

CDK4/6 inhibition in HR-positive early breast cancer: are we putting all eggs in one basket?



Elisa Agostinetto ,^{1,2} Rafael Caparica,¹ Evandro de Azambuja ¹

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Cyclin-dependent kinase 4–6 inhibitors (CDK4-6i) represent a major advance in the treatment of patients with HR-positive (HR+), HER2-negative (HER2–) metastatic breast cancer (mBC), having become the standard of care in first-line, and a valid treatment option in second-line in combination with endocrine therapy (ET).¹ These trials have consistently showed an improvement in progression-free survival and, some of them, in overall survival.

Although adjuvant ET significantly reduces the risk of recurrence and death among patients with HR+ early breast cancer (EBC), up to 20% of these patients will experience recurrences in the first 10 years, either with locoregional disease or with distant metastases, which is incurable in the latter scenario.² Therefore, it is of paramount importance to define new treatment strategies to minimise this recurrence risk and to improve patient outcomes.

Therefore, several studies are evaluating the efficacy of CDK4-6i with ET for patients with HR+/HER2– EBC. At the annual meeting of the European Society of Medical Oncology 2020, two of these ongoing studies were presented with controversial results: the MonarchE and the PALbociclib CoLaborative Adjuvant Study (PALLAS) studies (table 1). The open-label, phase III MonarchE study, included patients with HR+/HER– EBC at ‘high risk’ of relapse defined by ≥ 4 positive nodes, or 1–3 positive nodes with either tumours ≥ 5 cm, histological grade 3, or centrally assessed Ki-67 $\geq 20\%$.³ Patients were randomised to receive standard ET with or without abemaciclib, at a dosage of 150 mg administered twice daily for 2 years. Primary endpoint was invasive disease-free survival (IDFS). Overall, among the intention-to-treat population of 5637 patients, 323 events were observed. After a median follow-up of 15.5 months, the combination of abemaciclib and ET was associated with a significant IDFS

improvement (2-year IDFS rates 92.2% vs 88.7%, HR 0.75, 95% CI 0.60 to 0.93, $p=0.01$) and distant relapse-free survival (DRFS) (2-year DRFS rates 93.6% vs 90.3%, HR 0.72, 95% CI 0.56 to 0.92, $p=0.01$), compared with ET alone.³ By demonstrating a clinically meaningful absolute increase of 3.5% in 2-year IDFS, this was the first study to show positive results with a CDK 4/6i incorporated into the adjuvant treatment of patients with HR+/HER2– EBC. The addition of abemaciclib to ET increased the risk of gastrointestinal and haematological toxicities, and approximately 68% of patients required abemaciclib dose adjustment, around 17% discontinued it due to adverse events (AEs), and 6% of patients discontinued both abemaciclib and ET because of toxicity, compared with 0.8% of discontinuation in the ET arm. Of note, abemaciclib was associated with a non-negligible risk of venous thromboembolic events (2.3% vs 0.5% in the control arm) and interstitial lung disease (2.7% vs 1.2% in the control arm).³

Another open-label, phase III study evaluating CDK4-6i in the adjuvant setting, the PALLAS trial, randomly assigned 5760 stage II–III HR+/HER2– EBC patients to receive standard adjuvant ET with or without palbociclib (125 mg once daily on days 1–21, followed by 7 days off) for 2 years.⁴ Surprisingly, no improvement in IDFS was observed (HR 0.93, 95% CI 0.76 to 1.15; $p=0.51$), with these results crossing a futility boundary prespecified in the study statistical assumptions. No specific subgroup appeared to benefit from the addition of palbociclib to ET. Early discontinuation of palbociclib occurred in 42% of patients, and the majority was due to AEs (64%). Most common toxicities in palbociclib arm were haematological (neutropenia, 83% all grades and 61% grade 3–4), followed by fatigue (40% all grades, 2% grade 3–4) and upper respiratory tract infection (28% all grades, 1% grade 3–4).⁴ It will

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¹Academic Trials Promoting Team, Institut Jules Bordet, Bruxelles, Belgium

²Medical Oncology and Hematology Unit, Humanitas Clinical and Research Center – IRCCS, Humanitas Cancer Center, Rozzano, Milan, Italy

Correspondence to

Dr Evandro de Azambuja; evandro.azambuja@bordet.be

Table 1 Characteristics of study population and outcomes of PALLAS and MonarchE trials

	PALLAS		MonarchE	
	Palbociclib+ET	ET alone	Abemaciclib + ET	ET alone
N	2883	2877	2808	2829
Median age (range)	52 (25–90)	52 (22–85)	51 (23–89)	51 (22–86)
Menopausal status				
Pre	–	–	1221 (43.5%)	1232 (43.5%)
Post	–	–	1587 (56.5%)	1597 (56.5%)
Stage				
IA	–	–	2 (0.1%)	1 (0%)
IIA	504 (17.5%)	509 (17.7%)	323 (11.5%)	353 (12.5%)
IIB	968 (33.6%)	951 (33.1%)	389 (13.9%)	387 (13.7%)
III	1402 (48.6%)	1408 (48.9%)	2081 (74.1%)	2077 (73.4%)
T size				
T0, T1, Tx, Tis	557 (19.3%)	500 (17.4%)	780 (27.8%)	765 (27.0%)
T2	1603 (55.6%)	1636 (56.9%)	1369 (48.8%)	1419 (50.2%)
T3, T4	722 (25.0%)	741 (25.8%)	610 (21.7%)	612 (21.6%)
Nodal status				
0 LN	–	–	7 (0.2%)	7 (0.2)
1–3+LN	–	–	1119 (39.9%)	1143 (40.4%)
≥4 + LN	–	–	1680 (59.8%)	1679 (59.3%)
Grade				
G1	300 (10.4%)	313 (10.9%)	209 (7.4%)	215 (7.6%)
G2	1622 (56.3%)	1658 (57.6%)	1373 (48.9%)	1395 (49.3%)
G3	836 (29.0%)	767 (26.7%)	1090 (38.8%)	1066 (37.7%)
Ki67				
<20%	–	–	953 (33.9%)	973 (34.4%)
≥20%	–	–	1262 (44.9%)	1233 (43.6%)
Prior CT	2384 (82.7%)	2370 (82.4%)	2681 (95.5%)	2695 (95.3%)
Adjuvant ET				
Tamoxifen	923 (32.0%)	949 (33.0%)	857 (30.7%)	898 (32.1%)
Tamoxifen + ovarian suppression	–	–	192 (6.9%)	232 (8.3%)
AI	1954 (67.8%)	1918 (66.7%)	1928 (69.1%)	1891 (67.5%)
AI + ovarian suppression	–	–	410 (14.7%)	386 (13.8%)
Ovarian suppression (any time)	532 (18.5%)	604 (21.1%)	606 (21.7%)	627 (22.4%)
Median follow-up	23.7 months		15.5 months	
IDFS events	351 events (67% of expected events)		323 events (75% of expected events)	
IDFS	3 years IDFS 88.2 vs 88.5% HR 0.93; 95% CI 0.76 to 1.15; p=0.51		2 years IDFS 92.2 vs 88.7% HR 0.75; 95% CI 0.60–0.93; p=0.01	
DRFS	3 years DRFS 89.3 vs 90.7% HR 1.00; 95% CI 0.79 to 1.27; p=0.99		2 years DRFS 93.6 vs 90.3% HR 0.72; 95% CI 0.56 to 0.92; p=0.01	
Early CDK4-6i discontinuation due to AEs	770 (26.7%)		463 (16.5%)	
Most frequent AEs in CDK4-6i arm (any grade and grade 3–4)	Neutropenia (83% and 61%) Leucopenia (55% and 30%) Fatigue (40% and 2%) Upper respiratory tract infection (28% and 1%)		Diarrhoea (82% and 8%) Neutropenia (45% and 18%) Leucopenia (37% and 11%) Fatigue (38% and 3%) VTEs 2.3% ILD 2.7%	

AEs, adverse events; AI, aromatase inhibitor; CDK4-6i, cyclin-dependent kinase 4–6 inhibitor; CT, chemotherapy; DRFS, distant relapse-free survival; ET, endocrine therapy; IDFS, invasive disease-free survival; ILD, interstitial lung disease; VTEs, venous thromboembolisms.

be important to understand the impact of CDK4/6i in quality of life, which is still not reported in either trial.

The striking discrepancy between the results of these two trials puts the role of CDK4-6i in EBC into debate. How to explain such different findings? First, eligibility criteria in PALLAS relied only on the anatomic stage of disease (II and III), irrespectively of biological characteristics, and approximately 17.6% of patients with stage IIA disease were enrolled (vs 12% in MonarchE), suggesting that the latter population had an overall higher risk of recurrence. Also, in MonarchE, over 73% of patients had stage III disease compared with 48% in PALLAS, demonstrating a patient population at higher risk of relapse. This difference in the risk profile of the patient population might have played a role in the discrepant findings, reinforcing the importance of an adequate patient selection for achieving the desired outcomes in clinical trials.

Another hypothesis to explain these divergent results relies on the different activity of both CDK4-6i. Palbociclib and abemaciclib have unique pharmacological characteristics, despite belonging to the same class of CDK4-6i.⁵ Abemaciclib has a higher potency in terms of CDK4 and CDK6 inhibition, and requires a lower inhibitory concentration to block its target. Concerning spectrum activity, palbociclib is able to inhibit only CDK4 and CDK6, whereas abemaciclib has also activity against CDK9 (which could explain its peculiar gastrointestinal toxicities). Palbociclib has greater lipophilicity and different binding side chains, with less off-target interactions, compared with abemaciclib.⁵ Despite these pharmacological differences, both agents have demonstrated to improve outcomes in patients with HR+/HER2- mBC when combined with ET.⁶⁻¹² Nevertheless, no head-to-head comparison between the two CDK4-6i has ever been made.

Other reasons have been proposed to explain the discrepant results, including the higher discontinuation rate observed for palbociclib in the PALLAS trial as well as its intermittent schedule of administration. Regarding the MonarchE trial, more than 30% of patients in each arm received tamoxifen as ET, and only 8% of these in combination with ovarian suppression, which could be considered as a suboptimal treatment for high-risk patients. This should be taken into account when observing that more than 75% of the early recurrences observed in the control arm were distant metastases.

Further data are eagerly awaited from ongoing studies to shed light on the role of CDK4-6i in EBC. A recent press-release revealed that the PENELOPE-B study (NCT01864746), testing the addition of 1-year palbociclib to standard ET in patients with residual disease after the completion of neoadjuvant chemotherapy, did not meet its primary endpoint (IDFS). Complete results are expected in the next months. Beyond palbociclib and abemaciclib, data from another CDK4-6i, ribociclib, are expected from the ongoing NataLEE trial, which will evaluate adjuvant ET with or without ribociclib in around 4000 patients with HR+/HER2- EBC.¹³ Patients

with anatomic stage II (either N0 with grade 2-3 and/or Ki67 $\geq 20\%$ or N1) or III EBC are eligible, consisting of an 'intermediate' risk population when compared with PALLAS and MonarchE. Ribociclib is also being evaluated in two more studies in the adjuvant setting: the phase II EarLEE-1 study for high-risk patients,¹⁴ and the phase III EarLEE-2 for intermediate-risk patients.¹⁵ In the EarLEE-1 study, patients who received adjuvant chemotherapy for stage III disease or those with >2 mm residual disease in axillary lymph nodes and >10 mm in breast after neoadjuvant chemotherapy will be randomised to receive ribociclib or placebo for 2 years in combination with ET.¹⁴ The EarLEE-2 study was reported to be interrupted early for non-safety reasons.

Widening the concept of adjuvant setting, CDK4-6i are being evaluated also as preventive therapy after isolated locoregional recurrences of EBC. The POLAR study (NCT03820830) is an open-label, phase III study that aims to evaluate the addition of 3-year palbociclib to standard ET after a locoregional recurrence without evidence of distant metastasis. The hypothesis of the POLAR trial is that palbociclib, in combination with ET, may be active as adjuvant therapy in this specific subset of patients, who are at high risk of developing subsequent distant metastasis and whose 5-year survival probabilities ranges between 45% and 80%.¹⁶ By enrolling a very high-risk population, this study will further explore the hypothesis that patients with a high risk of recurrence may benefit more from adjuvant CDK4-6i.

The most important question that remains unanswered about CDK 4/6i in HR+/HER2- EBC is how to select patients who benefit from this treatment. Thus far, besides HR status, no biomarkers have proven to predict the benefit of CDK4-6i, and several studies are investigating the mechanisms of resistance and sensitivity to CDK 4-6 inhibition to answer this question.¹⁷⁻¹⁹ Another open question is the optimal duration of adjuvant treatment with CDK4-6i, which ranged in clinical trials from 1 year (for palbociclib in the PENELOPE-B study), to 2 and 3 years (for palbociclib and abemaciclib in the PALLAS and MonarchE studies and for ribociclib in the NataLEE study, respectively).

In conclusion, abemaciclib was the first CDK4-6i to demonstrate a significant improvement in IDFS in patients with HR+/HER2- EBC. A longer follow-up is essential to confirm this survival benefit. Likewise, a careful evaluation of its clinical relevance and financial impacts should be conducted, before these results may translate into a clinical practice change. The divergence with the results from the PALLAS trial in the same setting is not fully understood, while we can speculate about the role of patient selection, distinct pharmacodynamics profiles of CDK4-6i or treatment adherence. Ongoing studies will shed further light on the role of CDK4-6i in EBC, and, hopefully, will provide new predictive biomarkers which are eagerly awaited to better select patients who may benefit from this class of agents.



Twitter Elisa Agostinetto @ElisaAgostinett and Evandro de Azambuja @E_de_Azambuja

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ORCID iDs

Elisa Agostinetto <http://orcid.org/0000-0003-0295-7511>

Evandro de Azambuja <http://orcid.org/0000-0001-9501-4509>

REFERENCES

- Spring LM, Wander SA, Andre F, *et al.* Cyclin-Dependent kinase 4 and 6 inhibitors for hormone receptor-positive breast cancer: past, present, and future. *Lancet* 2020;395:817–27.
- Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. *Lancet* 2015;386:1341–52.
- Johnston SRD, Harbeck N, Hegg R, *et al.* Abemaciclib combined with endocrine therapy for the adjuvant treatment of HR+, HER2–, node-positive, high-risk, early breast cancer (monarchE). *JCO* 2020;JCO.20.02514.
- Mayer EL, Gnant MI, DeMichele A, *et al.* LBA12 Pallas: a randomized phase III trial of adjuvant palbociclib with endocrine therapy versus endocrine therapy alone for HR+/HER2– early breast cancer. *Ann Oncol* 2020;31:S1145.
- Marra A, Curigliano G. Are all cyclin-dependent kinases 4/6 inhibitors created equal? *NPJ Breast Cancer* 2019;5:27.
- Sledge GW, Toi M, Neven P, *et al.* Monarch 2: Abemaciclib in combination with fulvestrant in women with HR+/HER2– advanced breast cancer who had progressed while receiving endocrine therapy. *J Clin Oncol* 2017;35:2875–84.
- Goetz MP, Toi M, Campone M, *et al.* Monarch 3: Abemaciclib as initial therapy for advanced breast cancer. *J Clin Oncol* 2017;35:3638–46.
- Sledge GW, Toi M, Neven P, *et al.* The effect of abemaciclib plus fulvestrant on overall survival in hormone receptor–positive, ERBB2–negative breast cancer that progressed on endocrine therapy—MONARCH 2: a randomized clinical trial. *JAMA Oncol* 2020;6:116–24.
- Finn RS, Martin M, Rugo HS, *et al.* Palbociclib and letrozole in advanced breast cancer. *N Engl J Med* 2016;375:1925–36.
- Cristofanilli M, Turner NC, Bondarenko I, *et al.* Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2–negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. *Lancet Oncol* 2016;17:425–39.
- Rugo HS, Finn RS, Diéras V, *et al.* Palbociclib plus letrozole as first-line therapy in estrogen receptor-positive/human epidermal growth factor receptor 2–negative advanced breast cancer with extended follow-up. *Breast Cancer Res Treat* 2019;174:719–29.
- Turner NC, Slamon DJ, Ro J, *et al.* Overall survival with Palbociclib and fulvestrant in advanced breast cancer. *N Engl J Med* 2018;379:1926–36.
- Slamon DJ, Fasching PA, Patel R, *et al.* NATALEE: phase III study of ribociclib (ribo) + endocrine therapy (et) as adjuvant treatment in hormone receptor–positive (HR+), human epidermal growth factor receptor 2–negative (HER2–) early breast cancer (EBC). *J Clin Oncol* 2019;37:TPS597.
- Martin Jimenez M, Bachelot T, Barrios C, *et al.* EarLEE-1: a phase 3 study of ribociclib + endocrine therapy (et) for adjuvant treatment of patients (PTS) with hormone receptor-positive (HR+), human epidermal growth factor receptor 2–negative (HER2–), high-risk, early breast cancer (EBC). *Ann Oncol* 2017;28:v107.
- O'Shaughnessy J, Alba E, Bardia A, *et al.* Abstract OT3-05-06: EarLEE-2: a phase 3 study of ribociclib + endocrine therapy (et) for adjuvant treatment of patients with hormone receptor-positive (HR+), human epidermal growth factor receptor 2–negative (HER2–), intermediate-risk, early breast cancer. *Cancer Res* 2018;78:OT3-05-06 LP-OT3-05–6.
- Anderson SJ, Wapnir I, Dignam JJ, *et al.* Prognosis after ipsilateral breast tumor recurrence and locoregional recurrences in patients treated by breast-conserving therapy in five national surgical adjuvant breast and bowel project protocols of node-negative breast cancer. *J Clin Oncol* 2009;27:2466–73.
- Wander SA, Cohen O, Gong X, *et al.* The genomic landscape of intrinsic and acquired resistance to cyclin-dependent kinase 4/6 inhibitors in patients with hormone Receptor–Positive metastatic breast cancer. *Cancer Discov* 2020;10:1174–93.
- Álvarez-Fernández M, Malumbres M. Mechanisms of sensitivity and resistance to CDK4/6 inhibition. *Cancer Cell* 2020;37:514–29.
- Finn RS, Liu Y, Zhu Z, *et al.* Biomarker analyses of response to cyclin-dependent kinase 4/6 inhibition and endocrine therapy in women with treatment-naïve metastatic breast cancer. *Clin Cancer Res* 2020;26:110–21.