

Actionable Tumor Alterations and Treatment Protocol Enrollment of Pediatric and Young Adult Patients With Refractory Cancers in the National Cancer Institute–Children’s Oncology Group Pediatric MATCH Trial

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PURPOSE The National Cancer Institute–Children’s Oncology Group Pediatric MATCH trial aimed to facilitate evaluation of molecular-targeted therapies in biomarker-selected cohorts of childhood and young adult patients with cancer by screening tumors for actionable alterations.

PATIENTS AND METHODS Tumors from patients age 1-21 years with refractory solid tumors, lymphomas, or histiocytic disorders were subjected to cancer gene panel sequencing and limited immunohistochemistry to identify actionable alterations for assignment to phase II treatment arms. The rates of treatment arm assignment and enrollment were compared between clinical and demographic groups.

RESULTS Testing was completed for 94.7% of tumors submitted. Actionable alterations were detected in 31.5% of the first 1,000 tumors screened, with treatment arm assignment and enrollment occurring in 28.4% and 13.1% of patients, respectively. Assignment rates varied by tumor histology and were higher for patients with CNS tumors or enrolled at Pediatric Early Phase Clinical Trials Network sites. A reported history of prior clinical molecular testing was associated with higher assignment and enrollment rates. Actionable alterations in the mitogen-activated protein kinase signaling pathway were most frequent (11.2%). The most common reasons provided for not enrolling on treatment arms were patients receiving other treatment or poor clinical status.

CONCLUSION The Pediatric MATCH trial has proven the feasibility of a nationwide screening Protocol for identification of actionable genetic alterations and assignment of pediatric and young adult patients with refractory cancers to trials of molecularly targeted therapies. These data support the early use of tumor molecular screening for childhood patients with cancer whose tumors have not responded to standard treatments.

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INTRODUCTION

Although outcomes for children diagnosed with cancer have improved, effective treatment options for most recurrent cancers are limited and novel approaches are needed. Significant research effort has focused on interrogation of the genomic landscapes of pediatric cancers, providing insight into tumor biology and revealing potentially targetable genetic alterations in key signaling pathways.^{1,2} Clinical trials have demonstrated the benefit of such therapies for selected pediatric patients whose cancers harbor relevant (actionable) genetic alterations.³⁻⁵

These alterations each only occur in a fraction of pediatric tumors, however, and often in multiple

disease histologies,^{1,2} complicating efforts to evaluate novel molecularly targeted agents. Access to investigational molecularly targeted therapies in children has also presented a limitation to the performance of biomarker-selected trials.⁶ Moreover, data are limited regarding the frequency of actionable tumor alterations in recurrent pediatric cancers, and the utility of a molecular screening approach for pediatric patients is not known. The National Cancer Institute–Children’s Oncology Group Pediatric Molecular Analysis for Therapy Choice (NCI-COG Pediatric MATCH) trial was therefore developed to provide a national framework for trials of investigational molecularly targeted therapies in biomarker-selected populations.⁷

ASSOCIATED CONTENT

Appendix

Data Supplement Protocol

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

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CONTEXT

Key Objective

Cancer therapies targeting genetic alterations in key signaling pathways offer benefit for selected patients, but the utility of a molecular screening approach for children with refractory cancers is unknown. National Cancer Institute–Children’s Oncology Group Pediatric MATCH created a nationwide Protocol to facilitate enrollment in phase II trials of molecularly targeted therapies using next-generation sequencing to identify tumors harboring actionable genetic alterations. This analysis examined the frequency and spectrum of actionable tumor alterations in 1,000 patients and the resulting rates of treatment arm assignment and enrollment.

Knowledge Generated

Actionable genetic alterations in diverse genes were identified in 31% of tumors sequenced. Assignments to treatment arms were made for 28% of patients screened and 13% of patients enrolled in those studies.

Relevance

Next-generation tumor sequencing was effective at identifying actionable genetic alterations for investigational targeted therapies in pediatric and young adult patients with refractory cancers, supporting the use of molecular screening in this population.

The NCI-COG Pediatric MATCH screening Protocol (online only) allows enrollment of patients from COG institutions across the United States. Centralized tumor sequencing was performed, and patients with actionable tumor alterations were then eligible for phase II treatment arms of targeted therapies. We describe here the frequency and spectrum of alterations detected in the first 1,000 patients screened and the experience with treatment arm assignment and enrollment for children and young adults with advanced cancers enrolled in this national trial.

PATIENTS AND METHODS

Patient Selection and Clinical Data Collection

Patients age 1-21 years with treatment-refractory or recurrent solid tumors, non-Hodgkin lymphomas, or histiocytic disorders treated at US-based COG sites were eligible for the NCI-COG Pediatric MATCH screening trial (NCT03155620). Patients enrolled in the screening Protocol were required to have a tumor sample available for study testing (see the Biopsy Specimens and Tumor Testing section) or be planned to have a clinically indicated procedure to obtain such a sample. The trial was approved by the NCI Central Institutional Review Board, which serves as the Institutional Review Board of record for COG institutions. A written informed consent document was signed by all patients, and assent was obtained as appropriate. Patient demographic and clinical data were reported by study sites.

Selection of Study Drugs

Drugs studied in Pediatric MATCH (Fig 1 and Data Supplement, online only) were used as single agents. A Target and Agent Prioritization study committee (Data Supplement) longitudinally reviewed potential classes of agents and individual drugs and recommended agents for

inclusion in the trial.⁷ The study included 13 treatment arms with agents inhibiting a wide range of molecular targets (Fig 1); seven of these were activated with the screening Protocol, and six at later time points. Multiple arms with agents targeting mitogen-activated protein kinase (MAPK) signaling were included, collectively referred to as MAPK pathway arms: Arm E, selumetinib; Arm G, vemurafenib; Arm J, ulixertinib; and Arm M, tipifarnib.

Definition of Targetable Alterations

Lists of actionable molecular alterations were generated for each treatment arm on the basis of predefined levels of clinical and preclinical evidence (Fig 1 and Data Supplement). Actionable alteration lists for treatment arms were nonoverlapping except for the MAPK pathway arms. For patients with tumors harboring actionable alterations for more than one treatment arm, the arm with the highest level of evidence linking the alteration to the agent was prioritized. All treatment arms were histology-agnostic except Arms E (selumetinib) and G (vemurafenib) for which patients with low-grade glioma were ineligible because previous clinical trials of those agents had already established activity.^{8,9}

Biopsy Specimens and Tumor Testing

Formalin-fixed paraffin-embedded (FFPE) tumors submitted for Pediatric MATCH screening were required to have been obtained at any point after initial tumor recurrence or progression. A tumor sample from a diagnostic (pretreatment) procedure was only acceptable for use in screening for patients with high-grade gliomas of the brainstem or thalamus. The study Protocol advised that tumor samples that had been subjected to acid-based decalcification were generally not suitable for testing. All specimens were processed in the COG Biopathology Core laboratory at Nationwide Children’s Hospital. Isolated DNA

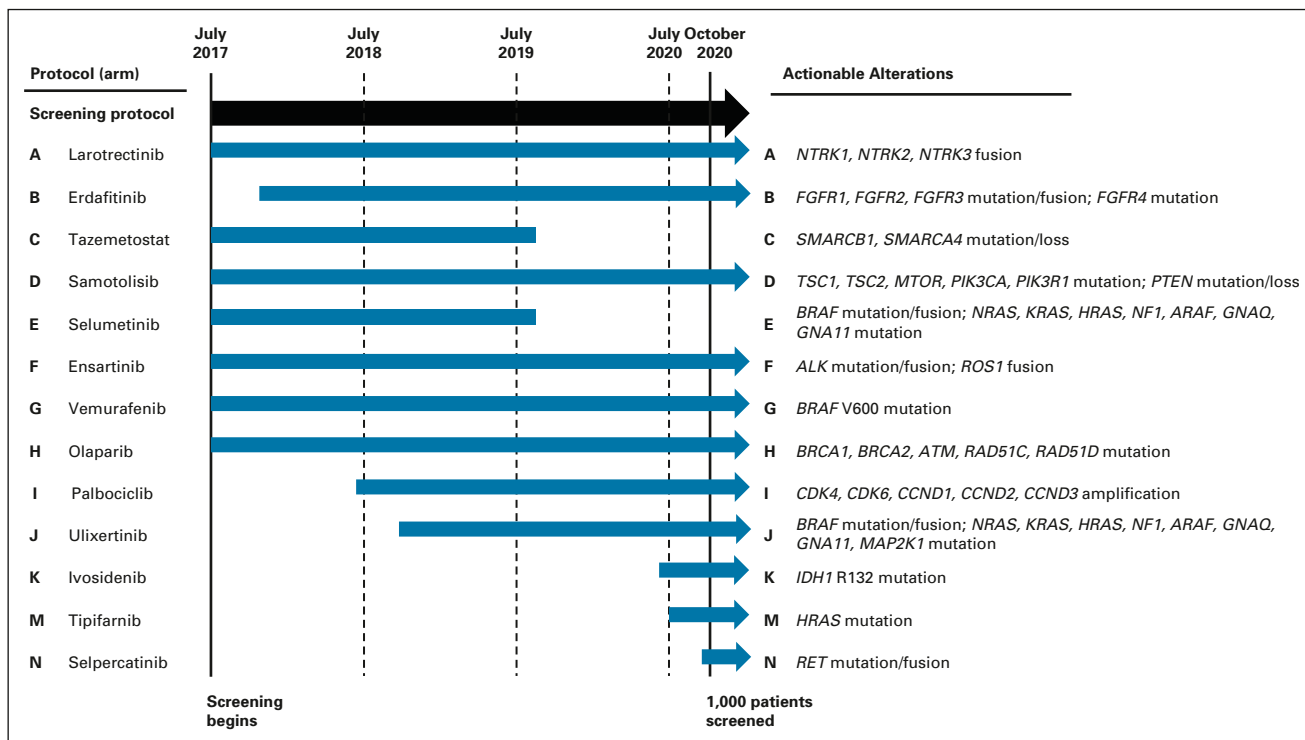


FIG 1. Pediatric MATCH trial arms and actionable cancer genes. The screening protocol and the seven treatment arms (A, C, D, E, F, G, and H) were activated in July 2017. Six additional treatment arms (B, I, J, K, M, and N) had been activated by the time the 1,000th patient screened was enrolled in October 2020. Arms C and E were closed after completion of study accrual.

and RNA for next-generation sequencing and slides for immunohistochemistry (IHC) were then sent to Pediatric MATCH laboratories (Data Supplement) for testing.

Next-Generation Sequencing and IHC Assays

DNA and RNA extracted from the FFPE tumor samples were sequenced using an OncoPrint AmpliSeq cancer gene panel (Thermo Fisher Scientific, Waltham, MA) designed for detection of single-nucleotide variants (SNVs), insertions and deletions, amplifications, and selected fusions in 159 cancer genes (Data Supplement).¹⁰ A variant allele fraction of 0.05 was required for reporting of SNVs and 0.10 for indels, with amplification defined as ≥ 7 gene copies. Copy number losses and consensus splice site mutations were not analyzed. Loss of protein expression for selected tumor suppressor genes (*SMARCB1*, *SMARCA4*, and *PTEN*) was evaluated by IHC; reflex testing for RB1 expression was performed only in tumors with an actionable alteration for Arm I (palbociclib). A software application (MATCHBOX) to facilitate processing and analysis of sequence data, treatment arm assignment, and patient tracking on the basis of that used for the adult NCI-MATCH trial was developed for the current study.^{10,11}

Study Definitions and Statistical Analysis

The study planned to screen 200-300 patients per year (17-25 per month), of which 10% were expected to have an actionable alteration of interest for which a treatment

Protocol was available. For the match rate feasibility analysis, the match rate along with the 95% score CI was assessed among patients with confirmed variant reports. The actionable alteration rate was defined as the fraction of tumors that had an actionable alteration detected for any study arm (regardless of slot availability). The treatment arm assignment (match) rate and enrollment rate were defined as the fraction of patients screened who were assigned to a treatment Protocol and the fraction of assigned patients who enrolled in a treatment arm, respectively. The 95% score type of CI was reported. Chi-square tests (or Fisher's exact tests as appropriate) were used to compare treatment arm matching and enrollment rates between groups. Statistical significance was set at P -values $< .05$. Data were analyzed using SAS version 9.4 and R version 4.0.2. Data as of December 31, 2020 were used in this article.

RESULTS

Patient Characteristics

The Pediatric MATCH screening Protocol was activated in July 2017. Tumor profiling was completed by December 2020 for 1,000 patients enrolled at 138 COG study sites in the United States between July 2017 and October 2020 (Appendix Fig A1, online only). The median screening Protocol enrollment rate was 28 patients per month over this period (range, 2-52; Appendix Fig A2, online only). Patient characteristics are summarized in Table 1. Patients

ranged in age from 1 to 21 years (median 13 years) with a slight predominance of males (55.6%). Adolescent and young adult patients (age 15-21 years) comprised 40.6% of the cohort. Most patients were White (69.0%) and of non-Hispanic or Latino ethnicity (72.7%). The median performance status score (Lansky or Karnofsky) was 90, with a score < 80 reported for 15.1% of patients. Fewer than half of the screened patients (45.2%) were enrolled at one of the

37 COG study sites in the United States that are members of the Pediatric Early Phase Clinical Trials Network (PEP-CTN).¹²

Solid tumors occurring outside the CNS comprised 72.3% of patient diagnoses, with CNS tumors in 24.6% and lymphomas/histiocytoses in 3.1% (Tables 1 and 2). Osteosarcoma (18.4%), rhabdomyosarcoma (12.0%), and Ewing sarcoma (10.4%) were most common; sarcomas as

TABLE 1. NCI-COG Pediatric MATCH Screening Trial Patient Characteristics

Characteristic	Screened Patients (n = 1,000)	Assigned to Trial Arms (n = 284)	Enrolled in a Trial Arm (n = 131)
Sex			
Female	444 (44)	125 (44)	57 (44)
Male	556 (56)	159 (56)	74 (56)
Median age, years (range)	13 (1-21)	12 (1-21)	13 (1-21)
Age categories, years			
< 5 years	119 (12)	40 (14)	15 (12)
≥ 5 and < 15 years	475 (48)	135 (48)	60 (46)
≥ 15 years	406 (41)	109 (38)	56 (43)
Race			
White	690 (69)	200 (70)	94 (72)
Black or African American	140 (14)	42 (15)	18 (14)
Asian	34 (3)	10 (4)	3 (2)
Native Hawaiian or Pacific Islander	8 (1)	2 (1)	2 (2)
American Indian or Alaska Native	3 (< 1)	0 (0)	0 (0)
Multiple races	14 (1)	2 (1)	1 (1)
Not reported	111 (11)	28 (10)	13 (10)
Ethnicity			
Hispanic or Latino	228 (23)	64 (23)	30 (23)
Not Hispanic or Latino	727 (73)	207 (73)	97 (74)
Not reported	45 (4)	13 (5)	4 (3)
Tumor category			
Non-CNS solid tumor	723 (72)	165 (58)	77 (59)
CNS solid tumor	246 (25)	109 (38)	52 (40)
Lymphoma/histiocytosis	31 (3)	10 (4)	2 (2)
History of prior clinical tumor profiling			
Yes	275 (28)	105 (37)	56 (43)
No	394 (39)	86 (30)	33 (25)
Not reported	331 (33)	93 (33)	42 (32)
Performance status (Lansky or Karnofsky)			
< 80	151 (15)	43 (15)	17 (13)
≥ 80	849 (85)	241 (85)	114 (87)
Enrolling institution			
PEP-CTN member	452 (45)	150 (53)	71 (54)
Not PEP-CTN member	548 (55)	134 (47)	60 (46)

NOTE. The table reflects data collected at screening enrollment. Data are reported as No. (%) unless otherwise indicated.

Abbreviations: NCI-COG, The National Cancer Institute–Children’s Oncology Group; PEP-CTN member, core or noncore member of the Pediatric Early Phase Clinical Trial Network (n = 37 institutions in the United States).

a group comprised 50.5% of the cohort. High-grade glioma (6.9%), neuroblastoma (6.0%), Wilms tumor (5.6%), and low-grade glioma (5.4%) were the only other tumor types observed in more than 5% of patients (Table 2). The remaining 353 patients (35.3%) had less frequent tumor types. In total, 80 different diagnoses were included in the study cohort (Data Supplement), with 61 of these found in fewer than 1% of patients.

Feasibility of Molecular Profiling

Tumors were submitted for 1,056 of 1,111 (95.0%) patients enrolled between July 2017 and October 2020 (Fig 2). Tumor screening was completed for 1,000 of these 1,056 patients (94.7%): the cohort being analyzed in this report. The RNA panel testing component of the assay was unsuccessful in 11.9% of these patients. The median and 75th percentile times from the receipt of the tumor sample

TABLE 2. Diagnoses and Matching Results of NCI-COG Pediatric MATCH Screening Trial Patients

Diagnosis	Patients Screened, No.	Patients Screened, %	Patients With aMOI, No.	Patients With aMOI, %	Patients Matched, No.	Patients Matched, %	Patients Enrolled, No.	Enrollment Rate, %
Non-CNS solid tumors	723	72.3	187	25.9	165	22.8	77	46.7
Osteosarcoma	184	18.4	31	16.8	28	15.2	14	50.0
Rhabdomyosarcoma	120	12.0	53	44.2	50	41.7	22	44.0
Ewing sarcoma	104	10.4	12	11.5	10	9.6	4	40.0
Neuroblastoma	60	6.0	27	45.0	25	41.7	9	36.0
Wilms tumor	56	5.6	6	10.7	6	10.7	1	16.7
Sarcomas—others	43	4.3	14	32.6	11	25.6	8	72.7
Undifferentiated sarcoma/NOS	26	2.6	4	15.4	4	15.4	2	50.0
Carcinomas	26	2.6	10	38.5	10	38.5	6	60.0
Synovial sarcoma	18	1.8	0	0.0	0	0.0	0	NA
Hepatoblastoma	15	1.5	2	13.3	2	13.3	0	0.0
Germ cell tumors	14	1.4	4	28.6	3	21.4	1	33.3
Malignant rhabdoid tumor	13	1.3	12	92.3	6	46.2	4	66.7
Desmoplastic small round cell tumor	10	1.0	2	20.0	2	20.0	1	50.0
Hepatocellular carcinoma	10	1.0	1	10.0	1	10.0	1	100.0
Other non-CNS tumor	24	2.4	9	37.5	7	29.2	4	57.1
CNS solid tumors	246	24.6	118	48.0	109	44.3	52	47.7
High-grade glioma	69	6.9	49	71.0	45	65.2	24	53.3
Low-grade glioma	54	5.4	39	72.2	37	68.5	13	35.1
Ependymoma	40	4.0	1	2.5	1	2.5	1	100.0
Medulloblastoma	26	2.6	6	23.1	6	23.1	1	16.7
Atypical teratoid/rhabdoid tumor	20	2.0	16	80.0	15	75.0	8	53.3
Mixed glial or glioneuronal tumor	12	1.2	4	33.3	4	33.3	4	100.0
Primitive neuroectodermal tumor	10	1.0	2	20.0	1	10.0	1	100.0
Other CNS tumor	15	1.5	1	6.7	0	0.0	0	NA
Lymphomas/histiocytoses	31	3.1	10	32.3	10	32.3	2	20.0
Lymphomas	18	1.8	6	33.3	6	33.3	0	0.0
Histiocytic disorders	13	1.3	4	30.8	4	30.8	2	50.0
All diagnoses	1,000	100.0	315	31.5	284	28.4	131	46.1

NOTE. Enrollment rate is defined as the fraction of patients matched who enrolled in a treatment protocol.

Abbreviations: aMOI, actionable mutation; NA not applicable; NCI-COG, The National Cancer Institute–Children’s Oncology Group; NOS, not otherwise applicable.

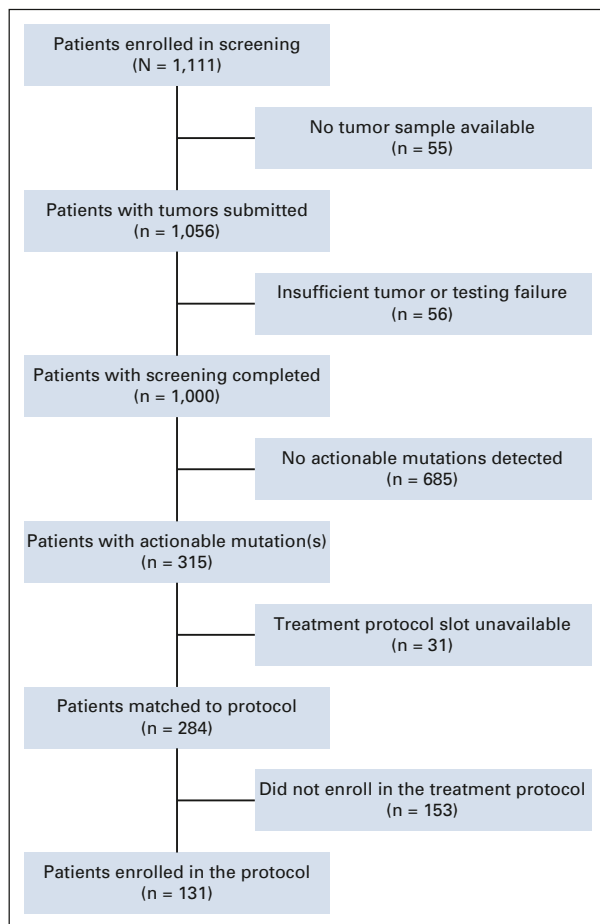


FIG 2. Patient flow diagram for Pediatric MATCH trial. Reasons provided for matched patients not enrolling in treatment protocols are described further in the Data Supplement.

to completion of tumor testing were 12 days and 16 days, respectively; the median time from screening Protocol enrollment to completion of tumor testing was 24 days (range 9–570 days). Grade 3 or higher biopsy-related adverse events were reported in 2 of 256 (0.8%) patients who had a clinically indicated procedure performed after study enrollment: one patient with headache (grade 3, probable attribution) and the other with surgical site infection and meningitis (grade 3, probable).

Treatment Protocol Assignment and Enrollment

At least one actionable tumor alteration for a study treatment arm was identified in 315 of 1,000 (31.5%) patients screened. Open treatment arm slots were not available for 31 patients with actionable tumor mutations; therefore, treatment arm assignments were made for 284 (28.4%) patients (95% CI, 25.7 to 31.3; Table 2 and Fig 2). A total of 131 patients, 13.1% of those screened (95% CI, 11.1%–15.3%), were enrolled in a treatment arm, yielding an enrollment rate of 46.1% among those patients for whom a treatment assignment was made. The most common reasons provided for not enrolling in a treatment arm

(Data Supplement) were patient receiving other treatment (32% of responses), poor clinical status (15%), lack of measurable disease (11%), or ineligible diagnosis (10%).

Factors Related to Treatment Assignment and Enrollment

No significant differences in the treatment arm match rate or enrollment rate were observed for patient sex, age, race, or ethnicity (Data Supplement). A reported history of prior molecular testing (38.2% v 21.8%, $P < .001$) and enrollment at a PEP-CTN site (33.2% v 24.5%, $P = .002$) were associated with significantly higher match rates. Higher enrollment rates were observed for patients with a reported history of prior molecular testing (53.3% v 38.4%, $P = .039$).

Patients with CNS tumors were nearly twice as likely as those with non-CNS solid tumors to be matched to treatment Protocols (44.3% v 22.8%, $P < .001$; Data Supplement); however, no difference in enrollment rate was observed ($P = .253$). Marked variability in match rates was observed across individual tumor types (Table 2). Of the common non-CNS solid tumors, match rates were highest in rhabdomyosarcoma (50 of 120, 41.7%) and neuroblastoma (25 of 60, 41.7%). Matches were much less frequent in other sarcomas, including osteosarcoma (28 of 184, 15.2%) and Ewing sarcoma (10 of 105, 9.6%). Treatment arm match rates for common CNS tumors were highest in low-grade glioma (37 of 54, 68.5%) and high-grade glioma (45 of 69, 65.2%).

Genomic Tumor Landscape

A total of 343 actionable alterations were detected in 315 tumors (Fig 3A and Data Supplement). DNA panel testing identified actionable mutations (SNVs or indels) in 206 tumors (20.6%) and amplifications in 48 tumors (4.8%), RNA testing revealed actionable fusions in 35 tumors (3.5%), and tumor IHC detected actionable tumor suppressor gene loss in 45 tumors (4.5%). Mutations or fusions in *BRAF* were most frequent (4.2%), followed by *SMARCB1* loss/mutation (3.9%), *CDK4* amplification (3.1%), *FGFR1* mutation/fusion (2.9%), and *NF1* mutation (2.4%; Fig 3B and Data Supplement). Actionable alterations in 11 genes were detected in more than 1% of patients.

The frequency of actionable alterations by treatment arm for the diagnoses occurring in more than 5% of patients is presented in Figure A3, online only and the Data Supplement. Alterations for MAPK pathway study arms (11.2%), Arm I (palbociclib, 4.8%), Arm C (tazemetostat, 4.6%), and Arm D (samotolisib, 4.2%) were most frequent. Actionable alterations for Arm B (erdafitinib) were common in CNS tumors (9.3%). Only 21 tumors (2.1%) harbored actionable alterations for more than one treatment arm (Data Supplement). Of these, eight were tumors with actionable alterations in both the MAPK and phosphatidylinositol-3-kinase/mammalian target of rapamycin (PI3K/MTOR) pathways. Since MAPK mutations are known to

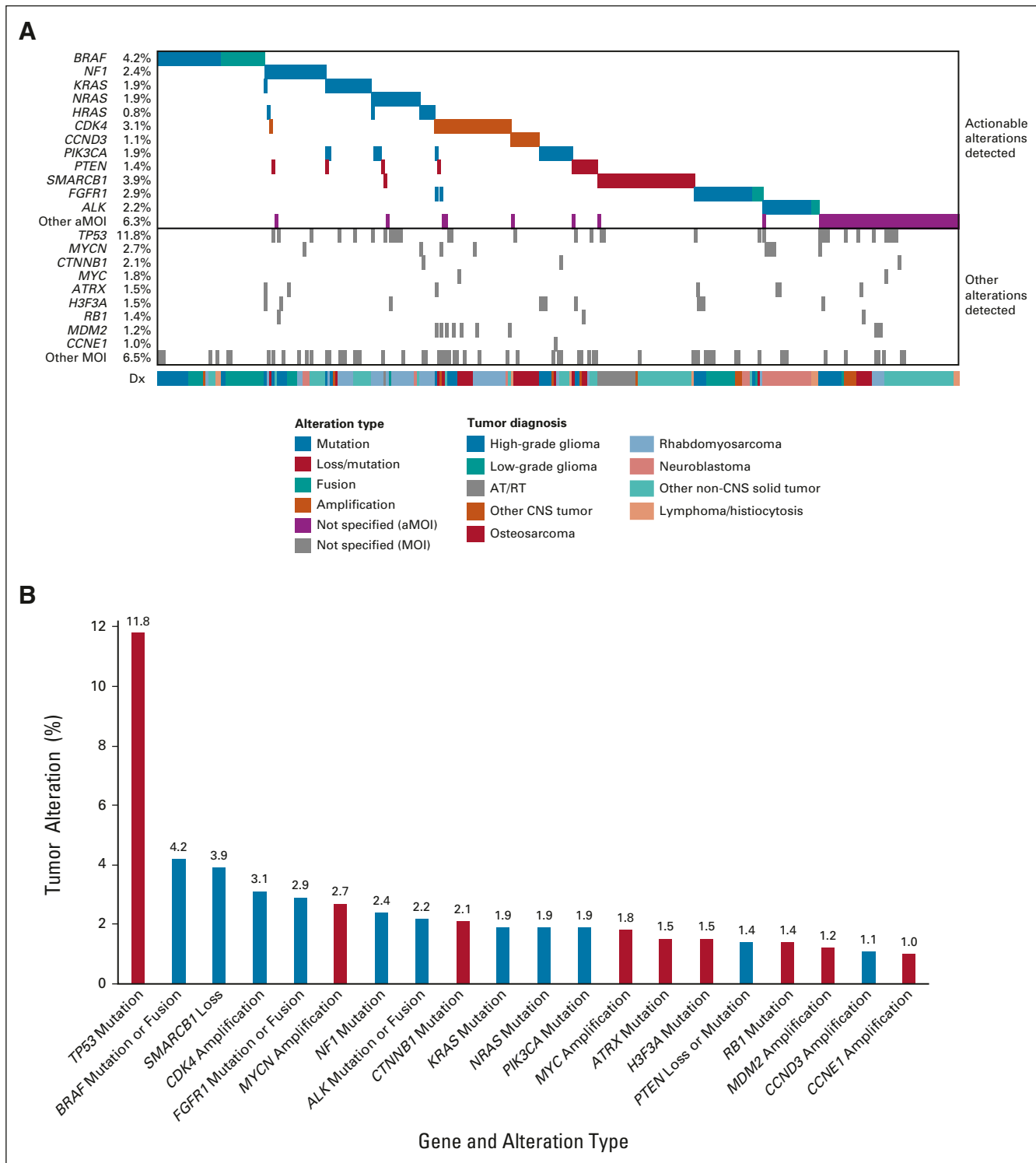


FIG 3. Genomic landscape of tumors with actionable alterations in the Pediatric MATCH trial (n = 315). A genomic waterfall plot (A) displaying the genes with most frequent actionable alterations at the top of the figure, categorized by variant type (mutation, loss/mutation, fusion, and amplification). Each tumor is represented by a column. The variant types for the less common actionable genes (shaded in purple) are not specified. Concurrent alterations in nonactionable genes occurring at a frequency of 1% or greater in the full study cohort are presented at the bottom of the figure. The lower bar categorizes the tumors on the basis of Dx. For the purposes of this figure, negative expression of SMARCB1, SMARCA4, or PTEN by IHC is assigned the loss/mutation variant type. (B) Twenty genes with tumor alterations detected in at least 1% of Pediatric MATCH patients screened. Actionable genes for Pediatric MATCH study arms are marked in blue. Genes with nonactionable alterations detected in patient tumors are marked in red. aMOI, actionable mutation; AT/RT, tumor histology of atypical teratoid rhaboid tumor; Dx, diagnosis; IHC, immunohistochemistry.

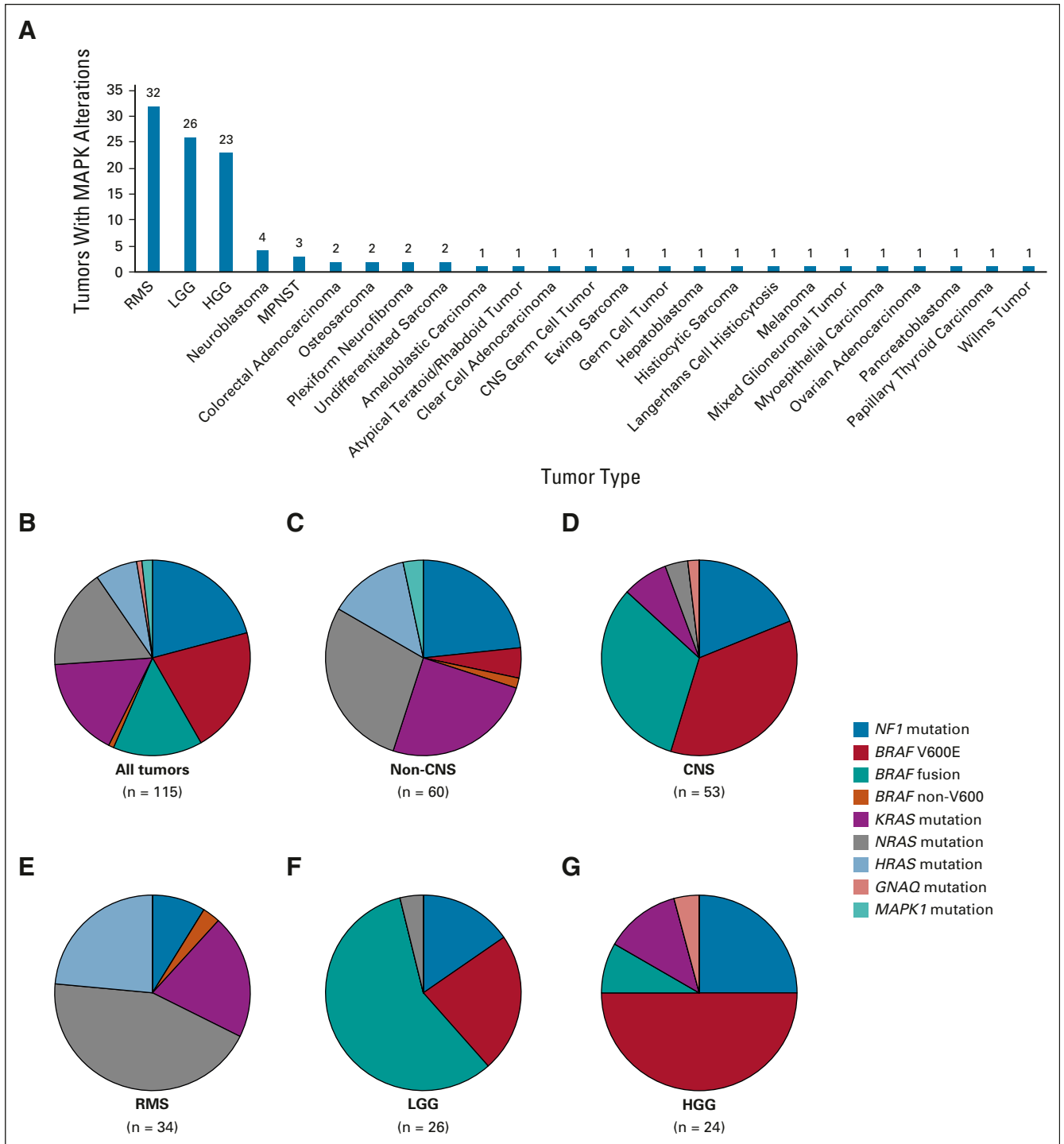


FIG 4. Actionable MAPK pathway alterations by tumor type. A total of 115 alterations were detected in 112 tumors. (A) Tumor diagnoses with actionable MAPK pathway alterations identified. (B-G) Specific MAPK alterations detected in selected diagnostic groups and tumor types. The number of alterations in each group is shown. (B) All tumors, (C) non-CNS solid tumors, (D) CNS solid tumors, (E) RMS, (F) LGG, and (G) HGG. HGG, high-grade glioma; LGG, low-grade glioma; MAPK, mitogen-activated protein kinase; MPNST, malignant peripheral nerve sheath tumor; RMS, rhabdomyosarcoma.

confer resistance to PI3K inhibitors, these patients were not eligible for assignment to the PI3K/MTOR inhibitor samotolisib (Arm D).

Actionable mutations for MAPK pathway arms were detected in 25 tumor types (Fig 4A). Rhabdomyosarcoma

(n = 32), low-grade glioma (n = 26), and high-grade glioma (n = 23) collectively comprised 72.3% of MAPK-altered tumors; the remaining 22 tumor types had four or fewer mutated tumors. The specific pattern of MAPK pathway alterations varied markedly by tumor type (Figs 4B-4G and

Data Supplement); for example, RAS gene mutations predominated in rhabdomyosarcoma (Fig 4E), whereas *BRAF* V600E and *NF1* mutations were most frequent in high-grade glioma (Fig 4F), and *BRAF* fusions accounted for more than half of the alterations in low-grade glioma (Fig 4G).

Cancer gene alterations that were not actionable for Pediatric MATCH treatment arms were detected in 347 tumors (Fig 3B and Data Supplement). Tumors with more than one nonactionable mutation were uncommon (9.8%). The nine genes with alterations occurring at a frequency of 1% or greater are shown in Figure 3B. Mutation of *TP53* was by far the most common (11.8%), followed by *MYCN* amplification (2.7%), *CTNNB* mutation (2.1%), and *MYC* amplification (1.8%).

DISCUSSION

The NCI-COG Pediatric MATCH trial has demonstrated the feasibility of a nationwide screening and centralized testing Protocol to select patients with tumors harboring actionable alterations for enrollment in clinical trials of molecularly targeted therapies. Study accrual exceeded projections, and tumor profiling was completed for the majority of patients, using predominantly archived FFPE samples. Although tumor biopsy was not part of the Pediatric MATCH Protocol, collection of adverse event data after study enrollment revealed few procedure-related adverse events. Most importantly, the screening Protocol has successfully matched patients to investigational therapies, with 28% of patients assigned to treatment arms and 13% enrolled in those trials.

The trial has provided access to clinical molecular screening and early-phase trials of molecularly targeted therapies for pediatric and young adult patients with cancer across the United States. The study cohort was geographically diverse (Appendix Fig A1), with patients screened and enrolled at 138 and 61 COG institutions, respectively, and representative of the race and ethnicity of the pediatric cancer population in the United States (Data Supplement). Nearly half of patients were enrolled in treatment arms at sites that are not members of the PEP-CTN (Table 1). Despite the known challenges of adolescent and young adult participation in clinical trials,^{13,14} patients age 15-21 years comprised more than 40% of patients screened. These data suggest that the study was broadly accessible to patients including those at COG institutions with less extensive access to investigational therapies.

Multiple factors might have affected the diagnoses and demographics of patients enrolled in the study, including technical challenges of sequencing FFPE tumor samples from bone biopsies, an inability to take pills for younger patients, and differential availability of competing trials for different tumor types. Despite this, Pediatric MATCH has provided a useful snapshot of the spectrum of refractory

solid tumor histologies (and their key molecular features) in pediatric and young adult patients, highlighting opportunities for further research. Although the tumor diagnoses were diverse (n=80), more than half of patients had sarcomas (Data Supplement). Except for rhabdomyosarcoma, a relatively low frequency of actionable alterations (16.4%) was observed in sarcomas (Table 2), demonstrating the need for alternative therapeutic strategies for these patients. Across the full cohort, the most frequently detected actionable genes (*BRAF*, *SMARCB1*, and *CDK4*) and pathways/functions (MAPK, CDK4/6, and MTOR/PI3K signaling) were consistent with previous genomic studies of pediatric cancers (Fig 3, Appendix Fig A3, and Data Supplement).^{1,2,15-19} Alterations in MAPK signaling genes (Fig 4) were by far the most common. Continuous drug development and incorporation of pediatric patients into innovative clinical trials targeting this pathway, including combination therapies, remains a high priority.

Comparison of data from Pediatric MATCH data and the adult NCI-MATCH trial, which used the same testing platform and a similar study design (albeit different treatment arms),¹¹ allows several observations regarding the feasibility of precision oncology strategies for childhood patients with cancer. First, analysis of archived FFPE tumor samples in Pediatric MATCH resulted in a similarly high profiling success rate (> 94%) as seen in the adult NCI-MATCH trial, which primarily used FFPE tumor samples that were collected from mandatory tumor biopsy procedures to obtain fresh tumor.¹¹ Second, despite the largely distinct cancer diagnoses in the two trials, the rates of actionable genetic alterations (31.5% pediatric v 37.6% adult) and treatment arm enrollment (13.1% pediatric v 12.4% adult) were also similar. Third, co-occurring resistance mutations that excluded patients from treatment arms were markedly less common in Pediatric MATCH as compared with the adult trial (2.1% v 34.7%).

Patients with a reported history of prior clinical molecular testing were significantly more likely to both match to and enroll in treatment arms, suggesting preferential enrollment of patients with tumors known to harbor actionable alterations. Most reasons provided for matched patients not enrolling on treatment arms (Data Supplement) could be considered issues of timing, with patients screened too late to receive treatment in the study (ie, after initiating alternative treatment for their refractory tumor or when poor clinical status precluded trial enrollment). Given the frequency of actionable alterations detected by Pediatric MATCH testing across most tumor types (Table 2 and Appendix Fig A3) and the increasing potential of those results to guide selection of both US Food and Drug Administration–approved and investigational therapies, early molecular testing for children and young adults with refractory cancers seems a reasonable strategy to inform treatment options in these patients.

Our trial design had several limitations that suggest opportunities to increase the rate of actionable alteration detection and trial enrollment. First, a more comprehensive tumor testing strategy could be used. Alternative approaches would be necessary to more comprehensively identify inactivating events (deletions and splice site mutations) in tumor suppressor genes (eg, *SMARCB1*, *NF1*, *PTEN*, *TSC1*, *TSC2*, *BRCA1*, and *BRCA2*) and fusion events between oncogenes (eg, *BRAF* and *NTRK* genes) and novel or uncommon partners. More comprehensive analysis of study tumors (including exome, whole genome, and transcriptome sequencing) will provide further insight into the additional yield of those approaches for identification of molecular targets.²⁰⁻²² Second, determination of alteration actionability could be made in real time following trial rules (Data Supplement) instead of using static variant lists. This would also facilitate the use of molecular profiling results from outside laboratories, increasing trial access for patients without available tumor for testing: an approach

that will be implemented in Pediatric MATCH beginning in early 2022.

In a minority of cases, alterations were classified as non-actionable in Pediatric MATCH that could be considered actionable for agents not included in the trial (Data Supplement), including biomarkers for US Food and Drug Administration–approved therapies (eg, *PTCH1* or *SMO* mutations for vismodegib) and molecular targets of investigational agents (eg, *PDGFRA* and *KIT* amplifications).^{23,24} Finally, a review of the most frequently identified non-actionable alterations detected (Figs 3B and Data Supplement) serves as a stark reminder that many of the most frequent genomic events in pediatric solid tumors (*TP53* and *CTNNB1* mutations, *MYC* and *MYCN* amplifications, and *EWSR-FLI1* fusions) remain therapeutic challenges. Novel strategies for targeting these genes and related pathways will be necessary to dramatically increase the potential clinical benefit of precision oncology strategies for childhood patients with cancer.

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CLINICAL TRIAL INFORMATION

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Actionable Tumor Alterations and Treatment Protocol Enrollment of Pediatric and Young Adult Patients with Refractory Cancers in the NCI-COG Pediatric MATCH Trial

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Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians ([Open Payments](#)).

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Patents, Royalties, Other Intellectual Property: Coinventor on current and pending patents related to cancer genes discovered through sequencing of several cancer types. Participants in royalty sharing related to those patents

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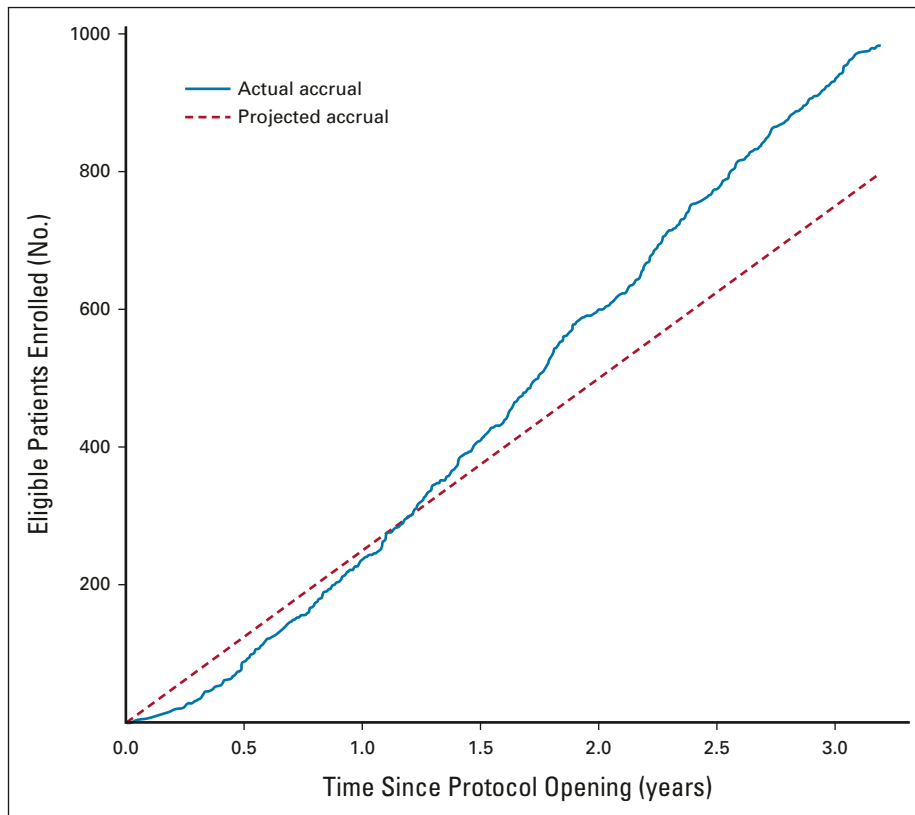


FIG A2. Projected and actual Pediatric MATCH screening protocol accrual.

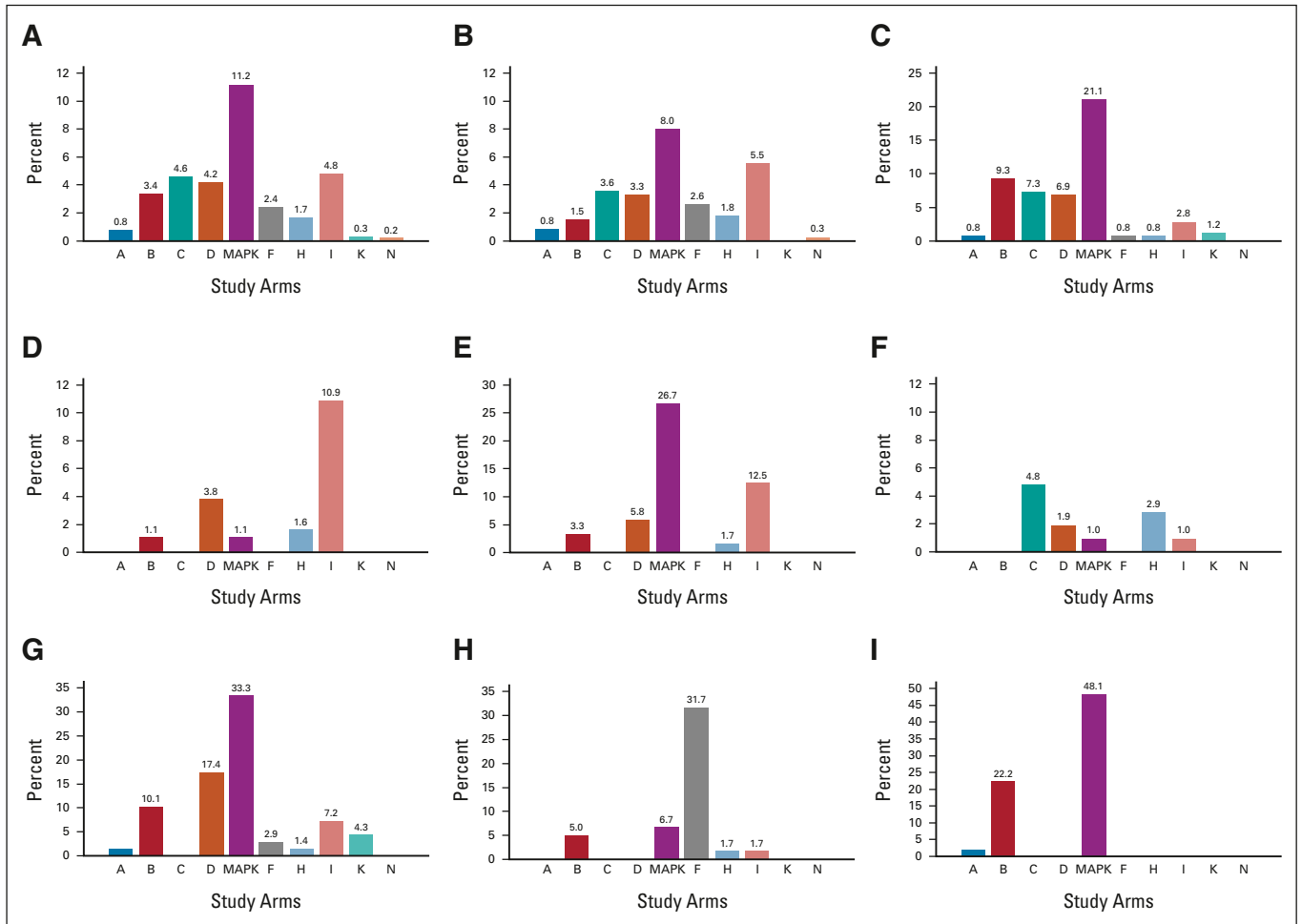


FIG A3. Actionable alteration rates for Pediatric MATCH study arms by tumor type. Study arms: A (larotrectinib), B (erdafitinib), C (tazemetostat), and D (samotolisib); MAPK arms (E, selumetinib; G, vemurafenib; J, ulixertinib; and M, tipifarnib), F (ensartinib), H (olaparib), K (ivosidenib), and N (selpercatinib). (A) All tumors, (B) non-CNS solid tumors, (C) CNS solid tumors, (D) osteosarcoma, (E) rhabdomyosarcoma, (F) Ewing sarcoma, (G) high-grade glioma, (H) neuroblastoma, and (I) low-grade glioma. MAPK, mitogen-activated protein kinase.