# #2307: Safety of CDK 4/6 inhibitors Combined with Radiotherapy in HR+/HER2- Metastatic Breast Cancer: A Meta-Analysis

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## Abstract

**Background:** Cyclin-dependent kinase 4/6 inhibitors (CDK4/6i) are crucial in the treatment of hormone-positive, HER2-negative (HR+/HER2-) metastatic breast cancer (MBC), with radiotherapy (RT) remaining an important modality for symptom control. With increasing clinical use of CDK4/6i in combination with RT, questions have emerged regarding its safety. Although formal prospective guidelines are lacking, increasing retrospective data and expert consensus has begun to inform practice, particularly around timing and toxicity management. This meta-analysis evaluates its safety and feasibility.

**Methods:** We systematically searched PubMed, Embase, Scopus and Cochrane CENTRAL (as of June 2025) to identify studies evaluating the safety of CDK4/6i + RT in HR+/HER2- MBC patients (pts). Eligible studies included those reporting safety outcomes such as grade ≥3 adverse events (AEs), dose reduction, or treatment discontinuations. Data were pooled using a random-effects model. We calculated pooled proportions (PP) and odds ratios (ORs) with 95% CIs. Statistical significance was set at p <0.05. Heterogeneity was assessed using the $I^2$ statistic (low: 0–25%, moderate: 26–50%, high: >50%). The protocol was registered with PROSPERO (CRD420251080439).

**Results:** Nineteen studies comprising 843 HR+/HER2- MBC pts treated with CDK4/6i and RT were included. The median follow-up was 18 months (IQR: 14.7–19.0), and median age was 58.8 years (IQR: 57.15–60.13). The PP of all hematological toxicity was 27.8% (95% CI: 15.6-44.5, $I^2$=85.7%, p< 0.0001), with neutropenia in 24.3% of pts (95% CI: 14.9-37.0, $I^2$=79.8%, p< 0.0001). Non-hematological toxicities were infrequent, with a PP of 5.4% (95% CI: 3.8-7.7, $I^2$=0.0%, p=0.986). Severe AEs (grade ≥3) occurred in 29.9% (95% CI: 19.8-42.5; $I^2$=79.3%; p<0.0001). Dose reduction due to toxicity occurred in 26.7% of pts (95% CI: 17.8-38.1, $I^2$=77.7%, p< 0.0001), while treatment discontinuation occurred in 6.3% (95% CI: 4.4-8.9, $I^2$=0.0%, p=0.69). When compared to CDK4/6i therapy alone, the addition of RT was not associated with significantly increased odds of neutropenia (1.13; 95% CI: 0.35–3.68; $I^2$=64.8%; p=0.85), dose reduction (1.06; 95% CI: 0.81–1.40; $I^2$=0%; p=0.58), or treatment discontinuation (0.75; 95% CI: 0.07–8.26; $I^2$=19.5%; p=0.66).

**Conclusion:** CDK4/6i + RT appear to be safe and generally well tolerated in HR+/HER2- MBC, with no significant increase in severe toxicities, dose reductions, or treatment discontinuation vs CDK4/6i alone, supporting feasibility in clinical practice. However, the evidence is limited to retrospective studies with heterogeneous designs, small cohorts, and short follow up, which may underestimate late or site-specific toxicities. Prospective studies with standardized toxicity reporting and stratification by radiation site, dose, and sequencing are needed to better assess long-term safety.

## Introduction

- Cyclin-dependent kinase 4/6 inhibitors (CDK 4/6i) are a standard systemic therapy for hormone–positive, HER2-negative (HR+/HER2-) metastatic breast cancer (MBC), with radiotherapy (RT) being important for symptom control.
- As the combined use of CDK 4/6i and RT increases in routine practice, questions have emerged regarding whether this approach leads to higher toxicity. Expert consensus has begun to inform practice, and available evidence is mostly retrospective.
- This study evaluated the safety of combining CDK 4/6i with RT in patients with HR+/HER2- MBC.

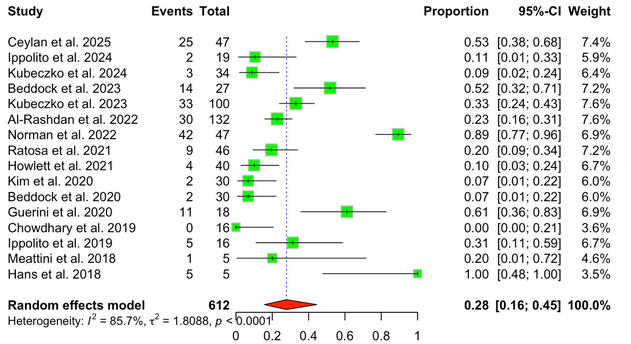
## Methods and Materials

- **Data Source:**
  - A systematic search of **PubMed, Embase, Scopus, and Cochrane CENTRAL** was conducted (June 2025).
- **Eligibility Criteria:**
  - Studies including adult patients with **HR+/HER2- MBC treated with CDK 4/6i combined with RT**.
  - Studies reporting **safety outcomes**, including severe (grade ≥3) adverse events, dose reductions, or treatment discontinuations.
  - Randomized trials, prospective or retrospective cohorts, or case series with ≥5 patients; Case reports, abstracts only, reviews, and non-English studies were excluded.
- **Statistical Analysis:**
  - Pooled proportions and odds ratios were calculated using a random-effects model**.**
  - Heterogeneity was assessed using the $I^2$ statistic (low: 0–25%, moderate: 26–50%, high: >50%).
  - Statistical significance was defined as a p-value < 0.05.
  - Analysis followed a pre-registered protocol (PROSPERO ID: CRD420251080439).

**Table 1. Adverse Events Associated with CDK4/6i+RT in HR+/HER2– MBC**

| Analysis | Effect Size (95% CI) | P-Value | $I^2$ (%) | Heterogeneity |
|---|---|---|---|---|
| **Proportion** | | | | |
| **All hematological AE** | 27.80% (15.6%–44.5%) | < 0.0001 | 85.70 | High |
| **Neutropenia** | 24.30% (14.9%–37.0%) | < 0.0001 | 79.80 | High |
| **Non-hematological AE** | 5.40% (3.8%–7.7%) | 0.9861 | 0.00 | Low |
| **All severe AE** | 29.90% (19.8%–42.5%) | < 0.0001 | 79.30 | High |
| **Dose reduction** | 26.70% (17.8%–38.1%) | < 0.0001 | 77.70 | High |
| **Dose discontinuation** | 6.30% (4.4%–8.9%) | 0.6927 | 0.00 | Low |
| **Odds Ratio** | | | | |
| **Neutropenia** | 1.131 (0.3479–3.6775) | 0.6972 | 64.80 | High |
| **Dose reduction** | 1.0628 (0.8057–1.4019) | 0.5746 | 0.00 | Low |
| **Dose discontinuation** | 0.7481 (0.0677–8.2623) | 0.6549 | 19.50 | Low |

**Figure 1. Proportion of Overall Hematological Toxicity (CDK4/6i + RT)**



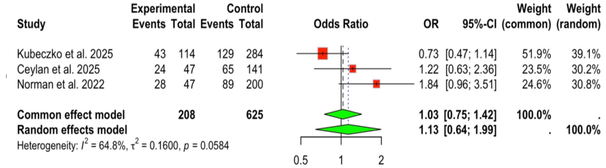

## Future Directions

- Prospective studies with **standardized toxicity reporting** and **stratification by radiation site, dose, and sequencing** are needed to better define long-term safety.
- **Stratify analyses by radiation site, dose, and treatment sequencing** to clarify factors influencing safety.
- Explore **optimal timing and integration of radiotherapy** with cyclin-dependent kinase 4/6 inhibitors to maximize safety and clinical benefit.

## Results

- **Study Overview:**
  - **19** studies, including **843 patients**, were analyzed.
  - Median age: **58.8 years.**
  - Median follow-up: **18 months**.
- **Toxicity Profile:**
  - Severe toxicities **(grade ≥3): 29.9%** (95% CI: 19.8-42.5; $I^2$=79.3%).
  - Overall **hematologic** toxicity: **27.8%** (95% CI: 15.6-44.5; $I^2$=85.7%).
  - **Neutropenia** (the most common event): **24.3%** (95% CI: 14.9-37.0; $I^2$=79.8%).
  - **Non-hematologic** toxicities: **5.4%** (95% CI: 3.8-7.7; $I^2$=0%).
- **Dose modifications:**
  - Dose reductions: **26.7%** (95% CI: 17.8-38.1; $I^2$=77.7%)
  - Treatment discontinuation: **6.3%** (95% CI: 4.4-8.9; $I^2$=0%).
- **Comparative Outcomes:**
  - **The addition of RT** did not increase toxicity risk compared to CDK 4/6i therapy alone.
  - **Neutropenia:** OR 1.13 (95% CI: 0.35–3.68; $I^2$ = 64.8%)
  - **Dose reduction:** OR 1.06 (95% CI: 0.81–1.40; $I^2$ = 0% )
  - **Treatment Discontinuation:** OR 0.75 (95% CI: 0.07–8.26; $I^2$ = 19.5%).

**Figure 2. Neutropenia Odds Ratio (RT vs No RT)**




## Conclusions

- **Combined use of CDK 4/6i and RT was safe** and generally **well tolerated**, with **no significant increase** in severe **toxicities**, dose reductions, or treatment discontinuation compared with CDK 4/6 inhibitor therapy alone.
- Existing evidence is based primarily on retrospective studies with heterogeneous designs and small cohorts, which may underestimate late or site-specific toxicities.

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## References

1. Finn RS, Martin M, Rugo HS, et al. Palbociclib and letrozole in advanced breast cancer. N Engl J Med. 2016;375(20):1925-1936. doi:10.1056/NEJMoa1607303.
2. Franco R, Shah C, Smith BD, et al. Safety of CDK4/6 inhibitors combined with radiotherapy in patients with metastatic breast cancer: a review of the literature. Curr Oncol. 2023;30(6):415.

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