#P881: COMPLETE TUMOR RESPONSE DURING FIRST-LINE ET PLUS CDK4/6i PREDICTS EXCELLENT CLINICAL OUTCOMES IN PATIENTS WITH HORMONE RECEPTOR-POSITIVE, HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR 2-NEGATIVE (HR+/HER2-) ADVANCED BREAST CANCER (ABC)

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BACKGROUND

- The combination of CDK4/6 inhibitors and endocrine therapy (ET) is the **standard first-line treatment** for patients with HR+/HER2- aBC.
- In some malignancies, **radiological complete response (CR)** predicts durable benefit, but its prognostic role in HR+/HER2- aBC treated with first-line ET plus CDK4/6 inhibitors has never been explored.

The aim of this study is to investigate the impact of achieving a radiological CR on survival outcomes, and to identify clinical and tumor-related factors associated with a higher likelihood of CR.

METHODS

- Dataset: PALMARES-2 (NCT06805812), multicenter observational Italian study enrolling HR+/HER2- aBC patients treated with 1L ET+CDK4/6i; data from 2nd study data cut-off (Jan 2025 - **Figure 1**).
- Objectives: *primary*: association between best radiologic response [(**CR**, partial response (**PR**), stable disease (**SD**), progressive disease (**PD**)] and **rwPFS**; *secondary*: impact of CR on **rwOS**, **rwTTC;** impact of CR in **endocrine sensitive** and **resistant** subgroups.
- Data and response: response assessed as per local practice (CT/FdG-PET/other) and classified as CR/PR/SD/PD; follow up ≥6 months required.
- Statistical analysis: standard descriptive statistics for covariate distribution; Kaplan-Meier and multivariable Cox model for rwPFS, rwTTC and rwOS assessment; logistic regression to identify CR predictors.

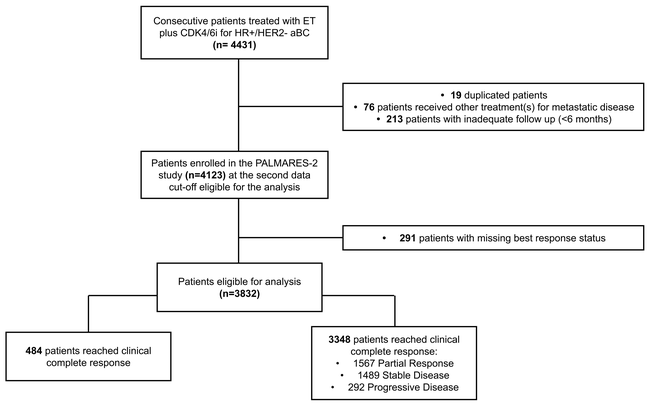


Figure 1. Study Flow chart.

RESULTS

Characteristic	Overall (N = 3,832)	CR (N = 484)	no-CR (N = 3,348)	p-value
Age	62 (53, 71)	59 (50, 68)	62 (53, 71)	<0.001
PS ECOG				<0.001
• 0	2,994 (78%)	431 (89%)	2,563 (77%)	
• 1	714 (19%)	50 (10%)	664 (20%)	
• ≥2	124 (3.2%)	3 (0.6%)	121 (3.6%)	
Sex and Menopausal status				<0.001
• Man	45 (1.2%)	3 (0.6%)	42 (1.3%)	
• Postmenopausal	3,107 (81%)	367 (76%)	2,740 (82%)	
• Premenopausal	680 (18%)	114 (24%)	566 (17%)	
Histology				0.13
• ILC	707 (18%)	84 (17%)	623 (19%)	
• NST	2,843 (74%)	374 (77%)	2,469 (74%)	
• Other	282 (7.2%)	26 (5.4%)	256 (7.6%)	
ER expression	90 (85, 95)	90 (90, 95)	90 (85, 95)	0.070
PgR expression	40 (5, 80)	50 (10, 80)	40 (4, 80)	0.019
Ki67 expression	20 (15, 30)	20 (15, 30)	20 (15, 30)	0.15
HER2low				0.074
• 0	1,600 (42%)	184 (38%)	1,416 (42%)	
• Low	2,232 (58%)	300 (62%)	1,932 (58%)	
Denovo sensitive				0.3
• De novo metastatic	1,235 (32%)	157 (32%)	1,078 (32%)	
• Endocrine Resistant	1,282 (33%)	148 (31%)	1,134 (34%)	
• Endocrine Sensitive	1,356 (34%)	179 (37%)	1,136 (34%)	
Number Metastatic Sites				<0.001
• 1	1,575 (41%)	255 (53%)	1,320 (39%)	
• 2	1,324 (35%)	157 (32%)	1,167 (35%)	
• 3	646 (17%)	53 (11%)	593 (18%)	
• ≥4	287 (7.5%)	19 (3.9%)	268 (8.0%)	
Liver Metastasis	824 (22%)	66 (14%)	758 (23%)	<0.001
Bone Metastasis	2,678 (70%)	296 (61%)	2,454 (71%)	<0.001
Lung Metastasis	979 (26%)	83 (17%)	896 (27%)	<0.001
SNC Metastasis	118 (3.1%)	7 (1.4%)	111 (3.3%)	0.026

Table 1. Patient baseline characteristics by radiological response (CR vs no-CR)

- Best response to 1L ET+CDK4/6i: **CR 12.6%** (n=484), PR 40.9%, SD 38.9%, PD 7.6%. Patient baseline characteristics in **Table 1**.
- Using multivariable Cox regression model (**Figure 2**), achieving CR remained the strongest independent predictor of prolonged rwPFS.
- Achieving **CR** was associated with markedly prolonged **rwPFS** (median 64 vs 25 months for PR/SD; aHR 0.39, p<0.001; **Figure 3A**), **rwTTC** (median not reached vs 35.3 months; aHR 0.25, p<0.001; **Figure 3B**), and **rwOS** (median not reached vs 64.9 months; aHR 0.24, p<0.001; **Figure 3C**).
- Higher age, ECOG PS, Ki67 level and metastatic burden, as well as endocrine resistance, were associated with lower probability of achieving CR, whereas higher ER tumor expression and the presence of node metastasis were associated with an increased probability (**Figure 4**).

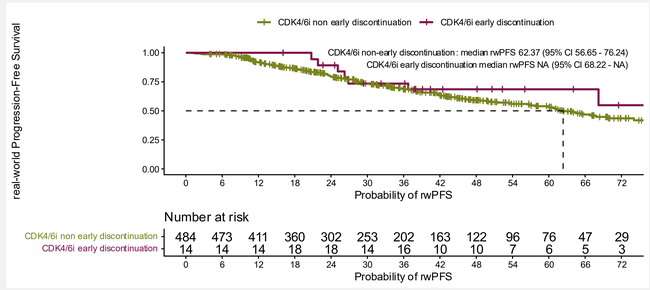
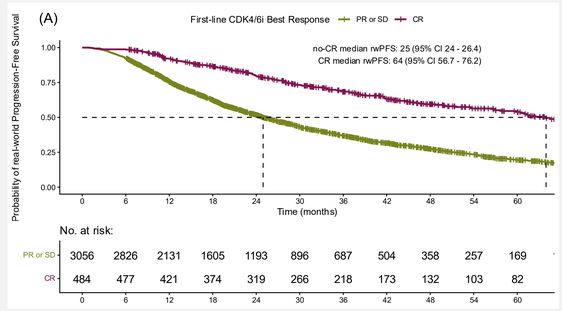
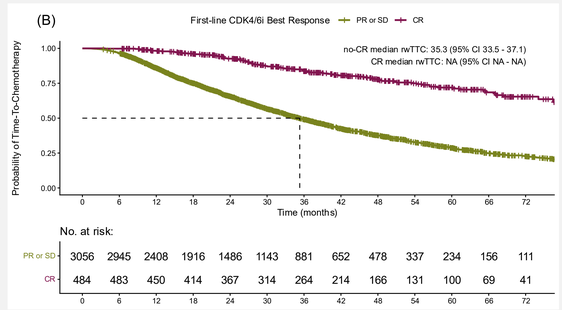


Figure 5. Time-dependent effect of CDK4/6i discontinuation on rwPFS in patients achieving CR on 1°-line ET+CDK4/6i.





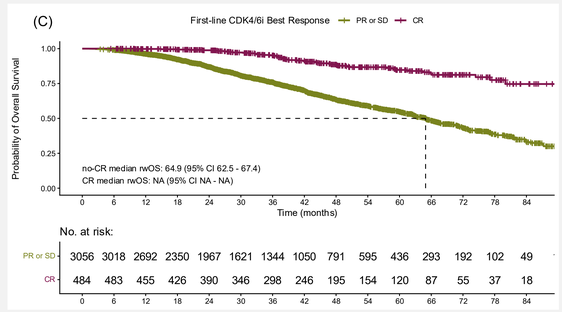


Figure 3. Kaplan-Meier curve of rw-PFS (A), rw-TTC (B) and rw-OS (C) according to best radiologic response: CR vs PR/SD.

- In both **endocrine-sensitive** and **endocrine-resistant** subgroups, CR was consistently associated with **longer rwPFS, rwTTC, and rwOS**, with median rwOS not reached in CR patients in either subgroup.
- Using time-dependent Cox regression model, **CDK4/6i discontinuation** due to **treatment toxicity** in patients achieving CR was not associated with lower rwPFS (**Figure 5**) or rwOS.

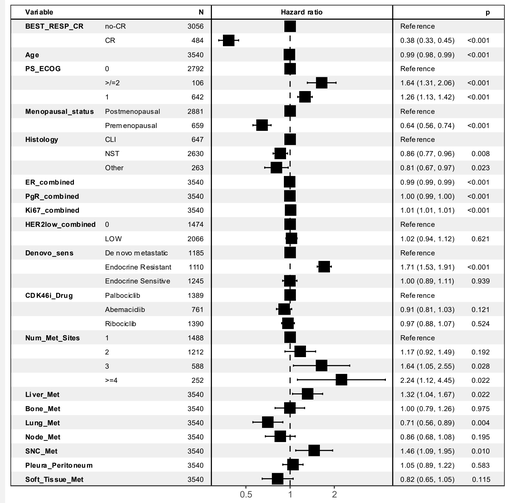


Figure 2. Multivariable Cox regression model evaluating the impact of CR and covariates on rwPFS.

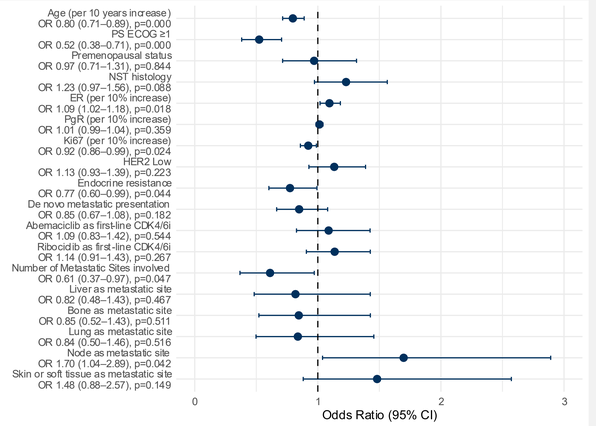


Figure 4. Logistic regression evaluating the effect of covariates on the probability of achieving CR.

Achieving CR on first-line ET+CDK4/6i in HR+/HER2- aBC is associated with excellent outcomes and may support more personalized management, including safer CDK4/6i dose reduction/discontinuation in case of toxicity and tailored radiologic follow-up.

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