



## Short communication

## CDK 4/6 inhibitors mired in uncertainty in HR positive and HER2 negative early breast cancer

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## ARTICLE INFO

## Article history:

Received 31 October 2020

Received in revised form

6 December 2020

Accepted 10 December 2020

Available online 13 December 2020

## Keywords:

Adjuvant therapy

Hormone receptor positive breast cancer

Cyclin-dependent kinase 4/6 inhibitors

Palbociclib

Abemaciclib

## ABSTRACT

Cell-cycle abnormalities are common in estrogen receptor- and/or progesterone receptor-positive, and HER2-non-overexpressing (HR+/HER2-) breast cancer, and have long been considered potential therapeutic targets. Cyclin-dependent kinase (CDK) 4/6 inhibitors have dramatically changed the therapeutic management of HR+/HER2-advanced breast cancer by prolonging progression-free and overall survival when given in combination with endocrine therapy. In this article, available data from PALLAS and monarchE trials regarding the efficacy and toxicity of adjuvant combined therapy with CDK 4/6 inhibitors and endocrine therapy in HR+/HER2-early breast cancer are reviewed, and relevant issues including study hypothesis, patient selection, and duration of follow-up are discussed.

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Breast cancer (BC) is a significant public health problem, accounting for approximately 24% of new cancers diagnosed in women each year worldwide [1]. According to the International Agency for Research on Cancer, nearly 2 million new cases were diagnosed in 2018 [1], and incident cases are expected to increase by almost 50% in the next two decades, rendering it the most prevalent cancer [2]. Seven percent of all cancer deaths are attributed to BC, making it the second leading cause of cancer-related deaths, and the first among females [1]. Among BC subtypes, defined by coupled hormone receptor (HR; estrogen receptor [ER] and/or progesterone receptor [PR]), and human epidermal growth factor receptor 2 [HER2] status, the most common is HR positive (ER-positive and/or PR-positive) and HER2 non-overexpressing (HER2 negative), hereinafter HR+/HER2-, comprising almost 70% of all newly diagnosed cases [2]. Given the large number of patients this represents, even small improvements in therapy may save thousands of lives annually.

Systemic treatment was initially employed along with surgery and radiotherapy for extensive loco-regional disease control, but became a main component of BC management once BC was recognized as a systemic disease at onset, due to the potential for

lymphatic, and blood dissemination [3]. Since then, the type of post-operative treatment given has been guided by the accumulated experience from treating patients with metastases. Starting from the late seventies, incremental progress has been primarily achieved through therapeutic escalation, both for chemotherapy, and endocrine therapy (ET) [4,5]. Nevertheless, especially in node positive cases, the cumulative risk of HR+/HER2- BC distant recurrences remained steady for decades, and optimal adjuvant systemic therapy for these early-stage high-risk patients is still recognized as an unmet clinical need. Of note, the risk of recurrence and death from HR+/HER2- BC vary over time. There is a sharp peak at 2 years, which defines the intrinsic endocrine resistant cases, and then a gradually decreasing plateau follows thereafter for at least 20 years from diagnosis [6]. These findings have implications for oncologists. An early adjuvant treatment effect may diminish with time. On the other hand, a lag time may exist before any pronounced effect is observed.

In advanced HR+/HER2- BC, Cyclin-Dependent Kinase (CDK) 4/6 inhibitors have been practice changing, and are now considered the standard of care, in combination with ET, for first or second lines of treatment. In early-stage HR+/HER2- BC, two different adjuvant trials have recently been reported that investigate the benefits of adding CDK4/6 inhibitors to ET. The results raise as many questions as answers provided.

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The PALLAS (NCT02513394) study assumed that therapeutic outcome in early-stage HR+/HER2- BC might be improved through the use of palbociclib [7]. The PALLAS investigators opened enrollment in September 2015 to a phase III study comparing adjuvant palbociclib plus the physician's choice of ET to ET alone in stage II/III disease. Palbociclib was administered at 125 mg/day as in the metastatic setting for 2 years concurrently with adjuvant ET. Patients were to enroll within 12 months of diagnosis and within 6 months of beginning adjuvant ET. The study focused on the superiority comparison between the combination arm and the ET arm; and assumed that 469 invasive disease-free survival (iDFS) events would provide 85% power to detect a hazard ratio of 0.75 at  $p = 0.05$ , and an absolute iDFS benefit of 4.4% at 5 years. In January 2020, after the second interim analysis showed the study was unlikely to reach the predefined efficacy criteria, the IDMC recommended that patients still on palbociclib would stop this treatment and continue ET alone; the trial will however continue its follow-up until at least 10 years. After a median follow-up of 23.7 (16.9–29.2) months, and 351 events, 3-year iDFS did not differ between the two arms (palbociclib and ET 88.2% versus ET alone 88.5%, Hazard Ratio (HR) 0.93, 95% confidence interval (CI) 0.76–1.15), crossing the pre-specified futility boundary. Was the PALLAS trial design wise? The crucial issue is whether the combination would enhance therapeutic benefit in high-risk BC. Among the 5760 patients, 4729 (82.1%) presented with stages IIB/III disease, but 1013 (17.6%) had stage IIA, potentially muddying the waters. However, the statistical assumption of PALLAS was event-rather than time-driven, and the futility analysis was conducted after 67% of the total expected events had occurred. Most of these events (76%) occurred in patients diagnosed with high-risk BC, ie patients with  $\geq 4$  involved nodes (N2), or with 1–3 involved nodes (N1) with either a tumor size of at least 5 cm (T3/T4), or histologic grade 3, and it is unlikely that enriching the study population with additional cases would have altered the outcome. This is evidenced by the exploratory subgroup analysis, which showed no advantage to palbociclib in high-as compared to lower-risk patients (HRs 0.89, 95%CI 0.70–1.13 versus 0.93, 95%CI 0.61–1.43,  $p = 0.87$ ). Should we have expected a greater benefit of palbociclib in stage III than in stage II BC patients? Although large primaries and nodal metastases may be enriched with the expression of cell cycle regulators [8–10], including the palbociclib targets, proliferation rates are not necessarily higher in stage III as compared to stage II, hence there is currently no biological rationale to expect a differential activity of palbociclib according to T-size and nodal status at presentation, and stage is a prognostic rather than a predictive factor for CDK 4/6 inhibitors.

The randomized controlled study monarchE [11], investigated the addition of another CDK 4/6 inhibitor, abemaciclib to adjuvant ET. This study included 5637 patients with high-risk disease, defined as the presence of at least N2, or N1 plus one or more of the following features: T3/T4; histologic grade 3; or centrally evaluated Ki67 levels of at least 20%. monarchE opened in July 2017 and is similar to PALLAS in terms of the primary endpoint, and study drug administration period. However, monarchE excluded patients with node-negative disease and allowed only up to 12 weeks of prior ET. During a median follow-up of approximately 15.5 months, the addition of abemaciclib, at a dose of 150 mg twice daily for up to 2 years, to standard of care ET reduced the risk for iDFS by a significant 25%. At the 2-year mark, 92.2% of patients who received abemaciclib plus ET were free from iDFS compared with 88.7% of those given ET alone.

The absence of statistical heterogeneity indicated consistency between the two trials in magnitude and direction of the relative risk of relapse sample estimates. Despite the wide 95%CI intervals, which indicated imprecise estimates, assuming in absolute terms a 2-year survival of 90% in the ET arm, the PALLAS Hazard Ratio

translated to a iDFS of 90.7% while that of monarchE to 92.4%, an absolute difference of 1.7%. Notwithstanding the above, PALLAS enrolled a group of patients who did not relapse as early as the those of the monarchE study, as suggested by the recurrence rates reported in Table 1 together with other major differences between the two trials.

Considering the mixed results of the PALLAS and monarchE trials, how does the addition of palbociclib compare with that of abemaciclib to ET? Multiple possibilities exist. First, abemaciclib can be administered continuously, and has greater inhibitory activity on CDK4 over CDK6 in enzymatic assays. Both properties have been credited for the differential effect of abemaciclib over palbociclib in the advanced BC setting [12–14], although there is no head-to-head comparison of the two agents and the differences eventually seen between clinical trials may be due to many confounding factors. Notably, abemaciclib and palbociclib have different toxicity profiles, with gastrointestinal and hematological adverse effects the most significant sequelae, respectively. The PALLAS study reported higher rates of discontinuation and interruption compared to monarchE (42% and 16.6%, respectively). The palbociclib discontinuation and interruption rate, primarily due to per protocol management of neutropenia, may have caused pharmacologic failure since patients cannot benefit from a drug they do not receive. Furthermore, drug discontinuation may be detrimental in itself. An exploratory analysis of post-progression-free survival, defined as the time from palbociclib progression until progression from further-line treatment, showed shorter duration of successive treatment line in patients previously treated with palbociclib as compared to those treated with endocrine therapy alone [13], suggesting a possible value in maintaining palbociclib beyond progression that merits to be explored in randomized phase 3 trials. Continuous dosing and other strategies, including lowering the dose according to toxicity to allow maintaining treatment (i.e. dose reductions are most likely less detrimental than dose interruptions) should be further investigated to find out the optimal palbociclib schedule [15]. Lastly, abemaciclib showed a greater progression free and overall survival advantages in patients with intrinsic endocrine resistant than endocrine sensitive tumors. For palbociclib, the opposite was true [13]. Given that the median duration of follow-up for both PALLAS and monarchE was less than 2 years, all events occurred in patients with intrinsic endocrine resistant tumors, and therefore limited benefit was derived from palbociclib over abemaciclib. If this hypothesis turns out to be correct, palbociclib could prevent delayed events in endocrine sensitive cases, hence a possible benefit might be seen with longer follow-up.

To be clear, PALLAS is a statistically negative trial, whereas monarchE is a statistically positive trial. To be equally clear, compared to study results of CDK4/6 inhibitors in metastatic disease, both trials were disappointing and raised important methodological concerns.

Planned interim analysis and secondary early trial discontinuation are essential to safeguard patient health. Given the high cost of long-term clinical trials, investing in studies unlikely to produce (positive) results, is unreasonable. The PALLAS and monarchE studies sought to quickly amass the required number of events for futility and efficacy analyses to save time, and probably money. Hence, almost 6000 patients were rapidly enrolled in each study to collect a maximum of 350 events in an extraordinarily short follow-up period of 2 years or less. If we were dealing with rapidly progressive disease, the strategy would be welcomed. However, in the context of HR+/HER2- BC, early- and long-term treatment effects are non-proportional. Early stoppage of clinical trials might well obscure important late effects. Alternatively, some adjuvant therapies may only show early benefits, with longer follow-up diluting those effects. It is therefore crucial to maintain follow-up for a

**Table 1**

Major differences between PALLAS and monarchE studies according to study patient population, experimental treatment and outcomes.

	PALLAS (n = 5760)	monarchE (n = 5637)
<b>STUDY PATIENT POPULATION</b>		
Stage, n (%)		
IA	0	3 (0.1)
IIA	1013 (17.6)	676 (12.0)
IIB	1919 (33.4)	776 (13.8)
III	2810 (48.9)	4158 (74.1)
missing data	18 (0.3)	24 (0.4)
<b>T-size, n (%)</b>		
0, 1, x, is	1057 (18.4)	1545 (27.8)
2	3239 (56.2)	2788 (50.2)
3, 4	1463 (25.4)	1222 (22.0)
missing data	1 (0.02)	82 (1.5)
<b>Nodal status, n (%)</b>		
0	750 (13.0)	14 (0.2)
1–3 positive nodes	2842 (49.3)	2262 (40.1)
≥4 positive nodes	2167 (37.6)	3359 (59.6)
missing data	1 (0.02)	2 (0.04)
<b>Grade, n (%)</b>		
1	613 (11.2)	424 (7.9)
2	3280 (59.7)	2768 (51.8)
3	1603 (29.2)	2156 (40.3)
missing data	264 (4.6)	289 (5.1)
<b>Ki67</b>		
<20%	NR	1926 (43.6)
≥20%	NR	2495 (56.4)
missing data	NA	1216 (21.6)
<b>EXPERIMENTAL TREATMENT</b>		
Drug	palbociclib	Abemaciclib
Schedule	3 weeks on/1 off	Continuous
Timing of initiation with respect to ET (months)	6	3
Discontinuation rate (%)	42	16.5
<b>OUTCOME</b>		
Median follow-up (months)	23.7	15.5
Events		
number	351	323
% of the total expected	67	75
% of the randomized patients	1.16	1.33
iDFS	3-year iDFS	2- year iDFS
	88.2 vs 88.5%	92.2 vs 88.7%
	HR 0.93	HR 0.75
	95%CI 0.76–1.15	95%CI 0.60–0.93
Recurrence rate (per 100 person-years)^		
Control arm	4.1	6.0
Experimental arm	4.2	4.1

NR = not reported; NA = not applicable; ET = endocrine therapy; iDFS = invasive disease free survival. ^Recurrence rate as calculated starting from the iDFS data, and assuming a constant rate of recurrence during the follow-up period.

longer period of time for both trials.

An additional methodological issue we cannot ignore is that HR interpretation in patients with favourable prognosis followed for a short period may be confounded by temporal fluctuations. In fact, the interval HR estimates over time may result wide because of the low observed events and detection of its fluctuations may be prevented even in the case that proportional hazard assumption is formally tested [16].

The PALLAS and monarchE studies followed an add on design where CDK inhibitors were given in combination with ET after conventional chemotherapy. The small incremental difference produced by abemaciclib is not surprising given that only 6% of patients relapsed and the strong neo-/adjuvant chemotherapy backbone in 96% of patients made a larger absolute benefit unlikely. Notwithstanding the above, the exploratory subgroup analysis did show some palbociclib effect in patients not exposed to chemotherapy (Hazard ratio 0.71, 95%CI 0.39–1.28), and in those with node negative (Hazard ratio 0.65, 95%CI 0.33–1.26) disease likely exposed to less intensive regimens. Considering that the benefit of abemaciclib was consistent with the absolute differences in disease free survival event rate of 3.5% and 1.8% reported for taxanes over

anthracyclines and anthracyclines over CMF in HR+/HER2- BC [17], and that possibly CDK inhibitors act as early as chemotherapeutic agents, their effect could be explored in the context of chemo-free adjuvant regimens, replacing rather than as additive to chemotherapy.

An additional issue is that neither in PALLAS nor in monarchE, there was a selection of patients based on biomarkers. This yielded a number-needed-to-treat (NNT) of 132 patients at the 3-year observation mark for the PALLAS study and 38 patients at the 2-year observation mark for the monarchE study [18]. The challenge lies in avoiding overtreatment. None of the available genomic signatures was developed nor can be used to select patients for treatment with CDK4/6 inhibitors [19]. However, their potential role in identifying high-risk patients, and assisting therapeutic decision with these agents should be explored. Despite intense research efforts, we still do not have a validated predictive biomarker to adequately select who is most likely to benefit from these agents [20]. There are however some promising molecular signals [21] and efforts should continue.

A final methodological issue is related to the wide 95%CI intervals of HRs, the primary measure of treatment effect. Wide 95%CI

intervals translate to estimates of NNT too imprecise to be clinically useful. For the PALLAS study the 95%CI intervals matched a minimum NNT to benefit of 38 patients, but also a minimum NNT to harm of 69 patients by 3 years since randomization. For the monarchE study the 95%CI intervals translated to a minimum and a maximum NNT to benefit by 2 years since randomization of 23 and 134 patients, respectively.

So where do we go from here? The clinical value of CDK 4/6 inhibitors plus ET in early stage HR+/HER2- BC will be further informed by results from currently ongoing studies including the NATALEE (NCT03701334), exploring a longer duration of adjuvant treatment with CDK 4/6 inhibitor with 3 years of adjuvant ribociclib, and the PENELOPE-B (NCT01864746), offering palbociclib specifically to patients not attaining a pathological complete response after neoadjuvant chemotherapy, that was announced not to have met its primary endpoint of IDFS [22]. In the meanwhile, if abemaciclib is approved, it will find a place in adjuvant therapy for patients with multiple involved lymph nodes or for those accepting of substantial toxicity for a marginal benefit. PALLAS and monarchE should be the last trials of their generation. It is simply not feasible to continue adding more therapy for all HR+/HER2-breast cancer patients selected solely on anatomic staging. The toxic effects, and costs, are just too great for too many, to benefit too few.

### Declaration of competing interest

SDC reports honoraria and advisory board from Novartis and Pierre-Fabre outside the scope of this work; she was the Italian coordinator of the PARSIFAL study (NCT02491983). LP declared no conflict of interest. FC declares consultancy role for: Amgen, Astellas/Medivation, AstraZeneca, Celgene, Daiichi-Sankyo, Eisai, GE Oncology, Genentech, GlaxoSmithKline, MacroGenics, Medscape, Merck-Sharp, Merus BV, Mylan, Mundipharma, Novartis, Pfizer, Pierre-Fabre, prIME Oncology, Roche, Sanofi, Samsung Bioepis, Seattle Genetics, Teva.

### Acknowledgement

SDC is the recipient of the IG 20774 grant from Fondazione Associazione Italiana Ricerca sul Cancro (AIRC).

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