Impact of Duration of Adjuvant Endocrine Therapy on Clinical Outcomes in BRCA pathogenic variant Carriers with HR+/HER2- Early Breast Cancer

Paola Zagami[1], Antonio Marra[1,2], Serena Perazzo[1], Grazia Castellano[1,2], Ambra Carnevale Schianca[1,2], Bianca Malagutti[1,2], Elisa Giordano[1,2], Mariarosaria Calvello[3], Monica Marabelli[3], Dario Trapani[1,2], Nicola Fusco[2,5], Elena Guerini Rocco[2,5], Sara Gandini[6], Elisabetta Munzone[4], Aliana Guerrieri-Gonzaga[3], Bernardo Bonanni[3], Giuseppe Curigliano[1,2]

[1] Early Drug Development for Innovative Therapies, European Institute of Oncology IRCCS, Milan, Italy, [2] Department of Oncology and Hemato-Oncology, University of Milano, Milan, Italy [3] Division of Cancer Prevention and Genetics, European Institute of Oncology IRCCS, Milan, Italy [4] Division of Medical Senology, European Institute of Oncology IRCCS, Milan, Italy [5] Division of Pathology, European Institute of Oncology IRCCS, Milan, Italy [6] Department of Experimental Oncology, European Institute of Oncology IRCCS, Milan, Italy.

BACKGROUND

There is limited evidence on the effect of extended adjuvant endocrine therapy (ET) in patients with hormone receptor-positive/HER2-negative (HR+/HER2-) early breast cancer (EBC) carrying germline BRCA (gBRCA) mutations compared to non-carriers.

We investigated the association between extended ET (eET), defined as therapy lasting more than 5 years, versus standard-duration ET and clinical outcomes in gBRCA mutation carriers with HR+/HER2- EBC.

METHODS

- This cohort study derived from an institutional database, including all consecutive patients with BC who underwent germline testing at the European Institute of Oncology (May 2002-Jan 2024).

Key inclusion criteria	Key exclusion criteria
Stage I-III invasive breast cancer	Stage IV de novo breast cancer
HR+/HER2- EBC	HR-/HER2+ EBC
BC diagnosis between January 2000 and December 2022	Lack of clinical/ follow-up data
Adjuvant endocrine therapy	Missed data on endocrine therapy

- Primary endpoints were distant relapse-free interval (DRFI) and invasive disease-free survival (iDFS), as defined by STEEP 2.0 criteria.
- Survival analyses were conducted using univariate and multivariate Cox proportional-hazard models, stratified for year of diagnosis, use of (neo)adjuvant chemotherapy, nodal status, tumor size and grade, stage, duration of ET, type of ET, BC surgery and BRCA mutations. Hazard ratio (HR) with 95% confidence interval (95%CI) were reported.
- Left-truncated models accounted for the interval between BC diagnosis and genetic testing. Landmark analysis was performed to calculate the cumulative incidence of events over time.

RESULTS

Among 1,225 eligible patients, the median duration of adjuvant ET was 60 months (IQR 49–74), with a median age of 41 years (IQR 36–47). The majority were premenopausal (79%, n=973), and 42% had stage I disease. Sixty percent received eET and 80% received LHRH agonists (Table 1).

Overall, 164 patients (13%) were gBRCA1/2 mutation carriers, mostly gBRCA2 (76%). Carriers were younger than non-carriers and more likely to have higher tumor stage (Table 1).

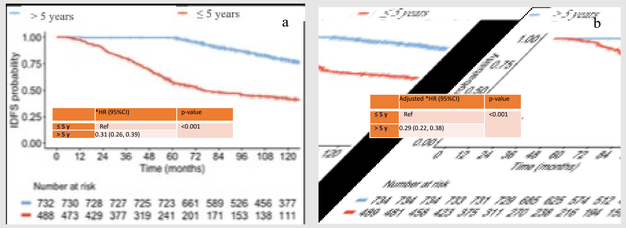
Table 1. Clinico-pathological characteristics of the patients.

Characteristic	Overall N = 1,225[1]	BRCA1/2 Status: Mutated N = 164[1]	BRCA1/2 Status: WT N = 1,061[1]	p-value[2]
Age Median (Q1, Q3)	41 (36, 47)	39 (35, 44)	42 (36, 48)	0.001
Adjuvant ET Type				0.3
AI	401 (33%)	49 (30%)	352 (33%)	
Tamoxifen	651 (53%)	86 (52%)	565 (53%)	
Tamoxifen, AI	173 (14%)	29 (18%)	144 (14%)	
ET Duration Median(Q1,Q3)	60 (49, 74)	60 (39, 71)	60 (50, 74)	0.049
Tumor Grade				<0.001
Low grade	804 (71%)	73 (47%)	731 (75%)	
Grade 3	332 (29%)	82 (53%)	250 (25%)	
N/A	89	9	80	
ET_Duration				0.071
>5 years	736 (60%)	88 (54%)	648 (61%)	
≤5 years	489 (40%)	76 (46%)	413 (39%)	
Menopausal_Status				0.065
NA	1 (<0.1%)	1 (0.6%)	0 (0%)	
Postmenopausal	251 (20%)	28 (17%)	223 (21%)	
Premenopausal	973 (79%)	135 (82%)	838 (79%)	
Stage				0.018
I	488 (42%)	50 (32%)	438 (43%)	
II	487 (42%)	80 (51%)	407 (40%)	
III	192 (16%)	27 (17%)	165 (16%)	
N/A	58 (0.8%)	7 (0.6%)	51	
Received neoadjuvant CT	93 (7.6%)	15 (9.1%)	78 (7.4%)	0.4
Received adjuvant CT	446 (36%)	92 (56%)	354 (33%)	<0.001

RESULTS

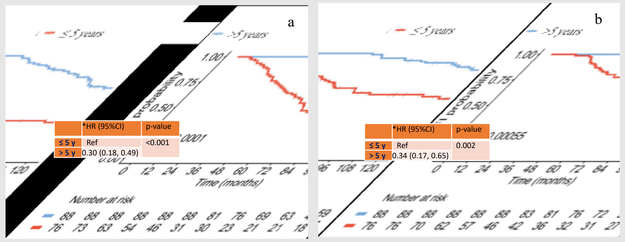
- At a median follow-up of 11.1 years (IQR [8.2–15.2]), extended ET was associated with significantly improved iDFS (HR [HR] 0.30, 95% CI 0.25–0.36, p<0.001) (Fig 1a) and DRFI (HR 0.29, 95% CI 0.22–0.38, p<0.001) (Fig.1b), compared to standard-duration ET. BRCA mutation status was associated to reduced iDFS (aHR 1.5, 95% CI 1.14–1.96, p=0.003), but not with DRFI.

Fig 1. iDFR (a) and DFRI (b) by extended endocrine therapy in the overall population



- In the subgroup of BRCA mutation carriers, with a median follow up of 12.3 years (IQR 9.3 vs 15.4), eET remained significantly associated with improved iDFS and DRFI compared to ET of 5 years or less (Fig 2).

Fig 2. DFR (a) and DFRI (b) by extended endocrine therapy in the overall population



*stratified for year of diagnosis, (neo)adjuvant chemotherapy, nodal status, tumor size and grade, stage, type of ET, BC surgery

RESULTS

- Landmark analysis showed that eET was consistently associated with improved DRFI at 60 months (aHR 0.21, 95% CI 0.13–0.33, p<0.001), 84 months (aHR 0.27, 95% CI 0.18–0.43, p<0.001), and 120 months (aHR 0.57, 95% CI 0.37–0.89, p=0.013) (Table 2).

Table 2. Cumulative Incidence of DRFI by BRCA/eET Group At 5, 7, and 10 Years (y)

Group	5-Year Risk	7-Year Risk	10-Year Risk
≤5y– gBRCA WT	25.3%	33.0%	38.3%
>5y– gBRCA WT	0.2%	4.0%	9.8%
≤5y–gBRCA-mutated	32.5%	40.4%	44.4%
>5y–gBRCA-mutated	0.0%	6.9%	13.3%

CONCLUSION

In this cohort of BRCA mutation carriers with HR+/HER2- early breast cancer, extended adjuvant ET (>5 years) was significantly associated with improved invasive disease-free survival and distant relapse-free interval compared to 5 years of ET. These findings support the potential benefit of prolonged endocrine therapy in this high-risk population.

CONTACT

Paola.Zagami@ieo.it

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