

CATCH: A Prospective Precision Oncology Trial in Metastatic Breast Cancer

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PURPOSE CATCH (Comprehensive Assessment of clinical features and biomarkers to identify patients with advanced or metastatic breast Cancer for marker driven trials in Humans) is a prospective precision oncology program that uses genomics and transcriptomics to guide therapeutic decisions in the clinical management of metastatic breast cancer. Herein, we report our single-center experience and results on the basis of the first 200 enrolled patients of an ongoing trial.

METHODS From June 2017 to March 2019, 200 patients who had either primary metastatic or progressive disease, with any number of previous treatment lines and at least one metastatic site accessible to biopsy, were enrolled. DNA and RNA from tumor tissue and corresponding blood-derived nontumor DNA were profiled using whole-genome and transcriptome sequencing. Identified actionable alterations were brought into clinical context in a multidisciplinary molecular tumor board (MTB) with the aim of prioritizing personalized treatment recommendations.

RESULTS Among the first 200 enrolled patients, 128 (64%) were discussed in the MTB, of which 64 (50%) were subsequently treated according to MTB recommendation. Of 53 evaluable patients, 21 (40%) achieved either stable disease (n = 13, 25%) or partial response (n = 8, 15%). Furthermore, 16 (30%) of those patients showed improvement in progression-free survival of at least 30% while on MTB-recommended treatment compared with the progression-free survival of the previous treatment line.

CONCLUSION The initial phase of this study demonstrates that precision oncology on the basis of whole-genome and RNA sequencing is feasible when applied in the clinical management of patients with metastatic breast cancer and provides clinical benefit to a substantial proportion of patients.

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INTRODUCTION

Metastatic breast cancer (mBC) is a systemic disease that currently still remains incurable despite the ongoing and gradual improvement in progression-free survival (PFS) and/or overall survival achieved with several recently approved targeted therapies.¹⁻¹¹ Patient stratification in this setting rarely goes beyond several well-established predictive biomarkers and is dominantly based on immunohistochemical staining of estrogen and progesterone receptors, also summarized as hormone receptors (HRs), followed by human epidermal growth factor receptor 2 (HER2), proliferation markers such as KI-67, and more recently, programmed death-ligand 1. Tumor DNA sequencing in mBC is currently still not common in standard clinical practice and is mostly reserved for determining the mutational status of actionable driver genes *ESR1*, *PIK3CA*, *ERBB2*, and *BRCA1/2*. More comprehensive molecular profiling using massively

parallel sequencing of tumors and corresponding nontumor controls is nowadays still dominantly performed within the framework of clinical and research-driven translational programs focusing almost exclusively on advanced-stage or metastatic cancers,¹²⁻¹⁶ with several focusing specifically on mBC.¹⁷⁻¹⁹ Moreover, as all these programs operate under the paradigm of precision medicine, the immediate goal is to use identified actionable alterations for further patient stratification and thus affect clinical decision making, especially if these alterations are successfully translated into individualized treatment options, which is the main task of an interdisciplinary molecular tumor board (MTB).

Herein, we report our single-center experience with CATCH (Comprehensive Assessment of clinical features and biomarkers to identify patients with advanced or metastatic breast Cancer for marker driven trials in Humans), which is a prospective precision

ASSOCIATED CONTENT

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

Despite recent advances in improving treatment outcomes of patients with metastatic breast cancer, patient stratification and optimal treatment allocation remains a challenging task. CATCH (Comprehensive Assessment of clinical features and biomarkers to identify patients with advanced or metastatic breast cancer for marker driven trials in Humans) is a prospective precision oncology program that aims at using existing markers as well as generating new knowledge on the basis of whole-genome and RNA sequencing to improve patient stratification, adapted therapies, and clinical outcomes.

Knowledge Generated

We report the data on the first 200 enrolled patients, of whom the majority were subject to a molecular tumor board and received treatment recommendations. Additionally, we provide an overview of identified biomarkers that were used for patient stratification.

Relevance

We show that substantial proportion of patients can benefit from recommended therapies when clinical decision making is guided by broad genomic techniques, further emphasizing the value of personalized treatment approaches in metastatic breast cancer.

oncology program using whole-genome sequencing (WGS) and RNA sequencing to guide therapeutic strategies in the clinical management of mBC. From June 2017 to March 2019, we enrolled 200 patients who were starting a new systemic treatment line and had either primary metastatic or progressive disease with any number of previous treatment lines and having at least one metastatic site accessible to biopsy at the time of enrollment (Table 1). DNA and RNA from biopsied tumor lesions and corresponding blood-derived nontumor DNA were systematically profiled using WGS and transcriptome sequencing for the purpose of individualized molecular diagnostics. The findings were presented within the MTB and integrated with clinical parameters to identify and prioritize tailor-made treatment recommendations for individual patients. We present here the data on the first 200 enrolled patients of an ongoing trial, with the emphasis on patient characteristics, predictive biomarkers, and treatment recommendations, as well as the rate of their translation into clinical setting and preliminary outcomes of treated patients.

METHODS

Patients with mBC eligible for CATCH were screened and consented upon presentation at the Division of Gynecological Oncology at the National Center for Tumor Diseases Heidelberg. They were eligible either if primary metastasized or upon disease progression with at least one metastatic tumor site accessible to biopsy at the time of enrollment, irrespective of previous treatment lines. Inclusion criteria, details on the enrollment, and in-depth information on the sample flow, molecular and bioinformatic analyses, development of rational treatment recommendations, and outcome assessment are outlined in the Data Supplement. The PFS ratio was calculated as the ratio between PFS under the MTB-recommended treatment (PFS2) and PFS under the immediate previous

treatment line (PFS1). In case of progression on MTB treatment and continuation of treatment after progression, PFS2 was counted only until the first progression was established.

RESULTS

Patient and Cohort Characteristics

Among the first 200 patients enrolled to CATCH, 64% (128/200) were discussed in the MTB, of which 127 were mBC cases. For one patient, diagnosis was changed to metastatic colon cancer after prior breast cancer history (Fig 1). Median age of 127 discussed patients with mBC at CATCH enrollment was 53 years (range, 27-79), with the median of 2 (range, 0-10) treatment lines received in metastatic setting before CATCH biopsy and a median of 2 (range, 1-6) metastatic sites affected (Table 1). Most of the profiled lesions were biopsied from the liver (51%), followed by lymph node (17%), breast (11%), skin (6%), and lung (3%) (Fig 2A). Although breast lesions (primary or recurrent) are not formally metastatic, they were still profiled if no metastatic lesions could be biopsied at the time of inclusion. The analysis of immunohistochemical-based HR and HER2 staining of sequenced lesions in the same subset of patients revealed 59.5% of them to be of the HR+/HER2- (or luminal HER2-) type, followed by 29.4% of HR-/HER2- (or triple-negative breast cancer), and 11.1% of HER2+, which is equally split between 5.55% of HR-/HER2+ and 5.55% of HR+/HER2+ (or luminal HER2+) (Fig 2B). For 16% (20/128) of the above cases, only WGS data were available as RNA sequencing could not be performed because of insufficient amount or quality of RNA.

Thirty-six percent (72/200) of enrolled patients were not discussed in the MTB as for a majority of those (44/200, 22% of all enrolled patients) sequencing could not be performed (exact reasons given in Fig 1). Importantly, half

TABLE 1. Patient Characteristics at CATCH Inclusion (n = 127)

Characteristic	No. (%)
Age, years	
Median (range)	53 (27-79)
Menopausal status at primary disease	
Premenopausal	44 (34.6)
Perimenopausal	10 (7.9)
Postmenopausal	51 (40.2)
NA	22 (17.3)
ECOG status	
0	68 (53.5)
1	44 (34.6)
> 1	10 (7.9)
NA	5 (4)
No. metastatic sites	
Median (range)	2 (1-6)
Metastatic sites	
Solitary hepatic	13 (10.2)
Solitary cerebral	1 (0.8)
Solitary lymphatic	5 (3.9)
Solitary bone	8 (6.3)
Multiple	100 (78.7)
Presence of visceral metastasis	
Yes	103 (81.1)
No	24 (18.9)
Primary metastatic	
Yes	36 (28.3)
No	81 (63.8)
NA	10 (7.9)
Primary tumor subtypes	
HR-/HER2-	30 (23.6)
HR-/HER2+	6 (4.7)
HR+/HER2-	76 (59.8)
HR+/HER2+	11 (8.7)
NA	4 (3.2)
CATCH biopsy subtypes	
HR-/HER2-	37 (29.1)
HR-/HER2+	7 (5.5)
HR+/HER2-	75 (59.1)
HR+/HER2+	7 (5.5)
NA	1 (0.8)
ER status of the CATCH biopsy	
Positive	82 (64.6)
Negative	44 (34.6)
NA	1 (0.8)

(Continued in next column)

TABLE 1. Patient Characteristics at CATCH Inclusion (n = 127)

Characteristic	No. (%)
(Continued)	
PgR status of the CATCH biopsy	
Positive	71 (55.9)
Negative	54 (42.5)
NA	2 (1.6)
HER2 status of the CATCH biopsy	
Positive	14 (11)
Negative	112 (88.2)
NA	1 (0.8)
Proliferation index of the CATCH biopsy	
5%-9%	10 (7.9)
10%-50%	58 (45.7)
> 50%	47 (37)
NA	12 (9.4)
PD-L1 status of the CATCH biopsy	
Positive	11 (8.7)
Negative	27 (21.3)
NA	89 (70)
Disease-free survival (from primary diagnosis till occurrence of first distant metastasis)	
≤ 2 years	51 (41)
> 2 years	76 (59)
No. pretreatment lines in the metastatic setting	
Median (range)	2 (0-10)
Previous treatments applied in the metastatic setting (220 individual therapies)	
CDK4/6 inhibitor	31 (14.1)
Chemotherapy	72 (32.7)
Endocrine therapy	52 (23.6)
Anti-HER2 therapy	13 (5.9)
Immune checkpoint inhibitor	9 (4.1)
Other	43 (19.5)

Abbreviations: CDK, cyclin-dependent kinase; ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; NA, not available; PD-L1, programmed death-ligand 1; PgR, progesterone receptor.

of these patients were still alive at the data cutoff, suggesting that there remains a possibility to rebiopsy them at next progression. Finally, as many enrolled patients were heavily pretreated (Table 1), 12% (24/200) of them died between sequencing and the MTB (Fig 1), which was especially common in the early phase of establishing the program with larger turnaround time between the biopsy and MTB (median 139 days for patients 1-100 and median 91 days for patients 101-200). Albeit not part of the

analyses presented here, the current median turnaround time between biopsy and MTB discussion in CATCH is 55 days.

Identified Biomarkers and Implementation of Treatment Recommendations

We analyzed predictive biomarkers used as rationale for the top three treatment recommendations among 127 patients discussed in the MTB and grouped them according to the type of aberration and drug class they are related to (Fig 3A). The purpose of this analysis was to summarize biomarkers and related events that have led to recommending a drug of a particular class in the real-world clinical setting. This differs from a typical landscape catalog of genomic and transcriptomic aberrations in mBC as the former was generated under implicit constraints set by specific pre-treatment history of analyzed patients and the availability of specific drugs within or outside clinical trials. In addition to already well-established actionable events such as mutations in *PIK3CA*, *ESR1*, and *BRCA1/2*, or amplifications and overexpression of ErbB family of receptor tyrosine kinases, we frequently observed aberrations suggesting pharmacologic targeting of pathways that are not routinely targeted in the clinical management of mBC and as such can be realized only within clinical trials or with an off-label use of drugs already approved in a different setting. For example, frequently observed amplification and/or overexpression of fibroblast growth factor receptors 1-4 (*FGFR1-4*) potentially leading to the overactivation of the FGFR signaling pathway²⁰ would suggest using either a specific pan-FGFR inhibitor^{21,22} or a pan-tyrosine kinase inhibitor (pan-TKI) that also targets FGFRs^{23,24} (Fig 3A). Similarly, overexpression of *RET* receptor tyrosine kinase, which has been already described in mBC,²⁵⁻²⁷ would argue for pharmacologic targeting of RET with a pan-TKI^{20,28} (Fig 3A). Furthermore, inactivating mutations or homozygous deletions of the *PTEN* tumor suppressor may argue for targeting the PI3K-AKT-mTOR pathway,²⁹⁻³² whereas similar events in *MAP3K1*, *MAP2K4*, and *NF1* would suggest targeting the mitogen-activated protein kinase (MAPK) pathway,^{33,34} depending on the context (Fig 3A). Finally, overexpression of the antibody-drug conjugate (ADC) target Trop2, encoded by *TACSTD2*, and mesothelin, encoded by *MSLN*, was also commonly observed and respective ADCs recommended, particularly among triple-negative breast cancers, as it suggests potential clinical efficacy of these agents in patients with tumors exhibiting such molecular features.³⁵⁻³⁷ Of note, commonly observed expression aberrations of FGFRs, RET, or targets of ADC in our cohort further illustrate the importance of RNA sequencing in the context of precision oncology, which was also recently proposed by the WINTHER trial.³⁸ Finally, linking biomarkers and treatment options in this way (Fig 3A, Data Supplement) allowed us to quantify and rank the most commonly suggested drug classes among treatment recommendations in this patient population (Fig

3B, dark blue bars). Comparison of the rates of treatment recommendations for specific drug classes (Fig 3B, dark blue bars) and their implementation rates in clinical practice (Fig 3B, dark red bars) revealed that certain types of treatments such as poly (ADP-ribose) polymerase (PARP), immune checkpoint, and cyclin-dependent kinase 4/6 inhibitors were more readily implemented in the clinic as opposed to pan-TKIs and MAPK pathway inhibitors, or FGFR-specific inhibitors and ADCs, most of which were only available within clinical trials. Of note, 85% of patients had a clinical trial recommended among the top three treatment recommendations, and 5% of patients were enrolled accordingly. Exact breakdown of reasons for the actual trial enrollment rate is provided in the Data Supplement.

In terms of germline variants, we observed pathogenic variants in 14% (18/127) of patients with mBC, where 6% (8/127) had pathogenic germline variants in *BRCA1/2*, known to have immediate therapeutic implications because of the approval of PARP inhibitors in this setting.^{9,10} This further increased to 11% (14/127) when considering additional cancer predisposition genes (*PALB2*, *CHEK2*, *ATM*, and *MUTYH*).

With regard to overall implementation of treatment recommendations in the clinic, 50% (64/127) of patients with mBC were treated according to the MTB recommendation (Fig 1). As there were no patients discussed in the MTB without a treatment recommendation (Data Supplement), lack of implementation was mostly because of other reasons, from which the most common was that patients still responded to the previous treatment line (21% of cases, 27/127; Fig 1). Together with the 6% of patients (8/127) who did not receive the treatment on the basis of the MTB, but received another therapy instead, they account for more than half of patients with mBC with no treatment implementation (55%, 35/64), who may potentially still receive molecularly guided treatment in the future. Sixteen percent (20/127) of analyzed cases could not receive MTB-recommended treatment since patients died before therapy implementation. In general, because of the high clinical pressure for achieving response in this population of heavily pretreated patients with progressive disease, we favored combination therapies whenever possible, as was also recently supported by the findings of the I-PREDICT study.³⁹ We recommended either combinations of different targeted therapies or combinations of targeted therapies and chemotherapies or endocrine therapies, provided that at least phase I study toxicity data were available for any given combination. As 72% (46/64) of all treated patients received off-label therapy and 81% (52/64) of them received combination therapies, managing toxicity becomes an important concern. Among these, 6% (4/64) had to stop the treatment completely before first treatment evaluation because of toxicity and were hence not evaluable for response (Fig 1).

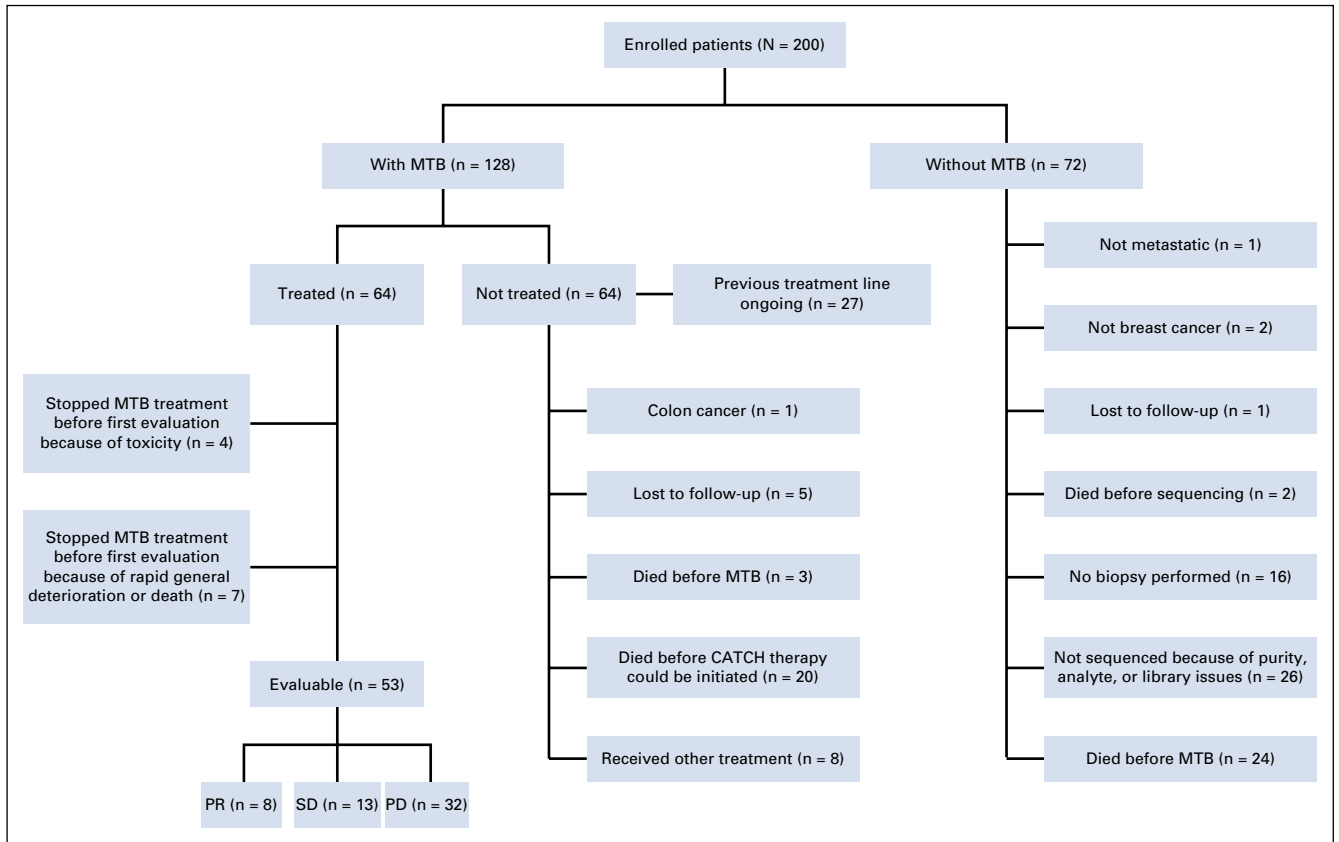


FIG 1. Flow diagram of the study outlining patients who were enrolled, discussed, or treated on the basis of MTB recommendation, as well as related dropout reasons. Outcomes are given as best responses. MTB, molecular tumor board; PD, progressive disease; PR, partial response; SD, stable disease.

Clinical Outcomes

Fifty-three of 64 patients treated according to MTB recommendation were evaluable for response (Fig 1), and of those, 40% (21/53) received clinical benefit. More specifically, 15% (8/53) of treated patients achieved partial response (PR) as best response while on MTB-

recommended treatment, whereas 25% (13/53) reached stable disease (SD) (Fig 1).

Furthermore, we compared the PFS2 with the PFS1 by calculating the PFS2-to-PFS1 ratio (PFS ratio) and observed that 30% (16/53) of evaluable patients exhibited improvement in PFS2 of at least 30% compared with PFS1

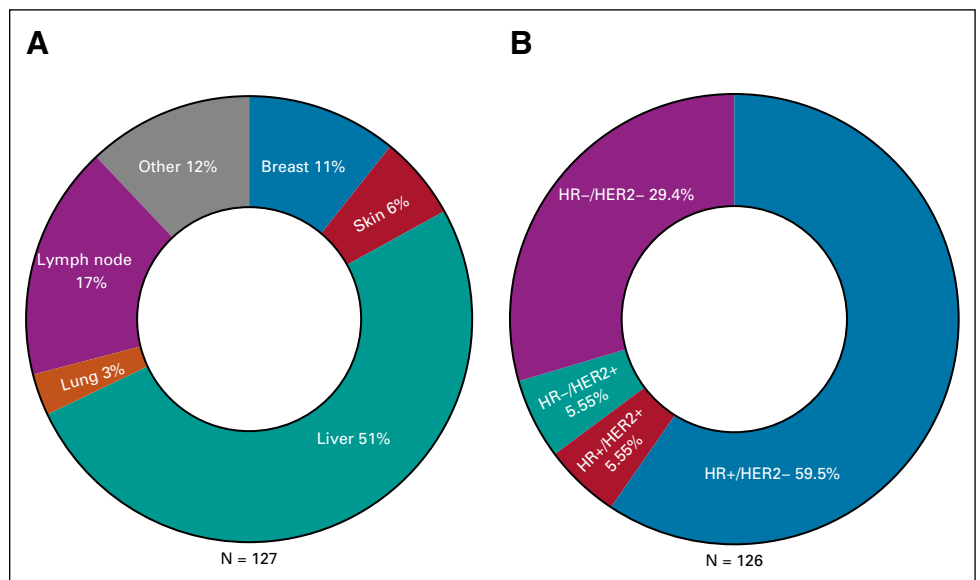


FIG 2. Features of sequenced samples among patients with metastatic breast cancer discussed in the molecular tumor board. (A) Localization of the biopsy. Other refers to adrenal gland, thoracic wall, soft tissue, muscle, ovary, and brain. (B) Histology of profiled lesions. Histology was not available for one sample (n = 126). HER2, human epidermal growth factor receptor 2; HR, hormone receptor.

FIG 3. Landscape of single-gene–based predictive biomarkers used for the top three treatment recommendations and the overview of recommendation and implementation rates across drug classes. (A) Biomarkers and the types of aberrations observed: SNVs or small insertions and/or deletions, amplifications and homozygous deletions as copy number changes, and expression aberrations (underexpression only for tumor suppressor genes, otherwise overexpression). Biomarkers are further stratified according to cellular pathways they belong to or the drug class they are targeted with. Shown are only biomarkers used for the top three treatment recommendations that were observed in at least three patients among 127 patients discussed in the molecular tumor board (MTB). Dark blue denotes pathogenic germline variants, *denotes presence of a truncating fusion. (B) Distribution of top three recommended treatments among patients discussed in the MTB (n = 127) and distribution of implemented treatments across patients treated according to one of the MTB recommendations (n = 64). Detailed list of drugs assigned to each class can be found in the Data Supplement. ADC, antibody-drug conjugate; AKT, AKR mouse strain thymoma; CDK, cyclin-dependent kinase; ERBB, erythroblastic leukemia viral (v-erb-b)oncogene; FGFR, fibroblast growth factor receptor; HER2, human epidermal growth factor receptor 2; ICI, immune checkpoint inhibitor; MAPK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; PI3K, phosphatidylinositol 3-kinase; SNV, single-nucleotide variant; TKI, tyrosine kinase inhibitor.

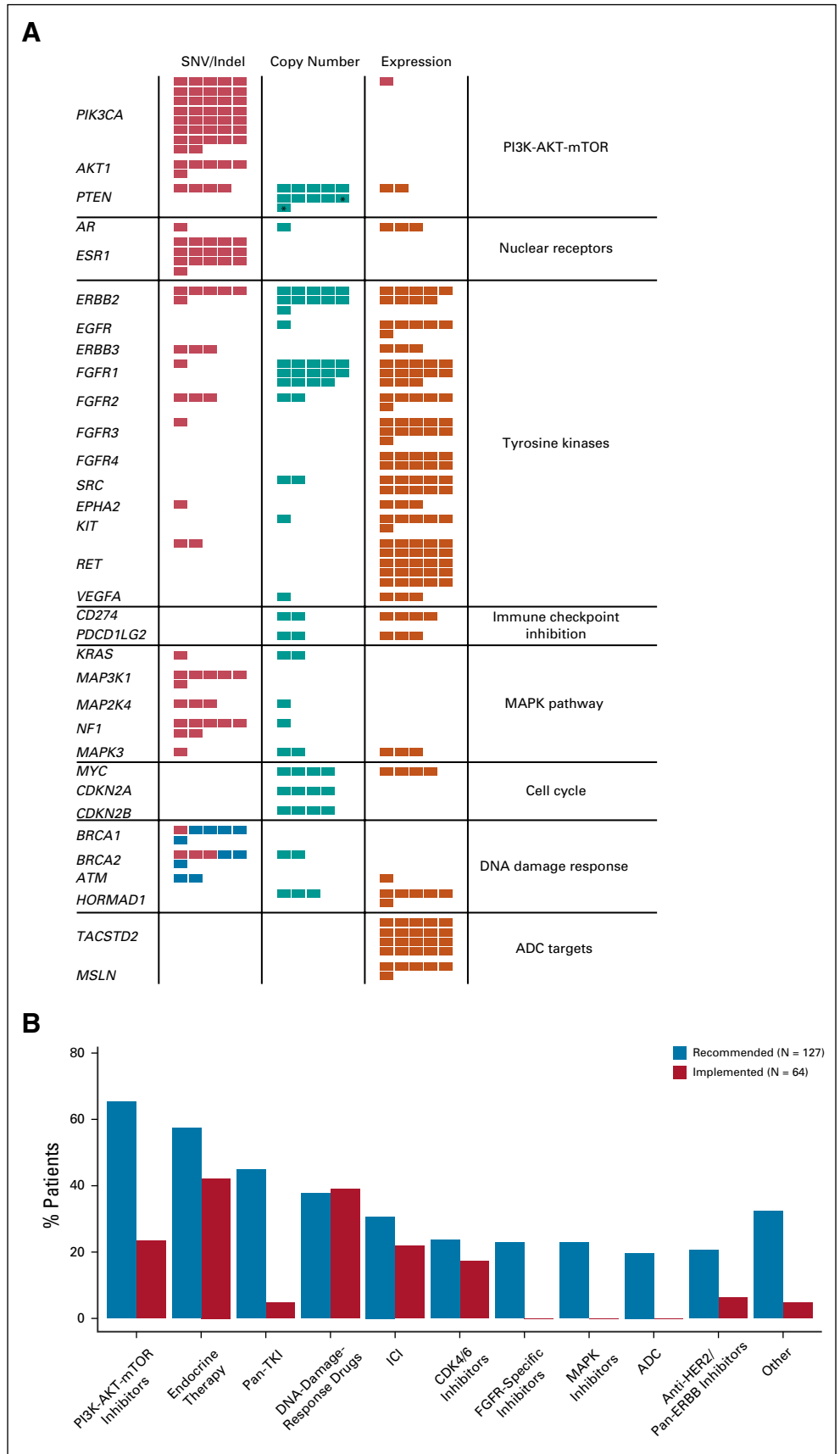
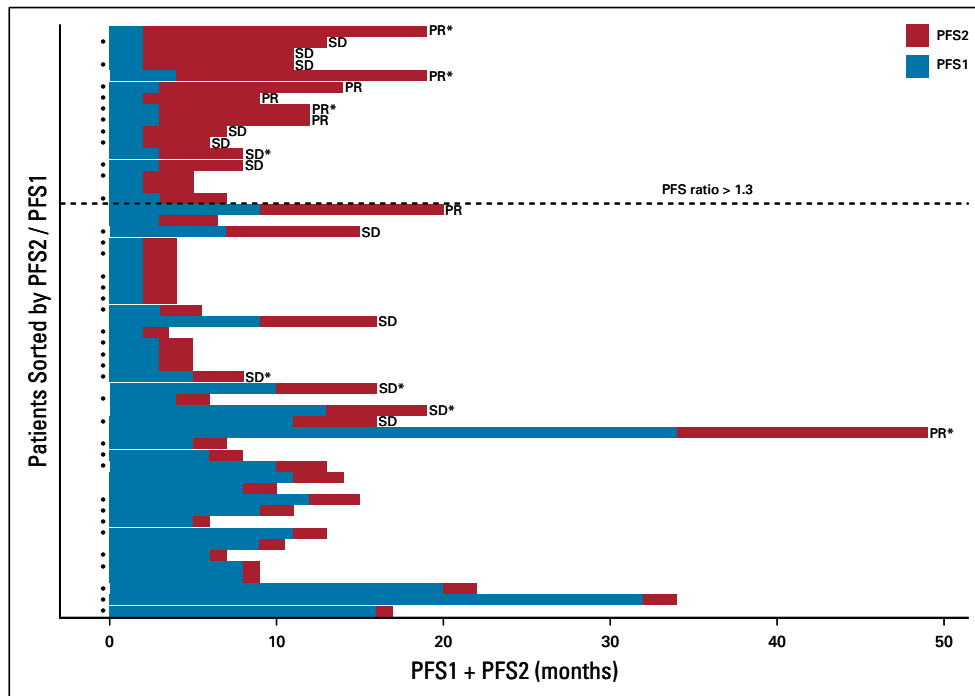


FIG 4. Clinical outcomes of evaluable patients (n = 53) treated with one of the molecular tumor board (MTB) recommendations shown as PFS and best response. Patients are sorted by the descending PFS2/PFS1 ratio, where PFS2 is PFS achieved while on MTB treatment and PFS1 is PFS achieved on treatment immediately preceding MTB treatment. * denotes ongoing treatments. • denotes off-label treatments. PFS, progression-free survival; PFS1, PFS under the immediate previous treatment line; PFS2, PFS under the MTB-recommended treatment; PR, partial response; SD, stable disease.



(Fig 4). Moreover, there are eight patients still on treatment who achieved at least an SD (Fig 4, denoted with a star), suggesting that the obtained PFS ratio may be even higher. Of note, even among patients who formally progressed when initially treated according to the MTB recommendation, there are currently two who still received clinical benefit (1 SD + 1 PR) when subsequently treated with the next available MTB-recommended therapy. Finally, we found no significant difference in overall survival between MTB-treated and non-MTB-treated patients (Data Supplement).

To illustrate the implementation of MTB decisions in the clinical setting and their impact on clinical outcome, we present two specific cases in more detail in the Data Supplement.

DISCUSSION

Continuous development of both sequencing technologies and accompanying computational algorithms has allowed us to interrogate breast tumor biology at an unprecedented and ever-increasing level of detail. We have used WGS and RNA sequencing to create a deep molecular snapshot of biopsied metastatic breast lesions to guide clinical decision making at the time of disease progression. This combined strategy enables maximal detection of genomic alterations along with concurrent analyses of both tumor and blood samples to discriminate germline from true somatic variants and to identify candidates in need of human genetic counseling. Furthermore, measuring expression levels also helps in distinguishing passengers from drivers in copy number variant analysis and provides information on

mutations being expressed or not. Taken together, the results presented by us require both techniques as such workflow removes the need for adaption and revalidation of used gene panels.

Evaluation of the first 200 patients enrolled into this program showed a promising treatment implementation rate of 50% (Fig 1), ie, every second patient discussed in the MTB had received one of the MTB-recommended treatments. Among 53 evaluable patients, 40% achieved clinical benefit (15% PR and 25% SD), with a PFS2/PFS1 ratio > 1.3 in 30% of patients (Fig 4). One of the critical prerequisites for successful implementation of treatment recommendations is drug availability. All therapies that are not in-label are available either within a clinical trial or if the drug is approved for another indication as off-label use, with the constraints to secure cost recovery from health insurance agencies. Given the relatively low trial enrollment rate post-MTB, which is a known limiting step in many precision oncology initiatives, and the high rate of off-label recommendations (70%, Fig 4 and Data Supplement), as well as favoring combination therapies, financial burden also becomes an important factor determining the success or failure of treatment implementation. This issue could be partly alleviated by enrolling more patients into clinical trials following our sequencing-based stratification. However, trials that would be ideally matched by the tumor molecular profile are not necessarily available locally, or even nationally, which may pose serious practical challenges for patients in palliative setting. Furthermore, using likely suboptimal drugs (eg, everolimus v alpelisib in *PIK3CA*-mutated HR+ mBC) and lacking toxicity data for many

rational combinations that would have been otherwise considered for implementation as off-label therapies present further obstacles to higher success rates in precision oncology. Thus, it is important to have a broad clinical trial portfolio accessible for an institution where precision oncology programs are carried out, including not only umbrella but also dedicated basket trials into which molecularly stratified patients will be fed. This has been already exemplified by the NCI-MATCH and TAPUR studies.^{12,13} Another, more fundamental reason for establishing a tighter link between precision oncology studies and clinical trials is that every treatment recommendation suggested by the MTB could be considered as a hypothesis on the treatment being able to achieve disease control. The strength or plausibility of each of these hypotheses is reflected in their ranking among all treatment suggestions, which correlates with assigned molecular evidence levels. Although the importance of biomarkers with lower evidence levels has yet to be established, this is precisely why testing these hypotheses should be ideally carried out in an independent clinical trial.

Apart from the ability to implement treatments suggested by the MTB in the clinic, the success of a precision oncology trial is also largely affected by the underlying features of the population at hand (Table 1). Established risk factors in mBC such as lines of pretreatment and the site and number of metastatic lesions present at the time of tumor sampling heavily affect the overall efficacy and outcomes following the administration of MTB-recommended treatments. Given that our patients were on average both heavily pretreated and with multiple metastatic lesions (Table 1), this should be also appropriately considered when interpreting response data (Figs 1 and 4). For example, it is known that the objective response rates (ORRs) to conventional chemotherapies in patients with mBC decrease substantially if administered beyond the first line.^{40,41} Similarly, tumor heterogeneity has been well-described in the context of evolving breast cancer metastases,^{42,43} which is also exemplified in the presented case 1 with discordant

response of different lesions to the same treatment (Data Supplement). Since all our patients had only a single lesion profiled, which, because of biopsy constraints and availability, may have not been the most recent one, this may have further affected response to chosen treatments.

With 15% (8/53) of evaluable patients achieving PR as the best response while on MTB-recommended treatment (Figs 1 and 4), ORR achieved so far in this heterogeneous and small patient population is comparable with the one achieved by conventional chemotherapies.^{40,44} Of note, this ORR achieved in our cohort with MTB-guided therapies as the median third-line treatment (range, 2-10) compares favorably with response rates achieved with capecitabine given as first- to third-line therapy of around 11% and eribulin of around 12% in patients who previously received two to five lines of chemotherapy.^{40,44} Another 25% (13/53) of evaluable CATCH patients achieved SD (Figs 1 and 4), translating into a 40% disease control rate in this heavily pretreated patient population. Moreover, the improvement in PFS of at least 30% while on personalized treatment as compared with the PFS achieved with the previous treatment line (PFS ratio > 1.3; Fig 4) could be observed in 30% (16/53) of evaluable patients, notably with some responders still appearing below this prespecified cutoff because of immature follow-up (Fig 4, below the dashed line). Importantly, the observed clinical outcomes in terms of both best response and PFS ratios also compare favorably with those in the cross-entropy high-throughput genomics MOSCATO 01 trial¹⁴ and the randomized phase II SHIVA trial,⁴⁵ as detailed further in the Data Supplement.

In conclusion, encouraging outcomes observed within CATCH have demonstrated that precision oncology on the basis of WGS and transcriptome sequencing is feasible when applied in the clinical management of mBC and suggest that its broader clinical implementation may be further justified as it has the potential to provide benefit to a substantial proportion of hard-to-treat patients with mBC.

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M.H., M.S., and S.E. shared first authors. P.L. and A.S. shared last authors.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Honoraria: Roche, Pfizer, Celgene, AstraZeneca, Amgen

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