

<https://doi.org/10.29289/259453942025V35S1059>

## CDK4/6 inhibitors in breast cancer: is it possible to predict response?

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**Introduction:** Up to 20% of luminal breast cancer patients present recurrent disease within ten years. The development of cyclin-dependent kinase 4 and 6 inhibitors (CDK4/6) has transformed treatment paradigms due to significant improvements in outcomes. However, no predictive biomarker has been identified despite extensive translational research. Additionally, evidence on CDK4/6 efficacy in specific populations (e.g., pathogenic germline carriers) and clinical scenarios (treatment sequencing, combinatorial strategies, and post-CDK4/6 therapy) remains limited. **Objective:** This study aimed to review clinical, histological, and genomic profile searching for predictive variables of better responses. **Methods:** This is a retrospective study of luminal breast cancer patients treated with three available CDK4/6: abemaciclib (AB), ribociclib (RIB), and palbociclib (PB), between 2018 and 2024. **Results:** A total of 378 patients were included, with a median age of 60 years; 38% were pre-menopausal. Median progression-free survival (PFS) and overall survival (OS) were 30 and 56 months (m), respectively. Most (65%) received CDK4/6 in 1L, 15% in 2L, and 20% in later lines. PFS and OS declined progressively: 1L (36/62m), 2L (22/52m), others (14/33m) ( $p < 0.01$ ). No significant PFS ( $p = 0.96$ ) or OS ( $p = 0.42$ ) differences were observed between CDK4/6 (AB 24/43m; RIB 25/45m; PB 27/45m). Patients with visceral metastasis had worse PFS/OS (28 vs. 32m,  $p = 0.009$ ; 49 vs. 60m,  $p = 0.01$ ). High Ki67 (>70%) predicted poorer outcomes (PFS 15 vs. 29m,  $p = 0.009$ ; OS 34 vs. 56m,  $p = 0.017$ ). **Conclusion:** These results may help refine patient selection and therapeutic strategies and serve as a basis for prospective studies aiming to validate predictive biomarkers in hormone receptor-positive metastatic breast cancer.

**Keywords:** breast cancer; immunohistochemistry.