Is There Still a Role for First-Line Single Agent Endocrine Therapy in HR+ and HER2– Advanced Breast Cancer?

Luca Malorni^{a,b} Laura Biganzoli^b

^a‘Sandro Pitigliani’ Translational Research Unit, Hospital of Prato, Istituto Toscano Tumori, Prato, Italy;

^b‘Sandro Pitigliani’ Medical Oncology Department, Hospital of Prato, Istituto Toscano Tumori, Prato, Italy

The management of patients with hormone receptor positive, HER2 negative (HR+ HER2–) metastatic breast cancer (MBC) has historically been based on endocrine therapy (ET) [1]. Endocrine resistance, both *de novo* and acquired, has impeded the clinical use of ET over decades, stimulating an exceptional effort in understanding mechanisms of resistance at a cellular and molecular level [2]. The development of targeted agents has recently changed the management paradigm of HR+ HER2– MBC. Such agents currently include the cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors palbociclib, ribociclib and abemaciclib, as well as everolimus, which targets the phosphatidylinositol 3-kinase (PI3K)-Akt-mammalian target of rapamycin (mTOR). All these agents have been shown to improve patient outcomes in combination with ET as compared to single-agent ET. The PALOMA-2, MONALEESA-2, and MONARCH-3 phase III trials demonstrated improvements in progression-free survival (PFS) in the front-line setting when a CDK4/6 inhibitor was used in combination with a non-steroidal aromatase inhibitor (nsAI) as compared to a single-agent nsAI [3–5]. These studies accepted patients with ‘*de novo*’ MBC and those who experienced relapse following a long disease-free interval (DFI) (>12 months) after the completion of adjuvant ET, therefore, representing a group with potentially high endocrine sensitivity.

Both palbociclib and abemaciclib have also shown significant prolongation of PFS when used in combination with fulvestrant in the PALOMA-3 [6] and MONARCH-2 phase III trials [7], respectively. In these studies, patients were permitted to receive study regimens as first-line therapy only if they had recurred during adjuvant ET or experienced a short DFI (<1 year) after adjuvant ET.

In all studies, the added toxicity of the combination with CDK4/6 inhibitors seemed manageable and did not result in significant rates of treatment discontinuation [4, 7–9].

Limited to the setting of nsAI pre-treated disease, the BOLERO-2 trial demonstrated the superiority of everolimus in combination with exemestane, compared with exemestane alone in women with

HR+ MBC after progression on an nsAI [10]. In this study, similar to PALOMA-3 and MONARCH-2 trials, patients with prior exposure to nsAI in the adjuvant setting and those who either had metastatic disease relapse during adjuvant HT or experienced a short DFI could be admitted to receive the study drugs as first-line therapy. Although efficacious in this combination, everolimus demonstrated a characteristic safety profile which requires appropriate management strategies to minimize the occurrence and severity of adverse events such as stomatitis, hyperglycemia, and pneumonitis [11].

Based on this data, combinations of ET and biologic agents are certainly an option for first-line therapy of those patients with HR+ HER2– MBC who have relapsed during adjuvant HT or have experienced a short DFI after adjuvant therapy with an nsAI and who are deemed suitable for ET. For these patients, appropriate regimens may be either a CDK4/6 inhibitor in combination with fulvestrant or everolimus in combination with exemestane, with the choice ultimately made according to individual preferences and clinical context.

However, the scenario of ‘*de novo*’ metastatic disease and of ‘nsAI-naïve’ patients merits additional consideration. Using single-agent hormonal therapy, a significant proportion (~50%) of patients can achieve disease responses lasting more than 12 months, with minimal side effects [12–14]. In this group of patients with high sensitivity to ET, any potential additional benefit bestowed by combinations incorporating a CDK4/6 inhibitor must be carefully weighed, taking into account additional toxicity and costs. In this context, identifying which subgroup of patients is most likely to benefit from the combination of ET and CDK4/6 inhibitors is therefore of critical importance in defining the most appropriate use of these compounds.

Unfortunately, despite many efforts in pre-clinical and translational studies, to date no tested biomarker has succeeded in distinguishing between those patients more likely to benefit from combination therapy with a CDK4/6 inhibitor, and those who may be

safely spared such an approach [15]. Similarly, from a clinical standpoint, subgroup analyses from the PALOMA-2 and MONALEESA-2 trials have so far failed to identify which patients may avoid combination treatment, as the hazard ratio for recurrence favored the combination arms for all the pre-defined subgroups. However, recent data derived from the MONARCH-3 study (a phase III randomized trial of abemaciclib plus a nsAI vs. placebo plus a nsAI in the front-line setting), suggested that those patients with a longer DFI (>36 months from the end of adjuvant ET) derived no benefit from the addition of abemaciclib [5]. Additionally, a lesser benefit from the combination was observed in the subgroup of patients with bone-only disease. This may suggest that those patients with clinical characteristics typical of strongly endocrine-responsive disease may be treated with single-agent hormonal treatment in the front-line setting, potentially saving the use of a CDK4/6 inhibitor for a later stage of the disease process. However, as this hypothesis derives from a single study with a relatively low number of patients assigned to these subgroups, these data require confirmation in a larger study.

In conclusion, the combination of targeted agents and ET is revolutionizing the approach to the management of HR+ HER2–

MBC. Clinical data currently support a scenario wherein most patients with an indication for front-line ET should receive a targeted agent. It is, however, possible to speculate that for selected patients with clinical characteristics suggestive of indolent, endocrine-sensitive disease, front-line treatment with single-agent hormonal treatment may still play a role. Clearly, more research is needed in this field to obtain solid biomarkers that may aid in patient selection.

Acknowledgements

We thank Amelia McCartney for her revision of this manuscript.

Disclosure Statement

L.M.: Lecture, Advisory board from AstraZeneca and Pfizer; research support from Pfizer.

L.B.: Consulting and advisory services, speaking or writing engagements, public presentations: AstraZeneca, Celgene, Lilly, Roche, Ipsen, Novartis, Pfizer, Pierre Fabre, Puma Biotechnology; Research support: Celgene.

References

- Migliaccio I, Malorni L, Hart CD, Guarducci C, Di Leo A: Endocrine therapy considerations in postmenopausal patients with hormone receptor positive, human epidermal growth factor receptor type 2 negative advanced breast cancers. *BMC Med* 2015;13:46.
- Osborne CK, Schiff R: Mechanisms of endocrine resistance in breast cancer. *Annu Rev Med* 2011;62:233–247.
- Finn RS, Martin M, Rugo HS, Jones S, Im SA, Gelmon K, Harbeck N, Lipatov ON, Walshe JM, Moulder S, Gauthier E, Lu DR, Randolph S, Dieras V, Slamon DJ: Palbociclib and letrozole in advanced breast cancer. *N Engl J Med* 2016;375:1925–1936.
- Hortobagyi GN, Stemmer SM, Burris HA, Yap YS, Sonke GS, Paluch-Shimon S, Campone M, Blackwell KL, Andre F, Winer EP, Janni W, Verma S, Conte P, Arteaga CL, Cameron DA, Petrakova K, Hart LL, Villanueva C, Chan A, Jakobsen E, Nusch A, Burdaeva O, Grischke EM, Alba E, Wist E, Marschner N, Favret AM, Yardley D, Bachelot T, Tseng LM, Blau S, Xuan F, Souami F, Miller M, Germa C, Hirawat S, O'Shaughnessy J: Ribociclib as first-line therapy for HR-positive, advanced breast cancer. *N Engl J Med* 2016;375:1738–1748.
- Goetz MP, Toi M, Campone M, Sohn J, Paluch-Shimon S, Huober J, Park IH, Tredan O, Chen SC, Manso L, Freedman OC, Garnica Jaffe G, Forrester T, Frenzel M, Barriga S, Smith IC, Bourayou N, Di Leo A: MONARCH 3: abemaciclib as initial therapy for advanced breast cancer. *J Clin Oncol* 2017;doi: 10.1200/JCO.2017.75.6155..
- Cristofanilli M, Turner NC, Bondarenko I, Ro J, Im SA, Masuda N, Colleoni M, DeMichele A, Loi S, Verma S, Iwata H, Harbeck N, Zhang K, Theall KP, Jiang Y, Bartlett CH, Koehler M, Slamon D: 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;17:425–439.
- Sledge GW, Jr., Toi M, Neven P, Sohn J, Inoue K, Pivrot X, Burdaeva O, Okera M, Masuda N, Kaufman PA, Koh H, Grischke EM, Frenzel M, Lin Y, Barriga S, Smith IC, Bourayou N, Llobart-Cussac A: 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;35:2875–2884.
- Verma S, Bartlett CH, Schnell P, DeMichele AM, Loi S, Ro J, Colleoni M, Iwata H, Harbeck N, Cristofanilli M, Zhang K, Thiele A, Turner NC, Rugo HS: Palbociclib in combination with fulvestrant in women with hormone receptor-positive/HER2-negative advanced metastatic breast cancer: detailed safety analysis from a multicenter, randomized, placebo-controlled, phase III study (PALOMA-3). *Oncologist* 2016;21:1165–1175.
- Harbeck N, Iyer S, Turner N, Cristofanilli M, Ro J, Andre F, Loi S, Verma S, Iwata H, Bhattacharyya H, Puyana Theall K, Bartlett CH, Loibl S: Quality of life with palbociclib plus fulvestrant in previously treated hormone receptor-positive, HER2-negative metastatic breast cancer: patient-reported outcomes from the PALOMA-3 trial. *Ann Oncol* 2016;27:1047–1054.
- Baselga J, Campone M, Piccart M, Burris HA 3rd, Rugo HS, Sahmoud T, Noguchi S, Gnant M, Pritchard KI, Lebrun F, Beck JT, Ito Y, Yardley D, Deleu I, Perez A, Bachelot T, Vittori L, Xu Z, Mukhopadhyay P, Lebewohl D, Hortobagyi GN: Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. *N Engl J Med* 2012;366:520–529.
- Rugo HS, Pritchard KI, Gnant M, Noguchi S, Piccart M, Hortobagyi G, Baselga J, Perez A, Geberth M, Cso-szi T, Chouinard E, Sriruninnimit V, Puttawibul P, Eakle J, Feng W, Baully H, El-Hashimy M, Taran T, Burris HA 3rd: Incidence and time course of everolimus-related adverse events in postmenopausal women with hormone receptor-positive advanced breast cancer: insights from BOLERO-2. *Ann Oncol* 2014;25:808–815.
- Robertson JF, Lindemann JP, Llobart-Cussac A, Rol-ski J, Felt D, Dewar J, Emerson L, Dean A, Ellis MJ: Fulvestrant 500 mg versus anastrozole 1 mg for the first-line treatment of advanced breast cancer: follow-up analysis from the randomized 'FIRST' study. *Breast Cancer Res Treat* 2012;136:503–511.
- Mouridsen H, Gershanovich M, Sun Y, Perez-Carrión R, Boni C, Monnier A, Apffelstaedt J, Smith R, Sleetboom HP, Jaenicke F, Pluzanska A, Dank M, Becquart D, Bapsy PP, Salminen E, Snyder R, Chaudri-Ross H, Lang R, Wyld P, Bhatnagar A: Phase III study of letrozole versus tamoxifen as first-line therapy of advanced breast cancer in postmenopausal women: analysis of survival and update of efficacy from the International Letrozole Breast Cancer Group. *J Clin Oncol* 2003;21:2101–2109.
- Robertson JFR, Bondarenko IM, Trishkina E, Dvorkin M, Panasci L, Manikhas A, Shparyk Y, Cardona-Huerta S, Cheung KL, Philco-Salas MJ, Ruiz-Borrego M, Shao Z, Noguchi S, Rowbottom J, Stuart M, Grinstead LM, Fazal M, Ellis MJ: Fulvestrant 500 mg versus anastrozole 1 mg for hormone receptor-positive advanced breast cancer (FALCON): an international, randomised, double-blind, phase 3 trial. *Lancet* 2016;388:2997–3005.
- Migliaccio I, Di Leo A, Malorni L: Cyclin-dependent kinase 4/6 inhibitors in breast cancer therapy. *Curr Opin Oncol* 2014;26:568–575.