Journal of Cancer Research and Clinical Oncology (2025) 151:185
https://doi.org/10.1007/s00432-025-06229-3

CORRESPONDENCE

From controversy to clarity: reimagining the role of CDK4/6 inhibitors in the adjuvant setting– a number needed to treat perspective

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Received: 23 April 2025 / Accepted: 9 May 2025

Dear Editor,

I read with interest the commentary by Tannock et al. titled "Why We Do Not Recommend That Women With Breast Cancer Receive Adjuvant Treatment With a CDK4/6 Inhibitor" (J Clin Oncol 2025;00:1–5) (Tannock et al. 2025). While the authors raise important concerns regarding toxicity and methodological issues in the monarchE and NATALEE trials, we believe a more nuanced perspective is warranted, particularly when considering the number needed to treat (NNT) in context with other established adjuvant therapies.

All clinical trials inherently contain biases. The authors focus extensively on informative censoring, yet this common limitation exists throughout oncological research (Templeton et al. 2020). The monarchE and NATALEE trials deserve scrutiny, but applying stricter methodological standards than historically used for other practice-changing studies creates an asymmetric evaluation framework.

An evidence-based assessment of treatment benefit can be enhanced by examining the NNT, which provides an intuitive metric for clinical relevance. In the monarchE trial, abemaciclib demonstrated a 6.4% absolute improvement in 4-year invasive disease-free survival (IDFS), yielding an NNT of 16. For NATALEE, ribociclib showed a 4.9% absolute benefit in 4-year IDFS, resulting in an NNT of 20 (Table 1). These values compare favorably with several established adjuvant therapies. For perspective, aromatase inhibitors versus tamoxifen yield an NNT of 29 for preventing recurrence at 5 years, and adjuvant chemotherapy in ER-positive disease has an NNT of 10–14 for recurrence prevention(Early Breast Cancer Trialists' Collaborative Group (EBCTCG) 2015; Early Breast Cancer Trialists' Collaborative Group (EBCTCG) 2005).

This analysis demonstrates that the magnitude of benefit from CDK4/6 inhibitors is clinically meaningful and in line with other interventions that have transformed breast cancer care. The sensitivity analyses referenced by Tannock and colleagues have their own limitations. Post-hoc analyses often rely on assumptions about missing data patterns that may not reflect reality and typically lack pre-specification, increasing analytical bias (Morris et al. 2014).

It is worth noting that despite methodological concerns, both abemaciclib and ribociclib demonstrated improved invasive disease-free survival across different patient populations and trial designs. This cross-trial consistency between monarchE and NATALEE suggests a genuine treatment effect (Slamon et al. 2024). The negative results of the PALLAS and PENELOPE-B trial can be attributed to palbociclib, a CDK4/6 inhibitor that has demonstrated inferior efficacy compared to abemaciclib and ribociclib in the metastatic setting. Furthermore, the mechanism of action of CDK4/6 inhibitors provides a sound biological rationale for effectiveness in the adjuvant setting, particularly in high-risk populations (Spring et al. 2020).

The evolution of cancer treatment has always involved passionate debate and refinement of approaches. The introduction of adjuvant chemotherapy, extended endocrine therapy, and targeted agents like trastuzumab all faced initial skepticism regarding their risk-benefit profiles (Hudis 2007). Early critiques focused on toxicity and questioned the magnitude of benefit, yet these treatments ultimately transformed outcomes for breast cancer patients.

Rather than categorical rejection of CDK4/6 inhibitors, we suggest focusing on identifying high-risk subgroups most likely to benefit, which could optimize the risk-benefit ratio. Recent translational research suggests certain molecular signatures may identify patients more likely to benefit from CDK4/6 inhibition (O'Leary et al. 2018). Additionally, emerging adaptive dosing protocols and improved

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Published online: 09 June 2025

Table 1 Number needed to treat comparison among adjuvant therapies in early breast cancer

Treatment Comparison	Endpoint	Time Point	Absolute Benefit	NNT
Abemaciclib + ET vs. ET	IDFS	4 years	6.4%	16
Ribociclib + ET vs. ET	IDFS	4 years	4.9%	20
AI vs. Tamoxifen	Recurrence	5 years	3.5%	29
AI vs. Tamoxifen	Mortality	10 years	2.1%	48
Trastuzumab + CT vs. CT	DFS	3 years	11.8%	9
Chemotherapy vs. None (ER+)	Recurrence	10 years	7–10%	10–14

ET: endocrine therapy; AI: aromatase inhibitor; CT: chemotherapy; IDFS: invasive Disease-Free survival; DFS: Disease-Free survival

supportive care measures may mitigate adverse events while preserving efficacy (Diéras et al. 2019).

Scientific progress in oncology demonstrates that early controversies often lead to refined approaches that ultimately benefit patients. The optimal integration of CDK4/6 inhibitors into adjuvant breast cancer treatment will likely emerge through continued investigation, improved patient selection strategies, and refined protocols addressing toxicity concerns.

The limitations identified by Tannock and colleagues should serve as a catalyst for improved trial design and reporting, but should be balanced against the potential benefits these agents may offer to appropriately selected patients with high-risk disease, particularly given their favourable NNT compared to established adjuvant therapies (Table 1). The oncology community would be best served by embracing this critical discourse as part of the scientific process while continuing to generate high-quality evidence to guide future practice.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00432-025-06229-3.

Author contributions A.O wrote the main manuscript and reviewed the manuscript.

Funding This letter received no specific funding from public, commercial, or not-for-profit organizations.

Data availability No datasets were generated or analysed during the current study.

Declarations

Competing interests The authors declare no competing interests.

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