Efficacy and Safety of PI3K Inhibitors on Hormone Receptor Positive, HER-2 Negative Advanced Breast Cancer: A Meta-Analysis of Phase III Randomized Controlled Trials

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Introduction

- The phosphoinositide 3-kinase pathway is crucial for cell growth, survival, and proliferation.
- The efficacy and safety of PI3K inhibitors in hormone receptor–positive, HER2-negative advanced breast cancer are an area of active investigation.

Methods

PubMed, Embase and Cochrane were systematically searched for randomized controlled trials (RCTs) phase III comparing PI3K inhibitors plus standard of care to placebo plus standard of care along in patients with hormone receptor-positive, HER2-negative advanced breast cancer.

OUTCOMES

- Progression-free survival (PFS)
- Overall survival (OS)
- Objective response rates (ORR)
- Clinical benefit rate (CBR)
- Adverse events (AEs)

A random-effects model was used to synthesize pooled hazard ratio (HR)/risk ratio (RR) with 95% confidence intervals (CIs).

Results

2992 patients

5 Randomized Controlled trials

- BELLE 2 2016
- BELLE 3 2017
- INAVO 120 2024
- SANDPIPER 2021
- SOLAR 1 2019

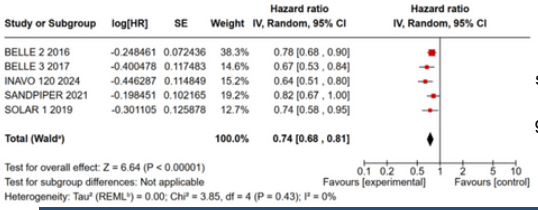
1650 (55.1%) PIK3 Inhibitors

1342 (44.9%) Placebo

MOST FRECUENT AEs

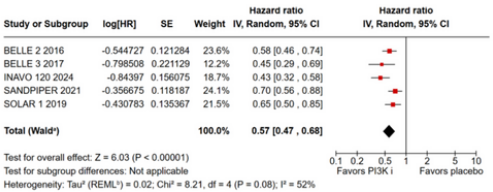
- Hyperglycemia (50.7%) - 16.5% were grade 3 or more.
- Diarrhea (44.6%) - 5.8% were grade 3 or more.
- Nausea (34.8%)
- Rash (32.4%) - 4.1% were grade 3 or more.
- Stomatitis (28.9%)

PROGRESSION FREE SURVIVAL - PIK3 GROUP



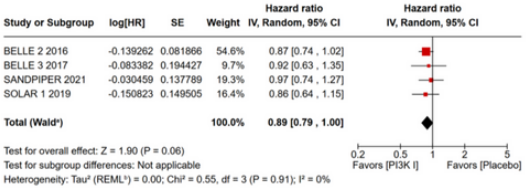
PFS was statistically significant in PI3K group (HR 0.65; 95% CI 0.58-0.81; p < 0.00001; I² 0%)

PROGRESSION FREE SURVIVAL - PIK3 MUTATION



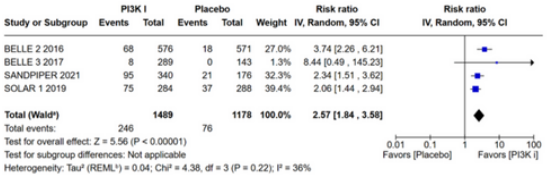
PFS was statistically significant in PI3K path-way activated population (HR 0.57; 95% CI 0.45-0.72; p <0.00001, I² 52%).

OVERALL SURVIVAL



OS was not statistically significant between the groups (HR 0.89; 95% CI 0.79-1.00; p 0.06; I² 0%).

OBJECTIVE RESPONSE RATES



ORR analysis and clinical benefit rate (CBR) were higher in PI3K inhibitors group (RR 2.57; 95% CI 1.84-3.58; p < 0.00001; I² 36%), (RR 1.62; 95% CI 1.38-1.91; p < 0.00001; I² 36%) respectively.

Conclusions

PI3K inhibitors demonstrate a favorable efficacy profile across key outcomes; however, toxicity remains a concern that may limit broader use. These findings support continued development to optimize dosing strategies, identify predictive biomarkers, and refine patient selection to maximize benefit while minimizing risk. Further randomized trials and real-world studies are needed to define their place in therapy and to compare head-to-head with alternative regimens.

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