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Access Program for Unapproved and Off-Label Drug Use in Pediatric *BRAF* V600E-Mutated Brain Tumors in Japan

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ABSTRACT

Programs allowing access to investigational drugs and off-label drug use for serious diseases have often been applied to pediatric cancers. A clinical study conducted under the Japanese "Patient-Proposed Healthcare Services" evaluated the efficacy and safety of dabrafenib plus trametinib in children with *BRAF* V600 mutant glioma (jRCTs071210071). This study successfully provided unapproved and off-label medications to four enrolled patients, two with low-grade glioma and two with high-grade glioma (median age: 10.5 years), until regulatory approval. The timeframe and data collection from such access programs need to be optimized for pediatric patients in accordance with the healthcare system of each nation.

1 | Introduction

Recent advances in precision medicine have led to the approval of various molecular targeted drugs. However, the development of molecular targeted therapy for pediatric cancer lags behind that for adults due to several reasons, including the limited market size for pharmaceutical companies, low tumor mutation burden in pediatric cancers [1], and the need for more complex studies for drug development in children.

To provide access to investigational therapies or drugs for off-label use for patients with life-threatening diseases, many countries have implemented early access and/or compassionate use programs. In Japan, two such programs were initiated in 2016. One is the "Expanded Access Program," which allows investigators to conduct clinical trials for patients excluded from the original clinical trial [2]. The other is the "Patient-Proposed Healthcare Services (PPHS)." Under the Japanese universal health insurance system, unapproved drugs cannot be used concomitantly with insurance-covered treatment. The PPHS exceptionally allows patients to receive unapproved or off-label therapies at their own expense, in addition to treatments covered by universal health insurance. It is applied as a clinical study for evaluating efficacy and safety, conducted by a designated hospital under

Abbreviations: AEs, adverse events; BPCA, Best Pharmaceuticals for Children Act; CRB, Certified Review Board; EU, European Union; FDA, U.S. Food and Drug Administration; HGG, high-grade glioma; IND, investigational new drug; LGG, low-grade glioma; MHLW, Japanese Ministry of Health, Labour and Welfare; MRI, magnetic resonance imaging; NCI CTCAE v5.0—JCOG, National Cancer Institute Common Terminology Criteria for Adverse Events v5.0—Japan Clinical Oncology Group; ORR, overall response rate; PFS, progression-free survival; PMDA, Pharmaceutical and Medical Drug Agency; PPHS, Patient-Proposed Healthcare Services; PREA, Pediatric Research Equity Act; PUT-RD, Protocole d'Utilisation Thérapeutique et de Recueil de Données; RANO, Response Assessment in Neuro-Oncology; RP2D, recommended phase II dose; SACHA, Secured Access to Innovative Medicines for Children with Cancer; SAE, serious adverse event.

the Japanese Clinical Trials Act [3] in response to a patient's request.

We here present the results of a clinical study conducted under PPHS, evaluating the efficacy and safety of dabrafenib plus trametinib in children with *BRAF* V600E-mutated progressive glioma, and discuss strategies for providing access to investigational drugs without delay and utilizing data from the program to expedite drug approval in pediatric oncology.

2 | Background of the PPHS Application

In 2021, a patient with relapsed high-grade glioma (HGG) harboring *BRAF* V600E mutation requested combination therapy with dabrafenib, a selective inhibitor of *BRAF* kinase, and trametinib, a selective *MEK* 1/2 inhibitor. Dabrafenib and trametinib had already been approved for treating adult cancers, including *BRAF* mutant melanoma and non-small cell lung cancer, in Japan in 2016 and 2018, respectively, but not yet for pediatric malignancies. A phase II clinical trial of these drugs in children or adolescents with *BRAF* V600 mutation-positive low-grade glioma (LGG) or relapsed or refractory HGG (NCT02684058) has recently reported promising results, with a 47% overall response rate (ORR) in the drug study group versus 11% in the standard chemotherapy group in the LGG cohort as first-line therapy [4] and with a 56% ORR in the HGG cohort [5]. At that time, the trial had concluded patient enrollment and was in the follow-up period, with no expanded clinical trial planned. For adults and adolescents aged 15 years and older, a multicenter, open-label, phase II clinical study was conducted under the PPHS (Japan Registry of Clinical Trials identifier: jRCTs031190104) [6] in Japan; however, children were not eligible for this study.

3 | Methods

In response to the patient's request, we initially assessed the feasibility of conducting a clinical study under PPHS with regard to both the timeframe and the potential utility of clinical study data for the drug approval process. Anticipating the patient's stable disease status following the second tumor removal until the initiation of the clinical study, we deemed it was appropriate to proceed. We anticipated that the data from the clinical study could serve as reference material when the pharmaceutical company seeks expansion of approval for dabrafenib and trametinib with data from their clinical trials. Subsequently, we started preparations for a single-center, open-label, clinical study under PPHS to evaluate the efficacy and safety of dabrafenib plus trametinib for *BRAF* V600 mutant progressive pediatric glioma. Planning for the study entailed developing a clinical study protocol and determining enrollment costs. Approval for the study was obtained from the Kyushu University Certified Review Board (CRB) (jRCTs071210071), and the Japanese Ministry of Health, Labour and Welfare (MHLW) authorized its conduct under PPHS.

Eligible patients, aged 1 to less than 15 years, were required to have histologically or cytologically diagnosed progressive glioma with *BRAF* V600 mutation, confirmed via a cancer gene panel test covered by Japanese universal health insurance, including OncoGuide NCC oncopanel test and FoundationOne CDx. Patients must have no standard therapy or have discontinued standard therapy due to disease progression or therapy-related toxicity. Tumor lesions had to be measurable or evaluable on magnetic resonance imaging (MRI) at enrollment. Patients with mutations activating *RAS* or *BRAF* fusion were excluded.

The dosage of dabrafenib (capsule or oral solution) and trametinib (tablet or oral solution) for combination therapy was determined based on the recommended phase II dose (RP2D) (NCT02124772). Patients received dabrafenib (5.25 mg/kg for patients aged <12 years; 4.5 mg/kg for patients aged ≥12 years, divided into two equal doses daily) and trametinib (0.032 mg/kg for patients aged <6 years and 0.025 mg/kg for patients aged ≥6 years, once daily) [7]. Treatment continued until disease progression.

The primary endpoint was the best overall response using Response Assessment in Neuro-Oncology (RANO) criteria within the first 16 weeks. Secondary endpoints were progression-free survival (PFS) and adverse events (AEs), defined by the National Cancer Institute Common Terminology Criteria for Adverse Events v5.0—Japan Clinical Oncology Group (NCI CTCAE v5.0—JCOG). Efficacy and safety data were compiled for each patient. Statistical analysis was not applied due to the small number of patients. Novartis provided dabrafenib and trametinib, including both approved adult formulations and unapproved pediatric formulations, free of charge, except for customs fees associated with importing the pediatric formulations, along with information regarding their dosage and safety.

4 | Results

Four patients, including two with LGG (optic glioma $n = 1$; ganglioglioma $n = 1$) and two with HGG (glioblastoma multiforme $n = 1$; HGG, specific diagnosis not possible $n = 1$) were enrolled. The median age at enrollment was 10.5 years (range: 8–11 years). Patient characteristics at baseline are presented in Table 1. Two patients initially received an unapproved trametinib oral solution and dabrafenib capsules for off-label use, based on their bodyweight. As they grew, they transitioned to trametinib tablets. The other two patients received the dabrafenib capsules and trametinib tablets from the beginning of the study. At 16 weeks, all patients showed stable disease, and no disease progression was observed in any of the four patients until the study's termination, as the study drugs, dabrafenib capsules and trametinib tablets, were approved for the target disease of this study and covered by insurance. The median PFS at the study's termination was 19 months (range: 19–22 months). The median duration of treatment in the clinical study was 17 months (range: 17–22 months). Among the two patients with LGG, one patient with optic glioma refractory to tumor resection and various chemotherapies, such as the Packer regimen (carboplatin, vincristine), vinblastine, and bevacizumab, experienced continued tumor shrinkage with dabrafenib plus trametinib and achieved a partial response at 52 weeks. The other patient with ganglioglioma in the medulla oblongata to the fourth ventricle showed improvement in hoarseness and hiccups, likely attributable to the tumor, after initiating dabrafenib plus trametinib. Both patients with HGG, including the patient who

TABLE 1 | Characteristics of the patients at baseline.

	Patient A	Patient B	Patient C	Patient D
Age, years	8	11	11	10
Sex	Female	Female	Female	Male
Lansky PS	90	100	100	100
Diagnosis	Optic glioma (pilocytic astrocytoma); LGG	Ganglioglioma; LGG	Glioblastoma multiforme; HGG	High-grade glioma specific diagnosis not possible; HGG
Results of the cancer gene panel test	OncoGuide NCC oncopanel test: *BRAF* V600E mutation No *BRAF* fusions *CDKN2A* WT *TP53* WT *IDH1*/*IDH2* WT	FoundationOne CDx: *BRAF* V600E mutation No *BRAF* fusions *CDKN2A*/*2B* WT *H3F3A* WT *TP53* WT *IDH1*/*IDH2* WT	FoundationOne CDx: *BRAF* V600E mutation No *BRAF* fusions *CDKN2A*/*2B* WT *H3F3A* WT *TP53* WT *IDH1*/*IDH2* WT	FoundationOne CDx: *BRAF* V600E mutation No *BRAF* fusions *CDKN2A* loss *CDKN2B* loss *H3F3A* WT *TP53* WT *IDH1*/*IDH2* WT
Prior therapy	Surgical resection Carboplatin/Vincristine Vinblastine Bevacizumab Bevacizumab/Temozolomide	Open biopsy alone	Surgical resection	Surgical resection Temozolomide Radiation
Complications	Reduced vision	Hoarseness Hiccups	Seizure Headache	Seizure
MRI finding	Enhanced mass in the optic chiasm T2-weighted lesions from bilateral optic tract to the cerebral peduncle, thalamus, basal ganglia to optic nerves	Enhanced mass in the medulla oblongata	T2-weighted lesions around the tumor resection cavity area in the right temporal lobe	T2-weighted lesions around the tumor resection cavity in the right frontal lobe

Abbreviations: HGG, high-grade glioma; LGG, low-grade glioma; MRI, magnetic resonance imaging; PS, performance status; WT, wild-type.

requested this therapy initially, maintained stable disease until the study's termination. Thirty-two AEs were reported, with 10 of them being determined to be related to the study treatments. Common treatment-related AEs included skin toxicity, such as erythema nodosum ($n = 4$), rash ($n = 1$), and fever ($n = 3$), which have been reported in previous studies [5, 7, 8]. One serious adverse event (SAE), Grade 3 infectious enterocolitis, determined to be unrelated to the study drugs, was reported, and the patient recovered after 9 days. No Grade 4/5 AEs were reported (Table S1).

Partial data from this study were submitted to the Pharmaceutical and Medical Drug Agency (PMDA), the Japanese regulatory agency evaluating the safety, efficacy, and quality of pharmaceuticals and medical devices, for the MHLW to make decisions regarding the expansion of the drug approval, as a reference by Novartis in addition to their original application data. In November 2023, *BRAF*-mutated progressive or relapsed solid tumors, including children with a bodyweight of 26 kg or more, were added to the approved indications covered by Japanese universal health insurance. As a result, this clinical study was terminated. Subsequently, in September 2024, dabrafenib oral solution and trametinib oral solution were approved for patients weighing 8 kg or more.

5 | Discussion

This study successfully provided unapproved and off-label drugs to pediatric patients without delay, and data from the study were submitted to the Japanese PMDA as a reference when expanding the Japanese insurance coverage for these drugs was requested. Several factors contributed to the success of this endeavor. First, pediatric formulations and dosage data were already established by a pharmaceutical company and provided for this study. Second, our hospital had established standard operating procedures to prepare for a clinical study under PPHS as a designated Clinical Research Core Hospital. Third, the patient remained clinically stable from the request for the drugs till the initiation of the study. However, there are several challenges associated with the PPHS. First, as the PPHS must be conducted as a clinical study, a significant amount of time is required to complete the necessary paperwork, in addition to the 6-week review period by the MHLW for PPHS authorization. In this study, the first patient was enrolled 6 months after the initial request, which included 2 months for writing the study protocol and obtaining CRB approval, 1 month for the MHLW review and PPHS authorization, and 3 months for making contracts with the pharmaceutical and clinical study insurance company, as well as establishing a study system, such as electronic data capture. The

TABLE 2 | Programs for patients with serious diseases to access to medicines for off-label use or investigational drugs.

Nation	Program		Aim	Requested by	Authorization	Timeframe	Costs	Data collection
United States	Expanded access program	Individual patient-emergency	Access to investigational drugs outside of clinical trials	Physicians in agreement with pharmaceutical company	FDA	Day 1 after FDA authorization by phone or other rapid means of communication	Depends on insurance. Most insurance companies do not pay for the drugs under the expanded access program	Safety report and summary of the results are submitted to the FDA
		Individual patient-non-emergency				A protocol under a new IND: 30-day waiting period for IND approval		
		Intermediate-size patient population				A protocol under an existing IND: no 30-day waiting period		
		Expanded access for widespread use				Both under a new or existing IND: 30-day waiting period by FDA		
European Union	Compassionate use recommendation (not a legal framework)		EMA's recommendation on how to use unauthorized drugs in compassionate use programs across the EU countries and the type of patient who may benefit from the drug	National competent authorities in EU countries	Not applicable	Not applicable	Not applicable	Not applicable
France	Early access authorization		Early access to investigational drugs intended to be marketed	Pharmaceutical company	HAS following review by ANSM	90 days	Drugs are covered or reimbursed by the universal healthcare insurance	Obligation to comply with PUT-RD
	Compassionate access	Compassionate access authorization	Access to drugs not intended to be marketed	Physicians for a named patient	ANSM	Most requests <48 hours		
		Compassionate prescription framework	Access to drugs marketed for other indications but not intended to be marketed for requested indications	The Ministry of Health or ANSM		Several months		

(Continues)

TABLE 2 | Continued

Nation	Program	Aim	Requested by	Authorization	Timeframe	Costs	Data collection
Japan	Patient-proposed healthcare services	Access to investigational drugs or medicines for off-label use and collection of safety and efficacy data for future approval	Designated hospital for a named patient	MHLW	6 weeks (additional time required for preparing the clinical study; e.g., 6 months)	Drug and costs for conducting the clinical study need to be paid by patients	Data collection in the clinical study
	Expanded access program	Access to investigational drugs for patients not eligible for the original clinical trial	Investigator of the original clinical trial	PMDA and MHLW	Several months	Covered by the investigator	Data collection in the clinical trial

Abbreviations: ANSM, the French National Agency for Medicines and Health Products Safety; EMA, European Medicines Agency; EU, European Union; FDA, U.S. Food and Drug Administration; HAS, the French National Authority for Health; IND, investigational new drugs; MHLW, the Japanese Ministry of Health, Labour and Welfare; PMDA, the Japanese Pharmaceutical and Medical Drug Agency; PUT-RD, the Protocole d'Utilisation Thérapeutique et de Recueil de Données.

extended time required for the application process might delay the start of treatment in critical cases. In fact, several patients who could not wait due to disease progression gave up on the PPHS request. Second, the costs associated with conducting a clinical study need to be borne by enrolled patients, in addition to the costs of study drugs. Although the pharmaceutical company provided the study drugs free of charge in this study, expenses related to conducting the study, including clinical study insurance participation fees and CRB review fees—approximately $3,150 per patient—placed a significant economic burden on the patients. Additionally, patients receiving the unapproved trametinib oral solution incurred a customs fee of $520 every 3 months for import costs. This study's participation fee calculation presented an additional challenge regarding amendments to the study protocol. We initially set the number of participants at four, based on our prior experience with *BRAF* V600E mutation-positive glioma cases at our hospital. However, we received inquiries from more than 10 potential candidates from other hospitals. The enrollment spots were filled quickly, preventing us from accommodating all potential candidates, including those requiring pediatric formulations of the study drugs. As the cost for each patient was calculated based on the original enrollment plan, expanding the number of participants during the study proved challenging. This created a dilemma within the PPHS framework, highlighting the tension between providing treatment opportunities and conducting a well-defined clinical study. Fortunately, at the time of our study's termination, another clinical study under PPHS of dabrafenib and trametinib targeting *BRAF* V600 mutant pediatric solid tumors (jRCTs011220017) was open, enabling us to share this information with potential patients. Third, as a clinical study under PPHS is not considered pivotal, a pivotal study is generally required for drug approval. Due to the small study population and the lack of controls, no definitive conclusions can be drawn regarding the treatment's efficacy, despite the observed median PFS of 19 months. Recently, a new framework allows data from clinical studies on rare diseases under the Japanese Clinical Trials Act to be used in requests for regulatory approval, provided certain requirements are met. These requirements include good study quality, proper consent acquisition, and sufficient evidence supporting the efficacy and safety of the study treatments. Further discussion on the application of this framework is warranted.

Many countries have programs for patients in life-threatening conditions with no other therapeutic options to access investigational therapies. Application for pediatric cancer patients, especially molecular targeted therapy, accounts for a large portion of these programs. For example, out of 2,901 unique single-patient investigational new drugs (IND) submitted to the Office of Oncologic Diseases in the U.S. Food and Drug Administration (FDA) between 2015 and 2020, 534 (18%) were for pediatric patients, with approximately 50% for tyrosine kinase inhibitors and 25% for other small molecules [9]. In Japan, seven out of 18 clinical studies under PPHS were for children with cancer, as of July 2024.

The contents of the access programs, such as timeframes and data collection, vary by country depending on the healthcare system and drug approval process. These programs in the United States, the European Union (EU), and Japan are summarized in Table 2. In the EU, each country has its own program. The primary goal of the expanded access program in the United States is to provide

requested drugs promptly, indicated by the fact that there is an emergency single-patient use IND. The median time for the FDA to grant a single-patient IND was 1 day [9]. In contrast, the PPHS in Japan aims to collect efficacy and safety data as a reference for future insurance coverage, and therefore, must be proceeded as a clinical study. The difference in goals of each program may be due to different healthcare systems. In the United States, where each insurance company decides its insurance coverage, the expanded access program prioritizes saving individual patients, considered separately from insurance. On the other hand, authorization of PPHS in Japan considers not only individual patients but also public benefits, as partial costs of the study under PPHS, including medical examination charges, are covered by universal health insurance. In Europe, France, which operates a universal health insurance system, has well-structured programs; the early access program and the compassionate access (Table 2). In 2022, 98% of requests for compassionate access authorization were processed within 48 hours [10]. The drugs provided through these programs are fully covered or reimbursed by the French universal health insurance. Data collection from the programs is emphasized. Through the Protocole d'Utilisation Thérapeutique et de Recueil de Données (PUT-RD), extensive data, including patient characteristics, safety, and efficacy from the early access program, are sent to the French National Authority for Health [11], and can be used to support the assessment of product value during reimbursement appraisals. Secured Access to Innovative Medicines for Children with Cancer (SACHA)—France, a prospective, multicenter, national observational registry established by the French Society of Pediatric Oncology in 2020, aims to collect clinical data from these programs or off-label drug use [12]. Through SACHA, access to these therapies is secured, and efficacy data are utilized to identify promising medical products.

These access programs are not a fundamental solution, as the ultimate goal is drug approval for pediatric use. Various initiatives, such as international collaboration on pediatric clinical trials, the Best Pharmaceuticals for Children Act (BPCA), and the Pediatric Research Equity Act (PREA) in the United States, as well as the Pediatric Regulation (EC) No 1901/2006 in the EU, have been launched to bridge the gap between adult and pediatric drug development. Concurrently, access programs work alongside these efforts, providing therapeutic options to patients affected by drug lag while potentially expediting drug approval in pediatric oncology.

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Conflicts of Interest

The study drugs, as well as information regarding their dosage and safety, were provided free of charge by Novartis. Koh-hei Sonoda received an honorarium from Novartis for chairing a lecture.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.