# Advanced Breast Cancer

Subjects: Allergy
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HER2 positive breast cancer represent about 20% of all breast cancer subtypes and it was considered the subtype with the worst prognosis until the discovery of therapies directed against the HER2 protein. The determination of the status of the HER2 must be very precise and well managed to identify this subtype, and there are very specific and updated guides that allow its characterization to be adjusted.

Keywords: HER2 positive breast cancer ; new drugs ; guidelines ; clinical trial

## 1. Treatment in First Line

The combination of taxane with trastuzumab and pertuzumab (CLEOPATRA TRIAL [1]: placebo plus trastuzumab plus docetaxel (control group) or pertuzumab plus trastuzumab plus docetaxel (pertuzumab group)) has shown impressive survival rates in patients with metastatic HER2-positive disease in the first line of treatment. After a median follow-up of 99.9 months [2], a median overall survival of 57.1 months in the pertuzumab group vs. 40.8 in the control group (without pertuzumab) was observed. This supposes an improvement of 16.3 months and a risk for death decreased by 31% (HR for overall survival: 0.68 95% CI, 0.56–0.84; $p < 0.001$).

Pertuzumab was well tolerated, and the toxicity was very low, with diarrhea, skin rash, headache, and muscle spasm being the most relevant. Nor were differences observed in cardiotoxicity, which was also very low [3]. With these data, the trastuzumab, pertuzumab, and taxane regimen were established as the standard first-line treatment in patients with HER2-positive MBC [4].

Although the analysis of overall survival in predefined subgroups indicated a consistent survival benefit, it is important to analyze the results in these subgroups. The majority of the patients were confirmed HER2 positive (91%), half were estrogen-receptor positive, and 77% had visceral disease. It is interesting that the 50% not received previous adjuvant or neoadjuvant therapy [1].

In the subgroup analysis, it was observed that the 88 patients who received prior treatment with neoadjuvant or adjuvant trastuzumab had an overall survival benefit with a hazard ratio of 0.68 (95% CI 0.30 to 1.55).

The early relapse subgroup was not represented in the CLEOPATRA trial, being a subgroup with a particularly poor prognosis [5]. However, the combination treatment with trastuzumab plus pertuzumab was approved in the first line regardless of the relapse time. In the EMILIA trial [6] (T-DM1 versus lapatinib plus capecitabine), this subgroup was included in a small proportion (15%), finding a benefit in favor of treatment with T-DM1, therefore the regulatory agencies approved the treatment with T-DM1 in this subgroup [4].

## 2. Improvement in This Area: Results of pi3ka Mutations

PIK3CA mutation is a signaling oncogenic that activates the (PI3K)/AKT/mTOR pathway and acts as an oncogenic driver and regulates cell growth, proliferation, survival, differentiation, angiogenesis and many other cell functions.

In the analysis of biomarkers with effect on survival benefit, PIK3CA was the only biomarker that showed prognostic effect, with longer median disease free survival (DFS) for patients whose tumors expressed wild-type versus mutated PIK3CA in both the control (13.8 vs. 8.6 months) and pertuzumab groups (21.8 vs. 12.5 months) [7]. Although patients with PIK3CA mutations also benefit from the combination with pertuzumab, the DFS is only 12 months. PIK3CA mutation identifies patients with high unmet needs, despite deriving DFS benefit from treatment with pertuzumab plus trastuzumab plus docetaxel. Thus, new trials combining HER2-targeted therapy and PIK3 inhibitors are currently underway.

There are some trials to investigate the role of PIK3CA inhibitors to improve the results in patients with PIK3CA mutations. One interesting trial is the Solti-1507, it is a phase Ib study of ipatasertib and anti-HER2 therapy in her2-positive advanced breast cancer with PIK3CA mutation (ipather) [8].

## 3. Improvement in This Area: Combination with Endocrinotherapy

Another approach is the use of antiHER2 therapy with endocrine-therapy in patients with hormonal receptor expression. In the CLEOPATRA trial, the benefit in overall survival for positive estrogen receptor was worse than negative estrogen receptors (HR 0.73 vs. HR: 0.57), so its addition to endocrine therapy could be an attractive approach [2]. Also, the CLEOPATRA trial does not allow maintenance endocrine therapy. Thus, the value of endocrine therapy in this setting is unknown.

In the PERTAIN trial [9], it was hypothesized that pertuzumab, trastuzumab, and an endocrine-therapy (aromatase inhibitor) may offer additional benefits compared with trastuzumab plus an aromatase inhibitor for HER2–positive and hormone receptor–positive MBC or locally advanced breast cancer (LABC) in first line. Induction intravenous docetaxel every 3 weeks or paclitaxel every week could be administered for 18 to 24 weeks at the investigator's discretion.

The median DFS was 18.89 months (95% CI, 14.09 to 27.66 months) in the pertuzumab plus trastuzumab arm and 15.80 months (95% CI, 11.04 to 18.56 months) in the trastuzumab arm (stratified hazard ratio, 0.65; 95% CI, 0.48 to 0.89; $p$ = 0.0070). In patients who did not receive induction chemotherapy, the pertuzumab plus trastuzumab showed a longer DFS (21.72 months) than trastuzumab arm (12.45 months; unstratified HR: 0.55; 95% CI, 0.34 to 0.88). Whereas patients who received induction chemotherapy the DFS was similar (16.8 months vs. 16.85; unstratified HR: 0.75; 95% CI, 0.50 to 1.13). Finally authors concluded that pertuzumab plus trastuzumab and an aromatase inhibitor is effective for the treatment of these patients.

## 4. Improvement in This Area: T-DM1 in First Line MBC

Treatment with T-DM1 in the first line is not indicated except for the early relapse subgroup, which has been previously commented upon, based on the results in favor of T-DM1 in the global series, but the benefit of T-DM1 in this subgroup is unknown.

The role of first-line T-DM1 was considered in the MARIANNE phase III randomized controlled trial, [10] which compared T-DM1, alone or with the combination of pertuzumab, trastuzumab, and taxane. This study showed a non-inferiority of TDM compared to the combination of pertuzumab, trastuzumab and taxane. Other series with retrospective studies [11] also showed poorer survival with T-DM1 compared to the combination of trastuzumab plus pertuzumab. Therefore, the combination of trastuzumab + pertuzumab + docetaxel remains the best first-line treatment option for metastatic breast cancer.

## 5. Improvement in This Area: Other First-Line Approaches

New active drugs and special scenarios has been studied and compared to standard treatment with the combination to trastuzumab plus pertuzumab. Trastuzumab deruxtecan and pyrotinib are very promising drugs that are being investigated their activity in first line treatment. New treatment with immune checkpoint inhibitors such as atezolizumab is also being studied in this situation. Finally, special situations such as positive receptors or brain metastasis are being investigated with specific therapy.

Other conditions that are being investigated are maintenance after a first line of standard treatment, such as the aforementioned maintenance with hormonal treatment (PERTAIN trial) or with AKT inhibitors (IPATHER). Moreover, the role of cyclin inhibitors (PALBOCICLIB) in this setting is currently being studied. **Table 1** summarizes trials that are ongoing in these conditions.

**Table 1.** New approaches in first line.

| Clinical Trial | Phase | Treatment Arm Study | Conditions | Enrollment |
|---|---|---|---|---|
| NCT04246502 | Phase II | Capecitabine plus pyrotinib | First Line | 200 |
| NCT03199885 | Phase III | Atezolizumab | First Line | 600 |
| NCT04784715 | Phase III | Trastuzumab deruxtecan | First Line | 1134 |

| Clinical Trial | Phase | Treatment Arm Study | Conditions | Enrollment |
|---|---|---|---|---|
| NCT03910712 | Phase II | Pyrotinib plus aromatase inhibitor | HR positive | 250 |
| NCT04088110 | Phase II | Pyrotinib plus aromatase inhibitor | HR positive | 77 |
| NCT04760431 | Phase II | Pyrotinib or tucatinib | Brain metastases | 120 |
| NCT04263298 | Phase III | Fulvestrant | Maintenance | 368 |
| NCT03304080 | Phase I/II | Palbociclib | HR positive | 36 |
| NCT 02947685 | Phase III | Palbociclib | Maintenance | 496 |
| NCT04253561 | Phase Ib | Ipatasertib | Maintenance | 25 |

## 6. Treatment in Second Line

The data with T-DM1 are very consistent for patients who progress to a first line. T-DM1 is an antibody-drug conjugate that is composed of an antibody targeting HER2 conjugated via a non-cleavable linker to DM1, an emtansine analogue that inhibits microtubules. We have very robust data suggesting that T-DM1 is highly effective in this setting initially based on the EMILIA data [12], which compared T-DM1 with capecitabine and lapatinib. In the primary progression-free survival analysis of EMILIA [6], median DFS was 9.6 months in the trastuzumab emtansine group and 6.4 months in the capecitabine plus lapatinib group (hazard ratio 0·65 [95% CI 0.55–0.77]; $p < 0.0001$). T-DM1 also significantly increased overall survival (30.9 vs. 25.1 months; HR, 0.68; 95% CI, 0.55–0.85; $p < 0.001$). This benefit was observed across all subgroups, regardless of hormone receptor status and site of metastatic disease. Fewer grade 3 or worse adverse events were reported for trastuzumab emtansine versus capecitabine plus lapatinib (41% vs. 57%).

Therefore, only a small number of patients in EMILIA have received previous pertuzumab treatment. Even so, a limitation of the EMILIA study is that it does not provide evidence regarding the efficacy of trastuzumab emtansine after a patient has been treated with trastuzumab plus pertuzumab combination [12].

In the TH3RESA phase 3 trial, [13] has also shown improved DFS and OS with T-DM1 in patients with HER2-positive MBC who have been exposed to 2 anti-HER2 lines of therapy, including trastuzumab and lapatinib. T-DM1 improved the final overall survival compared with treatment of physician's choice with a median overall survival pf 22.7 months vs. 15.8 months (HR 0.68 0.54–0.85; $p = 0.0007$).

Additional data for the use of trastuzumab emtansine in patients previously treated with HER2-targeted therapy plus chemotherapy will be obtained from real-world life studies. The Bahceci cohort [14] with 414 patients treated with T-DM1 in different lines, including anti HER2 therapy, shows an overall survival of 41 months, similar in first and second lines. However, in this cohort, there was a 30% of patients that are previously treated with lapatinib combinations and only 1% with pertuzumab combination. Battisti et al. [15] reported the Royal Marsden experience with T-DM1 in 128 patients with a 30% of previously treated with pertuzumab and shows a median disease-free survival and overall survival of 8 and 20 months respectively, and being very similar in the subgroup of patients who received prior treatment with pertuzumab.

The most important study to analyze T-DM1 after progression to previous treatments was the phase 3b KAMILLA study [16], with 2002 patients achieving a median disease-free survival and overall survival of 6.9 and 27.2 months respectively. Median DFS and OS decreased numerically with increasing prior lines of therapy. In patients with 0 to 1 prior lines of therapy, median DFS was 8.3 months, whereas in patients with 4 or more prior lines of therapy was 5.6 months. OS was 31.3 months in patients with 0 to 1 prior lines of therapy and 22.5 months in patients with 4 or more prior lines of therapy.

**Table 2** summarizes the results of the most important trials of T-DM1 for previously treated metastatic breast cancer and the survival for the T-DM1 treated patients.

**Table 2.** Main trials of TDM-1.

| Trial | Type | Size | Previous Treated | DFS | OS |
|---|---|---|---|---|---|
| EMILIA | Phase III | 991 | Trastuzumab and taxane | 9.6 | 30.9 |
| TH3RESA | Phase III | 602 | Trastuzumab and lapartinib | 6.2 | 22.7 |
| Baheci | RWD | 414 | 37% in second line | 12 | 41 |

| Trial | Type | Size | Previous Treated | DFS | OS |
|---|---|---|---|---|---|
| Battisti | RWD | 128 | 30% with pertuzumab | 8 | 20 |
| KAMILLA | Phase IIIb | 2020 | 22% in second line | 6.9 | 27.2 |

## 7. Treatment beyond Second Line

New agents have been developed in patients who had progressed on taxane, trastuzumab, pertuzumab, and T-DM1. **Table 3** lists the most developed drugs that will be explained below.

**Table 3.** New drugs after second line treatment.

| Drugs | Family |
|---|---|
| Lapatinib | TKI |
| Neratinib | TKI |
| Tucatinib | TKI |
| Trastuzumab deruxtecan | ADC |
| Margetuximab | Monlclonal Antibody |
| Pyrotinib | TKI |
| Trastuzumab duocarmazine | ADC |
| Palbociclib and abemaciclib | CDH 4/6 inhibitors |

## References


1. Baselga, J.; Cortés, J.; Kim, S.-B.; Im, S.-A.; Hegg, R.; Im, Y.-H.; Roman, L.; Pedrini, J.L.; Pienkowski, T.; Knott, A.; et al. Pertuzumab plus Trastuzumab plus Docetaxel for Metastatic Breast Cancer. N. Engl. J. Med. 2012, 366, 109–119.
2. Swain, S.M.; Miles, D.; Kim, S.-B.; Im, Y.-H.; Im, S.-A.; Semiglazov, V.; Ciruelos, E.; Schneeweiss, A.; Loi, S.; Monturus, E.; et al. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA): End-of-study results from a double-blind, randomised, placebo-controlled, phase 3 study. Lancet Oncol. 2020, 21, 519–530.
3. Swain, S.M.; Ewer, M.S.; Cortes, J.; Amadori, D.; Miles, D.; Knott, A.; Clark, E.; Benyunes, M.C.; Ross, G.; Baselga, J. Cardiac Tolerability of Pertuzumab Plus Trastuzumab Plus Docetaxel in Patients with HER2-Positive Metastatic Breast Cancer in CLEOPATRA: A Randomized, Double-Blind, Placebo-Controlled Phase III Study. Oncologist 2013, 18, 257–264.
4. Cardoso, F.; Paluch-Shimon, S.; Senkus, E.; Curigliano, G.; Aapro, M.; André, F.; Barrios, C.; Bergh, J.; Bhattacharyya, G.; Biganzoli, L.; et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann. Oncol. Off. J. Eur. Soc. Med. Oncol. 2020, 31, 1623–1649.
5. Láng, I.; Bell, R.; Feng, F.; Lopez, R.; Jassem, J.; Semiglazov, V.; Al-Sakaff, N.; Heinzmann, D.; Chang, J. Trastuzumab Retreatment after Relapse on Adjuvant Trastuzumab Therapy for Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer: Final Results of the Retreatment after Herceptin Adjuvant Trial. Clin. Oncol. 2014, 26, 81–89.
6. Verma, S.; Miles, D.; Gianni, L.; Krop, I.E.; Welslau, M.; Baselga, J.; Pegram, M.; Oh, D.-Y.; Diéras, V.; Guardino, E.; et al. Trastuzumab Emtansine for HER2-Positive Advanced Breast Cancer. N. Engl. J. Med. 2012, 367, 1783–1791.
7. Baselga, J.; Cortes, J.; Im, S.-A.; Clark, E.; Ross, G.; Kiermaier, A.; Swain, S. Biomarker Analyses in CLEOPATRA: A Phase III, Placebo-Controlled Study of Pertuzumab in Human Epidermal Growth Factor Receptor 2–Positive, First-Line Metastatic Breast Cancer. J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. 2014, 32, 3753–3761.
8. Oliveira, M.; Villagrasa, P.; Ciruelos, E.; Gavilá, J.; Cortegoso, A.; Henao, F.; Vega, E.; Bofill, J.S.; Quiroga, V.; García-Estevez, L.; et al. Abstract OT-35-01: Solti-1507 A phase ib study of ipatasertib and anti-her2 therapy in her2-positive advanced breast cancer with pik3ca mutation (ipather). Cancer Res. 2021, 81 (Suppl. 4), OT-35.
9. Rimawi, M.; Ferrero, J.-M.; Rodríguez, J.R.D.L.H.; Poole, C.; De Placido, S.; Osborne, C.K.; Hegg, R.; Easton, V.; Wohlfarth, C.; Arpino, G.; et al. First-Line Trastuzumab Plus an Aromatase Inhibitor, with or Without Pertuzumab, in

Human Epidermal Growth Factor Receptor 2–Positive and Hormone Receptor–Positive Metastatic or Locally Advanced Breast Cancer (PERTAIN): A Randomized, Open-Label Phase II Trial. J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. 2018, 36, 2826–2835.

10. Perez, E.A.; Barrios, C.; Eiermann, W.; Toi, M.; Im, Y.-H.; Conte, P.; Martin, M.; Pienkowski, T.; Pivot, X.; Burris, H.A.; et al. Trastuzumab Emtansine with or without Pertuzumab Versus Trastuzumab Plus Taxane for Human Epidermal Growth Factor Receptor 2–Positive, Advanced Breast Cancer: Primary Results From the Phase III MARIANNE Study. J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. 2017, 35, 141–148.
11. Schettini, F.; Conte, B.; Buono, G.; De Placido, P.; Parola, S.; Griguolo, G.; Fabi, A.; Bighin, C.; Riccardi, F.; Cianniello, D.; et al. T-DM1 versus pertuzumab, trastuzumab and a taxane as first-line therapy of early-relapsed HER2-positive metastatic breast cancer: An Italian multicenter observational study. ESMO Open 2021, 6, 100099.
12. Diéras, V.; Miles, D.; Verma, S.; Pegram, M.; Welslau, M.; Baselga, J.; Krop, I.E.; Blackwell, K.; Hoersch, S.; Xu, J.; et al. Trastuzumab emtansine versus capecitabine plus lapatinib in patients with previously treated HER2-positive advanced breast cancer (EMILIA): A descriptive analysis of final overall survival results from a randomised, open-label, phase 3 trial. Lancet Oncol. 2017, 18, 732–742.
13. Krop, I.E.; Kim, S.-B.; Martin, A.G.; LoRusso, P.M.; Ferrero, J.-M.; Badovinac-Crnjevic, T.; Hoersch, S.; Smitt, M.; Wildiers, H. Trastuzumab emtansine versus treatment of physician’s choice in patients with previously treated HER2-positive metastatic breast cancer (TH3RESA): Final overall survival results from a randomised open-label phase 3 trial. Lancet Oncol. 2017, 18, 743–754.
14. Bahçeci, A.; Paydaş, S.; Ak, N.; Ferhatoğlu, F.; Saip, P.M.; Seydaoğlu, G.; Bilici, M.; Şimşek, M.; Tekin, S.B.; Çalikuşu, Z.; et al. Efficacy and Safety of Trastuzumab Emtansine in Her2 Positive Metastatic Breast Cancer: Real-World Experience. Cancer Investig. 2021, 39, 473–481.
15. Battisti, N.M.L.; Rogerson, F.; Lee, K.; Shepherd, S.; Mohammed, K.; Turner, N.; McGrath, S.; Okines, A.; Parton, M.; Johnston, S.; et al. Safety and efficacy of T-DM1 in patients with advanced HER2-positive breast cancer The Royal Marsden experience. Cancer Treat. Res. Commun. 2020, 24, 100188.
16. Montemurro, F.; Ellis, P.; Anton, A.; Wuerstlein, R.; Delaloge, S.; Bonneterre, J.; Quenel-Tueux, N.; Linn, S.C.; Irahara, N.; Donica, M.; et al. Safety of trastuzumab emtansine (T-DM1) in patients with HER2-positive advanced breast cancer: Primary results from the KAMILLA study cohort 1. Eur. J. Cancer 2019, 109, 92–102.