

BRIEF ARTICLES

Cutaneous Toxicities of PI3K Inhibitors: A Series of Two Cases and Review of the Literature

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ABSTRACT

Phosphoinositide 3-kinase (PI3K) inhibitors are a class of antineoplastic agents currently approved for the treatment of multiple hematologic malignancies and breast cancer. These medications have specific molecular targets to limit toxicity; however, cutaneous adverse effects are frequently reported and can require cessation of therapy. Morbilliform, eczematous, psoriasiform, and pityriasis rubra pilaris-like eruptions are most common, though exfoliative dermatitis and Stevens-Johnson syndrome/toxic epidermal necrolysis have also been reported. We highlight two cases of photo-accentuated skin reactions to duvelisib, a p110- δ and p110- γ isoform inhibitor. Both cases required oral corticosteroids and interruption of therapy for definitive management due to severity. While one patient was able to tolerate re-challenge with duvelisib and continue on therapy, both patients experienced recurrence of cutaneous eruptions with repeat exposure, establishing a notable temporal correlation. Thus, these cases contribute a novel presentation of adverse reactions to PI3K inhibitors to existing literature.

INTRODUCTION

Phosphoinositide 3-kinase (PI3K) inhibitors are novel small molecule targeted inhibitors approved for the treatment of multiple hematologic malignancies, namely relapsed or refractory chronic lymphocytic leukemia (CLL), follicular lymphoma (FL), small lymphocytic lymphoma (SLL), and breast cancer.^{1,2} Isoform-specific PI3K inhibitors are a subclass of this broader category, consisting of agents targeting the p110- α isoform (alpelisib and tselisib), the p110- δ isoform (idelalisib), and the p110- δ and p110- γ isoforms (duvelisib).³ The specificity of these molecular targets allows for higher

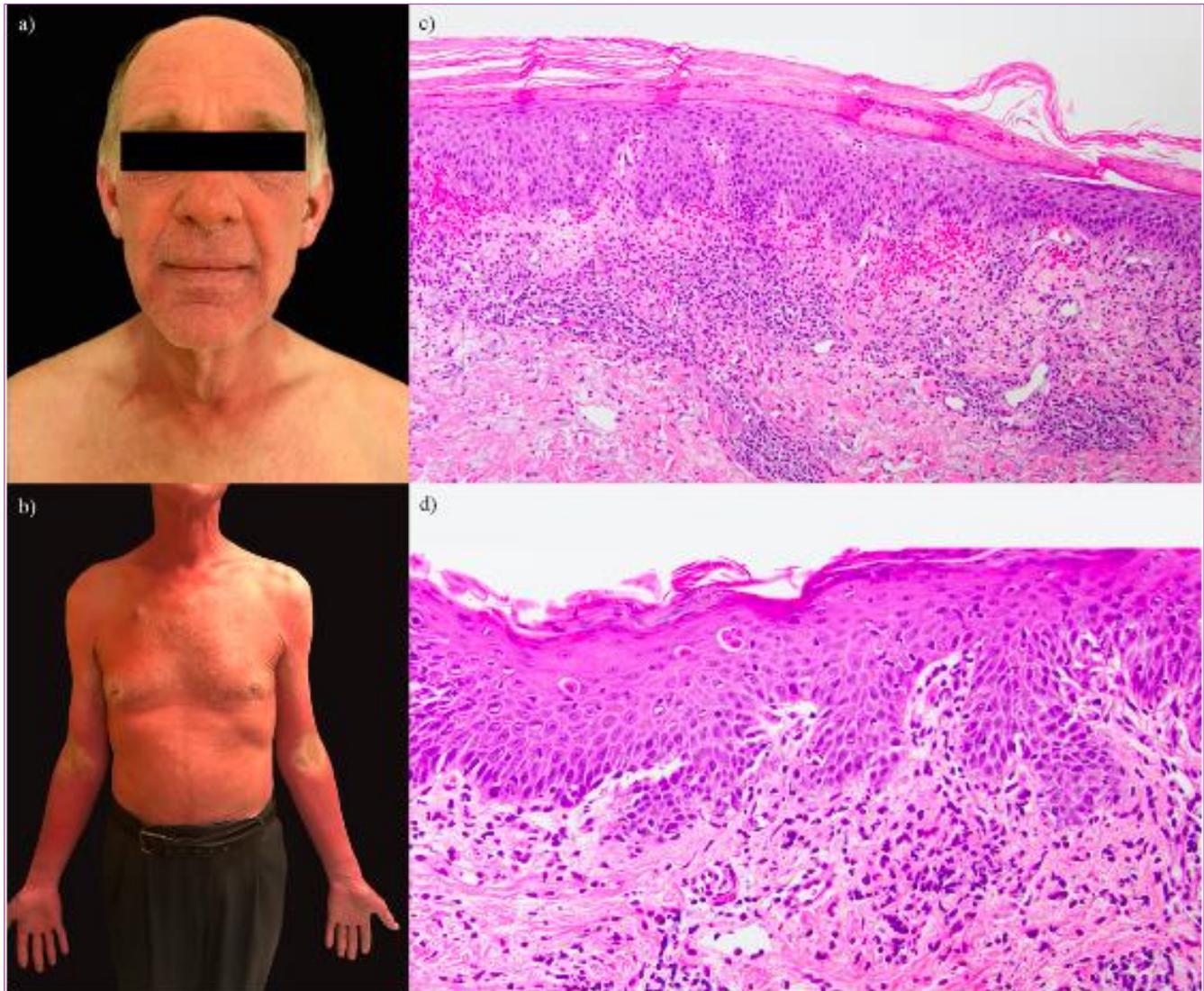
dosage while limiting toxicity; however, cutaneous, endocrine, and gastrointestinal toxicities are common. We report two photo-accentuated duvelisib-induced skin eruptions, both requiring interruption of therapy and resolving with systemic steroids.

CASE PRESENTATION**Case 1**

A 62-year-old man with a history of angioimmunoblastic T cell lymphoma (AITCL) presented with a pruritic skin eruption in the spring. The patient's AITCL

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Figure 1. Case 1 clinical image of the initial eruption reveals photo-accentuated erythematous scaly plaques on the face and neck (a). Clinical image of the recurrent eruption demonstrates pink-orange scaly plaques on the face, neck, trunk, and extremities with sparing of the antecubital fossae (b). Biopsies of the left forearm (c) and the left upper arm (d) show a chronic spongiotic dermatitis with scattered necrotic keratinocytes and a dermal infiltrate composed of lymphocytes and eosinophils (H&E, 100x, 200x).



had been previously treated with chemotherapy and autologous stem cell transplant, initially achieving complete remission. Recurrence of the AITCL prompted initiation of duvelisib three months prior to development of the skin eruption. On physical examination, the patient was noted to have erythematous, scaly thin plaques on the face, neck, dorsal hands and upper extremities with a psoriasiform appearance,

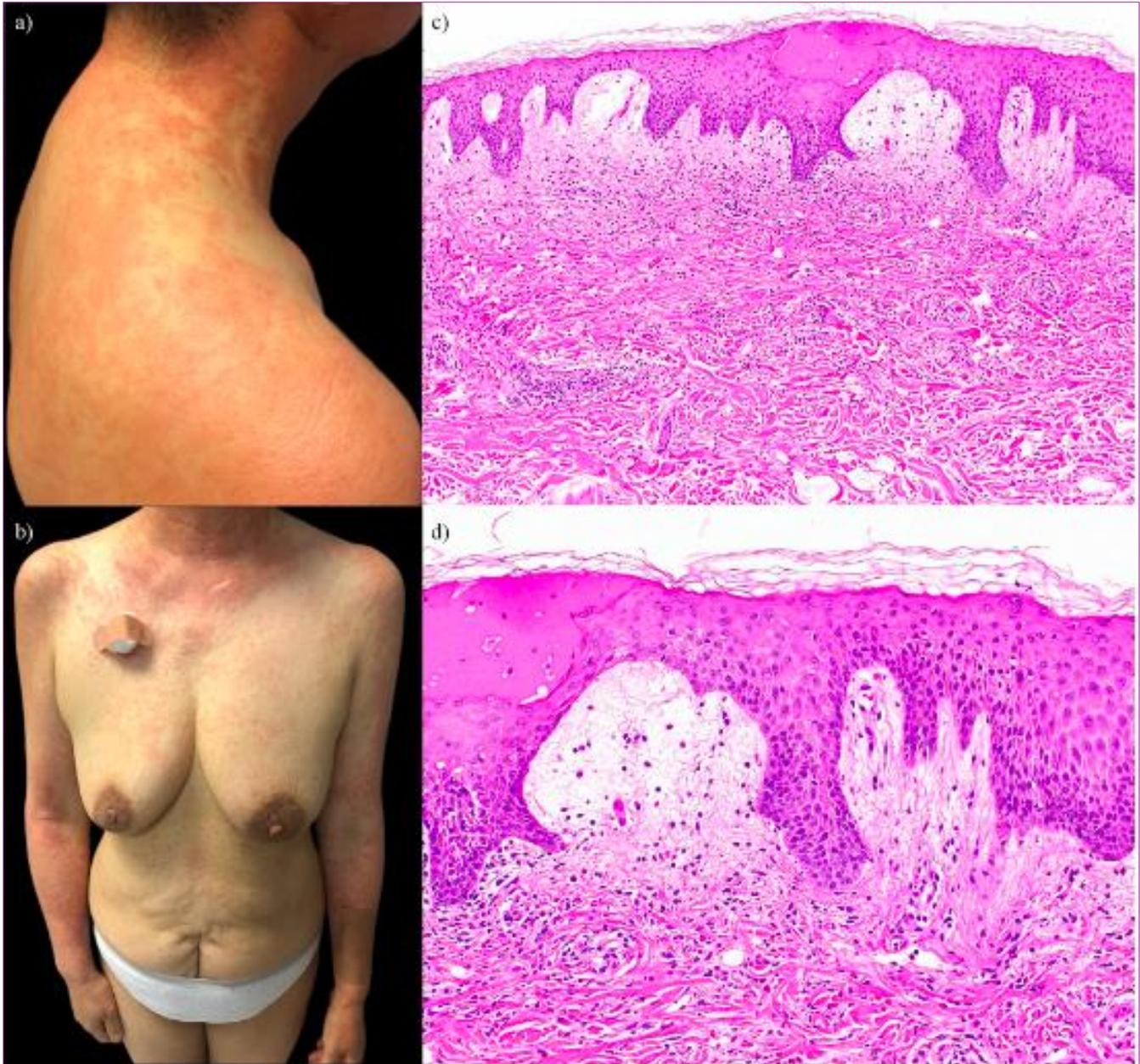
accentuated in sun exposed areas. This photo-accentuated psoriasiform eruption improved after duvelisib was held for 1 month due to a transaminitis.

One month after restarting the duvelisib, the patient presented with a new skin eruption. Physical examination revealed confluent, scaly, erythematous plaques on the face, scalp, and trunk (Figure 1a and 1b). There

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Figure 2. Case 2 clinical images reveal erythematous papules coalescing into plaques on the neck, shoulders, and forearms with photo-accentuation (**a, b**). Biopsy of the left arm (**c**) demonstrates a spongiotic epidermis with vesiculation, significant papillary dermal edema, and a perivascular and interstitial dermal infiltrate (H&E, 100x). Higher power (**d**) reveals a perivascular and interstitial infiltrate composed of lymphocytes and eosinophils (H&E, 200x).



were pink-orange scaly plaques on the bilateral palms with sharp demarcation at the wrists, well-demarcated pink plaques on the extremities, and areas of spared skin in flexural areas clinically resembling pityriasis interrupted due to the eruption; his skin

improved with oral and topical steroids, and then worsened with subsequent rechallenge of duvelisib. Multiple punch biopsies were performed throughout the evolution of the patient's rash. Histopathology demonstrated parakeratosis,

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Table 1. Previously Reported Cutaneous Toxicities of PI3K Inhibitors

	Age/ Sex	Malignancy	PI3K inhibitor	Time to reaction	Morphology	Histopathology	Reaction type	Treatment of cutaneous eruption	PI3K therapy outcome	Successful re- challenge (if interrupted)?	Associated adverse events
Case 1 (our case)	62 M	AITCL	Duvelisib	3 months	Photo-accentuated psoriasiform pink-orange scaly plaques on the face, neck, forearms, which generalized with areas of sparing	Parakeratosis, acanthosis, and spongiosis of epidermis, lymphocytic infiltrate with neutrophils and eosinophils in the upper dermis	Photo-accentuated PRP-like	Systemic corticosteroids, topical corticosteroids	Interrupted	No	Transaminitis
Case 2 (our case)	55 F	PTCL	Duvelisib	1 month	Photo-accentuated erythematous papules coalescing into plaques on the face, neck, arms	Perivascular and interstitial dermatitis with eosinophils	Photo-accentuated morbilliform eruption	Systemic corticosteroids, topical corticosteroids, oral antihistamines	Interrupted	Yes	Transaminitis, neutropenia, fatigue
Gabriel et al.	65 M	CLL	Idelalisib	3 months	Exfoliative rash with diffuse scaling of torso, extremities, tongue, glans penis, and desquamation of soles	Not performed	Exfoliative dermatitis	Not specified	Not specified	N/A	Transaminitis, normocytic anemia
Hammami et al.	56 M	FL	Idelalisib	4 months	Skin eruption, unspecified	Subacute spongiotic dermatitis, superficial dermal lymphohistiocytic infiltrate with eosinophils	Ecematous	Systemic corticosteroids	Discontinued	N/A	Colitis
Huilaja et al.	61 M	CLL	Idelalisib	1 months	Macular erythematous eruption with desquamation on upper arms/trunk, peeling on palms	Hyperkeratosis and focal parakeratosis, acanthotic thickening, focal spongiosis, perivascular lymphohistiocytic infiltrate with some eosinophils	Not specified	Oral corticosteroids, topical corticosteroids	Discontinued	N/A	Transaminitis
Machan et al.	82 F	FL	Idelalisib	11 months	Erythematous papules and plaques on back/buttocks with pustules of scalp/forehead	T-cell infiltration with psoriasiform epidermal hyperplasia, subcorneal pustule, and mild perivascular lymphocytic infiltrate	Psoriasiform	Topical corticosteroids	Interrupted	Yes	None
Dewan et al.	59 M	CLL	P110-delta inhibitor	17 months	Photodistributed erythematous papules and large plaques on arms/legs, which spread to face, scalp, trunk, soles	Psoriasiform epidermal hyperplasia, mild spongiosis, parakeratosis, intraepidermal/intracorneal neutrophils	Psoriasiform	Oral acitretin, topical corticosteroids, photoprotection	Interrupted	Yes	Not specified
	57 M	CLL	P110-delta/gamma inhibitor	15 days	Guttate papules and erythematous plaques with overlying micaceous scale on knees and intertriginous areas, nail pitting, palmoplantar pustules	Psoriasiform dermatitis with inflamed parakeratosis	Psoriasiform	Topical corticosteroids, topical tacrolimus, topical retinoid	Interrupted	Yes	Not specified
	81 M	SLL/CLL	P110-delta inhibitor	5 months	Thin erythematous papules coalescing into plaques with overlying micaceous scale on trunk/extremities	Spongiotic and suprabasilar acantholysis with superficial dermal lymphocytic infiltrate	Psoriasiform	Topical corticosteroids	Discontinued	N/A	Not specified
	72 M	MZL	P110-delta inhibitor	3 months	Thin erythematous plaques on gluteal cleft, inguinal folds; large plaques with overlying micaceous scale on neck, chest, extremities, scalp	Not performed	Psoriasiform	Topical corticosteroids	Discontinued (for colitis adverse effect)	N/A	Colitis
Dewan et al.	40s F	Anaplastic oligodendroglioma	Dual pan-class I PI3K inhibitor	4 days	Pruritic photodistributed orange-pink erythroderma with islands of sparing and overlying fine desquamative scale, palmoplantar keratoderma	Pityriasiform changes with alternating ortho and parakeratosis, spongiotic dermatitis, and numerous eosinophils	PRP-like	Systemic corticosteroids, oral acitretin, topical steroids, oral antihistamines	Not specified	N/A	Essential tremor
	60s M	CLL	Idelalisib	5 months	Diffuse orange-red erythroderma with islands of sparing, nonscarring alopecia, palmoplantar keratoderma	Pityriasiform changes with alternating ortho and parakeratosis, spongiotic dermatitis, and numerous eosinophils	PRP-like	Systemic corticosteroids, oral acitretin, topical corticosteroids, topical retinoids	Discontinued	N/A	Leukopenia, anemia, thrombocytopenia, suppurative adenitis
	60s M	SLL	Idelalisib	6 weeks	Diffuse orange-red patches with follicular prominence and islands of sparing over trunk/extremities	Subacute spongiotic dermatitis with pityriasiform scale and superficial perivascular lymphocytic infiltrate	PRP-like	Systemic corticosteroids, topical corticosteroids	Discontinued	N/A	Peripheral eosinophilia, transaminitis

Abbreviations: pityriasis rubra pilaris (PRP), angioimmunoblastic T cell lymphoma (AITCL), peripheral T cell lymphoma (PTCL), chronic lymphocytic leukemia (CLL), follicular lymphoma (FL), small lymphocytic lymphoma (SLL), marginal zone lymphoma (MZL).

acanthosis, and spongiosis of the epidermis and a lymphocytic infiltrate with occasional neutrophils and eosinophils in the upper dermis. Occasional necrotic keratinocytes were seen (Figure 1c and 1d). Repeat imaging demonstrated no evidence of lymphoma; his AITCL was considered to be in remission on duvelisib. Given worsening of the rash after multiple re-challenges, the patient was diagnosed with a photo-accentuated, duvelisib-induced PRP-like skin eruption.

Case 2

A 55-year-old woman with a history of primary refractory CD30-positive peripheral T cell lymphoma (PTCL) presented with a pruritic eruption on the face, neck, and upper extremities in the summer. The PTCL was previously treated with chemotherapy; however, duvelisib was initiated after repeat imaging and lymph node biopsy revealed progressive disease. One month after introducing duvelisib, the patient developed concurrent skin rash and transaminitis. Within five days, the rash progressed in severity and duvelisib was held. Physical examination revealed photo-accentuated erythematous papules coalescing into plaques on the face, chest, dorsal arms (Figure 2a and 2b). A punch biopsy of her left forearm was performed, and histopathologic analysis demonstrated a perivascular and interstitial dermatitis with eosinophils (Figure 2c and 2d). The patient was treated with topical triamcinolone, antihistamines, and an oral prednisone taper. Within three weeks, the rash significantly improved and duvelisib was resumed at a lower dose.

After resumption of duvelisib, the patient had persistent pruritus and xerosis, managed with oral antihistamines and topical emollients. Her rash recurred three and a half months later, albeit with markedly

decreased severity, and rapidly resolved with topical triamcinolone. She remains stable on duvelisib with complete tumor response. Given temporal association with duvelisib initiation and recurrence with re-challenge, the patient was diagnosed with duvelisib-induced photo-accentuated morbilliform skin eruption.

DISCUSSION

PI3K inhibitors block the PI3K/AKT/mTOR pathway, a signaling cascade that regulates cell proliferation, growth, motility, and survival through extracellular signaling. Isoform-specific PI3K inhibitors are a subclass that take advantage of this pathway's impact on oncogenesis.³ Cutaneous adverse events are commonly observed, occurring in 17-45% of patients, varying per isoform target.⁴⁻⁶ Though the majority of eruptions are mild, skin toxicities are the second most common grade 3 and 4 toxicity, per Common Terminology Criteria for Adverse Events (CTCAE) grading, for alpelisib and duvelisib.⁶

Cutaneous eruptions related to PI3K inhibitors present variably and can develop days to months after drug initiation (Table 1). A diffuse maculopapular rash with or without pruritus and xerosis is the most frequently reported skin manifestation; however phase I and II trials did not characterize cutaneous reactions with specific descriptors.³ Case reports have delineated various clinical presentations, including, but not limited to, eczematous, psoriasiform, and PRP-like eruptions, as well as exfoliative dermatitis and Stevens-Johnson syndrome/toxic epidermal necrolysis.^{3,5,7-12} Histopathology for specific eruptions largely resembles the clinical correlate, and non-specific eruptions commonly reveal perivascular and dermal infiltration by eosinophils and lymphocytes,

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with or without epidermal spongiosis.⁵ This report of two cases of PI3K inhibitor-induced rash adds photo-accentuated eruptions to the clinical presentations previously reported in the literature.

The pathophysiology of these toxicities is attributed to the effects of PI3K inhibition on subsets of lymphocytes, including T-regulatory cells and differentiation of Th1 and Th2 lymphocytes. Disruption in immune regulation and self-tolerance thus results in toxicities of an autoimmune nature.¹ Of note, PI3K inhibitors are effective photosensitizing agents and demonstrated potential utility in photodynamic therapy for cancer, thereby suggesting a possible mechanism underlying the photo-accentuated cutaneous toxicity noted in this case series.¹³ According to CTCAE guidelines, eruptions should be stratified by severity corresponding to body surface area involvement. Lower grade toxicities can be managed with high potency topical corticosteroids and antihistamines, whereas severe and persistent toxicities require systemic corticosteroids and possible interruption of PI3K inhibitor therapy. Notably, if therapy is interrupted, re-challenge at a lower dosage can be trialed. Close monitoring is paramount, as one in four patients experience recurrence of cutaneous toxicity with resumption of therapy, as reflected in this case series.⁵

While PI3K inhibitors are currently approved for a narrow range of malignancies, ongoing clinical trials present promising data for future utility in treatment of multiple solid tumors. Thus, the cutaneous toxicities of PI3K inhibitors merit recognition as the use of these agents expands.¹²

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References:

- Greenwell IB, Ip A, Cohen JB. PI3K Inhibitors: Understanding Toxicity Mechanisms and Management. *Oncology (Williston Park)*. 2017;31(11):821-828.
- Andre F, Ciruelos E, Rubovszky G, et al. Alpelisib for PIK3CA-Mutated, Hormone Receptor-Positive Advanced Breast Cancer. *N Engl J Med*. 2019;380(20):1929-1940.
- Nunnery SE, Mayer IA. Management of toxicity to isoform alpha-specific PI3K inhibitors. *Ann Oncol*. 2019;30 Suppl 10:x21-x26.
- Flinn IW, Patel M, Oki Y, et al. Duvelisib, an oral dual PI3K-delta, gamma inhibitor, shows clinical activity in indolent non-Hodgkin lymphoma in a phase 1 study. *Am J Hematol*. 2018;93(11):1311-1317.
- Ransohoff JD, Kwong BY. Cutaneous Adverse Events of Targeted Therapies for Hematolymphoid Malignancies. *Clin Lymphoma Myeloma Leuk*. 2017;17(12):834-851.
- Horwitz SM, Koch R, Porcu P, et al. Activity of the PI3K-delta,gamma inhibitor duvelisib in a phase 1 trial and preclinical models of T-cell lymphoma. *Blood*. 2018;131(8):888-898.
- Gabriel JG, Kapila A, Gonzalez-Estrada A. A Severe Case of Cutaneous Adverse Drug Reaction Secondary to a Novice Drug: Idelalisib. *J Investig Med High Impact Case Rep*. 2017;5(2):2324709617711463.
- Hammami MB, Al-Tae A, Meeks M, et al. Idelalisib-induced colitis and skin eruption mimicking graft-versus-host disease. *Clin J Gastroenterol*. 2017;10(2):142-146.
- Huilaja L, Lindgren O, Soronen M, Siitonen T, Tasanen K. A slowly developed severe cutaneous adverse reaction to idelalisib. *J Eur Acad Dermatol Venereol*. 2018;32(5):e192-e193.
- Machan S, Plaza C, Perez-Gonzalez Y, Rodriguez-Pinilla M, Requena L, Cordoba R. Management of psoriasis-like rash associated with idelalisib monotherapy in a patient with refractory follicular lymphoma: a case report. *J Med Case Rep*. 2020;14(1):35.
- Dewan AK, Sowerby L, Jadeja S, et al. Pityriasis rubra pilaris-like erythroderma secondary to phosphoinositide 3-kinase inhibition. *Clin Exp Dermatol*. 2018;43(8):890-894.
- Dewan AK, Gupta S, Bach DQ, et al. Psoriasiform eruptions secondary to phosphoinositide 3-kinase inhibition. *JAAD Case Rep*. 2019;5(5):401-405.
- Hayashida Y, Ikeda Y, Sawada K, et al. Invention of a novel photodynamic therapy for tumors using a photosensitizing PI3K inhibitor. *Int J Cancer*. 2016;139(3):700-711.

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