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Metastatic breast cancer

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Introduction

Breast Cancer (BC) accounts for 30% of the new cancer cases and 14% of cancer deaths in women in the US, according to statistics from 2017 [1]. At initial diagnosis, 10 % of BC patients have detectable metastases. However, women diagnosed with early stage BC who can access adequate multimodal treatment can achieve a cure probability of approximately 90% [2].

Because most patients with metastatic breast cancer ultimately die of their disease, with a median overall survival of ~2-3 years and a 5-year survival of only ~25% [3], the primary goal of therapy is palliation of symptoms and prolongation of life. On the other hand, it has had an improvement in the survival of patients with metastatic disease in recent decades as a result of more effective therapies, especially if they are more specific treatments in the different BC subtypes [4].

BC is a heterogeneous disease compromising different subtypes with diverse and specific properties, both clinically and biologically. Therefore, identification of BC subtypes is important to select the best therapeutic strategy [5]. BC is classified by Immunohistochemistry (IHC) markers such as Estrogen Receptor (ER), Progesterone Receptor (PR), human epidermal growth receptor 2 (HER2), and Ki67 (a proliferation index marker) in three principal subtypes: LUMINAL, HER2 positive and TRIPLE NEGATIVE. The prognosis and treatment of each of these subtypes is very different, so each of them will be specifically analyzed.

Luminal breast cancer

Defined as Hormone Receptor (HR)-positive, Human Epidermal growth Factor 2 (HER2) negative (HR+/HER2-) is the most common breast cancer subtype with a 70% approximately of metastatic BC [6].

Although this subtype is considered the best prognosis in the early stages, unfortunately, it has a significant residual risk of recurrence beyond the first 5 years, and metastases have been documented up to 20 to 30 years after the initial diagnosis [7]. Even though treatable, it is remains an incurable disease with a median overall survival of 2-3 years and a 5-year survival of only 25% [8].

Most of patients with metastatic disease are expected to experience progression of disease, certain clinical and tumor characteristics are useful in predicting prognosis. Patients with a long interval since initial diagnosis, excellent performance status, hormone receptor-positive disease that primarily involves bone or soft tissue, and only a few sites of visceral involvement are likely to have a better long-term prognosis [7].

The preferred treatment for luminal BC which should be endocrine therapy in the majority of cases, excluding those with visceral crisis and concern or proof of endocrine resistance. We can block the mechanism of endocrine action in two ways: With antiestrogens that compete directly with nuclear hormone receptors (tamoxifen and fulvestrant) or with Aromaratase Inhibitors (AI) that reduce estrogen levels in postmenopausal by inhibiting the enzymatic passage of androgens to estrogens (letrozole, anastrozole or exemestane).

All breast cancer guidelines concur with this recommendation [9] but unfortunately real life data studies show that most of these patients still receive chemotherapy as their first treatment, despite the lower efficacy and more toxicity [10].

The most important advance in the treatment of luminal BC over the last 2 years has been the introduction of a new class of agents, the CDK4/6 inhibitors, in combination with an endocrine agent. Growth of HR-positive breast cancer is dependent on Cyclin-Dependent Kinases (CDK) 4 and 6 that promote progression from G1 to the S phase of the cell cycle. CDK inhibitors block the cyclin D1-CDK 4/6 complex, prevent RB protein phosphorylation, stop the cell cycle from progressing to the S phase, thereby preventing cancer cell proliferation [11].

Three CDK4/6 inhibitors are currently under clinical development: Abemaciclib, ribociclib, and palbociclib. All three compounds showed promising results in phase I trials and many phase II and phase III. Currently, most of the countries have some of them available and the patients with this phenotype can benefit specially in the first line with an expected disease free survival around 24 months which would almost double that of the previously established treatment with antiestrogens or aromatase inhibitors alone.

In premenopausal or younger patients, the hormonal treatment has been less used to believe that these patients had less hormonal sensitivity and we needed to block ovarian function. Recently we have the data from the MONALEESA 7 [12] study that shows a very significant benefit in this subgroup of patients with a significant disease free survival and superior overall survival also with more than 42 months for treatment with the association of ribociclib + letrozole + ovarian block against hormonal treatment alone.

Fulvestrant is another effective option in this patient population. Fulvestrant is an estrogen receptor antagonist that blocks ER dimerization, increases ER turnover, and accelerates degradation of the receptor [13]. Fulvestrant was compared to tamoxifen in the first-line, advanced disease setting and shown to have similar efficacy [14]. The 250 mg dose of fulvestrant was also found to have a similar clinical benefit rate compared to IA in the second-line treatment of postmenopausal women with BC [15].

A higher dose of 500 mg of fulvestrant was found to be more effective than the 250 dose in the CONFIRM trial, showing a statistically significant improvement in PFS [16] and OS analysis that showed a 19% reduction in risk of death and a 4.1 month advantage in median OS [17]. The FIRST trial compared the 500 mg dose of fulvestrant to anastrozole and demonstrated a significantly longer median TTP of 23 versus 13 months and OS of 54 versus 48 months [18].

The confirmative phase III FALCON trial with a median follow-up of 25 months, PFS was prolonged with fulvestrant versus anastrozole (16.6 vs. 13.8 months; HR, 0.797; P = 0.049) [19]. These results suggest that fulvestrant could be acceptable as first-line therapy for metastatic disease in certain patients. But actually, with the impressive results with CDK4/6 inhibitors in the first line have moved the treatment with fulvestrant to the 2 line, where is one of the most recommended treatment options.

The use of second-line fulvestrant monotherapy is well tolerated, but has limited efficacy, in the CONFIRM trial was reported a median PFS of 6.5 and 5.5 months respectively [16]. One of the possible causes of this lack of effectiveness could be that many patients in this setting have already developed resistance to ET [17].

Studies have shown that common mechanisms of endocrine resistance include the upregulation of pathways downstream of ER signaling and adaptive cross-talk between ER and growth factor receptor signaling pathways [20]. Targeting the key biological pathways associated with endocrine resistance may be a rational approach for combination therapy with fulvestrant [21]. Clinical trials of several types of targeted therapy in combination with fulvestrant in the second-line setting are either ongoing or have recently reported data, but the majority of them had negative results and only SANDPIPER with taselisib, SOLAR-1 with apelisib and trials with CDK 4/6 inhibitors (MONARCH 2, PALOMA 3 and MONALEESA 3) reported positive results. In this context, the benefit is in disease free survival about 11 months for the combination versus 4 month in the fulvestrant alone. At present, overall survival data is not yet available because they are still immature [21].

A special situation is BC patients that progressed in course of adjuvant hormonotherapy with IA, although is a first line of the treatment in metastatic setting this patients have already received treatment with IA and their options of treatment is similar to second line so this patients could receive treatment with Fulvestrant with combination with CDK 4/6 inhibitors that have shown a better significant survival than fulvestrant alone with a DFS of 14-16 versus 9 months in the MONARCH 2 and MONALESSA 3 trial [21].

Another possible therapy is the combination of endocrine therapy (exemestane or fulvestrant) with the mTOR inhibitor, everolimus. This combination has shown a PFS benefit of 6 months, without a significant OS benefit, and with significant toxicity [22].

Cytotoxic chemotherapy is still an important therapeutic strategy for most BC patients with endocrine-resistant disease. Several agents have shown efficacy in the metastatic setting although there are no clear data to determine the optimal sequence or whether a combination strategy is better than a single-agent approach. Guidelines and international consensus statements recommend selecting chemotherapy according to each individual clinical scenario, with sequential administration of active single agents generally preferred to combinations of two chemotherapeutic agents except, for example, in patients requiring a rapid response [9].

The choice of chemotherapy will depend mainly on clinical factors that can predict a poor prognosis. The patients who present a relapse in the course of adjuvant hormonal treatment or in a short interval of finishing the adjuvance treatment (<24 months) have a poor prognosis and possibly the most benefit from a chemotherapy treatment is combination schemes with taxanes and antiangiogenics such taxol plus bevavizumab [23].

One important controversy is whether these patients who are progressing in the course of adjuvant treatment or with de novo advanced disease that we do not know their sensitivity to hormonal treatment if the best option would be to start treatment with chemotherapy and after inducing a response continue with hormonal maintenance treatment. There are not trials to compare this situation, only are retrospective analysis to show a similar effect and the greater tendency to start chemotherapy treatment and continue maintenance therapy in real life studies [24].

The combination of taxol plus bevacizumab have shown the best results, especially if the patients followed with a maintenance strategy with bevacizumab plus hormonotherapy or hormonotherapy alone. Tiainen et al [25] collects a series of 53 patients with a sequential treatment scheme with taxanes plus bevacizumab followed after induction response with hormonotherapy plus bevacizumab and reported an overall survival of 54 months.

In the LORENA study [26], a cohort with 120 BC patients treated with first line chemotherapy plus bevacizumab were analyzed the long-terms benefits. The patients who received maintenance hormone treatment had a better survival (25.3 months) compared to those who did not receive it [19] and with an impressive median overall survival of 58 months.

Several options exist for chemotherapy both for first and subsequent lines of therapy. The usual recommendations for patients pretreated with anthracyclines and taxanes are capecitabine, vinorelbine and eribulin, based on their efficacy and toxicity profile. Eribulin is one of the few agents to provide a survival gain, albeit small (2.5 months) in a heavily pretreated population of BC patients [27]. In a head-to-head comparison between eribulin and capecitabine, as first or second line therapy, there were no major differences between the drugs in efficacy but a different toxicity profile [28].

Recently has been published a randomized trial in BC patients with progression after endocrinotherapy with taxol weekly vs oral vinorelbine [29]. The survival benefit is similar in both treatment but the oral vinorelbine is more comfortable and less toxic than taxol so it is an interesting option for this BC patients.

In summary, although all international consensus recommends hormonal treatment as the first treatment option, there are many circumstances to consider in order to decide the best option. In the clearest situation, late relapses or metastatic debut, the option of the combination of inhibitors of CDK4 / 6 + IA can be considered the most appropriate, achieving global average survival rates exceeding 42 months or around 5 years.

In cases of early relapses the decision of the type of treatment is more compromised. The hormonal treatment offers worse results, so that the combination of CDK4/6 + fulvestrant achieves a median overall survival around 26 months. In this situation, although it is not exactly represented in the different studies, we could choose a chemotherapy treatment and continue with maintenance schemes where median survival can be achieved around 58 months.

Finally, after the progression to a first line of hormonal treatment, we could continue with hormonal treatments of 2 and 3 lines until the end of hormonal sensitivity and continue with chemotherapy treatment with oral dispensing drugs such as vinorelbine, reaching a median overall survival of 27 months. Below table summarizes all of these options with the results found.

Situation	Condition	Options	DFS	OS
First line	De novo or > 24 months end of adjuvant therapy	CDK4/6+IA	24 months	Not Done
Post menopausal				
Pre-menopausal		Ribocilib+IA+OS	24 months	70% alive in 42 months
Post menopausal	Early relapse	CDK4/6+FULVESTRANT	13 months	26 months
First line	Suitable to chemotherapy	Taxane + Bevacizumab	25 months	58 months
Second line	After IA	CDK4/6+FULVESTRANT	18 months	39 months
	After CDK4/6	FULVESTRANT	6 months	Not Done
	After QT	CDK4/6+FULVESTRANT	9 months	20 months
Third Line	Resposive to HT	Everolimus+exemestane	6 months	31 months
Resistence HT	After hormonotherapy	Oral vinorelvine	6 months	27 months
Late Lines	Heavily pretreated	Eribulin	4 months	15 months

HER2 Positive breast cancer

BC that overexpresses HER2 (HER2+) forms a subpopulation amounting to 15-20% of cases, with an aggressive clinical behavior [30]. Intense research efforts have yielded, starting with trastuzumab, a class of anti-HER2 agents that includes today 4 approved agents in the advanced setting – trastuzumab, lapatinib, pertuzumab and T-DM1.

These agents have doubled median Overall Survival (OS)-today surpassing 50 months, and more than tripled the 5-year survival rate [31].

According to international guidelines, patients with Metastatic HER2-positive BC (MBC) should be stratified according to prior exposure to trastuzumab and time elapsed between last dose and disease relapse [32]. Patients who have not been exposed to trastuzumab or who develop metastatic disease 6 months after adjuvant trastuzumab are candidates for first line treatment with a taxane, trastuzumab and pertuzumab (CLEOPATRA TRIAL) that achieved an impressive median overall survival around 50 months [33]. However, if disease progression occurs while on trastuzumab or with a treatment free interval of less than 6 months, direct second line treatment with T-DM1 is the best option [32].

About 80% of patients in the CLEOPATRA trial had not been treated with trastuzumab in adjuvant setting which is different from clinical practice in real life [34]. The results in these patients were superior to patients previously treated with trastuzumab (16.9 versus 21.6 months) but still being superior to the control arm without pertuzumab. However, in the second-line TDM-1 trial (EMILIA) [35] with only 16% of patients who did not receive trastuzumab in a metastatic line, the median survival was similar (21.9 months), so the treatment with TDM-1 in patients who progressed during adjuvant treatment with trastuzumab should be the best option.

TDM-1 is the most consistent option for treatment from patients HER2-positive BC previously treated with trastuzumab and a taxane, based on the EMILIA [35] trial patients treated with TDM-1 had significantly longer Progression-Free Survival (PFS; median 9.6 versus 6.4 months with capecitabine plus lapatinib; $p < 0.001$) and Overall Survival (OS; median 30.9 versus 25.1 months; $p < 0.001$) and fewer grade >3 Adverse Events (AEs; 41% versus 57%).

Following the use of T-DM1, lapatinib containing combinations or chemotherapy+ trastuzumab are standard options. Currently, many trials with new drugs are being developed but any of them having been approved. The only certain fact is that the maintenance of the blockage of the HER2 pathway still provides a benefit [32].

HER2 positive BC is still considered heterogeneous with implications in HER2 positive with positive hormonal receptors (ER+). Preclinical evidence suggests intense interconnection between the ER and HER2 signaling pathways, that the ER pathway is one of the mechanisms of resistance to anti-HER2 therapy [37]. Current treatment guidelines, however, do not propose distinct management strategies for ER+ and ER-HER2+ BC [29], partly due to disappointing results of initial trials testing enocrinotherapy in HER2+ patients, including TAnDEM, eLEcTRA and EGF107692, relegating the strategy either to patients who could not tolerate chemotherapy or to post chemotherapy empirical "maintenance strategies" [36].

More recent trials have renewed interest in ET strategies and carried out additional data. PERTAIN tested first line letrozole+ trastuzumab + pertuzumab vs letrozole+trastuzumab, with or without induction docetaxel (as per physician's choice), in 258 patients. PFS results showed a small, yet statistically significant, advantage to the dual blockade regimen (18 vs 15.8 months, HR 0.65, 95% IC 0.48–0.89, p=0.0070) [38]. Further new data comes from the ALTERNATIVE trial, which tested dual blockade with trastuzumab+lapatinib+Aromatase Inhibitor (AI) vs AI+trastuzumab or AI+lapatinib in second line or more. With 355 patients randomised, the PFS results show increased and significant benefit with dual blockade (11m vs 5.7m vs 8.3 m, respectively), though toxicity was slightly increased with the use of dual blockade [39].

In summary, most of the HER2 positive BC could receive the combination trastuzumab + pertuzumab + docetaxel, except for the BC that progresses in course or less than 12 months after finishing adjuvant with trastuzumab although there will be very few cases. In this scenario, a great advance has been achieved with a very significant survival improvement. It is also important to continue maintaining the blockage of the HER2 pathway in the successive lines that also produces a survival benefit. In cases with hormonal receptor expression, the maintenance strategy with hormonal treatment and the antiher2 block is a very good alternative. Below table summarizes all of these options with the results found.

Situation	Condition	Options	DFS	OS
First line	De novo or > 24 months end of adjuvant therapy	Trastuzumab+pertuzumab +docetaxel	21 months	50 months
First line	Trastuzumab < 24 months	Tdm-1	22 months	31 months
Second line	After first líne with anti her2	Tdm-1	22 months	31 months
Third line		Lapatinib+capecitabine	6 months	22 months
>Third line		Trastuzumab+qt	5 months	12 months
>Third line	Estrogen receptor negative	Lapatinib+trastuzumab	3 months	14 months

Triple negative breast cancer (TNBC)

Metastatic TNBC is associated with a more aggressive clinical course compared with other BC subtypes. Despite its high sensitivity to chemotherapy, advanced TNBC has poor outcome with conventional chemotherapy regimens with a higher frequency of progression, shorter Progression-Free Survival (PFS) and poorer OS. Chemotherapy remains the primary systemic treatment, with international guidelines supporting the use of single-agent taxanes or anthracyclines as first-line therapy .The median OS for metastatic TNBC is about 9-12 months with conventional cytotoxic agents [40].

The use of antiangiogenic drugs as bevacizumab in patients with TNBC has attracted considerable interest, primarily because of the lack of targeted therapy for these patients and failure of drugs developed in this setting, but also because of the observed effect of bevacizumab in the subgroup of patients with TNBC treated in the E2100 trial [41]. In these patients, median Progression Free Survival (PFS) was 10.6 months with bevacizumab plus paclitaxel versus 5.3 months with paclitaxel alone (hazard ratio [HR] 0.49; 95% Confidence Interval [CI] 0.34-0.70), and median Overall Survival (OS) was 20.5 versus 16.3 months (HR 0.89; 95% CI 0.66-1.19) [38]. These results was confirmed in other trials and metanalisis [42].

Recently the presence of tumor-infiltrating immune cells with expression of Programmed Death Ligand 1 (PD-L1) that can inhibit anticancer immune responses has been demonstrated [43]. Thus, the inhibition of Programmed Death 1 (PD-1) and PD-L1 may be a useful treatment strategy. In phase 1 trials, better results were observed in patients with high expression of PD-L1 who were receiving treatment with atezolizumab, pembrolizumab or avelumab.

The IMpassion130 trial [44] shows a clinical benefit with atezolizumab-nabpaclitaxel in the PD-L1-positive subgroup by a median progression free survival that was significantly longer by 2.5 months (7.5 months with atezolizumab plus nab-paclitaxel vs 5.0 months with placebo-nab-paclitaxel; hazard ratio for progression or death, 0.62), by a median overall survival that was 10 months longer at this interim analysis (25.0 months vs 15.5 months; hazard ratio for death, 0.62 [not statistically tested]), and a numerically higher objective response rate (58.9% vs 42.6%).

After progression of first line, the options to improve the survival are very disappointing. We could use different chemotherapy drugs as anthracyclin, capecitabine, vinorelbine or eribulin with an expected DFS about 4 months [45]. Patientes progressed after treatment with taxanes and anthracycline had very few options to treatment, only eribulin had shown a benefit in survival, in study 301, this subgroup of patients was randomized to treatment with eribulin versus capecitabine [46], finding a in overall survival (14 vs 9 months) so the treatment with eribulin should be the best option in this situation.

Given the low benefit of second or more lines treatment, one of the strategies used to achieve better survival is the concept of maintenance. There are meta-analyzes that confirm the usefulness of maintaining a chemotherapy treatment until progression but the implicit toxicity of these agents often limits this strategy [47]. One strategy that achieves great efficacy is to maintain treatment with antiangiogenics and changing the chemotherapy of taxanes with capecitabine. The IMELDA trial [48] showed significant and clinically meaningful improvements in both progression-free survival (7,6 months) and overall survival (39 months) when maintenance bevacizumab was combined with oral capecitabine compared with bevacizumab alone for maintenance treatment.

In this subgroup we have few possibilities given the lack of a specific treatment. The incorporation of agents directed against the expression of PDL1 of the tumor such as atezolizumab, have opened a new therapeutic window that has achieved a survival benefit. The schemes of taxanes with antiangiogenics followed by a maintenance strategy are the ones that produce the longest survival. When these treatments progress, the options for new treatment lines offer very discouraging results. Below table summarizes all of these options with the results found.

Situation	Condition	Options	DFS	OS
First line		Taxol + trastuzumab	11 months	20 months
First line	PDL-1 expression	Nab-paclitaxel+ Atezolizumab	7,5 months	25 months
Second line	After taxanes and anthracyclines	Eribuline	4 months	14 months

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. CA Cancer J Clin. 2017; 67: 7-30.
2. NIH Surveillance, Epidemiology, and End Results Program. Cancer Stat Facts-female breast cancer. 2015.
3. Global Status of Advanced/Metastatic Breast Cancer 2005e2015 Decade Report.
4. Kobayashi K, Ito Y, Matsuura M, Fukada I, Horii R, et al. Impact of immunohistological subtypes on the long-term prognosis of patients with metastatic breast cancer. Surgery today. 2016; 46: 821-826.
5. Dai X, Li T, Bai Z, Yang Y, Liu X, et al. Breast cancer intrinsic subtype classification, clinical use and future trends, Am. J. Cancer Res. 2015; 5: 2929-2943.
6. Howlader N, Altekruse SF, Li CI, Chen VW, Clarke CA, et al. US incidence of breast cancer subtypes defined by joint hormone receptor and HER2 status. JNCI: Journal of the National Cancer Institute. 2014; 106.
7. Pan H, Gray RG, Davies C, Peto R, Bergh JC, et al. Predictors of recurrence during years 5-14 in 46,138 women with ER+ breast cancer allocated 5 years only of endocrine therapy (ET). J Clin Oncol. 2016; 34: 505.
8. Howlader N, Noone AM, Krapcho M, Miller D, Bishop K, et al. SEER Cancer Statistics Review, 1975-2013. Bethesda, MD: National Cancer Institute. 2016.
9. Cardoso F, Costa A, Senkus E, Aapro M, André F, et al. 3rd ESO-ESMO international consensus guidelines for Advanced Breast Cancer (ABC 3). Breast. 2017; 31: 244-259.

10. Lobbezoo DJ, van Kampen RJ, Voogd AC, Dercksen MW, van den Berkmortel F, et al. In real life, one-quarter of patients with hormone receptor-positive metastatic breast cancer receive chemotherapy as initial palliative therapy: a study of the Southeast Netherlands Breast Cancer Consortium. Annals of Oncology. 2015; 27: 256-262.

11. Morikawa A, Henry NL. Palbociclib for the treatment of estrogen receptor–positive, HER2-negative metastatic breast cancer. Clin Cancer Res. 2015; 21: 3591-3596.

12. Hortobagyi GN, Stemmer SM, Burris HA, Yap YS, Sonke GS, et al. Ribociclib as First-Line Therapy for HR-Positive, Advanced Breast Cancer. N Engl J Med. 2016; 375:1738-1748.

13. Wakeling AE, Dukes M, Bowler J. A potent pure antiestrogen with clinical potential. Cancer Res. 1991; 15: 3867-3873.

14. Howell A, Robertson JF, Abram P, Lichinitser MR, Elledge R, et al. Comparison of fulvestrant versus tamoxifen for the treatment of advanced breast cancer in postmenopausal women previously untreated with endocrine therapy: A multinational, double-blind, randomized trial. Journal of Clinical Oncology. 2004; 22: 1605-1613.

15. Chia S, Gradishar W, Mauriac J. Double-blind randomized placebo controlled trial of fulvestrant compared with exemestane after prior nonsteroidal aromatase inhibitor therapy in postmenopausal women with hormone receptor positive advanced breast cancer: Results from effect. J Clin Oncol. 2008; 26: 1664-1670.

16. Di Leo A, Jerusalem G, Petruzelka L, Torres R, Bondarenko IN, et al. Results of the CONFIRM phase III trial comparing fulvestrant 250 mg with fulvestrant 500 mg in postmenopausal women with estrogen receptor-positive advanced breast cancer. J Clin Oncol. 2010; 28: 4594-4600.

17. Leo AD, Jerusalem G, Petruzelka L, Torres R, Bondarenko IN, et al. Final overall survival: Fulvestrant 500mg vs 250mg in the randomized CONFIRM trial. Journal of the National Cancer Institute. 2013; 106: djt337.

18. Ellis MJ, Llombart-Cussac A, Feltl D, Dewar JA, Jasiówka M, et al. Fulvestrant 500 mg versus anastrozole 1 mg for the first-line treatment of advanced breast cancer: Overall survival analysis from the phase II FIRST study. Journal of Clinical Oncology. 2015; 33: 3781.

19. Robertson JF, Bondarenko IM, Trishkina E, Dvorkin M, Panasci L, 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. The Lancet. 2016; 388: 2997-3005.

20. Selli C, Dixon J, Sims A. Accurate prediction of response to endocrine therapy in breast cancer patients: current and future biomarkers. Breast Cancer Res. 2016; 18:118.

21. Sammons S, Kornblum NS, Blackwell KL. Fulvestrant-Based Combination Therapy for Second-Line Treatment of Hormone Receptor-Positive Advanced Breast Cancer. Target Oncol. 2019; 14: 1-12.

22. Piccart M, Hortobagyi GN, Campone M, 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: 2357-2362.

23. Llombart-Cussac A1, Pivot X2, Biganzoli L3, Cortes-Funes H4, Pritchard KI5, et al. A prognostic factor index for overall survival in patients receiving first-line chemotherapy for HER2-negative advanced breast cancer: An analysis of the ATHENA trial. Breast. 2014; 23: 656-662.

24. Bonotto M, Gerratana L, Di Maio M, De Angelis C, Cinausero M, et al. Chemotherapy versus endocrine therapy as first-line treatment in patients with luminal-like HER2-negative metastatic breast cancer: A propensity score analysis. Breast. 2017; 31:114-120.

25. Tiainen L, Tanner M, Lahdenperä O, Vihinen P, Jukkola A, et al. Bevacizumab Combined with Docetaxel or Paclitaxel as First-line Treatment of HER2-negative Metastatic Breast Cancer. Anticancer Res. 2016; 36: 6431-6438.

26. Redondo A, Ramos Vázquez M, Manso L, Gil Gil MJ, Garau Llinas I, et al. Long-term response to first-line bevacizumab-based therapy in patients with metastatic breast cancer: Results of the observational "LORENA" study. Onco Targets Ther. 2018; 11: 5845-5852.

27. Cortes J, O'Shaughnessy J, Loesch D, Blum JL, Vahdat LT, et al. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): A phase 3 open-label randomised study. The Lancet. 2011; 377: 914-923.

28. Kaufman PA, Awada A, Twelves C, Yelle L, Perez EA, et al. Phase III open-label randomized study of eribulin mesylate versus capecitabine in patients with locally advanced or metastatic breast cancer previously treated with an anthracycline and a taxane. Journal of clinical oncology. 2015; 33: 594.

29. Aapro M, Ruiz-Borrego M, Hegg R, Kukielka-Budny B, Morales S, et al. Randomized phase II study evaluating weekly oral vinorelbine versus weekly paclitaxel in estrogen receptor-positive, HER2-negative patients with advanced breast cancer (NorBreast-231 trial). Breast. 2019; 45: 7-14.

30. Slamon D, Godolphin W, Jones L, Holt J, Wong S, et al. Studies of the HER-2/neu proto-oncogene in human breast and ovarian cancer. Science 1989; 244: 707-712.

31. Roth J, Bajaj P, Sullivan S, Reyes C, Antao V, et al. 263PSurvival gains from advances in first-line systemic therapy for HER2-positive metastatic breast cancer in the US, 1995-2015. Annals of Oncology. 2017; 28.

32. Cardoso F, Costa A, Senkus E, Aapro M, André F, et al. 3rd ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 3). Ann Oncol. 2017; 28: 16-33.

33. Baselga J, Cortés J, Kim SB, Im SA, Hegg R, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. N Engl J Med. 2012; 366: 109-119.

34. Seferina SC, Lobbezoo DJA, de Boer M, Dercksen MW, van den Berkmortel F, van Kampen RJW, et al. Real-life use and effectiveness of adjuvant trastuzumab in early breast cancer patients: A study of the southeast netherlands breast cancer consortium. Oncologist. 2015; 20: 856-863.

35. Verma S, Miles D, Gianni L, Krop IE, Welslau M, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. N Engl J Med. 2012; 367:1783-1791.

36. Pondé N, Brandão M, El-Hachem G, Werbrouck E, Piccart M. Treatment of advanced HER2-positive breast cancer: 2018 and beyond. Cancer Treat Rev. 2018; 67: 10-20.

37. Llombart-Cussac A, Cortés J, Paré L, Galván P, Bermejo B, Martínez N, et al. HER2-enriched subtype as a predictor of pathological complete response following trastuzumab and lapatinib without chemotherapy in early-stage HER2-positive breast cancer (PAMELA): An open-label, single-group, multicentre, phase 2 trial. Lancet Oncol. 2017; 18: 545-554.

38. Arpino G, Ferrero JM, De la Haba-Rodriguez J, Easton V, Schuhmacher C, et al. Abstract S3-04: Primary analysis of PERTAIN: A randomized, two-arm, open-label, multicenter phase II trial assessing the efficacy and safety of pertuzumab given in combination with trastuzumab plus an aromatase inhibitor in first-line patients with HER2-positive and hormone receptor-positive metastatic or locally advanced breast cancer.

39. Johnston SRD, Hegg R, Im SA, Park IH, Burdaeva O, et al. Phase III, Randomized Study of Dual Human Epidermal Growth Factor Receptor 2 (HER2) Blockade With Lapatinib Plus Trastuzumab in Combination With an Aromatase Inhibitor in Postmenopausal Women With HER2-Positive, Hormone Receptor-Positive Metastatic Breast Cancer: ALTERNATIVE. J Clin Oncol. 2018.

40. Kassam F, Enright K, Dent R, Dranitsaris G, Myers J, et al. Survival outcomes for patients with metastatic triple-negative breast cancer: Implications for clinical practice and trial design. Clinical breast cancer. 2009; 9: 29-33.

41. Miller K, Wang M, Gralow J, Dickler M, Cobleigh M, et al. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. New England Journal of Medicine. 2007; 357: 2666-2676.

42. Miles DW, Diéras V, Cortés J, Duenne AA, Yi J, et al. First-line bevacizumab in combination with chemotherapy for HER2-negative metastatic breast cancer: Pooled and subgroup analyses of data from 2447 patients. Ann Oncol. 2013; 24: 2773-2780.

43. Herbst RS, Soria JC, Kowanetz M, Fine GD, Hamid O, et al. Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. Nature. 2014; 515: 563-567.

44. Schmid P, Adams S, Rugo HS, Schneeweiss A, Barrios CH, et al. Atezolizumab and nab-paclitaxel in advanced triple-negative breast cancer. New England Journal of Medicine. 2018; 379: 2108-2121.

45. Oostendorp LJ, Stalmeier PF, Donders AR, van der Graaf WT, Ottevanger PB. Efficacy and safety of palliative chemotherapy for patients with advanced breast cancer pretreated with anthracyclines and taxanes: A systematic review. Lancet Oncol. 2011; 12: 1053-1061.

46. Kaufman PA, Awada A, Twelves C, Yelle L, Perez EA, et al. Phase III open-label randomized study of eribulin mesylate versus capecitabine in patients with locally advanced or metastatic breast cancer previously treated with an anthracycline and a taxane. Journal of clinical oncology. 2015; 33: 594.

47. Gennari A, Stockler M, Puntoni M, Sormani M, Nanni O, et al. Duration of chemotherapy for metastatic breast cancer: A systematic review and meta-analysis of randomized clinical trials. J Clin Oncol. 2011; 29: 2144-2149.

48. Gligorov J, Doval D, Bines J, Alba E, Cortes P, et al. Maintenance capecitabine and bevacizumab versus bevacizumab alone after initial first-line bevacizumab and docetaxel for patients with HER2-negative metastatic breast cancer (IMELDA): A randomised, open-label, phase 3 trial. Lancet Oncol. 2014; 15: 1351-1360.