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CDK4/6 inhibitors as adjuvant therapy in early breast cancer? Uncertain benefits, guaranteed harms

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ABSTRACT

CDK4/6 inhibitors are oral agents inhibiting key molecules of the cell cycle regulation. In patients with endocrine receptor positive (ER+), human epidermal growth factor receptor 2 negative (HER2-) breast cancer, the combination of CDK4/6 inhibitors with endocrine therapy is an effective treatment in the metastatic setting. Now, two studies in the adjuvant setting – MonarchE (2 years of abemaciclib) and NATALEE (3 years of ribociclib) – report positive invasive disease-free survival. Here, we re-evaluate these seminal trials. First, an excess drop-out or loss-to-follow up occurred early in the control arms of both studies. Since both trials are open-label, there is concern that the patients who drop-out do not do so at random but based on socioeconomic factors and alternative options. Is it possible that the results merely appear favorable due to loss to follow up? Based on re-constructed Kaplan-Meier curves, we concluded the results of these studies remain fragile, being prone to informative censoring. Secondly, adverse events were notably higher in both trials, and some of them, like COVID-19 related deaths in NATALEE, raise serious concerns. Third, the potential costs associated with CDK4/6 inhibition given as adjuvant therapy are unprecedented. The NATALEE strategy, in particular, could affect up to 35 % of patients with newly diagnosed breast cancer, which is the cancer with the highest incidence worldwide. Without confirmatory data based on a placebo-controlled trial, or better identification of patients that would benefit from the addition of CDK4/6 inhibitors in the adjuvant setting, we argue against their routine use as adjuvant therapy in ER+ /HER2- early breast cancer.

1. Introduction

Adjuvant treatment is offered to patients, some of whom are already cured, with the goal of reducing or eliminating recurrence in the fraction of patients whose cancer would otherwise return. All adjuvant treatments inherently result in overtreatment – exposing some cured patients to toxic drugs – but ideally this is offset by (1) preventing or delaying recurrence, and, as a result, the overall population (2) lives a longer and better life. Many adjuvant therapies meet this mark, and their use has been a success story in biomedicine [1].

CDK4/6 inhibitors are oral agents inhibiting key molecules of the cell cycle regulation. In patients with endocrine receptor positive (ER+), human epidermal growth factor receptor 2 negative (HER2-) breast cancer, the combination of CDK4/6 inhibitors with endocrine therapy – even if the optimal sequence is undetermined [2] – is considered the first-line standard therapy in the metastatic setting in patients with no

visceral crisis due to improvements in overall survival (OS) [3]. In recent years, buoyed by success in the metastatic setting, trials have tested these blockbuster drugs in the adjuvant space.

Now, two studies – MonarchE and NATALEE – report positive invasive disease-free survival (iDFS) results. The hazard ratios for iDFS were 0.68 and 0.75, respectively [4-6]. Both point to the conclusion that CDK4/6 inhibitors can avert or delay recurrence among people with ER+ /HER2- disease. While OS is immature, these results have captivated the oncology community and routine use of CDK4/6 inhibitors in the adjuvant space is rapidly becoming the new standard-of-care.

In this commentary, we re-evaluate these seminal trials. We note that in both studies there is excess drop-out or loss-to-follow up in the control arms. This occurs early in the study. Since both trials are open-label, there is concern that the patients who drop-out do not do so at random but based on socioeconomic factors and alternative options. In contrast, two other studies of CDK4/6 inhibitors – one using an open

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label design – have smaller imbalances in drop-out and are both negative. Is it possible that the results of MonarchE and NATALEE do not represent an increase in cured patients, but results merely appear favorable due to loss to follow up? Based on re-constructed Kaplan-Meier curves, we reached the provocative conclusion that the results of these seminal studies remain fragile. Further examination of toxicity, OS, and cost is warranted.

2. MonarchE and NATALEE trials

Both open-label phase 3 trials enrolled patients with ER+ /HER2-early breast cancer. MonarchE enrolled 5637 patients between July 2017 and August 2019 [4]. Eligibility criteria included patients having either ≥ 4 positive axillary lymph nodes or one to three nodes with additional high-risk factors (e.g., tumor size of 5 cm or larger or a high Ki-67 level). The study found adding 2 years of abemaciclib (150 mg twice a day) to endocrine therapy led to a significant improvement in iDFS compared to endocrine therapy alone. At 5 years, the absolute difference in iDFS was 7.6 % favoring abemaciclib (83.6 % vs. 76.0 %, $p < 0,001$) [6]. The drug was FDA-approved in the adjuvant setting in October 2021.

The NATALEE trial had wider inclusion criteria and enrolled 5101 patients between January 2019 and April 2021. Patients with stage II or III breast cancer, including patients with node-negative cancers, were randomly allocated to receive either 400 mg or ribociclib (21/28 days) over 3 years with non-steroidal aromatase inhibitor (NSAI, either letrozole or anastrozole), or only NSAI [5]. Premenopausal patients or men in both groups also received goserelin. The primary endpoint – iDFS – showed a statistical improvement in the ribociclib group, with an absolute difference at 3 years of 3.3 % (90.4 % vs. 87.1 %, $p = 0.003$).

MonarchE included higher risk patients with node-positive tumors. NATALEE also included patients with node-negative tumors. Tamoxifen was allowed in MonarchE but not in NATALEE. Neither trial demonstrated an OS gain, though OS is a secondary endpoint, and the data remain immature. The Table highlights key differences and similarities between trials.

3. Open-label design and informative censoring

A central question is whether informative censoring led to biased iDFS estimates in MonarchE and NATALEE. The open-label design – i.e. absence of a placebo-control – likely favored this bias. Early imbalance in drop-out undoes randomization if patients who quit are different from those who remain in the trial. High imbalance in early censoring may be driven by drug-toxicity (affecting the most toxic arm), or patient disappointment in the control group [7].

In both trials, patients disproportionately dropped-out from the control group right after randomization (Table). A likely explanation was patient disappointment after random allocation to the control group. Both studies also showed more toxicity in the experimental arm, potentially driving a fraction of patients to drop-out [7].

In MonarchE, researchers concluded that the reported gain could have been driven by informative censoring [8]. In NATALEE, 0.9 % and 4.3 % of patients did not receive the study treatment in the ribociclib and control groups, respectively. A fraction of patients may have dropped-out from the experimental therapy group due to side effects, while a fraction of patients from the control group may have dropped-out due to disappointment. The latter may represent more affluent patients, wealthier than those who remain in the trial, who may be at lower risk of disease recurrence because of factors (e.g., lifestyle and access to healthcare, generally) unrelated to cancer-specific treatment.

We explored this hypothesis after extracting synthetic individual patient-data from published Kaplan-Meier curves [9]. We ran a sensitivity analysis modeling a different scenario for 10 % of patients censored over the first time-point in each arm. After running a Cox

analysis, the iDFS was no longer statistically significant. This analysis is openly available for reproducibility (https://github.com/TimotheeMD/NATALEE_sensitivity). Sensitivity analyses conducted by independent groups like Meirson [8] or ours are inherently limited by the lack of access to individual patient data. Sensitivity analyses based on original data would ideally be needed.

Another source of disproportionate drop-out in NATALEE may have been the type of endocrine therapy in both arms. Contrary to MonarchE, patients could not receive tamoxifen due to drug interactions in NATALEE. Patients could enroll while already on adjuvant endocrine therapy (up to 12 months), and 13.4 % of them were receiving anti-estrogen therapy – likely tamoxifen. Those patients were probably lower-risk patients. If enrolled in NATALEE, they would have been switched to an NSAI, or NSAI plus goserelin, a combination recognized for its increased side effects. It is possible that those patients disproportionately left the trial after being allocated to the control arm, deciding to resume their previous endocrine therapy – tamoxifen.

Data from other trials support the hypothesis of informative censoring. Two phase 3 studies in comparable settings failed to find an iDFS benefit. In the PALLAS trial, an open-label trial investigating the addition of 2 years of palbociclib, the proportion of early drop-out were lower than in MonarchE and NATALEE (0.4 % and 0.8 % in the palbociclib and control groups, respectively) [10]. The placebo-controlled Penelope-B trial, testing 1 year of palbociclib, had no imbalance in early drop-outs (0,5 % in both arms) [11].

Overall, we maintain that the gains in iDFS reported in the MonarchE and NATALEE trials are potentially compromised by informative censoring.

4. What is clinically meaningful?

Large sample size allows one to find statistically significant differences, although not clinically relevant [12]. iDFS, the primary endpoint, was defined according to STEEP definition [13]. It is a time-to-event composite endpoint, meaning that many scenarios could count as an event: ipsilateral breast tumor recurrence, loco-regional invasive recurrence, distant recurrence, death from breast cancer, death from non-breast cancer or unknown cause, invasive contra-lateral breast cancer, or secondary primary invasive cancer (non-breast).

Composite endpoints increase the likelihood of a positive finding. However, it mixes scenarios with disparate clinical impact, where some are amenable to cure (e.g., loco-regional recurrence, or ipsilateral breast cancer recurrence), while others are more serious, including death.

The breakdown of composite endpoints is not always reported [14], but in MonarchE and NATALEE they are. In both trials, the “survival” part of the iDFS – i.e., the proportion of deaths among iDFS events – was minimal (50 patients, i.e. 6.0 % of events in MonarchE and 4.7 % – 20 patients – in NATALEE) [4,5]. Among all participants in the study, this is just 0,9 % in MonarchE and 0.4 % in NATALEE. In other words, iDFS gains were mostly driven by non-death events.

In early breast cancer, DFS trial-level surrogacy with OS has been suggested [15], though this study only examined 14 trials, while a larger study of 126 trials finds a moderate strength in correlation [16]. Trial-level surrogacy, however, has to be validated within a specific class of treatment. In the case of CDK4/6 inhibitors, such surrogacy has not yet been shown.

Overall, the clinical relevance of the iDFS benefit is undermined by a modest absolute gain, meaning that most patients do not benefit. The absolute iDFS increase – 7.6 % at 5 years with 2 years of abemaciclib and 3.3 % at 3 years with ribociclib – translates to a number needed to treat (NNT) of 13 and 30 patients, respectively, to prevent one event. Additionally, most are non-fatal events, including events potentially amenable to cure. Those NNTs are for a surrogate endpoint, as no survival benefit has been reported to date with CDK4/6 inhibitors given as adjuvant therapy. A thorough understanding of these concepts is important for better shared decision making between clinicians and

patients.

5. Neutropenia, COVID-19, and financial toxicity

Grade ≥ 3 adverse events were significantly higher with CDK4/6 inhibitors than in control groups (Table). In MonarchE, among 16 patients who experienced a grade 5 adverse events with abemaciclib (i.e., deaths), two were attributed to abemaciclib [4]. In NATALEE, patients in the ribociclib arm were more likely to experience a grade 5 adverse event (0.5 % vs. 0.2 %), with none related to ribociclib [5].

In NATALEE, a higher percentage of patients in the ribociclib arm tested positive for SARS-CoV-2 (19.3 % vs 12.7 % in the control arm), and more patients died from COVID-19, most occurring on treatment or within 30 days after the end of ribociclib (0,2 % vs 0,0 %, absolute numbers 4 vs 1). Similar imbalance was seen in MonarchE in COVID-19 cases (2,0 % vs 0,9 %), yet with smaller numbers, probably because the inclusion period ended before the COVID-19 pandemic. In MonarchE, 0,1 % and 0,0 % COVID-19 related deaths (absolute numbers 2 vs 1) were reported on treatment or up to 30 days after study treatment discontinuation in the abemaciclib and the control group, respectively.

What could explain the higher numbers of COVID-19 related deaths? Grade ≥ 3 neutropenia was more common with ribociclib (44 %) than with abemaciclib (20 %). Even though “no death [was] considered to be related to the trial treatment” in NATALEE according to the investigators, this signal should be closely followed.

Financial toxicity is defined as “both the objective financial burden and subjective financial distress from a cancer diagnosis and its treatment” [17]. We estimated, based on NATALEE’s results, that the cost to avert one iDFS event would be \$11,200,000. This estimation is based on the estimated average price per patient (\$370,000), multiplied by the NNT (30), considering the median exposure of ribociclib within the trial and dose reductions. Similar calculations, applied to the MonarchE trial, yielded \$5,700,000 to avert one event with the most recent efficacy update. Table 1.

Previously, the cost to avert events with agents approved by the FDA in the adjuvant setting ranged from \$820,000 to \$2,640,000 [18]. While RED BOOK prices used for these estimates do not always reflect what patients actually pay, prices can vary from country to country, and prices may change with additional indication approvals, therapies used in MonarchE and NATALEE would still set new records, potentially exacerbating financial toxicity.

6. A broad eligible population

Breast cancer has the highest incidence worldwide, with about 2,300,000 new cases in 2022. Among those, ER+ /HER2- breast cancers represent about 75 % of cases. In high income countries, stage II and III constitute 45 to 50 % of new cases [19]. Altogether, the NATALEE strategy (adjuvant ribociclib for 3 years) could affect up to 35 % of patients with newly diagnosed breast cancer.

7. Conclusion

Given the limitations we have detailed, we argue against the routine use of CDK4/6 inhibitors as adjuvant therapy in ER+ /HER2- early breast cancer. In one respect, the reported iDFS gains may be biased — potentially influenced by informative censoring, a likely consequence of the trials’ open-label design. On the other hand, the marginal increase in iDFS necessitates the treatment of a high number of patients to prevent a single event. The cost of this overtreatment is significant, not just in terms of toxicity — where most patients may see no benefit — but also in terms of financial burden. Moreover, adverse events were notably higher in both trials, some of them, like COVID-19 related deaths, raising serious concerns. Collectively, the potential financial costs associated with CDK4/6 inhibition as adjuvant therapy are unprecedented and safety costs are notable. The NATALEE strategy, in particular, could

Table 1

Key data from the MonarchE and the NATALEE trials, testing adjuvant CDK4/6 inhibitors in early breast cancer.

Trial name	MonarchE ¹		NATALEE	
Inclusion /exclusion criteria (summarized)	ER+ /HER2- node positive early breast cancer, with high-risk features for N1 patients		ER+ /HER2- stage II to III, including node negative, early breast cancer	
Design	Phase 3, open-label		Phase 3, open-label	
Experimental therapy	2 years abemaciclib+ control endocrine therapy		3 years ribociclib+ control endocrine therapy	
Control endocrine therapy (at least 5 years)	Physician’s choice: 1) antiestrogens (i.e. tamoxifen) 2) NSAI + /- GnHR agonist		1) NSAI in post-menopausal 2) NSAI + goserelin (GnHR agonist) in pre-menopausal and men	
Primary endpoint	iDFS*		iDFS*	
Sample Size	5637 patients		5101 patients	
Absolute iDFS gain ¹	7.6 % at 5 years, HR* = 0.68 (83.6 % vs. 76.0 %, p < 0.001)		3.3 % at 3 years, HR = 0.75 (90.4 % vs. 87.1 %, p = 0.003)	
NNT* ** (iDFS) ¹	13		30	
	Toxicity			
	Experimental	Control	Experimental	Control
Grade ≥ 3 events	49.9 %	6.9 %	62.6 %	17.8 %
Grade ≥ 3 neutropenia	19.6 %	0.9 %	43.8 %	0.8 %
SARS-CoV-2 positive	2.0 %	0.9 %	19.3 %	12.7 %
COVID-19 deaths ²	0,1 % (n = 2 including one suspicion)	0,0 % (n = 1)	0.2 % (n = 4)	0.0 % (n = 1)
Grade 5 events (deaths)	0.6 % ^o	0.4 %	0.5 % ^o	0.2 %
	iDFS breakdown of events			
Proportion of deaths among the iDFS events	8.9 %	4.0 %	6.9 %	3.0 %
	Censoring Data			
Proportion of patients not receiving the study treatment after randomization	0.5 %	1.1 %	0.9 %	4.3 %
	Financial Toxicity			
Estimated Average Cost per Patient	420,000 USD ^{oo}		370,000 USD ^{oo}	
Estimated Cost to Avert One iDFS event	5,700,000 USD ^{ooo}		11,200,000 USD ^{ooo}	

1: The efficacy data (iDFS and NNT) reported here for MonarchE are from the 5-year efficacy update [6]. Other data have been abstracted from the original publication [4] as they were not detailed in the update publication.

2: COVID-19 deaths reported here are those occurring on-therapy or up to 30 days after study treatment discontinuation (MonarchE) or ribociclib discontinuation (NATALEE).

* iDFS: invasive disease-free survival;

** HR: hazard ratio;

*** NNT: number needed to treat (rounded to the nearest whole number);

^o: two deaths were attributed to abemaciclib in MonarchE, none in NATALEE.

^{oo} rounded to the nearest 10,000 USD (calculations based on unrounded numbers)

^{ooo} rounded to the nearest 100,000 USD (calculations based on unrounded numbers)

affect up to 35 % of patients with newly diagnosed breast cancer, which is the cancer with the highest incidence worldwide. Until confirmatory data using a placebo-controlled trial are done, or there is a better identification of patients who would benefit from the addition of CDK4/6 inhibitors in the adjuvant setting, such strategies in routine use should be avoided. The call for more rigorous testing is echoed throughout the oncology community, highlighting the need for a reassessment of current protocols in light of these concerns. Systematic frameworks incorporating these and other considerations are needed to better evaluate clinical trials, generally.

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Vinay Prasad: Writing – review & editing, Supervision, Methodology. **Timothée Olivier:** Writing – review & editing, Validation, Supervision, Investigation, Formal analysis, Data curation, Conceptualization. **Sruthi Ranganathan:** Writing – review & editing, Writing – original draft. **Alyson Haslam:** Writing – review & editing, Supervision, Methodology.

Declaration of Competing Interest

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References

- [1] Parsons S, Maldonado EB, Prasad V. Comparison of drugs used for adjuvant and metastatic therapy of colon, breast, and non-small cell lung cancers. *JAMA Netw Open* 2020;3(4):e202488. <https://doi.org/10.1001/jamanetworkopen.2020.2488>.
- [2] Sonke GS, Van Ommen - Nijhof A, Wortelboer N, et al. Primary outcome analysis of the phase 3 SONIA trial (BOOG 2017-03) on selecting the optimal position of cyclin-dependent kinases 4 and 6 (CDK4/6) inhibitors for patients with hormone receptor-positive (HR+), HER2-negative (HER2-) advanced breast cancer (ABC). *LBA1000-LBA1000 JCO* 2023;41(17_suppl). https://doi.org/10.1200/JCO.2023.41.17_suppl.LBA1000.
- [3] National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Breast Cancerbreast.pdf. Accessed April 20, 2024. (https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf).
- [4] Johnston SRD, Toi M, O'Shaughnessy J, et al. Abemaciclib plus endocrine therapy for hormone receptor-positive, HER2-negative, node-positive, high-risk early breast cancer (monarchE): results from a preplanned interim analysis of a randomised, open-label, phase 3 trial. *Lancet Oncol* 2023;24(1):77–90. [https://doi.org/10.1016/S1470-2045\(22\)00694-5](https://doi.org/10.1016/S1470-2045(22)00694-5).
- [5] Slamon Dennis Lipatov Oleg, Zbigniew Nowecki, et al. Ribociclib plus endocrine therapy in early breast cancer. *N Engl J Med* 2024;390(12):1080–91. <https://doi.org/10.1056/NEJMoa2305488>.
- [6] Rastogi P, O'Shaughnessy J, Martin M. Adjuvant Abemaciclib Plus Endocrine Therapy for Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative, High-Risk Early Breast Cancer: Results From a Preplanned monarchE Overall Survival Interim Analysis, Including 5-Year Efficacy Outcomes. *JCO* 2024. <https://doi.org/10.1200/JCO.23.01994>.
- [7] Olivier T, Prasad V. Equal censoring but still informative: when the reasons for censoring differ between treatment arms. *Eur J Cancer* 2024;201:113942. <https://doi.org/10.1016/j.ejca.2024.113942>.
- [8] Meirson T, Goldstein DA, Gyawali B, Tannock IF. Review of the monarchE trial suggests no evidence to support use of adjuvant abemaciclib in women with breast cancer. *Lancet Oncol* 2023;24(6):589–93. [https://doi.org/10.1016/S1470-2045\(23\)00165-1](https://doi.org/10.1016/S1470-2045(23)00165-1).
- [9] Liu N, Zhou Y, Lee JJ. IPDfromKM: reconstruct individual patient data from published Kaplan-Meier survival curves. *BMC Med Res Methodol* 2021;21(1):111. <https://doi.org/10.1186/s12874-021-01308-8>.
- [10] Gnant M, Ducek AC, Frantal S, et al. Adjuvant palbociclib for early breast cancer: the PALLAS Trial Results (ABCSG-42/AFT-05/BIG-14-03). *JCO* 2022;40(3):282–93. <https://doi.org/10.1200/JCO.21.02554>.
- [11] Loibl S, Marmé F, Martin M, et al. Palbociclib for residual high-risk invasive HR-positive and HER2-negative early breast cancer—the Penelope-B trial. *JCO* 2021; 39(14):1518–30. <https://doi.org/10.1200/JCO.20.03639>.
- [12] Kay A, Higgins J, Day AG, Meyer RM, Booth CM. Randomized controlled trials in the era of molecular oncology: methodology, biomarkers, and end points. *Ann Oncol* 2012;23(6):1646–51. <https://doi.org/10.1093/annonc/mdr492>.
- [13] Tolaney SM, Garrett-Mayer E, White J, et al. Updated Standardized Definitions for Efficacy End Points (STEEP) in Adjuvant Breast Cancer Clinical Trials: STEEP Version 2.0. *JCO* 2021;39(24):2720–31. <https://doi.org/10.1200/JCO.20.03613>.
- [14] Walia A, Tuia J, Prasad V. Progression-free survival, disease-free survival and other composite end points in oncology: improved reporting is needed. *Nat Rev Clin Oncol* 2023;20(12):885–95. <https://doi.org/10.1038/s41571-023-00823-5>.
- [15] Untch M, PéroL D, Mayer EL, et al. Disease-free survival as a surrogate for overall survival in HR+/HER2- early breast cancer: A correlation analysis. *Eur J Cancer* 2024;202:113977. <https://doi.org/10.1016/j.ejca.2024.113977>.
- [16] Ng R, Pond GR, Tang PA, MacIntosh PW, Siu LL, Chen EX. Correlation of changes between 2-year disease-free survival and 5-year overall survival in adjuvant breast cancer trials from 1966 to 2006. *Ann Oncol* 2008;19(3):481–6. <https://doi.org/10.1093/annonc/mdm486>.
- [17] Carrera PM, Curigliano G, Santini D, et al. ESMO expert consensus statements on the screening and management of financial toxicity in patients with cancer. *ESMO Open* 2024;9(5). <https://doi.org/10.1016/j.esmoop.2024.102992>.
- [18] Mousavi I, Olivier T, Prasad V. Cost per event averted in cancer trials in the adjuvant setting from 2018 to 2022. *JAMA Netw Open* 2022;5(6):e2216058. <https://doi.org/10.1001/jamaoncol.2023.4837>.
- [19] Benitez Fuentes JD, Morgan E, de Luna Aguilar A, et al. Global stage distribution of breast cancer at diagnosis: a systematic review and meta-analysis. *JAMA Oncol* 2024;10(1):71–8. <https://doi.org/10.1001/jamaoncol.2023.4837>.