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EDITORIAL

Precision medicine in early breast cancer—beginning of a successful story?

Over the past 20 years, advances in genomic characterization of breast cancer enabled the constant evolution of clinically relevant subtypes from immunohistochemically defined groups, to molecular profiles,[1] and further individualization of driver alteration for each patient,[2] with the hope of identifying the targeted 'magic bullet' effective for each individual. Major advances across other tumor types with impressive results in controlling metastatic disease, such as epidermal growth factor receptor (EGFR)-mutated lung cancer or BRAF-mutated melanoma, paved the way toward transition of genomic medicine in the adjuvant setting with the approval of an EGFR inhibitor in lung cancer,[3] or the BRAF and MEK inhibitors in melanoma.[4] Better understanding of tumor biology helped us target non-oncogenic addiction, as demonstrated by adjuvant curative-intent use of poly (ADP-ribose) polymerase inhibitors in breast cancer.[5]

Due to its complexity and heterogeneity, breast cancer harbors many potentially targetable mutations involved in cancer progression or resistance to therapy. The probability of finding a relevant molecular feature depends on the biological subtype and the timing of tumor genomic evolution. Increased use of DNA sequencing made large trials possible that investigated the benefit of target-specific therapy. In the Safir-01 trial,[6] use of matched therapy according to genomic alterations was feasible albeit for a minority of patients (13%). Not all mutations bear the same therapeutic implication: therapy for alterations that are classified as level I/II by the European Society for Medical Oncology (ESMO) Scale for Clinical Actionability of Molecular Targets (ESCAT)[7] led to improved progression-free survival, but no benefit was observed for unselected alterations.[8] It also became apparent that certain biomarkers with established predictive value in other tumor types don't have the same predictive value in breast cancer, with the notable example of immune-related biomarkers in breast tumors.[9]

The COGNITIVE trial, whose preliminary results are reported in this issue of *ESMO Open*, proposes to use the concept in the early setting, and investigated the feasibility of genomic and transcriptomic profiling to identify biomarkers in patients with high risk for relapse after standard neoadjuvant chemotherapy (NACT) to guide genomics-driven targeted post-neoadjuvant therapy. Selection of higher-risk patients who do not achieve a pathological complete response (pCR) following neoadjuvant systemic therapy is a major advance that leads to improved patient outcomes, in triple-negative,[10] Her-2 positive[11] and, more recently, in high-risk germline BRCA-mutated cancers.[5] The principle investigated in this trial uses molecular analysis to evaluate genomics-guided targeted post-neoadjuvant therapy.

Specifically, the authors report on 213 assessable patients who received neoadjuvant systemic therapy. Of those, 171 (80%) underwent snap-frozen biopsies before treatment, while for the remaining 42 patients (20%) snap-frozen biopsies were taken after treatment in case of gross residual disease, or had formalin-fixed, paraffin-embedded (FFPE) tissue material retrieved from the surgical specimen.

The rate of pCR was 40.85% (87/213). Based on risk classification using pCR status and CPS+EG score,[12] 104 out of 213 (48.83%) patients were classified as high-risk patients. Post-neoadjuvant therapy consisted, in addition to endocrine therapy in case of hormone receptor-positive disease, of capecitabine (60/104), trastuzumab emtansine (T-DM1) (23/104), trastuzumab/pertuzumab (3/104) or trastuzumab/pertuzumab combined with capecitabine (1.92%; 2/104), while some patients were lost to follow-up (8/104).

Twenty-three patients were excluded from further analysis due to low tumor content or technical issues, which led to 81 patients who were evaluated by the molecular tumor board, and 70 patients were issued a therapeutic recommendation.

As the patients enrolled in this trial are potentially curable, besides standard adjuvant therapy, the authors reported using ESCAT criteria to propose one of the following additional therapies, through enrolment in one of the six arms of the ongoing companion study COGNITION-GUIDE: atezolizumab, inavolisib, ipatasertib, olaparib, sacituzumab govitecan and trastuzumab/pertuzumab. Details of treatment received are not available at this time.

Performance of tissue sampling for molecular profiling was reported. From the 168 patients who had a biopsy at diagnosis, 91.67% (154/168) possessed sufficient tumor cell content for subsequent whole-genome sequencing (WGS). Analysis of material post-neoadjuvant therapy proved more challenging: out of the 104 patients classified as high risk after NACT, only 60 patients were suitable for fresh-frozen biopsies, and the tumor cell content was sufficient for WGS which was available for 32 patients (30.77%). For the remaining 72 high-risk patients, DNA material extraction

was obtained from FFPE, which was successful in 51 patients. Overall, sequencing analysis post-NACT had a success rate of 77.8% (81/104).

Interestingly, the authors carried out a molecular analysis of evolutionary differences before and after NACT in a subset of 16 patients for which paired samples were available. The analysis revealed that most (86.4%) mutations in a patient were present in both the pre-treatment and the post-treatment samples, with the probable explanation that these mutations occurred early in the evolutionary tree and not as a consequence of treatment. Only 13.6% of putative drivers were lost or gained upon treatment, suggesting limited selective pressure on the genomes under NACT. An analysis was also carried out to assess the stability of mutational signatures in 12 patients, and the preliminary results suggest that most signatures remain stable after treatment, although a few cases of clonal evolution were found. Interestingly, the endocrine therapy with aromatase inhibitor was previously associated with a high clonal instability due to a selective growth advantage induced by estrogen deprivation.[13] A hypothesis worth investigating concerns potential specific susceptibility of luminal tumors to clonal evolution under selective therapeutic pressure.

Lastly, in the COGNITIVE trial, the molecular screening led to an unsuspected benefit: 17.28% of the patients had a pathogenic cancer-relevant germline variant identified, considering that half of these patients did not have a primary indication for genetic counselling. Consequently, broad genomic profiling improved the criteria of patient selection for optimized genetic counselling, with important implications for the patients and their family.

So, what have we learned? This study shows that genomic and transcriptomic profiling is feasible, with a success rate of nearly 80% in this patient population. Further development is needed as ∼20% of the patients would not potentially benefit from the post-NACT analysis if technology does not improve. The authors were able to issue a molecular tumor board additional treatment recommendation in the context of the COGNITION-GUIDE study, in ∼70% of the 104 patients considered high risk. This informs on the feasibility of genomics-driven targeted post-neoadjuvant therapy, but the efficacy of this approach remains to be proven by the results of the mentioned study. While the unsatisfactory outcomes for non-pCR patients justify research for additional intervention, and the rationale might be appealing, use of targeted therapy in the adjuvant, curative setting should be soundly founded on solid safety and efficacy data already assessed in the advanced breast cancer setting, which is not clear at this time for some of the therapies proposed.

This study focused on patients who did not achieve pCR, which is a good but not perfect prognostic parameter: while there is extensive evidence that pCR after NACT is correlated with a long-term survival benefit for triple-negative and Her2-positive tumors, its value for luminal tumors is still not clear.[14] Moreover, an important number of pCR patients will ultimately develop distant recurrence. An important addition to the informative value of this trial would be the identification, for the pCR patients, of prognostic genomic biomarkers obtained from the pre-treatment analysis that would allow the identification of these at-risk patients, despite having a pCR.

One of the additional adjuvant therapies proposed for the high-risk patients in the companion COGNITION-GUIDE study is immunotherapy. For breast cancer patients there are still no clear and definitive data as we have not fully understood the subtype-specific predictive factors to define the clinical benefit of immune therapy.[9] We hope that future analysis of this trial can provide data on tumor environment and the immune cell subtypes infiltrating breast tumors, as well as on the status of innate and adaptive immune response, ideally before and after neoadjuvant therapy, that would be extremely informative in order to advance our apprehension on the place of immunotherapy in early breast cancer treatment.

Although important progress has been made with the paradigm of risk-selected post-neoadjuvant therapies, our patients need us to identify new strategies to improve outcome, as many still relapse. Understanding the molecular features of these tumors, the dynamics of their evolution under neoadjuvant treatment as well as the potential therapy-induced selection holds the promise of enabling optimization of the subsequent treatment.

Effective implementation of such precision medicine will not be easy, and will need to resolve technical issues, diversity between and within tumors as well as accounting for their evolution through space and time. On a larger scale, basic questions of data interpretation, equal access to technologies and shared decision making with the patient as partner will need to be accounted for.[15] The COGNITION trial has the merit of attempting to tackle some of these issues, and represents a step towards translation of precision medicine into real benefits for patients, in a future where deep biological characterization of the tumor will become an essential part of the cancer care and treatment decision will largely incorporate genomics.

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