CDK4/6 Inhibitor Use and Risk of Therapy-Related Myeloid Neoplasms Following Chemotherapy for HR+/HER2- Breast Cancer: A Landmark Competing Risks Analysis

Jacqueline T Nguyen DO,[1] Arthur S Hong MD MPH,[2,3,4] Suraj R Rama MD,[3,4] Oscar Felipe Borja Montes MD,[1] Danh Q Nguyen MD MS[3,4]

[1] Division of Hematology & Oncology, University of Florida, Gainesville, FL
[2] Harold C Simmons Comprehensive Cancer Center, UT Southwestern Medical Center, Dallas, TX
[3] Parkland Health, Dallas, TX
[4] Department of Internal Medicine, UT Southwestern Medical Center, Dallas, TX

INTRODUCTION

- Therapy-related myeloid neoplasms (t-MN), including MDS and AML, are rare but serious complications of cytotoxic chemotherapy.
- Preclinical studies suggest cyclin-dependent kinase 4 and 6 inhibitors (CDK4/6i) may mitigate leukemogenesis by promoting hematopoietic stem cell quiescence.[1]

AIM

- To explore whether CDK4/6 inhibition is associated with reduced risk of t-MN in patients with breast cancer treated with chemotherapy.

METHODS

- Design: This was a retrospective cohort study using the TriNetX Research Network.
- Patients: We identified 34,055 adults with HR+/HER2- breast cancer who initiated anthracycline-, topoisomerase II inhibitor-, platinum-, or cyclophosphamide-based chemotherapy between January 2015 and December 2024 and survived free of t-MN through 365 days following treatment initiation.
- Outcome: Incident t-MN following chemotherapy initiation.
- Analysis: To mitigate immortal time bias, we performed a landmark analysis anchored at 365 days following chemotherapy initiation, with CDK4/6i exposure defined by receipt of CDK4/6i therapy within that window. Multivariable Fine-Gray subdistribution hazard models were used to account for the competing risk of death and adjust for age, race, ethnicity, metastatic disease, radiation, granulocyte colony-stimulating factor exposure, and comorbidity burden.

RESULTS

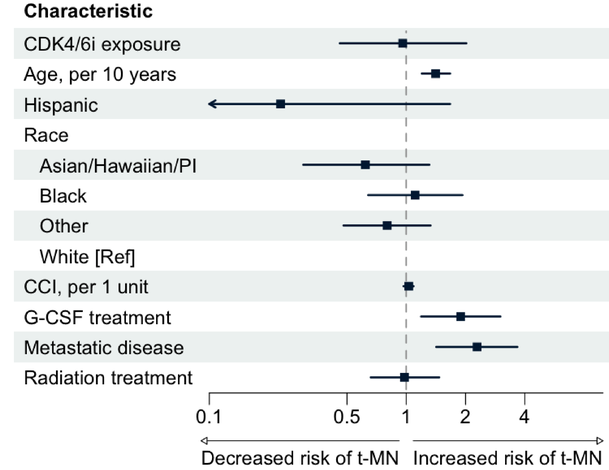
Cohort Characteristics

Characteristic	Overall (N=34,055)	No CDK4/6i (N=31,146)	CDK4/6i (N=2,909)
Age, y	55.7 (46.2, 65.1)	55.9 (46.3, 65.3)	53.3 (44.8, 62.9)
Hispanic	1,330 (3.9)	1,149 (3.7)	181 (6.2)
Race			
Asian	3,136 (9.2)	2,796 (9.0)	340 (11.7)
Black	3,095 (9.1)	2,810 (9.0)	285 (9.8)
Other	9,308 (27.4)	8,830 (28.4)	478 (16.4)
White	18,436 (54.3)	16,632 (53.5)	1,804 (62.1)
Metastatic disease	4,936 (14.5)	4,147 (13.3)	789 (27.1)
Radiation treatment	11,480 (33.7)	9,924 (31.9)	1,556 (53.5)
G-CSF treatment	4,611 (13.5)	4,259 (13.7)	352 (12.1)
CCI	3.0 (2.0, 8.0)	2.0 (2.0, 8.0)	8.0 (2.0, 9.0)
t-MN event rate	131 (0.4)	123 (0.4)	8 (0.3)

Data are shown as median (IQR) or n (%).
CCI=Charlson Comorbidity Index; G-CSF=granulocyte colony-stimulating factor; t-MN=treatment-associated myeloid neoplasm.

Multivariable Analysis of Factors Associated with Developing t-MN

Characteristic	sHR (95% CI)	P value
CDK4/6i exposure	0.96 (0.46, 2.02)	0.915
Age, per 10 years	1.41 (1.20, 1.67)	<0.001
Hispanic	0.23 (0.03, 1.67)	0.147
Race		
Asian/Hawaiian/PI	0.62 (0.30, 1.31)	0.211
Black	1.11 (0.64, 1.93)	0.701
Other	0.80 (0.48, 1.33)	0.397
White [Ref]		
CCI, per 1 unit	1.03 (0.97, 1.09)	0.353
G-CSF treatment	1.89 (1.19, 3.01)	0.007
Metastatic disease	2.29 (1.42, 3.67)	<0.001
Radiation treatment	0.98 (0.66, 1.47)	0.938



Subdistribution hazards ratios (sHR) were generated from multivariable Fine-Gray models adjusted for all variables shown.
CCI=Charlson Comorbidity Index; G-CSF=granulocyte colony-stimulating factor; t-MN=treatment-associated myeloid neoplasm.

CONCLUSIONS

- In this large real-world cohort of patients with HR+/HER2- breast cancer, CDK4/6i exposure was not associated with a significant reduction in t-MN risk.
- Interpretation is limited by the small number of incident t-MN events among CDK4/6i-treated patients (n=8) and potential residual confounding despite multivariable adjustment.
- Larger studies with sufficient follow-up and event accrual are needed to determine whether CDK4/6 inhibition confers meaningful protection against t-MN.

REFERENCES

1. Chan ICC, Zhang P, Pan X, et al. CDK4/6 inhibition mitigates chemotherapy-induced expansion of TP53-mutant clonal hematopoiesis. Nat Genet. 2026;58(3):582-592. doi:10.1038/s41588-026-02526-w

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