Breast cancer includes large numbers of genomic segments defined by genomic alteration on a putative oncogenic driver. Based on this background, it has been suggested to develop genomics-based trials where each patient receives a drug matched to the genomic alteration observed in the tumor. This approach has been evaluated in a molecular screening program called SAFIR01. This program has allowed defining limitation of the approach. First, the genomic test can not be provided in a significant proportion of patients for which % of cancer cells is low. This problem should be overcome by the development of in depth sequencing for clinical use. Second, the identification of oncogenic driver is challenging in breast cancer. Three solutions could be developed to overcome this issue. First, there is a need to develop catalogues of genes that are validated as cancer-related genes. Second, there is a need to better understand what are the rules that makes a genomic alteration a driver within a tumor. This includes clonal dominance, characteristics of the mutations, structure of amplicon etc etc. Third, there is a need to assess pathway activation. This could better understand the functional implication of the genomic alteration and could also allow identify drivers in patients without genomic alterations. Once the drivers have been identified, we then face the challenge of avoiding resistance to targeted therapies. There are currently three strategies to overcome this issue. First, there is a need to early identify subclones that mediate resistance to targeted therapies. Second, there is a need to combine targeted therapies with immunotherapeutics and DNA targeting agents. Finally, there is a need to better understand to what extent the level of intratumor heterogeneity (ITH) predicts resistance to targeted therapies, in order to exclude patients with high level of ITH from personalized medicine approaches.

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