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Molecular matching and treatment strategies for advanced stage lung cancer at Dartmouth-Hitchcock Medical Center: A three-year review of a Molecular Tumor Board

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ABSTRACT

Matching of actionable tumor mutations with targeted therapy increases response rates and prolongs survival in lung cancer patients. Drug development and trials targeting genetic alterations are expanding rapidly. We describe the role of a Molecular Tumor Board (MTB) in the design of molecularly informed treatment strategies in our lung cancer patient population.

Tumor DNA was sequenced using a 50-gene targeted next-generation sequencing panel. Cases were evaluated by a multidisciplinary MTB who suggested a course of treatment based on each patient's molecular findings.

During a three-year period, 21 lung cancer patients were presented at the MTB. All patients lacked common activating *EGFR* mutations and *ALK* rearrangements. One patient had Stage IIIb disease; all others were Stage IV; 18 patients had received ≥1 prior line of therapy (range 0–5). Suggestions for treatment with a targeted therapy were made for 19/21 (90.5%) patients, and four patients (21%) underwent treatment with a targeted agent, two as part of a clinical trial. Identified barriers to treatment with targeted therapy included: ineligibility for clinical trials (n = 2), lack of interest in study/distance to travel (n = 2), lack of disease progression (n = 2), poor performance status (n = 5), decision to treat next with immunotherapy (n = 3), and unknown (n = 1).

For the majority of lung cancer patients, the MTB provided recommendations based on tumor genetic profiles. Identified barriers to treatment suggest that presentation to the MTB at earlier stages of disease may increase the number of patients eligible for treatment with a genetically informed targeted agent.

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1. Introduction/Background

While cytotoxic chemotherapeutic agents have long been the foundation of systemic cancer treatment, the development of more specific targeted agents has rapidly progressed in the last 15 years. In many cases, these advances have resulted in superior outcomes for cancers which had a previously dismal prognosis. The beginning of molecular therapeutics can be traced to the 1960's with the discovery of the Philadelphia Chromosome in chronic myeloid leukemia (CML). However, it took over 30 years to develop the tyrosine kinase inhibitor imatinib to target the resulting *BCR-ABL* fusion oncogene. Imatinib was FDA-approved in 2001, turning once-rapidly fatal CML into a chronic disease.

Lung cancer is estimated to account for 225,000 new cases and 158,000 cancer deaths annually in the U.S [1]. This is expected to represent 26.5% of all cancer deaths in 2016 [1]. Fortunately, molecular therapeutics continue to play an increasingly important role in the treatment of lung cancer as the pace of drug development to approval has increased. At the time of this cohort analysis current molecular testing guidelines for the selection of therapy in patients with lung adenocarcinoma include at minimum, *EGFR* and *ALK* testing [2]. Subsequently, *ROS1, BRAF*, *NTRK*, *MET* and *RET* have been added due to the availability of recently approved drugs.

While a relatively small proportion of tumors harbor molecular alterations targetable by FDA-approved agents, an in silico prescription strategy, based on identification of the driver alterations and their druggability options suggests that up to 70% of tumors could potentially respond to treatments currently under clinical investigation [3]. A study from M.D. Anderson Cancer Center evaluated patients with advanced cancer that harbored genetic alterations, and compared the outcomes of those enrolled into genetically matched (n = 175) versus non-matched (n = 116) clinical trials [4]. The matched group had a higher overall response rate (27% vs. 5%; $P < 0.0001$), as well as longer overall survival (median, 13.4 vs. 9.0 months; $P = 0.017$). In July 2015, the phase II NCI-MATCH [Molecular Analysis for Therapy Choice (EAY131)] trial opened to determine whether genetically-informed targeted therapies would be effective regardless of cancer subtype. In this new area of molecular therapeutics, there is an increasing need for oncologists to have access to experts in molecular diagnostics and molecular biology to interpret molecular alterations. Herein, we describe the role of a Molecular Tumor Board (MTB) in the design of molecularly informed treatment strategies for our lung cancer patient population.

2. Patients and methods

2.1. MTB format

All patients were evaluated and treated at the NCI-designated Norris Cotton Comprehensive Cancer Center at Dartmouth-Hitchcock Medical Center. The primary treating oncologist of record determined which patients would benefit from molecular testing and requested presentation at the Molecular Tumor Board (MTB). The MTB was formed through collaboration with medical oncologists, hematologists, molecular and anatomic pathologists, genetic counselors, and basic science researchers with expertise in cancer genetics, signaling pathways, and molecular therapeutics. Patient-specific surgical pathology, clinical history, molecular testing results, and an in-depth summary of the significance of tumor mutations were presented monthly to the MTB. After discussion, final treatment suggestions and referral recommendations were made by the MTB and documented in the patient's medical record [5]. Tumor genetic profiles, MTB recommendations, and patient outcomes were then collected into an Institutional Review Board (IRB)-approved data set.

2.2. Tumor genetic profiling

In our institution, at the time of diagnosis of a lung adenocarcinoma, the diagnosing pathologist reflexively orders molecular testing; testing other histologic subtypes of lung cancer is by request of the treating oncologist. Testing was performed in the Clinical Laboratory Improvement Amendments-certified Dartmouth-Hitchcock Medical Center Department of Pathology and Laboratory Medicine's Laboratory for Clinical Genomics and Advanced Technology using validated methods [6,7]. After pathologist's review, macrodissection was performed to ensure ≥10% tumor cellularity. DNA was extracted from eight 4-μm sections of formalin-fixed paraffin-embedded tumor tissue using the Gentra PureGene Blood Kit Plus or Qiacube (Qiagen, Hilden, Germany) and quantified using PicoGreen (Promega, Madison, WI). Barcoded libraries were prepared from 10 ng of DNA using the Ion AmpliSeq Library Kit 2.0 with Ion AmpliSeq Cancer Hotspot Panel v2 per manufacturer's protocol (Life Technologies, Rockville, MD). This method generates 207 polymerase chain reaction (PCR) amplicons covering 2855 COSMIC-catalogued mutations across 50 cancer-related genes. Libraries were sequenced using the Ion Torrent Personal Genome Machine (PGM) System and Ion 318 Chips (Life Technologies, Rockville, MD). Sequencing reads were aligned to hg19, and variants were called using Torrent Suite Variant Caller Plugin v4.0. Variant annotation was performed using Golden Helix SNP and Variation Suite software v8.2.1. Filters were applied to remove benign polymorphisms, as well as synonymous variants. Potential germline polymorphisms were filtered from the variant call file based on an internally curated list of benign polymorphisms based on 1% population frequency in available population databases. The thresholds for calling a variant were ≥5% variant allelic fraction and ≥500-fold coverage; in our facility, tumor DNA is always sequenced to ˃1000-fold average coverage. A report detailing variants detected in the tumor and resultant amino acid changes was included in each patient's medical record. At that time, variants with FDA approved therapies or contraindications were listed as "clinically actionable" while other variants were listed as "not clinically indicated".

2.3. Variant analysis

Upon request for presentation at the MTB by the primary treating oncologist, each case was assigned to a member of the MTB to review. Publicly available tools and databases (*e.g.*, cBioPortal for Cancer Genomics) were queried to determine the frequency of a given mutation across patient populations. We then used databases (*e.g.*, PubMed, COSMIC, Google, MutationAssessor, UniProt, ClinVar, OncoKB, MyCancerGenome, clinicaltrials.gov,and dbSNP) to determine A) whether a given mutation was previously observed and evaluated, B) potential for germline mutation, C) relevant pathway(s) that may be affected by the mutation, D) available drugs (approved, off-label, or experimental) targeting the affected pathway(s), and E), the Level(s) of Evidence (*i.e.*, preclinical *in vitro* or *in vivo*, clinical case report, or clinical trial) (Table 1) [5] supporting a mutation-induced change in protein function and/or drug sensitivity. The results of this in-depth analysis are summarized and presented to the MTB for discussion and formation of treatment recommendations.

3. Results

3.1. Tumor types and mutated genes

The MTB at Dartmouth-Hitchcock Medical Center was formed in November 2013. This data set was locked for analysis in November 2016. During that three-year period, a total of 88 patients were presented to the MTB. Of these, 21 were lung cancer patients (23.9%). Tumor types included adenocarcinoma (n = 18), squamous (n = 1), and other (n = 2).

3.2. Impact on patient treatment and survival

Of the 21 lung cancer cases presented (Table 2), all patients lacked common (i.e., indicated for an FDA-approved drug) activating *EGFR* mutations and *ALK* rearrangements. One patient had Stage IIIb disease; all others were Stage IV; 18 patients had previously received ≥1 prior line of therapy (range 0–5). Suggestions for treatment with a targeted therapy were made for 19/21 (90.5%) patients, and four patients underwent treatment with a MTB-recommended targeted agent (21.1%), two as part of a clinical trial. Herein, we provide treatment histories for the four patients to illustrate how rational drug-mutation matching has impacted outcome (Fig. 2).

Patient 2 was a 51-year-old male diagnosed with Stage IV lung adenocarcinoma with symptomatic brain metastases. In 2013, molecular profiling of the primary lung tumor revealed mutations in *BRAF* (p.V600E) and *MET* (p.T992I). At the time, case reports and interim results of Phase II trials indicate that *BRAF* p.V600E-mutant lung cancers frequently respond to BRAF inhibition [8–11]. The MTB recommended treatment with BRAF and MEK inhibitors per clinical trial F12214: A Phase II study of the Selective BRAF Kinases Inhibitor GSK2118436 in Subjects With Advanced Non-small Cell Lung Cancer and BRAF Mutations [11]. The patient remained on therapy for 2 years and 3 months before progressing (Fig. 1A). He was next treated with the anti-PD1 antibody nivolumab. Of note, *BRAF* V600E became a FDA-approved indication with breakthrough designation of the combination of dabrafenib plus trametinib in 2015 followed by regular approval in 2017.

Patient 11 was a 77-year-old female diagnosed with Stage IV lung adenocarcinoma with lymph node involvement and bilateral pulmonary metastases. Molecular profiling of a lymph node biopsy with immunohistochemistry consistent with her primary lung tumor revealed mutations in *FGFR1* (p.A268P c.802G > C) and *TP53* (p.A159P). Although there were no data found on the A268P mutation, A268S variant had been reported in three colorectal cancer cell lines (COSM2960508). The MTB considered this a variant of uncertain significance, although the patient may be eligible for a FGFR inhibitor trial upon screening. She was enrolled in NCT02160041 a phase II trial of BGJ398, a selective FGFR 1/2/3 inhibitor, for patients with tumors with *FGFR* genetic alterations. (Fig. 1B). Unfortunately, the trial protocol designated that the patient terminate her participation due to the development of Grade III hypercalcemia and hypoglycemia shortly after initiation of treatment with the targeted agent. She was next treated with the oral EGFR inhibitor erlotinib as it was FDA-approved for second line therapy regardless of *EGFR* mutation status. However, she developed debilitating rash and diarrhea and discontinue erlotinib after one month. Subsequently, she was treated with nivolumab until disease progression. She died of disease eight months later.

Patient 16 was a 51-year-old female with metastatic adenocarcinoma of the lung with pleural-based and contralateral pulmonary metastasis. Molecular profiling of a lymph node biopsy metastasis revealed mutations in *KRAS* (p.G12V), *MET* (exon 14, p. R970C), and

Table 1
Levels of evidence supporting targeted therapies recommended by Molecular Tumor Board [5].

Level	Definition
1	FDA-approved agent for given indication; demonstration that patients with tumors bearing specific genetic alterations are more likely to respond than those without such alterations.
2	Agent met a clinical endpoint in a trial (objective response, PFS, or OS) with evidence of target inhibition; plausible evidence that tumors bearing a specific genetic alteration are predicted to respond.
3	Agent demonstrated evidence of clinical activity with evidence of target inhibition; some evidence that tumors bearing a specific genetic alteration are predicted to respond.
4	Preclinical evidence of anti-tumor activity and evidence of target inhibition; hypothesis that tumors bearing a specific alteration will respond.

Table 2
Lung cancer patients presented to the Molecular Tumor Board, mutations present, final recommendations, and barriers to treatment.

Patient Number	Tumor Board Date	Pathology	Stage	Mutations	AA change	DNA mutation	Prior Treatments	TB Recommendations - final recs	Targeted Therapy	Level of evidence	Barriers
1	12/19/13	Adenocarcinoma	IV	EGFR	p.E709_710 delinsD	c.2126_2129 delinsA	0	First line chemotherapy	no	n/a	n/a
				PIK3CA	p.E545K	c.1633 g > A					
2	12/19/13	Adenocarcinoma	IV	BRAF	p.V600E	c.1799T > A	1	Consider BRAF inhibitor trial.	yes	3	n/a
				MET	p.T9921	c. 2975C > T					
3	12/18/14	Adenocarcinoma	IV	KRAS	p.G12R	c.34G > C	2	NCT01798485 if willing to travel, CDK4/6 inhibitor trial for KRAS mutation NSCLC after progression on 2nd line therapy.	no	4	1
				SMO	p.C193Y	c.578G > A					
4	12/19/13	Adenocarcinoma	IV	TP53	p.Y88C	c.263A > G	1	Patient with poor performance status thus second line chemotherapy recommended, not fit for clinical trial.	n/a	n/a	n/a
				JAK3	p.V722I	c.2164G > A					
5	06/19/14	Adenocarcinoma	IV	MET	p.P814L	c.2441C > T	3	Continue maintenance chemotherapy, phase I MET inhibitor trial at progression. followed by MET inhibitor on trial at progression.	No	4	5
				TP53	p.G134E	c.401G > A					
6	07/17/14	Sarcomatoid	IV	TP53	p.G134E	c.401G > A	0	Consider EGFR inhibitor as second line therapy.	No	n/a	4
7	09/18/14	Adenocarcinoma	IV	RET	p.S653C	c.1958C > G	2	Evaluate tumor for KIF5B-RET fusion. Consider RET inhibitor.	No No	4	4
				TP53	p.L111R	c.332T > G					
8	10/16/14	Adenocarcinoma	IV	KRAS	p.G12C	c.34G > T	1	Continue first line chemotherapy. On progression, recommend treatment with RET/multi-kinase inhibitor Dovitinib.	No	4	2
				RET	p.E884V	c.2651A > T					
9	12/18/14	Adenocarcinoma	IV	KRAS	p.G12R	c.34G > C	1	Downstream KRAS target with Ganetespib clinical trial.	no	4	6
				SMO	p.C193Y	c.578G > A					
10	02/19/15	Adenocarcinoma	IIIB	CDKN2A	Exon 2 loss	c.*74-1G > T	1	Treatment with CDK4/6 inhibitor, on clinical trial such as LEE011.	no	3	1
				TP53	p.C110F	c.725G > T					
11	03/19/15	Adenocarcinoma	IV	FGFR1	p.A268P	c.802G > C	3	Continue chemotherapy, upon progression consider Signature trial arm for cancer FGFR dysregulation	yes	4	n/a
				TP53	p.A159P	c.475G > C					
12	05/21/15	Adenocarcinoma	IV	EGFR	p.L747S	c.2240T > C	2	EGFR mutation likely not activating and associated with erlotinib resistance. Consider off label treatment with JAK3 inhibitor. (V722I subsequently ckassified as polymorphism)	no	4	5
				JAK3	p.V722I	c.2164G > A					
13	05/21/15	Poorly differentiated carcinoma	IV	APC	p.E1299Q	c.3895G > C	2	APC and SMO mutations likely not drivers. Consider TP 53 clinical trials if patient is willing to travel.	no	4	3
				SMO	p.G529A	c.1586G > C					
				TP53	p.S241Y	c.722C > A					
14	09/24/15	Adenocarcinoma	IV	BRAF	p.G469V	c.1406G > T	2	PIK3CA inhibitor + MEK inhib combination trial, if available, otherwise MATCH EAY 131-R trial.	no	3	4
				PICK3CA	p.E545K	c.1633G > A					

(*continued on next page*)

Table 2 (*continued*)

Patient Number	Tumor Board Date	Pathology	Stage	Mutations	AA change	DNA mutation	Prior Treatments	TB Recommendations - final recs	Targeted Therapy	Level of evidence	Barriers
				STK11	p.F204fs	c.612delC					
15	10/22/15	Squamous	IV	PIK3CA	p.E542K	c.1624G > A	3	Continue immunotherapy, consider combination trial of PIK3CA/EGFR inhibitors or MATCH trial at progression	no	4	5
16	11/19/15	Adenocarcinoma	IV	KRAS	p.G12V	c.35G > T	1	MET change likely SNP, consider FISH for MET amplification, if present F15153 trial, Phase IB NCT01999972, or crizotinib. If MET amplification not present consider ATR or PARP inhibitor.	yes	4	n/a
				MET	p. R970C	c.2908C > T					
				ATM	p.D2725E	c.8175T > C					
17	11/19/15	Adenocarcinoma	IV	MET	p.T992I	c.2975C > T	2	MET change is likely a SNP. Consider bavituximab or CDK4/6 inhibitor clinical trial.	no	3	4
				CDKN2A	p.L63R	c.188T > G					
				TP53	p.C242F	c.725_726 GC > TT					
18	01/28/16	Adenocarcinoma	IV	SMAD4	p.D351G	c.1052A > G	5	Continue immunotherapy, consider traveling to a site where NCT02423343 open (Nivolumab + TGFBR1 inhibitor).	no	4	4
19	04/28/16	Adenocarcinoma	IV	MET	p.P814L	c.2441C > T	2	Consider phase I cMET inhibitor trial, EFGR inhibitor with pre-clinical data of higher response due to MET variant.	no	4	3
20	09/22/16	Adenocarcinoma	IV	PI3K	p.E542K	c.1624G > A	3	Consider PIK3CA inhibitors, GDC-0023 (taselisib) or MATCH trial.	no	3	2
21	11/17/16	Adenocarcinoma	IV	EGFR	p.S768I	c.2303G > T	0	Continue afatinib, at progression consider CDK4/6 given CDKN2A, consider p53-refolding drugs such as PRIMA-1 (APR246).	yes	2	n/a
				EGFR	p.V774 M	c.2320G > A					
				CDKN2A	p.P81H	c.242C > A					
				TP53	p.G245C	c.733G > T					

Barriers to choosing targeted therapy [1]: Ineligibility for study [2]; Lack of interest in study/travel [3]; Lack of progression [4]; Poor performance status [5]; Treated with immunotherapy [6]; Unknown.

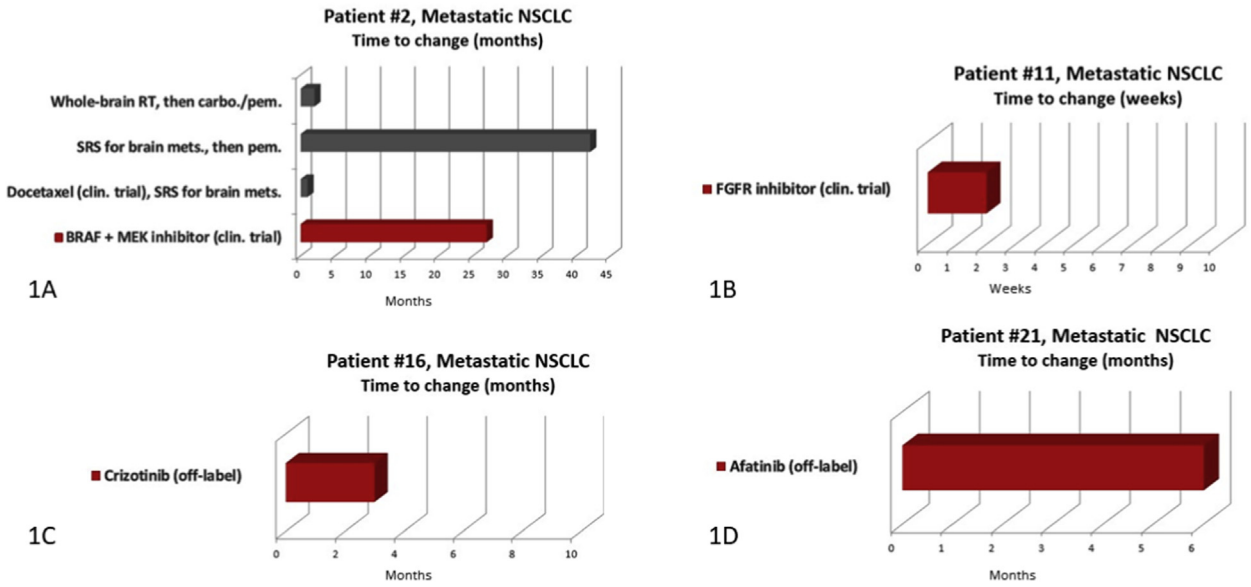

Fig. 1. Clinical course of four patients who received targeted therapies.

ATM (p.D2725E). This case highlights the benefits of reviewing and interpreting molecular findings in the context of a MTB. The *MET* p.R970C variant was included in the final report as "not clinically indicated". However, being in exon 14, this was initially interpreted by the treating oncologist as a *MET* exon 14 skipping mutation and the patient initiated crizotinib therapy prior to presentation at the MTB. The MTB noted that this *MET* variant was likely a single nucleotide polymorphism (SNP) and review of databases and the literature did not support this being an oncogenic variant. The MTB also noted that *ATM* variant may confer sensitivity to ATR or PARP inhibitors [12,13]. This led to recommendations for expanded testing to also include *MET* amplification. If *MET* amplification was identified, consider F15153 (INC280) trial, Phase IB NCT01999972, or crizotinib and if not present consider ATR or PARP inhibitor trial. Expanded testing was ultimately not performed. At the next follow up, approximately 3 months later, crizotinib was discontinued due to disease progression (Fig. 1C). This patient was then treated with the anti-PD1 antibody nivolumab.

Patient 21 was a 68-year-old female with metastatic adenocarcinoma of the lung with brain metastases. Molecular profiling of a lymph node biopsy with immunohistochemistry consistent with her primary lung tumor revealed mutations in *EGFR* (p.S768I and p.V774 M), *CDKN2A* (p.P81H), and *TP53* (p.G245C). The MTB concluded that the *EGFR* S768I mutation likely conferred sensitivity to the EGFR/HER2 dual inhibitor afatinib [14], while the V774 M mutation was predicted to not affect drug sensitivity. The *CDKN2A* P81H mutation was found to be rare and without functional data. However, *CDKN2A* alterations were noted to predict sensitization to CDK4/6 inhibition in preclinical studies. Finally, the MTB noted that the *TP53* G245C mutation has been shown to confer sensitivity to p53-refolding drugs such as PRIMA-1 (APR246) [15]. Concluding MTB recommendations were for first-line treatment with afatinib (which has subsequently been approved for these *EGFR* mutations). The patient was initiated on afatinib with primary tumor shrinkage noted on her initial two-month restaging exam. The patient remained on targeted treatment for 6 months duration (Fig. 1D) when she was found to have progression. She was next treated with carboplatin and pemetrexed with good response. At last follow up she remained on pemetrexed maintenance therapy.

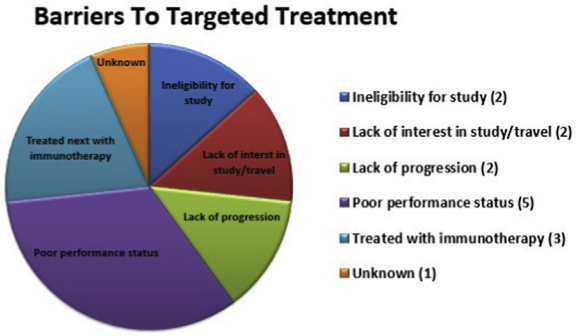

Fig. 2. Barriers to targeted treatment.

4. Discussion

4.1. Barriers to treatment with a targeted agent

These data demonstrate that the Dartmouth-Hitchcock Medical Center MTB model made recommendations for targeted therapy in the great majority of cases (90.5%). However, overall patient attainment of targeted medication was somewhat modest (21.1%). Barriers to treatment with MTB-recommended targeted therapy are illustrated in Fig. 2 and summarized in Table 2. Interestingly, identified barriers to treatment in this patient population did not include inability to pay for an off-label drug. The most common reason for not undergoing targeted treatment was poor performance status (n = 5, 33.3%). Conversely, two patients had yet to undergo targeted therapy due to lack of disease progression on current treatment (13.3%). This highlights the need for appropriate timing in molecular testing, and highlights that patients were often brought to the MTB in later stages of disease. This is a challenging patient population which typically has undergone multiple lines of prior therapy and, by default, are referred to the MTB because their tumors lack variants with FDA-approved therapies. As a MTB, we found that level 3–4 evidence (Table 1) was frequently all that was available when considering potential eligibility for a targeted clinical trial referral.

In those patients who were able to attain targeted medication, we saw a trend towards a decreased number of prior lines of therapy. In the group that ultimately underwent treatment with a targeted therapy (n = 4), the average number of prior therapies was 1.25. In the group for which recommendations for a targeted drug were made; however barriers impeded treatment, the average number of previous therapies was 1.82. This supports our conclusion that patients are more likely to receive targeted therapy when molecular testing is utilized early in the course of disease.

An additional factor when considering treatment with a targeted agent included the recent advances in the management of NSCLC with immunotherapy. Several patients presented during the first year of MTB were ultimately treated with immunotherapy (n = 3, 20%). Immunotherapy was not yet approved for use at the time of their case MTB discussion and ultimately presented a more appealing treatment at next progression. We also now know that several genetic alterations such as *STK11* co-mutation in *KRAS* mutant tumors as well as MSI, *POLE/POLD1* and tumor mutational burden may also be considerations when selecting immunotherapy.

Enrolling patients who lived outside of the immediate geography of the medical center on clinical trials proved a significant barrier given the burden of travel and extra testing. Several patients elected to have standard second-line chemotherapy locally, citing the inconvenience of increased travel to Dartmouth-Hitchcock Medical Center or to another NCI-designated Cancer Institute for a clinical trial (n = 2, 13.3%). Finally, a minority of patients were found ineligible for available trials (n = 2, 13.3%).

5. Conclusions

The Dartmouth-Hitchcock Medical Center MTB was able to optimize molecular treatment strategies for lung cancer patients. Nevertheless, patient attainment of molecularly targeted medication was moderate at best. As genetic profiling of tumors and trials targeting genetic alterations continue to increase, our data support the need for appropriate timing and consideration of early molecular testing in lung cancer patients. In this model, genetic alterations can become a permanent part of a tumor profile, thereby impacting treatment decisions for years after profiling is performed. A limitation of the 50 gene hotspot panel used for the patients presented here, is that it is designed to target the most common targetable alterations in solid tumors; however, on a monthly basis, there are more and more emerging molecular targets entering clinical trials that may not be encompassed by a targeted panel of this scale. Also, filtering germline variants, even benign polymorphism, can be challenging in tumor only testing and rely heavily on well curated clinical grade databases. Reporting of germline variants can potentially be misinterpreted as somatic variants with clinical implications, as in the case of patient 16. Increasing awareness of molecular profiling and presentation at the MTB has expanded the number of patients receiving targeted therapy at our institution; however, clinical trial enrollment continues to be a challenge.

Given the rapid advances and accessibility of genomic testing, many institutions are implementing similar MTBs in order to create a multidiciplinary approach to inform patient care decisions using this data [16–20]. In our MTB model, the multidisciplinary group interprets molecular information at the request of the treating physician, most often in patients with advanced stage disease. Detected variants may represent new pathways for treatment. It is educational and beneficial to the oncologic community as a whole to share these experiences and struggles that MTBs encounter as we are all facing similar challenges provided the vast increase in genomic medicine.

Declaration of competing interest

The authors have no conflicts of interest to disclose.

CRediT authorship contribution statement

Erica B. Bernhardt: Conceptualization, Methodology, Data curation, Writing - original draft. **Mary D. Chamberlin:** Data curation, Supervision, Writing - review & editing. **Ivan P. Gorlov:** Data curation. **Francine B. de Abreu:** Data curation, Methodology. **Katarzyna J. Bloch:** Supervision. **Jason D. Peterson:** Software, Data curation, Methodology. **Gregory J. Tsongalis:** Supervision. **Keisuke Shirai:** Methodology. **Konstantin H. Dragnev:** Methodology. **Todd W. Miller:** Data curation, Writing - original draft. **Laura J. Tafe:** Conceptualization, Methodology, Software, Data curation, Writing - original draft, Writing - review & editing.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.plabm.2020.e00174.

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