Cutaneous reactions in children treated with MEK inhibitors, BRAF inhibitors, or combination therapy: A multicenter study

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Background: Treatment with BRAF inhibitors (BRAFI) and MEK inhibitors (MEKI) causes cutaneous reactions in children, limiting dosing or resulting in treatment cessation. The spectrum and severity of these reactions is not defined.

Objective: To determine the frequency and spectrum of cutaneous reactions in children receiving BRAFI and MEKI and their effects on continued therapy.

Methods: A multicenter, retrospective study was conducted at 11 clinical sites in the United States and Canada enrolling 99 children treated with BRAFI and/or MEKI for any indication from January 1, 2012, to January 1, 2018.

Results: All children in this study had a cutaneous reaction; most had multiple, with a mean per patient of 3.5 reactions on BRAFI, 3.7 on MEKI, and 3.4 on combination BRAFI/MEKI. Three patients discontinued treatment because of a cutaneous reaction. Treatment was altered in 27% of patients on BRAFI, 39.5% on MEKI, and 33% on combination therapy. The cutaneous reactions most likely to alter treatment were dermatitis, panniculitis, and keratosis pilaris–like reactions for BRAFI and dermatitis, acneiform eruptions, and paronychia for MEKI.

Conclusions: Cutaneous reactions are common in children receiving BRAFI and MEKI, and many result in alterations or interruptions in oncologic therapy. Implementing preventative strategies at the start of therapy may minimize cutaneous reactions. (J Am Acad Dermatol 2021;84:1554-61.)

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Funding sources: Supported by National Institutes of Health grant P30 CA77598 using the Biostatistics and Bioinformatics Core shared resource of the Masonic Cancer Center, University of Minnesota and by the National Center for Advancing Translational Sciences of the National Institutes of Health award number UL1-TR002494.

Disclosure: Dr Moertel is a paid consultant to Recombinetics, Inc, investigating the NF1 pig model treated with selumetinib. Drs Boull and Gardeen, Author Abdali, Dr Li, Authors Potts and Rubin, and Drs Carlberg, Gupta, Hunt, Luu, Maguiness, Song, Vivar, Coughlin, Huang, and Lara-Corrales have no conflicts of interest to declare.

IRB approval status: Reviewed and approved by the University of Minnesota IRB.

Accepted for publication July 10, 2020.

Reprints not available from the authors.

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Published online July 17, 2020.

0190-9622/$36.00

https://doi.org/10.1016/j.jaad.2020.07.044

Key words: BRAF inhibitor; drug reaction; medical dermatology; MEK inhibitor; oncology; pediatric dermatology.

The mitogen-activated protein kinase (MAPK) pathway is an important regulator of cell proliferation that is aberrantly activated in up to 30% of human cancers.[1] Inhibitors of BRAF (BRAFI) and MEK (MEKI), upstream kinases in this pathway, are approved by the US Food and Drug Administration for adult use for treatment of multiple malignancies. Cutaneous toxicities are among the most common adverse effects in adults treated with BRAFI and MEKI.[2-23]

CAPSULE SUMMARY

- BRAFI and MEKI are known to cause cutaneous reactions in children.
- This study shows that cutaneous reactions are common in children on MEKI/BRAFI. One third of children had a treatment alteration/disruption due to a cutaneous reaction. Preventative skin care measures could help prevent many treatment alterations.

In the United States and Canada, BRAFI and MEKI are investigational in the pediatric population.[24] Children receive BRAFI/MEKI through clinical trials or compassionately for refractory tumors. A small, retrospective study of cutaneous reactions in children receiving trametinib for neurologic tumors found increased rates of follicular-based skin infections, xerotic dermatitis, acneiform eruptions, and paronychia.[25] A cross-sectional study of 22 children receiving MEKI, BRAFI, or MTOR inhibitors reported that 96% developed a cutaneous reaction, including follicular reactions, xerosis/eczematous changes, photosensitivity, hand-foot syndrome, and eruptive nevi.[26]

Most oncologic treatment protocols require holding or lowering the dose of MEKI or BRAFI for grade III cutaneous toxicities, but oncologists and families may also opt to modify treatment based on symptoms.[18] Dermatologists are frequently asked to evaluate patients on BRAFI and MEKI during therapy to prevent and treat cutaneous reactions, but these have not been fully delineated in the pediatric population. The aim of this study was to describe the frequency and spectrum of cutaneous reactions in children treated with BRAFI, MEKI, or combination therapy and the associated impact on oncologic therapy.

METHODS

After institutional review board approval, a multicenter retrospective study of patients at 11 clinical sites across the United States and Canada was undertaken. Investigators at each site identified patients within their institution who met the inclusion criteria of (1) age ≤18 years at the onset of treatment, (2) examination by a dermatologist at least once during treatment, (3) received BRAFI (dabrafenib and vemurafenib), MEKI (trametinib, cobimetinib, binimetinib, and selumetinib), or combination BRAFI/MEKI therapy at some point during a 6-year period (January 1, 2012, to January 1, 2018). There were no exclusion criteria, including no restriction on the duration, dose, or indication for BRAFI/MEKI therapy.

Investigators at each site reviewed the medical records of qualifying patients within their institutions and entered data into a shared REDCap repository (Vanderbilt University, Nashville, TN). Ten of the children had been included in other publications related to cutaneous reactions seen in 0children on targeted therapies.[25,27,28] Recorded data included patient demographics, treatment indication, presence of cutaneous reactions (predefined categories as well as a write-in option), grading of cutaneous reactions based on National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE),[29] and treatment interruptions or dose alterations due to cutaneous reactions.

Statistical analysis

Demographic and clinic measures such as medication type, reaction type, number of reactions per individual, and treatment interruptions were summarized descriptively. These measures were summarized by either the overall group, therapy type (BRAFI, MEKI, or combination), or prepubertal versus postpubertal group (<9 and ≥9 y). Fisher's exact test was used to compare percentages by group, and analysis of variance was used to compare the average number of reactions per individual across therapy type. Analyses were performed in R, version 3.6.0 (R Foundation for Statistical Computing, Vienna, Austria). *P* values less than .05 were considered statistically significant.

RESULTS

A total of 99 children met the inclusion criteria, including 46 girls and 53 boys, with an overall mean

Abbreviations used:

BRAFI:	inhibitor of BRAF
CNS:	central nervous system
cSCC:	cutaneous squamous cell carcinoma
CTCAE:	Common Terminology Criteria for Adverse Events
DRESS:	drug reaction with eosinophilia and systemic symptoms
KP:	keratosis pilaris
MAPK:	mitogen-activated protein kinase
MEKI:	inhibitor of MEK

age of 9.4 years (range, 1-18 y). Most were receiving single-agent therapy with BRAFI (44.4%) or MEKI (43.4%), and 12.1% were receiving combination therapy. BRAFI recipients were treated with dabrafenib (54.4%) or vemurafenib (45.5%). Most patients on MEKI received trametinib (90.7%); a few children received selumetinib (n = 1, 2.3%) or binimetinib (n = 3, 7%). The most common combination therapies were dabrafenib/trametinib (n = 5) and vemurafenib/trametinib (n = 3). The indications for BRAFI/MEKI therapy were a neural tumor of the central nervous system (CNS) (82.8%) including low- and high-grade CNS malignancies and optic gliomas, Langerhans cell histiocytosis (6.1%), plexiform neurofibroma (6.1%), malignant peripheral nerve sheath tumor (2%), mediastinal yolk sac tumor (1%), metastatic papillary thyroid carcinoma (1%), and myelodysplastic syndrome (1%).

Twenty-eight children (28%) were on drug study protocols that required routine dermatology visits. All children (99/99) in this study developed a cutaneous reaction, with a mean of 3.5 per BRAFI patient (range, 1-9), 3.7 reactions per MEKI patient (range, 1-10), and 3.4 per combination BRAFI/MEKI patient (range, 1-9). There was no statistically significant difference in the number of reactions based on drug class or single versus multiagent therapy ($P = .983$).

Cutaneous reactions varied by drug class (Table I). In those on BRAFI (n = 44), keratosis pilaris (KP)—like reactions (54.5%), photosensitivity (36.4%), and xerosis (36.4%) were most common. In MEKI recipients (n = 43), acneiform eruptions (67.4%), xerosis (58.1%), and paronychia (51.2%) were most prevalent. Patients on combination therapy (n = 12) developed reactions reflective of the individual medications, including xerosis (66.7%), dermatitis (33.3%), and photosensitivity (33.3%), but had lower rates of acneiform eruptions (25%) than those receiving single-agent MEKI (67.4%). Hair changes, including alopecia, curling, and lightening, were common in children on BRAFI (29.5%) and MEKI (23.3%). Twenty-nine other reactions were reported (Table II). These included hyperpigmentation and hypopigmentation, psoriasiform eruptions, oral and genital mucosal lesions, change in congenital nevi, epidermoid cyst, pruritus, lentigines, maculopapular eruption, petechial eruption, mottling, keloid, and lichen sclerosus.

Children were divided into 2 cohorts, based on age (<9 and ≥9 y), to approximate prepubertal and postpubertal status (Table III). Reactions differed based on patient age, with children 9 years and older being more likely to have acneiform eruptions in both BRAFI ($P = .054$) and MEKI ($P = .003$) than children younger than 9 years of age. There was a trend toward increased xerosis in younger children treated with MEKI, but this did not reach statistical significance ($P = .065$).

Cutaneous reactions resulted in treatment cessation in 3 patients and treatment alteration in 33% (33/99) of patients. Reactions that resulted in treatment cessation were pruritus (grade III, dual agent vemurafenib/trametinib), acneiform reaction (grade II, trametinib), and drug reaction with eosinophilia and systemic symptoms (DRESS) (grade IV, trametinib).

Of all patients with treatment alteration, 69.7% (23/33) had treatment held for a period of time, and 21.2% (7/33) had a dose reduction (Table IV). The highest percentage of treatment alterations, 66.7% (2/3) was seen in those on binimetinib, but only 3 study patients received this drug. Sixty percent (12/20) of vemurafenib-treated children and 41% (16/39) of trametinib-treated children experienced a treatment alteration.

Reaction grades were reported for most cutaneous reactions (92.8% for BRAFI, 91.5% for MEKI, 96.7% for combination therapy). A total of 10 grade III and 1 grade IV (DRESS) cutaneous reactions were noted. All grade III reactions occurred in patients on BRAFI. Grade III reactions included photosensitivity (n = 4), dermatitis (n = 3), panniculitis (n = 1), palmoplantar reaction (n = 1), pruritus (n = 1), and KP-like reaction (n = 1). Dermatitis was a common cause of treatment alteration (9/33), even though most of these reactions were grade I or II (Table V). Thirty percent of patients on BRAFI or MEKI monotherapy who developed dermatitis had a subsequent treatment alteration. Similarly, treatment was altered in 24% of those with an acneiform eruption.

DISCUSSION

To our knowledge, we performed the largest study to date that examines cutaneous reactions in children receiving BRAFI and MEKI therapy and found that these reactions are ubiquitous, usually multiple, and often alter oncologic therapy. All children in our cohort developed at least 1 cutaneous

Table I. Cutaneous reactions by drug class, n (%)

Reaction type	BRAFI (n = 44)	MEKI (n = 43)	Combination (n = 12)	Total (N = 99)	*P* value
Xerosis	16 (36.4)	25 (58.1)	8 (66.7)	49 (49.5)	.054
Acneiform eruption	8 (18.2)	29 (67.4)	3 (25.0)	40 (40.4)	<.001
Dermatitis	10 (22.7)	20 (46.5)	4 (33.3)	34 (34.3)	.025
Keratosis pilaris–like reaction	24 (54.5)	1 (2.3)	3 (25.0)	28 (28.3)	<.001
Alopecia and/or texture change	13 (29.5)	10 (23.3)	1 (8.3)	24 (24.2)	.628
Seborrheic dermatitis	10 (22.7)	11 (25.6)	2 (16.7)	23 (23.2)	.806
Paronychia	0 (0.0)	22 (51.2)	1 (8.3)	23 (23.2)	<.001
Photosensitivity	16 (36.4)	2 (4.7)	4 (33.3)	22 (22.2)	<.001
Palmoplantar hyperkeratosis	16 (36.4)	0 (0.0)	2 (16.6)	19 (19.2)	<.001
Eruptive nevi	10 (22.7)	1 (2.3)	3 (25.0)	14 (14.1)	.007
Folliculitis	3 (6.8)	8 (18.6)	1 (8.3)	12 (12.1)	.118
Panniculitis	7 (15.9)	0 (0.0)	3 (25.0)	10 (10.1)	.012
Oral ulcers/mucositis	0 (0.0)	3 (7.0)	1 (8.3)	4 (4.0)	.116
Angular cheilitis	0 (0.0)	3 (7.0)	0 (0.0)	3 (3.0)	.116
Nail changes	1 (2.3)	4 (9.3)	1 (8.3)	5 (5.0)	.202
Pyogenic granuloma	2 (4.6)	0 (0.0)	0 (0.0)	2 (2.0)	.494
Verrucous keratosis	2 (4.6)	0 (0.0)	0 (0.0)	2 (2.0)	.494
Excess facial hair	0 (0.0)	3 (4.7)	0 (0.0)	3 (3.0)	.116
DRESS	0 (0.0)	1 (2.3)	0 (0.0)	1 (1.0)	.494
Blepharitis	3 (6.8)	0 (0.0)	0 (0.0)	3 (3.0)	.241

BRAFI, Inhibitor of BRAF; *DRESS,* drug reaction with eosinophilia and systemic symptoms; *MEKI,* inhibitor of MEK.

Table II. Other reactions by drug class

Other reactions	Associated class	Associated medication
Hyperpigmentation	BRAFI	Dabrafenib
Change in congenital nevi	BRAFI	Dabrafenib
Epidermoid cyst	BRAFI	Dabrafenib
Pruritus	BRAFI	Dabrafenib, vemurafenib
Lentigines	BRAFI	Dabrafenib
Maculopapular eruption	BRAFI	Vemurafenib
Oral and genital mucosal lesions	BRAFI, MEKI	Vemurafenib, trametinib
Hypopigmentation	MEKI	Trametinib
Psoriasiform eruptions	MEKI	Trametinib
Petechial eruption	MEKI	Trametinib
Mottling	MEKI	Trametinib
Keloid	MEKI	Trametinib
Lichen sclerosus	MEKI	Trametinib

BRAFI, Inhibitor of BRAF; *MEKI,* inhibitor of MEK.

reaction, and some experienced up to 10 distinct reactions. Drug-associated cutaneous reactions significantly affected oncologic therapy, resulting in treatment alteration in one third of patients. However, the majority of reactions, as defined by the CTCAE, were mild, meeting criteria for grade I and II reactions, and there was no correlation between CTCAE grade and need for treatment alteration. One life-threatening reaction, DRESS, occurred in a patient receiving trametinib monotherapy.

Dermatitis and acneiform eruption were the most ;common treatment-altering reactions. Although these reactions may not involve a large body surface area, they can be symptomatic with pain or itch. In addition, the visible nature of acneiform eruptions can contribute to poor patient tolerance of this reaction. The CTCAE is limited to evaluating a cutaneous reaction based on the body surface area involved and its impact on activities of daily living. In some reactions (eg, acneiform eruption, alopecia), it considers psychosocial impact on severity grading, but this may be difficult to assess in a child. Ultimately, more precise assessment tools such as The Children's Dermatology Life Quality Index or the Visual Analog Scale for Itch may help oncologists and dermatologists objectively quantify the impact of cutaneous reactions.[30,31]

Cutaneous reactions in children were unique in quality and frequency compared to adults receiving similar therapies. Cutaneous squamous cell carcinomas (cSCCs) are reported in 20% to 36.1% of BRAFI-treated adults.[4,9,19,20] Reassuringly, no child in our cohort developed a cSCC. BRAFI-associated cSCCs are thought to arise because of paradoxical activation of the MAPK in cells that carry a RAS mutation.[32-34] Increasing age is associated with an increase in BRAF-associated cSCC.[35] Children likely carry a lower burden of keratinocytes with ultraviolet-induced RAS mutations that would have

Table III. Cutaneous reactions by age group, n (%)

Inhibitor	Reaction	0-8 years (n = 20)	9-18 years (n = 24)	Total (n = 44)	*P* value
BRAF	Keratosis pilaris–like reaction	10 (50.0)	14 (58.3)	24 (54.5)	.762
	Xerosis	6 (30.0)	10 (41.7)	16 (36.4)	.534
	Photosensitivity	5 (25.0)	11 (45.8)	16 (36.4)	.213
	Palmoplantar hyperkeratosis	6 (30.0)	8 (33.3)	15 (43.1)	.999
	Hair changes (alopecia/texture change)	4 (20.0)	9 (37.5)	13 (29.5)	.321
	Dermatitis	5 (25.0)	5 (20.8)	10 (22.7)	.999
	Seborrheic dermatitis	5 (25.0)	5 (20.8)	10 (22.7)	.999
	Eruptive nevi	5 (25.0)	5 (20.8)	10 (22.7)	.999
	Acneiform eruption	1 (5.0)	7 (29.2)	8 (18.2)	.054
	Panniculitis	1 (5.0)	6 (25.0)	7 (15.9)	.106
MEK	Acneiform eruption	8 (42.1)	20 (87.0)	28 (66.7)	.003
	Xerosis	14 (73.7)	10 (43.5)	24 (57.1)	.065
	Paronychia	10 (52.6)	12 (52.2)	22 (52.4)	.999
	Dermatitis	10 (52.6)	10 (43.5)	20 (47.6)	.757
	Seborrheic dermatitis	4 (21.1)	7 (30.4)	11 (26.2)	.726
	Hair changes (alopecia/texture change)	3 (15.8)	6 (26.1)	9 (21.4)	.477
	Folliculitis	4 (21.1)	4 (17.4)	8 (19.0)	.999
	Skin infection	3 (15.8)	2 (8.7)	5 (11.9)	.644

Table IV. Treatment alterations by drug class, n (%)

Medication alterations	BRAFI (n = 44)	MEKI (n = 43)	Combination (n = 12)	Total (N = 99)
Discontinued	0 (0.0)	2 (11.8)	1 (25.0)	3 (9.1)
Dose decrease	2 (16.7)	4 (23.5)	1 (25.0)	7 (21.2)
Held for period of time	10 (83.3)	11 (64.7)	2 (50.0)	23 (69.7)

BRAFI, Inhibitor of BRAF; *MEKI*, inhibitor of MEK.

the potential for BRAFI activation and subsequent neoplasia.

Although eruptive nevi were seen in 22.7% of children on BRAFI, there were no dysplastic nevi or melanomas diagnosed during the study period. Eruptive nevi were not biopsied because they appeared clinically benign. BRAFI-associated eruptive nevi have been associated with paradoxical activation of the MAPK pathway in BRAF wild-type melanocytes, without V600E mutations, explaining why children would also be affected.[36]

Children were much more likely to develop BRAFI-induced KP-like reactions (54.4%) compared to adults (reported rate, 1.7%-5.6%).[9] KP-like reactions range from mild, with follicularly based hyperkeratotic papules in the typical extensor locations, to severe, with involvement of the trunk, extremities, and face. There may brow thinning resembling ulerythema ophryogenes. The prevalence of KP-like reactions in our group approximates the prevalence of KP in healthy children. We speculate that BRAFI may exacerbate pre-existing KP in children prone to this condition, but we do not have baseline skin examination data to confirm this.[37,38]

Interestingly, the cutaneous reactions to BRAFI, including development of papillomatous lesions, palmar-plantar hyperkeratosis, hair texture changes, prominent KP, and cutaneous malignancies, mimic features of RASopathies, including Noonan, Costello, and cardiofaciocutaneous syndromes.[39] Systemic manifestations of RASopathies such as developmental delay and cardiac anomalies have not yet been reported in children receiving BRAFI.

MEKI-induced acneiform eruptions appear as inflammatory papules and pustules without comedones in areas with high sebaceous gland density. In MEKI-treated children, acneiform eruptions were quite common, with an overall rate of 67.4%, which increased to 87% in the 9- to 18-year-old cohort. This is a higher prevalence than reported in adults (62.5%-77%), suggesting that a predisposition to acne along with high sebaceous gland activity may be a risk factor.[11,20] As has been previously described, the

Table V. Reactions causing treatment alteration

Reaction	BRAF, n (%)*	MEK, n (%)*	Combination, n (%)	Total treatment alterations (n = 33), n (% of total)
Dermatitis	3 (30)	6 (30)	0 (0)	9 (27.3)
Acneiform eruption	0 (0)	7 (24)	0 (0)	7 (21.2)
Panniculitis	2 (29)	0 (0)	1 (33)	3 (9.1)
Paronychia	0 (0.0)	3 (14)	0 (0)	3 (9.1)
Keratosis pilaris–like reaction	2 (8)	0 (0)	1 (33)	3 (9.1)
Alopecia/texture change	0 (0)	1 (10)	0 (0)	1 (3.0)
Seborrheic dermatitis	0 (0)	1 (9)	0 (0)	1 (3.0)
Eruptive nevi	0 (0)	0 (0)	1 (330)	1 (3.0)
Photosensitivity	1 (6)	0 (0)	0 (0)	1 (3.0)
Other	4 (4)	3 (3)	2 (33)	9 (27.3)

*Total number of participants with reaction per drug class and percentage of patients with treatment interruption per reaction.

prevalence of acneiform eruptions was lower in those on combination BRAFI/MEKI therapy (40.4%) than in those on MEKI monotherapy.[11]

Paronychia were prevalent in children on MEKI (51.2%), which is consistent with other pediatric studies, but much more common than in adults (6%).[23,24,26] We postulate that children's higher physical activity level contributes, because preceding toe or nail trauma has been implicated in the pathogenesis of MEKI-induced paronychia.[40]

Our investigation supports the findings of prior smaller studies by confirming that cutaneous reactions in children on MEKI/BRAFI are universal. Both Song et al[26] and Boull et al[25] reported that 100% of children on MEKI or BRAFI experienced at least 1 cutaneous reaction. Children commonly experienced inflammatory reactions, including acneiform eruptions, paronychia, dermatitis, and panniculitis, but did not develop cutaneous malignancies. This study expands on previous literature by outlining the broad spectrum of reactions experienced by children on MEKI and BRAFI. A total of 33 unique cutaneous reactions developed in our patient group. Additionally, our data show that cutaneous reactions frequently alter treatment, highlighting the importance of preventing and treating reactions. The most common cutaneous reactions, including dermatitis and acneiform reactions, are also the most likely to alter therapy, suggesting that these should be targets for prevention efforts.

Because oncologists are most likely to be monitoring and treating cutaneous reactions, the implementation of prevention and treatment algorithms could significantly improve tolerance of BRAFI and MEKI. Gentle skin care practices, including use of a mild cleanser, avoidance of skin irritants, and use of a hypoallergenic emollient, should be suggested for all patients. Patients should also be counseled on effective photoprotective strategies. Patients on MEKI should receive education on nail-trimming techniques to minimize paronychia risk. These recommendations have previously been outlined in an algorithm by Song et al.[26]

Limitations

This study was retrospective and is limited by varied data gathering and reporting. The cutaneous reactions occurred while patients were receiving therapy with BRAFI and/or MEKI, but this does not prove causality. Only patients seen by a dermatologist were included in the analysis, which may have selected for individuals with more recalcitrant or severe cutaneous reactions. Approximately one third of patients required dermatologic examinations as part of their treatment protocols, but the remainder of patients were seen by a dermatologist as a result of cutaneous reactions. The number of follow-up visits varied among patients. For patients with single or few dermatology-focused visits, we were not able to accurately assess the timing of onset of cutaneous reactions. Finally, given the low number of patients on each medication, direct comparisons between reactions to medications in each class could not be performed.

CONCLUSIONS

Cutaneous reactions should be anticipated in children initiating therapy with BRAFI and/or MEKI. Reassuringly, life-threatening reactions and cutaneous malignancies are not common. Inflammatory reactions, including dermatitis, acneiform eruptions, panniculitis, and paronychia, frequently disrupt treatment, so better strategies to treat or prevent such reactions are needed.

Research reported in this publication was supported by National Institutes of Health grant P30 CA77598 using the

Biostatistics and Bioinformatics Core shared resource of the Masonic Cancer Center, University of Minnesota and by the National Center for Advancing Translational Sciences of the National Institutes of Health award number UL1-TR002494. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

This project was a result of collaboration from the Pediatric Dermatology Research Alliance.

This project was made possible by the support of our colleagues in pediatric oncology, including the following: Susan N. Chi, MD, assistant professor of pediatrics, Harvard Medical School, Department of Pediatric Oncology, Dana-Farber Cancer Institute; Stewart Goldman, MD, division head, Hematology, Oncology, Neuro-Oncology, and Stem Cell Transplantation, Ann & Robert H. Lurie Children's Hospital of Chicago; Angela Waanders, MD, MPH, director, Precision Medicine Oncology, Ann & Robert H. Lurie Children's Hospital of Chicago; Karen Gauvain, MD, associate professor, Division of Hematology/Oncology, Department of Pediatrics, Washington University School of Medicine in St Louis; Ashley Hite Meyer, CPNP, Division of Hematology/Oncology, Department of Pediatrics, Washington University School of Medicine in St Louis; Sarah E.S. Leary, MD, Division of Pediatric Hematology-Oncology, Seattle Children's Hospital, University of Washington School of Medicine; and Frank Y. Lin, MD and Jack M. Su, MD, Pediatric Hematology-Oncology, Texas Children's Cancer Center, Baylor College of Medicine, Texas Children's Hospital, Houston, Texas.

We thank the following investigators and industry sponsors for allowing us to include patients in clinical trials: Novartis (clinicaltrials.gov identifier: NCT02124772); Genentech, Dr Sabine Meuller, University of California, San Francisco, and Dr Theodore Nicolaides, New York University Langone Health (clinicaltrials.gov identifier: NCT01748149); and Dr Nathan Robinson, Children's Hospital of Los Angeles (clinicaltrials.gov identifier: NCT02285439).

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