Cyclin-dependent kinases 4 and 6 inhibitors (CDK4/6i) versus chemotherapy in luminal B early breast cancer: lessons from the CORALLEEN trial

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About 70% of all invasive breast cancers are hormone receptor (HR)-positive and human epidermal growth factor receptor 2 (HER2)-negative (1). Cyclin-dependent kinases 4 and 6 inhibitors (CDK4/6i) plus endocrine therapy represents nowadays the standard of care for pre- and post-menopausal women with HR-positive/HER2-negative advanced breast cancer both in the first- and second-line setting (2-5). Six studies have reported the efficacy of CDK4/6i in the neoadjuvant setting: PALLET, NeoPalAna, neoMONARCH, N007, CORALLEEN and NeoPAL (6-11). However, only the last two trials randomized patients between neoadjuvant endocrine treatment plus CDK4/6i *vs.* neoadjuvant chemotherapy (10,11). CORALLEEN, the study that is the main focus of this editorial, is a parallel arm, randomized, phase II trial conducted in 21 centers in Spain in which 106 postmenopausal women with HR-positive/HER2-negative, stage I–IIIA, luminal B by PAM50 (Prosigna) breast cancer were enrolled. A total of 52 patients received six cycles of ribociclib (600 mg daily for 21 days, every 4 weeks) plus letrozole (2.5 mg daily), while 54 patients received four cycles of doxorubicin (60 mg/m^2) and cyclophosphamide (600 mg/m^2) every 3 weeks followed by 12 cycles of weekly paclitaxel (80 mg/m^2). A PAM50 risk of relapse (ROR) prognostic score was evaluated for each patient at study entry. PAM50 ROR score was calculated by integrating gene expression data, tumor size and nodal status and three classes were assigned, namely low, intermediate and high ROR. Most patients had T2

tumors, no axillary node involvement, Ki67 expression level >14%, and a high-ROR disease at baseline (*Table 1*) (10). NeoPAL is also a non-comparative, phase II study in which 106 patients with HR-positive/HER2-negative, stage II–III, luminal B or node-positive luminal A PAM50-defined breast cancer were enrolled. A total of 53 patients received palbociclib (125 mg daily, 3 weeks on and 1 week off) plus letrozole (2.5 mg daily) for 19 weeks, while 53 patients received three cycles of FEC100 (5-fluorouracil 500 mg/m^2, epirubicin 100 mg/m^2, and cyclophosphamide 500 mg/m^2, every 3 weeks) followed by three cycles of docetaxel (100 mg/m^2, every 3 weeks). Similarly, to the Spanish study, most patients in NeoPAL had T2, luminal B, Ki67 expression ≥14%, and high-ROR breast cancers. However, in the NeoPAL trial patients with luminal A, node-positive disease were also allowed (*Table 1*) (11). Two strengths of both trials were: (I) a strong chemotherapy regimen in the non CDK4/6i arm; (II) the patient selection through a prognostic gene signature (PAM50), thus obtaining a homogenous study population (10,11). In a cohort of 1,691 patients with available PAM50 results, patients with luminal A subtype had a lower cumulative probability of dying from breast cancer compared to those with luminal B (7.1% *vs.* 16.2% at 10 years) (12).

How did CDK4/6i perform compared to chemotherapy in terms of clinical and radiological response? In the CORALLEEN study, chemotherapy seemed to be superior to CDK4/6i in terms of objective response rate (ORR)

Page 2 of 7

De Angelis et al. CDK4/6i *vs*. chemotherapy in luminal breast cancer

Table 1 Baseline characteristics in the CORALLEEN and NeoPAL trials

Characteristics	CORALLEEN trial		NeoPAL trial	
	Ribociclib arm (n=52)	Chemotherapy arm (n=54)	Palbociclib arm (n=53)	Chemotherapy arm (n=53)
Age, years				
Median [range]	63.0 [56.5–70.3]	64.0 [58.3–71.8]	65 [49–78]	62 [48–80]
Tumour size, n (%)				
T0–1	3 [6]	3 [6]	10 (19.2)	13 (26.0)
T2	40 [77]	43 [80]	38 (73.1)	36 (72.0)
T3	9 [17]	8 [15]	4 (7.7)	1 (2.0)
Lymph node status, n (%)				
N0	31 [60]	31 [57]	23 (43.4)	25 (47.2)
N1	19 [37]	22 [41]	30 (56.6)	28 (52.8)
N2	2 [4]	1 [2]	–	–
Tumour stage, n (%)				
I	2 [4]	2 [4]	–	–
II	43 [83]	45 [83]	49 (92.4)	52 (98.1)
III	7 [14]	7 [13]	4 (7.6)	1 (1.9)
Histological type, n (%)				
Invasive NOS	41 [79]	48 [89]	44 (83.0)	41 (77.4)
Lobular	10 [19]	6 [11]	7 (13.2)	10 (18.8)
Other	1 [2]	0 [0]	2 (3.8)	2 (3.8)
Grade, n (%)				
I	–	–	6 (11.3)	3 (5.6)
II	–	–	35 (66.1)	33 (62.3)
III	–	–	12 (22.6)	17 (32.1)
Intrinsic subtype, n (%)				
Luminal A	–	–	6 (11.3)	6 (11.3)
Luminal B	52 [100]	54 [100]	47 (88.7)	47 (88.7)
Ki67 expression, n (%)				
≤14%	3 [6]	2 [4]	15 (28.3)[‡]	18 (34.0)[‡]
>14%	49 [94]	51 [94][†]	38 (71.7)[§]	35 (66.0)[§]
ROR risk class, n (%)				
Intermediate	8 [15]	6 [11]	7 (13.2)	9 (17.0)
High	44 [85]	48 [89]	46 (86.8)	44 (83.0)

[†], Ki67 value is missing for 1 patient in chemotherapy arm in the CORALLEEN trial; [‡], patients with Ki67 <14% in the NeoPAL trial; [§], patients with Ki67 ≥14% in the NeoPAL trial. NOS, not otherwise specified.

Table 2 Efficacy parameters in the CORALLEEN and NeoPAL trials

Parameters	CORALLEEN trial		NeoPAL trial	
	Ribociclib arm (n=49)	Chemotherapy arm (n=52)	Palbociclib arm (n=53)	Chemotherapy arm (n=53)
Clinical-radiological response, n (%)				
ORR by MRI	28 (57.1)	41 (78.8)	–	–
ORR by US	–	–	25 (47.2)	24 (45.3)
ORR by physical examination	31 (63.3)	28 (53.8)	38 (71.7)	38 (71.7)
Breast conserving surgery	44 (84.6)[†]	39 (72.2)[†]	36 (69.2)[‡]	35 (68.6)[‡]
Pathological response, n (%)				
pCR (ypT0/Tis ypN0)	0 (0)	3 (5.8)	2 (3.8)[‡]	3 (5.9)[‡]
RCB 0–I	3 (6.1)	6 (11.8)	4 (7.7)[‡]	8 (15.7)[‡]
Biological response, median % [range]				
Ki67 level	3 [1–8]	10 [3–20]	3 [1–40]	9 [2–15]
Molecular response, n (%)				
Luminal A intrinsic subtype conversion	43 (87.8)	43 (82.7)	–	–
Other response measures, n (%)				
Low-ROR score	23 (46.9)	24 (46.2)	–	–
PEPI score 0	11 (22.4)	9 (17.3)	6 (11.5)[§]	8 (16.0)[§]

[†], in the CORALLEEN trial, 44 out of 52 evaluable patients in ribociclib arm and 39 out of 54 evaluable patients in chemotherapy arm received breast conserving surgery. [‡], in the NeoPAL trial, patients evaluable for breast conserving surgery, pCR and RCB were 52 and 51 in palbociclib arm and chemotherapy arm, respectively; pCR and RCB results were reported as per central review. [§], PEPI score for relapse-free survival was tested in 52 patients in palbociclib arm and 50 patients in chemotherapy arm; 9 out of 51 (17.6%) evaluable patients in palbociclib arm and 4 out of 50 (8.0%) evaluable patients in chemotherapy arm reported PEPI score 0 for breast cancer-specific survival. ORR, objective response rate; US, ultrasound; MRI, magnetic resonance imaging; pCR, pathologic complete response; Tis, tumour in situ; RCB, residual cancer burden; ROR, risk of relapse; PEPI, preoperative endocrine prognostic index.

assessed by magnetic resonance imaging (MRI). However, more patients in ribociclib arm received breast conserving surgery compared to chemotherapy arm. No differences between the two arms were suggested when ORR was evaluated by physical examination (*Table 2*) (10). NeoPAL also showed a similar ORR between the two treatment arms whether physical examination or ultrasound were used. Indeed, in this trial the same percentage of patients underwent breast conserving surgery in the two arms (*Table 2*) (11). Pathologic complete response (pCR) and residual cancer burden (RCB) of 0–I were low in both trials, with patients treated with chemotherapy appearing more likely to achieve pCR and RCB 0–I compared to the ones treated with CDK4/6i (*Table 2*) (10,11). Of note, pCR has been associated with improved event-free survival [hazard ratio 0.27, 95% confidence interval

(CI): 0.14–0.50] in high proliferative, HR-positive/ HER2-negative breast cancer (13). Moving to biological response, both trials showed greater reduction in Ki67 expression levels with CDK4/6i than with chemotherapy (*Table 2*) (10,11). Of note, this decrease in Ki67 could be underestimated due to Ki67 rebound occurring when CDK4/6i are suspended some days before surgery, as the NeoPalAna study has previously shown (7). This issue is mainly applicable to the CORALLEEN trial where 13.1 [standard deviation (SD) 14.6] was the mean number of days between the last dose of ribociclib and surgery (10). Conversely, in NeoPAL, patients should have been operated 24 hours after the last dose of palbociclib (11). However, in this trial the median time between the last dose of palbociclib and surgery was not reported (10,11). The conversion to luminal A subtype

Page 4 of 7

De Angelis et al. CDK4/6i vs. chemotherapy in luminal breast cancer

assessed by PAM50 at surgery was evaluated only in the CORALLEEN trial. A numerically higher percentage of conversion to luminal A subtype was observed in the ribociclib arm compared to chemotherapy arm (*Table 2*) (10). Thus, CDK4/6i could be at least as effective as chemotherapy in terms of Ki67 reduction and conversion to luminal A subtype. This was also the case when efficacy was assessed by combining clinicopathological and molecular variables. In the CORALLEEN study, similar rates of low-ROR score at surgery were found in the ribociclib and chemotherapy arms (10). ROR score was evaluated exclusively at baseline in the NeoPAL trial (*Table 2*) (11). Despite some numerical differences, similar percentages of patients with chemotherapy or CDK4/6i in both trials achieved preoperative endocrine prognostic index (PEPI) score 0 (*Table 2*) (10,11), known to be associated to more favorable relapse-free survival (14).

Results reported in the other four neoadjuvant trials are in line with those seen in the CDK4/6i arm of CORALLEEN and NeoPAL (6-9). In the NeoPalAna trial, patients received 4 weeks of anastrozole followed by 4 cycles of palbociclib plus anastrozole before surgery. In line with NeoPAL trial, 80.5% and 40.7% of patients reached ORR by physical examination and by ultrasound respectively, and no pCR was recorded. At the biological level, complete cell cycle arrest (CCCA, defined as Ki67 ≤2.7%) rate was significantly higher at cycle (C) 1 day (D) 15 with palbociclib plus anastrozole than that at C1D1 with anastrozole monotherapy (87% *vs.* 26%; P<0.001), both in luminal A (P=0.008) and luminal B (P=0.02) tumors (PAM50-defined) at baseline. Furthermore, PAM50 proliferation score (using a 11-gene signature) was significantly reduced from C1D1 to C1D15 (P<0.0001) and correlated with Ki67 drop at all timepoints (7). Also, in the PALLET study, there was no evidence that the addition of palbociclib to letrozole increased ORR measured by ultrasound (54.4% *vs.* 49.5%; P=0.20) or pCR rates (1.1% *vs.* 3.3%; P=0.43). Moreover, no difference in the proportion of patients that have undergone breast conserving surgery was seen (60.8% in palbociclib arm *vs.* 59.2% in letrozole arm). Conversely, median log-fold change in Ki67 (–4.1 *vs.* –2.2; P<0.001) and poly(ADP-ribose) polymerase (apoptosis, –0.80 *vs.* –0.42; P<0.001) was greater with palbociclib plus letrozole than letrozole alone, and there was a significant difference in CCCA (90.4% *vs.* 58.5%; P<0.001), too (6). In the neoMONARCH study, Ki67 at week 2 decreased by a geometric mean change of –93% in the abemaciclib plus anastrozole arm, –91% in the abemaciclib arm, and

–63% in the anastrozole arm (P<0.001). Moreover, patients treated with abemaciclib ± anastrozole reported a significant higher CCCA compared to anastrozole alone after 2 weeks (P<0.001). Furthermore, abemaciclib ± anastrozole led to a significant decrease of cell cycle-associated genes (*FOXM1*, *RRM2*, *CCNE1*, *MKI67*, *TOPO2A*) at 2 weeks (P<0.05) (8). Finally, in the small N007 study of 20 patients that received palbociclib and endocrine treatment, a clinical ORR of 85% and ORR by ultrasound of 70% were observed, and only one pCR was recorded. The mean value of Ki67 (P=0.044) and proliferation-associated genes (*BIRC5*, *UBE2C* and *DHCR7*; P<0.001), significantly decreased from baseline to surgery. A significant reduction in mean EndoPredict (EP) score occurred from baseline to surgery (6.87 *vs.* 5.25; P<0.0001) as well. Only 1 patient at surgery had PEPI 0 score, and 9 patients reached low EP clin score (9).

How do CDK4/6i compare to chemotherapy in the metastatic setting? Only 2 reported trials have directly addressed this question. The first one, is a phase III trial (PEARL) that enrolled 601 postmenopausal patients with HR-positive/HER2-negative metastatic breast cancer resistant to previous non-steroidal aromatase inhibitors (AIs), and allocated them to receive palbociclib plus exemestane (cohort 1)/fulvestrant [cohort 2, added after publication of data about *ESR1* mutations as mechanism of resistance to AIs (15)] or capecitabine alone. Palbociclib plus fulvestrant did not show a different median progression-free survival (PFS) compared to capecitabine alone [7.5 *vs.* 10 months (m); adjusted hazard ratio 1.09, 95% CI: 0.83–1.44; P=0.537]. Similarly, there was no improvement in median PFS in *ESR1* wild-type patients treated with palbociclib plus fulvestrant/exemestane compared to capecitabine alone (8.0 *vs.* 10.6 m; adjusted hazard ratio 1.08, 95% CI: 0.85–1.36; P=0.526). In terms of ORR, palbociclib plus fulvestrant was not superior to capecitabine (26.7% *vs.* 33.3%) (16). The second study (Young PEARL), was a phase II trial, in which 184 premenopausal women with HR-positive/HER2-negative metastatic breast cancer were randomized to receive palbociclib, exemestane, and leuprolide or capecitabine. All patients were previously treated with tamoxifen. Contrary to the PEARL study, the palbociclib arm showed a significant increase in median PFS compared to the chemotherapy arm (20.1 *vs.* 14.4 m; hazard ratio 0.659, 95% CI: 0.437–0.994; P=0.0235). No difference in ORR was detected (37% *vs.* 34% in the palbociclib and capecitabine arms, respectively; P=0.781) (17). In a network meta-analysis, no chemotherapy was significantly better than CDK4/6i and endocrine treatment in terms of PFS,

while CDK4/6i plus endocrine treatment was better than endocrine treatment alone (18). Thus, given the favorable toxicity profile of CDK4/6i over chemotherapy, this class of agents is the preferred option for 1st line treatment according to different guidelines. However, the metastatic setting is completely different from the early setting. In the early setting cure is the goal and thus strong data from a phase 3 trial are needed in order to demonstrate a non-inferiority of a CDK4/6i, chemotherapy-free regimen. We are not aware of any such trial ongoing in the general population. There is one trial in the elderly population, the European Organization for the Research and Treatment of Cancer (EORTC) APPALACHES trial that evaluates a chemotherapy-free, CDK4/6i and endocrine adjuvant treatment in elderly patients that will be otherwise candidates for adjuvant chemotherapy (NCT03609047).

Thus, we think that the CORALLEEN study could be most interesting in terms of identifying the patients that are resistant to CDK4/6i. Future translational research aiming to understand the mechanisms of primary treatment resistance in these patients is warranted. Apart from Ki67 and PAM50, no other biomarkers have been evaluated in the CORALLEEN and NeoPAL trials, so far. *PIK3CA* mutation status has not been associated with sensitivity to CDK4/6i. Indeed, in NeoPalAna and neoMONARCH studies Ki67 suppression and CCCA at C1D15 occurred regardless of *PIK3CA* mutation (7,8). In the PALOMA-3 trial, the addition of palbociclib to fulvestrant improved PFS regardless of *PIK3CA* mutation status (19). In the NeoPalAna study, significantly elevated mRNA expression levels of *CCND3*, *CCNE1*, and *CDKN2D* genes at C1D15 were found in the resistant group (7). Also, in the neoMONARCH study numerically high mRNA expression levels of *CCNE1* and *E2F1* at week 2 were found in resistant patients (8). These findings are supported by the PALOMA-3 trial results where high median *CCNE1* mRNA expression correlated with worse PFS (false discovery rate-adjusted P=0.0238) (20). Moreover, low expression of *RB1* mRNA was associated with resistance to abemaciclib monotherapy in the neoMONARCH trial (8). This is in line with previous results showing that inactivating mutations in the *RB1* gene might be associated with resistance to CDK4/6i (21). Genomic alterations of the fibroblast growth factor receptor (FGFR) or Hippo pathways have recently emerged as mechanisms of resistance to CDK4/6i in the metastatic setting (22,23), but they have not yet been explored in the early setting. Interesting data about immunomodulation mediated by CDK4/6i in the early

setting emerged from the neoMONARCH trial where the combination of abemaciclib plus anastrozole enhanced immune response genes related to INFγ production and PD-1 signaling, without increasing stromal tumor-infiltrating lymphocytes (TIL) levels (8). This is consistent with preclinical studies suggesting that CDK4/6i exposure might enhance the anti-tumor immune response (24). Results from ongoing, chemotherapy-free studies evaluating the combination of CDK4/6i and immunotherapy in the neoadjuvant setting (NCT03573648, NCT04075604, NCT04088032) are eagerly awaited.

In conclusion, although low-ROR score was observed at surgery in almost half of the patients treated with letrozole and ribociclib in the CORALLEEN trial, the prognostic significance of this low-ROR score at surgery has not been established as acknowledged by the authors. Thus, no statement can be made for these patients concerning their need or not for adjuvant chemotherapy. The role of adjuvant CDK4/6i in the early setting will be clarified from the large ongoing phase 3 adjuvant trials (NCT01864746, NCT02513394, NCT03155997, NCT03701334). The different neoadjuvant studies might serve as translational research platforms to help understand resistance to CDK4/6i but ultimately the results from these studies will need to be validated in the adjuvant studies. As of today, 806 patients have been enrolled in the six published neoadjuvant CDK4/6i trials, and >2,000 patients are being enrolled in additional neoadjuvant CDK4/6i trials (25). A collaborative effort using the samples from patients treated with CDK4/6i in the above neoadjuvant trials might provide important insights into the mechanisms of resistance to this class of compounds and help oncologists with an improved selection of women who may be spared chemotherapy.

Footnote

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Page 6 of 7

De Angelis et al. CDK4/6i *vs.* chemotherapy in luminal breast cancer

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