	68.85	25	13.66	p	p	p	p	p	p
Age										0.116	**0.001**	0.282	0.438	0.058	> 0.999
< 50	104	5	62.5	7	29.17	81	64.29	11	44.00						
≥ 50	79	3	37.5	17	70.83	45	35.71	14	56.00						
Histologic subtype										**0.09**	**< 0.001**	**0.003**	0.432	0.692	0.506
Invasive breast carcinoma of no special type	163	7	87.5	16	66.67	116	92.06	24	96.00						
Invasive lobular carcinoma	3	0	0	3	12.50	0	0.00	0	0.00						
Invasive metaplastic carcinoma	12	1	12.5	0	0.00	10	7.94	1	4.00						
Invasive carcinoma with apocrine differentiation	5	0	0	5	20.83	0	0.00	0	0.00						
Pretherapy histologic grade										0.412	**< 0.001**	**< 0.001**	0.139	0.474	0.268
1,2	30	2	25	12	50.00	15	11.90	1	4.00						
3	153	6	75	12	50.00	111	88.10	24	96.00						
ki-67										0.081	**0.001**	**0.011**	> 0.999	> 0.999	> 0.999
≤ 20%	17	0	0	8	33.33	8	6.35	1	4.00						
> 20%	166	8	100	16	66.67	118	93.65	24	96.00						
Pretherapy lymph node status										> 0.999	0.764	> 0.999	> 0.999	> 0.999	> 0.999
Core biopsy positive	123	4	50	18	75.00	84	66.67	17	68.00						
Core biopsy negative	27	1	12.5	3	12.50	19	15.08	4	16.00						
Unavailable	33	3	37.5	3	12.50	23	18.25	4	16.00						
Pretherapy tumor size, cm										0.241	0.076	> 0.999	0.395	0.197	> 0.999
≤ 2 cm	20	1	12.5	0	0.00	18	14.29	1	4.00						
> 2 cm	153	6	75	22	91.67	101	80.16	24	96.00						
Unavailable	10	1	12.5	2	8.33	7	5.56	0	0.00						
Posttherapy lymph node status										0.272	**0.001**	0.197	0.385	0.319	0.453
N0	103	4	50	6	25.00	80	63.49	13	52.00						
N1	41	1	12.5	11	45.83	21	16.67	8	32.00						
N2	21	2	25	3	12.50	13	10.32	3	12.00						
N3	18	1	12.5	4	16.67	12	9.52	1	4.00						
NACT regimen										0.845	0.563	**0.022**	0.399	**0.002**	0.718
PD-1 blockade containing therapy	37	1	12.5	4	16.67	30	23.81	2	8.00						
Others(including platinum-containing, and others)	55	3	37.5	5	20.83	32	25.40	15	60.00						
Anthracycline-taxane based	91	4	50	15	62.50	64	50.79	8	32.00						
Miller-Payne response										0.83	**< 0.001**	**0.009**	0.433	0.576	0.336
MP1	2	0	0.00	1	4.17	1	0.79	0	0.00						
MP2	54	4	50.00	13	54.17	31	24.60	6	24.00						
MP3	37	2	25.00	7	29.17	24	19.05	4	16.00						
MP4	29	1	12.50	2	8.33	19	15.08	7	28.00						
MP5	61	1	12.50	1	4.17	51	40.48	8	32.00						
Miller-Payne response										0.578	**< 0.001**	**0.001**	0.118	0.826	0.144
≥ 90%	90	2	25.00	3	12.50	70	55.56	15	60.00						
< 90%	93	6	75.00	21	87.50	56	44.44	10	40.00						

Table 3 (continued)

		FOXC1- /AR-		FOXC1- /AR+		FOXC1+ /AR-		FOXC1+ /AR+		FOXC1- /AR+ vs.			FOXC1+ /AR+ vs.			FOXC1- /AR- vs.
	n	n	%	n	%	n	%	n	%	FOXC1-/AR-	FOXC1+/AR-	p	FOXC1-/AR-	FOXC1+/AR+	p	FOXC1+ /AR- vs. FOXC1+ /AR+ p
	183	8	4.37	24	13.11	126	68.85	25	13.66	0.25		<0.001	0.643	0.01	0.458	0.263
Pathological response																
Non-pCR	130	7	87.50	24	100.00	81	64.29	18	72.00							
pCR	53	1	12.50	0	0.00	45	35.71	7	28.00							

Among the 44 patients, 34 patients who underwent FOXC1 testing were divided into a FOXC1-positive group (18 patients) and a FOXC1-negative group (16 patients). Compared to FOXC1-positive patients (94.44%, 17/18), FOXC1-negative patients (43.75%, 7/16) had a lower frequency of mutations affecting *TP53*(Supplemental Fig. 3A). Moreover, mutations affecting *PTEN* (3/16), *KMT2D* (4/16), *ANKRD11* (3/16), *FOXA1* (2/16), *TSC2* (2/16), *PIK3R1* (3/16), and *ARID1A* (3/16) were more frequently observed in FOXC1-negative patients. Mutations affecting *BRCA1* (3/18) and *CNR1* (2/18) were more frequently observed in FOXC1-positive patients.

Taken together, the identified alterations in non-pCR AR-positive TNBC patients and FOXC1-negative patients were mainly categorized as PI3K/AKT/mTOR pathway alterations, which may be targeted by PI3K and AKT inhibitors.

Discussion

The LAR subtype is a distinct subgroup of TNBC identified in a series of gene expression profiling studies and is dependent on AR signaling in TNBC [16]. According to previous studies, approximately 9–33% of TNBCs are of the LAR subtype [4, 6, 21, 22]. In surrogate IHC-based classification for TNBC subtyping, AR-positive TNBC has been regarded as IHC correlate of the LAR molecular subtype. In the present study involving 226 TNBC patients, the AR-positive TNBCs constituted 31.42% of the total TNBCs. All of the Invasive carcinomas with apocrine differentiation belonged to the AR-positive TNBCs. Invasive lobular carcinomas were almost exclusively of the AR-positive TNBCs. In contrast, nearly all of the Invasive metaplastic carcinomas were AR-negative TNBCs. Compared to AR-negative TNBC patients, AR-positive TNBC patients were older, had a lower histological grade, lower Ki-67 index, and more negative FOXC1 expression.

In this study, pCR was achieved in 12.68% (9/71) of AR-positive TNBC subgroup, which was significantly lower than that in AR-negative TNBCs (34.19%, 53/155). Studies by Anand et al. and Loibl et al. reported that AR expression could predict the response to chemotherapy and NACT in breast cancer patients [23, 24]. AR positivity in TNBC was found to be a reliable marker of a lack of response to cisplatin/paclitaxel chemotherapy [25]. High *AR* mRNA levels have been reported to be associated with lower pCR rates and better prognosis in breast cancer patients [26]. However, studies by Loibl et al. and Jongen et al. both reported no associations between AR expression and a pCR [24, 27]. These results indicate that AR is not a robust marker for predicting the pCR rate. In our study, although the pCR rate was significantly lower in AR-positive TNBCs, AR was not an independent predictor of pCR in TNBC. Meanwhile, all of the Invasive

Table 4 Univariate analysis of clinicopathologic variables and biomarkers associated with the NACT response in AR-positive TNBC patients

		Pathological response				
		pCR	%	non-pCR	%	p
	49	**7**	**14.29**	**42**	**85.71**	
AR						**< 0.001**
≤ 20%	11	6	54.55	5	45.45	
> 20%	38	1	2.63	37	97.37	
Pretherapy tumor size, cm						> 0.999
≤ 2 cm	1	0	0.00	1	100.00	
> 2 cm	46	7	15.22	39	84.78	
Histologic subtype						0.322
Invasive breast carcinoma of no special type	40	7	17.50	33	82.50	
others	9	0	0.00	9	100.00	
Pretherapy histological grade						0.167
3	36	7	19.44	29	80.56	
1,2	13	0	0.00	13	100.00	
Age						0.084
< 50	18	5	27.78	13	72.22	
≥ 50	31	2	6.45	29	93.55	
Pretherapy lymph node status						> 0.999
Core biopsy positive	35	5	14.29	30	85.71	
Core biopsy negative	7	1	14.29	6	85.71	
ki-67						0.322
≤ 20%	9	0	0.00	9	100.00	
> 20%	40	7	17.50	33	82.50	
FOXC1						**0.010**
Negative	24	0	0.00	24	100.00	
Positive	25	7	28.00	18	72.00	
Stromal TILs						0.737
≤ 9%	17	2	11.77	15	88.23	
≥ 10–49%	24	3	12.50	21	87.50	
≥ 50%	8	2	25.00	6	75.00	
Type of neoadjuvant chemotherapy						**0.003**
PD-1 blockade containing therapy	6	0	0	6	100.00	
Others(including platinum-containing, and others)	20	7	35.00	13	65.00	
Anthracycline-taxane based	23	0	0	23	100.00	

carcinomas with apocrine differentiation belonged to the AR-positive TNBCs, and also had a low pCR rate of 10% (1/10), which is in line with previous studies. Schwartz et al. reported none of the 10 triple-negative apocrine carcinomas achieved pCR after neoadjuvant chemotherapy [28]. Srivastava et al. also reported a low pCR in only 10% (1/10) apocrine tumors [29]. Multiple studies have shown that the LAR subtype is associated with a decreased pCR rate compared with other TNBCs [30, 31]. In the previous studies, approximately 10–25% of LAR TNBCs achieved pCR [6, 17, 30, 32]. These results should be interpreted with caution as none of these studies enrolled more than 30 LAR patients. A meta-analysis of 2826 TNBCs has shown that AR positivity is related to a lower risk of disease recurrence [33]. Nevertheless, different prognostic roles of AR in TNBC have also been reported. A previous study involving 263 TNBCs has revealed that AR positivity is associated with an increased risk of late distant disease-free survival events [11]. The majority of previous studies have reported that the LAR subtype patients are less aggressive. However, not all studies reveal better prognosis for LAR subtype patients compared with other TNBC subtypes. Jiang reported that patients with the LAR subtype had poorer prognoses than those with the IM subtype but better prognoses than those with the basal-like immune-suppressed (BLIS) and MES subtypes [4]. In the study of Hartung et al., patients with the LAR subtype were reported to have a worse clinical outcome than those patients without the LAR subtype [6]. In the present study, due to the short follow-up time, the DFS and OS were not significantly different between patients with the AR-positive TNBCs and AR-negative TNBCs.

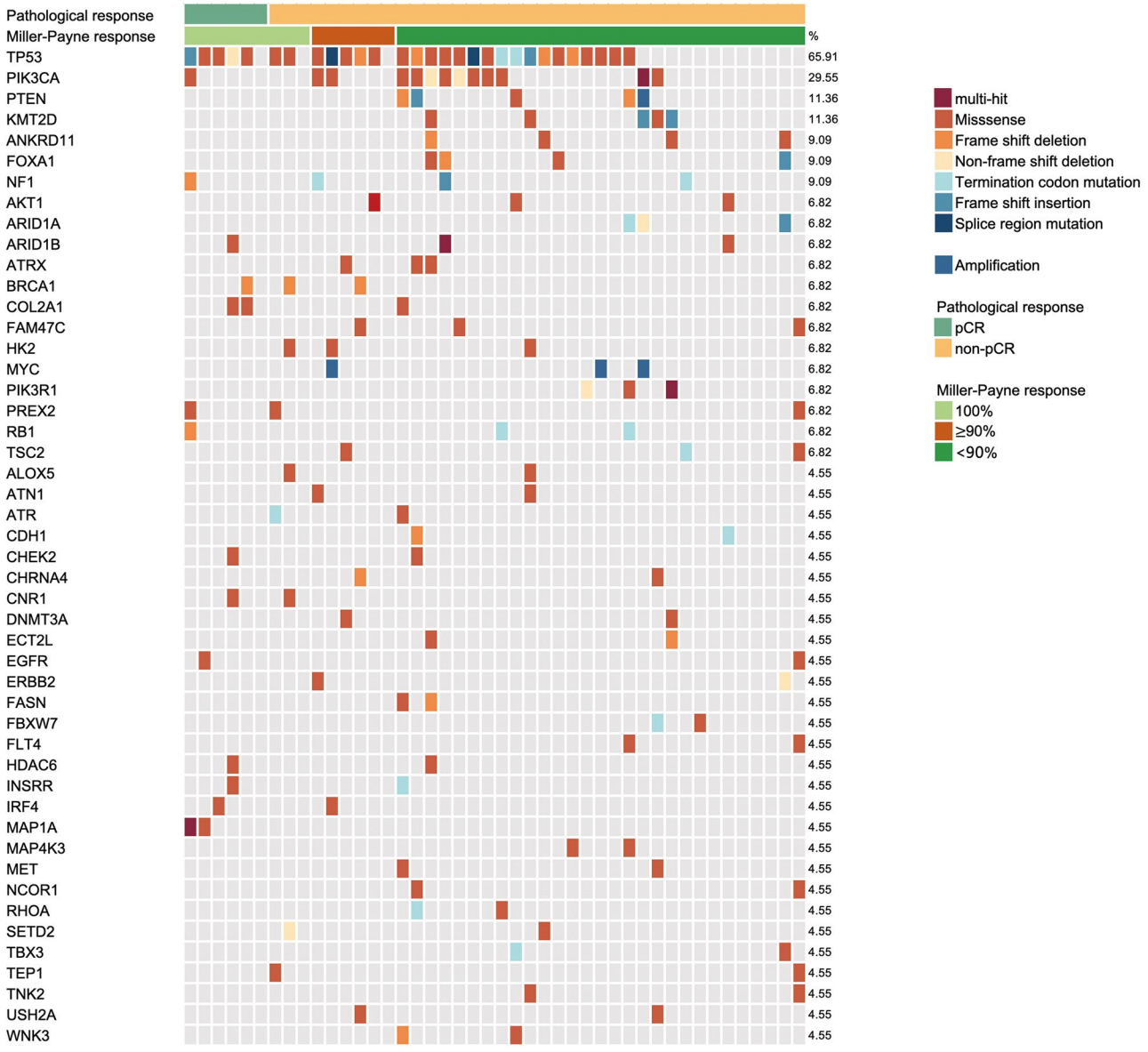

Fig. 4 Genomic landscape differences between the pCR and non-pCR AR-positive TNBC patients

The present data suggest that FOXC1 is an independent predictor of the NACT response in TNBC patients. High FOXC1 mRNA expression has been reported to be significantly related to the pathological response to NACT regardless of breast cancer subtype [18]. Moreover, consistent with previous studies [34, 35], the present study indicated that IDC-NOS and high Ki-67 values were associated with an increased pCR rate in TNBC patients. Additionally, FOXC1 was found to be expressed in a subset of AR-positive TNBCs (51.02%, 25/49), and patients with FOXC1-positive/AR-positive TNBCs showed a higher pCR rate compared to patients with FOXC1-negative tumors. FOXC1-positive/AR-positive TNBC patients who achieved a pCR had lower AR expression. Thus, the evaluation of FOXC1 expression may be of interest for the prediction of the NACT response for patients with TNBC and AR-positive TNBCs.

FOXC1 is a basal-like-specific biomarker in breast cancer [36]. The expression of FOXC1 in AR-positive TNBCs indicated that some AR-positive TNBCs presented with the basal-like PAM50 subtype phenotype. Multiple previous studies have indicated that some LAR subtype cases present a basal-like phenotype. In the study of Hartung et al.,40% (6/15) of LAR cases were classified as the basal-like subtype by PAM50, and non-basal-like LAR tumors had a better outcome than basal-like LAR tumors [6]. Zhao et al. reported that 33.33% (20/60) of LAR patients are classified into the basal-like subtype [13]. Another study reported that 21.43% (3/14) of LAR subtype patients are classified into the basal-like subtype [32].

In the present study, AR-positive TNBCs with FOXC1 expression had a significantly higher MP response rate and pCR rate than those without FOXC1 expression. In addition, AR-positive TNBCs without FOXC1 expression had a lower histological grade and lower Ki-67 expression. Collectively, these results might suggest that AR-positive TNBCs are also a heterogeneous group of tumors and that patients with FOXC1-positive tumors have more advanced clinicopathological features and are more sensitive to NACT compared to patients with FOXC1-negative tumors, which may partly explain the contradictory prognostic value and predictive value of AR in TNBC patients as reported in previous studies.

Furthermore, we examined the genomic alterations associated with NACT response of AR-positive TNBCs. The AR-positive TNBCs has been reported to have a high frequency of *PIK3CA* mutations. In the present study, the identified alterations in non-pCR AR-positive TNBCs were mainly categorized as PI3K/AKT/mTOR pathway alterations. *PIK3CA* mutation is associated with increased resistance to chemotherapy in TNBC. In AR-positive TNBCs, patients with alterations affecting the PI3K/AKT/mTOR pathway are less likely to derive benefit from NACT, but may be treated with PI3K and AKT inhibitors [37]. Activating *PIK3CA* mutations are enriched in AR-positive TNBC and confer sensitivity to the combination of PI3K and AR inhibitors [38]. Additionally, even for the enzalutamide-resistant LAR TNBCs, PIK3CA and AKT1 are potential therapeutic targets in PDX models [39]. In addition, *MYC* amplification was more frequently observed in non-pCR patients. *MYC* amplification and *PTEN* deletions or mutations are more common in patients with residual disease and may play a role in de novo or acquired chemotherapy resistance [40]. *KMT2D*, a histone methyltransferase gene, is mutated in numerous TNBC patients and is associated with detrimental outcomes in TNBC patients [41]. Inactivated mutations of *ARID1A*, a subunit of the SWI/SNF complex, have been found to be associated with carcinogenesis [42]. Cancer cells with *ARID1A* mutations demonstrate increased sensitivity to treatment with small molecule inhibitors of the PI3K/AKT pathway [43]. *FOXA1* mutations have also been detected in non-pCR AR-positive TNBC patients, suggesting the rational use of AR inhibitors. These data suggest that molecular analysis and FOXC1 evaluation of patients with the AR-positive TNBCs before NACT may help to predict the NACT response and to stratify patients to rational adjuvant trials with molecularly targeted agents, such as AR-targeting therapy and PI3K/AKT/mTOR inhibitors. In this study, immune-based therapy was an independent predictor of pCR in TNBCs. In terms of the AR-positive TNBC subgroup, univariate analysis revealed that the addition of platinum but not immunotherapy was significantly associated with higher pCR rates. The pCR rate of patients with high stromal TILs was slightly higher than that of patients with low and intermediate stromal TILs. A high abundance of TILs has been reported to be associated with a greater likelihood of achieving a pCR in TNBC [44]. However, whether the density of TILs is associated with the achievement of pCR in AR-positive TNBC patients is not clear. In the study of Thompson et al., LAR patients who achieved pCR presented increased myoepithelial, inflammatory cancer-associated fibroblasts (iCAFS), and endothelial cells compared to LAR non-responders, while decreased expression was observed with myofibroblastic cancer-associated fibroblasts (myCAFs), whereas no significant differences were observed among T cells, CD8 + T cells, and natural killer cells et al. [45]. Further investigations are needed to elucidate the microenvironment of AR-positive TNBCs/LARs that associated with NACT response. Further exploratory analysis in larger, independent cohorts would be needed to provide significant value for the alignment of AR-positive TNBCs with traditional chemotherapy versus targeted and immune-based therapies that are currently under clinical investigation.

The present study had several strengths and limitations. To date, this is the largest cohort of AR-positive TNBC patients who received NACT in which the clinicopathological features and genetic mutations associated with NACT response were investigated. Whether AR positivity serves as an adequate surrogate marker for the luminal androgen receptor (LAR) subtype and is sufficient for identifying AR - dependent tumors remains to be further confirmed. Zhao et al. reported that the two classification methods showed a high degree of agreement (Cohen's κ coefficient [κ] = 0.821) [7]. The LAR subtype is characterized by AR signaling. TBCRC 032 IB/II multicenter study suggested AR IHC alone might not be sufficient to identify AR signaling-dependent tumors [46]. FOXC1 has been identified as a basal-like specific marker. Due to the lack of sufficient follow - up time, it is unclear whether the expression of FOXC1 and the achievement of pathological complete response (pCR) contribute to the long - term outcomes of AR - positive TNBC patients. In addition, the treatment regimens utilized were heterogeneous in the current study and were an independent predictor of pCR in TNBC patients. Some of these patients were enrolled in clinical trials with the addition of platinum or immunotherapy. It has been reported that the addition of platinum agents and anti-PD-1 and anti-PD-L1 immunomodulatory antibodies can significantly increase pCR rate in TNBC patients [16, 47]. Moreover, in AR-positive TNBC patients, all of the seven patients who achieved pCR demonstrated positive FOXC1 expression and were treated with additional platinum; six cases showed relatively low AR expression. Therefore, the predictive value

of FOXC1 expression for pCR in AR-positive TNBCs should be interpreted with caution.

Conclusion

The present findings provided evidence that the AR-positive TNBCs is a molecularly heterogeneous disease that is worthy of further investigation. Compared to other TNBCs, the AR-positive TNBCs is associated with lower rates of pCR after NACT. FOXC1 is an independent predictive biomarker of the NACT response in TNBC patients, and patients with FOXC1-positive/AR-positive TNBCs demonstrate a higher pCR rate compared to FOXC1-negative/AR-positive TNBCs and FOXC1-negative/AR-negative TNBCs. The present results suggested that the FOXC1 level could potentially be utilized as a predictive marker for the efficacy of NACT for TNBC patients and the AR-positive TNBCs. Moreover, the present study revealed that the identified alterations in non-pCR patients with the AR-positive TNBCs were mainly categorized as PI3K/AKT/mTOR pathway alterations, thereby providing evidence that patients with the AR-positive TNBCs might gain benefits from PI3K/AKT/mTOR inhibitor.

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

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Author contributions
Conceived and designed the experiments: M. Li, R. Shui and W. Yang. Collected the data: M. Li, H. Lv, S. Zhou, and M. Cai. Analyzed the data: M. Li, S. Zhou, M.Cai and H. Lv. Wrote the paper: M. Li, and W. Yang. All authors read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Experiments and data generation were in accordance with the ethical standards of relevant national and international rules and regulations (GCP, Declaration of Helsinki). This study was approved by the Ethics Committee of Fudan University Shanghai Cancer Center, and each participant signed an informed consent document.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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