Molecular Tumor Boards

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The ability to decipher the molecular information in breast cancer offers the opportunity to identify genetic mutations, disturbed signal pathways, and new potential therapeutic targets. However, this flood of information mostly lacks in clinical relevance and therapeutic consequences.

Question 1: Is there high time for the implementation of molecular tumor boards for every patient?

Ettl: One must clearly differentiate between clinical practice and clinical research:

- No, it is not high time for the implementation of molecular tumor boards for every patient in clinical practice. In breast cancer, to date, there is no single approved drug that requires genomic profiling of the tumor. Also, one has to keep in mind that – at least based on current knowledge – breast cancer is different from lung cancer or melanoma, where approved drugs for certain genomic subtypes exist. Genomic profiling/next generation sequencing (NGS) can be used to identify clinical trial options for an individual patient.
- Yes, indeed it is high time for molecular tumor boards in the context of clinical research in order to further identify gene and pathway alterations of breast cancers to guide clinical research and to identify patients for clinical trials.

Marmé: No, it is not high time. Not for every patient and not in routine clinical practice! Nevertheless, NGS-based tumor profiling

is increasingly adopted by the oncologic community. The availability of such testing is used to attract patients in oncology practices, and research-oriented clinical cancer centers adopt NGS for most of their patients to promote investigator-initiated as well as pharma-sponsored clinical trials, as sites providing 'free' NGS testing may be more attractive for trial participation.

NGS, as a basic tool for molecular tumor boards, has become clinical practice not only since the recent Food and Drug Administration (FDA) marketing approval of such an NGS-based in vitro diagnostic test. For lung cancer, therapy based on selected information provided by such testing has greatly changed the current therapy landscape. However, breast cancer is currently lagging behind. And there is no therapy approved on the basis of such an NGS test. Thus far, treatment strategies based on molecular tumor boards have failed to demonstrate clinical benefit in prospective trials, like SHIVA and MOSCATO 01. There might be many explanations why these trials have not provided better results, ranging from limited number of pathways assessed to limited drug options and access to matched molecular therapies. In addition, before we adopt tissue-agnostic strategies widely it is important to accept that genomic as well as tissue context matter. A recent trial on neratinib in HER2-mutated cancers impressively demonstrated that some specific hot-spot mutations in HER2 were associated with response in one type but complete lack of efficacy in other tumor types. We are likely going to see data from larger clinical trials in breast cancer for targeted therapies against some of the few recurrent mutations, like PIK3CA, AKT1, and ESR1, and some of these alterations might prove to be clinically useful predictive factors. However, this can then be covered by small panels of genes and does not require a

molecular tumor board, which rather focuses on the ‘long tail’ of private non-recurrent alterations, tumor mutation burden, homologous recombination deficiency (HRD), and immune signatures. For the time being, I strongly recommend to support and pursue such precision oncology approaches within prospective and controlled programs to gain important insights.

Prat: I think this is an exciting area of active research that needs to be evaluated in a clinical trial or a research project. I believe that we are not ready yet to implement molecular tumor boards in the clinical setting for every patient. Before we do that, we need more evidence of the clinical validity – but especially of the clinical utility – of such an approach.

Question 2: Should every patient be discussed in a molecular tumor board or are there specific subgroups for which a molecular tumor board is appropriate for further treatment decision?

Ettl: Patients with metastatic breast cancer, who underwent standard therapies, have adequate performance status, and are willing to consider participation in a clinical trial, including breast cancer registries, should be discussed in a molecular tumor board.

Marmé: It seems obvious to focus on patients with the highest medical need and difficult-to-treat cancers, e.g. metastatic triple-negative breast cancers. However, although there are more treatment options for patients with metastatic luminal disease and disease dynamics are generally slower, eventually all of these patients will become resistant to therapy, and there is a need for novel approaches. In addition, NGS profiles might provide predictors of response or resistance to endocrine-based combinations including CDK4/6 and mTOR inhibitors in the future even though no useful predictors have been identified so far. Thus, there is no biological or clinical rationale to select patient subgroups for molecular tumor boards. Limited programs and resources, however, naturally lead to a selection of those patients with the highest clinical need, which can be found in all subgroups. Therapies based on molecular profiles might be more effective in earlier lines.

Prat: In a research project or a clinical trial platform, the tumor board might help to ‘guide’ a patient with a particular set of molecular alterations to clinical trial X versus Y. However, this recommendation is likely to be based on limited evidence, mostly coming from preclinical research. Therefore, I think the appropriate approach is to test particular molecular alterations (i.e. biomarkers) in prospective clinical trials, similarly as we do for drugs. Unless we do that, I am not sure we will obtain enough evidence to make ‘right decisions’.

Question 3: Should genetic profiling or sequencing be mandatory for every tumor patient? Is panel analysis or deep sequencing the appropriate method?

Ettl: Genomic profiling or sequencing should not be mandatory for every patient (see also answer to question 2). If used in a wrong way as well as indication, tools like NGS and molecular tumor boards can cause substantial harm to our patients by recommending the wrong drug and denying existing effective therapies the patient has not been treated with beforehand.

It is of great importance that we do not generate false hopes in our patients by not informing them about the fact that the likelihood of success (meaning the possibility of trial participation or effective off-label therapy with an approved drug) might be quite low.

In clinical practice, panel analysis seems to be the more reasonable approach. To further interpret clinical relevance of somatic sequencing results, it might also be necessary to carry out germline analysis. This implies genetic counseling of our patients.

Marmé: From an academic and research point of view, it might be desirable to sequence every tumor patient. Yet, as explained before, based on the clinical utility this cannot be made mandatory in routine clinical practice for every patient. Before doing so, data on clinical utility for specific patient subgroups needs to be available and the reimbursement issue needs to be solved. To clarify terminology, the term ‘panel analysis’ refers to the number of genes (mostly exons) that are sequenced. The term ‘panel’ refers to a limited number of genes, whereas whole exome sequencing (WES) implies coverage of all exomes. In contrast, whole genome sequencing (WGS) refers to the sequencing of the whole genome including intronic regions and other non-coding areas. Deep sequencing refers to sequencing a genomic region multiple, sometimes hundreds or even thousands of times. This is important if you want to detect rare subclonal events. The preferred method does ultimately dependent on the research question or application you are ultimately aiming at. If interested in the few recurrent mutations in breast cancer, a panel will suffice. If the focus is on rare private mutations to select patients for phase I trials etc., larger panel or whole exomes are needed. In an academic/research setting with unrestricted funding, WGS at a high coverage and additional RNA sequencing would be on my wish list. Novel HRD signatures, like HRDetect, are based on e.g. WGS, and neoantigen prediction does also imply information of expression of the epitope etc. In addition, RNA sequencing will help to identify novel potentially important fusion genes. However, this is far beyond clinical routine.

Prat: There is no doubt that if we want to make great progress in oncology, we must biologically characterize tumors at all possible levels and link this information with clinical outcomes. Clinical trials are the best context for doing this and for testing our hypotheses. However, we can also learn a lot from patients treated outside

of a clinical trial. Thus, I will always favor performing molecular profiling at the DNA, RNA, and protein level; however, this must be done in the context of clinical or translational research.

Question 4: How can we integrate molecular information in future trial designs?

Ettl: In breast cancer, there are only a few ‘common’ genomic alterations, and then there is a large variety of multiple alterations in only a very small number of patients. This makes it difficult to conduct fruitful clinical breast cancer studies. Thus, the future lies in basket trials where genotype-selected therapies are given. Also, confounding tumor/patient registries like the German PRAEG-NANT study, where data of thousands of patients with advanced breast cancer are collected and analyzed, will play a crucial role in further elucidating the clinical value of genotype-driven therapies. In my view, it should be mandatory that any patient who is discussed in a molecular tumor board should enter a trial or at least be followed within some kind of registry to collect data on treatment efficacy, side effects, and outcome.

Marmé: We should try to integrate molecular information already in early-phase clinical trials and by doing so gain information on which specific mutations within a gene or pathway predicts benefit in which specific tumor type – in order to then select groups based on molecular alteration and tissue of origin for further clinical development. The type of tissue should also be considered and a recent/new biopsy or ctDNA should be preferred as these are important to pick up molecular alterations like *ESR1* mutations and *BRCA* reversion mutations otherwise missed in the primary tumor.

Prat: This is critical. To approve a drug, it must undergo a series of steps from quality/safety of the product to clinical evidence demonstrating that it works (usually going from phase I to phase III trials). For biomarkers, we should be doing exactly the same. In other words, demonstrate that the biomarker is analytically valid, clinically valid, and clinically useful (i.e. clinical utility). In many instances, molecular information has been evaluated in retrospective tumor samples from clinical trials without properly powering the analysis. This does not allow to reach level 1 evidence. I think that we need to integrate these biomarkers prospectively and test their predictive value directly, just like we do with drugs and clinical trials every day.

Question 5: How should we manage the costs of molecular diagnostics?

Ettl: Costs of molecular diagnostics do not only include the costs of NGS but might also include the cost of expensive off-label therapies. As stated above: Since we are far from introducing

genomic profiling into clinical routine practice of breast cancer, if possible, the costs should be embedded within the setup of clinical trials and research programs.

Marmé: Considering the current data, who should cover the costs? Patients and/or health care providers/health insurance, or should testing rather be funded by pharmaceutical companies running these molecularly driven studies? Although sequencing costs are coming down, to incorporate these approaches in clinical routine would imply the off-label use of expensive therapies, adding considerably to these costs. Given the limited data on clinical efficacy, it does not seem justified to make patients or health care providers pay for this at this time. Setting up prospective controlled cooperative (inter-)national programs in which health insurances, academia, governmental bodies, and pharmaceutical companies cooperate to fund such trials and ascertain the best possible NGS methodologies, data management, bioinformatics, access to targeted drugs, and data quality would be desirable but will be difficult to implement.

Prat: This is challenging. Although the costs are dropping, molecular diagnostics are still expensive and require substantial resources. Thus, for biomarkers that have not yet shown clinical utility (in other words, they are not standard of care), these funds must come from large national or international research programs. For biomarkers that reach clinical utility and that show cost-effectiveness, these should be incorporated into routine clinical practice. This might be easier if the biomarker helps select which patients benefit from an expensive drug. If no expensive drug is behind the biomarker, things might be more challenging. For example, current prognostic gene expression-based tests that help identify patients with breast cancer who do not need adjuvant chemotherapy have not been widely implemented in the clinic in many countries despite showing clinical utility and being cost-effective.

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