# Supportive Oncodermatology in Pediatric Patients

Danny W. Linggonegoro, BS[a,b], Hannah Song, MD[a,b], Jennifer T. Huang, MD[a,b,*]

**KEYWORDS**

• Oncodermatology • Targeted therapy • Pediatric dermatology • Cutaneous reaction • Management

**KEY POINTS**

- Targeted cancer therapies block specific molecular pathways involved in the growth, progression, and spread of cancer.
- Pediatric dermatology literature is emerging on the specific types and prevalence of cutaneous reactions to targeted therapies that hone in on membrane-bound receptors (eg, BCR-ABL, EGFR, or SMO inhibitors), intracellular signaling targets (eg, BRAF, MEK, mTOR), and antiangiogenesis agents (eg, VEGF), as well as targeted immunotherapies.
- Information about the timing, severity, and treatment algorithm for these cutaneous reactions is most well described for BRAF, MEK, and EGFR inhibitors.
- Further research on the most common cutaneous reactions of targeted therapy in children, potential treatments, and prevention is crucial to better serve the needs of this population.

## INTRODUCTION

Cancer is an important cause of morbidity and mortality in children.[1] Targeted therapies have been developed to hone in on specific molecular pathways involved in the growth, progression, and spread of cancer. Although targeted therapies have become a focus of current anticancer drug development and are being increasingly used in pediatric populations, different cutaneous side effects have emerged with use of these therapies. Some targeted therapies result in dermatologic adverse events in nearly all treated children. Common reactions include xerosis, follicular and/or eczematous reactions, and hand-foot skin reactions. However, a subset of patients will experience adverse cutaneous effects that have the potential to lead to treatment cessation. In the authors' clinical experience, most children can be treated with topical and/or oral therapies without treatment breaks or cessation. Only rarely will children experience severe drug hypersensitivity reactions with internal organ involvement or Stevens-Johnson syndrome-like reactions requiring permanent drug cessation. Understanding the most common cutaneous reactions of targeted therapy in children and their treatments is crucial to better serve the needs of this population. In this article, the authors review common side effects of select targeted therapies and offer treatment options.

## DISCUSSION

### *Types of Targeted Therapies, Prevalence of Cutaneous Reactions, Management*

Targeted therapies are a type of cancer treatment that acts on membrane-bound receptors or intracellular signals to interfere with specific proteins that help tumors proliferate without regulation and resist apoptosis (**Fig. 1**).[3] The focus of this article is reactions to monotherapy with targeted therapeutics; however, combination therapy of different agents will also be discussed.

[a] Boston Children's Hospital, Dermatology Program, 300 Longwood Avenue, Fegan 6, Boston, MA 02115, USA;
[b] Harvard Medical School, 25 Shattuck St, Boston, MA 02115, USA
* Corresponding author. 300 Longwood Avenue, Fegan 6, Boston, MA 02115.
*E-mail address:* Jennifer.Huang@childrens.harvard.edu

Dermatol Clin 40 (2022) 203–214
https://doi.org/10.1016/j.det.2021.12.007

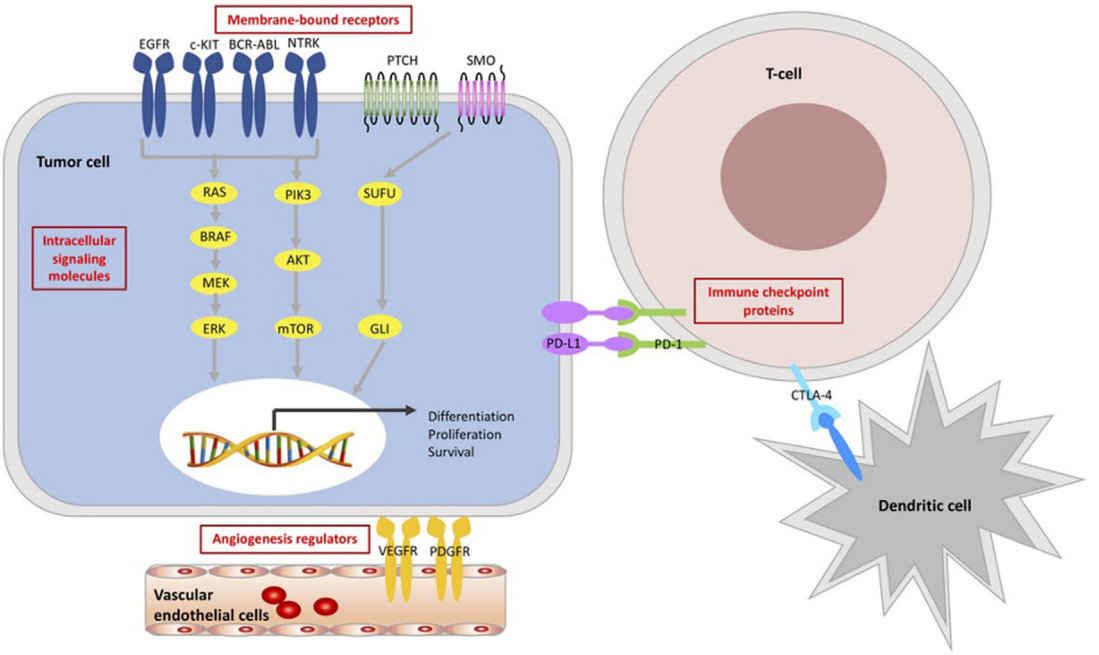


**Fig. 1.** Common molecules for targeted therapy in cancer. Therapies target membrane-bound receptors, intracellular signaling molecules, angiogenesis mediators, and immune checkpoint proteins to inhibit various steps of oncogenesis. From Carlberg, and colleagues; with permission from John Wiley & Sons.[2]

Classes of medications and brief mechanisms of action are reviewed. Each section includes incidence of cutaneous findings. Medication-specific treatment options are discussed in this section if any are available (**Table 1**). There are limited randomized clinical trials evaluating the effectiveness of management of cutaneous reactions in pediatric patients. Only reactions observed in pediatric patients are included. Dose reductions or switching to a different medication in the same class may be helpful for all these cutaneous reactions. Severe blistering skin reactions or skin reactions with internal organ involvement should prompt drug cessation. Dermatologists should work closely with oncologists to manage these complex patients.

## *Membrane-Bound Receptors or Intracellular Signaling Molecules*

Most targeted therapies are monoclonal antibodies or small-molecule drugs. Monoclonal antibodies target specific proteins on the surface of cancerous cells. Small-molecule drugs target specific substances inside the cell.

### *Membrane-bound receptors*

#### Tyrosine kinase receptors: BCR-ABL inhibitors

BCR-ABL inhibitors used in children include imatinib, dasatinib, and nilotinib. Translocation between the ABL tyrosine kinase gene on chromosome 9 and BCR gene on chromosome 22 leads to an oncogenic BCR-ABL1 fusion gene in hematopoietic stem cells. This fusion gene encodes a BCR-ABL protein kinase with constitutive tyrosine kinase activity leading to proliferative and antiapoptotic signaling responsible for hematologic malignancies.[4]

A maculopapular rash has been reported in 1.7% to 45.5% of pediatric patients.[5] Grade 1 to 2 periorbital edema has been reported in 25% of pediatric patients receiving imatinib.[6] Imatinib has a high degree of specificity for the platelet-derived growth factor receptor tyrosine kinase family, which is thought to regulate tissue fluid properties and is highly expressed in the dermal dendrocytes of periorbital tissue.[7] Rare cutaneous reactions include mucositis (6%), pruritus (2.3%), and madarosis (3%) in pediatric patients on BCR-ABL inhibitors.[5,8] Hypopigmentation has been reported in 1 case of a child with chronic myeloid leukemia being treated with imatinib.[9] The keratosis pilaris-like eruption associated with BCR-ABL has the characteristic perifollicular appearance, is generalized, and is variably associated with pruritus. In contrast, typical keratosis pilaris has a predilection for the lateral upper arms and legs and is usually asymptomatic. Pseudoporphyria has also been described in a few cases of children and adults receiving imatinib.[10] The onset of pseudoporphyria, occurring at months to years after imatinib initiation, appears to be significantly delayed compared with the other more commonly reported cutaneous reactions.[10] Dose reduction or cessation of imatinib resulted in complete resolution of the pseudoporphyria.[10]

**Table 1**
**Summary of dermatologic adverse events of targeted therapies and proposed management; management depends on the extent, severity, and underlying cause of the cutaneous reaction**

| Cutaneous Toxicities | Agents | Proposed Management |
|---|---|---|
| Maculopapular, acneiform, papulopustular rash | EGFR inhibitors[a]<br>BCR-ABL inhibitors[a]<br>SMO inhibitors<br>BRAF inhibitors<br>MEK inhibitors[a]<br>mTOR inhibitors[a]<br>AKT inhibitors<br>VEGF receptor tyrosine kinase inhibitors<br>CTLA-4 inhibitors | • Preemptive use of emollients, sunscreen, oral antibiotics, and topical steroids may be helpful<br>Mild:<br>• Topical steroids<br>• Topical antimicrobial wash (benzoyl peroxide)<br>• Dilute bleach baths<br>• Emollients<br>• Photoprotection<br>Moderate:<br>• Oral antibiotics<br>• Culture-driven antibiotics if secondary infection<br>Severe:<br>• Oral isotretinoin |
| Subcutaneous edema (periorbital, peripheral) | BCR-ABL inhibitors<br>BRAF inhibitors<br>mTOR inhibitors | • Limit salt intake<br>• Compression stockings<br>• Topical steroids<br>• Diuretics<br>• Topical phenylephrine<br>• Blepharoplasty for severe cases of periorbital edema |
| Mucosal changes (mucositis, angular cheilitis) | BCR-ABL inhibitors<br>MEK inhibitors<br>AKT inhibitors mTOR | • Antiseptic mouthwash without alcohol<br>• Topical analgesics<br>• Topical steroids<br>• Liquid, soft, or normal diet as tolerated |
| Pruritus | BCR-ABL inhibitors<br>EGFR inhibitors<br>AKT inhibitors<br>VEGF receptor tyrosine kinase inhibitors<br>CTLA-4 inhibitors | • Emollients<br>• Topical steroids<br>• Gentle skin care (short, warm showers; nonfragrance soaps; nonfragrance detergents)<br>• Oral antihistamines |
| Madarosis | BCR-ABL inhibitors<br>SMO inhibitors | • Usually reversible once responsible agent is discontinued<br>• Topical minoxidil |
| Hypopigmentation | BCR-ABL inhibitors<br>SMO inhibitors | • Usually reversible once responsible agent is discontinued |
| Keratosis pilaris-like eruption | BCR-ABL inhibitors<br>BRAF inhibitors | • Topical emollients<br>• Topical keratolytics<br>• Isotretinoin |
| Pseudoporphyria | BCR-ABL inhibitors | • Photoprotection<br>• Dose reduction or change targeted therapy |
| Xerosis | EGFR inhibitors<br>BRAF inhibitors<br>MEK inhibitors<br>mTOR inhibitors<br>AKT inhibitors<br>VEGF receptor tyrosine kinase inhibitors<br>CTLA-4 inhibitors | • Emollients<br>• Gentle skin care (short, warm showers; nonfragrance soaps; nonfragrance detergents) |

(*continued on next page*)

**Table 1**
***(continued)***

| Cutaneous Toxicities | Agents | Proposed Management |
|---|---|---|
| Trichomegaly | EGFR inhibitors | • Regular trimming and epilation to prevent obscuring vision, corneal erosions, irritation, and infection |
| Hypertrichosis | EGFR inhibitors | • Regular trimming |
| Alopecia | EGFR inhibitors<br>SMO inhibitors<br>BRAF inhibitors<br>MEK inhibitors<br>VEGF receptor tyrosine kinase inhibitors | • Topical minoxidil<br>• Usually reversible once responsible agent is discontinued |
| Hyperhidrosis | SMO inhibitors<br>CTLA-4 inhibitors | • Antiperspirants, topical anticholinergics<br>• Oral anticholinergics |
| Photosensitivity | BRAF inhibitors<br>MEK inhibitors | • Photoprotection |
| Hand-foot skin reaction | BRAF inhibitors<br>mTOR inhibitors<br>VEGF receptor tyrosine kinase inhibitors | • Topical steroids<br>• Topical keratolytics<br>• Emollients<br>• Topical analgesics<br>• Avoid friction of pressure points (thick socks and comfortable shoes) |
| Hair changes (changes in color or texture) | BRAF inhibitors<br>MEK inhibitors<br>VEGF receptor tyrosine kinase inhibitors | • Usually reversible once responsible agent is discontinued |
| Eruptive nevi | BRAF inhibitors<br>MEK inhibitors | • Photoprotection<br>• Baseline and routine skin examinations |
| Neutrophilic panniculitis | BRAF inhibitors | • Oral analgesics<br>• Compression garments<br>• Oral steroids<br>• Injected steroids<br>• Elevation of affected area |
| Hyperpigmentation | BRAF inhibitors | • Usually reversible once responsible agent is discontinued<br>• Photoprotection |
| Delayed wound healing | BRAF inhibitors<br>VEGF inhibitors | • Hold agent for 1 mo after surgery or until wound has healed |
| Paronychia | MEK inhibitors<br>EGFR inhibitors<br>mTOR inhibitors | • Gentle nail care (regular trimming once a week for fingernails and once a month for toenails; trim nails after showering; avoid trauma)<br>• Dilute bleach soaks<br>• Silver nitrate<br>• Topical steroids<br>• Culture driven topical or oral antibiotics |

[a] Most common medications with the associated dermatologic adverse reaction.

**Tyrosine kinase receptors: neurotrophic receptor tyrosine kinase inhibitors** Neurotrophic receptor tyrosine kinase (NTRK) inhibitors in children include entrectinib and larotrectinib. NTRK oncogenic fusions promote tumorigenesis via constitutive ligand-free activation of intracellular pathways that control cell-cycle progression, proliferation, apoptosis, and survival.[11,12] NTRK fusions are seen

more frequently in pediatric tumors than in adult tumors.[13] These pediatric tumors include infantile fibrosarcoma, cellular congenital mesoblastic nephroma, and papillary thyroid cancer.[13] Ongoing clinical trials are evaluating the optimal use of these drugs in children with NTRK fusions.[14] No cutaneous adverse effects have yet been reported with use of this targeted therapy.

**Tyrosine kinase receptors: EGFR inhibitors** Epidermal growth factor receptor (EGFR) inhibitors in children include erlotinib, cetuximab, gefitinib, and lapatinib. Acneiform rash is the most common type of skin toxicity reported in pediatric trials, with a prevalence of up to 67%.[15,16] Other common side effects include xerosis (48%), erythema (45%), pruritus (17%–21%), and trichomegaly (17%).[16] Clinical details regarding "erythema" were not available. Other rarer adverse reactions include hypertrichosis, alopecia, and cutaneous infection.[16] A study in pediatric patients receiving rapamycin and erlotinib reported 10% incidence of paronychia.[17] Time of onset of these cutaneous reactions in the pediatric population has not been described, but occurs within the first few weeks of treatment in adults.[18]

Practice guidelines for prevention and treatment of EGFR-inhibitor–associated dermatologic toxicities derive from approaches in adults (**Table 2**). Preemptive management of skin toxicity with emollients, sunscreen, oral doxycycline, and topical steroids showed a 50% decrease in the incidence of grade greater than 2 skin toxicities compared with the incidence in those who had reactive management of the cutaneous reactions.[19–21]

**G-protein-coupled receptor: smoothened inhibitors** Aberrant Hedgehog signaling has been implicated in carcinogenesis with a markedly increased risk of advanced basal cell carcinoma and medulloblastoma.[22,23] Although smoothened (SMO) inhibitors are not currently approved for pediatric patients, there are 2 clinical trials evaluating vismodegib and sonidegib for pediatric cancer.[24] Although sonidegib was well tolerated, premature growth plate changes were observed in prepubertal pediatric patients, which has limited their use.[24]

Cutaneous effects reported in a phase I and II clinical trial in children receiving sonidegib include alopecia (8.3%), madarosis (6.7%), and nail disorder (3.3%). Preliminary data in an ongoing trial in children receiving vismodegib have shown other cutaneous adverse effects, including hyperhidrosis, purpura, acneiform rash, and skin hypopigmentation.[25]

### *Intracellular signaling targets*

**Mitogen activated protein kinase pathway: BRAF inhibitors** BRAF inhibitors include vemurafenib and dabrafenib. The estimated prevalence of cutaneous reaction in patients receiving BRAF inhibitors is nearly 100% in children, and there are usually multiple reactions.[26,27] Time to onset of cutaneous reactions in children is not clear, but occurs within days to weeks in adults after initiation of BRAF inhibitors.[28] The most common cutaneous side effects of these agents include follicular eruptions, which impact 55% to 100% of patients receiving BRAF inhibitors. The follicular eruptions can present with keratosis pilaris-like reactions or comedonal eruptions and are typically distributed on the extremities and scalp.[26,27] Pruritic xerotic/eczematous dermatitis (36%–50%), photosensitivity (36%), hand-foot skin reactions (**Fig. 2**) with hyperkeratosis of pressure points of the palms and soles (36%–83%), and hair changes (changes in color or texture and alopecia; 30%) are other common cutaneous reactions. Inflammatory papules and pustules occurred in 18% of patients and were less common in children younger than 8 years (5%).[4,5] Other rarer reactions that have been reported include the following: eruptive nevi (23%) (**Fig. 3**), neutrophilic panniculitis (16%), periorbital edema, hyperpigmentation, delayed wound healing, erythema multiforme-like reaction, and severe photosensitivity reaction.[7]

**Mitogen activated protein kinase pathway: MEK inhibitors** MEK inhibitors include trametinib, cobimetinib, binimetinib, and selumetinib. In addition to cancer therapy, selumetinib has been approved by the Food and Drug Administration (FDA) for treatment of plexiform neurofibromas associated with neurofibromatosis-1. The estimated prevalence of cutaneous reactions in pediatric patients on an MEK inhibitor is 100%. Common reactions include acneiform eruptions (67%–87%) (**Figs. 4** and **5**), xerosis (58%–72.7%), and paronychia (36%–51%) (**Fig. 6**).[26,27] Other less common reactions include hair changes, including alopecia, curly hair texture, and hair lightening (18%–23.3%), seborrheic dermatitis (26%), folliculitis (19%), and angular cheilitis (7%–27.3%). Other rarer reactions (<10% prevalence) include photosensitivity, eruptive nevi, oral mucositis, nail changes, excess facial hair, psoriasiform eruption, and drug rash with eosinophilia and systemic symptoms-like reaction.

**PI3K/AKT/mTOR pathway: phosphatidylinositol-4,5-bisphosphate 3-kinase inhibitors** PI3K activates a signaling cascade that controls cellular proliferation, survival, and motility. PTEN is one of the more common inactivated tumor suppressor genes. Mutations in PTEN lead to lack of control of PIP3 levels and constitutive activation of

**Table 2**
**Epidermal growth factor receptor inhibitor associated acneiform rash treatment algorithm with grading based on the National Cancer Institute Common Terminology for Adverse Events, version 4.0**

| Grade of Acneiform Rash | Approach to Treatment |
|---|---|
| Grade 1: Papules and/or pustules covering <10% of the body surface area (BSA) with or without symptoms of pruritus or tenderness | • Emollients<br>• Photo-protection<br>• Low-potency topical steroids twice a day<br>• Topical antibiotics (clindamycin gel 1%, erythromycin gel/cream 3%; metronidazole cream/gel 0.75%–1%) twice a day for 4 wk<br>• If not improved, treat it as grade 2 rash |
| Grade 2: Papules and/or pustules covering 10%–30% of the BSA with or without symptoms of pruritus or tenderness; with psychosocial impact | • Oral antibiotics (doxycycline 200 mg or minocycline 200 mg daily) for 4–6 wk<br>• If not improved, treat it as grade 3 rash |
| Grade ≥3: Papules and/or pustules covering >30% of the BSA with or without symptoms of pruritus or tenderness; limiting self-care activities of daily living | • Low-dose isotretinoin (20–30 mg daily) for 2 mo<br>• If rash interferes with self-care activities, adjusting the dose of EGFR inhibitor until rash improves may be considered |

*Data from* Lupu I, Voiculescu V, Bacalbasa N, Prie B, Cojocaru I, Giurcaneanu C. Cutaneous adverse reactions specific to epidermal growth factor receptor inhibitors. J Med Life. 2015;8(Spec Issue):57-61.

PI3K signaling.[29] Currently, there are clinical trials in pediatric patients with osteosarcoma or Ewing sarcoma evaluating PI3K inhibitors BAY80-6946 and LY3023414; however, no cutaneous reactions have been reported.[30–32]

**PI3K/AKT/mTOR pathway: AKT inhibitors** AKT is activated downstream of PI3K, which transmits signals from cytokines, growth factors, and oncoproteins to multiple targets. AKT inhibitors include miransertib, perifosine, miltefosine, and MK2206. AKT inhibitors have been studied in children with proteus syndrome, ovarian carcinoma, and visceral leishmaniasis. Although there are no robust data describing cutaneous reactions of AKT inhibitors, mucositis, xerosis, pruritus, and maculopapular rash have been observed in a small sample of children receiving AKT inhibitors.[33,34]

**PI3K/AKT/mTOR pathway: mechanistic target of rapamycin inhibitors** Mechanistic target of rapamycin (mTOR) is activated further downstream of AKT. The mTOR inhibitors include everolimus, sirolimus, temsirolimus, and ridaforolimus. The most common cutaneous reaction in children taking mTOR inhibitors is mucositis, occurring in 83% of patients in a phase I study with 60% having a grade 3 adverse effect.[35] Xerosis occurred in 80% of pediatric patients. Other cutaneous side effects of mTOR inhibitors in children include follicular rash, nail changes, paronychia, hand-foot skin reaction, and peripheral edema.[27,36–40] A proposed treatment algorithm for cutaneous reactions for BRAF, MEK, and mTOR inhibitors includes baseline gentle skin care and sun protection (**Fig. 7**).

### *Antiangiogenesis*

Angiogenesis is a critical step in tumor growth and metastasis. Before a tumor can grow more than 1 to 2 mm, its cells require blood vessels for nutrients and oxygen.[41,42] Antiangiogenic agents target protein expression, receptors, and ligands in the vascular endothelial growth factor (VEGF) signaling pathway.

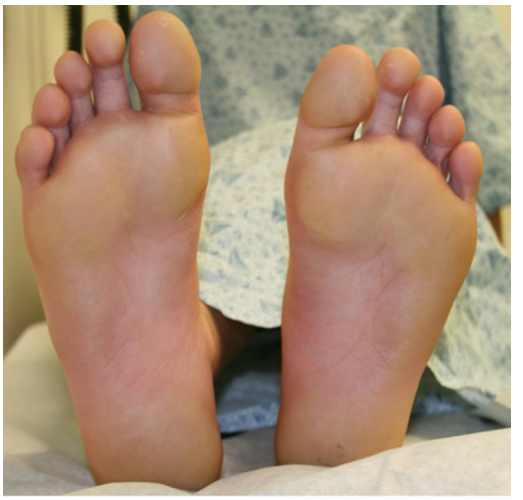

**Fig. 2.** Hand-foot skin reaction in a patient on a BRAF inhibitor.

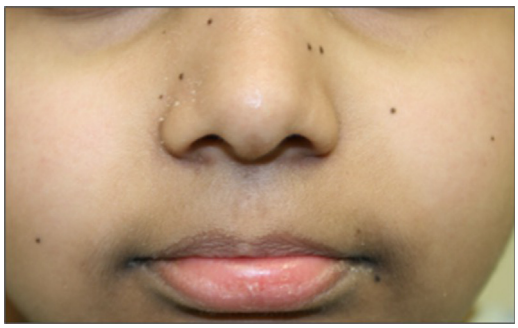

Fig. 3. Eruptive nevi in a patient on a BRAF inhibitor.

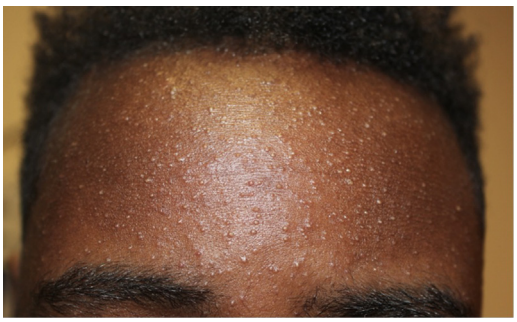

Fig. 5. Mild acneiform rash on the forehead in a patient receiving trametinib.

**Vascular endothelial growth factor and vascular endothelial growth factor receptor inhibitors** VEGF is a key mediator of vascular development in physiologic growth and embryogenesis; it also plays an important role in pathologic angiogenesis. VEGF is expressed ubiquitously in nearly all human cancers to date. Currently, it is the best-characterized proangiogenic cytokine.[41] Higher levels of VEGF have been associated with increased tumor vascularity, as well as rapid tumor growth, invasion, and metastasis. Blocking the VEGF pathway has thus been an important area of cancer drug development. Bevacizumab was the first anti-VEGF monoclonal antibody approved by the FDA and is one of the best-characterized VEGF inhibitors.

For patients taking bevacizumab after tumor resection, delayed wound healing was one of the more commonly reported adverse effects.[43] Surgical wound dehiscence and enterocutaneous fistula have also been reported.[44,45] Dehiscence of high-dose corticosteroid-induced striae at nonsurgical sites has been reported in 2 children receiving bevacizumab.[46,47] Some experts report that bevacizumab therapy should be delayed until complete surgical site healing or 4 weeks after surgery to avoid these complications.

**Multikinase inhibitors: vascular endothelial growth factor receptor tyrosine kinase inhibitors** VEGF receptor tyrosine kinase inhibitors currently being investigated for treatment of pediatric hematologic malignancy and solid tumors include sorafenib, sunitinib, and pazopanib.[48(p2)] Preliminary data reveal dose-limiting toxicities, including hand-foot skin reaction and maculopapular rash.[49] When sorafenib was administered concurrently with clofarabine and cytarabine, up to 67% of patients developed grade 2 hand-foot skin reaction or higher.[50] Increased pressure and friction, such as in the setting of wearing hard orthotics, may increase the risk of developing hand-foot skin reaction.[51] Up to 83% of patients on sorafenib monotherapy developed a maculopapular rash, and 50% developed xerosis.[52] Other cutaneous reactions associated with sorafenib monotherapy include lip discoloration, alopecia, hair color changes, and pruritus.[52–54] Hair color changes, most commonly in the form of pigmentary dilution, was the most common cutaneous

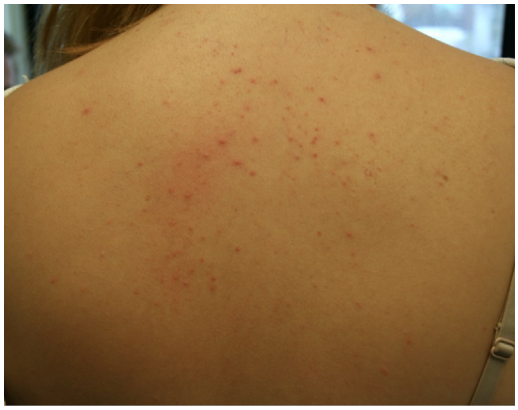

Fig. 4. Mild acneiform rash on the upper back in a patient receiving trametinib.

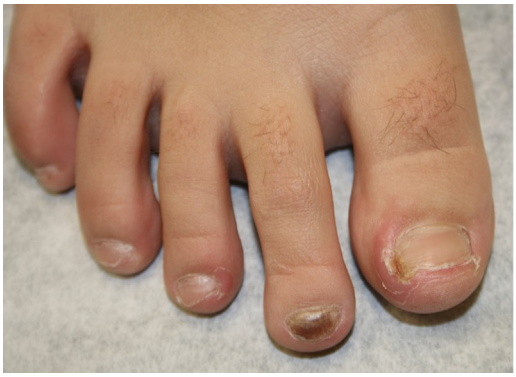

Fig. 6. Paronychia in a patient receiving trametinib.

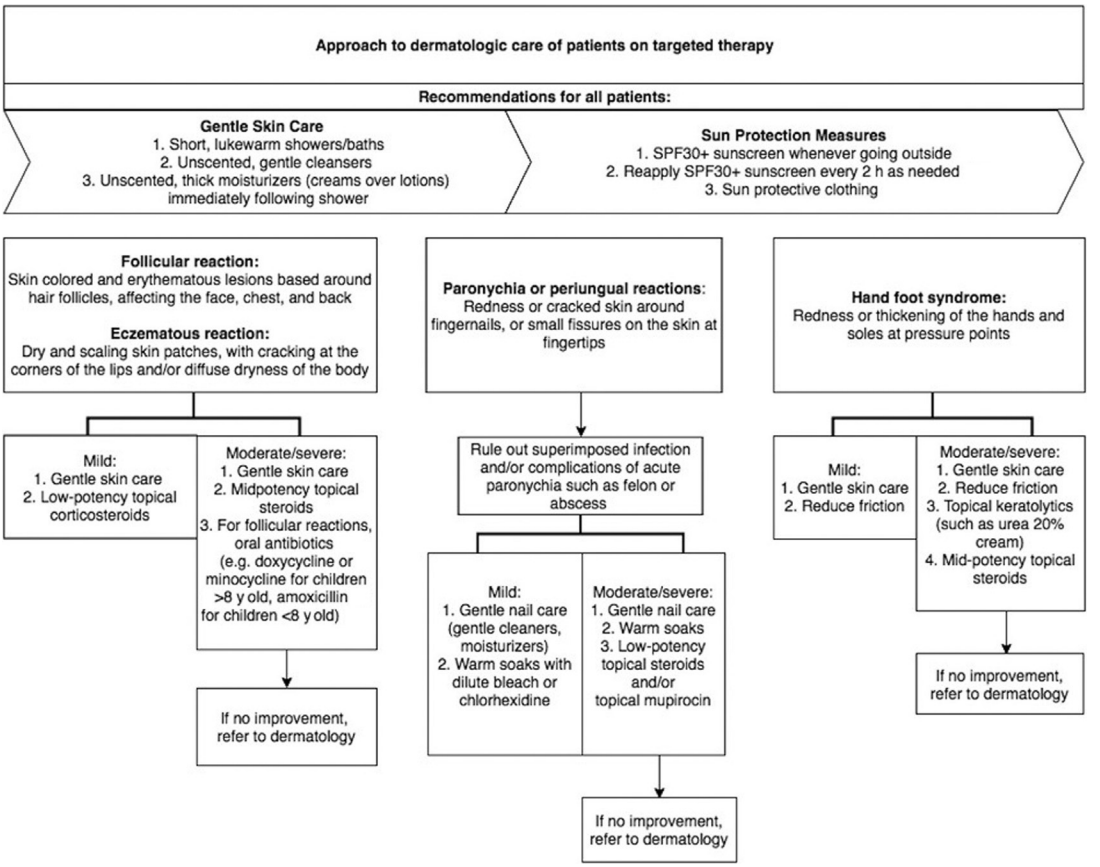


**Fig. 7.** Stepwise approach to initial dermatologic care of pediatric patients on BRAF, MEK or mTOR inhibitor monotherapy. (From Song H, Zhong CS, Kieran MW, Chi SN, Wright KD, Huang JT. Cutaneous reactions to targeted therapies in children with CNS tumors: A cross-sectional study. Pediatr Blood Cancer. 2019;66(6):e27682.)

adverse effect associated in pediatric patients receiving pazopanib (**Fig. 8**).[55] Other less common cutaneous effects include rash, urticaria, hand-foot skin reaction, xerosis, and generalized hypopigmentation. Notably, the incidence of cutaneous reactions with sorafenib is higher compared with pazopanib and sunitinib.[56] Patients receiving sorafenib also had the highest incidence of grade $\geq$3 rash compared with other VEGF receptor tyrosine kinase inhibitors.[56]

A clinical trial for treatment of sorafenib-induced hand-foot skin reaction with urea cream is currently underway.[57]

### *Targeted immunotherapy*

The immune system is able to detect and defend against abnormal cells, including cancerous cells. Tumor-infiltrating lymphocytes or TILs are found in and around tumors, and the presence of TILs are a positive prognostic indicator for oncology patients. Some cancerous cells can evade the immune system through mechanisms like genetic mutations to make themselves less detectable by immune cells. Targeted immunotherapy has been developed to upregulate the anticancer response. This section discusses the more recently developed dermatologic adverse effects of immune checkpoint

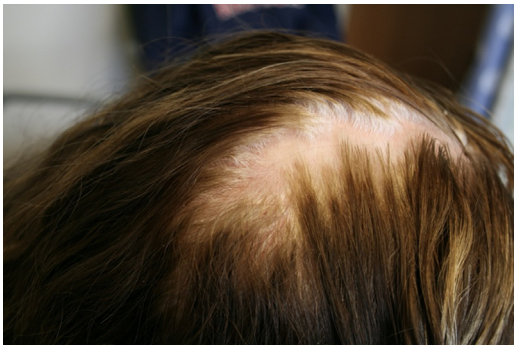

**Fig. 8.** Pigmentary dilution in a patient receiving pazopanib.

inhibitors, including inhibitors of cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), programmed death protein 1 (PD-1), and programmed death ligand 1 (PD-L1). The checkpoint proteins CTLA-4 and PD-1 are located on T cells and downregulate autoimmune responses. PD-L1 is a protein on the surface of cancer cells in addition to some normal cells. PD-1 on T cells binds to its partner protein PD-L1 on normal and/or cancer cells and thereby dampens the T-cell response. Checkpoint inhibitors work by blocking these checkpoint proteins from binding with their partner proteins, which prevents T cells from being downregulated and augments the immune response.

**Checkpoint inhibitors: cytotoxic T-lymphocyte-associated protein 4 inhibitors** Ipilimumab is a CTLA-4 inhibitor approved for use in pediatric patients 12 years of age or older.[58] A phase II trial of children between ages 12 and 18 years with stage III to IV malignant melanoma showed more cutaneous reactions in children taking 10 mg/kg versus children taking 3 mg/kg. These patients developed acne, xerosis, hyperhidrosis, pruritus, and rash.[59] Details describing the morphology of the rash were not available. Another phase II trial reported no grade 3 or 4 dermatologic adverse effects for children receiving treatment with ipilimumab.[60]

**Checkpoint inhibitors: programmed death protein-1 and programmed death ligand-1 inhibitors** PD-L1 inhibitors approved in pediatric populations include atezolizumab, avelumab, and durvalumab. In patients receiving nivolumab, several dermatologic adverse events were reported: maculopapular rash (11%), mucositis (1%), and Stevens-Johnson syndrome (1%).[61] In pediatric patients receiving pembrolizumab, dermatologic adverse events included rash (8%), pruritus (2%), and photosensitivity reaction (<1%).[62] In another retrospective cohort study with pediatric patients receiving immune checkpoint inhibitors either in combination (CTLA-4/PD-1) or as monotherapy, maculopapular eruption (50%) was the most common reaction. Among those who had any cutaneous reaction, a few (21%) of them were referred to dermatology.[63] There is 1 case report describing a patient with refractory acute lymphoblastic T-cell leukemia after allogeneic stem cell transplant who was treated with a PD-1 inhibitor. One week after administration, the patient developed acute graft-versus-host disease of the skin, liver, lung, central nervous system, and eyes.[64] Therefore, it is important to include graft-versus-host disease in the differential for an acute rash in a patient with a history of stem cell transplant who receives immunotherapy.

## SUMMARY

- Targeted cancer therapies block specific molecular pathways involved in the growth, progression, and spread of cancer.
- Pediatric dermatology literature is emerging on the specific types and prevalence of cutaneous reactions to targeted therapies that hone in on membrane-bound receptors (eg, BCR-ABL, EGFR, or SMO inhibitors), intracellular signaling targets (eg, BRAF, MEK, mTOR), and antiangiogenesis agents (eg, VEGF), as well as targeted immunotherapies.
- Data regarding the timing, severity, and treatment algorithm for these cutaneous reactions are most plentiful for BRAF, MEK, and EGFR inhibitors.
- Further research on the most common cutaneous reactions of targeted therapy in children, treatments, and prevention is crucial to better serve the needs of this population.

## CLINICS CARE POINTS

- Targeted cancer therapies induce a variable range of cutaneous toxicities that can be dose-limiting. Most common reactions in targeted therapies include follicular rash and xerosis.
- Data about onset of cutaneous reaction in pediatric populations are lacking, but onset in adults is within weeks.
- Preventative measures should be considered before starting targeted therapies.
- Dermatologists should tailor management to the type and severity of the cutaneous reaction.

## ACKNOWLEDGMENTS

Funding for this project was made possible by the Pediatric Dermatology Research Alliance (PeDRA)

## REFERENCES

1. Liu L, Oza S, Hogan D, et al. Global, regional, and national causes of child mortality in 2000–13, with projections to inform post-2015 priorities: an updated systematic analysis. Lancet 2015;385(9966):430–40.
2. Carlberg VM, Davies OMT, Brandling-Bennett HA, et al. Cutaneous reactions to pediatric cancer treatment part II: targeted therapy. Pediatr Dermatol 2021;38(1):18–30.

3. Targeted Therapy for Cancer - National Cancer Institute. 2014. Available at: https://www.cancer.gov/about-cancer/treatment/types/targeted-therapies. March 21, 2021.
4. Carofiglio F, Lopalco A, Lopedota A, et al. Bcr-Abl tyrosine kinase inhibitors in the treatment of pediatric CML. Int J Mol Sci 2020;21(12).
5. Belum VR, Washington C, Pratilas CA, et al. Dermatologic adverse events in pediatric patients receiving targeted anticancer therapies: a pooled analysis. Pediatr Blood Cancer 2015;62(5):798–806.
6. Geoerger B, Morland B, Ndiaye A, et al. Target-driven exploratory study of imatinib mesylate in children with solid malignancies by the Innovative Therapies for Children with Cancer (ITCC) European Consortium. Eur J Cancer 2009;45(13):2342–51.
7. Larson JSM. Severe periorbital edema secondary to imatinib mesylate for chronic myelogenous leukemia. Arch Ophthalmol 2007;125(7):985.
8. Drucker AM, Wu S, Busam KJ, et al. Rash with the multitargeted kinase inhibitors nilotinib and dasatinib: meta-analysis and clinical characterization. Eur J Haematol 2013;90(2):142–50.
9. Brazzelli V, Roveda E, Prestinari F, et al. Vitiligo-like lesions and diffuse lightening of the skin in a pediatric patient treated with imatinib mesylate: a noninvasive colorimetric assessment. Pediatr Dermatol 2006;23(2):175–8.
10. Mahon C, Purvis D, Laughton S, et al. Imatinib mesylate-induced pseudoporphyria in two children. Pediatr Dermatol 2014;31(5):603–7.
11. Albert CM, Davis JL, Federman N, et al. TRK fusion cancers in children: a clinical review and recommendations for screening. J Clin Oncol 2018;37(6):513–24.
12. Kheder ES, Hong DS. Emerging targeted therapy for tumors with NTRK fusion proteins. Clin Cancer Res 2018;24(23):5807–14.
13. Zhao X, Kotch C, Fox E, et al. NTRK fusions identified in pediatric tumors: the frequency, fusion partners, and clinical outcome. JCO Precis Oncol 2021;(5):204–14.
14. Laetsch TW, DuBois SG, Mascarenhas L, et al. Larotrectinib for paediatric solid tumours harbouring NTRK gene fusions: a multicentre, open-label, phase 1 study. Lancet Oncol 2018;19(5):705–14.
15. Trippett TM, Herzog C, Whitlock JA, et al. Phase I and pharmacokinetic study of cetuximab and irinotecan in children with refractory solid tumors: a study of the Pediatric Oncology Experimental Therapeutic Investigators' Consortium. J Clin Oncol 2009;27(30):5102–8.
16. Geoerger B, Hargrave D, Thomas F, et al. Innovative therapies for children with cancer pediatric phase I study of erlotinib in brainstem glioma and relapsing/refractory brain tumors. Neuro-Oncol. 2011;13(1):109–18.
17. Yalon M, Rood B, MacDonald TJ, et al. A feasibility and efficacy study of rapamycin and erlotinib for recurrent pediatric low-grade glioma (LGG). Pediatr Blood Cancer 2013;60(1):71–6.
18. Fakih M, Vincent M. Adverse events associated with anti-EGFR therapies for the treatment of metastatic colorectal cancer. Curr Oncol 2010;17(Suppl 1):S18–30.
19. Lacouture ME, Anadkat M, Jatoi A, et al. Dermatologic toxicity occurring during anti-EGFR monoclonal inhibitor therapy in patients with metastatic colorectal cancer: a systematic review. Clin Colorectal Cancer 2018;17(2):85–96.
20. Lacouture ME, Mitchell EP, Piperdi B, et al. Skin toxicity evaluation protocol with panitumumab (STEPP), a phase II, open-label, randomized trial evaluating the impact of a pre-emptive skin treatment regimen on skin toxicities and quality of life in patients with metastatic colorectal cancer. J Clin Oncol 2010;28(8):1351–7.
21. Lupu I, Voiculescu V, Bacalbasa N, et al. Cutaneous adverse reactions specific to epidermal growth factor receptor inhibitors. J Med Life 2015;8(Spec Issue):57–61.
22. McMillan R, Matsui W. Molecular pathways: the hedgehog signaling pathway in cancer. Clin Cancer Res 2012;18(18):4883–8.
23. Gorlin RJ, Goltz RW. Multiple nevoid basal-cell epithelioma, jaw cysts and bifid rib. N Engl J Med 1960;262(18):908–12.
24. Kieran MW, Chisholm J, Casanova M, et al. Phase I study of oral sonidegib (LDE225) in pediatric brain and solid tumors and a phase II study in children and adults with relapsed medulloblastoma. Neuro-Oncol. 2017;19(11):1542–52.
25. Vismodegib in treating younger patients with recurrent or refractory medulloblastoma - study results - ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/results/NCT01239316. March 20, 2021.
26. Boull CL, Gardeen S, Abdali T, et al. Cutaneous reactions in children treated with MEK inhibitors, BRAF inhibitors, or combination therapy: a multicenter study. J Am Acad Dermatol 2020. https://doi.org/10.1016/j.jaad.2020.07.044.
27. Song H, Zhong CS, Kieran MW, et al. Cutaneous reactions to targeted therapies in children with CNS tumors: a cross-sectional study. Pediatr Blood Cancer 2019;66(6):e27682.
28. Lacouture ME, Duvic M, Hauschild A, et al. Analysis of dermatologic events in vemurafenib-treated patients with melanoma. Oncologist 2013;18(3):314–22.
29. Rogers HA, Estranero J, Gudka K, et al. The therapeutic potential of targeting the PI3K pathway in pediatric brain tumors. Oncotarget 2016;8(2):2083–95.

30. Jiang N, Dai Q, Su X, et al. Role of PI3K/AKT pathway in cancer: the framework of malignant behavior. Mol Biol Rep 2020;47(6):4587–629.
31. Safety, tolerability, efficacy and pharmacokinetics of copanlisib in pediatric patients - no study results posted - ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/results/NCT03458728. March 20, 2021.
32. National Cancer Institute (NCI). NCI-COG pediatric MATCH (molecular analysis for therapy choice)- phase 2 subprotocol of LY3023414 in patients with solid tumors. clinicaltrials.gov. 2021. Available at: https://clinicaltrials.gov/ct2/show/NCT03213678. March 18, 2021.
33. Keppler-Noreuil KM, Sapp JC, Lindhurst MJ, et al. Pharmacodynamic study of miransertib in individuals with proteus syndrome. Am J Hum Genet 2019;104(3):484–91.
34. Fouladi M, Perentesis JP, Phillips CL, et al. A phase I trial of MK-2206 in children with refractory malignancies: a Children's Oncology Group Study. Pediatr Blood Cancer 2014;61(7):1246–51.
35. Morgenstern DA, Marzouki M, Bartels U, et al. Phase I study of vinblastine and sirolimus in pediatric patients with recurrent or refractory solid tumors. Pediatr Blood Cancer 2014;61(1):128–33.
36. Davies M, Saxena A, Kingswood JC. Management of everolimus-associated adverse events in patients with tuberous sclerosis complex: a practical guide. Orphanet J Rare Dis 2017;12(1):35.
37. Peterson DE, O'Shaughnessy JA, Rugo HS, et al. Oral mucosal injury caused by mammalian target of rapamycin inhibitors: emerging perspectives on pathobiology and impact on clinical practice. Cancer Med 2016;5(8):1897–907.
38. Fidan K, Kandur Y, Sozen H, et al. How often do we face side effects of sirolimus in pediatric renal transplantation? Transplant Proc 2013;45(1):185–9.
39. Hymes LC, Warshaw BL. Five-year experience using sirolimus-based, calcineurin inhibitor-free immunosuppression in pediatric renal transplantation. Pediatr Transplant 2011;15(4):437–41.
40. Hammer J, Seront E, Duez S, et al. Sirolimus is efficacious in treatment for extensive and/or complex slow-flow vascular malformations: a monocentric prospective phase II study. Orphanet J Rare Dis 2018;13. https://doi.org/10.1186/s13023-018-0934-z.
41. Glade-Bender J, Kandel JJ, Yamashiro DJ. VEGF blocking therapy in the treatment of cancer. Expert Opin Biol Ther 2003;3(2):263–76.
42. Carmeliet P. VEGF as a key mediator of angiogenesis in cancer. Oncology 2005;69(Suppl. 3):4–10.
43. Barone A, Rubin JB. Opportunities and challenges for successful use of bevacizumab in pediatrics. Front Oncol 2013;3. https://doi.org/10.3389/fonc.2013.00092.
44. Pasquale MDD, Castellano A, Sio LD, et al. Bevacizumab in pediatric patients: how safe is it? Anticancer Res 2011;31(11):3953–7.
45. Turner DC, Navid F, Daw NC, et al. Population pharmacokinetics of bevacizumab in children with osteosarcoma: implications for dosing. Clin Cancer Res 2014;20(10):2783–92.
46. Wheeler H, Black J, Webb S, et al. Dehiscence of corticosteroid-induced abdominal striae in a 14-year-old boy treated with bevacizumab for recurrent glioblastoma. J Child Neurol 2012;27(7):927–9.
47. Laugier O, Padovani L, Verschuur A, Gaudy-Marqueste C, André N. Necrotic ulcerated and bleeding striae distensae following bevacizumab in a palliative setting for gliobastomatosis cerebri. doi:10.3332/ecancer.2017.756
48. Kim A, Widemann BC, Krailo M, et al. Phase 2 trial of sorafenib in children and young adults with refractory solid tumors: a report from the Children's Oncology Group. Pediatr Blood Cancer 2015;62(9):1562–6.
49. Sorafenib tosylate in treating younger patients with relapsed or refractory rhabdomyosarcoma, Wilms tumor, liver cancer, or thyroid cancer - study results - ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/results/NCT01502410. March 21, 2021.
50. Inaba H, Panetta JC, Pounds SB, et al. Sorafenib population pharmacokinetics and skin toxicities in children and adolescents with refractory/relapsed leukemia or solid tumor malignancies. Clin Cancer Res 2019;25(24):7320–30.
51. Kusari A, Borok J, Han AM, et al. Hand-foot-skin reaction related to use of the multikinase inhibitor sorafenib and hard orthotics. Pediatr Dermatol 2018;35(4):e206–9.
52. NYU Langone Health. Phase II study of sorafenib in children and young adults with recurrent or progressive low-grade astrocytomas. clinicaltrials.gov. 2016. Available at: https://clinicaltrials.gov/ct2/show/NCT01338857. March 18, 2021.
53. Pfizer A. Phase I/II study of sunitinib in young patients with advanced gastrointestinal stromal tumor. clinicaltrials.gov. 2019. Available at: https://clinicaltrials.gov/ct2/show/results/NCT01396148. March 18, 2021.
54. Study of Sutent®/Sunitinib. SU11248) in subjects with NF-1 plexiform neurofibromas - study results - ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/results/NCT01402817. March 21, 2021.
55. Pazopanib Paediatric Phase II Trial Children's Oncology Group (COG) in solid tumors - study results - ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/results/NCT01956669. April 10, 2021.
56. Que Y, Liang Y, Zhao J, et al. Treatment-related adverse effects with pazopanib, sorafenib and sunitinib in patients with advanced soft tissue sarcoma: a

pooled analysis. Cancer Manag Res 2018;10:2141–50.
57. Kim JH. The effect of urea cream on sorafenib-associated hand-foot skin reaction in patients with Korean hepatocellular carcinoma patients: multicenter, prospective randomized double-blind controlled study. clinicaltrials.gov. 2019. Available at: https://clinicaltrials.gov/ct2/show/NCT03212625. March 18, 2021.
58. Merchant MS, Wright M, Baird K, et al. Phase I clinical trial of ipilimumab in pediatric patients with advanced solid tumors. Clin Cancer Res 2016;22(6):1364–70.
59. Phase 2 study of ipilimumab in children and adolescents (12 to < 18 years) with previously treated or untreated, unresectable stage III or stage IV malignant melanoma - study results - ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/results/NCT01696045. March 21, 2021.
60. Geoerger B, Bergeron C, Gore L, et al. Phase II study of ipilimumab in adolescents with unresectable stage III or IV malignant melanoma. Eur J Cancer 2017;86:358–63.
61. Davis KL, Fox E, Merchant MS, et al. Nivolumab in children and young adults with relapsed or refractory solid tumours or lymphoma (ADVL1412): a multicentre, open-label, single-arm, phase 1–2 trial. Lancet Oncol 2020;21(4):541–50.
62. Geoerger B, Kang HJ, Yalon-Oren M, et al. Pembrolizumab in paediatric patients with advanced melanoma or a PD-L1-positive, advanced, relapsed, or refractory solid tumour or lymphoma (KEYNOTE-051): interim analysis of an open-label, single-arm, phase 1–2 trial. Lancet Oncol 2020;21(1):121–33.
63. McCormack L, Thompson LL, Chang MS, et al. Cutaneous adverse events to immune checkpoint inhibitors in pediatric populations: a retrospective cohort study. J Am Acad Dermatol 2020. https://doi.org/10.1016/j.jaad.2020.11.033. S019096222033070X.
64. Boekstegers A-M, Blaeschke F, Schmid I, et al. MRD response in a refractory paediatric T-ALL patient through anti-programmed cell death 1 (PD-1) Ab treatment associated with induction of fatal GvHD. Bone Marrow Transplant 2017;52(8):1221–4.