

# Molecular Tumor Board–Assisted Care in an Advanced Cancer Population: Results of a Phase II Clinical Trial

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**PURPOSE** Multidisciplinary molecular tumor boards (MTBs) interpret next-generation sequencing reports and help oncologists determine best therapeutic options; however, there is a paucity of data regarding their clinical utility. The purpose of this study was to determine if MTB-directed therapy improves progression-free survival (PFS) over immediately prior therapy in patients with advanced cancer.

**METHODS** This single-arm, prospective phase II clinical trial enrolled patients with advanced cancer with an actionable mutation who received MTB-recommended targeted therapy between January 1, 2017, and October 31, 2020. MTB-recommended both on-label (level 1 evidence) and off-label (evidence levels 2 and 3) therapies. Of the 93 enrolled patients, 43 were treated frontline and 50 received second-line or greater-line therapy. The primary outcome was the probability of patients treated with second-line or greater-line MTB-directed therapy who achieved a PFS ratio  $\geq 1.3$  (PFS on MTB-directed therapy divided by PFS on the patient's immediately prior therapy). Secondary outcomes included PFS for patients treated frontline and overall survival and adverse effects for the entire study population.

**RESULTS** The most common disease sites were lung (35 of 93, 38%), gynecologic (17 of 93, 18%), GI (16 of 93, 17%), and head and neck (7 of 93, 8%). The Kaplan-Meier estimate of the probability of PFS ratio  $\geq 1.3$  was 0.59 (95% CI, 0.47 to 0.75) for patients treated with second-line or greater-line MTB-directed therapy. The median PFS was 449 (range 42-1,125) days for patients treated frontline. The median overall survival was 768 (range 22-1,240) days. There were four nontreatment-related deaths.

**CONCLUSION** When treated with MTB-directed therapy, most patients experienced improved PFS compared with immediately prior treatment. MTB-directed targeted therapy may be a strategy to improve outcomes for patients with advanced cancer.

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## INTRODUCTION

Oncology care is shifting toward individualized driver mutation-directed cancer treatment. The growing number of companion diagnostic tests, next-generation sequencing (NGS) tests, and targeted therapies approved by the US Food and Drug Administration (FDA) is the evidence of the focus on these precision medicine initiatives.<sup>1</sup>

Although many targeted therapies are more efficacious and tolerable than cytotoxic chemotherapy,<sup>2,4</sup> clinical use remains challenging because of the complexity of applying NGS results to patient care.<sup>5,6</sup> To overcome this challenge, many institutions have implemented multidisciplinary molecular tumor boards (MTBs)<sup>7-9</sup> to prescribe optimal targeted therapies. Furthermore, the availability of an MTB increases oncologists' willingness to use NGS tests.<sup>10</sup>

Although many institutions have implemented MTBs, data supporting their clinical utility are limited. A recent systematic review concluded that MTBs appear to improve clinical outcomes for patients with cancer; however, most of the existing literature is retrospective, observational, and underpowered for efficacy.<sup>11</sup> Two prospective studies demonstrated improvement in survival indices for patients with a wide variety of tumor types<sup>12</sup> and in patients with non-small-cell lung cancer (NSCLC).<sup>13</sup>

We report results from a phase II clinical trial of MTB-assisted care. We assessed the probability of patients receiving second-line or greater-line MTB-directed therapy that achieved a progression-free survival (PFS) ratio  $\geq 1.3$  compared with immediately prior therapy.

## ASSOCIATED CONTENT

### Data Supplement Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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## CONTEXT

### Key Objective

Do patients with advanced cancer experience survival benefit from molecular tumor board (MTB)-directed targeted therapy?

### Knowledge Generated

In this prospective phase II clinical trial, most patients treated with second-line or greater-line MTB-directed therapy experienced a superior progression-free survival compared with their most recent line of therapy. Patients treated with frontline MTB-directed therapy also experienced benefit.

### Relevance

These findings demonstrate that patients with advanced cancer with targetable mutations experience improved progression-free survival when treated with MTB-directed therapy.

## METHODS

### Study Design

The Markey Cancer Center (MCC) MTB therapy trial (ClinicalTrials.gov identifier: [NCT03089554](https://clinicaltrials.gov/ct2/show/study/NCT03089554)) is a single-institution, open-label, and single-arm prospective clinical trial. Patients were followed from time of consent until death.

Patient data were collected and reported using Research Electronic Data Capture (Nashville, TN)<sup>14,15</sup> hosted at the University of Kentucky and the OnCore Database (Advarra Inc, Columbia, MD), which is housed on secure servers maintained by the MCC Cancer Informatics Shared Resource Facility.

### Ethical Considerations

The study was performed in accordance with the US FDA International Conference on Harmonization Guidelines for Good Clinical Practice and Declaration of Helsinki. The Protocol was approved by the University of Kentucky Institutional Review Board (IRB approval #48018). Each patient provided written informed consent before trial participation. This trial was regularly monitored by the MCC Data and Safety Monitoring Committee, and all adverse event data were recorded.

### Study Population

Patients with cancer who had undergone NGS genomic testing, had an actionable mutation, no curative therapy options, and received an MTB-recommended therapy were eligible for inclusion. Initially, patients were required to have received prior cancer therapy; however, as genomic testing moved into the frontline setting, the Protocol was amended to include patients without prior therapy. A list of full eligibility criteria is available in the Protocol.

### Study Intervention

**Somatic profiling.** Before enrollment, patients underwent physician's choice somatic tumoral tissue or circulating tumoral deoxyribonucleic acid NGS testing at a commercial Clinical Laboratory Improvement Amendments-certified laboratory.

Tumor mutational burden (TMB), defined as the total number of somatic mutations per megabase (mut/Mb) of DNA, was

classified as low (1-5 muts/Mb), intermediate (6-9 muts/Mb), or high ( $\geq 10$  muts/Mb) on the basis of accepted ranges at study inception.<sup>16</sup> Biomarker status, including immunohistochemical hormone receptor, microsatellite instability (MSI), programmed death-1 (PD-1)/programmed death-ligand 1 (PD-L1) expression, and loss of heterozygosity (LOH) scores were reviewed when available.

**MTB structure and review.** The University of Kentucky MCC MTB serves as a consulting service where physicians submit cases for review. MTB participants include medical and gynecologic oncologists, genetic counselors, pharmacists, nurses, pathologists, radiologists, and basic scientists. Redacted patient history, histopathology, radiology, and genomic results are discussed. Each genomic pathogenic or likely pathogenic alteration is reviewed to determine its function, oncogenicity, availability of any targeted therapeutics, or clinical trials. MTB recommendations may include physician's choice standard therapy, clinical trial referral, targeted therapy with an FDA-approved on-label or off-label therapy, or additional testing, including recommendations for germline testing.

If a targeted therapeutic recommendation is made, on-label options are prioritized, followed by clinical trials and off-label options with the highest level of evidence. All recommendations are provided to the treating oncologist in a letter that includes evidence levels. The University of Kentucky Healthcare Pharmacy and Therapeutics Committee developed a consensus guideline for grading evidence, which is available in the Data Supplement. Level 1 evidence included FDA-approved indications and National Comprehensive Cancer Network guideline-recommended therapies. Evidence level 2 included drugs with an FDA-approved indication for the specific mutation in another disease type and phase II or III clinical trial evidence for activity in the disease of interest. Evidence level 3 included FDA-approved drugs for the specific mutation in another disease type with case report or phase I clinical trial evidence for activity in the disease of interest. Preclinical evidence or evidence of pathway inhibition was considered category 4 and not recommended.

## Outcome Measures

The prespecified primary end point was the probability of patients treated with second-line or greater-line MTB-directed therapy who achieved a growth modulation index (GMI)  $\geq 1.3$ . GMI is calculated as PFS2/PFS1, where PFS2 is PFS on MTB-directed therapy and PFS1 is PFS on the patient's immediately prior therapy. Von Hoff et al<sup>17</sup> previously used this definition to define clinical benefit. PFS was defined as the time interval between the treatment start date and the date of clinical or radiographic disease progression as documented by the treating physician, date of death, or date of last follow-up, whichever occurred first. As PFS is expected to decrease with each subsequent therapy, an improvement in subsequent PFS suggests clinical benefit.<sup>18</sup>

Prespecified secondary outcomes included overall survival for all patients and treatment-related adverse events. PFS for patients treated with frontline MTB-directed therapy was an additional outcome but was not prespecified because of the Protocol amendment. Documentation of treatment-related adverse events included event duration, severity, temporal relationship to the receipt of study therapy, and if event resulted in study withdrawal. Toxicities were graded according to Common Terminology Criteria for Adverse Events version 5.0.<sup>19</sup>

## Statistical Analysis

Sample size was calculated on the basis of research results from the study by Von Hoff et al.<sup>17</sup> In this study, the null hypothesis was that  $\leq 15\%$  of patients had PFS2/PFS1  $\geq 1.3$  and final results indicated that 27% of patients experienced PFS2/PFS1  $\geq 1.3$ .<sup>17</sup> The alternative hypothesis for the present study was that  $\geq 27\%$  of patients had GMI  $\geq 1.3$  versus a null hypothesis of  $\leq 15\%$  of patients had GMI  $\geq 1.3$ .<sup>17</sup> To obtain 85% power with a 5% significance level, 93 patients were required, with one interim analysis planned on enrollment of 37 patients on the basis of a two-stage Simon's design.<sup>20,21</sup> Stopping bound for futility was set at less than or equal to six patients with GMI  $\geq 1.3$ .

Patient demographic, disease, treatment, and molecular characteristics were assessed with descriptive statistics. Separate analyses were performed for patients treated with MTB-directed second or greater line of therapy (cohort 1) and patients treated with MTB-directed frontline therapy (cohort 2). Since ignoring censoring of PFS2 using a simple proportion could result in an underestimated probability  $P = P(\text{GMI} > 1.3)$ , the probability  $P = P(\text{GMI} > 1.3)$  was assessed by the Kaplan-Meier method.<sup>22</sup> For cohort 2, the Kaplan-Meier method was used to evaluate PFS with 95% binomial CIs.

## RESULTS

### Patients

Between January 1, 2017, and October 31, 2020, 679 patients underwent MTB review. Of the 591 patients with actionable mutations, 98 were enrolled in this study. Before

starting MTB-directed therapy, five patients were determined to be ineligible; 93 received the intervention (Fig 1). Accrual was stopped once the planned number of patients was enrolled. The median patient age was 63 (range 18-85) years; most were female (58 of 93, 62%), non-Hispanic (92 of 93, 99%), and White (88 of 93, 95%). Demographic and disease characteristics are summarized in Table 1. The most common disease sites were lung (35 of 93, 38%), gynecologic (17 of 93, 18%), GI (16 of 93, 17%), and head and neck (7 of 93, 8%).

Cohort 1 (n = 50) included advanced ovarian, NSCLC, and head and neck cancers treated with second-line or greater-line MTB-directed therapy. Cohort 2 (n = 43) included patients with NSCLC, gastroesophageal, head and neck, nonmelanoma skin, and other cancers treated with first-line MTB-directed therapy. Primary tumor sites, targets, treatments, level of evidence, and individual patient PFS outcomes are detailed in the Data Supplement (cohort 1<sup>24</sup> and cohort 2).

### Molecular Profiling

Treatment targets were identified using commercial (n = 89), in-house (n = 2), or trial-specific<sup>23</sup> (n = 2) genomic testing and are detailed in Table 1. Tissue NGS was performed for 92 (99%) patients, and blood circulating tumoral deoxyribonucleic acid was performed for one patient. Ninety-four percent (87 of 93) of patients were tested for at least one immunotherapy biomarker, including TMB (n = 81), MSI (n = 83), and/or PD-1/PD-L1 expression (n = 38).

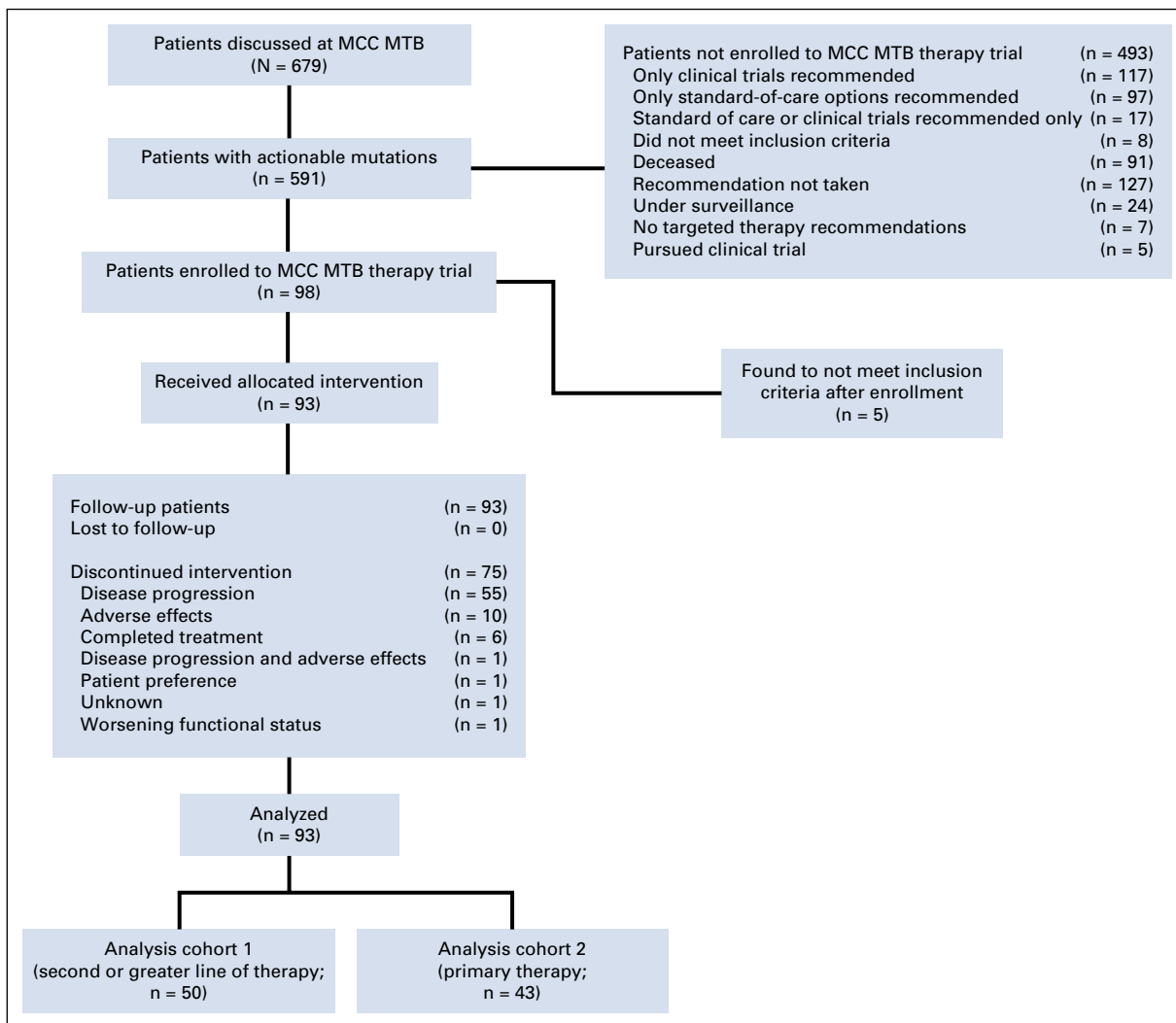
The most common genetic alterations included those in *TP53* (64 of 93, 69%), *CDKN2A* (23 of 93, 25%), *CDKN2B* (17 of 93, 18%), and *EGFR* (11 of 93, 12%). Among tumors evaluated for TMB, 24% (19 of 81) were high, 41% (33 of 81) were intermediate, and 36% (29 of 81) were low. MSI was present in 10% (8 of 83) of tumors tested, and 76% (29 of 38) of tumors evaluated for PD-L1 expression ( $\geq 1\%$  combined positive score) were positive.

Tumoral genomics, MTB-recommended targets, and received treatments are detailed in Figure 2. The most common targets were high TMB (26 of 93, 28%), PD-L1 expression (12 of 93, 13%), intermediate TMB (12 of 93, 13%), and *ERBB2* amplifications or mutations (11 of 93, 12%).

### Treatments

Immune checkpoint inhibitors were recommended for 59% (55 of 93) of participants, targeted high TMB for 47% (26 of 55), PD-L1 expression for 24% (13 of 55), intermediate TMB for 22% (12 of 55), and MSI for 9% (5 of 55). Immune checkpoint inhibitor therapy was recommended for one patient with PD-1 ligand 2 amplification (1 of 55, 2%) whose tumor also demonstrated PD-L1 positivity.

Small molecule inhibitors were recommended for 29% (27 of 93) of patients. Tyrosine kinase inhibitors (n = 10) included osimertinib (n = 4) and afatinib (n = 1), which targeted *EGFR* mutations; alectinib targeted an *ALK* fusion



**FIG 1.** Study flow diagram. Flow diagram shows identification of patients who underwent MTB review and subsequent enrollment in this trial. MCC, Markey Cancer Center; MTB, molecular tumor board.

(n = 1); crizotinib targeted an *ALK* rearrangement (n = 1); pazopanib targeted a *BCL2* rearrangement (n = 1); sorafenib targeted a *FLT3* mutation, and lapatinib was used in combination with trastuzumab to target an *ERBB2* amplification (n = 1). Poly-ADP ribose polymerase (PARP) inhibitors were used in eight patients, which targeted *BRCA2* (olaparib, n = 2; rucaparib, n = 1), *BRCA1* (rucaparib, n = 2), and *RAD51C* (rucaparib, n = 1) mutations and elevated LOH scores (niraparib, n = 1; rucaparib, n = 1). Mitogen-activated protein kinase (MEK) inhibitors targeted a *KRAS* mutation (cobimetinib, n = 1) and were used in combination with BRAF inhibitors (dabrafenib and trametinib, n = 3) to target *BRAF* V600E mutations. The mechanistic target of rapamycin inhibitor everolimus targeted an *NF2* mutation (n = 1) and a *PTEN* mutation (n = 1). Enasidenib, an isocitrate dehydrogenase-2 (IDH2) inhibitor, targeted an *IDH2* mutation (n = 1), and palbociclib, a cyclin dependent kinase 4/6 (CDK4/6) inhibitor, targeted a *CDK4* amplification (n = 1).

Trastuzumab was used in 11 (11 of 93, 12%) patients and targeted an *ERBB2* amplification (n = 9), point mutation (n = 1), and positive human epidermal growth factor receptor 2 immunohistochemistry (n = 1).

On-label therapies with level 1 evidence were recommended for 72% (67 of 93) of patients (cohort 1: 27 of 50; cohort 2: 40 of 43). Seven patients were treated with level 2–recommended therapies, and 19 were treated with level 3–recommended therapies. In cohort 1, five level 2 recommendations included an *ERBB2*-amplified salivary gland adenocarcinoma with trastuzumab and lapatinib, a *BRCA2*-mutated pancreatic cancer with a PARP inhibitor, a PD-L1–positive nonmelanoma skin cancer with pembrolizumab, and a neuroendocrine lung cancer with nivolumab. Before the site-agnostic FDA approval of pembrolizumab for high TMB,<sup>25</sup> one patient with anaplastic thyroid carcinoma in cohort 1 and one patient with squamous cell carcinoma arising from an ovarian teratoma in cohort 2 were treated with

**TABLE 1.** Baseline Demographic and Disease Characteristics in Patients Treated With MTB-Directed Therapy

Characteristic	No. (%)
Median age (years, range)	62 (18-85)
Sex	
Male	38 (41)
Female	55 (59)
Race	
White	88 (95)
Black or African American	3 (3)
Asian	1 (1)
Native Hawaiian or other Pacific Islander	1 (1)
Ethnicity	
Non-Hispanic	93 (100)
Primary site	
Lung and bronchus	35 (38)
NSCLC	34 (97)
Small cell lung cancer	1 (3)
Gynecologic	17 (18)
Ovarian, fallopian tube, and peritoneal	13 (77)
Uterine	4 (24)
GI	16 (17)
Gastroesophageal	9 (56)
Pancreatic	2 (13)
Colorectal and appendiceal	3 (19)
Liver	1 (6)
Anus	1 (16)
Head and neck	7 (8)
Thyroid gland	3 (3)
Leukemia	2 (2)
Breast	2 (2)
Nonmelanoma skin	5 (5)
Connective/soft tissue	2 (2)
Urinary tract	1 (1)
Unknown primary site	3 (3)
Stage	
I	2 (2)
II	2 (2)
III	10 (11)
IV	72 (82)
Not applicable <sup>a</sup>	2 (2)
Performance status	
ECOG score <sup>b</sup>	
0	16 (29)
1	32 (58)
2	7 (13)

(Continued in next column)

**TABLE 1.** Baseline Demographic and Disease Characteristics in Patients Treated With MTB-Directed Therapy (Continued)

Characteristic	No. (%)
Karnofsky scale <sup>c</sup>	
100	4 (8)
90	22 (45)
80	16 (33)
70	6 (12)
60	1 (2)
NGS type (No. of genes tested)	
FoundationOne CDx (324)	52 (34)
FoundationOne (315)	25 (27)
FoundationOne Heme (406)	4 (4)
UK Heme Panel (97)	2 (2)
Caris MI Tumor Seek (592)	2 (2)
Smart genomics (160)	2 (2)
NCI MATCH <sup>23</sup> (140)	2 (2)
ARUP <sup>d</sup>	2 (2)
Caris MI Profile (592)	1 (1)
Guardant360 (73)	1 (1)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; MTB, molecular tumor board; PD-L1, programmed death-ligand 1; NGS, next-generation sequencing; NSCLC, non-small-cell lung cancer.

<sup>a</sup>Staging was not applicable for two patients with hematologic malignancies.

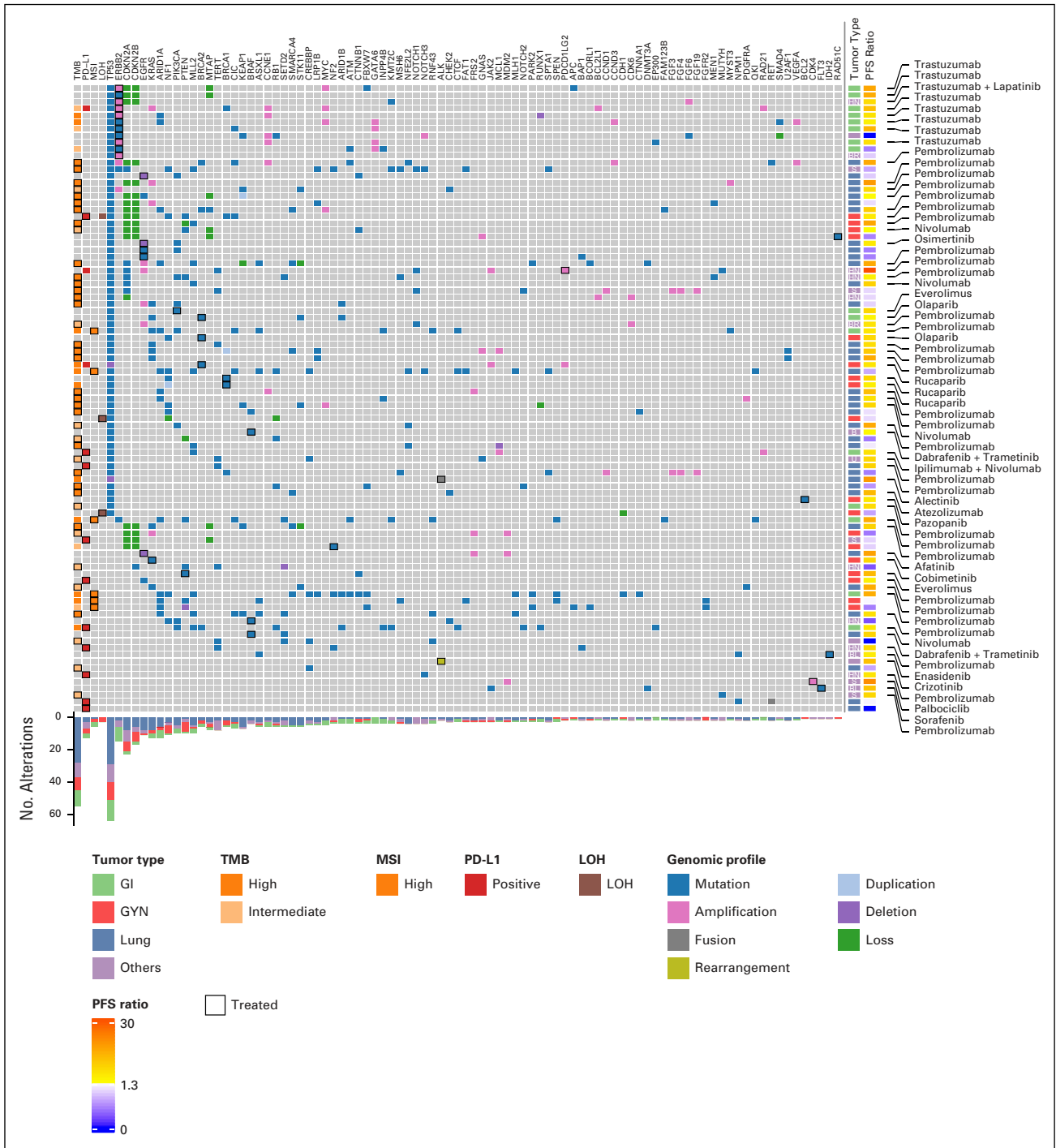
<sup>b</sup>ECOG score: 0, asymptomatic; 1, symptomatic but completely ambulatory; 2, symptomatic, < 50% in bed during the day.

<sup>c</sup>Karnofsky scale: 100, normal, no complaints, no evidence of disease; 90, able to perform normal activity, minor signs or symptoms of disease; 80, normal activity with effort, some signs or symptoms of disease; 70, cares for self, unable to perform normal activity or to do active work; 60, requires occasional assistance, but is able to care for most of personal needs.

<sup>d</sup>ARUP, tests evaluated for PD-L1, expression.

pembrolizumab for this indication. One patient with a *BRAF* V600E–mutated head and neck sarcoma was treated with BRAF and MEK inhibitors.

Level 3 recommendations (n = 19) were common in cohort 1 (n = 18) and included treatment of a *PTEN*-mutated ovarian cancer (n = 1), an *NF2*-mutated ovarian cancer (n = 1), and a *PIK3CA*-mutated cholangiocarcinoma (n = 1) with mechanistic target of rapamycin inhibitors; an *ALK*-rearranged mesothelioma with an ALK inhibitor (n = 1)<sup>24</sup>; a *BRAF* V600E–mutated anaplastic thyroid cancer with BRAF and MEK inhibitors (n = 1); a *KRAS*-mutated ovarian cancer with a MEK inhibitor (n = 1); and a *CDK4*-amplified liposarcoma with a CDK4/6 inhibitor (n = 1). Trastuzumab targeted an *ERBB2*-mutated neuroendocrine tumor (n = 1). Immune checkpoint inhibitors were recommended as a level 3 recommendation for PD-L1 positivity in head and neck mesothelioma (n = 1) and ovarian cancer (n = 1) and targeted intermediate TMB in appendiceal (n = 1), large cell neuroendocrine ovarian (n = 1), breast (n = 1), Hurthle cell thyroid (n = 1) cancers and



**FIG 2.** Genomic profiles, recommendations, and MTB-directed targeted therapy, and outcomes of patients enrolled in this trial. Genes and biomarkers are displayed in columns. Rows demonstrate individual tumor profiles, targeted therapy, and PFS ratio for each patient. GYN, gynecologic; LOH, loss of heterozygosity; MSI, microsatellite instability; MTB, molecular tumor board; PD-L1: programmed death-ligand 1; PFS, progression-free survival; TMB, tumor mutational burden.

retroperitoneal (n = 1) and head and neck (n = 1) sarcomas. Pembrolizumab was recommended for an MSI endometrial carcinoma (n = 1) before the FDA site-agnostic approval,<sup>26</sup> and niraparib was recommended for an ovarian cancer with an elevated LOH score (n = 1) as a level 3 recommendation before this FDA approval.<sup>27</sup> In cohort 2, one nonmelanoma

skin cancer with an intermediate TMB was treated with pembrolizumab.

**Efficacy and Survival**

As of April 15, 2021, the probability of patients treated with second-line or greater-line MTB-directed therapy achieving

GMI  $\geq 1.3$  was 0.54 (27 of 50); 95% CI, 0.40 to 0.68; the null hypothesis of 0.15 was rejected ( $P < .0001$ ). A Kaplan-Meier estimate of  $P(\text{GMI} \geq 1.3)$ , which accounted for censoring, was 0.59 (95% CI, 0.47 to 0.75; Fig 3A). The median baseline PFS1 for this cohort was 145 (range 35-1767) days, the median PFS2 was 186 (range 22-1,240) days, and the median GMI was 2.053 as estimated by the Kaplan-Meier method. Individual patient PFS2/PFS1 ratios are illustrated in Figures 3B and 4.

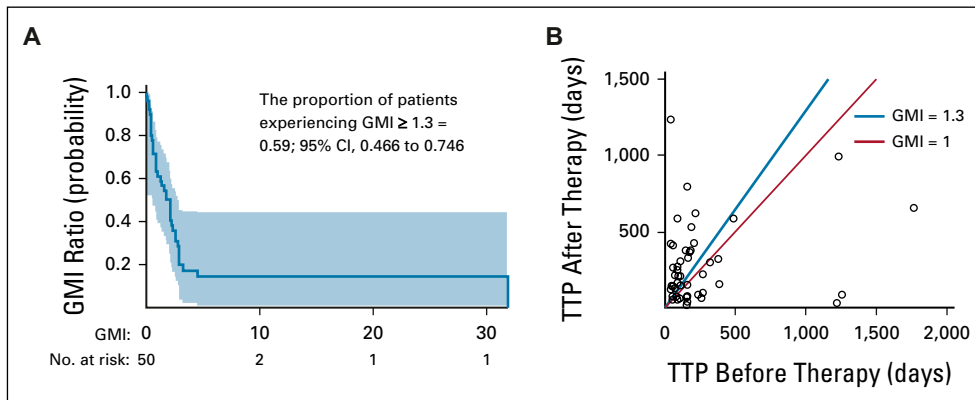
We compared survival outcomes for patients treated with second-line or greater-line MTB-directed therapy by evidence level (level 1 v level 2 or 3 evidence; Data Supplement). The Kaplan-Meier estimate of  $P(\text{GMI} \geq 1.3)$  was 0.61 (95% CI, 0.39 to 0.77), and the median PFS ratio was 2.053 (95% CI, 0.85 to 2.88) for patients treated with therapies with level 1 evidence. The Kaplan-Meier estimate of  $P(\text{GMI} \geq 1.3)$  was 0.57 (95% CI, 0.34 to 0.74), and the median PFS ratio was 1.551 (95% CI, 0.54 to 2.56) for patients treated with therapies with level 2 or 3 evidence. There was no difference between these groups (log-rank test;  $P = .54$ ), suggesting that benefit of MTB-directed therapy was similar regardless of the evidence level.

In cohort 2, the Kaplan-Meier estimate of the median PFS on MTB-directed frontline therapy was 449 (range 42-1,125) days (Data Supplement). In the entire cohort, the

median overall survival on MTB-directed therapy was 768 (range 22-1,240) days (Data Supplement).

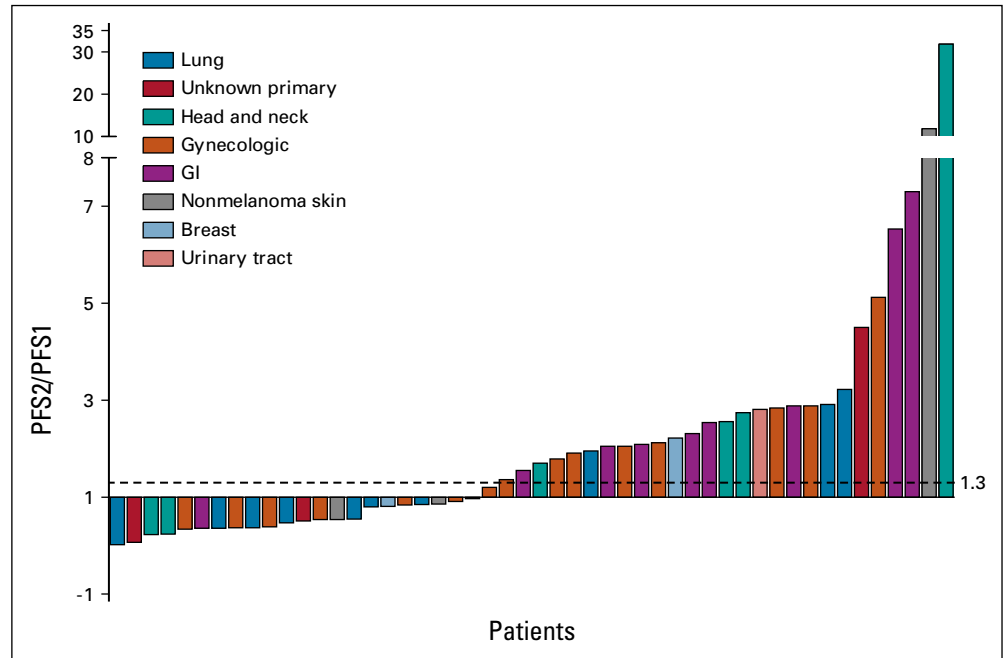
Exceptional responses were noted in both cohorts. One patient with head and neck squamous cell carcinoma treated with pembrolizumab experienced a PFS2/PFS1 of 31.79. Although the indication for this on-label therapy was *PDCD1LG2* amplification, which is predictive of clinical response in this disease,<sup>28</sup> this patient was subsequently tested for PD-L1 expression, which was also positive. One patient with a *PTEN*-mutated ovarian cancer experienced a PFS2/PFS1 ratio of 5.12 on (evidence level 3) everolimus, consistent with a previous report suggesting benefit in this population.<sup>29</sup> Before the FDA site-agnostic approval of pembrolizumab for high TMB,<sup>25</sup> one patient with squamous cell carcinoma arising from an ovarian teratoma was treated with frontline MTB-directed (evidence level 2) pembrolizumab for a TMB of 25 and experienced a PFS of 880 days.

Poor responses were also noted for patients treated with on-label therapies. These included a PD-L1–positive NSCLC treated with pembrolizumab (PFS2/PFS1 = 0.02), an *ERBB2*-amplified esophageal adenocarcinoma treated with trastuzumab (PFS2/PFS1 = 0.36), an MSI endometrial cancer treated with pembrolizumab (PFS2/PFS1 = 0.37), and two ovarian cancers treated with PARP inhibitors for a



**FIG 3.** Growth modulation index among patients treated with second-line or greater-line MTB-directed therapy (cohort 1;  $n = 50$ ). (A) GMI analysis for 50 patients who had prior therapy PFS data. Larger GMI values represent higher PFS2/PFS1 ratios, indicating superior PFS on MTB-directed therapy (PFS2). Survival probability indicates the probability of obtaining or exceeding a particular GMI. A GMI  $\geq 1.3$  suggests the benefit of subsequent therapy. The simple proportion of patients experiencing GMI  $\geq 1.3$  (27 of 50) is 0.54. To provide an accurate estimation, the Kaplan-Meier method accounts for censoring of PFS2 and is 0.59. The Hall-Wellner band indicates the 95% CI, 0.466 to 0.746. (B) Individual patients' time to progression (days) on prior therapy (x axis) and MTB-directed therapy (y axis) is delineated by a circle. The blue line indicates GMI = 1.3. Patients to the left of the blue line demonstrated the most benefit from MTB-directed therapy with some long-term survivors. The red line indicates GMI = 1.0. Patients with GMI = 1.0 conferred the same benefit from MTB-directed therapy as they with their most recent therapy. GMI, growth modulation index; MTB, molecular tumor board; PFS, progression-free survival; TTP, time to progression.

**FIG 4.** Waterfall plot detailing individual PFS ratio (PFS2/PFS1) values for patients treated with second-line or greater-line MTB-directed therapy (cohort 1; n = 50). A larger PFS2/PFS1 value indicates a greater benefit of MTB-directed therapy. MTB, molecular tumor board; PFS, progression-free survival.



*RAD51C* mutation (PFS2/PFS1 = 0.39) and an elevated LOH score (PFS2/PFS1 = 0.54).

### Safety

A summary of adverse event data is available in the Data Supplement. All-grade adverse events occurred in 23% of patients (21 of 93). Grade 3 events were experienced by 17% (16 of 93) and included GI (14 events, nine patients) and respiratory, thoracic, and mediastinal (nine events, five patients) disorders. Grade 4 events occurred in two patients (2 of 93, 2%) and included neutropenia (1 of 93, 1%) and nonfatal respiratory failure (1 of 93, 1%). While on study, two patients died of progressive disease and two patients died of sepsis. One patient died of sepsis related to aspiration pneumonia 5 days after pembrolizumab administration. A separate patient died of sepsis resulting from a chronic pelvic abscess 15 days after nivolumab administration. Neither of the deaths were determined to be drug-related on independent reviews by the study investigators and treating physicians.

### DISCUSSION

This prospective phase II trial demonstrated a survival benefit of MTB-directed therapy over immediately prior therapy. The probability of patients treated with MTB-directed second-line or greater-line therapy experiencing GMI  $\geq 1.3$  was 0.59. These results are superior to those previously reported by Von Hoff et al,<sup>17</sup> where 27% (18 of 66) of patients demonstrated a PFS ratio  $\geq 1.3$ <sup>17</sup> and comparable with those reported by Radovich et al,<sup>30</sup> which showed that 43% (19 of 44) of patients achieved a PFS ratio  $\geq 1.3$ . Differences are likely related to increased availability of targeted therapies, including immune checkpoint inhibitors.

The patients most likely to achieve a PFS ratio  $\geq 1.3$  in these publications were breast and colon cancers<sup>17</sup> and sarcomas.<sup>30</sup> Although our study enrolled few patients with sarcoma and breast cancer, 8 of 9 (89%) patients with GI cancer, 4 of 5 (80%) patients with head and neck cancer, and 8 of 14 (57%) patients with gynecologic cancer experienced PFS2/PFS1  $\geq 1.3$ . This demonstrates the benefit of MTB-directed care across a wide variety of tumor types.

Personalized cancer therapies are quickly becoming approved for multiple molecular targets and primary disease sites. This results in more difficult decisions for patients whose tumors harbor more than one actionable mutation. MTBs may help oncologists choose the most efficacious therapy option, especially when multiple options are available. Although a benefit of the MTB is identifying off-label therapies, oncologists are more likely to use NGS testing to support on-label therapies.<sup>10</sup> The present study demonstrates similar evidence of benefit for patients treated with on-label and off-label therapies, which supports the continuous practice of MTB off-label recommendations.

Although most MTB studies include few or no patients treated with up-front targeted therapy, patients treated with frontline MTB-directed therapy in this study experienced a median PFS of 14.9 months (449 days). Sixty percent (26 of 43) of patients in this cohort had advanced or metastatic NSCLC, where NGS sequencing and targeted therapy are frontline.<sup>31</sup> Our findings echo the report of Koopman et al,<sup>32</sup> describing a median PFS equal to 6.3 months in patients with NSCLC receiving MTB-directed frontline therapy. Although 60% of patients treated with frontline MTB-directed therapy in our study had a diagnosis of NSCLC, the other 40% with varying histologies also benefitted.



Frequency of adverse events was consistent with previous MTB studies,<sup>33</sup> and toxicities were as expected for the anticancer agents used in the study.

A strength of this study is its prospective, interventional design. As most previous MTB-related studies are observational, we provide evidence of benefit of MTB-directed care. The statistical design with the use of the novel GMI end point and the Kaplan-Meier method to adjust for censoring is another strength as it compares MTB-directed therapy with the patients' immediately prior therapy, allowing the patient to serve as their own control. Of the 139 patients whom the MTB identified to be eligible for at least one clinical trial, five patients pursued these opportunities. It is important to note that these patients were excluded from this analysis as we felt that it was unethical to count their outcomes in two clinical trials.

Limitations include the possibility of selection bias as this was a single-arm study that only enrolled patients with an actionable mutation and received MTB-directed therapy; therefore, benefit is confined to patients with targetable mutations. This study was conducted at a single-institution tertiary referral center with a largely rural, Appalachian population and may not be generalizable to other

populations. Furthermore, this was an unblinded, non-randomized study with clinical disease assessments and PFS calculated by the study investigators. This could result in less precise assessment and bias in ascertaining PFS; however, patients were usually managed by the same treating oncologist for both regimens, and measurement error is likely similar between the MTB-directed and immediately prior regimens. To minimize bias, study investigators used predefined criteria to assess PFS.

Finally, because of the markedly better-than-anticipated outcomes demonstrated in the planned interim analysis, only 50 patients were enrolled into cohort 1 despite initial sample size calculations requiring 93 patients to detect  $GMI \geq 1.3$  in 27% of patients. As a result, an IRB-approved Protocol modification permitted enrollment of patients treated with frontline MTB-directed therapy into a second cohort to total 93 patients.

In conclusion, this prospective study demonstrates that patients with advanced cancer with targetable mutations experience survival benefit when receiving MTB-directed care. Additional trials in disease-specific populations and with randomized designs are warranted.

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## CLINICAL TRIAL INFORMATION

[NCT03089554](https://clinicaltrials.gov/ct2/show/study/NCT03089554)

## DATA SHARING STATEMENT

Anonymized data sets may be available upon request. Requests for access to data may be obtained by contacting the corresponding author.

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## REFERENCES

- Colomer R, Mondejar R, Romero-Laorden N, et al: When should we order a next generation sequencing test in a patient with cancer?. *EClinicalMedicine* 25:100487, 2020
- Zhao TT, Xu H, Xu HM, et al: The efficacy and safety of targeted therapy with or without chemotherapy in advanced gastric cancer treatment: A network meta-analysis of well-designed randomized controlled trials. *Gastric Cancer* 21:361-371, 2018
- Schwaederle M, Zhao M, Lee JJ, et al: Association of biomarker-based treatment strategies with response rates and progression-free survival in refractory malignant neoplasms: A meta-analysis. *JAMA Oncol* 2:1452-1459, 2016
- Jardim DL, Schwaederle M, Wei C, et al: Impact of a biomarker-based strategy on oncology drug development: A meta-analysis of clinical trials leading to FDA approval. *J Natl Cancer Inst* 107:djv253, 2015
- Gray SW, Hicks-Courant K, Cronin A, et al: Physicians' attitudes about multiplex tumor genomic testing. *J Clin Oncol* 32:1317-1323, 2014
- Kurzrock R, Colevas AD, Olszanski A, et al: NCCN oncology research program's investigator steering committee and NCCN best practices committee molecular profiling surveys. *J Natl Compr Canc Netw* 13:1337-1346, 2015
- Bourret P, Cambrosio A: Genomic expertise in action: Molecular tumour boards and decision-making in precision oncology. *Social Health Illn* 41:1568-1584, 2019
- Burkard ME, Deming DA, Parsons BM, et al: Implementation and clinical utility of an integrated academic-community regional molecular tumor board. *JCO Precis Oncol* 10.1200/PO.16.00022, 2017
- Walko C, Kiel PJ, Kolesar J: Precision medicine in oncology: New practice models and roles for oncology pharmacists. *Am J Health Syst Pharm* 73:1935-1942, 2016
- Freedman AN, Klabunde CN, Wiant K, et al: Use of next-generation sequencing tests to guide cancer treatment: Results from a nationally representative survey of oncologists in the United States. *JCO Precis Oncol* 2:1-13, 2018
- Larson KL, Huang B, Weiss HL, et al: Clinical outcomes of molecular tumor boards: A systematic review. *JCO Precis Oncol* 5:1122-1132, 2021
- Kato S, Kim KH, Lim HJ, et al: Real-world data from a molecular tumor board demonstrates improved outcomes with a precision N-of-One strategy. *Nat Commun* 11:4965, 2020
- Huang B, Chen Q, Allison D, et al.: Molecular tumor board review and improved overall survival in non-small-cell lung cancer. *JCO Precis Oncol* 5:1530-1539, 2021
- Harris PA, Taylor R, Thielke R, et al: Research electronic data capture (REDCap)—A metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 42:377-381, 2009
- Harris PA, Taylor R, Minor BL, et al: The REDCap consortium: Building an international community of software platform partners. *J Biomed Inform* 95:103208, 2019
- Goodman AM, Kato S, Bazhenova L, et al.: Tumor mutational burden as an independent predictor of response to immunotherapy in diverse cancers. *Mol Cancer Ther* 16:2598-2608, 2017
- Von Hoff DD, Stephenson JJ Jr., Rosen P, et al: Pilot study using molecular profiling of patients' tumors to find potential targets and select treatments for their refractory cancers. *J Clin Oncol* 28:4877-4883, 2010
- Bailey CH, Jameson G, Sima C, et al.: Progression-free survival decreases with each subsequent therapy in patients presenting for phase I clinical trials. *J Cancer* 3:7-13, 2012
- Lichtman SM: Pharmacokinetics and pharmacodynamics in the elderly. *Clin Adv Hematol Oncol* 5:181-182, 2007
- Jung SH, Kim KM: On the estimation of the binomial probability in multistage clinical trials. *Stat Med* 23:881-896, 2004
- Koyama T, Chen H: Proper inference from Simon's two-stage designs. *Stat Med* 27:3145-3154, 2008
- Wu J, Chen L, Wei J, et al: Phase II trial design with growth modulation index as the primary endpoint. *Pharm Stat* 18:212-222, 2019
- Flaherty KT, Gray RJ, Chen AP, et al: Molecular landscape and actionable alterations in a genomically guided cancer clinical trial: National Cancer Institute Molecular Analysis for Therapy Choice (NCI-MATCH). *J Clin Oncol* 38:3883-3894, 2020
- Patel RA, Lin M, Harper MM, et al: Pediatric patient with peritoneal mesothelioma harboring ALK rearrangement. *Curr Probl Cancer Case Rep* 4:100074, 2021
- United States Food and Drug Administration: FDA Approves Pembrolizumab for Adults and Children With TMB-H Solid Tumors, 2020. <https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-pembrolizumab-adults-and-children-tmb-h-solid-tumors>
- United States Food and Drug Administration: FDA Grants Accelerated Approval to Pembrolizumab for First Tissue/Site Agnostic Indication, 2017. <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-pembrolizumab-first-tissuesite-agnostic-indication>
- United States Food and Drug Administration: FDA Approves Niraparib for HRD-Positive Advanced Ovarian Cancer, 2019. <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-niraparib-hrd-positive-advanced-ovarian-cancer>
- Yearley JH, Gibson C, Yu N, et al: PD-L2 expression in human tumors: Relevance to anti-PD-1 therapy in cancer. *Clin Cancer Res* 23:3158-3167, 2017

29. Wheeler JJ, Moulder SL, Naing A, et al: Anastrozole and everolimus in advanced gynecologic and breast malignancies: Activity and molecular alterations in the PI3K/AKT/mTOR pathway. *Oncotarget* 5:3029-3038, 2014
30. Radovich M, Kiel PJ, Nance SM, et al: Clinical benefit of a precision medicine based approach for guiding treatment of refractory cancers. *Oncotarget* 7:56491-56500, 2016
31. Ettinger DS, Wood DE, Aisner DL, et al: NCCN Clinical Practice Guidelines in Oncology: Non-small Cell Lung Cancer. Version 7.2021. 2021. [https://www.nccn.org/professionals/physician\\_gls/pdf/nscl.pdf](https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf)
32. Koopman B, van der Wekken AJ, Elst A, et al: Relevance and effectiveness of molecular tumor board recommendations for patients with non-small-cell lung cancer with rare or complex mutational profiles. *JCO Precis Oncol*:393-410, 2020
33. Réda M, Richard C, Bertaut A, et al: Implementation and use of whole exome sequencing for metastatic solid cancer. *EBioMedicine* 51:102624, 2020

