Asian Journal of Current Research in Clinical Cancer
ISSN: 3062-4444
2022, Volume 2, Issue 1, Page No: 60-73

Available online at: www.galaxypub.co/page/journals

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Implementing a Molecular Tumor Board in Routine Clinical Practice: Four-Year Experience from a German Single Center

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Received: 19 November 2021; **Revised:** 18 February 2022; **Accepted:** 21 February 2022

ABSTRACT

Precision oncology faces two major hurdles: rapidly pinpointing actionable molecular alterations and making such targeted interventions accessible to a wide patient population. We report a four-year experience of the Molecular Tumor Board (MTB) at the Comprehensive Cancer Center Freiburg, Germany, highlighting workflow refinements and practical implementation strategies. This retrospective study includes 488 patients evaluated from February 2015 to December 2018. The MTB provided personalized molecular diagnostics, therapy recommendations based on molecular profiles, monitored adherence to these recommendations, and tracked clinical outcomes, including overall survival. Most patients (90.6%) had advanced (stage IV) cancers and had received an average of 2.1 prior treatment lines. Nearly all patients (99.8%) received diagnostic guidance, and treatment suggestions were made for 264 cases (54.1%), with 212 cases (43.4%) involving therapies tailored to molecular findings. Recommendations were implemented in 76 patients (28.8%), resulting in stable disease in 19 patients (25.0%), partial response in 17 (22.4%), and complete remission in five (6.6%). Among those receiving MTB-guided therapy, 28.9% achieved an objective response, representing 4.5% of the total cohort. Optimization of MTB operations increased the number of cases reviewed per session without compromising adherence or outcomes. Our experience demonstrates that molecular-guided cancer therapy can be effectively integrated into routine clinical practice, yielding a modest but meaningful and durable disease control rate.

Keywords: Personalized oncology, Molecular tumor board, Precision medicine, Molecular profiling, Targeted therapy, Cancer management

How to Cite This Article: Kim JH, Park SW, Lee MY. Implementing a Molecular Tumor Board in Routine Clinical Practice: Four-Year Experience from a German Single Center. Asian J Curr Res Clin Cancer. 2022;2(1):60-73. https://doi.org/10.51847/BbqgoHWY2t

Introduction

Oncology continues to be one of the most rapidly advancing fields in medicine, exemplified by 28 FDA drug approvals between 2018 and 2019, including numerous targeted therapies and immunotherapies [1, 2]. Notably, for the first time, tumor-agnostic drugs such as pembrolizumab for MSI-H, MMRd, or TMB-H metastatic tumors [3–5], and larotrectinib for tumors with NTRK gene fusions [6] have received approval, underscoring the growing role of molecular and genetic testing in clinical decision-making. Early trials failed to demonstrate clear benefits [7–10], yet subsequent studies increasingly support the feasibility and efficacy of precision oncology [11–17]. Despite these advances, cancer remains the second leading cause of death worldwide, with over 9 million fatalities in 2018 [18].

The expanding number of therapies and clinical trials, coupled with more accessible and affordable molecular profiling, provides new treatment avenues, especially for patients who have exhausted standard-of-care options. Additionally, growing knowledge of predictive biomarkers and mechanisms of therapy resistance is rapidly reshaping treatment strategies. To keep pace with these developments and provide patients with state-of-the-art molecular diagnostics and therapy recommendations, the University Medical Center Freiburg established a Molecular Tumor Board (MTB) in March 2015. Here, we present a comprehensive four-year analysis detailing patient characteristics, molecular diagnostics, treatment recommendations, adherence, and clinical outcomes.

Building upon our 2018 proof-of-concept study [19], we focus on structural and organizational improvements that enabled a threefold increase in annual cases while maintaining the clinical utility of molecularly guided therapies.

Materials and Methods

MTB organization and patients

Founded in March 2015, the MTB at Freiburg comprises a multidisciplinary team of physicians, molecular pathologists, biologists, and bioinformaticians from over 16 departments. The MTB is open to all cancer patients, with a focus on individuals lacking standard treatment options or those with rare tumors. This retrospective, single-center study includes 488 patients discussed at the MTB from March 2015 to December 2018. Patient registration occurs via an online platform, with the treating physician providing the initial case presentation. Molecular diagnostic recommendations are made according to entity-specific and general standard operating procedures (SOPs), which are regularly updated. Treatment recommendations are issued following interdisciplinary discussion and presentation of molecular results by pathology and bioinformatics teams, with levels of molecular evidence documented. The study was approved by the local institutional review board (protocol 369/19), and all patients provided written informed consent.

Molecular diagnostics

The MTB guides tissue sampling for molecular analyses and may recommend re-biopsies when necessary. Routine molecular analyses (RMA) are conducted in accredited laboratories, including immunohistochemistry (IHC) with an immuno-oncology (IO) panel, MMRd testing, NTRK testing, in situ hybridization, MSI testing, and targeted next-generation sequencing (tNGS; Supplementary Procedures). The IO panel assesses CD3, CD4, CD8, PD1, and PD-L1 using combined positivity score (CPS), tumor proportion score (TPS), and immune cell (IC) scoring [20]. MSI testing is performed using either standard mononucleotide and dinucleotide panels [21, 22] or a commercial five-marker panel (Promega, Walldorf, Germany) with additional pentanucleotide controls [23]. NTRK testing uses IHC and/or RNA-fusion NGS analysis.

Extended genetic analyses (EGA), including whole-exome sequencing (WES) and RNA sequencing (RNA-Seq), are performed primarily on FFPE tissue (86.5%) or fresh-frozen samples (13.5%). WES is conducted on microdissected tumor DNA and matched germline DNA to distinguish somatic from germline variants. Variants with ≥10% allele frequency and <0.1% population frequency in gnomAD are reported, and classified using ClinVar, InterVar, COSMIC, dbSNP, cancer hotspot databases, and drug-gene interactions (DGIdb). Mutation signatures are analyzed with YAPSA and COSMIC signatures, copy number alterations with Control-FREEC, and tumor mutational burden (TMB) is calculated for WES samples, with >10 mutations/Mb classified as TMB-H. BRCAness is assessed via the AC3 mutational signature. RNA fusions are identified with FusionCatcher, and gene expression is quantified using STAR.

tNGS panels include hotspot panels (8-, 15-, 48-gene), BRCA1/2 panels, and myeloid panels, analyzed on tumor tissue and processed through Illumina pipelines. Variants are annotated based on population frequency, cancer hotspots, COSMIC, dbSNP, and Condel, and variants not included in existing databases are assessed for clinical relevance using literature and expert review.

Results and Discussion

From March 2015 through December 2018, the MTB evaluated 488 patients, resulting in 1,072 total case discussions—averaging slightly over two sessions per patient. Across 95 board meetings, sessions typically included 16 specialists from multiple departments, along with experts in molecular pathology, molecular biology, and bioinformatics. Following the adoption of entity-specific diagnostic SOPs in 2017, the number of cases reviewed per 90-minute session rose dramatically, from an average of 5.8 cases in 2015 to nearly 20 cases in 2018, effectively tripling throughput. The median interval from initial case submission to the first treatment recommendation was 42 days.

Patient profile

Patients were a median age of 54 years at their first MTB discussion (range 1–88), with a balanced gender distribution (52.9% male, 47.1% female). Most patients (96.5%, n = 470) presented with solid tumors, and the majority (78.5%, n = 383) had metastatic disease. Tumor types most frequently represented included lower

gastrointestinal tract cancers (13.9%, n = 68), pancreatic cancers (10.2%, n = 50), and central nervous system tumors (9.2%, n = 45). Patients had undergone a median of 2.1 prior therapies, with 16.2% (n = 79) having received more than three lines of treatment. Referrals to the MTB were largely driven by progression after standard-of-care therapy (78.1%, n = 381) or by the need for guidance in managing rare tumor types (10.5%, n = 51).

Table 1. Patient characteristics.

Characteristic	No.	(%)
Total	488	
Sex		
Female	230	(47.1)
Male	258	(52.9)
Median Age	54	range (1–88)
Patients with Solid Tumors: Stage at Presentation	470	(96.5)
Metastatic Disease	383	(81.5)
Localized Disease	86	(18.3)
Complete Remission	1	(0.2)
Tumor type		
Lower GI tract	68	(13.9)
Pancreas	50	(10.2)
Upper GI tract	42	(8.6)
Central nervous system	45	(9.2)
Unknown Primary Site	37	(7.6)
Hepatobiliary	30	(6.1)
Thyroid	30	(6.1)
Soft tissue and bone	37	(7.6)
Gyn (others)	18	(3.7)
Head and neck	19	(3.9)
Breast	21	(4.3)
Urogenital	12	(2.5)
Ovary	12	(2.5)
Dermatologic	18	(3.7)
Hematologic	17	(3.5)
Lung	16	(3.3)
Neuroendocrine	10	(2.0)
Other	6	(1.2)
Previous Lines of Therapy	2.05	(0–12)
0	66	(13.6)
1	152	(31.2)
2 to 3	192	(39.2)
>3	79	(16.2)
Unknown	1	(0.2)
Reason for Referral		
Progression to standard of care treatment	381	(78.1)

Rare Tumor	51	(10.5)
Young Age	29	(5.9)
Unknown Primary Site	20	(4.1)
Other	7	(1.4)

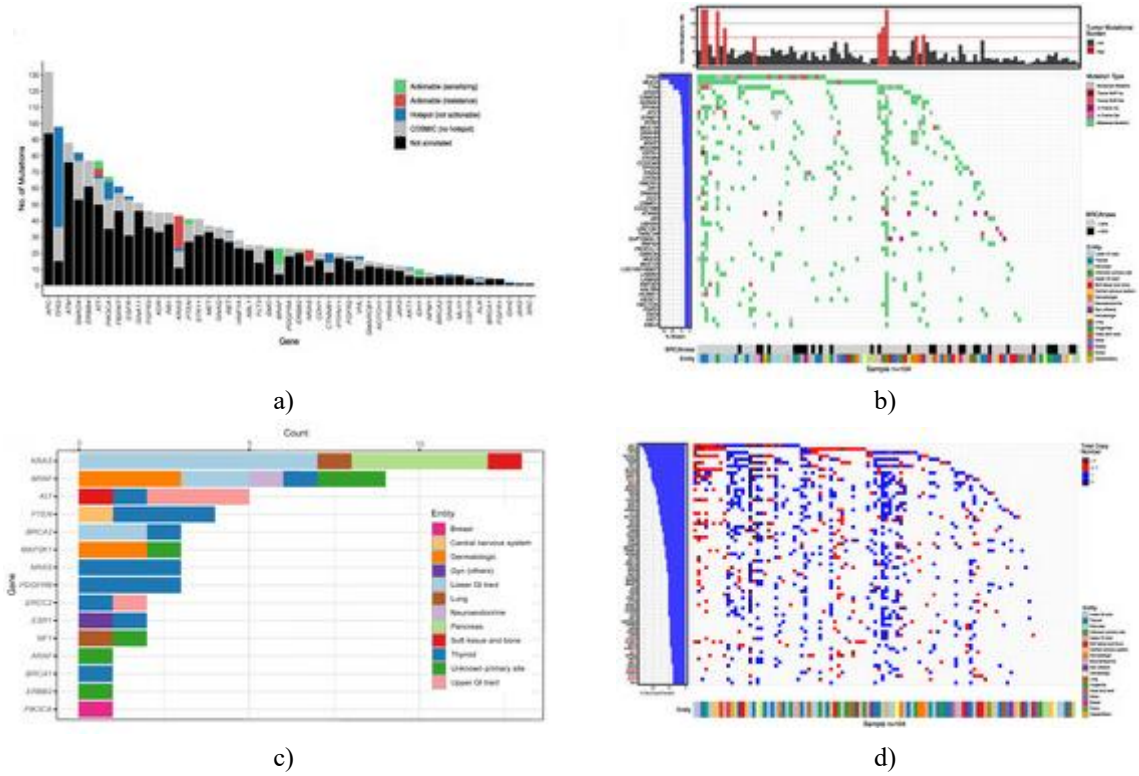
Molecular diagnostic testing

Diagnostic guidance was provided for nearly all patients (487 of 488, 99.8%), with the sole exception being a patient with Burkitt lymphoma who was instead referred to the specialized lymphoma board. Following regularly updated SOPs, the MTB recommended both tumor-specific and broader molecular tests. The broader tests included MSI, MMR, IO-panel, and NTRK assessments. Nearly all patients (485, 99.4%) received at least one routine molecular analysis (RMA) recommendation, while over one-third (183, 37.5%) were advised to undergo extended genetic analyses (EGA; **(Table 2)**). Overall, 615 of the 762 proposed diagnostic procedures (80.7%) were actually completed. Reasons for non-implementation included technical limitations such as insufficient tumor tissue for RMA or inadequate tumor DNA for EGA (44.9%), medical considerations (17.7%), and patient death (18.4%).

Table 2. Results.

Recommendations	**No.**	**(%)**
Meetings	95	
Case Discussions (per patient average)	499	(2.5)
Recommendations	1411	
Diagnostic	762	(54.0)
Treatment	367	(26.0)
No treatment recommendation	224	(15.9)
Conditional treatment recommendation	58	(4.1)
Patients with diagnostic recommendations	487	(99.8)
Routine molecular analysis	485	(99.4)
Extended genetic analysis	183	(37.5)
Rebiopsy	40	(5.2)
Other	14	(1.8)
Patients with Treatment recommendations	264	
Not implemented	188	(71.2)
Implemented	76	(28.8)
Stable disease (off-label)	19 (13)	(25.0)
Partial response (off-label)	17 (12)	(22.4)
Complete remission (off-label)	5 (5)	(6.6)
Disease control rate (off-label)	41 (30)	(8.4)

Among the implemented routine molecular analyses (RMA, n = 3,550), the majority consisted of immunohistochemistry (IHC, n = 2,599), targeted NGS panels (tNGS, n = 412), and in situ hybridizations (n = 227). The 48-gene tNGS panel was the most commonly applied assay (n = 221), identifying a total of 502 COSMIC-annotated mutations **(Figure 1a)**. The five genes most frequently mutated were APC, TP53, ATM, SMAD4, and ERBB4. Variants with potential therapeutic relevance (n = 343) were annotated using the OncoKB database [24] and included both drug-sensitizing mutations—such as BRAF, IDH1, KIT, and PIK3CA—and resistance-associated alterations in KRAS, NRAS, and KIT.



a) b)

c) d)

Figure 1. Results of sequencing: (a) The bar plot depicts the number of sequence variants detected in tumor DNA using the 48-gene panel for 221 patients. Colors indicate non-targetable COSMIC- (grey) and non-targetable hotspot mutations (blue). Actionable variants are shown in green (drug-sensitizing) and red (drug-resistance) based on the OncoKB classification. (b) The heatmap depicts the 50 most frequently mutated somatic genes of the 104 patients analyzed by whole-exome sequencing (WES). The colors indicate tumor entities, type of mutation, tumor mutational burden and BRCAness-score (= AC3−signature). Only mutations with a variant allele frequency greater than 10% and a minor allele frequency less than 0.1% were considered. (c) The bar diagram depicts all mutations that were annotated as targetable by the OncoKB classification. The colors indicate tumor entities. (d) The heatmap depicts copy number variations of the most frequently affected oncogenes. The colors indicate tumor entities and the total copy number per oncogene. Gene copy number gains that were annotated as targetable by the OncoKB algorithm are depicted in red.

Extended genetic analyses and sequencing results

Extended genetic analyses (EGA) were recommended for 183 patients (37.5%), comprising whole-exome sequencing (WES) with or without RNA-seq for 180 patients and RNA-seq alone for 3 patients. EGA was prioritized for younger patients (<50 years), those with rare tumor types, or cases in which routine molecular analyses (RMA) failed to reveal actionable targets. Re-biopsies were suggested for 40 patients (8.2%) when tumor material was insufficient due to low tissue quantity, low tumor cell content, or long intervals between biopsy and MTB presentation.

WES was successfully performed in 104 patients (21.3%), identifying a total of 10,484 mutations. Among these, 2,064 were COSMIC-annotated mutations—including 64 within known hotspot regions—and 8,420 were previously unreported somatic variants **(Figures 1b and 1c)**. According to TARGET and DGIdb databases, 1,987 mutations were classified as potentially actionable, while the OncoKB database identified 53 mutations with direct clinical relevance. The most frequently mutated genes included TP53, KRAS, APC, BRAF, and AR. Copy number variations (CNVs) were detected in both oncogenes and tumor suppressor genes **(Figures 1d)**, with high-level gains (>7 copies) in oncogenes highlighted as potential therapeutic targets per OncoKB annotation.

Tumor mutational burden (TMB) was calculated as a surrogate for neoantigen load and predictive marker for immune checkpoint blockade (ICB) responsiveness. TMB-high (>10 mutations/Mb) tumors were observed in 10 of 104 patients (9.6%). Mutational signatures reflecting exogenous and endogenous processes were also assessed [25, 26], including the AC3 signature associated with homologous recombination repair defects and BRCA-like

("BRCAness") tumors. Tumors with a BRCAness phenotype may respond to PARP inhibitors or DNA-damaging agents [27–29]. A positive BRCAness score (>20%) was observed in 29 of 104 patients (27.9%; **(Figure 1b)**).

Treatment recommendations

Interdisciplinary interpretation of molecular data resulted in treatment recommendations for 264 of 488 patients (54.1%), with a total of 367 recommendations issued. The majority were off-label therapies (248/367; 67.6%), followed by referrals to clinical trials (67/367; 18.3%), and standard in-label treatments (52/367; 14.2%). Recommended therapies primarily included single-agent targeted therapy (TT, 159/367; 43.3%), immune checkpoint inhibitors (ICB, 102/367; 25.1%), and combination regimens (CT, 92/367; 25.1%).

Recommendations were classified according to levels of molecular evidence, following an approach refined for German MTBs [30]. Most recommendations were supported by clinical trial or cohort evidence in the same tumor entity (m1, 166/367; 45.2%) or a different tumor type (m2, 92/367; 25.1%), whereas a smaller fraction relied on preclinical evidence (m3, 101/367; 27.5%) or biological rationale alone (m4, 4/367; 1.1%).

Therapies were implemented in 76 of the 264 patients (28.8%) who received a recommendation. The type, implementation rate, and outcomes of recommended therapies are summarized in **Figure 2**. Among implemented off-label therapies, recommendations based on RMA included tNGS (18/82; 22.0%) and IHC (17/82; 20.7%), while those based on EGA were implemented in 12 patients (14.6%). Non-implementation was primarily due to deferred recommendations for patients stable under current therapy (44/188; 23.4%), medical contraindications (43/188; 22.9%), or patient death (35/188; 18.6%).

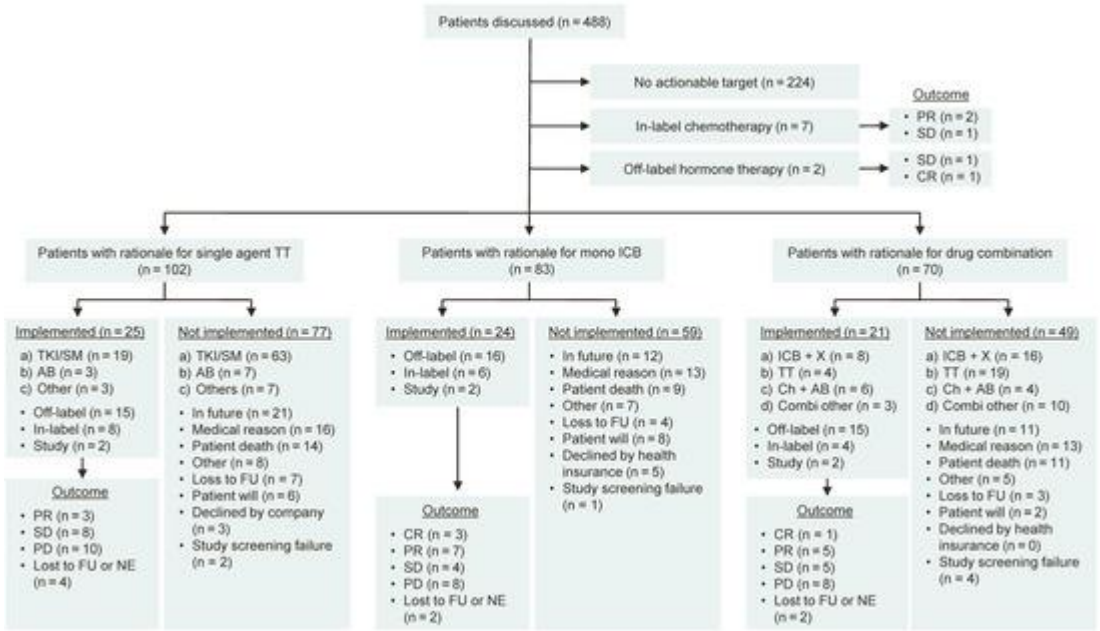


Figure 2. Patient flow through the MTB and subsequent treatment outcomes. Responses were evaluated using RECIST v1.1. Panels (a–d) represent distinct drug categories. Abbreviations: PR = partial remission, SD = stable disease, PD = progressive disease, ICB = immune checkpoint blockade, TT = targeted therapy, TKI = tyrosine kinase inhibitor, SM = small molecule, AB = antibody, ICB + X = ICB combined with another agent, Ch + AB = chemotherapy plus antibody, FU = follow-up, NE = not evaluable.3.4. Clinical Outcomes

Among the 76 patients who implemented MTB-recommended therapies, 19 achieved stable disease (SD; 25.0%), 17 experienced partial responses (PR; 22.4%), and five attained complete remission (CR; 6.6%). Across the full cohort of 488 patients, this corresponds to an objective response rate (ORR) of 4.5% and a disease control rate (DCR) of 8.4%. Within the group achieving disease control, 30 patients had received off-label treatments (6.1% of the total population), of which 23 were guided explicitly by molecular profiling (4.7%).

To evaluate the clinical benefit of these molecularly guided therapies, progression-free survival on the MTB-recommended treatment (PFS2) was compared with the PFS of the immediately preceding therapy (PFS1). A ratio of PFS2 to PFS1 ≥ 1.3 is generally considered indicative of a meaningful response in advanced cancer [17, 31–

35]. Using the modified PFS ratio (mPFSr) approach [36], three patients were excluded due to insufficient or adjusted PFS1 data. Among the remaining 20 patients, 17 who received strictly molecularly matched off-label therapy met the SD criterion and had an mPFSr ≥ 1.3, resulting in an adjusted DCR of 3.5%.

Detailed clinical data for patients achieving at least SD on off-label treatments from March 2017 to December 2018 (n = 16) are summarized in **Table 3**. Earlier outcomes for 14 patients treated between March 2015 and February 2017 have been reported previously [19]. Two cases with exceptional responses—medullary thyroid carcinoma and pleomorphic xanthoastrocytoma—are highlighted corresponding case reports [37, 38].

Table 3. Patients with disease control under off-label treatment since 2017.

Cancer Type	Rationale for Treatment Recommendation	Board Recommendation	EL	L	R	PFS2 (Weeks)	PFS1 (Weeks)	PFSr	Outcome
Adrenocortical Carcinoma	Favorable immunotherapy markers (TPS 2%, CPS 3, IC-Score 0). Evidence of chromosomal instability (copy number variations in 16 oncogenes and 28 tumor suppressor genes). Elevated tumor mutational burden (11.07 mutations/Mb).	Nivolumab (based on NCT02832167 trial for rare tumors)	m2C	off	SD	36	37	1.0	Stable disease maintained for 36 weeks
		Pembrolizumab	m2C	off	SD	53	3	17.5	Stable disease maintained for 53 weeks
Colorectal Cancer (CRC)	Favorable immunotherapy markers (TPS 5%, CPS 10, IC-Score 1).	Atezolizumab combined with cobimetinib	m2C	off	PR	76	11	6.9	Partial response lasting 76 weeks, followed by transition to best supportive care
Cancer of Unknown Primary (CUP)	Signet ring cell histology from unknown primary, with chromosomal instability including extreme EGFR amplification (×338 copies).	Cetuximab combined with FOLFIRI	m2A	off	SD	25	31	0.8	Stable disease for 25 weeks, then progression with new ascites; switched to paclitaxel plus ramucirumab
Histiocytosis	Erdheim-Chester disease harboring BRAF V600E mutation.	BRAF inhibition using vemurafenib or dabrafenib	m1B	off	PR	>133	51	>2.6	Started with vemurafenib; switched to dabrafenib after 10 weeks due to toxicity. Excellent partial response on cardiac MRI at 39 weeks, leading to maintenance pegylated interferon.

									Partial response continues
Meningioma	Anaplastic histology. Immunohistochemistry reveals intense somatostatin receptor expression in 100% of tumor cells.	Octreotide	m3	off	SD	18	n.a.	n.a.	Stable disease for 18 weeks, then progression requiring resection. PFS1 not applicable (no prior systemic therapy; only surgery and radiotherapy)
Mesothelioma	Unfavorable immunotherapy markers (TPS <1%, CPS 10, IC-Score 1), but literature reports responses to checkpoint blockade [39].	Pembrolizumab	m1C	off	SD	32	56	0.6	Stable disease for 32 weeks, followed by patient death
Pleomorphic Xanthoastrocytoma (PXA)	BRAF V600E mutation present.	BRAF inhibition with dabrafenib plus trametinib	m1C	off	CR	>64	n.a.	n.a.	Complete response for 64 weeks and continuing. PFS1 not applicable (no prior systemic therapy; only surgery and radiotherapy)
Prostate Cancer	Pathogenic BRCA2 alteration.	Platinum chemotherapy followed by olaparib maintenance	m2A	off	SD	31	7	4.5	Stable disease for 31 weeks, then progression
Salivary Gland Cancer	Immunohistochemistry shows robust androgen receptor expression in 90% of tumor cells.	Degarelix combined with bicalutamide	m1C	off	CR	66	n.a.	n.a.	Complete response for 66 weeks, then progression with new metastases. PFS1 not applicable after R0 resection and adjuvant radiochemotherapy
Sarcoma	Whole-exome sequencing indicates BRCAness score of 29%.	Olaparib combined with trabectedin	m3	off	SD	6	4	1.3	Stable disease at first imaging (2 weeks). Palliative radiotherapy initiated for pain, complicated by esophagitis and pancytopenia,

									leading to death at 6 weeks
Thyroid Cancer (Anaplastic)	Favorable immunotherapy markers (TPS 5%, CPS 9, IC-Score 1). Trial access available.	Pembrolizumab combined with lenvatinib	m2C	off	PR	>53	16	>3.3	Partial response for 53 weeks and ongoing
	Favorable immunotherapy markers (TPS >80%, with intratumoral TILs).	Pembrolizumab	m2C	off	CR	25	7	3.0	Complete response achieved, but fatal pulmonary hemorrhage at 21 weeks
	Favorable immunotherapy markers (TPS 5%, intratumoral TILs). Chromosomal instability with marked PDGFRA (×28) and PDGFB (×29) amplification.	Pembrolizumab combined with lenvatinib	m2C	off	CR	83	16	3.9	Complete response for 83 weeks and ongoing. Lenvatinib stopped after 52 weeks
	RNA sequencing reveals activated FGFR3 pathway.	FGFR3 inhibition with lenvatinib	m3	off	SD	11	n.a.	n.a.	Strong clinical benefit with regression of local recurrence and symptom improvement. Treatment halted after 14 weeks due to weight loss; subsequent progression and death
Thyroid Cancer (Medullary)	RET M918T mutation.	Selpercatinib	m1A	off	PR	35	15	2.3	Radiographic partial response. Calcitonin dropped from 8554 pg/mL to 12 pg/mL. Response persists

Among the 488 patients evaluated, 41 experienced disease stabilization or tumor response following the recommended treatment. Progression-free survival was measured according to RECIST version 1.1, with median PFS2 reaching 53 weeks (range, 6–238 weeks), markedly exceeding median PFS1 of 16 weeks (range, 3–16 weeks; $p = 0.003$). Additionally, we report on 16 off-label responders that have not been published previously, discussed between March 2017 and December 2018. For each patient, we provide the diagnostic findings that guided board recommendations, along with the level of evidence, labeling, treatment outcome, PFS1, PFS2, PFS ratio (PFSr = PFS2/PFS1), and overall result. Four patients lacked prior systemic therapy and therefore PFS1 and PFSr could not be calculated. Abbreviations used include PR (partial response), SD (stable disease), n.a. (not applicable), CUP (cancer of unknown primary), IO-Panel (immuno-oncology panel), TPS (tumor proportion score), CPS (combined positive score), IC-Score (immune cell score), TILs (tumor-infiltrating lymphocytes), CNV (copy number variation), and PXA (pleomorphic xanthoastrocytoma).

To determine the effect of molecular tumor board (MTB) recommendations on overall survival (OS), survival times were analyzed using Kaplan–Meier estimates, starting from the patient's initial MTB presentation. To

reduce bias, the analysis included only patients with stage IV disease (n = 340) and excluded those who had died before therapy initiation (n = 53) or already had disease control at the time of recommendation (n = 37). Patients who received and followed the recommended therapy (n = 73) achieved a median OS of 18 months (95% CI, 11–30 months), which was significantly longer than patients who did not implement recommendations (n = 100; median OS = 8 months, 95% CI, 7–12 months; p = 0.008) and those who received no recommendation (n = 167; median OS = 8 months, 95% CI, 7–12 months; p = 0.003)

In this retrospective series, we evaluated 488 patients, the majority of whom (n = 442; 90.6%) had stage IV malignancies, consecutively referred to a single-institution molecular tumor board (MTB) between March 2015 and December 2018. Most referrals were due to progression after standard-of-care therapies (78.1%) or the presence of rare tumor types (10.5%, **(Table 1)**). Following both entity-specific and general diagnostic standard operating procedures (SOPs), nearly all patients (n = 487; 99.8%) were recommended for individual molecular testing, with a high adherence rate of 80.7% to these diagnostic recommendations. These findings allowed the MTB to provide individualized treatment recommendations for over half of the cohort (n = 264; 54.1%), of which roughly one-third (n = 76; 28.8%) ultimately received the suggested therapy. Across all recommended treatments, the overall response rate (ORR) was 4.5%, and the disease control rate (DCR) was 8.4%. These results are in line with reports from other MTBs, such as Baltimore (24%, 16%, 9%), Cleveland (49%, 11%, 3.2%), and Vienna (54%, 23%, n.a.). Although an ORR of 4.5% appears low, it must be interpreted in the context of a heavily pretreated, advanced-stage patient population. Reasons for non-implementation included patient death (18.6%) and poor performance status (7.5%), indicating that even a small proportion of patients achieving disease control reflects a meaningful clinical benefit.

Our SOP-driven, stepwise molecular diagnostic approach proved both time- and cost-efficient, with a median interval of 42 days from the first MTB discussion to the initial treatment recommendation. Most recommendations (85.4%) were made without additional, resource-intensive exploratory genomic analyses (EGA), which were used in 14.6% of cases, including patients undergoing upfront whole-exome sequencing (WES) or RNA sequencing, such as those with carcinoma of unknown primary, rare malignancies, or younger patients. When RMA did not identify actionable targets and the patient's condition allowed, EGA was performed as a secondary diagnostic step. Clinical effectiveness was highlighted by the OS benefit observed in stage IV patients receiving recommended treatments (median OS 18 months; 95% CI, 11–30 months), compared with patients who did not receive recommendations (median OS 8 months; 95% CI, 7–12 months; p = 0.003) or did not implement them (median OS 8 months; 95% CI, 7–12 months; p = 0.008). However, the survival analysis has limitations: small sample sizes prevented propensity score matching, leaving potential confounding factors uncontrolled.

Comparing these results with our 2018 proof-of-concept study (198 patients), treatment recommendation rates remained stable (55.1% vs. 52.5%), while implementation rates were consistently low (28.8% vs. 31.7%), with medical reasons (22.9%) and patient death (18.6%) as the main barriers. We hypothesize that a streamlined workflow for off-label treatment access, based on pre-agreed criteria, could improve timely treatment uptake. To facilitate this, the MTB plans to provide formal applications to healthcare providers along with recommendations for treating physicians.

Over time, patient outcomes remained stable (DCR 7.6% vs. 9.6%), while case volumes per 90-minute MTB session increased significantly (18.0 vs. 8.1). Workflow efficiency improvements included pre-assigning patients to entity-specific experts at least four days before discussion, establishing a regular SOP update process (2017), automated WES reporting within two days of raw data receipt, pre-meeting communication of detailed diagnostic results to the expert, and preparation of draft recommendations for discussion and approval during the meeting.

Our report is in line with prospective precision oncology trials that demonstrated the impact of molecular driven therapies on patient outcome [11–13, 40] underlining the importance of upscaling MTBs in order to facilitate treatment access to cancer patients who lack standard treatment options. A survey from van der Velden *et al*. revealed that in the Netherlands < 50% of hospitals and only 5% of non-academic hospitals had access to an MTB in 2017 [41]. To address this medical need, we opened the MTB to patients treated by external hospitals and private practice oncologists in June 2016. External referrals to the MTB increased from an average of 1.1 patients per session in 2016 to 1.7 in 2018. To further grant MTB-access to more cancer patients and to reduce discrepancies in care, related to diverse bioinformatics workflows [42] and heterogeneous standards for interpretation of molecular aberrations [43], the comprehensive cancer centers of southwest Germany upscaled referrals and harmonized their workflows and SOPs in 2020. This network initiative (Zentrum für Personalisierte Medizin, ZPM, Baden-Württemberg, Germany) also established a digital cloud that collects molecular diagnostic

results and clinical follow-up data. This data will be used to identify both positive and importantly also negative correlations between molecular biomarker-driven therapies and outcomes. Accessible and effective drugs or clinical trials may therefore be identified easier and faster. Health care providers expressed an intrinsic interest to support and fund the establishment of the German ZPM-network since the increasing number of off-label requests from oncologists [44] will be streamlined through specialized MTBs allowing a harmonized and fast decision process with evidence based recommendations.

A primary objective of the MTB is to expand patient access to molecularly guided clinical trials. In partnership with the on-site early clinical trial unit (ECTU), the Freiburg MTB oversees numerous innovative phase I and II basket studies. Potential candidates are pre-screened promptly to identify both on-site and external trial opportunities, ensuring rapid access to appropriate molecularly stratified studies. Compared to our initial 2018 report, the rate of trial recommendations increased from 12.5% to 20.2%, a figure comparable to recent reports from Paris (13.2%) and London (20%). Insights from MTB patients who demonstrated exceptional responses have facilitated the development of two investigator-initiated early-phase trials: ATLEP (DRKS00013336) and SORATRAM (DRKS00015849).

A central challenge for MTBs is the rapidly evolving landscape of predictive biomarkers for targeted and immuno-oncology therapies. Immune checkpoint blockade (ICB) therapies, for example, have broadened the spectrum of potential off-label indications, including melanoma, lung, and renal cancers. In our cohort, established biomarkers such as PD-L1 expression, microsatellite instability (MSI), and tumor mutational burden (TMB) guided off-label ICB monotherapy or combination therapy in 108 patients (22.1%), with 28 (25.9%) ultimately receiving treatment. Within this subgroup, the disease control rate (DCR) was 57.1% (16 of 28). Positive IO-panel status correlated with better outcomes (39.3% vs. 17.9% in negative panels). Notably, all seven patients with anaplastic thyroid cancer exhibited positive IO-panels with TPS ≥ 5, indicative of immune "hot" tumors; all but one achieved disease control, including two complete remissions. These findings highlight the MTB's role in facilitating early patient access to promising therapies, exemplified by pembrolizumab's tumor-agnostic FDA approval following Keynote-158.

The identification of new biomarker-driven therapies and clinical trial opportunities depends heavily on the MTB panel's expertise. The team is structured into entity-specific molecular oncology experts, molecular pathologists, bioinformaticians, and translational scientists, enabling rigorous evaluation of the rapidly expanding precision oncology literature.

The introduction of FDA-approved combination therapies since the 2012 approval of trastuzumab plus pertuzumab with docetaxel has increased both the likelihood and magnitude of treatment responses, while addressing primary and acquired resistance mechanisms. Reflecting this trend, the MTB's combination therapy recommendations have risen from 18.3% in 2018 to 28.5% currently. Among 70 patients advised to receive combination therapy, 21 (30%) implemented the recommendation, achieving a DCR of 52.4% (11 of 21). Importantly, none of these therapies were discontinued due to toxicity, demonstrating both their feasibility and the growing complexity of contemporary anti-cancer treatment, underscoring the importance of structured molecular diagnostics.

Conclusion

This retrospective review of 488 patients managed by the Freiburg MTB from 2015 to 2018 illustrates the successful evolution from proof-of-concept to routine clinical implementation. Despite significant increases in case volume and workflow complexity, molecularly guided precision oncology remains effective for a meaningful subset of advanced-stage patients who have exhausted standard-of-care options.

Acknowledgments: None

Conflict of Interest: None

Financial Support: This work was funded by the Comprehensive Cancer Center Freiburg (CCCF), core support for molecular diagnostics in and by the Institute for Surgical Pathology and by a grant to M.B. (Melanie Boerries), N.v.B. and S.L. by the German Cancer Consortium (DKTK, Award Number L628) and the local steering committee of DKTK partner site Freiburg. This work was further supported by the Deutsche

Forschungsgemeinschaft (DFG) through SFB 850, Z1 (H.B., M.B. (Melanie Boerries), and S.L.) and a Heisenberg professorship (T.B.), BW-VAPO funded the Ministry of Science, Research and the Arts of Baden-Württemberg (T.B., C.P., and M.B. (Melanie Boerries)), by a grant of the German Society of Internal Medicine (DGIM), the German Cancer Consortium (DKTK, Award number FR01-376) and Deutsche Krebshilfe (grant number DKH 70114112) to ALI, by the BMBF through the framework of the e:Med research and funding concept, DeCaRe (FKZ 01ZX1409B) to M.B. (Melanie Boerries). M.B. (Martin Boeker) and M.B. (Melanie Boerries). are further supported and PM funded through the BMBF medical informatics initiative (consortium MIRACUM FKZ 01ZZ1801B). The authors greatly acknowledge the team of the Genomics and Proteomics Core Facility, German Cancer Research Center/DKFZ, Heidelberg, Germany for their sequencing service. R.H., J.W. and J.D.A. are funded by the Berta-Ottenstein-Programme for Clinician Scientists, Faculty of Medicine, University of Freiburg.

Ethics Statement: None

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