



Molecular downstaging: a new paradigm for neoadjuvant endocrine therapy

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Comment on: Prat A, Saura C, Pascual T, *et al.* Ribociclib plus letrozole versus chemotherapy for postmenopausal women with hormone receptor-positive, HER2-negative, luminal B breast cancer (CORALLEEN): an open-label, multicentre, randomised, phase 2 trial. *Lancet Oncol* 2020;21:33-43.

Submitted Jul 20, 2020. Accepted for publication Aug 04, 2020.

doi: [10.21037/atm-20-5406](https://doi.org/10.21037/atm-20-5406)

View this article at: <http://dx.doi.org/10.21037/atm-20-5406>

The indication for neoadjuvant endocrine therapy (NET), alone or in combination with other biological agents, is not well established. Hormone receptor (HR)-positive human epidermal growth factor receptor 2 (HER2)-negative breast cancers (BC) are generally less responsive to neoadjuvant treatments, resulting in pathological complete response (pCR) rates of 10–20% and 5% with chemotherapy (1) and endocrine therapy (2), respectively. Given the longer time needed to obtain a response from endocrine therapy compared to chemotherapy, NET was initially considered an option only for elderly patients with inoperable tumours not eligible for neoadjuvant chemotherapy (NAC) (3,4). In the last 20 years, several trials have demonstrated the benefit of NET in downstaging the primary tumour and achieving breast conserving surgery. Nevertheless, none of these studies was able to establish a final recommendation for patients' selection and duration of treatment because underpowered, with different duration of treatment and different primary endpoints. A meta-analysis (5), published in 2016 including 3,490 patients from 20 clinical trials, compared NET to NAC and found that NET with an aromatase inhibitors (AI) yielded comparable clinical and radiological responses with similar rates of breast conservation. As expected, the toxicity was less in patients treated with NET. The meta-analysis also confirmed that AI are more effective than tamoxifen. Selection criteria for NET and duration of treatment, especially if combined with biological agents, remain open questions. Dixon *et al.* (6) showed, that patients who received neoadjuvant letrozole beyond 3 months had a better clinical response

rate compared to patients treated for 3 months only (83.5% *vs.* 69.8%, respectively). Given the mechanism of action of endocrine treatment, a longer duration seems to have an important role in downstaging and downsizing the tumour (7,8). The addition of CDK4/6 inhibitors to standard endocrine treatment could increase the efficacy and has opened the possibility to avoid the chemotherapy in early stage. In this article we will comment on the results of CORALEEN trial and we will review the most recent literature on NET plus CDK4/6 inhibitors.

NET gives a window of opportunity to study endocrine sensitivity in a dynamic fashion. Several endpoints have been tested to evaluate the efficacy of NET. We now have enough evidence that pCR is not a surrogate endpoint of survival for well-differentiated BC, namely luminal A-like subtype (9). This is however not the case for luminal B-like tumours, where a possible prognostic role has been reported, though not as strong as for HER2-positive and triple negative BC (9,10). The ALTERNATE study (11) presented at the 2020 ASCO meeting, which evaluated the efficacy of either anastrozole, fulvestrant or its combination in patients with stage II–III HR-positive BC, confirmed the clinical utility of Ki-67 changes as an early marker of endocrine sensitivity. Patients with Ki-67 >10% at week 4 or 12 were recommended to go off protocol-directed endocrine therapy and switch to NAC. Using this strategy, less than 2% of patients progressed during treatment. The Preoperative Endocrine Prognostic Index score (PEPI score), first tested in the P024 neoadjuvant trial and validated in the IMPACT trial (12), is largely used instead

of pCR in trials evaluating NET. It combines tumour size and nodal status, as well as Ki-67 and ER expression post-NET. However, nor the change in Ki-67 or the PEPI score take in consideration the genomic features of the tumour, which have been shown to be prognostic in the early stage, and to identify the benefit of adjuvant chemotherapy.

The “Neoadjuvant Multi-Agent Chemotherapy or Letrozole plus Ribociclib in Luminal B/HER2-negative BC” (CORALLEEN trial) (13), is a randomized phase II study designed testing the hypothesis of a molecular downstaging through the PAM50 signature. Patients with high-risk luminal-B tumours were randomized to receive the CDK4/6 inhibitor ribociclib in combination with endocrine treatment for 24 weeks or standard anthracycline and taxane-containing chemotherapy. Molecular downstaging was defined as the switch from baseline high/intermediate risk-of-relapse (ROR) group, as defined by the PAM50 molecular signature, plus clinicopathological features, to a low ROR group (14). The study population included patients with stage I–IIIA BC, tumour size >2 cm and luminal-B genomic profile—the latter assessed at baseline, during treatment and at surgery. The authors aimed to validate the hypothesis that the addition of CDK4/6 to standard NET offers the possibility to induce a molecular downstaging therefore to avoid adjuvant chemotherapy in luminal B-like tumours.

The ROR risk score is the first composite biomarker which incorporates the genomic status according to the PAM50 panel. Currently, no genomic tool is approved to support the recommendation of neoadjuvant treatment and molecular signatures, such as Oncotype DX and MammaPrint, are approved in adjuvant setting (15,16).

The authors reported that among 106 patients enrolled, 87% were high ROR-risk and 16% intermediate risk at the diagnosis. The rate of conversion to low-ROR risk was similar for ribociclib and chemotherapy arms (46.9% *vs.* 46.1%), with a rate of pCR higher in the chemotherapy arm (5.8% *vs.* 0%). The conversion in low-ROR risk after 15 days of treatment occurred in 96% of cases in ribociclib arm and in only 37% in the chemotherapy arm, suggesting the potential role of CD4/6 inhibitors to induce an early molecular downstaging. While the survival data has been not collected, the authors proposed molecular downstaging as a potential biomarker of the benefit of CDK4/6 inhibitors in the neoadjuvant setting. However, the CORALLEEN study was not designed and powered for this aim.

Will the CORALLEEN trial set a new standard of care for HR-positive early BC patients? Probably not, considering

that it was designed with an exploratory goal. However, this trial offers new important insight and establishes a new paradigm of study for HR-positive HER2-negative tumours—traditionally considered as poorer responders to neoadjuvant approach. This trial has underlined how important is to choose and validate the most suitable biomarkers tailored to type of tumour and class of drugs.

Previous experience with CDK4/6 inhibitors in the neoadjuvant setting have produced mixed results, with different surrogate endpoints used to evaluate efficacy and outcome (*Table 1*).

The NeoPAL trial (17), which included patients with PAM50 luminal B-like tumour or luminal A-like with nodal involvement, compared standard chemotherapy with anthracycline and taxane *vs.* letrozole plus palbociclib. The experimental arm with palbociclib was associated with low rate of pCR compared to chemotherapy but encouraging responses in decreasing of Ki-67 levels as biomarker of cell proliferation. In the PALLET trial (19) with endocrine treatment alone or in combination with palbociclib, the change in the mitotic rate (Ki-67) was also used as a biomarker of response. The addition of palbociclib to letrozole enhanced significantly the suppression of cell proliferation assessed by Ki-67. Similar findings regarding decline in Ki-67 have been shown with anastrozole and/or abemaciclib in NeoMONARCH trial (21). Confirming the role in inhibiting proliferation, the NeoPalAna trial (20), with the sequential use of AI followed by palbociclib, showed a Ki-67 <2.7% observed after 15 days of the combination treatment, namely a comparative complete cell cycle arrest (CCCA)—especially in less differentiated tumours. The N007 study (22), a pivotal trial (n=20 patients) with palbociclib and letrozole administered for 16 weeks, showed a clinical response rate of 85%, with 40% of complete response. Furthermore, EndoPredict score, a multigene score that combines the expression of proliferative and ESR1 signalling/differentiation-associated genes, was reduced after treatment, suggesting a suppressive effect of the combination on proliferation pathways. Recently, the first results of FELINE trials (24) has been presented and showed no significant benefit of the addition of ribociclib to AI alone in term of PEPI score at time of surgery. The data about survival outcome have not been presented yet. Alongside trials with CD4/6 inhibitors, other targeted therapies have been investigated in this setting. For instance, in a randomized phase II neoadjuvant trial, the PIK3CA inhibitor taselisib, has been demonstrated to be more effective than letrozole alone in terms of

Table 1 Clinical trials with CDK4/6 or biological agents in combination with endocrine treatment in neoadjuvant setting

| Trial | Phase | Experimental arm | Control arm | Duration of the treatments | N of patients | Primary endpoint | Results |
|------------------|-------|--------------------------------|------------------|----------------------------|---------------|----------------------------|--|
| NEOPAL (17) | II | L + P | FEC ×3 → D ×3 | 19 w | 106 | RCB0/I | 7.7% vs. 15% |
| NeoPalAna (18) | II | ANA → ANA + P; ANA + P | – | 5 mo.; 6 mo. | 50 | CCCA after 15 d | 26% vs. 87% (P<0.001) |
| PALLET (19) | II | L → P; P → L; P + L | L alone | 14 w | 307 | CRR; Ki-67 changes | 54.3% vs. 49.5%; 4.1 vs. 2.2 (P<0.001) |
| MONALEESA-1 (20) | II | L + R (400 mg); L + R (600 mg) | L alone; L alone | N.A. | 14 | Ki-67 reduction rate | 96% vs. 69%; 92% vs. 69% |
| NeoMONARCH (21) | II | ABE; ABE + ANA | ANA | 14 w | 223 | Ki-67 reduction rate | 92.6% vs. 63.2% |
| N007 (22) | II | L + P | – | 16 w | 20 | CRR | CRR in 17/20 pts; CR in 8/20 pts |
| LORELEI (23) | II | L + taselisib | L + pl | 16 w | 334 | CRR | Overall: 50% vs. 39%; PIK3CAm: 38% vs. 56%; overall: 2% vs. 1%; PIK3Cam: 1% vs. 0% |
| CORALLEEN (13) | II | R + L | AC → Pac | 24 w | 106 | Low-ROR risk after surgery | 46.9% vs. 46.1% |
| FELINE (24) | II | L + Ri; L + Rc | L | 24 w | 32; 28 | PEPI score 0 at surgery | 25.4% vs. 25.8% |

L, letrozole; P, palbociclib; FEC, 5-fluoro-uracil, epirubicin and cyclophosphamide; D, docetaxel; Ri, ribociclib intermittent; Rc, ribociclib continuous; RCB, residual cancer burden; PEPI, Preoperative Endocrine Prognostic Index; ANA, anastrozole; CCCA, complete cell cycle arrest (Ki-67 <2.7%); CCR, clinical response rate (Ki-67 <2.7%); CR, complete response; pCR, pathological complete response; pl, placebo; Pac, paclitaxel; w, weeks; mo., months; N.A., not available.

objective response rate as assessed by magnetic resonance imaging (MRI) in the overall study patients population and PIK3A mutant cohort (23). Despite the heterogeneity of these studies in terms of different control arms, primary endpoints and duration of the treatment, the addition of biological agents seems to enhance the efficacy of endocrine treatment as monotherapy. None of these studies have been able to demonstrate the superiority of NET compared to chemotherapy and none of the biomarkers used to define the response has been validated with survival outcome data. The results of CORALLEEN open new perspectives for the design of trials for early-stage luminal-like BC eligible for a neoadjuvant approach. The choice of luminal-B like population is instrumental to demonstrate that, not only in the metastatic setting but also in early stage, chemotherapy may be omitted in a subset of patients.

pCR, largely used as primary endpoint in neoadjuvant trials, seems to be a questionable predictive factor of survival outcome in patients with endocrine-sensitive tumours. The best biomarker to select patients who could avoid chemotherapy has not been well-defined yet and

several questions remain unsolved regarding both surgery and medical goals. The design of future NET clinical trials should include specific endpoints to address the unmet needs in this field, considering the drugs utilized and the characteristics of the disease. Large powered studies are needed to validate the prognostic and predictive value of these endpoints. Additionally, in the evaluation of the risk of recurrence, genomic profiling of the tumour may give more comprehensive reproducible data on tumour aggressiveness compared to traditional Ki-67. The challenge is translating the precision medicine approach from the metastatic setting to the curative setting. The CORALLEEN study represents an important milestone in this direction.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned

by the editorial office, *Annals of Translational Medicine*. The article did not undergo external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/atm-20-5406>). The authors have no conflicts of interests to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Ferraro E, Fornier MN. Molecular downstaging: a new paradigm for neoadjuvant endocrine therapy. *Ann Transl Med* 2020;8(24):1694. doi: 10.21037/atm-20-5406