A Real-World-Data Retrospective Cohort Study of Low Estrogen Receptor Positive Early Breast Cancer: Natural History and Treatment Outcomes.

Shahla Bari (✉ shahlabari19@gmail.com)

University of South Florida <https://orcid.org/0000-0002-8459-8518>

David Boulware

Moffitt Cancer Center

Jiannong Li

Moffitt Cancer Center

Loretta Loftus

Moffitt Cancer Center

Aixa Soyano

Moffitt Cancer Center

Zena Jameel

Moffitt Cancer Center

Hung Khong

Moffitt Cancer Center

Brian Czerniecki

Moffitt Cancer Center

Ricardo Costa

Moffitt Cancer Center <https://orcid.org/0000-0002-3303-3234>

Research Article

Keywords: Breast cancer, estrogen receptor, low-positive, recurrence free survival

Posted Date: January 18th, 2022

DOI: <https://doi.org/10.21203/rs.3.rs-792365/v2>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

**A real-world-data retrospective cohort study of low estrogen receptor positive
early breast cancer: natural history and treatment outcomes.**

Running head- Assessing ER low cut points using real world data.

Authors: Shahla Bari^a, David Boulware^b, Jiannong Li^b, Loretta Loftus^c, Aixa Soyano Muller^c, Zena Jameel^d, Hung Khong^c, Brian J. Czerniecki^c, Ricardo L. B. Costa^c

^a Department of Hematology/Oncology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL.

^b Department of Biostatistics, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL.

^c Department of Breast Oncology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL.

^d Department of Anatomic and clinical pathology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL.

Abstract word count: 231

Text word count: 2469

Number of Tables/Figures: 4/3

Number of supplementary figures 1

Corresponding author

Ricardo L. B. Costa

12902 Magnolia drive, MKC-BRPROG

Tampa, FL 33612

Phone: 813.745.3806 Fax 813.745.7287

Email: ricardo.costa@moffitt.org

Orcid ID 0000-002-3303-3234

Conflicts of Interest: R. L. B. Costa received honorarium from Bristol Meyers Squib, Pfizer, Athenex Oncology, Daiichi Sankyo and Astra Zeneca. All other authors declare no conflicts of interest.

32
33 **Declarations**

34 **Funding:** Shula's Foundation.

35 **Ethical Approval:** Institutional Review Board approval of the study protocol was
36 obtained from WCG IRB prior to study conduct and included a waiver of informed
37 consent.

38 **Informed Consent:** This article does not contain any studies with human participants
39 which would require informed consent.

40 **Availability of data and materials:** The data that support the findings of this study
41 have been originated by Flatiron Health, Inc. These de-identified data may be available
42 upon request and are subject to a license agreement with Flatiron Health; interested
43 researchers should contact DataAccess@flatiron.com to determine licensing terms.

44 **Acknowledgements:** Editorial assistance was provided by the Moffitt Cancer Center's
45 Office of Scientific Writing by Dr. Paul Fletcher, Daley Drucker, and Mikael Michalik. No
46 compensation was given beyond their regular salaries. This work has been supported in
47 part by the Biostatistics & Bioinformatics Shared Resource at the H. Lee Moffitt Cancer
48 Center & Research Institute, a comprehensive cancer center designated by the National
49 Cancer Institute and funded in part by Moffitt's Cancer Center Support Grant (P30-
50 CA076292).

Abstract

Purpose: Estrogen receptor–positive (ER⁺) breast cancer (BC) is a heterogeneous disease with an ongoing debate regarding the optimal cutoff point for clinically relevant ER expression. We used a real-world database to assess prognostic and predictive values of lower ER expression levels on treatment outcomes with endocrine therapy.

Methods: We used a nationwide electronic health record– (EHR-) derived deidentified database. Descriptive statistics were used to evaluate the association between ER expression, tumor characteristics, and treatment patterns among patients with early-stage BC. We used Kaplan-Meier survival curves to estimate relapse-free survival (RFS) and overall survival (OS). To assess an optimal ER expression level cut point, association between ER⁺ expression and clinical outcomes were performed.

Results: Among 4697 patients with early-stage BC, 83 (1.76%) had ER⁺-low BC (ER expression, 1%-9.99%), and 36 (0.8%) had ER⁺-intermediate BC (10%-19.9%). ER⁺-low tumors were associated with higher tumor grade, larger size and higher axillary tumor burden than ER⁺-high tumors ($\geq 20\%$ ER expression). African Americans had a higher prevalence of both triple-negative BC (TNBC; 21%) and ER⁺-low BC (22%) than ER⁺-high tumors (8%). Patients with ER⁺-low and ER⁺-intermediate tumors had survival outcomes similar to patients with TNBC and worse survival outcomes than patients with ER⁺-high tumors ($P < .001$). Tumors with $<20\%$ ER expression were associated with worse outcomes.

Conclusions: Patients with ER expression levels $< 20\%$ BC have poor clinical outcomes similar to those with TNBC.

Key words: Breast cancer; estrogen receptor; low-positive; recurrence free survival

Introduction

Breast cancer (BC) is the most common malignancy worldwide. In 2020, an estimated 279100 new cases were diagnosed in the United States alone [1]. Hormone receptor–positive (HR⁺) BC is the most common subset (~60%) and is defined by the 2010 American Society of Clinical Oncology (ASCO) and College of American Pathology (CAP) guidelines as a tumor with at least 1% of cancer nuclei that stain positive for HRs for estrogen or progesterone by immunohistochemistry [2]. Notwithstanding the clinical importance of pathological assessments of both HRs, decisions pertaining to endocrine therapy (ET) are largely based on expression levels of estrogen receptors (ERs), and progesterone receptors are largely accepted as a prognostic biomarker.

The current definition of ER positivity (ER⁺) presents an obvious caveat, as it does not encompass the biological heterogeneity inherent in the wide distribution of ER expression levels between tumors. Moreover, it suggests that patients with BCs with varying levels of ER expression have similar natural histories and derive similar benefit from approved and developing ETs. This is an incorrect premise. Data show that patients with tumors harboring lower levels of ERs have a poor prognosis similar to patients with strictly defined triple-negative BC (TNBC); patients with TNBC have a 3-year absolute risk of BC recurrence of 30% despite multimodality therapy [3-5]. The results of a meta-analysis of 21457 patients with early-stage BC showed that ER⁺-low status (i.e., ligand-based assay, HR <10 fmol/mg cytosol protein) was not significantly associated with clinical benefit from adjuvant ET [6]. Current guidelines for ER testing in BCs, published by ASCO and CAP, define ER⁺-low tumors as cancer with 1% to 10% staining for ERs and affirms the optimal cut point for ER positivity using the universally

adopted immunohistochemistry scoring system [7]. It is remarkable that this revision recognizes that most of the trials supporting the benefit of adjuvant ET for early ER⁺ BC conducted in the 1990s used quantitative measures of HRs that are no longer routinely used.

Albeit their poor prognosis and apparent lack of benefit from ETs, treatment development for patients with BCs with lower levels of ERs has been stagnant as these patients are not allowed to participate in clinical trials for patients with TNBC under the assumption of better outcomes and benefit from endocrine therapies. This is important as *Developmental Therapeutics* have gained momentum and continues to develop treatments targeted to strictly defined subsets of BCs (i.e., TNBC vs. ER⁺ BCs). This is evidenced by a new surge in clinical trials that assess the efficacy of new agents targeting ERs (e.g., selective estrogen receptor modulators [SERMs] and degraders [SERDs]) [8].

We conducted a large real-world retrospective study of patients with early-stage BC to improve current understanding of the prevalence and natural history of tumors with lower levels of ER expression and treatment patterns of patients with this disease. Moreover, we retrospectively assessed the prognostic and predictive values of an alternative definition of ER⁺-low BC in relation to treatment outcomes with ET.

Methods

Data source

This retrospective cohort study used the nationwide Flatiron Health electronic health record– (FEHR-) derived deidentified database. This is a real-world longitudinal database that comprises deidentified patient-level structured and unstructured data, which were curated via technology-enabled abstraction [9, 10]. The database originated from approximately 280 US cancer clinics (~800 sites of care). The majority of patients were from community oncology settings, and relative community/academic proportions may vary depending on study cohort.

Our cohort (N = 9386) included patients with early-stage BC diagnosed between January 2011 and May 2020. Institutional Review Board approval of the study was obtained prior to study conduct and included a waiver for informed consent. The data were deidentified and subject to obligations to prevent reidentification and protect patient confidentiality. The dataset included patient-related and tumor-related variables, including epidemiological, clinical, and pathological data as well as age at diagnosis, race, ethnicity, menopausal status, tumor size, grade, Ki-67 (%), number of lymph nodes involved, chemotherapy, and ET histories. HRs and human epidermal growth factor receptor 2 (HER2) expressions were assessed locally in accordance with standard immunohistochemistry nuclei staining by a local pathologist. Expression of HRs and HER2 was measured as the percent of nuclei staining and membrane staining, respectively. HER2 amplification was assessed according to locally assessed fluorescent in situ hybridization.

Recurrence-free survival (RFS) was defined as the time in months from the date of first treatment to the date of diagnosis of metastasis, first local recurrence, or death, whichever occurred first; patients without these data were censored at the last date

known alive. Overall survival (OS) was defined as the time from the date of first treatment to the date of death; patients without these data were censored at the last date known alive.

Real-world cohort key inclusion and exclusion criteria

Inclusion criteria used to select cases from the FEHR BC cohort included having a diagnosis of histologically proven stage I-III BC and receiving surgical treatment for BCs with curative intent. Exclusion criteria were having carcinoma *in situ*, metastatic BC and having HER2⁺ BC. Patients who received chemotherapy before or after surgical treatment were classified as having received perioperative chemotherapy. Information on perioperative chemotherapy, ET, and radiation therapy was abstracted. Because of the diversity in the number of chemotherapy regimens, these regimens were classified as anthracycline- and taxane-containing, anthracycline-only and taxane-only regimens, and *other*. Anastrozole, exemestane, letrozole and tamoxifen were classified as ET. Patients were followed from the date of resection (index date) until the date of biopsy-proven tumor recurrence, death, or last follow-up. Patients with >90 days between diagnosis and first Flatiron Health–reported structured activity were excluded to avoid missing treatment data. Furthermore, any patient with <90 days of follow-up from the index date was excluded.

Statistical methods

Among 9386 early-stage BC patients, 3490 had missing or incomplete ER, PR, or HER2 status and/or did not have at least 90 days of follow-up. A further 1299 patients

163 had HER2⁺ BC and were also excluded from the final analysis, leaving 4697 evaluable
164 patients (634 with TNBC and 4063 with ER⁺ BC).

165 Initially, descriptive characteristics were described by using means (standard
166 deviations) and medians (ranges) for continuous variables and frequencies for
167 categorical variables. The ER⁺-low and ER⁺-intermediate cohorts were compared using
168 the Kruskal-Wallis test for continuous variables and Fisher exact test for categorical
169 variables.

170 A training dataset and test dataset were established by dividing the ER⁺ dataset into
171 two-thirds training and one-third test data. The range of ER percent staining values was
172 divided into 10 levels, with 10% increments. A cut point analysis was performed on the
173 training dataset using the Contal and O'Quigley method [11], which enabled us to
174 assess the optimum cut point of ER⁺ staining, which was correlated with RFS using Cox
175 proportional hazards regression. Because the analysis did not identify a cut point that
176 was adequately and significantly differentiated from other cut points, we used 20% as a
177 clinically reasonable cut point ($P < .0001$). New exploratory ER⁺-low and ER⁺-high
178 groups were defined by this cut point (1%-19.9% vs $\geq 20\%$).

179 We then performed Kaplan-Meier survival curves for RFS and OS for both the training
180 and test sets. Furthermore, a multivariable Cox proportional hazards survival analysis
181 was used on the training set and adjusted for age, radiotherapy, and ET. This model
182 was then used on the test set, and the c-statistic was used to check for model fit.
183 Hazard ratios and 95% confidence intervals are reported. All analyses were performed
184 in SAS v 9.4 (Cary, NC).

Results

In the total cohort of 9386 patients with early-stage BC, only 4697 were evaluable (634 with TNBC and 4063 with ER⁺ BCs). Only 83 cases were classified as ER⁺ low (ER expression 1%-9.99%). Median follow-up was 36 months (range 17-60).

Baseline demographics and clinical, treatment, and outcome patterns

The majority (72%) of patients were White, and African Americans represented 10% of the cohort analyzed. There were 38 males in this dataset. Median age in years at diagnosis of BC was 63 (range, 24-84 years), and most women were postmenopausal (72%). Eighty-two percent of patients had invasive ductal carcinomas, 12% had lobular carcinomas, and 47% had grade 2 tumors. Up to 63% of patients received adjuvant radiation therapy, and 37% underwent mastectomies (Table 1). Patients with ER⁺ tumors had significantly longer RFS and OS than patients with TNBC (Figure 1).

Distribution of ER expression and pathological characteristics

A total of 4063 patients with ER⁺/HER2⁻ early-stage BC were included in our analysis, of whom 83 (1.8%) had ER⁺-low (ER staining, 1%-9.99%) and 36 (0.8%) had ER⁺-intermediate (ER staining 10%-19.99%) BC. Both TNBC and ER⁺-low tumors were more commonly observed among patients <60 years of age. Patients with higher ER expression were typically older. African American patients had a higher frequency of both TNBC (28% vs 12.4%) and ER⁺-low (3.7% vs 1.6%) BC and lower frequency of ER⁺-high (66.7 vs 85.2%) tumors compared to the Caucasians. The majority of ER⁺-high tumors had low to intermediate histological grades, whereas most tumors with

lower levels of ER expression were grade 3 (Table 1). Patients with ER⁺-high tumors were also diagnosed with smaller tumors and lower axillary tumor burden than those with ER⁺-low tumors.

Clinical outcomes of patients with ER⁺-low and -intermediate early-stage BCs

There was no statistically significant difference between the epidemiological, clinical, and pathological characteristics of patients with ER⁺-low and ER⁺-intermediate tumors (Table 2). Surgical and radiation treatment patterns were similar between these two groups. More patients in the ER⁺-intermediate group received adjuvant ET (unadjusted $P = .005$) as well as adjuvant chemotherapy with both anthracycline- and taxane-containing perioperative regimens (unadjusted, $P = .009$). In univariate analyses, patients with ER⁺-low and ER⁺-intermediate tumors had OS and RFS similar to patients with TNBC (Figure 2). The low number of patients in the ER⁺-low and ER⁺-intermediate groups precluded multivariate analyses.

Sensitivity analyses of ER cut point

Kaplan-Meier survival curves for both RFS and OS showed that patients with tumors harboring ER expression levels between 1% and 19.9% had significantly poorer outcomes than patients with expression rates $\geq 20\%$ (Figure 3). Furthermore, a multivariable Cox proportional survival analysis was performed on the training set and showed a statistically significant association between higher expression of ERs ($\geq 20\%$) and improved RFS (HR, 0.55; 95% CI, 0.33-0.96; $P = .02$) and OS (HR, 0.5; 95% CI, 0.27-0.9; $P = .02$) (Harrell's c statistics, 0.677 for RFS and 0.698 for OS) (Table 3). Univariate analyses showed no significant differences in treatment effect of ET on RFS

and OS when comparing patients with ER⁺-low (1-9.99%) and ER⁺-intermediate tumors (10-19.99%) (Table 4) suggesting similar outcomes when ET is given. Finally, patients with ER⁺-low tumors had improved RFS when treated with ET (Supplemental figure 1).

Discussion

ER⁺ BC is a heterogeneous disease, not only in its natural history but also in reference to its wide distribution of ER expression levels between tumors; cases of low expression represent a small proportion of cases of BC. The optimal cut point that indicates reliable prognostic ER expression and predictive information of ET benefit remains to be determined. Historically, any level of ER expression has been considered to be positive, which is counterintuitive and misleading, as tumors harboring lower levels of ERs will likely not respond to ET. In parallel, tumors with low expression rates of ERs are universally excluded from contemporary clinical trials for patients with TNBC. The corollary is that the ER⁺-low BC subset remains an orphan disease. With an increasing number of clinical trials aiming to develop new ETs (e.g., SERDs and SERMs), a better understanding of the natural history of and possible benefit from ET remains an unmet need in developmental therapeutics for patients with ER⁺-low BCs.

We conducted a large real-world retrospective cohort study of 4697 participants with early-stage ER⁺ BC or TNBC. In this cohort, the natural history of patients with early-stage BCs was similar to previously published literature [12]. Our results indeed suggest that ER⁺-low BC (expression, 1%-9.99%) represents a small subset (1.8%) of patients with ER⁺ BC. These tumors presented pathological features and prognosis similar to those of patients with TNBC. We observed a continuous association between ER

expression and clinical outcomes and therefore chose 20% as a clinically reasonable cut point for further analyses. In our cohort, patients with tumors harboring ER expression rates between 10% and 19.9% (intermediate levels) presented similar clinicopathological features, natural histories, and treatment patterns to those with ER⁺-low BCs (1%-9.99%); however, anthracycline- and taxane-containing chemotherapy regimens were more commonly administered to patients with tumors with ER⁺-intermediate tumors. Moreover, ER⁺-intermediate patients had similar RFS and OS as ER⁺-low patients, irrespective of ET use but the latter group of patients seem to still derive benefit from adjuvant ET. We observed that an incremental expression of ER is associated with improved outcomes, further suggesting that the binary categorization of ER expression represents a simplification of continuous biological phenomena. Based on our findings, a balanced discussion should be conducted in patients with ER⁺-low and ER⁺-intermediate breast cancer when deciding on adjuvant ET as possible benefits need to be weighed against toxicities, including arthralgia, fatigue, thrombosis, osteoporosis, fatigue[13] etc. If patient and physician collaboratively decide to forego adjuvant ET, these patients should be informed about higher risk of cancer recurrence and closely monitored.

Our study has limitations inherent to real-world retrospective cohort studies. There were missing data, which prevented us from including important variables, such as chemotherapy and nodal staging, into our adjusted analyses. Assessments of ER expression were not centrally reviewed, it is uncertain that all sites that contributed data followed strictly ASCO-CAP guidelines for ER, PR and Her2 testing. Additionally, the number of ER⁺-low and ER⁺-intermediate tumors was relatively small compared to other

subtypes, limiting exploratory statistical comparisons and multivariable adjustments. Further, data on genomic markers (e.g., Oncotype Dx scores) on all patients in this real-world database is not available , therefore we are unable to comment on biomarkers to predict benefit of chemo or lack of benefit from ET. In addition, Flatiron database lacks information on histological features of breast cancer recurrences to differentiate between invasive vs. non-invasive recurrent cancers which if available would have been ideal[14]. Nonetheless, this is a large retrospective study that uses real-world data, which thereby increases the external validity of our findings. Given the low frequency of ER⁺-low tumors, the conduction of large prospective studies assessing the prognostic and predictive value of lower ER expression is practically unfeasible. However retrospectively studies evaluating prospectively collected tumor samples and data from large phase 3 trails assessing the efficacy of adjuvant ET may be feasible and favored to address this unmet need.

This study therefore fills an important gap in our knowledge of the natural history of ER⁺-low and ER⁺-intermediate tumors.

Conclusions

Findings from this real-world retrospective study suggest that patients with ER expression rates <20% have poor outcomes. Future clinical trials for patients with TNBC should allow for participation of patients with ER-low BCs.

References

1. Siegel RL, Miller KD, Jemal A (2020) Cancer statistics, 2020. CA: a cancer journal for clinicians 70:7-30. doi: 10.3322/caac.21590
2. Hammond ME, Hayes DF, Dowsett M, Allred DC, Hagerty KL, Badve S, Fitzgibbons PL, Francis G, Goldstein NS, Hayes M, Hicks DG, Lester S, Love R, Mangu PB, McShane L, Miller K, Osborne CK, Paik S, Perlmutter J, Rhodes A, Sasano H, Schwartz JN, Sweep FC, Taube S, Torlakovic EE, Valenstein P, Viale G, Visscher D, Wheeler T, Williams RB, Wittliff JL, Wolff AC (2010) American Society of Clinical Oncology/College Of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. J Clin Oncol 28:2784-2795. doi: 10.1200/JCO.2009.25.6529
3. Landmann A, Farrugia DJ, Zhu L, Diego EJ, Johnson RR, Soran A, Dabbs DJ, Clark BZ, Puhalla SL, Jankowitz RC, Brufsky AM, Ahrendt GM, McAuliffe PF, Bhargava R (2018) Low Estrogen Receptor (ER)-Positive Breast Cancer and Neoadjuvant Systemic Chemotherapy: Is Response Similar to Typical ER-Positive or ER-Negative Disease? Am J Clin Pathol 150:34-42. doi: 10.1093/ajcp/aqy028
4. Prabhu JS, Korlimarla A, Desai K, Alexander A, Raghavan R, Anupama C, Dendukuri N, Manjunath S, Correa M, Raman N, Kalamdani A, Prasad M, Gopinath KS, Srinath BS, Sridhar TS (2014) A Majority of Low (1-10%) ER Positive Breast Cancers Behave Like Hormone Receptor Negative Tumors. Journal of Cancer 5:156-165. doi: 10.7150/jca.7668
5. Raghav KP, Hernandez-Aya LF, Lei X, Chavez-Macgregor M, Meric-Bernstam F, Buchholz TA, Sahin A, Do KA, Hortobagyi GN, Gonzalez-Angulo AM (2012) Impact of low estrogen/progesterone receptor expression on survival outcomes in breast cancers previously classified as triple negative breast cancers. Cancer 118:1498-1506. doi: 10.1002/cncr.26431
6. Davies C, Godwin J, Gray R, Clarke M, Cutter D, Darby S, McGale P, Pan HC, Taylor C, Wang YC, Dowsett M, Ingle J, Peto R (2011) Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. Lancet (London, England) 378:771-784. doi: 10.1016/s0140-6736(11)60993-8
7. Allison KH, Hammond MEH, Dowsett M, McKernin SE, Carey LA, Fitzgibbons PL, Hayes DF, Lakhani SR, Chavez-MacGregor M, Perlmutter J, Perou CM, Regan MM, Rimm DL, Symmans WF, Torlakovic EE, Varella L, Viale G, Weisberg TF, McShane LM, Wolff AC (2020) Estrogen and Progesterone Receptor Testing in Breast Cancer: ASCO/CAP Guideline Update. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 38:1346-1366. doi: 10.1200/jco.19.02309
8. Howell SJ, Johnston SR, Howell A (2004) The use of selective estrogen receptor modulators and selective estrogen receptor down-regulators in breast cancer. Best Pract Res Clin Endocrinol Metab 18:47-66. doi: 10.1016/j.beem.2003.08.002
9. Ma X, Long L, Moon S, Adamson BJS, Baxi SS (2020) Comparison of Population Characteristics in Real-World Clinical Oncology Databases in the US: Flatiron Health, SEER, and NPCR. medRxiv:2020.2003.2016.20037143. doi: 10.1101/2020.03.16.20037143
10. Benjamin Birnbaum NN, Katharina Seidl-Rathkopf, Monica Agrawal, Melissa Estevez, Evan Estola, Joshua Haimson, Lucy He, Peter Larson, Paul Richardson (2020) Model-

- assisted cohort selection with bias analysis for generating large-scale cohorts from the EHR for oncology research. In:
11. Tunes-da-Silva G, Klein JP (2011) Cutpoint selection for discretizing a continuous covariate for generalized estimating equations. *Computational statistics & data analysis* 55:226-235. doi: 10.1016/j.csda.2010.02.016
 12. Liedtke C, Mazouni C, Hess KR, Andre F, Tordai A, Mejia JA, Symmans WF, Gonzalez-Angulo AM, Hennessy B, Green M, Cristofanilli M, Hortobagyi GN, Puztai L (2008) Response to neoadjuvant therapy and long-term survival in patients with triple-negative breast cancer. *J Clin Oncol* 26:1275-1281. doi: 10.1200/JCO.2007.14.4147
 13. Berkowitz MJ, Thompson CK, Zibecchi LT, Lee MK, Streja E, Berkowitz JS, Wenziger CM, Baker JL, DiNome ML, Attai DJ(2021). How patients experience endocrine therapy for breast cancer: an online survey of side effects, adherence, and medical team support. *J Cancer Surviv.* :29-39. doi: 10.1007/s11764-020-00908-5.
 14. Tolaney SM, Garrett-Mayer E, White J, Blinder VS, Foster JC, Amiri-Kordestani L, Hwang ES, Bliss JM, Rakovitch E, Perlmutter J, Spears PA, Frank E, Tung NM, Elias AD, Cameron D, Denduluri N, Best AF, DiLeo A, Baizer L, Butler LP, Schwartz E, Winer EP, Korde LA (2021). Updated Standardized Definitions for Efficacy End Points (STEEP) in Adjuvant Breast Cancer Clinical Trials: STEEP Version 2.0. *J Clin Oncol.*2720-2731. doi: 10.1200/JCO.20.03613.

364 **Tables.**365 **Table 1a. Cohort description**

Characteristics	[ALL] N=4697	Triple negative N=634	ER+ low N=83	ER+ intermediate N=36	ER+ high N=3944	p.overall
Gender:						0.079
Female	4659 (99.2%)	634 (13.6%)	83 (1.78%)	36 (0.77%)	3906 (83.8%)	
Male	38 (0.81%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	38 (100%)	
Race:						<0.001
White	3126 (72.5%)	388 (12.4%)	50 (1.60%)	24 (0.77%)	2664 (85.2%)	
Black or African American	432 (10.0%)	122 (28.2%)	16 (3.70%)	6 (1.39%)	288 (66.7%)	
Asian	123 (2.85%)	9 (7.32%)	1 (0.81%)	1 (0.81%)	112 (91.1%)	
Other Race	633 (14.7%)	72 (11.4%)	7 (1.11%)	5 (0.79%)	549 (86.7%)	
Ethnicity:						0.340
Hispanic or Latino	308 (6.56%)	51 (16.6%)	7 (2.27%)	3 (0.97%)	247 (80.2%)	
Non-Hispanic	4389 (93.4%)	583 (13.3%)	76 (1.73%)	33 (0.75%)	3697 (84.2%)	
MenopausalStatus:						0.021
N/A - patient is male	37 (0.79%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	37 (100%)	
Perimenopausal	114 (2.43%)	16 (14.0%)	1 (0.88%)	2 (1.75%)	95 (83.3%)	
Postmenopausal	3400 (72.4%)	436 (12.8%)	54 (1.59%)	24 (0.71%)	2886 (84.9%)	
Premenopausal	843 (17.9%)	126 (14.9%)	21 (2.49%)	5 (0.59%)	691 (82.0%)	
Unknown/not documented	303 (6.45%)	56 (18.5%)	7 (2.31%)	5 (1.65%)	235 (77.6%)	
Histology:						<0.001
Unknown.	6 (0.13%)	1 (16.7%)	0 (0.00%)	0 (0.00%)	5 (83.3%)	
Ductal	3829 (81.5%)	581 (15.2%)	75 (1.96%)	31 (0.81%)	3142 (82.1%)	
Lobular	579 (12.3%)	10 (1.73%)	3 (0.52%)	2 (0.35%)	564 (97.4%)	
Mixed	107 (2.28%)	9 (8.41%)	1 (0.93%)	1 (0.93%)	96 (89.7%)	
Other	176 (3.75%)	33 (18.8%)	4 (2.27%)	2 (1.14%)	137 (77.8%)	
TumorGrade:						<0.001
Grade 1	1144 (24.6%)	10 (0.87%)	4 (0.35%)	3 (0.26%)	1127 (98.5%)	
Grade 2	2247 (48.2%)	113 (5.03%)	15 (0.67%)	11 (0.49%)	2108 (93.8%)	
Grade 3	1267 (27.2%)	508 (40.1%)	61 (4.81%)	22 (1.74%)	676 (53.4%)	
KI67:						<0.001
<20%	1161 (51.1%)	28 (2.41%)	10 (0.86%)	1 (0.09%)	1122 (96.6%)	
>=20%	1112 (48.9%)	285 (25.6%)	30 (2.70%)	14 (1.26%)	783 (70.4%)	
Clinical T stage:						<0.001
1	893 (54.0%)	110 (12.3%)	14 (1.57%)	5 (0.56%)	764 (85.6%)	
2	537 (32.5%)	135 (25.1%)	16 (2.98%)	7 (1.30%)	379 (70.6%)	
3	223 (13.5%)	64 (28.7%)	6 (2.69%)	3 (1.35%)	150 (67.3%)	
Clinical N stage:						<0.001
0	1095 (71.7%)	160 (14.6%)	19 (1.74%)	9 (0.82%)	907 (82.8%)	
1	338 (22.1%)	100 (29.6%)	10 (2.96%)	4 (1.18%)	224 (66.3%)	

Characteristics	[ALL] N=4697	Triple negative N=634	ER+ - low N=83	ER+ - intermediate N=36	ER+ - high N=3944	p.overall
2	94 (6.16%)	31 (33.0%)	3 (3.19%)	1 (1.06%)	59 (62.8%)	
PrimaryRadiotherapy:						0.922
No/unknown	1709 (36.4%)	237 (13.9%)	29 (1.70%)	14 (0.82%)	1429 (83.6%)	
Yes	2988 (63.6%)	397 (13.3%)	54 (1.81%)	22 (0.74%)	2515 (84.2%)	
EndocrineTherapy:						0.000
No	938 (20.0%)	588 (62.7%)	42 (4.48%)	8 (0.85%)	300 (32.0%)	
Yes	3759 (80.0%)	46 (1.22%)	41 (1.09%)	28 (0.74%)	3644 (96.9%)	
Chemotherapy:						<0.001
Anthracycline without taxane	56 (1.19%)	12 (21.4%)	0 (0.00%)	3 (5.36%)	41 (73.2%)	
Taxane without anthracycline	593 (12.6%)	132 (22.3%)	15 (2.53%)	4 (0.67%)	442 (74.5%)	
Taxane and anthracycline	746 (15.9%)	270 (36.2%)	36 (4.83%)	19 (2.55%)	421 (56.4%)	
Other	81 (1.72%)	13 (16.0%)	0 (0.00%)	2 (2.47%)	66 (81.5%)	
No info on chemo	3221 (68.6%)	207 (6.43%)	32 (0.99%)	8 (0.25%)	2974 (92.3%)	
Surgery:						<0.001
Mastectomy	2885 (62.9%)	330 (11.4%)	42 (1.46%)	20 (0.69%)	2493 (86.4%)	
Other	1704 (37.1%)	280 (16.4%)	41 (2.41%)	16 (0.94%)	1367 (80.2%)	
Age	63.0 [53.1;71.5]	58.7 [50.1;67.6]	54.9 [44.4;67.0]	60.7 [54.6;66.1]	63.9 [53.9;72.1]	<0.001
Follow_up (months)	36.0 [17.0;60.0]	34.0 [16.0;58.0]	30.5 [14.2;57.8]	30.0 [16.5;51.0]	37.0 [17.0;60.0]	0.073

366
367
368
369
370
371
372
373
374
375
376
377
378
379
380
381
382
383
384
385
386
387
388
389
390
391
392
393
394
395

Table 1b: cohort description of ER+ low and ER + intermediate.

Characteristics	[ALL] N=119	ER ⁺ - low N=83	ER ⁺ - intermediate N=36	p.overall
Race:				0.883
White	74 (67.3%)	50 (67.6%)	24 (32.4%)	
Black or African American	22 (20.0%)	16 (72.7%)	6 (27.3%)	
Asian	2 (1.82%)	1 (50.0%)	1 (50.0%)	
Other Race	12 (10.9%)	7 (58.3%)	5 (41.7%)	
Ethnicity:				1.000
Hispanic or Latino	10 (8.40%)	7 (70.0%)	3 (30.0%)	
Non-Hispanic	109 (91.6%)	76 (69.7%)	33 (30.3%)	
MenopausalStatus:				0.237
Perimenopausal	3 (2.52%)	1 (33.3%)	2 (66.7%)	
Postmenopausal	78 (65.5%)	54 (69.2%)	24 (30.8%)	
Premenopausal	26 (21.8%)	21 (80.8%)	5 (19.2%)	
Unknown/not documented	12 (10.1%)	7 (58.3%)	5 (41.7%)	
Histology:				0.941
Ductal	106 (89.1%)	75 (70.8%)	31 (29.2%)	
Lobular	5 (4.20%)	3 (60.0%)	2 (40.0%)	
Mixed	2 (1.68%)	1 (50.0%)	1 (50.0%)	
Other	6 (5.04%)	4 (66.7%)	2 (33.3%)	
TumorGrade:				0.250
Grade 1	7 (6.03%)	4 (57.1%)	3 (42.9%)	
Grade 2	26 (22.4%)	15 (57.7%)	11 (42.3%)	
Grade 3	83 (71.6%)	61 (73.5%)	22 (26.5%)	
KI67:				0.238
<20%	11 (20.0%)	10 (90.9%)	1 (9.09%)	
>=20%	44 (80.0%)	30 (68.2%)	14 (31.8%)	
Clinical T stage:				1.000
1	19 (37.3%)	14 (73.7%)	5 (26.3%)	
2	23 (45.1%)	16 (69.6%)	7 (30.4%)	
3	9 (17.6%)	6 (66.7%)	3 (33.3%)	
Clinical N stage:				1.000
0	28 (60.9%)	19 (67.9%)	9 (32.1%)	
1	14 (30.4%)	10 (71.4%)	4 (28.6%)	
2	4 (8.70%)	3 (75.0%)	1 (25.0%)	
PrimaryRadiotherapy:				0.838
No/unknown	43 (36.1%)	29 (67.4%)	14 (32.6%)	
Yes	76 (63.9%)	54 (71.1%)	22 (28.9%)	
EndocrineTherapy:				0.007
No	50 (42.0%)	42 (84.0%)	8 (16.0%)	
Yes	69 (58.0%)	41 (59.4%)	28 (40.6%)	
Chemotherapy:				0.004

Characteristics	[ALL] N=119	ER ⁺ low N=83	ER ⁺ intermediate N=36	p.overall
Anthracycline without taxane	3 (2.52%)	0 (0.00%)	3 (100%)	
Taxane without anthracycline	19 (16.0%)	15 (78.9%)	4 (21.1%)	
Taxane and anthracycline	55 (46.2%)	36 (65.5%)	19 (34.5%)	
Other	2 (1.68%)	0 (0.00%)	2 (100%)	
No info on chemo	40 (33.6%)	32 (80.0%)	8 (20.0%)	
Surgery:				0.766
Mastectomy	62 (52.1%)	42 (67.7%)	20 (32.3%)	
Other	57 (47.9%)	41 (71.9%)	16 (28.1%)	
Age	58.6 [47.2;66.4]	54.9 [44.4;67.0]	60.7 [54.6;66.1]	0.130
Follow_up (months)	30.0 [15.0;54.0]	30.5 [14.2;57.8]	30.0 [16.5;51.0]	0.910

398

Abbreviations: Estrogen Receptor, ER.

Triple negative defined as ER and PR <1% staining; ER⁺ low 1%-9.99% staining; ER⁺ intermediate 10%-19.99%; ER⁺-high ≥20% staining.

399

Table 2. Comparison between ER low⁺ and ER intermediate⁺ groups

Characteristics		Group		P value*
		ER ⁺ - low n = 83	ER ⁺ - intermediate n = 36	
Ethnicity	Hispanic or Latino	7 (8.43)	3 (8.33)	1.000
	Non-Hispanic	76 (91.57)	33 (91.67)	
Race	Asian	1 (1.35)	1 (2.78)	.727
	Black or African American	16 (21.62)	6 (16.67)	
	Other	7 (9.46)	5 (13.89)	
	White	50 (67.57)	24 (66.67)	
Menopausal Status	Perimenopausal	1 (1.2)	2 (5.56)	0.214
	Postmenopausal	54 (65.06)	24 (66.67)	
	Premenopausal	21 (25.3)	5 (13.89)	
	Unknown/not documented	7 (8.43)	5 (13.89)	
Histology	Ductal	75 (90.36)	31 (86.11)	0.694
	Lobular	3 (3.61)	2 (5.56)	
	Mixed	1 (1.2)	1 (2.78)	
	Other	4 (4.82)	2 (5.56)	
Tumor Grade	Grade 1	4 (5)	3 (8.33)	0.229
	Grade 2	15 (18.75)	11 (30.56)	
	Grade 3	61 (76.25)	22 (61.11)	
KI67	<20%	10 (25)	1 (6.67)	0.255
	≥20%	30 (75)	14 (93.33)	
Clinical T stage	1	14 (38.89)	5 (33.33)	1.000
	2	16 (44.44)	7 (46.67)	
	3,4	6 (16.67)	3 (20)	
Clinical N stage	0	19 (59.38)	9 (64.29)	1.000
	1	10 (31.25)	4 (28.57)	
	2,3	3 (9.38)	1 (7.14)	
Primary Radiotherapy	No/unknown	29 (34.94)	14 (38.89)	0.684
	Yes	54 (65.06)	22 (61.11)	
Surgery	mastectomy	42 (50.6)	20 (55.56)	0.691

Table 2. Comparison between ER low* and ER intermediate* groups

Characteristics		Group		P value*
		ER ⁺ - low n = 83	ER ⁺ - intermediate n = 36	
Endocrine therapy	other	41 (49.4)	16 (44.44)	0.005
	Yes	42 (50.6)	8 (22.22)	
	No	41 (49.4)	28 (77.78)	
Chemotherapy	Other	0 (0)	2 (7.14)	0.009
	Anthracycline without taxane	0 (0)	3 (10.71)	
	Taxane without anthracycline	15 (29.41)	4 (14.29)	
	Taxane and anthracycline	36 (43)	19 (53)	
Age (years)	Mean	55.62	59.53	.130
	Median	54.91	60.65	
	Minimum	26.99	31.05	
	Maximum	80.06	81.46	
	Standard deviation	13.33	11.66	
Follow-up (months)	Mean	55.62	59.53	.130
	Median	54.91	60.65	
	Minimum	26.99	31.05	
	Maximum	80.06	81.46	
	Standard deviation	13.33	11.66	

Abbreviations: ER, Estrogen Receptor, ER

** ER⁺- low 1%-9.99% staining and ER⁺- intermediate 10%-19.99% staining.

* The non-parametric P value is calculated by the Kruskal-Wallis test for numerical covariates and Fisher exact test for categorical covariates.

Table 3. Cox proportional hazards regression -Comparative analysis of recurrence free survival (RFS) and overall survival of ER⁺- High and ER⁺- low tumors.

Recurrence-free survival analysis of maximum likelihood estimates									
Parameter		Degree of freedom	Parameter estimate	Standard error	Chi-Square	P value	Hazard ratio	95% Hazard ratio confidence limits	
*ER ⁺ -High/Her2 ⁻	Ref ER ⁺ -low/ Her2 ⁻	1	-0.59231	0.26311	5.0678	.024	0.553	0.330	0.926
Age under 50	Ref (50 or above)	1	-0.14587	0.15137	0.9286	.335	0.864	0.642	1.163
Endocrine therapy	Ref (no)	1	-0.89719	0.17325	26.8186	<.001	0.408	0.290	0.573
Primary radiotherapy	Ref (no)	1	-0.55534	0.11269	24.2846	<.001	0.574	0.460	0.716

Fitting model to the test set, at 3 years recurrence-free survival, Harrell's c-statistic = 0.677.

Overall Survival Analysis of Maximum Likelihood Estimates									
ER ⁺ - High/Her2 ⁻	Ref (ER ⁺ -low/ Her2 ⁻)	1	-0.69144	0.30380	5.1799	.023	0.501	0.276	0.908
Age under 50	Ref (50 or above)	1	-0.60046	0.20565	8.5258	.004	0.549	0.367	0.821
Endocrine therapy	Ref (no)	1	-0.79007	0.20488	14.8702	.001	0.454	0.304	0.678
Primary radiotherapy	Ref (no)	1	-0.63333	0.13218	22.9577	<.001	0.531	0.410	0.688

Fitting model to the test set, at 3 years overall survival, Harrell's c-statistic = 0.698.

Abbreviations: CI, confidence interval, CI; ER, estrogen receptor; Ref, reference.

*ER⁺- low 1%-19.9% staining; ER⁺ -high ≥20% staining.

Table 4. Endocrine therapy treatment effect (univariate analysis)

Parameter	Recurrence free survival				Overall survival		
	Patients, no.	Events, no.	HR (95% CI)	P value	Events, no.	HR (95% CI)	P value
Patient who received ET							
ER ⁺ - low (1-9.99%)	41	5	Ref	Ref	3	Ref	Ref
ER ⁺ - intermediate (10-20%)	28	5	1.47 (0.42, 5.08)	.545	5	2.57 (0.61, 10.77)	.196
Patient who did not receive ET							
ER ⁺ - low (1-9.99%)	42	16	Ref	Ref	10	Ref	Ref
ER ⁺ - intermediate (10-20%)	8	2	0.38 (0.05,2.86)	.346	1	n/a	n/a

Abbreviations: CI, confidence interval; ER, estrogen receptor; HR, hazard ratio; n/a, not applicable; Ref, reference, inadequate sample size to estimate.

Figure legends

Fig. 1 Clinical outcomes of patients with ER+ and TNBC BCs. Triple negative defined as ER/PR < 1% staining and HER2- (i.e., IHC 0/1+ and non-amplified); ER+ ≥ 1% staining. Abbreviations: Breast cancer, BC; Estrogen Receptor, ER; Human Epidermal growth factor receptor 2, HER2; immunohistochemistry (IHC).

Fig. 2 Clinical outcomes of patients with TN, low-, intermediate- and High-ER+ BCs. Triple negative defined as ER and PR < 1% staining, ER⁺- low 1-9.99% staining, ER⁺-inter, 10-19.99%, ER⁺- high ≥ 20% staining. Abbreviations: Breast cancer, BC; Estrogen Receptor, ER; Human Epidermal growth factor receptor 2, HER2; triple negative, TN.

Fig. 3 Clinical outcomes of patients with ER low positive vs. ER high positive BCs. ER⁺- low 1-19.9% staining and ER⁺- high ≥ 20% staining. Abbreviations: Breast cancer, BC; Estrogen Receptor, ER.

Supplementary Fig 1. Kaplan Meyer curve demonstrating recurrence free survival of ER⁺ low and ER + Intermediate patients who received ET vs those who did not. Abbreviation- ER⁺- low 1-9.99% staining, ER⁺-inter, 10-19.99%, ER⁺, ET-Endocrine therapy

Figures

Figure 1. Clinical outcomes of patients with ER+ and TNBC BCs.

Figure 1

Clinical outcomes of patients with ER+ and TNBC BCs. Triple negative defined as ER/PR < 1% staining and HER2- (i.e., IHC 0/1+ and non-amplified); ER+ ≥ 1% staining. Abbreviations: Breast cancer, BC; Estrogen Receptor, ER; Human Epidermal growth factor receptor 2, HER2; immunohistochemistry (IHC).

Figure 2. Clinical outcomes of patients with TN, low-, intermediate- and High-ER+ BCs.

Figure 2

Clinical outcomes of patients with TN, low-, intermediate- and High-ER+ BCs. Triple negative defined as ER and PR < 1% staining, ER+ - low 1-9.99% staining, ER+ - inter, 10-19.99%, ER+ - high $\geq$ 20% staining. Abbreviations: Breast cancer, BC; Estrogen Receptor, ER; Human Epidermal growth factor receptor 2, HER2; triple negative, TN.

Figure 3. Clinical outcomes of patients with ER low positive vs. ER high positive BCs.

Abbreviations: Breast cancer, BC; Estrogen Receptor, ER.
ER+ low 1-19.9% staining and ER+ high $\geq 20\%$ staining.

Figure 3

Clinical outcomes of patients with ER low positive vs. ER high positive BCs. ER+ - low 1-19.9% staining and ER+ - high $\geq 20\%$ staining. Abbreviations: Breast cancer, BC; Estrogen Receptor, ER.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Supplementary material ER Cutpoint breast Cancer Res Treat.pdf](#)