Hormone Receptor-Positive / HER2-Negative Early Breast Cancer High-Risk Population: An Algorithm for Optimization Systemic Adjuvant Treatment Based on 2022 Updates

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ABSTRACT: Prognostic and predictive factors for early and late distant distance recurrence risk in estrogen-receptor positive and HER2-receptor negative early breast cancer are well known, but not all these variables work equally for the prediction. The following are the most widely accepted variables for categorizing risk levels: clinic-pathologic features (tumor size, lymph node involvement, histological grade, age, menopausal status, Ki-67 expression, estrogen, and progesterone expression), primary systemic treatment response (pathologic response and/or Ki-67 downstaging), and gene expression signatures stratification. Treatment guidelines from cancer societies and collaborative groups, online predict-tools, real-world data and experts' opinion recommends different adjuvant strategies (chemotherapy, endocrine therapy, ovarian suppression, olaparib, or abemaciclib) depending on the low (< 10%), intermediate (10%-20%) or high-risk of distance recurrence at least in the first 5 years. Multiple randomized prospective trials were updated in 2022, that evidence allow us to perform a stratification of risk in pre- and postmenopausal women with estrogen-receptor positive and HER2-receptor negative early breast cancer based on a combination of clinic-pathologic features and genomic assays and guide the adjuvant systemic treatment recommendation for those with high risk.

KEYWORDS: Estrogen-receptor positive, early breast cancer, high risk, adjuvant treatment

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Introduction

Nowadays, there is not a unique definition of clinical high risk (cHR) of systemic recurrence in estrogen-receptor positive (ER+) and HER2-receptor negative (HER2–) early breast cancer (EBC). There are so many guidelines from different cancer societies and collaborative groups, online predict-tools, real-world data, and experts' opinion that arbitrarily define the high risk of distance recurrence cut-off value between 10% and 20%, specifically high risk over 20%. Some have coincidences, but there is still a lack of a consensus. Clinical and pathological features such as tumor size, lymph node (LN) involvement, Ki-67 and hormone-receptors expression, histological grade (G), age, menopausal status, and primary systemic treatment (PST) response are the most well-known risk factors. Lately, the gene expression signatures (GES) have come to reclassify patients in low, intermediate, or high risk of relapse according to genetic factors more than the heterogenous clinicopathological criteria; unfortunately its use in daily practice is still limited due to their costs and clinical utility (prognostic value with or without predictive value).

On the contrary, there are some online validated tools, such as Adjuvant! Online (no longer available), PREDICT Breast Cancer tool (https://breast.predict.nhs.uk),[1] CTS5 Calculator (late distant recurrence prediction, https://cts5-calculator.com)[2] INFLUENCE 2.0 (https://pubmed.ncbi.nim.nih.gov/34338943/)[3]and others, which help physicians and their patients to quantify the risk of local and/or distance recurrence, the risk for a secondary breast cancer, or the potential benefit of specific adjuvant treatments, becoming in a decision-making support.

Furthermore, it is not only important the absolute risk of recurrence, but also about the distribution of early (⩽ 5 years) and late distant recurrence (beyond 5 years) to design a tailored-adjuvant systemic strategy for each patient.

The aim of this article is to present the common definition of cHR and to present a treatment algorithm based on last update of clinical trials.

Genomic Definition of High Risk

Several GES have demonstrated their clinical utility to identify patients with genomic low (gLR) or high risk (gHR) that benefit with adjuvant chemotherapy (ACT). Clinical low risk for ER+ EBC patients was defined using Adjuvant! Online (modified version 8.0, MINDACT's criteria) as greater than 88% breast cancer specific survival capability at 10 years, without systemic therapy to account for the average absolute benefit of adjuvant endocrine therapy (AET).

Two important randomized and prospective trials utilized the same definition to include patient with high or low clinical risk, MINDACT study[4] (with MammaPrint and BluePrint, MP/BP) and TAILORx study[5] with Oncotype Dx Recurrence Score (RS), similar studies but with different design looking

for prognostic and predictive value of the GES over the clinical stratification. For ER+ pN0, cHR was defined by T > 2 cm and G2 or G3, T > 1 cm and G3, or T > 3 cm and G1 in both studies. For ER+ pN1, only in the MINDACT trial, cHR was defined by T > 2 cm and G1, and G2 or G3 with any size. In both trials, Ki-67 expression was depreciated and the age was considered for subgroup analysis.

For MP/BP, the classification of genomic risk is dichotomic, gLR or gHR despite LN involvement. For Oncotype Dx, the genomic risk is stratified in categories, the low RS (gLR): 0 to 10, 11 to 15, 16 to 20, 21 to 25, and high RS ⩾26 (gHR). In the last update of TAILORx study, a new subgroup of patients with age ⩽ 50 years and a RS between 21 and 25, jumped from gLR to gHR despite low or high clinical risk. The absolute benefit with ACT in terms of iDFS ranged from 6% to 12% at 9 years of follow-up.[6]

The SWOG-S1207 trial evaluated the potential benefit of adding 1 year of everolimus (mTOR inhibitor) to AET in four cHR and gHR subgroups of patients defined by (a) T ⩾ 2 cm, pN0-pN1mic, and RS > 25 or MammaPrint-high; (b) pN1 and either: RS > 25, MP-high or G3; (c) ⩾ 4 positive LN; and (d) neoadjuvant chemotherapy (NCT) and residual disease with ⩾ 1 positive LN (ypN+). The final overall analysis recently published demonstrated no benefit of everolimus plus AET in the adjuvant setting.[7] The S1207 study included 32% of premenopausal patients, after a median follow-up of 50.5 months, everolimus was associated with improved iDFS (hazard ratio [HR] = 0.63 [95% confidence interval [CI]: 0.43-0.93]) and overall survival (OS; HR = 0.48 [95% CI: 0.26-0.88]) in this specific subgroup of patients.[8,9]

The RxPONDER trial analyzed the benefit of ACT in pre and postmenopausal women with ER+/HER2– EBC with cHR (pN1) and gLR defined by RS ⩽ 25. Last update showed no benefit adding ACT among postmenopausal women with pN1 and RS ⩽ 25 (similar results as in TAILORx). On the contrary, premenopausal patients achieved an overall benefit in iDFS with ACT of 5.2%, ranges from 3.9% to 6.2%; because of this result, the recommendation of use Oncotype Dx in premenopausal patients with pN1 is controversial. In addition, the rate of ovarian function suppression (OFS) plus tamoxifen, OFS with an aromatase inhibitor (AI), or OFS plus tamoxifen and an AI within 1 year of study entry was 5%, 12%, and 3%, respectively. It is possible that therapy-induced amenorrhea contributes to the benefit but it should be noted that many women with CT-induced amenorrhea continue to have premenopausal estradiol levels.[10,11]

Is the number of positive LN a determinant of which GES to use?

First, nowadays the use of GES for ER+/HER2– EBC ⩾ 4 positive LN is not recommended in clinical practice, some trials are ongoing in this setting. Second, either MINDACT (48% pN1 patients) and RxPONDER (100% pN1 patients) studies recruited patients with one to three positive LN, the subgroup of patients with three positive LN were underrepresented in both trials, 11% and 9%, respectively. Despite positive results achieved in both studies, an open question persists, is the prospective data enough to offer GES for patients with three positive LN or ACT continues to be the standard of care?

There are different GES with clinical validation studies but without clinical utility due to lack of prospective randomized clinical trials validating their positive or negative predictive power for ACT (PROSIGNA,[7] EndoPredict,[12] Breast Cancer Index [BCI],[13] others), that's why MP/BP and Oncotype Dx are more frequently used world-wide.

Clinical Definition of High-Risk

Classically, a cHR ER+/HER2– EBC are defined as tumors that are bigger than 2 cm and/or has direct extension to chest wall, skin, or both (T4a-d); with high grade, N2/3 nodal involvement, or has a Ki-67 value greater or equal than 20%.[14]

The Early Breast Cancer Trialist Collaborative Group (EBCTCG) meta-analysis (91 trials, n: 71.194 patients) showed outcomes of patients with ER+ EBC with a median follow-up of 20 years after 5 years of adjuvant tamoxifen and were disease-free at 5 years. The cumulative risk of distance recurrence ranges from 13% to 18% in ER+ pT1 pN0 to 41% to 57% in ER+ pT2 pN2.[14]

The BIG 1-98 study, is a four-arm, randomized trial comparing adjuvant letrozole versus tamoxifen (either treatment received for 5 years) and their sequences (2 years of one treatment plus 3 years of the other) for postmenopausal women with ER+ EBC. About 14% of postmenopausal patients included in this trial were cHR, defined by: pT3, pN2-3, G3 or Ki-67 ⩾ 20%.[15]

Several trials with CDK4/6-inhibitors in combination with ET in the neo/adjuvant setting included patients with ER+/HER2– EBC with intermediate and cHR. In Table 1, the inclusion criteria are listed for the most important studies. Some of these studies (Penelope B) use a score called CPS + EG scoring system estimating the relapse probability based on clinical and pathological stage (CPS) + ER status + histologic grade (EG). The scores range from 0 to 6, and higher scores indicating worse prognosis.[16]

The OlympiA trial, allowed world-wide approval of olaparib in the adjuvant setting for germline BRCA1/2-mutated HER2-negative EBC. Two settings were included, patients with residual disease after NCT and patients after ACT. cHR in the HR+ subgroup was defined by (a) pathologic status after NCT: no pCR and CPS + EG ⩾ 3 and (b) patients that performed ACT: ⩾ 4 positive LN.[18]

Currently, the most novel drug family that are participating in the adjuvant scenario are the oral selective ER degrader (SERD). In this sense, the EMBER-4 study, evaluate a new SERD, Imlunestrant as extended ET (EET) after 2 to 5 years of AET, designed for men, pre and postmenopausal women with cHR of late distant recurrence. Three groups were included: (a)

Table 1. CDK4/6 Inhibitors Trials in Early Setting.

STUDY	CLINICAL-PATHOLOGICAL HIGH-RISK INCLUSION CRITERIA	CDK4/6 INHIBITOR
PALLAS[6]	Anatomic stage II or III	Palbociclib for 2 years
NATALEE[17]	Stage IIA: N1, or N0 G3, or N0 G2 if any of the following features: Oncotype Dx RS ⩾26, EndoPredict High Risk, Prosigna/PAM50 High Risk, MammaPrint High Risk or Ki-67 ⩾ 20 Stage IIB or III	Ribociclib for 3 years
PENELOPE-B[16]	Very high risk with residual disease after neoadjuvant treatment (CPS-EG score ⩾ 3 or ⩾ 2 and ypN+)	Palbociclib for 1 year
monarchE[8]	Cohort 1: ⩾ pN2 or ⩾ pN1 and G3 or pT3 Cohort 2: pN1 and Ki-67 ⩾ 20 _ prior NCT permitted.	Abemaciclib for 2 years

Abbreviations: CPS + EG scoring system, clinical and pathological stage (CPS) + estrogen-receptor status + histologic grade; G, histological grade; N, lymph node involvement; NCT, neoadjuvant chemotherapy; T, tumor size.

patients with ⩾ 4 positive LN, (b) patients with one to three positive LN and one other criteria (T ⩾ 5 cm, G3, T > 2 to < 5 cm and G2), and (c) patients without LN compromise and one other criteria (T ⩾ 5 cm, T > 2 to < 5 cm and G3). Recruitment is ongoing.[19]

Ki-67, Role in Clinical Decision-Making

Multiple trials in neo/adjuvant setting tried to reach the optimal prognostic and predictive value, and the right cut-off value of the Ki-67 biomarker.

In the meta-analysis by de Azambuja et al (12.155 patients; 38 studies were evaluable for DFS, and 35 studies for OS), Ki-67/MIB-1 positivity is associated with higher probability of relapse in all patients (HR = 1.93 [95% CI: 1.74-2.14]; $P < .001$), in pN0 patients (HR = 2.31 [95% CI: 1.83-2.92]; $P < .001$), and in LN positive patients (HR = 1.59 [95% CI: 1.35-1.87]; $P < .001$). Furthermore, Ki-67/MIB-1 positivity is associated with worse survival in all patients (HR = 1.95 [95% CI: 1.70-2.24]; $P < .001$), pN0 patients (HR = 2.54 [95% CI: 1.65-3.91]; $P < .001$, and LN positive patients (HR = 2.33 [95% CI: 1.83-2.95]; $P < .001$).[20]

The ADAPT trial stratified HR+/HER2– EBC patients in the neoadjuvant setting based on baseline Ki-67 and Oncotype Dx (RS 0-11 and RS 12-25), and Ki-67 value after short course (3 weeks) of neoadjuvant ET (stratification post-treatment in ET-responders versus poor-responders). Based on endocrine response assessment, patients were selected for prolonged ET or CT before surgery. The 5 years distant disease-free survival (5y-dDFS) in the age < 50 group was 96.8% and 97.4% in the RS 0 to 11 and RS 12 to 25/ET-responders subgroups, respectively. On the contrary, the 5y-dDFS in the age > 50 group was 96.1% and 95.1% in the RS 0 to 11 and RS 12 to 25/ET-responders subgroups, respectively. The trial allowed to identify a subgroup of low-risk premenopausal patients that could avoid CT in the early setting.[21]

Nowadays, Ki-67 needs to be used together with tumor burden and biology, and no single validated Ki-67 baseline cut-off value for clinical decision-making.

Are All Premenopausal Patients Considered High Risk?

Two of the main studies for premenopausal patients, SOFT and TEXT trials, evaluated the role of ET versus ET plus OFS or ovarian ablation (OA), included 17% and 26% of patients with cHR criteria, respectively. Similar criteria of the BIG 1-98 study (pT3, pN2-3, G3 or Ki-67 ⩾ 20%), including age under 40 years, and progesterone-receptor expression (PR) sub-analysis. At 8 years of follow-up, the PR expression showed a negative interaction with distance recurrence rate, the lower the expression, the higher incidence of distance recurrence, range from 15% to 20% with PR-expression of 20% to 49% and < 20%, respectively.[22]

There were no prospective trials evaluating the right adjuvant systemic treatment for very young women (⩽ 35 years). Several questions remain unanswered in this subgroup of patients regarding who benefits for ACT, who needs OFS/OA plus tamoxifen or AI, and is there a place for only adjuvant tamoxifen.

Nowadays, just by the age, most of them received ACT with or without OFS/OA plus ET. Only by expert panel recommendation, ACT may be spare in the subgroup of very young with ER+/HER2–, pT1, pN0, G1, lymph-vascular invasion absent and low Ki-67 expression (Luminal-A-like).[23,24]

Degree of Absolute Benefit With Adjuvant Systemic Treatment and Subgroup Analysis in Clinical Trials

Adjuvant chemotherapy

The true role of giving ACT to patients with ER+ EBC has been better defined in recent years. The use of GES in patients

with low, intermediate, or high clinical risk has allowed for optimization of treatment in patients with gHR or gLR.[25]

The EBCTCG conducted an individual patient meta-analysis with over 37 000 patients, randomizing adjuvant polychemotherapy regimens with standard regimens versus increasing the frequency of administration, demonstrating a decrease in the risk of recurrence, breast cancer-specific mortality, and all-cause mortality at 10 years of 28.0% versus 31.4% (relative risk [RR] 0.86, 95% CI: 0.82–0.89, $P < .0001$); 18.9% versus 21.3% (RR 0.87, 95% CI: 0.83–0.92, $P < .0001$), 22.1% versus 24.8% (RR 0.87, 95% CI: 0.83–0.91, $P < .0001$), respectively. Therefore, the use of dose-dense regimens is recommended in patients under 70 years of age, opting for an anthracycline-based, alkylating, and taxane-based regimen.[26]

In recent years, several collaborative groups have attempted to de-escalate the use of anthracyclines.

The PlanB, SUCCESS, and MASTER studies showed that the combination of cyclophosphamide plus docetaxel (TC) for four to six cycles can be a safe option with fewer adverse effects in patients with discordant cLR/gHR and for those with pN1.[27-30]

ABC Trials is a series of three adjuvant trials, women were randomly assigned to TC for six cycles (TC6) or to a standard doxorubicin and cyclophosphamide (AC) with a taxane (TaxAC) regimen. US Oncology Research (USOR) 06-090 compared TC6 with docetaxel, doxorubicin, and cyclophosphamide (TAC6). National Surgical Adjuvant Breast and Bowel Project (NSABP) B-46-I/USOR 07132 compared TC6, TAC6, or TC6 plus bevacizumab. NSABP B-49 compared TC6 with several standard AC and taxane combination regimens. Before any analysis of individual trials, a joint efficacy analysis of TC versus the TaxAC regimens was planned, with iDFS as the primary end point. Patients who received TC6 plus bevacizumab on NSABP B-46-I/USOR 07132 were not included. The median follow-up time was 3.3 years and the HR for TC6 versus TaxAC was 1.2 (95% CI: 0.97-1.49), which triggered early reporting for futility. The 4-year iDFS was 88.2% for TC6 and was 90.7% for TaxAC ($P = .04$). Tests for treatment interaction by protocol, hormone receptor status, and nodal status were negative. The TaxAC regimens improved iDFS in patients with cHR HER2– EBC compared with the TC6 regimen.[31]

Recent long-term analysis of the GIM-2 study was presented at ESMO2022, the trial evaluated four arms of treatment: the pivotal treatment anthracyclines times four followed by taxanes times four, dose-dense (Q2) versus triweekly (Q3), and the efficacy of adding fluorouracil to anthracyclines. Target population, cHR (all LN positive) ER+ EBC. After 15 years of follow-up, in the ER+ population, dose-dense ACT improved outcomes in terms of DFS with an absolute benefit of 7% (62% Q2 versus 55% Q3), HR 0.81 (95% CI: 0.69-0.96, $P = .0129$), and OS with an absolute benefit of 5%, HR 0.78 (95% CI: 0.63-0.96, $P = .0191$). Authors concluded and recommended that dose-dense ACT should be considered for all patients with LN positive EBC irrespective of number of positive LNs and irrespective of ER expression. Similarly, fluorouracil demonstrated that it does not add benefit in DFS, reason why it should be avoided in the anthracyclines scheme.[32]

Frail and older patients ($\geq$ 70 years) are special populations to tailored-adjuvant treatment. HOPE study showed that the use of anthracycline-based, alkylating, and taxane-based regimens had a three times higher relative dose intensity index $\leq$ 85%, resulting in a 11% decrease in 5-year survival.[33]

Adjuvant endocrine therapy

According to ESMO guidelines for the management of ER+/HER2– EBC, more aggressive treatment should not be indicated, considering age as the only factor and the same prognostic and predictive factors should be considered.[34]

In general, luminal tumors in young patients present with larger tumors, greater axillary involvement, and in the luminal subtype with higher histological grade or Ki-67.

In this increased risk of recurrence, different studies have tried to answer the following questions related to adjuvant treatment in premenopausal patients with luminal breast cancer: which patients will we prescribe LHRH analogues? and what's the duration of LHRH analogues treatment?

In the Int 0142 trial, OFS plus ET results in more adverse events such as sexual dysfunction and other menopausal symptoms without improvement in outcomes. In addition, this study was unable to determine long-term benefit because it was closed early, and the included population (pN0) had a lower risk of recurrence.[27]

After 13 years of follow-up, the joint analysis of SOFT and TEXT studies showed that OFS plus exemestane significantly improved DFS and distant recurrence-free interval, but not OS compared with tamoxifen plus OFS. Consequently, the authors suggest that OFS should be considered in selected cases in combination with exemestane (over tamoxifen plus OFS) mainly in cHR patients and should be offered for 5 years.[22,35]

The ASTRRA trial demonstrated positive results in event-free survival with 2 years of treatment with tamoxifen plus OFS. This finding suggests that adding OFS to TAM should be considered for those who remain in a premenopausal state or resume ovarian function after N/ACT and longer follow-up is needed to fully evaluate the OS benefit.[36]

Extended endocrine therapy

After 5 years of AET, breast cancer recurrences continued to occur steadily throughout the study period from 5 to 20 years. The risk of distant recurrence was strongly correlated with the original tumor size, LN status, age and grade, with risks ranging from 10% to 41%.[37]

What evidence indicates that we should consider EET?

Many trials were performed, and many are ongoing to answer this question, in different populations (cHR, gHR, etc), with different duration (7, 8, 10, or 15 years), switch or maintenance same ET, and trying to validate GES to identify residual late distance recurrence risk. MA 17.R, GIM4, DATA, NSABP B-42, IDEAL, ABCSG 16, and other studies are good examples of these strategies. In general, the cHR patients recruited were: 30% to 55% pN1 and 10% to 15% pN2-3. The MA 17.R study, designed to evaluate the longest duration of endocrine blockage, showed DFS benefit in specific subgroups, those who recieved only tamoxifen previously, pN+ and pT2-3, but without any benefit in OS. Another important result was the finding that 7 to 8 years versus 10 years of EET was equal in terms of DFS.[37] In general, the HR ranges in the overall analysis of these trials between 0.78 and 1.00. The counterpart of these strategies are the risk of osteoporosis (8% to 21%), bone fractures (5% to 10%) and the rate of discontinuation 20% to 40%.

The panel experts of ASCO Clinical Practice Guideline recommends that women with pN+ should receive EET including an AI for up to a total of 10 years of AET. Many women with pN0 should be considered for EET despite modest or scanty absolute benefit in OS (consider EET especially after initial 5 years of tamoxifen). A substantial proportion of the benefit for extended adjuvant AI therapy was derived from prevention of second breast cancers. Shared decision-making between clinicians and patients is appropriate for decisions about EET, including discussions about the absolute benefits in the reduction of breast cancer recurrence, the prevention of second breast cancers, and the impact of side effects.[38-40]

Retrospective analysis of tumor block from randomized trials with second- and third-generation GES allowed to identify patients for EET recommendation. From all (Oncotype-DX, EndoPredict, Prosigna/PAM50, Ki-67, IHC4, CTS5 calculator, BCI, others), only BCI-high (BCI between 51 and 100) for pT1-3, pN0, or pN1 without distance recurrence after 5 years AET, validated its prognostic value of late relapse and predicted EET benefit.[41,42]

CDK4/6 inhibitors

The monarchE study evaluated the role of abemaciclib as adjuvant systemic therapy administered for 2 years in combination with AET versus AET alone in pre- or postmenopausal women or men with cHR HR+/HER2– EBC (see Table 1) with or without N/ACT, with an interval of ⩽ 16 months from surgery and ⩽ 12 weeks from the onset of ET.

The primary endpoint was iDFS that was met in the preplanned interim analysis at 15.5 months median follow-up. A statistically significant increase in iDFS was observed in patients receiving the combination, thus granting approval for cohort 1, the largest subpopulation of the study. In a subsequent analysis at 27.1 months median follow-up, 91% of patients in cohort 1 were outside the study treatment period (2 years) with an absolute benefit in iDFS of 2.8%. At 42.0 months of follow-up (cut-off at July 1, 2022), the first interim OS analysis was presented and the iDFS was updated to 4 years. In intention-to-treat, there was a reduction in the risk of developing an iDFS event of 33.6% with an HR of 0.664 (95% CI: 0.57-0.76, $P < .0001$) with an increase in absolute benefit of 6.4% (85.6% in abemaciclib plus ET arm versus 79.4% in ET arm). OS data remain immature with an HR of 0.929 ($P = .5027$).[43,44]

In contrast, palbociclib, another CDK4/6 inhibitor, failed to demonstrate a decrease in iDFS in the PALLAS[45,46] study, which had different selection criteria and a shorter administration time than the monarchE study. A study is currently underway with ribociclib, another CDK4/6 inhibitor that is already approved in first- and second-line metastatic disease, with the intention of demonstrating a decrease in iDFS as the primary outcome in the NATALEE study.[17]

PARP inhibitors

The OlympiA study allowed the approval of olaparib (PARP enzyme inhibitor) as adjuvant systemic therapy in HER2– EBC with cHR of systemic recurrence and pathogenic or probably pathogenic variants of the germline BRCA1 and/or BRCA2 genes. Olaparib versus placebo were administered orally for 1 year after completion of local treatment and N/ACT. Patients had completed at least six cycles of CT, 95% of which were based on anthracyclines and taxanes. The primary endpoint of the OlympiA study was 3 year iDFS. The iDFS at 4 years for the olaparib group was 82.7% compared to 75.4% for the placebo group, the absolute benefit 7.3% (95% CI: 3.0%-11.5%). In terms of overall survival, olaparib showed a significant improvement compared to the control group with a HR of 0.68 (95% CI: 0.47-0.97) and *P*-value .009. The OS at 4 years was 89.8% in the olaparib group and 86.4% in the placebo group, the absolute benefit 3.4% (95% CI: 0.1-6.8%). The ITT population analyses in the subgroup of HR+ patients (18.2% of the intervention group and 17.2% of the control group), had an OS of 89.2% for the olaparib group and 86.3% for the control group with a HR of 0.89 (95% CI: 0.44-1.78) and iDFS of 80.1% for the olaparib group and 76.6% for the control group with a HR of 0.68 (95% CI: 0.402-1.13).

The approval of olaparib by FDA and EMA was made for the global population with inclusion criteria in the study independently of two clear subgroups that did not benefit from the addition of adjuvant olaparib: those who received platinum salts as part of their NCT and the subgroup of patients with HR+/HER2– EBC.[18,47]

mTOR inhibitors

In conjunction with recently published data of the SWOG-S1207 study described above, the phase III randomized trial UNIRAD

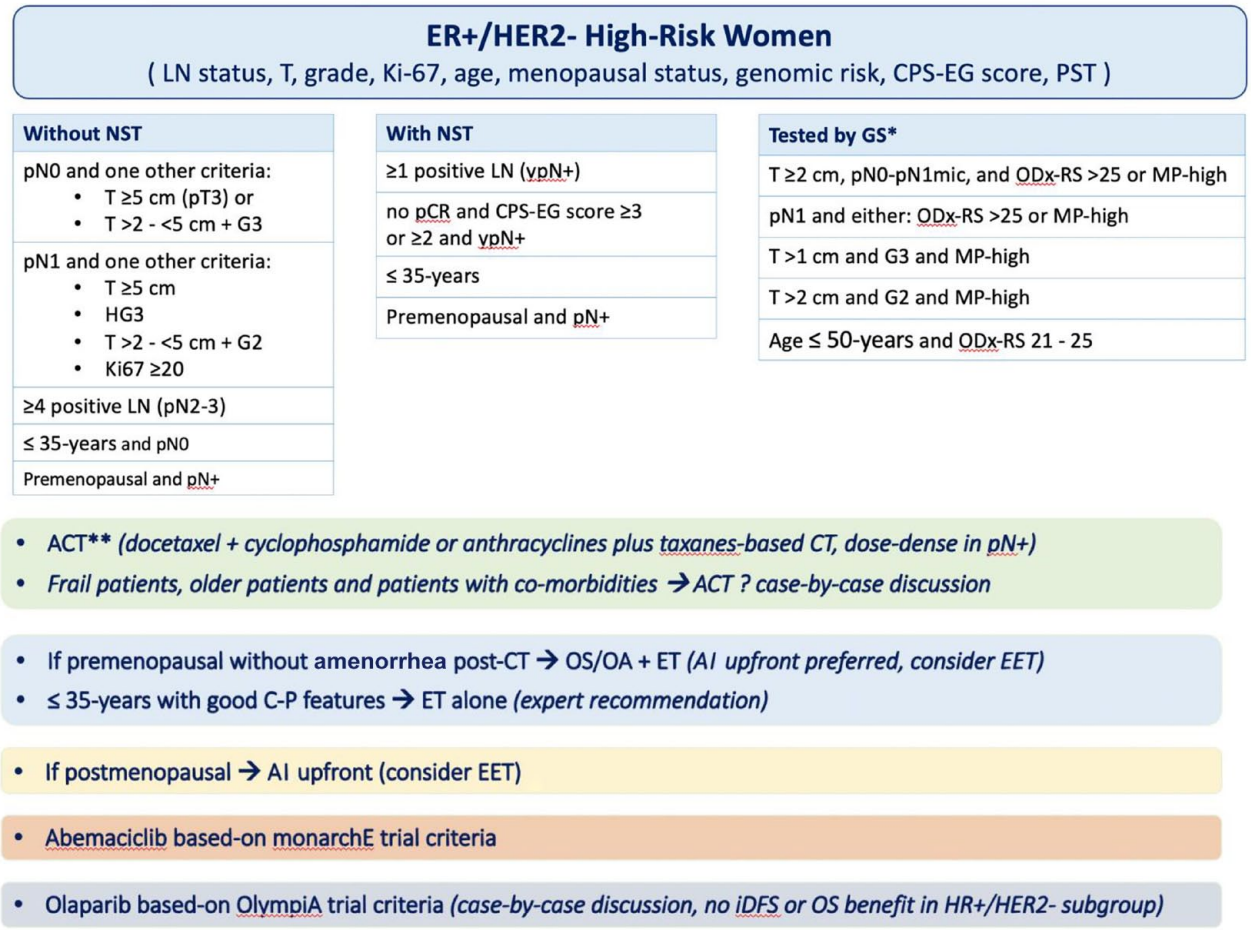

Figure 1. ER+/HER2- High-Risk Breast Cancer and Adjuvant Systemic Treatment Recommendations.
AI indicates aromatase inhibitor; C-P, clinic-pathologic; CPS, CPS + EG scoring system estimates the relapse probability based on clinical and pathological stage (CPS) + estrogen-receptor status + histologic grade (EG); ETT, extended endocrine therapy; HG, histologic grade; iDFS, invasive disease-free survival; LN, lymph-nodes; OS, overall survival; OS/OA, ovarian suppression/ovarian ablation; PST, primary systemic treatment.
*Other GS: EndoPredict high risk, Prosigna/PAM50 high risk.
**ACT, adjuvant chemotherapy, if no PST.

failed to demonstrate benefit adding everolimus to AET in patients with cHR defined by pN2 or ypN1 or pN1 + EndoPredict Clinic high (cut-off value > 3.3). After first interim analysis at 3 years, trial was stopped for futility. DFS was 88% versus 89% for the intervention and control group, respectively (HR 0.95, $P = .77$).[48]

We face all these scenarios in our daily clinical practice. Based on subgroup analysis of clinical trials presented here for cHR ER+/HER2− breast cancer women, we propose a selection criterion for adjuvant systemic treatment, discussing case-by-case with the multidisciplinary team, summarized in Figure 1.

Conclusions

It seems for cHR and/or gHR pre- or postmenopausal women de-escalation strategies in the adjuvant setting is so difficult to achieve and in the last decade the experts' discussions revolve around how to introduce another drug in combination or in sequencing to improve outcomes, but patient profile for each indication is a doubt. In general, the absolute benefit with new treatment strategies (CDK4/6i, PARPi, etc) range from 2% to 8% reducing the incidence of invasive events (huge number of patients needed to treat to spare one recurrence), but with a scanty or null benefit in survival. The cost? First of all, an impairment in quality of life, lower treatment compliance, work and social life disorders; and on the contrary, an economic impact in local health systems. Clearly, until we reach much more and deep understanding of each molecular and phenotypic ER+ subtypes we cannot provide the best benefit with curative intention to every patient. Nowadays, ACT with anthracyclines plus taxanes, AET with AI, EET, and OFS/OA for premenopausal women, abemaciclib or olaparib in selective patients is the standard of care. De-escalation seems not an option.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

Daniel González-Hurtado: Conceptualization; formal analysis; resources; writing – original draft.
Sergio Rivero: Conceptualization; Formal analysis; Writing – original draft; Writing – review & editing.
Juan Carlos Samamé Pérez-Vargas: Supervision; Writing – review & editing.
Fernando E. Petracci: Conceptualization; data curation; formal analysis; investigation; methodology; project administration; supervision; writing – original draft; writing – review & editing.

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