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Two genomic tests identify groups of patients most likely to benefit from new drugs

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New results from a long-running trial to identify which new drugs or combinations of drugs are most effective in which types of breast cancer, show that two genomic tests are bringing the era of truly personalised medicine ever nearer.

Professor Laura van 't Veer, leader of the Breast Oncology Program at the University of California San Francisco, USA, told the 30th EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics in Dublin, Ireland, today: "Effective breast cancer treatment depends on recognising the biology of the tumour. MammaPrint and BluePrint are two tests that recognise disease that is at risk of early recurrence and the different molecular sub-types."

I-SPY 2 TRIAL is a phase II randomised clinical trial testing several promising new drugs, alone or in combination, alongside standard chemotherapy in women with newly diagnosed breast cancer at high risk of early recurrence. By studying the genetic signature of the tumours, the researchers hoped to identify more precisely subgroups of patients who would respond to particular treatments.

"This will allow us to tailor treatment further so that the right anti-cancer drugs can be given to the right patients who have the highest chance of response, and so that patients who are unlikely to respond can be prioritised to receive another therapy," said Prof van 't Veer.

In the first part of her presentation to the meeting, she described how

refining information from the MammaPrint test, which looks at the activity of 70 genes in breast cancer tissue, provided information on how patients' tumours would respond to the treatments, depending on whether it classified the patients as "high risk" (MP1) or "ultra-high risk" (MP2).

"MammaPrint is a prognostic signature used to predict the likelihood of a patient experiencing an early recurrence of her breast cancer in the absence of chemotherapy. In this study we tested the hypothesis that MP1/2 status is associated with tumour response, and we looked to see whether any association might depend on hormone or HER2 receptor status, as well as the treatment regimen the patients were receiving," said Prof van 't Veer.

"We found that, as hypothesised, the 'ultra-high risk' MP2 patients had higher rates of complete pathologic response than the lower risk, MP1 patients."

A total of 483 (49%) of the 986 patients were identified as being MP2, and they were 2.62 times more likely to have their tumours disappear completely (pathologic complete response—pCR) compared to MP1 patients. When the results were adjusted according to which treatment they had received, and whether or not their cancer was driven by hormones or HER2 receptors, the pCR rate for MP2 patients was 2.43 times higher than that of MP1 patients.

Further analysis according to which cancer drugs they were receiving, showed that MP2 patients were more likely to achieve pCR if they were taking veliparib/carboplatin, neratinib, ganitumab, TDM1/pertuzumab or pembrolizumab in addition to the standard paclitaxel treatment alone or in combination with trastuzumab. Analysis of responses according to types of receptors showed that MP2 patients with cancers that were hormone receptor positive (HR+) and HER2 positive (HER2+) were 3.62 times more likely to achieve pCR than MP1 patients, while those

who were HR+ and HER2- were 3.2 times more likely to achieve pCR compared to MP1 patients. This was not found in HR- HER+ patients.

"The most basic message of this study is that a prognostic signature that predicts good outcome in patients with a low risk signature when foregoing chemotherapy can also, when further stratified, be used to predict response in high-risk signature patients who receive chemotherapy or targeted therapies. In short, this is a prognostic signature that is also predictive. The clinical implications will need to be further developed, but these data suggest that MP1/2 status might be a useful adjunct in predicting which patients are likely to respond to which drugs or combinations," said Prof van 't Veer.

In the second part of her presentations from I-SPY 2, Prof van 't Veer described how the BluePrint 80-gene signature test was used to classify 375 HR+HER2- patients by biological subtype, as having either basal, luminal or HER2 subtype breast cancer. Although all patients in the study belong to the same 'receptor' subtype (HR+HER2-), there can be differences in tumour biology reflected in gene expression patterns measured by BluePrint. The luminal biological subtype is similar to a 'typical' HR+HER2- tumour driven by the hormones oestrogen and progesterone, and it has a relatively low rate of cell proliferation. The basal biological subtype resembles triple negative tumours (which do not have receptors for the hormones oestrogen and progesterone and the HER2 protein), and it has a higher rate of cell proliferation. The HER2 biological subtype is driven by the HER2 protein activating signalling pathways at the level of individual genes; this is something that is possible even in HR+HER2- tumours, but is rare.

Prof van 't Veer and her team hypothesised that HR+HER2- tumours classified as basal by BluePrint would be more responsive to targeted chemotherapy than the more typical luminal cancers.

"We used the BluePrint molecular subtype/signature test to classify I-SPY 2 patients as having luminal, basal or HER2 biological subtype breast cancers. We then focused on HR+HER2- patients, who were all classified as either luminal or basal, and performed an analysis to assess whether subtype was associated with complete pathologic response to chemotherapy and targeted therapy given before surgery, and, if so, to identify the subtype that is more responsive to therapy. We also looked at survival outcomes by subtype and tumour response.

"This analysis showed that patients with HR+HER2- breast cancers of basal subtype as assessed by BuePrint were more likely to achieve a complete pathologic response than patients with luminal-type breast cancers. In addition, we showed that though patients with luminal cancers were less likely to respond with a complete pathologic response, non-responding HR+HER2- luminal patients had superior long-term survival outcomes compared to non-responding HR+HER2- basal patients."

Patients with basal subtype cancers were approximately four times more likely to achieve pCR than patients with luminal cancer, regardless of which therapy they were receiving. In addition, the researchers found an association between subtype as assessed by BluePrint and the MammaPrint MP1 or MP2 classes; 77% of the HR+HER2- basal patients were also 'ultra-high risk' MP2 types, compared to only 9% of HR+HER2- luminal patients.

"These findings suggest that BluePrint can identify a subset of patients with HR+HER- basal tumours who are more likely to respond to neoadjuvant chemotherapy," said Prof van 't Veer. "The overlap between BluePrint basal subtype and MP2 class suggests that different predictive signatures may identify similar sets of patients who are most likely to respond to a particular investigational drug."

I-SPY 2 is ongoing and recruiting patients. So far, 15 investigational drugs have entered the trial. The results presented today include control treatments and the first ten drugs, most of which target particular biological processes or recruit the immune system to kill cancer cells. Seven of these first ten have proved to be at least twice as good as standard chemotherapy (which is given in the control arm of the trial), two were dropped as they failed to show a big benefit over standard treatment, and one was stopped because it was too toxic for patients.

Professor Charles Swanton of the Francis Crick Institute, London, UK, is scientific co-chair of the EORTC-NCI-AACR Symposium and was not involved in the research. He said: "These are exciting results from I-SPY 2 TRIAL and show how understanding the underlying biology of a person's cancer has enormous potential for predicting not only their risk of an early recurrence, but also for how their cancer is likely to respond to particular therapies. This will help us to choose the most effective treatment for individual patients and so improve their chances of surviving breast cancer."

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