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How To Use and Sequence Systemic Therapy in Stage III Luminal Breast Cancer?

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1. Abstract

Luminal (HR+/HER2-) breast cancer (BC) is the most frequent BC subtype and is highly heterogenous. Stage III is associated with a high risk of relapse. Clinical benefit can be expected from the (neo-) adjuvant use of various systemic therapies. No trials are available specifically for patients with stage III. In this narrative review, we summarize the available evidence and provide recommendations on the use and timing of different neoadjuvant systemic therapies in this high-risk population.Neoadjuvant systemic treatment is the most used approach in this setting. In premenopausal patients, neoadjuvant chemotherapy (NAC) is often preferred, as small studies have shown it to be superior to endocrine therapy (ET). The most used regimen is dose-dense anthracycline-cyclophosphamide followed by taxanes. For postmenopausal patients, neoadjuvant endocrine therapy (NET) has demonstrated similar pathological and clinical response rates compared to both NAC and ET combined with CDK4/6 inhibitors. NET can be recommended as the first-line treatment, particularly for elderly or frail patients.Pathological complete response is not an optimal surrogate endpoint for survival in luminal BC. Alternative endpoints, such as residual cancer burden, should be further explored. Despite not being investigated specifically in stage III, gene expression profiling (GEP) determination at diagnosis or dynamic KI67 evolution after 2-4 weeks of NET could help clinicians and patients to guide the need of chemotherapy. Many treatment options are available for stage III luminal BC, in this review we provide evidence and guidance for optimal use and sequence of (neo-) adjuvant therapies for these patients.

2. Introduction

Invasive breast cancer (BC) can be classified in different immunohistochemical subtypes depending on the expression of estrogen receptor (ER), progesterone receptor (PR) and epidermal growth factor receptor 2 (HER2). Among these subtypes, in the Western world, approximately 85% of BC are hormone-receptor (HR+)/HER2-, classified as luminal BC [1]. Transcriptomic analysis has shown that depending on the level of expression of genes related to proliferation, luminal tumors can be further divided in luminal A or B. At the histopathological level luminal B tumors are associated with higher grade and lower level of PR expression by immunohistochemistry. [2]. The international KI67 working

group has issued some guidelines in this regard having three cutoffs: low (< 5%), intermediate (6-30%) and high (31-100%). Clinical utility of KI67 immunohistochemistry in BC remains limited to prognosis assessment in stage I or II breast cancer while stage III tumors in general require all available treatment modalities to decrease the generally high risk of relapse. In case of low KI67 (no chemotherapy) or high KI67 (chemotherapy indicated), gene expression profiling (GEP) may not be needed. In case of intermediates values they recommend the use of GEP (2). The advent of prognostic and predictive GEP has provided more clues to better understand the heterogeneity and prognosis of the different molecular subtypes both for prognosis and benefit of (neo)adjuvant chemotherapy. Remarkably, 5-30% of HR-positive BC are not luminal A or B by intrinsic molecular GEP tests like PAM50 or MammaPrint/Blueprint but rather HER2-enriched or basal-like [3]. These non-luminal tumors by GEP harbor different characteristics such as lower ER-expression levels and estrogen dependency, higher sensitivity to chemotherapy, poor response to (some) CDK4/6 inhibitors (CDK4/6-i) and poorer outcomes [4-7]. In the last decade, therapeutic strategies in high risk early luminal BC have evolved, incorporating NAC and improving patient selection for adjuvant chemotherapy through GEP. Additionally, endocrine-based therapies have been increasingly used in the neoadjuvant setting or in window of opportunity trials [8-11]. Stage III BC is a heterogenous group consisting of large tumors and/or positive lymph nodes, usually implying an indication for chemotherapy [12]. In the most recent AJCC UICC 8th edition, the exact definition has become rather complex [13]. Stage IIIA can be considered primarily operable in principle, while IIIB and IIIC indicate locally more advanced disease making upfront surgery often not feasible [14].Currently, there are no clear guidelines on the optimal use and sequencing of different systemic therapies in patients with stage III luminal BC. This narrative review primarily aims to outline the current status of neoadjuvant treatment and its future prospects, particularly in the context of growing interest in de-escalation of therapeutic approaches and the incorporation of molecular biomarkers for optimal selection of (neo)adjuvant treatments.

2.1. Neoadjuvant Chemotherapy (NAC) in Luminal Breast Cancer

The main goals of NAC are to provide effective systemic treatment to prevent cancer recurrence (equivalent to adjuvant treatment) and to downsize the primary tumor and lymph nodes in view of de-escalating surgery. For now, adjusting treatment based on response to NAC is not standard of care in luminal breast cancer in contrast to HER2+ and triple negative breast cancers where response on NAC determines drug choice in adjuvant setting.

The recommendation that chemotherapy can be used in the neo-adjuvant setting as alternative for adjuvant chemotherapy is based on data from the landmark NSABP B-18 trial [15]. In this trial, there was no difference in disease-free survival (DFS) or overall survival (OS) in patients with stage II or III BC who were randomly assigned to doxorubicin/cyclophosphamide either before or after surgery.There is no direct evidence from randomized phase III clinical trials regarding the optimal NAC regimen in patients with HR+/HER2- BC. The choice of regimen follows data and guidelines extrapolated from the adjuvant setting. Anthracycline regimens have been the standard for years, while the addition of taxanes and dose-dense administration have further improved outcome and survival and has become the reference in luminal BC [16]. Nevertheless, concerns regarding both short- and long-term side effects associated with anthracyclines (mainly cardiovascular disease and acute myeloid leukemia) have resulted in a rise of non-anthracycline based regimens. In the adjuvant setting, docetaxel-cyclophosphamide provides similar efficacy (although most trials compared with non-dose-dense anthracycline regimens) and showed significantly lower cardiac toxicities and leukemia [17]. However, subgroup analysis suggests that patients with high tumor burden, defined by four or more involved lymph nodes, and those with lobular tumors might benefit more from anthracycline-containing chemotherapy, at least in terms of DFS [18].Unfortunately, none of the pivotal NAC trials have specifically focused on stage III luminal BC but dose dense anthracycline-cyclophosphamide followed by taxanes appears to be the most appropriate NAC approach, unless use of anthracycline is contra-indicated.

2.2. Neoadjuvant Endocrine Therapy (NET) in Luminal Breast Cancer

ET targets the tumoral estrogen signaling pathway. By reducing estrogen levels or blocking the estrogen receptor, the pivotal role of estrogen for the growth and differentiation of BC, is inhibited [19]. Given the recurrence rate, especially in stage III, chemotherapy and ET should both be used to achieve best results. The question is when to use them best and whether the sequence really matters.Spring et al. [20].Conducted a meta-analysis of prospective, randomized trials to evaluate the effects of NET on primary endpoints such as clinical response rate, BCS rate and pathologic complete response (pCR) in 3.490 HR+ BC. All primary endpoints were similar to what has been observed with NAC, yet with significantly better tolerability [1].A systematic review reports that one out of three patients (30%) become eligible for BCS after treatment with NET. The highest surgical conversion rate of 75.9% was found after NET with letrozole 2.5 mg/d during four to eight months [20]. Several studies aimed to determine the optimal duration of NET consistently show higher objective response rates (ORR) with prolonged treatment, ranging from 20% to 70% within 3-4 months of NET and reaching up to 88% within 12 months before surgery [21-24]. pCR was achieved in 2.5-17.5%

cases, increasing with longer drug exposure [25].Currently, there is no consensus concerning the optimal duration of NET. The St Gallen 2023 panel recommends a minimum duration of 6 months or continuing treatment until the maximum response is achieved [26].

2.3. Neoadjuvant Systemic Therapy Trials According to Menopausal Status In Luminal Breast Cancer

Several trials compared NET with NAC, as well as NET combined with CDK 4/6 inhibitors or other combinations, analyzing postmenopausal and premenopausal patients separately, as highlighted below. We report the most relevant trials and show the percentage of included patients with stage III tumors (or clinically T3-4 and cN2-3 if stage was not available).

2.3.1. Postmenopausal Women

a) NET monotherapy

Third-generation aromatase inhibitors (AI) (anastrozole, letrozole and exemestane) are considered standard of care for NET. Among postmenopausal patients several randomized phase III trials (Table 1) have compared AIs to tamoxifen. The findings consistently point toward the superior response rates associated with AIs (ORR > 60% with AI versus (vs.) 30-45% with tamoxifen).

Results from a biomarker analysis of the IMPACT and P024 trials suggest that higher baseline estrogen receptor levels by ER staining correlate with an increased likelihood of an ORR to NET [23,24]. In light of these findings, strong ER expression by immunohistochemistry (defined as an Allred score of 6-8, obtained by the sum of the score obtained by the percentage of positive tumor cells and the score obtained by the intensity of staining) was associated with response rate greater than 60% vs. 35-50% in tumors with Allred score 3-5 [27]. Moreover, higher plasma estradiol concentrations were recently reported to be associated with a significantly greater response to AI in the POETIC trial [28].

In conclusion, NET is a feasible treatment option for postmenopausal patients with early luminal BC, but very few data on its benefit in stage III setting are available.

b) NET vs. NAC

In postmenopausal patients, few data are available regarding direct comparison between chemotherapy and ET in the neoadjuvant setting. Two studies have evaluated the use of anthracyclines and taxanes in comparison to AI (Table 2).

Semiglazov et al. have recruited 239 postmenopausal patients in a phase II trial, to undergo either neoadjuvant anthracycline-taxane based chemotherapy or NET with exemestane or anastrozole for 3 months prior to surgery. The primary endpoint was ORR. No statistically significant differences were observed when comparing the two arms (64.5% vs. 63.6%, p-value > 0.5) [29]. The limited duration of NET (3 months) might have underestimated the efficacy of NET.

In the phase II GEICAM/2006-03 trial, Alba et al. enrolled 44 postmenopausal patients undergoing NAC vs. NET with exemestane. The primary endpoint was response through magnetic resonance imaging. The results indicated no clear difference in clinical response in patients treated with NAC compared to NET (57% vs. 52%, p-value = 0.78) [30)].

In conclusion, NET and NAC perform similarly in postmenopausal patients with luminal BC in terms of clinical and radiological responses. Very few patients with stage III were assessed in these trials. While NET is better tolerated, it is important to recognize that most of these patients will still require chemotherapy, either in the neoadjuvant or adjuvant setting.

c)NET + NAC concomitant

The cytostatic impact of ET prompts questions about whether the cytotoxicity of chemotherapy might diminish in cells whose cell cycle is slowed down by ET, suggesting a potential antagonistic effect [31]. Clinical studies in the adjuvant setting in node positive BC patients concluded that concomitant use of chemotherapy and tamoxifen had no positive effect on DFS and OS compared to sequential use, and sequential treatment remained standard [32-34]. Reported toxicity was similar. The current standard sequential use of ET and chemotherapy results in a significant period (months) in which patients do not receive ET despite the tumor being highly hormone sensitive. A meta-analysis of Ergun et al. summarized 5 randomized trials (each with 10-40% of stage III) comparing NET (4 studies with AI, 1 with Tamoxifen) plus concomitant NAC vs. NAC, and showed that the combination arm has significantly higher ORR (82% vs. 72.7%, odds ratio (OR) 1.77), but with low pCR rates in both arms (6.5% vs. 3.8%, OR 1.72) [35].

The concomitant administration of NET and NAC cannot be considered a standard of care at present in early luminal BC but given the absence of reliable evidence concerning superiority of sequential therapy it seems unnecessary to delay the start of this highly effective treatment. The combination of AI and chemotherapy appears to increase the response rate without an increase in side effects. Nevertheless, there is a need for further randomized phase III studies reporting survival outcomes.

d)NET + CDK 4/6-i

CDK4/6-i are an innovative class of agents approved for first and second line in the metastatic setting in combination with ET, based on progression-free survival and OS improvement in phase III trials [36-38]. More recently, abemaciclib and ribociclib have shown invasive disease-free survival benefit (iDFS) in the adjuvant setting [39,40]. In MonarchE, there was a high proportion of patients with stage III (73.4 %) while Natalee study included a lower number of stage III (59.6%) [41].

The growing interest of ET with CDK4/6-i has led to the evaluation of this combination in the neoadjuvant setting (Table 3 and 4). NET + CDK 4/6 inhibitor has first been compared

with NET monotherapy. Although the study designs, primary endpoints and patient numbers vary across different studies, results consistently show enhanced antiproliferative activity as measured by a higher KI67 decline and complete cell cycle arrest (CCCA, defined as KI67 < 2.7%) when adopting the combination strategies. However, clinical response and pCR were similar. Clinical response when adding CDK4/6-i to NET, assessed through radiological response, ranged between 40% and 55%, consistent with previous clinical trials employing AI monotherapy. Nevertheless, pCR rates with the combination of CDK4/6-i plus AI are very low. In the neoMONARCH 2 trial, pCR was obtained in 3.7% of patients, whereas in NeoPalAna not a single pCR was achieved [42,43]. Similarly, in the PALLET trial, no differences were observed between the experimental (palbociclib + letrozole) and control arm (letrozole) in terms of pCR [44].The FELINE trial showed higher CCCA rates with ribociclib, yet a rebound increase of KI67 at 2 weeks post-discontinuation and at surgery was observed. This has raised concerns because some patients may experience only temporary rather than persistent benefits from this approach [45]. Similar findings were reported in the NeoPalAna trial with palbociclib [43] (Table 3).Unfortunately, only a minority of included patients in these trials were stage III. Given the discrepancies between KI67 suppression and clinical response, it remains uncertain whether adding CDK4/6 inhibition to NET translates into a clinical benefit. NET monotherapy remains the standard of care when applying a neoadjuvant approach with ET.This combination of CDK4/6-i and NET has also been compared with chemotherapy. The CORALLEEN trial represents the first prospective neoadjuvant trial to adopt molecular downstaging as primary efficacy endpoint. This trial randomized 106 postmenopausal patients with HR+/HER2- BC Luminal B (assessed by Prosigna assay) to either standard NAC or letrozole + ribociclib for 24 weeks. Molecular downstaging, defined as the switch from baseline high/intermediate risk-of-relapse (ROR) group to a low ROR group, occurred at similar rates in the ribociclib + letrozole and chemotherapy arms (46.9% vs. 46.1%), but with less toxicity. Gene-expression data gathered from post-treatment samples could offer valuable insights into the mechanism of resistance to neoadjuvant treatments and potentially drive subsequent strategies after neoadjuvant therapy [46].In the NeoPAL trial the combination of letrozole and palbociclib led to a profound decrease in KI67 levels, equivalent to that obtained by NAC, translating into very encouraging BC specific survival and relapse-free survival (RFS) (47,48). Nevertheless, pCR was low both with NET and NAC (Table 4).Also here, few patients with stage III were included in these trials, but we can conclude that NET + CDK4/6 inhibition performs similarly to NAC for the clinically relevant endpoints.

Table 1: Randomized trials comparing different endocrine agents in the neoadjuvant setting. ORR: objective response rate (determined by clinical examination); BCS: breast conservative surgery.
*indicates statistically significant difference

	n	Treatment	Duration	ORR	BCS	Stage III
Ellis et al, 2001 (22)	324	Letrozole Tamoxifen	4 months	61%* 40%	48%* 36%	T/N not mentioned separately
Eiermann et al, 2001 (24)	324	Letrozole Tamoxifen	4 months	55%* 36%	45%* 35%	T3 = 156 (48%)
Smith et al, 2005 (23)	330	Anastrozole Tamoxifen Anastrozole + Tamoxifen	3 months	37% 36% 39%	44%* 31% 24%	T/N not mentioned separately Median diameter by caliper = 3.8 - 4 cm
Ellis et al, 2011 (83)	374	Exemestane Letrozole Anastrozole	4 months	63% 75%* (only in comparison to exemestane) 69%	48% 42% 64%	T3-T4 = 95 (25%)

Table 2: Neoadjuvant endocrine therapy (NET) vs. neoadjuvant chemotherapy (NAC) trials in postmenopausal patients. EC: epirubicine and cyclophosphamide; ORR: objective response rates either determined by clinical examination or radiological examination using magnetic resonance imaging (underlined); BCS: breast conservativesurgery,pCR:pathologicalcompleteresponse.
PM: postmenopausal patients; ITT: intention to treat
*indicates statistically significant difference.

	n	Treatment	Duration	ORR	BCS	pCR	Stage III
Semiglazov et al, 2007 (29)	239 post-menopausal	Doxorubicine paclitaxel Exemestane or anastrozole	3 months	64.5% 63.6%	24% 33%*	6% 3%	118 (49%) T3-T4 = 129 (53%) N2 = 41 (17%)
Alba et al, 2012 (30)	44/95 post-menopausal	EC – docetaxel Exemestane	24 weeks	57% in PM 52% in PM	47% in ITT 56% in ITT		T3-T4 = 23/95 (24%) N2 = 2/95 (2%)

Table 3: Neoadjuvant endocrine therapy (NET) + CDK 4/6 inhibitor vs. NET monotherapy. CCCA: complete cell cycle arrest defined as KI67≤ 2.7%; PEPI: preoperative endocrine prognostic index; PCR: pathological complete response.
*indicates statistical significance.

	n	Treatment	Outcome (1)		Outcome (2)		Stage III (n)
PALLET: Johnston et al, 2018 (44)	307	A: Letrozole B: Letrozole ◊ letrozole + palbociclib C: Palbociclib ◊ letrozole + palbociclib D: Palbociclib + letrozole	Clinical response	49.5% (A) 54.3% (B, C, D)	KI67 decline ≤ 2.7%	59%* (A) 90% (B,C,D)	T/N not mentioned separately Inclusion criteria: T ≥ 2 cm.
neoMONARCH2: Hurvitz et al, 2020 (42)	223	A: Anastrozole + abemaciclib B: Abemaciclib C: Anastrozole	Change in KI67 (C1d1 - C1d15)	68%* (A vs C) 58%* (B vs C) 14%	pCR	3.7% = 7/190 patients who underwent surgery	31 (14%)
FELINE: Khan et al, 2020 (45)	120	Letrozole + ribociclib Letrozole	PEPI 0	25% 25%	KI67 decline ≤ 2.7%	92% 52%*	T/N not mentioned separately

Table 4: Neoadjuvant endocrine therapy (NET) + CDK 4/6 inhibitor vs. chemotherapy.
FEC: 5FU epirubicinecyclofosfamide; RCB: residual cancer burden; pCR: pathological complete response; DC: doxorubicin cyclofosfamide.

	n	Treatment	Outcome (1)		Outcome (2)		Stage III
NEOPAL: Cottu et al, 2018 (47)	106	Letrozole + palbociclib FEC - docetaxel	RCB 0-1	8% 16%	pCR	3.8% 5.9%	5 (4%)
CORALLEEN (Lum3 by PAM50): Prat et al, 2020 (84)	106	Letrozole + ribociclib DC - paclitaxel	PAM50 low at surgery	47% 46%	RCB 0-1	6% 12%	14 (13%)

2.4. Premenopausal Women

a) NET monotherapy

Data on the efficacy and safety of NET in premenopausal women is scarce. This specific population has often been excluded from neoadjuvant trial, especially those without chemotherapy due to concerns about undertreatment. Younger age is associated with a higher risk of recurrence and increased benefit of chemotherapy [49].One study, the phase 3 STAGE trial, compared 24 weeks of pre-operative goserelin with either anastrozole or tamoxifen in 197 pre-menopausal women. Patients in the anastrozole group had a clinical response rate of 70.4% vs. 50.5% in the Tamoxifen group (p = 0.004) [50]. Unfortunately, this study only included cT2N0 tumors but it is the only available data on NET in this setting.

b) NET vs. NAC

Kim et al. [51] compared tamoxifen + ovarian function suppression (OFS) to anthracycline- and taxane based chemotherapy in premenopausal women. There was a higher clinical response in the NAC arm (83.7% vs. 52.9%, p-value = 0.046), but both arms showed similar low rates of pCR (3.4% vs. 1.2%, p-value < 0.005) and no significant difference in BCS (13.8 vs. 11.5%, p-value = 0.531) or KI67 changes [51]. These findings are consistent with the GEICAM/2006 trial: the NAC arm reported higher clinical responses, but only in the group with high baseline KI67 >10% (67% vs. 42%, p-value = 0.075) and not in the low KI67 group (p-value = 0.74). In this trial the NET arm consisted of exemestane + OFS [30].

With the available data, it seems most logical to start NAC in stage III luminal disease in premenopausal patients. However, many of these studies did not incorporate OFS as part of the adjuvant ET and overlooked the OFS induced by chemotherapy itself. It can be speculated that the degree of benefit seen with chemotherapy in younger women is at least partially due to endocrine effects, suggesting that the use of NET should be further explored in this setting [52,53].

2.5. Neoadjuvant Immunotherapy in Luminal Breast Cancer

Patients with clinically and genomically high risk disease have a roughly 20% risk of recurrence at 10 year, despite the use of (neo-)adjuvant systemic therapies, demanding additional or alternative treatment options to further improve prognosis. As such, immune checkpoint inhibition may enhance endogenous anticancer immunity when combined with chemotherapy [54]. Data from two recent phase III trials, the CHECKMATE-7FL (CK7FL) and KEYNOTE-756 (KN756), show a benefit of adding neoadjuvant immunotherapy to chemotherapy in luminal BC (Table 5), leading to increased pCR (24% vs. 14-16%) [55-57]. However, the implications on long-term outcome have not been reported yet.In the CK7FL, a greater benefit from the addition of immunotherapy was observed in tumors with tumor infiltrating lymphocytes (TILs) > 1%. However, it remains unclear whether the observed benefit of Nivolumab is due to a more immunogenic microenvironment, different tumor characteristics or both [58]. In both trials the magnitude of pCR benefit was higher in PD-L1 positive tumors, especially with higher PD-L1 scores. In KN756, the PD-L1 positivity rate was 76% on the DAKO 22C3 assay using the combined positive score criteria, while CK7FL reported a 35% positivity rate using the Ventana SP142 assay for immune cell infiltration. This discrepancy is likely attributed to differences in the scoring methods [59]. In the recent I-SPY2 analysis, researchers identified biomarkers to predict response to immunotherapy. In this trial, adding pembrolizumab to standard chemotherapy more than doubled the estimated pCR rates (30% vs. 13%) [60]. In this study, they also identified an immune signature, the ImPrint signature which could identify BC patients with immune active tumors as denoted by enrichment of several immune related pathways. It involves 53 genes and could predict pCR following PD1 inhibition [61].Moreover, luminal BC showing Mammaprint index scores between -0.570 and -1 (also referred to as Mammaprint high 2) are more immunogenic, as evidenced by greater presence of immune cells and upregulation of antigen presentation genes when compared to so called MammaPrint high 1 tumors (Mammaprint index score between 0 and -0.569) [62]. MammaPrint high 2 tumor status seems to be a promising predictive biomarker of immunotherapy benefit in this population and warrants further validation as a biomarker to select patients for neoadjuvant chemo-immunotherapy treatment (SWOG S2206 trial, NCT06058377).Preclinical models suggest synergistic activity of CDK4/6-i and immune checkpoint inhibition through multiple mechanisms, including enhanced tumor antigen presentation, decreased immunosuppressive regulatory CD4+ T

cells proliferation and modulated T cell activation by reducing the expression of inhibitory receptors such as PD-1 [63]. The ImmunoADAPT study (NCT03573648) is currently investigating if the addition of palbociclib can enhance the response rates of avelumab in patients with stage II/III HR+/HER2- BC.

In conclusion, neoadjuvant immunotherapy added to chemotherapy in luminal BC is a promising approach, but better patient selection and long-term outcome data are needed before this can be applied in routine clinical practice.

Table 5: Neoadjuvant immunotherapy. EC: epirubicine cyclophosphamide; DC: doxorubicine cyclophosphamide; pCR: pathological complete response.

	n	Treatment	Outcome		Stage III
KEYNOTE-756: Cardoso et al (56).	1278	Pembrolizumab + paclitaxel - EC/DC Placebo + paclitaxel - EC/DC	pCR	24.3%* 15.6%	T3-T4 = 463 (36%) N+ = 1152 (90%)
CheckMate 7FL: Loi et al (55)	510	Nivolumab + paclitaxel - EC/ DC Placebo + paclitaxel- EC/DC	pCR	24.5%* 13.8%	223 (43%)
I-SPY2 analysis: Nanda et al (60)	250 54% HR+/HER2-	Pembrolizumab + paclitaxel - DC Paclitaxel - DC	pCR	34.2% 13.6%	Stage not mentioned Median tumor size on MRI: 3.6-3.9 cm. N+ = 220 (88%)

2.6. Role of Gene Expression Profiling

GEP such as Oncotype DX® and MammaPrint® can predict the risk of recurrence of HR+/HER2- early BC, and more importantly the benefit of adjuvant chemotherapy [9,10]. MINDACT, TAILORx or Rx-PONDER trials however only contained small proportions of stage III luminal disease.In the non-randomized, real-world, FLEX registry, patients with MammaPrint high 2 (-1.000 to -0.570) Blueprint Luminal B have a lower risk of recurrence at 3 years (11.3%) if they received adjuvant anthracycline-based regimen instead of Taxotere Cyclophosphamide. No difference was seen in luminal MammaPrint high 1 (-0.569 to 0.000) patients. This trial included only 5.4% of T3-T4 and 23.6% of node positive patients [64]. In the future, GEP with MammaPrint could help clinicians to decide who may benefit more from anthracyclines-regimen (MammaPrint high 2). On the other end, patients with a 70-gene ultralow-risk BC (+0.356 to +1.000) have shown excellent survival but very few stage III tumors were present in those datasets including MINDACT trial [65]. Performing GEP on core biopsies could also be of interest in the neoadjuvant setting to better select patients for NAC vs. NET [60]. In a meta-analysis of 1744 patients with HR+/HER2- patients, pCR to NAC was considerably higher among high OncotypeDX recurrence score (RS) BC (RS > 25 vs RS <25, 11% vs. 1%; p-value < 0.001) [66]. RS inversely correlated with NET sensibility in another meta-analysis of 691 tumors with low-intermediate RS (RS < 25, OR 4.60; p-value < 0.001) [67].Recently, it has also been shown that MammaPrint high 2 tumors had significantly higher pCR rates after NAC compared to MammaPrint high 1 tumors: 22-29% vs. 6-10% [68].This concept is currently under evaluation in the phase II PLATO study (NCT03900637). BC classified as low risk based on GEP will receive NET (letrozole), whereas those classified as high risk will receive NAC (anthracycline-cyclophosphamide followed by taxanes). Its primary endpoint is the conversion rate from BCS-ineligible to BCS-eligible patients.

2.7. Role of Tumor Histology

Invasive breast carcinoma of no special type (IBC-NST) accounts for +/- 70% of all BC cases. Invasive lobular carcinoma (ILC) is the second most common subtype of BC, accounting for 5-15%. ILC has some unique clinical and pathological features that distinguish it IBC-NST. ILC exhibits a distinct dyscohesive and infiltrative growth pattern, primarily due to the loss of the cell adhesion molecule E-cadherin [69]. This growth pattern often makes ILC challenging to detect mammographically and clinically, contributing to its presentation at a more advanced T stage. Additionally, ILC is more likely to be multifocal and bilateral. Clinical BC research often does not differentiate between IBC-NST and ILC. However, these are distinct types, both in terms of pathological characteristics and treatment responses. In general, ILCs respond poorly to NAC. Current guidelines recommend NAC primarily to facilitate surgery for locally advanced ILC tumors. However, pCR rates for ILC are reported to be lower than those for IBC-NST [70]. Loss of E-cadherin protein expression, due to alterations in its encoding gene CDH1, is the most frequent oncogenic event in ILC. Synthetic lethality approaches have

shown promising antitumor effects of ROS1 inhibitors in models of E-cadherin-defective BC in in vivo studies and provide the rationale for testing their clinical activity in patients with ILC [71]. The optimal approach towards stage III ILC may need specific future studies.

2.8. Assessment of Response to Neoadjuvant Therapies in Luminal Breast Cancer

The optimal strategy to evaluate tumor response and clinical benefit of new therapies in luminal BC is still a matter of debate. Both in terms of timing (when to conduct the first reevaluation and frequency of subsequent assessments) and methodology (clinical response, radiological response, BCS rate).

a) pCR and Residual Cancer Burden (RCB)

While downsizing the breast tumor to enable BCS is a common indication for the use of NET, it is important to recognize that a pCR is not required to achieve BCS, and the presence of residual breast and axillary disease at time of surgery is expected. In ALTERNATE, the largest NET trial to date, pCR following 6 months of NET was 0.8% [72]. Different pooled analysis showed also a lower pCR rate after NAT in luminal BC (5-30%) compared to TNBC (20-62%) and HER2-positive disease (18-74%) and a weaker association between pCR and EFS [73,74]. This raises questions about the appropriateness of using pCR as surrogate marker of response in luminal BC [75].

RCB is a valuable method to accurately measure the extent of residual disease at the time of surgery and is statistically significantly associated with long-term outcomes after NAC [76]. RCB is assessed based on four factors: the size and cellularity of the residual breast tumor, as well as the number and size of nodal metastases, ranging from RCB-0 (which represents pCR) to RCB-III (which indicates extensive residual disease) [76].In a recent meta-analysis including 5161 patients, RCB showed a linear effect on long-term outcomes, including a subgroup (n = 1775) with luminal BC. RCB of 0-I is linked to improved EFS compared to RCB II-III after NAC [77]. However, the prognostic value of RCB after NET remains largely unexplored while PEPI score (see below) is more validated in that setting. In the NeoPAL trial, fewer patients achieved RCB-0/I with letrozole and palbociclib compared to NAC (7.7% vs. 15.7%) [47].

b) KI67

In postmenopausal women, the early decrease of KI67 after a ‘window of opportunity’ period of NET with an AI seems to be a significant predictor of treatment effectiveness and long-term survival. The IMPACT trial showed that lower levels of KI67 expression after 2 weeks of NET were significantly associated with higher RFS. The P024 trial demonstrated that post-treatment KI67 levels on surgical specimens after 4 months of NET were also significantly linked to RFS and BC specific survival. Both trials revealed that on-treatment KI67 expression had a stronger association with long-term outcomes compared to KI67 at baseline.The POETIC trial tested the hypothesis that KI67 levels after 2 weeks of NET could combine the intrinsic prognostic value of baseline KI67 with the predictive value of changes in KI67 expression. KI67 was analyzed immunohistochemically in a core biopsy at baseline (KI67B) and in either a core biopsy or the excision biopsy taken at surgery (KI672w), and was estimated as the percentage of cancer cells staining positive. In this trial, 4480 postmenopausal women with HR+ BC (2% cT3) were randomized to receive either AI for 2 weeks before surgery, or no pre-surgical treatment. In patients with high KI67B(≥10%), KI672w revealed interesting findings. Those patients whose KI67 remained ≥10% were at statistically significant risk of recurrence compared with those whose KI67 decreased to < 10% and adjuvant chemotherapy seems advantageous. Five-year recurrence risk was 21.5% and 8.4%, respectively [78]. Nevertheless, there is no evidence that this window of opportunity approach outperforms efficacy compared to the strategy using upfront surgery and postoperative GEP to determine adjuvant chemotherapy indication.

Based on the prognostic value of KI67 staining levels, the ACOSOG Z1013 and ALTERNATE trials recommend that patients with KI67 levels (>10%) after 2 to 4 weeks of NET should consider switching to NAC. In the ALTERNATE trial, nearly all patients with baseline KI67 ≤ 10% maintained low at week 4, indicating limited value for on-treatment biopsy in this group.In the phase III WSG-ADAPT trial women with intermediate risk cancer, defined by the OncotypeDX RS of 12-25, were stratified by KI67 changes after a short period of ET exposure. ET responders, based on the 3-week change in KI67 to ≤ 10%, were allocated to adjuvant ET without chemotherapy (experimental arm) and ET non-responders (KI67 > 10%) received adjuvant chemotherapy followed by ET. In the overall population, ET-responders had 5 years iDFS of 95.6%. The patients included in this study had mostly low-stage BC (only 2.8% of T3-T4, 0.8% N2-N3). A NET strategy based on RS and KI67 change could be considered for further development and validation in clinical trials before being implemented in clinical practice [79].

c) Preoperative Endocrine Prognostic Index (PEPI)

The PEPI score, a prognostic model incorporating post-treatment pathological stage and biomarker status in patients treated with NET, was developed based on the P024 study cohort and clinically validated in the IMPACT and Z1013 trials. Tumors with a PEPI score 0 were associated with excellent long-term outcomes (relapse-free survival of 97% at 3y and 96.3% at 5y) (23,24). A modified PEPI (mPEPI) score, excluding ER Allred score because fulvestrant downregulates ER expression, is being prospectively validated in ALTERNATE, a randomized trial of patients with stage II/III luminal BC treated with fulvestrant and/or anastrozole. Preliminary results show that rates of endocrine-sensitive disease (mPEPI score of 0) are similar between treatment arms ranging

between 18.6% and 22.7% [80].

d)Treatment efficacy score (TES)

Recently, the I-SPY Consortium developed a statistical tool called the TES to quantify the difference of pathologic responses across various RCB values observed in trial arms. The authors illustrated that higher TES values in a reference arm were associated with a greater shift towards lower RCB values in a corresponding experimental arm. This tool may accurately identify less effective treatment regimens, irrespective of improvements in pCR rates. Moreover, the correlation between TES and survival outcomes was stronger than the correlation between differences in pCR rates and survival. This suggests that the TES might potentially serve as an early surrogate endpoint for predicting survival differences at the trial arm level, although further validation and integration into other studies are needed [81].

3. Discussion and conclusion

In the absence of specific trials for stage III luminal BC, data are often extrapolated from clinical trials including lower stage luminal BC. We summarized key messages and recommendations on the use and sequence of neoadjuvant systemic therapy (Table 6).Stage III luminal BC generally requires surgery, radiotherapy, chemotherapy, ET, and CDK4/6-i, but the optimal sequence of those remains challenging. Upfront multidisciplinary team discussion is crucial.Based on the available evidence, NAC can be considered as the most standard approach, when chemotherapy is needed anyhow. Dose-dense anthracycline-cyclophosphamide followed by taxanes is recommended as regimen, unless use of anthracycline is contra-indicated.NET represents a feasible and effective treatment option (mainly in postmenopausal patients) with similar clinical responses and BCS rates but less toxicity than chemotherapy. Currently, there is no consensus concerning the optimal duration of NET. In the majority of NET trials, patients were treated for 3-6 months and the St Gallen 2023 panel recommended a minimum duration of 6 months of treatment with AI. Given the lack of clear benefit when adding a CDK 4/6-i, the standard remains to give an AI in monotherapy. Young age/ premenopausal status, signs of limited endocrine sensitivity such as reduced ER expression (< 50% ER positive cells) and/or absent PR expression reinforce the decision to start NAC rather than NET. Age and frailty status can have important impact on treatment choice, with a much more pronounced role of initial ET approach with increasing age and frailty. However robust conclusions to guide appropriate patient selection cannot be drawn yet.Upfront ET during a 2-to-4-week window of opportunity, with information on KI67 evolution, could be of help in the decision for further treatment with NAC or NET, like observed in the POETIC trial, but is currently not standard. There is an unmet need for stage III specific trials to further optimize this (neo-) adjuvant approach. Patient selection should be guided by GEP-based risk stratification rather than just disease staging. ‘High risk’ patients based on genomic scores should be directed towards new biomarker driven approaches, using NAC as the comparator arm. Meanwhile, those considered ‘low risk’ should be assessed for ‘de-escalation’ strategies with NET as a reference. GEP determination on diagnostic biopsy might help to guide clinicians in deciding who will benefit from neoadjuvant chemotherapy and who could be spared the morbidity [82]. These new trials should implement new endpoints, since the simple dichotomy between pCR and non-pCR does not accurately predict long-term outcomes in luminal disease. Using a more discriminative index like PEPI score would better assess the benefit of new therapies.In summary, we conclude that the approaches to NAC and NET in (stage III) luminal BC are transitioning toward interim assessment-driven, risk-based treatment modulation. Dissecting the heterogeneity of this cancer type will necessarily rely on the design of biomarker-based studies.

Table 6: Recommendations on the use and sequence of systemic therapy in stage III luminal breast cancer. NAC: neoadjuvant chemotherapy; GEP: gene expression profiling; ET: endocrine therapy; NET: neoadjuvant endocrine therapy; ER estrogen receptor; PR progesterone receptor; BC: breast cancer; BCS: breast conservative surgery; CDK4/6-I : CDK4/6 inhibitor.

General principles	
- Upfront multidisciplinary team discussion = crucial. - NAC = most standard approach when chemotherapy is needed anyhow. - GEP with Mammaprint on diagnostic biopsy or ET during 2-to-4-week window of opportunity could help better select patients in the future for NET vs. NAC.	
In favor of NAC	In favor of NET
- Young age/premenopausal status. - Limited endocrine sensitivity: low ER (< 50% ER positive cells) and/or absent PR expression. - Inflammatory BC. - cN2/3 nodal disease. - T4 tumors or large primary tumor relative to breast size in patients who desire BCS. - High risk GEP.	- Older age. - Frail. - High endocrine sensitivity.
Type of NAC	Type of NET

- Dose dense anthracyclines follow by taxanes for high stage luminal BC (unless contraindication). - Docetaxel Cyclophosphamide can be an alternative but limited data. - Consider GEP for benefit anthracyclines (Mammaprint high 2).	- AI monotherapy for at least 6 months (no proven benefit so far of combination with CDK4/6-i) - Aromatase inhibitor > Tamoxifen.
Post-surgery systemic therapy	
- Chemotherapy to be considered depending on initial therapy, obtained response if NET was administered, and general health status. - Consider extended use ET after 5 years given high baseline stage. - Abemaciclib (2 years) or Ribociclib (3 years) if patients fit the MonarchE of NATALEE criteria. - Olaparib in case of germline BRCA mutation fitting OLYMPIA criteria. - Adjuvant bisphosphonates.	

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