Belgian clinical practice guidelines for the treatment of patients with HER2-positive advanced breast cancer

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SUMMARY

HER2-targeted agents are the central component of HER2-positive metastatic breast cancer (MBC) treatment. The combination of trastuzumab, pertuzumab and a taxane is the preferred first-line regimen in most settings. For patients with disease relapse after adjuvant therapy, treatment decisions in the first-line are influenced by the treatment-free interval and the regimens used in the (neo)adjuvant setting. T-DXd has been recently established as the preferred second-line therapy. T-DM1, or the combination of tucatinib, trastuzumab and capecitabine, are reasonable third-line options, although efficacy and safety data of these regimens after prior exposure to T-DXd are lacking. In fourth and later lines, trastuzumab duocarmazine, neratinib plus capecitabine, margetuximab plus chemotherapy, lapatinib-based combinations or the continuation of trastuzumab with different chemotherapy partners are valid alternatives.

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INTRODUCTION

Human epidermal growth factor receptor 2 (HER2) overexpressed and/or amplified breast cancer (BC) represents approximately 15-20% of all breast cancers and is characterised (if untreated) by an aggressive behavior, a high risk of relapse and a worse prognosis.[1] The incorporation of HER2-targeted therapies into treatment algorithms significantly reduced the risk of recurrence and improved survival of patients with both early and metastatic HER2-positive BC.[2–5] Particularly in the metastatic setting, since the demonstration of the benefit of trastuzumab and chemotherapy, the first anti-HER2 therapy to be approved for clinical use, several other agents have shown significant activity, including other monoclonal antibodies, tyrosine kinase inhibitors, and antibody-drug conjugates.[5–8] However, the increasing availability of active agents, overlapping indications, and different toxicity profiles have increased the complexity of the decision-making process. On behalf of the *Belgian Society of Medical Oncology* Breast Cancer Taskforce, we review available evidence supporting therapeutic decisions and propose a treatment algorithm for patients with HER2-positive metastatic breast cancer (MBC).

FIRST-LINE TREATMENT

The gold standard first-line therapy for patients with previously untreated HER2-positive MBC was established by the phase III CLEOPATRA trial.[5] In this study, 808 women with HER2-positive MBC were treated with trastuzumab and docetaxel and randomly assigned to treatment with pertuzumab or placebo every three weeks, until disease progression or intolerable side effects.[5] The three-agent combination of trastuzumab plus pertuzumab and a taxane (THP) improved the progression-free survival (PFS) (median PFS 18.7 *vs* 12.4 months, HR 0.69; 95% CI 0.59-0.81; P < 0.001, with and without pertuzumab, respectively) and overall survival (OS) (median OS 57.1 *vs* 40.8 months, HR 0.69; 95% CI 0.58-0.82) in comparison with trastuzumab/docetaxel.[5] If tolerated, docetaxel should be given for at least six cycles, followed by maintenance trastuzumab/pertuzumab until disease progression.[9] Although docetaxel was used as chemotherapy backbone in the CLEOPATRA trial, it is reasonable to assume that other taxanes represent acceptable chemotherapy alternatives. The single-arm PERUSE study enrolled 1,436 patients with HER2-positive locally advanced or MBC for treatment with trastuzumab and pertuzumab combined with a taxane and demonstrated comparable OS between docetaxel, paclitaxel or nab-paclitaxel (median OS of 66.5, 64.0 and 70.9 months, respectively).[10] If taxanes are contraindicated, less toxic chemotherapy partners may be considered, including vinorelbine, oral cyclophosphamide (older patients) and capecitabine.[9,11,12] For patients who prefer to avoid chemotherapy-based treatment regimens or who have comorbidities or performance status that preclude the use of cytotoxic agents, HER2-targeted therapy without chemotherapy (for patients with hormone receptor negative disease) or in combination with endocrine therapy (hormone receptor positive disease) might be considered.[13,14]

SECOND-LINE TREATMENT

The antibody drug conjugate (ADC) trastuzumab emtansine (T-DM1) was considered the standard treatment after trastuzumab and a taxane progression with or without pertuzumab in the metastatic setting, largely based on the results of the EMILIA trial.[15] In this study, 991 patients with HER2-positive MBC who had previously been treated with trastuzumab and a taxane were randomised to treatment with T-DM1 or lapatinib plus capecitabine and demonstrated an improvement in PFS (median PFS 9.6 *vs.* 6.4 months; HR 0.65, 95% CI 0.55-0.77) and in OS (median OS 30.9 *vs.* 25.1 months; HR 0.68; 95% CI, 0.55 to 0.85) favouring the T-DM1 arm.[15] However, nearly a decade after the presentation of the EMILIA trial, recently presented data from the DESTINY-Breast-03 study have changed treatment paradigms in this clinical setting.[16] In this phase III trial, another ADC, trastuzumab deruxtecan (T-DXd), was compared to T-DM1 in 524 patients with HER2-positive MBC previously treated with a taxane and trastuzumab.[16] Treatment with T-DXd 5.4 mg/kg once every three weeks resulted in improved overall response rate (79.7% *vs* 34.2%) and PFS (HR 0.28, P = 7.8x10-22), with a twelve month PFS rate of 75.8% with T-DXd versus 34.1% with T-DM1.16 Although OS data were immature, a numerical improvement in OS favouring T-DXd was observed (HR 0.56; P = 0.0071), which did not meet the predefined significance boundary at the time of this analysis.[16] Importantly, although there was a safety concern due to fatal cases of drug-related interstitial lung disease (ILD) observed in the phase II DESTINY-Breast01 study, and although ILD occurred in 10.5% of patients treated with T-DXd in the DESTINY-Breast03 study, there were only 0.8% grade 3 according to common terminology criteria for adverse events [CTCAE] criteria, and no fatal events were reported.[8,17]

THIRD-LINE TREATMENT AND BEYOND

In patients previously treated with trastuzumab- and T-DM1-based therapy, tucatinib, an oral tyrosine kinase inhibitor (TKI) that is selective for the kinase domain of HER2 with minimal inhibition of epidermal growth factor receptor (EGFR), demonstrated significant activity.[7] In the HER2CLIMB study, heavily pre-treated patients with HER2-positive MBC (median of four prior lines of therapy) were randomly assigned to receive either tucatinib 300 mg orally twice

daily or placebo, in combination with trastuzumab (conventional dosing) and capecitabine (1000 mg/m² twice daily).[7] After a median follow-up of 29.6 months, tucatinib-based therapy significantly increased PFS (median PFS 7.6 *vs* 4.9 months, HR 0.57, 95% CI 0.47-0.70) and OS (median OS 24.7 *vs* 19.2 months, HR 0.73, 95% CI 0.59-0.90).[18] Importantly, 291 patients with central nervous system (CNS) involvement were included in HER2CLIMB, including those with treated and stable, treated and progressing or previously untreated CNS disease.[19] In this population with baseline brain metastases (BM), tucatinib treatment was associated with reduced risk of intracranial progression or death (CNS-PFS HR 0.32; 95% CI, 0.22 to 0.48), and OS improvement (HR 0.58; 95% CI, 0.40 to 0.85).[19] Considering these data, although HER2CLIMB was conducted in a third-line setting, tucatinib can be considered as a reasonable second-line alternative, especially for selected patients with BM.[9] The appropriate representation of patients with BM in HER2CLIMB and the significant levels of CNS activity demonstrated by this agent were recognised in the approvals by regulatory agencies such as the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) which specifically mentioned the inclusion of patients with CNS involvement in the indication statements.[20,21] Finally, considering that HER2CLIMB included patients with HER2-positive MBC after previous treatment with at least two anti-HER2 drugs, this regimen may, in rare situations, be considered a first-line alternative for patients with early relapse after treatment with trastuzumab, pertuzumab and T-DM1 in the early setting.

Trastuzumab deruxtecan may also be considered a third-line option for patients not previously treated with this agent in second-line. In the single-arm, phase II DESTINY-Breast01 study, T-DXd yielded an overall response rate (ORR) of 60.9% (95% CI, 53.4 to 68.0%) and a median PFS of 16.4 months (95% CI, 12.7 to not reached) in patients previously treated with trastuzumab- and T-DM1-based therapies (median number of previous cancer regimens of six).[17] T-DM1 is another third-line treatment alternative for patients not exposed to this agent in previous lines (although there are no data about the efficacy of T-DM1 after T-DXd exposure). In the TH3RESA study, T-DM1 was compared with treatment of physician's choice (TPC) in 602 patients previously treated with trastuzumab and lapatinib.[22] Patients treated with T-DM1 had an improvement in PFS (median PFS 6.2 *vs* 3.3 months; HR 0.53, 95% CI 0.42-0.66) and OS (median OS 22.7 *vs* 15.8 months; HR 0.68, 95% CI 0.54-0.85).[22]

As a general principle, continued anti-HER2 blockade is considered a standard clinical practice beyond disease progression.[9] The definition of standards of care in subsequent lines is strongly influenced by previous lines of treatment, response to prior therapies, disease-free interval, different toxicity profiles between agents, comorbidities/patients' performance status, treatment availability and patient's preferences. Additional treatment options include sequential trastuzumab-based strategies (in combination with different chemotherapy backbones), TKIs, and other monoclonal antibodies and ADCs.

Margetuximab is an Fc-engineered anti-HER2 antibody that was compared with trastuzumab (both in combination with chemotherapy) in the SOPHIA trial, which included patients who had experienced disease progression after at least two lines of anti-HER2 therapy.[23] In this study, margetuximab-based therapy was associated with a very modest PFS improvement (median PFS 5.8 *vs* 4.9 months; HR 0.76, 95% CI 0.59-0.98) without improvement in OS.[23] Based on this result, margetuximab has been approved by the FDA (not yet approved by the EMA).

The phase III NALA trial enrolled 621 patients with at least two previous lines of HER2-directed therapy for treatment with capecitabine in combination with either lapatinib or neratinib, an irreversible pan-HER TKI.[24] The combination of neratinib and capecitabine improved median PFS (median PFS 8.8 *vs* 6.6 months; HR 0.76, 95% CI 0.63-0.93), with no significant impact on OS in comparison with lapatinib and capecitabine.[24]

Trastuzumab duocarmazine is another HER2-targeted ADC that demonstrated activity in late lines of treatment in the recently presented phase III SYD985.002/TULIP trial.25 In this study, trastuzumab duocarmazine was compared to TPC in patients who had received at least two prior lines of treatment, or previous treatment with T-DM1.[25] Trastuzumab duocarmazine therapy was associated with an improvement in PFS (median PFS 7.0 *vs* 4.9 months, HR 0.64, 95% CI 0.49–0.84), with no improvement in OS at the time of this analysis.[25] Importantly, eye toxicity was reported by 78.1% of patients treated with trastuzumab duocarmazine, accounting for a treatment discontinuation rate of 20.8% in this arm.[25] An ongoing clinical trial (NCT04983238) is evaluating the safety and efficacy of sodium thiosulfate eye drops to reduce ocular toxicity in patients treated with this agent.

Finally, ARX788, a site-specific anti-HER2 ADC, demonstrated low systemic toxicity and promising activity in the phase I ACE-Breast-01 trial, with an ORR of 74%, a disease control rate of 100% and median PFS has not been reached in a heavily pre-treated population.[26]

Lapatinib is another HER2-targeted TKI approved for the treatment of HER2-positive MBC.[27] The EGF104900 study randomised patients who experienced progression on prior trastuzumab-containing regimens to receive either lapa-

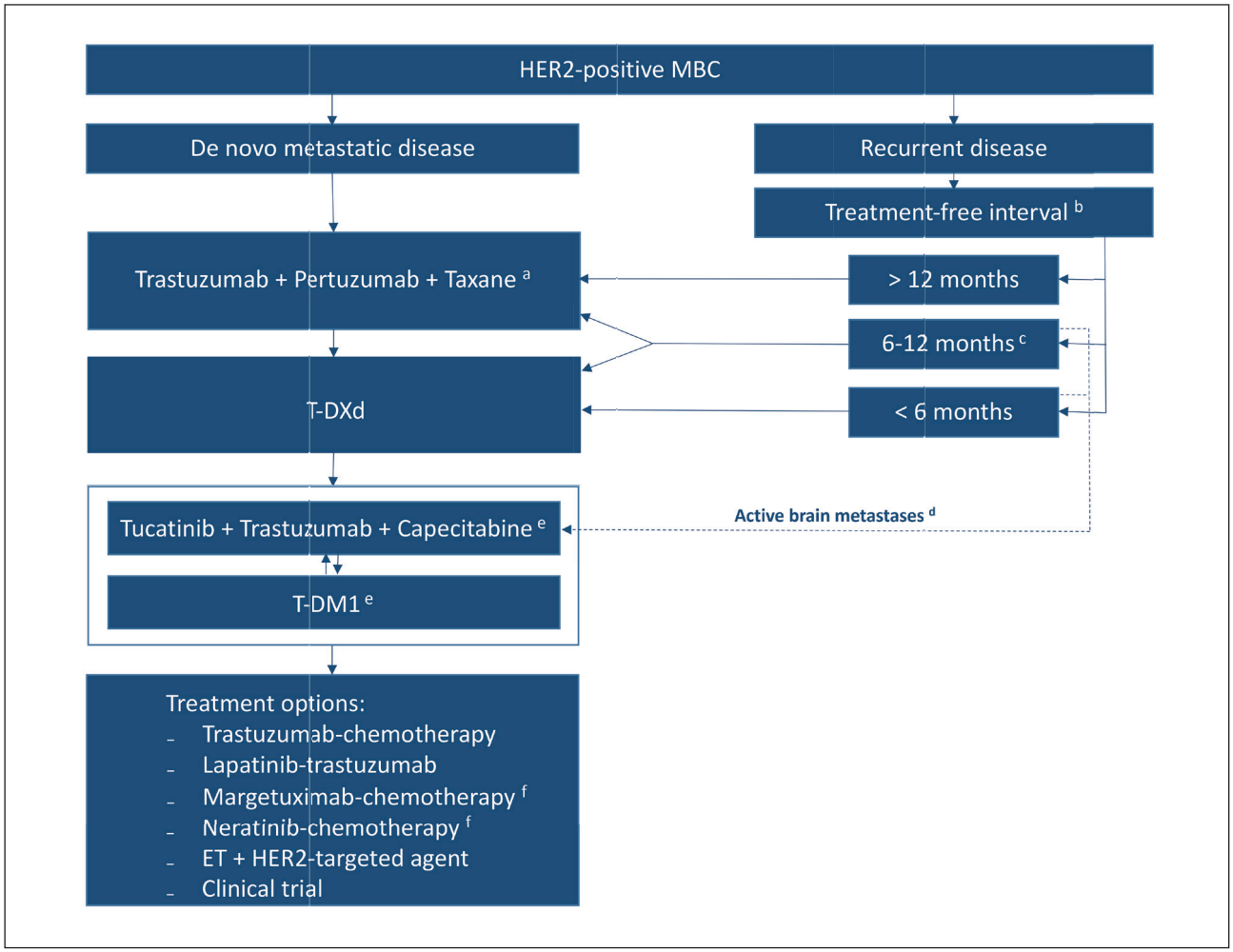

FIGURE 1. Treatment algorithm for patients with HER2-positive locally advanced unresectable or metastatic breast cancer.
a. Trastuzumab may be combined with endocrine therapy (ET) if chemotherapy is contraindicated. ET should be added as maintenance therapy concomitantly with trastuzumab and pertuzumab after the discontinuation of chemotherapy.
b. Time elapsed between completion of HER2-targeted systemic therapy and diagnosis of metastatic disease.
c. T-DXd and THP are the preferred first-line therapies for patients treated with pertuzumab-containing and pertuzumab-free adjuvant regimens, respectively.
d. For patients with short DFI and pre-treated with T-DM1 in the early setting, presenting with active brain metastases not requiring or not eligible for immediate local treatment, tucatinib-trastuzumab-capecitabine can be considered the preferred treatment option before T-DXd based on current evidence.
e. There is no direct evidence supporting an optimal sequence of treatment after progression to T-DXd.
f. Not EMA-approved.

tinib alone or in combination with trastuzumab.[28] In this study, the combination of lapatinib with trastuzumab improved PFS (HR 0.74; 95% CI, 0.58 to 0.94) and OS (HR 0.74; 95% CI, 0.57 to 0.97) in comparison with lapatinib monotherapy.[28] However, these data should be analysed with caution considering the characteristics of the population included in this trial in regards to treatment standards at the time the study was designed, which are markedly different from current standard practice (i.e. no prior exposure to pertuzumab, ADC or other TKI).

DISEASE RELAPSE AFTER (NEO)ADJUVANT THERAPY

For patients who experience unresectable or metastatic recurrence after (neo)adjuvant HER2-targeted treatment, therapeutic decisions are largely influenced by the therapy used in the (neo)adjuvant setting, treatment-free interval, and previous toxicities (*Figure 1*). Patients who experience disease recurrence more than twelve months after the end of adjuvant systemic therapy should be managed along the lines recommended for patients with *de novo* metastatic disease

KEY MESSAGES FOR CLINICAL PRACTICE

1. **The treatment landscape for patients with HER2-positive advanced breast cancer is rapidly evolving.**
2. **As first-line therapy, the combination of trastuzumab, pertuzumab and a taxane remains the preferred choice for the majority of patients.**
3. **In the second-line setting, trastuzumab deruxtecan should be considered the preferred therapy in most clinical scenarios.**
4. **There is no direct evidence supporting an optimal sequence of treatment after progression to T-DXd.**
5. **T-DM1 and tucatinib in combination with trastuzumab and capecitabine are reasonable third-line options. Tucatinib-based therapy may be considered particularly in patients with brain metastases.**

(e.g., trastuzumab, pertuzumab and taxane combination as preferred first-line therapy).[5] For patients with a treatment-free interval of less than six months, we recommend T-DXd-based first-line therapy, regardless of the therapeutic regimen used in the curative setting, based on the results of DESTINYBreast-03 trial.[16] For patients who experience recurrence with a treatment-free interval of six to twelve months, therapeutic decisions must be individualised and may vary according to the regimen used in the early setting, namely: 1) T-DXd could be considered if the regimen used in the early setting included pertuzumab, based on the DESTINYBreast-03 study[16], and 2) for patients treated with pertuzumab-free adjuvant regimens (i.e., trastuzumab monotherapy or T-DM1), in the absence of consensus, the combination of trastuzumab, pertuzumab and taxane is an appropriate option.

CONCLUSION

The treatment landscape of HER2-positive MBC is rapidly evolving with the incorporation of novel anti-HER2 therapies that significantly improved the survival of patients with HER2-positive MBC. Several HER2-targeted agents have recently been incorporated into clinical practice, increasing the complexity of the decision-making and treatment tailoring process. A multidisciplinary patient-centred approach is essential for optimising treatment sequencing.

REFERENCES

1. Loibl S, Gianni L. HER2-positive breast cancer. Lancet. 2017;389(10087):2415-29.
2. Cameron D, Piccart-Gebhart MJ, Gelber RD, et al. Eleven years' follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive early breast cancer: final analysis of the HERceptin Adjuvant (HERA) trial. Lancet. 2017;389(10075):1195-205.
3. Piccart M, Procter M, Fumagalli D, et al. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer in the APHINITY Trial: 6 Years' Follow-Up. J Clin Oncol. 2021;39(13):1448-57.
4. von Minckwitz G, Huang CS, Mano MS, et al. Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer. N Engl J Med. 2019;380(7):617-28.
5. Swain SM, Miles D, Kim SB, 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(4):519-30.
6. Diéras V, Miles D, Verma S, 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(6):732-42.
7. Curigliano G, Mueller V, Borges VF, et al. Updated results of tucatinib versus placebo added to trastuzumab and capecitabine for patients with pretreated HER2+ metastatic breast cancer with and without brain metastases (HER2CLIMB). J Clin Oncol. 2021;39(15_suppl):1043.
8. Cortés J, Kim SB, Chung WP, et al. Trastuzumab Deruxtecan versus Trastuzumab Emtansine for Breast Cancer. N Engl J Med. 2022;386(12):1143-54.
9. Gennari A, André F, Barrios CH, et al. ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. Ann Oncol. 2021;32(12):1475-95.
10. Miles D, Ciruelos E, Schneeweiss A, et al. Final results from the PERUSE study of first-line pertuzumab plus trastuzumab plus a taxane for HER2-positive locally recurrent or metastatic breast cancer, with a multivariable approach to guide prognostication. Ann Oncol. 2021;32(10):1245-55.
11. Wildiers H, Tryfonidis K, Dal Lago L, et al. Pertuzumab and trastuzumab with or without metronomic chemotherapy for older patients with HER2-positive metastatic breast cancer (EORTC 75111-10114): an open-label, randomised, phase 2 trial from the Elderly Task Force/Breast Cancer Group. Lancet Oncol. 2018;19(3):323-36.
12. Andersson M, Lidbrink E, Bjerre K, et al. Phase III randomized study com-

paring docetaxel plus trastuzumab with vinorelbine plus trastuzumab as first-line therapy of metastatic or locally advanced human epidermal growth factor receptor 2-positive breast cancer: the HERNATA study. J Clin Oncol. 2011; 29(3):264-71.

13. Rimawi M, Ferrero JM, de la Haba-Rodriguez J, 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. 2018;36(28):2826-35.
14. Cortés J, Fumoleau P, Bianchi GV, et al. Pertuzumab monotherapy after trastuzumab-based treatment and subsequent reintroduction of trastuzumab: activity and tolerability in patients with advanced human epidermal growth factor receptor 2-positive breast cancer. J Clin Oncol. 2012;30(14):1594-600.
15. Verma S, Miles D, Gianni L, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. N Engl J Med. 2012;367(19):1783-91.
16. Cortes J, Kim S, Chung W. Trastuzumab deruxtecan (T-DXd) *vs* trastuzumab emtansine (T-DM1) in patients (Pts) with HER2+ metastatic breast cancer (mBC): Results of the randomized phase III DESTINY-Breast03 study. Ann Oncol. 2021;32(suppl_5):S1283-S1346.
17. Modi S, Saura C, Yamashita T, et al. Trastuzumab Deruxtecan in Previously Treated HER2-Positive Breast Cancer. N Engl J Med. 2020;382(7):610-21.
18. Curigliano G, Mueller V, Borges V, et al. Tucatinib *vs* Placebo Added to Trastuzumab and Capecitabine for Patients with Pretreated HER2+ Metastatic Breast Cancer with and without Brain Metastases (HER2CLIMB): Final Overall Survival Analysis. Ann Oncol. 2022;33(3):321-9.
19. Lin NU, Borges V, Anders C, et al. Intracranial Efficacy and Survival With Tucatinib Plus Trastuzumab and Capecitabine for Previously Treated HER2-Positive Breast Cancer With Brain Metastases in the HER2CLIMB Trial. J Clin Oncol. 2020;38(23):2610-9.
20. Shah M, Wedam S, Cheng J, et al. FDA Approval Summary: Tucatinib for the Treatment of Patients with Advanced or Metastatic HER2-positive Breast Cancer. Clin Cancer Res. 2021;27(5):1220-6.
21. EMA. Tukysa. European Medicines Agency. Published December 9, 2020. Accessed January 5, 2022. https://www.ema.europa.eu/en/medicines/human/EPAR/tukysa
22. Krop IE, Kim SB, Martin AG, et al. 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(6):743-54.
23. Rugo HS, Im SA, Cardoso F, et al. Efficacy of Margetuximab *vs* Trastuzumab in Patients With Pretreated ERBB2-Positive Advanced Breast Cancer: A Phase 3 Randomized Clinical Trial. JAMA Oncol. 2021;7(4):573-84.
24. Saura C, Oliveira M, Feng YH, et al. Neratinib Plus Capecitabine Versus Lapatinib Plus Capecitabine in HER2-Positive Metastatic Breast Cancer Previously Treated With ≥ 2 HER2-Directed Regimens: Phase III NALA Trial. J Clin Oncol. 2020;38(27):3138-49.
25. Saura C, O'Shaughnessy J, Aftimos P. LBA15 - Primary outcome of the phase III SYD985.002/TULIP trial comparing [vic-]trastuzumab duocarmazine to physician's choice treatment in patients with pre-treated HER2-positive locally advanced or metastatic breast cancer. Ann Oncol. 2021;32(suppl_5):S1283-S1346.
26. Hurvitz SA, Park H, Frentzas S, et al. Safety and unique pharmacokinetic profile of ARX788, a site-specific ADC, in heavily pretreated patients with HER2-overexpresing solid tumors: Results from two phase 1 clinical trials. J Clin Oncol. 2021;39(suppl_15):1038.
27. Geyer CE, Forster J, Lindquist D, et al. Lapatinib plus Capecitabine for HER2-Positive Advanced Breast Cancer. N Engl J Med. 2006;355(26): 2733-43.
28. Blackwell KL, Burstein HJ, Storniolo AM, et al. Overall survival benefit with lapatinib in combination with trastuzumab for patients with human epidermal growth factor receptor 2-positive metastatic breast cancer: final results from the EGF104900 Study. J Clin Oncol. 2012;30(21):2585-92.