Precision medicine improves outcomes in metastatic breast cancer

For breast cancers that have spread, a randomized phase II clinical trial shows that using genomic analysis to target therapies can improve outcomes, but only in people with a genetic alteration that has previously been associated with antitumour activity in clinical trials.

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At a glance

Study design: A phase II randomized trial evaluating the efficacy of targeted therapies matched to genomic alterations.

Population: 1,462 individuals with metastatic breast cancer underwent genomic analysis; 238 were randomized to targeted or maintenance therapy.

Analysis: Targeted therapy improved survival when matched to genomic alterations previously associated with drug sensitivity.

Conclusion: Targeted treatment decisions should be based on firm evidence that genomic alterations are clinically relevant.

The unmet medical need

Around 600,000 women worldwide died in 2020 because of metastatic breast cancer, in which tumours have spread to other parts of the body. The disease is driven in part by genetic alterations, and DNA analyses have shown that the genetic changes involved vary considerably between cancers[1]. Oncologists now use multigene DNA sequencing to identify the driver genomic alterations for each person's cancer[2] and try to offer a matched targeted therapy — one that blocks the molecular mechanisms activated by a certain alteration. Although this method is widely used, it remains unclear how best to use the results, and there is little evidence that the approach improves outcomes. The ESMO Scale for Clinical Actionability of Molecular Targets (ESCAT)[3] was developed to improve the interpretation of genomic sequencing for clinical use. ESCAT is a framework that ranks genomic alterations in six tiers according to evidence about their value as clinical targets[3]. Tier I alteration–drug matches are associated with improved outcomes in rigorous clinical trials. Tier II matches show antitumour activity, but the benefit to individuals is less certain. The clinical use of mutations in lower tiers is supported by relatively weak evidence.

The study and its findings

To evaluate the clinical benefit of genomic sequencing and its interpretation by ESCAT, we performed a comparative randomized trial called SAFIR02. In total, 1,462 people with metastatic breast cancer underwent genomic analysis and 646 had genomic alterations that could be targeted. Of those, 238 people took part in two subsequent trials that compared standard chemotherapy to a targeted therapy that was matched with the individual's genomic alteration (Fig. 1). The efficacy of targeted therapies was assessed according to the ESCAT classification of the genomic alteration being blocked.

The trial showed that targeted therapies matched to genomics extended the period before the disease progressed further (called progression-free survival) when genomic alterations were classified as tier I or II according to ESCAT (adjusted hazard ratio, 0.41; 90% confidence interval, 0.27–0.61; $P < 0.001$). (A hazard ratio of one indicates no difference in survival between the two treatment groups.) In a subgroup analysis, no improvement in progression-free survival was observed in the targeted therapies arm compared with maintenance chemotherapy (unadjusted hazard ratio, 1.15; 95% confidence interval, 0.76–1.75) for people whose cancer had an ESCAT alteration that did not fall into tiers I or II.

The SAFIR02 trial provides evidence that genomic sequencing improves outcomes for a subset of people. It suggests that genome-sequencing results should be used to guide treatment decisions only for people whose cancers have a tier I/II genomic alteration according to ESCAT.

Outlook for the future

- Although the present study focused on people with metastatic breast cancer, its main findings should apply to other types of cancer, but this should be tested in further trials.
- Future targeted drug development and clinical trials could also increase the number of mutations classed as ESCAT tier I or II.
- The present study used a limited number of drugs, and did not formally test a specific DNA-sequencing technology.
- The next frontier in the field of cancer precision medicine is to integrate profiles of DNA, RNA, proteins and the tumour microenvironment into a comprehensive portrait that guides treatment decisions. Research that combines applied mathematics with experimental biology will aim to model the cancer biology of each person on the basis of these bespoke molecular portraits.

Fabrice Andre and **Gustave Roussy** are at the University of Paris Saclay, Villejuif, France.

EXPERT OPINION

"This is the first report of a prospective randomized clinical trial testing a genomic assay to select the optimal maintenance therapy, versus conventional maintenance chemotherapy (standard of care). This trial represents a major step in developing a new cohort of innovative trials based on a conceptual design in modern personalized medicine."

Alessandra Gennari is at the University of Piemonte Orientale, Novara, Italy.

FIGURE

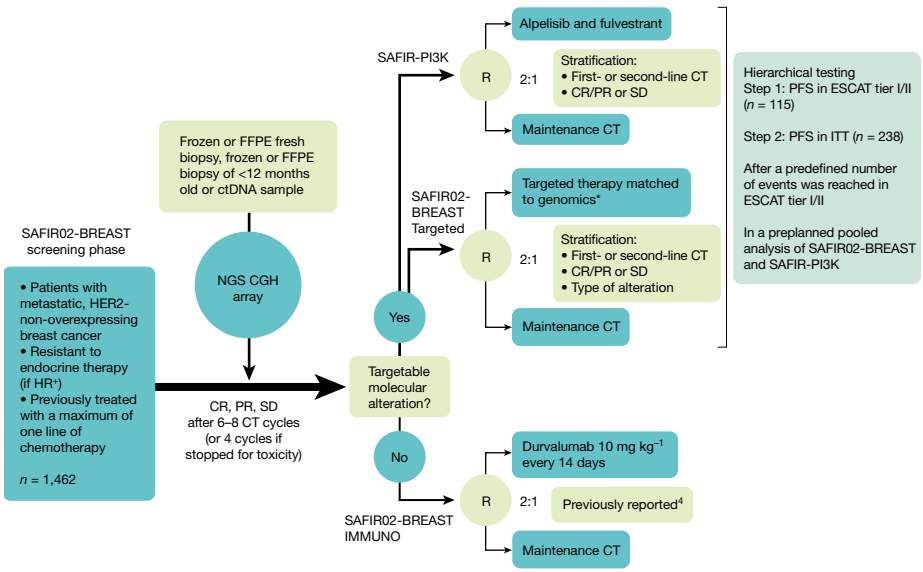

Figure 1 | Design of a randomized trial evaluating targeted therapies based on genomic analysis. People with metastatic breast cancer without overexpression of the receptor HER2, which promotes cancer-cell growth, and who had received no more than one line of chemotherapy were selected. A biopsy was done unless one had been performed less than 12 months before inclusion; the biopsy was frozen or formalin-fixed and paraffin-embedded (FFPE). If a biopsy was not feasible, a plasma sample was obtained to analyse circulating tumour DNA (ctDNA). Multigene next-generation sequencing (NGS) and comparative genomic hybridization (CGH) arrays were performed. After six to eight cycles of chemotherapy (CT), individuals who met the inclusion criteria and had a genomic alteration that could be targeted by a drug available in the trial were randomized (R) into two trials (SAFIR02-BREAST Targeted and SAFIR-PI3K) and received either targeted therapy matched to their cancer's genomics or maintenance chemotherapy. The trial used hierarchical testing, starting with the population of individuals whose cancers have ESCAT tier I/II alterations, followed by the overall population. SAFIR02-BREAST IMMUNO trial results were published previously[4]. *Drugs included olaparib, capivasertib, vistusertib, AZD8931, vandetanib, bicalutamide, AZD4547 and selumetinib. CR, complete remission; ESCAT, ESMO Scale of Clinical Actionability of Molecular Targets; HR, hormone receptor; ITT, intention to treat; PFS, progression-free survival; PR, partial remission; SD, stable disease.

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FROM THE EDITOR

This study uses a logical, practical trial design to show how genomic profiling for cancer can be beneficial in the clinic. It provides a framework for transforming the wealth of available genomic information into scores that can match people to the most-effective treatments.

Victoria Aranda, Senior Editor, *Nature*