

original report Personalized Medicine in the Oncology Clinic: Implementation and Outcomes of the Johns Hopkins Molecular Tumor Board

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Purpose Tumor genomic profiling for personalized oncology therapy is being widely applied in clinical practice even as it is being evaluated more formally in clinical trials. Given the complexities of genomic data and its application to clinical use, molecular tumor boards with diverse expertise can provide guidance to oncologists and patients seeking to implement personalized genetically targeted therapy in practice.

Methods A multidisciplinary molecular tumor board reviewed tumor molecular profiling reports from consecutive referrals at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins over a 3-year period. The tumor board weighed evidence for actionability of genomic alterations identified by molecular profiling and provided recommendations including US Food and Drug Administration–approved drug therapy, clinical trials of matched targeted therapy, off-label use of such therapy, and additional tumor or germline genetic testing.

Results One hundred fifty-five patients were reviewed. Actionable genomic alterations were identified in 132 patients (85%). Off-label therapies were recommended in 37 patients (24%). Eleven patients were treated off-label, and 13 patients were enrolled onto clinical trials of matched targeted therapies. Median progression-free survival of patients treated with matched therapies was 5 months (95% CI, 2.9 months to not reached), and the progression-free survival probability at 6 months was 43% (95% CI, 26% to 71%). Lack of locally available clinical trials was the major limitation on clinical actionability of tumor profiling reports.

Conclusion The molecular tumor board recommended off-label targeted therapies for a quarter of all patients reviewed. Outcomes were heterogeneous, although 43% of patients receiving genomically matched therapy derived clinical benefit lasting at least 6 months. Until more data become available from precision oncology trials, molecular tumor boards can help guide appropriate use of tumor molecular testing to direct therapy.

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INTRODUCTION

The advent of low-cost, next-generation DNA sequencing (NGS) technologies has led to an explosion in individual tumor molecular profiling with the goal of identifying personalized therapeutic matches for patients with cancer. Case reports and clinical trials attest to the clinical utility of targeting driver gene mutations in cancer types other than those in which the drug is approved for clinical use, such as *BRAF* V600 mutations in cancers other than melanoma.¹ Ongoing efforts, such as the National Cancer Institute Molecular Analysis for Therapy Choice (NCI-MATCH;

ClinicalTrials.gov identifier: NCT02465060) and the ASCO Targeted Agent and Profiling Utilization Registry (TAPUR; ClinicalTrials.gov identifier: NCT02693535) trials, aim to identify genomic predictors of response for targeted therapies against diverse genetic variants that may be difficult to study clinically because of their rarity outside of specific disease types.² However, the use of tumor sequencing in clinical practice has outpaced the implementation and completion of such trials. Surveys have indicated that many oncologists are unsure how to interpret tumor sequencing data and whether their patients will have access to targeted

therapies on the basis of the reports (ie, how actionable the findings are in reality).³ In response to these concerns, we established a multidisciplinary Genetic Alterations in Tumors With Actionable Yields (GAITWAY) molecular tumor board at our institution (Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD) to assist providers with interpretation and use of tumor molecular profiling data. Here, we present our approach to using tumor molecular profiling and our 3-year experience, with associated patient outcomes.

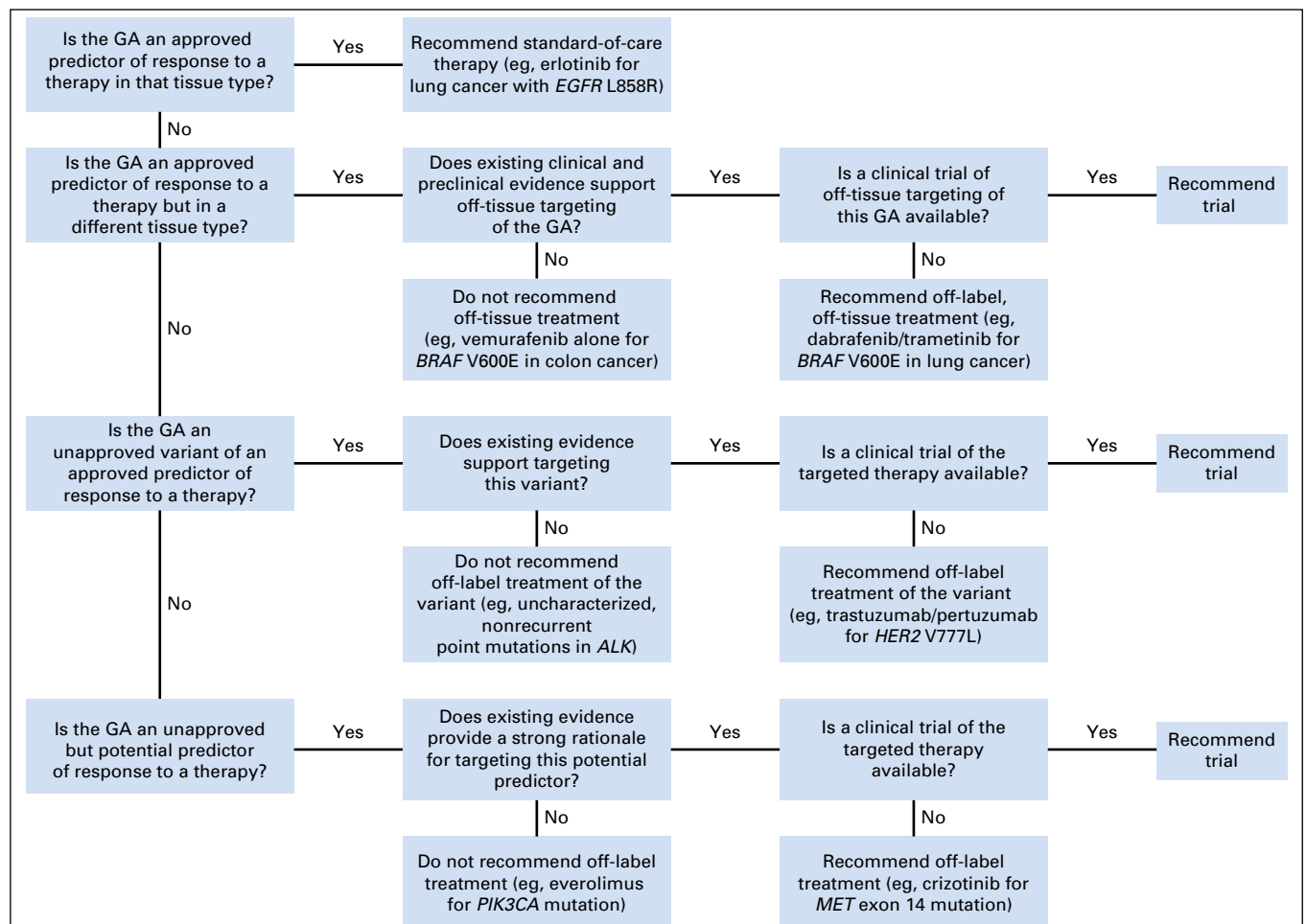
METHODS

The GAITWAY tumor board began meeting weekly in September 2013. Attendees included adult and pediatric medical oncologists representing diverse subspecialties, molecular pathologists with NGS expertise, genetic counselors, phase I clinical trial investigators, research coordinators, a patient advocate, and medical oncology fellows. Tumor testing was ordered by the referring oncologist without the board's input. The referring

oncologist provided the board with the molecular profiling report(s) and the patient's oncologic and family history. A written summary of the board's discussion and recommendations was provided to the referring oncologist.

The board reviewed Clinical Laboratory Improvement Amendments–approved NGS cancer gene panel tests from a variety of providers, including Foundation Medicine (Cambridge, MA; FoundationOne, n = 120), Personal Genome Diagnostics (Baltimore, MD; Cancer Select-203 or Cancer Select-88, n = 25), Memorial Sloan Kettering Cancer Center MSK-IMPACT (New York, NY; n = 5), Caris Life Sciences (Irving, TX; MI Profile, n = 3), and several others. Personal Genome Diagnostics and MSK-IMPACT included normal tissue control sequencing and filtered out most germline variants. A small number of reports included multiplatform testing, including NGS, fluorescence in situ hybridization, and protein immunohistochemistry. Only one test used circulating tumor DNA from plasma as the source material (Personal Genome Diagnostics, Lung Select).

Fig 1. Genetic Alterations in Tumors With Actionable Yields (GAITWAY) tumor board approach to therapeutic recommendations on the basis of tumor genomic analyses. GA, genomic alteration.



Medical records for consecutive patients referred to the board from September 2013 through September 2016 were accessed under a protocol approved by the Johns Hopkins institutional review board. Patient characteristics were analyzed using

descriptive statistics. Progression-free survival (PFS) was measured from the first date of treatment with a genomically matched therapy or next nonmatched therapy after tumor board evaluation until the date of disease progression or death, whichever came first. Progression was determined by imaging studies or clinician assessment. Responses were assessed according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Probability of PFS was estimated using the Kaplan-Meier method. Alive patients without progression were censored at the date of last radiographic assessment. Statistical analyses were performed using R software v.3.3.1.

Table 1. Patient Demographic Characteristics and Distribution of Tumor Types

Characteristic	Patients, No. (%)
Total	155
Sex	
Female	101 (65)
Male	54 (35)
Median age, years (range)	56 (17-89)
Race	
White	118 (76)
African American/African	24 (15)
Asian	6 (4)
Other	5 (3)
Unknown	3 (2)
No. of prior lines of therapy for metastatic disease, mean (range)	2.0 (0-11)
Tumor type	
Breast triple negative	32
Breast ER positive/HER2 negative	21
Breast HER2 positive (ER positive or negative)	3
Lung adenocarcinoma	14
Lung squamous carcinoma	6
Lung adenosquamous	1
Head and neck squamous carcinoma	11
Neuroendocrine carcinoma/small-cell carcinoma/atypical carcinoid	8
Salivary gland/duct	7
Glioblastoma/anaplastic astrocytoma	6
Unknown primary site	5
Adenoid cystic carcinoma	5
Hepatobiliary/ampullary/duodenal	5
Pancreas adenocarcinoma	4
Cholangiocarcinoma	4
Sarcoma	4
Endometrial	3
Prostate	2
Stomach	2
Colon	2
Ovary	1
Other*	11

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2.

*Sinonasal undifferentiated carcinoma, anaplastic ependymoma, appendiceal mucinous carcinoma, testicular choriocarcinoma, esthesioneuroblastoma, inflammatory myofibroblastic tumor, ameloblastoma, medullary kidney cancer, lacrimal gland carcinoma, skin adnexal carcinoma, and acinar pancreas cancer.

Criteria for Actionability of Genomic Alterations

The board considered a genetic alteration actionable if one of the following conditions was met: it offered a target for a drug approved by the US Food and Drug Administration (FDA) for the patient's tumor type; it offered a target for a drug approved by the FDA for another tumor type; it offered a target for a drug on a clinical trial; or it was a potential germline mutation for a hereditary cancer predisposition syndrome. The board's approach to recommending genomically guided therapy is shown in Figure 1. The board had a relatively high threshold for considering a genetic variant as the basis for off-label use of a targeted therapy. Genetic alterations with drugs that specifically targeted the affected protein were of highest priority. In contrast, although many genes could potentially be linked to activation of the mammalian target of rapamycin (mTOR) pathway (eg, *NF1*, *PIK3CA*, *FBXW7*), the board generally did not recommend off-label use of mTOR inhibitors, given that the genetic link to mTOR was indirect or variants in these genes did not predict mTOR inhibitor benefit in clinical correlative studies.^{4,5} Similarly, *CCND1* amplification and *CDKN2A/B* loss or mutation were not considered a high-level rationale for off-label use of the CDK4/6 inhibitor palbociclib because these alterations had not been shown to predict therapeutic benefit in breast cancer.⁶ Although multi-kinase inhibitors like pazopanib are often suggested as a match for *FGFR1-3* amplifications,⁷ the board thought there was insufficient evidence to recommend off-label use and instead preferred clinical trials of fibroblast growth factor receptor (FGFR) inhibitors. The board was more liberal in recommending clinical trials for the alterations discussed earlier, even when the genetic alteration was not directly targeted by the investigational agent (eg, considering *KRAS* mutations as rationale for an

MEK inhibitor trial). The rationale for some recommendations changed over time as new data and literature emerged relevant for a given target. The board's approach to evaluating specific variants in genes is further described in the Appendix.

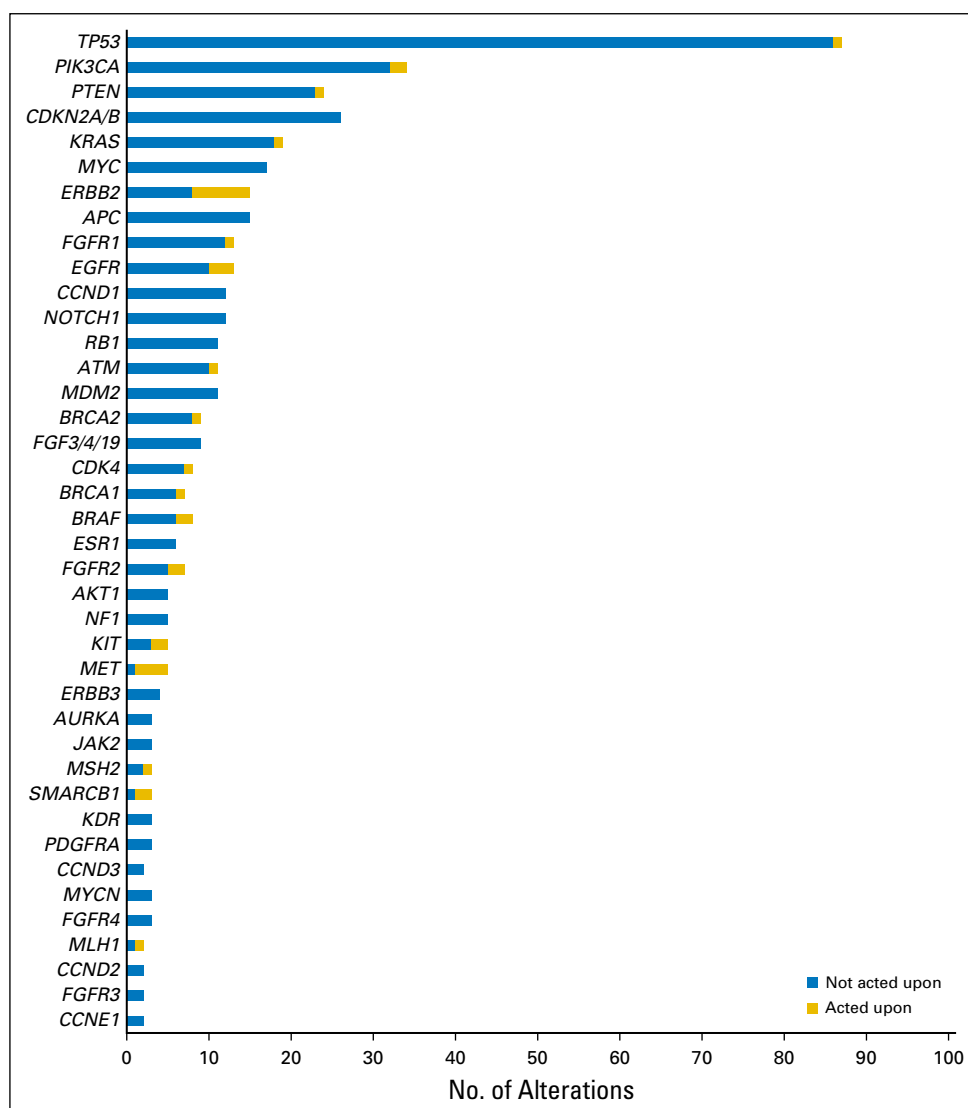
RESULTS

From September 2013 through September 2016, 157 cases representing 155 patients were reviewed by the GAITWAY tumor board (two patients had subsequent tumor sequencing and were reviewed twice). Patient demographic characteristics and distribution of tumor types are listed in Table 1. The most frequent tumor types were breast cancer (n = 56), lung cancer (n = 21), and squamous cell carcinoma of the head and neck (n = 11). The breast cancer cases included 20 patients with triple-negative disease previously reviewed as part of Individualized Molecular Analyses Guide Efforts

(IMAGE), an institutional precision oncology feasibility trial.⁸ The mean number of lines of prior systemic therapy for metastatic disease was two lines (range, zero to 11 lines). Follow-up information was available for 129 patients (83%). The main reason for lack of follow-up was that the patient was seen only once for a second opinion.

The average number of genetic alterations per tumor was 4.8 (range, zero to 16 alterations), excluding variants of uncertain significance or equivocal amplifications. The average number of genetic alterations considered actionable by the board was 1.9 (range, zero to six alterations). Genes recurrently altered across samples were similar to those reported from other series,⁹⁻¹¹ although the relative frequencies were influenced by the case mix seen by our tumor board (Fig 2). In terms of targetable pathways, the phosphatidylinositol-3 kinase (PI3K) pathway was most frequently altered (63 alterations),

Fig 2. Frequency of genomic alterations. Actionable genomic alterations and selected nonactionable alterations are shown. For actionable genes, the number of patients in whom an action was taken is shown. Actions taken included therapy assignment, germline testing, or microsatellite instability evaluation.



followed by the G₁ cell cycle checkpoint (61 alterations) and FGFR pathways (30 alterations).

The board identified a potentially actionable genomic alteration in 132 patients (85%; Fig 3). Four patients (3%) received therapies approved by the FDA for their tumor type. Thirty-seven patients (24%) had a recommendation for off-label use of an FDA-approved therapy (Table 2 and Appendix Table A1). Twenty-four patients (15%) received a nonstandard, genetically matched therapy off-label (n = 11) or on a clinical trial (n = 13). Reasons patients did not receive recommended off-label therapy are detailed in Figure 3. In no case was the treating oncologist unable to prescribe or obtain a recommended off-label drug as a result of denial by insurance.

A clinical trial was recommended as an option for 129 patients (83%; including 34 patients who also had a recommendation for off-label therapy), but only 13 patients were enrolled onto a recommended trial (Fig 3). In a number of patients, the trial recommendation was qualified, because there was no clinical evidence that the alterations were predictive of benefit. The most frequent alterations that led to a qualified recommendation were *KRAS* or *MDM2* mutations and alterations activating the G₁ cell cycle checkpoint (*CDKN2A/B*, *CCND1*, and *CDK4*). Stronger recommendations were made for

trials targeting the FGFR or PI3K pathways, but only four patients were treated on such trials, largely because of lack of availability. Twenty-five patients who investigated clinical trial options were not eligible, could not access a trial for reasons of geographical proximity, or had worsening performance status (Fig 3).

Outcomes of Patients Receiving Matched Targeted Therapy

Follow-up information was available for all 24 patients treated with a matched therapy on a clinical trial or off-label. Two patients had recently initiated therapy, and response assessment was not yet available. With a median follow-up of 7.0 months, the median PFS of patients treated with genomically matched therapy was 5 months (95% CI, 2.9 months to not reached), and the 6-month PFS probability was 43% (95% CI, 26% to 71%; Fig 4A). The median PFS for 54 patients with available follow-up information whose next therapy was nonmatched was 2.97 months (95% CI, 2.4 to 5.13 months), and 6-month PFS was 20% (95% CI, 11% to 35%). Demographic characteristics of the two cohorts are listed in Appendix Table A2. Fifty percent of patients receiving genomically matched therapy had a PFS more than double their PFS on prior therapy (Fig 4B). Two patients

Fig 3. CONSORT diagram of patients discussed at the molecular tumor board. Note, all numbers do not add up because some patients are counted in more than one category (eg, had an actionable alteration for a clinical trial and also were recommended off-label use or had an actionable alteration for therapy and also for germline analysis). (*) One patient with *KRAS* mutation for whom the board recommended a clinical trial only but who was prescribed off-label trametinib by his primary oncologist. FDA, US Food and Drug Administration; NED, no evidence of disease; PS, performance status.

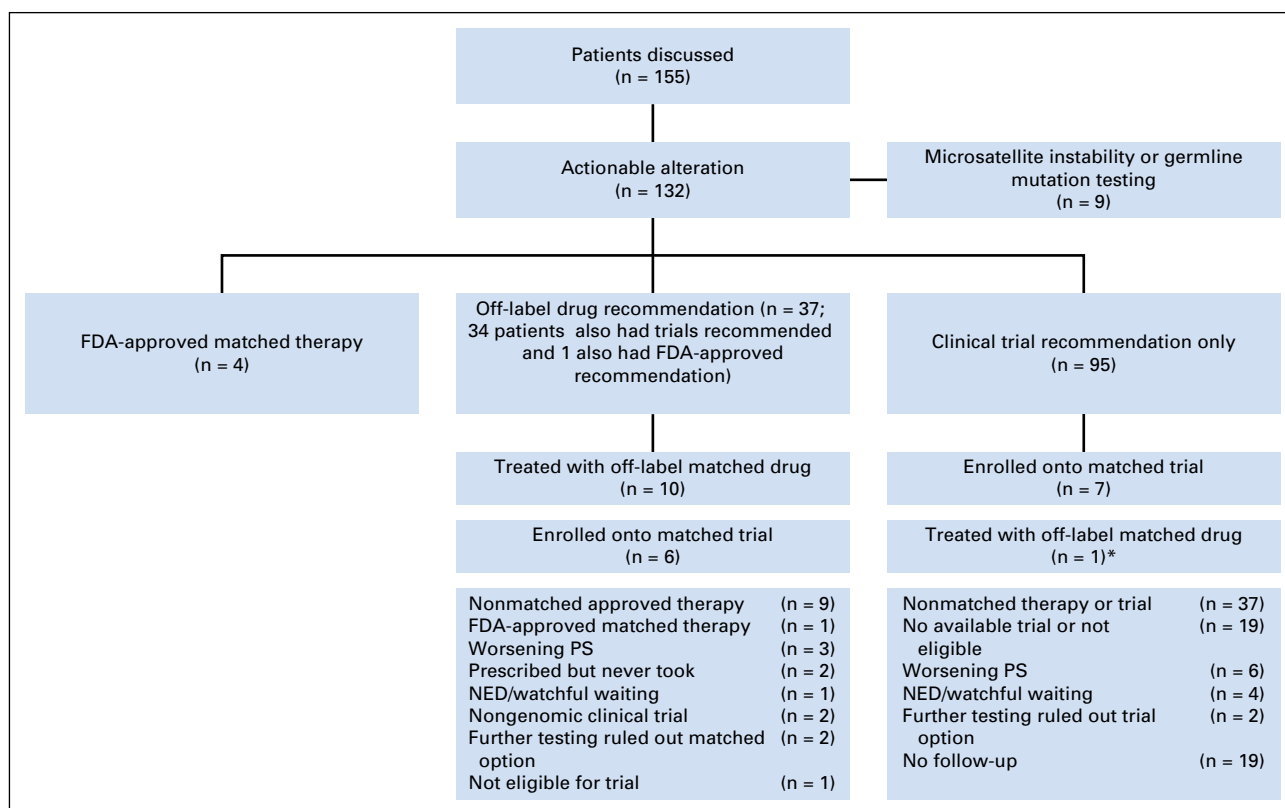


Table 2. Patients Who Received Matched Targeted Therapies or for Whom the Board Recommended Off-Label Use of Targeted Therapies

Cancer Type	Actionable Alteration	Board Recommendation	Treatment and Outcome
Inflammatory myofibroblastic tumor	<i>ALK</i> G1202R, <i>RANBP2-ALK</i> fusion	Cabozantinib off label or clinical trial	Cabozantinib; SD for 5 months, hospice
Breast, triple negative*	<i>BAP1</i> E498fs*38, loss; <i>EGFR</i> R108K	PARP inhibitor trial or lapatinib/capecitabine off label	Olaparib/carboplatin trial: SD for 4 months
Ameloblastoma	<i>BRAF</i> V600E	Dabrafenib/trametinib off label	Dabrafenib/trametinib; PR for 8 months, then PD after medication supply ran out; now back on therapy
Glioblastoma	<i>BRAF</i> G469R	Trametinib off label	Trametinib prescribed but never started as a result of intervening medical complications and worsening PS
Stomach	<i>BRAF</i> D594N	Trametinib or sorafenib off label	PD, PS decline, hospice
Lung adenocarcinoma	<i>BRAF</i> G469S	Trametinib or sorafenib off label	Nivolumab with SD, then died
Lung adenocarcinoma	<i>BRAF</i> V600E	Dabrafenib/trametinib off label	Immunotherapy, then chemotherapy with PR
Pancreas acinar cell carcinoma†	<i>SND1-BRAF</i> fusion	Trametinib or selumetinib off label	NED, not requiring therapy
Supraglottic larynx squamous carcinoma	<i>BRC1</i> Q905*	PARP inhibitor trial or olaparib off label (qualified recommendation given uncertainty of <i>BRC1</i> germline status)	Chemotherapy, PD, hospice within 1 month
Poorly differentiated INI-1–deficient carcinoma	<i>BRC1</i> C61G, <i>SMARCB1</i> loss	PARP inhibitor trial or olaparib off label (qualified recommendation given uncertainty of <i>BRC1</i> germline status) or EZH2 inhibitor trial or single-patient IND for alisertib	Tazemetostat (EZH2 inhibitor) trial targeting <i>SMARCB1</i> loss; response assessment pending
Breast, metaplastic, ER positive, PgR negative, HER2 negative	<i>BRC1</i> Q94*	PARP inhibitor trial or olaparib off label	Olaparib; PR at 2 months, then PD after 5 months
Glioblastoma	<i>BRC2</i> F1546fs*22	PARP inhibitor trial or olaparib off label or platinum	Pursued alternative clinical trial, radiation, bevacizumab
Pancreas adenocarcinoma	<i>BRC2</i> S599fs*1, splice site 794-37_794-del37	PARP inhibitor trial or olaparib off label or platinum chemotherapy	Not eligible for PARP inhibitor trial; no further follow-up available
Lung squamous carcinoma	<i>CDK4</i> amplification, <i>CDKN2A/B</i> loss	CDK4/6 inhibitor trial only	Palbociclib trial; PD after 12 weeks
Lung adenocarcinoma	<i>EGFR</i> G719S, S768I	Afatinib (FDA indication)	Afatinib for 8 months; mixed response (PR of mass originally sequenced, PD contralateral mass)
Lung adenocarcinoma	<i>EGFR</i> H773_V774insH	No recommendation at time of review; was receiving definitive chemoradiation	AUY922 (HSP90 inhibitor) trial upon recurrence; SD for 9 months, ongoing

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Table 2. Patients Who Received Matched Targeted Therapies or for Whom the Board Recommended Off-Label Use of Targeted Therapies (Continued)

Cancer Type	Actionable Alteration	Board Recommendation	Treatment and Outcome
Lung adenocarcinoma	<i>EGFR</i> D770_N771insY	AUY922 (HSP90 inhibitor) trial	AUY922 trial; PD, off study after 1 month
Malignant peripheral nerve sheath tumor	<i>EGFR</i> duplication exons 18-26	Afatinib off label	Had already started temozolomide/pazopanib; died within 2 months
Biliary tract adenocarcinoma	<i>EGFR</i> amplification 19-fold (<i>KRAS</i> wild type)	Cetuximab or panitumumab off label	Had neoadjuvant chemotherapy, resection, and more chemotherapy
Breast, triple negative*	<i>ERBB2</i> D769H, V777L	Trastuzumab/lapatinib; trastuzumab/chemotherapy; lapatinib/capecitabine	Trastuzumab/capecitabine (after 6 weeks of trastuzumab alone); SD for 9 months
Breast, HER2 positive, ER positive	<i>ERBB2</i> amplification (equivocal)	Trastuzumab with endocrine therapy (FDA indication)	Trastuzumab with endocrine therapy; was and remains NED after radiation for brain metastatic recurrence
Breast, HER2 positive	<i>ERBB2</i> amplification; <i>MTOR</i> E2104K	Trastuzumab/pertuzumab/docetaxel (FDA indication) (qualified recommendation for everolimus off label on the basis of <i>MTOR</i> variant)	Trastuzumab/pertuzumab for 3 months, PD, added docetaxel: near CR of nodes (now not measurable)
Lung adenocarcinoma	<i>ERBB2</i> L755S	Various HER2-targeted therapies: trastuzumab ± chemotherapy, afatinib, T-DM1	Trastuzumab/pertuzumab on trial; PR at 12 months, continues on therapy
Skin adnexal carcinoma	<i>ERBB2</i> FISH ratio 2.1	Various HER2-targeted therapies	Trastuzumab/pertuzumab trial; CR after 2 cycles
Lung adenocarcinoma	<i>ERBB2</i> exon 20 insertion E770_A771insAYVM (equivalent to A775_G776insYVMA)	Afatinib off label (but approved for lung cancer)	Was benefitting from chemotherapy, then died
Lung adenocarcinoma (known <i>EGFR</i> mutated)	<i>ERBB2</i> amplification, <i>EGFR</i> E746_A750del	Trastuzumab/pertuzumab/taxane or trastuzumab/pertuzumab or trastuzumab/lapatinib or T-DM1 or trastuzumab + <i>EGFR</i> kinase inhibitor off label	PS declined; died within several weeks of tumor board
Salivary duct	<i>ERBB2</i> S310F	Trastuzumab + pertuzumab or afatinib or trastuzumab + chemotherapy; off label or on trial	Trastuzumab/pertuzumab on trial; response assessment pending
Lacrimal gland	<i>ERBB2</i> amplification	Trastuzumab ± pertuzumab ± taxane off label	Awaiting assessment of current chemotherapy
Squamous cell carcinoma hypopharynx	<i>ERBB2</i> amplification	Trastuzumab ± pertuzumab ± taxane off label or on trial	HER2 1+ by IHC; received chemotherapy
High-grade neuroendocrine carcinoma	<i>ERBB3</i> G284R	Afatinib or trastuzumab + lapatinib; off label	Immunotherapy trial for 2 cycles; died
Rhabdomyosarcoma	<i>FGFR1</i> N577K	Pazopanib (FDA indication)	Pazopanib; on therapy 4 months, no restaging; died of PD
Breast, triple negative	<i>FGFR2</i> amplification	FGFR inhibitor trial	Lucitanib (FGFR inhibitor) trial; PD after 1 cycle

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Table 2. Patients Who Received Matched Targeted Therapies or for Whom the Board Recommended Off-Label Use of Targeted Therapies (Continued)

Cancer Type	Actionable Alteration	Board Recommendation	Treatment and Outcome
Cholangiocarcinoma	<i>FGFR2-WAC</i> fusion	FGFR inhibitor trial	BGJ398 (FGFR inhibitor) trial; SD for 6 months
Duodenal adenocarcinoma‡	<i>JAK2</i> V617F	Ruxolitinib (qualified recommendation pending verification that mutation was present in tumor)	Mutation determined to be from contaminating blood cells (patient had polycythemia vera)
Breast, ER positive	<i>KIT</i> V560G	Imatinib off label	Imatinib; worsening respiratory failure, discontinued therapy after 7 days, comfort care
Appendiceal mucinous carcinoma	<i>KRAS</i> G12V, <i>GNAS</i> amplification	MEK inhibitor on trial only	Trametinib off label for 4 months with PD
Breast, triple negative*	<i>MAP2K1</i> amplification	MEK inhibitor trial or off label	Trametinib off label; early clinical response (skin nodules), then PD after several weeks
Lung adenocarcinoma	<i>MET</i> exon 14 splice; <i>MET</i> amplification (equivocal)	Crizotinib off label	Crizotinib off label; SD for 21 months, ongoing
Lung adenocarcinoma	<i>MET</i> amplification	Crizotinib off label	Prescribed crizotinib, but never started as a result of medical and social circumstances
Anaplastic astrocytoma	<i>MET</i> amplification 8.9-fold, <i>MET</i> R731Q, <i>KIT</i> amplification 5-fold	Crizotinib or cabozantinib off label	Cabozantinib off label; clinical and radiographic response after 3 weeks, treatment stopped during episode of zoster, followed by rapid PD (on treatment 1 month)
Lung adenocarcinoma (known <i>EGFR</i> exon 21 mutation)	<i>MET</i> exon 14 splice (<i>EGFR</i> mutation not found in biopsy specimen)	Add crizotinib to erlotinib	Erlotinib/crizotinib; SD for 6 months, ongoing
Breast, ER positive	<i>PIK3CA</i> H1047R, R88Q	Continue on BKM120 (PI3K inhibitor)/fulvestrant trial	BKM120/fulvestrant trial; SD for 6 months
Breast, ER positive, PgR positive	<i>PIK3CA</i> E545K	PI3K inhibitor trial	BYL719 (PI3K inhibitor)/protein-bound paclitaxel trial; on cycle 3 with tumor marker decline and SD
Colon	<i>PTCH1</i> P681L	Vismodegib on trial or off label	PS worsened, hospice
Lung adenosquamous carcinoma	<i>RET KIF5B-RET</i> fusion	Cabozantinib off label or on trial	Cabozantinib clinical trial; PR after 2 months, then off study for debility; continued cabozantinib off label for 1 month, then leptomeningeal PD
Lung adenocarcinoma	<i>RICTOR</i> amplification, <i>STK11</i> G276fs*11	Everolimus on trial or off label	Received chemotherapy then radiation
Medullary kidney cancer	<i>SMARCB1</i> Y47*	Alisertib single-patient IND	Received chemotherapy then nivolumab and experienced progression; died before alisertib could be given (IND obtained)

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Table 2. Patients Who Received Matched Targeted Therapies or for Whom the Board Recommended Off-Label Use of Targeted Therapies (Continued)

Cancer Type	Actionable Alteration	Board Recommendation	Treatment and Outcome
Cholangiocarcinoma	<i>STK11</i> spl598-2A>C	Everolimus or temsirolimus; on trial or off label	Temsirolimus added to capecitabine; PD after 1 month
Mucoepidermoid carcinoma	<i>TSC2</i> V1711M	Everolimus (qualified recommendation; mutation not well characterized) on trial or off label	Received chemotherapy then pembrolizumab

NOTE. A more detailed version of this table including all genomic alterations in the tumors is available as Appendix Table A1.

Abbreviations: CR, complete response; ER, estrogen receptor; FDA, US Food and Drug Administration; FGFR, fibroblast growth factor receptor; FISH, fluorescent in situ hybridization; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; IND, investigational new drug application; NED, no evidence of disease; PARP, poly (ADP-ribose) polymerase; PD, progressive disease; PgR, progesterone receptor; PR, partial response; PS, performance status; SD, stable disease; T-DM1, trastuzumab emtansine.

*Previously reported.⁸

†This patient's *BRAF* fusion has been previously reported.¹²

‡Details of this patient's case are discussed in another report.¹³

with *ERBB2* missense mutations, one with triple-negative breast cancer (reported previously⁸) and one with lung adenocarcinoma, have had prolonged disease control on human epidermal growth factor receptor 2 (HER2) antibody-based therapy. The patient with lung cancer had progression after four cycles of platinum doublet chemotherapy and has achieved a partial response after 12 months on a clinical trial of trastuzumab and pertuzumab. This is notable because there have been few reports of *ERBB2*-mutant tumors benefiting from HER2 antibody-based therapy in the absence of chemotherapy or small-molecule HER2 kinase inhibitors.^{14,15} Two patients with lung adenocarcinoma with *MET* exon 14 skipping splice site mutations have had prolonged stable disease (21 months and 6 months, ongoing) on crizotinib, in line with recent reports.^{16,17} A patient with *BRAF*V600E-mutated ameloblastoma experienced a partial response lasting 8 months to dabrafenib and trametinib, again consistent with a previous case report.¹⁸

Evidence for Tumor Evolution and Heterogeneity

Five patients had tumor sequencing performed more than once (in three patients, the multiple reports were reviewed at a single tumor board session). Sequencing of metastatic sites of disease progression on targeted therapy revealed new genetic alterations consistent with pre-existing tumor heterogeneity or acquired drug resistance. A patient with an inflammatory myofibroblastic tumor with an *RANBP2-ALK* rearrangement at diagnosis was initially treated with crizotinib with an excellent response, followed by ceritinib. Repeat sequencing at the time of progression on

ceritinib showed the same *RANBP2-ALK* fusion as well as an acquired *ALK* G1202R mutation, which confers resistance to both crizotinib and ceritinib.¹⁹ The board reviewed preclinical data on the G1202R mutation and identified activity of cabozantinib as well as newer investigational ALK inhibitors against G1202R or the analogous mutation in *ROS1*.^{20,21} The patient was treated with off-label cabozantinib, with stable disease lasting 5 months.

A patient with *EGFR* exon 21-mutated lung adenocarcinoma with an excellent response to erlotinib developed a new progressing lesion, which was biopsied and sequenced. Sequencing showed a *MET* exon 14 skipping splice site mutation that had not been present when the tumor was initially sequenced, but no *EGFR* mutation. The board noted that distinct tumor clones with *EGFR* and *MET* mutations could account for the mixed response to erlotinib, and the patient was treated with erlotinib plus crizotinib on the basis of tolerability of the combination in a phase I trial.²² His disease has been stable for 6 months, and treatment is ongoing.

A second patient who had lung cancer with an *EGFR* exon 19 deletion mutation had tumor sequencing after experiencing progression on many lines of targeted therapy including erlotinib, afatinib and cetuximab, and osimertinib. Sequencing showed the *EGFR* exon 19 deletion as well as amplification of *ERBB2*, which has been described as an acquired resistance mechanism in *EGFR*-mutated lung cancer treated with EGFR inhibitors.²³ The board recommended HER2-targeted therapy; unfortunately, the patient's clinical condition deteriorated, and she died without receiving another line of therapy.

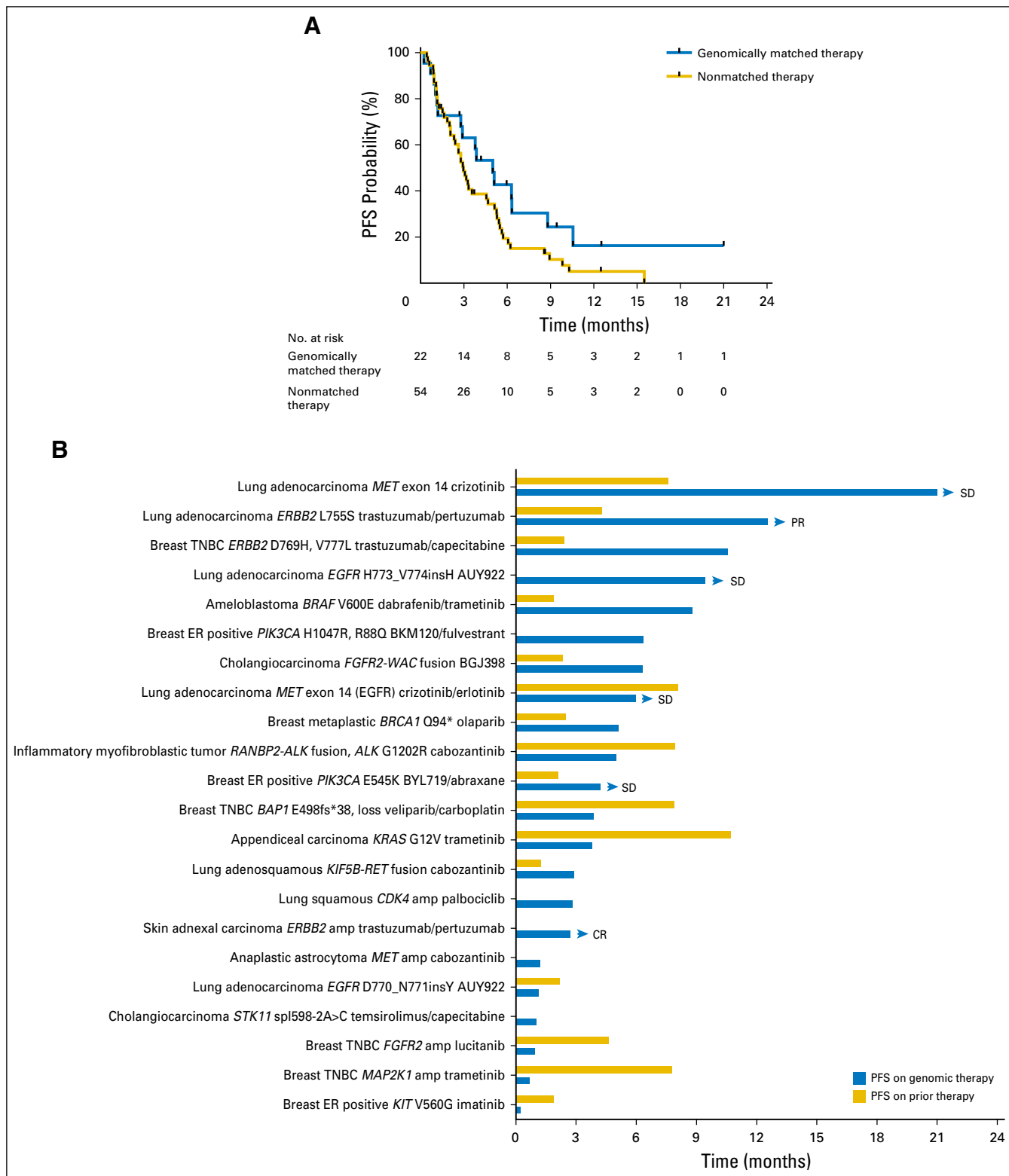


Fig 4. (A) Progression-free survival (PFS) of patients treated with genomically matched therapy (n = 22) or nonmatched therapy (n = 54). All patients with

Germline Evaluation Prompted by Tumor Sequencing

The board recommended further clinical or genetic evaluation for a possible germline cancer-predisposing variant for 46 patients. Many of the

patients with breast cancer had already had germline testing. The board examined mutant allele frequencies, if available, to determine the likelihood of the alterations being germline. However, because tumor sequencing platforms have not

follow-up who were treated with genomically matched therapy are included in the analysis, including one patient who was treated with off-label trametinib for a *KRAS* mutation when the board had recommended a clinical trial. (B) PFS and PFS on immediate prior therapy for individual patients treated with genomically matched therapies. Eight patients either had no prior systemic therapy for metastatic disease or insufficient documentation of prior therapy. Arrowheads indicate patients continuing on treatment. amp, amplification; CR, complete response; ER, estrogen receptor; PR, partial response; SD, stable disease; TNBC, triple-negative breast cancer.

been validated specifically for germline testing, the board recommended genetic counseling to consider dedicated germline analysis. Three patients had additional tumor testing for microsatellite instability, and all were microsatellite stable. Six patients had germline testing for *BRCAl/2*, *PTEN*, *TP53*, and other genes; all were germline nonmutated.

DISCUSSION

This report adds to the growing literature on precision oncology guided by a molecular tumor board. Our series is one of the largest to date to include patient outcomes. Although this was not a prospective clinical trial and treating oncologists were not bound by the board's recommendations, the molecular tumor board attempted to apply a consistent standard of principles when assessing each patient. Our criteria for evaluating individual mutations and levels of supporting evidence for actionability are similar to those applied in the NCI-MATCH trial.^{2,24} The board preferred direct rather than indirect drug-gene matches and rarely advocated multikinase inhibitors off-label when the target had not been extensively validated as predictive. We found a high frequency of actionable genomic alterations, similar to previous reports^{9,11,25,26}; however, lack of available clinical trials and a higher threshold for recommending off-label use of targeted therapies reduced the rate of therapeutic use in our patients.

A limitation of our study is that the board reviewed only those patients referred to it. Thirty-eight percent of our patients had genomic variants that could have made them eligible for one of the NCI-MATCH treatment arms, which is higher than the estimated match rate of 23% with the current NCI-MATCH arms open.²⁷ This likely reflects the case mix of patients seen at our cancer center and referred to our tumor board, which was perhaps enriched for variants the referring physician considered actionable.

Lack of locally available trials was a leading reason for lack of application of matched, targeted therapies, as noted by others.⁸⁻¹⁰ Immunotherapy also emerged as a compelling therapeutic alternative for many patients. Almost all of our patients were reviewed before the NCI-MATCH trial opened at our institution. NCI-MATCH and TAPUR offer access to genomically targeted therapies for a variety of targets that would be difficult for any single cancer center to have in its clinical trial portfolio. Such trials could partially solve the leading barrier to actionability noted here.

Despite these limitations, 15% of our patients were treated with matched targeted therapies on a clinical trial or with off-label drugs. Although the PFS of patients treated with genomically matched therapies compared favorably with that of patients receiving nonmatched therapies, our study was not designed to test the superiority of a genomically guided approach for all patients. The small sample size, retrospective nature of the analysis, and heterogeneous patient population subject to referral bias all limit the utility of such a comparison. The non-genomically treated patients had fewer actionable alterations than the genomically treated cohort and had a different distribution of tumor types. Nonetheless, half of the patients receiving genomically matched therapy had a PFS more than double their prior PFS, and several had prolonged duration of benefit. The patients who benefited most from matched therapy had alterations in genes such as *ERBB2*, *BRAF*, *EGFR*, and *MET*, for which there is currently patient-level response data from clinical trials, case series, and case reports. As with prospective trials of precision oncology,²⁸ outcomes of series such as ours will be impacted by the criteria used to match targeted therapies to genetic variants found in patients' tumors. We cannot rule out that our conservative approach toward actionability prevented us from observing greater clinical benefit, but we believe that more liberal off-label use of targeted agents is unlikely to produce better outcomes than we observed. Reasons for the limited benefit of single-agent targeted therapies have been reviewed elsewhere.²⁹

Even when off-label drug use was recommended for a highly actionable mutation, some patients experienced rapid disease progression that precluded them from starting or continuing such therapies. The optimal timing of tumor sequencing has yet to be determined, but the experience of these patients suggest that the review of genomic actionability should take place earlier in the disease course. However, we documented several patients in whom repeat tumor sequencing demonstrated new genomic findings consistent with either pre-existing heterogeneity or clonal evolution. Improvements in the use of NGS panels on cell-free circulating tumor DNA from plasma may allow sampling of tumor heterogeneity and enable serial monitoring of acquired resistance and clonal dynamics in the face of targeted therapy.^{8,30,31}

The board also reviewed patients for whom it disagreed with a prior interpretation and use of tumor profiling data. In one instance, a patient had discontinued an approved chemotherapy drug to

which she had been responding (docetaxel) because a tumor profiling biomarker (TUBB3 immunohistochemistry) predicted lack of benefit. A patient with HER2-positive breast cancer was treated ineffectively for several months with enzalutamide on the basis of the tumor staining positive for androgen receptor. The board instead recommended treating the patient with pertuzumab, an FDA-approved therapy, to which she responded. The circumstances of these patients show the value a molecular tumor board can add and highlight that standard-of-care therapies should still be considered as viable and often preferred options, because approved therapies for a given cancer type have high levels of evidence to support their use.

Our standard for recommending off-label use may be more stringent than that used at some other centers or by individual practicing oncologists. Whereas 73% of our patients had a variant for

which off-label drug use was suggested by the commercial sequencing provider and 55% had a variant that would have enabled use of an FDA-approved drug on the TAPUR trial, our board recommended off-label use in only 24% of patients. In the absence of more data or practice guidelines, patients and providers have some discretion about where to set the threshold. Large data-sharing efforts and publication of series such as this one will be essential to expand public knowledge about the clinical actionability of genetic variants and outcomes associated with precision oncology as currently practiced.³² We support ongoing trials like NCI-MATCH and TAPUR in the belief that, as much as possible, precision oncology should be carried out in the context of clinical trials so we can replace educated guesswork with evidence.

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APPENDIX

Methods

For uncommon variants in well-established cancer driver genes (eg, non-V600 *BRAF* mutations), the board considered factors including recurrence of that specific mutation in databases such as Catalogue of Somatic Mutations in Cancer (Zhan F, et al: *Blood* 108:2020-2028, 2006), sequencing data accessed at cBioPortal (Cerami E, et al: *Cancer Discov* 2:401-404, 2012), and in published studies; location in a known protein domain; evidence that the variant could be a germline single nucleotide polymorphism; and preclinical functional characterization—to show whether the variant was biologically activating and whether it demonstrated sensitivity or resistance to known drugs. The board generally did not recommend targeting amplifications reported as equivocal or mutations that were clearly subclonal relative to other mutations in the tumor. In some cases, reported variants of uncertain significance were evaluated for potential treatment implications.

Table A1. Patients Who Received Matched Targeted Therapies or for Whom the Board Recommended Off-Label Use of Targeted Therapies

Cancer Type	Alterations	Board Recommendation	Treatment and Outcome
Inflammatory myofibroblastic tumor	ALK G1202R, RANBP2-ALK fusion <i>PALB2</i> splice site 2748 +1G>T <i>SMAD4</i> loss	Cabozantinib off label or clinical trial	Cabozantinib; SD for 5 months, hospice
Breast, triple negative	BAP1 E498fs*38, loss EGFR R108K <i>TP53</i> A276G <i>PALB2</i> L1045F	PARP inhibitor trial or lapatinib/capecitabine off label	Olaparib/carboplatin trial: SD for 4 months
Ameloblastoma	BRAF V600E <i>NF1</i> N2676D <i>SMO</i> L412F	Dabrafenib/trametinib off label	Dabrafenib/trametinib; PR for 8 months, then PD after medication supply ran out; now back on therapy
Glioblastoma	BRAF G469R <i>NF1</i> S436*	Trametinib off label	Trametinib prescribed but never started as a result of intervening medical complications and worsening PS
Stomach	BRAF D594N <i>SMO</i> P352L	Trametinib or sorafenib off label	PD, PS decline, hospice
Lung adenocarcinoma	BRAF G469S <i>TP53</i> Y220C <i>LRB1B</i> Q3419* <i>SF3B1</i> V701F	Trametinib or sorafenib off label	Nivolumab with SD, then died
Lung adenocarcinoma	BRAF V600E <i>PDGFRB</i> V125Wfs*18 <i>TP53</i> R175H	Dabrafenib/trametinib off label	Immunotherapy, then chemotherapy with PR
Pancreas acinar cell carcinoma	SND1-BRAF fusion <i>MCL1</i> amplification <i>SF3B1</i> K700E subclonal	Trametinib or selumetinib off label	NED, not requiring therapy
Supraglottic larynx squamous carcinoma	BRCA1 Q905* <i>DNMT3A</i> A910V <i>CDKN2A</i> p16 H83Y/p14ARF A97V <i>TP53</i> P142fs*7 <i>APC</i> W685* <i>CREBBP</i> R1446L <i>EPHB1</i> R865W <i>RB1</i> V520fs*3	PARP inhibitor trial or olaparib off label (qualified recommendation given uncertainty of <i>BRCA1</i> germline status)	Chemotherapy, PD, hospice within 1 month
Poorly differentiated INI-1-deficient carcinoma	BRCA1 C61G <i>SMARCB1</i> loss <i>CHEK2</i> truncation intron 2	PARP inhibitor trial or olaparib off label (qualified recommendation given uncertainty of <i>BRCA1</i> germline status) or EZH2 inhibitor trial or single-patient IND for alisertib	Tazemetostat (EZH2 inhibitor) trial targeting <i>SMARCB1</i> loss; response assessment pending
Breast, metaplastic, ER positive, PgR negative, HER2 negative	BRCA1 Q94* <i>TP53</i> C238Y	PARP inhibitor trial or olaparib off label	Olaparib; PR at 2 months, then PD after 5 months
Glioblastoma	BRCA2 F1546fs*22 <i>NF1</i> loss <i>PIK3CA</i> R88Q <i>CDKN2A/B</i> loss <i>EPHB1</i> V322I <i>SETD2</i> rearrangement exon 3	PARP inhibitor trial or olaparib off label or platinum	Pursued alternative clinical trial, radiation, bevacizumab
Pancreas adenocarcinoma	BRCA2 S599fs*1, splice site 794-37_794-del37 <i>KRAS</i> G12V <i>CDKN2A</i> deletion p16INK4a exons 1-2 and p14ARF exon 2 <i>APC</i> G2070fs*1, P2018fs*26 <i>SMAD4</i> P198fs*4	PARP inhibitor trial or olaparib off label or platinum chemotherapy	Not eligible for PARP inhibitor trial; no further follow-up available
Lung squamous carcinoma	CDK4 amplification <i>CDKN2A/B</i> loss <i>KDR</i> amplification <i>KIT</i> amplification <i>PDGFRA</i> amplification <i>GLI1</i> amplification <i>MDM2</i> amplification <i>PRKCI</i> amplification (equivocal) <i>TP53</i> K164E <i>APC</i> S1362F <i>FRS2</i> amplification	CDK4/6 inhibitor trial only	Palbociclib trial; PD after 12 weeks

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Table A1. Patients Who Received Matched Targeted Therapies or for Whom the Board Recommended Off-Label Use of Targeted Therapies (Continued)

Cancer Type	Alterations	Board Recommendation	Treatment and Outcome
Lung adenocarcinoma	EGFR G719S, S768I	Afatinib (FDA indication)	Afatinib for 8 months; mixed response (PR of mass originally sequenced, PD contralateral mass)
Lung adenocarcinoma	EGFR H773_V774insH APC Q1067*	No recommendation at time of review; was receiving definitive chemoradiation	AUY922 (HSP90 inhibitor) trial upon recurrence; SD for 9 months, ongoing
Lung adenocarcinoma	EGFR D770_N771insY EGFR amplification equivocal CDK4 amplification MYC amplification GLI1 amplification NFKB1A amplification NKX2-1 amplification TP53 V197E	AUY922 (HSP90 inhibitor) trial	AUY922 trial; PD, off study after 1 month
Malignant peripheral nerve sheath tumor	EGFR duplication exons 18-26 ATRXK2174fs*7 CDKN2A/B loss CIC truncation exon 5 RPTOR amplification	Afatinib off label	Had already started temozolomide/pazopanib; died within 2 months
Biliary tract adenocarcinoma	EGFR amplification 19-fold TP53 R213Q BMP1A R417C GNA11 R38_E39 dup HIST1H2BD ex1 K13fs XPO1 T118S SLC12A7-TERT rearrangement	Cetuximab or panitumumab off label	Had neoadjuvant chemotherapy, resection, and more chemotherapy
Breast, triple negative*	ERBB2 D769H, V777L PIK3CA M1043V GNAS amplification (equivocal) AURKA amplification (equivocal) TP53 R273H ARFRP1 amplification (equivocal) EMSY amplification	Trastuzumab/lapatinib; trastuzumab/chemotherapy; lapatinib/capecitabine	Trastuzumab/capecitabine (after 6 weeks of trastuzumab alone); SD for 9 months
Breast, HER2 positive, ER positive	ERBB2 amplification (equivocal) IGF1R R595H TP53 R248Q MAP2K4 G111fs*22	Trastuzumab with endocrine therapy (FDA indication)	Trastuzumab with endocrine therapy; was and remains NED after radiation for brain metastatic recurrence
Breast, HER2 positive	ERBB2 amplification MTOR E2104K EGFR R108K (subclonal) CRKL amplification FGFR1 amplification GNAS amplification SRC amplification TOP1 amplification AURKA amplification TP53 R110L mutation ZNF217 amplification ZNF703 amplification	Trastuzumab/pertuzumab/docetaxel (FDA indication) (qualified recommendation for everolimus off label on the basis of MTOR variant)	Trastuzumab/pertuzumab for 3 months, PD, added docetaxel: near CR of nodes (now not measurable)
Lung adenocarcinoma	ERBB2 L755S ATM N2267I, 4901 +1G>T FGFR1 448+3G>A FGFR2 D334Y NOTCH1 G1015D	Various HER2-targeted therapies: trastuzumab ± chemotherapy, afatinib, T-DM1	Trastuzumab/pertuzumab on trial; PR at 12 months, continues on therapy
Skin adnexal carcinoma	ERBB2 FISH ratio 2.1 EGFR amplification (equivocal) PIK3CA E545K AURKA amplification ARFRP1 amplification (equivocal) FAT1 R806H GNAS amplification (equivocal) NFKB1A amplification (equivocal) TP53 S241F ZNF217 A671T, amplification	Various HER2-targeted therapies	Trastuzumab/pertuzumab trial; CR after 2 cycles
Lung adenocarcinoma	ERBB2 exon 20 insertion E770_A771insAYVM (equivalent to A775_G776insYVMA)	Afatinib off label (but approved for lung cancer)	Was benefitting from chemotherapy, then died

(Continued on following page)

Table A1. Patients Who Received Matched Targeted Therapies or for Whom the Board Recommended Off-Label Use of Targeted Therapies (Continued)

Cancer Type	Alterations	Board Recommendation	Treatment and Outcome
Lung adenocarcinoma (known <i>EGFR</i> mutated)	<i>ERBB2</i> amplification <i>EGFR</i> E746_A750del <i>FANCD2</i> 2716-4A>T splice site <i>TP53</i> V173L	Trastuzumab/pertuzumab/taxane or trastuzumab/pertuzumab or trastuzumab/lapatinib or T-DM1 or trastuzumab + <i>EGFR</i> kinase inhibitor off label	PS declined; died within several weeks of tumor board
Salivary duct	<i>ERBB2</i> S310F <i>FANCA</i> R1400C <i>FANCB</i> M1? <i>FANCM</i> Y1918C <i>MAP2K4</i> D263Cfs*4 <i>TSC2</i> N187H Microsatellite stable	Trastuzumab + pertuzumab or afatinib or trastuzumab + chemotherapy; off label or on trial	Trastuzumab/pertuzumab on trial; response assessment pending
Lacrimal gland	<i>ERBB2</i> amplification <i>IDH2</i> amplification 3.5-fold indeterminate <i>APC</i> K1593Sfs*57 (3%) K1878Rfs*4 (3%) <i>AR</i> Q58L (5%) <i>CDKN2A</i> W15X (2%) <i>GNAQ</i> T96S (3%) <i>POLE</i> 1924-4C>T (12%) <i>SUFU</i> P24Rfs*72 (3%) <i>TET2</i> K655Nfs*45 (3%) <i>TP53</i> L330Dfs*5 (32%) MSI high	Trastuzumab ± pertuzumab ± taxane off label	Awaiting assessment of current chemotherapy
Squamous cell carcinoma hypopharynx	<i>ERBB2</i> amplification <i>PTCH1</i> F109fs*27 <i>CCND1</i> amplification <i>CDKN2A/B</i> loss <i>IGF1R</i> amplification <i>MYCL1</i> amplification <i>TP53</i> E180* <i>FGF19</i> / 3/4 amplification <i>NOTCH1</i> E1595* <i>RAD51</i> truncation exon 10	Trastuzumab ± pertuzumab ± taxane off label or on trial; vismodegib on trial or off label (qualified on the basis of uncertainty about status of other <i>PTCH1</i> allele)	HER2 1+ by IHC; received chemotherapy
High-grade neuroendocrine carcinoma	<i>ERBB3</i> G284R <i>ATM</i> R3008C <i>CDKN2A/B</i> loss <i>APC</i> H929fs*26, T1556fs*3 FAM123BQ335* <i>MAP3K1</i> splice site 2369+1G>G	Afatinib or trastuzumab + lapatinib; off label	Immunotherapy trial for 2 cycles; died of PD
Rhabdomyosarcoma	<i>FGFR1</i> N577K <i>APC</i> R1858Q <i>NF1</i> H2123N <i>PIK3CA</i> G118D, T1025A <i>PTPN11</i> A5775	Pazopanib (FDA indication)	Pazopanib; on therapy 4 months, no restaging; died of PD
Breast, triple negative	<i>FGFR2</i> amplification <i>PTEN</i> D24G <i>TP53</i> R175H <i>LRP1B</i> duplication exons 68-72	FGFR inhibitor trial	Lucitanib (FGFR inhibitor) trial; PD after 1 cycle
Cholangiocarcinoma	<i>FGFR2-WAC</i> fusion <i>PTEN</i> loss <i>CDKN2A/B</i> loss	FGFR inhibitor trial	BGJ398 (FGFR inhibitor) trial; SD for 6 months
Duodenal adenocarcinoma	<i>JAK2</i> V617F <i>CCND3</i> amplification <i>CDK4</i> amplification <i>ERBB3</i> amplification <i>VEGFA</i> amplification <i>GLI1</i> amplification <i>MDM2</i> amplification <i>SMAD4</i> E538*	Ruxolitinib (qualified recommendation pending verification that mutation was present in tumor)	Mutation determined to be from contaminating blood cells (patient had polycythemia vera)
Breast, ER positive	<i>KIT</i> V560G <i>AKT1</i> amplification <i>EGFR</i> amplification <i>PTEN</i> loss exon 1 <i>RICTOR</i> amplification <i>TP53</i> splice site 920-2A>G <i>ESR1</i> D538G	Imatinib off label	Imatinib; worsening respiratory failure, discontinued therapy after 7 days, comfort care
Appendiceal mucinous carcinoma	<i>KRAS</i> G12V <i>GNAS</i> amplification <i>ATR</i> L610* <i>AURKA</i> amplification <i>CCND2</i> amplification <i>TP53</i> R175H	MEK inhibitor on trial only	Trametinib off label for 4 months with PD

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Table A1. Patients Who Received Matched Targeted Therapies or for Whom the Board Recommended Off-Label Use of Targeted Therapies (Continued)

Cancer Type	Alterations	Board Recommendation	Treatment and Outcome
Breast, triple negative*	MAP2K1 amplification <i>CCNE1</i> amplification <i>MCL1</i> amplification <i>MYC</i> amplification <i>TP53</i> N247K, R175H-subclonal, T253N <i>CREBBP TRAP1-CREBBP</i> fusion <i>SETD2</i> T2354A	MEK inhibitor trial or off label	Trametinib off label; early clinical response (skin nodules), then PD after several weeks
Lung adenocarcinoma	MET exon 14 splice MET amplification (equivocal) <i>CDKN2A/B</i> loss <i>MDM2</i> amplification	Crizotinib off label	Crizotinib off label; SD for 21 months, ongoing
Lung adenocarcinoma	MET amplification <i>JAK2</i> K607N <i>ATR</i> K829* <i>TP53</i> G266V <i>ARID1A</i> R391* <i>TOP2A</i> R736L	Crizotinib off label	Prescribed crizotinib, but never started as a result of medical and social circumstances
Anaplastic astrocytoma	MET amplification 8.9-fold <i>MET</i> R731Q <i>KIT</i> amplification 5-fold <i>IDH1</i> R132H <i>NF1</i> F2714Vfs*16 <i>TP53</i> R273C	Crizotinib or cabozantinib off label	Cabozantinib off label; clinical and radiographic response after 3 weeks, treatment stopped during episode of zoster, followed by rapid PD (on treatment 1 month)
Lung adenocarcinoma (known <i>EGFR</i> exon 21 mutation)	MET exon 14 splice (<i>EGFR</i> mutation not found in biopsy specimen) <i>AKT1</i> E40K <i>RBI</i> T774Pfs*36	Add crizotinib to erlotinib	Erlotinib/crizotinib; SD for 6 months, ongoing
Breast, ER positive	PIK3CA H1047R, R88Q <i>FGFR1</i> amplification <i>TP53</i> E285K <i>CDH1</i> D746fs*24 <i>RBI</i> splice <i>ZNF703</i> amp	Continue on BKM120 (PI3K inhibitor)/fulvestrant trial	BKM120/fulvestrant trial; SD for 6 months
Breast, ER positive, PR positive	PIK3CA E545K <i>CCND1</i> amplification <i>FGF19</i> amplification <i>FGF3</i> amplification <i>FGF4</i> amplification <i>PRSS8</i> amplification <i>TET2</i> Q943*, subclonal*	PI3K inhibitor trial	BYL719 (PI3K inhibitor)/protein-bound paclitaxel trial; on cycle 3 with tumor marker decline and SD
Colon	PTCH1 P681L <i>ATM</i> R189K <i>TP53</i> R248W <i>APC</i> E1295*, W1049* <i>FGF10</i> N159K	Vismodegib on trial or off label	PS worsened; hospice
Lung adenosquamous carcinoma	RET KIF5B-RET fusion <i>ERBB3</i> amplification <i>CDKN2A/B</i> loss <i>MDM2</i> amplification <i>CDK4</i> amplification	Cabozantinib off label or on trial	Cabozantinib clinical trial; PR after 2 months, then off study for debility; continued cabozantinib off label for 1 month, then leptomeningeal PD
Medullary kidney cancer	SMARCB1 Y47*	Alisertib single-patient IND	Received chemotherapy then nivolumab and experienced progression; died before alisertib could be given (IND obtained)
Lung adenocarcinoma	STK11 G276fs*11 <i>RICTOR</i> amplification <i>FGFR4</i> amplification <i>KRAS</i> amplification <i>CCNE1</i> amplification <i>TP53</i> G154V, M237_C238del <i>FGF10</i> amplification	Everolimus on trial or off label	Received chemotherapy then radiation
Cholangiocarcinoma	STK11 spl598-2A>C <i>KRAS</i> amp <i>BRCA2</i> K3326* <i>ATM</i> S1905* <i>CDKN2A/B</i> loss	Everolimus or temsirolimus on trial or off label	Temsirolimus added to capecitabine; PD after 1 month

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Table A1. Patients Who Received Matched Targeted Therapies or for Whom the Board Recommended Off-Label Use of Targeted Therapies (Continued)

Cancer Type	Alterations	Board Recommendation	Treatment and Outcome
Mucoepidermoid carcinoma	TSC2 V1711M	Everolimus (qualified recommendation; mutation not well characterized) on trial or off label	Received chemotherapy then pembrolizumab

NOTE. Alterations serving as the basis for board recommendation of off label use or as basis of matched therapy actually received are shown in bold. Other alterations in the tumor are also shown.

Abbreviations: CR, complete response; ER, estrogen receptor; FDA, US Food and Drug Administration; FGFR, fibroblast growth factor receptor; FISH, fluorescent in situ hybridization; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; IND, investigational new drug application; MSI, microsatellite instability; NED, no evidence of disease; PARP, poly (ADP-ribose) polymerase; PD, progressive disease; PgR, progesterone receptor; PR, partial response; PS, performance status; SD, stable disease; T-DM1, trastuzumab emtansine.

Table A2. Demographic Characteristics of the Genomically Matched and Non-Genomically Matched Cohorts of Patients Analyzed for Progression-Free Survival in Figure 4

Characteristic	No. of Patients (%)		P
	Genomic (n = 22)	Nongenomic (n = 54)	
Age, years, median (range)	58.5 (17-73)	56 (25-81)	1.00
No. of prior lines of therapy for metastatic disease, mean (range)	2.2 (0-8)	1.8 (0-10)	.43
Sex			
Male	7 (32)	34 (37)	.79
Female	15 (68)	20 (63)	
No. of alterations, mean (range)	5.5 (2-10)	4.4 (1-10)	.08
No. of actionable alterations, mean (range)	2.5 (0-5)	1.7 (0-6)	.04
Tumor type			
Breast triple negative	4 (18)	13 (24)	.76
Breast ER positive/HER2 negative	4 (18)	8 (15)	.74
Lung adenocarcinoma	5 (23)	4 (7)	.11
Lung other	2 (9)	3 (6)	.62
Cholangiocarcinoma	2 (9)	2 (4)	.57
SCC head and neck	0 (0)	6 (11)	.17
Salivary gland	0 (0)	4 (7)	.32
Brain tumor	1 (5)	3 (6)	1.00
Endometrial	0 (0)	3 (6)	.55

NOTE. Continuous data were compared by *t* test, and categorical data were compared by Fisher's exact test using GraphPad version 5.0 software.

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; SCC, squamous cell carcinoma.