Giuseppe Curigliano | giuseppe.curigliano@ieo.it

Short-term risk of recurrence in patients with HR+/ HER2− early breast cancer treated with endocrine therapy in randomized clinical trials: a meta-analysis

Giuseppe Curigliano,[1] Eva M. Ciruelos,[2,3] Kevin Kalinsky,[4] David Proudman,[5] Dave Nellesen,[5] Priscilla Lopez,[5] Samantha Kaufhold,[5] Olivia Shane,[5] Adrienne Kwok,[5] Vaidyanathan Ganapathy,[6] Adaeze Q. Amaefule,[6] Agnes Lteif,[6] Peter A. Fasching,[7] Erika Hamilton[8]

[1]European Institute of Oncology, IRCCS, and University of Milano, Milano, Italy; [2]SOLTI Cancer Research Group, Barcelona, Spain; [3]Hospital Universitario 12 de Octubre, Madrid, Spain; [4]Winship Cancer Institute at Emory University, Atlanta, GA, USA; [5]Analysis Group, Inc., San Francisco, CA, USA; [6]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; [7]University Hospital Erlangen, Comprehensive Cancer Center Erlangen–European Metropolitan Region of Nuremberg, and Department of Gynecology and Obstetrics, Friedrich-Alexander University Erlangen-Nuremberg, Erlangen, Germany; [8]Breast and Gynecologic Cancer Research Program, Sarah Cannon Research Institute, Nashville, TN, USA.

KEY FINDINGS & CONCLUSIONS

- HR+/HER2− EBC may recur over decades after initiating adjuvant treatment, but a substantial number of patients also recur while receiving adjuvant therapy
  - This meta-analysis of >30,000 patients (stage I-IIIC) in HR+/HER2− EBC trials published from 2013 to now found substantial risk of invasive recurrence at 3- (7%) and 5-yrs (12%) while receiving adjuvant ET ± CT, across stage I-IIIC HR+/HER2− EBC
- Approximately 40% of patients across the 14 trials had N0 disease. While risk of invasive recurrence at 3-yrs for N0 patients (stage I-IIIC) was 5%, the risk was higher among N0 cohorts with high genomic risk at 7% (n >2,000)
- Among N0 patients in the control arm of CDK4/6i trials, which included only patients with stage II-III disease, the 3-year invasive recurrence risk while receiving ET was 10%
- These findings indicate that there is greater heterogeneity among patients with stage I-IIIC HR+/HER2− EBC with N0 disease and the risk is not driven solely by LN status
- This meta-analysis demonstrates that patients with HR+/HER2− EBC treated with current standard-of-care adjuvant ET ± CT, including select patients with N0 disease with high-risk features, still have a notable risk of early recurrence and indicates a need for optimal risk reduction strategies

Scan to obtain:
- Poster

Poster presented at: 2024 NCODA International Fall Summit; October 23-25; Orlando, Florida.
This study is sponsored by Novartis Pharma AG.

INTRODUCTION

- The standard-of-care treatment for hormone receptor-positive/human epidermal growth factor receptor-negative (HR+/HER2−) early breast cancer (EBC) has been adjuvant endocrine therapy (ET) ± chemotherapy (CT) for the last 20 yrs[1]
- Patients with HR+/HER2− EBC remain at risk of both early (≤5 yrs) and late (>5 yrs) recurrences despite standard-of-care adjuvant ET, regardless of nodal status[2,3]
- Several meta-analyses have been previously published on risk of breast cancer recurrence, although none exist that include cohorts initiating ET within the last decade, in which practice patterns in the adjuvant setting have changed substantially[2,4]
- Furthermore, there are no published meta-analyses on this topic since the publication of recent EBC trials investigating cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) treatments.[18-23] Considering these trials is important to obtain a more complete picture of recurrence risk in recent studies, including patients treated with ET alone[5-23]
- Here we present a meta-analysis of short-term invasive recurrence risk among ET ± CT arms in randomized controlled trials (RCTs) of patients with stage I-IIIC HR+/HER2− EBC, including recent CDK4/6i trials, to address these gaps in the literature

METHODS

- A systematic literature review of published adjuvant ET HR+/HER2− EBC trials (2013 or later) was performed. Trials investigating adjuvant ET ± CT as active or control arm and meeting additional criteria were included (**Table 1**); extended ET trials were excluded since these trials did not report outcomes during the first 5 yrs of adjuvant therapy
- Data on age, nodal status, grade, menopausal status, genomic risk score, and adjuvant treatments, where available, were extracted from selected studies
- Survival curves were digitized to obtain landmark invasive disease-free or disease-free survival estimates (iDFS/DFS) at 3 and 5 yrs[a]
- A meta-analysis of iDFS/DFS proportions using a random-effects model with double arcsine transformation was conducted; risk of invasive recurrence was calculated using the formula: 100 – iDFS/DFS to report risk at 3- and 5-yr landmarks for all patients with stage I-IIIC HR+/HER2− EBC, regardless of nodal status. 5-yr rates are reported where available
- 3-yr risk was analyzed separately using trials that reported iDFS/DFS by lymph node (LN) status (N0: 0 LN, N1: 1-3 LN, N+: any positive LN) and menopausal status
- Risk estimates were also reported separately for control arms of CDK4/6i trials
- Where data were available, sensitivity analyses of the risk of recurrence among patients with stage I-IIIC disease were performed
  - Sensitivity analysis 1 only included trials with fewer than 30% of patients with stage I or tumor size ≤2 cm (T1)
  - Sensitivity analysis 2 limited the ET ± CT cohorts from non-CDK4/6i trials to patients with low to medium risk of recurrence scores based on genomic testing (ie, excluded PlanB trial cohort with Oncotype DX recurrence score [RS] <25; TAILORx, Oncotype DX RS <26; and RxPONDER)

[a]For DFS, only included trials where the definition of DFS was identical to the Standardized Definitions for Efficacy End Points (STEEP) definition of DFS (invasive, ipsilateral breast tumor recurrence, local or regional invasive recurrence, distant recurrence, death [from breast cancer, nonbreast cancer, or unknown cause], invasive, contralateral breast cancer, or second primary invasive cancer [nonbreast cancer]).

Table 1. PICOS Criteria for Systematic Review

PICOS element	Inclusion criteria	Exclusion criteria
Population	• Patients with stage I-IIIC HR+/HER2− EBC, any nodal status	• Individuals who do not have EBC, or are not HR+/HER2− • Subpopulation analysis, other than by stage or nodal status, mentioned as exclusion
Interventions	• Adjuvant ET as listed in NCCN guidelines (aromatase inhibitors [anastrozole, letrozole, exemestane], tamoxifen)[a]	• Neo-adjuvant ET and ET extension trials (if patients are not followed from ET initiation)
Outcomes	• iDFS and/or DFS rates (3-yr and 5-yr where available)	• No disease-free survival data
Study design	• Phase 3 RCTs	• Any study design other than phase 3 RCTs • Post hoc analysis • Systematic literature review
Language	• English	• Language other than English
Publication date	• 2013 - present	• Prior to 2013

DFS, disease-free survival; EBC, early breast cancer; ET, endocrine therapy; HR+/HER2−, hormone receptor-positive/human epidermal growth factor receptor-negative; iDFS, invasive disease-free survival; NCCN, National Comprehensive Cancer Network; PICOS, population intervention comparator outcome study design; RCT, randomized controlled trial.
[a]Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer V.2.2024. ©National Comprehensive Cancer Network, Inc. 2024. All rights reserved. Accessed [January 19, 2024]. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

RESULTS

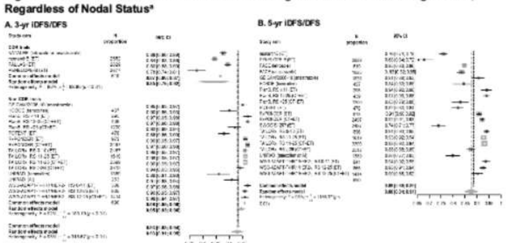
- 14 RCTs met the criteria for the systematic literature review and were further chosen for data extraction for the meta-analysis (1,353 studies screened, 1,316 excluded, 22 included) (**Table 2**)
- Data were extracted for 31,012 patients (stage I-IIIC) on ET ± CT, among whom 40.8% were N0, 56.7% were N+, and nodal status was not reported for 2.5% (**Table 2, Figure 1**)

Table 2. EBC Trials Included for Meta-Analysis and Patient Characteristics

RCT	Trial start, yr	Country	Age, median	Nodal status, %		Grade, %		Genomic risk categories,%
				N0	N+	G1	G2-G3	
HOBOE[5]	2003	Italy	Let: 44.9; Tam: 44.7	Let: 55%; Tam: 55%	Let: 45%; Tam: 45%	Let: 9%; Tam: 10%	86%	NR
FACE[6]	2005	Multiple	62	0%	100%	NR	NR	NR
TAILORx[7,8]	2006	Multiple	55-56 (by arm)	100%	0%	RS 0-10, ET: 34%; RS 11-25, ET: 29%; RS 11-25, CT+ET: 29%; RS ≥26, CT+ET: 7%	RS 0-10, ET: 66%; RS 11-25, ET: 70%; RS 11-25, CT+ET: 71%; RS ≥26, CT+ET: 90%	RS 0-10: 16.7%; RS 11-25: 69.1%; RS ≥26: 14.3%
GEICAM[9]	2006	Spain	62	46%	54%	19%	73%	NR
PlanB[10]	2009	Germany	56	59%	41%	5%	93%	RS 0-11: 17.4%; RS 12-25: 58.4%; RS >25: 20.8%
RxPONDER[11]	2011	Multiple	57.5	0%	N1: 100%	24%	74%	RS 0-13: 42.8% RS 14-25: 57.2%
SWOG 1207[12]	2011	Multiple	54	NR	NR	NR	NR	RS >25: 100%
POTENT[13]	2012	Japan	51	37%	43%	11%	87%	NR
WSG ADAPT[14]	2012	Germany	ET arms: 57-58; CT+ET: 48	RS 0-11, ET: 76%; RS 12-25, ET: 73%; RS 12-25, CT+ET: 53%	RS 0-11, ET, N1: 24%; RS 12-25, ET, N1: 27%; RS 12-25, CT+ET, N1: 39%	RS 0-11, ET: 14%; RS 12-25, ET: 10%; RS 12-25, CT+ET: 5%	RS 0-11, ET: 80%; RS 12-25, ET: 85%; RS 12-25, CT+ET: 90%	RS 0-11: 29.1%; RS 12-25: 70.9%
UNIRAD[15,16,17]	2013	Multiple	53.5	0%	100%	7%	89%	NR
PENELOPE-B[18]	2014	Multiple	48	12%	88%	6%	94%	NR
PALLAS[19,20]	2015	Multiple	52	13%	87%	6%	27%	NR
monarchE[21,22]	2017	Multiple	51	0.2%	99%	8%	87%	RS ≥26: 100%
NATALEE[23]	2019	Multiple	NR	13%	87%	9%	84%	RS ≥26: 100%

CT, chemotherapy; ET, endocrine therapy; Let, letrozole; N, node; NR, not reported; RCT, randomized controlled trial; RS, recurrence score; Tam, tamoxifen.

Figure 1. 3- and 5-Year iDFS/DFS in Patients With Stage I-IIIC Disease Receiving ET ± CT, Regardless of Nodal Status[a]

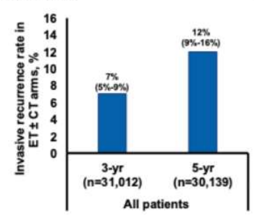


CDK, cyclin-dependent kinase; CT, chemotherapy; ET, endocrine therapy; iDFS, invasive disease-free survival; RS, recurrence score.
[a]iDFS/DFS proportions presented in figure.

Risk of invasive recurrence among patients with stage I-IIIC disease receiving ET ± CT, regardless of nodal status

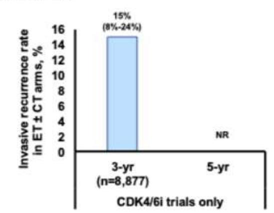
- The 3-yr pooled invasive recurrence risk across patients with stage I-IIIC disease receiving ET ± CT, regardless of nodal involvement (12 trials; n=31,012), was 7% (**Figure 2**)
- The corresponding 5-yr pooled risk (12 trials; n=30,139) was 12% (**Figure 2**)
- The 3-yr pooled invasive recurrence risk across ET ± CT arms in the 4 CDK4/6i trials, which included stage II-III patients (n=8,877), was 15%; corresponding 5-yr results were not reported for all CDK4/6i trials (**Figure 3**)
- The 5-yr risk was similar between those who were premenopausal or age <50 yrs (9%; n=5,882) and postmenopausal or age ≥50 yrs (11%; n=9,851) (**Figure 4**)

Figure 2. Invasive Recurrence Risk at 3 and 5 years in Patients With Stage I-IIIC Disease in All 14 RCTs[a]



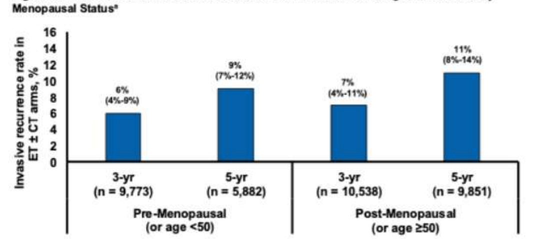
CT, chemotherapy; ET, endocrine therapy; RCT, randomized controlled trial.
[a]ET ± CT control arms (study arms excluded).

Figure 3. Invasive Recurrence Risk at 3 and 5 years in Patients With Stage II-III Disease in the Control Arm of CDK4/6i Trials[a,b]



CT, chemotherapy; ET, endocrine therapy; NR, not reported; RCT, randomized controlled trial.
[a]ET ± CT control arms (study arms excluded). [b]All enrolled patients in the CDK4/6i trials were stage II-III, regardless of trial I/E criteria.

Figure 4. Invasive Recurrence Risk at 3 and 5 Years in Patients With Stage I-IIIC Disease by Menopausal Status[a]

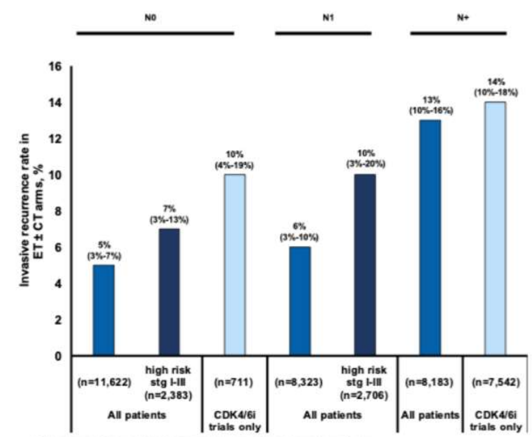


CT, chemotherapy; ET, endocrine therapy.
[a]ET ± CT control arms (study arms excluded).

Risk of invasive recurrence among patients with stage I-IIIC disease receiving ET ± CT, by nodal status

- The 3-yr pooled invasive recurrence risk across patients with stage I-IIIC disease on ET ± CT was 5% for N0 (4 trials; n=11,622), 6% for N1 (4 trials; n=8,323), and 13% for N+ (4 trials; n=8,183) disease (**Figure 5**)
- The 3-yr pooled invasive recurrence risk across ET ± CT arms in the 4 CDK4/6i trials, which included stage II-III patients (n=8,877), was 10% for patients with N0 (2 trials; n = 711) and 14% for N+ (3 trials; n=7,542) (**Figure 5**)

Figure 5. Invasive Recurrence Rate at 3 Years in Patients With Stage I-IIIC Disease Receiving ET ± CT Arms by Nodal Status[a,b,c]



CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; CT, chemotherapy; ET, endocrine therapy; RS, recurrence score; Stg, stage.
[a]ET ± CT control arms (study arms excluded). [b]All enrolled patients in the CDK4/6i trials were stage II-III, regardless of trial I/E criteria. [c]High risk stage I-III excluded ET cohorts with RS of low to medium (PlanB trial, Oncotype DX RS <25; TAILORx, Oncotype DX RS <26; and RxPONDER).

Sensitivity analyses

- Sensitivity analysis 1. If only trials with fewer than 30% patients with stage I or T1 were considered (5 trials; n=8,722), the 5-yr pooled invasive recurrence risk across ET ± CT arms regardless of nodal status was 21%
- Sensitivity analysis 2. For non-CDK4/6i trials reporting both nodal status and genomic risk, if ET ± CT cohorts with low to medium genomic risk scores were excluded, the 3-yr pooled invasive recurrence risk across patients with stage I-IIIC disease was 7% among patients with N0 (4 trials; n=2,383) and 10% among those with N1 disease (3 trials; n=2,706) (**Figure 5**)

References

1. Loibl S, et al. *Ann Oncol.* 2024;35(2):159-182. **2.** Pan H, et al. *N Engl J Med.* 2017;377:1836-1846. **3.** Pedersen RN, et al. *J Natl Cancer Inst.* 2022;114(3):djab202. **4.** Salvo EM, et al. *Breast.* 2021;57:5-17. **5.** Perrone F, et al. *Eur J Cancer.* 2019;118:178-186. **6.** Smith I, et al. *J Clin Oncol.* 2017;35(10):1041-1048. **7.** Sparano J, et al. Cancer Res; 2023; 83 (5 suppl) GS1-05. **8.** Sparano JA, et al. *N Engl J Med.* 2018;379(2):111-121. **9.** Ruiz-Borrego M, et al. *Breast Cancer Res Treat.* 2019;177(1):115-125. **10.** Nitz U, et al. *Breast Cancer Res Treat.* 2017;165(3):573-583. **11.** Kalinsky K, et al. *N Engl J Med.* 2021;385(25):2336-2347. **12.** Chavez M, et al. *Cancer Res.* 2023; 83 (5 suppl): GS1-07. **13.** Toi M., et al. *Lancet Oncol.* 2021;22(1):74-84. **14.** Nitz UA, et al. *J Clin Oncol.* 2022;40(23):2557-2567. **15.** Bachelot T, et al. *J Clin Oncol.* 2022;40(32):3699-3708. **16.** Bachelot T, et al. *Annals of Oncology.* 2021;32(4):574-575. **17.** Cottu PH, et al. *Annals of Oncology.* 2021;32:S425. **18.** Loibl S, et al. *J Clin Oncol.* 2021;39(14):1518-1530. **19.** Gnant M, et al. *J Clin Oncol.* 2022;40(3):282-293. **20.** Mayer EL, et al. Lancet Oncol. 2021;22(2):212-222. **21.** Johnston SRD, et al. Lancet Oncol. 2023;24(1):77-90. **22.** Harbeck N, et al. *Annals of Oncology.* 2023; 34: S1256. **23.** Hortobagyi GN, et al. *J Clin Oncol.* 2023. 41, Number 17_suppl.

Disclosures

G Curigliano reports other from Roche, Novartis, Lilly, Pfizer, AstraZeneca, Daiichi Sankyo, Ellipsis, Veracyte, Exact Science, Celcuity, Merck, BMS, Gilead, Sanofi, and Menarini, during the conduct of the study. **E M Ciruelos** reports personal fees from Roche, Lilly, Novartis, and Pfizer, during the conduct of the study. **K Kalinsky** reports employment stock of spouse from EQRX, Grail (prior employee); personal fees for advisory/consulting from Eli Lilly, Pfizer, Novartis, AstraZeneca, Daiichi Sankyo, Puma, 4D Pharma, Oncosec, Immunomedics, Merck, Seattle Genetics, Mersana, and Cyclocel; institutional research funding from Genentech/Roche, Novartis, Lilly, AstraZeneca, Daiichi Sankyo, and Ascentage. **D Proudman, D Nellesen, P Lopez, S Kaufhold, O Shane, and A Kwok** report employment for Analysis Group, Inc., a consulting company which received funding from Novartis for this study. **V Ganapathy** reports employment from Novartis. **A Q Amaefule** has nothing to disclose. **A Lteif** reports employment and stock ownership from Novartis. **P A Fasching** reports personal fees for advisory boards from Novartis, Pfizer, Daiichi Sankyo, AstraZeneca, Eisai, Merck Sharp & Dohme, Lilly, Pierre Fabre, Seagen, Roche, Hexal, Agendia, Sanofi Aventis, Gilead, institutional funding grant from BioNtech, Cepheid; research grant from Pfizer. **E Hamilton** reports grant to institution for fees associated with clinical trial from Novartis; grant to institution from Pfizer, Genentech/Roche, Lilly, Puma Biotechnology, Daiichi Sankyo, Mersana, Boehringer Ingelheim, Cascadian Therapeutics, AstraZeneca, Hutchison MediPharma, OncoMed, MedImmune, Stem CentRx, Curis, Verastem, Zymeworks, Syndax, Lycera, Rgenix, Millennium, Tapimmune, BerGenBio, Medivation, Tesaro, Kadmon, Eisai, H3 Biomedicine, Radius Health, Acerta Pharma, Takeda, MacroGenics, AbbVie, Immunomedics, Fujifilm, eFFECTOR Therapeutics, Mallinckrodt, Merus, Nucana, TetraLogic Pharmaceuticals, PharmaMar, Regeneron, Leap Therapeutics, Taiho Pharmaceutical, EMD Serono, Syros, Clovis, CytomX, InventisBio, Oncothyreon, and Novartis; nonfinancial support—payment or reimbursement of exact amount of expenses from Genentech/Roche, Lilly, Daiichi Sankyo, AstraZeneca, Tesaro, Eisai, Novartis, EMD Serono, Clovis, Amgen, Bayer, Bristol Myers Squibb, Genzyme, Helsinn Therapeutics, HERON, Lexicon, Medivation, Merck, Roche, Sysmex, Guardant Health, and Foundation Medicine; personal fees for consulting from Flatiron; payment to institution for consulting services from Pfizer, Genentech/Roche, Lilly, Puma Biotechnology, Daiichi Sankyo, Mersana, Boehringer Ingelheim, Cascadian Therapeutics, and Eisai.

Acknowledgements

Medical editorial assistance was provided by Nucleus Global, Ltd, and Novartis Healthcare Pvt. Ltd, Hyderabad, India, and funded by Novartis Pharmaceuticals Corporation.
The authors had final responsibility for the poster.