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# Retrospective analysis of outcomes of HR-positive/HER2-negative early-stage breast cancer patients from adjuvant GEICAM studies and El Álamo IV registry


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GEICAM spanish breast cancer group

## INTRODUCTION

Adjuvant endocrine therapy (ET) reduces the risk of recurrence and death in hormone receptor (HR)-positive/human epidermal growth factor receptor 2 (HER2)-negative early breast cancer (EBC)[1] and is the standard of care in these patients regardless the use of chemotherapy (CT). However, recurrences are still common, with risk of recurrences ranging from 10% to 41%[2].

The combination of CDK4/6 inhibitors with ET, have demonstrated an improvement in outcomes in patients with intermediate and high-risk HR-positive/HER2-negative EBC:

The **monarchE study**[3] showed a benefit in invasive Disease-Free Survival (iDFS) in patients with **high-risk** HR-positive/HER2-negative breast cancer with two years of **abemaciclib** plus standard ET: 5-year iDFS rate in the abemaciclib + ET arm was 83.6% compared to 76.0% in the ET alone arm.

The **NATALEE study**[4], showed that the addition of 3 years of **ribociclib** to ET improves the 4-year iDFS compared with ET alone (88.5% versus 83.6%) in patients with **intermediate and high-risk** HR-positive/ HER2-negative EBC patients.

Understanding the risk of recurrence and timing of relapse in a real population of EBC treated in recent years can be of great help when interpreting the results of trials with new adjuvant drugs.

**Fig. 1. iDFS in the monarchE study**

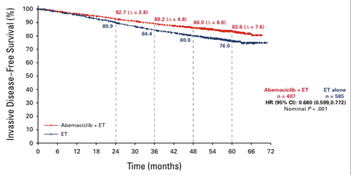
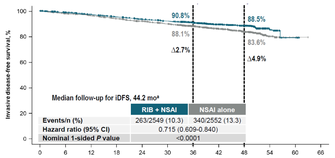



**Fig. 2. iDFS in the NATALEE study**




## OBJECTIVES

✓ **Co-Primary Objectives and Endpoints:**

- **Invasive Disease-Free Survival (iDFS) at 10 years:** defined as the time from adjuvant ET initiation to the first date of diagnosis of any of the following events: ipsilateral (local/regional) invasive breast cancer (BC) recurrence, distant BC recurrence, contralateral invasive BC, second non-breast invasive cancer and death due to any cause, whatever occurs first.
- **Distant Disease-Free Survival (DDFS) at 10 years:** defined as the time from adjuvant ET initiation to the first date of diagnosis of any of the following events: distant BC recurrence, second non-breast cancer and death due to any cause, whatever occurs first.
- **Overall Survival (OS) at 10 years:** defined as the date of adjuvant ET initiation to the date of death from any cause.

✓ **Secondary Objectives and Endpoints :**

- **Yearly Invasive Relapse Rate (yIRR) at years 1 to 10:** defined as the proportion of patients with ipsilateral (local/regional) invasive BC recurrence or distant BC recurrence per year.
- **Yearly Distant Relapse Rate (yDRR) at years 1 to 10:** defined as the proportion of patients with distant BC recurrence per year (either as first or subsequent recurrence if first recurrence is local/regional).
- **Yearly Death Rate at 1-10 years:** defined as the proportion of deaths per year.

## MATERIALS AND METHODS

✓ The analysis included data from HR-positive/HER2-negative EBC patients with lymph node-negative (N0) or lymph node-positive (N+) disease, treated with adjuvant ET that were enrolled in El Alamo IV registry and 5 adjuvant studies (GEICAM/9805[5]: TAC* vs. FAC* in N0; GEICAM/2003-02[6]: FAC* vs. FAC-wP* in N0; GEICAM/9906[7]: FEC* vs. FEC-wP* in N+; GEICAM/2003-10[8]: EC-T* vs. ET-X* in N+; GEICAM/2006-10[9]: fulvestrant [3 years] + anastrozole [5 years] vs anastrozole [5 years] in N0 and N+).

✓ Patients were eligible if they meet all the following criteria: Stage I-III, HR-positive/HER2-negative disease, have received adjuvant ET.

✓ **Patients (n=8,825) were divided into 3 cohorts according to their risk of recurrence:** Cohort 1 (high-risk: stage III), Cohort 2 (intermediate-risk: T2N1, T0N1, T1N1, **T3N0 or T2N0 plus either histological Grade (G)3, or GX/G2 with Ki-67 ≥20%) and Cohort 3 (low-risk: stage I and T2N0** plus either G1, or GX/G2 with Ki-67 <20%).

***Abbreviations: A:** doxorubicin, **C:** cyclophosphamide, **E:** epirubicin, **F:** fluorouracil, **H:** trastuzumab, **T:** docetaxel, **wP:** weekly paclitaxel, **X:** capecitabine.

**Table 1. Patients' distribution by study**

| | GEICAM/ 9805 | GEICAM/ 2003-02 | GEICAM/ 9906 | GEICAM/ 2003-10 | GEICAM/ 2006-10 | *El ÁLAMO IV* | Total |
|---|---|---|---|---|---|---|---|
| Cohort 1 | 0 | 0 | 257 | 336 | 146 | 1030 | 1769* |
| Cohort 2 | 65 | 193 | 417 | 616 | 347 | 1541 | 3179* |
| Cohort 3 | 323 | 906 | 0 | 0 | 256 | 2392 | 3877 |
| Total | 388 | 1099 | 674 | 952 | 749 | 4963 | 8825 |

*95.0% and 80.1% of patients had N+, respectively.

**Table 2. Baseline characteristics**

Median age was 55 years (range 19-90), most patients were female (99.5%) and 82.5% had invasive ductal carcinoma.

| | Cohort 1 N= 1,769 | Cohort 2 N= 3,179 | Cohort 3 N= 3,877 | Total N= 8,825 |
|---|---|---|---|---|
| **Histopathological grade, n (%)** | | | | |
| G1, well differentiated | 226 (12.8%) | 550 (17.3%) | 1070 (27.6%) | 1,846 (20.9%) |
| G2, moderately differentiated | 776 (43.9%) | 1356 (42.6%) | 1782 (46.0%) | 3,914 (44.3%) |
| G3, poorly differentiated | 485 (27.4%) | 972 (30.6%) | 625 (16.1%) | 2,082 (23.5%) |
| GX, unknown | 282 (15.9%) | 301 (9.5%) | 400 (10.3%) | 983 (11.1%) |
| **Menopausal status, n (%)*** | | | | |
| Postmenopausal | 651 (37.1%) | 1241 (39.2%) | 1295 (33.6%) | 3187 (36.3%) |
| Premenopausal | 1075 (61.2%) | 1871 (59.1%) | 2516 (65.2%) | 5462 (62.2%) |
| Not available | 31 (1.8%) | 55 (1.7%) | 48 (1.2%) | 134 (1.5%) |
| **Ki-67, n (%)** | | | | |
| < 20% | 557 (31.5%) | 937 (29.5%) | 1,792 (46.2%) | 3,286 (37.2%) |
| ≥ 20% | 587 (33.2%) | 976 (30.7%) | 1,207 (31.1%) | 2,770 (31.4%) |
| Unknown | 625 (35.3%) | 1,266 (39.8%) | 878 (22.6%) | 2,769 (31.4%) |
| **Prior CT, n (%)**** | | | | |
| No | 198 (11.2%) | 377 (11.9%) | 1,587 (40.9%) | 2,162 (24,5) |
| Yes | 1,571 (88.8%) | 2,802 (88.1%) | 2,290 (59.1%) | 6,663 (75.5) |
| **Type of adjuvant ET, n (%)***** | | | | |
| SERM | 651 (36.9%) | 1,150 (36.2%) | 1,378 (35.5%) | 3,179 (36.1%) |
| SERM + Aromatase Inhibitors | 532 (30.2%) | 972 (30.6%) | 1,256 (32.4%) | 2,760 (31.3%) |
| Aromatase Inhibitors | 505 (28.6%) | 881 (27.7%) | 1,112 (28.7%) | 2,498 (28.3%) |
| Aromatase inhibitors + SERD | 74 (4.2%) | 167 (5.3%) | 123 (3.2%) | 364 (4.1%) |
| Other | 2 (0.2%) | 6 (0.1%) | 8 (0.2%) | 16 (0.1%) |

*Only considering female patients: 1757 in Cohort 1, 3167 in Cohort 2 and 3859 in Cohort 3.
** Anthracycline-based CT was the most used regimen in 52.2% of patients (38.5%, 48.5%, and 66.2% in Cohort 1, 2, and 3, respectively).
***ET was unknown in 5 patients from Cohort 1 and 3 from Cohort 2. The median exposure time to adjuvant ET was 5 years (range: 0.-15 years), similar across all cohorts.

## RESULTS

### Invasive-Disease-Free Survival, Distant Disease-Free Survival and Overall Survival

At 5 and 10 years, iDFS were 87.9% and 74.3%, DDFS were 89.5% and 77.7%, and OS were 94.0% and 84.2%, respectively

**Fig. 3. Kaplan-Meier Plot for iDFS by Cohorts**

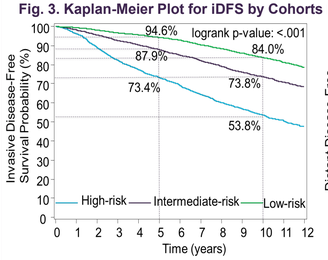



**Fig. 4. Kaplan-Meier Plot for DDFS by Cohorts**

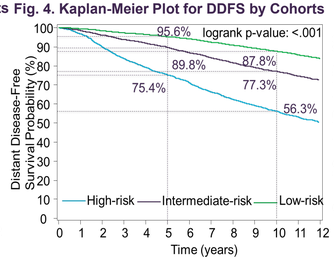
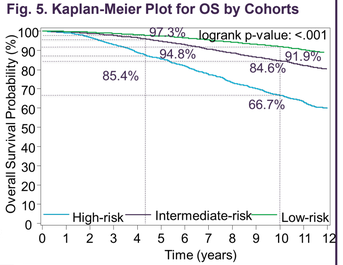



**Fig. 5. Kaplan-Meier Plot for OS by Cohorts**




| Cohort | Events n(%) | Censored n(%) | Median (95% CI) | Hazard Ratio, p |
|---|---|---|---|---|
| Cohort 1 | 871 (49.2%) | 898 (50.8%) | 11.1 (10.3-12.2) | 3.31 (3.01-3.64), p<0.001 |
| Cohort 2 | 925 (29.1%) | 2254 (70.9%) | 16.7 (15.3- ) | 1.63 (1.49-1.80), p<0.001 |
| Cohort 3 | 800 (20.6%) | 3077 (79.4%) | | |

| Cohort | Events n(%) | Censored n(%) | Median (95% CI) | Hazard Ratio, p |
|---|---|---|---|---|
| Cohort 1 | 825 (46.6%) | 944 (53.4%) | 12.2 (11.1-12.7) | 4.08 (3.67-4.53), p<0.001 |
| Cohort 2 | 798 (25.1%) | 2381 (74.9%) | | 1.83 (1.65-2.04), p<0.001 |
| Cohort 3 | 612 (15.8%) | 3265 (84.2%) | | |

| Cohort | Events n(%) | Censored n(%) | Median (95% CI) | Hazard Ratio, p |
|---|---|---|---|---|
| Cohort 1 | 649 (36.7%) | 1120 (63.3%) | 14.6 (14.1- ) | 4.26 (3.77-4.81), p<0.001 |
| Cohort 2 | 567 (17.8%) | 2612 (82.2%) | | 1.81 (1.60-2.05), p<0.001 |
| Cohort 3 | 433 (11.2%) | 3444 (88.8%) | | |

### Invasive Relapse Rate, Distant Relapse Rate and Death Rate

High-risk Intermediate-risk Low-risk

**Fig. 6. IRR at 1-10 years**

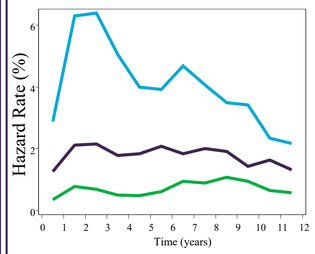



**Fig. 7. DRR at 1-10 years**

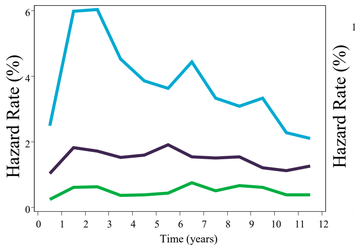
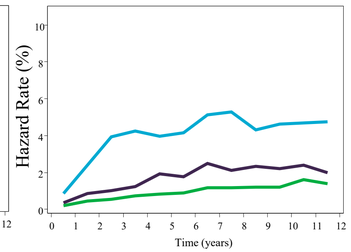



**Fig. 8. DR at 1-10 years**




## CONCLUSIONS

- **Intermediate-risk pts have a 5 and 10-y iDFS of 87.9% and 73.8%, and 5 and 10-y OS of 94.8% and 84.6%.**
- **The IRR, DDR and DR increased steadily in the intermediate-risk cohort (as in the low-risk cohort), in contrast to the high-risk cohort (where earlier peaks are observed).**
- **Longer Follow-up of the NATALEE study is needed to see the potential benefit of adjuvant ribociclib in the intermediate-risk patients.**

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