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Personalized medicine: Present and future of breast cancer management

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Contents

Abstract

Breast cancer is the first cause of cancer in women worldwide. Recent molecular analyses have shown that it is not a single disease but a mixture of several diseases with different biological behaviors, which should lead to treatment customization for each patient. Personalized medicine is based on tumor and/or patient molecular profiles. This new way to think oncology is currently applied at different stages of breast cancer management, including prognosis, prediction of treatment efficacy, and development of new therapies *via* new kinds of clinical trials. These trials are not only based on tumor site but also on tumor genetic characterization using genomic tools such as gene expression profiling, array-CGH or next-generation sequencing technologies. The aim of personalized medicine is to tailor treatment according to the specificities of a single disease in a given patient. In this review, we present the advances in treatment personalization which are currently used in daily practice as well as the technologies and therapies under investigation in various clinical trials.

Keywords: Breast cancer; Personalized medicine; Molecular profiling

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1. Introduction

Breast cancer (BC) is the first cause of death by cancer in women worldwide, with nearly 465,000 deaths in 2011 [1]. BC is a heterogeneous disease with several clinical, pathological and prognostic subgroups. Such diversity is the result of a large range of molecular alterations. Since a decade, high-throughput technologies have allowed to better understand this molecular complexity, poorly reflected by usual histo-clinical features and scarcely exploited by former therapeutic approaches.

Personalized medicine has been defined by the National Health Institute and the Food and Drug Administration (FDA) as "an emerging practice of medicine that uses an individual's genetic profile to guide decisions made in regard to the prevention, diagnosis, and treatment of disease" (accessed January 3rd, 2013) and as the best way to obtain "the best medical outcomes by choosing treatments that work well in a given person according to its genomic profile, or with certain characteristics in blood or cell surface proteins" [2]. The first goal of this new way to think oncology is to define new subgroups of patients more homogeneous in terms of therapeutic response and outcome. Molecular classifications should allow clinicians to improve the treatment of each class. These biomarkers must be specific, measurable, reliable, and linked to specific biological processes [3]. They can be identified at molecular (DNA, RNA, proteins) or cellular levels, using biological fluids (blood, serum, plasma, urines), tissues, or morphological and functional radiological assessments. They should improve diagnosis, prognostic evaluation, treatment or follow-up when compared to usual features [4].

This review will present the main biomarkers, currently available and under development, in BC. The development of a more tailored medicine will be based on prognostic biomarkers guiding the indication or not of systemic therapy, and predictive biomarkers guiding the choice of a given systemic therapy, in both adjuvant and metastatic settings.

2. Prognostic and predictive biomarkers in early breast cancers

2.1. Molecular subtypes

For many years, breast cancer has been considered as a single disease displaying variable clinical, morphological and biological features. Some of these features have a prognostic and/or predictive value useful for guiding the indications for adjuvant systemic treatment (chemotherapy (CT), hormone therapy (HT), HER2 inhibitors): patient's age, pathological tumor size, axillary lymph node involvement, grade, vascular emboli, expression of hormone receptors (HR, including estrogen receptor (ER) and progesterone receptor (PR)) defined using immunohistochemistry (IHC), and expression of HER2 (IHC) and/or *ERBB2* amplification (*in situ* hybridization technologies). Because IHC has a few limitations (reproducibility, standardization and quality controls), alternative ways to define HR and HER2 status are being explored. They include quantitative measurement of mRNA expression based on DNA microarrays or quantitative RT-PCR [5–7], and multigene expression signatures of pathway activity, theoretically more reliable than single protein or gene expression [8]. Among the numerous other tested biomarkers, the uPA (urokinase-type plasminogen activator) protease and its inhibitor PAI-1 (plasminogen activator inhibitor-1), both markers of invasion, have reached the highest level of evidence with the validation of their value both prognostic and predictive for benefit of adjuvant CT in a prospective randomized trial [9]. In node-negative patients, low uPA/PAI1 protein expression levels were associated with better outcome, whereas the benefit of adjuvant CT was higher in patients with high uPA/PAI1 levels [9]. Today, uPA/PAI1 assessment is considered by ASCO as a level 1 biomarker for node-negative early BC [10], but is very rarely used for practical reasons (ELISA test from 50 mg of cytosol protein sample extracted from frozen tumor sample).

More than 10 years ago, gene expression profiling based on DNA microarrays [11] revealed the molecular heterogeneity of BC [11]. A new molecular classification was defined, dividing BC in at least 5 biologically and clinically relevant subtypes [12,13]: luminal A (LA), luminal B (LB), basal-like (BL), HER2-enriched and normal-like (NL). These subtypes are linked to major molecular alterations such as HR and HER2 expression and proliferation and to mammary cell types. They are found across all BC stages, from *in situ* carcinoma [14] to inflammatory [15] and metastatic tumors [16], and display epidemiological specificities, different rates of therapeutic response and different outcomes. LA tumors are less proliferative, poorly chemosensitive but highly sensitive to HT. In the opposite LB, HER2-enriched and BL cases are generally resistant to HT but sensitive to CT [17]. Since these subtypes incorporate many of the prognostic and predictive features used in previous recommendations, the 2011 Saint-Gallen Consensus Conference based its recommendations on the molecular subtypes [18]. For practical reasons, the subtypes were approximated using four IHC markers (ER, PR, HER2, Ki67) [19] rather than gene expression profiles [20], even if a genomic test – the *Breast BioClassifier/PAM50* (50 genes, Nanostring Technologies®, USA) – has been recently commercialized and can be applied to paraffin-embedded BC samples. Systemic therapy recommendations followed the subtype classification: LA tumors require only endocrine therapy that is also given to patients with LB tumors. Chemotherapy is indicated for most patients with LB tumors, HER2+ tumors also treated with trastuzumab, and triple-negative ductal tumors. These recommendations have been essentially unchanged during the 2013 Saint-Gallen conference [21] for HER2+ tumors and triple-negative ductal tumors. But because the main clinical issue concerns the selection of patients with HR+/HER2− tumor (node-negative or with less than four positive nodes) candidate for adjuvant

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CT and HT or for HT alone, efforts were done to refine the classification of luminal BC.

They were first centered on proliferation. Ki67 assessment using IHC is the most frequently used proliferation test and recommendations have been recently published [22]. Ki67 expression not only correlates with a poorer outcome [23–26], but also with a higher sensitivity to neo-adjuvant CT, notably to the anthracycline and taxane combinations [17,24,27]. But this predictive value remains controversial. In the International Breast Cancer Study Group Trials VIII and IX, there was no benefit to add CT to HT in node-negative HR-positive tumors with high Ki67 levels [28]. Within HR-negative tumors from the GeparTrio trial [29], Ki67 level had no predictive value for pathological response to CT and its impact within HER2-positive tumors has been poorly explored. In the 2011 Saint-Gallen recommendations, a 14% cut-off for Ki67 positivity was retained to distinguish LA (<14%) from LB (>14%) tumors. But this cut-off was questioned during the 2013 Conference [21], and alternate additional markers were proposed to define LB tumors. They include the IHC level of PR: a moderate or strong expression (>20%) was proposed as an additional restriction in the definition of LA tumors, whereas a low or negative expression defined LB tumors. However, because of the known variability of IHC and absence of clear standardization, a few multigene expression signatures were also proposed, when available, as alternate additional criteria to distinguish LB from LA tumors: the PAM50 classifier that defines the five molecular subtypes including LA and LB, and three prognostic signatures (Recurrence Score, *Mammaprint*, and *Endopredict*; see below), which define low-risk tumors that correspond for more than 80% of cases to LA tumors. The most recommended signature by the Expert panel was the Recurrence Score shown (retrospectively) as predictive of CT efficacy in prospective clinical trials.

2.2. Prognostic and predictive multigene signatures

Besides the molecular subtypes, prognostic multigene classifiers have also been reported (Table 1). Their goal is to avoid overtreatment in patients with early BC, notably node-negative, by providing arguments to decrease the indications of adjuvant CT. Prognostic utility, reproducibility and reliability of these classifiers are now admitted both by the MAQC consortium [30,31] and by meta-analyses [32,33]. The PAM50 (prediction analysis of microarray) classifier provides also a risk of relapse (ROR) score correlated to survival in ER-positive/negative node-negative patients [20], and in ER-positive node-negative/positive patients treated with adjuvant tamoxifen therapy [34]. It uses a non-PCR-based technology and is applicable to paraffin-embedded samples. Of note, the ROR score also predicted neoadjuvant chemotherapy efficacy with a negative predictive value for pathological complete response (pCR) of 97% [30].

Mammaprint (Agendia®, The Netherlands) is a 70-gene prognostic signature initially developed and validated in a panel of hundreds patients with node-negative tumors — whatever was their HR status – from 3 retrospective series [34–36]. Its prognostic value was then demonstrated in patients with node-positive disease [35,37] and in post-menopausal patients between 55 and 70 years of age [38]. Since its FDA approval, it has been the first commercialized DNA microarray predictor. *Mammaprint* is also predictive for pathological response to neoadjuvant chemotherapy [39] and benefit of adjuvant chemotherapy [40].

Oncotype DX © (Genomic Health®, CA, USA) is another predictor based on the expression of 21 genes including 16 genes of interest and 5 reference genes: the resulting Recurrence Score classifies breast tumors in 3 groups according to their 10-year risk of relapse (low, intermediate or high). These genes are analyzed by quantitative RT-PCR (qRT-CPR) on FFPE (formalin-fixed paraffin-embedded) samples. This test is focused on node negative HR-positive tamoxifen-treated BC [41,42]. It has been retrospectively validated on samples from prospective trials and is largely used in the USA. Its prognostic value was also demonstrated in node-positive tumors [43]. The Recurrence Score is also predictive for pathological response to neoadjuvant chemotherapy [44,45] and for benefit of adjuvant chemotherapy [42,46].

Node negative HR-positive BC can also be classified with the *Breast Cancer Index* © (Biotheragnostics®, CA, USA). This classifier is based on the combination of the HOXB13/Il17BR ratio [47,48] and the 5-gene *Molecular grade index* [49]. It results in 2 groups of low and high risk of 10-year relapse. This classifier is also associated with pathological response to primary chemotherapy [50]. The Genomic Grade Index (GGI; *MapQuant* ©, Ipsogen®, France) includes 97 genes involved in cell proliferation [51], and aims to class grade 2 tumors in 2 groups of poor (high genomic grade) and good (low genomic grade) prognosis. Like the other classifiers, GGI is associated with pathological response to primary chemotherapy [52].

Endopredict (Sividon Diagnostic®, Germany) is a more recently published signature focused on HR-positive and HER2-negative node-negative/positive BC [53,54]. Eleven genes (including 8 genes of interest and 3 reference genes) have been explored using qRT-PCR performed on 964 FFPE samples treated by adjuvant HT. This prognostic score has then been validated on 1702 independent tumors from 2 prospective trials. It segregates BC into 2 groups according to their distant relapse risk.

IHC-derived classifiers have also been developed The IHC4 score, which combines four IHC parameters (ER, PR, HER2 and Ki67), was defined on 1000 patients from the ATAC trial, and validated on 786 independent patients [55]. IHC measurements were done in a controlled setting. The authors showed that the inclusion of the Recurrence Score measured by *Oncotype DX* © into the IHC4 score provided little additional prognostic information, suggesting that the amount of prognostic information contained in four widely performed IHC assays is similar to that in the Recurrence Score.

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Table 1
Currently commercialized prognostic gene expression signatures.

Multigenic signature	PAM50/Prosigna	Mammaprint	Oncotype	Breast Cancer Index	MapQuant	EndoPredict
Technologies	DNA microarray/qRT-PCR	DNA microarray/qRT-PCR	qRT-PCR	qRT-PCR	DNA microarray/qRT-PCR	qRT-PCR
Number of genes	50	70	21	7	97/9	11
Samples	Frozen/FFPE	Frozen/FFPE under development	FFPE	FFPE	Frozen/FFPE	FFPE
Inclusion criteria	HR+ pN− or 1–3N+	pN− or 1–3N+	HR+ pN−	HR+ pN−	HR+ grade II	HR+ HER2−
Results	Molecular subtypes, risk of relapse	Risk of relapse	Risk of relapse	Risk of relapse	Risk of relapse	Risk of relapse
Level of evidence	II	III	I	III	III	I
FDA approval	Yes	Yes	No	No	No	No
ASCO/NCNN guidelines	No	No	Yes	No	No	No
Evaluation in prospective randomized trial	No	MINDACT	TAILORx	No	No	No
Company	Nanostring (USA)	Agendia (The Netherlands)	Genomics Health (USA)	bioTheragnostics (USA)	Ipsogen/Qiagen (France)	Sividon Diagnostic (Germany)

qRT-PCR, real-time polymerase chain reaction; FFPE, formalin-fixed, paraffin-embedded; pN, pathological lymph node; HR, hormone receptors.

Some of these multigenic classifiers are already approved by the FDA and commercialized in some countries, where their use is increasing and has led to an overall decreased use of adjuvant CT in patients with HR-positive BC [56]. In the 2013 Saint-Gallen recommendations [21], the recurrence Score and the *Mammaprint* signature are proposed to help decisions of adjuvant CT in HR+/HER2− patients. However, costs and availability preclude their application in many countries and their real benefits in cancer care improvement are still discussed and have to be confirmed by the results of prospective randomized trials. The MINDACT (*Microarray In Node-Negative Disease may Avoid ChemoTherapy*) European trial has included nearly 6600 patients between 2007 and 2001 [57] and assesses the prognostic value of the *Mammaprint* signature. The TAILORx (*Trial Assigning Individualized Options for Treatment Rx*) evaluates *Oncotype DX* © in nearly 10,000 patients included from 2006 to 2010 [58].

Another approach is the definition of signatures able to predict the response to a specific CT. A 30-gene classifier (the *DLDA-30* score) was identified to predict pCR in patients receiving paclitaxel and FAC neoadjuvant chemotherapy [59]. It was prospectively validated in a randomized trial comparing this therapy to FAC alone [60]. However its predictive value was not higher than those of clinical data. Predictors of response to anthracyclines have been reported for HR-negative tumors [61]. In the adjuvant setting, we have developed a signature able to predict outcome after anthracycline therapy in node-positive BC [62], and tested its prognostic value in the SA02 prospective trial, the results of which are awaited. The REMAGUS 04 trial randomized patients with HER2-negative early breast cancers not eligible to conservative surgery between two arms: conventional CT (4 cycles of FEC followed by 4 cycles of docetaxel) *versus* CT guided by the assessment of the *DLDA-30* score and *TOP2A* expression [63]. *DLDA-30* high-risk tumors received 12 weekly paclitaxel injections followed by 4 FEC courses; *DLDA-30* low-risk and TOP2A-positive cases received 4 cycles of FEC followed by 4 cycles of docetaxel; *DLDA-30* low-risk and TOP2A-negative tumors received 6 courses of docetaxel associated with capecitabine. The primary objective was to improve the pCR rate. This study was stopped after a pre-planned interim analysis because of a low pCR rate (<10%) in the capecitabine subgroup. No difference between arms was observed.

3. Personalized medicine and metastatic breast cancer

3.1. Where to assess tumor molecular profile?

3.1.1. Primary tumor and/or metastasis?

The treatment of patients with of metastatic BC is based on several clinicopathological features such as age, menopausal status, performance status, comorbidities, disease-free interval, previous treatments and number and localization of metastases. As in the adjuvant setting, HR and HER2 expression analyses are the main biological tools currently used in daily practice. They represent the first step to more personalized treatments.

50–80% of HR-positive advanced BC are sensitive to HT, whereas only 5–10% of negative cases can be improved by

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this therapy [64]. There is a quantitative correlation between ER levels and sensitivity to HT: the higher the number of ER-positive cells, the better HT results [65,66]. However no clear threshold exists to exclude HT activity. This is why HT can be prescribed if at least 1% of tumor cells are stained. No biological factor has yet been identified to select which kind of HT should be the most effective. Another point is that HR expression has been correlated to a partial resistance to chemotherapy. HER2 overexpression and/or amplification are warranted to prescribe HER2-inhibitors. Trastuzumab, pertuzumab or lapatinib efficacy depends on IHC and/or *in situ* hybridization results [67,68]. It is of note that HER2 overexpression has been retrospectively correlated to resistance to HT in HR-positive tumors. However, HT benefits in this population are not null, justifying the use ofHT in patients with HER2-positive HR-positive tumor [69,70].

However a question is arising: where to assess HR and HER2 status: primary tumor or mestatatic site? Until recently, molecular characteristics of the primary tumor were used to guide treatment choices for metastatic patients. In the 80s, phenotypic differences between primary lesions and metastases were reported [71,72]. That was confirmed in more recent retrospective studies exploring HR and HER2 expression on both primary and metastatic tumors [73–83]. Mismatches have been identified in 10–40% of cases for HR expression (notably HR loss), and in nearly 10% of cases for HER2. Several explanations could be proposed: methodological bias, tumor heterogeneity or clonal selection. Even if phenotypic modifications are not yet fully understood, they induce therapeutic changes in 12% [84] to 20% [76] of cases. Biopsy for pathological exploration of a suspected metastasis may decrease the risk of wrong diagnosis with identification of benign lesions or second primary tumors [76]. Phenotypic differences between primary and metastatic tumors have a prognostic value. ER loss was associated with a 2-fold increase of death risk, compared to patients with stable ER status [78,85]. In a series of 182 HER2-positive patients, nearly 25% displayed HER2 loss in metastases sites, notably in case of previous CT, with a reduced survival in this population [82]. Liedtke et al. have studied 789 recurrent BC including 231 with ER, PR and HER2 measurements available on both primary and metastatic tumors. The rate of phenotypic differences was 18%, 40% and 13% for ER, PR and HER2, respectively. Moreover these alterations were associated with a poorer outcome [77]. The authors suggested two explanations. First, the poorer outcome could be induced by the pathological exploration, because of measurement bias leading to wrong diagnoses and treatments. Second, the poorer outcome could be induced by a real change in tumor phenotype, leading to a more aggressive behavior. Botteri showed in a retrospective comparative study including 200 patients with liver metastases that survival was similar with or without metastases examination [86]. However within the 100 biopsied patients, 18 presented phenotypic modifications leading to treatment changes. These patients had a longer survival than other biopsied patients. A recently published prospective trial described the results, including the survival impact, of metastases biopsy [87]. Pathological examination of metastases was performed for 80% of 121 BC with metastases at diagnosis. Mismatch rates were 16% for ER, 40% for PR and 10% for HER2. Treatment was modified for 14% of patients. After a 1-year follow-up, patients with phenotypic discrepancy did not experiment a poorer outcome, maybe thanks to treatment modifications in this population. These observations have been recently confirmed in a meta-analysis [88].

In conclusion, metastasis biopsy is recommended to confirm diagnosis in equivocal cases such as unique lesions, history of multiple primary cancers, or doubt after clinical and radiological explorations. In other cases, if biopsy procedure is safe, it should be performed to confirm diagnosis and to evaluate HR and HER2 expression. Nevertheless stopping targeted therapies in case of loss of expression in secondary lesions is not currently recommended because of the putative tumor heterogeneity. Thus, pathological examination of metastases is more used to add new therapeutics options than to eliminate previously used therapies.

3.1.2. Could we evaluate the metastatic disease using circulating agents? Analysis of circulating tumor DNA and circulating tumor cells

Non-invasive procedures are under investigation to avoid the potential adverse events and discomfort of biopsies, and the failures or mistakes due to tumor heterogeneity [89]. Circulating tumor cells (CTC) identification and quantification can be performed using *Cellsearch* © (Veridex®, NJ, USA), the only technology approved by the FDA. It is based on the analysis of a small volume of peripheral blood (7.5 ml) in order to detect epithelial cells with CD45-negative and cytokeratin (CK8, 18 and 19)-positive staining. High CTC levels (≥5 cells/7.5 ml) in metastatic BC patients correlate with poor outcome (median overall survival of 10.1 *versus* 18 months, $p = 0.001$). The modification of CTC rate after one course of CT is a predictive factor, with a PFS (progression-free survival) of 7.0 months in the cases of CTC decrease under 5 cells/7.5 ml *versus* 2.1 months in the other cases ($p < 0.001$) [90]. These prognostic and predictive values of CTC have been validated in retrospective trials [91–93] and in a large prospective trial [94]. Large prospective studies are warranted to confirm CTC predictive value after treatment combining CT and targeted therapies such as trastuzumab or bevacizumab [94–96].

However, even if *Cellsearch* © has been approved by the FDA, it is not yet the case for the European Medical Agency, and it is not recommended in daily practice by ASCO guidelines [10]. Indeed, this technology has not yet demonstrated prospectively an impact on survival or quality of life. Prospective trials are in progress to confirm clinical utility of CTC in breast cancer care.

The METABREAST trial (Fig. 1), founded by the French STIC (*Soutien aux Techniques Innovantes et Coûteuses*) program, is a multicenter randomized trial designed to show the

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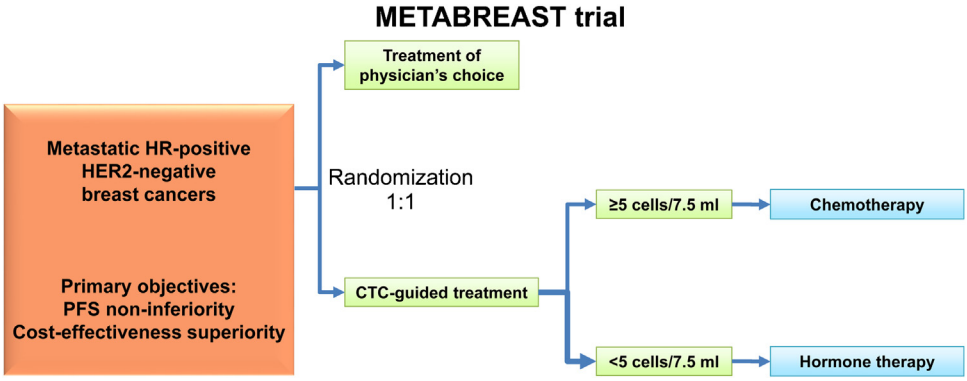

Fig. 1. METABREAST trial: phase III trial based on circulating tumor cell levels at baseline in metastatic breast cancer [97] (HR, hormone receptors; PFS, progression-free survival; CTC circulating tumor cells).

non-inferiority of CTC identification for PFS, and superiority of the CTC arm for the cost-effectiveness evaluation (co-primary endpoints). The inclusion of 994 HR-positive HER2-negative patients with metastatic BC is planned. Patients are randomized between treatment based on clinician's choice and treatment based on CTC assessment. In the CTC arm, patients with ≥5 cells/7.5 ml will receive CT, whereas those with <5 cells/7.5 ml will receive HT as first-line treatment [97]. Two other trials are exploring early CTC count changes during chemotherapy. The SWOG0500 trial randomized patients treated with first-line CT and with high CTC rate after the first cycle between therapy modification guided by usual clinical and radiological features *versus* early therapy modification based on CTC count. Primary endpoint was OS. The authors confirmed the prognostic value of CTC with a median OS of 13 months for patients with high CTC levels not modified after one cycle of chemotherapy *versus* 35 months for patients with low CTC levels at diagnosis. They showed that early treatment modification based on CTC count after 3 weeks of treatment did not affect OS [98]. In the CirCe01 trial, 300 patients with high CTC levels before a third line CT are randomized between standard management and therapy guided by CTC count after 1 course of treatment. Patients with CTC decrease under 5 cells/7.5 ml continue the same therapy until the next clinic-radiological assessment whereas patients with ≥5 cells/7.5 ml start another treatment. Primary endpoint is OS.

CTC phenotype may also be used. The DETECT III trial includes patients with HER2-negative metastatic BC with at least 1 HER2-positive CTC/7.5 ml. Patients are randomized between standard treatments *versus* the same molecules associated to lapatinib. Primary objective is PFS [99].

Circulating tumor DNA (CTDNA) profiling with high-throughput technologies is also under investigation [100,101]. Fifty-two metastatic BC patients were prospectively analyzed in a study comparing different monitoring options: imaging, CA 15-3 serum level, CTC count, genomic alterations identified on tumor tissue and CTDNA [102]. Most of patients (30/52) presented genomic alterations on tumor tissue. Ninety-seven percent of these alterations could be identified on CTDNA using digital PCR or tagged-amplicon deep sequencing technologies. In this population, tumor modifications based on radiological assessment were more correlated to CTDNA modifications than to CTC or CA 15-3 changes. The same authors recently showed that CTDNA deep sequencing can identify mutations associated with resistance to chemotherapy [103].

3.2. How to assess tumor molecular profile?

DNA microarray technology has dramatically changed our knowledge about BC. Another technology is continuing to improve BC understanding: next generation sequencing (NGS). It allows sequencing of several genes in a same time, from tens of them to the whole genome. Results can be obtained in 1–15 days according to the length of the amplicons studied [104]. This new sequencing technology, quicker and cheaper than the classical Sanger technique, can identify already known or unknown mutations. It is of note that experiments are currently performed on frozen samples, even if analyses of a limited number of genes can also be done on FFPE samples. This new approach also leads to data flow enhancement, and thus to a need in development of new bioinformatics tools.

Some recently published articles have describe NGS in BC [105–109]. New mutations with low frequency (lower than 5–10%) have been identified. The genes involved in these mutations can often be pooled in similar biological processes, including some involved in resistance to endocrine therapy [105].

3.3. How to develop new targeted therapies?

The next step after the identification of multiple but rare alterations is the development of dedicated therapies. Hundreds of targeted drugs are under investigation, both in monotherapy and in association. These therapies will potentially be effective in small tumor subsets presenting the corresponding alterations. This new concept will make out

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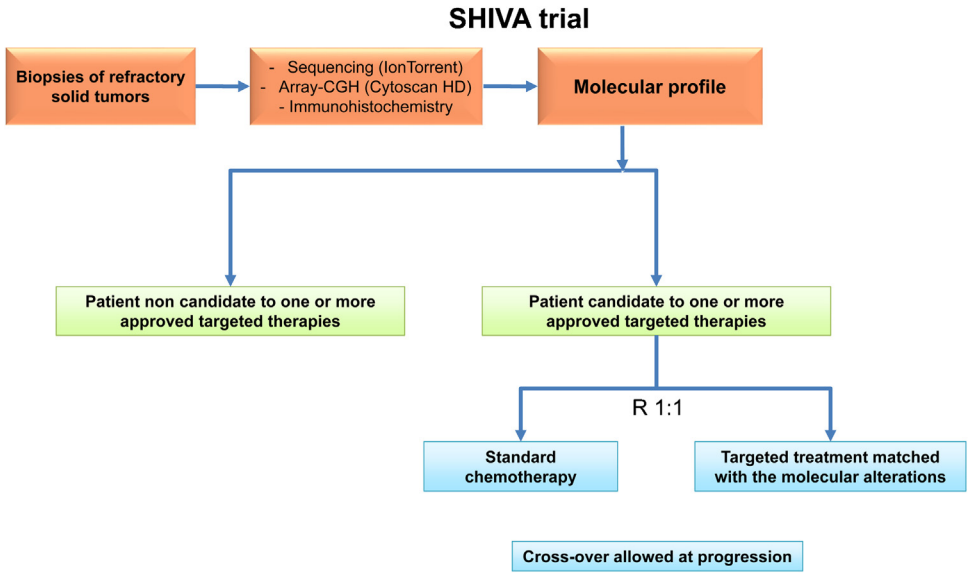

Fig. 2. SHIVA trial: phase II trial analyzing molecular alterations to evaluate if systemic treatment based on these alterations may increase progression-free survival [113].

of date the usual design of clinical trials based on the development of a therapy in the whole population followed by the search for predictive biomarkers. New strategies based on tumor genomic profile will guide patients to dedicated early phase trials. Since focused on small populations, these trials will be shorter, cheaper and will theoretically use more effective therapies.

Different biological alterations may be identified. Huge abnormalities such as genomic instability potentially correlated with DNA damage response alterations and PARP inhibitors sensitivity, pathways activations (RAS, MYC, KIT) [110], but also gene mutations (*EGFR*, *BRAF*, etc.), translocations (*ALK-EML4*, etc.) or amplifications (*HER2*). Von Hoff et al. studied 86 patients with refractory metastatic cancers [111]. They evaluated the expression of 61 genes using IHC and gene expression profiling. One putative target was identified in 84 patients, and 66 received a genomic-guided therapy. Eighteen patients presented a 1.3-fold longer PFS when compared to the PFS observed under the previous treatment line. In the same way, among thousands of patients included in phase 1 trials at the MD Anderson Cancer Center, 40.2% had at least one molecular alteration. Within this population, patients with matching therapies had higher overall response rates (27% *vs.* 5%); longer time to treatment failure (5.2 *vs.* 2.2 months) and longer OS (13.4 *vs.* 9.0 months, $p = 0.017$). The authors have noted that the use of a matched targeted treatment was an independent prognostic factor in patients displaying molecular alterations [112]. The SHIVA French trial is a proof of concept randomized phase II trial for patients with refractory solid tumors (Fig. 2) [113]. From a tumor biopsy, a molecular profile of the disease is established using IHC, array-CGH and sequencing of 46 genes using *Ion Torrent*™ (Life Technologies®, San Francisco, CA, USA). If a molecular alteration is identified for which an approved targeted agent is available in the trial, patients are randomized between therapy based on the molecular profile and conventional therapy based on investigator's choice. Primary endpoint is PFS after randomization. Thousand patients need to be screened to randomize 200 cases. About 10 already available drugs are proposed: imatinib (KIT, ABL, RET), everolimus (AKT, mTOR, PTEN, PI3K), vemurafenib (BRAF), sorafenib (PDGFR, FLT-3), erlotinib (EGFR), trastuzumab and lapatinib (HER2), dasatinib (SARC, LCK, YES, EPHA2), tamoxifen and letrozole (ER), and abiraterone (AR).

Metastatic BC has also been studied with this strategy. The French SAFIR01 prospective trial, launched by UNICANCER, has included 423 patients in a 16-month period. Pathological examination of metastases was performed using array-CGH and sequencing of mTOR pathway genes (*PI3K*, *PTEN* and *AKT*). When a molecular targetable alteration was observed, the patient was directed toward a dedicated early phase clinical trial. Tumor molecular profile was obtained for 64% of patients, with 69% presenting one or more targetable alteration. The first preliminary results showed that 26 patients had actually received a targeted therapy with clinical benefits for 8 patients [114]. The MOSCATO (MOlecular Screening for CAncer Treatment Optimization) trial reproduces the SAFIR01 design in advanced solid tumors. Of note, one of the main limitations of this biopsy-driven therapeutic targeting is the emerging concept of intra-tumoral heterogeneity [89,115].

4. Conclusion

The concept of personalized medicine is currently used in BC management, in both adjuvant and metastatic settings,

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even if several aspects are still under investigation. Analyzes can be performed not only on tumor tissue but also on circulating tumor cells and DNA. Prognostic or predictive gene expression signatures, designed to improve treatment decision are already used or in development for localized and metastatic diseases. In metastatic BC, several studies have assessed or are evaluating therapeutic strategies based on tumor genomic alterations identified by array-CGH or next-generation sequencing tools.

The "El Dorado" of oncology may be reached with the theory of "one cancer, one patient, one treatment". However the reality is currently limited to the use of high-throughput technologies in order to assemble patients in more homogeneous populations, and to give them specific targeted therapies. Nevertheless this approach will face several challenges and issues before its translation to the clinic: quick access to genomic explorations; development of new tools in bioinformatics, statistics and clinical research; new ways to think drugs development due to the high number of tumor subsets and biomarkers identified by these tools. Finally, these technologies will have to minimally impact cancer management costs to allow clinicians to offer these advances to all patients.

Conflict of interest

None.

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