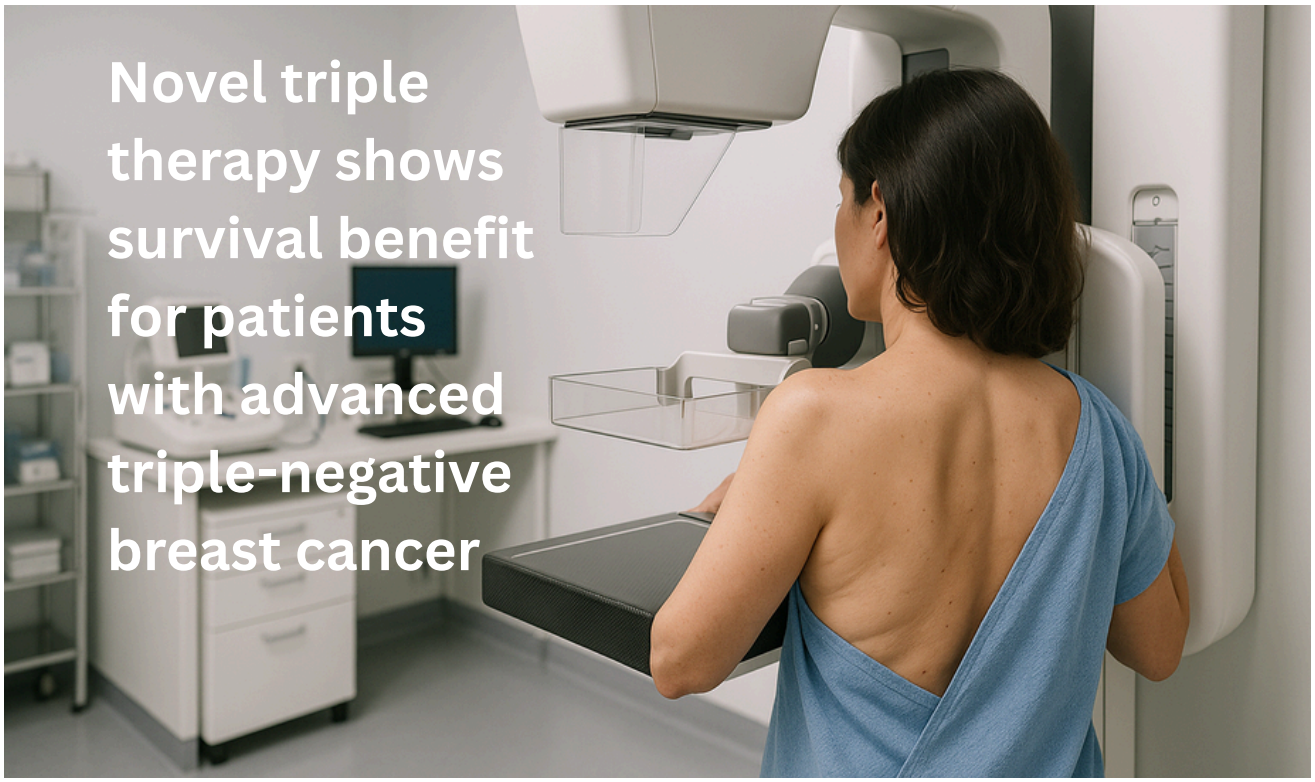

Novel triple therapy shows survival benefit for patients with advanced triple-negative breast cancer

by Cliff Dominy PhD

A new triple drug combination therapy can extend the overall survival time for patients with breast tumours resistant to conventional chemotherapy.

The INAVO120 Trial showed a statistically significant survival benefit for patients with advanced triple-negative breast cancer.

In the study, a novel tumour inhibitor combined with two other anti-tumour drugs extended overall survival time for patients with advanced stage recurrent breast cancer.

The trial reported that patients receiving the triple therapy experienced a survival benefit of 7 additional months compared to those on a dual therapy regimen and 44 additional months relative to current standard of care therapy.

The study …

INAVO120 was published in the May 2025 edition of the New England Journal of Medicine [1]. It reported updated data from the original INAVO120 paper which came out earlier in the year [2]. All three drugs in the triple therapy target different cancer mechanisms involved in supporting the tumour's growth.

The INAVO120 trial was a phase 3, double-blind, randomized study conducted across 28 countries, enrolling 325 patients between January 2020 and September 2023. The study randomly assigned 161 patients to receive inavolisib combined with palbociclib and fulvestrant, while 164 patients received palbociclib and fulvestrant only.

Each drug in the therapy targets a different tumour pathway. The intervention drug, inavolisib, is a novel antibody-drug conjugate which targets the PIK3CA nutrient sensor involved in redirecting energy to growing tumours. By contrast, palbociclib, a CDK4/6 inhibitor, interferes with the tumour cells replication cycle. The third drug, fulvestrant, degrades the estrogen receptor, reducing the sex hormones' influence on tumour development.

Patients eligible for the study were those without diabetes and with locally advanced or metastatic triple-negative breast cancer who experienced disease recurrence within 12 months after completion of primary therapy. The primary outcome was progression-free survival, whilst the secondary endpoint of the study was the objective response rate of patients to the new drug, inavolisib.

The goal of INOVA120 was to evaluate the benefit of the third drug inavolisib, in the progression-free survival of patients with advanced disease. The palbociclib and fulvestrant dual therapy functioned as the placebo arm in the new study.

And the results …

The results were statistically significant. After a median follow-up of 34.2 months in the triple therapy group and 32.3 months in the dual therapy (placebo) group, the results showed compelling efficacy. The median overall survival reached 34.0 months in patients receiving triple therapy compared to 27.0 months in the placebo group, with a statistically significant survival benefit of 33% relative to the dual therapy arm.

The survival probabilities showed consistent benefit across all time points, with 96.8% of triple therapy patients alive at 6 months compared to 90.1% in the placebo group, and 56.5% versus 46.3% respectively at 30 months.

The objective response rate, the percentage of patients showing a benefit from the treatment, was higher in the triple therapy group at 62.7% compared to 28.0% in the placebo group ($P<0.001$). There was a 58% reduction in the risk of disease progression or death with triple therapy.

The downside …

Any new therapy carries the risk of side effects. The triple therapy intervention had a 6.8% dropout rate versus 0.6% in the dual therapy arm. The most commonly reported side effect was raised blood sugar, blurred vision and gastrointestinal complaints. Deaths of participants in both arms were attributed to the underlying breast cancer rather than the therapy.

THE MANY FACES OF BREAST CANCER

Breast cancer is the most common form of cancer in women and has the second highest mortality rate after lung cancer. Breast tumours can be classified by the cell types in which they form, with invasive ductal carcinoma accounting for 80% of all cases. They can also be classified by the molecular mechanisms which drive their growth. If tumour progression is facilitated by the HER2 growth factor, monoclonal antibodies targeting HER2 - such as Herceptin, show good efficacy in treating the disease. Herceptin plus chemotherapy has a 37% improvement in overall survival over chemotherapy alone [3.] The patient's 10-year survival expectancy is now 84%.

In the absence of HER2-driven growth, drugs such as tamoxifen provide a significant survival benefit of 47% increase over 25 years [4.] The challenge is to treat the remaining subset of breast tumours, the so-called triple negative cancers, which account for 10-15% of all breast cancer cases. Triple negative breast cancer is aggressive, typically striking women of African descent, younger women under the age of 40, and those who carry the BRCA1 gene mutation. These tumours are hormone receptor positive (both estrogen and progesterone), HER2 negative and have mutations in the pI3K signalling pathway. PI3K, is normally involved in cell growth and metabolism, but when overexpressed, can drive tumour formation in a variety of cancer types.

Strengths and limitations

The INAVO120 trial was a well-powered controlled trial designed to detect a therapeutic benefit of inavolisib in the treatment of triple-negative breast cancer. The patients were recruited internationally, suggesting that the INAVO120 results were both robust and generalizable.

The authors noted the results may be more pronounced if applied as a first-line therapy in a newly diagnosed cancer population where drug resistance has not yet developed.

A limitation of the trial was the highly selected patient population in terms of their genetic mutation profile and overall metabolic health. A larger study, started earlier in the disease progression, will be required to establish the clinical usefulness of triple therapy in a broader population.

In summary, the INAVO120 trial represents an important step forward for women in the advanced stages of a life-threatening disease. The success of this combination therapy opens new avenues for research into multi-pathway targeting strategies and may inform the development of similar approaches for other cancer types.

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