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Advances in the Treatment of Hormone Receptor-Positive Metastatic Breast Cancer

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Editorial

Despite advances in therapy, approximately one-third of women with localized breast cancer develop distant metastases [1]. Metastatic Breast Cancer (MBC) is generally considered incurable with a median 5-year survival of less than 25% [1]. Hormone Receptor (HR)-positive breast cancer, defined by over expression of the estrogen and/or progesterone receptors, accounts for over 70% of breast cancer [1]. Herein, recent advances in the treatment of HR-positive MBC are reviewed.

Endocrine therapy is considered the mainstay of treatment for HR-positive MBC. Guidelines recommend sequential endocrine therapy for most women with HR-positive MBC, even in the presence of modest burden of visceral disease [2]. Chemotherapy is generally reserved for patients at risk of visceral crisis and/or hormone resistant disease.

Tamoxifen was the first widely used front-line endocrine therapy for patients with MBC on the basis of a favorable toxicity profile compared to other treatments [3]. The TARGET trial established aromatase inhibitor therapy as the preferred first-line option for postmenopausal patients with HR-positive MBC [4]. The study demonstrated equivalent efficacy of anastrozole when compared to tamoxifen in the treatment of MBC (median time to progression (TTP) 8.2 *vs.* 8.3 months) with an improved toxicity profile including reduced incidence of thromboembolic events and vaginal bleeding. The non-steroidal aromatase inhibitors, letrozole and anastrozole, are largely used interchangeably. However, preclinical studies have suggested that letrozole is more potent than anastrozole [5]. A randomized, open-label phase III study that enrolled 713 postmenopausal patients with MBC who had progressed on tamoxifen compared letrozole and anastrozole [6]. The study reported no significant difference in TTP between the two drugs (median TTP 5.7 months in both arms), but did report an improved overall response rate with letrozole (19.1% *vs.* 12.3%, P=0.01). The recently reported FALCON trial compared first-line treatment with fulvestrant *vs.* anastrozole for patients with HR-positive MBC, and reported a statistically significant improvement in Progression-Free Survival (PFS) with fulvestrant (16.6 *vs.* 13.8 months; P=0.05) [7]. As such, both non-steroidal aromatase inhibitors and fulvestrant are reasonable frontline endocrine options for patients with metastatic disease when considering monotherapy. These endocrine therapies are able to achieve disease control and prolong PFS, but endocrine resistance remains a challenge in the treatment of HR-positive MBC, both in pre-treated patients (acquired resistance) and in untreated patients (*de novo* resistance). Thus, novel combinatorial strategies have been developed to overcome endocrine resistance.

mTOR Inhibition

Activation of the PI3K/AKT/mTOR pathway has been implicated in resistance to endocrine therapy in HR-positive breast cancer [8]. Everolimus is an oral rapamycin analog that inhibits the mTORC1 complex, which regulates translation, transcription, cell cycle progression, and survival [9]. Everolimus has been studied in combination with anti-estrogen therapy in the treatment of HR-positive MBC. The randomized phase II TAMRAD study compared tamoxifen in combination with everolimus to tamoxifen alone in 111 postmenopausal patients with HR-positive MBC that had progressed on aromatase inhibition [10]. The study reported an increased clinical benefit rate (61% *vs.* 42%; P=0.05) as well as improved TTP and Overall Survival (OS) with the combination. There was a 55% reduction in the risk of death with the combination (exploratory P<0.01). The randomized, double-blind phase III BOLERO-2 study compared exemestane in combination with everolimus to exemestane alone in 724 patients with HR-positive MBC who had progressed on previous therapy with a non-steroidal aromatase inhibitor [11]. The study reported more than doubling of the PFS with the combination (7.8 months *vs.* 3.2 months; P<0.01), resulting in FDA approval. However,

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no improvement in OS was seen (31.0 months *vs.* 26.6 months; P=0.14) [12]. Everolimus has also been tested in combination with fulvestrant in postmenopausal patients with HR-positive MBC after progression on aromatase inhibitor. The randomized, double-blind phase II prECOG 0102 trial reported a longer PFS with fulvestrant in combination with everolimus compared to fulvestrant alone in 130 patients that had progressed on aromatase inhibition (10.4 *vs.* 5.1 months; P=0.02) [13]. mTOR inhibitors have largely been used for HR-positive MBC to extend the duration of endocrine therapy by overcoming resistance to anti-estrogen therapy. Due to the lack of survival impact, the toxicity associated with therapy and the recent reports of significant PFS improvements when CDK 4/6 inhibitors are combined with hormone therapy in the first-line setting, mTOR inhibitors are not typically incorporated into frontline therapy.

CDK 4/6 Inhibition

Cyclin D1 is a regulator of cyclin-dependent kinases 4 and 6, which in turn are required for the cell cycle G1 to S phase transition [14]. Cyclin D1 is also a direct transcriptional target of the estrogen receptor, indicating that these pathways are linked [15]. Increased activity of cyclin D1 activity through various mechanisms and resultant over activation of the cyclin D1-CDK 4/6 pathway is common in HR-positive breast cancer [16]. As such, CDK 4/6 inhibitors have been evaluated for the treatment of HR-positive MBC. PALOMA-1 was a phase II trial that randomized 165 postmenopausal patients with untreated HR-positive MBC to receive letrozole with or without the CDK 4/6 inhibitor palbociclib [17]. The study reported a doubling of PFS in the palbociclib containing arm (20.2 *vs.* 10.2 months; P<0.01), which resulted in accelerated FDA approval of palbociclib and letrozole as combination first-line treatment for postmenopausal patients with HR-positive MBC. The randomized, double-blind Phase III PALOMA-2 trial confirmed these findings (PFS 24.8 months for palbociclib and letrozole *vs.* 14.5 months for placebo and letrozole; P<0.01) [18]. Neither trial resulted in a statistically significant improvement in overall survival with the combination, although data from the PALOMA-2 trial is not mature at this time. Palbociclib has also been evaluated in combination with fulvestrant after progression on endocrine therapy. The randomized, double-blind, placebo-controlled phase III PALOMA-3 trial reported a significantly longer PFS with fulvestrant in combination with palbociclib compared to fulvestrant alone (9.5 *vs.* 4.6 months; P<0.01) in 521 patients that had previously progressed on endocrine therapy, leading to FDA approval of this combination for second-line treatment of HR-positive MBC [19].

Studies with other CDK 4/6 inhibitors have resulted in similar findings. In the randomized, placebo-controlled phase III MONALEESA-2 trial, letrozole in combination with ribociclib extended PFS compared to letrozole alone in 668 postmenopausal patients with HR-positive MBC in the front-line metastatic setting (PFS not reached *vs.* 14.7 months at interim analysis; P<0.01), leading to FDA approval of this combination [20]. Similarly, in the randomized, placebo-controlled phase III MONARCH-3 trial, letrozole or anastrozole in combination with abemaciclib extended PFS compared to letrozole or anastrozole alone in 493 postmenopausal patients with HR-positive MBC in the front-line metastatic setting (PFS not reached *vs.* 14.7 months at interim analysis; P<0.01) [21]. The randomized, double-blind phase III MONARCH-2 study reported a significantly longer PFS with fulvestrant in combination with abemaciclib compared to fulvestrant alone (16.4 *vs.* 9.3 months; P<0.01) in 669 patients with HR-positive MBC progressing on endocrine therapy [22]. The phase II MONARCH-1 study reported single agent activity of abemaciclib in patients with HR-positive MBC that had previously progressed on endocrine therapy and chemotherapy [23]. The study reported an objective response rate of 19.7% in 132 patients, who had previously received a median of 3 lines of prior systemic therapy in the metastatic setting with the majority of patients (90%) having visceral disease at the time of study enrollment.

These studies have established the efficacy of CDK 4/6 inhibition in combination with endocrine therapy. However, many questions remain unanswered. It is unclear if all patients should be treated with CDK 4/6 inhibitors in the front-line setting. Many patients experience long duration of disease control with anti-estrogen agents alone. Predictive biomarkers of response and resistance are necessary to avoid the widespread use of these high cost agents and to spare patients who might do well with anti-estrogen therapy alone from unnecessary toxicity. The optimal dosing schedule of CDK 4/6 inhibition remains unclear. Both palbociclib and ribociclib are dosed 3 weeks on followed by 1 week off due to the neutropenia caused by these agents, while abemaciclib is dosed continuously as it has a lower incidence of associated neutropenia. Theoretically, it is felt there might be rebound of cell cycle progression upon drug withdrawal and thus, potential benefit of a continuous dosing schedule. An ongoing clinical trial is investigating an alternative dosing schedule of palbociclib, dosed 5 days on and 2 days off each week without any weeks off drug (NCT03007979). Another unresolved question is whether CDK 4/6 inhibition should be continued beyond progression with an alternative endocrine agent. Several ongoing clinical trials are investigating this question (NCT02732119, NCT02632045, NCT02871791, NCT02684032). Finally, due to the success of these agents in the metastatic setting, CDK 4/6 inhibition is also being evaluated in the early-stage curative setting. Two ongoing randomized, multicenter phase III trials are evaluating the role of palbociclib in combination with endocrine therapy as adjuvant therapy for patients with early-stage HR-positive BC: the Palbociclib Collaborative Adjuvant Study (PALLAS, NCT02513394) and the PEBELOPE-B (NCT01864746), which is evaluating the addition of adjuvant palbociclib in patients with residual disease after neo-adjuvant chemotherapy and surgery.

Novel Strategies

Development of novel strategies is ongoing for the treatment of HR-positive MBC. BELLE-3 is a randomized phase III trial that investigated the combination of the PI3K inhibitor buparlisib with fulvestrant compared to fulvestrant alone in 432 patients that had progressed on aromatase inhibitor therapy and combination endocrine therapy and everolimus [24]. The study reported a PFS of 3.9 months with the combination compared to 1.8 months with fulvestrant alone. Among patients with PIK3CA mutations, PFS was 4.7 months in the buparlisib arm *vs.* 1.6 months in the placebo arm.

RAD1901 is a non-steroidal, oral Selective Estrogen Receptor Degrader (SERD), which has been tested in patients with heavily pretreated HR-positive MBC [25]. Confirmed partial responses were seen patients who had previously progressed on fulvestrant and palbociclib. Further, responses were seen in patients harboring mutations in the gene coding for the estrogen receptor (ESR1), which has been associated with acquired endocrine resistance in patients with HR-positive MBC.

Immune checkpoint inhibitors have been very successful in other tumor types with modest results in breast cancer. The phase I b JAVELIN trial evaluated the anti-programmed death-ligand 1 (PD-L1) antibody avelumab and enrolled 69 patients with heavily pretreated HR-positive MBC [26]. Response was seen in 2.8% of patients with HR-positive disease. Checkpoint inhibition in combination with other therapies is also being explored. In the I-SPY2 trial, the anti-PD-1 antibody pembrolizumab was added to standard neo-adjuvant chemotherapy in patients with Stage II-III HER2-negative disease [27]. In 40 patients with HR-positive disease, the pathological complete response rate increased from 13% to 34% with the addition of pembrolizumab. An upcoming clinical trial at Cedars-Sinai Medical Center will test the combination of pembrolizumab and radiation therapy in the preoperative setting in patients with localized HR-positive breast cancer. Similar strategies are ongoing in patients with metastatic disease (NCT03051672).

As novel targeted therapies are developed for the treatment of HR-positive MBC, predictive biomarkers of response and resistance are increasingly needed to guide therapy. Further, molecular characterization of tumor progression is necessary to continue to develop new strategies to overcome resistance. Ongoing advances in translational science are essential to the development of new treatment strategies for HR-positive MBC.

References

1. O'Shaughnessy J. Extending survival with chemotherapy in metastatic breast cancer. Oncologist. 2005;10(3):20-9.
2. Rugo HS, Rumble RB, Macrae E, Barton DL, Connolly HK, Dickler MN, et al. Endocrine therapy for hormone receptor-positive metastatic breast cancer: american society of clinical oncology guideline. J Clin Oncol. 2016;34(25):3069-103.
3. Litherland S, Jackson IM. Antioestrogens in the management of hormone-dependent cancer. Cancer Treat Rev. 1988;15(3):183-94.
4. Bonneterre J, Thürlimann B, Robertson JF, Krzakowski M, Mauriac L, Koralewski P, et al. Anastrozole versus tamoxifen as first-line therapy for advanced breast cancer in 668 postmenopausal women: results of the Tamoxifen or Arimidex Randomized Group Efficacy and Tolerability study. J Clin Oncol. 2000;18(22):3748-57.
5. Bhatnagar AS, Brodie AM, Long BJ, Evans DB, Miller WR. Intracellular aromatase and its relevance to the pharmacological efficacy of aromatase inhibitors. J Steroid Biochem Mol Biol. 2001;76(1-5):199-202.
6. Rose C, Vtoraya O, Pluzanska A, Davidson N, Gershanovich M, Thomas R, et al. An open randomised trial of second-line endocrine therapy in advanced breast cancer. comparison of the aromatase inhibitors letrozole and anastrozole. Eur J Cancer. 2003;39(16):2318-27.
7. Robertson JFR, Bondarenko IM, Trishkina E, Dvorkin M, Panasci L, Manikhas A, et al. 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(10063):2997-3005.
8. Schiff R, Massarweh SA, Shou J, Bharwani L, Mohsin SK, Osborne CK. Cross-talk between estrogen receptor and growth factor pathways as a molecular target for overcoming endocrine resistance. Clin Cancer Res. 2004;10(1 Pt 2):331S-6S.
9. Wullschleger S, Loewith R, Hall MN. TOR signaling in growth and metabolism. Cell. 2006;124(3):471-84.
10. Bachelot T, Bourgier C, Cropet C, Ray-Coquard I, Ferrero JM, Freyer G, et al. Randomized phase II trial of everolimus in combination with tamoxifen in patients with hormone receptor-positive, human epidermal growth factor receptor 2-negative metastatic breast cancer with prior exposure to aromatase inhibitors: a GINECO study. J Clin Oncol. 2012;30(22):2718-24.
11. Yardley DA, Noguchi S, Pritchard KI, Burris HA 3rd, Baselga J, Gnant M, et al. Everolimus plus exemestane in postmenopausal patients with HR(+) breast cancer: BOLERO-2 final progression-free survival analysis. Adv Ther. 2013;30(10):870-84.
12. Piccart M, Hortobagyi GN, Campone M, Pritchard KI, Lebrun F, Ito Y, et al. Everolimus plus exemestane for hormone-receptor-positive, human epidermal growth factor receptor-2-negative advanced breast cancer: overall survival results from BOLERO-2†. Ann Oncol. 2014;25(12):2357-62.
13. Kornblum N, Manola J, Klein P, Ramaswamy B, Brufsky A, Stella PJ, et al. Abstract S1-02: PrECOG 0102: A randomized, double-blind, phase II trial of fulvestrant plus everolimus or placebo in post-menopausal women with hormone receptor (HR)-positive, HER2-negative metastatic breast cancer (MBC) resistant to aromatase inhibitor (AI) therapy. Cancer Res. 2016;77(4):S1-2.
14. Satyanarayana A, Kaldis P. Mammalian cell-cycle regulation: several Cdks, numerous cyclins and diverse compensatory mechanisms. Oncogene. 2009;28(33):2925-39.
15. Yu Q, Sicinska E, Geng Y, Ahnström M, Zagozdzon A, Kong Y, et al. Requirement for CDK4 kinase function in breast cancer. Cancer Cell. 2006;9(1):23-32.
16. Arnold A, Papanikolaou A. Cyclin D1 in breast cancer pathogenesis. J Clin Oncol. 2005;23(18):4215-24.
17. Finn RS, Crown JP, Lang I, Boer K, Bondarenko IM, Kulyk SO, et al. The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study. Lancet Oncol. 2015;16(1):25-35.
18. Finn RS, Martin M, Rugo HS, Jones S, Im SA, Gelmon K, et al. Palbociclib and letrozole in advanced breast cancer. N Engl J Med. 2016;375(20):1925-36.
19. Cristofanilli M, Turner NC, Bondarenko I, Ro J, Im SA, Masuda N, et al. 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(4):425-39.
20. Hortobagyi GN, Stemmer SM, Burris HA, Yap YS, Sonke GS, Paluch-Shimon S, et al. Ribociclib as first-line therapy for hr-positive, advanced breast cancer. N Engl J Med. 2016;375(18):1738-48.
21. Leo AD, Toi M, Campone M, Sohn J, Paluch-Shimon S, Huober J, et al. MONARCH 3: Abemaciclib as initial therapy for patients with HR+/HER2- advanced breast cancer. Proceedings of ESMO Congress Abstract 236O_PR; 2017 Sep 08-12; Madrid, Spain.
22. Sledge GW, Toi M, Neven P, Sohn J, Inoue K, Pivot X, et al. 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(25):2875-84.
23. Dickler MN, Tolaney SM, Rugo HS, Cortés J, Diéras V, Patt D, et al. MONARCH 1, A phase II study of abemaciclib, a cdk4 and cdk6 inhibitor, as a single agent, in patients with refractory hr+/her2- metastatic breast cancer. Clin Cancer Res. 2017;23(17):5218-24.
24. Leo AD, Lee KS, Ciruelos E, Lønning P, Janni W, O'Regan R, et al. Abstract S4-07: BELLE-3: A phase III study of buparlisib + fulvestrant in postmenopausal women with HR+, HER2–, aromatase inhibitor-treated, locally advanced or metastatic breast cancer, who progressed on or after mTOR inhibitor-based treatment. SABCS Abstract 16-S4-07; 2016 Dec 06-10; San Antonio, Texas.

25. Bardia A, Kabos P, Elledge R, Wang D, Shen J, Garner F, et al. Evaluation of RAD1901, a novel investigational, selective estrogen receptor degrader (SERD), for the treatment of ER-positive (ER+) advanced breast cancer. Proceedings of ASCO Annual Meeting; 2017 Jun 2-6; Illinois, USA; J Clin Oncol. 2017;35.

26. Dirix LY, Takacs I, Nikolinakos P, Jerusalem G, Arkenau H-T, Hamilton EP, et al. Avelumab (MSB0010718C), an anti-PD-L1 antibody, in patients with locally advanced or metastatic breast cancer: A phase Ib JAVELIN solid tumor trial. Proceedings of the 2016 San Antonio Breast Cancer Symposium; 2016 Dec 6-10; San Antonio, TX. Philadelphia (PA): AACR; Cancer Res 2017;77(4 Suppl):S4-07.

27. Nanda R, Liu MC, Yau C, Asare S, Hylton N, Veer LV, et al. Pembrolizumab plus standard neoadjuvant therapy for high-risk breast cancer (BC): Results from I-SPY 2. Proceedings of ASCO Annual Meeting; 2017 Jun 2-6; Illinois, USA; J Clin Oncol. 2017;35.