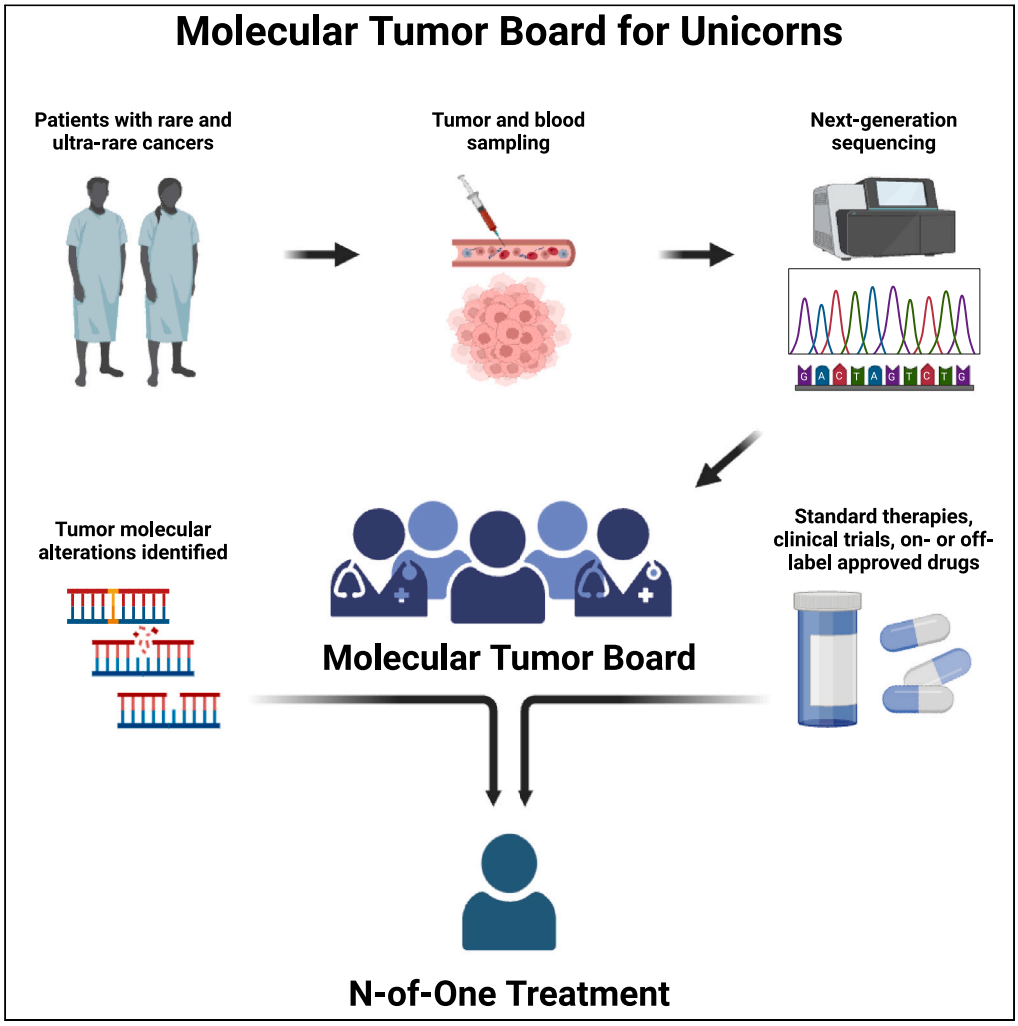
iScience

CellPress
OPEN ACCESS

Article

Molecular Tumor Board for Unicorns: Outcomes for rare and ultra-rare cancers using an N-of-One personalized treatment strategy



Bryan H. Louie, Shumei Kato, Jordan S. Lim, ..., Jason K. Sicklick, Scott M. Lippman, Razelle Kurzrock

b1louie@health.ucsd.edu (B.H.L.)
smkato@health.ucsd.edu (S.K.)
teoam@gmail.com (R.K.)

Highlights

Treatment of rare and ultra-rare cancers is an unmet need

We implemented the Molecular Tumor Board (MTB), a personalized approach to treatment

The MTB matched therapies to molecular alterations in rare/ultra-rare tumors

Patients with higher degrees of matching experienced improved clinical outcomes

Louie et al., iScience 27, 110465
August 16, 2024
https://doi.org/10.1016/j.isci.2024.110465

iScience

CellPress
OPEN ACCESS

Article

Molecular Tumor Board for Unicorns: Outcomes for rare and ultra-rare cancers using an N-of-One personalized treatment strategy

Bryan H. Louie,[1,9,11,*] Shumei Kato,[1,9,*] Jordan S. Lim,[1] Ki Hwan Kim,[2] Hyo Jeong Lim,[3] Ryosuke Okamura,[4] Suzanna Lee,[1] Lisa Kim,[1] Jason K. Sicklick,[5] Scott M. Lippman,[1,10] and Razelle Kurzrock[6,7,8,10,*]

SUMMARY

Treatment of rare/ultra-rare tumors is an unmet need due to a lack of standardized therapies and clinical trials. We developed the Molecular Tumor Board (MTB), a multidisciplinary team that integrates molecular profiling to generate personalized, N-of-One treatments for advanced cancers. This study evaluates 112 patients with rare/ultra-rare tumors who presented to the MTB and were evaluable for clinical therapeutic outcome. Overall, 46/112 patients (41%) received a treatment regimen with a high degree of matching between tumor molecular alterations and drugs given (reflected by a high Matching Score ($\geq$50%)). Patients with a high versus low Matching Score experienced significantly longer progression-free survival ($p = 0.005$) and overall survival ($p = 0.047$), and higher rates of clinical benefit (stable disease $\geq$6 months, partial response, or complete response) (54% vs. 32% $p = 0.027$). The MTB facilitated personalized N-of-One matching of drugs to tumor molecular alterations, which was associated with improved clinical outcomes in patients with rare/ultra-rare cancers.

INTRODUCTION

In the United States, approximately 20% of the cancer burden is due to rare cancers, which are defined by an incidence of <6 per 100,000 people.[1,2] Among cancers that fit this definition, there are 181 different cancer types. Of these rare tumors, 119 cancers are considered ultra-rare (defined by an incidence rate of <2 per 100,000),[3] which comprise approximately 3% of the total cancer burden.[1] Furthermore, rare/ultra-rare cancers occur predominantly in younger patients with 71% of tumors occurring in children and adolescents and <20% occurring in patients older than 65 years old.

Due to the low numbers of rare/ultra-rare tumor cases, the diagnosis and clinical management of these patients is difficult.[1,4,5] First, early detection of rare tumors is challenging because screening options are impractical due to the low incidence rates.[6] As a result, rare cancers are consistently diagnosed at later stages, with 59% of rare cancers diagnosed at locally advanced or metastatic stages versus only 45% of common cancers diagnosed at late stages.[1] In addition, treatment of rare cancers is particularly challenging, because most data are collected from case studies or small series, making it problematic to determine the efficacy of therapies for widespread practice.[5] As a result, patients with rare malignancies face a decreased 5-year survival rate of 47% in comparison to the 67% 5-year survival rate associated with common cancers.[7] This is due in part to the lack of treatment options and in part to the late-stage diagnosis of rare cancers.

The poor prognosis of many rare/ultra-rare cancers is also compounded by the lack of standard treatment options and the fact that patients are ineligible for many clinical trials. To address this, several initiatives such as the International Rare Cancers Initiative as well as the National Clinical Trial Network in the United States, have aimed at developing clinical trials for rare cancers.[8,9] Alternatively, modifications to traditional clinical trial design to maximize recruitment and minimize sample size have been suggested for the treatment of rare cancers.[10] One particular alternative to treating rare/ultra-rare tumors is the N-of-One strategy, a precision medicine approach that focuses on the individual patient and choosing the optimal treatment based on each patients' specific characteristics.[11]

[1]Center for Personalized Cancer Therapy and Division of Hematology and Oncology, Department of Medicine, UC San Diego Moores Cancer Center, La Jolla, CA, USA
[2]Division of Hematology and Medical Oncology, Department of Internal Medicine, Seoul National University Boramae Medical Center, Seoul, Republic of Korea
[3]Department of Internal Medicine, Veterans Health Service Medical Center, Seoul, Republic of Korea
[4]Department of Surgery, Kyoto University Hospital, Kyoto, Japan
[5]Division of Surgical Oncology, Department of Surgery, and Department of Pharmacology, UC San Diego Health Sciences, San Diego, CA, USA
[6]WIN Consortium for Precision Medicine, Paris, France
[7]Medical College of Wisconsin Cancer Center and Genomic Sciences and Precision Medicine Center, Milwaukee, WI, USA
[8]University of Nebraska, Omaha, NE, USA
[9]These authors contributed equally
[10]These authors contributed equally
[11]Lead contact
*Correspondence: b1louie@health.ucsd.edu (B.H.L.), smkato@health.ucsd.edu (S.K.), teoam@gmail.com (R.K.)
https://doi.org/10.1016/j.isci.2024.110465

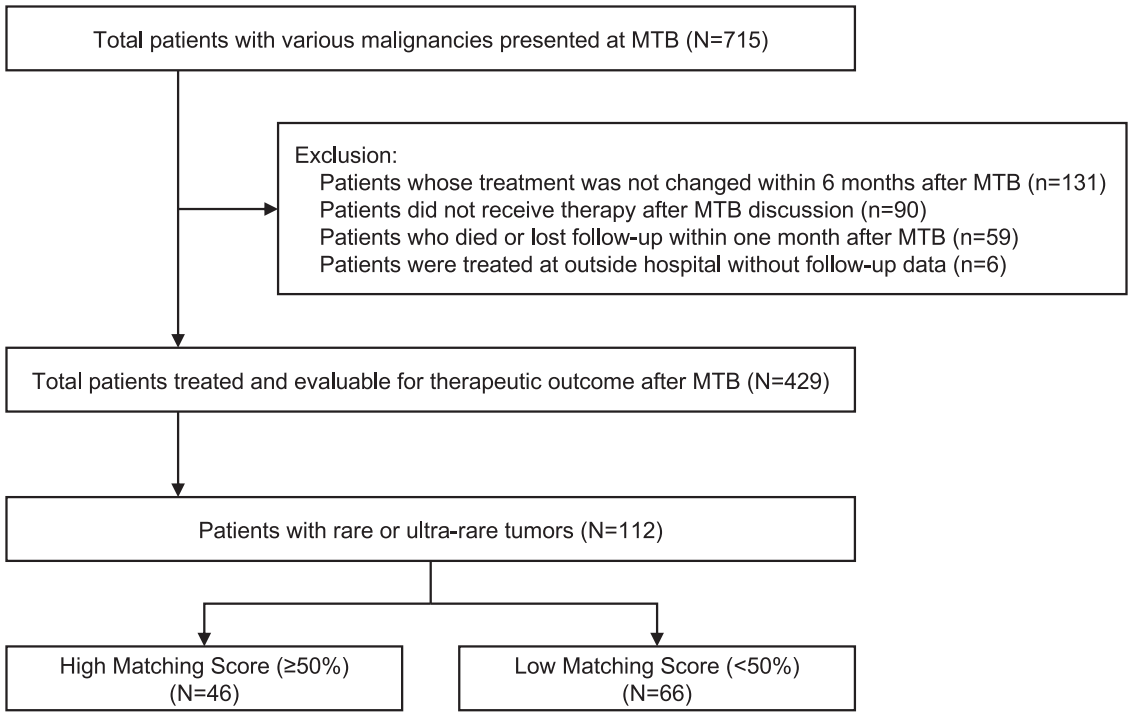


Figure 1. CONSORT diagram of patients who presented to the face-to-face Molecular Tumor Board (MTB)

Among 715 patients who presented to the MTB, there were 112 patients with rare or ultra-rare tumors that were given treatment and assessable for therapeutic outcome following MTB discussion.

We implemented an N-of-One precision medicine strategy in the form of The University of California San Diego (UCSD) Molecular Tumor Board (MTB). This multidisciplinary group evaluates molecular profiling data, as well as pathology, imaging, and clinical information in a comprehensive review of each cancer patient to develop N-of-One treatment plans.[12–15] The concept of the molecular tumor board has been a recent development in the cancer treatment paradigm with promising results in several studies.[13,14,16,17] However, to our knowledge, there has yet to be a substantial molecular tumor board experience specifically evaluating rare/ultra-rare tumors. Our study suggests that utilizing molecular profiling and matching therapies to tumor molecular alterations, as facilitated by the MTB, is associated with improved clinical outcomes in patients with rare/ultra-rare tumors.

RESULTS

Patient characteristics

In total, there were 112 patients with rare/ultra-rare cancers that were presented at the face-to-face MTB between December 2012 and September 2018 (Figure 1; Table 1). Within this cohort, the median age was 60 years (range: 3–92). Sixty-one patients (54%) were women, and 51 patients (46%) were men. All patients had advanced/metastatic disease. Thirty-six patients (32%) had been treated with ≥3 prior lines of therapy, and 76 patients (68%) had been treated with <3 prior lines of therapy, of which 33 were on first line therapy after MTB presentation. Of the rare/ultra-rare cancers, the most common diagnosis was biliary cancer (23% [26/112]), followed by sarcoma (20% [22/112]), other GI malignancies (including appendiceal and duodenal cancer) (11% [12/112]), rare gynecological cancers (10% [11/112]), and CNS malignancies (9% [10/112]) (Table 1).

Molecular profiling of rare/ultra-rare tumors revealed a complex landscape of molecular alterations

The MTB evaluated all molecular profiling reports performed by clinical-grade laboratories for each patient. Tissue next-generation sequencing (NGS) was performed in 106 patients at four different laboratories and blood-derived cell-free DNA (cfDNA) analysis was performed in 40 patients at two laboratories (Table S1).

Analysis of tissue NGS (N = 106) across the cohort of rare/ultra-rare cancers revealed that *TP53* was the most altered gene (37% [39/106]), followed by *CDKN2A/B* (18% [19/106]), *KRAS* (14% [15/106]), *PIK3CA* (14% [15/106]), and *APC* (9% [10/106]) (Figure 2A). Alterations detected by tissue NGS included mutations, rearrangements, deletions, amplifications, insertions, and multiple aberrations of genes.

Among rare/ultra-rare cancers with blood-derived cfDNA profiling (N = 40), the most altered genes were *TP53* (33% [13/40]) followed by *PIK3CA* (18% [7/40]), *ERBB2* (13% [5/40]), *APC* (10% [4/40]), and *RAF1* (10% [4/40]) (Figure 2B). Alterations detected by cfDNA profiling included mutations, amplifications, and multiple aberrations of genes.

Table 1. Baseline demographics of patients with rare/ultra-rare tumors presented at the Molecular Tumor Board (MTB) and assessable for therapeutic outcome (*N* = 112)

Total patients with rare/ultra-rare cancers (*N* = 112)	
Period	December 2012–September 2018
Median age at MTB (years) (range)	60 (3–92)
Sex, N (%)	Female, 61 (54%); Male, 51 (46%)
Diagnosis	N, patients (%)
Biliary cancer	26 (23%)
Sarcoma	22 (20%)
Other GI malignancy	12 (11%)
Appendiceal cancer	11
Duodenal cancer	1
Gynecological cancer	11 (10%)
Uterine cancer[a]	5
Cervical cancer[a]	2
Ovarian cancer[a]	2
Fallopian tube carcinoma	1
Vulvar squamous cell carcinoma	1
CNS malignancy	10 (9%)
Medullary thyroid carcinoma	1 (1%)
Other malignancies[a]	30 (26%)
Cancer of unknown primary	5
Anal squamous cell carcinoma	3
Metastatic cutaneous squamous cell carcinoma	3
Gastroesophageal adenocarcinoma	2
Renal cell carcinoma[a]	2
Renal collecting duct adenocarcinoma	1
Metastatic cutaneous basal cell carcinoma	1
Hepatocellular carcinoma	1
Pleuropulmonary blastoma	1
Parotid gland carcinoma	1
Penile squamous cell carcinoma	1
Peritoneal carcinoma	1
Rectal neuroendocrine carcinoma	1
Desmoid-type fibromatosis	1
Undifferentiated pleomorphic sarcoma	1
Submandibular gland adenocarcinoma	1
Thymoma	1
Urachal adenocarcinoma	1
Adrenal cortical carcinoma	1
Sclerosing epithelioid fibrosarcoma	1

Abbreviations: CNS, central nervous system; GI, gastrointestinal; MTB, Molecular Tumor Board.
[a]For these renal and gynecologic tumors, the histologic subtype was rare/ultra-rare.

Importantly, no two patients had an identical molecular profile.

High Matching Score was associated with longer progression-free survival and overall survival

Of the 112 patients with rare/ultra-rare cancers that were evaluable for treatment outcome, 46 (41%) patients were assigned a high Matching Score (≥50%), indicating a better match between the treatment regimen given and the tumor molecular alterations present. The remaining 66 (59%) patients were assigned a low Matching Score (<50%).

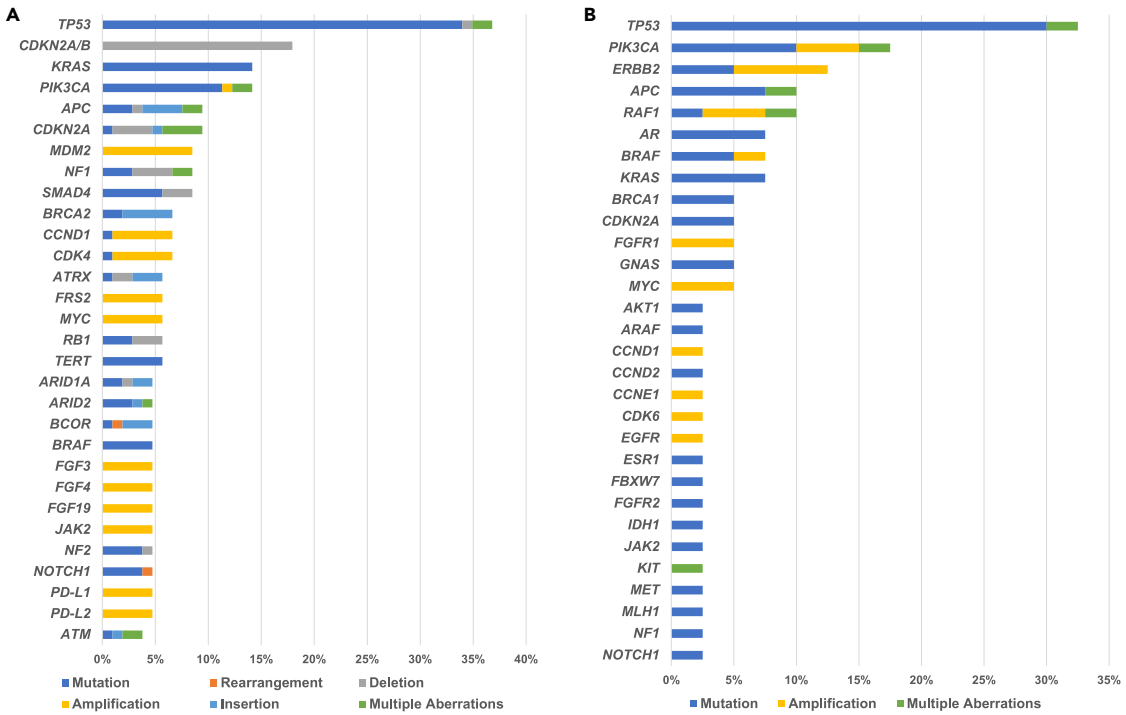


Figure 2. Frequency of pathogenic genomic alterations from tissue NGS and cfDNA of rare/ultra-rare tumors

(A) Alterations from tissue next-generation sequencing (NGS) (N = 106).

(B) Alterations from blood-derived cell-free DNA (cfDNA) sequencing (N = 40). Colored bars show the percent of patients with the specific type of molecular alteration for each gene.

Patients with a high Matching Score (≥50%) exhibited significantly longer progression-free survival (PFS) (hazard ratio [HR], 0.54; 95% confidence of interval (CI), 0.35–0.83; p = 0.005; univariate analysis) and overall survival (OS) (HR, 0.59; 95% CI, 0.35–0.99; p = 0.047; univariate analysis) in comparison to patients with a low Matching Score (<50%) (Figure 3A and 3B). After multivariate analysis, the association between high Matching Score and improved PFS remained significant (HR, 0.55; 95% CI, 0.36–0.85; p = 0.007) and the association between high Matching Score and improved OS maintained a trend toward statistical significance (HR, 0.60; 95% CI, 0.36–1.02; p = 0.058); no other factors had a statistically significant impact on PFS or OS with multivariate analysis (Table 2).

High Matching Score was associated with increased clinical benefit (SD ≥ 6 months/PR/CR)

Similar to previous studies, we used response evaluation criteria in solid tumors (RECIST) criteria/physician assessment to define patients who experienced clinical benefit from treatment.[15,18] Patients who exhibited stable disease (SD) ≥ 6 months, partial response (PR), or complete response (CR) per RECIST criteria were assigned to the clinical benefit (SD ≥ 6 months/PR/CR) category. The remaining patients who had progressive disease (PD), or stable disease <6 months, were characterized as not having clinical benefit from treatment. Subsequently, patients with high Matching Score (≥50%) experienced a significantly higher rate of clinical benefit (54% [23/43]) than patients with low Matching Score (<50%) (32% [20/63]) (odds ratio [OR], 0.40; 95% CI, 0.18–0.90; p = 0.027; univariate analysis) (Figure 4). With multivariate analysis, the relationship between high Matching Score and clinical benefit remained statistically significant (odds ratio [OR], 0.41; 95% CI, 0.19–0.93, p = 0.033) (Table 3).

DISCUSSION

Rare and ultra-rare tumors represent a challenge in cancer treatment due to their complex molecular profiles and lack of proven standardized therapies. Several precision medicine strategies that employ molecular profiling to identify actionable tumor alterations have shown benefit across a variety of cancers.[12,15,19–23] Some studies suggest that this approach may be a better strategy for treating rare malignancies.[24,25] In this present study, we evaluated the experience of the Molecular Tumor Board (MTB) at the University of California San Diego, Center for Personalized Cancer Therapy and demonstrate the utility of this N-of-One precision medicine strategy in treating rare/ultra-rare tumors.

Overall, 112 patients with multiple types of rare (<6 per 100,000 people) and ultra-rare (<2 per 100,000 people) cancers were presented to the MTB and evaluable for therapeutic outcome (Table 1).[1–3] It should be noted that most of the patients that were considered inevaluable in this study (Figure 1) were given that denotation because they did not receive a change of therapy at all after MTB or they did not receive a change of therapy within six months. The reason for this was that our physicians were strongly encouraged to present patients at MTB while the patients were doing well on their current therapy, so that back up plans could be created with a long runway before progression. This is

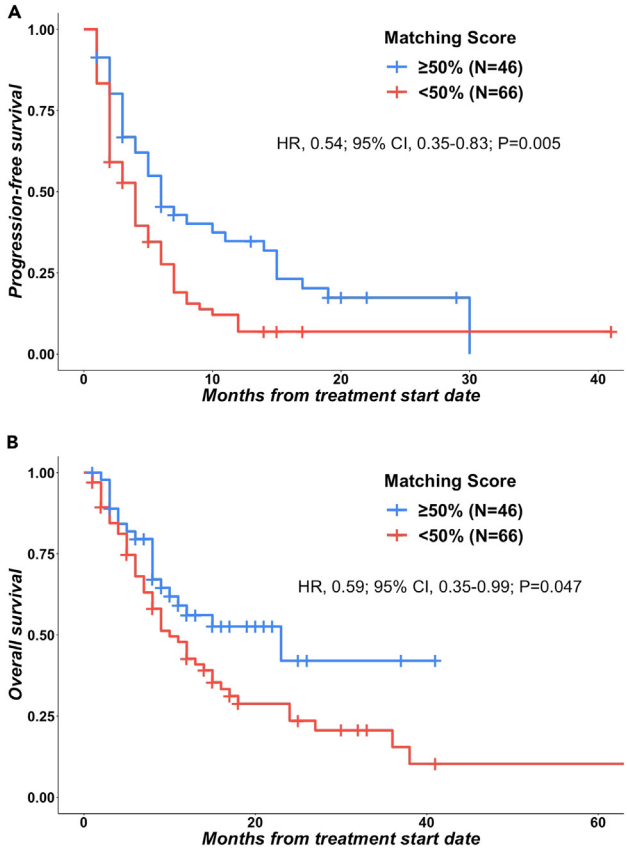


Figure 3. Progression-free and overall-survival in patients with high (≥50%) versus low (<50%) Matching Score (*N* = 112)

(A) Progression-free survival (PFS) was significantly longer in patients with high (≥50%) Matching Score versus low (<50%) Matching Score (hazard ratio [HR], 0.54; 95% CI, 0.35–0.83; p = 0.005, univariate Cox regression) (N = 112). Median PFS: high (≥50%) Matching Score, 5.93 months (95% CI: 3.57–8.30); low (<50%) Matching Score, 3.90 months (95% CI: 2.77–5.03).

(B) Overall survival (OS) was significantly longer in patients with high (≥50%) Matching Score versus low (<50%) Matching Score (hazard ratio [HR], 0.59; 95% CI, 0.35–0.99; p = 0.047, univariate Cox regression). Median OS: high (≥50%) Matching Score 22.97 months (95% CI: 5.06–40.87), low (<50%) Matching Score, 9.63 months (95% CI: 6.28–12.99).

because once patients progress, they often have little time for backup management plan preparation. Our model is quite different from the situation with many molecular tumor boards, where patients are presented at time of progression.

Subsequently, the MTB utilized multiple clinical-grade molecular tests including tissue NGS, blood-derived cfDNA, mRNA, and immunohistochemistry to characterize targetable tumor alterations. Molecular profiling was performed in all patients, which revealed a diverse array of pathogenic alterations, with the most common mutations consistent with those seen in similar studies of rare tumors (Figure 2).[24–26]

After MTB discussion, 46 patients received a drug regimen that was highly matched to tumor alterations (Matching Score ≥50%) while 66 patients received treatment with a lower degree of matching (Matching Score 0–49%). Subsequently, patients with high versus low degrees of tumor-to-therapy matching experienced significantly longer progression-free survival (p = 0.005) and overall survival (p = 0.047), and higher rates of clinical benefit (SD ≥ 6 months/PR/CR) (p = 0.027). Notably, there were no other factors in our analysis that were significantly associated with outcome (Table 2; Table 3). Thus, the Matching Score herein was predictive of outcome in our 112 evaluable patients with rare/ultra-rare tumors, which has been previously demonstrated in our other studies in 83 and 76 evaluable patients, respectively in our prior publications.[19,27]

Of note, to properly customize therapy to individual tumors, some combinations that were given had not been previously evaluated in phase I studies. It is important to balance the risk of such combinations with the benefit. Therefore, we have previously shown in our prior publications that, by using toxicity data gleaned from thousands of patients treated with specific drug combinations in the literature as well as by initial dose reductions for *de novo* combinations, *de novo* combinations can be both safe and effective.[19,27]

In summary, the findings of our current study indicate that matching therapies to tumor molecular alterations, may be a viable precision medicine approach to treating rare and ultra-rare cancers. Using multiple molecular profiling modalities, the MTB evaluated patients with various types of rare/ultra-rare malignancies and developed N-of-One treatments. The N-of-One treatment strategy may be especially important because no two patients had an identical molecular profile. Patients who received treatment with high versus low degrees of matching between tumor alterations and therapy experienced improvement in all outcome parameters. Importantly, prospective trials such as the

Table 2. Association between patient and treatment characteristics, PFS and OS (*N* = 112)

Characteristics		PFS					OS				
Univariate					Multivariate[a]		Univariate			Multivariate[a]	
N			Median (months) (95% CI)	HR (95% CI)	*p* value	HR (95% CI)	*p* value	Median (months) (95% CI)	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age, years	≥60	57	4.43 (3.57–5.30	1.05 (0.70–1.58)	0.824	–	–	11.10 (6.77–15.44)	1.12 (0.69–1.81)	0.655	–	–
	<60	55	4.03 (2.41–5.65)	–	–	–	–	12.33 (6.44–18.23)	–	–	–	–
Sex	Male	51	3.13 (1.58–4.69)	1.13 (0.75–1.71)	0.555	–	–	14.70 (10.73–18.67)	0.91 (0.56–1.47)	0.694	–	–
	Female	61	4.53 (2.87–6.20)	–	–	–	–	9.63 (6.78–12.49)	–	–	–	–
Biliary or GI malignancy	Yes	38	4.80 (2.49–7.11)	0.87 (0.57–1.34)	0.534	–	–	12.03 (6.39–17.68)	0.93 (0.55–1.56)	0.778	–	–
	No	74	4.03 (3.10–4.97)	–	–	–	–	11.97 (7.31–16.62)	–	–	–	–
Matching Score (%)	≥50%	46	5.93 (3.57–8.30)	0.54 (0.35–0.83)	0.005	0.55 (0.36–0.85)	0.007	22.97 (5.06–40.87)	0.59 (0.35–0.99)	0.047	0.60 (0.36–1.02)	0.058
	<50%	66	3.90 (2.77–5.03)	–	–	–	–	9.63 (6.28–12.99)	–	–	–	–
Number of prior lines of therapy	≥3	36	4.40 (1.84–6.96)	1.02 (0.66–1.56)	0.944	–	–	9.63 (7.07–12.19)	1.50 (0.91–2.46)	0.111	1.45 (0.88–2.38)	0.147
	<3	76	4.20 (3.08–5.32)	–	–	–	–	13.13 (6.91–19.36)	–	–	–	–
Number of drugs following MTB	>1	66	4.87 (2.87–6.86)	0.72 (0.47–1.08)	0.111	0.75 (0.50–1.14)	0.181	12.03 (6.53–17.54)	0.84 (0.52–1.35)	0.465	–	–
	1	46	3.13 (1.45–4.82)	–	–	–	–	11.10 (5.66–16.54)	–	–	–	–
Immunotherapy	Yes	25	5.03 (0.87–9.20)	0.84 (0.51–1.38)	0.488	–	–	15.33 (6.46–24.21)	1.02 (0.57–1.86)	0.938	–	–
	No	87	4.20 (3.37–5.03)	–	–	–	–	11.97 (8.67–15.27)	–	–	–	–

Abbreviations: CI, confidence interval; GI, gastrointestinal; HR, hazard ratio; MTB, Molecular Tumor Board; OS, overall survival; PFS, progression-free survival.

[a]Covariates with *p* value < 0.2 by univariate analysis were included in multivariate analysis.

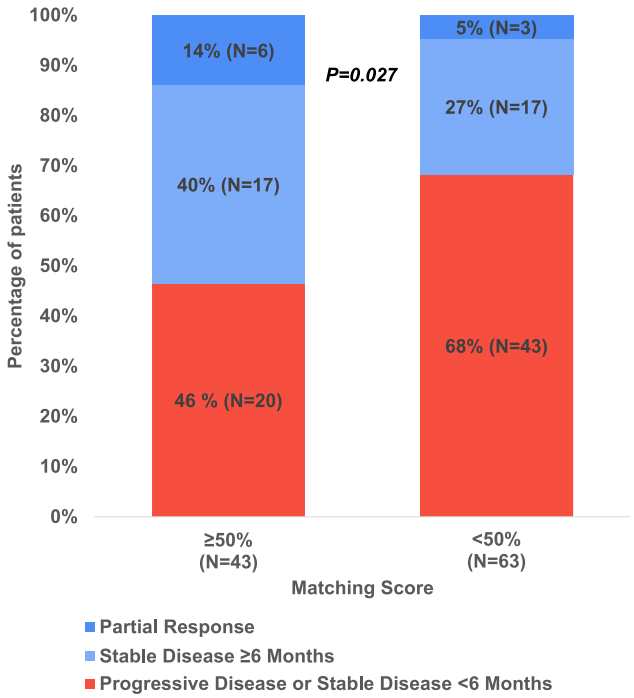


Figure 4. Clinical benefit rate (SD ≥ 6 months/PR/CR) based on Matching Score (*N* = 106*)

Clinical benefit rate (SD ≥ 6 months/PR/CR) was significantly higher among patients who received therapy with high (≥50%) Matching Score (23/43 [54%]) when compared to patients with low (<50%) Matching Score (20/63 [32%]) (p = 0.027, univariate analysis). *Six of 112 patients were not evaluable for response since these patients had ongoing SD that was less than 6 months at the time of data cutoff. Abbreviations: CR, complete response; PR, partial response; SD, stable disease.

Target Rare Cancer Knowledge (TRACK) trial (NCT04504604) and the DETERMINE trial in the UK are currently ongoing to further explore the use of molecular profiling and treatment matching strategies for rare and ultra-rare cancers.[28,29] In conclusion, our study suggests that using multi-omic profiling to identify and target actionable molecular alterations in rare and ultra-rare cancers may be a valuable treatment option in these historically difficult-to-treat tumors. Future prospective trials as well as more precise matching algorithms built with machine learning are warranted to further evaluate this approach.

Limitations of the study

There were several limitations to this study. First, this was not a randomized controlled clinical trial but rather a retrospective review of real-world data from the MTB. As such, we are not able to control for all confounding variables. Second, the rare/ultra-rare cancer types in this study were limited to those that were presented to the MTB, and therefore selection bias may be present. Furthermore, due to the presence of different cancer types in this study, we are unable to apply our findings to individual cancer histologies. However, this might also suggest the possibility of generalizing the outcomes of our study to rare and ultra-rare tumors, rather than a single cancer type. Though it still may be difficult to apply a one-size-fits-all approach due to tumor heterogeneity and differences in histological types and treatment outcomes. Third, another study limitation is that some actionable alterations were not matchable because the drugs to be used may have been contraindicated in individual patients due to co-morbidities or the drugs were not available for use (generally because insurance and our medication acquisition process could not acquire all off-label drugs); finally, some patients may have needed drugs that were available only through a secondary clinical trial and the patient did not meet eligibility criteria. Fourth, we used Cox regression analysis to determine correlations. Although this statistical method is commonly utilized for this purpose, it has limitations: its linearity formula cannot capture non-linear connections; and it assumes that the influence of the patient's variables is constant throughout time, limiting the approach to producing proportionate patient prediction at all follow-up time points. Finally, our prior study in the pan-cancer setting has shown a linear relationship between Matching Score and outcome.[27] However, in the current paper, focused on rare/ultra-rare cancers, the small number of patients in sub-cohorts precludes robust statistical analysis of this issue, which warrants investigation in future larger studies.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

- KEY RESOURCES TABLE
- RESOURCE AVAILABILITY
  - Lead contact

Table 3. Association between patient and treatment characteristics and clinical benefit rate (SD ≥ 6 months/PR/CR) (*N* = 106)

		Clinical benefit rate (SD ≥ 6 months/PR/CR)					
				Univariate		Multivariate[b]	
Characteristics		N[a]	SD ≥ 6 months/PR/CR (N, %)	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Age, years	≥60	52	21 (40%)	1.02 (0.47–2.20)	0.970	–	–
	<60	54	22 (41%)	–	–	–	–
Sex	Male	49	19 (39%)	1.15 (0.53–2.50)	0.728	–	–
	Female	57	24 (42%)	–	–	–	–
Biliary or GI malignancy	Yes	36	16 (44%)	0.79 (0.35–1.77)	0.560	–	–
	No	70	27 (39%)	–	–	–	–
Matching Score (%)	≥50%	43	23 (54%)	0.40 (0.18–0.90)	0.027	0.41 (0.19–0.93)	0.033
	<50%	63	20 (32%)	–	–	–	–
Number of prior lines of therapy	≥3	34	15 (44%)	0.81 (0.35–1.84)	0.609	–	–
	<3	72	28 (39%)	–	–	–	–
Number of drugs following MTB	>1	62	29 (47%)	0.53 (0.24–1.19)	0.124	0.55 (0.24–1.26)	0.157
	1	44	14 (32%)	–	–	–	–
Immunotherapy	Yes	24	11 (46%)	0.76 (0.30–1.89)	0.551	–	–
	No	82	32 (39%)	–	–	–	–

Abbreviations: CI, confidence interval; CR, complete response; GI, gastrointestinal; MTB, Molecular Tumor Board; OR, odds ratio; PR, partial response; SD, stable disease.

[a]Six of 112 patients were not evaluable for response since these patients had ongoing SD that was less than 6 months at the time of data cutoff; hence it was too early for evaluation of this parameter.

[b]Covariates with *p* value < 0.2 by univariate analysis were included in multivariate analysis.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.isci.2024.110465.

ACKNOWLEDGMENTS

This work was supported in part by the Joan and Irwin Jacobs Fund and by National Cancer Institute at the National Institutes of Health (grant no. NIH P30 CA023100 [R.K.]). R.K. is also funded in part by 5U01CA180888-08 and 5UG1CA233198-05. Graphical abstract created at BioRender.com.

AUTHOR CONTRIBUTIONS

R.K. and S.K. designed and directed the study. B.H.L., S.K., and R.K. drafted the manuscript. B.H.L. and S.K. analyzed and interpreted the data. J.S.L., K.H.K., H.J.L., R.O., S.L., and L.K. collected and compiled the data. S.K., R.O., S.L., J.K.S., S.M.L, and R.K. were involved in the Molecular Tumor Board. All authors have read and approved the manuscript.

DECLARATION OF INTERESTS

R.K. has received research funding from Boehringer Ingelheim, Debiopharm, Foundation Medicine, Genentech, Grifols, Guardant, Incyte, Konica Minolta, MedImmune, Merck Serono, Omniseq, Pfizer, Sequenom, Takeda, and TopAlliance and from the NCI; as well as consultant and/or speaker fees and/or advisory board/consultant for Actuate Therapeutics, AstraZeneca, Bicara Therapeutics, Inc., Biological Dynamics, Caris, Datar Cancer Genetics, Daiichi, EISAI, EOM Pharmaceuticals, Iylon, LabCorp, Merck, NeoGenomics, Neomed, Pfizer, Prosperdtx, Regeneron, Roche, TD2/Volastra, Turning Point Therapeutics, X-Biotech; has an equity interest in CureMatch Inc. and IDbyDNA; serves on the Board of CureMatch and CureMetrix, and is a co-founder of CureMatch. J.K.S. receives consultant fees from Deciphera, Aadi, and Grand

Rounds; serves as a consultant for CureMatch, received speakers fees from Deciphera, La-Hoffman Roche, Foundation Medicine, Merck, QED, and Daiichi Sankyo; and owns stock in Personalis. J.S.L is a shareholder of Guardant Health.

Received: June 21, 2023
Revised: May 6, 2024
Accepted: July 2, 2024
Published: July 5, 2024

REFERENCES

1. DeSantis, C.E., Kramer, J.L., and Jemal, A. (2017). The burden of rare cancers in the United States. CA. Cancer J. Clin. *67*, 261–272. https://doi.org/10.3322/caac.21400.
2. Munoz, J., and Kurzrock, R. (2012). Targeted therapy in rare cancers–adopting the orphans. Nat. Rev. Clin. Oncol. *9*, 631–642. https://doi.org/10.1038/nrclinonc.2012.160.
3. Stacchiotti, S., Frezza, A.M., Blay, J.-Y., Baldini, E.H., Bonvalot, S., Bovée, J.V.M.G., Callegaro, D., Casali, P.G., Chiang, R.C., Demetri, G.D., et al. (2021). Ultra-Rare Sarcomas: A Consensus Paper From the Connective Tissue Oncology Society Community of Experts on the Incidence Threshold and the List of Entities. Cancer *127*, 2934–2942. https://doi.org/10.1002/cncr.33618.
4. Blay, J.-Y., Coindre, J.-M., Ducimetière, F., and Ray-Coquard, I. (2016). The value of research collaborations and consortia in rare cancers. Lancet Oncol. *17*, e62–e69. https://doi.org/10.1016/S1470-2045(15)00388-5.
5. Komatsubara, K.M., and Carvajal, R.D. (2016). The promise and challenges of rare cancer research. Lancet Oncol. *17*, 136–138. https://doi.org/10.1016/S1470-2045(15)00485-4.
6. Gates, T.J. (2014). Screening for Cancer: Concepts and Controversies. AFP *90*, 625–631.
7. Gatta, G., Ciccolallo, L., Kunkler, I., Capocaccia, R., Berrino, F., Coleman, M.P., De Angelis, R., Faivre, J., Lutz, J.M., Martinez, C., et al. (2006). Survival from rare cancer in adults: a population-based study. Lancet Oncol. *7*, 132–140. https://doi.org/10.1016/S1470-2045(05)70471-X.
8. Keat, N., Law, K., Seymour, M., Welch, J., Trimble, T., Lascombe, D., and Negrouk, A. (2013). International rare cancers initiative. Lancet Oncol. *14*, 109–110. https://doi.org/10.1016/S1470-2045(12)70570-3.
9. Schott, A.F., Welch, J.J., Verschraegen, C.F., and Kurzrock, R. (2015). The National Clinical Trials Network: Conducting Successful Clinical Trials of New Therapies for Rare Cancers. Semin. Oncol. *42*, 731–739. https://doi.org/10.1053/j.seminoncol.2015.07.010.
10. Billingham, L., Malottki, K., and Steven, N. (2016). Research methods to change clinical practice for patients with rare cancers. Lancet Oncol. *17*, e70–e80. https://doi.org/10.1016/S1470-2045(15)00396-4.
11. Lillie, E.O., Patay, B., Diamant, J., Issell, B., Topol, E.J., and Schork, N.J. (2011). The n-of-1 clinical trial: the ultimate strategy for individualizing medicine? Per. Med. *8*, 161–173. https://doi.org/10.2217/pme.11.7.
12. Parker, B.A., Schwaederlé, M., Scur, M.D., Boles, S.G., Helsten, T., Subramanian, R., Schwab, R.B., and Kurzrock, R. (2015). Breast Cancer Experience of the Molecular Tumor Board at the University of California, San Diego Moores Cancer Center. JOP *11*, 442–449. https://doi.org/10.1200/JOP.2015.004127.
13. Schwaederle, M., Parker, B.A., Schwab, R.B., Fanta, P.T., Boles, S.G., Daniels, G.A., Bazhenova, L.A., Subramanian, R., Coutinho, A.C., Ojeda-Fournier, H., et al. (2014). Molecular Tumor Board: The University of California San Diego Moores Cancer Center Experience. Oncol. *19*, 631–636. https://doi.org/10.1634/theoncologist.2013-0405.
14. Patel, M., Kato, S.M., and Kurzrock, R. (2018). Molecular Tumor Boards: Realizing Precision Oncology Therapy. Clin. Pharmacol. Ther. *103*, 206–209. https://doi.org/10.1002/cpt.920.
15. Kato, S., Kim, K.H., Lim, H.J., Boichard, A., Nikanjam, M., Weihe, E., Kuo, D.J., Eskander, R.N., Goodman, A., Galanina, N., et al. (2020). Real-world data from a molecular tumor board demonstrates improved outcomes with a precision N-of-One strategy. Nat. Commun. *11*, 4965. https://doi.org/10.1038/s41467-020-18613-3.
16. Larson, K.L., Huang, B., Weiss, H.L., Hull, P., Westgate, P.M., Miller, R.W., Arnold, S.M., and Kolesar, J.M. (2021). Clinical Outcomes of Molecular Tumor Boards: A Systematic Review. JCO Precis. Oncol. *5*, 1122–1132. https://doi.org/10.1200/PO.20.00495.
17. Luchini, C., Lawlor, R.T., Milella, M., and Scarpa, A. (2020). Molecular Tumor Boards in Clinical Practice. Trends Cancer *6*, 738–744. https://doi.org/10.1016/j.trecan.2020.05.008.
18. Eisenhauer, E.A., Therasse, P., Bogaerts, J., Schwartz, L.H., Sargent, D., Ford, R., Dancey, J., Arbuck, S., Gwyther, S., Mooney, M., et al. (2009). New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur. J. Cancer *45*, 228–247. https://doi.org/10.1016/j.ejca.2008.10.026.
19. Sicklick, J.K., Kato, S., Okamura, R., Schwaederle, M., Hahn, M.E., Williams, C.B., De, P., Krie, A., Piccioni, D.E., Miller, V.A., et al. (2019). Molecular profiling of cancer patients enables personalized combination therapy: the I-PREDICT study. Nat. Med. *25*, 744–750. https://doi.org/10.1038/s41591-019-0407-5.
20. Louie, B.H., Kato, S., Kim, K.H., Lim, H.J., Okamura, R., Eskander, R.N., Botta, G., Patel, H., Lee, S., Lippman, S.M., et al. (2022). Pan-cancer molecular tumor board experience with biomarker-driven precision immunotherapy. npj Precis. Onc *6*, 67–68. https://doi.org/10.1038/s41698-022-00309-0.
21. Louie, B.H., Kato, S., Kim, K.H., Lim, H.J., Lee, S., Okamura, R., Fanta, P.T., and Kurzrock, R. (2022). Precision medicine-based therapies in advanced colorectal cancer: The University of California San Diego Molecular Tumor Board experience. Mol. Oncol. *16*, 2575–2584. https://doi.org/10.1002/1878-0261.13202.
22. Rodon, J., Soria, J.-C., Berger, R., Miller, W.H., Rubin, E., Kugel, A., Tsimberidou, A., Saintigny, P., Ackerstein, A., Braña, I., et al. (2019). Genomic and transcriptomic profiling expands precision cancer medicine: the WINTHER trial. Nat. Med. *25*, 751–758. https://doi.org/10.1038/s41591-019-0424-4.
23. Patel, S.P., Othus, M., Chae, Y.K., Giles, F.J., Hansel, D.E., Singh, P.P., Fontaine, A., Shah, M.H., Kasi, A., Baghdadi, T.A., et al. (2020). A Phase II Basket Trial of Dual Anti-CTLA-4 and Anti-PD-1 Blockade in Rare Tumors (DART SWOG 1609) in Patients with Nonpancreatic Neuroendocrine Tumors. Clin. Cancer Res. *26*, 2290–2296. https://doi.org/10.1158/1078-0432.CCR-19-3356.
24. Kato, S., Kurasaki, K., Ikeda, S., and Kurzrock, R. (2018). Rare Tumor Clinic: The University of California San Diego Moores Cancer Center Experience with a Precision Therapy Approach. Oncol. *23*, 171–178. https://doi.org/10.1634/theoncologist.2017-0199.
25. Groisberg, R., Hong, D.S., Roszik, J., Janku, F., Tsimberidou, A.M., Javle, M., Meric-Bernstam, F., and Subbiah, V. (2018). Clinical Next-Generation Sequencing for Precision Oncology in Rare Cancers. Mol. Cancer Ther. *17*, 1595–1601. https://doi.org/10.1158/1535-7163.MCT-17-1107.
26. Morfouace, M., Stevovic, A., Vinches, M., Golfinopoulos, V., Jin, D.X., Holmes, O., Erlich, R., Fayette, J., Croce, S., Ray-Coquard, I., et al. (2020). First results of the EORTC-SPECTA/Arcagen study exploring the genomics of rare cancers in collaboration with the European reference network EURACAN. ESMO Open *5*, e001075. https://doi.org/10.1136/esmoopen-2020-001075.
27. Sicklick, J.K., Kato, S., Okamura, R., Patel, H., Nikanjam, M., Fanta, P.T., Hahn, M.E., De, P., Williams, C., Guido, J., et al. (2021). Molecular profiling of advanced malignancies guides first-line N-of-1 treatments in the I-PREDICT treatment-naïve study. Genome Med. *13*, 155. https://doi.org/10.1186/s13073-021-00969-w.
28. Subbiah, V., Groisberg, R., Skefos, C., Cleary, J.M., Subbiah, I.M., Palma, J., Oster, M., Young, S.W., Elvin, J.A., Sicklick, J.K., et al. (2021). TCF-001 TRACK (Target Rare Cancer Knowledge): A national patient-centric precision oncology trial for rare cancers. J. Clin. Orthod. *39*, TPS3143. https://doi.org/10.1200/JCO.2021.39.15_suppl.TPS3143.
29. Determine Overview (2022 (Cancer Research UK). https://www.cancerresearchuk.org/funding-for-researchers/our-research-infrastructure/our-centre-for-drug-development/determine-overview.

STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Software and algorithms		
SPSS Statistics Software, version 28	IBM	https://www.ibm.com/

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the lead contact, Bryan H. Louie (b1louie@health.ucsd.edu).

Materials availability

This study did not generate new unique reagents.

Data and code availability

- Pertinent data reported in this paper will be shared by the lead contact upon reasonable request.
- This paper does not report original code
- Any additional information required to reanalyze the data reported in this paper is available from the lead contact upon reasonable request.

METHOD DETAILS

Molecular tumor board

The Molecular Tumor Board (MTB) is a multidisciplinary team developed by and operating within the University of California San Diego (UCSD) Center for Personalized Cancer Therapy. Similar to a traditional tumor board, this team was composed of a diverse group of clinicians, including medical, radiation, and surgical oncologists, radiologists, and pathologists. In addition, to aid in the evaluation of molecular data and advanced therapeutic applications, this team also incorporated bioinformaticians, geneticists, basic/translational scientists, medication acquisition specialists, and clinical trial coordinators/navigators. The MTB's primary mode of evaluation was in-person meetings, several times a month, that aimed to discuss patient cases that were referred by primary treating physicians. These meetings were facilitated by senior and mid-level medical oncologists, and organized by an MTB project manager, who provided comprehensive agendas that included de-identified patient information, such as age, sex, diagnosis, pathology, and treatment history, as well as molecular diagnostic reports from Clinical Laboratory Improvement Amendments (CLIA)-licensed and College of American Pathologists (CAP)-accredited laboratories.

The MTB discussions evaluated all available patient information, including laboratory tests, imaging, and pathology, with a focus on identifying molecular alterations in tumors across multiple profiling methods. The team then sought to determine whether there were any drugs, either approved by the Food and Drug Administration (FDA) or in clinical trials, that might address the cellular pathways that were impacted by the molecular alterations present. Once potential viable drugs were proposed by the MTB, a medication acquisition specialist and clinical trial coordinator/navigator then assisted with medication ordering, clinical trial screening, and obtaining consent. The MTB maintained strict adherence to Health Insurance Portability and Accountability Act (HIPAA) standards for patient privacy, and all recommendations and meeting notes were reviewed and verified by an MTB physician organizer and the presenting physician before being recorded in the patient's medical record. Ultimately, the MTB was considered an advisory body, and all recommendations were presented to the patients' primary oncologist, who ultimately made the final treatment decisions.

Patients and therapy

The patients in this study represent a sub-cohort, drawn from a larger group of 715 patients with various types of cancer who were presented at the face-to-face MTB between December 2012 and September 2018, and subsequently 429 patients who were assessable for clinical therapeutic outcome following MTB discussion (Figure 1).[15] Patients were usually excluded if they did not receive treatment after MTB presentation, their treatment did not change within six months after MTB presentation (i.e., continued on prior therapy), or they died or were lost to follow-up within one month after presenting to the MTB. From this cohort, this current study assesses 112 patients with various types of rare/ultra-rare cancers who presented to the MTB (Table 1). De-identified patient characteristics were obtained from electronic medical records. The study abided by all procedures established and approved by the Institutional Review Board (IRB) for the UCSD-Profile Related Evidence Determining Individualized Cancer Therapy (PREDICT) study (NCT02478931) and any other studies for which patients gave consent.

Molecular profiling

Next-generation sequencing (NGS) of solid tissue DNA and/or cell-free circulating tumor DNA (cfDNA) was performed on tissue and blood in one of several CLIA-certified laboratories (See Table S1): Foundation Medicine (https://www.foundationmedicine.com/), Tempus (https://www.tempus.com/), Guardant (https://guardanthealth.com/), University of California San Diego Health (https://health.ucsd.edu/), Paradigm (https://www.paradigmdx.com/), Caris (https://www.carislifesciences.com/). The sequencing panels included 15–313 genes for tissue and 66–173 for blood-derived cell-free circulating tumor DNA (cfDNA). In addition, select patients received testing for mRNA expression, protein immunohistochemistry (IHC) and immune biomarkers. All molecular diagnostics tests were chosen by the attending physician. The MTB did not consider gene alterations that were categorized as variants of unknown significance (VUS) as potential alterations that could be targetable by drugs.

Matching Score

The Matching Score was a metric assigned to each patient based on the percentage of pathogenic tumor alterations that were targeted by the drugs administered after MTB presentation. Blinded investigators calculated the Matching Score through a *post hoc* analysis based on administered drugs, without any knowledge of the treatment outcomes. Tumor molecular alterations considered in the Matching Score calculation included mutations, rearrangements, deletions, amplifications, insertions, and multiple aberrations of genes. As previously described, the Matching Score calculation included assessment of all NGS characterized variants (but not VUS) as well as mRNA expression, protein expression, and immunotherapy biomarkers in specific cases.[19]

The Matching Score was computed by dividing the number of molecular alterations targeted by the administered drugs by the total number of pathogenic tumor alterations present. A higher score indicates a better match between drugs and alterations (ranging from 0%, unmatched, to 100% completely matched). Further details regarding the Matching Score calculation have been previously published.[19] Consistent with prior studies, patients were categorized into high Matching Score ($\geq$50%) and low Matching Score (<50%) groups.[15,19,20] Additional details regarding patient characteristics, molecular alterations, therapies received, and Matching Score are provided in Table S2.

QUANTIFICATION AND STATISTICAL ANALYSIS

The study summarized patient characteristics and molecular profiling information using descriptive statistics. The main measures of outcome were progression-free survival (PFS), overall survival (OS), and clinical benefit rate (stable disease (SD) $\geq$ 6 months, complete response (CR), partial response (PR)). PFS was defined as the time between treatment start date after MTB presentation and the date of progression, which was assessed by clinical evaluation or imaging. OS was defined as the time between treatment start date after MTB presentation and the date of death or last follow-up. If a patient's tumor had not progressed at the last follow-up date, they were censored for PFS, and if they were still alive at the last follow-up date, they were censored for OS. RECIST criteria were used to assess clinical response.[18] The study used Kaplan-Meier analysis and Cox regression to compare patient subgroups for survival analysis. Univariate Cox regression was performed on all covariates to evaluate correlation with survival. Subsequently, multivariate analysis included covariates with p-values <0.2 by univariate analysis. To compare clinical benefit rates between different subgroups of patients, binomial logistic regression was utilized. Univariate binomial logistic regression was performed for all covariates to evaluate correlation with clinical benefit rate. Subsequently, multivariate binomial logistic regression included only covariates with p-value <0.2 by univariate analysis. Significance level was set at p-values $\leq$0.05, and statistical analyses were conducted using R and SPSS Statistics software. Statistical details are reported in the results, tables, and figures.