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Editorial

Neoadjuvant Endocrine Therapy for Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Breast Cancer

Pengcheng Jin[1], Xiawei Li[2,3], Yunxiang Zhou[4,5,*]

[1]Department of Surgical Oncology, The First People's Hospital of Linhai, 317000 Taizhou, Zhejiang, China
[2]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Harvard University, Boston, MA 02138, USA
[3]Department of General Surgery, The Second Affiliated Hospital, Zhejiang University School of Medicine, 310009 Hangzhou, Zhejiang, China
[4]Department of Breast Surgery and Oncology, The Second Affiliated Hospital, Zhejiang University School of Medicine, 310009 Hangzhou, Zhejiang, China
[5]Cancer Institute (Key Laboratory of Cancer Prevention and Intervention, China National Ministry of Education), The Second Affiliated Hospital, Zhejiang University School of Medicine, 310009 Hangzhou, Zhejiang, China
*Correspondence: yxzhou@zju.edu.cn (Yunxiang Zhou)

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Neoadjuvant therapy enables tumor downstaging to facilitate breast conserving surgery (BCS), allows assessment of treatment sensitivity, provides prognostic information, and serves as an experimental platform in breast cancer research [1,2]. Although chemotherapy remains the predominant neoadjuvant modality, responses vary widely across breast cancer subtypes [1]. Notably, hormone receptor-positive, human epidermal growth factor receptor 2-negative (HR+/HER2–) disease, the most common subtype (~70% of cases) [3], exhibits particularly low pathological complete response (pCR) rates to neoadjuvant chemotherapy (NCT) (0%–8%) [4], far below those of triple-negative or HER2+ tumors (30%–50%) [1].

Initially reserved for elderly or chemotherapy-ineligible patients, neoadjuvant endocrine therapy (NET) has proven to be a safe and effective strategy in HR+/HER2– breast cancer, achieving objective response rates (ORRs) and BCS rates comparable to NCT [5]. Nevertheless, its clinical application remains limited [6]. Key challenges remain regarding optimal patient selection, treatment regimens and duration, reliable response endpoints, and strategies for subsequent adjuvant therapy.

1. Optimizing Patient Selection and Treatment Strategies

Current guideline recommendations support consideration of NET for HR+/HER2– patients in whom the indications for chemotherapy are uncertain [7], and for patients with strong HR expression who have comorbidities or low-risk luminal tumors as determined by clinicopathologic/genomic features [8]. Since adjuvant chemotherapy does not benefit all patients with HR+/HER2– breast cancer and can be omitted in low-risk cases [9], the routine use of NCT for chemosensitivity testing or downstaging may be questioned. Consequently, tumors deemed low risk by guideline-endorsed genomic assays (e.g., the 21-gene Oncotype DX or 70-gene MammaPrint tests) [7,8] are therefore logical candidates for less toxic neoadjuvant approaches such as NET [10]. Indeed, direct evidence links the 21-gene Recurrence Score with clinical response to preoperative letrozole [11], and data from the DANCER trial indicate that MammaPrint low-risk patients treated with cyclin-dependent kinase 4/6 (CDK4/6) inhibitor plus NET had lower preoperative endocrine prognostic index (PEPI) and residual cancer burden (RCB) scores [12]. Similarly, the PLATO trial demonstrated that triaging patients by MammaPrint (high-risk to NCT, low-risk to NET) substantially increased BCS eligibility while sparing low-risk patients unnecessary chemotherapy toxicity [13].

Three pivotal trials have demonstrated that aromatase inhibitor (AI)-based NET yields superior clinical benefit compared with tamoxifen in postmenopausal women, establishing AIs as the preferred agents in this population [14–16]. For premenopausal patients, current guidelines recommend either an AI combined with ovarian function suppression (OFS) or tamoxifen with or without OFS [8]. Although maximal response to NET may take 6–12 months to evolve [17,18], the commonly employed neoadjuvant interval in clinical practice is 4–6 months [8,10,19]. Treatment may be extended in patients who continue to derive clinical benefit [10].

A major recent focus has been the incorporation of CDK4/6 inhibitors into NET. Multiple neoadjuvant trials have evaluated CDK4/6 inhibitor plus endocrine therapy—either in comparison with chemotherapy (e.g., NeoPal [20,21], CORALLEEN [22,23], and CARABELA [24,25] trial) (Table 1, Ref. [20–25]) or versus endocrine monotherapy (e.g., PALLET [26], FELINE [27], and neoMONARCH trial [28]). The addition of CDK4/6 inhibitors enhances tumor proliferation suppression, yet fails to improve pCR rates, ORRs, disease control rates, or PEPI scores compared with NCT or NET alone [20,22,25,26,28,29]. Further work is needed to identify subgroups most likely to benefit. The DANCER trial introduced a two-step, biomarker-driven framework utilizing baseline parameters and dynamic circulating tumor DNA monitoring to better stratify patients

Table 1. Neoadjuvant trials comparing cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor plus endocrine therapy versus chemotherapy in hormone receptor–positive, human epidermal growth factor receptor 2–negative (HR+/HER2–) breast cancer.

Trial	Disign	Population	Intervention	ITT N	Primary endpoint	Main findings	Ref
NeoPAL	Randomized (1:1), open-label, phase II	Stage II–IIIA, ER+/HER2–, PAM50 luminal B/A with node+, not eligible for BCS, postmenopausal	Palbociclib + letrozole vs. FEC→T	106 (53/53)	RCB 0–I rate	RCB 0–I: 4 (7.7%) vs. 8 (15.7%); pCR: 3.8% vs. 5.9%; PEPI-0: 17.6% vs. 8.0%; CRR/BCS similar; 40-month PFS: 86.7% vs. 89.9%	Efficacy [20], survival [21]
CORALLEEN	Randomized (1:1), open-label, phase II	Stage I–IIIA, HR+/HER2–, PAM50 luminal B, tumor ≥2 cm, postmenopausal	Ribociclib + letrozole vs. AC→wP	106 (52/54)	PAM50 low-ROR rate	Low-ROR: 46.9% vs. 46.1%; RCB 0–I: 6.1% vs. 11.8%; PEPI-0: 22.4% vs. 17.3%; significantly better HRQoL	Efficacy [22], HRQoL [23]
CARABELA	Randomized (1:1), open-label, phase II	Stage II–III, HR+/HER2–, Ki67 ≥20.0%	Abemaciclib + letrozole (± LHRHa) vs AC→wP	200 (100/100)	RCB 0–I rate	RCB 0–I: 13.0% vs. 18.0%; CRR: 78% vs. 71%; PEPI-0: 14% vs. 26% (p = 0.03); Ki67 rebound (2w→surgery): 17% vs. 2% ($p <$ 0.0001); Median RS (surgery): 22 vs. 19 (p = 0.028); RS downstaging (>25→≤25): 20% vs. 36% (p = 0.024)	[24,25]

Abbreviations: ITT, intention-to-treat; ER, estrogen receptor; BCS, breast-conserving surgery; FEC→T, 5-fluorouracil + epirubicin + cyclophosphamide followed by docetaxel; RCB, residual cancer burden; pCR, pathological complete response; PEPI, preoperative endocrine prognostic index; ROR, risk of relapse; HRQoL, health-related quality of life; CRR, clinical response rate; PFS, progression-free survival; AC→wP, doxorubicin + cyclophosphamide followed by weekly paclitaxel; LHRHa, luteinizing hormone–releasing hormone agonist; RS, recurrence score.

likely to benefit from treatment [12]. Targeting the PI3K/AKT/mTOR (PAM) pathway, an axis implicated in proliferation and endocrine resistance, has also been explored in the neoadjuvant setting, but whether PAM inhibition adds additional benefit to NET remains uncertain [30,31].

2. Assessing Response and Refining Clinical Decision-Making

pCR to neoadjuvant therapy provides important prognostic information, although its association is weakest in the HR+ subtype [32–34]. RCB after NCT has established prognostic value across breast cancer subtypes, including HR+/HER2– tumors [35], though its significance following NET remains unclear. In fact, pCR rates after preoperative treatment are extremely low in the HR+/HER2– population, even reaching 0% in some reports, irrespective of NCT or NET [13,36,37]. The largest NET trial to date, ALTERNATE, reported a pCR rate of only 0.3% (3/933) after 6 months of NET [38].

Early changes in Ki67 levels following short-term (2–4 weeks) endocrine therapy exhibit predictive value for long-term outcomes and can assist in guiding treatment decisions [39–44]. Consequently, Ki67 and derived indices such as complete cell cycle arrest (CCCA; Ki67 $\leq$ 2.7%) are widely used as primary endpoints in NET trials [12,26,28,43,45,46]. Ellis and colleagues developed the PEPI score, which integrates postoperative tumor size, nodal status, ER level, and Ki67 to estimate relapse risk after NET [47]. PEPI has been validated in multiple cohorts (IMPACT [15], ACOSOG Z1031 [42], JFMC34-0601 [48]). Additionally, changes in gene-expression profiles after NET are increasingly considered as measures of molecular downstaging and as exploratory prognostic or surrogate endpoints in clinical studies [22,49,50].

There is no universally accepted strategy for adjuvant systemic therapy following NET, and whether to add adjuvant chemotherapy remains a clinically difficult decision. Generally, patients with clinical or genomic high-risk features and those with unexpectedly extensive residual disease after NET (e.g., $\geq$4 positive lymph nodes) are commonly recommended to receive adjuvant chemotherapy [10]. In practice, most NET trials determine postoperative systemic therapy regimens based on baseline clinicopathologic features, treatment response, gene-expression profiles, RCB score, and local practice guidelines [12,15,39,46,48,51]. The ALTERNATE study employed a modified PEPI (mPEPI) score to guide postoperative treatment. Patients with mPEPI 0 (ypT1-2N0/N1mic/Ki67 $\leq$2.7%) did not receive chemotherapy, whereas patients with mPEPI $>$0 were recommended to receive adjuvant chemotherapy [52]. Long-term follow-up from such trials will be critical to define the prognostic and predictive utility of mPEPI after NET.

Author Contributions

YZ and PJ conceived and designed the study. XL contributed to the interpretation of the results. YZ critically revised the manuscript, supervised the research, and guided the discussion. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest. Yunxiang Zhou is serving as one of the Editorial Board members and one of the Guest Editors of this journal. We declare that Yunxiang Zhou had no involvement in the review of this article and has no access to information regarding its review. Full responsibility for the editorial process for this article was delegated to Michael H. Dahan.

Declaration of AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work, the authors used ChatGPT-5.1 in order to check spelling and grammar. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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