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Clinical Trial Results

Phase II study of vemurafenib in children and young adults with tumors harboring BRAF V600 mutations: NCI-COG pediatric MATCH trial (APEC1621) Arm G

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Abstract

Background: This is a phase II subprotocol of the NCI-COG Pediatric MATCH study evaluating vemurafenib, a selective oral inhibitor of BRAF V600 mutated kinase, in patients with relapsed or refractory solid tumors harboring BRAF V600 mutations.

Methods: Patients received vemurafenib at 550 mg/m^2 (maximum 960 mg/dose) orally twice daily for 28-day cycles until progression or intolerable toxicity. The primary aim was to determine the objective response rate and secondary objectives included estimating progression-free survival and assessing the tolerability of vemurafenib.

Results: Twenty-two patients matched to the subprotocol and 4 patients (18%) enrolled. Primary reasons for non-enrollment were ineligibility due to exclusions of low-grade glioma (n = 7) and prior BRAF inhibitor therapy (n = 7). Enrolled diagnoses were one each of histiocytosis, ameloblastoma, Ewing sarcoma, and high-grade glioma, all with BRAF V600E mutations. Treatment was overall tolerable with mostly expected grade 1/2 adverse events (AE). Grade 3 or 4 AE on treatment were acute kidney injury, hyperglycemia, and maculopapular rash. One patient came off therapy due to AE. One patient (glioma) had an objective partial response and remained on protocol therapy for 15 cycles.

Conclusion: There was a low accrual rate on this MATCH subprotocol, with only 18% of those who matched with BRAFV600 mutations enrolling, resulting in early termination, and limiting study results (ClinicalTrials.gov Identifier: NCT03220035).

Key words: vemurafenib; BRAF V600 mutations; pediatric match.

Lessons learned

- The study demonstrated the challenge of conducting trials of targeted therapies in rare cohorts in the context of available FDA approved agents and evidence for the use of combination therapy in the relevant pathway.
- Consistent with previous data, Vemurafenib appears to be tolerable in pediatric patients and offers a potential treatment option in patients with pediatric cancers with BRAFV600 mutations, including high-grade gliomas.

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Discussion

Vemurafenib is a selective oral inhibitor of the oncogenic BRAF V600 mutated kinase approved by the FDA for the treatment of metastatic melanoma with BRAF V600E mutations as identified on an FDA approved test[1]; however, not all BRAF mutations appear to be the primary driver of tumor progression.[2] This trial aimed to determine response rate in pediatric patients harboring BRAF V600 mutations, excluding low-grade glioma patients with BRAF V600 mutations due to known prior data demonstrating response to BRAF inhibitors.[3] This subprotocol is part of the comprehensive NCI-COG Pediatric MATCH Trial which proved an effective strategy in identifying pediatric patients eligible with BRAF V600 mutations. Twenty-two patients were matched to this study which aligned with the expected match rate based on the literature.[4] However, fewer than 20% of matched patients actually enrolled on this subprotocol, primarily due to having an ineligible diagnosis of low-grade glioma (n = 7), prior therapy with a BRAF inhibitor (n = 7), and other reasons (n = 4) including not meeting eligibility criteria such as poor performance status or low platelet count. The treatment was overall well-tolerated with the majority of adverse events being expected in grades 1 and 2, and one patient coming off therapy due to grade 3 hyperglycemia (n = 1). One patient with high-grade glioma had a sustained objective partial response for 15 cycles and had long-term tolerability (progression-free survival (PFS) of 12.9 months; Figure 1). Unfortunately, due to poor accrual, the study was terminated early, highlighting the challenges of clinical trial completion for rare pediatric cancers, especially where the increased availability of tumor molecular sequencing and multiple commercially available BRAF inhibitors allow providers to treat patients outside of clinical trials. In addition, new studies with combinatorial approaches (such as targeting MEK/BRAF) to overcome resistance pathways are now available. The response observed in this study demonstrates the potential benefit of vemurafenib in patients with BRAF V600 mutated cancers; however, further conclusions could not be established.

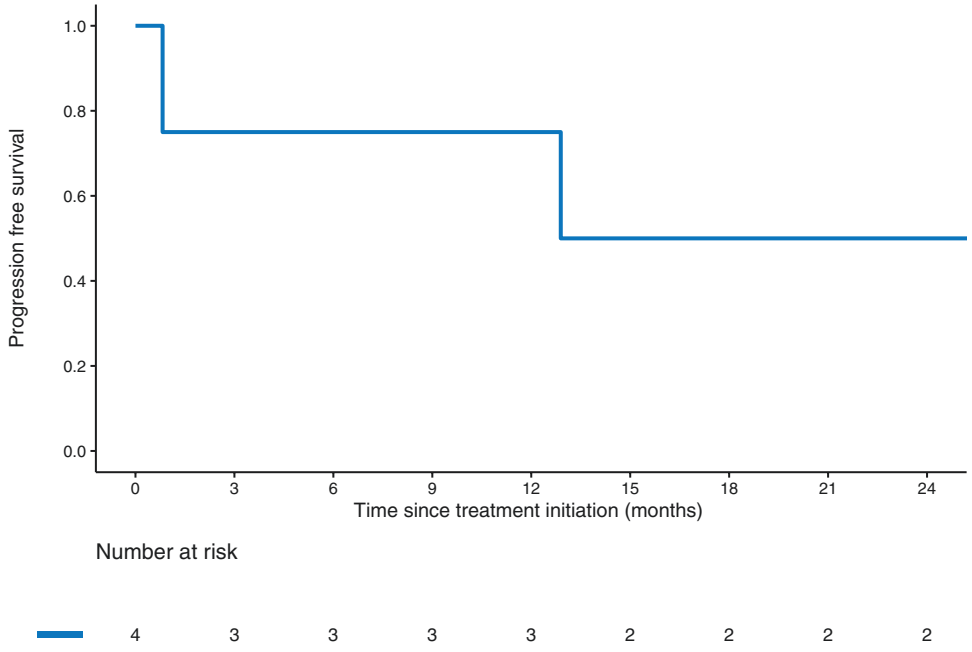

Figure 1. Progression-free survival of the treated patients.

Trial Information	
Disease	Advanced solid tumors, non-Hodgkin lymphoma, or histiocytic disorders with BRAF V600E mutations
Stage of disease/treatment	Relapsed or refractory/Vemurafenib
Prior therapy	Patients must have fully recovered from the acute toxic effects of all prior anti-cancer therapy and must meet the following minimum duration from prior anti-cancer directed therapy prior to enrollment; if after the required timeframe, the numerical eligibility criteria are met, eg, blood count criteria, the patient is considered to have recovered adequately Cytotoxic chemotherapy or other anti-cancer agents known to be myelosuppressive: ≥21 days after the last dose of cytotoxic or myelosuppressive chemotherapy (42 days if prior nitrosourea) Anti-cancer agents not known to be myelosuppressive (eg, not associated with reduced platelet or absolute neutrophil count [ANC] counts): ≥7 days after the last dose of agent Antibodies: ≥21 days must have elapsed from the infusion of the last dose of antibody, and toxicity related to prior antibody therapy must be recovered to grade ≤1 Corticosteroids: If used to modify immune adverse events related to prior therapy, ≥14 days must have elapsed since the last dose of corticosteroid Hematopoietic growth factors: ≥14 days after the last dose of a long-acting growth factor (eg, pegfilgrastim) or 7 days for short-acting growth factor; for growth factors that have known adverse events occurring beyond 7 days after administration, this period must be extended beyond the time during which adverse events are known to occur; the duration of this interval must be discussed with the study chair and the study-assigned research coordinator Interleukins, interferons, and cytokines (other than hematopoietic growth factors): ≥21 days after the completion of interleukins, interferon, or cytokines (other than hematopoietic growth factors) Stem cell infusions (with or without total-body irradiation [TBI]): (1) allogeneic (non-autologous) bone marrow or stem cell transplant, or any stem cell infusion including donor lymphocyte infusion (DLI) or boost infusion: ≥84 days after infusion and no evidence of graft versus host disease (GVHD); (2) autologous stem cell infusion including boost infusion: ≥42 days Cellular therapy: ≥42 days after the completion of any type of cellular therapy (eg, modified T cells, natural killer (NK) cells, dendritic cells, etc.) Radiation therapy (XRT)/external beam irradiation including protons: >=14 days after local XRT; ≥150 days after TBI, craniospinal XRT, or if radiation to ≥50% of the pelvis; ≥42 days if other substantial bone marrow (BM) radiation; Note: radiation may not be delivered to "measurable disease" tumor site(s) being used to follow response to subprotocol treatment Radiopharmaceutical therapy (eg, radiolabeled antibody, iobenguane I-131 [131I-MIBG]): ≥42 days after systemically administered radiopharmaceutical therapy Patients must not have received prior exposure to a BRAF inhibitor (eg, vemurafenib, dabrafenib, or encorafenib)
Type of study	Open label, single-arm, phase II
Primary Endpoint	Overall response rate (ORR) defined as complete response + partial response determined by response evaluation criteria in solid tumors (RECIST) v 1.1.
Secondary Endpoints	Progression-free survival (PFS) was defined as the time from the initiation of protocol treatment to the occurrence of any of the following events: disease progression or recurrence or death from any cause. PFS along with confidence intervals was estimated using Kaplan-Meier method. Percentage of patients experiencing grade 3 or higher adverse events evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Drug Information	
Generic/working name	Vemurafenib
Company name	N/A
Drug type	Small molecule inhibitor
Drug class	Selective inhibitor of BRAF V600 kinase
Dose	550 mg/m^2/dose BID (maximum 960 mg BID)
Route	Oral
Schedule of administration	Twice daily (BID)

Patient Characteristics	
Number of patients, male	1 (treated)
Number of patients, female	3 (treated)
Stage	Relapsed/refractory
Age: median (range)	10 years (range 6-18 years)
Number of prior systemic therapies: median (range)	1 (range 1-3)
Performance status: Karnofsky/Lansky	100: 2 90: 1 80: 1
Cancer types or histologic subtypes	CNS tumors, astrocytoma, high grade glioma, 1; histiocytic disorders, 1; ameloblastic carcinoma, 1; Ewing sarcoma

Primary Assessment Method	
Title	NCI-COG Pediatric MATCH (Molecular Analysis for Therapy Choice): Phase II subprotocol of vemurafenib in patients with tumors harboring actionable BRAF V600 Mutations
Number of patients screened	22 matched
Number of patients enrolled	4
Number of patients evaluable for toxicity	4
Number of patients evaluated for efficacy	4
Evaluation method	RECIST 1.1
Response assessment, CR	0 (0%)
Response assessment, PR	1 (25%)
Response assessment, SD	0 (0%)
Response assessment, PD	1 (25%)
Median duration assessments, PFS	12.9 months (95% CI: 0.82-NA)
Response duration	12.9 months
Duration of treatment	1.2 months

Outcome notes

Two out of 4 (50%) patients were removed from protocol therapy during cycle 1. One of these patients, diagnosed with Ewing sarcoma, had clinical or radiographic evidence of progressive disease. The second, diagnosed with ameloblastic carcinoma, had adverse events requiring removal from protocol therapy, so the response to study therapy is unknown. The third patient (with a histiocytic disorder) demonstrated non-compliance that in the opinion of the investigator did not allow for ongoing participation and was removed from study therapy during cycle 2. The fourth patient, diagnosed with a high-grade glioma, had a partial response (PR) before coming off therapy after cycle 15 due to progressive disease (PD).

Assessment, Analysis, and Discussion	
Completion	Study completed
Investigator's assessment	There were signs of activity; unfortunately, study needed to be terminated prematurely due to poor accrual

BRAF is a key element of the RAS/RAF/MEK/ERK pathway, and mutations in the *BRAF* gene, most commonly at the V600 site, create a constitutively active kinase that leads to downstream cancer cell proliferation.[5] Mutations in BRAF V600E have been frequently identified in melanomas as well as a diversity of other cancers including colorectal cancer, non-small cell lung cancer, papillary thyroid cancer, diffuse gliomas, cholangiocarcinoma, hairy cell leukemia, and Langerhans cell histiocytosis (LCH), prompting the development of targeted therapies to inhibit these mutated proteins.[5] While many BRAF V600 mutated tumors occur predominantly in adult patients, a number of these cancers also are common in pediatric malignancies, such as histiocytic disorders (LCH), melanomas, and papillary thyroid carcinoma, as well as a large fraction of pediatric brain tumors, including low- and high-grade gliomas, and rare tumors such as clear cell sarcoma and pediatric metanephric tumor.[6-20]

Vemurafenib is a selective oral inhibitor of the oncogenic BRAF V600 mutated kinase and is currently FDA approved for the treatment of patients with unresectable or metastatic melanoma and Erdheim-Chester Disease with BRAF V600E mutations.[21] Interestingly, in adults, not all patients with BRAF mutations respond to BRAF monotherapy, highlighting the heterogenous pattern of BRAF activation within, and between histologies.[22] It remains unknown whether all pediatric tumors that harbor BRAF V600 mutated kinase will respond to BRAF V600 inhibitors but given the increasing number of pediatric tumors found to have BRAF V600 mutations, this selective inhibitor offers a promising therapy. Although there are various case reports in the literature and experiential knowledge of providers of responses of pediatric tumors, such as gliomas, to vemurafenib and other BRAF inhibitors, few prospective studies have evaluated the response of BRAF mutated tumors to these targeted agents. Previous reports have shown varying responses (some sustained) with toxicities similar to those found in adults.[14,23-25] The safety and efficacy study for children with recurrent/refractory BRAFV600E mutant gliomas (NCT01748149) determined the MTD/RP2D of vemurafenib to be 550 mg/m^2 PO BID,[26] which was the dose administered in this study. In that study, vemurafenib in children with recurrent or progressive BRAF V600E mutant brain tumors, many of whom were heavily pretreated, resulted in a partial response in 5 out of 19 patients, and one complete response with tolerable toxicities.[26]

This trial was a subprotocol of the Pediatric MATCH study, a phase II trial of vemurafenib in children with relapsed or refractory solid tumors, lymphomas, or histiocytic disorders with activating BRAF V600 mutations. The primary aim was to determine an objective response rate, with secondary aims of estimating progression-free survival and obtaining additional information regarding safety and tolerability. Unfortunately, this arm was closed early due to poor accrual. Only 4 of the 22 patients who were matched to vemurafenib treatment were enrolled in the treatment arm (Table 1). Fourteen of the patients who matched to the trial therapy were not eligible due to their diagnoses, as low-grade gliomas were not eligible (n = 7) due to known activity of BRAF inhibition in these tumors, or due to prior treatment with vemurafenib or other agents targeting BRAF V600 mutated kinase

such as dabrafenib alone or in combination with trametinib (n = 7). The poor accrual highlights the difficulty in enrolling pediatric subjects in studies where the medications utilized are already FDA approved for other indications and commercially available. Tumor sequencing is also widely available through various sources. Thus, providers can order molecular testing and start targeted therapies without enrolling patients in clinical trials. Not only is vemurafenib commercially available, but other BRAF V600 targeted agents are available such as dabrafenib, which has demonstrated notable responses in pediatric tumors.[27,28] In addition, data to suggest combinatorial treatment with agents such as an MEK inhibitor may improve response and availability of these agents off study and/or studies of combination therapy may also limit the desire to enroll on a monotherapy trial.[29,30]

Treatment with vemurafenib was overall well-tolerated with the majority of adverse events being grade 1-2; however, grade 3 events did occur in 1 patient, who ultimately came off therapy. However, larger studies in the pediatric population are needed to accurately determine the rate of rare events such as secondary squamous cell carcinoma in patients treated with BRAF V600 targeted therapies. One patient on this trial with a high-grade glioma did have a sustained response, with the best response being confirmed PR, and remained on study therapy for 15 cycles with a PFS of 12.9 months (Figure 1). This response highlights the potential benefit of vemurafenib and other BRAF-directed therapies in patients with aggressive pediatric cancers.

Prescribing targeted therapies off-label may offer benefits for practitioners, patients, and families, but it can also serve to decrease enrollment in trials utilizing these agents, limiting controlled analyses of biomarker-selected cohorts of patients with rare tumors and the ability to share knowledge within the literature. Data sharing is critical to gaining approval for the widespread use of new medications, providing evidence-based guidance to providers, facilitating insurance authorization, and most importantly, improving patient outcomes. Since BRAF-mutated tumors in general are relatively uncommon, especially in the pediatric population, this study could have provided the infrastructure to treat many patients and follow responses over time. Potential solutions to poor accrual in pediatric oncology trials of rare diseases with even rarer molecular cohorts include offering combination therapies for synergistic effect, novel testing platforms only available on the study, and earlier access to agents in development for evaluation in children. The approval of the TRK fusion inhibitor larotrectinib is a prime example of including children in the early phase of drug development which ultimately led to the accelerated development of a tumor-agnostic drug relevant to pediatric cancer.[31] Until larger-scale studies can be performed in pediatrics, barriers to both FDA approval and insurance coverage of these agents will remain.

Clinical trials are the gold standard for assessing the effectiveness and safety of new medical treatments and have led to significant breakthroughs in patient outcomes. This is especially notable in the field of pediatric oncology where diagnoses are rare and patient numbers are small, but past trials have led to such achievements as improving survival in childhood leukemia.[32,33] The most common reason for a trial to close prematurely is due to poor accrual, estimated in up to 20%-40% of trials investigating cancer therapies.[34-37] Until we are able to overcome barriers to pediatric clinical trial enrollment, future progress in the treatment of pediatric cancer is at risk.

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Additional information: AeRang Kim is the principal investigator.

Conflicts of interest

J.M.R. reports research funding from the NCI P30 CA15083 (RF) and consulting/advisory relationship with Elucida Oncology. A.J. reports stock ownership in Gilead Sciences. The other authors indicated no financial relationships.

Data availability

The data underlying this article are available in this article and in the ClinicalTrials.gov PRS system (protocol registration and results system) and can be accessed with the ClinicalTrials.gov ID: NCT03220035.

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Table

Table 1. NCI-COG pediatric MATCH trial patient characteristics.

Characteristics	Treated		Overall
	Yes (*N* = 4)	No (*N* = 18)	Matched patients (*N* = 22)
Sex			
Female	1 (75%)	13 (72%)	14 (64%)
Male	3 (25%)	5 (28%)	8 (36%)
Median age, years (range)	10 [6, 18]	12[1, 20]	12 [1, 20]
Age categories, years			
< 5 years	0 (0%)	1 (6%)	1 (4%)
≥ 5 years and <15 years	3 (75%)	11 (61%)	14 (64%)
≥ 15 years	1 (25%)	6 (33%)	7 (32%)
Race			
White	2 (50%)	16 (89%)	18 (82%)
Black or African American	2 (50%)	1 (5%)	3 (14%)
Not reported/unknown	0 (0%)	1 (5%)	1 (4%)
Ethnicity			
Not Hispanic or Latino	3 (75%)	14 (78%)	17 (77%)
Hispanic or Latino	1 (25%)	4 (22%)	5 (23%)
Diagnosis			
CNS tumors—astrocytoma	1 (25%)	15 (83%)	16 (73%)
Histiocytic disorders	1 (25%)	1 (5%)	2 (9%)
Other[a]	1 (25%)	1 (5%)	2 (9%)
CNS tumors—mixed glial or glioneuronal tumor	0 (0%)	1 (5%)	1 (4%)
Ewing sarcoma	1 (25%)	0 (0%)	1 (4%)

[a]Other diagnosis in the treated cohort is ameloblastic carcinoma (*n* = 1). Another diagnosis in the untreated cohort is melanoma (*n* = 1). The table reflects data collected at screening enrollment. Data are reported as no. (%) unless otherwise indicated.