Precision neoadjuvant treatment with Artificial Intelligence assisted subtyping in HR+/HER2- breast cancer: a randomized, open-label, phase 2 trial FASCINATE-N

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Abstract

In this phase 2 trial, patients with stage II-III HR+/HER2- breast cancer were categorized into endocrine-based and targeted-based group based on previously proposed similarity network fusion (SNF) subtyping by digital pathology classification and randomly assigned (1:1) to receive precision or control treatment. Precision treatments included six cycles of dalpicilib (CDK4/6 inhibitor) plus endocrine therapy every 4 weeks for endocrine-based group and six cycles of targeted therapy (SHR-1316 [PD-L1 inhibitor] for SNF2, fuzuloparib [PARP1 inhibitor] for SNF3 and apatinib [VEGFR inhibitor] for SNF4) plus nab-paclitaxel and carboplatin every 4 weeks for targeted-based group. Control treatment was nab-paclitaxel plus carboplatin every 4 weeks for six cycles. The primary endpoint was pathological complete response (pCR). (ClinicalTrials.gov: NCT05582499).

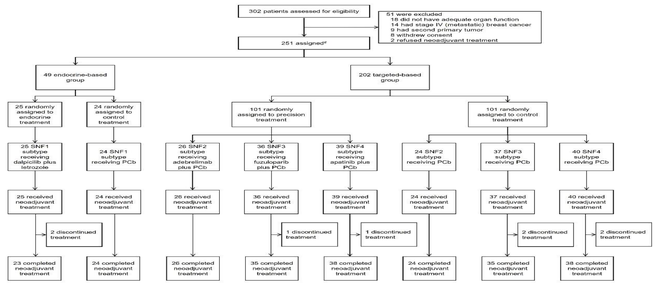


Figure 1. Trial profile

Introduction

Breast cancer is the most common malignant tumor for women worldwide, of which 70% are hormone receptor-positive (HR+) /human epidermal growth factor receptor 2-negative (HER2−) subtype. The current strategies for HR+/HER2- disease include neoadjuvant chemotherapy (NCT), neoadjuvant endocrine therapy (NET) and NCT/NET combined with targeted therapies or immune checkpoint inhibitors. It is important to further explore appropriate neoadjuvant treatment strategies.
HR+/HER2- breast cancer exhibits significant heterogeneity and numerous efforts have been made to interpret its molecular characteristics.
We have conducted an umbrella phase 2 trial to evaluate subtyping-based neoadjuvant treatments for breast cancer1. Here, we present the findings on AI assisted subtyping in HR+/HER2- to identify effective neoadjuvant precision treatments based on endocrine-based and targeted-based group.

Methods and Materials

Our team previously conducted next-generation DNA and RNA sequencing combined with metabolomics and proteomics analyses focused on these challenges[2]. By using large-scale multi-omics data and similarity network fusion (SNF), HR+/HER2- breast cancer was divided into two groups. Endocrine-based group (SNF1: canonical luminal) representing a group of patients resembling the traditional luminal breast cancer most likely to be sensitive to endocrine therapy, while targeted-based group included several SNF subtypes (SNF2: immunogenic, SNF3: proliferative and SNF4: RTK-driven) with distinct biological and clinical features and might derive benefit from subtype-specific targeted treatments, including immune checkpoint inhibitors, PARP inhibitors and RTK inhibitors. We further developed a digital pathology classification approach employing convolutional neural networks derived from pathology whole-slide images (WSIs) to classify molecular subtypes. The efficacy of Artificial Intelligence (AI)-assisted precision treatment based on the SNF subtyping system for HR+/HER2- breast cancer demands additional clinical validation.
Female patients with HR+/HER2- breast cancers were stratified into two distinct therapeutic cohorts: an endocrine-based (EB) therapy group and a targeted-based (TB) therapy group, then randomized to receive either precision treatment or control treatment.
Patients in the EB group were randomly assigned to receive endocrine treatment: dalpicilib (CDK4/6 inhibitor, 150 mg orally once daily from day 1 to day 21) plus letrozole (2.5 mg orally once daily) with or without goserelin (for premenopausal patients, 3.6 mg intramuscularly every 4 weeks) in a 28-day per cycle for six cycles; or chemotherapy in the control group with nab-paclitaxel (100 mg/m2 intravenously on day 1, day 8, and day 15) plus carboplatin (AUC = 1.5 intravenously on day 1, day 8, and day 15), in a 28-day per cycle for six cycles (PCb). Patients in the TB group were randomly assigned to receive subtype-specific precision treatments, listed as follows: SHR-1316 (PD-L1 inhibitor, 10 mg/kg intravenously on days 1 and 15) plus PCb in a 28-day per cycle for six cycles for SNF2; fuzuloparib (PARP1 inhibitor 50 mg orally twice daily) plus PCb in a 28-day per cycle for six cycles for SNF3; and apatinib (VEGFR inhibitor, 250 mg orally daily) plus PCb in a 28-day per cycle for six cycles for SNF4; or PCb for six cycles in the control group.
The primary endpoint was pCR rate, defined as pathological stage (post neoadjuvant, abbreviated yp) ypT0/Tis ypN0.

Results

302 patients were screened, and 251 patients were randomly assigned (Figure 1). Through Bayesian monitoring method, the pCR rates of the first 60 patients in each group of target-based therapy indicated that the pCR rate was significantly higher in patients receiving precision treatment compared with those receiving control treatment, so the enrolment was stopped, and 251 patients were ultimately enrolled. 49 (19.5%) patients were assigned to the EB group, and 202 (80.5%) patients were assigned to the TB group, which included 50 (19.9%) patients with the SNF2 subtype, 73 (29.1%) with the SNF3 subtype, and 79 (31.5%) with the SNF4 subtype. The baseline characteristics were well balanced (Table 1).
The pCR rate was significantly higher in the precision therapy group compared with the control group (14/126, 11.1% [90% CI, 6.8 to 16.8] vs. 5/125, 4.0% [90% CI, 1.6 to 8.2], P = 0.033) (Figure 2A). In the EB group, no patients receiving endocrine treatment achieved pCR, whereas one patient in the control group did (0/25, 0.0% [90% CI, 0.0 to 11.3] vs. 1/24, 4.2% [90% CI, 0.2 to 18.3], P = 0.490) (Figure 2B). In the TB group, the pCR rate was significantly higher in patients receiving precision treatment compared with those receiving control treatment (14/101, 13.9% [90% CI, 8.6 to 20.8] vs. 4/101, 4.0% [90% CI, 1.4 to 8.8], P = 0.026) (Figure 2C).
Grade 3-4 TRAEs occurred in 40.0% (10/25) of endocrine treatment group and 45.8% (11/24) of control group in the EB group and 40.6% (41/101) of precision treatment group and 43.6% (44/101) of control group in the TB group. Dose adjustment was required for 10 patients receiving endocrine treatment and 11 patients receiving control treatment in the EB group, and 17 patients receiving precision treatment and 13 patients receiving control treatment in the TB group. Treatment discontinuation due to TRAEs was observed in 4 patients receiving endocrine treatment and 3 patients receiving chemotherapy in the EB group, and 3 patients receiving precision treatment and 4 patients receiving control treatment in the TB group. No treatment-related deaths were reported in either group.

Conclusions

This study explored a new insight for the neoadjuvant therapy for HR+/HER2- early breast cancer via subtyping it to endocrine-base group and targeted-based group. Precision therapy could improve the benefit of neoadjuvant therapy for HR+/HER2- breast cancer patients. NET plus CDK4/6 inhibitor was verified to replace chemotherapy with better tolerance in the endocrine-base group while precision therapy was proved promising clinical activity and manageable safety profile in the targeted-based group.

Discussion

This study for the first time prospectively applies endocrine-based and targeted-based subtyping to guide precision neoadjuvant treatment with increased pCR rate for HR+/HER2- breast cancer. We employed this method based on digital pathology and deep learning for SNF subtyping in the current study, as well as LINUX trial (NCT05594095) for metastatic patients progressed with CDK4/6 inhibitor treatment with endocrine therapy for metastatic disease and trials exploring precision therapy in first-line (NCT05949541, NCT05205200, NCT05759546, NCT06612814, NCT05759572, NCT06447623), confirmed the value of SNF subtyping in guiding precision treatment[3,4]. Our findings highlight guiding neoadjuvant precision treatment by SNF subtyping for patients with HR+/HER2- breast cancer showed potential clinical benefits.

Characteristic	Endocrine-based group (N = 49)		Targeted-based group (N = 202)		Total (N = 251)
	Endocrine treatment (N = 25)	Control treatment (N = 24)	Precision treatment (N = 101)	Control treatment (N = 101)	
Age, yr					
Median (range)	46 (32-68)	48 (35-68)	43 (26-70)	46 (25-68)	45 (25-70)
<40	6 (24.0)	4 (16.7)	33 (32.7)	29 (28.7)	72 (28.7)
40-59	17 (68.0)	16 (66.7)	57 (56.4)	62 (61.4)	152 (60.6)
≥60	2 (8.0)	4 (16.7)	11 (10.9)	10 (9.9)	27 (10.8)
Menopausal status					
Premenopausal	17 (68.0)	16 (66.7)	70 (69.3)	69 (68.3)	172 (68.5)
Postmenopausal	8 (32.0)	8 (33.3)	31 (30.7)	32 (31.7)	79 (31.5)
Clinical tumor size					
T2	19 (76.0)	16 (66.7)	66 (65.3)	60 (59.4)	161 (64.1)
T3	1 (4.0)	4 (16.7)	15 (14.9)	20 (19.8)	40 (15.9)
T4	5 (20.0)	4 (16.7)	20 (19.8)	21 (20.8)	50 (19.9)
Clinical nodal stage					
N0	2 (8.0)	1 (4.2)	10 (9.9)	10 (9.9)	23 (9.2)
N1	9 (36.0)	10 (41.7)	61 (60.4)	60 (59.4)	140 (55.8)
N2	14 (56.0)	13 (54.2)	30 (29.7)	31 (30.7)	88 (35.1)
Tumor stage					
II	9 (36.0)	7 (29.2)	45 (44.6)	46 (45.5)	107 (42.6)
III	16 (64.0)	17 (70.8)	56 (55.4)	55 (54.5)	144 (57.4)
ER expression					
≤50%	1 (4.0)	0 (0.0)	3 (3.0)	6 (5.9)	10 (4.0)
>50%	24 (96.0)	24 (100.0)	98 (97.0)	95 (94.1)	241 (96.0)
PgR expression					
≤50%	11 (44.0)	9 (37.5)	51 (50.5)	58 (57.4)	129 (51.4)
>50%	14 (56.0)	15 (62.5)	50 (49.5)	43 (42.6)	122 (48.6)
Ki-67 index					
≤10%	7 (28.0)	5 (20.8)	13 (12.9)	21 (20.8)	46 (18.3)
>10%	18 (72.0)	19 (79.2)	88 (87.1)	80 (79.2)	205 (81.7)

Abbreviations: ER, estrogen receptor; PgR, progesterone receptor.

Table 1. Characteristics of the patients in the intention-to-treat population at baseline.

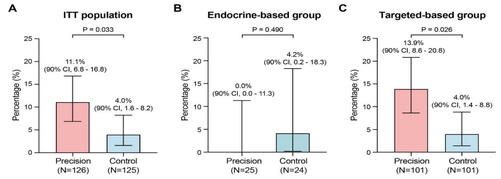


Figure 2. Pathological complete responses.

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References

1. Zuo, WJ., et al. Rational and trial design of FASCINATE-N: a prospective, randomized, precision-based umbrella trial. Ther Adv Med Oncol 16, 17588359231225032 (2024).
2. Jin, X., et al. Molecular classification of hormone receptor-positive HER2-negative breast cancer. Nature Genetics 55, 1696-1708 (2023).
3. Lei Fan, et al. Precision Treatment with Artificial Intelligence Assisted Subtyping Enhances Therapeutic Efficacy in HR+/HER2- Breast Cancer: The LINUX Platform Trial. Cancer Cell 2025 Accept.
4. Xiuzhi Zhu, et al. Subtyping-directed Precision Treatment Refines Traditional One-size-fits-all Therapy for HR+/HER2- Breast Cancer. Cancer Research 2025 Accept.

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