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Case Report

CDK4/6 Inhibition and Stereotactic Radiotherapy in Oligometastatic HR+/HER2− Breast Cancer: Evidence of Immunogenic Modulation and Pseudoprogression

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Abstract

Background: A combination of cyclin-dependent kinase 4/6 inhibitors (CDKi) and radiotherapy (RT) may enhance antitumoral immunity, yet clinical evidence of this interaction in HR+/HER2− metastatic breast cancer (MBC) remains limited. This study evaluates the impact of combined CDKi and stereotactic body radiotherapy (SBRT) on immune biomarkers and treatment response. Methods: We report a case of a 51-year-old woman with oligometastatic HR+/HER2− MBC involving the sacrum. Clinical management included letrozole plus palbociclib and SBRT (30 Gy in 3 fractions). Serial Neutrophil-to-lymphocyte ratio (NLR) measurements, MRI, and PET-CT scans were used to monitor systemic immune modulation and treatment efficacy over a five-year period. Results: Baseline NLR was 1.068. Following four weeks of CDKi, NLR decreased by 44.7% (0.591). Post-SBRT, a further 17.8% reduction was observed (nadir 0.486). Five months post-RT, MRI showed a volumetric increase in sacral lesions despite clinical improvement. Subsequent PET-CT demonstrated a complete metabolic response, confirming the MRI findings as pseudoprogression. As of January 2026, the patient remains in sustained complete metabolic remission. Conclusion: The integration of CDKi and SBRT might induce an immune-mediated antitumoral response, evidenced by dynamic NLR reductions and radiologic pseudoprogression. Multimodal imaging is essential to differentiate immune-mediated swelling from true progression in this setting.

Keywords: breast cancer; CDK4/6; CDK; cyclin; immune response; immunomodulation; NLR; radiation; radiotherapy; SBRT

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1. Introduction

Radiotherapy plays a central role in several aspects of the treatment of metastatic breast cancer (MBC), as more than half of metastatic patients present bone involvement [1],

for which palliative radiotherapy might be beneficial. Remarkably, in case of low burden of disease, stereotactic body radiotherapy (SBRT) might also be beneficial in terms of survival [2]. Combining radiotherapy with systemic treatment acts as a double-edged sword: although concomitant administration may improve antitumor efficacy, it could also increase the risk of toxicity in healthy tissues [3].

Cyclin-dependent kinase 4/6 inhibitors (CDKi) are a cornerstone in the treatment of MBC [4]. Pre-clinical models suggest that CDKi act as radiosensitizers by impairing homologous recombination-mediated DNA repair [5,6]. Retrospective clinical data support this synergy, demonstrating robust local control in metastatic breast cancer, maintaining a generally manageable safety profile [7–9].

Beyond direct cytotoxicity, both modalities promote an immunostimulatory environment. CDKi enhance antigen presentation and interferon production while depleting regulatory T-cells [10,11], a process that might be complemented by RT immunostimulant effects. Indeed, tumor irradiation induces apoptotic and immunogenic cell death, promoting neoplastic antigen release and neoantigen formation, enhancing antigen expression, and inducing the release of pro-inflammatory cytokines and chemokines, ultimately increasing T-cell infiltration [12,13].

Neutrophil-to-lymphocyte ratio (NLR) has emerged as a significant prognostic marker for patients undergoing CDKi [14] but has not yet been evaluated in the setting of combined RT and CDKi.

In this paper we report a case of long-term complete metabolic remission in oligometastatic hormone receptor–positive (HR+), a HER2-negative breast cancer treated with CDK4/6 inhibition and SBRT, highlighting the impact of CDKi and SBRT on NLR and their potential immunostimulatory effects.

2. Case Report

A premenopausal woman aged 51 presented in August 2013 with a self-detected right breast mass. Comorbidities included obesity and arterial hypertension. Mammography and ultrasound imaging revealed a 20 mm spiculated lesion and ipsilateral axillary lymphadenopathy. Core biopsy demonstrated grade 2 non-special-type invasive carcinoma with estrogen receptor (ER) expression of 90%, Ki-67 expression of 20%, and no HER2 expression (score 0). Axillary cytologic analysis confirmed nodal metastases. Staging PET-CT identified additional uptake at L3 vertebra, consistent with de novo stage IV disease.

The patient received neoadjuvant epirubicin/cyclophosphamide chemotherapy with LHRH analog, followed by radiotherapy to L3 vertebra (39 Gy in 13 fractions). Post-treatment PET-CT demonstrated complete metabolic response in all disease sites. In March 2014, she underwent quadrantectomy and axillary dissection. Histology revealed a partial response, confirming a grade 2 NST invasive carcinoma staged ypT2 ypN1a (2/16 positive lymph nodes) with ER expression 90%, PgR expression 80%, Ki-67 expression 24%, and HER2-negative. Adjuvant endocrine therapy with tamoxifen plus LHRH analog was started after surgery and radiotherapy at a dose of 44 Gy in 15 fractions to the right breast, and a 10 Gy sequential boost to the involved quadrant was completed in September 2014.

The patient continued endocrine therapy and remained disease-free until October 2020, when a PET-CT was performed due to refractory sacral pain, revealing hypermetabolic activity in the right side of the sacrum. In December 2020, she underwent a contrast-enhanced pelvic MRI, which detected a lesion on the sacral side of the right sacroiliac joint and a faint signal alteration involving the left sacral wing. CT-guided biopsy of the right sacral lesion, performed in February 2021, demonstrated metastatic breast adenocarcinoma (ER expression 80%, PgR expression 70%, HER2-negative). The patient underwent a repeat

pelvic MRI in March 2021 (Figure 1). Following a multidisciplinary review of the imaging, both sacral lesions were deemed consistent with metastatic disease.

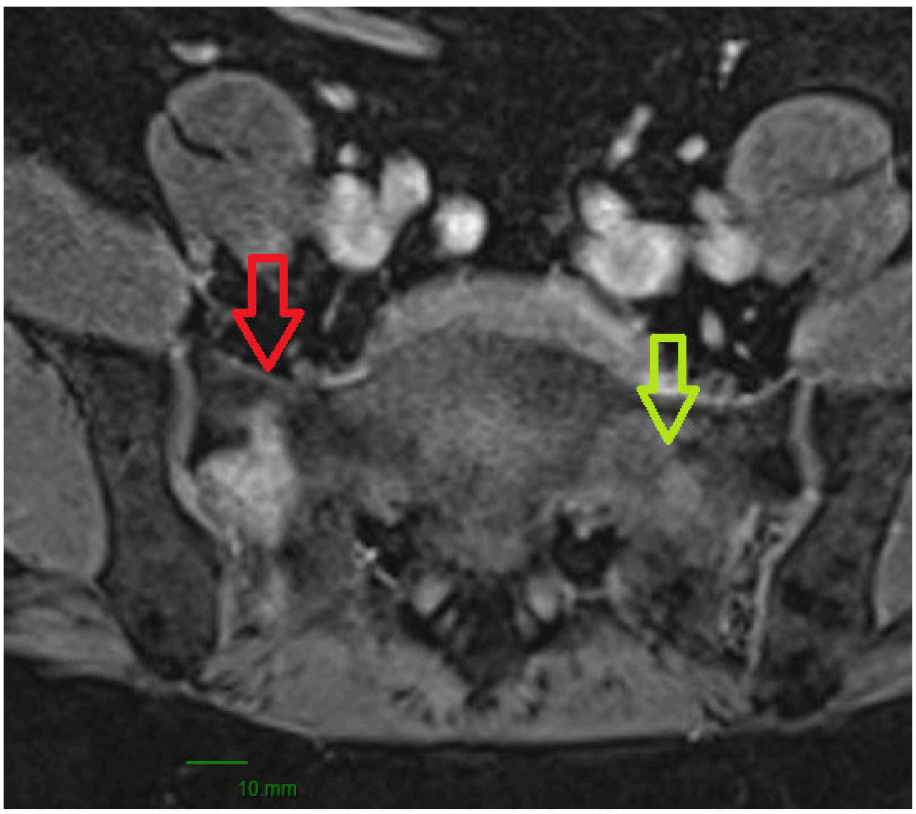
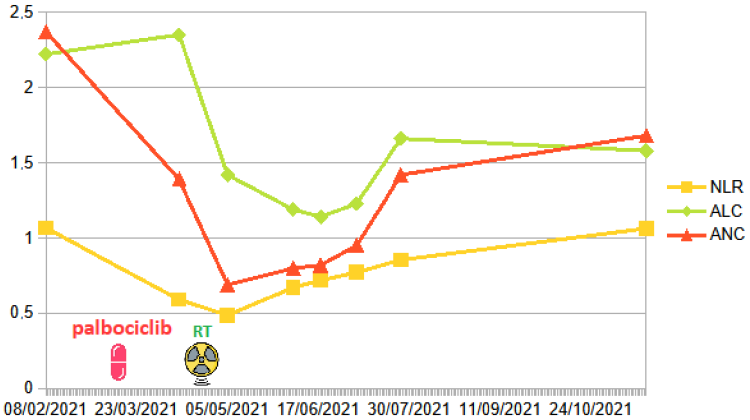


Figure 1. T1 vibe sequence of the baseline pelvic contrast-enhanced MRI performed in March 2021, demonstrating a lesion in the right ala of the sacrum (red arrow) and a faint signal alteration of the root of the left sacral wing (green arrow).

On 12 March 2021, the patient started a new line of treatment with letrozole plus palbociclib. Baseline neutrophil-to-lymphocyte ratio (NLR) before start of treatment was 1.068.

The NLR trend during treatment is presented in Figure 2.



	08/02/2021	12/04/2021	05/05/2021	05/06/2021	18/06/2021	05/07/2021	26/07/2021	19/11/2021
NLR	1.068	0.591	0.486	0.672	0.719	0.772	0.855	1.063
ALC	2.22	2.35	1.42	1.19	1.14	1.23	1.66	1.58
ANC	2.37	1.39	0.69	0.8	0.82	0.95	1.42	1.68

Figure 2. Trend of neutrophil-to-lymphocyte ratio (NLR), absolute lymphocyte count (ALC, K/μL), and absolute neutrophil count (ANC, K/μL). Administration of palbociclib is represented as a pill sign and of radiotherapy (RT) as radiation sign. Date is reported in "Day Month Year" format.

After four weeks of CDK4/6 inhibition, NLR declined to 0.591, representing a 44.7% reduction from baseline.

Following multidisciplinary discussion, SBRT was administered to the two sacral lesions involving S1 (30 Gy in 3 fractions, 19–22 April 2021). Two weeks after SBRT, NLR further decreased to 0.486, corresponding to a 17.8% reduction compared to post-CDKi start and a 54.5% reduction compared to baseline.

A repeated MRI performed in September 2021 (Figure 3) demonstrated a complete response of the left sacral lesion and a slight dimensional increase of the lesion in the right sacral ala from 15 × 12 mm to 15 × 15 mm.

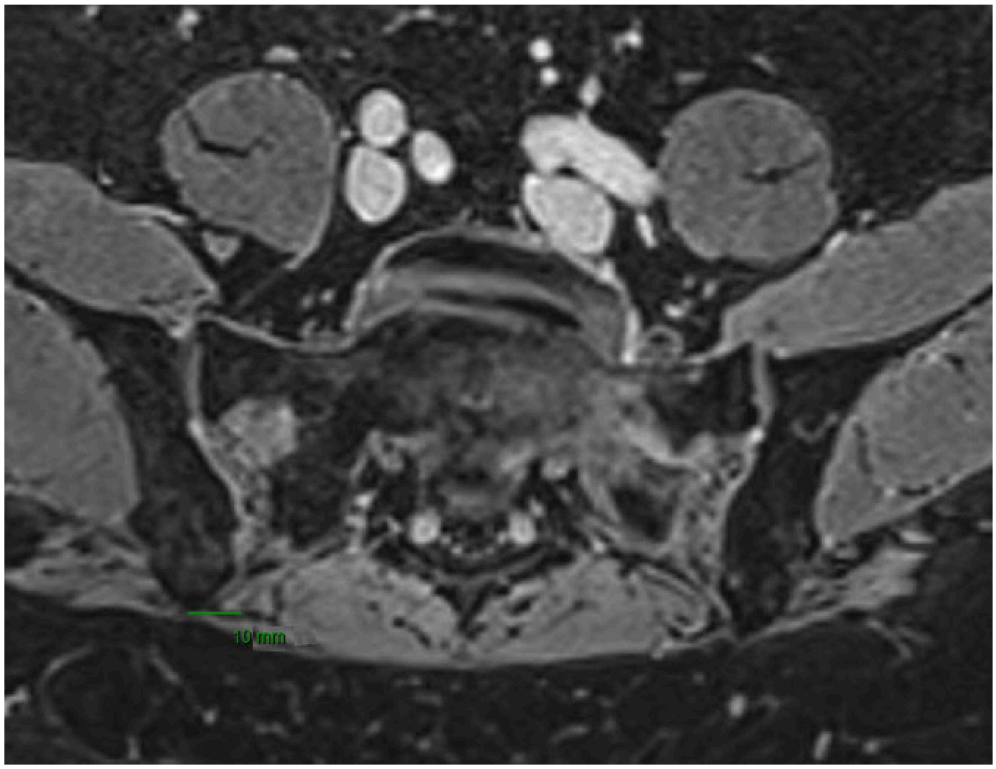


Figure 3. MRI performed in September 2021. The lesion remained T1 hypointense and T2FS hyperintense, without diffusion restriction. The findings were consistent with treatment-induced pseudoprogression, but actual progression could not be ruled out.

A PET-CT performed in November 2021 demonstrated complete resolution of FDG uptake, with no evidence of metabolically active diseases. The discordance between MRI enlargement and complete metabolic response was interpreted as pseudoprogression.

During the months following SBRT, NLR gradually increased, reaching 1.063 approximately seven months post-radiotherapy, nearly identical to pre-treatment baseline.

Serial PET-CT scans performed every six months, including the latest in January 2026, have confirmed sustained complete metabolic response. The patient remains on palbociclib and letrozole and maintains no evidence of disease (NED) almost five years after RT.

3. Discussion

This case of durable remission in oligometastatic breast cancer highlights the potential synergy between radiotherapy and CDKi in enhancing the antitumoral immune response.

Beyond their classic mechanism of inducing cell cycle arrest in the G1 phase by preventing the phosphorylation of the retinoblastoma (Rb) protein, pre-clinical data demonstrate that CDKi possess significant immunostimulatory activity. This is mediated through multiple mechanisms, including upregulation of MHC class I expression, suppression of

regulatory T-cell population, enhanced cytotoxic T-cell activation and interferon pathway stimulation [10,11]. In previous studies, CDKi significantly reduced neutrophils, Tregs, and neutrophil-to-lymphocyte ratio [15].

In this case, the early reduction in the NLR from 1.068 to 0.591 one month after CDKi initiation suggests systemic immune modulation. NLR is a validated prognostic biomarker in breast cancer, as lower values typically correlate with improved survival and treatment response. Specifically, in the context of CDK4/6 inhibition, a decreasing NLR has been associated with better clinical outcomes and a shift toward a more favorable, "inflamed" tumor microenvironment [16,17].

Radiotherapy may also foster an antitumoral immune response through multiple mechanisms [12,13]. Fractionated schemes with a high dose per fraction, such as those used for SBRT, hold increased immunostimulant potential compared to other schedules, as they can induce immunogenic cell death (ICD). This process releases damage-associated molecular patterns (DAMPs), activates the cGAS-STING pathway, and promotes dendritic cell priming [18,19].

In this case, SBRT further reduced the NLR to 0.486 (an additional reduction of 17.8%). This pattern supports a positive immunogenic interaction where CDKi "primes" the immune system and SBRT provides the "in situ vaccine" effect through ablative cell death.

Therefore, the combination of the two modalities could potentially improve the anti-neoplastic response.

As NLR represents the ratio between neutrophil and lymphocyte counts in peripheral blood, its reduction is not necessarily indicative of immune activation, but may also result from treatment-induced neutropenia. Nonetheless, in previous series, breast cancer patients treated with CDKi who developed grade 4 neutropenia had significantly higher baseline NLR, suggesting that pre-treatment neutrophil count does not confer protection against neutropenia and thus supporting the role of NLR as a marker of systemic inflammation. In this case, as shown in Figure 2, lymphocyte count also decreased, albeit less markedly than neutrophil count. This finding, in conjunction with the observed pseudoprogression and subsequent durable disease control, suggests a potential immunomodulatory effect. However, the contribution of neutropenia cannot be completely ruled out.

Five months after SBRT, MRI showed an approximately 25% increase in lesion volumetric product. The presentation was characterized by an absence of diffusion restriction, which is more suggestive of treatment-induced modifications. Subsequent PET-CT demonstrated a complete metabolic response, corroborating previous MRI findings as representative of pseudoprogression. This also highlights the importance of multimodality imaging in discriminating pseudoprogression from actual disease progression [20].

Pseudoprogression is a clinical phenomenon where a tumor appears to increase in size or new lesions appear on imaging, followed by a subsequent decrease in tumor burden. This is not representative of treatment failure but rather reflects the recruitment of immune cells (such as T-lymphocytes and macrophages), localized edema, and stromal remodeling within the tumor site [21].

While pseudoprogression is a well-described hallmark of immune checkpoint inhibitor therapy, it is less frequently reported in HR+/HER2− breast cancer treated with endocrine therapy and CDKi [22,23].

A key limitation that remains is the uncertainty of how pseudoprogression should guide clinical practice, though it must be considered when combining SBRT and CDKi to ensure accurate response assessment, as well as to prevent premature treatment discontinuation.

While SBRT can induce long-term control as a single modality, the initial reduction in NLR after palbociclib and the further decrease after RT suggest that both treatments exerted an immunomodulatory effect that might have contributed to the durable remission.

As NLR is a ratio between neutrophil and lymphocyte counts in peripheral blood, its reduction is not necessarily due to immune activation but can also be determined by treatment-induced neutropenia. Nonetheless, in previous series [24], breast cancer patients treated with CDKi who developed grade 4 neutropenia had significantly higher baseline NLR, suggesting that pre-treatment neutrophil count has no protective effect against neutropenia and confirming NLR as a marker of an inflammatory state.

In this case, as shown in Figure 2, lymphocyte count was also reduced, albeit less markedly than neutrophil count. This, in conjunction with the pseudoprogression and subsequent lasting control, suggests an immunomodulatory effect. Nonetheless, the impact of neutropenia could not be completely ruled out.

Notably, the NLR nadir preceded these imaging changes, and normalization occurred months later as immune equilibrium was restored. Despite the NLR returning to baseline, durable remission persisted, suggesting that early dynamic shifts reflecting the activation phase of the immune system may be more prognostically informative than steady-state values.

Radiotherapy demonstrated high efficacy in pre-treated patients as well [25], and this case also confirms the possibility of complete response and long lasting disease control of SBRT in the metastatic setting.

While the predictive value of NLR in guiding clinical decision-making is not yet established, its role as a biomarker is under active investigation. An ongoing multicenter trial is evaluating NLR trends in patients with metastatic breast cancer treated with CDKi and radiotherapy, aiming to clarify the impact of systemic inflammatory markers on treatment outcomes.

4. Conclusions

This case supports the hypothesis that selected oligometastatic patients may achieve prolonged control when local ablative therapy is combined with immune-modulating systemic agents. The integration of CDK4/6 inhibition and metastasis-directed SBRT led to a reduction in NLR, suggesting an immunomodulating activity, coherently with previous pre-clinical and preliminary clinical experiences. This was confirmed by radiologic pseudoprogression of the irradiated sites, followed by sustained metabolic complete response, underscoring the importance of multimodal imaging and the awareness of immune-related phenomena in breast cancer.

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Conflicts of Interest: The authors declare no conflicts of interest.

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