Outcome of Children and Adolescents With Relapsed/Refractory/Progressive Malignancies Treated With Molecularly Informed Targeted Drugs in the Pediatric Precision Oncology Registry INFORM

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ABSTRACT

PURPOSE INFORM is an international pediatric precision oncology registry, prospectively collecting molecular and clinical data of children with recurrent, progressive, or very high-risk malignancies. We have previously identified a subgroup of patients with improved outcomes on the basis of molecular profiling. The present analysis systematically investigates progression-free survival (PFS) and overall survival (OS) of patients receiving matching targeted treatment (MTT) with the most frequently applied drug classes and its correlation with underlying molecular alterations.

METHODS A cohort of 519 patients with relapsed or refractory high-risk malignancies who had completed a follow-up of at least 2 years or shorter in the case of death or loss to follow-up was analyzed. Survival times were compared using the log-rank test.

RESULTS MTT with anaplastic lymphoma kinase (ALK), neurotrophic tyrosine receptor kinase (NTRK), and B-RAF kinase (BRAF) inhibitors showed significantly improved PFS ($P = .012$) and OS ($P = .036$) in comparison with conventional treatment or no treatment. However, analysis of the four most commonly applied MTT groups, mitogen-activated protein kinase (MEK- n = 19), cyclin-dependent kinase (CDK- n = 23), other kinase (n = 62), and mammalian-target of rapamycin (mTOR- n = 20) inhibitors, did not reveal differences in PFS or OS compared with conventional treatment or no treatment in patients with similar molecular pathway alterations. We did not observe differences in the type of pathway alterations (eg, copy number alterations, single-nucleotide variants, InDels, gene fusions) addressed by MTT.

CONCLUSION Patients with respective molecular alterations benefit from treatment with ALK, NTRK, and BRAF inhibitors as previously described. No survival benefit was observed with MTT for mutations in the MEK, CDK, other kinase, or mTOR signaling pathways. The noninterventional character of a registry has to be taken into account when interpreting these data and underlines the need for innovative interventional biomarker–driven clinical trials in pediatric oncology.

ACCOMPANYING CONTENT

Data Supplement

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INTRODUCTION

Outcomes of childhood cancer have significantly improved over the past 50 years, but still cancer remains the leading cause of disease-related death in children living in high-income countries.[1-4] Over the past decade, international collaborative efforts have been made to investigate newly emerging techniques in refining diagnosis and implementing innovative targeted treatment strategies for children with high-risk cancer.[5-8] These efforts have resulted in establishing INFORM (Individualized Therapy for Relapsed Malignancies in Childhood)[8-10] and other pediatric precision oncology programs.[6,7,11-21]

CONTEXT

Key Objective

Improving outcomes of children with recurrent, progressive, or very high-risk malignancies has been the goal of several pediatric precision oncology programs. First data publications show the significant impact of molecular tumor profiling in this vulnerable patient population. We have investigated survival times of patients receiving matching targeted treatment (MTT) with the most commonly applied MTTs in the INFORM registry.

Knowledge Generated

Patients with respective molecular alterations benefit from treatment with anaplastic lymphoma kinase, neurotrophic tyrosine receptor kinase, and B-RAF kinase inhibitors. The four most commonly applied MTTs are cyclin-dependent kinase, mitogen-activated protein kinase, other RTKi, and mammalian target of rapamycin inhibitors. Here, no clinical benefit was seen with MTT from one these drug classes.

Relevance

To our knowledge, this is the first report that investigates activity signals of several MTTs in this particular patient population. The lack of detection of activity signals for these commonly applied MTTs indicates the urgent need for innovative, biomarker-driven, single- and combination-agent clinical drug trials for children with cancer.

First data publications confirm the significant impact of molecular tumor profiling. Data from the INFORM registry showed improved progression-free survival for a subset of patients receiving matched targeted treatment (MTT) on the basis of a very high priority–level molecular target following the previously established target prioritization algorithm.[8,9] Within this patient group, a large proportion of patients with different malignancies received MTT with anaplastic lymphoma kinase (ALK), neurotrophic tyrosine receptor kinase (NTRK), or B-RAF kinase (BRAF) inhibitors; these findings are in line with the already published efficacy data of MTT with drugs of one of these three classes.[17,18,22-24] However, availability of activity data of targeted drugs in pediatric oncology is lagging behind adult oncology, because of scarcity of innovative pediatric interventional trials as comprehensively reviewed by Laetsch et al.[25] In contrast to our previous report about MTT on the basis of a very high priority–level target, the present analysis focuses on the clinical outcome of patients receiving the most frequently applied MTTs within the group of small molecule inhibitors in this real-world clinical setting of the INFORM registry. Our goal was to investigate activity signals to support a scientific and clinical rationale for the development of innovative single or combination mechanism of action–based clinical trials on the basis of individual molecular alterations.

METHODS

The INFORM Registry—Summary of Patient Characteristics and Procedures

As previously described, INFORM is an ongoing, international, noninterventional, precision oncology registry, prospectively collecting clinical and molecular data of pediatric patients with relapsed, progressive, or high-risk malignancies.[9] It investigates a predefined molecular target prioritization algorithm, on the basis of the alteration type and disease-specific relevance.[8,9] A total of 72 centers enrolled patients in Austria (n = 5), Finland (n = 5), Germany (n = 396), Greece (n = 3), Poland (n = 2), Sweden (n = 36), Switzerland (n = 13), and the Netherlands (n = 59).[9] Eligible patients age 0-21 years were included, as well as patients age up to 40 years with a primary pediatric malignancy diagnosed before age 21 years. Malignancies registered included hematologic malignancies and solid and CNS tumors.[9] Fresh-frozen tumor samples from the current disease episode and nonmalignant material were subjected to centralized molecular analysis consisting of whole-exome sequencing, low-coverage whole-genome sequencing, RNA sequencing, RNA-based gene expression array, and DNA methylation analysis.[9] The reported results were ranked on a seven score scale from very high to very low (priority level 1-7) on the basis of the type of molecular alterations as previously described by van Tilburg et al.[8,9] Results were discussed in weekly molecular tumor boards with an interdisciplinary expert panel and the treating oncologist. Ultimate clinical decision making on treatment options remained within the primary oncologist's responsibility.[9] Target reports and clinical follow-up data of each patient were collected in a web-based clinical trial database (MARVIN XClinical).[9]

The study was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. All patients or their legally acceptable representative, or both (if possible), provided written informed consent. Approvals for the study protocol (and any modifications thereof) were obtained from independent ethics committees and the institutional review board at each participating center. The

study was registered with the German Clinical Trial Register, number DRKS00007623.

Matching Target Treatment Analysis

The present analysis was performed in the previously described cohort of 519 patients. Patients enrolled between January 21, 2015, and September 30, 2019, who had completed a follow-up of at least 2 years or shorter in the case of earlier study participation termination because of, for example, death or being lost to follow-up, were included.[9] Patients receiving MTT on the basis of their first molecular analysis were selected for this report. Some tumors were analyzed at several points in time. However, MTT resulting from subsequent episodes with molecular profiling were not included in the analysis. All MTT drugs were sorted by generic drug names as reported in the raw data and grouped into their respective drug classes. Patients were included in the analysis once MTT had been documented, regardless of duration of treatment or other concomitant treatments such as conventional chemotherapies, other MTTs, radiation therapy, or surgery. In case multiple MTTs were documented for a single patient, this patient was accounted for in each MTT drug class, respectively; for example, if a patient received a mammalian target of rapamycin inhibitor (mTORi) and another kinase inhibitor (OKI), this patient was included in the mTORi and OKI drug class, separately. However, it is important to note that the drug classes are not compared against each other. For each of the four most commonly applied MTT drug classes, patients were stratified into three groups for survival analysis:

1. patients receiving MTT on the basis of a respective molecular alteration in the tumor regardless of the priority level,
2. patients with a tumor harboring a respective molecular alteration who received conventional treatment or no treatment at all, and
3. patients with tumors without a respective molecular alteration who received treatment with a targeted drug from one of the selected drug classes (non-MTT; eg, patient with neuroblastoma and alteration in *ALK* [single-nucleotide variant] and *MYCN* [amplification] received treatment with cyclin-dependent kinase [CDK] inhibitor [CDKi] ribociclib).

Within the selected drug classes, clinically established and tumor-specific actionable molecular alterations were analyzed according to the alteration type (eg, copy number alterations, single-nucleotide variants [SNVs], InDels, gene fusions, outlier expressions, and expression of fusion transcripts) and priority level (1-7).[8,9] Briefly, very high–priority targets contain directly actionable genetic alterations, high- and moderate-priority targets are genetic alterations in a known cancer driver, intermediate targets contain genetic hits known to sensitize to a given drug, or highly overexpressed oncogenes and borderline and low-priority targets involve expression changes in oncogenic pathways, and very low–priority targets show only circumstantial evidence of links to actionable drug targets.[8,9] To assess whether a positive signal could be detected using this method, survival times of patients receiving treatment with clinically proven effective targeted drugs from the BRAFi, ALKi, and NTRKi classes were included as an internal positive control.

Statistical Analysis

Progression-free survival (PFS) and overall survival (OS) were compared using the log-rank test. PFS and OS durations were calculated on the basis of the date that all necessary samples for molecular analysis were received and the date that an event was first documented in the web portal. An event was defined as the reported date of disease progression (PFS) or death (OS). In case death or disease progression occurred in the time between registration and sample receipt completion, patients were excluded from PFS analysis. In case death occurred in the time between registration and sample receipt completion, patients were excluded from OS analysis.

RESULTS

Of 1,051 patients registered between January 21, 2015, and September 30, 2019, 519 patients met the criteria for survival analysis on the basis of eligibility, successful molecular analysis, and availability of clinical follow-up data (Fig 1A) as described previously.[9] Six patients died, and five had progressive disease before completion of sample receipt. Therefore, 513 patients were included for OS and 508 for PFS analysis. As previously reported, the median PFS and OS of this cohort were 118 (95% CI, 106 to 145) and 290 (95% CI, 257 to 343) days.[9] Of 519 patients, 147 (28%) patients received MTT on the basis of any reported molecular target priority level (level 1-7), and 372 (72%) patients did not receive targeted drugs but conventional therapy (eg, chemotherapy, radiation or surgery) or no treatment or a targeted drug without the presence of a matching molecular target (non-MTT). 185 MTTs were applied in 147 patients, including small molecule inhibitors, biologicals, and miscellaneous other targeted treatments (Fig 1B). All MTT drugs and their frequency of use are listed in Table 1. The four most commonly applied MTT drug classes were CDKi (applied ×23), mitogen-activated protein kinase inhibitors (MEKi; applied ×19), OKI (applied ×62), and mTORi (applied ×20; Fig 2). The most commonly applied MTT within the class of OKI included dasatinib (applied ×21) and ponatinib (applied ×11). It was not deemed appropriate to further divide the large group of OKI into target-drug subcategories because of small case numbers. Within the class of MEKis, the most commonly applied drug was trametinib (applied ×18), within mTORi everolimus (applied ×10) and within CDKi palbociclib (applied ×15; Table 1). The most commonly applied MTTs within the group of clinically proven effective targeted drugs with ALKi (applied ×20), BRAFi (applied ×5), and NTRKi (applied ×6), were crizotinib (applied ×11), dabrafenib (applied ×4), and larotrectinib (applied ×6), respectively (Table 1). In this group (ALKi, BRAFi, NTRKi), a significant improvement in median PFS and OS was observed when

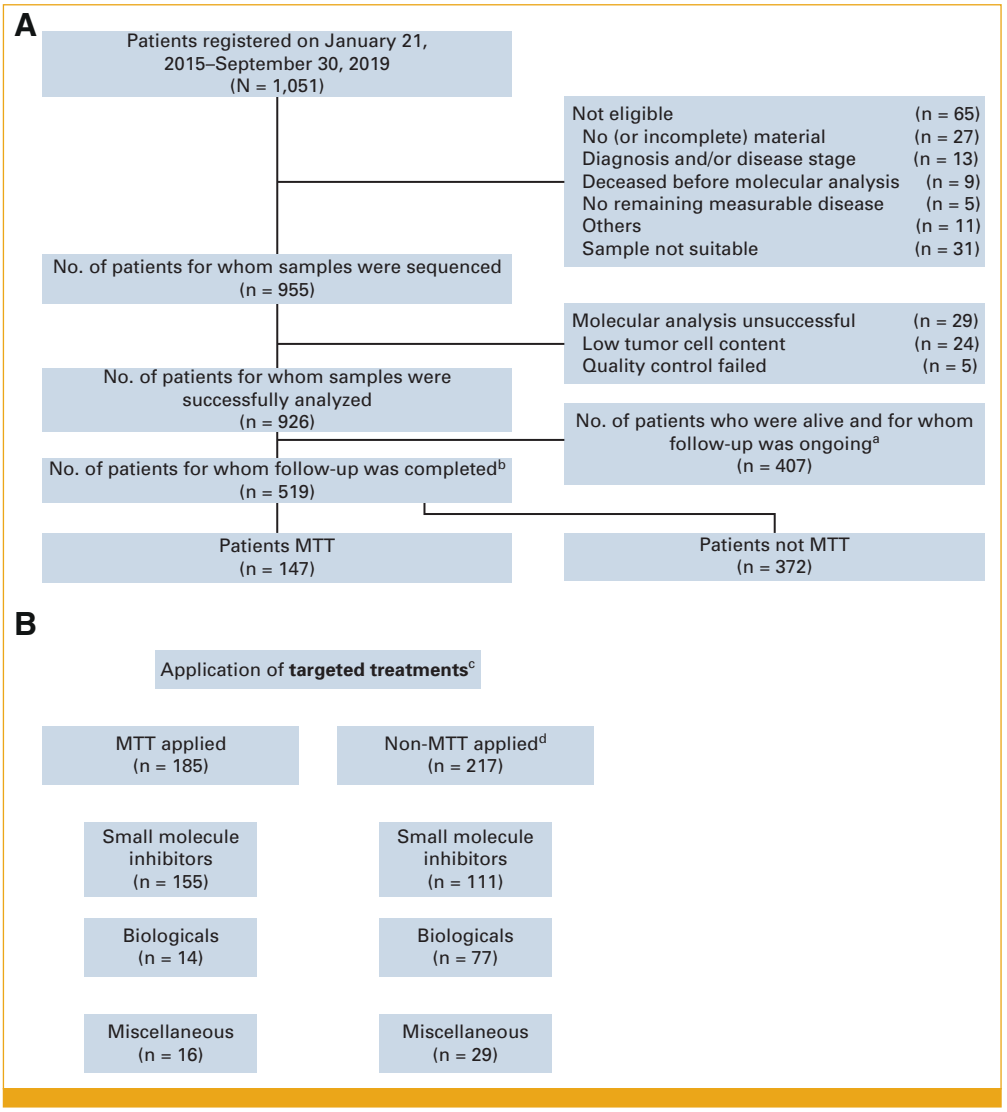

FIG 1. (A) CONSORT diagram of patient disposition. [a]Registered after October 1, 2017, still alive, and with ongoing follow-up (because a regular follow-up of 2 years was not complete) at the data cutoff. [b]At least a regular follow-up of 2 years was completed, lost to follow-up, or deceased. This includes patients registered after October 1, 2017, who were lost to follow-up or deceased. (B) Application of targeted treatments. [c]Each targeted treatment on the basis of the first molecular target report is accounted for here; thus, patients receiving multiple targeted treatments occur multiple times. [d]Non-MTT is defined as treatment with a targeted drug in the absence of a respective molecular pathway alteration. MTT, matching targeted treatment; non-MTT, nonmatching targeted treatment.

compared with patients harboring respective actionable molecular alterations who did not receive MTT (PFS = 153 days; 95% CI, 96 to 531; $P = .012$; OS = 340 days; 95% CI, 181 to 659; $P = .036$; Figs 3A and 3B and Table 2). Non-MTT was not included in the survival analysis since only one patient received non-MTT with an ALK inhibitor (patient with neuroblastoma without *ALK* alteration treated with crizotinib). Molecular priority–level (1-7) distribution is as follows: (1) ALKi ×10, BRAFi ×3, and NTRKi ×3 and (2) ALKi ×3, BRAFi ×2, NTRKi ×3,[26] ALKi ×3,[26] ALKi ×2,[26] and ALKi ×1.

Analysis of OS and PFS duration of the four most commonly applied MTT drug classes revealed no significant survival benefit in comparison with conventional or no treatment in patients with respective actionable molecular alterations and in comparison with patients receiving one of those targeted drugs without the presence of the respective molecular target (non-MTT; Figs 4A-4D). Molecular priority–level (1-7) distribution is as follows: (1) MEKi ×4 and OKI ×4, (2) CDKi ×10, MEKi ×7, OKI ×7, and mTORi ×1, and (3) CDKi ×9, MEKi ×4, OKI ×7, mTORi ×8,[26] CDKi ×3, MEKi ×4, OKI ×13, mTORi ×1,[26] OKI ×25, mTORi ×7,[26] CDKi ×1, OKI ×1, mTORi ×1,[26] and mTORi ×1. For CDKi, non-MTT was not included since only one patient received non-MTT with a CDKi (patient with neuroblastoma and alteration *ALK* (single nucleotide variant) and *MYCN*

TABLE 1. MTTs With Small Molecule Inhibitors by Drug Class and Frequency of Application

Inhibitor	No.
BRAF inhibitors	5
Dabrafenib	4
Vemurafenib	1
mTOR inhibitors	20
Everolimus	10
Rapamycin	1
Sirolimus	8
Temsirolimus	1
ALK inhibitors	20
Ceritinib	8
Crizotinib	11
Lorlatinib	1
CDK inhibitors	23
Palbociclib	15
Ribociclib	8
NTRK inhibitors	6
Larotrectinib	6
MEK inhibitors	19
Cobimetinib	1
Trametinib	18
Other Kinase inhibitors	62
AKT inhibitor	1
Capivasertib	1
EGFR inhibitor	2
Afatinib	2
FGFR inhibitor	1
Erdafitinib	1
JAK inhibitor (JAK1&2)	1
Ruxolitinib	1
Multiple target kinase inhibitors	57
Cabozantinib	1
Lenvatinib	1
Midostaurin	2
Pazopanib	6
Ponatinib	11
Regorafenib	3
Sorafenib	9
Dasatinib	21
Imatinib	1
Nilotinib	2

Abbreviations: AKT, serine/threonine protein kinase; ALK, anaplastic lymphoma kinase; BRAF, B-RAF kinase; CDK, cyclin-dependent kinase; EGFR, epidermal growth factor receptor; FGFR, fibroblast growth factor receptor; JAK, janus kinase; MEK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; MTT, matching targeted treatment; NTRK, neurotrophic receptor tyrosine kinase; OKI, other kinase inhibitor.

(amplification) treated with CDK inhibitor ribociclib). Median PFS and OS including 95% CI and *P* value for the MEKi, CDKi, OKI, and mTORi drug classes are listed in Table 2. The distribution of tumor diagnoses per MTT drug class is presented in Table 3. Of 17 patients enrolled in clinical drug trials, one was treated with crizotinib, three with ceritinib, one with dabrafenib, five with larotrectinib, one with pazopanib, and three with ribociclib.[9] Molecular alterations for target evidence levels (level 1-7) included copy number alterations, SNVs, InDels, gene fusions, outlier expression of individual genes, and expression of fusion transcripts (Data Supplement Table 1). Nineteen of 155 patients received treatment with at least two drugs from one of the here-analyzed drug classes (Data Supplement Table 2). A detailed survival analysis by target and priority level was performed, in addition. However, within each of the selected drug classes, case numbers for distinct molecular alterations were too small to generate meaningful results.

DISCUSSION

The present analysis in this real-world clinical setting of the INFORM registry confirmed a significant survival benefit for patients receiving MTT with ALK, NTRK, and BRAF inhibitors and whose tumors harbor respective molecular targets regardless of tumor diagnosis and relapse status and previous treatments, when compared with conventional treatment or no treatment. The four most commonly applied drug classes outside of these specific examples were CDK, MEK, other kinase, and mTOR inhibitors. In patients with tumors harboring respective molecular alterations, no detectable activity signal was observed for MTT with one of these four drug classes when compared with conventional treatment or no treatment in patients with potential targets. In addition, no survival benefit was seen with the application of a targeted drug from one of these four classes in patients whose tumors did not harbor a respective molecular target (non-MTT).

In this analysis, it is possible that potential activity signals in the four drug classes investigated here are missed, because of obvious limitations inherent to the registry character of INFORM. These limitations lie in the noninterventional status of this real-world clinical registry (eg, treatment choices are not defined a priori nor other treatments excluded), less strict eligibility criteria, and different timing and method of response evaluations in comparison with a clinical trial.[9] Because of the heterogeneity of tumor diagnoses, previously applied treatments, and potential other concomitant treatments, it is possible that activity signals were diluted. For example, the OKI group includes a rather heterogeneous group of different MTTs. To investigate effects caused by these variables, the controlled environment of a clinical trial with appropriate statistical power would be

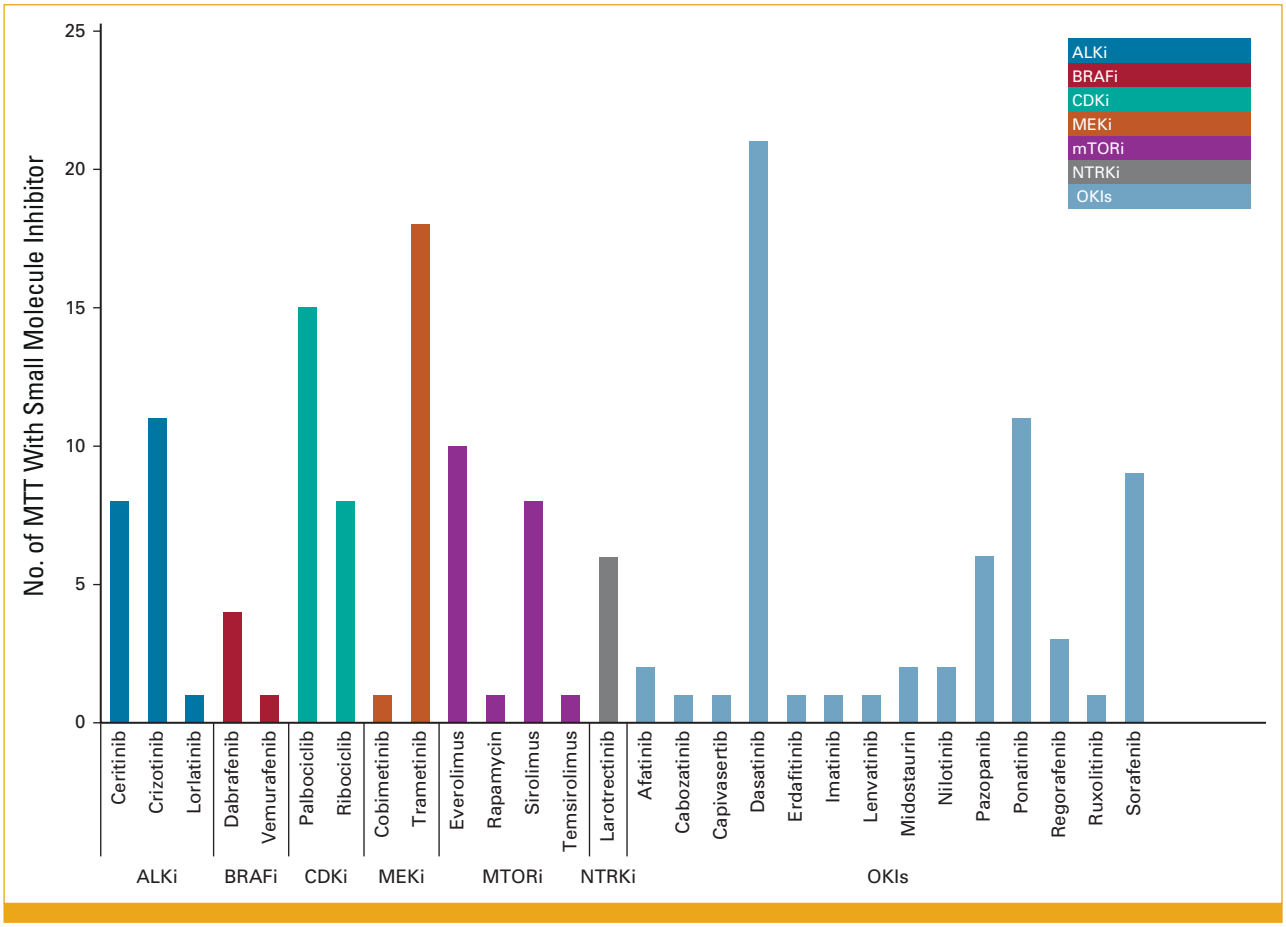

FIG 2. Frequency of MTTs with small molecule inhibitors. ALK, anaplastic lymphoma kinase; ALKi, anaplastic lymphoma kinase inhibitor; BRAF, B-RAF kinase; BRAFi, B-RAF kinase inhibitor; CDK, cyclin-dependent kinase; CDKi, cyclin-dependent kinase inhibitor; MEK, mitogen-activated protein kinase; MEKi, mitogen-activated protein kinase inhibitor; mTOR, mammalian target of rapamycin; mTORi, mammalian target of rapamycin inhibitor; NTRK, neurotrophic receptor tyrosine kinase; NTRKi, neurotrophic receptor tyrosine kinase inhibitor; OKI, other kinase inhibitor.

necessary. This also holds true for the group of patients who did not receive any MTT, which now consists of patients who received different treatment modalities and combinations thereof. Furthermore, clinical trials would allow for a distinct evaluation regarding activity of molecular pathway alterations and respective molecularly targeted drugs in each of the four here-discussed MTT classes. The same is true for the group of patients who did not receive any MTT, which consists of patients who received different treatment modalities and combinations thereof. This might serve as the basis for further investigations into (combination) targeted treatment strategies. Of note, patients could only belong to the MTT group if they had started targeted therapy. Patients progressing or dying before the start of MTT therapy by definition belong to the non-MTT group. Therefore, the present survival analyses are limited by an immortal time bias. Despite these limitations, this analysis provides first insights into the correlation of molecular alterations and accordingly applied targeted drugs that are commonly used in this particularly vulnerable patient population.

To our knowledge, this report is one of the first to investigate activity signals of several commonly applied targeted treatments in relapsed, progressive, or high-risk pediatric malignancies regardless of tumor diagnosis and molecular target evidence level in a large patient cohort from an international pediatric precision oncology registry. Previous reports of large pediatric precision oncology registries such as ZERO,[6,7,17-19] p-MATCH,[12-14] MOSCATO,[15] GAIN/iCat2,[16] the European MAAPYACTS pediatric molecular profiling trial,[11] and INFORM[8-10] demonstrate the clinical value and feasibility of molecular tumor profiling in this unique patient population, but did not report on lower-level molecular targets and survival with commonly applied drugs on such a large scale.[6-9,11,13,15,19,27,28] Furthermore, the implementation of scoring algorithms for molecular alterations in conjunction with tumor diagnosis and targeted treatment options have demonstrated promising effects; for example, as previously reported, in this INFORM patient cohort, patients benefitted from MTT for very high–priority level targets.[9,16] Of note, ALK, NTRK, and BRAF pathway alterations are over-represented in the very high–level evidence

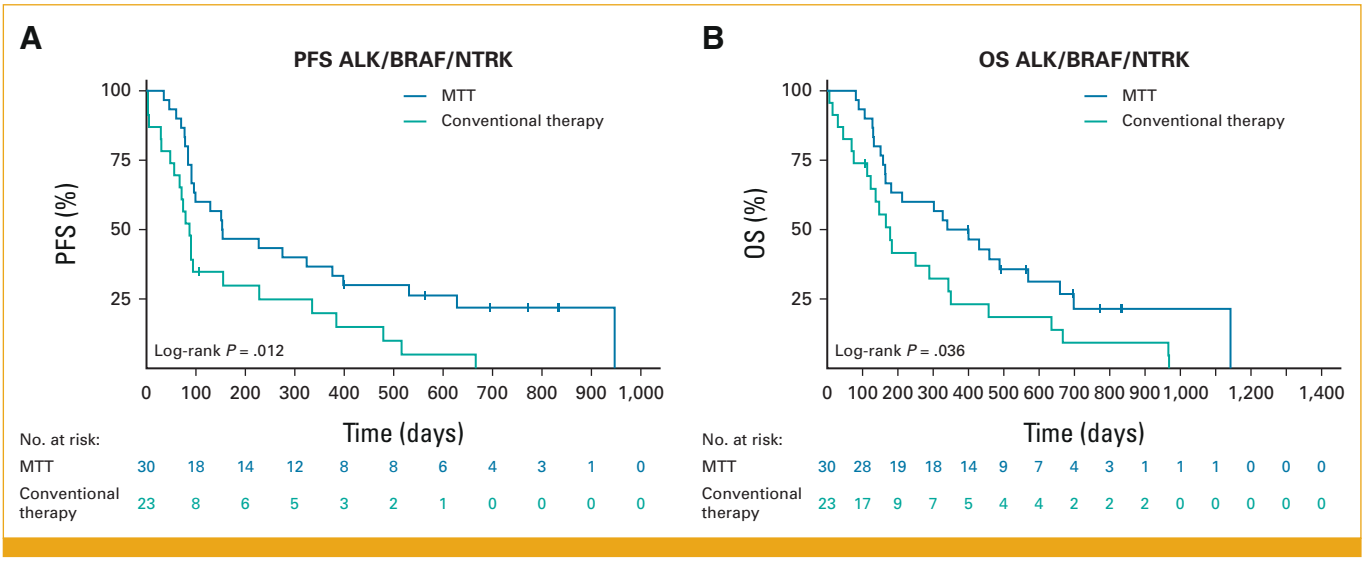

FIG 3. Survival analyses. (A) PFS of patients with ALK, BRAF, or NTRK genetic alterations receiving MTT with ALKi, BRAFi, or NTRKi, respectively, versus patients with respective molecular alterations who received conventional treatment or no treatment ($P = .012$). (B) OS of patients receiving MTT with ALK, BRAF, or NTRK genetic alterations receiving ALKi, BRAFi, or NTRKi versus other patients with respective molecular alterations who received conventional treatment or no treatment ($P = .036$). ALK, anaplastic lymphoma kinase; ALKi, anaplastic lymphoma kinase inhibitor; BRAF, B-RAF kinase; BRAFi, B-RAF kinase inhibitor; MTT, matching targeted treatment; NTRK, neurotrophic receptor tyrosine kinase; NTRKi, neurotrophic receptor tyrosine kinase inhibitor; OS, overall survival; PFS, progression-free survival. MTT, defined as treatment with a targeted drug in the presence of a respective molecular pathway alteration. Conventional therapy, defined as treatment including surgery, radiation therapy, conventional chemotherapy, and no treatment.

group.[9] Therefore, it is not unexpected that MTT with ALK, NTRK, and BRAF inhibitors demonstrates a statistically significant benefit in PFS and OS duration in the present analysis, despite the inclusion of all target evidence levels. This is also in line with the current clinical application of these MTTs.[17,18,22-24] However, overall, only a small number of patients (42 of 519) harbor molecular alterations with very high–level evidence targets.[9] As opposed to the target-focused approach in a previously published report of the same cohort,[9] the present analysis focuses on the most

TABLE 2. Tumor Diagnosis Distribution per MTT Drug Class

TUMOR Diagnosis	ALKi	BRAFi	CDKi	MEKi	mTORi	NTRKi	OKIs
ALL							2
AML							2
Desmoplastic small round cell tumor			1		1		2
Ependymoma			1	1			2
Ewing sarcoma		1	1	1	3		10
High-grade glioma (incl. DIPG)	3	2	2	4	5		8
Medulloblastoma			1	1	3		1
Neuroblastoma	11	1	4	1			3
Osteosarcoma	2		3	1	3		5
Others		1		3	3	1	10
Other soft tissue sarcomas	2		5	3	1	5	7
Rhabdomyosarcoma	1		5	4			3
Rhabdoid tumor							2
Total count of patients receiving MTT per drug class	19	5	23	19	19	6	57

Abbreviations: ALKi, anaplastic lymphoma kinase inhibitor; BRAFi, B-RAF inhibitor; CDKi, cyclin-dependent kinase inhibitor; DIPG, diffuse intrinsic pontine glioma; MEKi, mitogen-activated protein kinase inhibitor; mTORi, mammalian target of rapamycin inhibitor; MTT, matching targeted treatment; non-MTT, nonmatching targeted treatment; NTRKi, neurotrophic tyrosine kinase inhibitor; OKI, other kinase inhibitor.

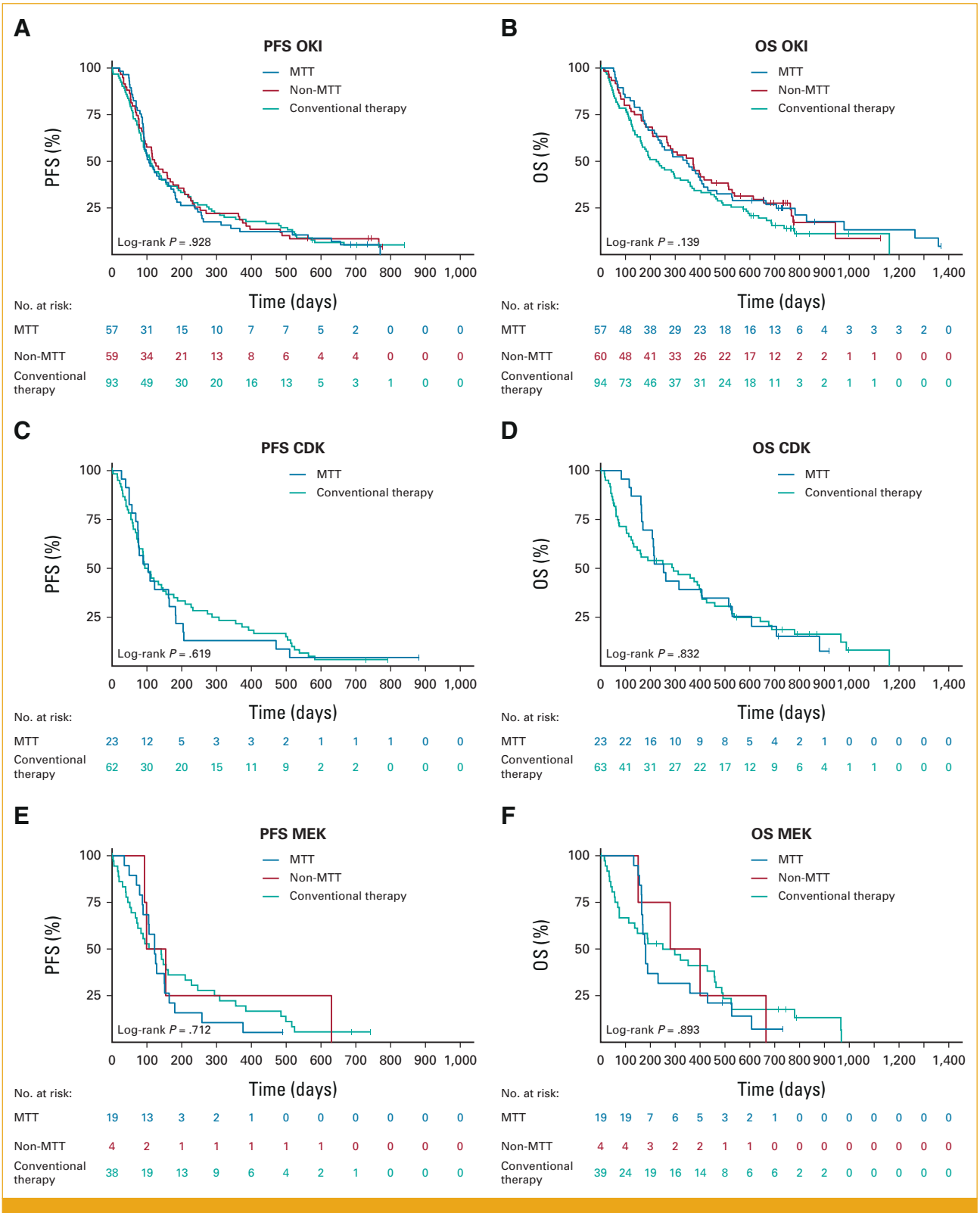

FIG 4. Survival analyses. (A) PFS of patients receiving MTT with OKIs versus other patients with respective molecular alterations who received conventional treatment or no treatment (P = .928). (B) OS of patients receiving MTT with OKIs versus other patients with respective molecular alterations who received conventional treatment or no treatment (P = .139). (C) PFS of patients receiving MTT with CDKi versus other patients with respective molecular alterations who received conventional treatment or no treatment (P = .619). (D) OS of patients receiving MTT with CDKi versus patients with respective molecular alterations who received conventional treatment or no treatment (P = .832). (continued on following page)

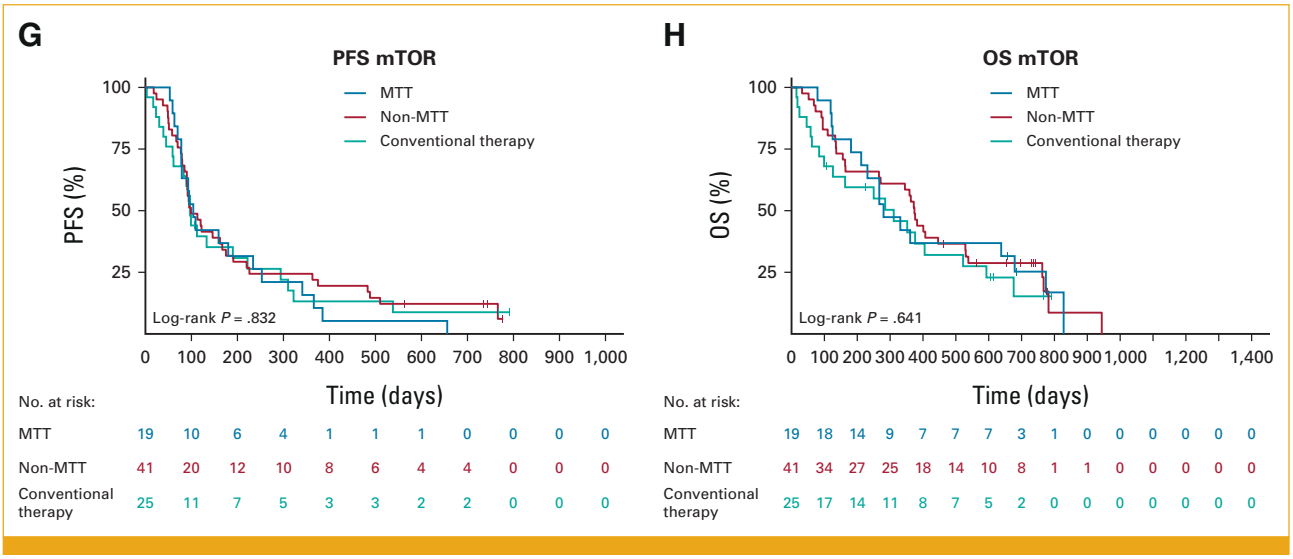

FIG 4. (Continued). (E) PFS of patients receiving MTT with MEKi versus other patients with respective molecular alterations who received conventional treatment or no treatment ($P = .712$). (F) OS of patients receiving MTT with MEKi versus other patients with respective molecular alterations who received conventional treatment or no treatment ($P = .893$). (G) PFS of patients receiving MTT with mTORi versus other patients with respective molecular alterations who received conventional treatment or no treatment ($P = .832$). (H) OS of patients receiving MTT with mTORi versus other patients with respective molecular alterations who received conventional treatment or no treatment ($P = .641$). CDK, cyclin-dependent kinase; CDKi, cyclin-dependent kinase inhibitor; MEK, mitogen-activated protein kinase; MEKi, mitogen-activated protein kinase inhibitor; mTOR, mammalian target of rapamycin; mTORi, mammalian target of rapamycin inhibitor; MTT, matching targeted treatment; OKI, other kinase inhibitor; OS, overall survival; PFS, progression-free survival. Non-MTT, defined as treatment with a targeted drug in the absence of a respective molecular pathway alteration. MTT, defined as treatment with a targeted drug in the presence of a respective molecular pathway alteration. Conventional therapy, defined as treatment including surgery, radiation therapy, conventional chemotherapy, and no treatment.

commonly applied drug classes and also includes lower priority–level targets. The majority of patients carry lower evidence–level targets for which clinical significance and related implications for treatment are yet to be further investigated. The lack of clear activity signals for the group of patients who received MTT with frequently applied compounds from the MEK, CDK, other kinase, and mTOR inhibitor drug classes, regardless of their priority level or tumor diagnosis, is surprising considering their frequent usage in this patient population. Although outliers were observed, after thorough analysis of those individual patients, we did not observe any target/MTT relationship that would explain their particularly long PFS. The clear lack of availability of sound scientific data for the application of (combination of) drugs studied in this analysis emphasizes the urgent need for innovative biomarker-driven combination treatment clinical trials. International efforts in this direction are being made, including the INFORM2 series of multinational biomarker-driven seamless phase I/II combination trials, the European AcSéESMART study (ClinicalTrials.gov identifier: NCT02813135) and pMATCH in the United States, among others.[10,13,15,29]

TABLE 3. Median PFS and OS in Days per MTT Drug Class

	Median PFS (95% CI)			
MTT Class	MTT	Non-MTT	Conventional Treatment/No Treatment	*P*
MEKi	122 (105 to 180)	126 (93 to 630)	123 (71 to 228)	.712
CDKi	104 (75 to 183)		98 (77 to 177)	.619
OKI	106 (92 to 169)	122 (92 to 206)	110 (90 to 155)	.928
mTORi	104 (79 to 341)	99 (90 to 175)	97 (83 to 294)	.832

	Median OS (95% CI)			
MTT Class	MTT	Non-MTT	Conventional Treatment/No Treatment	*P*
MEKi	181 (169 to 527)	340 (151 to 665)	250 (137 to 464)	.893
CDKi	253 (208 to 607)		293 (133 to 408)	.832
OKI	347 (231 to 431)	372 (267 to 515)	224 (166 to 360)	.139
mTORi	280 (231 to 828)	374 (271 to 530)	311 (126 to 593)	.641

Abbreviations: CDKi, cyclin-dependent kinase inhibitor; MEKi, mitogen-activated protein kinase inhibitor; mTORi, mammalian target of rapamycin inhibitor; MTT, matching targeted treatment; OKI, other kinase inhibitor; OS, overall survival; PFS, progression-free survival.

In conclusion, no difference in survival was seen in patients treated with frequently applied MTT classes in comparison with standard-of-care therapies in children with relapsed, recurrent, or high-risk malignancies. The lack of activity signals for these commonly applied MTTs may be due to the inherent limitations of a registry and low case number. It is

important to note that our data do not prove that the here-analyzed MTTs do not work in this particular patient population. Therefore, it is of utmost importance to intensify efforts of preclinical and early-phase clinical trial evaluations of these frequently applied targeted drug classes in relation to distinct biomarkers. An example for an international collaboration tasked with preclinical in vivo evaluation of drugs in pediatric tumor models including molecular biomarkers in large single-mouse trials using hundreds of PDX models is the ITCC-P4[30] program. Further layers of molecular and functional data (eg, gene signatures, liquid biopsy methodologies, single-cell sequencing technologies, proteomics, drug sensitivity profiling) will be incorporated in INFORM/ITCC trials in the future. All these efforts may lead to changes in the understanding of the relevance of targets with respect to targeted drugs and potentially improve target evidence–level algorithms, such as the algorithm used in INFORM.[8] Finally, our data show that only a limited number of patients are being enrolled in clinical trials. However, to improve care and decrease potentially toxic side effects and uncontrolled off-label drug use, it is crucial to increase the availability of and recruitment for early phase biomarker-driven clinical (combination) drug trials particularly designed for this vulnerable patient population.

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DATA SHARING STATEMENT

Whole-exome sequencing, low-coverage whole-genome sequencing, RNA sequencing, and methylation data generated by this study are available from the European Genome Archive, accession number EGAS00001005112.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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