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Cutaneous Toxicity of Ribociclib in Hormone Receptor-Positive/HER2-Negative Advanced Breast Cancer: Frequency, Dermatologic Management, and Prognostic Significance

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Abstract

Ribociclib is an approved cyclin-dependent kinase 4/6 inhibitor for the treatment of hormone receptor–positive (HR+), human epidermal growth factor receptor 2–negative (HER2−) advanced breast cancer (ABC) when combined with endocrine therapy. Although pivotal clinical trials have clearly described hematologic, hepatic, and cardiac toxicities, data regarding ribociclib-associated cutaneous adverse events (CAEs) are still scarce. This retrospective cohort study included all patients with HR+/HER2− ABC who were treated with ribociclib at the Humanitas Cancer Center from June 2017 through December 2022. Clinical and pathological variables were collected together with the frequency, type, and management of CAEs attributed to ribociclib. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 5.0. Progression-free survival (PFS) was assessed using the Kaplan–Meier method, and comparisons between groups were conducted with the log-rank test. Out of 91 treated patients, 13 (14.3%) developed ribociclib-related CAEs, with a mean time to onset of 3.9 months. Eczematous dermatitis represented the most common manifestation (53.8%), followed by maculopapular eruptions (15.4%). Pruritus was present in all 13 affected patients. Severity was classified as grade 3 in 8 cases, grade 2 in 4 cases, and grade 1 in 1 case. A multidisciplinary strategy combining ribociclib dose modification with dermatologic therapies (oral antihistamines, emollient creams, topical and/or systemic corticosteroids) enabled treatment continuation in the majority of patients. After a median follow-up of 20 months, median PFS was 13 months (range, 1–66), and patients who experienced CAEs showed significantly improved PFS curves (P = .04).This analysis characterizes the incidence and clinical spectrum of ribociclib-induced CAEs. Integrating structured dermatologic management into routine oncologic practice may help limit treatment discontinuation and could contribute to improved long-term clinical outcomes.

Keywords: Ribociclib, Eczematous dermatitis, Progression-free survival, Metastatic breast cancer, Endocrine therapy

Introduction

Cyclin-dependent kinase 4 and 6 inhibitors (CDK4/6i) have substantially reshaped the management of hormone receptor–positive (HR+), human epidermal growth factor receptor 2–negative (HER2−) advanced breast cancer (ABC). The addition of CDK4/6 inhibitors to endocrine therapy (ET) has led to significant gains in response rates and survival outcomes among patients with HR+/HER2− ABC [1–6]. As a result, these agents have received regulatory approval in combination with nonsteroidal aromatase inhibitors (NSAIs) for endocrine-sensitive disease or with fulvestrant, particularly in endocrine-resistant settings.

Currently, three CDK4/6 inhibitors—palbociclib, ribociclib, and abemaciclib—are widely used in clinical practice. Treatment selection is influenced by individual patient characteristics, including comorbid conditions, concomitant medications, and differences in toxicity

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profiles. Updated results from pivotal clinical trials have demonstrated a significant overall survival (OS) benefit for ribociclib combined with ET compared with ET alone, with a median OS of 58.7 months versus 48.0 months for placebo [7]. Moreover, extended follow-up data from the MONALEESA-3 trial confirmed a marked OS improvement with ribociclib plus fulvestrant compared with placebo plus fulvestrant (median OS: 53.7 vs 41.5 months) [8].

In the context of endocrine-resistant disease, the MONARCH-2 trial reported a statistically significant OS advantage for abemaciclib plus fulvestrant relative to ET alone (46.7 vs 37.3 months) [9]. At present, mature OS results are not available for abemaciclib combined with NSAI in the MONARCH-3 study [3]. Meanwhile, palbociclib plus ET has shown numerical, but not statistically significant, improvements in median OS [10, 11]. Notably, long-term follow-up exceeding 6 years in the PALOMA-3 trial demonstrated a clinically meaningful OS benefit of 6.8 months for palbociclib plus fulvestrant compared with placebo plus fulvestrant in patients with HR+/HER2− ABC who had progressed on prior ET [12].

Across multiple studies evaluating the three approved CDK4/6 inhibitors, treatment-related toxicities have generally been manageable through supportive care, dose reductions, and/or temporary treatment interruptions [1–6, 13–15]. Hematologic adverse events—such as neutropenia, anemia, and thrombocytopenia—represent the most common toxicities associated with CDK4/6i-based regimens. Beyond these hematologic effects, which occur in approximately 70% of patients, each CDK4/6 inhibitor exhibits a distinct non-hematologic safety profile. Abemaciclib is frequently associated with diarrhea (87%) and fatigue (43%), whereas ribociclib is more commonly linked to hepatotoxicity (12%) and early, reversible, concentration-dependent QT interval prolongation (11%) [16, 17].

Multiple dermatologic toxicities have been documented in both randomized trials and real-world settings among patients treated with cyclin-dependent kinase 4/6 inhibitors (CDK4/6i). The most frequently reported manifestations include alopecia, inflammatory skin reactions, and pruritus [1–6, 18, 19]. These adverse events are clinically meaningful not only due to their negative impact on health-related quality of life, but also because they may necessitate dose modification or complete discontinuation of anticancer therapy. When CDK4/6i were administered in combination with endocrine therapy (ET), alopecia was observed in 23% of patients, compared with 9.6% among those receiving ET alone, with abemaciclib showing the highest associated risk. Cutaneous adverse events and pruritus were reported in approximately 15%–20% of patients treated with CDK4/6i plus ET, whereas severe reactions (grade ≥3) were rare, occurring in fewer than 1% of cases [20, 21]. Despite these observations, available literature provides limited detail regarding the clinical presentation of these skin toxicities, and their potential relationship with treatment efficacy and patient outcomes remains largely unexplored [18–20, 22].

Skin-related toxicities were included among reported adverse events in the MONALEESA-2, MONALEESA-3, and MONALEESA-7 trials. Specifically, MONALEESA-2 documented 74 cases (22%) of CAEs and maculopapular eruptions of any grade (G). In MONALEESA-3, pruritus was reported in 96 patients (20%), while CAEs occurred in 89 patients (18%). In the MONALEESA-7 trial, CAEs were observed in 43 patients (13%), pruritus in 31 patients (9%), and xerosis in 27 patients (8%) [2, 6, 23]. Although pivotal trials mainly described nonspecific and low-grade dermatologic reactions, the published literature contains several case reports and small series illustrating a broad spectrum of ribociclib-associated skin disorders, including severe and clinically challenging presentations [24–26].

Based on these considerations, we conducted a retrospective observational cohort study aimed at systematically evaluating the frequency and clinical features of dermatologic adverse events attributable to ribociclib, as well as their implications for treatment tolerability and effectiveness in a real-world population of patients with HR+/HER2− advanced breast cancer (ABC) treated with ribociclib plus ET. Additionally, we investigated potential clinical factors predictive of CAE development. Finally, in accordance with emerging evidence, we explored whether the occurrence of CAEs might be associated with improved prognosis [27].

Materials and Methods

Study design and population

This retrospective observational study included all consecutive patients diagnosed with HR+/HER2− ABC who initiated treatment with ribociclib in combination with ET between June 2017 and December 2022 at IRCCS Humanitas Research Hospital (Milan). Patients

who transferred care to other institutions during treatment were excluded from the analysis. Data were extracted from electronic medical records, including demographic variables (age at diagnosis), baseline clinicopathologic features (comorbid conditions, prior allergic history and/or dermatologic disease, Eastern Cooperative Oncology Group [ECOG] Performance Status, American Joint Committee on Cancer stage, and histologic characteristics), treatment-related information (type of ET, ribociclib starting dose, dose interruptions, and permanent discontinuation), and clinical outcomes (best observed response and disease progression).

For study-specific purposes, both cutaneous and non-cutaneous adverse events were systematically collected. Recorded variables included the type of dermatologic reaction, latency from treatment initiation, severity graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0, clinical evolution, and therapeutic management. Cutaneous events were considered causally related to ribociclib when the Naranjo probability score was ≥5 [28]. Alopecia was excluded from the CAE category, as adnexal toxicities were outside the scope of the present analysis. Evaluation and management of CAEs were performed through close collaboration between oncologists and a dedicated dermatologist.

The study protocol was approved by the Independent Ethical Committee of IRCCS Humanitas Research Hospital (protocol number ONC/OSS-06/2023). Written informed consent for both treatment and the use of anonymized clinical data for research purposes was obtained from all participants. The study was conducted in compliance with the Declaration of Helsinki.

Ribociclib was administered to all patients at the standard initial dose of 600 mg orally once daily following a 3-weeks-on/1-week-off schedule, in combination with ET. Endocrine therapy consisted of either letrozole (2.5 mg orally once daily) or fulvestrant (500 mg intramuscularly on days 1, 14, and 28, and every 28 days thereafter), with or without a luteinizing hormone–releasing hormone (LHRH) analog according to menopausal status. Clinical evaluations were performed every 4 weeks during the first 3 months and subsequently every 4–8 weeks, or more frequently if clinically required. Radiologic tumor assessments were carried out using computed tomography or magnetic resonance imaging according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. Dose adjustments and treatment discontinuation followed approved prescribing guidelines.

Study objectives

The primary aim of this study was to quantify the incidence of ribociclib-related CAEs in the analyzed cohort. Secondary objectives included detailed characterization of CAE subtype, severity, duration, management strategies, and clinical outcome, as well as identification of potential predictors associated with CAE development. An exploratory objective was to assess whether CAE occurrence correlated with improved survival outcomes.

Statistical analysis

Categorical variables were summarized using frequencies and percentages, while continuous variables were described using medians and ranges. Associations between candidate clinical predictors and the development of CAEs were evaluated using logistic regression models. Progression-free survival (PFS), defined as the interval from the first administration of ribociclib to disease progression or death, was estimated using the Kaplan–Meier method. Comparisons between patients with and without CAEs were performed using the log-rank test. All statistical tests were two-sided, and statistical significance was defined as $P \leq .05$ following Bonferroni adjustment for multiple comparisons. Statistical analyses were conducted using STATA software (version 15; StataCorp, 2017; Stata Statistical Software: Release 16; College Station, TX, USA: StataCorp LLC).

Results and Discussion

Patient demographics and therapy details

The analysis encompassed 91 individuals with advanced breast cancer receiving ribociclib therapy. Patient profiles are outlined in **Table 1**. Ribociclib-triggered cutaneous adverse events (CAEs) occurred in 14.3% of cases (n = 13). Other toxicities included all-grade neutropenia in 55.1% (n = 43), hepatobiliary issues in 11.5% (n = 9), and QT interval prolongation in 8.9% (n = 7). Specifically, CAEs affected 5 patients on ribociclib combined with fulvestrant and 8 on ribociclib plus letrozole. Among the latter, only 2 were premenopausal and also received an LHRH analog. No concomitant drugs showed documented interactions with ribociclib. Three of the 13 patients with CAEs had prior allergies to

iodinated contrast agents, succinylcholine, opioids, or nickel sulfate.

Table 1. Baseline features of patients developing CAEs versus those who did not.

	No CAEs	CAEs
N (%)	78 (85.7)	13 (14.3)
ECOG PS		
0		10 (76.9)
1	59 (75.6)	3 (23.1)
Allergies	19 (24.4)	3 (23.1)
History of skin disease	21 (26.9)	3 (23.1)
Recurrent ABC	0 (0.0)	10 (76.9)
De novo ABC	41 (52.6)	3 (23.1)
Luminal A	37 (47.4)	6 (46.2)
Luminal B	20 (25.6)	7 (53.8)
First-line therapy	58 (74.4)	12 (92.3)
HT companion	71 (91.1)	
Fulvestrant		5 (38.5)
Letrozole		6 (46.2)
LHRHa + letrozole	10 (12.8)	2 (15.4)
LHRHa + fulvestrant	39 (50.0)	0 (0.0)
Best response	28 (35.9)	
CR	1 (1.3)	2 (15.4)
PR		6 (46.2)
SD		4 (30.8)
PD	10 (12.8)	1 (7.7)
	19 (24.4)	
	43 (55.1)	
	6 (7.7)	

Percentages are calculated within each subgroup (with or without skin reactions).

Abbreviations: CAEs, cutaneous adverse events; PS, performance status; ABC, advanced breast cancer; HT, hormonal therapy; LHRHa, luteinizing hormone–releasing hormone analog; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Features and handling of skin toxicities linked to ribociclib

Details on ribociclib-associated CAEs and their handling are presented in **Table 2.** Average onset time from therapy initiation to initial CAE appearance was 3.9 months (range: 0.4–14.4). Most cases involved significant skin involvement (G3 in 8 patients, G2 in 4, G1 in 1). Pruritus accompanied every instance of ribociclib-induced CAE. In 2 patients, isolated pruritus constituted the sole manifestation. Apart from itching, predominant patterns were eczematous dermatitis (n = 7, 53.8%) and maculopapular eruptions (n = 2, 15.4%). Single occurrences included urticarial and lichenoid reactions.

Table 2. Patient profiles and clinical aspects in cases of ribociclib-induced CAEs.

Patient ID	Age (years)	Known Allergies	Concomitant Oncologic Agents	Time to Onset of CAEs (months)	CAE Type and Grade	Affected Areas	Treatment Approach	Recurrence of CAE, Grade	Management of Recurrence	Response to Ribociclib

7	6	5	4	3	2	1
73	70	72	74	69	67	69
None	None	None	None	None	None	Iodinated contrast media
Letrozole	Fulvestrant	Letrozole	Fulvestrant	Letrozole	Letrozole, denosumab	Fulvestrant
0.4	3.5	4.1	3.0	6.1	14.4	0.7
Pompholyx/dyshidrotic eczema (eczematous dermatitis), G3	Nummular eczema (eczematous dermatitis), G3	Lichenoid dermatitis, G1	Maculo-papular reaction, G2	Pruritus, G2	Eczematous dermatitis, G3	Eczematous dermatitis, G3
UL	H, N, T, UL, LL	T, UL, LL	LL	UL, LL	T, UL	H, N, T, UL, LL
Ribociclib interruption and dose reduction (400 mg)	Ribociclib interruption and dose reduction (400 mg), betamethasone dipropionate 0.05% cream	Ribociclib interruption, moisturizer cream	Ribociclib interruption and dose reduction (400 mg)	Ribociclib withdrawal, desloratadine 5 mg daily, switch to palbociclib	Ribociclib interruption and dose reduction (400 mg), methylprednisolone aceponate 0.1% cream, cetirizine 10 mg daily	Ribociclib interruption and dose reduction (400 mg), methylprednisolone aceponate 0.1% cream, cetirizine 10 mg daily
No	No	Yes, G3	Yes, G3	No	Yes, G1	Yes, G1
-	-	Ribociclib dose reduction	Switch to palbociclib	-	-	-
SD	SD	PR	PR	PR	SD	SD

8	45	Opioids, nickel sulphate	LHRHa, letrozole	4.0	Eczematous dermatitis, G3	T, UL; LL	Ribociclib interruption and dose reduction (400 mg), betamethasone dipropionate 0.05% cream, cetirizine 10 mg daily	Yes, G3	Dupilumab 300 mg q2week	PR
9	75	None	Letrozole	1.2	Eczematous dermatitis, G2	UL	Ribociclib interruption and dose reduction (400 mg)	No	-	CR
10	65	None	Fulvestrant	2.3	Pruritus, G2	T, UL; LL	Ribociclib interruption	No	-	CR
11	58	Succinylcholine chloride	Fulvestrant	3.2	Maculo-papular reaction, G3	T, UL; LL	Ribociclib withdrawal	-	-	PR
12	46	None	LHRHa, letrozole	5.0	Urticaria, G3	T, UL; LL	Ribociclib interruption and dose reduction (400 mg), prednisone 25 mg daily, levocetirizine 5 mg daily, betamethasone dipropionate 0.05% cream	Yes, G3	Switch to palbociclib	PR
13	67	None	Letrozole	2.6	Eczematous dermatitis, G3	N, UL, LL	Ribociclib interruption and dose reduction (400 mg), prednisone 10 mg daily, methylprednisolone aceponate 0.1% cream	No	-	PD

Pruritus occurred universally. Grading of skin toxicities followed the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

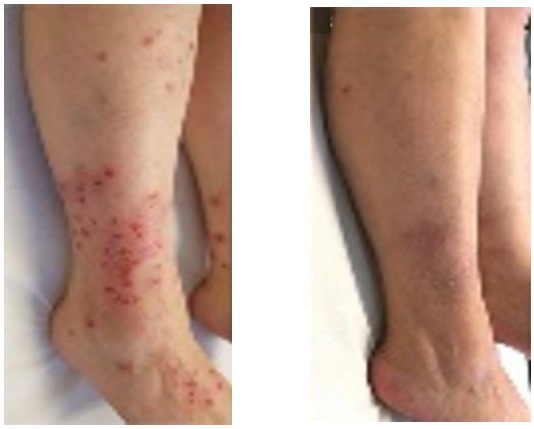
Abbreviations: CAEs, cutaneous adverse events; CR, complete response; H, head; LHRHa, luteinizing hormone–releasing hormone analog; LL, lower limbs; N, neck; PR, partial response; SD, stable disease; T, trunk; UL, upper limbs.

In total, 10 patients (76.9%) underwent temporary ribociclib suspension followed by resumption at the reduced dose of 400 mg daily. Of these, 4 required dose adjustment for combined skin and non-skin toxicities, mainly neutropenia (3 cases) or QT prolongation (1 case). Initial management comprised oral antihistamines, emollient creams, topical corticosteroids, and/or oral steroids. Despite efficacy, CAE recurrence affected 6 patients (46.1%). Individual dermatologic patterns are described in the following sections.

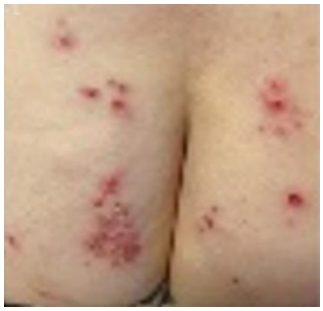
Eczematous dermatitis

Eczema-like presentations dominated ribociclib-related CAEs (7/13 patients; 53.8%). Grading reached G3 in 6 cases and G2 in 1. Two G3 patients reported prior allergies (one to iodinated contrast, another to opioids and nickel sulfate). Lesions invariably involved the upper limbs **(Figure 1)**; extension to the trunk occurred in 10 patients and to the head/neck in 2. Therapy started with potent topical corticosteroids plus non-sedating oral antihistamines. Every patient with eczematous features required a brief ribociclib hold and subsequent dose lowering. Recurrence emerged in 3 of 7 upon restarting 400 mg daily ribociclib, graded G1 in 2 instances. One patient experienced G3 relapse, prompting dupilumab 300 mg subcutaneously every 2 weeks. This individual currently sustains a partial response at 12 months, with full resolution of eczema (**Figure 2**), allowing ongoing ribociclib administration.

Figure 1. Pompholyx-type (dyshidrotic) eczema affecting the right hand. This G3-grade eczematous eruption appeared in a 73-year-old female following the initial cycle of ribociclib.



a) b)



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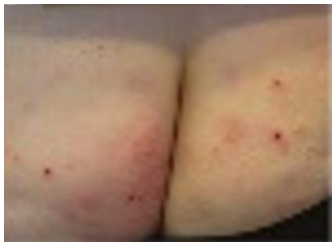


d)

Figure 2. Severe (G3) eczematous rash in a 45-year-old female with prior allergies to opioids and nickel sulfate, emerging 4.0 months into ribociclib therapy. Excoriated plaques distributed across trunk, upper, and lower extremities (a, c). Near-total resolution of lesions achieved after 18 weeks of dupilumab 300 mg subcutaneously every 2 weeks (b, d).

Maculopapular eruption

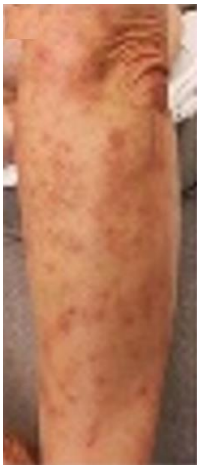
Maculopapular patterns occurred in 2 cases (15.4%). A 74-year-old female developed G2 involvement in the lower extremities and feet. Therapy was paused briefly, then restarted at 400 mg/day, but G3 flare led to permanent cessation of ribociclib and transition to palbociclib, which exhibited superior skin tolerance. The other case, a 58-year-old female with succinylcholine chloride sensitivity, manifested diffuse G3 maculopapular changes that fully resolved after drug withdrawal; ribociclib was not reinitiated, proceeding instead with fulvestrant monotherapy until disease advancement.

Urticarial pattern

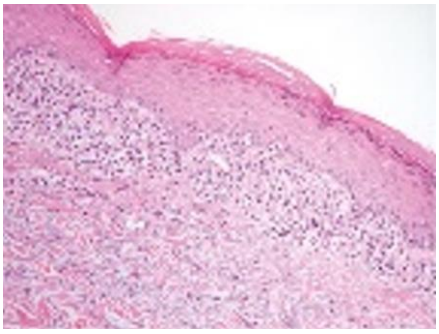
One 46-year-old female exhibited G3 urticaria across the trunk, upper, and lower limbs around 5 months post-ribociclib start. Administration halted, with prescription of oral prednisone 25 mg daily, levocetirizine 5 mg daily, and betamethasone dipropionate 0.05% topical cream. Rechallenge provoked G3 recurrence, necessitating a switch to palbociclib, which was tolerated well dermatologically.

Lichenoid reaction

A 72-year-old female manifested mild (G1) lichenoid changes on the trunk, upper, and lower extremities 4.1 months after ribociclib commencement. Biopsy confirmed lichenoid features histologically (**Figure 3**). Early handling involved emollients and cycle delay at full dose. Progression to G3 during the next administration prompted a reduction to 400 mg daily, yielding full clearance.



a)



b)

Figure 3. Itchy macules and papules along the extensor aspect of the left forearm in a 72-year-old female after 4.1 months on ribociclib (a). Histology revealed compact hyperkeratosis, hypergranulosis, and lymphocytic band-like infiltrate in the upper dermis (hematoxylin and eosin, ×20 original magnification; b).

Isolated pruritus without visible primary rash

Two females, aged 69 and 65 years, displayed sole G2 itching at 6.1 and 2.3 months post-ribociclib initiation, respectively. The former needed drug cessation plus desloratadine 5 mg daily orally, whereas the latter resolved completely via cycle postponement alone. No further itching episodes occurred, though the first case transitioned to palbociclib.

Factors predicting CAEs and outcome implications

Luminal A subtype (high ER/PgR, low Ki67) approached borderline relevance univariately (P = .038), but lost significance following Bonferroni adjustment for multiple comparisons.

With a median follow-up of 20 months, the overall median PFS reached 13 months (range 1–66). Individuals developing CAEs demonstrated superior PFS estimates (P = .04).

The pivotal MONALEESA studies supporting ribociclib approval noted cutaneous side effects among toxicities. Detailed characterization of ribociclib-specific skin reactions remains scarce, however. A comprehensive review of CDK4/6 inhibitors identified 13 distinct dermatologic toxicity patterns across the class. Alopecia predominated, though adnexal events fell outside our scope. Bullous eruptions often mandated ribociclib cessation. Additional reported entities encompassed Stevens-Johnson syndrome/toxic epidermal necrolysis, vitiligo-like depigmentation, erythema dyschromicum perstans, toxic epidermal necrolysis, radiation recall dermatitis, Henoch-Schönlein purpura, leukocytoclastic vasculitis, subacute/chronic cutaneous lupus, and histiocytoid Sweet syndrome [18].

Earlier investigations centered predominantly on palbociclib-associated dermatotoxicity [19], with ribociclib data largely confined to registrational trials and isolated reports [18, 22, 24-26].

Here, in a real-life cohort of 91 HR+/HER2− advanced breast cancer cases, ribociclib provoked skin reactions in 14.3%. Average latency to onset was 3.9 months from commencement. Eczematous forms prevailed, trailed by maculopapular, urticarial, and lichenoid types. Pruritus universally accompanied ribociclib-linked skin events. Most eczematous instances were moderate, controllable via temporary hold, dose lowering, and coordinated multidisciplinary care. Permanent discontinuation arose in 2 patients from toxicity; 10 restarted at 400 mg/day (2 later converting to palbociclib). Simple cycle delay sufficed for complete reversal in one instance.

Besides contemplating temporary cessation of ribociclib until the adverse event resolves (particularly for moderate to severe instances), the handling of skin-related side effects involved standard dermatological treatments. Specifically, for grade 1 events, topical moisturizers and frequent application of hydrating

creams are advised, with low-potency corticosteroids considered for persistent cases. For grade 2–3 events, moderate- to high-potency topical corticosteroids and/or oral corticosteroids warrant consideration. Antihistamines can be incorporated to relieve pruritus across all grades. Regardless of severity, prompt referral to a dermatologist is essential for improved diagnostic precision and tailored treatment, including specialized options, based on the presentation. In moderate to severe (grade 2–3) cutaneous events, pausing ribociclib until resolution of the adverse event is recommended as standard practice. **Figure 4** provides a streamlined illustration of potential strategies for managing skin toxicities associated with ribociclib.

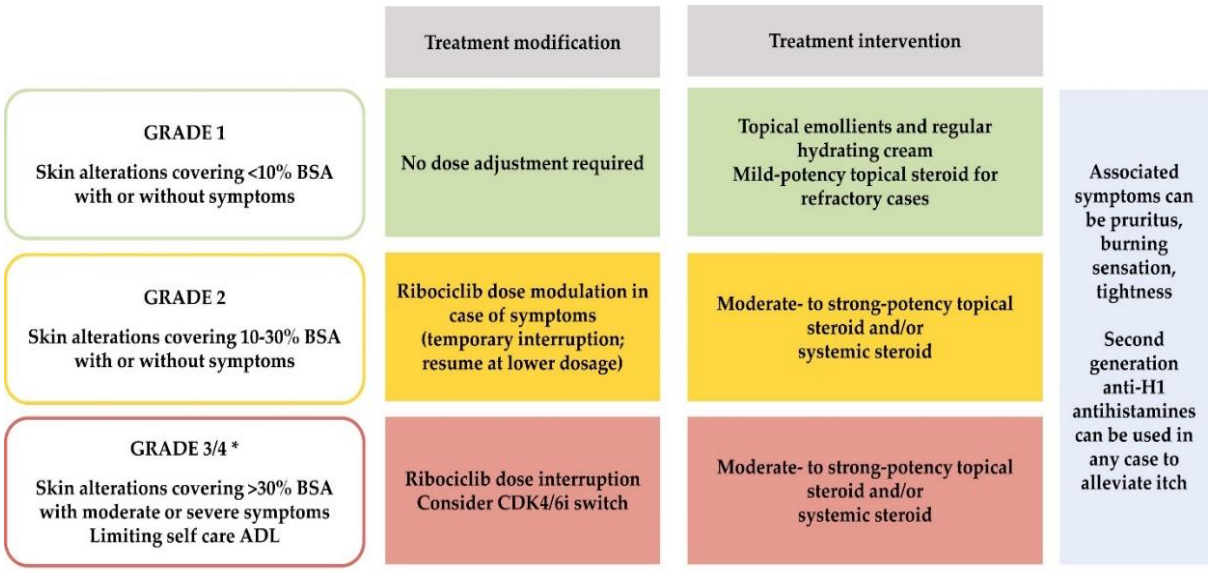


Figure 4. Management of ribociclib-related cutaneous adverse reactions. Abbreviations: BSA, body surface area; ADL, activities of daily living; CDK4/6i, cyclin dependent kinase 4/6 inhibitor; CTCAE, Common Terminology Criteria for Adverse Events.

No clinical factors predictive of cutaneous adverse events (CAEs) were identified in our analysis. However, discovering biomarkers via ongoing research remains an important goal for future investigations, as their validation could facilitate integration into everyday oncology practice. These biomarkers, combined with dermatology input, might help minimize or prevent skin toxicities.

Progression-free survival (PFS) analysis revealed a superior curve among patients who developed CAEs (P = .04). This aligns with prior reports indicating improved outcomes in patients exhibiting CAEs during therapy with anti-epidermal growth factor receptor agents across various malignancies, such as non–small cell lung cancer and colorectal cancer (CRC). For example, in individuals with lung cancer receiving erlotinib monotherapy or cetuximab combined with chemotherapy, early onset of CAEs correlated with substantially enhanced PFS and overall survival (OS). [29, 30] Comparable links between CAEs and treatment benefits have been observed with cetuximab and panitumumab in CRC studies. [27] Nevertheless, the practical implications of this correlation between CAEs and therapeutic efficacy require verification in larger cohorts.

Moreover, the mechanisms driving cutaneous toxicities merit additional exploration. Research in a rat model suggests that inhibition of adenosine 5′-triphosphate (ATP) could contribute to skin injury, given ribociclib's competitive blockade of ATP-binding sites on CDK4/6. The investigation proposed that ATP supplementation might aid in treating such damage, though this finding awaits confirmation in human subjects. [31]

The findings of this study must be viewed considering two primary limitations. Firstly, its single-center design

may limit generalizability due to the modest cohort size. Secondly, our data showed predominantly severe skin events (8 patients with grade 3, 4 with grade 2, and 1 with grade 1), differing from results in registration trials. This discrepancy likely stems from undercapture of mild (grade 1) CAEs in the retrospective review, as such events are often managed easily and resolve quickly, leading patients to omit reporting them during oncology appointments.

Conclusion

This work highlights that multidisciplinary coordination in treating advanced breast cancer (ABC) is vital for timely control of therapy-related toxicities. A collaborative strategy incorporating ribociclib dose adjustments and targeted skin interventions avoided permanent drug withdrawal in most cases (69.2%). Adopting this model in standard practice could improve compliance and maximize outcomes for these patients. Indeed, sustaining CDK4/6 inhibitor therapy while preserving quality of life poses a key ongoing challenge in managing HR+/HER2− ABC.

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Conflict of Interest: Armando Santoro reported advisory boards for Bristol-Myers-Squibb (BMS), Servier, Gilead, Pfizer, Eisai, Bayer, Merck Sharp and Dohme (MSD); consultancy for Arqule, Sanofi, Incyte; speaker's bureau for Takeda, BMS, Roche, Abb-Vie, Amgen, Celgene, Servier, Gilead, AstraZeneca, Pfizer, Arqule, Lilly, Sandoz, Eisai, Novartis, Bayer, MSD (all outside the submitted work). Rita De Sanctis reported honoraria for advisory board consultancy from Novartis, Istituto Clinico Gentili, Amgen, EISAI, Lilly, Gilead, and Ipsen (all outside the present work). The other authors indicated no financial relationships.

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