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REVIEW ARTICLE

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Adjuvant systemic treatment in luminal breast cancer — what else apart from hormone therapy?

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Oncology in Clinical Practice
DOI: 10.5603/ocp.50816

ISSN 2450–1654
e-ISSN 2450–6478

ABSTRACT

The luminal subtype [hormone receptor (HR) expression and absence of HER2 overexpression] occurs in more than 70% of patients with early breast cancer. These patients are characterized with a differentiated prognosis depending on the stage and the biological aggressiveness of the tumor, which can be assessed by examining the degree of HR expression, histological malignancy (grade, G), the severity of tumor cell proliferation (Ki67 index) or gene expression in a molecular test. Besides, the young age of the patient, especially under 35 years, is associated with a worse prognosis. In all patients with HR expression, indications for adjuvant hormone therapy should be considered. However, in patients with a higher risk of relapse and death, there are additional systemic treatment options that can reduce this risk: chemotherapy and targeted drugs (cyclin-dependent kinase 4/6 inhibitors, PARP inhibitor for patients with germline *BRCA 1/2* mutation). The aim of the review is to discuss indications for these forms of adjuvant therapy in HR+ HER2– patients.

Keywords: luminal breast cancer, adjuvant chemotherapy, palbociclib, abemaciclib, ribociclib, olaparib, *BRCA1/2* mutation, anthracyclines, taxoids

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Introduction

Most breast cancers express hormone receptors (HR) without overexpression of HER2. Such a subtype is called luminal. According to the definition presented in the recommendations of the European Society for Medical Oncology (ESMO), luminal phenotype A is characterized by estrogen receptor (ER) expression, high progesterone receptor expression (PR > 20%) and low Ki67 expression (below the median value of local laboratory results for tumors expressing HR, approx. 20%), or a low-risk molecular signature. The luminal B phenotype is characterized by ER expression, low PR expression (< 20%), high Ki67 expression, or a high-risk molecular signature.

According to a study by Yang H et al. [1], among 329770 breast cancer patients registered in the SEER database in the years 2010–2016, 73% were diagnosed with an HR-expressing cancer subtype without HER2 overexpression. About 96% of them had no distant metastases at the time of diagnosis. In other words, adjuvant systemic treatment, which aims to reduce the risk of relapse and prolong life, is most often administered in such patients.

Hormone therapy (HT) is the adjuvant treatment of choice in breast cancer patients with the ER+/HER2– phenotype, while indications for additional adjuvant chemotherapy result from the individual risk of recurrence and patient preferences [ESMO and the Polish Society of Clinical Oncology (PTOK) recommendations] [2, 3]. The risk of recurrence is determined on the basis of clinical and pathological features. In dubious situations, molecular tests or the Magee Equation calculator may help determine

Received: 27.12.2024 Accepted: 02.01.2025 Early publication: 07.02.2025

the individual risk of recurrence. Computer models of risk recurrence, for example, PREDICT (www.predict.nhs.uk) [4], are helpful tools for estimating the benefits of systemic adjuvant therapy in individual clinical situations. For several years, ESMO recommendations emphasized the relationship between the immunohistochemical subtype (IHC) of breast cancer and the risk of recurrence. Chemotherapy is recommended mainly in patients with luminal subtype B, but it may also be used in patients with luminal subtype A, especially in those with cancers in advanced local and regional stages. Before we found out about the prognostic value of subtypes, the risk of recurrence and the resulting possible indications for chemotherapy had been determined on the basis of clinical-pathological features. These recommendations are still in force [3]. Chemotherapy is preferable in cancers with low HR expression, high histological grade (G3), high proliferation, involvement of at least 4 lymph nodes, tumor size > 5 cm, in patients willing to undergo cytotoxic treatment, and (according to the more recent version of the recommendations) in patients at high risk confirmed by a molecular test. Chemotherapy is not preferable in cancers with a high expression of HR, low grade (G1), low proliferation rate, lack of lymph node involvement, tumor size up to 2 cm, in patients refusing to take chemotherapy, and patients at low-risk confirmed by a molecular test.

American recommendations of the National Comprehensive Cancer Network (NCCN) [5] also suggest that clinical and pathological factors help make decisions about chemotherapy, but it is noteworthy that the authors recommend doing the Oncoptype DX molecular test, which is regarded as a regular element of the diagnostic algorithm in postmenopausal patients at the pT1b-3N0-1 stage and in premenopausal patients at the pT1b-3N0 stage.

This review aims to summarize indications for adjuvant chemotherapy and targeted therapy in HR+ HER2– patients.

Why should adjuvant chemotherapy be considered in HR+ HER2– patients?

Knowledge about the value of adjuvant chemotherapy in patients with breast cancer has been summarized and consolidated after the publication of 2 meta-analyses by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG), presenting results of clinical trials conducted from the 1970s.

A study including data from 145,000 patients obtained in 194 clinical trials, published in 2005, showed that the introduction of multidrug chemotherapy over a 15-year follow-up:

— reduced the relative risk of death due to breast cancer by about 30% in patients <50 years of age and about 12% in patients aged 50–69 years;
— reduced the relative risk of recurrence by 37% in patients < 50 years of age and about 19% in patients aged 50–69 years [6].

The benefit is evident in ER+ and ER- patients receiving and not receiving tamoxifen (TAM), with and without lymph node involvement, and undergoing different types of chemotherapy [cyclophosphamide, methotrexate, fluorouracil (CMF), anthracycline-based, other]. The publication also summarized the benefit of adjuvant HT, showing that in ER+ patients, 5 years of TAM therapy reduced the relative risk of recurrence by 41% and the risk of breast cancer-related death by 34% in 15-year follow-up.

Another EBCTCG meta-analysis published in 2012 focused not only on the benefits of adjuvant chemotherapy but also compared different chemotherapy regimens [7]. It has been shown that in patients with HR expression receiving TAM for 5 years, administration of anthracycline-based chemotherapy or CMF reduced the risk of death from breast cancer by 6.8% if patients were younger than 55 years and by 6.5% if patients were 55–69 years old in 10-year follow-up. The authors noted that the benefit of chemotherapy (i.e. reducing the risk of death due to breast cancer throughout the next 10 years) depended on the absolute risk of recurrence and death, which, in the case of patients with HR expression, was the risk observed after implementation of optimal HT. A low absolute risk is associated with a small benefit from chemotherapy. The authors of the meta-analysis highlighted a weak point of their study — lack of data on tumor gene expression and quantitative data on IHC results, which would help to more accurately predict the risk of recurrence and death and possible chemosensitivity.

These meta-analyses summarized results of clinical trials conducted for over 30 years. However, diagnostic and therapeutic methods used at that time are now at least partially obsolete. Nevertheless, the above-mentioned results allow us to conclude that every patient with invasive breast cancer can potentially benefit from adjuvant chemotherapy. However, the absolute magnitude of this benefit depends on the risk of recurrence and death and, at low risk, may be clinically insignificant and generate unnecessary toxicity.

Thus, the question is how to identify potential candidates for adjuvant chemotherapy. Over the past 20 years, methods of diagnosing and treating early breast cancer have significantly evolved, chemotherapy regimens have changed, new hormonal drugs and targeted drugs have been invented, and IHC and molecular diagnostics have also developed. Thus, on the one hand, more effective HT considerably reduces the risk in patients with HR expression, and on the other hand, new tools identifying patients at lower risk have been designed (Fig. 1).

In the following sections, traditional and more recent tools for determining the risk of recurrence and death

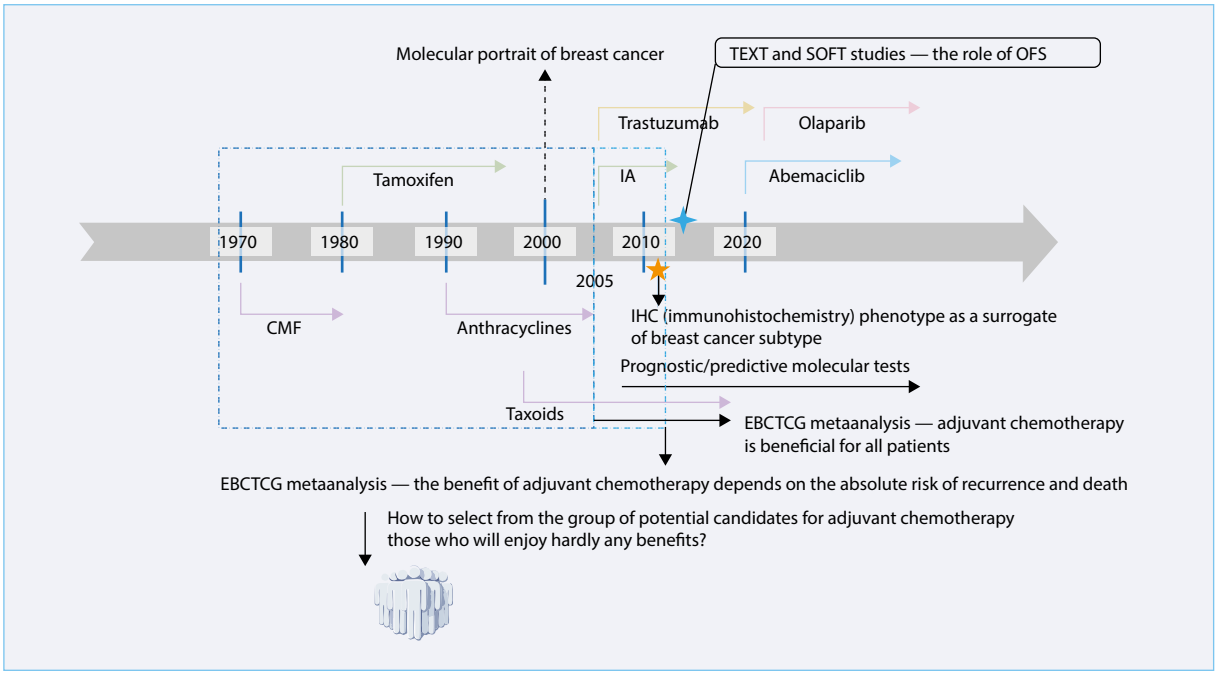

Figure 1. Schematic summary of the history of adjuvant treatment of breast cancer. The timeline marks the moments of introduction of the most important drugs into adjuvant therapy, description of the 'molecular portrait' of cancer, and introduction of immunohistochemical subtype (IHC) tests to assess breast cancer phenotypes; AI — aromatase inhibitor; CMF — cyclophosphamide, methotrexate, fluorouracil; EBCTCG — Early Breast Cancer Trialists' Collaborative Group; OFS — ovarian function suppression

due to breast cancer and their possible predictive value for chemotherapy will be discussed.

Prognostic value of clinical and pathological risk factors in patients with HR+ HER2– breast cancer

The EBCTGC meta-analysis published in 2017 presented clinical and pathological risk factors for recurrence and death due to breast cancer based on 20-year follow-up of 74 000 patients undergoing adjuvant HT [8]. It is important that 64% of them also received adjuvant chemotherapy. Parameters related to the disease stage, its biology, and patients' age were taken into account. Higher stages, especially nodal involvement, were associated with higher risk of recurrence during 5 years of HT and throughout further follow-up which, in total, could be as long as 20 years. Factors such as age under 35, G3, and Ki67 ≥ 20% were also associated with higher risk of relapse in the short and long term. In contrast, low PR expression and HER2 overexpression increased the risk of relapse during 5-year HT but were insignificant in longer follow-up. A higher stage increased the risk of breast cancer-related death both during 5 years of HT and in subsequent follow-up. Similarly, G3 and low PR expression increased the risk of death in the first 5 years and later. In contrast, patients under 35 years of age, with Ki67 ≥ 20% and overexpression of HER2 exhibited an increased risk of death during 5 years of HT.

Wangchinda and Ithimakin, in an article published in 2016 [9], attempted to identify clinical and pathological factors associated with recurrence observed later than 5 years after surgery. Both cited studies show that patients with HR expression may experience late recurrences — even throughout 20 years after surgery — the situation of late recurrence may affect up to 40% of patients with recurrent breast cancer. The authors demonstrated an association between large tumor size (> 2 cm), lymph node involvement, and a high histological malignancy and early recurrence. Conversely, late relapses correlated with high ER expression, PR expression, and absence of HER2 overexpression.

Prognostic and predictive value for chemotherapy of luminal subtypes A and B

A distinction of breast cancer subtypes based on IHC parameters appeared for the first time in the recommendations issued after the St. Gallen Conference in 2011 [10]. However, the first article describing breast cancer subtypes was published in 2000 in *Nature*. Its authors, Perou and Sorlie [11], created a "genetic portrait of breast cancer," based on molecular examination of

tumors from 42 patients. They distinguished the following molecular subtypes: basal, HER2-positive, normal-breast-like, and luminal, i.e. characterized by HR expression. The following year, the authors published a second article. This time, it examined the molecular profiles of 78 patients and grouped them into prognostic categories, which made it possible to distinguish a subcategory with worse prognosis in patients with luminal cancer [12].

Thus, originally, breast cancer subtypes were distinguished based on genetic/molecular profiles. Due to the difficulty of using this typing in clinical practice at that time, it was not until 10 years after the first publications that the St. Gallen recommendations distinguished IHC surrogates of genetic subtypes. According to the first definition from 2011, the surrogate of luminal subtype A was characterized by ER and/or PR expression, lack of HER2– overexpression, and Ki67 < 14%. On the other hand, the luminal B subtype was distinguished by ER and/or PR expression and HER2+ or Ki67 ≥ 14%. Two years later, the definitions of IHC subtypes have been slightly modified [13]. Luminal subtype A was characterized by ER expression and PgR expression ≥ 20%, absence of HER2 overexpression, and low expression of Ki67 (no fixed cut-off point, suggested values were < 14% or < 20%, inter alia) or low risk of recurrence in a multigenic molecular assay. The definition of luminal subtype B without HER2 overexpression is based on the following criteria: ER expression and absence of HER2 overexpression and at least 1 of these traits: high expression of Ki67 or PgR < 20% or a high risk of recurrence in a multigenic molecular assay.

The above recommendations and their subsequent amendment were based on research data, mainly of a retrospective-prospective nature.

The Ki67 cut-off value of 13.25%, which best distinguished between tumors with luminal A and B genetic subtypes (2011 definition), was determined by Cheang et al. [14].

The revised definition from 2013 was based on the results of a study by Prat et al. [15], who showed that patients with luminal subtype A, defined according to 2011 St. Gallen recommendations are characterized by higher PR expression (> 20%), lack of HER2 and G1.

In addition to the above definitions, for practical reasons (i.a. low prevalence of Ki67 assessment before 2011, difficulties in establishing cut-off points), there is a third, less official definition of luminal subtypes based on HR, HER2 expression, and histological grade. In an article by Brouckaert et al. [16], patients expressing HR without HER2 overexpression were classified into luminal subtype A for G1 or G2 and the luminal subtype B for G3; there were significant differences in the prognosis of both subgroups. Van Maaren et al. [17] assessed the risk of recurrence in patients undergoing radical surgery for breast cancer in 2005 in the Netherlands. Their study used luminal subtype definitions based on histological grades. Of 8062 patients enrolled in the study, 56% were diagnosed with luminal subtype A and 26% with luminal type B. Local recurrence occurred throughout 10-year follow-up in 3.7% and 5% of patients, respectively, regional recurrence occurred in 1.7% and 4.5%, respectively, and distant recurrence was observed in 9.5% and 20%, respectively. Lobular carcinoma occurred in 10% of patients (83.1% — luminal subtype A, and 12.7% — luminal subtype B) and had worse prognosis than in patients with luminal ductal carcinoma.

Although histological grade and Ki67 expression refer to tumor cell proliferation, they are differently assessed. The degree of histological malignancy has 3 features: the mitotic rate, degree of gland formation, and nuclear grade or atypia. Each component is assessed on a 3-point scale in the microscopic section stained with hematoxylin and eosin. The Ki67 protein can be detected in the cell nucleus during the cell cycle. Therefore, its expression reflects the mitotic rate, but it is assessed with IHC. Each method has its own evaluation algorithms. Despite good standardization of methods, a lack of reproducibility by different doctors and laboratories is possible. The result may also be affected by tissue processing (the tissue may undergo necrosis) or the method of its collection (core needle biopsy, surgical specimen). Although G3 and high expression of Ki67 in breast cancer may correlate with each other, these results usually do not coincide when assessed in the same group of patients [18, 19].

Immunohistochemical surrogates of breast cancer subtypes were used in studies in subsequent years when the benefit of adjuvant chemotherapy in patients with luminal A carcinoma had been questioned. These retrospective studies included patients with luminal subtype A distinguished by the IHC method, but different definitions of this subtype were used in different studies. Most of these studies did not show that adding chemotherapy to adjuvant hormone therapy is beneficial [20–25]. One exception is the work by Haque et al. [24] published in 2018. The authors collected data from the National Cancer Data Base for 8548 patients with pT1-3N1 luminal A breast cancer diagnosed in the years 2004–2014. Sixty-one percent of them received adjuvant chemotherapy in addition to hormone therapy. Chemotherapy appeared to be beneficial as overall survival (OS) of all patients included in the analysis and of patients younger than 50 years of age increased comparing with patients without chemotherapy. Chemotherapy did not provide such a benefit in patients aged 51–60 years ($p = 0.116$), 61–70 years ($p = 0.222$), or >70 years ($p = 0.239$). The publication showed a growing tendency to waive chemotherapy over time: 14% in 2004–2005 and 41% in 2012–2014. This form of

Table 1. Retrospective studies in which the effectiveness of adjuvant chemotherapy was evaluated in patients with luminal A breast cancer distinguished by immunohistochemical subtype (IHC)

Study	IHC definition of luminal A subtype	Conclusions
Han 2015 [20]	G1–2 or Ki67<15%, ER+ and/or PgR+ and HER2–	In patients with N2 the trend towards reducing the risk of relapse and death with chemotherapy, but in patients N0 and N1 the opposite trend
Herr 2019 [21]	HR+, HER2– and G1–2	No benefit of chemotherapy (OS, DFS) in patients with N1 and in patients with N2
Diessner 2016 [22]	HR+, HER2– and G1–2	No benefit of chemotherapy (RFS) regardless of lymph node involvement, age, tumor size, G1/2 features chemotherapy alone worse than chemohormonal therapy — prognosis similar to that of patients without systemic treatment
Park 2017 [23]	ER+, HER2– and Ki67 < 14%	No benefit of chemotherapy (OS, DFS)
Haque 2018 [24]	G1, ER+, PR+, HER2–	Chemotherapy was associated with a benefit in OS in all patients included in the analysis and in patients younger than 50 years of age, chemotherapy did not provide such a benefit in patients aged 51–60 years, 61–70 years or > 70 years
Li 2020 [25] metaanalysis	Luminal A (various definitions)	Chemotherapy does not improve the prognosis in all patients (OS HR = 1.73; DFS/RFS HR = 1.22), nor in those with lymph node involvement (OS HR = 1.86; DFS/RFS HR = 1.30)

DFS — disease-free survival; HR — hazard ratio; OS — overall survival; RFS — relapse-free survival

treatment was also less often used in older patients, in academic centers, in patients after lumpectomies, and in cancers in less advanced local stages.

Unfortunately, the retrospective nature of the research presented in Table 1 means that the quality of the evidence is poor. However, the results allow us to hypothesize that patients with high HR expression and low proliferation (i.e. G1–2, Ki67 < 14/15%) probably benefit from chemotherapy added to HT, but the value is insignificant.

On the other hand, Zhao et al. [26] tried to determine whether patients with luminal B carcinoma benefit from the addition of chemotherapy to adjuvant HT. The researchers included 1372 patients with breast cancer at stage TNM I–III and with ER expression, diagnosed in the years 1998–2005. The authors identified the luminal B phenotype (according to the 2011 definition of St. Gallen: ER+, HER2- and G3 or ER+ and HER2+) in 432 patients (31%). HER2 overexpression was present in 179 patients from this group (41%), and adjuvant anti-HER2 treatment was received by 6% of them. After the 105 months of follow-up, recurrence was observed in 56 patients (13%). The authors found no differences in disease-free survival (DFS) and OS for all HER2+ and HER2– patients but in patients ≥ 60 years of age, the HER2+ feature was associated with worse DFS [hazard ratio (HR) = 3.23; p = 0.017] and OS (HR = 3.06; p = 0.027). The study showed that the administration of adjuvant chemotherapy was associated with a benefit in DFS (HR = 0.3; p = 0.034) and OS (HR = 0.2; p = 0.013), which was not dependent on the HER2 feature (DFS: HR = 1.65; p = 0.37; OS: HR = 1.65; p = 0.39) or PR expression (DFS: HR = 1.8; p = 0.37; OS: HR = 2.3; p = 0.25). Unfortunately, the retrospective nature of the study and participation of HER2+ patients, whose treatment was also very different from current standards, significantly reduced the level of reliability of the presented data.

In conclusion, although the determination of the IHC phenotype of breast cancer has a prognostic value, unfortunately, the data on its predictive value are based on weak evidence from retrospective studies. In addition, there is a lack of reliable data on the predictive value for adjuvant chemotherapy of individual parameters that determine the phenotype, such as Ki67 expression, histological grade, or PR expression, even though the results of numerous studies indicate their prognostic value [27–33]. Viale et al. [27] evaluated Ki67 expression in tumors of patients participating in two randomized clinical trials that compared the efficacy of adjuvant HT and chemo-hormonal therapy (CMF + TAM ± goserelin *vs.* TAM ± goserelin) in patients without lymph node involvement [27]. The investigators did not confirm a predictive value of high Ki67 expression (≥ 19%) for adjuvant chemotherapy. A retrospective study conducted by Criscitiello et al. [34] showed that adjuvant chemotherapy increases DFS in patients with Ki67 ≥ 32% (HR = 0.35). In modern research, the preoperative treatment model is used to assess the sensitivity of breast cancer with different IHC characteristics to chemotherapy. Several projects used high expression of Ki67, G3, and low/no expression

Table 2. The most popular commercial molecular tests used to predict prognosis in patients with early breast cancer

	Oncotype DX	PAM50/ /prosigna	MammaPrint (agencies)	BluePrint (agencies)	EndoPredict	Breast Cancer Index
Number of evaluated genes	21	50	70	80	11	7
Material	Formalin--fixed paraffin--embedded tissue	Formalin--fixed paraffin--embedded tissue	Fresh-frozen tissue or paraffin block	Formalin--fixed paraffin--embedded tissue	Formalin--fixed paraffin--embedded tissue	Formalin--fixed paraffin--embedded tissue
Clinical value	Prognosis Predictive value for chemotherapy	Prognosis (including late relapses > 5 years) Distinguishing between intrinsic subtypes	Prognosis Predictive value for chemotherapy	Distinguishing between intrinsic subtypes	Prognosis (including late relapses > 5 years)	Prognosis (including late relapses >5 years)
Validation of the predictive value for adjuvant chemotherapy in prospective studies	TAILORx (patients N0) RxPONDER (patients N1)	–	MINDACT (patients N0 and N1)	–	–	–

of PR in patients with hormone-sensitive cancer as potential predictive factors for chemotherapy. These parameters correlate with a higher chance of achieving a pathologically confirmed complete response (pCR) thanks to chemotherapy [35–38], but also with worse prognosis [36–38].

With regard to patients with ER expression and absence of PR expression, it is worth emphasizing that their prognosis is worse and does not depend on what adjuvant therapy they receive compared to patients with cancer positive for both receptors [39]. However, for them, adjuvant hormone therapy is a valuable and recommended treatment option as it significantly reduces the risk of death throughout 10 years of follow-up compared to the lack of hormone therapy (HR = 0.58; $p < 0.001$) [40].

The role of multigenic molecular tests in determining indications for adjuvant chemotherapy

Table 2 presents the five most popular commercial molecular tests used to determine the prognosis of patients with early breast cancer: Oncotype DX, MammaPrint, PAM50, EndoPredict, Breast Cancer Index [41, 42]. Their prognostic value was validated in retrospective-prospective studies. Histopathological material for molecular testing was obtained from patients participating in previous clinical trials or population studies, and then the data from these patients underwent statistical analysis to assess the prognostic value of the results of individual tests. The PAM50 test also allows assessing the molecular subtype of breast cancer [43]. Its findings integrated with the clinical factor, i.e. tumor size, make up the risk-of-recurrence score (ROR) [44]. The result of the EndoPredict test is also integrated with prognostic clinical factors such as tumor size and lymph node status to give "EPclin" tool [45]. It helps evaluate the risk of late relapses and thus, indirectly, possible indications for prolonged hormone therapy. However, only two of the presented tests. i.e. Oncotype DX and MammaPrint, have so far been tested for their predictive value for chemotherapy in large prospective clinical trials with long follow-up.

Oncotype DX

The result of the Oncotype DX test is a recurrence score (RS), with a value of 0–18, which indicates a low risk of recurrence, 18–31 — an intermediate risk of recurrence, and a score of ≥ 31 — a high risk of recurrence. The prognostic value of the test and the predictive value for chemotherapy of the high-risk signature were demonstrated in prospective-retrospective analyses [46]. In postmenopausal patients with lymph node involvement, the prognostic categories of low (40% of patients), intermediate (28%), and high risk (32%) were associated with 10-year DFS rates (60%, 49%, and 43% respectively), and 10-year OS rates (77%, 68%, and 51%, respectively) [47]. The same study showed that high RS (≥ 31) was a strong predictor of the benefit from cyclophosphamide, doxorubicin, fluorouracil

(CAF) chemotherapy added to HT (10-year DFS rates for patients treated and not treated with chemotherapy — 55% *vs.* 43%; p = 0.033; HR = 0.59).

In patients without lymph node involvement receiving adjuvant HT, different RS values were also associated with different rates of 10-year distant recurrence-free survival (DRFS: 96.8%, 90.9%, and 60.5% for low, intermediate, and high-risk signatures, respectively) [46]. The addition of chemotherapy [CMF, methotrexate, fluorouracil (MF)] to HT was associated with significant DRFS benefit in patients at high risk with RS ≥ 31 (rates of 10-year DRFS without and with chemotherapy 60% *vs.* 88%; p < 0.001). In this study, a low-risk signature occurred in 54% of patients, intermediate in 21%, and a high-risk signature in 25% of patients.

The prospective studies aimed to answer the questions of whether the addition of chemotherapy to HT brings an additional benefit for patients with intermediate risk without lymph node involvement and patients with low and intermediate risk and N1 nodal stage. These issues were addressed in the TAILORx and RxPONDER studies, respectively. For the purpose of the cited studies, different than original ranges of RS values were adopted: low ≤ 10, intermediate 11–25, and high ≥ 26 [48]. This procedure aimed to minimize the chance that high-risk patients would not receive the chemotherapy they deserved. After publication of the findings, the result of the commercially performed molecular test is interpreted according to new limits of RS risk groups adopted in the trials.

The TAILORx study included 10273 patients with a tumor size ranging from 0.6 cm to 5 cm without involvement of lymph nodes, with HR expression, and without HER2 overexpression, both pre- and postmenopausal [49]. Patients with Oncotype DX test result RS 0-10 were treated with HT, while patients with high risk (RS ≥ 26) were treated with chemotherapy and HT. The researchers focused on patients with intermediate risk (RS 11–26, 60% of patients), assigned to two arms: they received HT or a combination of hormone therapy and chemotherapy. It was a non-inferiority study. The primary endpoint of the study was to demonstrate that HT alone is no less effective than chemo-hormonal therapy for invasive disease-free survival (IDFS; non-inferiority limit HR = 1.322). In the study, the rates of 9-year IDFS were 83.3% *vs.* 84.3% for HT and chemo-hormonal treatment, HR = 1.08; 95% confidence interval (CI) 0.94–1.24; p = 0.26, respectively. The percentages of 9-year OS were 93.9% and 93.8%, respectively. The 9-year IDFS rates for low- and high-risk patients were 84% and 75.7%, respectively, and the 9-year OS rates were 93.7% and 89.3%, respectively.

A subgroup analysis showed that the benefit from the addition of chemotherapy could be achieved by premenopausal patients and patients < 50 years of age. For patients < 50 years of age, the absolute differences in 9-year IDFS rates in favor of chemotherapy were 3.5 % for RS 11–15, 9 % for RS 16–20, and 6.3 % for RS 21–25, respectively.

The RxPONDER study was dedicated to patients with T1-3N1 stage, HR expression, lack of HER2 overexpression, and low and intermediate risk in the Oncotype DX test (RS ≤ 25) [50]. The study involved 5083 premenopausal (33.2%) and postmenopausal patients. They were assigned to 2 arms: HT or chemotherapy with HT. The primary endpoint of the study was to check the effect of chemotherapy on IDFS and to assess whether the relative benefit of chemotherapy increases with a higher RS value. It was shown that the benefit of chemotherapy differed significantly and depended on the menopausal status of patients (p = 0.008). Hence, separate analyses were carried out in both subgroups.

In postmenopausal patients, no benefit of chemotherapy was demonstrated (HR = 1.02, 5-IDFS 91.9% *vs.* 91.3% for HT and chemotherapy combined with HT, respectively). In premenopausal patients, a significant gain from the addition of chemotherapy was noted, the difference in 5-year IDFS rates was 5 % (89% *vs.* 94%; HR = 0.60; p = 0.002). The relative gain from chemotherapy did not increase with a higher RS value.

Potential benefits of chemotherapy were observed for premenopausal patients. Thus, it was questioned whether this effect did not depend on ovarian suppression caused by cytotoxic agents. However, it should be remembered that these studies were not designed to assess the efficacy of ovarian function suppression (OFS) and such an interpretation is not justified.

MammaPrint

The MammaPrint test result divides patients into 2 prognostic categories: low- and high-risk. The prognostic value of this test was confirmed in retrospective-prospective studies [51].

The prospective MINDACT study aimed to assess the clinical utility of the test added to standard clinical and pathological criteria in selecting patients for adjuvant chemotherapy [52]. The study included 6693 pre- and postmenopausal patients patients with various subtypes of breast cancer [HR+ HER2– 81%, HER2+ 9.5%, triple negative breast cancer (TNBC) 9.6%] at pT1-3N0-1 stage.

The patients were subjected to a double assessment of prognosis, which was performed: with a clinical tool, i.e. the Adjuvant online calculator, and a genetic tool — the MammaPrint test. Hormone therapy was used in patients with low clinical risk and low genetic risk. Patients with high clinical risk and high genetic risk were treated with chemotherapy and HT. On the other

hand, patients whose results in both assessments were not consistent were administered HT or chemotherapy with HT. The investigators focused on patients with high clinical risk and low genetic risk. The primary endpoint of the study was to determine if patients in whom chemotherapy has not been implemented will demonstrate a non-inferior rate of 5-year DMFS compared to patients who have undergone chemotherapy combined with HT. The lower limit of the 95% confidence interval for non-inferiority was 92%. Patients with low clinical risk were assumed to have a 10-year breast cancer-specific survival (BCSS) rate without adjuvant chemotherapy of more than 92% for HR negative and >88% if HR positive and the mean absolute benefit of HT was 4%.

After a 5-year of follow-up, the DMFS rate in patients with high clinical risk and low genetic risk not receiving chemotherapy was 94.7% (95% CI 92.5–96.2). Such a result indicated that waiving chemotherapy was acceptable for these patients and did not significantly worsen the prognosis. Nevertheless, the 5-year DMFS rate in patients who received chemotherapy was higher by 1.5% .

After an 8-year follow-up, DMFS rates in patients at high clinical risk and low genetic risk receiving and not receiving chemotherapy were 92.0% (95% CI 89.6–93.8) and 89.4% (86.8–91.5; HR = 0.66; 95% CI 0.48–0.92), respectively [53]. An exploratory analysis of the results in the HR+ HER2– subgroup was performed. Patients aged ≤ 50 years demonstrated the values of 93.6% *vs.* 88.6%, respectively, indicating a 5% absolute gain from chemotherapy. On the other hand, in patients aged > 50 years, the application of chemotherapy did not bring any benefits (rates of 8-year DMFS: 90.2% *vs.* 90%, respectively).

Results of the MINDACT study indicate that in patients with pT1-3N0-1 stage with high clinical risk and low genetic risk, chemotherapy is not necessary, and its omission will not significantly worsen the prognosis. Chemotherapy, however, is associated with a small benefit that seems to occur in patients aged ≤ 50. These results refer to HR+ HER2– patients. For other breast cancer subtypes, there are currently different standards of adjuvant treatment than those described in the MINDACT study; moreover, such patients were a minority in the study.

Multigenic molecular tests in clinical practice — summary

In 2022 Andre et al. [41] published recommendations endorsed by the American Society of Clinical Oncology (ASCO), summarizing the clinical value of popular molecular tests. These tests were intended for patients with HR expression and without HER2. If the patient is premenopausal and has lymph node involvement, performing the test is of no additional value when deciding on chemotherapy, as such patients should be treated with cytotoxic agents regardless of test results. If the premenopausal patient does not have metastases in the lymph nodes and is in the pT1-3 stage, chemotherapy may be waived in patients with low risk (RS 0–10) and patients with RS 11–15, for whom treatment with cytotoxic agents is associated with insignificant benefits. In postmenopausal patients, the tests are helpful in the case of pT1-3N0-1 stage; chemotherapy can be waived in patients at low and intermediate risk (RS < 26). It is preferable to perform the Oncotype DX regardless of the menopausal status (if indicated by stage), or MammaPrint in postmenopausal patients, as these tests are based on the highest quality evidence.

Magee equation calculator

The Magee decision algorithm has been adopted by the Department of Pathology at the University of Pittsburgh School of Medicine [54]. It aims to select patients in whom performing the Oncotyope DX molecular test would bring additional benefits when deciding on adjuvant chemotherapy [55]. The calculator helps to determine, based on pathological and clinical features, in which patients the risk of recurrence and death is intermediate and molecular testing would provide additional knowledge about prognosis. The Magee equation calculator includes information about the exact number of points on the Nottingham score used to assess the histological grade (G), the expression of both hormone receptors reported in the h-score, the expression of Ki67 and HER2, and tumor size. The result of the test allows the patient to be classified into 3 prognostic groups: a value of ≥ 31 indicates need for chemotherapy, a value of < 18 or ≤ 25 with a low mitotic index indicates no benefit from chemotherapy, while in patients with a score of 18–25 and a mitotic index of 2–3 or a score > 25 and < 31, the Oncotype DX molecular test is justified, as it may help to decide about chemotherapy. Unfortunately, to perform calculations according to the Magee equation, data that are usually available to a pathologist and not a clinician are needed.

Computer risk calculator

Predict is a useful tool that helps to calculate 1) the risk of breast cancer-related death after 5, 10, and 15 years of follow-up and 2) benefits of various forms of adjuvant systemic therapy in patients undergoing radical surgery [56]. It is an algorithm based on statistical estimation of individual data from almost

6000 patients treated in the United Kingdom (UK) in the years 1999–2003 and validated in a group of 23000 patients. The calculator has been updated several times; currently, version 2.2 is used. The following data are required to calculate the risk: the patient age, menopausal status, expression of ER, HER2, Ki67, histological grade, number of lymph nodes involved, and possible manifestations of clinical symptoms of breast tumor. According to the Cambridge Breast Unit (UK), a decision to administer adjuvant chemotherapy should be made on the basis of a calculation of the potential absolute 10-year gain from this type of treatment. If it is less than 3%, chemotherapy is not recommended, for the value ranging from 3% to 5% it should be considered, and for a gain > 5% — chemotherapy is recommended.

Which adjuvant chemotherapy regimen should be chosen in HR+ HER2– patients? The role of anthracyclines

The role of anthracyclines as a component of adjuvant chemotherapy was confirmed by the results of the 2012 EBCTCG meta-analysis [7]. It showed that the benefit in reducing the risk of death due to breast cancer with the doxorubicin, cyclophosphamide (AC) regimen is similar to that of CMF chemotherapy if 4 courses of AC are used [risk ratio (RR) = 0.98; 95% CI 0.89–1.08]; it exceeds CMF benefit if the total dose of doxorubicin is bigger than 240 mg/m^2 or the total dose of epirubicin is bigger than 360 mg/m^2 (RR = 0.80; 95% CI 0.72–0.88; absolute gain after 10 years — 4.1%). Administration of a higher dose of anthracycline also improved overall survival (RR = 0.84; 95% CI 0.76–0.92; 3.9 percentage points). Adjuvant chemotherapy with anthracycline has also been shown to reduce both the risk of recurrence (RR = 0.73; 95% CI 0.68–0.79; 8%) and the risk of death from any cause (RR = 0.84; 95% CI 0.78–0.91; 5 points) compared to no chemotherapy at all. The cited article also demonstrated the benefit of adding taxoid to AC chemotherapy as sequential treatment applied to both reducing the risk of relapse (RR = 0.84; 95% CI 0.78–0.91; absolute gain at 8 years — 4.6%) and death from any cause (RR = 0.86; 95% CI 0.79–0.93; 3.2%) compared to AC.

Nowadays, the role of taxoid regimens is well established in clinical practice, the omission of anthracyclines because of their expected late cardiac and hematological toxicity is a matter of debate. Unfortunately, most studies evaluating the role of anthracyclines in adjuvant therapy included patients with different phenotypes because, at the time of recruitment, the assessment of HER2, PR, or Ki67 expression was not a standard procedure. Therefore, there are not much data on this issue in patients with HR+ HER2– breast cancer.

One of the first major studies investigating the possibility of omission of anthracyclines in adjuvant therapy was USOR 9735. Its results became the basis for the widespread use of the docetaxel, cyclophosphamide (TC) regimen in clinical practice [57]. Among the study participants, 71% expressed HR, and HER2 status was assessed in only 17% of patients. After seven years of follow-up, the effectiveness of 4 TC cycles was shown to surpass 4 AC cycles in terms of the DFS (81% *vs.* 75%; p = 0.033; HR = 0.74) and OS (87% *vs.* 82%; p = 0.032; HR = 0.69) rates. The prevalence of TC was independent of age, lymph node involvement, or HR expression. It should be noted, however, that greater efficacy of regimens based on both anthracyclines and taxoids had been previously observed. Hence, 4 AC cycles appear to be a suboptimal comparator, and the TC regimen should be rather compared to treatment containing drugs from both groups [7].

Studies aiming to compare adjuvant chemotherapy with sequential or concomitant treatment containing anthracycline and taxoid to 6 cycles of TC [58–63] were presented in Table 3.

Unfortunately, as mentioned above, these studies included patients with different cancer phenotypes. The percentage of patients expressing HR ranged from 69% to 92%, and the DBCG07 READ study also included patients with HER2 overexpression [58]. In addition, the specific designs of some studies are worth to be noted. The inclusion criterion in the DBCG07 READ study was normal expression of the *TOP2A* gene, and in the HORG study, chemotherapy in the control arm was used in the dose-dense pattern [59]. These were phase III studies, most of which were *non-inferiority*. The results of the studies are contradictory and do not give a clear answer to whether it is possible to give up anthracyclines without worsening treatment outcomes, especially in patients with a higher risk of relapse and death.

In 2023, the EBCTCG published a meta-analysis [64] on this topic. Data from 18103 patients participating in 15 clinical trials were analyzed. It was shown that the addition of anthracycline to chemotherapy with taxoid, compared to anthracycline-free regimens, reduced the relative risk of relapse by 14% (p = 0.0004). This translates into a 2.6% absolute gain after 10 years, regardless of ER expression, age, lymph node involvement or grading. It was also shown that the risk of death due to breast cancer was reduced by 12% (p = 0.027; absolute gain after 10 years — 1.6 %). There was no significant difference in overall survival (p = 0.066).

The authors of the meta-analysis pointed out that the greatest benefit was obtained by patients treated with a combination of anthracycline, docetaxel, and cyclophosphamide. Compared to regimens containing

Table 3. Publications referring to the value of anthracyclines in adjuvant chemotherapy for luminal carcinoma. Sequential or concomitant treatment containing anthracycline and taxoid was compared to anthracycline-free taxoid-based chemotherapy

Study	N	Patients' characteristics	Treatment	Results/conclusions
Ejlertsen 2017, DBCG07 READ Phase III [58]	2012	Normal *TOP2A* gene, ≥ 1 risk factor: N+ (55%) or N0 and ≤ 39 years of age/T ≥ 20 mm/G2–3/ER–/HER2+ (11%)	3 × EC (90/600) → 3 × D (100) *vs.* 6 × TC (75/600)	TC has not been proved to be more effective (5 DFS, DDFS and OS) Subgroup analysis: greater benefit of TC in premenopausal and G3 patients
Mavroudis 2016, HORG Phase III, non-inferiority [59]	650	HER2– and N+ (N1–3 in 63% of patients) HR+ in 88% of patients	4 × ddFEC (500/75/500) → 4 × ddD (75) *vs.* 6 × TC (75/600)	It has not been proved that TC is not worse than ddA + T (3y DFS 91.1% *vs.* 89.5%; HR = 1.147; 95% CI 0.716–1.839; p = 0.568)
Blum 2017, ABC trials Phase III, non-inferiority [60]	4242	HER2– HR+ 69%, N0 41%, N1–3ww 44%, G3 51%	TaxAC *vs.* 6 × TC (75/600)	It has not been proven that TC is not worse than TaxAC (4y IDFS 88.2% *vs.* 90.7%; HR = 1.202; 95% CI 0.97–1.49) Unplanned subgroup analysis: TC not worse in patients HR+ N0
Harbeck 2017, WSG Plan B Phase III, non-inferiority [61]	2449	HER2–, ≥ 1 risk factor: N+ or N0 and ≤ 35 years/T ≥ 20 mm/G2–3/ ↑uPA/PAI-1; for patients HR+ pN0-1 RS > 11 according to Oncotype DX HR+ in 82% of patients	4 × EC (90/600) → 4 × D (100) *vs.* 6 × TC (75/600)	TC not worse than EC → D (but during the study a protocol correction in the statistical analysis)
Janni 2018, WSG Plan B + SUCCESS C — pooled analysis [62]	3547	–	–	No differences in DFS and OS Subgroup analysis: longer DFS and OS with sequential treatment in pN2-3 patients, especially if lobular carcinoma
Yu 2021, phase III, non-inferiority [63]	1571	pT1-3N+ or N0 with an additional risk factor HR+ in 92% of patients (luminal A — 21%, luminal B — 71%)	4EC → 12 × pacliataxel *vs.* 3FEC → 3T *vs.* 6 × TC (75/600)	TC non-inferior to 4EC-12P (5y DFS 85% *vs*. 85.9%; HR = 1.05; 90% CI 0.79–1.39; p = 0.048)

CI — confidence interval; D — docetaxel ; ddFEC — dose dense 5-fluorouracil, epirubicin and cyclophosphamide; ddD — dose dense docetaxel; DDFS — distant disease free survival; DFS — disease free survival; EC — epirubicin and cyclophosphamide; ER — estrogen receptor; HR+ — hormonal receptor expression positive; HR — hazard ratio ; IDFS — invasive disease free survival; OS — overall survival; uPA/ PAI-1 — urokinase-type plasminogen activator/plasminogen activator inhibitor-1 ; RS — recurrence score; TC — docetaxel and cyclophosphamide

a similar cumulative dose of docetaxel with cyclophosphamide but without anthracycline, there was a 42% lower relative risk of relapse (p < 0.0001; absolute gain at 10 years — 8.7%) and a 35% lower risk of death due to breast cancer (p = 0.0034; absolute gain — 4.2 %). The efficacy of anthracycline and taxoid administered sequentially, was similar to that of chemotherapy with a higher cumulative dose of docetaxel and cyclophosphamide without anthracycline in terms of the risk of recurrence (RR = 0.94; 95% CI 0.83–1.06) and death (RR = 0.92; 95% CI 0.77–1.09). These differences may have been due to the use of higher cumulative doses of anthracycline and taxoid if given in concomitant way compared to sequential regimens. The authors noted that regimens with higher cumulative doses and higher dose intensity were more effective.

The authors also assessed the risk of acute myeloid leukemia, and it was 0.18% in patients treated with anthracyclines compared to 0.03% in patients treated with non-anthracycline regimens (p = 0.013), which corresponded to approximately 1 additional case in 700 patients. In two studies using chemotherapy with docetaxel and cyclophosphamide with or without anthracycline, the incidence of adverse events G ≥ 3 was similar (50.1% *vs.* 49.7%).

Taken together, the above data indicate that 4 cycles of TC are a more advantageous option than 4 cycles of AC, and sequential treatment with taxoid and anthracycline is more effective than 4 cycles of TC. Sequential chemotherapy compared to 6 cycles of TC is probably associated with slightly higher efficacy. Results of the cited meta-analysis indicate a benefit of concomitant

administration of anthracycline and taxoid, as in the doxorubicin and docetaxel (AT) or doxorubicin, docetaxel and cyclophosphamide (TAC) regimens, but it should be remembered that this treatment is more toxic. The efficacy of the TAC regimen (6 cycles) compared to the doxorubicin, 5-fluorouracil and cyclophosphamide (FAC) regimen in patients with lymph node involvement was documented in the study by Martin et al. [65]. It is worth noting that the TAC regimen was administered with antibiotic or granulocyte growth factor prophylaxis. Despite this, febrile neutropenia occurred in more than 20% of patients receiving the TAC regimen. Treatment was associated with a significantly higher incidence of other hematological and non-hematological complications.

Cyclin-dependent kinase 4/6 inhibitors in adjuvant therapy

Cyclin-dependent kinase 4/6 inhibitors (iCDK4/6) in combination with the first-line or second-line palliative HT are currently the 1st choice drugs in patients with HR expression without HER2 overexpression. Palbociclib, ribociclib, and abemaciclib added to an aromatase inhibitor (AI) or to fulvestrant significantly prolong progression-free survival (PFS) compared to hormone therapy alone [66–72]. Moreover, the addition of abemaciclib to fulvestrant [72] and the addition of ribociclib to fulvestrant [71] or to AI [67, 69, 71] prolongs OS. This significant improvement in prognosis for patients with metastatic breast cancer made researchers focus on the use of iCDK4/6 in adjuvant therapy, particularly in patients at high risk of early recurrence.

Each of the listed drugs has been tested for the aforementioned indication.

Abemebaciclib and ribociclib are currently approved for adjuvant therapy based on the results of the MonarchE and NATALEE studies. However, palbociclib was first tested in the treatment of early breast cancer. Its combination with adjuvant HT has been the subject of two clinical trials, both of which were found to be negative.

Palbocyclib

The randomized phase III PALLAS study aimed to determine the value of adding palbociclib to adjuvant HT in HR+ HER2– patients with stage II and III (TNM IIA 18% *vs.* IIB 32% *vs.* III 50%) [73]. The study included patients who had completed local treatment and perioperative chemotherapy [neoadjuvant chemotherapy in 34% of patients (inclusion in the study regardless of pathological response), adjuvant chemotherapy in 50% of patients]. According to the inclusion criteria, HT had to be started within 12 months of diagnosis, and inclusion in the study had to begin within 6 months of the HT commencement. In total, 5796 patients were assigned in equal numbers to each arm. They received 2-year palbociclib treatment (125 mg/d after, days 1–21, cycle lasting 28 days) in combination with HT or HT alone. Hormonal treatment had to last at least 5 years. Forty-six percent of patients included in the study were premenopausal; 67% of participants started with AI. In 22% of patients, a gonadotropin-releasing hormone analogue (aLHRH) was used. The primary endpoint of the study was IDFS, secondary i.a.: DRFS and OS. A final analysis of the results, after 31 months of follow-up, showed no significant differences in treatment outcomes in the two arms. The 4-year IDFS rates were 84% in both groups (HR = 0.96; p = 0.65). No differences were found in the secondary endpoints, either. The subgroups analysis did not show any differences in IDFS results [stratification, i.a. depending on the stage (I + IIA and IIB + III), nodal status, grading, use or absence of chemotherapy or age (≤ 50 and > 50 years)]. No new adverse reactions were reported with palbociclib. An additional preplanned subgroup analysis did not demonstrate the benefit of palbociclib in stage IIA patients.

The phase III PENELOPE-B study enrolled patients with HR expression (≥ 1%), without HER2 overexpression, who did not achieve pCR after preoperative chemotherapy containing taxoid and were at high risk of relapse according to the clinical pathological staging-estrogen receptor grading score (CPS-EG ≥ 3) or CPS-EG 2 and ypN+ (after protocol amendment 9/12/2015) [74]. The CPS-EG response assessment system takes into account the tumor staging before and after surgery, ER expression, and histological grade and has a prognostic value. The same system for assessing response to preoperative chemotherapy was used in the OlympiA study for patients with HR expression. According to the PENELOPE-B study protocol, preoperative chemotherapy had to last at least 16 weeks, including the taxoid part — at least 6 weeks. Adjuvant radiotherapy could be used according to local indications. Patients were assigned to two arms in equal numbers and received 13 cycles of palbociclib or placebo on days 1–21 of a 28-day cycle in combination with HT. The primary endpoint was IDFS. Altogether, 1250 patients were included in the study, 50% of whom were premenopausal. CPS-EG 2 was present in 39% of patients, ypN2-3 in 50% of patients; half of the patients started HT with TAM, and 33% of premenopausal patients received aLHRH. The addition of palbociclib did not significantly improve IDFS (HR = 0.93; p = 0.525), and no differences were found in the subgroup analysis. Adverse reactions mainly included infectious and vascular complications occurring with similar frequency in both arms. Serious fatal adverse reactions were reported in 8 patients (2 in the palbociclib group and 6 in the placebo group).

Abemaciclib

The efficacy of abemaciclib as adjuvant therapy was evaluated in the phase III MonarchE study, which enrolled 5637 HR-expressing patients without HER2 overexpression and at high risk of relapse [75]. The patients underwent surgery and, depending on the indications, radiotherapy and perioperative chemotherapy, which were allowed but not necessary.

The inclusion criteria were:

1) cohort 1 (91% of patients):
— involvement of at least 4 lymph nodes (60% of patients),
— or involvement of 1–3 nodes and at least 1 additional risk factor: tumor ≥ 5 cm or G3
and
2) cohort 2 (9% of patients):
— involvement of 1–3 nodes, Ki67 ≥ 20%, G1–2, T < 5 cm.

Patients with inflammatory breast cancer, occult breast cancer, and a history of thromboembolic complications were ineligible. Before enrollment, the patients were allowed to receive up to 12 weeks of HT after completion of other forms of systemic adjuvant therapy. Enrollment in the study had to take place within 16 months of surgery. Stratification was made on the basis of previous chemotherapy (neoadjuvant, adjuvant, none), menopausal status upon diagnosis, and the region in which the study was conducted (North America/Europe, Asia, others). Patients were assigned to two arms in equal numbers — standard HT with or without abemaciclib (150 mg, 2 times daily for 2 years). After that, HT continued to be applied for a total of 5–10 years; the "crossover" was not allowed. The primary endpoint was IDFS, the secondary, i.a., DRFS, OS, and safety. The median age of the patients was 51 years, and about 13% of patients were younger than 40 years. The majority of patients in the study were women (99.4%), about 57% were postmenopausal, and 10% of patients did not express PR. Over 95% of patients underwent RT and chemotherapy (including 37% neoadjuvant, 58% adjuvant, and 3.5% both; over 80% of patients were treated with anthracycline and taxoid). In total, 68.3% of patients received AI as the first type of HT (14% in combination with ovarian suppression), and 31.4% received TAM (7.6% with OFS). Ovarian suppression was used in about 22% of patients. Fourteen percent of patients received drugs affecting bone metabolism.

A preplanned efficacy interim analysis showed a benefit of abemaciclib in the 2-year IDFS range in the treatment population (92.2% *vs.* 88.7%; p = 0.01; HR = 0.75). After a longer follow-up (median 42 months), a sustained significant benefit was noted from the addition of abemaciclib to complementary HT. The values of 4-year IDFS were 86% *vs.* 79.4%, respectively (HR = 0.664; p < 0.0001). A similar number of deaths was recorded in both groups (5.6% and 6%, respectively; HR = 0.929; p = 0.50). At 54 months of the follow-up, the benefit of abemaciclib (IDFS HR = 0.680; 95% CI 0.599–0.772 and DRFS HR = 0.675; 95% CI 0.588–0.774) was maintained, and the absolute differences in the 5-year IDFS and DRFS rates were 7.6% and 6.7%, respectively. Fewer deaths were reported in patients receiving iCDK4/6 (208 *vs.* 234), but the difference was statistically insignificant [76]. In cohort 1 defined by clinicopathologic risk factors, experimental treatment reduced the relative risk of invasive disease by 35% (HR = 0.653), and in cohort 2 defined, i.a., by high Ki67 expression, by 23% (HR = 0.773). The relative risk reduction in distant recurrence in both cohorts was 35% (HR = 0.652) and 24% (HR = 0.764), respectively. Furthermore, in patients from cohort 1, Ki67 expression was assessed in pre-treatment biopsy material, and its value appeared to be prognostic, but not predictive, for treatment with abemaciclib. Two thousand and three patients demonstrated a high Ki67 value, whereas in 1914 patients the value was low. In both subgroups, a similar reduction in the risk of invasive disease was achieved with the use of iCDK4/6. In the first subgroup, the values of 4-year IDFS were 83.6% *vs.* 74.7% (HR = 0.618), and in the second subgroup, they were 88.8% *vs.* 82.4% (HR = 0.624) [77]. A subgroup analysis during the 1st efficacy interim analysis suggested a lower benefit in patients ≥ 65 years of age. However, after a longer follow-up, the benefit of treatment with abemaciclib appeared to be similar in both age groups. Older patients were more likely to have poorer performance status and more comorbidities, but the frequency of adverse reactions and quality of life (assessed by the FACT-B form) were similar in both groups. Older patients were more likely to require dose reductions and discontinuation of treatment. On the other hand, the benefit of iCDK4/6 appears to be similar in patients with different abemaciclib dose intensities [78]. The efficacy of abemaciclib depending on the menopausal status of patients was also analyzed. In premenopausal patients, experimental treatment reduced the relative risk of invasive disease by 42% and in postmenopausal patients by 22% (HR = 0.785; p = 0.0268) [79]. The choice of hormonal drug was well-balanced in both arms for both subgroups of patients. Postmenopausal patients were more likely to start hormone therapy with AI (89%) and premenopausal patients with TAM (58%), and few of them received aLHRH (30%). It is also noteworthy that the choice of initial HT in premenopausal patients varied greatly depending on the region (HT started with TAM in 95% of patients in Japan, 78% in Germany, 44% in the US, and 8% in China). In premenopausal patients, the benefit of experimental treatment for

IDFS and DRFS was similar regardless of the type of initiated HT drug (IDFS p = 0.350, DRFS p = 0.335). Yet, a greater number of invasive disease-defining events in the HT alone group were reported for TAM (13%) compared to AI (9%). At the 1st interim analysis, the median duration of treatment with abemaciclib was 14 months. Sixty-eight percent of patients required dose adjustment due to adverse reactions (57% missed doses, 41% dose reduction). Approximately 17% of patients discontinued abemaciclib prematurely due to adverse reactions, but most of them continued HT. In 6% of patients, both kinds of treatment were discontinued, while in the control arm, the proportion of patients with premature HT termination due to toxicity was 0.8%. The most common adverse reactions of abemaciclib were diarrhea, neutropenia, fatigue, and, in controls, arthralgia, hot flush, and fatigue. G3 adverse reactions were reported in 46% of patients treated experimentally (among others, neutropenia 20%, leukopenia 11%, diarrhea 8%) and in 13% of patients in the control arm, respectively. Diarrhea was an adverse reaction significantly more often reported in the quality-of-life questionnaire by patients taking abemaciclib [75]. Thromboembolic complications occurred in 2.3% of patients in the experimental arm and 0.5% in the control arm, including more frequently patients receiving TAM (pulmonary embolism 0.9% *vs.* 0.1%). Interstitial lung disease was reported in a similar number of patients [2.7% (0.3% G3) and 1.2% (1 G3 case), respectively]. Two deaths reported in the study were considered possibly related to abemaciclib toxicity (diarrhea and pneumonia). In accordance with current regulatory indications, abemaciclib in combination with HT is indicated for adjuvant treatment of patients with hormone receptor-positive and non-HER2 overexpressing breast cancer with lymph node metastases and high risk of recurrence. The Ki67 criterion initially included in the indications was withdrawn in March 2023.

Ribociclib

The efficacy of ribociclib in the adjuvant treatment of patients with HR+ HER2– breast cancer was evaluated in a randomized, open-label, phase III NATALEE study [80]. It included patients with stage IIA, IIB, and III breast cancer [according to the criteria of the 8th edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual], regardless of the menopausal status. Patients with stage IIA and unaffected lymph nodes (T2N0) had to have an additional risk factor such as G3 or G2 with Ki67 ≥ 20% or a molecular/genomic high risk (Oncotype DX RS ≥ 26 or high-risk signature in Prosigna/PAM50, MammaPrint, or EndoPredict tests). One of the exclusion criteria was the previous use of a selective estrogen receptor modulator (SERM). Patients were eligible for the study if perioperative HT was initiated within 12 months before randomization. Possible perioperative chemotherapy and radiotherapy had to be completed at least 14 days before randomization. Patients were equally assigned to two arms; they received ribociclib 400 mg/d (3 weeks on, then 1 week off) + HT (letrozole 2.5 mg/d or anastrozole 1 mg/d, ± goserelin in premenopausal women and men), or HT alone. Treatment with ribociclib lasted 36 months, and with HT at least 60 months. The primary endpoint was IDFS (STEEP criteria), and the secondary endpoints were, i.a., relapse-free survival (RFS), OS, and safety. In total, 5101 patients were enrolled in the study in equal numbers. After a median follow-up of 44 months, in all participants assigned to the experimental arm, ribociclib was discontinued; 63% of patients completed 3 years of the therapy as planned, and 20% of patients discontinued ribociclib treatment due to toxicity. The experimental treatment showed a statistically significant benefit compared to standard HT in terms of IDFS (HR = 0.715; 95% CI 0.609–0.840; p < 0.0001). The rates of 3-year IDFS were 90.8% and 88.1%, respectively (absolute gain of 2.7%), and the rates of 4-year IDFS were 88.5% *vs.* 83.6% (absolute gain of 4.9%). The benefit of adding ribociclib to HT was noted in the subgroups which were distinguished on the basis of the lymph node involvement status (absolute gain in 4-year IDFS in N0 patients — 5.1%, in N+ patients — 5 %) and stage (absolute benefit in 4-year IDFS in patients with stage II — 4.3%; stage III — 5.9%). The combined treatment was associated with a significant benefit in distant disease free survival (DDFS; HR = 0.715; 95% CI 0.604–0.847). The results for OS are immature [81]. In the experimental arm, the most common adverse reactions were neutropenia and arthralgia, and in the control arm, they were arthralgia and hot flashes.

While 74% of patients with advanced breast cancer taking ribociclib at a dose of 600 mg had a prolonged QTc at any severity, the incidence of this complication was 62% in patients taking ribociclib at a dose of 400 mg. Adding ribociclib to AI (aromatase inhibitor) was associated with maintaining a similar quality of life as in patients receiving HT alone [82].

In September 2024, ribociclib in combination with AI was approved by the Food and Drug Administration (FDA) for adjuvant treatment of patients with HR+HER2- stage II-III breast cancer with a high risk of recurrence.

It is worth noting that there are several differences in registration studies of abemaciclib (MonarchE) and ribociclib (NATALEE) which may affect the choice of therapy for individual patients.

In the NATALEE study, the duration of treatment with a iCDK4/6 was longer than in MonarchE

(3 *vs.* 2 years). In addition, the ribociclib study used broader inclusion criteria. Only patients with lymph node involvement were eligible for the MonarchE study, also an additional risk factor was required in patients with the N1 nodal stage. Patients at stages III, IIB, and IIA (N+) were included in NATALEE, and an additional risk factor was required in patients IIA (N0). According to these, adjuvant ribociclib treatment could be indicated in up to 45% of patients with early breast cancer (while abemaciclin only in 10%). Thus, a much larger group of patients at relatively low risk of relapse would be exposed to long and potentially toxic treatment. In addition, this will certainly pose a serious challenge for institutions financing the therapy.

Moreover, results of molecular tests to assess the risk of recurrence (i.a. Oncotype DX or MammaPrint) in some patients with stage IIA (N0, G2, Ki67 < 20%) were used as inclusion criteria in the NATALEE study. These tests are still not reimbursed from public funds in Poland. The strength of the NATALEE study is the fact that all premenopausal patients received aLHRH with AI because hormonal therapy with ovarian suppression is currently the optimal choice for high-risk premenopausal patients, and its use definitely confirms the effectiveness of therapy in the control arm. Of course, ovarian suppression was mandatory with AI treatment, and a combination of ribociclib with AI was necessary due to increased risk of cardiac complications when ribociclib was combined with tamoxifen.

Olaparib

In patients with HR+ HER2– breast cancer and in the case of *BRCA1/2* germline mutation, adjuvant treatment with olaparib can be indicated. It is estimated that about 5% of unselected breast cancer patients are carriers of pathogenic or possibly pathogenic mutations in these genes. The chance of carrying the mutation is greater if the patient has her own and family history of cancers, especially breast cancer and ovarian cancer. *BRCA1* mutation carriers are characterized by a high predisposition to develop triple-negative cancer, while *BRCA2* mutation carriers have relatively higher chances of developing HR+ cancer. There is evidence that *BRCA 1/2* germline mutations in early breast cancer patients correlate with an increased risk of recurrence [83]. The GeparOcto study included high-risk patients with different phenotypes of breast cancer who were candidates for preoperative chemotherapy. In the case of luminal B breast cancer, one of the inclusion criteria was lymph node involvement. Seventeen percent of the study participants had the HR+ HER2– phenotype, and 14% of them had a germline *BRCA1/2* mutation.

Olaparib registration in adjuvant therapy was based on the results of a double-blind phase III OlympiA study [84]. It included patients without HER2 overexpression with pathogenic or possibly pathogenic germline *BRCA1* or *BRCA2* mutations and high risk of recurrence. The inclusion criteria were as follows: completion of local treatment, including radiotherapy (it had to be completed 2–12 weeks before the commencement of olaparib treatment). Patients were also supposed to complete perioperative chemotherapy (at least 6 cycles) containing anthracycline, taxoid, or both. The use of platinum compound was allowed. In the case of preoperative chemotherapy, its use also as an adjuvant was not allowed. Most (82%) patients participating in the study were diagnosed with triple-negative breast cancer. In such cases, the inclusion criteria were the absence of pCR after neoadjuvant chemotherapy or, in the case of primary surgery, lymph node involvement, or tumor size ≥ 2 cm. Eighteen percent of study participants were diagnosed with HR+ breast cancer (defined as IHC expression in ≥ 1% of breast cancer cells). For these patients, inclusion criteria were involvement of at least 4 lymph nodes in the case of primary surgery and adjuvant chemotherapy, or in the case of preoperative chemotherapy, absence of pCR, and a CPS-EG score of at least 3. The method of its calculation is presented in Table 4. Adjuvant therapy with hormonal drugs (87%) and bisphosphonate was administered according to local recommendations. Altogether, 1836 patients were assigned in equal numbers to two arms; they were treated with olaparib (300 mg 2 days) or placebo for 1 year (52 weeks). Patients were stratified, i.a., depending on HR expression (±), chemotherapy timing (preoperative or adjuvant), and use of platinum compound (yes/no). The primary endpoint was IDFS, and the secondary endpoints were i.a., DDFS, OS, and safety. Most (72%) study participants were carriers of the germline *BRCA1* mutation, 50% of patients underwent neoadjuvant chemotherapy, 93% of patients were treated with anthracycline and taxoid in perioperative treatment, and 26% of patients were treated with platinum; 62% of study participants were premenopausal. Among HR+ patients, 87% had hormonal therapy (tamoxifen 41%, AI 52%, and LHRH 24%), and 45% of patients had ovariectomy before or after randomization. An interim analysis performed after a 2.5-year follow-up showed a significant benefit of experimental treatment in terms of 3-year IDFS (86% *vs.* 77%; HR = 0.58; p < 0.001).

A second interim analysis (median follow-up of 3.5 years) confirmed a benefit in 4-year IDFS (83% *vs.* 75.4%; HR = 0.63) [85]. A significant gain was also shown in 4-year OS (90% *vs.* 86.4%; HR = 0.68; p = 0.009). In HR+ HER2– patients, these values were as follows: the 4-year IDFS rates 80.1% *vs.* 76.6%, and the 4-year OS rates 88 *vs.* 86%, respectively.

Table 4. Method of calculating the pathological staging-estrogen receptor grading score (CPS-EG) ratio

Feature		Points
Clinical stage according to AJCC	0	0
	IIA	0
	IIB	1
	IIIA	1
	IIIB	2
	IIIC	2
Pathological stage according to AJCC	0	0
	I	0
	IIA	1
	IIB	1
	IIIA	1
	IIIB	1
	IIIC	2
Estrogen receptor expression	Lack of expression	1
Histological grade	G3	1
CPS-EG index = total number of points for the following characteristics: clinical stage + pathological stage + ER expression + G		

AJCC — American Joint Committee on Cancer; ER — estrogen receptor

The toxicity data of olaparib were consistent with those reported in previous studies. In the drug group, the dose reduction rate was 25%, compared to 5.2% in the placebo group. Adverse events leading to treatment discontinuation were reported in 10.8% and 4.6% of patients, respectively. The most common adverse reactions leading to olaparib withdrawal were nausea (2.2%), anemia (1.8%), fatigue (1.6%), and decreased neutrocyte counts (1%). Adverse reactions of ≥ G 3 severity reported in patients treated with a PARP inhibitor (iPARP) included anemia (8.7%), neutropenia (4.9%), leukopenia (3.0%), fatigue (1.8%), and lymphopenia (1.3%). Serious adverse reactions occurred in a similar number of patients in the olaparib and placebo groups (8.7% and 8.6%, respectively). Fatal serious side effects were cardiac arrest in one patient treated with olaparib, 1 case of acute myeloid leukemia, and 1 case of ovarian cancer in a patient treated with placebo. Particular attention was paid to adverse reactions such as pneumonitis, pneumonitis after RT, acute myeloid leukemia/myelodysplastic syndrome (AML/MDS), and new primary neoplasms other than AML/MDS. No differences in their frequency were noted in both groups. There were 2 cases of AML/MDS in patients treated with PARPi and 3 cases in patients in the placebo group. Patients in OlympiA reported that the side effects associated with treatment were limited and resolved after treatment discontinuation. Although fatigue reported by patients was more severe in the olaparib arm, no clinically significant difference was found in the assessments performed at 6, 12, 18, and 24 months after the treatment was initiated. Evaluation carried out at 6 and 12 months of the therapy showed higher severity of nausea and vomiting in patients taking olaparib [86].

In germinaline *BRCA1/2* mutation carriers with HR+ HER2– breast cancer, there may be indications for the use of both iCDK4/6 and olaparib in adjuvant therapy. Apart from obvious reimbursement issues, there is a lack of data on the safety of the combination of both therapies, which are toxic to the bone marrow. In practice, it will be necessary to choose one targeted agent. The fact that it prolongs IDFS and OS makes Olaparib use favorable. In addition, data from retrospective studies suggest that the efficacy of cyclin-dependent kinase 4/6 inhibitor in palliative treatment of breast cancer may be lower in carriers of pathogenic germline *BRCA1/2* mutations compared to the general population and patients with the wild types of these genes [87, 88].

Conclusions

In patients with HR+ HER2– breast cancer, regardless of the risk of recurrence and indications for other types of adjuvant systemic therapy, adjuvant HT is the standard of care. Currently, we have data on the effectiveness of various hormonal treatment strategies. The choice of hormonal drugs depends on the patient's menopausal status, expected toxicity, but also the risk of relapse [89]. Postmenopausal patients benefit more from AI administered for 5 years or for shorter period sequentially with TAM compared to TAM applied for 5 years, regardless of the stage. Prolongation of hormone therapy with AI and/or TAM by over 5 years improves DFS with no effect on OS, and the benefit is particularly evident in patients with more advanced stages. In premenopausal patients, on the other hand, ovarian function suppression (OFS) increases the efficacy of oral medications and is necessary when using AI. Regardless of the patient's menopausal status, extending TAM to 10 years, compared to TAM 5 years, is associated with an additional benefit in DFS and OS.

In addition to HT, in patients with HR+ HER2– breast cancer with a high risk of relapse, adjuvant chemotherapy and targeted treatment with abemaciclib or ribociclib or olaparib may be indicated. Although inclusion criteria for targeted therapies have been defined in registration studies, indications for chemotherapy are not clearly

Table 5. Possibilities of systemic adjuvant therapy in patients with HR+ HER2– breast cancer depending on the risk factors

Risk factor	Severity		
ER expression	< 10%	> 10%	
PR Expression	< 20%		≥ 20%
Histological grade	G3	G2	G1
Ki67	≥ 20%		< 20%
pN	N2	N1	N0
pT	≥ T3	T2	T1
Oncotype DX RS (optional)	≥ 26	11–25	0–10
Treatment			
Postmenopausal patients	AI or TAM → AI or AI → TAM better than TAM HT ≥ 5 lat (± bisphosphonate)		TAM (if it meets all of the above)
	± chemotherapy		–
Premenopausal patients	OFS + AI/TAM (± bisphosphonate)		TAM (if it meets all of the above)
	Chemotherapy	Chemotherapy (N1 or RS ≥ 16)	–
± 1 of the targeted drugs regardless of the menopausal status In Poland, only olaparib is reimbursed	Abemaciclib N2 or N1 + T3/ G3	-	–
	Ribociclib — TNM III, IIB, IIA (T0–1N1 or T2N0 and G3/Ki67 ≥ 20%/ RS ≥ 26)		–
	Olaparib for *gBRCA1/2*mut+ patients N2 or non-pCR and CPS + EG ≥ 3	–	–

AI — aromatase inhibitor; CPS + EG — pathological staging-estrogen receptor grading score; ER — estrogen receptor; G — grading; *gBRCA1/2mut+* — pathogenic or possibly pathogenic germline mutations in *BRCA1* or *BRCA2* genes; non-pCR — lack of pathologically confirmed complete response after preoperative chemotherapy; OFS — ovarian function suppression; PR — progesterone receptor; RS — recurrence score; Tam — tamoxifen

expressed and are based on results of numerous clinical trials conducted over decades.

Clinical features of low risk of dissemination and death speak against the use of chemotherapy: high expression of HR, G1 and low proliferation, lack of lymph node involvement, and primary tumor size up to 2 cm. Indications for chemotherapy can result from low expression of HR, G3, high proliferation, massive lymph node involvement, and the size of the primary tumor over 5 cm. In addition to the above-mentioned extreme clinical situations, there is a huge group of patients with intermediate-risk features, which does not facilitate making decisions about chemotherapy. A molecular test can be helpful, especially in their case. Among the various tests available on the market, Oncotype DX and MammaPrint seem to be optimal because their role in the decision-making algorithm was confirmed in prospective studies. These tests are indicated for patients with HR+HER2- breast cancer and stage pT1-3N0-1 if postmenopausal or pT1-3N0 if premenopausal. In Poland, molecular tests are not reimbursed from public funds.

Bisphosphonate is an additional option for adjuvant treatment. Patients with natural or artificial menopause benefit from its application (reduction in the risk of death due to breast cancer, recurrence, and bone metastases). In all patients, regardless of the menopausal status, bisphosphonates lower the risk of bone metastases and pathological bone fractures.

Computer risk calculators, e.g. Predict, help calculate the risk of death and possible benefit of adjuvant treatment.

Table 5 summarizes the possibilities of systemic adjuvant therapy in patients with HR+ HER2– breast cancer depending on the risk factors.

Article Information and Declarations

Author contributions

S.D.-S.: conception and design, acquisition of data, analysis and interpretation of data, drafting the article, final approval of the version to be published; P.P.: analysis and interpretation of data, drafting the article and revising it critically for important intellectual content, final approval of the version to be published.

Funding

None.

Acknowledgments

None.

Conflict of interest

S.D-S.: declare no conflict of interest.
P.P.: professional fees from Novartis, AstraZeneca, Eli Lilly.

Supplementary material

None.

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