Clinical Oncology xxx (2017) 1–4

Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Editorial

Are Cyclin-dependent Kinase 4/6 Inhibitors Needed for all Oestrogen Receptor-positive Metastatic Breast Cancers?

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Received 23 May 2017; accepted 19 June 2017

Endocrine therapy is the primary treatment approach for patients with oestrogen receptor-positive (ER+) metastatic breast cancer (MBC), and for postmenopausal women an aromatase inhibitor, such as anastrozole or letrozole, has been the standard of care for the past 15 years [1]. However, the disease in some patients with ER+ MBC shows *de novo* 'primary' resistance to hormonal treatments and can progress quickly, whereas in all other patients who initially respond to an aromatase inhibitor the disease will eventually progress showing acquired 'secondary' resistance. Improving initial clinical response rates to endocrine therapy, and prolonging the duration of those responses while maintaining quality of life, has been an important clinical research goal in ER+ MBC. In recent years efforts have focused on the addition of agents targeted to pathways contributing to endocrine resistance that may improve tumour responses and delay progression. Growth factor receptor inhibitors and agents that target various signal transduction pathways have all been investigated with varying levels of success [2]. However, to date the only approach that has been consistently effective in combination with endocrine therapy is to co-target the cell cycle, in particular by the addition of a cyclin-dependent kinase (CDK) 4/6 inhibitor.

Palbociclib is an orally bioavailable small-molecule inhibitor of CDK 4 and 6 [3]. In preclinical studies, palbociclib was highly active against ER+ breast cancer cell lines and is synergistic with endocrine therapies [4]. A randomised phase II study (PALOMA-1) showed significantly improved progression-free survival (PFS) with the addition of palbociclib to letrozole versus letrozole alone as first-line therapy for patients with ER+, human epidermal growth factor receptor 2-negative (HER2−) MBC [5]. The recently reported primary results from the phase III study (PALOMA-2) in 666 patients in the first-line setting also showed a significant improvement in PFS with palbociclib plus letrozole with a median of 24.8 months compared with 14.5 months for placebo plus letrozole (hazard ratio 0.58; 95% confidence interval 0.46–0.72; $P < 0.001$) [6]. In those patients with measurable disease there was a significantly better objective response rate for the combination (55.3% versus 44.4%, odds ratio 1.55; 95% confidence interval 1.05–2.28). The most frequent toxicity with the addition of palbociclib was neutropenia, which was managed by appropriate dose delay and subsequent dose reduction. Unlike chemotherapy, the incidence of serious complications associated with neutropenia, such as fever/infection, was extremely low (<2%). Similar data have also been reported for the oral CDK 4/6 inhibitor ribociclib with letrozole compared with letrozole alone in a phase III study (MONALEESA-2) in 668 patients, with a similar 46% improvement in PFS [7]. Based on these highly significant results and manageable side-effect profile palbociclib with letrozole was approved in the USA (2015) and EU (2016), with ribociclib plus letrozole being approved more recently in the USA (2017). As such this approach is now considered an effective first-line treatment option in international treatment guidelines for patients with advanced ER+/HER2− breast cancer [8,9].

These are undoubtedly impressive results, with the largest improvement ever seen in PFS for first-line endocrine therapy in ER+ MBC. In both of the phase III trials, subgroup analysis showed that benefit was seen in all groups of patients, regardless of prior adjuvant endocrine therapy use, the age of the patient or indeed visceral or bone as the dominant site of metastases [6,7]. The separation in the Kaplan-Meier curves occurred early in both studies, suggesting that those patients with early progression on an aromatase inhibitor alone (primary endocrine resistance) can benefit from the combination, in addition to the significant prolongation of PFS for all patients, which implies that the combination may also delay the development of secondary endocrine resistance. This is a stark

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http://dx.doi.org/10.1016/j.clon.2017.06.016

Please cite this article in press as: Johnston SRD, Are Cyclin-dependent Kinase 4/6 Inhibitors Needed for all Oestrogen Receptor-positive Metastatic Breast Cancers? Clinical Oncology (2017), http://dx.doi.org/10.1016/j.clon.2017.06.016

contrast to results seen in other recent first-line endocrine therapy studies, such as SWOG-0226, where the Kaplan-Meier curves initially fell steeply in the first 3–4 months but then separated later [10]. This suggested that only a small proportion of patients in the SWOG-0226 trial derived benefit from fulvestrant plus anastrozole compared with anastrozole alone, which on subgroup analysis seemed to be those who were endocrine therapy naive or with long disease-free intervals since primary diagnosis, factors that are well known to predict for endocrine responsiveness.

So does the quantum of clinical benefit seen in the CDK 4/6 first-line clinical trials that occurred for most patients treated with the combination mean that all first-line therapy in ER+ MBC should now be the combination of a CDK 4/6 inhibitor with an aromatase inhibitor? These novel therapies are both expensive and not yet readily available in many countries. Instead, can we select those patients who would probably benefit and respond in the first-line setting based on any molecular biomarkers rather than clinical features, such as prior therapies received, disease-free interval or distribution of disease sites? In addition, is there an optimal sequencing strategy that would mean targeted combinations could be more appropriately reserved for second- or third-line settings?

In terms of tumour-based molecular predictors for response to CDK 4/6 inhibitors, research efforts in the clinical trials have yielded little so far other than ER expression itself. Indeed it was the preclinical observation that palbociclib was much more effective in luminal breast cancer subtypes that prompted clinical development to be initiated in ER+ disease [4]. In the PALOMA-1 trial, patients were then selected in the second part of the study to only include those where an archival tumour biopsy had shown either cyclin D1 (*CCND1*) amplification or loss of the negative regulator p16, both of which were thought to be putative biomarkers for an activated cell cycle. However, clinical benefit was seen regardless of *CCND1*/p16 status [5]. In the more recent PALOMA-2 first-line study, additional biomarkers were assessed by both qualitative and quantitative means in the primary tumour, including expression of ER, the retinoblastoma protein, which regulates CDK activation, Ki67 as an indicator of cell proliferation, in addition to cyclin D1 and p16 status [11]. Once again, no biomarkers were identified as being predictive of clinical benefit for the combination. Likewise, in a separate second-line ER+ MBC study where palbociclib plus fulvestrant was superior to fulvestrant alone (PALOMA-3) [12], attempts were made to see which patients derived most benefit, only this time using circulating tumour DNA taken at study entry to measure for mutations in either the *ESR1* gene or *PIK3CA* gene, both of which are thought to be predictors for endocrine resistance. The advantage of this approach was to have more contemporaneous tumour-related biomarkers from the metastatic setting that could indicate the biology of the treated disease, rather than relying on archival tissue [13]. However, despite this, benefit for the combination occurred regardless of whether patients had a wild-type or mutant *ESR1* or *PIK3CA* status [14].

Given the challenges of finding biological predictors of response in the metastatic setting, studies in the neo-adjuvant setting are ongoing, where biopsies are taken from the primary breast tumour *in situ* before and during drug exposure to biological response to therapy. In particular, the PALLET trial conducted in the UK and the USA is assessing the benefit of adding palbociclib to letrozole in 306 post-menopausal women with ER+ early breast cancer using changes in cell proliferation (as measured by Ki-67 expression) as the primary end point, with extensive protein and RNA sequence molecular analyses to identify the molecular profile of both endocrine resistant tumours that do not respond to aromatase inhibitors and also the biomarkers that predict a good response to the addition of a CDK 4/6 inhibitor. It is unclear whether PALLET will substantially assist the choice of therapies in the metastatic setting, but instead it is designed to help identify those patients with early stage breast cancer in the future for whom adjuvant CDK 4/6 therapy for 2 years could be an important additional therapy once results from the ongoing adjuvant trials (PALLAS) become available.

So, in the absence of biomarkers that might predict who needs CDK 4/6 inhibitors in the first-line ER+ MBC setting, is the default position that we should treat everybody with this combination from the outset of presentation with advanced ER+ metastatic disease? Certainly, the subgroup analyses within both the PALOMA-2 and MONALEESA-2 studies would imply that all patients may benefit from combination therapy compared with an aromatase inhibitor alone [6,7]. However, various clinical and patient-related factors should also be considered, as we already know that many patients with ER+ MBC can have excellent long-lasting responses with endocrine therapy alone. For example, a 76-year-old woman relapsing with two or three isolated asymptomatic bone metastases 15 years after her primary diagnosis can respond very well to an aromatase inhibitor alone, often for several years. Known clinical predictors of a good response to endocrine therapy include strong ER+ expression in the tumour, a long disease-free interval, non-visceral sites of metastases and also the absence of prior endocrine therapy exposure. Indeed, in the recently reported FALCON trial that compared fulvestrant 500 mg versus anastrozole in patients with ER+ advanced breast cancer who had never received any prior endocrine therapy, the median PFS in those with non-visceral sites of disease (i.e. bone, soft tissue) with fulvestrant was 22.3 months compared with 13.4 months for anastrozole (hazard ratio 0.59; 95% confidence interval 0.42–0.84) [15]. This would imply that in the correctly chosen clinical subgroup of patients with ER+ MBC, prolonged responses to endocrine therapy alone can occur. Thereafter, at progression, combined therapies, such as palbociclib and fulvestrant, as shown in the PALOMA-3 trial [8], or exemestane and the mTOR inhibitor everolimus, as shown in the BOLERO-2 trail [16], both more than double PFS in the second-line setting compared with an endocrine agent alone. By contrast, a 56-year-old woman relapsing 6 years after primary treatment with nodal disease together with asymptomatic lung and small volume liver metastases may do better with

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