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Reimbursement in the Context of Precision Oncology Approaches in Metastatic Breast Cancer: Challenges and Experiences

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Keywords
Metastatic breast cancer · Genomics-guided therapies · Reimbursement · Precision oncology · Translational oncology

Abstract
Background: Precision oncology programs using next-generation sequencing to detect predictive biomarkers are extending therapeutic options for patients with metastatic breast cancer (mBC). Regularly, based on the recommendations of the interdisciplinary molecular tumor board (iMTB), an inclusion in a clinical trial is not possible. In this case, the German health insurance system allows for the application of reimbursement for an off-label drug use. Here, we describe the current challenges and our experience with reimbursement of molecular therapies in mBC. ***Methods:*** A total of 100 applications for reimbursement of off-label therapies recommended by an iMTB were filed for patients with mBC, of which 89 were evaluable for this analysis. The approval rate was correlated with the molecular level of evidence of the respective therapy according to the National Center for Tumor Diseases (NCT) and European Society for Medical Oncology Scale for Clinical Actionability of molecular Targets (ESCAT) classification as well as with pretreatment therapy lines. ***Findings:*** Overall, 53.9% (48/89) of reimbursement applications were approved. Applications for therapies based on level of evidence m1 (NCT classification), tier I and II (ESCAT classification) had a significantly and clinically relevant increased chance of reimbursement, while a greater number of previous treatment lines had no significantly increased chance of approval, though a trend of approval toward higher treatment lines was detectable. ***Interpretation:*** Currently, the German jurisdiction seems to aggravate the clinical implementation of clinically urgently needed molecular therapies.

Introduction

In Germany, an increasing number of precision oncology programs are arising such as the MASTER [1] and CATCH programs [2] or the initiative of Centers for Personalized Medicine (ZPM) [3] which offer detailed genomic and transcriptomic analysis based on next-generation sequencing (NGS). The predictive value of

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molecular alterations identified in those programs are discussed in an interdisciplinary molecular tumor board considering the molecular level of evidence and the clinical background leading to individual therapy recommendations. The molecular level of evidence for respective therapies is assessed according to the National Center for Tumor Diseases (NCT) classification [4] or the European Society for Medical Oncology (ESMO) Scale for Clinical Actionability of molecular Targets (ESCAT) classification [5]. Recommendations can comprise therapies approved by the European Medicines Agency (EMA), therapies within clinical trials, or off-label treatments. Based on the report of the molecular tumor board, off-label therapies can be applied for cost reimbursement by health insurance companies. In Germany, applications for reimbursement are usually reviewed by the medical service of the health insurance companies (Medizinischer Dienst der Krankenkassen, MDK) relying on criteria specified in accordance with §2 paragraph 1a Sozialgesetzbuch V of the German jurisdiction. In this analysis, we evaluated the clinical implementation rate of genomics-guided recommended therapies based on reimbursement applications for patients with metastatic breast cancer (mBC) and correlated the approval rate with the molecular level of evidence and clinical parameters.

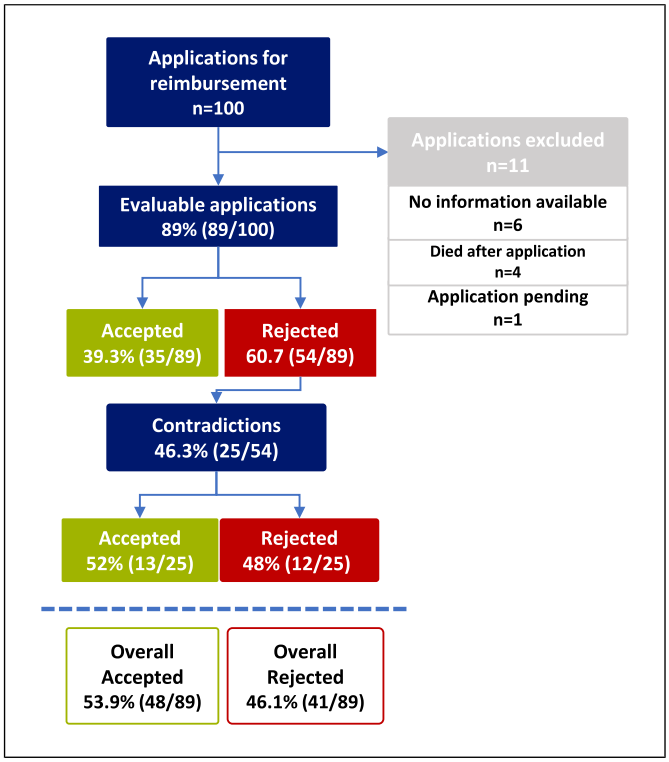

Fig. 1. Consort diagram displaying the number of initial, evaluable, and excluded applications as well as initial acceptances/rejections, acceptances/rejections after contradiction, and overall acceptances/rejections. The applications were prepared by the physicians in our outpatient service and sent to the respective health insurance company by the respective patient.

Materials and Methods

Within this study, the clinical implementation rate of off-label therapies for patients with mBC recommended within molecular precision oncology programs was evaluated. The report of the interdisciplinary molecular tumor board was discussed with the respective patient in the gynecological outpatient clinic of the NCT in Heidelberg. In case where molecular therapy was clinically indicated an application was prepared by our physicians and submitted by the patient to the health insurance company, which initiated an assessment of the application via MDK. If the application was rejected, a contradiction was written and submitted in certain cases.

The level of evidence for the recommended therapy was assessed during this study as described by the NCT [4] and ESCAT classification [5]. All different subtypes of mBC have been regarded as different entities. In cases where treatment combinations were applied for, the level of evidence from both drugs was determined separately, and the weaker level of evidence was ultimately assigned. Since not all levels of evidence were stated in all applications, a retrospective evidence level classification was carried out for all cases considering only data available at the time the application was written.

The levels of evidence were compared by calculating the rate difference of the acceptance of two levels of evidence as a point estimate and their Wilson confidence interval (95%) using the DescTools package in R (version 4.2.1). A clinically relevant result was regarded as rate difference of 40%. The two-tailed Mann-Whitney U test was used for the statistical comparison of the number of palliative lines of therapy for acceptances and rejections. *p* values were calculated using GraphPad Prism v8.4.2 for Windows 10 (GraphPad Software LLC).

Results

A total of 100 applications were submitted from January 2018 to September 2021. Four patients died shortly after the application. For 6 patients, no information about the application procedure was reported from the patient and one application was still pending. Altogether, applications from 89 patients were evaluable for analysis (shown in Fig. 1). The median age at the time of application was 52 years and the median Eastern Cooperative Oncology Group (ECOG) performance score was 1. The subtypes of BC were distributed as follows: triple-negative BC (TNBC) 46/89 (51.7%), hormone receptor (HR) positive/human epidermal growth factor receptor (HER2) negative (HR+ HER2−) 34/89 (38.2%), HR+ HER2+ 7/89 (7.9%), HR− HER2+ 2/89 (2.2%).

Acceptances and Rejections

A total of 35/89 (39.3%) applications were initially approved and 54/89 (60.7%) rejected. A total of 25/35 (71.4%) of the rejected patients filed an appeal against the decision. In 13/25 (52%) of the cases, the appeal was successful. In total, 48/89 (53.9%) of the applications were finally accepted by the health insurance companies, and 41/89 (46.1%) were rejected (shown in Fig. 1). A total of

25/89 (28.1%) of the patients took the risk of starting therapy despite rejection of reimbursement. An attempt was made to investigate the reasons for initial rejections considering the three assessment criteria specified in accordance with §2 paragraph 1a Sozialgesetzbuch V of the German jurisdiction, i.e., (i) an incurable disease must be present, (ii) a not entirely improbable chance of a noticeable positive effect on the course of the disease (medical evidence) must be expected, and (iii) no approved standard therapies must be available.

In total, 38 reviews by the surveyors of the MDK were available. In 29/38 (76.3%) cases, the evidence for benefit from the molecular-guided therapy was considered insufficient by the reviewer. In all 38 reviews, it was acknowledged that mBC is incurable and that alternative approved therapies are still available. We examined next the two arguments of lacking evidence and remaining therapies to better understand which applications had a higher chance of acceptance.

Distribution of Molecular Level of Evidence according to NCT Classification

Figure 2a–e shows the distribution of levels of evidence according to the NCT classification across initial approvals and rejections (shown in Fig. 2a, b), across final approvals and rejections after the contradiction process (shown in Fig. 2c) as well as the distribution across all applications delivered (shown in Fig. 2d) and across the reviews stating evidence as not sufficient after first review (shown in Fig. 2e). Due to the small number of cases, evidence m1A, m1B, m1C and m2A, m2B, m2C were combined into the categories m1 and m2 (shown in Fig. 2b–e). Patients with a treatment option with m1 evidence compared to patients with a treatment option with m2 (rate difference 27.9%, CI 95% 3.3–49.3%) had a statistically significant but not clinically relevant chance of approval, while m1 evidence compared to m3 (rate difference 44.8%, CI 95% 6.4–67.8%) and m4 (rate difference 53.3%, CI 95% 24.3–70.1%) had a significantly and clinically relevant increased chance of approval. Treatment options of m2, m3, or m4 evidence did not show an increased chance of approval compared to each other (shown in Fig. 3a).

Distribution of Molecular Level of Evidence according to ESCAT Classification

Figure 2f–j show the distribution of evidence according to ESCAT criteria across initial approvals and rejections (shown in Fig. 2f, g), across final approvals and rejections after the contradiction process (shown in Fig. 2h), as well as the distribution across all written applications (shown in Fig. 2i) and across the reviews stating evidence as not sufficient after first review (shown in Fig. 2j). Due to the small number of cases, evidence tiers IA, IB, IC, IIA, IIB, IIIA, IIIB, IVA, IVB were combined into the categories tiers I, II, III, and IV (shown in Fig. 2g–j). Patients with a treatment option of tier I evidence had a significantly and clinically relevant increased chance of approval compared to patients with a treatment option of tier IV evidence (rate difference 57.8%, CI 95% 21.7–76.2%) and tier X evidence (rate difference 54.3%, CI 95% 24.1–72.4%) as well as patients with tier II evidence compared to patients with tier IV (rate difference 42.5%, CI 95% 3.4–66.3%). Evidence levels at tier II compared to tier X, tier III compared to tier IV, and tier II to tier X were significantly but not clinically relevantly increased (shown in Fig. 3b).

Distribution of the Number of Lines of Therapy

On median and average, patients received 4 lines (range, 0–13) of palliative therapy lines before application. Patients with HR+ and/or HER2+ tumor, for whom more therapies are available due to targeted treatment options, had significantly more palliative therapy lines at application compared to patients with TNBC (Mann-Whitney U test, p value 0.01029, CI 95%) (shown in Fig. 4a). However, neither in the overall population (Mann-Whitney U test, p value 0.07384, CI 95%) (shown in Fig. 4b) nor in the subgroup of patients with an HR+ and/or HER2+ tumor (Mann-Whitney-U, p value 0.1685, CI 95%) (shown in Fig. 4c) or TNBC (Mann-Whitney U test, p value 0.07045, CI 95%) (shown in Fig. 4d), a greater number of previous treatment lines had a significantly increased chance of approval, though a trend of approval toward higher treatment lines was detectable.

Implementation of Molecular Therapy

Molecular therapies were implemented in 60/89 (67.4%) patients. The objective response rate (ORR) 1–3 months after start of the molecular-guided therapy was 16.7% and the clinical benefit rate (complete or partial response, or stable disease) was 45%. In 5% (3/60) of patients, therapy was discontinued due to adverse events before the first staging. 6.7% (4/60) of the patients had not yet started their therapy, and 11.7% (7/60) were still under therapy in November 2021, the cut-off used for this analysis. The median duration of therapy was 3 months (shown in online suppl. Table 1; for all online suppl. material, see https://doi.org/10.1159/000533902).

The average time between the molecular tumor board and the start of molecular-guided therapy was 134 days, with a median of 103 days (range, 14–503 days). Between the molecular tumor board and the start of therapy, patients received an average of 1.7 lines (range, 0–4 lines) of therapy.

Discussion

The challenges in NGS-based analysis were summarized in the 2013 report of the National Human Genome Research Institute (NHGRI), focusing on the limited evidence, the limited consensus on which genomic

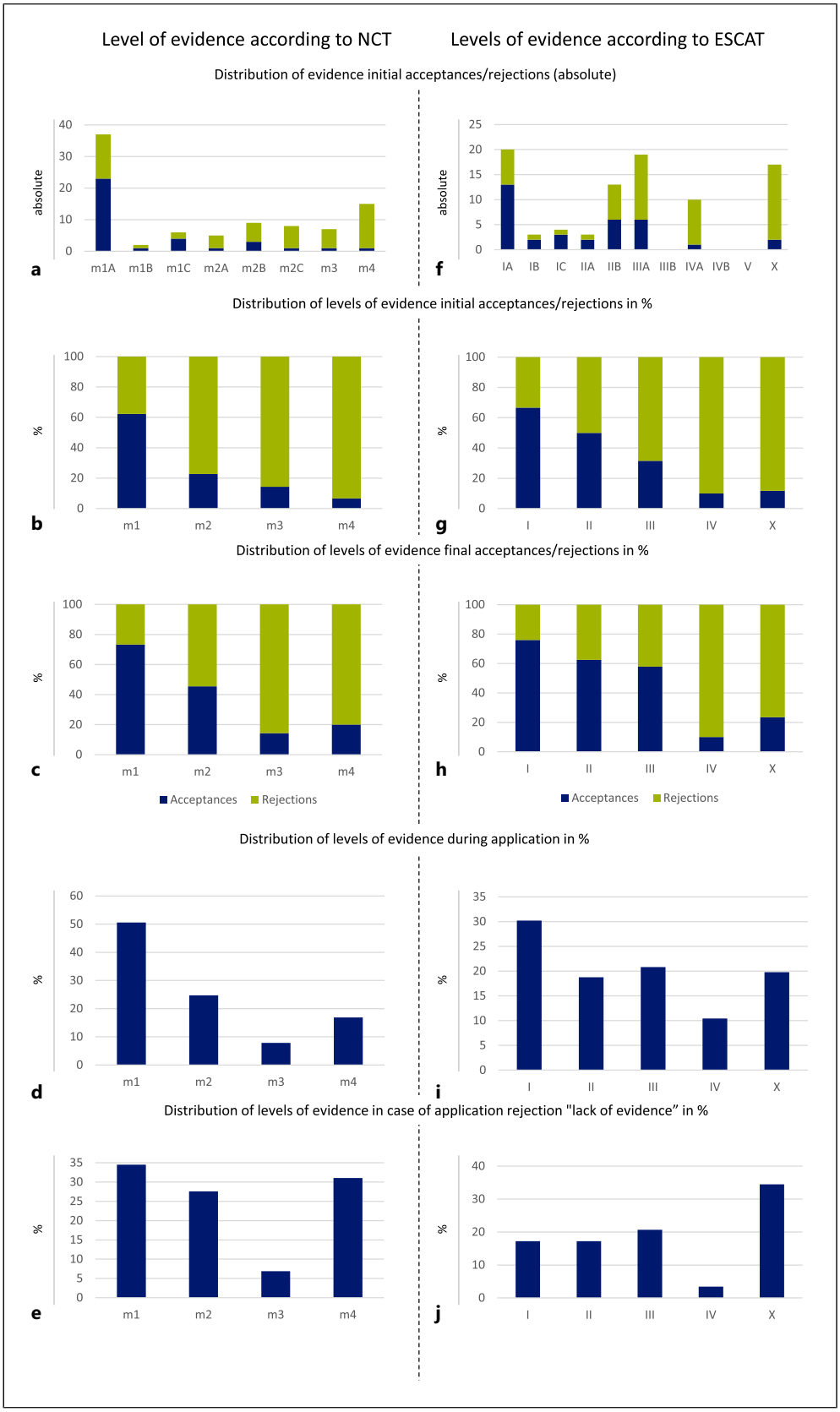

Fig. 2. Distribution of levels of evidence according to NCT (**a–e**) and ESCAT criteria (**f–i**). **a**, **f** Absolute distribution of evidence over initial acceptances and rejections. **b**, **c**, **g**, **h** Distribution of evidence in % within initial and final acceptances and rejections. **d**, **i** Distribution of evidence at application in %. **e**, **j** Distribution of evidence in expert opinions stating evidence as not sufficient.

variants are clinically relevant, and the lack of reimbursement at the diagnostic and therapeutic level [6]. While diagnostics can more and more be covered in registry studies [7–14], there are still various burdens in clinical implementation of genomics-guided treatments outside clinical trials.

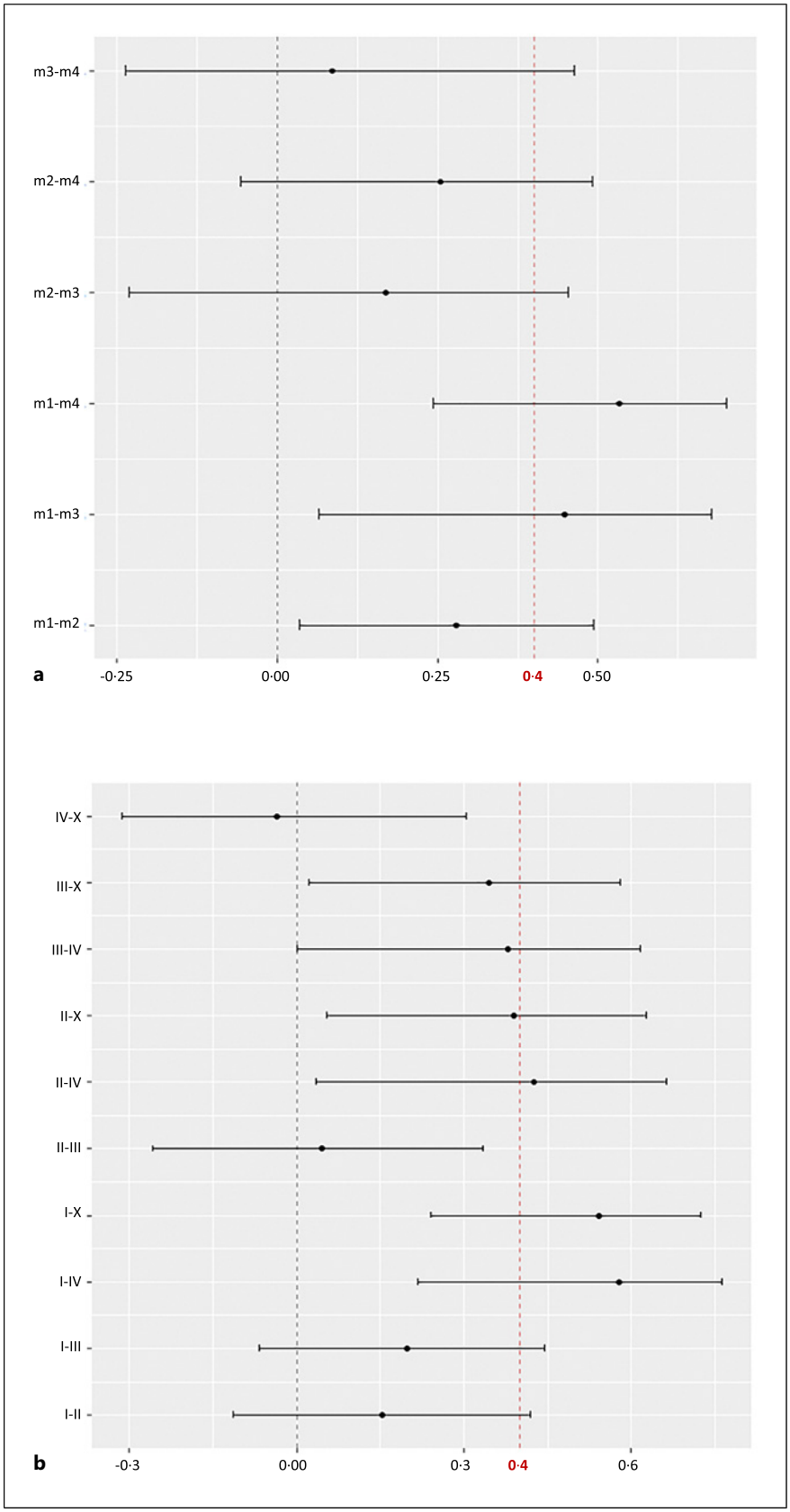

Fig. 3. Rate difference of acceptance as point estimate between two evidence levels and the corresponding 95% confidence interval for levels of evidence of the NCT classification (**a**) and ESCAT classification (**b**). A clinically relevant result was regarded as rate difference of 40%.

Herein, we sought to understand which applications have a significantly and clinically relevant increased chance of reimbursement. Treatment options with NCT m1 evidence (i.e., predictive markers within the same entity) had a significantly increased and clinically relevant chance of acceptance. In contrast, no significant and

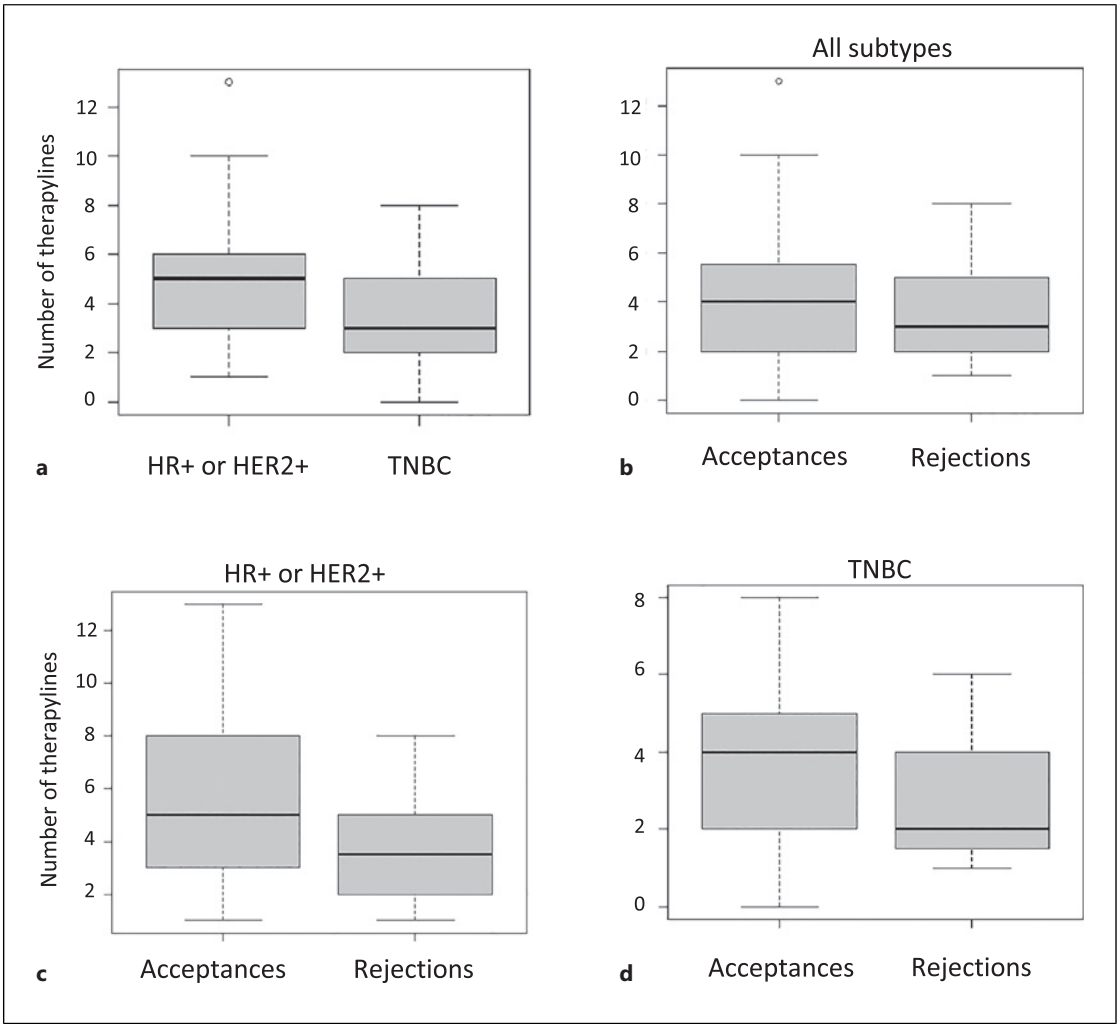

Fig. 4. a Boxplot of number of palliative lines of systemic therapies in TNBC and HR+ and/or HER2+ patients. Boxplots of palliative lines of therapy across acceptances and rejections overall (**b**), in HR+ or HER2+ BC (**c**), and TNBC (**d**).

clinically relevant differences existed in the approval of treatments with levels m2, m3, or m4, respectively. Considering the ESCAT classification system, therapy recommendations assessed as tier I (i.e., substance ready for routine use) and tier II (investigational targets are likely to define patients who benefit), had a significantly clinically relevant increased chance of reimbursement. That therapies for which sufficient data are available are preferentially accepted is reasonable. Still, we expected that recommendations with NCT m2 evidence (biomarkers transferred from different entities) or ESCAT tier III (clinical benefit previously demonstrated in other tumor type or for similar molecular targets) were more clinically relevant and accepted over lower levels of evidence. Still, we see that the transferability of biomarkers to another entity has always had to be assessed in the overall individual context and the final decision is challenging for the respective reviewer.

Considering the number of approved lines of systemic treatments for mBC (at least >7 in-label therapies are currently approved in Germany), the argument of still existing in-label therapies plays an important role for rejection. However, we found a trend of therapy approval toward higher therapy lines but no statistical significance. While most trials in mBC are conducted within first and second lines, data for chemotherapeutics in later lines are scarce. Nevertheless, ORR in later lines decreases dramatically. For example, capecitabine achieved an ORR of 24% in first-line HER2-negative BC within the RIBBON-1 trial [15], while capecitabine had an ORR of only 11.5% versus eribulin 11% [16] as first-third-line therapy. The cohort analyzed herein received the genomics-guided therapy on average as forth-line therapy and achieved an ORR of 16.7%. This highlights the efficacy of molecular therapies, which might even be higher if

administered earlier in the course of disease. However, since approved lines of therapy are one of the dominant reasons for refusal according to German jurisdiction, it is indeed difficult for the individual reviewer to grant genomics-guided therapies in early lines based on the German jurisdiction. Nevertheless, it is possible in special cases, mostly due to intolerabilities or pronounced chemorefractoriness.

An average of 1.7 lines of therapies had to be applied between tissue collection for NGS and start of the molecular therapy. It is known that intermediate systemic treatments can alter the genetic landscape and expression of cancer cells [17–19]. It is currently unclear which impact systemic treatments given between tissue collection for NGS and start of the genomics-guided therapy might have on efficacy and outcome.

Considering the steadily growing datasets regarding the success of precision oncology, a substantial number of patients are tempted to pay for their genomics-guided off-label therapies themselves, driven by the desperation of the incurable disease and the resulting poor prognosis with approved therapies. This aspect is reflected in the high number of patients (28.1%) who started the therapy without reimbursement. Less privileged patients and their families could experience severe disadvantages compared to richer patients, as they either cannot pay for the treatment in the first place or are driven to the brink of financial ruin by costs of therapy. Still, there is an obligation to provide information about the genomics-guided off-label treatment options within the framework of translational programs. The access to off-label therapies deemed effective based on validated levels of evidence like the NCT/ESCAT system must be facilitated.

Conclusion

Importantly, this study is not intended to diminish the work of the reviewers of the applications who have to take difficult decisions and are hereby bound to the German jurisdiction. It is more about to show the challenges of dealing with the complexity of reimbursement in the context of biomarker-driven therapy recommendations considering the molecular evidence and clinical parameters within the given framework of the German jurisdiction, which in our view is currently not fully meeting the demands of translational oncology approaches and thereby causing the high rejection rate. Entities with a high number of approved therapies are even more disadvantaged. Together, new avenues need to be established to make molecular therapies more accessible to all patients with cancer.

Statement of Ethics

This research study was conducted retrospectively from data obtained from the clinical translational register program (ethic number S-164/2017; approved by the Ethics Committee of the Medical Faculty Heidelberg) of the gynecological departure of the University Hospital Heidelberg and the German Cancer Research Center. Informed consent was obtained from all individual participants included in the study within the clinical translational register program of the gynecological departure of the University Hospital Heidelberg and the German Cancer Research Center. Patients signed informed consent regarding publishing their data.

Conflict of Interest Statement

Constantin Pixberg has received speaker's fee from Merck Sharp and Dohme (MSD). Mario Hlevnjak has received speaker's fee from Merck Sharp and Dohme (MSD) and holds stocks from Aadi Biosciences, Astellas Pharma, BioInvent International, BioNTech, Deciphera Pharmaceuticals, Exelixis, GSK, Guardant Health, Illumina, Immatics, ImmunoGen, Jazz Pharmaceuticals, Mersana Therapeutics, Merus, Mirati Therapeutics, OSE Immunotherapeutics, PharmaMar, Replimune, Rigel Pharmaceuticals, and Veru. Sabine Heublein has received research funding from Novartis; speaker's fee from Clovis, Astra Zeneca, and Pfizer; travel grants from MSD; and participates on a data safety monitoring board or advisory board from MSD and Novartis.

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Author Contributions

Constantin Pixberg: conceptualization, data curation, formal analysis, methodology, project administration, supervision, validation, data interpretation, visualization, writing – original draft, and writing – review and editing. Markus Schulze: formal analysis, methodology, validation, data curation, data interpretation, visualization, and writing – review and editing. Lars Buschhorn, Jan Philipp Suppelna, Andreas Mock, and Sabine Heublein: data curation, formal analysis, methodology, data interpretation, and writing – review and editing. Mario Hlevnjak: formal analysis, methodology, and writing – review and editing. Eva Schumacher-Wulf and Andreas Schneeweiss: conceptualization, data interpretation, and writing – review and editing.

Data Availability Statement

The published data have been obtained from the clinical translational register program of the gynecological departure of the University Hospital Heidelberg and the German Cancer Research Center. The authors reserve the right to release the raw data upon request.

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