First large scale trial of whole-genome cancer testing for clinical decision-making reported

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For the first time, researchers have conducted a large trial in which they tested the entire genome of individual breast cancers to help personalize treatment. They released their findings at the ESMO 2012 Congress of the European Society for Medical Oncology in Vienna.

In recent years, a number of drugs have been developed that target specific genetic alterations in cancer. To choose which of these drugs are suitable for individual patients, some genetic testing is performed. "In most of these cases, these genetic testing approaches only analyze a limited number of genes," said study author Dr Fabrice André from Institute Gustave Roussy, Villejuif, France.

The theoretical benefit of whole genome testing is that this approach can identify both frequent and rare unexpected genomic events. "In addition, it allows us to quantify the level of genomic instability, and to detect whether driver mutations are associated with genomic alterations involved in resistance to targeted agents," Dr André said.

In terms of healthcare delivery and policy, developing whole-genome approaches also means new bioassays do not need to be designed for each new target discovered in cancer.

In the SAFIR01 trial, Dr André and colleagues developed a program where the entire genome from a biopsy of a metastatic lesion was analyzed prospectively for individual patients with metastatic breast cancer. They used array CGH (aCGH) and Sanger sequencing to identify

the genetic alterations in the metastatic tissue, which allowed them to identify which genes were mutated, amplified or deleted. This genomic information was prospectively used to propose different targeted therapies. The study was conducted and sponsored by UNICANCER and funded by the French National Cancer Institute.

As of 23 September 2012, biopsies had been performed in 402 breast cancer patients, including 26 patients for whom analyses are ongoing. Of those, a genomic result could be generated in 276 patients, including whole genome analysis in 248. A genomic alteration "targetable" by an anticancer drug was found in 172 of those patients, Dr André said. Interestingly, around 20% of the patients presented a very rare and sometimes unexpected genomic alteration, highlighting the need for whole genome approaches.

"The main message is that whole genome approaches can be delivered in the context of daily practice in large cohorts, allowing us to identify targets that can be inhibited in a high proportion of patients, leading to anti-tumor effects. This study suggests that time has come to bring personalized medicine to the cancer field," Dr André said.

Although only a minority of patients needed an investigational agent since the biopsy, 26 patients so far received a targeted agent matched to the genomic alteration. The goal is to reach more than 80 patients treated with a targeted agent.

"When results from the SAFIR01 trial and its pilot phase are pooled, 18 out of 48 patients treated according to whole genome analysis presented evidence of antitumor activity," Dr André said.

"In the future, we think that whole-genome approaches to genomic testing of cancer will be the standard of care since they provide a broad picture of genomic alterations and an easy way to test biomarkers," Dr

André concluded.

Commenting on the data, Dr Peter Dubsky, Associate Professor of Surgery at the Medical University of Vienna (who was not involved in the study) said: "SAFIR01 is a remarkable accomplishment that has moved personalized molecular dissection of breast cancer into a setting that is, in principle, transferable into clinical practice."

"The investigators have been able to analyze large parts of the individual breast cancer genome and have furthermore been successful in identifying molecular alterations with a good chance of responding to specific treatments," Dr Dubsky said. "In other words, they create the possibility of identifying 'drug-able' targets in women showing progression of metastatic disease. Both the technical achievement and the organizational and ethical hurdles overcome by the French consortium represent dedicated and clinically relevant research at its best."

"The French consortium has opened a new door to more personalized treatment of advanced breast cancer," Dr Dubsky said. "Clinical research will have to address the clinical utility of such approaches compared to current standards."

Several questions remain to be discussed, Dr Dubsky said: "The biopsy of metastases (especially in order to obtain high-quality DNA) is not always feasible, is expensive and may lead to additional morbidity. Given the recent insights from next generation sequencing techniques, it is worth asking how relevant tissue from the metastatic site is. In other words, in the future would fresh tissue from the primary be sufficient to screen for drug targets?"

"It is also important to mention that the definition of breast cancer subtypes is already a clinical reality in the treatment of advanced and

early disease. Oncologists are able to dissect breast cancer subtypes based on hormone receptors, the expression of Her2-neu and markers for differentiation and proliferation of the tumor. Whole genome approaches will have to be compared to this current gold standard in terms of their clinical utility."

Recently, the targeting of the PI3K/mTOR pathway using mTOR inhibitor in combination with exemestane has lead to a major improvement of clinical benefit in women with metastatic hormone receptor-positive and Her2neu negative breast cancer, Dr Dubsky said. "It is noteworthy that this target was based on molecular research. The patients to benefit from this new treatment combination however were selected clinically: women who had developed endocrine resistance to prior endocrine treatment were selected and showed a remarkable clinical benefit rate. The clinical trials providing this evidence were successful without individual molecular identification of the treatment target."

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