https://doi.org/10.29289/259453942025V35S1011

CDK4/6 inhibitor plus endocrine therapy after progression on CDK4/6 inhibition in HR+/HER2- advanced breast cancer: a systematic review and meta-analysis (ReIGNITE study)

Luiz Felipe Costa de Almeida[1], Luís Felipe Leite da Silva[1], Mariana Gouveia[2], Brenda Ernst[3], Jesse Lopes da Silva[4], Andreia Cristina de Melo[4], Paolo Tarantino[5], Felipe Batalini[3]

[1]Universidade Federal Fluminense, Department of Medical Sciences – Niterói (RJ), Brazil.
[2]Hospital 9 de Julho, Departament of Clinical Oncology, DASA – São Paulo (SP), Brazil.
[3]Mayo Clinic, Department of Medical Oncology – Phoenix (AZ), United States of America.
[4]Instituto Nacional de Cancer, Division of Clinical Research and Technological Development – Rio de Janeiro (RJ), Brazil.
[5]Dana-Farber Cancer Institute, Department of Medical Oncology – Boston (MA), USA.

Objective: To systematically evaluate the efficacy and safety of cyclin-dependent kinase 4 and 6 inhibitors (CDK4/6) combined with endocrine therapy (ET) compared to ET alone in patients with hormone receptor-positive and human epidermal growth factor receptor-type 2-negative (HR+/HER2-) advanced breast cancer who progressed to prior CDK4/6 therapy. **Methods:** This systematic review and meta-analysis adhered to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines and was registered in the International Prospective Register of Systematic Reviews (PROSPERO), under CRD420251007031). Randomized clinical trials were identified through comprehensive searches on PubMed, Cochrane, Embase databases, and in ASCO, ESMO, and SABCS conference proceedings. The primary outcome was progression-free survival, analyzed using hazard ratios (HR) with a random-effects model and 95% confidence intervals (CI). Adverse effects were evaluated through pooled odds ratios (OR). **Results:** Five randomized clinical trials encompassing 1,184 patients were included. Overall, CDK4/6 plus ET significantly improved progression-free survival versus ET alone, yielding a HR of 0.72 (95%CI 0.56–0.92; p<0.05). Subgroup analyses highlighted superior efficacy when patients switched to a different CDK4/6 following progression (HR 0.61; 95%CI 0.48–0.77; p<0.05), whereas continuation of the same agent showed no significant benefit (HR 0.93; 95%CI 0.68–1.28; p=0.15). Genetic profiling demonstrated that patients harboring PIK3CA mutations experienced notable progression-free survival improvement (HR 0.71; 95%CI 0.52–0.98; p<0.05), whereas no significant benefit was observed among patients with ESR1 mutations (HR 0.86; 95%CI 0.60–1.24; p=0.06). CDK4/6 plus ET significantly increased odds of anemia (OR 2.67; 95%CI 1.45–4.93; p<0.05), neutropenia (OR 19.27; 95%CI 9.94–37.35; p<0.05), thrombocytopenia (OR 4.51; 95%CI 2.20–9.25; p<0.05), and diarrhea (OR 4.29; 95%CI 1.28–14.39; p<0.05) compared to ET alone. **Conclusion:** Treatment with CDK4/6 combined with ET beyond CDK4/6 progression demonstrated significant clinical benefit in HR+/HER2- advanced breast cancer, particularly when switching between different CDK4/6. Patients with PIK3CA mutations notably benefitted from this strategy. These findings provide critical insights for the refinement of future clinical guidelines.

Keywords: cyclin-dependent kinase inhibitor proteins; breast neoplasms; meta-analysis.