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Supplemental Table for:
Implementation of a Molecular Tumor Board: The Impact on Treatment Decisions for 35 Patients Evaluated at Dartmouth-Hitchcock Medical Center
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Table S2. Summary of 35 cases evaluated by MTB.

Patient #	Diagnosis	Primary (P), Recurrent (R), or Metastatic (M)	*n* lines of prior therapy	DNA-seq of archived (A, yrs) or recently sampled (R, <1 yr) tumor	Mutated gene(s)	Amino acid change(s) (p.___)	DNA mutation(s) (c.___)	MTB interpretation and recommendation	Level of evidence supporting recommended targeted therapy [Ref.]	Followed MTB-recommended treatment? yes or no (reason)	Subsequent treatment
1	Rhabdo-myosarcoma	M	3	R	*TP53*	R141H	421_422delinsCA	Recommend treatment with standard therapy; referral for genetic counseling to rule out germline mutation.	NA	NA	SOC chemotherapy
2	NSCLC, adeno. (*ALK*-normal)	M	0	A (3 y)	*EGFR* *PIK3CA*	709_710del-insD E545K	2126_2129delinsA 1633g>A	*EGFR* mutation may result in decreased activation. *PIK3CA* mutation may confer sensitivity to PI3K inhibitor. Recommend treatment with standard first-line chemotherapy.	NA	NA	SOC chemotherapy
3	NSCLC, adeno. (*ALK*-normal)	M	2	R	*BRAF* *MET*	V600E T992I	1799T>A 2975C>T	*BRAF* mutation may confer resistance to EGFR inhibitor and sensitivity to BRAF inhibitor. Recommend treatment with BRAF inhibitor.	2 [1-3]	Yes	BRAF inhibitor (Phase II trial)
5	NSCLC, adeno. (*ALK*-normal)	M	1	R	*KRAS* *SMO*	G12R C193Y	34G>C 578G>A	*KRAS* mutation confers resistance to EGFR-targeted therapy. Recommend treatment with standard second-line therapy, followed by clinical trial with Hedgehog inhibitor or CDK4/6 inhibitor (in-house clinical trial).	3 [4]	NA	SOC chemotherapy
6	NSCLC, adeno (*ALK*-normal)	M	1	R	*KIT* *MET* *TP53* *JAK3*	M541L N375S Y88C V722I	1621A>G 1124A>G 263A>G 2164G>A	Recommend treatment with standard second-line therapy; pt. has poor PS, trial not recommended.	NA	NA	SOC chemotherapy and RT
8	Leiomyo-sarcoma	M	6	A (4 y)	ND			Re-biopsy and analyze with larger gene panel; consider Phase I trials; referral for germline genetic testing.	NA	No (responding to SOC)	NA
9	CRC	M	7	A (3 y)	*KDR* *APC* *TP53*	Q1149E E1291fs R43H	3445C>G 3867_3871del AAAAG 128G>A	*KDR* mutation lies in kinase domain, may be associated with sensitivity or resistance to VEGF inhibitor; recommend re-biopsy and sequencing of current tumor; recommend Phase I trials.	NA	No (pt. declined trial options)	SOC chemotherapy
10	Melanoma	M	2	R	*BRAF* *PIK3CA*	V600E Y1021*	1799T>A 3063C>G	*BRAF* mutation sensitizes to BRAF inhibitor. Recommend treatment with	1 [5, 6]	Yes	BRAF + MEK inhib.

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					MET	E355K	1063G>A	BRAF inhibitor (+/- MEK inhibitor). *PIK3CA* mutation of unknown significance; upon disease progression, consider trial with PI3K inhibitor.			[Dabrafenib + Trametinib (approved)]
11	CRC	M	1	A (4 y)	*KRAS* *APC* *TP53*	G12V P1440fs R141C	35G>T 4318delC 421C>T	*KRAS* mutation associated with resistance to EGFR inhibitors. Recommend treatment with MEK (+/- PI3K) inhibitor.	3 [7]	No (pt. declined therapy)	herbal, alternative medicine
12	CRC	M	2	A (3 y)	*BRAF* *PIK3CA* *KIT* *APC* *ERBB2*	V600E H1047Y G51K R858* V842I	1799T>A 3139C>T 152G>A 2572C>T 2524G>A	*BRAF* mutation confers resistance to EGFR inhibition. *PIK3CA* mutation may confer resistance to BRAF inhibition. *ERBB2* mutation induces kinase activation and possibly confers sensitivity to HER2 kinase inhibitors. Recommend treatment with PI3K inhibitor, PI3K and BRAF inhibitors, or BRAF and EGFR inhibitors.	3 [8-10]	No (pt. declined trial options)	None
13	Naso-pharyngeal CA	M	2	R	ND			Consider Phase I trials.	NA	No (pt. declined trial options)	SOC chemotherapy
14	Pilocytic astrocytoma	P	0	R	*PIK3CA*	Q546E	1636C>G	Tumor type is associated with neurofibromatosis type 1 (NF1), and suggestive of germline mutations; recommend referral for genetic counseling. *PIK3CA* mutation is likely activating; consider treatment with PI3K inhibitor upon disease progression.	NA	NA	Surgery as SOC, then observation
15	CRC	P	0	R	*PIK3CA* *TP53*	E542K R196*	1624G>A 586C>T	*PIK3CA* mutation is activating; consider treatment with PI3K inhibitor upon recurrence. Recommend treatment with standard first-line therapy.	3 [11-13]	NA	SOC chemotherapy
16	Salivary gland CA	M	2	R	*PIK3CA* *HRAS*	E545K Q61R	1633G>A 182A>G	*PIK3CA* mutation is activating and may confer sensitivity to PI3K inhibitor. *HRAS* mutation may be associated with resistance to standard therapies. Evaluate amplification of EGFR and ERBB2 status, as clinical studies suggest potential correlation with response to receptor-targeted therapy. Consider treatment with PI3K inhibitor.	3 [11-13]	No (disease is stable on SOC)	SOC chemotherapy
17	CRC	M	7	A (4 y)	*KRAS* *TP53*	G13D R43H	38G>A 128G>A	Re-biopsy a current tumor and perform genetic analysis with larger gene panel.	NA	No (pt. not interested in traveling for treatment)	SOC chemotherapy

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18	Melanoma	M	0	R	*FGFR3* *CDKN2A* *TP53*	G691R P81L S241F	2071G>A 242C>T 722C>T	*FGFR3* mutation lies in kinase domain, may alter kinase activity. *CDKN2A* mutation may predict sensitivity to CDK4/6 inhibitor. Consider treatment with FGFR3/multi-kinase inhibitor Dovitinib, or CDK4/6 + MEK inhibitors in ongoing trial.	3 [14-19]	No (pt. requested care closer to home)	SOC Ipilimumab
19	Epithelioid hemangio.	M	2	R	ND			Consider Phase I trials.	NA	No (progressive disease)	None (pt. died)
20	NSCLC adeno. (*ALK*-normal)	M	1	R	*MET* *TP53*	P814L G134E	2441C>T 401G>A	*MET* mutation does not lie in kinase domain; unknown effect on sensitivity to MET inhibitor. Consider MET inhibitor trial upon disease progression.	3 [20]	NA	SOC Pemetrexed
21	Unknown primary	M	2	R	*PIK3CA*	E542K	1624G>A	*PIK3CA* mutation is activating, may confer sensitivity to PI3K inhibitor. Recommend treatment with PI3K inhibitor in ongoing Phase II clinical trial.	3 [11-13]	No (pt. has declining PS)	None (pt. died)
22	Breast CA (ER+, HER2-)	M	6	R	*PIK3CA*	H1047R	3140A>G	*PIK3CA* mutation is activating and may confer sensitivity to PI3K pathway inhibitor. Recommend SOC treatment with Everolimus (mTORC1 inhibitor) + Exemestane.	1 [21, 22]	Yes	SOC Everolimus + Exemestane
23	Anaplastic ependy-moma[1] (seq by Foundation Medicine)	M	2	A (3 y)	*NF1* *PIK3R1* *PTPN11* *CDKN2A* *TP53* *MSH2* *MSH6* *BRIP1* *MLL2* *SETD2*	N1465fs*2 R301* V428M R80* R248Q null F1088fs*5 S624L A2169T R2510H	4332+2T»C NR NR NR NR exons 1-3 NR NR NR T1652fs*i4	*PTPN11* (Shp-2) and *NF1* mutations may confer sensitivity to MEK and PI3K pathway inhibitors. *PIK3R1* mutation may activate JNK and ERK pathways. Recommend treatment with MEK inhibitor. Loss of MSH2 function may confer synthetic lethality with methotrexate; consider treatment.	4 [23-36]	Yes	Methotrexate (approved); upon subsequent disease progression, switched to Trametinib (MEK inhibitor), off-label
24	Glioblastoma multiforme (1p/19q-normal; *MGMT*-methylated)	R	1	R	*PIK3CA*	Y1021C	3062A>G	*PIK3CA* mutation may be activating and confer sensitivity to PI3K/mTOR pathway inhibitors. Recommend treatment with PI3K inhibitor in clinical trial upon disease progression.	3 [11-13]	No (pt. has declining PS)	SOC Bevacizumab
25	Cholangio-carcinoma	M	1	R	*MET* *TP53*	N375S R148K	1124A>G 443G>A	*MET* mutation may be benign polymorphism. Consider clinical trials with MET- or P53-directed therapies.	3 [37, 38]	No (pt. has declining PS)	SOC

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26	CRC	M	2	A (2 y)	*KRAS* *APC*	G12C T1420fs	38G>A 4255delinsAA	*KRAS* mutation suggests proteasome addiction and synthetic lethality to topoisomerase inhibitors in preclinical studies, but clinical evidence is lacking. Recommend clinical trials.	4 [39]	No (stable disease on SOC)	SOC Yttrium-90 (Y-90)
27	CRC	M	5	A (7 y)	*TP53* *JAK3*	splice site V722I	376-1G>A 2164G>A	Re-biopsy a current tumor and perform genetic analysis with larger gene panel. Recommend clinical trials.	NA	No	NR
28	Basal cell CA & Gorlin's Syndrome	M	5	R	*MET* *SMO* *TP53*	E168D G529V R248W	504G>T 1586G>T 742C>T	Impact of *MET* mutation is unknown, could confer sensitivity to MET inhibitor. Impact of *SMO* mutation is unknown, could confer sensitivity to SMO inhibitor. Recommend treatment with SMO inhibitor (Vismodegib is approved).	1 [37, 40, 41]	No (progressive disease, hospice referral)	None
29	NSCLC adeno. (*ALK*-normal)	M	0	R	*MET* *TP53*	N375S G134E	1124A>G 401G>A	*MET* mutation may be polymorphism. Consider clinical trials with MET inhibitor.	3 [20]	No (pt. declined treatment)	None
30	Breast CA (ER-, PR-, HER2+)	M	2	R	*FLT3*	S684P	2050T>C	*FLT3* mutations are common in AML, but rare in breast cancer. Treatment with a multi-kinase inhibitor that inhibits FLT3 (such as Dovitinib or Sorafenib) may have activity.	2 [42-45]	No (pt. died)	None (pt. died)
31	Melanoma	R	1	R	*NRAS*	Q61K	181C>A	*NRAS* mutation may be associated with sensitivity to MEK inhibitor. Use of adjuvant therapy is an option in the context of a clinical trial.	3 [46, 47]	NA	SOC surveillance
32	Breast CA (ER+, HER2-)	M	1	R	*PIK3CA* *APC* *TP53* *SRC*	H1047R A1340T R273H E527K	3140A>G 4018G>A 818G>A 1579G>A	*PIK3CA* mutation is activating. *SRC* is rarely mutated in breast cancer, but preclinical evidence indicates that *SRC* mutation is activating. Recommend treatment with SOC first-line anti-estrogen therapy. Upon disease progression, recommend treatment with SRC inhibitor.	3 [11-13, 48-51]	NA (stable disease on SOC)	SOC fulvestrant
33	NSCLC adeno. (*ALK*-normal)	M	2	R	*RET* *TP53*	S653C L111R	1958C>G 332T>G	Evaluate tumor for *KIF5B-RET* fusion. Consider treatment with RET inhibitor.	2 [52-54]	No (declining PS; hospice care)	SOC
34	CRC	P	0	R	*ALK* *PIK3CA* *PIK3CA* *APC* *PTEN* *PTEN*	R1181C E81K R88Q E1526 R130Q E299	3541C>T 241G>A 263G>A 4576G>T 389G>A 895G>T	*ALK* mutation lies in kinase domain; patient has history of mental retardation, and family history of colon cancer; consider germline testing for *ALK* mutation, as similar lesions are associated with increased risk of neuroblastoma.	NA	Yes (pursuing germline testing; stable disease on SOC)	SOC chemotherapy

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					RB1 *TP53*	E137* splice site	409G>T 163+2T>G	*PTEN* mutation(s) is inactivating, and R130Q is a germline mutation associated with Cowden's Syndrome, which would confer high risk for other malignancies. Recommend germline testing for *PTEN* mutation.			
35	Breast CA (ER+, HER2+)	M	4	R	*APC*	E1317Q	3949G>C	Recommend SOC, and tumor genetic profiling with larger gene panel.	NA	NA	SOC
36	NSCLC adeno. (*ALK*-normal)	M	0	R	*KRAS* *RET*	G12C E884V	34G>T 2651A>T	Recommend treatment with first-line SOC; upon disease progression, treat with RET/multi-kinase inhibitor Dovitinib.	2 [52-54]	NA (stable disease on SOC)	SOC chemotherapy
37	Breast CA (ER+, HER2-)	M	1	R	*APC*	E1299Q	3895G>C	Recommend continuation of SOC anti-estrogen therapy	NA	NA (stable disease on SOC)	SOC

Fluorescence in situ hybridization (FISH) analysis was performed on tumor types for relevant gene amplifications and rearrangements, including *ERBB2* (HER2) amplification in breast cancers (PathVysion HER2 kit, Abbott Molecular), *ALK* rearrangements in lung adenocarcinomas (*ALK* break-apart FISH kit, Abbott Molecular), and 1p/19q deletions in gliomas (mail-out test). MGMT promoter methylation testing was also performed on gliomas (mail-out test). Findings are indicated in second column as appropriate.

Abbreviations: ND- None detected; NR- not reported; NA- not applicable; pt.- patient; PS- performance status; SOC- standard of care; RT- radiation therapy; inh.- inhibitor; NSCLC- non-small cell lung cancer; CA- carcinoma; CRC – colorectal carcinoma; adeno.- adenocarcinoma; ER+/- indicates estrogen receptor alpha status; HER2+/- indicates HER2 proto-oncogene status; epithelioid hemangio.- epithelioid hemangioendothelioma.

Levels of evidence supporting targeted therapies recommended by Molecular Tumor Board:
Level 1: FDA-approved; demonstration that patients with tumors bearing specific genetic alterations are more likely to respond than those without such alterations.
Level 2: Agent met a clinical endpoint (objective response, PFS, or OS) with evidence of target inhibition; plausible evidence that tumors bearing a specific genetic alteration are predicted to respond.
Level 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.
Level 4: Preclinical evidence of anti-tumor activity and evidence of target inhibition; hypothesis that tumors bearing a specific alteration will respond.

[1]Additional mutations of unknown significance detected in tumor from Patient 23 include *APC*: C451R, R2525C; *EPHA3*: K365fs*6; *GNA11*: R60C; *MAP3K1*: R288Q; *PRKAR1A*: S155L; *TSHR*: N406fs*6; *ARID2*: A61V; *FANCA*: L1143V; *HGF*: E248D; *MED12*: Q2120_Q2121>HQQQQQ; *SMARCB1*: A359T; *BCL6*: R640Q; *FANCE*: S266L; *KDM5C*: R1445H, R787Q; *MTOR*: L1453P; *TET2*: A277P; *DOTL1*: P1470L; *FGFR4*: R83M; *KIT*: R686C; *NTRK2*: T748M; *TGFBR2*: R479W.

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