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Breast Cancer in 2013: Genomics, drug approval pathways, and optimal treatment duration

Adrian V. Lee and Nancy E. Davidson

Departments of Pharmacology & Chemical Biology, Human Genetics, and Medicine, Women's Cancer Research Center, Magee-Womens Research Institute, University of Pittsburgh, 204 Craft Avenue, Pittsburgh, PA 15238, USA (A. V. Lee). University of Pittsburgh Cancer Institute and University of Pittsburgh Medical Center Cancer Center, 5150 Center Avenue, Pittsburgh, PA 15232, USA (N. E. Davidson)

Abstract

2013 was another rich year for breast cancer research. Advances in high throughput technologies continue to refine our knowledge of the molecular biology of breast cancer, and are beginning to give insight into cancer evolution, drug resistance, and deployment of precision therapeutics.

Two comprehensive reports of pan-cancer genomic analysis compared breast cancer to multiple other cancer types. A pan-cancer analysis of somatic point mutations and small insertions/deletions in 12 cancer types in TCGA showed that breast cancer has one of the lowest mutation rates in solid tumors with on average ~3,000 somatic mutations/tumor (range ~90 – 60,000)¹. Breast cancers were enriched for mutations in *TP53*, *PIK3CA*, *GATA3*, *MAP3K1*, *CDH1* and *MLL3*. Alexandrov et al.² examined somatic mutations from ~7,000 cancers and found a rate of mutation in breast cancer that was strikingly similar to that seen in the TCGA pan-cancer analysis. Breast cancers showed foci of hypermutation, termed kataegis, which were associated with large structural rearrangements. Specific types of base pair mutation were strongly associated with tumors harboring loss of *BRCA1* or *BRCA2*. The team also identified a unique signature of base pair mutation that is consistent with activity of endogenous genes, APOBECs, a family of cytidine deaminases which normally convert cytidine to uracil. Several other studies in 2013 revealed overexpression of and functional roles for APOBECs in breast and other cancers, suggesting that this may be a mechanism to generate mutations in cancer. Taken together, reports in the last 2–3 years have comprehensively identified somatic point mutations and small insertions/deletions in primary breast cancer. However, the breast cancer genomics story is clearly not over as most large sequencing studies have focused on primary breast cancer. Recent reports of sequencing in metastasis have described mutations (such as in *ESR1* described later) that are absent, or present at very low frequencies in primary breast cancer (e.g. in rare subclones), supporting the need for study of metastases.

TCGA and other large projects have struggled to address the extent of genomic intra-tumor heterogeneity (ITH). Sequencing of distinct tumor regions, and single cells, has revealed

tremendous ITH; however, determining the extent and clinical significance of ITH is hampered by the difficulty in obtaining repeated tissue biopsies. An attractive alternative is examination of circulating cancer DNA in plasma (circulating-free DNA or cfDNA), the so called ‘liquid biopsy’. 2013 saw two reports on longitudinal analysis of whole exome and genome sequencing of cfDNA in breast cancer patients. Whole exome sequencing on cfDNA collected over 1–2 years from patients with advanced breast cancer showed that mutations in liquid biopsies arose or increased in frequency coincident with development of clinical therapeutic resistance³. In one patient, treatment with tamoxifen and trastuzumab was followed by an increase in truncation of MED1, an estrogen receptor co-activator known to be involved in tamoxifen resistance. Subsequent treatment of the patient with lapatinib and capecitabine was followed by an increase in a splicing mutation in GAS6, the ligand for AXL which has been shown to cause resistance to lapatinib³. Dawson et al.⁴ used whole exome and whole genome sequencing of cfDNA to design patient-specific assays for longitudinal monitoring. cfDNA was detected in 29/30 (97%) patients with advanced breast cancer, whereas elevated CA15-3 and circulating tumor cells were only detected in 78 and 87% respectively. Importantly, an increase in cfDNA was noted months before confirmation of progression by CT scan. These studies, and others, highlight the potential utility of using cfDNA to monitor disease burden and progression, and hopefully identify targets to treat the disease and prevent the molecular evolution of drug resistance.

Perhaps the greatest surprise in breast cancer genetics/genomics in 2013 was the identification of estrogen receptor alpha (ER, *ESR1*) mutations in breast cancer metastases. As ER is such a central driver and target in breast cancer, most researchers had surmised that it must be mutated in some endocrine-resistant tumors. However, very few mutations have been identified despite intensive efforts; for example, TCGA identified somatic mutations in *ESR1* in only 2 out of 825 primary breast cancers (0.2%). The landscape changed dramatically when the analysis was shifted from primary breast cancer to biopsies of advanced hormone-resistant disease. In a herculean effort designed to sequence and characterize patient-derived xenografts, Ellis et al.⁵ identified *ESR1* somatic mutations in advanced breast cancers that were obtained from patients who were refractory to anti-hormonal therapy. This finding was substantiated in two subsequent studies. Robinson et al.⁶ identified somatic *ESR1* mutations in 6 out of 11 (55%) patients with advanced breast cancer. Toy et al.⁷ identified mutations in 9 out of 36 (25%) ER+ advanced breast cancers as well as 5/44 (11%) derived from participants in the BOLERO-2 clinical trial. Importantly, these mutations were found almost exclusively in advanced ER+ breast cancers, particularly after treatment with an aromatase inhibitor rather than an antiestrogen. The somatic mutations clustered in the ligand binding domain of ER, and structure-function studies showed these mutations change receptor conformation and result in ligand-independent activity. Together these studies open up a new avenue for studying hormone action and developing new therapies in ER+ advanced breast cancer, such as inhibitors which specifically target mutant ER.

The use of massively parallel sequencing to personalize genomic-directed breast cancer therapy is rapidly becoming a reality. However, the number of approved “targeted” drugs remains small, and the path to their clinical development and testing is unacceptably long.

Last year the FDA provided guidelines for the use of pathologic complete response (pCR) as an endpoint to support accelerated approval of new agents in the setting of neoadjuvant treatment of high-risk early-stage breast cancer. In 2013, Pertuzumab (Perjeta, Genentech) was the first agent to receive such approval for neoadjuvant treatment of early stage HER-2-overexpressing breast cancer (<http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm370393.htm>) It is hoped that the use of pCR as an endpoint will accelerate the development of new therapeutics needed to tackle the diverse array of somatic mutations found in breast cancer.

Finally 2013 also brought reports of four large clinical trials designed to optimize our use of active targeted agents. The ATLAS trial compared 10 years versus 5 years of tamoxifen in 12,894 women with early breast cancer⁸. Continued tamoxifen resulted in decreased breast cancer recurrence and mortality after 10 years of tamoxifen compared to stopping tamoxifen after 5 years; however, the greatest effect was seen from years 10–15 where extended tamoxifen showed a recurrence rate ratio of 0.75 and a mortality rate ratio of 0.71. This result was confirmed in the aTTom trial reported in preliminary fashion in 2013. While these results, combined with previous studies of extended aromatase inhibitor use after tamoxifen, point to the value of extended adjuvant hormone therapy, this model does not hold true for all therapies. Indeed, the PHARE and HERA trials together showed that 6 months of adjuvant trastuzumab therapy cannot be regarded as a substitute for 1 year of trastuzumab⁹ and 2 years of trastuzumab is not more beneficial in reducing recurrence of HER2 positive breast cancer than 1 year¹⁰. There are likely many explanations for the difference between optimal length of adjuvant tamoxifen and trastuzumab therapy, but one might be the relative indolence of ER-positive disease where endocrine therapies like tamoxifen act to control the dormancy of micro-metastases. This suggests that there will need to be extensive optimization of targeted therapies.

We expect that 2014 and beyond will continue to extend our knowledge about breast cancer research and treatment. New techniques are allowing unprecedented investigation into the underpinnings of breast cancer that will likely have a major impact upon treatment and prevention.

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Key advances

- Breast cancer mutations detected in circulating-free DNA by whole exome and genome sequencing change with therapeutic resistance, and can reflect disease progression.
- The Estrogen receptor alpha gene (ESR1) is mutated in some hormone-resistant advanced breast cancers. The mutations alter ER activity and may represent novel targets.
- Extended adjuvant hormone therapy is more efficacious, but extended adjuvant trastuzumab therapy is not. Each targeted therapy will likely require mechanism-based optimization.