Editorial

Genomic mutational profiles of metastatic breast cancer: obtaining them early and during the continuum of oncological care

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The era of incorporating tumor genomic profiling in metastatic breast cancer (MBC) management using histopathology, immunohistochemistry, and fluorescence *in situ* hybridization information for tailoring cancer treatment is on the horizon. Commercialized tumor profiling using next-generation sequencing (NGS) with massive parallel sequencing and high-throughput technology is now available at an affordable price. A caveat is that NGS diagnostics should be performed in a Clinical Laboratory Improvement Amendments-certified and College of American Pathologists-accredited academic or commercial laboratory. Outside clinical trial settings, an increasing number of clinical oncologists feel comfortable accepting this technology, and some have already considered it as an essential companion diagnostic test in determining potentially actionable targets for oncological therapeutics. Deep sequencing is required to identify mutations within the tumor proper because normal cell contamination can occur and tumors themselves likely contain multiple subclones of cancer cells (1).

Perou *et al.*, from the Norway/Stanford group, published the molecular characterization of breast cancer using complementary DNA microarrays representing 8,102 human genes 18 years ago (2). Breast oncologists can ultimately use the traditional histopathological characterization of tumor grade and identify the expression of hormone receptors (HRs): estrogen receptors and progesterone receptors, human epidermal growth factor receptor type 2 (HER2), and Ki-67, by recognizing molecular portraits derived from hierarchical clustering to therapeutically segregate breast cancer into five types with distinct tumor behaviors: luminal A, luminal B/HER2-negative, luminal B/HER2-positive, HER2-enriched, and triple-negative breast cancer (TNBC) (3). Luminal A predicts the response to endocrine therapy, and HER2-positive predicts the response to anti-HER2-targeted agents. However, precision oncology requires knowledge of the status of actionable genomic alterations in primary and/or metastatic tumors to predict treatment response and match the most appropriate drug for better clinical outcomes.

Breast cancer is always among the most frequently assessed cancers for genomic mutations using NGS, accounting for approximately one-fourth of all cancer types submitted for this purpose (4). Patients with MBC can benefit by clinical actionability with recommendations to enroll in a therapeutic clinical trial, FDA-approved therapy, or off-label approved therapy. Further options include changing from the current treatment course when clinically actionable molecular alterations are detected by NGS, discontinuing ineffective targeted therapy because of newly discovered evidence on treatment resistance, employing germline mutation testing, and assigning diagnostic reclassification because of a new understanding of the cancer (5).

A study from the MD Anderson Cancer Center, Houston shows that in a significantly large number (n=354) of patients with breast cancer at various stages

subjected to an analysis of 46 commonly known cancer-related genes, 62.1% of patients harbored alterations in at least one of these genes. HR+/HER2– tumors have the highest frequency (38%) of *PIK3CA* mutations (6). Triple-negative cancers have a greater number of *TP53* mutations (62%). This study showed that the top four most frequently mutated genes were *TP53* (39%), *PIK3CA* (31.7%), *AKT1* (6%), and *ATM* (3.9%) (6). In patients with MBC, the concordance of genomic alterations detected between the primary and metastatic tumors was 77%, whereas 21% showed additional mutations in metastatic samples, which may reflect tumor adaptation to stress from antineoplastic treatments.

On December 27, 2016, Lefebvre *et al.*, from the French cooperative group, published their retrospective analysis of the mutational profile of MBC in *PLoS Medicine* (7). The study analyzed whole-exome NGS large-scale data of 216 tumor-blood pairs from patients with MBC accrued at the previous four French multicenter trials (8-10) using bioinformatics. It aimed to characterize the mutational signature and identify mutations available for clinical actionability. The paper provides sequence data deposited in publicly assessable websites and up to 19 additional tables or figures available online.

The study disclosed that 12 driver genes (*AKT1*, *CBFB*, *CDH1*, *CDKN2A*, *ESR1*, *GATA3*, *MAP2K4*, *MAP3K1*, *PIK3CA*, *PTEN*, *RB1*, *and TP53*) were statistically significant mutated in MBC. Eight genes (*AGRN*, *EDC4*, *ESR1*, *FRAS1*, *FSIP2*, *IGFN1*, *OSBPL3*, *and PALB2*) were more frequently mutated in MBC than in early breast cancer (7). Notably, patients with at least one mutation in the eight enriched genes have a nearly two-fold increased risk of death [adjusted hazard ratio (aHR)=1.97; 95% confidence interval (CI), 1.34–2.89; P=0.001] compared to patients with zero mutations.

The French study also revealed that 6% of patients with HR+/HER2– with MBC presented mutations in TSC1 and/or TSC2 genes of the mammalian target of rapamycin (mTOR) pathway; other actionable genes include *ALK*, *ERBB4*, and *NOTCH3*, which were more frequently mutated in HR+ MBC. The multivariate Cox proportional hazards model shows that patients with TNBC harbor a nearly two-fold increase in risk of death compared to patients with HR+/HER2– MBC; the aHR is 1.91 [95% CI, 1.16–3.16; P=0.011] (7).

Tumor genomic profiles may evolve even under stress from endocrine therapy. Gellert *et al*. very recently reported the results of an extension study of the POIETIC trial conducted in the United Kingdom, investigating the impact of mutational profiles obtained from whole-exome sequencing on the treatment response to a short-term, neoadjuvant hormonal treatment using an aromatase inhibitor for luminal-type breast cancer in postmenopausal women (11). The investigators found six genes frequently mutated that were related to the antiproliferative response to the aromatase inhibitor: *ABCA13*, *CDH1*, *FLG*, *mixed-lineage leukemia 3* (*MLL3*), *PIK3CA*, and *TP53*. *CDH1*, an *E-cadherin* gene, and *MLL3* have been identified in breast cancers, with the former more commonly found in lobular carcinoma. The investigators concluded that *TP53* mutations are associated with poor response to estrogen deprivation therapy (11).

Two new driver genes, *ESR1* and *RB1*, were observed in the French study. The *ESR1* mutation, which only occurred in the hormone receptor domain, has a prevalence of 19% in patients with HR+ MBC; it is associated with resistance to endocrine therapy. However, *TSC1* and *TSC2* mutations, accounting for 6% of mutations when present, are associated with everolimus sensitivity (7). The most innovative finding of the paper is that the investigators have noticed that *RB1* mutations are enriched in 5% of cases of MBC, which is associated with primary resistance to CDK4 inhibitors such as palbociclib. In a double-blind, randomized trial in postmenopausal patients with ER+/HER2– advanced breast cancer, front-line treatment with palbociclib-letrozole resulted in significantly longer progression-free survival than with letrozole alone (12). The authors suggest that *RB1* mutation should be further studied as a negative predictive marker for selecting a CDK4 inhibitor. Somatic *RB1* mutations have been previously reported to be associated with resistance to anthracycline chemotherapy (13).

In the clinical setting of genomics-informed anticancer decision-making, the absence of a tissue diagnosis of a metastatic tumor is frequently encountered, which may be due to a patient's refusal or because the diagnostic procedure is too risky to perform. Bertucci *et al.* performed a comparative genomic analysis of 23 pairs of primary breast cancers and paired metastases using whole-genome, array-comparative genomic hybridization and NGS of 365 cancer-associated genes and found that genes with recurrent amplifications showed 100% (*ERBB2*, *FGFR1*), 96% (*CCND1*), and 88% (*MYC*) concordance between primary and paired metastatic tumors (14). Their results suggest that NGS genotyping of the primary tumor is adequate in guiding anticancer therapies if metastatic sampling is not

feasible.

Activating point mutations in *PIK3CA* in breast cancer has been extensively studied in the past, particularly in estrogen receptor-positive luminal-type tumors, as the status of *PIK3CA* mutation should be determined to select targeted agents acting on the phosphoinositide-3 kinase (PI3K) pathway. The PI3K-AKT-mTOR pathway is frequently altered in breast cancer, including activating point mutations in *PIK3CA* or *AKT1* genes in approximately 30% of cases (6,15), and PTEN inactivation, the negative regulator of the PI3K-AKT-mTOR pathway, occurs in 10% of cases. The mutation is associated with paclitaxel resistance (16). Daneshmand *et al.* from the University of Ottawa, demonstrated that even the frequently occurring *PIK3CA* mutations in breast cancer osseous metastatic samples [3+/6 (50%)] accurately reflect the *PIK3CA* mutation status in the primary tumor (17). PI3K pathway alterations have also been investigated in patients with TNBC. A study using semiconductor-based sequencing on a cohort of 104 well-annotated TNBC specimens revealed that nearly 30% mainly had *PIK3CA* mutations (22.1%), but mutations and amplifications/deletions in other PI3K-associated genes (7.7%) were detected in the 104 TNBC formalin-fixed, paraffin-embedded specimens (18). The importance of *PIK3CA* mutations is its druggable pathway. Buparlisib (BKM120) (16), a pan-class I PI3K inhibitor, and pictilisib (GDC-0941), an experimental PI3K inhibitor (19), are effective in overcoming resistance to antineoplastics beyond phase I clinical trials.

A genomic profile of somatic mutations revealed using NGS diagnostics is essential for implementing precision medicine in patients with MBC. Even when a mutation is not currently actionable, it may become druggable in the near future because of the fast-evolving technology and drug development milieu. As to the time and manner of incorporating NGS molecular results into clinical practice, it is no longer a question of why, but instead when and how to interpret the NGS results which may be a game-changer in the management of patients with MBC.

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References

1. Guffanti A, Iacono M, Pelucchi P, et al. A transcriptional sketch of a primary human breast cancer by 454 deep sequencing. BMC Genomics 2009;10:163.
2. Perou CM, Sørlie T, Eisen MB, et al. Molecular portraits of human breast tumours. Nature 2000;406:747-52.
3. Calza S, Hall P, Auer G, et al. Intrinsic molecular signature of breast cancer in a population-based cohort of 412 patients. Breast Cancer Res 2006;8:R34.
4. Johnson DB, Dahlman KH, Knol J, et al. Enabling a genetically informed approach to cancer medicine: a retrospective evaluation of the impact of comprehensive tumor profiling using a targeted next-generation sequencing panel. Oncologist 2014;19:616-22.
5. Hirshfield KM, Tolkunov D, Zhong H, et al. Clinical Actionability of Comprehensive Genomic Profiling for Management of Rare or Refractory Cancers. Oncologist 2016. [Epub ahead of print]
6. Roy-Chowdhuri S, de Melo Gagliato D, Routbort MJ, et al. Multigene clinical mutational profiling of breast carcinoma using next-generation sequencing. Am J Clin Pathol 2015;144:713-21.

7. Lefebvre C, Bachelot T, Filleron T, et al. Mutational Profile of Metastatic Breast Cancers: A Retrospective Analysis. PLoS Med 2016;13:e1002201.
8. André F, Bachelot T, Commo F, et al. Comparative genomic hybridisation array and DNA sequencing to direct treatment of metastatic breast cancer: a multicentre, prospective trial (SAFIR01/UNICANCER). Lancet Oncol 2014;15:267-74.
9. Jovelet C, Ileana E, Le Deley MC, et al. Circulating Cell-Free Tumor DNA Analysis of 50 Genes by Next-Generation Sequencing in the Prospective MOSCATO Trial. Clin Cancer Res 2016;22:2960-8.
10. Le Tourneau C, Delord JP, Gonçalves A, et al. Molecularly targeted therapy based on tumour molecular profiling versus conventional therapy for advanced cancer (SHIVA): a multicentre, open-label, proof-of-concept, randomised, controlled phase 2 trial. Lancet Oncol 2015;16:1324-34.
11. Gellert P, Segal CV, Gao Q, et al. Impact of mutational profiles on response of primary oestrogen receptor-positive breast cancers to oestrogen deprivation. Nat Commun 2016;7:13294.
12. Finn RS, Martin M, Rugo HS, et al. Palbociclib and Letrozole in Advanced Breast Cancer. N Engl J Med 2016;375:1925-36.
13. Berge EO, Knappskog S, Lillehaug JR, et al. Alterations of the retinoblastoma gene in metastatic breast cancer. Clin Exp Metastasis 2011;28:319-26.
14. Bertucci F, Finetti P, Guille A, et al. Comparative genomic analysis of primary tumors and metastases in breast cancer. Oncotarget 2016;7:27208-19.
15. Cejalvo JM, Pérez-Fidalgo JA, Ribas G, et al. Clinical implications of routine genomic mutation sequencing in PIK3CA/AKT1 and KRAS/NRAS/BRAF in metastatic breast cancer. Breast Cancer Res Treat 2016;160:69-77.
16. Martín M, Chan A, Dirix L, et al. A randomized adaptive phase II/III study of buparlisib, a pan-class I PI3K inhibitor, combined with paclitaxel for the treatment of HER2- advanced breast cancer (BELLE-4). Ann Oncol 2016. [Epub ahead of print].
17. Daneshmand M, Hanson JE, Nabavi M, et al. Detection of PIK3CA Mutations in Breast Cancer Bone Metastases. ISRN Oncol 2012;2012:492578.
18. Kriegsmann M, Endris V, Wolf T, et al. Mutational profiles in triple-negative breast cancer defined by ultradeep multigene sequencing show high rates of PI3K pathway alterations and clinically relevant entity subgroup specific differences. Oncotarget 2014;5:9952-65.
19. Pictilisib stalls advanced ER+/PR+ breast cancer. Cancer Discov 2015;5:OF5.

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