EJCRIM
European Journal
of Case Reports
in Internal Medicine

# DELAYED-ONSET VITILIGO IN METASTATIC HR+/HER2– BREAST CANCER DURING LONG-TERM RIBOCICLIB THERAPY

Elias Tayar[1], Dhatri Kodali[1,2]

[1] Department of Internal Medicine, HCA Healthcare Clear Lake, Houston, USA
[2] Texas Oncology, Webster, USA

**Corresponding author's e-mail:** Elias.tayar@hcahealthcare.com

**Received:** 27/11/2025
**Accepted:** 03/12/2025
**Published:** 23/12/2025

**Conflicts of Interests:** The Authors declare that there are no competing interests.
**Patient Consent:** Signed informed consent for the publication of this case was obtained from the patient.
**Acknowledgments:** This research was supported (in whole or in part) by HCA Healthcare and/or an HCA Healthcare affiliated entity. The views expressed in this publication represent those of the author(s) and do not necessarily represent the official views of HCA Healthcare or any of its affiliated entities.
**This article is licensed under a Commons Attribution Non-Commercial 4.0 License**

**How to cite this article:** Tayar E, Kodali D. Delayed-onset vitiligo in metastatic HR+/HER2– breast cancer during long-term ribociclib therapy. *EJCRIM* 2025;**12**: doi:10.12890/2025_006043

## ABSTRACT

Vitiligo is a rare cutaneous adverse event associated with cyclin-dependent kinase 4/6 (CDK4/6) inhibitors. We report a 56-year-old woman with de novo metastatic $HR^+/HER2^-$ breast cancer who developed vitiligo several years into long-term ribociclib therapy. She was initially treated with palbociclib plus letrozole and later transitioned to a reduced dose of ribociclib due to cytopenias and coverage limitations. After 3 years on ribociclib, she developed asymptomatic hypopigmented patches on her hands and face. Dermatologic evaluation confirmed vitiligo. Treatment was conservative with topical corticosteroids, and ribociclib was continued without interruption. Her metastatic disease remained stable with durable oncologic control. This case highlights delayed-onset vitiligo as an uncommon immune-mediated toxicity during prolonged CDK4/6 inhibitor therapy and demonstrates that such lesions do not necessitate discontinuing effective cancer treatment.

## KEYWORDS

Breast cancer, cyclin-dependent kinase 4/6 inhibitors, ribociclib, vitiligo

## LEARNING POINTS

- This case highlights that cutaneous autoimmune-like toxicities, while concerning in appearance, do not necessarily warrant discontinuation of an effective anticancer drug if they are mild.
- Oncologists and dermatologists should be aware of CDK4/6 inhibitor-associated vitiligo, even late in the treatment timeline, and approach it with a collaborative management strategy.
- Moving forward, further research into the immunological or apoptotic mechanisms of this toxicity may shed light on why it occurs and how best to treat it.

EFIM
European Federation of Internal Medicine

Publisher
smc media srl

## INTRODUCTION

Cyclin-dependent kinase 4/6 inhibitors such as ribociclib have significantly improved progression-free and overall survival in patients with advanced $HR^+/HER2^-$ breast cancer[1]. Ribociclib is an orally administered selective CDK4/6 inhibitor that, in combination with endocrine therapy, has become a standard of care for hormone receptor-positive, HER2-negative ($HR^+/HER2^-$) advanced breast cancer. By blocking CDK4/6-mediated phosphorylation of retinoblastoma protein, Ribociclib arrests the cell cycle in G1 and thereby inhibits cancer cell proliferation[2]. These agents are generally well tolerated[2]. Common toxicities include myelosuppression, fatigue, and mild dermatologic effects (e.g. alopecia, rash, pruritus). However, rare cutaneous adverse events such as vitiligo-like depigmentation have been reported in association with CDK4/6 inhibitor therapy[3]. Drug-induced vitiligo or vitiligo-like leukoderma is a known phenomenon with some cancer therapies, particularly immune checkpoint inhibitors in melanoma and certain targeted therapies[3]. Nonetheless, vitiligo occurring during CDK4/6 inhibitor treatment is exceedingly uncommon. We describe a case of metastatic breast cancer in which vitiligo developed after prolonged ribociclib therapy, and we discuss this in the context of the emerging literature on this rare adverse effect.

## CASE DESCRIPTION

A 56-year-old woman was diagnosed in 2016 with de novo metastatic breast cancer, presenting with an advanced breast mass and diffuse bone metastases. The tumour was oestrogen receptor (ER)–positive, progesterone receptor (PR)–positive, and HER2-negative.

Following diagnosis, she was initiated on first-line therapy with palbociclib in combination with letrozole. She remained on this regimen for several years; however, palbociclib was ultimately discontinued due to recurrent cytopenias. In 2020, she was transitioned to ribociclib at a reduced dose of 400 mg daily (administered 3 weeks on and 1 week off) along with continued letrozole.

The patient achieved durable disease control on ribociclib, maintaining stable metastatic disease for several years without radiologic progression. Approximately 3–4 years after starting ribociclib, she developed new, asymptomatic hypopigmented patches on the hands and face *(Fig. 1)*. Dermatologic evaluation, including Wood's lamp examination, confirmed sharply demarcated depigmented macules consistent with vitiligo. A punch biopsy from a depigmented area on the forearm showed loss of epidermal melanocytes with focal pigment incontinence, supporting the diagnosis of vitiligo. She had no prior history of vitiligo or other autoimmune disorders.

Given the mild and purely cosmetic nature of the depigmentation and her ongoing clinical benefit from therapy, ribociclib was continued without interruption. The vitiligo was managed conservatively with topical corticosteroids, leading to stabilization of the lesions. She remained on ribociclib and letrozole with persistent disease control and no further progression of her cutaneous findings.



*Figure 1. Photograph of the patient's hands showing vitiligo lesions during ribociclib therapy. There are depigmented, milk-white patches with well-defined borders over the dorsal hands and knuckles. The lesions are symmetrical and confined to sun-exposed areas of the hands and distal forearms. No erythema or scaling is present.*

## DISCUSSION

Vitiligo-like depigmentation (VLD) is a rare adverse effect of cancer therapy, recently described in patients receiving CDK4/6 inhibitors[4–8]. To date, only a limited number of cases have been reported in the literature, including several single-case reports and one retrospective series[4–8]. The onset of VLD during CDK4/6 inhibitor treatment has typically been within the first year of therapy. In a recent report evaluating cases of ribociclib-induced vitiligo-like lesions, the median time to onset was approximately 9–10 months[9]. In contrast, our patient developed vitiligo after about 3-4 years on ribociclib, which is a substantially delayed onset compared to most published cases. This suggests that vitiligo can develop even during long-term therapy, and clinicians should remain vigilant for cutaneous changes throughout the course of treatment.

The pathogenesis of therapy-induced vitiligo is not fully understood. CDK4/6 inhibitors induce cell-cycle arrest and may trigger melanocyte apoptosis, which could contribute to depigmentation[5]. An immune-mediated mechanism is also likely involved. Vitiligo occurring in cancer patients has been most extensively documented in those receiving immunotherapy for melanoma, where the appearance of vitiligo is often correlated with a favourable tumour response[10]. In our case, the patient's vitiligo-like lesions emerged at a time when her disease was well controlled on ribociclib, raising the question of whether the drug's influence on the immune environment might have contributed to both the cutaneous effect and tumour suppression. A recent study of 2 patients with ribociclib-induced vitiligo-like toxicity noted an "exceptional" therapeutic response in those cases, hinting at a possible association between depigmentation and improved oncologic outcomes[9]. While it is premature to draw conclusions, these observations

align with the paradigm seen in melanoma and suggest that ribociclib-induced vitiligo could potentially be a marker of immune activation against the tumour. Further research and accumulation of cases will be needed to determine any prognostic significance of this phenomenon in breast cancer. From a management perspective, drug-induced vitiligo poses a therapeutic challenge. In reported cases, various treatments such as topical corticosteroids, calcineurin inhibitors, and phototherapy have been tried, typically with limited success in restoring pigmentation[4–8]. The response of CDK4/6 inhibitor-induced vitiligo to therapy has been discouraging in almost all cases, and the aim should be to halt the progression of depigmentation rather than to achieve full re-pigmentation[4–8]. In many instances, depigmented patches persist despite treatment, and some areas may remain permanently white even after discontinuation of the offending drug[4]. Fortunately, in our patient the vitiligo-like reaction was primarily cosmetic and did not necessitate interrupting effective cancer therapy. None of the reported patients with CDK4/6 inhibitor-associated vitiligo, except one, had a prior history of vitiligo, indicating that this adverse effect arises *de novo* due to therapy[8]. Interdisciplinary management is recommended: dermatologic evaluation can help confirm the diagnosis and guide symptomatic treatment, while oncologists can make informed decisions about continuing therapy. Patient education is important to alleviate anxiety, as the sudden appearance of vitiligo can be distressing, though it is benign.

This case highlights the potential for immune-mediated cutaneous toxicity during prolonged CDK4/6 inhibitor therapy. Although vitiligo remains a rare adverse event, emerging literature suggests a possible association between CDK4/6 inhibition and immune activation, potentially leading to melanocyte destruction. The delayed onset of vitiligo after several years of ribociclib therapy, following prior exposure to palbociclib, raises the possibility of cumulative immune modulation or differential immunologic effects among CDK4/6 inhibitors. Importantly, the patient maintained excellent disease control on a reduced dose of ribociclib, indicating that lower doses may still confer durable efficacy in selected patients with hormone receptor–positive metastatic breast cancer; however, the development of vitiligo does not appear to be dose dependent.

## CONCLUSION

We have presented a rare case of delayed-onset vitiligo in a patient with metastatic $HR^+/HER2^-$ breast cancer during prolonged ribociclib therapy. Despite the unusual timing, the vitiligo exhibited a benign course and was effectively managed with topical agents alone. The patient's life-prolonging cancer therapy was continued uninterrupted, resulting in ongoing disease control. This case highlights that cutaneous autoimmune-like toxicities, while concerning in appearance, do not necessarily warrant discontinuation of an effective anticancer drug if they are mild. Oncologists and dermatologists should be aware of CDK4/6 inhibitor-associated vitiligo, even late in the treatment timeline, and approach it with a collaborative management strategy. Moving forward, further research into the immunological or apoptotic mechanisms of this toxicity may shed light on why it occurs and how best to treat it. Recognizing and treating such adverse events promptly can ensure patients derive maximum benefit from breakthrough therapies like CDK4/6 inhibitors without compromising safety or quality of life.

## REFERENCES


1. Hortobagyi GN, Stemmer SM, Burris HA, Yap YS, Sonke GS, Paluch-Shimon S, et al. Ribociclib as First-Line Therapy for HR-Positive, Advanced Breast Cancer. *N Engl J Med* 2016;**375**:1738-1748. doi: 10.1056/NEJMoa1609709. Erratum in: *N Engl J Med* 2018;**379**:2582. doi: 10.1056/NEJMx180043
2. O'Leary B, Finn RS, Turner NC. Treating cancer with selective CDK4/6 inhibitors. *Nat Rev Clin Oncol* 2016;**13**:417-430. doi: 10.1038/nrclinonc.2016.26
3. Raschi E, Fusaroli M, La Placa M, Ardizzoni A, Zamagni C, Poluzzi E, et al. Skin Toxicities with Cyclin-Dependent Kinase 4/6 Inhibitors in Breast Cancer: Signals from Disproportionality Analysis of the FDA Adverse Event Reporting System. *Am J Clin Dermatol* 2022;**23**:247-255. doi: 10.1007/s40257-021-00645-0
4. Chan OB, Su JC, Yazdabadi A, Chan A. Drug induced vitiligo-like depigmentation from a CDK 4/6 inhibitor. *Asia Pac J Clin Oncol* 2022;**18**:e154-e156. doi: 10.1111/ajco.13585
5. Silvestre Torner N, Aguilar Martínez A, Echarri González MJ, Tabbara Carrascosa S, Román Sainz J, Gruber Velasco F. Ribociclib-induced Vitiligo: a Case Report. *Dermatol Pract Concept* 2022;**12**:e2022045. doi: 10.5826/dpc.1202a45
6. Anjaneyan G, Keechilat P, Duraisamy P, Eapen M. Ribociclib-induced extensive vitiligo-like lesions: possible pathomechanisms with clinical, dermoscopic and histological correlation. *BMJ Case Rep* 2022;**15**:e248782. doi: 10.1136/bcr-2022-248782
7. Sharaf B, AlMasri R, Abdel-Razeq N, Salama O, Hamad I, Abunasser M, et al. Vitiligo-Like Lesions in a Patient with Metastatic Breast Cancer Treated with Cyclin-Dependent Kinase (CDK) 4/6 Inhibitor: A Case Report and Literature Review. *Clin Cosmet Investig Dermatol* 2022;**15**:5-10. doi: 10.2147/CCID.S344867
8. Sollena P, Nikolaou V, Soupos N, Kotteas E, Voudouri D, Stratigos AJ, et al. Vitiligo-like lesions in patients with advanced breast cancer treated with cycline-dependent kinases 4 and 6 inhibitors. *Breast Cancer Res Treat* 2021;**185**:247-253. doi: 10.1007/s10549-020-05914-w
9. Pasqualoni M, Orlandi A, Palazzo A, Garufi G, Cannizzaro MC, Pontolillo L, et al. Case report: Vitiligo-like toxicity due to ribociclib during first-line treatment of metastatic breast cancer: two cases of premature interruption of therapy and exceptional response. *Front Oncol* 2023;**13**:1067264. doi: 10.3389/fonc.2023.1067264
10. Nakamura Y, Tanaka R, Asami Y, Teramoto Y, Imamura T, Sato S, et al. Correlation between vitiligo occurrence and clinical benefit in advanced melanoma patients treated with nivolumab: A multi-institutional retrospective study. *J Dermatol* 2017;**44**:117-122. doi: 10.1111/1346-8138.13520