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Impact of prior CDK4/6 inhibitor treatment on the efficacy of everolimus and exemestane or fulvestrant in hormone receptor positive HER-2 negative (HR+/HER2-) metastatic breast cancer (MBC). A restropective analysis of 144 patients

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Abstract

- **Purpose**: Everolimus plus endocrine therapy is a standard treatment in HR+/HER2- MBC. Although, in BOLERO-2 trial1 no one of these patients received treatment with CDK4/6 inhibitor, which is the standard first line nowadays. The purpose of this study is to evaluate progression-free survival (PFS) and overall survival (OS) according to prior CDK4/6 inhibitor exposure in patients treated with everolimus plus exemestane or fulvestrant.
- **Methods**: Retrospective analysis of women > 18 years with HR+/HER2- MBC treated in our center with the combination of everolimus plus exemestane or fulvestrant between October 2010 and October 2023.
- **Results**: 144 patients included, 93 with prior CDK4/6 inhibitor treatment and 51 with no prior CDK4/6 inhibitor. Median PFS 7.4 months in the overall population, 8.2 month if previously treated with CDK 4/6 and 6.1 months if no previously treated with CDK4/6 inhibitor.
- **Conclusion**: Patient who received prior CDK4/6 inhibitor had a trend to lower PFS and OS with everolimus + endocrine treatment than those who did not received, although this difference was not statistically significant.

Introduction

- Everolimus in combination with exemestane is approved for the treatment of HR+/HER2- MBC based on the BOLERO-2 trial (2012) results with increased PFS for the combination compared with exemestane alone (10.6 vs 4.1 months).
- PrE01022 analyzed the efficacy of fulvestrant and everolimus in patients who has become resistant to aromatase inhibitor. This study showed a median PFS of 10.3 month with the combination compared with 5.1 with fulvestrant alone.
- Since the CDK4/6 inhibitor (palbociclib, ribociclib, abemaciclib) combined with endocrine therapy has became standard first-line treatment, data on the effectiveness of everolimus plus exemestane after progression on CKD4/6 inhibitor remain limited.
- Some retrospective studies such as Hanjie et al3, and smaller series like Cook M et al4, have reported modest benefit with exemestane plus everolimus in this setting.
- Our objective is to compare PFS and OS according to prior CKD4/6 inhibitor exposure in patients treated with everolimus plus exemestane or fulvestrant.

Methods and Materials

- **Study design**: Retrospective single center study.
- **Population**: Women > 18 year with HR+/HER2- MBC treated with the combination of everolimus plus exemestane or everolimus plus fulvestrant between October 2010 and October 2023.
  - **cohort 1** patients without previous CDK4/6 inhibitor.
  - **cohort 2** patient with previous CDK/6 inhibitor (palbociclib or ribociclib).
- **Endpoints**:
  - **Primary:** PFS according to prior CDK4/6 inhibitor treatment.
  - **Secondary:** OS in these same population.
- **Statistical Tools**: Data described using medians for continuous variables, and frequency and percentages for categorical. Long rank test to compared PFS and OS between groups. Cox proportional hazard to compute HR. p values two-sided with 0,05 as level of significance.
- **Analysis**: conducted June 2025. IRB-approved.

Patient Characteristics	Overall population N= 144	No prior CDK4/6 N= 51	Prior CDK 4/6 n= 93
Age at primary tumor diagnosis	53,54 (32-19)	59.3 (27-77)	58.3 (34.3-80.8)
Age at dissemination	59,1 (34-80)	58,9	59,02 (34-80)
Postmenopause	111 (77%)	42 (82%)	69 (74%)
Stage IV at diagnosis	49 (34%)	13 (25.4%)	36 (38.7%)
Previous endocrine lines on metastatic setting			
1	87 (53.4%)	19 (37.2%)	68 (73%)
2	41 (28.4%)	22 (43.13%)	19 (20.4%)
3	13 (9%)	7 (13.7%)	6 (6.6%)
4	3 (2%)	3 (5.8%)	0 (0%)
Previous chemotherapy on metastatic setting	39 (27%)	22 (43.1%)	17 (18.2%)
Last treatment line duration	17.5 months (0.92-74.7)	13.3 months (0.9-38.2)	19.7 months (1.6-74.7)
Everolimus concomitant endocrine treatment			
Fulvestrant	44 (30.5%)	1 (2%)	43 (46.2%)
Exemestane	100 (69.4%)	50 (98%)	50 (53.7%)

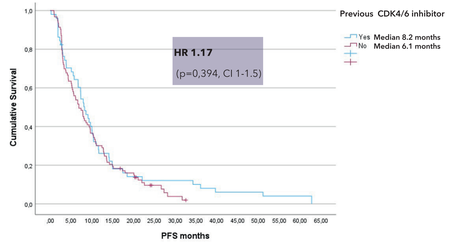
Table 1: Baseline Characteristics

Results

144 women included. Median follow up 31.3 month (2.23-103).
Table 1 highlights baseline characteristics.

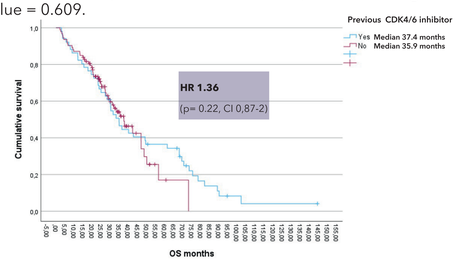
Progression free survival:

- 137 events. Cohort 1: 51 (100%); cohort 2: 87 (93.5%).
- Median PFS: 7.8 months in the overall population (95%CI 6.5 to 9 months), 8.2 month in cohort 1 (95%CI 6.2 to 10.3 months) and 6.1 months in cohort 2 (95% CI 4.8 to 9 months). Stratified long rank p value =0.392.
- No statistical significance even adjusted for age, previous treatment lines, previous treatment line duration.



Overall survival:

- 90 events. Cohort 1: 44 (86%); Cohort 2: 46 (49%).
- Median OS: 35.5 months in the overall population (95% CI 28.4 to 42.4 months), 37.4 month in cohort 1 (95%CI 28 to 47 months) and 35.9 months in cohort 2 (95% CI 27.7 to 42 months). Stratified long rank p value = 0.609.



Cox regression model for OS:

Variable	HR (95% CI)	P-value
Prior CDK4/6 inhibitor	HR 1,36 (1,0-1,6)	0,39
Prior chemotherapy	2,41 (1,50-3,87)	< 0,001
Prior hormonal lines	0,68 (0,52-0,88)	0,003

Discussion

- **Everolimus combined with endocrine therapy remains an active treatment** option after progression on CDK4/6 inhibitor. Although we observed a trend toward shorter PFS and OS in patient previously exposed to CDK4/6 inhibitor, was not an independent predictor of worse outcomes in the multivariable analysis.
- A higher number of **prior hormonal therapy lines was associated with improved survival**.
- Prior c**hemotherapy for metastatic disease** identified a subgroup with more aggressive biology and **poorer prognosis**.
- Our results are **aligned with real world studies** such as Mo et al. and Cook et al, supporting the continued role of everolimus after CDK 4/6 inhibitor failure, although the magnitude of benefit appears smaller than that reported in the pre CDK 4/6 inhibitor era.
- Hankie M and colleagues, with a larger series of 192 patients, reported significant difference in PFS but not in OS. The PFS and OS reported in our study are better than the reported in the previous mentioned.
- **Limitations** to the study: retrospective, did not reported hormone receptor status, Ki67, ESR1 mutation status, or presence of visceral metastases, witch may have impacted outcomes.

CONCLUSIONS

- Everolimus plus endocrine therapy provides a maintained therapeutic benefit in patients with HR+/HER2- metastatic breast cancer after progression on CKD 4/6 inhibitor . Prior CDK 4/6 exposure dos not appear to independently compromise treatment efficacy.
- These results support everolimus-based therapy as a reasonable option in the post-CDK 4/6 setting, while the optimal sequencing of targeted therapies in HR+/HER2- MBC continues to evolve.
- Prospective studies are warranted to refine patient selection and confirm the impact of prior treatment exposure on outcomes.

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