Study opens new prospects for developing new targeted therapies for breast cancer

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A study led by prominent breast cancer experts from Europe and the US has revealed a number of potentially important prospects for targeted therapies, and brings opportunities of truly personalised therapy for breast cancer a step closer, researchers said at the 5th IMPAKT Breast Cancer Conference in Brussels, Belgium.

The IMPAKT meeting presents cutting edge, 'translational' breast cancer research that is beginning to have an impact for patients.

This current study was led by Dr Martine Piccart, Director of Medicine at the Jules Bordet Institute in Brussels, and Dr Jose Baselga, Associate Director at Memorial Sloan-Kettering Cancer Center, New York.

The researchers used modern sequencing technology to characterise the genetic aberrations of cancer genes present in tumour samples from a well-defined cohort of advanced postmenopausal patients who were enrolled in the BOLERO-2 clinical trial.

"The results of this study generated hypotheses for developing more rational targeted therapy combinations based on the specific genetic aberrations present in each individual tumour," Dr Piccart said.

"This work, together with previous works published last year, highlights again the genetic heterogeneity of breast cancer. These results show that tumours that may look very similar at the clinical level, can be genetically very different, suggesting that they may require different

treatment strategies."

"There is still a long way to go before we will be able to offer truly personalised therapies to cancer patients, and support for research such as this will be critical to accelerate this process," Dr Piccart said.

The study involved postmenopausal women with advanced breast cancer that was hormone receptor positive and HER2 negative taking part in the BOLERO-2 phase III trial. The trial showed that everolimus plus exemestane significantly improved progression-free survival, response rate and clinical benefit rate versus placebo plus exemestane. Although benefits were seen in all prospectively defined subgroups of women who took part, the researchers noted some variations, partially due to genetic differences in molecular determinants of everolimus sensitivity and interactions between the oestrogen receptor and mTOR pathways.

In the current analysis, researchers used next-generation sequencing to assess genetic alterations in archival tumour specimens from 230 tumours. They analysed coding regions of 182 cancer-related genes for sequence and copy number variations.

All patients had at least one genetic alteration, and 98% had more than 2, the researchers report. A total of 173 different genes were altered in at least one of the tumour samples. Among the frequently mutated genes were PIK3CA, TP53 and ARID1A.

"Some mutations were found to cluster into similar pathways, for which targeted therapies could potentially be used," Dr Piccart said.

"Although in many cases we cannot be sure what effect the mutations have on the tumour characteristics or the clinical efficacy of treatments, we did find that mutations in the tumour suppressor gene PTEN were associated with loss of protein expression and function."

The authors also found an increased mutation rate for the oestrogen receptor, a key player in breast cancer, between primary and metastatic samples, which highlights potentially clinically relevant differences between the primary and metastatic disease for this group of hormone-receptor positive patients.

More generally, the results illustrate that this kind of sequencing is feasible in phase III studies, the researchers say.

"The ability to carry on large-scale sequencing in phase III trials will potentially help us understand why some patients did show a good clinical response to the investigated drugs whereas others did not. Also, being able to sequence cancer genes in well-described clinically homogeneous cohorts of clinical trials will help to build new hypotheses regarding future targeted treatment strategies."

Dr Fabrice Andre from the Department of Medical Oncology at Institut Gustave Roussy, Villejuif, France, who was not involved in the research, said the study has two major impacts for clinical research.

First, he said, it suggests that next generation sequencing can be applied in the daily practice using archival samples. This opens new avenues for the development of personalised medicine trials. Second, by discovering new genomic segments, this study will certainly lead to the development of new biomarker-driven trials.

"This is a pioneering study in the field of personalised therapy for breast cancer since it shows for the first time that next generation sequencing can be applied to 'real-life' samples of patients with breast cancer. Until now, most of the data from next generation sequencing have been obtained with frozen tissue specifically for this purpose," Dr Andre said.

"Interestingly, this study, done in patients who have relapsed, shows an

increased frequency of mutations in important genes like ESR1, IGF1R. This could lead to the development of new trials testing compounds against these genomic segments," Dr Andre said.

Following this study, prospective trials are needed to test whether the use of genomics could improve outcomes for patients, he said. "Also, we still need a comprehensive analysis of metastatic tissue in order to better develop drugs and understand the metastatic phenomenon. These two purposes will be addressed in the large pan-European effort called PRISM and led by Breast International Group (BIG)."

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