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REVIEW ARTICLE

Diagnosis and Management of Dermatologic Adverse Events from Systemic Melanoma Therapies

Christopher J. Fay[1] · Samantha Jakuboski[2] · Beth Mclellan[3] · Blair S. Allais[1] · Yevgeniy Semenov[4] · Cecilia A. Larocca[1] · Nicole R. LeBoeuf[1]

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Abstract

The advent of protein kinase inhibitors and immunotherapy has profoundly improved the management of advanced melanoma. However, with these therapeutic advancements also come drug-related toxicities that have the potential to affect various organ systems. We review dermatologic adverse events from targeted (including BRAF and MEK inhibitor-related) and less commonly used melanoma treatments, with a focus on diagnosis and management. As immunotherapy-related toxicities have been extensively reviewed, herein, we discuss injectable talimogene laherparepvec and touch on recent breakthroughs in the immunotherapy space. Dermatologic adverse events may severely impact quality of life and are associated with response and survival. It is therefore essential that clinicians are aware of their diverse presentations and management strategies.

Key Points

Systemic melanoma treatments have improved survival in patients but are associated with significant specific dermatologic adverse events.

Dermatologic adverse events from melanoma treatments are common, and prompt recognition and management can improve patient quality of life and cancer outcomes.

1 Introduction

Melanoma is the fifth most common cancer in the USA, representing 5.2% of all new cancer diagnoses [1, 2]. An estimated 2.1% of the population is expected to develop melanoma during their lifetime, with the incidence increasing in the USA [2]. While new cases have been on the rise, the death rates have slowly been in decline [1, 2]. Improvements in earlier-stage detection, as well as new treatment options, especially for patients with advanced-stage melanoma, are contributing to this improvement. Systemic therapies for advanced melanoma include inhibitors of V-raf murine sarcoma viral oncogene homolog B1 (BRAF) and mitogen and extracellular-regulated protein kinase (MEK); talimogene laherparepvec (T-VEC); and immune checkpoint inhibitors (ICIs); with additional novel therapies in clinical trials. However, these therapies are not without side effects, and specific dermatologic adverse events (dAEs) are associated with each drug class. The range of clinical presentations is diverse, and when severe, can result in treatment discontinuation. Interestingly, these dAEs are also often associated with therapeutic response. In this review, we will focus on the diagnosis and management of dermatologic adverse events (dAEs) from melanoma therapies, so that dermatologists and oncologists will be positioned to best identify the culprit agent and mitigate toxicity, improving both melanoma and quality-of-life-threatening outcomes.

Christopher Fay and Samantha Jakuboski are co-first authors.

✉ Nicole R. LeBoeuf
nleboeuf@bwh.harvard.edu

[1] Department of Dermatology, Brigham and Women's Hospital, and the Center for Cutaneous Oncology, Dana-Farber/Brigham and Women's Cancer Center, Harvard Medical School, Boston, MA, USA

[2] Loyola University Stritch School of Medicine, Maywood, IL, USA

[3] Department of Dermatology, Albert Einstein College of Medicine, Bronx, NY, USA

[4] Department of Dermatology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

2 Targeted Therapies: BRAF and MEK Inhibitors

Among the revolutionary advancements in metastatic melanoma treatment in the last decade are drugs targeting BRAF and MEK. BRAF and MEK are two protein kinases involved in the Ras/Raf/MEK mitogen-activated protein kinase (MAPK) cell signaling pathway for cell replication and growth (Fig. 1). Mutations anywhere along this pathway, especially in BRAF and MEK genes, can result in uncontrolled cell growth and division, leading to tumorigenesis [3, 4]. Fifty percent of patients with metastatic melanoma have *BRAF* mutations, with 80% of the mutations caused by the substitution of valine by glutamic acid at position 600 (BRAF V600E) [3]. This mutation induces a 500-fold increase in BRAF activity. Patients with BRAF V600E mutations respond to both BRAF inhibitors (BRAFi) and MEK inhibitors (MEKi). Mutations substituting valine for lysine (V600K) comprise around 15% of BRAF mutations and also respond to BRAF and MEK inhibition. BRAFi (dabrafenib, vemurafenib, encorafenib) and MEKi (trametinib, cobimetinib, binimetinib) stop oncogenic signaling. Their implementation has led to improved survival in patients [5–7]. Somatic testing is recommended for patients with stage III and IV melanoma to guide treatment. These therapies individually have notable, specific dAEs. However, BRAFi and MEKi are now rarely used as monotherapy in the treatment of melanoma, as combination therapy with these two classes of drugs increases efficacy and decreases adverse events [8]. Nonetheless, the clinical experience of their use in melanoma treatment has been helpful for understanding adverse events when these medications are used as monotherapy in other malignancies. Skin toxicities from BRAF and MEK inhibitors and management strategies are summarized in Table 1 [9].

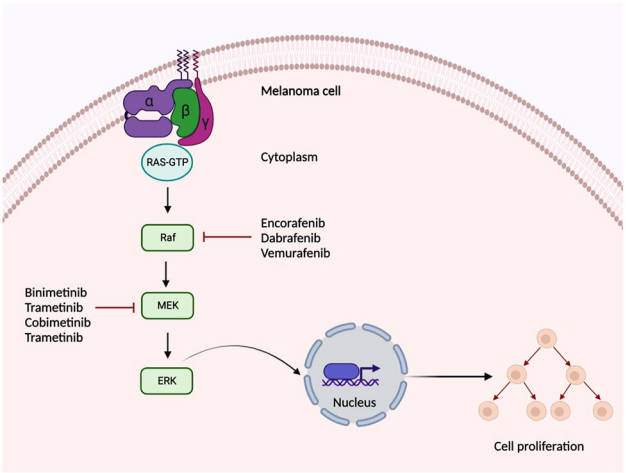

Fig. 1 The RAS/RAF/MEK/ERK pathway is activated when a ligand binds to a growth factor or cytokine receptor, inducing the binding of the protein Grb2 with SOS, a guanine nucleotide exchange factor (not shown). SOS exchanges GDP for GTP on RAS (HRAS, NRAS, and KRAS), a GTPase on the inner plasma membrane. This conformation induces RAS activation, leading to the recruitment and subsequent activation of the protein kinase RAF (ARAF, BRAF, and CRAF), initiating a phosphorylation signaling cascade with sequential phosphorylation of MEK (MEK1 and MEK2), MAPK, and MYC. The latter translocates into the nucleus and upregulates genes involved in cell growth and division. Mutations anywhere along this pathway, especially in BRAF and MEK genes, can result in uncontrolled cell growth and division, leading to tumorigenesis

2.1 BRAFi (Vemurafenib, Dabrafenib, Encorafenib)

dAEs impact up to 95% of patients on BRAFi monotherapy [10]. Other important adverse effects include fever, headache, arthralgia, and fatigue [11]. Here, we focus on the most common dAEs, though awareness of other toxicities can help identify the culprit drug in patients on combination therapy.

2.1.1 Inflammatory Reactions

2.1.1.1 Maculopapular/Morbilliform Eruptions Transient morbilliform eruptions are the earliest eruptions that arise and are common dAE form BRAF inhibition [10]. The eruption is pruritic and includes both macules and papules, expanding centripetally from the trunk [12]. Patients with morbilliform eruptions should undergo laboratory evaluation to assess for evidence of systemic hypersensitivity, including complete blood count with differential, transaminases, and urinalysis to look for eosinophilia, hepatic involvement, and nephritis, respectively. If symptomatic, topical steroids, oral antihistamines, and emollients may be considered as first-line treatment [10, 12]. For higher-grade reactions, those not responsive to topical steroids and antihistamines, or in cases associated with systemic hypersensitivity, oral steroids may be considered, with dose reduction and treatment discontinuation reserved as last-line intervention [10, 12].

2.1.1.2 Severe Cutaneous Adverse Reactions While most morbilliform exanthems are overall benign behaving, evaluation for severe cutaneous adverse reactions (SCAR), such as drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens–Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), is warranted [13–15]. If an eruption is accompanied by edema or lymphadenopathy and DRESS is suspected, the following labs can be obtained to aid in the diagnosis: a complete blood count (CBC) with dif-

Table 1 Summary of management strategies for common adverse effects of BRAF inhibitors and MEK inhibitors

Side effect	Pharmacological interventions	Nonpharmacological interventions
BRAF inhibitors		
Maculopapular/morbilliform eruptions [10, 12]	Low-grade reactions: topical steroids and oral antihistamines High-grade reactions: consider oral steroids	Bland emollients
Acneiform/papulopustular eruptions [12, 18-22]	Topical steroids (triamcinolone 0.1% for the body, hydrocortisone 2.5% for the face), topical clindamycin lotion, tetracyclines for more severe cases Refractory cases: low-dose oral isotretinoin (10–20 mg every other day), or consider oral steroids	Sun protection: Wide brimmed hat Long sleeved shirts Broad spectrum, SPF 30+ sunscreen Avoid sunlight exposure from 11:00AM-3:00PM
	Non-steroidal anti-inflammatory drugs, topical and intralesional corticosteroids More severe cases: consider oral steroids (low doses often effective)	Not applicable
Sweet's-like dermatosis [30]	Dapsone, colchicine, or consider oral steroids	
Photosensitivity	Not applicable	Sun protection
Secondary squamous neoplasms [33, 44-46]	Topical and intralesional 5-fluorouracil, systemic retinoids, intralesional methotrexate, photodynamic therapy (if multiple)	Surgical removal Wide-local excision Mohs micrographic surgery Curettage and electrodesiccation Total body skin exam every six months for the first two years and then annually
Melanocytic nevi	Not applicable	Sun protection Skin exam every 4–6 weeks → every month for first six months of therapy → every eight weeks Surgical excision for melanomas
Hand-foot skin reaction [10, 22, 34, 48, 49]	Grade 1: 20-40% urea cream, 6% salicylic acid Grade 2: topical class I and II steroids (ointment based) Grade 3: dose reduction Symptom control: COX-2 inhibitors (celecoxib 200mg BID)	Grade 0: prevention includes wearing well-fitting shoes, urea-based creams, and using emollients prior to strenuous or repetitive activity Grade 1 and 2: bland emollients Grade 3: antimicrobial soaks, liquid bandages, temporary discontinuation of treatment
MEK inhibitors		
Acneiform eruptions [12, 18-22]	As above	Sun protection
Morbilliform eruptions [60-61]	Low-grade reactions: topical steroids and oral antihistamines High-grade reactions: consider oral steroids	Bland emollients
Xerosis with pruritus [19, 22]	Keratolytics (salicylic acid, lactic acid, zinc oxide) Medium to high potency topical steroids Skin glues for fissures	Emollients (Eucerin and Cetaphil) Behavioral modifications Short showers with tepid water Avoid soap in shower except in axilla and groin Avoidance of harsh soap
Alopecia [63, 64]	Scalp: topical minoxidil 2-5% Eyelashes: bimatoprost 0.03% ophthalmic solution	Not applicable

Table 1 (continued)

Side effect	Pharmacological interventions	Nonpharmacological interventions
Paronychia [11, 19, 53, 65, 66]	High potency topical steroids Antimicrobial soaks and topicals Topical silver nitrate Culture guided antibiotics (tetracyclines can be used empirically) Timolol	Trim nails, wear gloves, and well-fitting shoes Nail lacquers may be used Partial nail avulsion for significant granulation tissue
MEK inhibitor-induced dusky erythema [67]	Suspend MEK inhibitor therapy Topical steroids Consider oral steroids	Not applicable

ferential to evaluate for atypical lymphocytes, eosinophilia, thrombocytopenia, and other hematological disorders; a complete metabolic panel to evaluate liver and kidney involvement; and viral serologies, including human herpesvirus 6 (HHV-6), Epstein–Barr virus (EBV), and cytomegalovirus (CMV) [16]. When SJS/TEN is on the differential, physical examinations should evaluate for skin tenderness, erosions, bullae, and mucosal involvement; importantly, these reactions are exceedingly rare. We also recommend early skin biopsy, such as fresh frozen or STAT formalin-fixed to rapidly assess for full thickness epidermal necrosis when SJS/TEN is suspected. Grade 4 cutaneous side effects, including DRESS requiring hospitalization and SJS/TEN require collaborative management between dermatology, oncology, and additional consultants as needed. Cancer treatment interruption or discontinuation is almost always required.

2.1.1.3 Acneiform/Papulopustular Eruptions Papulopustular eruptions also present early during therapy and are less common than morbilliform drug eruptions when combination therapy is used [17]. The eruptions are similar to those seen with epidermal growth factor inhibitors (EGFRi), consisting of inflammatory pustules and open and closed comedones, but can present more diffusely, most commonly on the face and trunk (Fig. 2) [17]. Management of acneiform eruptions includes topical steroids (triamcinolone 0.1% for the body, hydrocortisone 2.5% for the face), topical clindamycin lotion, and may include metronidazole cream, mupirocin, and/or tretinoin 0.05% cream in certain circumstances, depending on the pattern of involvement and degree of dryness [18, 19]. Doxycycline or minocycline can be added for more severe cases. If the eruption is refractory to these measures, low-dose oral acitretin (10 mg every other day to daily), isotretinoin (10–20 mg daily), or oral steroids can be considered [12, 20, 21]. For more severe eruptions (grade 3 and above), therapy interruption can be considered while toxicities are addressed [18, 22].

2.1.1.4 Panniculitis The development of neutrophilic panniculitis, which presents as tender, subcutaneous nodules most commonly on the lower legs (Fig. 3), is a rare side effect of BRAFi that can occur as early as 1 week after treatment initiation and clinically resembles erythema nodosum (EN) [23–26]. Evaluation of patients with EN-like lesions should include an inquiry of symptoms including concomitant arthralgias, fever, and myalgias; and laboratory workup consisting of CBC, C-reactive protein, creatine kinase, and a complete metabolic panel [23]. A skin biopsy is warranted and should be considered to ensure no subcutaneous metastases of melanoma, or other etiologies such as vasculitis [23]. Conservative management is generally sufficient for first-line management of panniculitis. Nonsteroidal antiin-

flammatory drugs should be initiated early to decrease the risk of anticancer therapy interruption [26]. Topical and intralesional corticosteroids can also be employed as a treatment strategy [23]. If treatment escalation is needed, oral corticosteroids, such as prednisone (as low as 5 mg daily is often sufficient) until nodule resolution, can be considered [27]. Interruption in therapy or dose reduction in BRAFi may also be needed, with re-escalation once symptoms have sufficiently improved [23].

2.1.1.5 Sweet's-Like Dermatosis Sweet's syndrome is a neutrophilic disorder and rare side effect of BRAFi [28, 29]. Patients present with abrupt-onset, asymmetric, tender erythematous juicy plaques and nodules most commonly on the upper extremities [30]. Extracutaneous manifestations include pyrexia, arthralgias, headache, fatigue, and conjunctivitis [30]. This condition can be drug induced, as with BRAFi, malignancy associated, especially with hematological cancers, and autoimmune associated. Biopsy is diagnostic and is characterized by papillary dermal edema with neutrophils in the reticular dermis without vasculitis [31]. Systemic corticosteroids are considered first-line treatment, and antineutrophilic agents, such as dapsone or colchicine, can be considered as steroid-sparing agents [30].

2.1.2 Photosensitivity

Of the BRAFi, vemurafenib is associated with the highest incidence of photosensitivity, specifically to ultraviolet A (UVA) light (315–400 nm), with 23–67% of melanoma patients experiencing symptomatic photosensitivity (Fig. 4) [7, 10, 32–34]. Photosensitivity reactions include

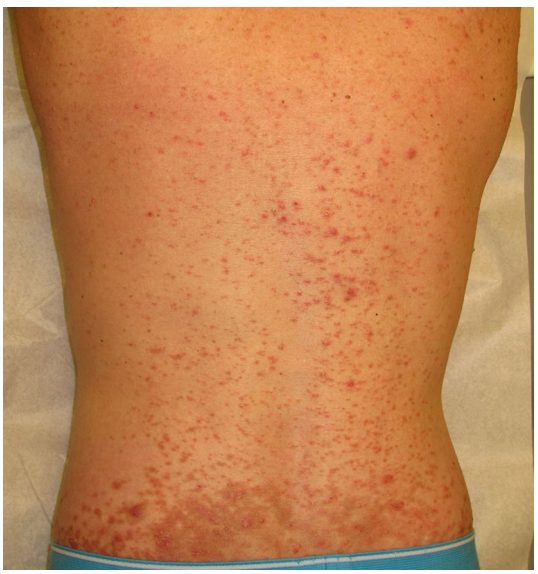

Fig. 2 BRAF inhibitor acneiform eruption (Photo courtesy of Nicole LeBoeuf, MD, MPH)

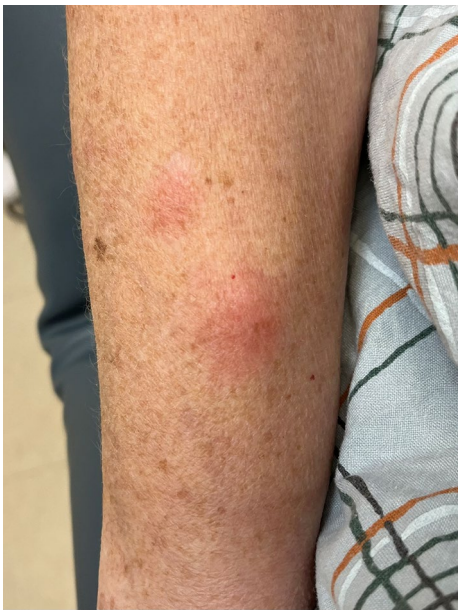

Fig. 3 BRAF inhibitor panniculitis (Photo courtesy of Nicole LeBoeuf, MD, MPH)

both immediate and delayed reactions, with a median time to onset of 1.7 weeks after starting BRAF therapy [10]. In an extended follow-up of a phase III randomized clinical trial comparing vemurafenib with dacarbazine in patients with previously untreated, metastatic melanoma harboring a BRAF V600E mutation (BRIM-3 trial), 37% and 4% of melanoma patients taking vemurafenib had a grade 1/2 and grade 3 photosensitivity skin reaction, respectively, compared with 5% of patients with a grade 1/2 reaction in the dacarbazine group [7, 35]. Immediate reactions to UV light include erythema, edema, burning, and blistering. Delayed reactions include cheilitis and facial erythematous eruptions. The metric used to determine photosensitivity is the minimal erythema dose (MED), which is the UV threshold dose needed for a person to get a sunburn (perceptible erythema). In patients taking BRAFi, the MED for UVA light remains depressed until approximately 2 weeks after discontinuation [32, 36]. Reactions due to increased photosensitivity include blistering sunburns and solar urticaria [36]. However, not all BRAFi cause the same degree of photosensitivity as vemurafenib. Patients on dabrafenib, for example, have a higher MED than patients on vemurafenib (20 J/cm^2 and 12 J/cm^2, respectively) [6, 37, 38]. In a multicenter, open-label, phase 3 randomized control trial comparing dabrafenib with dacarbazine, only 3 out of 187 patients (3%) receiving dabrafenib experienced what the authors described as phototoxic reactions [6]. Management of photosensitivity relies primarily on patient education on sun protection and avoidance. Patients should avoid peak sun exposure, wear sun-protective clothing and broad-brimmed hats, and should liberally apply a

broad-spectrum sunscreen (preferably a physical blocker) with a sun protection factor (SPF) of 30 or above every 2 h. Importantly, UVA can penetrate through most window glass and thus, daily application is warranted.

2.1.3 Keratinocyte and Melanocytic Neoplasms

BRAFi can paradoxically induce keratinocyte proliferation, leading to disordered keratinization and secondary skin neoplasia. Hand–foot skin reaction (HFSR), though inflammatory, is at least in part a disorder of keratinocyte proliferation. Neoplasia, such as verrucous lesions, cutaneous squamous cell carcinoma (SCC), keratoacanthoma (KA), and melanocytic lesions, are induced by BRAFi [10]. Secondary skin neoplasms can arise within 2 months of initiation of therapy [10]. The mechanism through which BRAFi promote secondary skin tumors is paradoxical activation of the MAPK pathway in cells with a preexisting rat sarcoma (*RAS*) mutation and wild-type *BRAF* [39–43].

Other BRAFi-induced dAEs of epidermal proliferation to be aware of are cystic and milia-like lesions, seborrheic keratoses, actinic keratoses, benign verrucous neoplasms and keratosis pilaris [40].

2.1.3.1 Squamous Cell Carcinoma and Keratoacanthomas In the phase III trial comparing dabrafenib with dacarbazine in patients with previously untreated stage IV or unresectable stage III BRAFV600E mutation-positive melanoma, 6% of patients receiving dabrafenib developed SCCs or KAs (Fig. 5), compared with 0% for the control group [6]. Vemurafenib is associated with an even higher incidence of SCC: in the BRIM-3 trial, 12% of patients on vemurafenib developed cutaneous SCC, compared with < 1% of the dacarbazine group [5]. Additionally, 8% of patients in the treatment group developed KA compared with 0% in the control [5]. In an extended follow-up analysis, the percentages of patients receiving vemurafenib who developed SCC and KA were 19% and 10%, respectively, compared with < 1% for each dAE in the control [7]. Oral retinoids (acitretin dosed 10 mg every other day up to 25 mg daily) may be used to treat and prevent these squamous neoplasms. In most cases, reactive squamous atypia should be treated nonsurgically. Actinic keratoses and benign squamous neoplasms can be treated with cryotherapy or standard topicals, such as 5-fluorouracil (5-FU), imiquimod, or combination 5-FU with calcipotriene [33]. For squamous atypia and well-differentiated lesions, topical and intralesional steroids, intralesional 5-fluorouracil, photodynamic therapy, and electrodesiccation and curettage can be considered [44–46]. For refractory, quickly growing, or invasive neoplasms in anatomically important areas, surgery can be considered, employing excision or Mohs based on standard criteria. Dose reduction or discontinuation is rarely required.

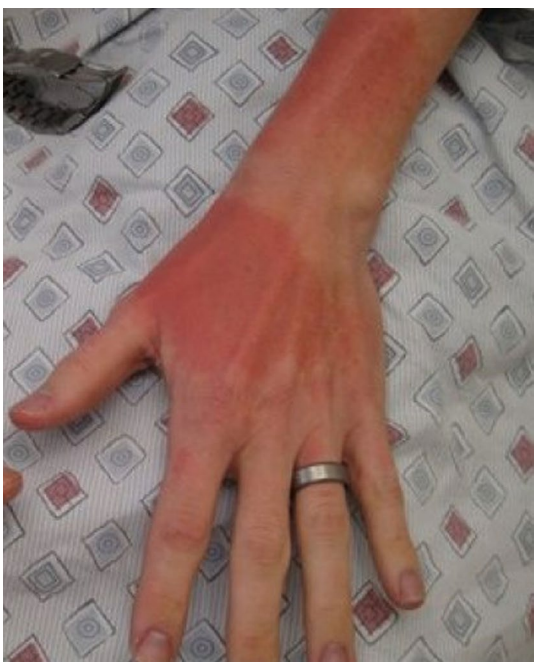

Fig. 4 BRAF inhibitor photosensitivity, with watch removed for photograph (Photo courtesy of Nicole LeBoeuf, MD, MPH)

2.1.3.2 Melanocytic Nevi BRAFi have been associated with the development of melanocytic nevi (termed eruptive nevi) and the growth and pigmentation of existing nevi within a year of starting treatment [8, 33, 42]. For patients on vemurafenib, eruptive nevi occur in 10% of patients [34]. There is also an increased incidence of second primary cutaneous melanomas due to BRAFi [34]. It is important to closely monitor new and changing nevi and maintain a low threshold to biopsy suspicious lesions.

2.1.3.3 Hand–Foot Skin Reaction Hand–foot skin reaction (HFSR) is a condition characterized by painful, white–yellow hyperkeratotic plaques at pressure points with surrounding and underlying erythema on the palms and soles (Fig. 6) [47]. It is seen in patients receiving all three approved BRAFi therapies, but is most common in patients treated with vemurafenib, with an incidence of up to 60% [34]. To prevent HFSR, patients should be advised to avoid heat and friction, wear well-fitting shoes or orthopedic shoe inserts designed to avoid pressure and friction, and moisturize their hands and feet with urea-based creams; thick ointment-based emollients should be liberally applied prior to strenuous or repetitive activity [10, 22, 34, 48]. Urea-based creams and high-potency topical steroids can be used to prevent and treat HFSR, with BRAFi dose reduction or treatment postponement in severe cases [10, 34, 49].

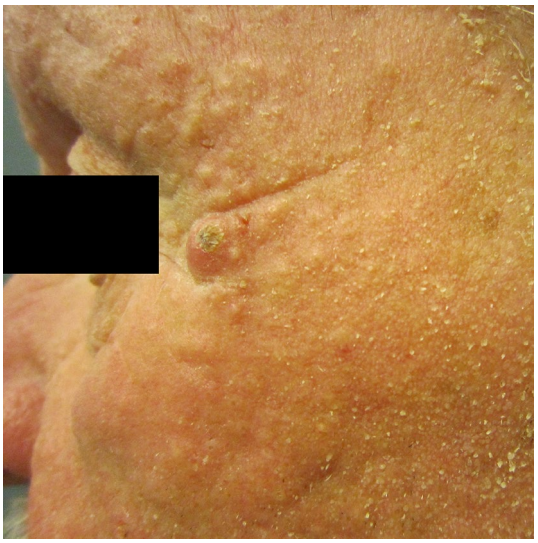

Fig. 5 BRAF inhibitor keratoacanthoma (Photo courtesy of Nicole LeBoeuf, MD, MPH)

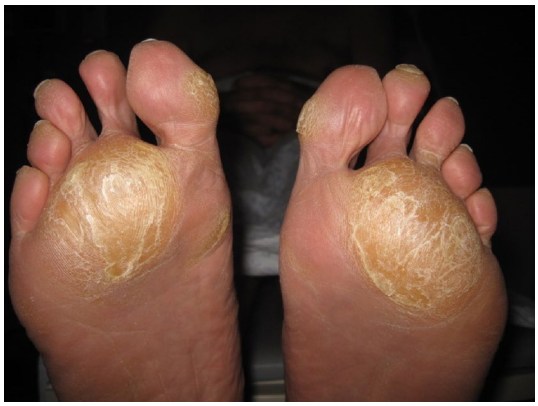

Fig. 6 BRAF inhibitor hand–foot skin reaction (Photo courtesy of Nicole LeBoeuf, MD, MPH)

2.1.4 Hair Changes

BRAFi can induce alopecia and hair texture changes (Fig. 7). In a prospective study ($n = 11$), nonscarring, diffuse alopecia was observed in 100% of patients on vemurafenib [5, 50]. The actual incidence of clinically relevant thinning may be closer to 25% as described in cohort studies and meta-analyses [51, 52]. Furthermore, patients on BRAFi can develop changes in hair thickness, texture, and color [53]. Patients with traditionally straight hair may notice that they develop gray hair and curls after starting BRAFi therapy [8, 53]. Textural abnormalities can also be observed, with a transition to coarser and more brittle hair [8]. Scalp seborrheic dermatitis and pityriasis amiantacea, characterized by thick adherent scale on the scalp, have also been reported in patients receiving BRAFi [53].

2.2 MEKi (Selumetinib, Trametinib, Binimetinib, and Cobimetinib)

The first MEKi, trametinib, was approved for the treatment of metastatic melanoma in 2013 [54]. The side effect profile of MEKi is generally similar to that of EGFRi, with some nuances [19]. As with BRAFi, MEKi are rarely used as monotherapy in the treatment of melanoma, since combination therapy with BRAFi has shown increased efficacy and decreased dAEs. They are used as monotherapy for some histiocytic disorders, are under investigation in combination with checkpoint blockade in some solid tumors, and are used in a subset of patients with metastatic mucosal and uveal melanoma, although results are mixed [55–58]. The most common adverse events from MEKi therapy include fever and edema, which can complicate the cutaneous examination when considering the most common dAEs. dAEs include exanthematous morbilliform eruptions, acneiform eruptions, photosensitivity, xerosis with pruritus, hair and nail disorders, and panniculitis, as well as the uncommon dAE of MEKi-induced dusky erythema. Unlike BRAFi, MEKi are not associated with secondary skin malignancies.

2.2.1 Papulopustular/Acneiform Eruptions

The most common dAEs of MEKi are papulopustular acneiform eruptions on the chest, upper back, and in a seborrheic dermatitis-like distribution on the central face and scalp [11, 20]. Unlike acne, these drug-induced eruptions lack comedones. These affect 40–93% of patients taking MEKi and are similar to the acneiform rashes induced by EGFRi [11, 59].

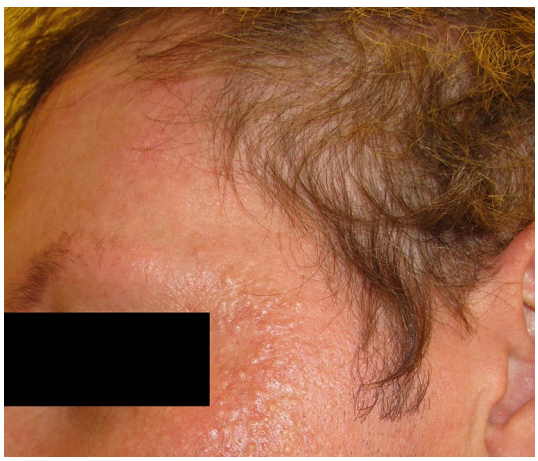

Fig. 7 BRAF inhibitor alopecia and hair texture changes (Photo courtesy of Nicole LeBoeuf, MD, MPH)

Like EGFRi-induced acneiform eruptions, these rashes may result in part from drug-induced production of chemokines by epidermal keratinocytes; this results in inflammation and local immunosuppression [11]. Patients may experience pruritus and burning, and develop colonization or secondary infections from bacteria such as *Staphylococcus aureus* [11]. For acneiform eruptions with secondary infection not responsive to initial treatment approaches, culture should be obtained and antibiotics added based on susceptibilities. As with BRAFi, photosensitivity may occur with MEKi therapy, and can cause flares of the acneiform inflammatory process. Management is similar to the aforementioned treatment for BRAFi-induced acneiform eruptions.

2.2.2 Morbilliform Eruptions

As with BRAFi, MEKi can also cause morbilliform exanthems (Fig. 8). This is dose dependent, occurs early in treatment, and is generally mild and transient [60, 61]. Management involves topical steroids, emollients, antihistamines, and, if refractory, oral steroids [60, 61]. As with all morbilliform eruptions, when extensive, laboratory evaluation and full skin and mucosal examination should be performed to evaluate for a SCAR.

2.2.3 Xerosis with Pruritus

Xerosis is a common side effect for patients on MEKi and can lead to pruritus or eczematous dermatitis. In patients receiving trametinib, for example, 22% experience xerosis [62]. First-line treatments include bland emollients, with ointments and creams preferred over lotions [19]. For patients with skin fissures, medium- to high-potency topical steroids and skin glues can be used [22]. Patients should also be counseled to take short showers (less than 15 minutes) with tepid water, avoiding the use of harsh soaps and using soap only in the axilla and groin.

2.2.4 Hair Disorders

In addition to cutaneous adverse effects, hair disorders can also be precipitated by MEKi in up to 17% of patients. Eyelash trichomegaly, grade 1 alopecia, and hair depigmentation have been observed [63]. Topical minoxidil 2–5% for scalp alopecia and bimatoprost 0.03% ophthalmic solution for the eyelashes may be used to help with hair regrowth [63, 64].

2.2.4.1 Nail Disorders Paronychia is an often painful inflammation of the nail folds that can impact the quality of life of patients on MEKi (Fig. 9). Avoidance of trauma and pressure on the nails is key for minimizing the impact of these symptoms [11]. Patients can be advised to wear gloves and well-fitting shoes for water work and significant activity [11]. Nails should be trimmed. While patients may use nail lacquers, polish hardeners should be avoided [11]. Patients presenting with paronychia can be treated with high-potency topical steroids, antimicrobial soaks and topicals, culture-guided oral antibiotics (tetracycline antibiotics can be considered empirically given antiinflammatory properties), partial nail avulsion and, when granulation tissue is present, topical silver nitrate, cautery, and/or timolol can be helpful [19, 53, 65, 66].

2.2.5 MEKi-Induced Dusky Erythema

A rare dAE associated with MEKi treatment was first described in 2012 by Patel et al. MEKi-induced dusky erythema presents with red to violaceous urticarial or targetoid-like plaques, papules, and macules on the extremities and trunk, with central duskiness and erythematous halos, resembling erythema multiforme (Fig. 10) [59, 67, 68]. This eruption can occur anywhere from a few weeks to a few months after starting a MEKi and is most commonly seen in patients receiving combination therapy with BRAFi [67]. For patients with MEKi-induced dusky erythema, MEKi therapy should be temporarily suspended. First-line treatment is topical or oral steroids [67]. Once improved, MEKi rechallenge is possible with close monitoring of skin and mucosa, given the resemblance of this eruption to erythema multiforme [67].

2.3 BRAFi/MEKi Combination Therapy

Resistance to BRAFi monotherapy by activating mutations in *MEK* prompted combination therapy of BRAFi with

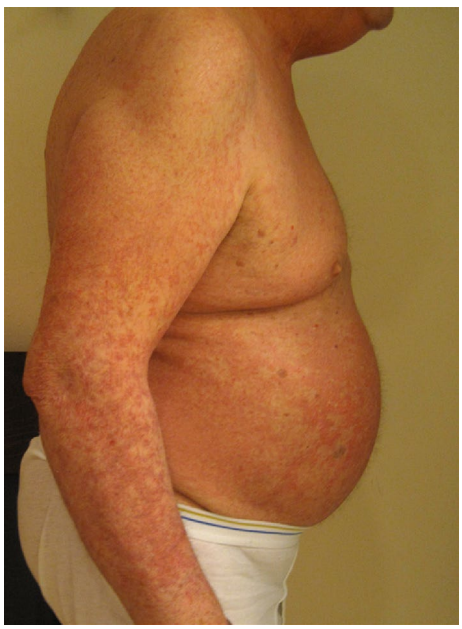

Fig. 8 MEK inhibitor morbilliform eruption (Photo courtesy of Nicole LeBoeuf, MD, MPH)

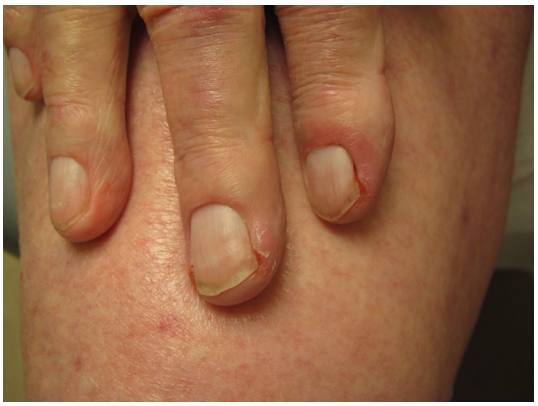

Fig. 9 MEK inhibitor paronychia (Photo courtesy of Nicole LeBoeuf, MD, MPH)

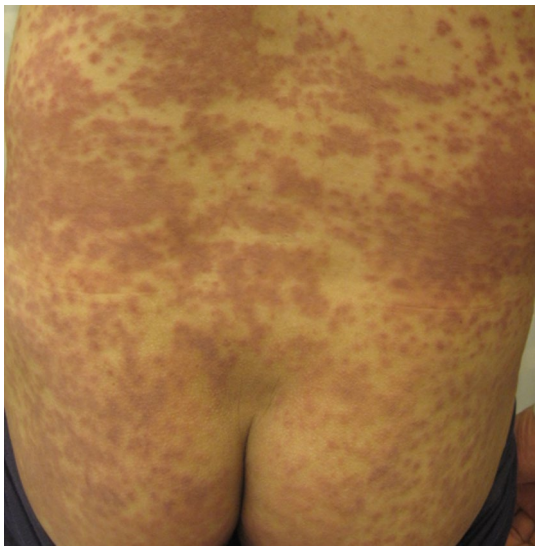

Fig. 10 MEK inhibitor-induced dusky erythema (Photo courtesy of Nicole LeBoeuf, MD, MPH)

MEKi. Combination therapy (dabrafenib plus trametinib, vemurafenib plus cobimetinib, encorafenib plus binimetinib) has improved overall survival (OS) and progression-free survival (PFS) when compared with either therapy alone [69–71]. When BRAFi and MEKi are used together, patients experience fewer grade 3 or grade 4 toxicities and require fewer dose interruptions or changes [70, 72]. dAEs—such as rash, acneiform dermatitis, hyperkeratosis, primary melanomas, alopecia, hand–foot syndrome, and toxicities of epidermal proliferation—are decreased with combination therapy when compared with BRAFi or MEKi alone.[8, 69, 70, 72–74] Combination therapy does not appear to reduce the risk of BRAFi-induced panniculitis or keratosis pilaris [26].

The impact of combination therapy on photosensitivity varies by trial. In the COLUMBUS trial, photosensitivity was seen in 24% of patients on vemurafenib, 4% on encorafenib, and 5% on combination therapy [70]. In the coBRIM trial, however, photosensitivity was more common in patients receiving combination therapy (34% in the cobimetinib and vemurafenib versus 20% in the vemurafenib and placebo groups) [35]. Therefore, it is crucial to counsel patients taking combination therapy on the importance of sun protection and avoidance.

Rates of dAEs in BRAFi and MEKi combination therapy and monotherapy are summarized in Table 2. Lastly, extracutaneous side effects to be mindful of in these patients include cardiovascular (hypertension, decreased ejection fraction), ocular (retinopathy), and gastrointestinal toxicities (diarrhea, nausea, vomiting), as they tend to be higher in patients on combination therapy compared with those on vemurafenib monotherapy [70]. Patients on combination therapy also more commonly experience pyrexia, and it is usually more severe [69].

2.4 ERKi

Resistance to BRAFi and MEKi has prompted research into downstream targets of the RAS/RAF/MAPK pathway [75]. While there are currently no US Food and Drug Administration (FDA)-approved therapies to target and inhibit ERK for the treatment of melanoma, preclinical and phase I trials are underway [75]. Since these drugs are not used in clinical practice, their dermatologic toxicities are only briefly reviewed. As an example, in a phase I trial of a novel ERKi, ulixertinib, dAEs were common with a median onset of 3 weeks, and they were similar to the dAEs of BRAFi and MEKi. These included acneiform rash (33%), maculopapular exanthem (27%), pruritus (25%), unspecified rash (23%), xerosis (11%), alopecia (10%), photosensitivity (3%), and erythema multiforme (0.7%) [76]. Nineteen percent of all patients had grade 3 dAEs, 29% had grade 2 dAEs, and 32% had grade 1 dAEs [76]. No patient experienced grade 4 or 5 dAEs [76]. Treatment options for these toxicities should reflect the management of similar morphologies as outlined above for BRAFi and MEKi [76].

3 Intralesional Therapy

In 2015, the FDA approved T-VEC for injectable but unresectable cutaneous, subcutaneous, and nodal lesions for patients with melanoma recurrence after an initial surgery [77, 78]. To date, it remains the only approved oncolytic virus for any purpose in the USA, although there are three

Table 2 Rates of cutaneous adverse effects in BRAF inhibitor and MEK inhibitor combination therapy and monotherapy

	coBRIM study [35]						COMBI-d study [69, 71]						COLUMBUS study [70]						COMBI-V study (72)					
	Cobimetinib plus vemurafenib ($n = 247$)			Vemurafenib plus placebo ($n = 246$)			Dabrafenib plus trametinib[a] ($n = 209$)			Dabrafenib plus placebo ($n = 211$)			Encorafenib plus binimetinib ($n = 192$)		Encorafenib ($n = 192$)		Vemurafenib ($n = 186$)		Dabrafenib plus trametinib ($n = 350$)			Vemurafenib ($n = 349$)		
Cutaneous adverse effect (%)																								
Grade	Any	2	3 +	Any	2	3+	Any	2	3+	Any	2	3 +	1–2	3+	1–2	3+	1–2	3 +	Any	2	3+	Any	2	3 +
Rash	73%[b]	–	17%[b]	68%[b]	–	16%[b]	24%	3%	0%	20%	2%	< 1%	13%	2%	19%	2%	26%	3%	22%	–	1%	43%	–	9%
Acneiform eruption	–	–	–	–	–	–	8%	2%	0%	3%	1%	0%	–	–	–	–	–	–	6%	–	–	6%	–	1%
Cutaneous squamous cell carcinoma	4%	–	4%	13%	–	13%	3%	0%	3%	9%	0%	9%	–	3%	–	8%	–	17%	1%[c]	–	1%[c]	18%[c]	–	17%[c]
Keratoacanthoma	2%	–	1%	9%	–	9%	–	1	–	–	–	–	2%	–	6%		8%	3%						
New primary melanoma	–	–	–	–	–	–	< 1%	0%	< 1%	2%	1%	< 1%	0%	0%	5%	2%	1%	4%	1%	–	–	2%	–	–
Xerosis	–	–	–	–	–	–	9%	0%	0%	14%	1%	0%	14%	–	30%	–	23%	–	–	–	–	–	–	–
Photosensitivity	34%	–	3%	20%	–	0%	–	–	–	–	–	–	4%	1%	4%	0%	23%	1%	4%	–	0%	22%	–	< 1%
Skin papilloma	–	–	–	–	–	–	1%	0%	0%	18%	3%	0%	6%	0%	9%	0%	17%	0%	2%	–	0%	23%	–	1%
Hyperkeratosis	10%	–	< 1%	27%	–	3%	6%	0%	0%	33%	6%	< 1%	14%	1%	34%	4%	29%	–	4%	–	0%	25%	–	1%
Alopecia	17%	–	< 1%	31%	–	< 1%	5%	0%	0%	26%	2%	0%	14%	0%	56%	0%	37%	0%	6%	–	0%	39%	–	< 1%
Hand–foot skin reaction	–	–	–	–	–	–	6%	1%	< 1%	27%	8%	< 1%	7%	0%	38%	14%	13%	1%	4%	–	0%	25%	–	< 1%
Pruritus	–	–	–	–	–	–	7%	1%	0%	11%	1%	0%	10%	1%	21%	1%	11%	0%	–	–	–	–	–	–

Key: –, not reported or combined with another line item

[a]Data from the updated progression-free survival analysis of the double-blind phase 3 COMBI-d study

[b]Per the authors of coBRIM, the term "rash" includes maculopapular rash and morbilliform rash, among other terms

[c]Cutaneous squamous cell carcinoma and keratoacanthoma combined

other oncolytic viruses approved in other countries [79]. T-VEC is a live, replicating herpes simplex virus (HSV)-1 genetically modified for increased safety, preferential replication in tumor cells, induction of host immunity with expression of granulocyte–macrophage colony stimulating factor (GM-CSF) and deletion of multiple viral genes [80]. There have been no known reports of household contact transmissions [77], although rarely both patients receiving or hospital staff preparing the injection have reported herpetic lesions [81–83]. T-VEC patients or providers with concern of possible herpetic lesions should contact Amgen at 1-855-IMLYGIC (1-855-465-9442) for additional testing, as they are currently recruiting for an ongoing, post-marketing study to better characterize the risk of herpetic infection (NCT02910557). The T-VEC mechanism of action is summarized in Fig. 11.

The use of T-VEC has been somewhat limited due to logistical concerns surrounding injection therapy and concerns of those who do not yet have experience with the oncolytic virus, as it has a favorable toxicity profile with a low rate of grade 3 or 4 adverse events [77, 84]. Fatigue, chills, pyrexia, nausea, and influenza-like illness are the most common adverse events [77]. The following dAEs are well established: injection-site reactions, vitiligo-like depigmentation, and "cellulitis."

3.1 Injection-Site Reaction

Nearly one-third (28.4%) of patients receiving T-VEC experience injection-site pain [85]. Acetaminophen or indomethacin can be utilized for either prevention or treatment of the pain (in addition to treating fever or chills) [77, 86]. Prophylactic use of acetaminophen the evening of the injection may prevent constitutional side effects and injection-site symptoms that tend to occur 24–48 h after injection. Patient education and counseling should occur before the intralesional injection, so patients can be prepared for possible injection-site pain.

3.2 Vitiligo-Like Depigmentation

Vitiligo-like depigmentation (VLD) is the most frequent dAE secondary to T-VEC, with a rate of 6.2% in the Oncovex GM-CSF Pivotal Trial in Melanoma (OPTiM), a randomized, open-label phase III trial in patients with unresectable stage IIIB–IVM1c melanoma comparing T-VEC and subcutaneous GM-CSF as a control [84]. The depigmentation onset occurred after a median time of 22 weeks (interquartile range, 9–36 weeks). VLD is known to present in melanoma patients, even before the introduction of T-VEC, due to immunity against shared antigens of melanoma and melanocytes [87]. Autoimmunity against shared antigens is likely augmented secondary to T-VEC-induced release of tumor-derived antigens as well as the accumulation of tumor antigen-presenting dendritic cells promoted by GM-CSF. In two case reports of T-VEC-induced VLD, the patients were in complete remission at the time of publication (16 and 20 months) [88]. The two patients had VLD at both the injection site and more distant locations, which suggested a systemic effect. Similar to ICI induced VLD [89], T-VEC induced VLD may be an indication of response to therapy and associated with positive long-term results [88]. All patients with VLD should be counseled on sun protective practices including the use of broad-spectrum sunscreen and protective clothing to prevent burns of depigmented skin [90]. Currently, the only FDA-approved treatment for vitiligo is the Janus kinase inhibitor cream ruxolitinib, approved in 2022 [91]. Patients with grade 1 VLD may start topical corticosteroids twice daily [92]. Following general guidelines for vitiligo, ultrapotent and potent corticosteroids may be used on the body, but the face, neck, and intertriginous areas should be treated with mid-potency topical corticosteroids [93]. For grade 2 VLD, both topical corticosteroids twice daily and phototherapy in a controlled setting may be recommended [92]. Collaborative management between dermatology and oncology is warranted, and continuation of T-VEC treatment encouraged [92].

3.3 Cellulitis

The only grade 3 or 4 adverse event occurring in ≥ 2% patients receiving T-VEC in OPTiM was "cellulitis," which affected 2.1% of patients [84]. Cellulitis of any grade affected 5.8% of patients. Cellulitis is a clinical diagnosis characterized by erythema and pain, and in the setting of T-VEC, is regarded as an inflammatory response to the injected organism. Herpes cellulitis from T-VEC clears within 24–48 h and is self-limiting [86]. This is in contrast to bacterial cellulitis, which may complicate the injection site, is persistent, and may be associated with persistent fever and leukocytosis. If bacterial cellulitis is suspected, cultures should be performed, and antibiotic therapy initiated. Patients who are immunosuppressed or those experiencing symptomatic or progressive erythema should be started on empiric treatment with antibiotics [94].

Real-world data suggest dAEs may be more diverse than was seen in trials. Granulomatous dermatitis at the injection site, panniculitis, and Sweet's-like neutrophilic dermatosis have been reported [95–97].

Although T-VEC and ICI combination therapy is still undergoing investigation, adverse events appear to be similar to their known safety profiles without new toxicities [85]. In practice, T-VEC is often added in close proximity to other ICIs (when the effect of the ICI is likely still present) or in combination with ICIs in patients who have developed

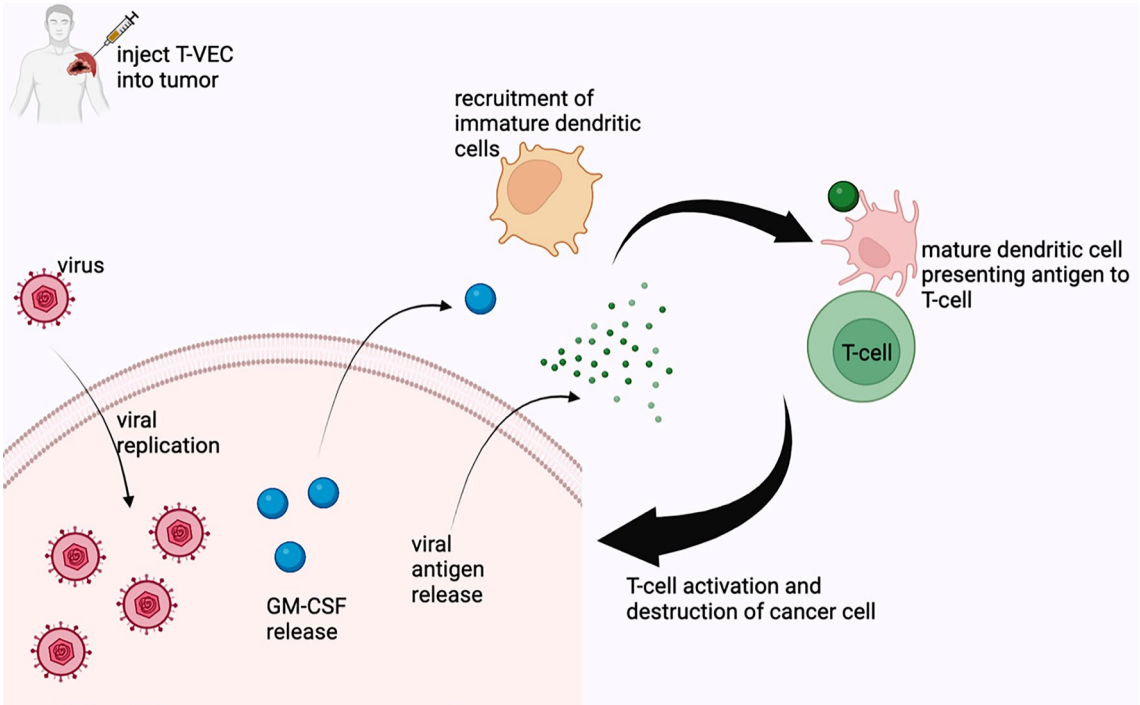

Fig. 11 Lysis of the cancer cells allows new viral particles to be released for continued infection of other tumor cells. Additionally, T-VEC promotes release of tumor-derived antigens in an immunogenic fashion that is strengthened by expression of GM-CSF. There is accumulation and maturation of dendritic cells, and it is thought that through both the tumor antigen release and viral progeny producing GM-CSF there is improved cross-priming of CD8+ T cell response by the dendritic cells

resistant cutaneous, subcutaneous or nodal metastases. The rate of dAEs is 33.2% and 38.7% for ICI therapy alone and combination T-VEC and ICI therapy, respectively [98]. When controlling for sex, race/ethnicity, age at ICI initiation, ICI type, Charlson Comorbidity Index, and cancer type, however, there is a two-fold (hazard ratio, 1.96; $p = 0.009$) increase in the risk of dAEs in the patients receiving the combination therapy.[98]

4 Systemically Administered Immunotherapy

The immune system is tasked with differentiating self and non-self and harnessing this system has led to profound success in advancing the treatment of melanoma. Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1) immune checkpoint pathways negatively regulate T cell activity and are frequently exploited by tumor cells [99]. Inhibiting PD-1 and CTLA-4, the two most clinically important checkpoints, increases activation of the immune system. A recent population-level analysis found the overall incidence of ICI-induced clinically relevant dAEs to be 25.1%, and the median time to onset was 113 days [100]. Female sex has been associated with higher rates of dAEs [101]. Immune-related side effects are associated with ICI therapy response and patient survival [102, 103]. As checkpoint-induced toxicities and their management have been extensively reviewed [11, 104–106], here we discuss novel agents minimally discussed in the literature.

A new, first-in-class, fixed-dose combination of nivolumab and relatlimab (Opdualag™) for unresectable or metastatic melanoma was approved by the FDA in March 2022 [107]. Relatlimab is a monoclonal antibody targeting lymphocyte activation gene-3 (LAG-3), which is an activation-induced, CD4-related cell surface molecule [108]. Activated CD4+ T helper cells, cytotoxic CD8+ T cells, and a subset of other immune cells express LAG-3 [109], and IL-2, IL-7, and IL-12 all promote upregulation of LAG-3 expression [110]. LAG-3 mediates T cell homeostasis and negatively regulates T cell expansion and pool size [109, 111]. Melanoma cells exploit this pathway, with MHC II on melanoma cells engaging with LAG-3 on tumor-infiltrating leukocytes to protect against Fas-mediated apoptosis [112]. The survival benefit of dual checkpoint inhibition of LAG-3 and PD-1 was recently shown in a randomized, double-blinded, phase II/III trial in patients with metastatic or unresectable melanoma comparing fixed dose combination therapy with relatlimab–nivolumab to nivolumab alone [113].

In patients receiving relatlimab–nivolumab, the median PFS was 10.1 months (95% CI, 6.4 to 15.7 months), which was more than double the median PFS of 4.6 months (95% CI, 3.4 to 5.6 months) in nivolumab alone. Notably the relatlimab–nivolumab group had a longer PFS than nivolumab alone regardless of BRAF mutation status, American Joint Committee on Cancer metastasis stage of the tumor, lactate dehydrogenase level, or tumor burden.

In terms of safety, 18.9% of patients receiving relatlimab–nivolumab experienced grade 3 or 4 treatment-related adverse events, compared with 9.7% of the patients receiving nivolumab alone [113]. Increased lipase, alanine aminotransferase, aspartate aminotransferase, and fatigue were the most frequent grade 3 or 4 treatment-related adverse events in the relatlimab–nivolumab group. Of note, 14.6% of patients in the relatlimab–nivolumab group had treatment-related adverse events (any grade) that led to discontinuation, in comparison with 6.7% of the nivolumab only group. However, quality-of-life assessments were high and comparable between both groups in the study. Overall, no new safety signals emerged with the relatlimab–nivolumab combination, and the adverse events were favorable in comparison with nivolumab plus ipilimumab combination therapy [114].

The most observed dAEs of combination relatlimab-nivolumab therapy were "rash" and vitiligo-like depigmentation. Importantly, the use of clinical trial data remains limited in understanding specific toxicities from ICIs, as eruptions are often bluntly described as "rash" with little additional diagnostic specificity.

4.1 Rash

Of patients receiving relatlimab-nivolumab, 9% developed an immune-mediated rash of any grade, with 3.4% experiencing grade 2 and 0.6% experiencing grade 3 adverse reactions [113, 115]. Immune-mediated rash resulted in 1.4% of patients having treatment interruptions, although there were no patients who had to permanently discontinue the treatment [115]. Systemic corticosteroids were used in 88% of the patients with immune-mediated rash, which effectively resolved the rash in 70% of these patients. One-quarter of patients who required treatment interruption with relatlimab–nivolumab experienced a recurrence of the rash after reinitiating therapy. As use of relatlimab–nivolumab combination therapy expands, providers should anticipate a diversity of specific dAEs, such as those seen with other ICIs: lichenoid reactions, psoriasis, Grover's disease, bullous pemphigoid, dermatomyositis, vasculitis, Sjogren's syndrome, sarcoidosis, and Sweet's syndrome, among others [104, 116]. Ideally, these toxicities should be described and reported as specifically as possible.

4.2 Vitiligo-Like Depigmentation

VLD occurred in 10.4% of patients receiving relatlimab–nivolumab (Fig. 12) [113]. While studies on LAG-3 inhibition monotherapy are limited, this rate is lower than the 16.5% seen with nivolumab monotherapy in the 3 year follow-up of the phase III trial of patients with advanced melanoma [117]. Interestingly, in one study investigating VLD in patients on ICIs, responders to the therapy were found to have downregulation of LAG-3 [118]. Some authors have argued that VLD in anti-PD-1 therapies is clinically and biologically distinct from vitiligo: anti-PD-1 induced VLD has been described as flecked depigmented macules that coalesce into patches that do not exhibit Koebnerization and occur on skin commonly exposed to the sun [106, 119]. More recently, other authors have concluded that this may represent active vitiligo with similar disease mechanisms [120]. As mentioned above, all patients with VLD should be counseled on sun protective practices including broad-spectrum sunscreen and sun protective clothing [90]. There is no definitive treatment for VLD, and it does not require treatment unless it begins to negatively impact quality of life. Other treatment is similar to T-VEC-induced vitiligo (above).

Fig. 12 Immunotherapy-induced vitiligo-like depigmentation on Wood's lamp examination (Photo courtesy of Nicole LeBoeuf, MD, MPH)

5 Therapies Used in the Refractory Setting

5.1 Topical Imiquimod

Though not a systemic therapy, topical imiquimod can induce systemic and cutaneous adverse events and has been used off-label for various stages of melanoma. In practice, imiquimod may be used across the melanoma spectrum, from in situ to metastatic disease. It is used as an adjunct in patients who decline surgery, for those whom resection is not practical or when previous resections have not been successful, for cutaneous metastasis not otherwise responsive to systemic or intralesional therapy, and in patients who are not candidates for these or other surgical approaches [121]. Imiquimod is an immunomodulatory agent with antiviral and antitumor properties that is FDA approved for the treatment of genital and perianal warts, superficial truncal and extremity basal cell carcinoma, and actinic keratoses [122, 123]. Its mechanism of action is via toll-like receptor-7 mediated release of inflammatory cytokines, such as interferon-α, IL-6 ,and TNF-α [122, 124]. For in situ lesions, imiquimod has shown clearance rates up to 100% when used both as first-line treatment and after incomplete excision, though recurrence rates remain an area of investigation [125–129]. Topical imiquimod is used in the treatment of advanced melanoma with in-transit or distant metastatic cutaneous lesions, with most evidence derived from case reports [130, 131]. dAEs of topical imiquimod include pruritus, burning, erythema, and scaling in addition to crusting, vesicles, erosions, and weeping. These dAEs resolve with cessation of the drug. For open, weeping erosions, topical antimicrobials may be used [132, 133]. Additionally, imiquimod-induced localized vitiligo-like depigmentation confirmed with histopathology has been reported in patients being treated for genital warts, basal cell carcinoma, and extramammary Paget disease [134–137]. Though not fully understood, the pathogenesis may be due in part to the stimulation of toll-like receptors on melanocytes and the subsequent inhibition of melanogenesis with increased apoptosis of melanocytes [138, 139]. When imiquimod is applied to cosmetically sensitive areas and on patients with darker skin phototypes, the potential consequences of depigmentation and hypopigmentation can be significant. Though there has been no data on the use of ruxolitinib in imiquimod-induced vitiligo, this, along with cessation of imiquimod, may be considered. Lastly, imiquimod has been reported to induce and exacerbate psoriasis at both local and distant sites from application [140, 141]. The mechanism is thought to be due in part to imiquimod's involvement in the IL-17 and IL-23 axis [142]. Treatment follows standard psoriasis guidelines, which include myriad options such as topical corticosteroids, topical vitamin D analogs, topical calcineurin inhibitors, and phototherapy for mild psoriasis; in the setting of active malignancy, the general approach to systemic agents includes apremilast and IL17/12/23 inhibitors considering comorbidities and malignancy status [143]. TNF inhibitors are generally avoided, though research on their impact on malignancy response is ongoing.

5.2 Imatinib Mesylate

The protooncogene KIT may be mutated in melanoma. It is a receptor tyrosine kinase that is involved in cell growth, division, and survival, especially in melanocytes. Mutations in KIT are most commonly seen in mucosal and acral melanoma [144, 145]. Imatinib is a receptor kinase inhibitor of Abl, KIT, and platelet-derived growth factor receptor. It is most commonly used in the treatment of chronic myelogenous leukemia and gastrointestinal stromal tumor, and has been used as a second-line treatment for metastatic or unresectable melanomas with *KIT* mutations, although durable responses and best overall response rates are low with limited clinical efficacy in metastatic melanoma [121, 146–149]. Imatinib is generally well tolerated, but dAEs are common [150]. These include morbilliform exanthems, psoriasiform eruptions, periorbital edema, hyperpigmentation, and hypopigmentation [150, 151]. Less common conditions reported with imatinib treatment include SJS and neutrophilic dermatoses, and diverse dAEs reported as individual cases [151]. Treatments for these conditions are as previously discussed.

5.3 Larotrectinib and Entrectinib

Neurotrophic tyrosine receptor kinase (*NTRK*) gene fusions are found in approximately 28% of spitzoid melanomas, 2.5% of acral melanomas, and less than 1% of cutaneous or mucosal melanomas [152]. For melanoma patients with *NTRK* gene fusions who have progression of their metastatic or unresectable disease despite immunotherapy and/or BRAF therapy, the National Comprehensive Cancer Network (NCCN) guidelines recommend the use of tropomyosin kinase (Trk) inhibitors larotrectinib and entrectinib as second-line therapy [121, 153, 154]. dAEs appear to be rare and are not well documented; only toxicities with incidences of 15% were reported in the pivotal trial [153, 155]. dAEs with entrectinib are better reported; in an integrated analysis of three phase I/II trials of 54 adults with metastatic or locally advanced solid tumors positive for NTRK fusions who received entrectinib, dAEs included rash (6%), skin pain (4%), hyperesthesia (3%), and pruritus (2%) [155, 156]. Notably, no melanoma patients were included in this study.

Table 3. Current Phase III Trials with Novel Mechanisms in Melanoma Therapy

Drug	Route	Mechanism of action	Population	NCT	Status
IO102-IO103 plus pembrolizumab	Injection; intravenous	IDO and PD-L1 inhibitor; anti-PD-1	Unresectable or Metastatic Melanoma	NCT05155254	Recruiting
DCaT-RNA	Vaccination	Targeted antigen-presenting cells	Uveal melanoma typed positive for monosomy 3 and without evidence for metastases	NCT01983748	Recruiting
Bempegaldesleukin combined with nivolumab	Intravenous	CD122-preferential IL-2 pathway agonist; anti-PD-1	Unresectable or metastatic melanoma	NCT03635983	Active, not recruiting
Bempegaldesleukin combined with nivolumab	Intravenous	CD122-preferential IL-2 pathway agonist; anti-PD-1	Stage III or IV melanoma that has been surgically resected	NCT04410445	Active, not recruiting
Pembrolizumab combined with lenvatinib	Intravenous; oral	Anti-PD-1; inhibition of multiple receptors of tyrosine kinases	Unresectable or metastatic melanoma	NCT04889118 NCT03820986	Active, not recruiting
Cyclophosphamide, fludarabine, TIL, IL-2	Intravenous	Alkylating agent; purine analog; targeted lymphocytes; keeps TIL active	Unresectable or metastatic melanoma	NCT02278887	Active, not recruiting
Natural dendritic cells	Vaccination	Antigen-presenting cells	Stage IIIB and IIIC melanoma patients after complete radical lymph node dissection or sentinel node procedure	NCT02993315	Active, not recruiting
Melphalan	Percutaneous hepatic perfusion	Alkylating agent	Hepatic dominant metastatic ocular melanoma	NCT02678572	Active, not recruiting
Vitamin D	Oral	Numerous effects	Stage IB to III melanoma with only surgical treatment	NCT01748448	Active, not recruiting
Daromun	Intralesional	Immunocytokine preferentially targeting tumor cells	Surgically resectable stage IIIB or IIIC metastatic melanoma	NCT03567889	Recruiting
Melatonin	Oral	Tryptophan derivative with various physiological effects	Uveal melanoma with tumor size T3d or higher	NCT05502900	Recruiting
HBI-8000 combined with nivolumab	Oral; intravenous	Inhibitor of class I HDAC; anti-PD-1	Unresectable or metastatic melanoma	NCT04674683	Recruiting
L19IL2/L19TNF	Intralesional	IL-2 and TNF fused to L19 antibody	Stage IIB/C melanoma	NCT02938299	Recruiting

IDO indoleamine-pyrrole 2,3-dioxygenase, *PD-L1* programmed death ligand 1, *PD-1* programmed cell death protein 1, *DCaT-RNA* dendritic cell loaded with autologous tumor RNA, *IL* interleukin, *TIL* tumor-infiltrating lymphocytes, *HDAC* histone deacetylases, *TNF* tumor necrosis factor, *BCG* bacilli Calmette-Guerin, *TLR* toll-like receptor

6 Additional Ongoing Clinical Trials

Striving toward better patient outcomes and improved quality of life while undergoing anticancer therapy relies on novel research. There are currently over 1000 clinical trials investigating melanoma therapies that are either soon to be recruiting, recruiting, enrolling by invitation, or active [157]. Of note, therapies under investigation include those classically used to treat hematologic malignancy, such as navitoclax (ClinicalTrials.gov Identifier: NCT01989585) or histone deacetylase inhibitors (ClinicalTrials.gov Identifier: NCT04674683). Importantly, these therapies are not associated with significant rates of specific skin toxicities. For the purpose of this review article, we have summarized the current phase III clinical trials of melanoma therapies (systemic and not systemic) with novel mechanisms that may introduce new dAEs in Table 3.

7 Conclusions

There has been remarkable progress in therapeutic strategies for patients with advanced melanoma over the recent decades. As we utilize new additions in our therapeutic armamentarium, we also see a diversity of drug-related toxicities. In this review, we focus on diagnosis and management of dAEs of targeted therapies as well as less commonly used melanoma treatments. Specific recognition of the presentations and knowledge of mitigation strategies for dAEs is critical for decreasing patient morbidity and mortality. Dermatologists and oncologists must be prepared to diagnose and manage these adverse events promptly, while minimizing disruptions to the anticancer therapy regimen. Ultimately, the ability to diagnose a specific toxicity and attribute it to the correct drug allows patients to maximize cancer treatment, only removing an agent or therapeutic class when absolutely necessary.

As novel therapies and combinations are trialed, there will undoubtedly be an increase in the number of patients suffering from dAEs. We hope that dermatologists and oncologists will persistently continue to educate themselves on emerging specific toxicities to maximize patient quality of life as well as cancer outcomes.

Declarations

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Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication The patients whose medical photographs are included in this article have provided written consent for having their photographs taken and published.

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Author contributions First draft: SJ and CF; critical review, writing, and revisions: SJ, CF, BM, BSA, CL, NL.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin. 2019;69(1):7–34.
2. Surveillance E, and End Results Program. Cancer stat facts: melanoma of the skin. National Cancer Institute; 2022. https://seer.cancer.gov/statfacts/html/melan.html. Accessed 8 Aug 2022.
3. Patel H, Yacoub N, Mishra R, White A, Long Y, Alanazi S, et al. Current advances in the treatment of BRAF-mutant melanoma. Cancers. 2020;12(2):482.
4. Dhillon AS, Hagan S, Rath O, Kolch W. MAP kinase signalling pathways in cancer. Oncogene. 2007;26(22):3279–90.
5. Chapman PB, Hauschild A, Robert C, Haanen JB, Ascierto P, Larkin J, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med. 2011;364(26):2507–16.
6. Hauschild A, Grob JJ, Demidov LV, Jouary T, Gutzmer R, Millward M, et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. Lancet. 2012;380(9839):358–65.
7. McArthur GA, Chapman PB, Robert C, Larkin J, Haanen JB, Dummer R, et al. Safety and efficacy of vemurafenib in BRAF(V600E) and BRAF(V600K) mutation-positive melanoma (BRIM-3): extended follow-up of a phase 3, randomised, open-label study. Lancet Oncol. 2014;15(3):323–32.
8. Heinzerling L, Eigentler TK, Fluck M, Hassel JC, Heller-Schenck D, Leipe J, et al. Tolerability of BRAF/MEK inhibitor combinations: adverse event evaluation and management. ESMO Open. 2019;4(3): e000491.
9. Macdonald JBMD, Macdonald BBA, Golitz LEMD, LoRusso PDO, Sekulic AMDP. Cutaneous adverse effects of targeted therapies. J Am Acad Dermatol. 2014;72(2):203–18.
10. Lacouture ME, Duvic M, Hauschild A, Prieto VG, Robert C, Schadendorf D, et al. Analysis of dermatologic events in vemurafenib-treated patients with melanoma. Oncologist. 2013;18(3):314–22.
11. Lacouture M, Sibaud V. Toxic side effects of targeted therapies and immunotherapies affecting the skin, oral mucosa, hair, and nails. Am J Clin Dermatol. 2018;19(Suppl 1):31–9.
12. Russo I, Zorzetto L, Chiarion Sileni V, Alaibac M. Cutaneous side effects of targeted therapy and immunotherapy for advanced melanoma. Scientifica. 2018;2018:5036213.

13. Ros J, Munoz-Couselo E. DRESS syndrome due to vemurafenib treatment: switching BRAF inhibitor to solve a big problem. BMJ Case Rep. 2018.
14. Torres-Navarro I, de Unamuno-Bustos B, Botella-Estrada R. Systematic review of BRAF/MEK inhibitors-induced severe cutaneous adverse reactions (SCARs). J Eur Acad Dermatol Venereol. 2021;35(3):607–14.
15. Lytvyn Y, Mufti A, Sachdeva M, Maliyar K, Yeung J. Stevens–Johnson syndrome and toxic epidermal necrolysis reactions to BRAF and MEK inhibitors in patients with melanoma: a systematic review. J Am Acad Dermatol. 2021;85(4):981–3.
16. Kardaun SH, Sidoroff A, Valeyrie-Allanore L, Halevy S, Davidovici BB, Mockenhaupt M, et al. Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: does a DRESS syndrome really exist? Br J Dermatol. 2007;156(3):609–11.
17. Petukhova TA, Novoa RA, Honda K, Koon HB, Gerstenblith MR. Acneiform eruptions associated with vemurafenib. J Am Acad Dermatol. 2013;68(3):e97–9.
18. Heinzerling L, Eigentler TK, Fluck M, Hassel JC, Heller-Schenck D, Leipe J, et al. Tolerability of BRAF/MEK inhibitor combinations: adverse event evaluation and management. ESMO Open. 2019;4(3):e000491.
19. Balagula Y, Barth Huston K, Busam KJ, Lacouture ME, Chapman PB, Myskowski PL. Dermatologic side effects associated with the MEK 1/2 inhibitor selumetinib (AZD6244, ARRY-142886). Investig New Drugs. 2011;29(5):1114–21.
20. Caruana M, Hatami A, Marcoux D, Perreault S, McCuaig CC. Isotretinoin for the treatment of severe acneiform eruptions associated with the MEK inhibitor trametinib. JAAD Case Rep. 2020;6(10):1056–8.
21. Bierbrier R, Lam M, Pehr K. A systematic review of oral retinoids for treatment of acneiform eruptions induced by epidermal growth factor receptor inhibitors. Dermatol Ther. 2022;35(5):e15412.
22. Macdonald JB, Macdonald B, Golitz LE, LoRusso P, Sekulic A. Cutaneous adverse effects of targeted therapies: part I: inhibitors of the cellular membrane. J Am Acad Dermatol. 2015;72(2):203–18 (**quiz 19–20**).
23. Mossner R, Zimmer L, Berking C, Hoeller C, Loquai C, Richtig E, et al. Erythema nodosum-like lesions during BRAF inhibitor therapy: report on 16 new cases and review of the literature. J Eur Acad Dermatol Venereol. 2015;29(9):1797–806.
24. Choy B, Chou S, Anforth R, Fernandez-Penas P. Panniculitis in patients treated with BRAF inhibitors: a case series. Am J Dermatopathol. 2014;36(6):493–7.
25. Monfort JB, Pages C, Schneider P, Neyns B, Comte C, Bagot M, et al. Vemurafenib-induced neutrophilic panniculitis. Melanoma Res. 2012;22(5):399–401.
26. Zimmer L, Livingstone E, Hillen U, Domkes S, Becker A, Schadendorf D. Panniculitis with arthralgia in patients with melanoma treated with selective BRAF inhibitors and its management. Arch Dermatol. 2012;148(3):357–61.
27. Ferreira J, Toda-Brito H, Moura MC, Sachse MF, Costa-Rosa J. BRAFi-associated panniculitis - an emerging side effect with a variable histological picture: report of two cases and review of the literature. J Cutan Pathol. 2017;44(3):307–9.
28. Pattanaprichakul P, Tetzlaff MT, Lapolla WJ, Torres-Cabala CA, Duvic M, Prieto VG, et al. Sweet syndrome following vemurafenib therapy for recurrent cholangiocarcinoma. J Cutan Pathol. 2014;41(3):326–8.
29. Yorio JT, Mays SR, Ciurea AM, Cohen PR, Wang WL, Hwu WJ, et al. Case of vemurafenib-induced Sweet's syndrome. J Dermatol. 2014;41(9):817–20.
30. Vashisht P, Goyal A, Hearth Holmes MP. Sweet syndrome. Treasure Island: StatPearls; 2022.
31. Cohen PR. Sweet's syndrome—a comprehensive review of an acute febrile neutrophilic dermatosis. Orphanet J Rare Dis. 2007;2:34.
32. Brugiere C, Stefan A, Morice C, Cornet E, Moreau A, Allouche S, et al. Vemurafenib skin phototoxicity is indirectly linked to ultraviolet A minimal erythema dose decrease. Br J Dermatol. 2014;171(6):1529–32.
33. Mattei PL, Alora-Palli MB, Kraft S, Lawrence DP, Flaherty KT, Kimball AB. Cutaneous effects of BRAF inhibitor therapy: a case series. Ann Oncol. 2013;24(2):530–7.
34. Boussemart L, Routier E, Mateus C, Opletalova K, Sebille G, Kamsu-Kom N, et al. Prospective study of cutaneous side-effects associated with the BRAF inhibitor vemurafenib: a study of 42 patients. Ann Oncol. 2013;24(6):1691–7.
35. Ascierto PA, McArthur GA, Dreno B, Atkinson V, Liszkay G, Di Giacomo AM, et al. Cobimetinib combined with vemurafenib in advanced BRAF(V600)-mutant melanoma (coBRIM): updated efficacy results from a randomised, double-blind, phase 3 trial. Lancet Oncol. 2016;17(9):1248–60.
36. Eberlein B, Biedermann T, Hein R, Posch C. Vemurafenib-related photosensitivity. J Dtsch Dermatol Ges. 2020;18(10):1079–83.
37. Gabeff R, Dutartre H, Khammari A, Boisrobert A, Nguyen JM, Quereux G, et al. Phototoxicity of B-RAF inhibitors: exclusively due to UVA radiation and rapidly regressive. Eur J Dermatol. 2015;25(5):452–6.
38. Trojaniello C, Festino L, Vanella V, Ascierto PA. Encorafenib in combination with binimetinib for unresectable or metastatic melanoma with BRAF mutations. Expert Rev Clin Pharmacol. 2019;12(3):259–66.
39. Huang V, Hepper D, Anadkat M, Cornelius L. Cutaneous toxic effects associated with vemurafenib and inhibition of the BRAF pathway. Arch Dermatol. 2012;148(5):628–33.
40. Heidorn SJ, Milagre C, Whittaker S, Nourry A, Niculescu-Duvas I, Dhomen N, et al. Kinase-dead BRAF and oncogenic RAS cooperate to drive tumor progression through CRAF. Cell. 2010;140(2):209–21.
41. Poulikakos PI, Zhang C, Bollag G, Shokat KM, Rosen N. RAF inhibitors transactivate RAF dimers and ERK signalling in cells with wild-type BRAF. Nature. 2010;464(7287):427–30.
42. Chen FW, Tseng D, Reddy S, Daud AI, Swetter SM. Involution of eruptive melanocytic nevi on combination BRAF and MEK inhibitor therapy. JAMA Dermatol. 2014;150(11):1209–12.
43. Su F, Viros A, Milagre C, Trunzer K, Bollag G, Spleiss O, et al. RAS mutations in cutaneous squamous-cell carcinomas in patients treated with BRAF inhibitors. N Engl J Med. 2012;366(3):207–15.
44. Alloo A, Garibyan L, LeBoeuf N, Lin G, Werchniak A, Hodi FS Jr, et al. Photodynamic therapy for multiple eruptive keratoacanthomas associated with vemurafenib treatment for metastatic melanoma. Arch Dermatol. 2012;148(3):363–6.
45. Que SKT, Compton LA, Schmults CD. Eruptive squamous atypia (also known as eruptive keratoacanthoma): definition of the disease entity and successful management via intralesional 5-fluorouracil. J Am Acad Dermatol. 2019;81(1):111–22.
46. Shimizu I, Cruz A, Chang KH, Dufresne RG. Treatment of squamous cell carcinoma in situ: a review. Dermatol Surg. 2011;37(10):1394–411.
47. Lilly E, Burke M, Kluger H, Choi J. Pregabalin for the treatment of painful hand-foot skin reaction associated with dabrafenib. JAMA Dermatol. 2015;151(1):102–3.
48. Anderson R, Jatoi A, Robert C, Wood LS, Keating KN, Lacouture ME. Search for evidence-based approaches for the prevention and palliation of hand-foot skin reaction (HFSR) caused by the multikinase inhibitors (MKIs). Oncologist. 2009;14(3):291–302.

49. Peuvrel L, Quereux G, Saint-Jean M, Brocard A, Nguyen JM, Khammari A, et al. Profile of vemurafenib-induced severe skin toxicities. J Eur Acad Dermatol Venereol. 2016;30(2):250–7.
50. Cebollero A, Puertolas T, Pajares I, Calera L, Anton A. Comparative safety of BRAF and MEK inhibitors (vemurafenib, dabrafenib and trametinib) in first-line therapy for BRAF-mutated metastatic melanoma. Mol Clin Oncol. 2016;5(4):458–62.
51. Blank CU, Larkin J, Arance AM, Hauschild A, Queirolo P, Del Vecchio M, et al. Open-label, multicentre safety study of vemurafenib in 3219 patients with BRAF(V600) mutation-positive metastatic melanoma: 2-year follow-up data and long-term responders' analysis. Eur J Cancer. 2017;79:176–84.
52. Belum VR, Marulanda K, Ensslin C, Gorcey L, Parikh T, Wu S, et al. Alopecia in patients treated with molecularly targeted anticancer therapies. Ann Oncol. 2015;26(12):2496–502.
53. Mir-Bonafe JF, Saceda-Corralo D, Vano-Galvan S. Adverse hair reactions to new targeted therapies for cancer. Actas Dermosifiliogr (Engl Ed). 2019;110(3):182–92.
54. Hoffner B, Benchich K. Trametinib: a targeted therapy in metastatic melanoma. J Adv Pract Oncol. 2018;9(7):741–5.
55. Steeb T, Wessely A, Ruzicka T, Heppt MV, Berking C. How to MEK the best of uveal melanoma: a systematic review on the efficacy and safety of MEK inhibitors in metastatic or unresectable uveal melanoma. Eur J Cancer. 2018;103:41–51.
56. Falchook GS, Lewis KD, Infante JR, Gordon MS, Vogelzang NJ, DeMarini DJ, et al. Activity of the oral MEK inhibitor trametinib in patients with advanced melanoma: a phase 1 dose-escalation trial. Lancet Oncol. 2012;13(8):782–9.
57. Tacastacas JD, Bray J, Cohen YK, Arbesman J, Kim J, Koon HB, et al. Update on primary mucosal melanoma. J Am Acad Dermatol. 2014;71(2):366–75.
58. Diamond EL, Durham BH, Ulaner GA, Drill E, Buthorn J, Ki M, et al. Efficacy of MEK inhibition in patients with histiocytic neoplasms. Nature. 2019;567(7749):521–4.
59. Janne PA, Shaw AT, Pereira JR, Jeannin G, Vansteenkiste J, Barrios C, et al. Selumetinib plus docetaxel for KRAS-mutant advanced non-small-cell lung cancer: a randomised, multicentre, placebo-controlled, phase 2 study. Lancet Oncol. 2013;14(1):38–47.
60. de Golian E, Kwong BY, Swetter SM, Pugliese SB. Cutaneous complications of targeted melanoma therapy. Curr Treat Options Oncol. 2016;17(11):57.
61. Macdonald JB, Macdonald B, Golitz LE, LoRusso P, Sekulic A. Cutaneous adverse effects of targeted therapies: part II: inhibitors of intracellular molecular signaling pathways. J Am Acad Dermatol. 2015;72(2):221–36 (**quiz 37–8**).
62. Kim KB, Kefford R, Pavlick AC, Infante JR, Ribas A, Sosman JA, et al. Phase II study of the MEK1/MEK2 inhibitor Trametinib in patients with metastatic BRAF-mutant cutaneous melanoma previously treated with or without a BRAF inhibitor. J Clin Oncol. 2013;31(4):482–9.
63. Rubio-Gonzalez B, Juhasz M, Fortman J, Mesinkovska NA. Pathogenesis and treatment options for chemotherapy-induced alopecia: a systematic review. Int J Dermatol. 2018;57(12):1417–24.
64. Glaser DA, Hossain P, Perkins W, Griffiths T, Ahluwalia G, Weng E, et al. Long-term safety and efficacy of bimatoprost solution 0.03% application to the eyelid margin for the treatment of idiopathic and chemotherapy-induced eyelash hypotrichosis: a randomized controlled trial. Br J Dermatol. 2015;172(5):1384–94.
65. Sun Q, Antaya RJ. Treatment of MEK inhibitor-induced paronychia with doxycycline. Pediatr Dermatol. 2020;37(5):970–1.
66. Martinez-de-Espronceda I, Bernabeu-Wittel J, Azcona M, Monserrat MT. Recalcitrant trametinib-induced paronychia treated successfully with topical timolol in a pediatric patient. Dermatol Ther. 2020;33(1): e13164.
67. Patel U, Cornelius L, Anadkat MJ. MEK inhibitor-induced dusky erythema: characteristic drug hypersensitivity manifestation in 3 patients. JAMA Dermatol. 2015;151(1):78–81.
68. Bancalari B, Algarra MA, Llombart B, Nagore E, Soriano V, Sanmartin O, et al. Dusky erythema secondary to anti-MEK therapy. Melanoma Res. 2019;29(4):449–51.
69. Long GV, Stroyakovskiy D, Gogas H, Levchenko E, de Braud F, Larkin J, et al. Dabrafenib and trametinib versus dabrafenib and placebo for Val600 BRAF-mutant melanoma: a multicentre, double-blind, phase 3 randomised controlled trial. Lancet. 2015;386(9992):444–51.
70. Dummer R, Ascierto PA, Gogas HJ, Arance A, Mandala M, Liszkay G, et al. Encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with BRAF-mutant melanoma (COLUMBUS): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol. 2018;19(5):603–15.
71. Long GV, Stroyakovskiy D, Gogas H, Levchenko E, de Braud F, Larkin J, et al. Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. N Engl J Med. 2014;371(20):1877–88.
72. Robert C, Karaszewska B, Schachter J, Rutkowski P, Mackiewicz A, Stroiakovski D, et al. Improved overall survival in melanoma with combined dabrafenib and trametinib. N Engl J Med. 2015;372(1):30–9.
73. Sanlorenzo M, Choudhry A, Vujic I, Posch C, Chong K, Johnston K, et al. Comparative profile of cutaneous adverse events: BRAF/MEK inhibitor combination therapy versus BRAF monotherapy in melanoma. J Am Acad Dermatol. 2014;71(6):1102 e1-1109 e1.
74. Carlos G, Anforth R, Clements A, Menzies AM, Carlino MS, Chou S, et al. Cutaneous toxic effects of BRAF inhibitors alone and in combination with MEK inhibitors for metastatic melanoma. JAMA Dermatol. 2015;151(10):1103–9.
75. Savoia P, Fava P, Casoni F, Cremona O. Targeting the ERK signaling pathway in melanoma. Int J Mol Sci. 2019;20(6):1483.
76. Wu J, Liu D, Offin M, Lezcano C, Torrisi JM, Brownstein S, et al. Characterization and management of ERK inhibitor associated dermatologic adverse events: analysis from a nonrandomized trial of ulixertinib for advanced cancers. Investig New Drugs. 2021;39(3):785–95.
77. Larocca CA, LeBoeuf NR, Silk AW, Kaufman HL. An update on the role of talimogene laherparepvec (T-VEC) in the treatment of melanoma: best practices and future directions. Am J Clin Dermatol. 2020;21(6):821–32.
78. SanFilippo A, Agarwala SS. FDA panels support approval of T-VEC for metastatic melanoma. HEM/ONC Today. 2015;16(10):7.
79. Lauer UM, Beil J. Oncolytic viruses: challenges and considerations in an evolving clinical landscape. Future Oncol. 2022;18(24):2713–32.
80. Kohlhapp FJ, Kaufman HL. Molecular pathways: mechanism of action for talimogene laherparepvec, a new oncolytic virus immunotherapy. Clin Cancer Res. 2016;22(5):1048–54.
81. Soh JM, Galka E, Mercurio MG. Herpetic Whitlow—a case of inadvertent inoculation with melanoma viral therapy. JAMA Dermatol. 2018;154(12):1487–8.
82. Louie RJ, Perez MC, Jajja MR, Sun J, Collichio F, Delman KA, et al. Real-world outcomes of talimogene laherparepvec therapy: a multi-institutional experience. J Am Coll Surg. 2019;228(4):644–9.
83. Kimmis BD, Luu Y, Dai H. Disseminated herpes infection following talimogene laherparepvec administration. JAMA Dermatol. 2022;158(4):456–7.
84. Andtbacka RHI, Collichio F, Harrington KJ, Middleton MR, Downey G, Hrling K, et al. Final analyses of OPTiM: A

randomized phase III trial of talimogene laherparepvec versus granulocyte-macrophage colony-stimulating factor in unresectable stage III–IV melanoma. J Immunother Cancer. 2019;7(1):145.
85. Ribas A, Chesney J, Long GV, Kirkwood JM, Dummer R, Puzanov I, et al. 1037O MASTERKEY-265: a phase III, randomized, placebo (Pbo)-controlled study of talimogene laherparepvec (T) plus pembrolizumab (P) for unresectable stage IIIB–IVM1c melanoma (MEL). Ann Oncol. 2021;32:S868–9.
86. Rehman H, Silk AW, Kane MP, Kaufman HL. Into the clinic: Talimogene laherparepvec (T-VEC), a first-in-class intratumoral oncolytic viral therapy. J Immunother Cancer. 2016;4(1):53.
87. Cui J, Bystryn JC. Melanoma and vitiligo are associated with antibody responses to similar antigens on pigment cells. Arch Dermatol. 1995;131(3):314–8.
88. Iglesias P, Ribero S, Barreiro A, Podlipnik S, Carrera C, Malvehy J, et al. Induced vitiligo due to talimogene laherparepvec injection for metastatic melanoma associated with long-term complete response. Acta Derm Venereol. 2019;99(2):232–3.
89. Quach HT, Dewan AK, Davis EJ, Ancell KK, Fan R, Ye F, et al. Association of anti-programmed cell death 1 cutaneous toxic effects with outcomes in patients with advanced melanoma. JAMA Oncol. 2019;5(6):906–8.
90. Boada A, Carrera C, Segura S, Collgros H, Pasquali P, Bodet D, et al. Cutaneous toxicities of new treatments for melanoma. Clin Transl Oncol. 2018;20(11):1373–84.
91. Rosmarin D, Pandya AG, Lebwohl M, Grimes P, Hamzavi I, Gottlieb AB, et al. Ruxolitinib cream for treatment of vitiligo: a randomised, controlled, phase 2 trial. Lancet. 2020;396(10244):110–20.
92. Belum VR, Benhuri B, Postow MA, Hellmann MD, Lesokhin AM, Segal NH, et al. Characterisation and management of dermatologic adverse events to agents targeting the PD-1 receptor. Eur J Cancer. 2016;60:12–25.
93. Rodrigues M, Ezzedine K, Hamzavi I, Pandya AG, Harris JE, Vitiligo WG. Current and emerging treatments for vitiligo. J Am Acad Dermatol. 2017;77(1):17–29.
94. Stevens DL, Bisno AL, Chambers HF, Dellinger EP, Goldstein EJ, Gorbach SL, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the infectious diseases society of America. Clin Infect Dis. 2014;59(2):147–59.
95. Everett AS, Pavlidakey PG, Contreras CM, De Los Santos JF, Kim JY, McKee SB, et al. Chronic granulomatous dermatitis induced by talimogene laherparepvec therapy of melanoma metastases. J Cutan Pathol. 2018;45(1):48–53.
96. Long TH, Shinohara MM, Argenyi ZB, Thompson JA, Gardner JM. Panniculitis in a patient with pathologic complete response to talimogene laherparepvec treatment for recurrent, in-transit melanoma. J Cutan Pathol. 2018;45(11):864–8.
97. Lee K, Pouldar D, Shiu J, Elsensohn A, de Feraudy S. The histological spectrum of talimogene laherparepvec (TVEC) injections—neutrophilic and chronic granulomatous dermatitis. J Cutan Pathol. 2019;46(2):165–7.
98. Leung B, Wan G, Zhang S, Chen W, Cohen S, Boland G, et al. Increased risk of cutaneous immune-related adverse events in patients treated with talimogene laherparepvec and immune checkpoint inhibitors: a multi-institutional cohort study. J American Acad Dermatol. 2023;88(6):1265–70.
99. Buchbinder EI, Desai A. CTLA-4 and PD-1 pathways: similarities, differences, and implications of their inhibition. Am J Clin Oncol. 2016;39(1):98–106.
100. Wongvibulsin S, Pahalyants V, Kalinich M, Murphy W, Yu KH, Wang F, et al. Epidemiology and risk factors for the development of cutaneous toxicities in patients treated with immune-checkpoint inhibitors: a United States population-level analysis. J Am Acad Dermatol. 2022;86(3):563–72.
101. Bui AN, Bougrine A, Buchbinder EI, Giobbie-Hurder A, LeBoeuf NR. Female sex is associated with higher rates of dermatologic adverse events among patients with melanoma receiving immune checkpoint inhibitor therapy: a retrospective cohort study. J Am Acad Dermatol. 2022;87(2):403–6.
102. Hussaini S, Chehade R, Boldt RG, Raphael J, Blanchette P, Maleki Vareki S, et al. Association between immune-related side effects and efficacy and benefit of immune checkpoint inhibitors—a systematic review and meta-analysis. Cancer Treat Rev. 2021;92: 102134.
103. Tang K, Seo J, Tiu BC, Le TK, Pahalyants V, Raval NS, et al. Association of cutaneous immune-related adverse events with increased survival in patients treated with anti-programmed cell death 1 and anti-programmed cell death ligand 1 therapy. JAMA Dermatol. 2022;158(2):189–93.
104. Sibaud V. Dermatologic reactions to immune checkpoint inhibitors: skin toxicities and immunotherapy. Am J Clin Dermatol. 2018;19(3):345–61.
105. Park BC, Jung S, Chen ST, Dewan AK, Johnson DB. Challenging dermatologic considerations associated with immune checkpoint inhibitors. Am J Clin Dermatol. 2022;23(5):707–17.
106. Quach HT, Johnson DB, LeBoeuf NR, Zwerner JP, Dewan AK. Cutaneous adverse events caused by immune checkpoint inhibitors. J Am Acad Dermatol. 2021;85(4):956–66.
107. Paik J. Nivolumab plus relatlimab: first approval. Drugs. 2022;82(8):925–31.
108. Workman CJ, Rice DS, Dugger KJ, Kurschner C, Vignali DA. Phenotypic analysis of the murine CD4-related glycoprotein, CD223 (LAG-3). Eur J Immunol. 2002;32(8):2255–63.
109. Workman CJ, Cauley LS, Kim IJ, Blackman MA, Woodland DL, Vignali DA. Lymphocyte activation gene-3 (CD223) regulates the size of the expanding T cell population following antigen activation in vivo. J Immunol. 2004;172(9):5450–5.
110. Sun H, Sun C, Xiao W. Expression regulation of co-inhibitory molecules on human natural killer cells in response to cytokine stimulations. Cytokine. 2014;65(1):33–41.
111. Wei SC, Duffy CR, Allison JP. Fundamental mechanisms of immune checkpoint blockade therapy. Cancer Discov. 2018;8(9):1069–86.
112. Hemon P, Jean-Louis F, Ramgolam K, Brignone C, Viguier M, Bachelez H, et al. MHC class II engagement by its ligand LAG-3 (CD223) contributes to melanoma resistance to apoptosis. J Immunol. 2011;186(9):5173–83.
113. Tawbi HA, Schadendorf D, Lipson EJ, Ascierto PA, Matamala L, Castillo Gutierrez E, et al. Relatlimab and nivolumab versus nivolumab in untreated advanced melanoma. N Engl J Med. 2022;386(1):24–34.
114. Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. N Engl J Med. 2015;373(1):23–34.
115. Nivolumab and relatlimab-rmbw. Am J Health Syst Pharm. 2022;79(13):1025–30.
116. Le TK, Kaul S, Cappelli LC, Naidoo J, Semenov YR, Kwatra SG. Cutaneous adverse events of immune checkpoint inhibitor therapy: incidence and types of reactive dermatoses. J Dermatol Treat. 2022;33(3):1691–5.
117. Ascierto PA, Long GV, Robert C, Brady B, Dutriaux C, Di Giacomo AM, et al. Survival outcomes in patients with previously untreated BRAF wild-type advanced melanoma treated with nivolumab therapy: three-year follow-up of a randomized phase 3 trial. JAMA Oncol. 2019;5(2):187–94.
118. Hermann N, Maul LV, Ameri M, Traidl S, Ziadlou R, Papageorgiou K, et al. Clinical presentation and prognostic features in patients with immunotherapy-induced vitiligo-like

depigmentation: a monocentric prospective observational study. Cancers. 2022;14(19):4576.
119. Larsabal M, Marti A, Jacquemin C, Rambert J, Thiolat D, Dousset L, et al. Vitiligo-like lesions occurring in patients receiving anti-programmed cell death-1 therapies are clinically and biologically distinct from vitiligo. J Am Acad Dermatol. 2017;76(5):863–70.
120. Fukuda K, Harris JE. Vitiligo-like depigmentation in patients receiving programmed cell death-1 inhibitor reflects active vitiligo. J Am Acad Dermatol. 2018;78(1):e15–6.
121. National Comprehensive Cancer Network. Melanoma: Cutaneous (Version 3.2022). https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf. Accessed 1 Nov 2022.
122. Hanna E, Abadi R, Abbas O. Imiquimod in dermatology: an overview. Int J Dermatol. 2016;55(8):831–44.
123. Hyde MA, Hadley ML, Tristani-Firouzi P, Goldgar D, Bowen GM. A randomized trial of the off-label use of imiquimod, 5%, cream with vs without tazarotene, 0.1%, gel for the treatment of lentigo maligna, followed by conservative staged excisions. Arch Dermatol. 2012;148(5):592–6.
124. Urosevic M, Maier T, Benninghoff B, Slade H, Burg G, Dummer R. Mechanisms underlying imiquimod-induced regression of basal cell carcinoma in vivo. Arch Dermatol. 2003;139(10):1325–32.
125. Naylor MF, Crowson N, Kuwahara R, Teague K, Garcia C, Mackinnis C, et al. Treatment of lentigo maligna with topical imiquimod. Br J Dermatol. 2003;149(Suppl 66):66–70.
126. Spenny ML, Walford J, Werchniak AE, Beltrani V, Brennick JB, Storm CA, et al. Lentigo maligna (melanoma in situ) treated with imiquimod cream 5%: 12 case reports. Cutis. 2007;79(2):149–52.
127. Buettiker UV, Yawalkar NY, Braathen LR, Hunger RE. Imiquimod treatment of lentigo maligna: an open-label study of 34 primary lesions in 32 patients. Arch Dermatol. 2008;144(7):943–5.
128. Kai AC, Richards T, Coleman A, Mallipeddi R, Barlow R, Craythorne EE. Five-year recurrence rate of lentigo maligna after treatment with imiquimod. Br J Dermatol. 2016;174(1):165–8.
129. Mora AN, Karia PS, Nguyen BM. A quantitative systematic review of the efficacy of imiquimod monotherapy for lentigo maligna and an analysis of factors that affect tumor clearance. J Am Acad Dermatol. 2015;73(2):205–12.
130. Turza K, Dengel LT, Harris RC, Patterson JW, White K, Grosh WW, et al. Effectiveness of imiquimod limited to dermal melanoma metastases, with simultaneous resistance of subcutaneous metastasis. J Cutan Pathol. 2010;37(1):94–8.
131. Heber G, Helbig D, Ponitzsch I, Wetzig T, Harth W, Simon JC. Complete remission of cutaneous and subcutaneous melanoma metastases of the scalp with imiquimod therapy. J Dtsch Dermatol Ges. 2009;7(6):534–6.
132. Alessi SS, Sanches JA, Oliveira WR, Messina MC, Pimentel ER, Festa NC. Treatment of cutaneous tumors with topical 5% imiquimod cream. Clinics. 2009;64(10):961–6.
133. Cantisani C, Lazic T, Richetta AG, Clerico R, Mattozzi C, Calvieri S. Imiquimod 5% cream use in dermatology, side effects and recent patents. Recent Pat Inflamm Allergy Drug Discov. 2012;6(1):65–9.
134. Gowda S, Tillman DK, Fitzpatrick JE, Gaspari AA, Goldenberg G. Imiquimod-induced vitiligo after treatment of nodular basal cell carcinoma. J Cutan Pathol. 2009;36(8):878–81.
135. Brown T, Zirvi M, Cotsarelis G, Gelfand JM. Vitiligo-like hypopigmentation associated with imiquimod treatment of genital warts. J Am Acad Dermatol. 2005;52(4):715–6.
136. Li W, Xin H, Ge L, Song H, Cao W. Induction of vitiligo after imiquimod treatment of condylomata acuminata. BMC Infect Dis. 2014;14:329.
137. Rodrigues M, Ezzedine K, Hamzavi I, Pandya AG, Harris JE, Vitiligo WG. New discoveries in the pathogenesis and classification of vitiligo. J Am Acad Dermatol. 2017;77(1):1–13.
138. Yu H, Cen J, Lin X, Cheng H, Seifert O. Imiquimod induced vitiligo-like lesions-A consequence of modified melanocyte function. Immun Inflamm Dis. 2022;10(1):70–7.
139. Kim CH, Ahn JH, Kang SU, Hwang HS, Lee MH, Pyun JH, et al. Imiquimod induces apoptosis of human melanocytes. Arch Dermatol Res. 2010;302(4):301–6.
140. Wu JK, Siller G, Strutton G. Psoriasis induced by topical imiquimod. Australas J Dermatol. 2004;45(1):47–50.
141. Patel U, Mark NM, Machler BC, Levine VJ. Imiquimod 5% cream induced psoriasis: a case report, summary of the literature and mechanism. Br J Dermatol. 2011;164(3):670–2.
142. van der Fits L, Mourits S, Voerman JS, Kant M, Boon L, Laman JD, et al. Imiquimod-induced psoriasis-like skin inflammation in mice is mediated via the IL-23/IL-17 axis. J Immunol. 2009;182(9):5836–45.
143. Armstrong AW, Read C. Pathophysiology, clinical presentation, and treatment of psoriasis: a review. JAMA. 2020;323(19):1945–60.
144. Torres-Cabala CA, Wang WL, Trent J, Yang D, Chen S, Galbincea J, et al. Correlation between KIT expression and KIT mutation in melanoma: a study of 173 cases with emphasis on the acral-lentiginous/mucosal type. Mod Pathol. 2009;22(11):1446–56.
145. Curtin JA, Busam K, Pinkel D, Bastian BC. Somatic activation of KIT in distinct subtypes of melanoma. J Clin Oncol. 2006;24(26):4340–6.
146. Ugurel S, Hildenbrand R, Zimpfer A, La Rosee P, Paschka P, Sucker A, et al. Lack of clinical efficacy of imatinib in metastatic melanoma. Br J Cancer. 2005;92(8):1398–405.
147. Carvajal RD, Antonescu CR, Wolchok JD, Chapman PB, Roman RA, Teitcher J, et al. KIT as a therapeutic target in metastatic melanoma. JAMA. 2011;305(22):2327–34.
148. Hodi FS, Corless CL, Giobbie-Hurder A, Fletcher JA, Zhu M, Marino-Enriquez A, et al. Imatinib for melanomas harboring mutationally activated or amplified KIT arising on mucosal, acral, and chronically sun-damaged skin. J Clin Oncol. 2013;31(26):3182–90.
149. Wyman K, Atkins MB, Prieto V, Eton O, McDermott DF, Hubbard F, et al. Multicenter Phase II trial of high-dose imatinib mesylate in metastatic melanoma: significant toxicity with no clinical efficacy. Cancer. 2006;106(9):2005–11.
150. Ugurel S, Hildenbrand R, Dippel E, Hochhaus A, Schadendorf D. Dose-dependent severe cutaneous reactions to imatinib. Br J Cancer. 2003;88(8):1157–9.
151. Pretel-Irazabal M, Tuneu-Valls A, Ormaechea-Pérez N. Adverse skin effects of imatinib, a tyrosine kinase inhibitor. Actas Dermo-Sifiliográficas (English Edition). 2014;105(7):655–62.
152. Forschner A, Forchhammer S, Bonzheim I. NTRK gene fusions in melanoma: detection, prevalence and potential therapeutic implications. J Dtsch Dermatol Ges. 2020;18(12):1387–92.
153. Drilon A, Laetsch TW, Kummar S, DuBois SG, Lassen UN, Demetri GD, et al. Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. N Engl J Med. 2018;378(8):731–9.
154. Drilon A, Siena S, Ou SI, Patel M, Ahn MJ, Lee J, et al. Safety and antitumor activity of the multitargeted Pan-TRK, ROS1, and ALK inhibitor entrectinib: combined results from two phase I trials (ALKA-372-001 and STARTRK-1). Cancer Discov. 2017;7(4):400–9.
155. Espinosa ML, Abad C, Kurtzman Y, Abdulla FR. Dermatologic toxicities of targeted therapy and immunotherapy in head and neck cancers. Front Oncol. 2021;11: 605941.

156. Doebele RC, Drilon A, Paz-Ares L, Siena S, Shaw AT, Farago AF, et al. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1–2 trials. Lancet Oncol. 2020;21(2):271–82.
157. ClinicalTrials.gov U.S. National Library of Medicine. https://clinicaltrials.gov/. Accessed 26 Oct 2022.