New Systemic Therapy Strategies for HER2-Positive Metastatic Breast Carcinoma

Introduction

Molecular biological typing of breast carcinoma makes it possible to pursue individual, targeted treatment plans. After the discovery of overexpression of the receptor tyrosine kinase (RTK) HER2/neu (ErbB-2) in invasive breast carcinoma and its importance as a prognostic factor, the anti-HER2 antibody trastuzumab was developed as the first targeted therapeutic option for the treatment of HER2-positive (HER2+) breast carcinoma [1, 2]. Further developments in the treatment of this aggressive subtype led to a significantly improved therapy offering with numerous different anti-HER2 therapies now available for early-stage and metastatic cases, leading to a significant improvement in the prognosis for HER2+ breast carcinoma; historically very poor, this is now comparable to the prognosis for luminal A tumors [3, 4]. With the constant development of new HER2-directed therapies, treatment decisions become increasingly complex. After integrating the latest research results into current recommendations and guidelines, the algorithm developed by the Breast Committee of the Working Group for Gynecological Oncology (AGO) may be helpful in applying the multiple treatment options available in the different lines of therapy.

HER2 Classification

Based on the ASCO/CAP (American Society of Clinical Oncology/College of American Pathologists) Guideline, HER2 status is classified as positive or negative based on evidence of receptor overexpression through immunohistochemistry (IHC) and/or gene amplification using in situ hybridization (ISH). Even in cases of an ambiguous IHC finding (2+) and a discrepancy between the HER2/centromere 17 ratio and the number of HER2 signals (ISH groups 2–4), the 2023 update continued to classify these patients as either positive or negative, confirming the 2018 update (Table 1). A category for borderline cases in the event of unclear findings has not been introduced [5]. In approximately 15% of all breast carcinoma cases, overexpression of the protein and/or amplification of the DNA of HER2 is detected [6]. In addition, around 60% of HER2-negative breast carcinoma cases show a low level of HER2 expression (so-called HER2-low tumors); this is defined as IHC 1+ or 2+ without gene amplification (ISH-) [7]. Recently, it has been shown that HER2-low tumors also respond to new anti-HER2 therapies [8, 9].

Anti-HER2-Directed Treatment of HER2-Positive Breast Cancer

Systemic therapy with targeted anti-HER2 agents in combination with chemotherapy is clearly at the forefront in the treatment of HER2+ breast cancer. Anti-HER2 therapies can be divided into antibodies, tyrosine kinase inhibitors (TKI), and antibody-drug conjugates (ADC) (Fig. 1).

The monoclonal anti-HER2 antibody trastuzumab (Tz) binds to the extracellular domain of HER2, thereby inhibiting the growth of HER2-dependent tumor cells [12]. In 2001, Slamon et al. showed for the first time that adding Tz to first-line chemotherapy (1 L CT) conferred a clear survival advantage in metastatic disease. While monotherapy is less effective, especially with low HER2 expression, the combination with CT has a synergistic effect [2, 13]. In the phase III NRG Oncology/NSABP B-47 study, the addition of Tz to CT in the adjuvant treatment of invasive disease with a high risk of recurrence did not show any benefit for HER2-low tumors [14]. The alternative route of administration by subcutaneous injection was comparable to standard infusion (HannaH) [15, 16]. In addition, the market for Tz-biosimilars is constantly evolving [17]. Pertuzumab (Pz) binds to an epitope located further from the cell membrane than Tz, and thus inhibits the dimerization of HER2 and HER3; this means that adding Pz to Tz plus CT results in an additional benefit (FDA approval already granted) [21].

In antibody-drug conjugates (ADC), an anti-HER2 antibody is coupled to a cytostatic agent (payload), so that the cytostatic agent is transported specifically into HER2-positive tumor cells. After binding to HER2 and uptake of the complex, the cytostatic agent is released. Tz-emtansine (T-DM1) is a conjugate of Tz with the microtubule inhibitor DM1 (maytansine derivative) [22]. Tz-deruxtecan (T-DXd; DS-8201a) consists of Tz and a topoisomerase-I inhibitor that has an antitumor effect, even in tumors with low HER2 expression [23]. T-DXd also acts on neighboring tumor cells due to its membrane-permeable payload (bystander effect) [24]. Other conjugates currently being researched in clinical trials include Vic-Tz-duocarmazine (SYD985), consisting of a Tz-like antibody with the alkylating substance duocarmycin, and...
PF-06804103, an anti-HER2 antibody conjugated with the microtubular inhibitor Aur0101 [25, 26].

Oral TKIs bind to the intracellular tyrosine kinase domain of HER2, and possibly also HER1/EGFR and HER4 depending on selectivity (HER3 lacks a functional tyrosine kinase domain). Lapatinib (GW572016) binds reversibly to HER1 and HER2 (dual TKI) [27]. Neratinib (HKI-272) is an irreversible pan-HER inhibitor [28]. Tucatinib (ONT-380) selectively binds to the tyrosine kinase domain of HER2 and has minimal inhibition of HER1; this may have an influence on its side effect profile compared with dual or pan-HER inhibitors [29]. Pyrotinib, an irreversible pan-HER inhibitor, received conditional approval in China in 2018 [30].

**Side Effects of Anti-HER2 Therapies**

Side effect profiles differ depending on the type of anti-HER2 therapy. Cardiac dysfunction (congestive heart failure) is the most significant side effect associated with the administration of Tz, especially when administered after anthracycline-containing CT (doxorubicin or epirubicin) [2]. Adding Pz to Tz plus docetaxel leads to an increased occurrence of gastrointestinal events, especially diarrhea, but not to increased cardiac toxicity [18, 31]. Cardiac side effects are rarely observed with T-DM1 or T-DXd [32, 33]. Thrombocytopenia, including severe cases, is one of the most common side effect of T-DM1. Bleeding and elevated aminotransferases also occur more frequently [32, 34]. With T-DXd, the increased occurrence of interstitial lung disease (ILD), including reported fatalities, is a particular concern. Rapid diagnosis and treatment of ILD are important in this context [35, 36]. Alopecia occurs very frequently with T-DXd and was observed in almost half of patients in the DESTINY-Breast01 study [33]. With T-duocarmazine, ocular events (conjunctivitis, keratitis) and ILD/pneumonitis are of particular relevance. Gastrointestinal events occur more frequently during treatment with an oral tyrosine kinase inhibitor (lapatinib, neratinib, tucatinib, pyrotinib) [37, 38, 39, 40]. In addition, skin reactions are often observed with lapatinib, and elevated aminotransferases are observed with tucatinib [37, 38].

**Primary Treatment of Early HER2-Positive Breast Cancer**

When treating early stage HER2+ breast cancer, (neo)adjuvant CT treatment in combination with 1 year of anti-HER2 treatment with Tz or PzTz is standard. In stage I cancers, primary surgery is performed, followed by adjuvant treatment with Tz for 1 year in combination with paclitaxel based on the APT study. This study included patients with a tumor size of up to 3 cm and mainly node-negative disease. A 12-week treatment with paclitaxel plus Tz, followed by Tz for 1 year, was associated with a low risk of recurrence [41]. Long-term data from the 7-year analysis support the use of this regimen in this patient population [42]. If there is a discrepancy between clinical (cT1 and cN0) and postoperative histopathological (pT ≥2 and/or pN+) findings, the use of neoadjuvant chemotherapy (NACT) and, if necessary, post-neoadjuvant strategies is no longer possible. In this situation, the adjuvant treatment is extended, with the use of polychemotherapy with Tz or TzPz (in node-positive cases) [43, 44]. In the case of hormone receptor-positive (HR+) disease, the adjuvant Tz-based regimen can be extended to include subsequent treatment with neratinib [10, 11].

From stage II, neoadjuvant treatment with a PzTz-based regimen is given (phase II NeoSphere) [45]. Post-neoadjuvant treat-
Treatment of Metastatic HER2-Positive Breast Carcinoma

In a proportion of patients, breast carcinoma recurs after the primary treatment (secondary metastatic disease occurs in approx. 80 % of cases). In addition, a proportion of patients is diagnosed at the metastatic stage (approximately 20 % of patients are diagnosed with de novo metastatic breast cancer). Treatment in the metastatic stage is stratified according to the type of primary treatment and the duration of the therapy-free interval (TFI), and also depends on the presence of brain metastases. The incidence of brain metastases is high in HER2+ disease (25–50 %), and these often develop during the early lines of treatment. In the case of progression with brain metastases and stable extracranial treatment, the option of local treatment while maintaining systemic therapy may be considered. Treatment options that were already used in the early therapy stage can be administered repeatedly in the advanced stage, especially if there has been a TFI of at least 6–12 months since the last treatment administration.

For the majority of patients, a combination of Pz, Tz, and a taxane (docetaxel or paclitaxel) is the standard 1 L treatment for metastasis, including brain metastases. In the pivotal study CLEOPATRA, the combination therapy with dual anti-HER2 blockade plus docetaxel was significantly superior to the combination with Tz plus docetaxel. After an 8-year follow-up period, with the addition of Pz, there was an OS rate of 38 % compared to 23 % in the placebo group. The median OS was 57.1 months (95 % CI 50–72) vs. 40.8 months (95 % CI 36–48) (HR 0.69; 95 % CI 0.58–0.82), and the median PFS was 18.7 months (95 % CI 17–22) vs. 12.4 months (95 % CI 10–14) (HR 0.69; 95 % CI 0.59–0.81) [48]. The results from the long-term follow-up therefore confirmed the statistically significant results from previous analyses [18, 31]. The duration of taxane treatment is determined on an individual basis. With tolerable toxicity, at least 6 cycles are recommended, although the dose may be adjusted. Anti-HER2 treatment should be given until disease progression, if the toxicity is tolerated; for HR+ disease, it should be given in combination with endocrine treatment (ET) as a maintenance therapy.

In second-line treatment (2 L), T-DXd has recently replaced T-DM1 as standard therapy based on the results of the DESTINY-Breast03 study [49]. Administration of T-DXd to patients pretreated with Tz plus taxane prolonged the PFS to a median of 28.8 months compared to 6.8 months with T-DM1 (HR 0.33; 95 % CI 0.26–0.43; nominal p < 0.0001). Median OS had not yet been achieved after a follow-up period of over 2 years, with 72 (28 %) OS events in the T-DXd group vs. 97 (37 %) in the T-DM1 group (HR 0.64; 95 % CI 0.47–0.87; p = 0.0037) [50]. The benefits of T-DXd were observed in all of the subgroups studied; even patients who had stable brain metastases at the time of enrolment in the study benefited from the treatment. Another 2 L option in cases of active brain metastases is a tucatinib-based regimen (capecitabine plus Tz plus tucatinib). Otherwise, this regimen is preferred as a third line of treatment (see below). In the single-arm, phase II DESTINY-Breast01 study [33], which led to T-DXd being approved from the third line of treatment, the median PFS in the heavily pretreated cohort (with a median of 6 previous lines of therapy) of patients who had already received T-DM1 treatment was 19.4 months after a 20-month follow-up period [51]. After a further 9 months of follow-up, the median OS was 28.4 months with 91 (49.5 %) OS events [52]. These results were confirmed in the phase III DESTINY-Breast02 study. After previous progression under T-DM1, the median PFS in the T-DXd arm was 17.8 months compared to 6.9 months for treatment of the physician’s choice; the median OS was 39.2 months vs. 26.5 months [53]. From the third line of treatment, several therapeutic alternatives may be considered; the choice depends on both the previous treatment and the time of progression, as well as on the location of metastasis, tolerability, comorbidities, and patient characteristics and preferences. There is no optimal sequence for this [54, 55]. The addition of tucatinib to Tz and capecitabine led to a clinically significant prolongation of PFS and OS in the highly pretreated cohort of patients (median of 4 previous lines of therapy) in the phase II HER2CLIMB study who had already previously received Tz and Pz and T-DM1; this was observed especially in the group of patients with brain metastases. Brain metastases were identified in almost half of the patient cohort at the time of enrolment in the study. After a median follow-up of 14 months, the median PFS was 7.8 vs. 5.6 months (HR 0.54; 95 % CI 0.42–0.71; p < 0.001); in patients with brain metastases 7.6 vs. 5.4 months (HR 0.46; 95 % CI 0.31–0.67; p < 0.001) [40]. In the extended follow-up (30 months), an OS of 24.7 months was achieved with the tucatinib combination compared to 19.2 months with the placebo combination (HR 0.73; 95 % CI 0.59–0.90; p = 0.004). The 1-year rate of intracranial PFS was 0 % in the control arm (Tz plus capecitabine), rising to 40 % with the addition of tucatinib (35 % in active and 53 % in stable brain metastases) [56]. The previous standard 2 L treatment was based on the EMILIA study, in which a comparison of T-DM1 with capecitabine plus lapatinib showed a significantly prolonged median PFS (9.6 months vs. 6.4 months; HR 0.65; 95 % CI 0.55–0.77; p < 0.001) and OS (30.9 months vs. 25.1 months; HR 0.68; 95 % CI 0.55–0.85; p < 0.001) under T-DM1; this was confirmed in the descriptive final OS analysis [32, 57]. The efficacy of T-DM1 from the third line of treatment was also validated in the TH3RESA study. After previous treatments with Tz and lapatinib as well as a taxane, the median PFS (6.2 months vs. 3.3 months; HR 0.53; 95 % CI 0.42–0.66; p < 0.0001) and OS (22.7 months vs. 15.8 months; HR 0.68; 95 % CI 0.54–0.85; p = 0.0007) was significantly longer with T-DM1 compared to treatment of the physician’s choice [34, 58]. In the NALA study, neratinib plus capecitabine showed a significant PFS advantage over lapatinib plus capecitabine after at least 2 previous lines of therapy (8.8...
months vs. 6.6 months; HR 0.76; 95% CI 0.63–0.93; p = 0.0059) with a median follow-up of 30 months. CNS interventions with neratinib were also less common (cumulative incidence 22.8% vs. 29.2%; p = 0.43) [39]. Lapatinib plus capecitabine was the standard 2L treatment prior to T-DM1. After progression under an anthracycline, a taxane, and Tz, combination therapy was clearly superior to monotherapy in terms of PFS (HR 0.57; 95% CI 0.43–0.77; p < 0.001; EGF100151 study) [37, 59]. In addition, after progression under Tz (median of 3 previous Tz-based lines of therapy), CT-free dual HER2 blockade with lapatinib plus Tz resulted in an improvement in PFS compared to the administration of lapatinib alone (HR 0.73; 95% CI 0.57–0.93; p = 0.008; EGF104900 study) [60].

Other CT-free treatment options for HR+ disease include combinations of anti-HER2 treatment and ET. TAnDEM, eLeCTRA, and EGF30008 were the first phase III studies to demonstrate a benefit by adding an anti-HER2 treatment to an aromatase inhibitor (AI) in the 1L setting. The addition of Tz to anastrozole (TAnDEM) and letrozole (eLeCTRA), respectively, and lapatinib to letrozole (EGF30008), resulted in a significantly longer PFS [61, 62, 63]. A further increase in efficacy was achieved with dual anti-HER2 treatment in the PERTAIN study, the median PFS with an AI (anastrozole or letrozole) in combination with PzTz was 18.9 months vs. 15.8 months (Tz) (HR 0.65; 95% CI 0.48–0.89; p = 0.0070). Only ET was allowed as a previous systemic therapy [64]. In the ALTERNATIVE study (EGF114299), the administration of Tz plus lapatinib in combination with an AI after previous ET and (neo)adjuvant/1L Tz plus CT resulted in a median PFS of 11.0 months vs. 5.6 months (Tz) (HR 0.62; 95% CI 0.45–0.88; p = 0.0063). The differences between the two anti-HER2 therapies were not significant (AI plus Tz vs. AI plus lapatinib: 5.6 months vs. 8.3 months) [65]. Moreover, inhibition of cyclin-dependent kinases 4 and 6 (CDK4/6) with abemaciclib resulted in a significantly longer PFS (HR 0.56; 95% CI 0.43–0.73; p < 0.0001) [69]. After a median follow-up of 15.7 months, initial results from the phase II PERMEATE study also indicate activity in brain metastases. The intracranial response rate was 74.6% in radiotherapy-naive brain metastases and 42.1% in cases of progression after radiotherapy [70]. In the TULIP study, for Tz-duo-carmazone vs. CT of the physician’s choice, the median PFS in the heavily pretreated patient cohort (median of 4 previous lines of therapy) was 7.0 months vs. 4.9 months (HR 0.64; 95% CI 0.49–0.84; p = 0.002) [71]. Results from the first phase I study also indicate efficacy in HER2-low tumors [8]. PF-06804103 showed a promising antitumor effect in a small phase I study in heavily pretreated patients with HER2+ solid tumors (advanced breast carcinoma and stomach cancer), with a preliminary response rate of 52.4% [72].

New Combination Therapies

New combination therapies offer the possibility of synergistic antitumor activity from different substance classes, making it possible to overcome resistance to anti-HER2 therapy. The addition of inhibitors of cyclin-dependent kinases 4 and 6 (CDK4/6) offers another option for CT-free combination therapy, especially in HR+ breast cancer; this was first included in the AGO algorithm with the 2023 update. Besides the triple combination with abemaciclib, the addition of palbociclib to Tz (with or without ET) shows promising results in the heavily pretreated (2–4 previous treatments in the metastatic setting) HR+ patient population of the phase II PATRICIA study. The PFS rates at 6 months were 42.8% and 46.4% respectively in the HR+ cohort without or with letrozole, but only 33.3% in the HR-negative cohort. In particular, the luminal (PAM50) subtype was associated with an advantage in terms of PFS (median PFS 10.6 months vs. 4.2 months in non-luminal disease) [75]. Based on these results, recruitment was stopped and a new cohort with HR+/HER2+ advanced disease and a luminal A/B PAM50 gene signature was set up in order to demonstrate the superiority of the combination of palbociclib, Tz, and ET compared to treatment of the physician’s choice (T-DM1, CT plus Tz or ET plus Tz) in this patient population (PATRICIA II) [76]. Further studies are currently researching the role of CDK4/6 inhibitors in patients with HR+/HER2+ breast carcinoma. The goal of the phase III PATINA study is to demonstrate superiority in terms of prolonged PFS when palbociclib is added to a standard anti-HER2 treatment (Tz + Pz) plus ET after induction with chemotherapy. To investigate the influence of PI3KCA mutations on the development of resistance to maintenance therapy with palbociclib, Tz ± Pz, and ET, a PFS comparison according to PI3KCA mutation status is planned as a translational research objective [77]. The phase III DETECT V study is investigating a combination of dual anti-HER2 treatment (PzTz), ET, and ribociclib with a combination of PzTz and CT, followed by maintenance therapy with PzTz, ET, and ribociclib. Ribociclib was added to the treatment following an amendment approximately 3 years after the start of the study. The majority of patients included in the unplanned first interim
analysis were enrolled before this amendment (see above for a presentation of the data) [67].

Results from previous clinical trials support the combination with immunotherapy, especially in PD-L1-expressing (PD-L1+) tumors, to enhance the antitumor immunological response. In the single-arm phase Ib/II PANACEA study, a combination of Tz with the PD-1 inhibitor pembrolizumab in Tz-resistant tumors achieved a response in 15% of patients with PD-L1+ tumors. In contrast, there was no response in tumors with negative PD-L1 status [78]. In the phase II KATE2 study, a possible advantage was seen with the addition of the PD-L1 inhibitor atezolizumab to T-DM1 in PD-L1+ tumors (median PFS 8.5 months vs. 4.1 months; stratified HR 0.60; 95% CI 0.32–1.11; p = 0.099). However, in the overall population, there was increased toxicity with no clinically significant PFS prolongation [79]. The phase Ib/II DESTINY-Breast07 study is currently investigating the addition of various combination partners, including the PD-L1 inhibitor durvalumab, to T-DXd [80].

In addition, combinations with inhibitors of the phosphoinositide 3-kinase (PI3K)/AKT-kinase signaling pathway offer additional therapeutic approaches, especially in tumors with PIK3CA mutations and overactivated PI3K signaling, which leads to anti-HER2 resistance. PIK3CA mutations are the most common genetic changes in patients with advanced HER2+ breast cancer, accounting for up to 40% of all mutations; they are associated with a poorer prognosis compared to wild-type tumors in treatment with anti-HER2 agents in both the advanced [81, 82] and the early (neo)adjuvant [83, 84] therapy setting. However, there are differences with regard to substance classes; for example, the action of T-DM1 is independent of PIK3CA mutation status [82, 85, 86]. The results from a single-arm phase I study suggest that a combination therapy with the PI3K inhibitor alpelisib and T-DM1 shows some therapeutic activity following progression after a Tz-based treatment. The response rate was 43%, and even after prior T-DM1 treatment was still 30% [87]. Preliminary results from the single arm phase Ib-IPATHER study suggest that the addition of

![Fig. 2 Treatment options for HER2-positive metastatic breast carcinoma in 1L, 2L, 3L+ according to the AGO treatment algorithm. Data according to [73]. * docetaxel (++) , paclitaxel (++), nab-paclitaxel (+), vinorelbine (+, secondary metastatic only); ‡ only in cases of recurrence after at least 6–12 months; † prioritization (HER2CLIMB).](image-url)
the AKT inhibitor ipatasertib (± ET) to maintenance therapy with PzTz after 1 L THP in patients with PIK3CA-mutated tumors is effective and well tolerated [88]. The phase Ib B-PRECISE-01 study investigating the PI3K inhibitor MEN1611 in combination with Tz ± fulvestrant showed the first promising results with regard to tolerability and duration of therapy in heavily pretreated patients with PIK3CA-mutated tumors [89]. The phase III EPIK-B2 study is currently investigating the addition of alpelisib to maintenance therapy with PzTz after induction therapy with THP in PIK3CA-mutated advanced breast carcinoma [90].

“HER2-low”

According to the classification of HER2 status in the ASCO/CAP Guideline, the use of anti-HER2-directed therapies is indicated in HER2 + tumors (i.e., IHC 3 + and/or with gene amplification) [5]. However, with evidence of a therapeutic effect from new ADCs in tumors with low HER2 expression (so-called HER2-low; i.e., IHC 1 + or 2 + without gene amplification), in future the binary classification system (positive/negative) will no longer be adequate as a predictive factor for a response to anti-HER2 treatment; accordingly, it will be necessary to extend the currently recognized criteria for HER2 positivity. Based on results from the phase III-DESTINY-NY-Breast04 study [91], approval of T-DXd has been extended to include patients with unresectable or metastatic HER2-low breast carcinoma who have received prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy. This took effect in August 2022 in the USA, and in January 2023 in Europe. T-DXd showed a significantly longer PFS (9.9 months vs. 5.1 months; HR 0.50; p < 0.001) and OS (23.4 months vs. 16.8 months; HR 0.64; p = 0.001) in patients with metastatic HER2-low breast carcinoma [9]. Based on this, the ASCO/CAP Guideline was re-evaluated. This review confirmed the 2018 update, but acknowledged that metastatic patients with an IHC finding of 1 + or 2 + without gene amplification may be eligible for anti-HER2 therapies, with T-DXd currently being the only treatment option [5].

Conclusion

The steady development of anti-HER2-directed therapies leads to increasingly better options for treating HER2 + breast carcinoma.
While THP remains the standard 1 L treatment in the metastatic setting, T-DXd is the new standard 2 L treatment. Combination therapy with tucatinib remains another valid 2 L option, especially in patients with active brain metastases. A variety of different options are available as follow-up therapies. Further research on the mechanisms of resistance development and possible synergistic activities will lead to new combination therapies, and will also make it possible to optimize the sequence of later therapy lines. With the addition of CDK4/6 inhibitors, PI3K inhibitors, or checkpoint inhibitors, the identification of molecular characteristics going beyond HER2 positivity is becoming increasingly relevant.

With the approval of T-DXd extended to allow treatment of HER2-low tumors, it can now be used to treat not only HER2-positive patients, but also patients with HER2-low tumors. This means that an additional 60 % of breast cancers classified as HER2-negative, with a score of IHC 1+ or 2+ with a simultaneous negative ISH result (ISH−), may benefit from anti-HER2-directed therapy [7]. Relaxing the strict limits for therapeutic application will contribute to a further improvement in the treatment of advanced breast carcinoma, leading to a change in clinical practice.

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Conflict of Interest

The author has received honoraria for lectures and advisory work from: Roche, Novartis, Pfizer, pfm, Eli Lilly, Onkorissen, Seagen, AstraZeneca, Eisai, Amgen, Samsung, Canon, MSD, GSK, Daiichi Sankyo, Gilead, Sirius Pintuition, Pierre Fabre, ExactSciences; study support from: EndoMag, Mammutome, MenlMedical, Gilead, Hologic, ExactSciences; Reimbursement of travel and conference expenses from: Eli Lilly, ExactSciences, Pierre Fabre, Pfizer, Daiichi Sankyo, Roche

Literatur


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