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Overall survival with first versus second-line use of CDK4/6 inhibitors in HR+/HER2- advanced breast cancer

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Background

The phase 3, randomized SONIA trial (NCT03425838) evaluated the optimal timing of cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) use in patients with hormone receptor positive (HR+), HER2 negative (HER2-) advanced breast cancer (ABC), comparing addition to first-line (aromatase inhibitor [AI]) versus second line (fulvestrant) endocrine therapy. We previously reported that first-line CDK4/6i use did not significantly improve progression-free survival after two lines of therapy (PFS2; primary endpoint) compared to second line use (hazard ratio [HR] 0.87; 95% CI 0.74-1.03) and was associated with greater toxicity and higher drug costs. Here we present the prespecified overall survival (OS) analysis.

Methods

A total of 1,050 patients were randomized 1:1 to AI + CDK4/6i followed by fulvestrant or AI followed by fulvestrant + CDK4/6i. OS was a key secondary endpoint analyzed using log-rank testing and Cox proportional hazards modeling. This prespecified analysis was triggered when all patients had ≥3 years of follow-up.

Results

At a median follow-up of 58.5 months, 606 deaths (58%) had occurred, and 263 patients (25%) remained on study treatment. Median OS was 47.9 months with first-line CDK4/6i and 48.1 months with second line CDK4/6i (HR 0.91; 95% CI 0.77-1.07, *P* = 0.24), showing no significant or clinically meaningful difference. Results were consistent across all predefined subgroups, including CDK4/6i type (palbociclib or ribociclib). A post-hoc subgroup analysis suggests an OS benefit with first-line use in premenopausal patients (HR 0.53; 99% CI 0.27–1.02), but not in postmenopausal patients (HR 1.00; 99% CI 0.80–1.25; P for interaction = 0.01). Among patients who discontinued second line treatment, 85% (CDK4/6i first) and 84% (CDK4/6i second) received subsequent anti-cancer therapy, with similar treatment patterns. No new safety signals were observed.

Conclusions

First-line CDK4/6i use does not confer a statistically significant or clinically meaningful overall survival benefit over second line use in HR+/HER2- ABC, despite more toxicity and higher costs. Exploratory data suggest an OS benefit with first-line use in premenopausal patients.

Clinical trial identification

NCT03425838.

Legal entity responsible for the study

BOOG Study Center representing the Dutch Breast Cancer Research Group (BOOG).

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Disclosure

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