Title page

Title:

Systemic therapy for early breast cancer in older adults: current status and prospects.

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Abstract

Purpose of review

In this review, we describe the evidence on the efficacy and the safety of systemic treatments for the management of early breast cancer (EBC) in older individuals

Recent findings

Chemotherapy has a temporary impact on quality of life for older EBC patients and improves survival outcomes for those with oestrogen receptor (ER)-negative disease. Benefits were seen also in the context of comorbidities, although these may be influenced by selection bias. The Cancer and Aging Research Group-Breast Cancer tool can predict the risk of severe toxicities on chemotherapy in older patients. Gene expression profiling is less frequently used in older adults although it holds promise to better inform patient selection also in this age group.

Post-neoadjuvant systemic therapy and novel agents remains poorly described in older patients with EBC. No disease-free survival benefits were seen in older patients receiving abemaciclib plus adjuvant endocrine therapy.

Summary

Chemotherapy is beneficial for selected older patients with high-risk, ER-negative EBC. Although its impact on QoL is temporary, preferences, higher risk of toxicity and competing risks need to be carefully considered. Open questions remain on novel therapeutic approaches and gene expression profile in older EBC patients and more real-world evidence is warranted.

Keywords

Early breast cancer, older, systemic therapy

INTRODUCTION

Age is a key risk factor for breast cancer.(1) Nonetheless, older individuals are less frequently offered guideline-concordant care with a substantial degree of treatment variation at national and international level.(2) Older adults are heterogeneous and may be affected by comorbidities, functional problems, cognitive impairments, polypharmacy, malnutrition, psychological distress and lack of social support. These issues may have a significant impact on efficacy and safety of anticancer treatments. establishes a major health disparity in this age group.(3) Since chronological age alone is a poor descriptor of fitness in this population, geriatric assessments are instrumental to determine the best course of action where effects on quality of life may frequently overcome survival concerns.(4)

These considerations are relevant also to inform early breast cancer (EBC) management in this population. In this article, we review the evidence on the patterns of use, the efficacy and the safety of systemic treatment agents in older adults with EBC and discuss new insights and their impact on clinical practice. The completed and ongoing studies in this setting are outlined in Table 1-2.

TEXT OF REVIEW

Chemotherapy

Efficacy

Adjuvant chemotherapy is offered less frequently with increasing age.(5) However, a marked selection bias impacts on the interpretation of systemic treatment patterns in this age group, involving a lower prevalence of screen-detected disease at presentation,(6) a more indolent biology,(7) and the less frequent use of gene expression profiling (GEP).(8)

Prospective and retrospective evidence suggest a benefit of chemotherapy on disease-specific survival and overall mortality in older adults with oestrogen receptor (ER)-negative EBC.(9-11) The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis demonstrated that for patients aged ≥70 years, the proportional reductions in risk of recurrence were similar to those seen in younger postmenopausal women but no longer statistically significant.(12) A 15% reduction in mortality for women treated with adjuvant chemotherapy was documented in a retrospective SEER series of patients ≥65 years with hormone receptor (HR)-negative EBC,(9) although those aged ≥70 years were less frequently offered chemotherapy. Similarly, a SEER database analysis of stage I-III patients ≥65 years showed lower chemotherapy uptake after the age of 75 years, along with a survival benefit on chemotherapy only in patients with ER-negative, node-positive breast cancer.(10)

Although prospective trial data are lacking, a pooled analysis of Cancer and Leukemia Group B (CALGB) trials including patients with node-positive EBC showed similar incremental benefits with chemotherapy in older and younger patients with EBC and worse mortality in those ≥65 years.(13) The US Oncology Trial 9735 documented a similar improved efficacy of docetaxel/cyclophosphamide (TC) versus doxorubicin/cyclophosphamide (AC) in older and younger individuals.(14) The French Adjuvant Study Group 08 trial demonstrated a reduction in the risk of relapse for patients ≥65 years with node-positive EBC receiving chemotherapy in addition to tamoxifen with no overall survival benefit.(15) However, prospective studies have previously failed to recruit older patients.(16)

Recently, the Bridging The Age Gap study recruited 3416 women with EBC aged 70 years and older in 56 breast units in England and Wales between 2013 and 2018.(17) The trial included geriatric assessments in order to correlate baseline fitness and tumour risk of recurrence with treatment patterns and recurrence and survival outcomes. Among 2811 patients undergoing surgery, this study documented that only 27.8% of those who were fit and had a high risk of recurrence received chemotherapy, that might suggest under-treatment. A benefit of chemotherapy on metastatic recurrence was observed in unmatched patients with high-risk EBC and in a propensity score-matched analysis adjusting for age, stage and fitness. Nonetheless, no overall or disease-specific survival benefits were seen in the overall population. Consistently with previous analyses, an overall and breast cancer-specific survival benefit was seen only in patients with ER-negative disease.

A national population-based registry analysis investigated the impact of chemotherapy on survival outcomes on data regarding 1130 women aged ≥70 years with primary triple-negative EBC ≥5mm retrieved from the Swedish National Breast Cancer Register, the Swedish Patient Register, and the Swedish Cause of Death Register.(18) In this study, 63.5% of patients did not receive chemotherapy. Similarly to previous data, a significant benefit in breast cancer-specific and overall survival was observed at 5 years for patients receiving chemotherapy versus not in the overall cohort and in a propensity score-matched analysis adjusting for age, tumour size, grade, nodal status and comorbidities.

A recent National Cancer Database propensity-matched analysis including data from women aged ≥70- years with surgically treated stage I-III triple-negative breast cancer diagnosed in 2004-2014 evaluated a similar question.(19) At a median follow-up of 38.3 months, the study showed better overall survival outcomes at 5 years for those receiving chemotherapy compared with those who did not received it. The benefit persisted in a propensity score-matched analysis (adjusting for age, comorbidities, tumour grade, tumour size, nodal status, and receipt of radiotherapy) also for those with node-negative EBC and those with a Charlson-Deyo comorbidity score greater than 0. This study provides further support for the use of chemotherapy in older patients with triple-negative EBC.

Additional evidence is now also available for older patients with luminal EBC. A recent US National Cancer Database (NCD) analysis including 1,592 patients aged ≥70 years with a Charlson/Deyo comorbidity score of 2-3 and node-positive, ER-positive, human epidermal growth factor receptor 2 (HER2)-negative disease undergoing surgery in 2010-2014 investigated the impact of adjuvant chemotherapy on survival outcomes with propensity matching.(20) As expected, this study showed that chemotherapy was offered to younger patients with higher risk EBC. In a matched cohort analysis, the investigators documented no impact of chemotherapy on overall survival; however, better survival outcomes were observed when adjusting for confounding factors including age, comorbidities, facility type and location, stage and use of endocrine therapy and radiotherapy. Nonetheless, selection bias remains a significant limitation of this retrospective analysis.(21)

A 10-year update of the CALGB 49907 trial has also recently been published.(11) In this study, 633 patients aged ≥65 years with EBC were randomized to either standard chemotherapy (four cycles of AC or six cycles of cyclophosphamide/methotrexate/fluorouracil [CMF]) versus capecitabine. Recurrence-free survival rates were superior for those receiving standard regimens compared with those treated with capecitabine, especially in those with HR-negative disease. On the other hand, no differences in overall survival were seen in the context of the effect of competing risks of mortality in an older patient population. This analysis confirms that the use of alternative chemotherapy regimens is not a standard of care in the older age group. The ELDA study showed worse quality of life (QoL) for those receiving docetaxel versus CMF in the absence of any survival benefit.(22) The Ibandronate with or without Capecitabine in Elderly Patients study did not show any survival advantage with the use of oral capecitabine chemotherapy versus ibandronate alone (with endocrine therapy where indicated) in older patients with EBC.(23) Anthracycline-free regimens may be particularly attractive in the older age group to minimise the risk of cardiac toxicity and in view of the superior efficacy of four cycles of TC versus four cycles of AC observed in a recent meta-analysis.(24)

GEP holds promise for the identification of older patients with ER-positive, HER2-negative EBC most likely to benefit from cytotoxic treatments. Recently, a SEER analysis including 363,876 women aged 18-69 years and 147,107 women aged ≥70 years diagnosed with ER-positive disease from 2004 to 2014 evaluated the validity of

OncotypeDx® Recurrence Score (RS) in the older age group.(8) Fewer patients ≥70 years underwent RS compared with their younger counterparts, although its distribution was similar between the two cohorts. In this analysis, the high-risk categorization of patients based on RS predicted higher hazards of death also in women aged ≥70 years but in the older group there was no association of chemotherapy with decreased mortality.

The potential influence of comorbidities on the benefits of using GEP is also a key consideration in older patients. A study including data from population studies and clinical trials simulated the effect of chemotherapy based age and comorbidities in women with HR-positive, HER2-negative EBC with a RS ≥26.(25) The investigators demonstrated that among patients aged ≥65 years, only those aged 65-74 years with no or low/moderate comorbidities derive benefits from the addition of chemotherapy to endocrine therapy. Therefore, GEP and chemotherapy should be considered only in women aged <75 years in the absence of severe comorbidities.

Ongoing studies such as the ASTER70 trial will elucidate the role of GEP in this specific age group.(26) On the other hand, online prediction tools are also commonly used in this setting, although in older patients NHS PREDICT is less accurate to predict outcomes at 10 years, in the context of comorbidities and in those ≥80 years.(27) On the other hand, the Age Gap Decision tool overcomes these limitations with the inclusion of data on comorbidities and activities of daily living in the algorithm.(28)

Finally, post-neoadjuvant systemic therapy options remains poorly investigated in older individuals. The CREATE-X study of adjuvant capecitabine for patients with residual invasive EBC following preoperative chemotherapy recruited patients aged 25-74 years.(29)

Safety

Chemotherapy toxicity and mortality are more frequent in older EBC patients.(30, 31) A chemotherapy duration longer than 3 months is associated with more frequent toxicities.(32) This parameter is included also in the Cancer and Aging Research Group-Breast Cancer (CARG-BC) score.(32) The score includes 8 predictors: anthracycline use, stage, planned treatment duration, abnormal liver function,

anaemia, falls, limited walking and lack of social support. Its validation study enrolled 473 patients aged ≥65 years with stage I-III disease and demonstrated higher rates of grade 3-5 toxicity, hospitalizations and reduced dose intensity in patients with higher risk scores.

Age is a key risk factor for haematological toxicities(30, 33, 34) and primary granulocyte colony stimulating factors prophylaxis is recommended for older adults receiving chemotherapy.(35, 36) Older patients experience higher rates of congestive heart failure on chemotherapy.(37) Age and history of diabetes are also predictors of neurotoxicity on taxanes.(38, 39)

QoL effects are meaningful in older individuals. The Bridging The Age Gap study enrolled 3,416 patients aged ≥70 years diagnosed with operable breast cancer in 2013-2018 who underwent geriatric assessments at trial enrolment.(40) Among 1,520 patients with high-risk EBC, 24.7% received chemotherapy. At 6 months, chemotherapy had a significant negative impact on several QoL domains measured by the European Organisation for Research and Treatment of Cancer (EORTC)-QLQ-C30, BR23 and ELD15 scales and by the EQ-5D-5L scale. However, these effects were no longer significant at 18-24 months in unmatched and matched cohort of patients. This study suggests that chemotherapy has a temporary effect on QoL outcomes for older patients with EBC, which typically resolves within two years. These findings confirm the results of previous analyses showing that the effect of chemotherapy on these outcomes is temporary.(41)

Targeted agents

Anti-HER2 therapy

Adjuvant trastuzumab is beneficial for patients with HER2-positive EBC regardless of age.(42, 43) A 47% reduction in the relative risk of mortality was observed in a meta-analysis of older patients receiving trastuzumab plus chemotherapy versus chemotherapy alone in this setting.(44) Conversely, age and lower left ventricular ejection fraction are risk factors for cardiac toxicity for patients receiving trastuzumab.(45-47) Early treatment discontinuation in 15-40% of patients (especially ≥80 years and in the presence of comorbidities).(48) Nonetheless, the overall incidence of cardiac toxicity remains low and reversible with appropriate medical interventions.(49) Therefore, although adequate cardiac monitoring is crucial in this setting, anti-HER2 agents are standard of care for older patients with early HER2-positive disease as recommended by the International Society of Geriatric Oncology consensus.(50)

The chemotherapy backbone may represent a challenge for older patients with HER2-positive EBC. Anthracycline-free regimens are reasonable in this setting.(50) The RESPECT study randomized 275 patients aged 70-80 years with HER2-positive EBC to trastuzumab alone versus its combination with chemotherapy.(51) At a mean follow-up of 4.1 years, the trial failed to show non-inferiority of trastuzumab alone versus trastuzumab plus chemotherapy. Nonetheless, in this population omitting chemotherapy was associated with a survival loss of less than 1 month at 3 years. The study also documented a detrimental impact of chemotherapy on global QoL at 2 and 12 months, whereas this was no longer observed at 36 months.(52) Therefore, omitting chemotherapy and pursuing single-agent trastuzumab (along with endocrine therapy in case of ER-positive EBC) may be appropriate in vulnerable patients.

The duration of treatment with trastuzumab is a key consideration for older patients. Although 81.7% of older individuals were able to complete a one-year course of adjuvant trastuzumab in a retrospective study, age and comorbidities are associated with earlier discontinuations.(48) No age-specific analyses have been included in the studies investigating shorter courses of treatment.(53-55) Despite one year of trastuzumab remains standard of care,(50) a shorter course may be considered for patients with lower-risk EBC at increased cardiac risk.

Novel anti-HER2 agents remain poorly investigated in older individuals. Only a minority of patients recruited in the trials of pertuzumab, neratinib or trastuzumab emtansine were older.(56-58) Therefore, more research is needed to evaluate their benefit and safety in this age group.

Endocrine therapy

Older patients should be considered for endocrine therapy similarly to their younger counterparts. Nonetheless, age-specific data are sparse and omitting this treatment option might not be detrimental for patients aged 60-74 years with EBC ≤10mm with grade 1 ductal or grade 1-2 lobular histology.(59)

Aromatase inhibitors (AI) have better efficacy compared with tamoxifen.(60) However, myalgia and arthralgia may limit adherence. AI can induce osteoporosis and cardiovascular risk, while tamoxifen may increase the risk of venous thromboembolism, endometrial cancer and fatty liver disease. Despite the role of AIs following five years of tamoxifen is well supported by survival benefits, their impact after using an AI upfront has more modest impact.(61)

Cyclin-dependent kinase 4/6 inhibitors

Cyclin-dependent kinase 4/6 inhibitors are a valuable palliative treatment option also in the older age group.(62) In the curative setting, evidence is still limited. Subgroup analysis of the monarchE study did not confirm any invasive disease-free or distant relapse-free survival benefit in patients ≥65 years which represent 15.1% of those recruited. (63) A longer follow-up/more events are needed to define the role of this strategy in older patients.

CONCLUSION

Whilst the benefit of chemotherapy is well established in older patients with high-risk, ER-negative EBC, its role for those with ER-positive disease is still questionable and supported by limited retrospective data involving substantial selection bias. Additional insight may be provided by a more frequent use of GEP to get a better understanding of tumour biology and predicted benefits on cytotoxic treatments in the context of patients' global health. Although the effect of chemotherapy on QoL outcomes appears to be temporary, the routine implementation of chemotherapy toxicity prediction tools such as CARG-BC offers a unique opportunity to support the use of geriatric assessments to better inform treatment decisions in this population.

The management of EBC in this age group requires careful consideration of a complex framework of needs, including competing risks that may mitigate survival gains, impacts on QoL and functional status and a higher risk of severe toxicities. Therefore, shared decision-making is critical to inform systemic treatment choices in older patients with EBC.

KEY POINTS

- Additional evidence supports the efficacy of chemotherapy in older patients with triple receptor-negative breast cancer.
- Retrospective data show a survival benefit with the use of chemotherapy also in older patients with node-positive, oestrogen receptor-positive disease and comorbidities, although these findings may be influenced by selection bias and lead to significant risk of overtreatment in this population.
- The Cancer and Aging Research Group-Breast Cancer tool is an useful tool to predict the risk of severe complications on chemotherapy for older patients with early breast cancer
- The impact of chemotherapy on quality of life is temporary in older patients with operable breast cancer.
- The role of gene expression profile and novel targeted agents in this setting remains poorly described.
- Adding chemotherapy to trastuzumab is beneficial for older patients with early HER2-positive breast cancer with limited impact on quality of life outcomes.

TABLES

Table 1 – Completed clinical trials of adjuvant systemic therapy for older patients with early breast cancer.

Trial	Accrual (n)	Key eligibility criteria	Design	Geriatric assessment included	Objective(s)	Results
French Adjuvant Study Group 08 (FASG 08) trial	338	Age ≥65 years Operable breast cancer Previous mastectomy/lumpectomy plus axillary dissection Axillary nodal involvement Any hormone receptor status	Randomized phase 3 Arm 1: epirubicin 30mg on day 1, 8, 15 every 28 for 6 cycles + tamoxifen 30mg for 3 years Arm 2: tamoxifen 30mg for 3 years March 1991 – April 2001	No	Primary: 6-year DFS Secondary: 6-year OS	6-year DFS: 72.6% vs 69.3% (p 0.14) 6-year OS: 79.8% vs 79.1% (p 0.41) Risk of relapse 1.93 with Tamoxifen vs Epirubicin-Tamoxifen (p 0.005) Six cycles of Epirubicin completed in 96.9% of patients
Ibandronate with or without Capecitabine in Elderly Patients (ICE) study	1,358	Age ≥65 years pN+ or pN0 with pT≥2cm or grade 2-3 or HR-negative CCI ≤2	Randomised phase 3 Arm 1: capecitabine 2000mg/m^2 on day 1-14 for 6 cycles + ibandronate 50mg po daily or 6mg IV every 4 weeks for 2 years Arm 2: ibandronate 50mg po daily or 6mg IV every 4 weeks for 2 years	No	Primary: 5-year DFS	3-year DFS: 85.4% vs 84.3% 6-year DFS: 78.8% vs 75.0% DFS: HR 1.04 (95% CI 0.84-1.29, p 0.7012)
ELderly Docetaxel Adjuvant (ELDA) Study	302	Age 65-79 years Resected early breast cancer Average to high risk of recurrence	Randomised phase 3 Arm 1: weekly docetaxel 35mg/m2 days 1, 8, 15 every 4 weeks for 4-6 cycles Arm 2: CMF for 4-6 cycles July 2003 – April 2011	Yes	Primary: DFS Secondary: QOL	DFS: HR 1.21 (95% CI 0.83-1.76, p 0.32) OS: HR 1.34 (95% CI 0.80-2.22, p 0.26) Worse QOL on docetaxel vs CMF (nausea/vomiting, appetite loss, diarrhoea, body image, future perspective, treatment side effects, alopecia)

ACTION	4 (planned: 1,000)	Age >70 years WHO PS)-1 Resected early breast cancer High risk of relapse within 5 years ER Allred score ≤5	Randomised phase 3 Randomisation 1: Arm 1: No chemotherapy Arm 2: AC or EC for 4 cycles Randomisation 2 (for Arm 2): Arm A: 3-weekly administration Arm B: 2-weekly administration + pegylated G-CSF	No	Primary: RFS Secondary: DFS, OS, compliance, safety, tolerability, QOL	Trial closed due to poor recruitment
Bridging the Age Gap in Breast Cancer	3,416	Age ≥70 years Operable breast cancer pT1-3 N0-1 M0 No previous early breast cancer within 5 years	Observational 2013 - 2018	Yes	Developing a predictive tool to tailor treatment options for older women according to breast cancer factors and their fitness/frailty Developing a Decision Support Instrument (DESI) to assist older women making informed decisions about their preferred treatment	Chemotherapy given to 27.8% of fit patients with high-risk disease Chemotherapy associated with: Reduced risk of metastatic recurrence (HR 0.36, 95% CI 0.19-0.68) No OS or BCSS benefit In ER-negative patients: improved OS (HR 0.20, 95% CI 0.08-0.49) and BCSS (HR 0.12, 95% CI 0.03-0.44) Negative impact of chemotherapy on QOL at 6 months resolving by 18 months
Cancer and Leukemia Group B (CALGB) 49907 study	633	Age ≥65 years Stage I-III breast cancer pT ≥1cm any HR status	Randomised phase 3 non-inferiority study Arm 1: Capecitabine 2000mg/m^2 on day 1-14 for 6 cycles Arm 2: AC for 4 cycles or CMF for 6 cycles September 2001 – December 2006	No	Primary: 5-year RFS Secondary: OS, BCSS	10-year RFS: 50% vs 56% (HR 0.80, p 0.03) 10-year BCSS: 82% vs 88% (HR 0.62, p 0.03) 10-year OS: 56% vs 62% (HR 0.84, p 0.16)
RESPECT	275	Age 70-80 years Resected early breast cancer HER2-positive	Randomised phase 3 non-inferiority Arm 1: trastuzumab	Yes	Primary: DFS Secondary: OS, RFS, adverse events, CGA	3-year DFS: 89.5% vs 93.8% (HR 1.36, 95% CI 0.72-2.58, p 0.51)

			Arm 2: trastuzumab + chemotherapy (weekly paclitaxel or docetaxel or AC or EC or CMF or TC of docetaxel/carboplatin)			3-year RMST: -0.39 difference (95% CI -1.71-0.93, p 0.56) 3-year RFS: 92.4% vs 95.3% (HR 1.33, 95% CI 0.63-2.79, p 0.53) Clinically meaningful QOL deterioration on chemotherapy at 2 months (31% vs 48%, p 0.0.16) and 1 year (19% vs 38%, p 0.009) Detrimental impact of chemotherapy on global QOL, morale and activity capacity

Abbreviations: DFS: disease-free survival; HR: hormone receptor; CCI: Charlson Comorbidity Index; AC: doxorubicin/cyclophosphamide; CMF: cyclophosphamide/methotrexate/5-fluorouracil; RFS: relapse-free survival; BCSS: breast cancer-specific survival; QOL: quality of life; HR: hazard ratio; CI: confidence interval; ER: oestrogen receptor; HER2: human epidermal growth factor receptor 2; CGA: comprehensive geriatric assessment, EC: epirubicin/cyclophosphamide; TC: docetaxel/cyclophosphamide; RMST: restricted mean survival time; ECOG: Eastern Cooperative Oncology Group; PS: performance status.

Table 2 – Ongoing clinical trials of adjuvant systemic therapy for older patients with early breast cancer.

Trial	Anticipated accrual (n)	Eligibility	Design	Geriatric assessments included	Endpoints	Cooperative group/sponsor	Description	Identifier	Status
Exercise in Older Women With Breast Cancer During Systemic Therapy (BREACE)	100	Age ≥65 years Resected or advanced breast cancer ECOG PS ≤2	Randomised Arm 1: Breast cancer exercise intervention Arm 2: Control November 2018 – December 2021	Yes	Primary: Change in the 30-second chair stand test Secondary: gait speed, walk test, handgrip strength, stair climb, adherence, physical activity, QOL, anxiety/depression, adverse events, survival	Herlev and Gentofte Hospital University of Copenhagen	Investigate the effect of an exercise-based intervention among older participants with breast cancer treated with adjuvant or first-line systemic therapy.	NCT03656731	Recruiting
Cognitive Function in Older Women With Stage I, Stage II, or Stage III Breast Cancer Receiving Hormone Therapy	72	Age ≥65 years Stage I-III HR-positive breast cancer Postmenopausal Suitable for anastrozole or letrozole	Observational case-control October 2007 – January 2011	Yes	Cognitive function	City of Hope Medical Center National Cancer Institute	Study cognitive function in older postmenopausal women with stage I, stage II, or stage III breast cancer receiving hormone therapy and in healthy volunteers	NCT00681928	Completed
A Breast Cancer Treatment Decision Aid for Women Aged 70 and Older	312	Age ≥70 years Primary breast cancer T ≤3cm ER-positive, HER2-negative	Randomised July 2016 – July 2024	Yes	Primary: Change in Decisional Conflict Scale Secondary: Knowledge score, preferences, anxiety, QOL, decision regret, satisfaction, acceptability	Dana-Farber Cancer Institute Beth Israel Deaconess Medical Center	Evaluate a decision aid to help women aged 70 and older decide on treatment for their breast cancer	NCT02823262	Recruiting
Cognition in Older Breast Cancer Survivors: Treatment Exposure, APOE and Smoking History	540	Age ≥60 years Postmenopausal Stage I-III breast cancer	Observational case-control April 2014 – April 2021	Yes	Neurocognitive outcomes	Memorial Sloan Kettering Cancer Center City of Hope Medical Center	Assess cognition in older women who are survivors of breast cancer and either did or did not receive chemotherapy are affected by	NCT02122107	Not recruiting

							treatment, compared to older women who have never had cancer		
Liposomal Doxorubicin Compared With Observation or Cyclophosphamide and Methotrexate in Treating Older Women Who Have Undergone Surgery for Breast Cancer (CASA)	77	Age >65 years Resected early breast cancer Not suitable for endocrine therapy or standard chemotherapy HR-negative Postmenopausal ECOG PS ≤2	Randomised Arm 1: PDL 20 mg/m^2 IV for 16 weeks Arm 2: metronomic cyclophosphamide and methotrexate for 16 weeks Arm 3: No chemotherapy August 2005 – December 2011	No	Primary: BCSS Secondary: adverse events, QOL, DFS, OS, causes of death, sites of failure, second (non-breast) malingnancies	International Breast Cancer Study Group	Compare the breast cancer-free interval in elderly women with resectable, hormone receptor-negative breast cancer treated with PDL vs observation or PDL vs cyclophosphamide and methotrexate.	NCT00296010	Not recruiting
Trastuzumab in Treating Older Women With Early-Stage Breast Cancer	56	Age ≥60 years Early breast cancer HER2-positive ECOG PS ≤2 Life expectancy >6 months	Single-arm November 2008 – January 2019	Yes	Primary: cardiac events Secondary: physiologic biomarkers of heart failure, pro-inflammatory cytokines, QOL, functional status, cognition, mental status, DFS, OS	Cynthia Owusu, MD, Case Comprehensive Cancer Center National Cancer Institute	Study the side effects of trastuzumab and its efficacy in older women with early-stage breast cancer.	NCT00796978	Not recruiting
Elevate!: An Elderly Breast Cancer Cohort Study	200	Age ≥70 years Non-metastatic breast cancer Any subtype	Observational February 2019 – November 2028	No	Adjuvant treatment recommendations Adherence Barriers to treatment and adherence Treatment patterns	Dana-Farber Cancer Institute Susan G. Komen Breast Cancer Foundation	Understanding how the investigators can improve upon breast cancer and health outcomes for older participants with breast cancer.	NCT03818087	Recruiting
Novel Social Media Intervention For Older Br CA Patients	47	Age ≥60 years Stage I-III breast cancer Requiring systemic	Single-arm February 2016 – June 2021	No	Primary: feasibility Secondary: usability, overall	Dana-Farber Cancer Institute CURE Foundation	Evaluating how engaging in an online support community may improve the	NCT02639208	Not recruiting

		anticancer therapy			satisfaction, desirability		experience of older patients receiving chemotherapy		
ATOP Trial: Adjuvant Ado-Trastuzumab Emtansine (T-DM1) for Older Patients With Human Epidermal Growth Factor Receptor 2 (HER2)-Positive Breast Cancer	200	Age ≥60 years Stage I-II breast cancer HER2-positive ECOG PS ≤2	Single-arm August 2018 – January 2025	No	Primary: IDFS at 5 years Secondary: RFS, OS, site of first recurrence, toxicities, cardiac events	Dana-Farber Cancer Institute Susan G. Komen Breast Cancer Foundation Gateway for Cancer Research	Evaluate the efficacy of trastuzumab emtansine in older patients with HER2-positive stage I-III breast cancer.	NCT02414646	Not recruiting
Adjuvant Palbociclib in Elderly Patients With Breast Cancer (Appalaches)	366	Age ≥70 years Stage II-III breast cancer ER-positive HER2-negative ECOG PS ≤2	Randomised phase 3 Arm 1: standard endocrine therapy for ≥5 years + palbociclib 125mg daily for 21 days every 28 days for 2 years Arm 2: standard endocrine therapy for ≥5 years June 2019 – June 2032	Yes	Primary: distant recurrence-free interval Secondary: BCSS, OS, discontinuation rate	European Organisation for Research and Treatment of Cancer	Assess the efficacy of the combination of at least 5 year endocrine therapy and 2 year-palbociclib as adjuvant systemic treatment instead of adjuvant chemotherapy followed by endocrine therapy in older patients with stage II-III ER-positive/HER2-negative early breast cancer.	NCT03609047	Recruiting
Adjuvant Systemic Treatment for (ER)-Positive HER2-negative Breast Carcinoma in Women Over 70 According to Genomic Grade (GG): Chemotherapy + Endocrine Treatment Versus Endocrine Treatment (ASTER 70s)	2000	Age ≥70 years Resected early breast cancer ER-positive HER2-negative ECOG PS ≤2	Randomised Arm 1: endocrine therapy Arm 2: endocrine therapy + chemotherapy (TC, AC, MC) March 2012 – March 2026	Yes	Primary: OS Secondary: DFS, EFS, toxicity, geriatric assessment, mortality, QOL, cost-effectiveness	UNICANCER	Evaluate the benefit of adjuvant chemotherapy on overall survival for elderly patients with breast cancer, in a sub group with a high risk of relapse according to Genomic Grade test.	NCT01564056	Not recruiting

Gene Polymorphisms and Gene Products as Biological Markers of Aging and Correlation With Clinical Geriatric Assessment, Tolerance of Chemotherapy and Outcome in Elderly Breast Cancer Patients (EBS)	110	Age ≥70 years Early breast cancer Suitable for adjuvant systemic therapy	Observational case-control September 2012 – September 2014	Yes	Impact on biological markers	Universitaire Ziekenhuizen Leuven	Evaluate the biology of aging in breast cancer patients, and study the impact of chemotherapy on aging related blood biomarkers.	NCT00849758	Completed
An Open Label Phase II Trial to Investigate the Cardiac Effects of Pegylated Liposomal Doxorubicine (Caelyx) in Elderly Breast Cancer Patients With New Imaging and Biochemical Techniques	16	Age ≥65 years Early breast cancer requiring adjuvant chemotherapy ECOG PS ≤2	Single-arm January 2006 – April 2007	Yes	Impact on cardiac strain rate imaging	Universitaire Ziekenhuizen Leuven	Evaluate the cardiac effects of liposomal doxorubicin n elderly patients (65y or older) with early breast cancer who are candidate for adjuvant chemotherapy with new non-invasive techniques, i.e. strain rate imaging, classical echocardiography, and special blood tests measuring troponin I and BNP.	NCT00284336	Completed

Abbreviations: DFS: disease-free survival; HR: hormone receptor; CCI: Charlson Comorbidity Index; AC: doxorubicin/cyclophosphamide; CMF: cyclophosphamide/methotrexate/5-fluorouracil; RFS: relapse-free survival; BCSS: breast cancer-specific survival; QOL: quality of life; HR: hazard ratio; CI: confidence interval; ER: oestrogen receptor; HER2: human epidermal growth factor receptor 2; CGA: comprehensive geriatric assessment, EC: epirubicin/cyclophosphamide; TC: docetaxel/cyclophosphamide; RMST: restricted mean survival time; ECOG: Eastern Cooperative Oncology Group; PS: performance status; PDL: pegylated doxorubicin hydrochloride liposome; IDFS: invasive disease-free survival; MC: liposomal non pegylated doxorubicin/cyclophosphamide.

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Authors' contributions

Dr Battisti and Dr Biganzoli conceived the article, reviewed and interpreted the available evidence, wrote and edited the manuscript.

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