Systemic Therapy

20

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20.1 Cytotoxic Agents

Cytotoxic agents still have to be considered an important backbone in the treatment for many patients with breast cancer in the adjuvant as well as the metastatic setting; especially those who are not considered hormone-sensitive or who have developed endocrine resistance. The following overview addresses drugs that are registered and/or currently used in breast cancer.

20.1.1 Topoisomerase II Inhibitors

20.1.1.1 Anthracyclines

The biological functions of topoisomerase II (Top2) are complex and include a critical role in DNA replication and transcription as well as chromosome segregation. Top2 uses hydrolysis of ATP to cut the DNA double helix and is involved in the unwinding of DNA for transcription and replication.

Broadly, Top2-targeting drugs fall into two classes, so-called Top2 poisons and Top2 catalytic inhibitors. The first class of Top2 poisons comprises most of the clinically active agents, like anthracyclines, etoposide, and mitoxantrone. Their precise mode of action leading to clinical activity is not fully understood and the dominant effects likely differ from agent to agent. Top2 poisons lead to an accumulation of high levels of persistent covalent trapping of Top2 in DNA cleavage complexes.

Anthracyclines stabilize the topoisomerase II complex after it has broken the DNA chain for replication, preventing the DNA double helix from being resealed and thereby preventing the progress of replication. Top2 poisons cause DNA damage including DNA double strand breaks and proteins covalently bound to DNA. In addition, anthracyclines and mitoxantrone function as intercalators whereas etoposide is a non-intercalating Top2 poison. The induction of DNA double strand breaks rapidly leads to a DNA damage response, as reflected by ATM phosphorylation, γH2AX and RAD51 foci formation. Anthracyclines also elicit a variety of Top2 independent effects, including formation of free radicals, membrane damage and DNA–Protein crosslinks [1]. Anthracyclines belong to the most active agents in the treatment of breast cancer. The most commonly used anthracylines are epirubicin and doxorubicin (Table 20.1). In Europe anthracyclines have been used for the treatment of metastatic breast cancer since the 1980s, whereas in the U.S. their approval by the Food and Drug Administration (FDA) followed somewhat later in 1990. The optimal dose of anthracyclines has not been fully established; however, there is an agreement that the therapeutic window is between 20 and 25 mg/m^2/week for doxorubicin and 30–40 mg/m^2/week for epirubicin. Schedules using lower doses have shown significantly lower efficacy and schedules using higher doses, especially of doxorubicin, have shown no increase in efficacy but higher toxicity.

In metastatic disease anthracyclines are nowadays mostly used as monotherapy since the sequential use of single agents is generally regarded as the standard. The use of combination chemotherapy should be restricted to visceral crisis situations, rapid disease progression or strong symptomatic burden [2]. However, as many patients have been pretreated with anthracyclines since they have become standard of care in the adjuvant setting, the use in the metastatic disease has decreased considerably. Anthracycline rechallenge is complicated by their maximum cumulative dose.

In the (neo)adjuvant setting, as per label, anthracyclines originally were approved for primary, node-positive breast cancer, regardless of hormone receptor (HR) or HER2 status. However, since decisions on adjuvant chemotherapy today are more dependent on tumor biology than on stage, they are also routinely used in node-negative primary breast cancer as long as chemotherapy is indicated and there are no relevant comorbidities or cardiac risks.

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Table 20.1 A summary of selected topoisomerase II inhibitors in breast cancer

Medication	Trade name® (examples)	Dosing (mg/m^2 BSA)	Precautions	Selected interactions	Selected side effects
Epirubicin	Farmorubicin	90–120 q3w in adjuvant regimens 20–30 q1w as a single agent, e.g., in MBC	Save IV application (severe tissue necrosis may occur in case of extravasation); monitor cardiac function; do not exceed maximum cumulative dose; dose reduction in case of liver impairment	Inhibitors and inducers of CYP3A4 and p-GP, Interferone, H2-antihistaminics (e.g., cimetidine)	left ventricular dysfunction, chronic heart failure, acute cardiac toxicity in form of arrhythmias, myelosuppression, AML/MDS, mucositis, severe tissue damage/necrosis, thrombophlebitis/phlebosclerosis vomiting, alopecia
Doxorubicin	Adriamycin, Adriblastin	Single agent 60–75 q3w 40–60 in combinations regimens		Inhibitors and inducers of CYP3A4 and p-GP, Interferone, H2-antihistaminics (e.g., cimetidine)	left ventricular dysfunction, chronic heart failure, acute cardiac toxicity in form of arrhythmias, myelosuppression AML/MDS, mucositis, severe tissue damage/necrosis, thrombophlebitis/phlebosclerosis, vomiting, alopecia
Pegylated liposomal doxorubicin	Caelyx, Doxil	40–50 q4w	Monitor cardiac function		Myelosuppression, mucositis, nausea and vomiting, left ventricular dysfunction, and chronic heart failure (lower risk compared to non-liposomal formulations), local tissue toxicity, dermatologic toxicity, palmar-plantar erythrodysesthesia/ (hand–foot-skin syndrome), hypersensitivity reaction
Mitoxantrone		12–14 IV q3w	Do not exceed maximum cumulative dose (160–200 mg/m^2) Dose modifications according to myelotoxicity and liver impairment Monitor cardiac function if anthracycline-pretreated or cardiovascular risk factors		Myelosuppression, congestive heart failure, secondary leukemia, transient ECG alterations, local tissue damage in case of paravasation, nausea and vomiting, mucositis, alopecia, blue discoloration of urine, and sclerea Cumulative max dose 160–200 mg/m^2
Liposomal doxorubicin	Myocet	60–75 q3w in combination with cyclophosphamide (600) q3w	monitor cardiac function; dose reduction in case of liver impairment		Myelosuppression, febrile neutropenia, cardiotoxicity, nausea and vomiting, mucositis, elevation of liver enzymes, hypersensitivity reactions, local tissue toxicity, alopecia, asthenia/fatigue

These highlights do not include all the information needed to use the respective drugs safely and effectively. See full prescribing information for all information needed to use these agents safely. We do not take responsibility for the correctness of the content

For (neo)adjuvant therapy, they are used as part of combination regimens, most frequently in combination with cyclophosphamide, followed by the sequential administration of taxanes or in three drug combinations with 5-fluorouracil and cyclophosphamide or docetaxel and cyclophosphamide (Table 20.2).

Historically, anthracyclines substituted the adjuvant CMF regimen not based on superiority. Two National Surgical Adjuvant Breast and Bowel Project (NSABP) studies (B-15 and B-23) showed that 4 cycles of AC (doxorubicin [60 mg/m^2], cyclophosphamide [600 mg/m^2]) were equivalent to six cycles CMF with regard to disease-free survival (DFS) and overall survival (OS). Significantly shorter duration of therapy, less frequent applications, and improved tolerability supported the use of AC instead of CMF [3, 4]. In the Cancer and Leukemia Group B (CALGB) 9344 trial, dose escalations of doxorubicin from 60 to up 90 mg/m^2 in combination with cyclophosphamide (600 mg/m^2) did not improve efficacy of the AC combination any further [5]. Subsequently, several studies have demonstrated superiority

Table 20.2 Selected (neo)adjuvant chemotherapy regimens recommended by the NCCN and/or the German AGO guidelines [305, 306] and regimens of commonly used

Setting	Regimen		Cytotoxic agents	Dosing (mg/m^2)	Schedule, cycles
HER2-negative	AC-T_w	AC followed by weekly Paclitaxel	Doxorubicin Cyclophosphamide	60 600	q3w × 4
			Paclitaxel	80	qw × 12
	EC-T_w	EC followed by weekly Paclitaxel	Epirubicin Cyclophosphamide	90 600	
			Paclitaxel	80	qw × 12
	AC-Doc	AC followed by three-weekly Docetaxel	Doxorubicin Cyclophosphamide	60 600	q3w × 4
			Docetaxel	100	q3w × 4
	EC-Doc	EC followed by three-weekly Docetaxel	Epirubicin Cyclophosphamide	90 600	q3w × 4
			Docetaxel	100	q3w × 4
	TAC (DAC)	Docetaxel/Doxorubicin/Cyclophosphamide	Docetaxel Doxorubicin Cyclophosphamide	75 50 500	q3w × 6
	ddAC-ddT	Dose-dense AC followed by dose-dense Paclitaxel	Doxorubicin Cyclophosphamide	60 600	q2w × 4
			Paclitaxel	175	q2w × 4
	ddEC-ddT	Dose-dense EC followed by dose-dense Paclitaxel	Epirubicin Cyclophosphamide	90 600	q2w × 4
			Paclitaxel	175	q2w × 4
	ddAC-T_w	Dose-dense AC followed by weekly Paclitaxel	Doxorubicin Cyclophosphamide	60 600	q2w × 4
			Paclitaxel	80	qw × 12
	ddEC-T_w	Dose-dense AC followed by weekly Paclitaxel	Epirubicin Cyclophosphamide	90 600	q2w × 4
			Paclitaxel	80	qw × 12
	DC	Docetaxel/cyclophosphamide	Docetaxel Cyclophosphamide	75 600	q3w × 4
	Classic CMF	CMF	Cyclophosphamide Methotrexat 5-Fluorouracil	600 IV d 1 + 8 or 100 p.o. d 1– 14 40 IV d 1 + 8 600 i.v. d 1 + 8	q4w × 6
	FEC-DOC	FEC followed by Docetaxel	5-Fluorouracil Epirubicin Cyclophosphamide	500 100 500	q3w × 3
			Docetaxel	100	q3w × 3
	iddETC	Dose-intense, dose-dense epirubicin followed sequentially by paclitaxel and cyclophosphamide	Epirubicin Paclitaxel Cyclophosphamide	150 225 2000	q2w × 3, q2w × 3, q2w × 3

(continued)

Table 20.2 (continued)

Setting	Regimen		Cytotoxic agents	Dosing (mg/m^2)	Schedule, cycles
HER2-positive	AC − T + Tras	EC followed by paclitaxel** + trastuzumab	Doxorubicin Cyclophosphamide	60 600	q3w × 4
			Paclitaxel Trastuzumab	80 2 (4)[a] mg/kg (6 mg/kg)	qw × 12 qw × 12 (q3w to complete 1 year)
	EC − T + Tras	EC followed by paclitaxel** + trastuzumab	Epirubicin Cyclophosphamide	90 600	q3w × 4
			Paclitaxel Trastuzumab	80 2 (4)[a] mg/kg (6 mg/kg)	qw × 12 qw × 12 (q3w to complete 1 year)
	AC − T + Tras + Per*	AC followed by paclitaxel** + trastuzumab + pertuzumab*	Doxorubicin Cyclophosphamide	60 600	q3w × 4
			Paclitaxel Trastuzumab (Pertuzumab)*	80 2 (4[a]) mg/kg (6 mg/kg) 420 mg absolute (840 mg[a]) [a]*loading dose*	qw × 12 qw × 12 (q3w to complete 1 year) q3w during neoadjuvant therapy
	EC – T/Tras ±Per*	EC followed by paclitaxel** + trastuzumab + pertuzumab*	Epirubicin Cyclophosphamide	90 600	q3w × 4
			Paclitaxel Trastuzumab (Pertuzumab)*	80 2 (4[a]) mg/kg (6 mg/kg) 420 mg absolute (840 mg[a]) [a]*loading dose*	qw × 12 qw × 12 (q3w to complete 1 year) q3w during neoadjuvant therapy
	TCH ± pertuzumab	Docetaxel/Carboplatin/Trastuzmab/±Pertuzumab	Docetaxel Carboplatin Trastuzumab (Pertuzumab)*	75 AUC6 2 (4[a]) mg/kg (6 mg/kg) 420 mg absolute (840 mg[a]) [a]*loading dose*	q3w q3w qw × 12 (q3w to complete 1 year) q3w during neoadjuvant therapy
	Paclitaxel + trastuzumab	Paclitaxel/Trastuzumab	Paclitaxel Trastuzumab	80 2 (4)* mg/kg (6 mg/kg)	qw × 12 qw × 12 (q3w to complete 1 year)

*Pertuzumab is currently only approved for *neoadjuvant* therapy in patients with HER2-positive breast cancer at high risk of recurrence. **Paclitaxel might be substituted by docetaxel. These highlights do not include all the information needed to use the respective drugs safely and effectively. See full prescribing information for all information needed to use these agents safely. We do not take responsibility for the correctness of the content

of anthracycline-containing combination regimens over CMF, most using higher doses or longer treatment schedules. The Canadian MA.5 study, which compared six cycles of $FE_{120}C$ (colloquially known as "Canadian FEC") with an administration of epirubicin (60 mg/m^2) and 5-FU (500 mg/m^2) both on day 1 and 8 and oral cyclophosphamide (75 mg/m^2) per day through days 1–14 in a 28-day cycle to classical CMF demonstrated a 5-year event-free survival of 63 % for patients treated with FEC in comparison to 53 % for patients treated with CMF ($p < 0.009$). The corresponding overall survival rates were 77 and 70 %, respectively, ($p < 0.03$) [6]. The benefit was

maintained with longer follow-up [7]. The NEAT and BR9601 trial, two phase III trials from the U.K., investigated the efficacy of epirubicin (100 mg/m^2) given for four cycles (q3w) followed by four cycles of CMF compared to six and eight cycles of CMF, respectively. The epirubicin-containing regimens demonstrated an improved relapse-free and overall survival at 5 years in a combined analysis (76 % vs. 69 % and 82 % vs. 75 %; both $p < 0{,}001$, respectively) [8]. In a phase III trial conducted by the Spanish Breast Cancer Research Group (GEICAM), six cycles of FAC q3w (500/50/500) proved to be superior to six cycles CMF in terms of DFS and OS, an effect predominantly seen in node-negative patients [9].

The French Adjuvant Study Group (FASG) investigated the effect of dose intensity of epirubicin in their randomized phase III FASG05 trial. They compared six cycles of $FE_{50}C$ to six cycles of $FE_{100}C$. Patients receiving $FE_{100}C$ had a significantly improved DFS and OS (5-year OS rates: 77.4 % vs. 65.3 %, $p = 0.007$) [10, 11]. A similar dose–response relationship was seen in 2 phase III trials in metastatic breast cancer (MBC) with improved response rates, time to progression and DFS for $FE_{100}C$ [12, 13]. Prior to the taxane era, $FE_{100}C$, also known as "French FEC," was a popular standard regimen for adjuvant chemotherapy of early breast cancer (EBC) in Europe. Epirubicin doses of 50 mg/m^2 in adjuvant combination regimens are considered underdosed.

Overall, trials comparing anthracycline-based chemotherapy to CMF regimens have been heterogeneous in terms of dose intensity, cumulative anthracycline dose as well as in terms of results. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) performed an individual patient data meta-analysis of randomized adjuvant trials including over 14,000 patients in trials comparing anthracycline-based regimens to standard CMF. In this meta-analysis four cycles of standard AC were equivalent to standard CMF (overall mortality RR 0.97, $p = 0.55$). However, anthracycline-based regimens with higher cumulative dosages than standard 4 × AC (epirubicin ≥ 90 mg/m^2 per cycles or a cumulative dose of >360 mg/m^2 and doxorubicin ≥60 mg/m^2 per cycle or a cumulative dose of >240 mg/m^2; e.g., FEC or FAC) were significantly more effective in reducing breast cancer and overall mortality (OS: RR 0.84; $p = 0.0002$). The superiority was seen independent of age, hormone receptor (HR) status, differentiation, tamoxifen use or lymph node status [14]. Prior to the implementation of taxane-based regimens, FAC and FEC were considered as widely accepted standard therapies. However, considering the proven benefit of taxanes in adjuvant therapy today, anthracycline-based, non-taxane-containing regimens are only used in exceptions. Table 20.2 gives a summary of the recommended and most frequently used adjuvant chemotherapy regimens.

Anthracycline-related toxicities

Anthracyclines can cause severe tissue necrosis if extravasation occurs. Therefore, careful intravenous administration is a prerequisite. If extravasation is suspected, administration needs to be stopped and close observation and plastic surgery consultation are recommended. If blistering or ulceration occurs, wide excision with split-thickness skin grafting is indicated. Intermittent application of ice for 15 min. q.i.d. for three days may be helpful. The role of local administration of drugs (e.g., dexrazosan [Savene®, Totect™]) has not been clearly established. The most frequent acute toxicity is neutropenia with a risk of febrile neutropenia that is usually below the threshold of 20 %, which is the threshold for primary G-CSF prophylaxis in most guidelines in the absence of patient-related risk factors. Only the three drug combination TAC has a febrile neutropenia rate of above 20 % and mandates primary G-CSF (and potentially antibiotics) prophylaxis [15]. Alopecia, mucositis, nausea & vomiting and thrombophlebitis/phlebosclerosis are further acute toxicities observed with anthracyclines.

Long-term toxicities of anthracyclines have long been recognized and remain of concern. They include congestive heart failure, acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS).

Cardiotoxicity

Cardiac toxicity of anthracyclines is attributed to the generation of free radicals and death of cardiomyocytes as a result of oxidative stress. This so-called type I cardiotoxicity is distinct from trastuzumab-related type 2 cardiotoxicity, which in contrast is generally considered reversible and dose independent. The risk of systolic dysfunction and congestive heart failure is directly related to the lifetime cumulative dose with an estimated risk of congestive heart failure of around 1 % for present standard doses of doxorubicin of 240 mg/m^2 (e.g., 4 cycles of AC) but increasing to around 5 % for cumulative doses of 400 mg/m^2 to near to 15 and 25 % for doses of 500 and 550 mg/m^2, respectively [16]. At equimolar doses, epirubicin is less cardiotoxic than doxorubicin [17]. In a pooled analysis of eight FASG trials, the rate of congestive heart failure after 7 years was 1.4 % for epirubicin-treated patients at a cumulative dose of about 300 mg/m^2 as compared to 0.2 % in CMF treated patients or controls [18]. However, cumulative doses administered in adjuvant epirubicin-containing regimens are considerably higher and the same dose effect as for doxorubicin also applies to epirubicin. At a cumulative dose of 900 mg/m^2, the expected rate of congestive heart failure is 4 %, which rises to 15 % for doses of 1000 mg/m^2 [19]. In the MA.5 trial with a cumulative dose of epirubicin of 720 mg/m^2 [given as 60 mg/m^2 on day 1 and 8 of each of cycles (q4w)] per protocol, the rate of congestive heart failure was 1.1 % compared to 0.3 % in the CMF group [7]. Long-term

follow-up of the FASG05 trial reported congestive heart failure in 2.3 % of patients available for evaluation and treated with a cumulative dose of epirubicin of 600 mg/m^2 and 0 % in the $FE_{50}C$ arm [20]. Rates of systolic dysfunction (without signs of CHF) measured as a decrease of LVEF of more than 10–15 % or below or near to 50 % are reported to be higher. However, the clinical relevance of these observations is unclear. Risk of cardiotoxicity is increased by additional risk factors such as age, prior mediastinal radiation (e.g., Mantel field for Hodgkin lymphoma), hypertension, diabetes and other cardiovascular risk factors. In addition to the risk of type 1 cardiotoxicity, prior therapy with anthracyclines also increases the risk of trastuzumab-related type 2 toxicity [21].

Maximum cumulative doses of 450 mg/m^2 for doxorubicin and 900 mg/m^2 are usually given according to different sources including manufacturers. However, the best option to minimize cardiotoxicity is to restrict cumulative doses to 360 and 720 mg/m^2, respectively, and be cautious when treating patients older than 65 and with borderline LVEF (50–55 %) where anthracycline-free alternatives should be considered. Reassuringly, all contemporary and widely used anthracycline-containing adjuvant regimens remain well below these strict thresholds and yield CHF rates of 1–2 % or less in patients without risk factors.

AML, MDS

The second long-term toxicity, which causes concern, is a low but increased risk of secondary acute myelogeneous leukemia (AML) and myelodysplastic syndromes (MDS). Treatment-associated AML/MDS occurring after chemotherapy is associated with complex cytogenetics, high-risk karyotypes, and a poorer prognosis compared to de novo AML [22]. Like in congestive heart failure, the risk is proportional to the dose of anthracyclines used. In addition, the cumulative risk of AML/MDS is also related to the dose of cyclophosphamide given, a drug frequently combined with anthracyclines in the adjuvant treatment of primary breast cancer (PBC) [23].

A review of follow-up data of almost 10,000 patients from 19 trials in an effort to investigate the rate of AML/MDS after epirubicin chemotherapy demonstrated an 8-year cumulative risk of 0.55 % in patients treated with epirubicin-containing regimens. Nearly all had also received cyclophosphamide. In patients with cumulative doses of epirubicin and cyclophosphamide equal or less then contemporary (at that time) regimens (E: ≤ 720 mg/m^2; C: ≤ 6300 mg/m^2) the cumulative risk was only 0.37 % and near to that of patients treated with tamoxifen alone or epirubicin-free chemotherapy. In contrast, the risk increased to up to 4.97 % in patients receiving substantially higher doses of both drugs [24]. In a combined analysis of six NSABP trials investigating different intensities of AC, patients treated with four cycles of standard AC (60/600) had a 5-year cumulative rate of AML/MDS of 0.21 %. Similarly to the data for epirubicin, the risk increased with increasing doses of cyclophosphamide (up to 1 %) and the use of breast irradiation [23]. Wolff et al. reported 51 patients who developed acute leukemia after breast cancer amongst 20,000 patients with stage I-III breast cancer treated within Centers of the National Comprehensive Cancer Network. The 5- and 10-year incidence of marrow neoplasm in patients treated with surgery only was 0.05 and 0.2 % but 0.27 and 0.49 % in patients who received adjuvant chemotherapy. Rates for patients receiving adjuvant chemotherapy plus radiation were similar (0.32 and 0.51 %, respectively) [25]. In an observational study based on data from the Surveillance, Epidemiology and End Results (SEER) database including almost 65,000 women with nonmetastatic breast cancer of whom about 10,000 received adjuvant chemotherapy, the 10-year absolute risk of AML as identified by claims for its treatment was 1.8 % as compared to 1.2 % in those not treated with adjuvant chemotherapy. Radiotherapy in this study did not increase the risk of AML [26]. The study has its limitations as it only included patients over the age of 66 and data on the drug schedules and dosages used were not available and the diagnoses of AML and chemotherapy use were deducted from Medicare claims. MDS for example cannot be identified by claims. In Europe, dose-dense, dose-intensified adjuvant regimens are considered a possible standard for patients with high nodal stage. The regimen developed by Moebus et al. provided a 10 % OS benefit at 10 years for patients with four or more involved lymph nodes. After a median follow-up of 62 months, the trial reported four AML cases in the 658 patients (0.61 %) treated with the intensified regimen (cumulative dose of epirubicin: 450 mg/m^2 and cyclophosphamide: 7500 mg/m^2) versus none in the conventionally scheduled arm (cum. dose of epirubicin: 360 mg/m^2 and cyclophosphamide: 2400 mg/m^2). The background lifetime risk of AML is estimated to be 0.4 %. Therefore, contemporary adjuvant anthracycline-based chemotherapy regimens add only little to this absolute risk and the benefits of adjuvant chemotherapy, if indicated wisely, outweigh these risks largely [27].

Continuing role of anthracyclines in adjuvant chemotherapy and alternative anthracycline-free regimens

The compelling efficacy and routine use of taxanes in PBC combined with concerns about the long-term anthracycline-related toxicities (AML, MDS and congestive heart failure, etc.) started a debate if anthracyclines are still indispensable in the adjuvant chemotherapy for early stage breast cancer. Two prominent randomized trials have

addressed this question in both HER2-negative as well as HER2-positive disease. The US Oncology 9735 phase III trial (n = 1016) demonstrated superior disease-free as well as overall survival for four cycles of TC (docetaxel, cyclophosphamide) over four cycles of AC (doxorubicin, cyclophosphamide) [28]. Most patients in the trial had HR-positive disease, half were node-negative, and only a minority (11 %) had four or more involved lymph nodes. Thus, applicability of the results cannot confidently be extended to patients with high-risk breast cancer. However, the trial was not designed to investigate the efficacy of a non-anthracycline-containing regimen compared to an anthracycline/taxane combination. Shulman et al. failed to prove non-inferiority of four or six cycles weekly paclitaxel to AC in a large randomized phase III trial in patients with none to three involved axillary lymph nodes (n = 3871) [29]. A second trial provides support for anthracycline-free adjuvant chemotherapy in HER2-positive disease. The Breast Cancer International Research Group 006 phase III trial (BCIRG006; n = 3222) [21, 30] randomized patients to either AC-T (without trastuzumab), AC-T with trastuzumab (AC-TH) or TCbH (Docetaxel, Carboplatin, and Trastuzumab). Both trastuzumab containing regimens were superior to AC-T in terms of DFS. There was a small non-significant numerical difference in DFS events between AC-TH and TCbH in favor of AC-TH, however, this was counterbalanced by a fivefold increase of congestive heart failure at 10 years (n = 21 vs. n = 4) and an increased risk of treatment-associated leukemia (n = 8 vs. n = 1) for the AC-TH arm [30]. Subgroup analysis stratified by nodal status suggests a similar efficacy in of AC-TH and TCbH even in patients with four or more involved lymph nodes. The trial was not powered to detect differences between the AC-TH and TCbH arm. Trastuzumab may also be added to other non-anthracycline-based regimens like TC [31, 32] or weekly paclitaxel, however, so far there are only data from single-arm trials. Trastuzumab is very effective in HER2-positive disease and optimizing the chemotherapy backbone in this setting might not be of such importance. Hence, these results cannot be generalized to HER2-negative disease in which effective targeted therapies (other than endocrine) are not available. Robust evidence supports the use of anthracycline- **and** taxane-based combinations, and cumulative anthracycline doses used in contemporary regimens convey a low risk of long-term toxicity. However, the data support the omission of anthracyclines in patients at risk of anthracycline toxicity, e.g., older patients, those with risk factors for CHF or patients at the lower end of the spectrum of recurrence risk [27]. In fact in the U.S. the use of anthracyclines has substantially decreased over the last years [33, 34]. Evidence of superiority or non-inferiority of an anthracycline-free taxane-based regimen over an anthracycline and taxane combination is needed before anthracyclines could be omitted across all patient subgroups. Ongoing trials like the WSG PlanB trial (NCT01049425) and the US Oncology "TIC/TAC" trial (NCT00493870), both comparing TC to TAC will answer this question but results are still pending. Until these data are available, anthracyclines remain an integral part of adjuvant chemotherapy for many women with PBC.

Liposomal anthracyclines

Anthracyclines are considered among the most effective drugs for the treatment of breast cancer. Yet, their use is limited by a cumulative (cardio-) toxicity. This is a major limitation of treatment for metastatic breast cancer and often precludes anthracycline rechallenge which is not uncommon practice for taxanes for example. Nonetheless, liposomal formulations of doxorubicin are available, which exhibit a significantly reduced cardiotoxicity and differ considerably from nonencapsulated doxorubicin in their toxicity profile and pharmacokinetics. Pegylated liposomal doxorubicin (PLD; Doxil/Caelyx®) has been licensed in Europe for the treatment of metastatic breast cancer in patients at increased cardiac risk based on a phase III trial demonstrating comparable efficacy to doxorubicin but a significantly reduced cardiotoxicity even at higher cumulative doses [35]. PLD is also characterized by lower rates of alopecia and myelosuppression but higher rates of mucositis and palmar-plantar erythrodysesthesia (see Table 20.1). Due to the relatively high rate of PPE, PLD is frequently used at a dose of 40 mg/m^2 as opposed to the 50 mg/m^2 in the label [36]. In the U.S. as well as in Europe it is also approved for the treatment of recurrent ovarian cancer, AIDS-related Kaposi's sarcoma, and multiple myeloma. Non-pegylated liposomal doxorubicin (Myocet®) has been approved in Europe and Canada as a first-line treatment of metastatic breast cancer in combination with cyclophosphamide based on superior TTP in a phase III trial [37]. Like PLD, it is associated with a significantly reduced cardiotoxicity but due to its different pharmacokinetic profile, it produces less PPE [38]. Although data are limited, liposomal formulations of doxorubicin appear to be more effective in patients previously treated with anthracyclines and there is a rationale for a rechallenge with liposomal anthracyclines in some circumstances [38].

Mitoxantrone and other topoisomerase II inhibitors

In some European countries like Germany, mitoxantrone is approved for the treatment of metastatic breast cancer as well as for the treatment of hormone-refractory prostate cancer and in combination regimens for acute nonlymphocytic leukemia, whereas the FDA label only includes prostate cancer and acute leukemia. In early trials mitoxantrone as a single agent has been shown to be similarly active or at most only marginally less active when directly compared to single agent doxorubicin (n = 325) as a second-line therapy [39] or

compared to $FE_{50}C$ in the first-line setting ($n = 260$) [40], however, with significantly reduced toxicity in terms of nausea and vomiting, mucositis, alopecia as well as cardiotoxicity (Table 20.1). The most frequent toxicity is myelosuppression and infections. Cardiotoxicity, even if less frequent when compared to doxorubicin and epirubicin, can occur and cumulative doses of >160 mg/m^2 should be avoided. Special caution should be taken in anthracycline-pretreated patients and patients with cardiovascular disease or risk factors. Despite its proven activity and approval at least in parts of the world, mitoxantrone hardly has a role in the treatment of metastatic breast cancer mostly due to the frequent anthracycline use in the adjuvant setting and the availability of several drugs with proven single agent activity and favorable toxicity profiles. Etoposide and other topoisomerase II inhibitors are not approved for the treatment of breast cancer.

20.1.2 Tubulin Inhibitors

Tubulin inhibitors are a class of drugs that bind to tubulin. Alpha- and β-tubulin are the main components of microtubules, which are key components of the cytoskeleton and exert important functions in eukaryotic cells. They build up the mitotic spindle and are important for intracellular organelle transport, axonal transport, and cell motility. By binding to β-tubulin, tubulin inhibitors interfere with either microtubule polymerization or depolymerization, which interrupts proper function of the mitotic spindle. The first tubulin-binding drug, colchicine, was isolated from the autumn crocus but is not used in cancer therapy.

Vinca alkaloids, taxanes, epothilones, and halichondrins represent the tubulin inhibitors currently used as cytotoxic agents. They have originally all been isolated from plants or microorganisms and differ in their binding sites and exact mode of action in inhibiting microtubule dynamics.

20.1.2.1 Taxanes

Taxane-based chemotherapeutic agents lead to the inhibition of the mitotic progress (M-phase) by the stabilization of microtubuli during mitosis, resulting in a cell cycle arrest at the G2 phase. This prevents further cell proliferation or maturation [41].

Until the early 1990s, taxanes were mainly isolated from the bark (paclitaxel) and the needles (docetaxel) of the pacific yew tree (*Taxus brevifolia*). Meanwhile, a semi-synthetic production method has been adopted, avoiding shortages in supply as a result of the limitation of natural resources. Due to the hydrophobic behavior of both substances, lipid-based solvents are needed (Cremophor EL, Triton), along with special IV (intravenous) infusion tubes. This can induce hypersensitivity reactions, which are manageable when corticosteroids and antihistamines are given as premedication before and after the start of taxane-based chemotherapy.

Nab-paclitaxel is a polyethoxylated castor oil-free albumin-bound paclitaxel and does not require this premedication. Paclitaxel and docetaxel are approved for the treatment of patients with primary and metastatic breast cancer (MBC), nab-paclitaxel currently only for MBC.

Docetaxel and Paclitaxel

In primary breast cancer (PBC), paclitaxel- and docetaxel-containing regimes can be regarded as the preferred (neo-)adjuvant treatment options if chemotherapy is indicated, regardless of nodal status and hormone receptor status. They are either used as single agents in sequential regimes after anthracyclines (e.g., combined with cyclophosphamide), e.g., EC-D (epirubicin/cyclophosphamide—docetaxel), A(E)C-P (epirubicin or doxorubicin/cyclophosphamide—paclitaxel) or concurrently in combination with anthracyclines and/or cyclophosphamide (TC, TAC; Table 20.2). Dose-dense schedules mainly use paclitaxel based on a better tolerability.

Several large randomized trials in node-positive and node-negative EBC as well as the result from several meta-analyses have provided solid evidence for the benefit of taxanes in the adjuvant therapy for breast cancer. In the PACS-01 study, conducted in node-positive disease, three cycles of $FE_{100}C$ followed by three cycles of docetaxel (100 mg/m^2) were associated with an 18 % reduction of the relative risk of relapse ($p = 0.012$) as well as a 27 % reduction of the relative risk of death ($p = 0.017$) compared to a control arm consisting of six cycles of $FE_{100}C$. The effect was mainly seen in the subgroup of patients who were 50 years or older [42].

BCIRG-001 compared six cycles of $FA_{50}C$ to six cycles of DAC (75/50/500 mg/m^2) in node-positive PBC. After 10 years of follow-up the docetaxel-containing regimen demonstrated a 7 % absolute improvement in both disease-free (HR 0.8, $p = 0.004$) and overall survival (HR 0.74, $p = 0.002$) [43, 44]. Similarly, the GEICAM9805 study, comparing the same regimens in node-negative, high-risk EBC, demonstrated a 6 % improvement in DFS from 82 to 88 % for DAC versus FAC at a median follow-up of 77 months (HR 0.68, $p = 0.01$). GEICAM9805 has not yet been able to demonstrate a significant OS benefit, but at the time, the results were reported, the number of events was small and a numerical trend in favor of DAC could be observed (OS events: DAC 24, FAC 36) [45]. In the WSG-AGO EC-Doc trial, the sequential EC-Doc regimen provided improved EFS and OS compared to six cycles of $FE_{100}C$ in intermediate risk node-positive breast cancer (pN1): 5-year EFS: 89.8 % versus 87.3 % ($p = 0.038$); 5-year OS: 94.5 % versus 92.8 % ($p = 0.034$). These

differences appear marginal. However, a subgroup analysis stratified by centrally determined Ki-67 (at a cut-off of 20 %) demonstrated a significantly greater benefit in luminal B-like tumors with an EFS benefit of 89 % versus 74 % (HR 0.39, 95 % CI 0.18—0.80), whereas luminal A-like tumors did not derive any benefit at all. The test for interaction between treatment and Ki-67 was positive [46].

In the BCIRG005 study, which directly compared EC-Doc to DAC in node-positive EBC, both regimens proved equally effective in terms of DFS and OS. Estimated 5-year disease-free survival rates were 79 % in both groups (HR 1.0; 95 % CI, 0.86–1.16; $p = 0.98$) and 5-year overall survival rates were 88 % and 89 %, respectively (HR, 0.91; 95 % CI, 0.75–1.11; $p = 0.37$). Results were similar in subgroups stratified by numbers of involved lymph nodes or hormone receptor status. However, both regimens differed in their toxicity profiles with DAC being more myelosuppressive and EC-Doc resulting in higher rates of peripheral polyneuropathy.

The Eastern Cooperative Oncology Group (ECOG) trial E1199 addressed the issue, which taxane and schedule would be the most beneficial. For this purpose, patients were randomized after four cycles of AC to either paclitaxel or docetaxel, both given every 3 weeks for four cycles or in a weekly fashion for 12 applications. After a median follow-up of 12 years, both weekly paclitaxel and three-weekly docetaxel significantly improved DFS (HR 0.84, $p = 0.011$ and HR 0.79, $p = 0.001$, respectively) and marginally improved OS (HR 0.87, $p = 0.09$ and HR 0.86, $p = 0.054$, respectively) as compared to three-weekly paclitaxel. An exploratory subgroup analysis suggests substantial benefit from weekly paclitaxel within the subgroup of triple-negative patients in terms of DFS (HR 0.69, $p = 0.01$) and OS (HR 0.69, $p = 0.02$) [47].

Thus, when paclitaxel is used as a single agent sequentially to anthracyclines in adjuvant therapy it appears to be more effective when administered in a weekly fashion as compared to three-weekly paclitaxel. On the other hand, three-weekly docetaxel seems more effective compared to weekly docetaxel [47]. Similar results have been demonstrated for metastatic disease [48, 49].

An exploratory subgroup analysis of the CALGB-9344 study [5, 50] questioned if estrogen receptor-positive, HER2-negative patients benefited from taxanes as the investigators were unable to demonstrate any benefit in this subgroup. Other trials like GEICAM 9805, BCIRG-001, and the PACS-01 studies, however, were able to demonstrate a benefit regardless of ER status [51]. In the WSG-AGO EC-Doc study the taxane benefit in the ER-positive population was restricted to patients with luminal B-like tumors as determined by Ki-67 staining (>20 %) [46]. It can be reasonably argued that low-risk luminal A-like tumors, which are likely not to benefit from chemotherapy at all, will in turn also not benefit from the addition of taxanes.

Two large meta-analyses provide evidence that the benefit from the addition of taxanes in the adjuvant therapy for EBC is independent of node and hormone receptor status [52, 53]. The meta-analysis conducted by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) confirms the benefit in ER-positive patients [14].

Thus, taxane-containing combinations or sequential regimens constitute the preferred therapy for early node-negative and -positive breast cancer if adjuvant chemotherapy is indicated. The pivotal question is to define the subgroup of patients with estrogen receptor-positive tumors which should receive adjuvant chemotherapy. The distinction between luminal A- and B-like tumors either by multigene signatures or a combination of grading and Ki-67 is currently recommended by the St. Gallen international consensus expert panel for this purpose [54]. Patients thought to benefit from adjuvant chemotherapy on this basis should be offered taxane (and anthracycline)-based regimens.

Today, docetaxel is also commonly used in alternative anthracycline-free adjuvant regimens both in HER2-negative and -positive EBC, especially in patients with cardiovascular disease or risk factors who are at higher risk of cardiotoxicity (see Table 20.1). The US Oncology 9735 phase III trial provides evidence that four cycles of a combination of docetaxel and cyclophosphamide lead to an improved overall survival compared to four cycles of AC. However, so far, DC has not been compared to a contemporary anthracycline and taxane-containing regimen. In Her2-positive EBC the combination of docetaxel, carboplatin, and trastuzumab, explored in BCIRG 006, offers a similarly efficacious anthracycline-free option with significantly reduced cardiotoxicity and fewer cases of secondary leukemia.

The side effects of taxanes are shown in Table 20.3. They include myelosuppression, mucositis/stomatitis, hand–foot skin reaction, nail disorders, arthralgia, elevated liver enzymes, diarrhea and obstipation, and fluid retention. One of the most compromising side effects is peripheral polyneuropathy, which occurs in more than 10 % (more than 20 % for Paclitaxel in E1199, [55]). However, severe grade 3/4 PNP is relatively rare and occurs in only 0–8 % of patients [55, 56]. In most cases polyneuropathy resolves after stopping taxane-based chemotherapy but unfortunately, this can take several months or even years. However, formal long time follow-up of PNP in large randomized trials has not been reported and the proportion of underreported yet relevant long-lasting PNP might be considerable.

Similarly to the adjuvant setting, weekly administration of paclitaxel is the preferred regimen for metastatic disease because it has demonstrated superior DFS and OS when

compared to 3-weekly paclitaxel [49]. Docetaxel given every 3 weeks has also demonstrated superiority over 3-weekly paclitaxel and remains the most widely used schedule for docetaxel [28]. Several trials have investigated a diverse range of taxane-based combinations. O'Shaughnessy et al. have even demonstrated a superior overall survival for the combination of docetaxel and capecitabine when compared to docetaxel alone [57]. However, few patients in the monotherapy arm received capecitabine as a post-study treatment [58]. In addition, the combination causes considerable toxicity and its use has not been widely adopted into clinical practice. Similar results have been demonstrated for the combination of paclitaxel and gemcitabine [59]. Today it is widely accepted that taxanes, like other agents used in the metastatic setting, should be used as single agents. So far, no trial has been able to demonstrate superiority of a combination regimen over the sequential use of the same drugs in terms of survival. Combinations provide higher response rates and longer PFS, but also have an inferior therapeutic index and should be reserved for situations of rapidly progressive, life-threatening disease when a rapid remission and high response rates are the main goal [2].

Nab-Paclitaxel

Unlike conventional paclitaxel, this solvent-free formulation of nanoparticle albumin-bound paclitaxel is thought to utilize the natural albumin binding and transport pathways, specifically gp60 and caveolin-mediated transcytosis, to achieve enhanced drug delivery to the tumor [59, 60].

A phase III trial compared *nab*-paclitaxel to conventional paclitaxel in patients with MBC. 454 patients were randomly assigned to either *nab*-paclitaxel 260 mg/m^2 intravenously (q3w) without premedication (n = 229) or standard paclitaxel 175 mg/m^2 intravenously (q3w) with premedication (n = 225). Results showed that response rates were significantly higher (33 vs. 19 %, $P > 0.001$) and time to progression was significantly longer (23.0 vs. 16.9 weeks; HR 0.75, $P > 0.006$) in the *nab*-paclitaxel group compared to conventional solvent-based paclitaxel. Although the dosage of *nab*-paclitaxel was 49 % higher than standard paclitaxel, the incidence of grade 4 neutropenia was significantly lower for nab-paclitaxel (9 vs. 22 %, $P < 0.001$). Grade 3 sensory neuropathy was more common in the nab-paclitaxel arm than in the standard paclitaxel arm (10 vs. 2 %, $P < 0.001$), but improved rapidly (median, 22 days). No hypersensitivity reactions occurred with *nab*-paclitaxel despite the absence of premedication and shorter administration time [61]. *Nab*-paclitaxel was approved by the FDA in 2005 as monotherapy for patients with advanced breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated. In Europe, the EMA (European Medicines Agency) approved *nab*-paclitaxel in 2008 as monotherapy after failure of first-line chemotherapy. Patients should have received prior anthracyclines. Based on the observation that conventional paclitaxel is more effective when administered in a weekly schedule [49] as well as on emerging phase II data [62], *nab*-paclitaxel is frequently used in a weekly schedule despite the fact that this has not been confirmed in a phase III trial. There is some debate on the ideal weekly dosage, but practical- and evidence-based considerations suggest doses between 100 and 125 mg/m^2 given on 3 out of 4 weeks [63]. In the recent randomized neoadjuvant phase III GeparSepto trial, *nab*-Paclitaxel (12 × 125 mg/m^2 weekly) followed by four cycles of EC led to a significantly higher pCR rate (38 %, ypT0 ypN0) compared to standard solvent-based weekly paclitaxel (29 %, $p = 0.001$), an effect that was even more pronounced in triple-negative disease, further supporting the superior efficacy of *nab*-paclitaxel [64, 65].

20.1.2.2 Epothilones (Ixabepilone)

Another tubulin-targeted agent is ixabepilone, a semi-synthetic analog of epothilone B. Similar to taxanes, it leads to microtubule stabilization. However, taxanes and ixabepilone are structurally unrelated and bind to tubulin in a distinct manner and at distinct binding sites. Ixabepilone can retain activity in taxane-resistant tumor cells.

Two large phase III trials of ixabepilone in combination with capecitabine compared to single agent capecitabine demonstrated significantly superior response rates (35 % vs. 14 % and 43 % vs. 29 %, respectively) as well as PFS (5.8 vs. 4.2 months and 6.2 vs. 4.2 months, respectively). However, the combination did not lead to an improved OS and was associated with significantly increased toxicity, including 70 % grade 3/4 neutropenia and 20–24 % of grade 3/4 peripheral neuropathy. Furthermore, slightly more treatment-associated deaths were observed in the combination arms (3 % vs. 1 %) [66, 67]. Other commonly observed toxicities were anemia, leucopenia, thrombocytopenia, fatigue/asthenia, myalgia/arthralgia, alopecia, nausea, vomiting, stomatitis/mucositis, diarrhea, and musculoskeletal pain [67–70].

In October 2007, the FDA approved ixabepilone for the treatment of aggressive metastatic or locally advanced breast cancer no longer responding to currently available chemotherapy regimes. Ixabepilone is indicated in combination with capecitabine or as monotherapy for the treatment of patients with metastatic or locally advanced breast cancer resistant to treatment with an anthracycline and a taxane or as monotherapy in patients resistant to anthracycline, taxanes, and capecitabine. In contrast, the EMA has refused a marketing authorization for ixabepilone because of its unfavorable therapeutic index [71].

Table 20.3 Summary of selected tubulin-targeted cytotoxic agents in breast cancer

Medication	Trade name® (examples)	Dosing (mg/m^2 BSA)	Precautions	Interactions	Selected side effects
Paclitaxel	Taxol	135–250 q3w; 80–90* weekly. *e.g., in combination with bevacizumab. Paclitaxel is then given at days 1, 8, 15 q4w	Premedication to prevent severe hypersensitivity reactions including corticosteroids, diphenhydramine and H2-antagonists; use PVC free IV lines, etc.; dose reductions in case of liver function impairment	Interaction with inhibitors and inducer of CYP3A4 and CYP2C8	Polyneuropathy, dysgeusia, myelosuppression, stomatitis/mucositis, palmar-plantar erythrodysesthesia (hand–foot-skin syndrome), fatigue, arthralgia, nausea, vomiting, diarrhea, musculoskeletal pain, pulmonary toxicity (interstitial pneumonitis, pulmonary fibrosis, ARDS), hepatotoxicity (hyperbilirubinemia, elevated transaminases), hypersensitivity reaction (can be severe), skin and nail changes, alopecia, injection site reactions, fluid retention
Docetaxel	Taxotere	75–100 q3w	Premedication to prevent severe hypersensitivity reactions including corticosteroids, diphenhydramine and H2-antagonists; use PVC free IV lines, etc.; dose reductions in case of liver function impairment	Interaction with inhibitors and inducer of CYP3A4	Polyneuropathy, dysgeusia, myelosuppression, febrile neutropenia, stomatitis/mucositis, palmar-plantar erythrodysesthesia (hand–foot-skin syndrome), pulmonary toxicity (interstitial pneumonitis, pulmonary fibrosis, ARDS), hepatotoxicity (hyperbilirubinemia, elevated transaminases), fatigue, arthralgia, nausea, vomiting, diarrhea, musculoskeletal pain, hypersensitivity reaction (can be severe), skin and nail changes, alopecia, injection site reactions, fluid retention
Nab-Paclitaxel	Abraxane	260 q3w; weekly schedules are widely used (dose range 100–150 q3/4w)	Dose reductions in case of liver function impairment	Interaction with inhibitors and inducer of CYP3A4 and CYP2C8	Polyneuropathy, dysgeusia, myelosuppression, stomatitis/mucositis, hand–foot-skin syndrome, pulmonary toxicity (interstitial pneumonitis, pulmonary fibrosis, ARDS), hepatotoxicity (hyperbilirubinemia, elevated transaminases), fatigue, arthralgia, nausea, vomiting, diarrhea, musculoskeletal pain, hypersensitivity reaction (significantly less frequent than with pacli- and docetaxel), skin and nail changes, alopecia, fluid retention, injection site reactions

(continued)

Table 20.3 (continued)

Medication	Trade name® (examples)	Dosing (mg/m^2 BSA)	Precautions	Interactions	Selected side effects
Ixabepilone	Imprexa	40 q3w	Premedication with an H1-and H2-antagonists, dose reductions in case of liver function impairment; dose should be capped at 2.2 m^2 BSA; Must not be used in patients with hypersensitivity against drugs formulated with cremophor (e.g., paclitaxel), patients with AST or ALT > 2.5 × ULN or bilirubin > 1 × ULN must not be treated with ixabepilone in combination with capecitabine	Interaction with inhibitors and inducer of CYP3A4	Peripheral neuropathy, myelosuppression, stomatitis/mucositis, hand–foot syndrome fatigue/asthenia, alopecia, nausea, vomiting, diarrhea, musculoskeletal pain (myalgia/arthralgia), anorexia, abdominal pain, nail disorder, hypersensitivity reactions
Vinorelbine	Navelbine	30 weekly	Save IV application, dose reduction in case of liver function impairment	Interaction with inhibitors and inducer of CYP3A4	myelosuppression, polyneuropathy, nausea and vomiting, constipation, elevated liver enzymes, mucositis, injections site reactions and local tissue damage (including necrosis), pulmonary toxicity (interstitial pneumonitis, ARDS, bronchospasm)
Eribulin	Halaven	1.23 mg/m^2 d1, 8 q3w (equivalent to eribulin mesylate: 1,4 mg/m^2 d1, 8 q3w)	Dose reductions in case of impaired liver and renal function ECG monitoring in patients with heart disease	Interaction with drugs that prolong QT interval	Neutropenia, peripheral neuropathy, fatigue/asthenia, alopecia, nausea

These highlights do not include all the information needed to use the respective drugs safely and effectively. See full prescribing information for all information needed to use these agents safely. We do not take responsibility for the correctness of the content

20.1.2.3 Vinca Alkaloids (Vinorelbine)

Vinca alkaloids are a class of drugs originally isolated from the Madagascar periwinkle plant (*Catharanthus roseus, syn. Vinca rosea*).

Vinblastine, vincristine, vinorelbine, vindesine, and vinflunin are the most widely used members of this class of drugs. Vinorelbine is the only vinca alkaloid currently approved for the treatment of breast cancer (in the EU). Vinca alkaloids bind tubulin at a different binding site compared to taxanes. Unlike taxanes, which prevent tubulin depolymerization, vinca alkaloids inhibit tubulin polymerization, thereby preventing microtubule formation and the proper function of the mitotic spindle.

Single agent vinorelbine has demonstrated activity against advanced breast cancer in a range of single-arm phase II trials including 45–157 patients each. In the first-line setting, vinorelbine, given at a dose of 30 mg/m^2 (qw), demonstrated objective response rates between 35 and 50 % with a time to treatment failure ranging from 5 to 6 months and a median duration of response of 9 months. Median overall survival in trials reporting OS was between 15 and 18 months [72–76]. In more heavily pretreated patients, response rates ranged from 16 to 36 % with a median duration of response of 5–8.5 months and a median overall survival of 14.5–16 months [73, 77, 78].

The number of randomized trials investigating the role of vinorelbine in breast cancer in any setting is very limited. A randomized phase III trial comparing vinorelbine to melphalan in 183 anthracycline-pretreated patients run in the early 1990s demonstrated vinorelbine to be superior to melphalan with a response rate of 16 % versus 9 % and a significantly improved TTP and OS [79]. A large randomized phase III trial compared single agent vinorelbine to a combination of vinorelbine and gemcitabine. Single agent vinorelbine had a significantly shorter PFS of 4 versus 6 months ($p = 0.0028$) and a numerically smaller response rate of 26 % versus 36 % ($p = 0.09$). However, overall survival did not differ between both treatment arms (V: 16.4 months and VG: 15.6, $p = 0.8$) [80]. A trial directly comparing vinorelbine to capecitabine was prematurely

closed after inclusion of only 46 patients, but efficacy was similar for the two drugs with significantly different toxicity profiles [81]. Unlike in Europe, where vinorelbine is approved for the treatment of non-small-cell lung cancer (NSCLC) and metastatic breast cancer after failure of anthracyclines or taxanes in the 1990s, vinorelbine has only gained approval for NSCLC in the US.

The main dose-limiting toxicity of vinorelbine is neutropenia, which can occur as grade 3/4 in more than 50 % of patients if vinorelbine is used as a single agent. Peripheral neuropathy is usually mild and only rarely occurs as grade 3/4 in about 3 % of patients (single agent). Vinorelbine can cause phlebitis and inflammation at the injection site. Care has to be taken to correctly position the IV catheter or needle as severe local tissue necrosis may occur in rare cases. Rarer side effects include interstitial pulmonary disease (in rare cases severe ARDS), bronchospasm, cardiac ischemia and diarrhea. Vinorelbine rarely causes apparent alopecia. An oral formulation, which has demonstrated activity, has been marketed and registered in Europe for the same settings [82, 83]. Vinorelbine is mostly used as second- or third-line therapy. In addition, vinorelbine has shown good efficacy in combination with trastuzumab [84].

20.1.2.4 Eribulin

Eribulin is a structurally modified synthetic analog of halinchondrin B, a natural compound isolated from a rare Japanese marine sponge (Halichondria okadai). Like most tubulin-targeted agents, it impairs the proper function of the mitotic spindle leading to a G2-M cell cycles arrest and inhibiting cell proliferation. However, unlike other antimitotic drugs such as taxanes and vinca alkaloids which inhibit microtubule growth and shortening, eribulin predominantly inhibits microtubule polymerization and leads to the sequestration of tubulin into nonproductive aggregates. Microtubule shortening remains largely unaffected [85].

Eribulin was first approved as a monotherapy by the FDA in 2010 and the EMA in 2011 for the treatment of metastatic breast cancer in women who have received two or more prior chemotherapies for advanced disease. Prior therapy should have included anthracyclines and a taxane, either in the adjuvant or metastatic setting. The approval was based on results from the EMBRACE study (study 305; NCT00388726), a randomized phase III trial that included patients with 2–5 prior lines of chemotherapy for advanced disease and compared eribulin to treatment of physician's choice (TPC). The study demonstrated a significant improvement in overall survival (HR 0.81; $p = 0.041$) in favor of eribulin [86]. A second large phase III trial directly compared eribulin to capecitabine as first- to third-line therapy for metastatic breast cancer previously treated with anthracyclines and taxanes. This study (E301; NCT00337103) failed to demonstrate a superiority of eribulin over capecitabine (OS HR 0.88; $p = 0.056$). Neither PFS nor ORR differed between the two therapies [87]. A pooled analysis of the two trials confirmed the OS benefit of eribulin versus control and suggested a more pronounced benefit in HER2-negative and triple-negative subgroups [88]. In the EU, the indication for eribulin has been expanded to patients with only one prior line of chemotherapy in the advanced/metastatic setting. The most common side effects of eribulin are neutropenia, fatigue/asthenia, alopecia, peripheral neuropathy and nausea.

20.1.3 Alkylating Agents

20.1.3.1 Cyclophosphamide

Cyclophosphamide is a widely used anticancer drug and is listed on the World Health Organization's List of Essential Medicines. It is a member of the oxazaphosphorine family of mustard-alkylating agents and was first synthesized in 1958 by Norbert Brock and has since been used to treat a range of diseases [89]. Cyclophosphamide itself is a prodrug that needs to be activated by the cytochrome P450 in the liver. The resulting metabolite is called 4-hydroxy-cyclophosphamide (4-OH-CPA). It has to undergo β-elimination to yield phosphoramide mustard and acrolein. Phosphoramide mustard alkylates both DNA and proteins and forms DNA crosslinks both between and within DNA strands at guanine N-7 positions. These inter- and intrastrand crosslinks are irreversible and finally lead to apoptosis [90]. The intracellular release of the active alkylating agent also leads to direct inhibition of DNA polymerases [91]. Cyclophosphamide is one of the best known agents of this class and has a long history in the treatment of all kinds of cancers. Even today, more than 50 years after its introduction, it is one of the most widely used chemotherapeutic agents. Cyclophosphamide is nowadays part of the majority of chemotherapeutic regimes in the treatment of breast cancer in the adjuvant and neoadjuvant setting but is less frequently used in the metastatic setting. It is also used in the treatment of other types of cancers such as leukemia, multiple myeloma, or retinoblastoma. When used as a single agent in the treatment of breast cancer, response rates between 10 and 50 % were observed.

Cyclophosphamide is one of the agents that made up the first successfully implemented adjuvant chemotherapy regimen consisting of cyclophosphamide, methotrexate, and 5-fluoruracil, the CMF regimen, which significantly reduced the risk of recurrence and improved overall survival, compared to observation [92, 93]. CMF is rarely used today and cyclophosphamide is usually given as part of combination regimes, mostly together with anthracyclines, e.g., doxorubicin

Table 20.4 Selected alkylating agents used in the treatment of breast cancer

Medication	Trade name® (examples)	Dosing (mg/m^2 BSA)	Precautions	Interactions	Selected side effect
Cyclophosphamide	Endoxan	Varies between several different adjuvant regimens., e.g., 500 mg/m^2 IV q3w, as part of the "CAF" protocol or 600 mg/m^2 IV d1, 8 q4w as part of the "CMF" regimen. And up to as high as 2000 mg/m^2 in dose-intensified, dose-dense ETC (see Table 20.2) Or 50 mg p.o. daily as part of a oral metronomic therapy in combination with methotrexate (2 × 2.5 mg p. o. d 1, 2 q1w)	>1000 mg/m^2: uroprotection with MESNA, sufficient hydration, exclude urinary obstruction	Several. Refer to prescribing information	Myelosuppression, immunosuppression, amenorrhea, ovarian failure, infertility, alopecia, nausea, vomiting, mucositis, hemorrhagic cystitis, nephrotoxicity, cardiotoxicity (e.g., hemorrhagic perimyocarditis), pulmonary toxicity, secondary malignancies (e.g., AML/MD and bladder cancer). Can cause fetal harm.
Bendamustin	Ribomustin	120–150 mg/m^2 IV day 1, 2 q4w; no standard dose/schedule defined for breast cancer. Bendamustin is not approved for the treatment of breast cancer	None	None	Myelosuppression, mucositis, stomatistis, nausea, vomiting, alopecia. Can cause fetal harm

These highlights do not include all the information needed to use the respective drugs safely and effectively. See full prescribing information for all information needed to use these agents safely. We do not take responsibility for the correctness of the content

(AC) or epirubicin (EC) followed by a taxane but also in combination with docetaxel (see Table 20.4) [4, 31, 94, 95].

Cyclophosphamide also plays a role in metronomic chemotherapeutic regimens, often in combination with methotrexate. In heavily pretreated patients, such metronomic regimens (CM) provide response rates of around 20 % [96]. Recently, the same regimen given for 12 months as maintenance therapy in a randomized phase trial (IBCSG 22-00) after adjuvant chemotherapy has demonstrated some signs of activity at least in the high-risk subpopulation of node-positive, triple-negative patients [97]. For these low-dose cyclophosphamide regimens, alternative modes of action are proposed and low-dose cyclophosphamide is rather thought to induce beneficial immunomodulatory effects, e.g., by eliminating regulatory T cells and in metronomic dosing schedules also antiangiogenic effects [89, 98]. In addition, high-dose cyclophosphamide is also used as an immunosuppressant to treat severe and refractory autoimmune diseases like lupus because high doses cause general lymphodepletion.

Side effects of cyclophosphamide include nausea and vomiting, bone marrow suppression, alopecia, fatigue, amenorrhea, hemorrhagic cystitis, nephrotoxicity and secondary malignancies. The urotoxic effect of cyclophosphamide is caused by acrolein, one of its metabolites. The risk can be minimized by securing adequate hydration, excluding urinary tract obstruction, avoiding night time dosage and the administration of MESNA at higher doses of cyclophosphamide. MESNA (sodium 2-mercaptoethan sulfonate) binds and neutralizes acrolein [99]. As cyclophosphamide significantly increases the risk of premature menopause and infertility, younger patients in the adjuvant setting need to be offered counseling on fertility preservation (as with all adjuvant chemotherapy regimens) prior to the start of therapy. Cyclophosphamide also has procarcinogenic effects and can lead to secondary malignancies including leukemia, MDS, skin cancer, bladder cancer, and other malignancies. The risk of treatment-related AML (t-AML) appears to be dose dependent, but is also influenced by additional factors including other agents, e.g., anthracyclines which can also increase the risk. T-AML is often preceded by MDS and often associated with complex cytogenetics and a worse prognosis compared to de novo AML. Cyclophosphamide at high doses can also induce cardiac toxicity, which can manifest as a range of conditions, including hemorrhagic perimyocarditis.

20.1.3.2 Bendamustine

Another substance of this group is bendamustine (Table 20.4), which has structural similarities to both alkylating agents and purine analogs. Its function is not yet entirely clear, but it has demonstrated to be noncross resistant with other alkylating drugs [100].

It is a long-known cytotoxic agent, which was once widely used in the former German Democratic Republic for a variety of cancers types. It is mainly indicated for

hematological malignancies like Hodgkin's, non-Hodgkin's disease, multiple myeloma, but there are promising results for bendamustine in breast cancer patients as second- or third-line chemotherapy [101]. In a phase III trial, the combination of bendamustine, cyclophosphamide, and 5-fluorouracil was compared with conventional CMF as first-line treatment for MBC and achieved a longer progression-free survival [102]. Current ongoing studies are evaluating new schedules, doses, and the management of toxicities and combinations with other cytotoxic agents (e.g., NCT00661739, NCT00705250) to optimize cancer therapy with bendamustine. Bendamustine seems to have a favorable range of side effects, especially for heavily pretreated patients with metastasized breast cancer. In a phase II study, the main side effects reported were myelosuppression, infection, mucositis, and diarrhea. Those events mostly occurred within grade 1–2 and were well manageable [100, 103]. However, due to a range of alternative effective drugs and several other reasons, bendamustine is currently not frequently used in the treatment of breast cancer and has not been approved for this indication either.

20.1.4 Platinum-Based Chemotherapeutic Agents

Cisplatin and carboplatin are widely used drugs to treat various types of cancers, including sarcomas, a range of carcinomas (e.g., small cell lung cancer, and ovarian cancer), lymphomas, and germ cell tumors as well as breast cancer (Table 20.5). Platinum-based agents form complexes within the cells, which induce intra- and interstrand crosslinks, which result in double strand breaks during replication and ultimately the induction of apoptosis.

The activity of platinum salts in breast cancer was first demonstrated in the 1980s in several small trials, with cisplatin achieving response rates of 47–54 % in previously untreated patients. However, a considerably lower activity (RR ~ 10 %) was observed in more heavily pretreated patients [104–109]. These data suggest a dose and pretreatment-dependent activity. With the introduction of anthracyclines and taxanes as effective but less toxic therapies, interest in platinum therapies for breast cancer decreased. Investigators regained interest in platinum salts for breast cancer when in the 2000s several preclinical studies reported an outstanding efficacy of platinum in BRCA-mutated cancer cells and in addition, new regimens to manage toxicities have been established.

The strong interest in platinum-based therapies that mainly focused on TNBC were based on phenotypic similarities between BRCA1-associated breast cancer and triple-negative disease or more precisely the basal-like subtype. Roughly 80 % of BRCA1-associated tumors are basal like. However, the majority of basal-like tumors are not BRCA-associated but sporadic. Yet, the shared phenotype led to the speculation that sporadic basal-like tumors might also share defects in homologous recombination (HR) with their BRCA-associated counterparts, yet, caused by different mechanisms and might therefore have a similar sensitivity to platinum salts [110]. The double strand breaks induced by platinum salts during replication require homologous recombination (HR) as an error-free DNA repair mechanism. If cells harbor HR defects, error-prone compensatory repair mechanisms step in and lead to a high degree of genomic instability, finally resulting in the death of the tumor cells. Preclinical data pointed to an extraordinary sensitivity to platinum agents of BRCA-associated breast and ovarian cancers. However, it took a long time until randomized trials provided first evidence that at least a subgroup of TNBC patients might specifically benefit from platinum-based chemotherapy. Several studies in unselected TNBCs revealed discouraging results [111–113]. Finally, the TNT trial randomized 376 patients with metastatic TNBC to either carboplatin or docetaxel as a head-to-head comparison. There were no significant differences in terms of ORR, PFS, and OS in the overall study population. However, an exploratory analysis revealed a significant benefit from carboplatin over docetaxel in *BRCA1/2* mutation carriers, with an ORR of 68 % versus 33 % and a PFS of 6.8 months versus 4.8 months. A test for interaction between BRCA status and therapy was positive, providing evidence that BRCA mutations but not TNBC status or basal-like subtype predicts benefit from platinum salts in breast cancer [114].

Several trials have investigated the role of carboplatin in the neoadjuvant setting in patients with TNBC. With one exception, they have all demonstrated increased pathologic complete response (pCR) rates for the platinum-based regimens. The GeparSixto trial and the CALGB 40603 trial reported an increase in pCR rates (ypT0/is ypN0) of 10.5 and 13 % by the addition of carboplatin to anthracycline- and taxane-based combinations in TNBC [115, 116]. Recently, carboplatin, when added to four cycles of neoadjuvant *nab*-paclitaxel, increased pCR rates by 17.2 % compared to gemcitabine in TNBC [117]. So far, only the GeparSixto and CALGB 40603 have reported preliminary survival data. In GeparSixto, the addition of carboplatin led to a 10 % improvement in 3-year DFS (HR 0.56; $p = 0.035$) [118], whereas in the CALGB 40603 the increased pCR rates did not result in an improved survival [119]. In the GeparSixto trial, the benefit from the addition of carboplatin in terms of pCR and event-free survival was not restricted to BRCA-mutated patients but seen in BRCA wild-type patients as well [118]. The use of carboplatin against TNBC in the (neo)adjuvant setting cannot be regarded as a standard until additional data on survival are available. Thus far, in the (neo)adjuvant setting, carboplatin is only used as a

Table 20.5 Platinum-based cytotoxic agents used in the treatment of breast cancer

Medication	Trade name® (examples)	Dosing	Precautions	Interactions	Selected adverse effects
Cisplatin		30–75 mg/m^2, e.g., q3w, various regimens	Dose reduction according to GFR. Ensure sufficient hydration prior to and after cisplatin infusion (1000–2000 ml each)	Avoid further nephrotoxic drugs	Myelosuppression, renal toxicity, alopecia, marked nausea and vomiting, neurotoxicity, ototoxicity, electrolyte disturbances, allergic/anaphylactic reactions
Carboplatin		Area under the curve (AUC), e.g., as calculated by the "Calvert formula": Total dose (mg) = (target AUC) × (GFR + 25), e.g., AUC 4–6 q3w or AUC 2 q1w as a single agent or in combination	Dose reduction according to GFR	None	Myelosuppression, renal toxicity (less than cisplatin), alopecia, nausea, vomiting, neurotoxicity and ototoxicity (less than cisplatin), electrolyte disturbances, allergic/anaphylactic reactions

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standard treatment option in HER2-positive breast cancer in combination with docetaxel and trastuzumab (and pertuzumab).

There is no data to suggest that in breast cancer either cis- or carboplatin was superior to the other. However, due to the reduced toxicity, particularly with regard to renal and ototoxicity, carboplatin is often preferred over cisplatin. The adverse reactions of carboplatin and cisplatin consist of myelosuppression affecting all lineages, including the risk of severe thrombopenia, nephrotoxicity, neurotoxicity, ototoxicity, nausea and vomiting, allergic and anaphylactic reactions.

In addition to the significantly reduced nephrotoxicity and ototoxicity of carboplatin, nausea, and vomiting are also less severe and more easily controlled, compared to cisplatin. In turn, myelosuppression appears to be more severe with carboplatin including higher rates of grade 3/4 thrombopenia.

20.1.5 Antimetabolites

Methotrexate, 5-FU, capecitabine and gemcitabine are antimetabolites frequently used in the treatment of metastatic breast cancer (Table 20.6).

20.1.5.1 Methotrexate (MTX)

Methotrexate (MTX) is a widely used antimetabolite with a wide range of indications including the therapy of several cancer types, like breast cancer, trophoblast diseases, leukemia, lymphomas and as an intrathecal application to treat meningeal carcinomatosis or primary CNS lymphomas. In addition, it is also used for the conservative management of extrauterine pregnancy, severe forms of rheumatoid arthritis and psoriasis. It is available as IV, IT, IM as well as oral formulations.

MTX competitively inhibits dihydrofolate reductase (DHFR), an enzyme involved in tetrahydrofolate synthesis [120]. Folic acid is a crucial enzyme in the de novo synthesis of thymidine, which is essential for DNA synthesis. Folate is also essential for the synthesis of purine and pyrimidine bases. MTX therefore inhibits DNA as well as RNA synthesis.

In breast cancer it has mostly been used in combination with cyclophosphamide and 5-fluorouracil (CMF), in the metastatic as well as the adjuvant setting. Adjuvant CMF was the first adjuvant therapy to be successfully established for the therapy of primary breast cancer. It has been replaced by "standard" AC or EC not based on superiority but rather due to the shorter duration and better tolerability of the latter regimens. Subsequently, anthracycline-containing regimens with higher cumulative doses and longer duration proved to be more effective, which is reflected by the EBCTCG meta-analysis [14]. The CMF regimen today is infrequently used as an anthracycline-free option.

MTX has also demonstrated some activity as part of a metronomic regimen consisting of oral cyclophosphamide (50 mg per day continuously) and oral MTX (5 mg on day 1 and 2, qw). It is not used as monotherapy.

To prevent excessive bone marrow and gastrointestinal toxicity from higher doses of MTX (>100 mg/m^2 BSA), folinic acid (leucovorin rescue) has to be given at the appropriate time after the administration of MTX.

Table 20.6 Antimetabolites used in the treatment of breast cancer

Medication	Trade name® (examples)	Dosing (mg/m^{2}BSA)	Precautions	Interactions (selected examples)	Selected side effects
Methotrexate		E.g., 40 mg/m^2 IV on days 1 and 8 of each cycle as part of the classic CMF protocol in combination with cyclophosphamide and 5-FU or as part of a metronomic therapy at a dose 5 mg/d on day 1 and 2, q1w, in combination with continuous oral cyclophosphamide (50 mg/d)	Dose reduction in case of renal impairment, MTX elimination also impaired in patients with ascites and pleural effusion. leucovorin rescue (calcium folinate) is mandatory at higher doses (>100 mg/m^2)	Unexpectedly severe bone marrow suppression, aplastic anemia, and gastrointestinal toxicity have been reported with concomitant administration of some nonsteroidal anti-inflammatory drugs (NSAIDs)	Myelosuppression, mucositis, stomatitis, diarrhea, hepatotoxicity, pulmonary toxicity (including. interstitial pneumonitis), skin toxicity, renal failure Can cause fetal damage or death
5-Fluorouracil		As part of the classic CMF protocol: 600 mg/m^2 IV in combination with cyclophosphamide and MTX q4w As part of the FAC or FEC regimen: 500 mg/m^2 in combination with doxorubicin or epirubicin and cyclophosphamide, q3w Several other dosing schedules are used in the treatment for other malignancies		Methotrexate, leucovorin (calcium folinate) increases efficacy and toxicity. Brivudin und Sorivudin. 5-FU may lead to unexpected severe toxicity in patients with dihydropyrimidindehydrogenase (DPD) deficiency	Myelosuppression, palmar-plantar erythrodysesthesia, alopecia, nail changes, mucositis, stomatitis, diarrhea, nausea, vomiting, CNS toxicity, allergic reactions, cardiac toxicity including ECG changes, hepatotoxicity
Capecitabine	Xeloda	2 × 1000–1250 daily p. o. d1-14 q3w	Dose reductions for renal impairment (GFR 30–50 ml/min.), contraindicated in patients with a GFR < 30 ml/min	Methotrexate, Leucovorin, coumarin-type anticoagulants May lead to unexpected severe toxicity in patients with dihydropyrimidindehydrogenase (DPD) deficiency	Myelosuppression, palmar-plantar erythrodysesthesia, diarrhea, dehydration, cardiotoxicity, renal impairment
Gemcitabine	Gemzar	Approved for breast cancer at a dose of 1250 mg/m^2 on days 1 and 8 of each cycle in combination with paclitaxel (175 mg/m^2 given on day 1) q3w. Other dosing regimens, not officially approved in breast cancer include gemcitabine monotherapy at a does of 1000 mg/m^2 d 1, 8, 15 q4w or at doses from 750 mg/m^2 d 1, 8 q3w, e.g., in combination with cisplatin		Cisplatin, radiosensitizer	Myelosuppression, nausea and vomiting, pulmonary toxicity (including cases of ARDS), hepatotoxicity, hemolytic uremic syndrome, skin rash, capillary leak syndrome, peripheral edema, posterior reversible encephalopathy. Gemcitabine may exacerbate toxicity of radiotherapy

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20.1.5.2 Capecitabine, 5-Fluourouracil (5-FU)

Capecitabine is a prodrug which is enzymatically converted to 5-FU by carboxyesterase, cytidine deaminase, and thymidine phosphorylase in the liver and in tumor cells. 5-FU (and capecitabine) exerts it cytotoxic effects via the inhibition of thymidylate synthase, blocking the synthesis of the pyrimidine thymidine, a nucleoside required for DNA replication.

5-FU has a long history in breast cancer and has been used as part of an adjuvant regimen consisting of 5-FU, epi- or doxorubicin, and cyclophosphamide (FEC, FAC). Recently, a large randomized phase III trial (GIM-2), however, demonstrated, that 5-FU did not add any benefit to the combination of epirubicin and cyclophosphamide followed by paclitaxel [121]. It has now been replaced by modern anthracycline-/taxane-based regimens (Table 20.6).

Capecitabine has been approved based on a series of phase II/III trials as monotherapy for metastatic breast cancer after failure of anthracycline- and taxane-containing therapies. Response rates for capecitabine monotherapy range between 14 and 29 %, with a TTP and OS of 3.1–7.9 and 10.1–29.4 months, respectively across all settings [122–124]. Based on a randomized phase III trial in the first-line setting, capecitabine has also been approved in combination with docetaxel after prior anthracycline-based therapies. This trial is one of the few chemotherapy trials for MBC which have demonstrated a significant overall survival for the combination over docetaxel monotherapy. However, the regimen produces considerable toxicity, including high rates of febrile neutropenia, and there are some questions about subsequent therapies [57, 58]. Therefore, it mainly remains a valuable option in situations which require rapid responses, otherwise sequential monotherapies are generally preferred due to their better therapeutic index.

In the US, capecitabine is also approved in combination with ixabepilone in otherwise resistant metastatic breast cancer. However, due to an unfavorable therapeutic index and risk of severe toxicities, this combination has not been approved by the EMA in Europe. In contrast, capecitabine in Europe but not the US has been granted approval as first-line therapy for MBC in combination with bevacizumab. Further, capecitabine is used in combination with lapatinib or trastuzumab for the treatment of HER2-positive breast cancer. It is also used to treat colorectal cancer and gastric cancer.

Capecitabine has also been investigated in the adjuvant setting as an adjunct to anthracycline- and taxane-based regimens. However, none of these regimens provided evidence of a benefit from the addition of capecitabine in unselected patients [125–128]. Some studies suggest that there might be a role for capecitabine in selected patients with primary breast cancer. The GeparTrio trial demonstrated a survival benefit from switching to a noncross-resistant regimen consisting of capecitabine and vinorelbine in patients with luminal type breast cancers not responding to two cycles of neoadjuvant docetaxel, doxorubicin, and cyclophosphamide (TAC) [129]. Very recently, a phase III trial in the post-neoadjuvant setting demonstrated an overall survival benefit of 6 months from capecitabine in Asian patients not achieving a pCR after anthracycline- and taxane- containing neoadjuvant chemotherapy [130]. Whether this effect can be extrapolated in other ethnicities is unclear.

One of the most frequent and compromising side effects are hand–foot syndrome (HFS, Palmar-plantar erythrodysesthesia) with an incidence of up to 20 % and diarrhea. HFS can become very painful and significantly impair daily activities and quality of life. An association between hand–foot syndrome and efficacy has been suspected but is still unproven. In general, the side effects are manageable with dose interruptions or reductions and a complete termination of therapy is rarely necessary. Diarrhea can be severe and potentially life-threatening in rare cases, especially if capecitabine is given in combination with lapatinib. Useful guidelines for management of chemotherapy-induced diarrhea have been developed by the American Society of Clinical Oncology (ASCO) [131]. Other adverse events include myelosuppression, stomatitis, nausea and vomiting, abdominal pain, dehydration, and hyperbilirubinemia.

Capecitabine is metabolized and inactivated by dihydro-pyrimidin-dehydrogenase (DPD). Polymorphisms within this gene can result in DPD-deficiency and patients are at risk of severe, potentially life-threatening toxicities. Use of capecitabine should be avoided in patients with known DPD-deficiency.

20.1.5.3 Gemcitabine

Gemcitabine is another chemotherapeutic agent which acts as an antimetabolite. It is a nucleoside analog (2″,2′-difluoro-deoxycytidine; dFdC) that is phosphorylated intracellularly [132–134] by deoxycytidine kinases and interferes with DNA replication. The diphosphate inhibits ribonucleotide reductase that is crucial for the production of deoxynucleotide triphosphates needed for normal DNA synthesis, whereas the triphosphate is incorporated into the DNA instead of deoxycytidine triphosphate [132–134].

A series of phase II studies, none including more than 41 evaluable patients, has investigated the activity of gemcitabine as monotherapy for MBC. In chemotherapy-naïve patients, response rates vary between 14.3 and 37 %, whereas in anthracycline- and taxane-pretreated patients, response rates between 0 and 23 % where observed. In pretreated patients, activity as single agent is modest, but the toxicity profile is favorable [135].

Due to the lack of overlapping toxicities and the expectation of noncross resistance, gemcitabine has been investigated in combination regimens, e.g., with taxanes. In a registrational

phase III first-line trial, Albain et al. compared paclitaxel as a single agent (175 mg/m^2, q3w) to the combination of paclitaxel and gemcitabine (175 mg/m^2, d1/1250 mg/m^2, d1, 8; q3w). The trial demonstrated a significant 3-month improvement in OS, the trial's primary endpoint (18.6 vs. 15.8 months, $p = 0.048$) as well as response rates (41.4 vs. 26.2 %, $p < 0.001$) and TTP [59, 136]. Toxicity, mainly in terms of myelosuppression was also significantly increased. Today, three-weekly paclitaxel can no longer be considered a standard, as weekly schedules have demonstrated significantly improved response rates, TTP, and overall survival [49]. In a head-to-head comparison of docetaxel plus gemcitabine versus docetaxel plus capecitabine, a regimen which has provided a significantly improved OS over single agent docetaxel, no significant differences in terms of efficacy or toxicity could be discovered [136, 137]. Based on the phase III trial, gemcitabine has been approved by the FDA and EMA in combination with paclitaxel for the first-line treatment of metastatic breast cancer after failure of prior adjuvant anthracycline-containing therapy, unless anthracyclines are contraindicated (Table 20.6). In addition, gemcitabine is used in the treatment of ovarian cancer, pancreatic cancer, and non-small-cell lung cancer.

Trials trying to demonstrate a benefit from the addition of gemcitabine to adjuvant regimens have failed thus far.

Side effects of gemcitabine include nausea and vomiting, myelosuppression, pulmonary toxicity including ARDS, hepatotoxicity (transaminitis), haematuria, rash, hemolytic uremic syndrome (HUS), capillary leak syndrome, and posterior reversible encephalopathy. Gemcitabine exacerbates toxicity of radiotherapy and administration should be avoided within 7 days of radiotherapy.

20.2 Targeted Therapies

20.2.1 Human Epidermal Growth Factor Receptor 2 (HER2)-Targeted Therapies

20.2.1.1 Trastuzumab

The Human Epidermal Growth Factor Receptor 2 gene (HER2), a member of the erbB epidermal growth factor receptor tyrosine kinase family, has been independently described by several groups in the mid 1980s [138–141] (Table 20.7).

HER2 is also referred to as HER2/neu or ErbB-2. Shortly thereafter, Slamon and colleagues provided evidence that the HER2 gene was overexpressed and amplified in 20–30 % of patients with EBC. They further found HER2 overexpression/amplification to be a strong and independent prognostic factor in this setting [142, 143]. Several groups, including researchers at Genetech Inc. have developed murine monoclonal antibodies against the extracellular domain of HER2, which proved to be potent inhibitors of cell growth in HER2 overexpressing human breast cancer xenografts. The most potent of these antibodies, muMAB 4D5, was in turn humanized to minimize the generation of human anti-mouse immune responses possibly neutralizing its effects in humans. The resulting chimeric antibody was called trastuzumab and entered clinical trials. Since then an unprecedented success story in the therapy of breast cancer has begun [144].

In a multinational phase II trial 222 patients who had received one or two chemotherapies for MBC were treated with trastuzumab monotherapy. The response rate was 15 % with a median duration of response of 9.1 months within the intention to treat population. However, in patients with HER2 ampflification the response rate was 19 % compared to 0 % in patients who were found to be negative by fluorescence in situ hybridization (FISH) [145]. In a phase II study carried out in the first-line setting the response rate for single agent trastuzumab amounted to 26 % (35 % in HER2 amplified) [146].

A pivotal first-line phase III trial randomized 469 HER2 overexpressing patients to either chemotherapy alone or in combination with trastuzumab. Patients who had received anthracyclines in the adjuvant setting received paclitaxel 175 mg/m^2 three-weekly, the remaining were mainly treated with doxorubicin/cyclophosphamide, both for six cycles. The addition of trastuzumab significantly improved response rates (32 % vs. 50 %, $p < 0.001$), PFS (4.6 months vs. 7.4 months, $p < 0.001$) and overall survival (20.3 months vs. 25.1 months, $p = 0.046$). Over 70 % of patients received open-label trastuzumab as one of the subsequent therapies, which might have obscured the real survival benefit from trastuzumab. In the subgroup of patients treated with paclitaxel combined with trastuzumab, response rates were increased from 17 to 41 % and PFS from 3 months to 6.9 months [147]. An additional phase II study ($n = 186$) provided further evidence of the efficacy of trastuzumab in combination with docetaxel. The addition of trastuzumab to docetaxel in the first-line treatment of patients with HER2-positive breast cancer improved response rates from 34 to 61 % ($p = 0.0002$) as well as overall survival from 22.7 to 31.2 months. This OS benefit was observed despite 57 % crossing over to trastuzumab upon progression as part of the trial. In fact, OS in patients who did not cross over to trastuzumab was merely 16.6 months [148]. The combination of trastuzumab and vinorelbine proved equally effective as trastuzumab plus docetaxel in the randomized phase III HERNATA trial, of which the first has a favorable tolerability [84]. This combination has not been approved by the FDA or EMA.

Table 20.7 HER2-directed therapies

Anti-Her2 Agent	Trade name® (examples)	Mode of action	Dosing	Interactions	Selected side effects
Trastuzumab	Herceptin	Humanized monoclonal antibody targeting the extracellular domain of the HER2 protein Inhibition of HER2-signalling, antibody-dependent cellular cytotoxicity (ADCC)	2 mg/kg body weight per week after a loading dose of 4 mg/kg or 6 mg/kg body weight per week after a loading dose of 8 mg/kg; 600 mg absolute as a 5 min subcutaneous injection (EMA, EU)		Cardiotoxicity, infusion reactions, skin rash, flu-like symptoms, headache, diarrhea, nausea, vomiting, fatigue, abdominal pain, pulmonary toxicity including cough, dyspnea, interstitial pneumonitis, ARDS, exacerbation of chemotherapy-induced neutropenia, anemia, myalgia Trastuzumab can cause fetal harm (e.g., oligohydramnion, pulmonary hypoplasia, etc.)
Lapatinib	Tykerb (USA), Tyverb (EU)	HER-1 and HER-2 receptor tyrosine kinase inhibitor (TKI) Inhibits autophosphorylation of HER1 (EGFR) and HER2 and downstream signalling	1250 mg daily p.o. in combination with capecitabine (2000 mg/m^2 d 1–14, q3w); 1500 mg p.o. daily in combination with letrozol 1000 mg p.o. daily in combination with trastuzumab	Interaction with inhibitors and inducer of CYP3A4 and CYP2C8	Diarrhea, nausea, vomiting, skin rash, erythema multiforme, fatigue, arthralgia, cardiotoxicity, headache, abdominal pain, loss of weight, hepatotoxicity, e.g., elevation of liver enzymes, interstitial lung disease, paronychia Lapatinib can cause fetal harm. Lapatinib should be administered with caution to patients who have or may develop prolongation of QTc
Pertuzumab	Perjeta	Humanized monoclonal antibody directed against the dimerization domain of HER2. Pertuzumab inhibits the interaction of HER2 with other HER family members. Ligand-activated signaling from HER2:HER1 and HER2:HER3 heterodimers is thereby inhibited	420 mg pertuzumab (absolute) q3w following a loading dose of 840 mg (absolute)		Cardiotoxicity (left ventricular dysfunction), infusion reactions, anaphylactic reactions, diarrhea, nausea, vomiting, fatigue, skin rash, loss of weight, neutropenia, febrile neutropenia, elevated liver enzymes
Trastuzumab-Emtansin (T-DM1)	Cadcyla	Antibody–drug conjugate consisting of the humanized monoclonal antibody trastuzumab, directed against HER2 covalently linked to emtansine (DM-1), a potent anti-microtubule agent. T-DM1 is internalized upon binding to the HER2 receptor on HER2 overexpressing cells and the cytotoxic agents is released intracellularly	3.6 mg/kg body weight q3w	CYP3A4 inhibitors	Thrombocytopenia, hepatotoxicity, elevation of liver enzymes, hyperbilirubinemia, nodular regenerative hyperplasia, pulmonary toxicity (e.g., interstitial lung disease, pneumonitis), infusion related reactions, anaphylaxis, cardiotoxicity, peripheral neuropathy Can cause embryofetal death or birth defects
Afatinib	Giotrif, Gilotrif		40 mg p.o./d (max. 50 mg/d) Currently approved for lung cancer only. Phase II/III trials in breast cancer negative	P-gp inhibitors	Diarrhea, interstitial lung disease, bullous and exfoliative skin disorders, hepatoxicity, hepatic toxicity, keratitis Embryofetal toxicity

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As a result of these trials trastuzumab has been approved by the FDA in 1998 for the first-line therapy of HER2-positive breast cancer in combination with paclitaxel or as a single agent as second or third-line therapy. In Europe trastuzumab was approved by the EMA in 2000 and is now registered for first-line therapy in combination with paclitaxel and docetaxel or as a single agent after two prior chemotherapies for metastatic disease including anthracyclines and taxanes. In Europe, trastuzumab has consecutively also been approved for the treatment of metastatic disease in combination with anastrozol in HER2- and HR-positive disease for patients without prior trastuzumab therapy for MBC (see below), as well as in combination with lapatinib, a TKI directed against epidermal growth factor receptor (EGFR) and HER2 for patients with HER2-positive and HR-negative disease having failed prior therapy with trastuzumab in combination with chemotherapy [149, 150].

A randomized phase III trial compared the combination of anastrozol and trastuzumab to anastrozol alone in trastuzumab-naïve patients who have had no prior therapy for metastatic HER2- and ER-positive breast cancer. Response rates as well as PFS were significantly improved in the combination arm, however, at a low level. The ORR was 20.3 % in the combination arm compared to 6.8 % in the monotherapy arm ($p = 0.018$) and PFS was 4.8 months compared to 2.8 months ($p = 0.0016$), respectively. OS did not show a significant improvement (23.9 vs. 28.5, $p = 0.33$) [150].

Several strategies have been investigated for patients progressing on or after treatment with trastuzumab. In a phase II trial ($n = 156$) conducted by the German Breast Group, patients who had progressed after prior first-line therapy containing taxane and trastuzumab were randomized to either capecitabine alone or in combination with trastuzumab. The trial was prematurely closed due to slow accrual. However, the "treatment beyond progression" arm demonstrated significantly higher response rates (48 % vs. 27 %, $p = 0.01$) and a prolonged TTP (8.5 months vs. 5.8 months, HR 0.69; $p = 0.03$). The OS was longer in patients treated with capecitabine plus trastuzumab. However, this observation did not reach statistical significance (25.5 months vs. 20.4 months, $p = 0.26$) [151].

There is further evidence for the strategy to continue treatment with trastuzumab after disease progression from a phase III trial investigating the combination of trastuzumab and lapatinib versus lapatinib alone in this setting. An overall survival benefit was seen in patients with HER2-positive and HR-negative disease [149, 152].

Further treatment options for patients progressing on or after treatment with trastuzumab will be discussed in subsequent sections on lapatinib, pertuzumab and T-DM1.

Based on its activity against metastatic HER2-positive breast cancer, several studies analyzed the benefit of trastuzumab in the (neo)adjuvant setting.

In early randomized neoadjuvant trials, like the NOAH trial, pathologic complete response rates showed a twofold increase due to trastuzumab, resulting in unprecedented pCR rates, which were confirmed in additional neoadjuvant trials, like TECHNO and GeparQuattro [153–157]. The achievement of a pCR was strongly correlated with survival in those trials, which have reported survival.

One of the pivotal trials in the adjuvant setting was the HERA trial ($n = 5099$). It started in 2001 as an international multicenter trial and randomized patients to either 1 or 2 years of trastuzumab or to observation alone after completion of standard neoadjuvant or adjuvant chemotherapy in women with HER2-positive, node-positive, or high-risk node-negative breast cancer (NCT00045032). It was shown that after a median follow-up of 8 years the addition of one year of trastuzumab significantly reduced the relative risk for death by 24 % (82.7 % vs. 77.4 %%; HR 0.76, $p = 0.0005$) in the intention to treat population. 8-year DFS was 71.2 % versus 64.8 % (HR 0.76, $p < 0.0001$) in the ITT analysis. These benefits were observed despite 52.1 % of patients in the observation arm crossing over to trastuzumab prior to a DFS event after the first results of the trial were released [158, 159]. In contrast, continuing trastuzumab for 2 years instead of one did not improve outcomes any further [159].

At the same time, two large randomized adjuvant trials in North America investigated the efficacy of 12 months of trastuzumab, added to a sequential adjuvant regimen consisting of doxorubicin/cyclophosphamide (AC) followed by paclitaxel. Trastuzumab was either started concomitantly to weekly[1] or three-weekly[2] paclitaxel or sequentially after completion of chemotherapy[3] and compared to the same adjuvant regimens without trastuzumab. The trials were very similar in design and the FDA and National Cancer Institute (NCI) allowed a joint efficacy analysis of both trials. The definitive OS analysis showed that adjuvant trastuzumab led to a relative reduction in mortality by 37 %, accompanied by a relative improvement in DFS by 40 %. 10-year OS rates improved from 75.2 to 84 % (HR 0.63, $p < 0.001$) and DFS rates from 62.2 to 73.7 % (HR0.60, $p < 0.001$), respectively [160, 161]. The N9831 trial also compared concomitant (starting with paclitaxel) to sequential adjuvant trastuzumab. The concomitant arm revealed a 5-year DFS rate of 84.4 % compared to 80.1 % in the sequential arm (HR 0.77, $p = 0.02$). However, this did not meet the prespecified statistical criteria to be significant in this interim analysis [162]. Today, the concomitant administration of trastuzumab to paclitaxel in sequential regimens is a common practice and a standard of care based on these results.

[1] in NCCTG N9831 and NSABP B31.
[2] in NSABP B31.
[3] in N9831.

The Breast Cancer International Research Group 006 phase III trial (BCIRG 006; $n = 3222$) randomized patients to either AC-T with (AC-TH) or without trastuzumab (AC-T) or TCbH (docetaxel, carboplatin and trastuzumab) [21]. Both trastuzumab containing regimens were superior to AC-T in terms of DFS. There was a small nonsignificant numerical difference in DFS events between AC-TH and TCbH in favor of AC-TH. However, this was counterbalanced by a fivefold increase of congestive heart failure at 10 years (21 vs. 4) and an increased risk of treatment-associated leukemia (8 vs. 1) in the AC-TH arm. [21, 30] The trial was not powered to detect differences between the AC-TH and the TCbH arm.

In the FinHer trial HER2-positive patients ($n = 232$) were randomized to receive trastuzumab or not for 9 weeks in parallel to either three cycles of docetaxel or vinorelbine, followed by $FE_{100}C$ as adjuvant therapy. Despite the short duration of therapy, the addition of trastuzumab led to an improvement in DFS from 78 to 89 % at 3 years (HR 0.42, $p = 0.01$) and a nonsignificant improvement of 3-year OS from 89.7 to 96.3 % (HR 0.41, $p = 0.07$) [163].

The French PHARE trial investigated whether a shorter duration of trastuzumab was enough. In this non-inferiority trial 6 months of trastuzumab failed to meet the criteria to prove non-inferiority compared to 1 year of adjuvant trastuzumab, which remains the current standard of care [164]. The HERA trial additionally compared one versus 2 years of adjuvant trastuzumab. No significant benefit was seen from continuing trastuzumab beyond 1 year [165].

As a consequence of these data, the FDA first granted approval to adjuvant trastuzumab in 2006. It is currently labeled as part of a regimen consisting of doxorubicin, cyclophosphamide, either paclitaxel, or docetaxel or in combination with docetaxel and carboplatin or as a single agent following multimodality anthracycline-based therapy. In 2006, trastuzumab was approved as adjuvant therapy for HER2+ EBC in Europe. In addition, the EMA recently approved a subcutaneous formulation of a fixed dose of trastuzumab based on the neoadjuvant phase III HannaH trial [166].

One of the main side effects of trastuzumab is cardiac dysfunction. Trastuzumab-related cardiotoxicity is distinct from type 1 cardiotoxicity observed with anthracyclines, in such a way that there is no dose/effect relationship and it is mostly reversible upon discontinuation of therapy. HER2 is also expressed on cardiomyocytes and is thought to be implicated in the repair of cell damage.

The definition of cardiac events slightly differed within the large randomized adjuvant trials. However, the trials report results within the same order of magnitude. After 8-years of follow-up the HERA trial reported rates of severe congestive heart failure (CHF, NYHA III & IV) of 0.8 % in the trastuzumab containing arms (1- and 2-years, sequentially) versus 0 % in the control arm. The rate of confirmed significant drops in LVEF (>10 % and below 50 %) was 7.2 % for 2 years and 4.1 % versus 0.9 % in the 1 year and control group, respectively. Acute recovery occurred in more than 80 % of patients [167]. In a long-term safety analysis NSABP B31 and N9831 reported cardiac events mainly defined as NYHA III & IV CHF in 4.0 and 3.4 % for the concomitant arms compared to 1.3 and 0.6 % in the control arms, again with a high rate of spontaneous recovery upon cessation of trastuzumab [168, 169]. One point worthy of note is that 6.9 % of patients in NSABP B31 had unacceptably low post-AC LFEV measurements, precluding the start of trastuzumab therapy altogether [168]. The rate of cardiac death within the trials was very low and did not significantly differ between experimental and control arms. It is mandatory to assess left ventricular ejection fraction (LVEF) prior to initiation of trastuzumab and at regular intervals during treatment.

Apart from infrequent infusion reactions, which are easily controlled, trastuzumab is well tolerated, and especially, hematologic toxicities are negligible. Another rare but potentially serious adverse reaction is pulmonary toxicity, e.g., in the form of interstitial pneumonitis.

20.2.1.2 Lapatinib

Lapatinib is a small molecule dual tyrosine kinase inhibitor (TKI) directed against epidermal growth factor receptor (EGFR; syn. HER1) and HER2. Lapatinib inhibits receptor signaling by binding to the ATP-binding pocket of the HER1/HER2 protein kinase domain, preventing self-phosphorylation and subsequent activation of the signal cascade. Therefore, it could potentially abrogate signaling from constitutively active HER2 receptors, e.g., caused by shedding of the extracellular domain of the HER2 receptor, which cannot be inhibited by trastuzumab and in addition from HER1/HER2 heterodimers.

In a phase III study, the combination of lapatinib and capecitabine compared to capecitabine alone resulted in a prolonged TTP of 6.2 versus 4.3 months (HR 0.57, $p < 0.001$) and an increased response rate of 23.7 % compared to 13.9 % (OR 1.9, $p = 0.017$). OS in the ITT population was not significantly improved, however, the trial was stopped early as it met prespecified criteria for superiority and crossover to the combination was offered to patients in the control arm. The benefit was achieved without an increase in serious toxic effects or symptomatic cardiac events in patients with normal left ventricular ejection fraction at baseline [170–172]. Based on this trial, lapatinib was approved in combination with capecitabine in 2006 for the treatment of patients with advanced or metastatic HER2-positive breast cancer, who had received prior therapies, including anthracyclines, taxanes and trastuzumab (second or third line). In a direct comparison of capecitabine

plus either lapatinib or trastuzumab as part of a large randomized phase III trial (CEREBEL), however, the lapatinib-based combination was inferior to trastuzumab plus capecitabine [173]. An attempt to prove benefit of lapatinib in patients with HER2-negative MBC in a large randomized phase III trial based on its property to inhibit EGFR in addition to HER2 failed [174].

Subsequently, the indication for lapatinib has been expanded in the US and Europe to include the combination of lapatinib and letrozol in HER2 and HR-positive patients. However, the underlying phase III trial was run in the first-line setting and patients had neither been pretreated with trastuzumab nor an aromatase inhibitor [175, 176]. The combination of lapatinib plus letrozol was tested against letrozol alone and demonstrated a significantly improved PFS and ORR, yet, without an improvement in OS. There are no comparisons of lapatinib (or trastuzumab) plus an AI versus trastuzumab plus chemotherapy, for which a clear survival benefit has been demonstrated in first-line therapy. This combination might be an alternative for patients who are not candidates for chemotherapy or with a very low disease burden, although the efficacy is lower than the combination of trastuzumab and chemotherapy. In Europe, the indication for lapatinib has also been expanded to include the combination of lapatinib and trastuzumab for trastuzumab refractory HER2-positive, HR-negative patients. A randomized phase III trial showed a significant improvement in OS from 9.5 to 14 months (HR 0.74, $p = 0.026$), which was restricted to the HR-negative subgroup (HR 0.68, $p = 0.012$) [149, 152]. However, today there are other compelling treatment options after progression on or after treatment with trastuzumab (see below).

The most common side effect, which leads to a discontinuation of lapatinib is diarrhea. Skin rash and elevation of liver enzymes are further common side effects of lapatinib. Although rarely life-threatening, the physical and psychosocial distress associated with these dermatologic reactions may reduce compliance with EGFR inhibitors [177–179]. There are data suggesting that the occurrence and severity of rash might correlate with clinical response [180], but the final confirmation of this correlation is still pending. Cardiac toxicity is a major concern in drugs targeting HER2 based on the data from trastuzumab. Perez et al. analyzed cardiac toxicity in 3689 patients treated with lapatinib within phase I–III trials. There was a 1.3 % incidence of symptomatic and asymptomatic decreases in LVEF in patients treated with lapatinib compared to 0.7 % in patients from comparator arms within these trials [181]. Thus, the cardiac toxicity of lapatinib appears to be comparably small [182].

In the neoadjuvant setting, the NeoALTTO study demonstrated promising results for lapatinib in combination with trastuzumab and chemotherapy. The dual HER2 blocking strategy lead to an almost twofold increase in pCR rates compared to chemotherapy plus trastuzumab alone [181, 183]. In its adjuvant counterpart, the ALTTO trial ($n > 8000$), however, the dual inhibition of HER2 by trastuzumab and lapatinib disappointingly did not significantly improve DFS or OS [184]. The experimental arm investigating chemotherapy and lapatinib as the single anti-HER2 agent was closed early due to inferiority to the standard arm of chemotherapy plus trastuzumab, an observation in keeping with results from several neoadjuvant trials [183, 185–187].

20.2.1.3 Pertuzumab

Pertuzumab (Perjeta®) is a fully humanized monoclonal antibody directed against the dimerization domain of HER2, preventing homo- as well as heterodimerization of HER2 with other HER family members, including the EGFR, HER3 and HER4 [188]. As a result, pertuzumab inhibits downstream signaling of two key signal pathways regulating cell growth and survival: the mitogen-activated protein kinase (MAPK) pathway and the phosphatidylinositol-3-kinase (PI3K) pathway. Inhibition of these signaling pathways can result in cell growth arrest and apoptosis [189]. In addition, it is thought to contribute to antibody-dependent cell-mediated cytotoxicity (ADCC).

The efficacy and safety of pertuzumab have been investigated in two phase II and one phase III trial in MBC. The phase II trials included patients who had received at least three prior lines of chemotherapy and had progressed on trastuzumab. Patients received pertuzumab plus trastuzumab without chemotherapy. In BO17929 ($n = 66$), the combination demonstrated significant antitumor activity with a response rate of 24.2 % and a median PFS of 5.5 months [190]. To determine if the observed effect was a result of the combination of pertuzumab and trastuzumab or mainly pertuzumab alone, a second cohort was recruited which was initially treated with single agent pertuzumab with trastuzumab added in upon progression of disease. Results for the monotherapy with pertuzumab were disappointing (ORR 3.4 %) but activity could be recovered by the addition of trastuzumab (ORR 17.9 %), providing solid evidence that the clinical benefit is only obtained by the combination of the two antibodies [191].

The main evidence for the efficacy of pertuzumab plus trastuzumab was obtained from the pivotal CLEOPATRA trial. In this large randomized, placebo-controlled phase III trial, patients were randomized to docetaxel plus trastuzumab and either pertuzumab or placebo as first-line therapy for HER2-positive breast cancer. Patients were allowed to have received prior (neo)adjuvant chemotherapy with or without trastuzumab if the disease-free interval was more than 12 months. Response rates in the pertuzumab group were significantly increased from 69.3 to 80.2 % ($p = 0.001$) as was median PFS (Δ 6.1 months; HR 0.62, $p < 0.001$). The effect size observed in patients who had

received prior trastuzumab was identical. However, even more striking was an unprecedented improvement of OS by 15.7 months from 40.8 to 56.6 months (HR 0.68, $p < 0.001$) [192–194]. These results have clearly defined the new standard for the first-line treatment of HER2-positive metastatic breast cancer. In Europe and the US, pertuzumab has been approved in combination with docetaxel and trastuzumab for the treatment of patients with HER2-positive advanced breast cancer, who have not received prior anti-HER2 or chemotherapy for metastatic disease.

In addition, two neoadjuvant phase II trials, the NeoSphere and the TRYPHAENA trial demonstrated superior pCR rates for the dual blockade with pertuzumab and trastuzumab. Taken together with the large survival benefit in metastatic disease, these data have led to the approval of pertuzumab in combination with trastuzumab and chemotherapy in the neoadjuvant setting, based on pCR as a possible surrogate for survival.

In the Neosphere trial, 417 patients with HER2 + primary breast cancer and tumors larger than 2 cm were randomized to four cycles of docetaxel in combination with either trastuzumab or pertuzumab alone or the combination of both. A chemotherapy-free treatment option consisting of the combination of trastuzumab and pertuzumab was also investigated. Patients receiving docetaxel in combination with pertuzumab and trastuzumab achieved a pCR rate of 45.8 %, which was significantly higher than that in the docetaxel/trastuzumab group (29 %; $p = 0.0063$). The chemotherapy-free treatment arm achieved a pCR rate of 16.8 % (31 % for HER2+/HR− patients) and the docetaxel/pertuzumab combination 23 % [195].

The TRYPHAENA trial was designed to evaluate the safety and tolerability of trastuzumab and pertuzumab in combination with either anthracycline-based or carboplatin-based neoadjuvant chemotherapy. 225 patients were randomized to three cycles of FEC followed by three cycles of docetaxel and either trastuzumab and pertuzumab concurrently with the entire adjuvant chemotherapy or beginning with docetaxel. The third arm received a combination of docetaxel (75 mg/m^2), carboplatin (AUC5), trastuzumab, and pertuzumab. PCR rates (ypT0 ypN0) ranged from 45.3 to 51.9 %, with the highest pCR rate observed in the anthracycline-free treatment arm. The FDA and EMA have now approved pertuzumab in combination with chemotherapy for neoadjuvant therapy in HER2-positive patients with a high risk of recurrence [196].

The main adverse reactions observed with pertuzumab (in combination with trastuzumab and chemotherapy) are diarrhea, neutropenia, febrile neutropenia and asthenia. Cardiac safety is a main concern in HER2-directed therapy, especially in dual HER2-blockade. However, the addition of pertuzumab to trastuzumab in the available trials only marginally increased the rates of cardiac events. In the CLEOPATRA trial, the rate of symptomatic congestive heart failure was 1.8 % in the combination group compared to 1.0 % in patients only receiving trastuzumab. The rate of decline of LVEF by more than 10 % and below the 50 % threshold was also slightly higher (6.6 % vs. 3.8 %), however, the majority of patients recovered spontaneously after cessation of treatment with pertuzumab and trastuzumab [197, 198].

20.2.1.4 Ado-Trastuzumab Emtansine, T-DM1

T-DM1 (Kadcyla®) is a novel antibody–drug conjugate composed of emtansine covalently linked to trastuzumab. Emtansine, a maytansine derivative, is a highly potent anti-microtubule agent. Trastuzumab specifically directs the linked emtansine against HER2-overexpressing cells, thereby minimizing exposure of normal tissue and increasing the therapeutic window.

The EMILIA trial randomized 991 patients, who had previously been treated with a taxane and trastuzumab, to either lapatinib/capecitabine or T-DM1. Compared to capecitabine and lapatinib, T-DM1 significantly prolonged the median PFS from 6.4 to 9.6 months (HR 0.65, $p < 0.001$) as well as overall survival from 25.1 to 30.9 months (HR 0.68, $p < 0.001$). Moreover, T-DM1 also demonstrated a lower overall toxicity and was generally well tolerated. Rates of adverse events of grade ⩾3 were higher for lapatinib/capecitabine than for patients treated with T-DM1 (57 % vs. 41 %) [199, 200]. Based on the EMILIA study, the FDA and EMA granted T-DM1 approval in 2013 for the treatment of patients with HER2-positive metastatic breast cancer who have previously been treated with a taxane and trastuzumab. Patients must have received prior therapy for metastatic disease or must have relapsed within 6 months after completing adjuvant therapy.

An additional large phase III trial (TH3RESA) comparing T-DM1 to a physician's choice of treatment in patients, who had previously been treated with at least two lines of HER2-directed therapies for advanced disease, including trastuzumab, lapatinib and a taxane provides further evidence for the efficacy and tolerability of T-DM1. In this heavily pretreated population, with more than half of patients having received at least three prior lines of therapy for advanced disease, T-DM1 significantly prolonged PFS from 3.3 to 6.2 months (HR 0.528, $p < 0.0001$) as well as OS from 15.8 to 22.78 months (HR 0.68, $p = 0.0007$) [201, 202].

The most prominent grade 3/4 adverse events of T-DM1 are thrombocytopenia and elevated liver enzymes. Cardiac events were low in both trials.

Based on data from EMILIA and TH3RESA, T-DM1 is now the standard of care as second-line therapy of HER2-positive MBC, as well as in later lines if prior therapy did not include T-DM1 [203].

T-DM1 does also appear to have some activity in CNS metastasis. A subgroup analysis of the EMILIA trial focusing on patients with brain metastasis at baseline demonstrated a longer OS in patients treated with T-DM1 (26.8 vs. 12.9 months; HR 0.38, $p = 0.008$) [204]. In addition, several case series document response of brain metastases to T-DM1 [205, 206].

Given the benefit from the addition of pertuzumab to trastuzumab plus docetaxel observed in CLEOPATRA, a large randomized phase III trial, the MARIANNE trial, set to investigate the combination of T-DM1 and pertuzumab in the first-line setting. MARIANNE randomized 1095 women with HER2-positive MBC to either trastuzumab plus a taxane or to T-DM1 plus either placebo or pertuzumab. Surprisingly, none of the treatment arms showed a significantly improved PFS (13.7, 14.1, and 15.2 months, respectively) [207] and OS data are still immature. Thus, standards for first and second-line treatment choices remain unaffected.

The role of T-DM1 in the (neo)adjuvant setting is currently scrutinized in several trials. The ADAPT trial recently reported a pCR rate (ypT0/is ypN0) of 41 % in HER2- and HR-positive patients treated with only four cycles of T-DM1 (± endocrine therapy) [208].

20.2.1.5 New HER2-Directed Agents and Combinations Under Investigation

Currently a new generation of HER2-directed TKIs is under investigation. The most extensively studied members are neratinib and afatinib, both irreversible inhibitors, neratinib directed against HER1, −2 and −4, and afatinib a pan-HER inhibitor. For both agents, diarrhea is a main dose-limiting toxicity [199].

Afatinib has failed to demonstrate a benefit in phase II and III trials in breast cancer (LUX-Breast 1 and 3) and is unlikely to gain approval for HER2-positive MBC [209, 210].

Neratinib has yielded some positive data in clinical trials and has recently demonstrated to prolong invasive disease-free survival (iDFS) in the ExteNET trial (NCT00878709), which randomized patients with HER2-positive PBC within 1 year after completion of adjuvant trastuzumab to either 1 year of neratinib or placebo. IDFS was significantly improved in the group treated with neratinib (HR 0.73, $p = 0.023$), an effect that was exclusively observed in the HR-positive subgroup (HR 0.57, $p = 0.004$) [211]. These data are in contrast to data from the extended (2 years) trastuzumab arm in the HERA trial [159].

Based on the hypothesis, that downstream activation of the PI3K-Akt-mTOR pathway can be responsible for trastuzumab resistance, preclinical data have demonstrated that resistance to trastuzumab can be reversed by the addition of everolimus, an oral mTOR inhibitor blocking the PI3K pathway (see also Table 20.8) [212]. The combination of chemotherapy, trastuzumab, and everolimus has been investigated in two phase III trials for MBC, BOLERO-1, and BOLERO-3. The two trials demonstrated no or only a marginal benefit in terms of DFS [213, 214]. Nonetheless, it was indicated that HR-negative patients might derive more benefit from adding everolimus to trastuzumab. However, at this point there is no role for everolimus in the therapy of HER2-positive metastatic breast cancer. Several PIK3CA inhibitors such as alpelisib (BYL719), taselisib, and pilaralisib are currently being investigated in HER2+ breast cancer [65]. The addition of bevacizumab, a recombinant humanized monoclonal antibody against VEGF, to trastuzumab and chemotherapy has not improved outcomes in early or metastatic breast cancer in two large randomized phase III trials (AVAREL, BETH) [80, 81].

20.2.2 Antiangiogenic Agents

Neo-angiogenesis is one of the hallmarks of cancer implicated in tumor growth, invasion, and metastasis. It is a prerequisite for the progression of solid tumors. Inhibition of tumor angiogenesis is therefore regarded as an attractive therapeutic target. Table 20.9 summarizes antiangiogenic therapies used or investigated in breast cancer.

20.2.2.1 Bevacizumab

Bevacizumab (Avastin®) is a recombinant humanized monoclonal IgG1 antibody that binds to vascular endothelial growth factor A (VEGF-A), one of the most potent pro-angiogenic factors and inhibits its biologic activity in vitro and in vivo assay systems [215]. Bevacizumab prevents the interaction of VEGF with its receptors (Flt-1 and KDR) on the surface of endothelial cells, which normally leads to endothelial cell proliferation and new blood vessel formation. Administration of bevacizumab to xenotransplant models of colon cancer in mice caused reduction of microvascular growth and inhibition of metastatic disease progression. Therapies that inhibit VEGF may have multiple effects on angiogenesis and tumor growth, most importantly, reducing the tumor's blood supply, preventing the development of new blood vessels in the tumor and facilitating the delivery of chemotherapy to the tumor cells, which can be explained by the concept of "normalization of tumor vasculature" [216–218].

Based on preclinical findings demonstrating activity of bevacizumab in breast cancer, bevacizumab was tested in MBC initially as monotherapy. Cobleigh et al. evaluated the safety and efficacy in a phase I/II dose escalation trial in patients with previously treated MBC [219]. The overall response rate was 9.3 % (confirmed response rate, 6.7 %) and the median duration of confirmed response was

Table 20.8 Endocrine therapies and targeted agents used in combination with endocrine therapy

Agent	Trade name® (examples)	Mode of action	Dosing	Interactions	Selected adverse effects
Tamoxifen	Nolvadex	Selective estrogen receptor modulator. Tamoxifen is a prodrug that needs to be metabolized into several active metabolites including endoxifen	20 mg daily p.o.	Interaction with inhibitors of CYP2D6 Strong inhibitors of CYP2D6 should be avoided as they might lead to significantly reduced levels of active metabolites May increase anticoagulant effects if used in combination with coumarin-type anticoagulants	thromboembolic events, raised blood triglyceride levels, vaginal bleeding, endometrium hyperplasia, endometrial polyps and endometrial cancer, headache, vaginal discharge and dryness, pruritus vulvae, fluid retention, hot flushes, menopausal symptoms, hair thinning, mood disturbances, visual disturbances, including corneal changes, retinal vein thrombosis, retinopathy and cataracts, fatigue, elevation of liver enzymes, fatty liver may cause fetal harm
Exemestan Anastrozol Letrozol	Aromasin Arimidex Femara	Steroidal irreversible aromatase inhibitor Nonsteroidal AI Nonsteroidal AI	25 mg daily p.o. 1 mg daily p.o. 2.5 mg daily p.o.	CYP450 enzymes	Loss of bone mineral density, osteoporosis, fractures, fatigue, raised blood triglyceride, hypercholesterinemia, vaginal dryness, vaginal bleeding, headache, hot flushes, increased sweating, night sweats, menopausal symptoms, arthralgia, headache, nausea, vomiting, skin rash, hair thinning, elevation of liver enzymes
Goserelin Leuprorelin	Zoladex Enantone Gyn	GnRH (gonadotropin-releasing hormone)- agonist	3.6 mg q4w s.c. (the 10.8 mg q12w dose is only approved for the treatment of prostate cancer) 3.75 mg q4w s.c. or IM (not US)	None	Fatigue, hot flushes, increased sweating, loss of bone mineral density, osteoporosis, hypertension, hypotension, headache, arthralgia, menopausal symptoms, decreased libido, vaginitis, seborrhea, peripheral edema, emotional lability, depression, hypersensitivity reactions
Fulvestrant	Faslodex	Selective estrogen receptor downregulator	500 mg q4w IM with an additional dose on day 15 of the first cycle	None	Nausea, vomiting, constipation, diarrhea, abdominal pain, headache, back pain, hot flushes, sore throat, vaginal bleeding, thromboembolic events Due to its intramuscular injection, fulvestrant should be used with great caution in patients with bleeding disorders, thrombocytopenia or taking anticoagulants
Everolimus	Afinitor	An oral mTOR inhibitor targeting mTORC1, one of the two mTOR complexes	10 mg daily p.o.	CYP3A4, p-GP; inhibitors and inducers should be avoided	Hyperglycemia, hypertriglycerinemia, hypercholesterinemia, noninfectious pneumonitis, infections, infestations, oral ulcerations, renal impairment, anemia, lymphopenia, neutropenia, thrombocytopenia, impaired wound healing. Avoid live vaccines and close contact with those who have received live vaccines. Can cause fetal harm

(continued)

Table 20.8 (continued)

Agent	Trade name® (examples)	Mode of action	Dosing	Interactions	Selected adverse effects
Palbociclib (other cdk4/6 inhibitors in clinical development are ribociclib and abemcaciclib)	Ibrance	an oral cdk4/6 inhibitor	125 mg once daily taken 21 days followed by 7 days off-treatment	CYP3A inhibitors and inducers (should be avoided)	neutropenia, leukopenia, infections, febrile neutropenia, fatigue, nausea, anemia, stomatitis, headache, diarrhea, thrombocytopenia, constipation, alopecia, vomiting, rash, and decreased appetite, pulmonary embolism can cause fetal harm

These highlights do not include all the information needed to use the respective drugs safely and effectively. See full prescribing information for all information needed to use these agents safely. We do not take responsibility for the correctness of the content

Table 20.9 Antiangiogenic agents

Agent	Trade name	Mode of action	Dosing	Interactions	Selected adverse effects
Bevacizumab	Avastin	Humanized monoclonal anti-VEGF a monoclonal IgG1 antibody	10 mg/kg q2w or 15 mg/kg q3w IV (for breast cancer) in combination with paclitaxel or capecitabine as first-line treatment of MBC EMA approval, not approved for breast or ovarian cancer by the FDA		Proteinuria, hypertension, hypertensive crisis, hemorrhage, arterial and venous thromboembolic events, surgery and wound healing complications, gastrointestinal perforations and fistulae, reversible posterior leukoencephalopathy syndrome (RPLS), fatigue, nausea, vomiting, mucositis, stomatitis, fatigue, congestive heart failure, may increase risk of osteonecrosis of the jaw. Bevacizumab may cause fetal harm.
Sorafenib	Nexavar	Multi-tyrosine kinase inhibitor with antiproliferative (RAF, c-KIT, Flt-3) and anti-angiogenic (VEGFR-2, PDGFR-β) effects	800 mg/d (400 mg twice daily) p.o. Not approved for breast cancer, has failed to provide evidence of efficacy in phase II/III trials	Interaction with inhibitors and inducer of CYP3A4	Palmar-plantar erythrodysesthesia, skin rash, severe skin toxicity, hypertension, (hypertensive crisis), hemorrhage, nausea, vomiting, diarrhea, drug induced hepatitis (monitor liver enzymes), myelosuppression, electrolyte disturbances including hypophosphatemia, QT prolongation, cataract, arterial and venous thrombosis, gastrointestinal perforations. Can cause fetal harm
Sunitinib	Sutent	Multi-tyrosine kinase inhibitor with antiproliferative (c-KIT, CSF1R) and anti-angiogenic (VEGFR-R, PDGFR) effects	GIST and RCC: 50 mg orally once daily, with or without food, 4 weeks on treatment followed by 2 weeks off. pNET: 37.5 mg orally once daily, with or without food, continuously without a scheduled off-treatment period. Not approved for the treatment of breast cancer. Negative findings from phase II/III trials	Interaction with inhibitors and inducer of CYP3A4	Hepatotoxicity, proteinuria, hemorrhage, QT interval prolongation, hypertension, wound healing and surgical complications, left ventricular dysfunction, thyroid dysfunction, hypoglycemia, dermatologic toxicities including erythema multiforme and Stevens–Johnson syndrome, osteonecrosis of the jaw, thromboembolic events Sunitinib can cause fetal harm

(continued)

Table 20.9 (continued)

Agent	Trade name	Mode of action	Dosing	Interactions	Selected adverse effects
Aflibercept (VEGF-Trap)	Zaltrap	Fully human soluble VEGF receptor fusion protein targeting vascular endothelial growth factor (VEGF)	4 mg/kg body weight q2w IV in combination with FOLFIRI approved for mCRC Not approved for breast cancer		Proteinuria, hypertension (hypertensive crisis), fatigue, nausea, vomiting, mucositis, stomatitis, hemorrhage, epistaxis, wound healing disturbances, gastrointestinal perforations and fistulae, arterial and venous thromboembolic events, neutropenia (in combination with chemotherapy), infusion and hypersensitivity reactions, reversible posterior leukoencephalopathy syndrome (RPLS) May cause fetal harm.
Ramucirumab	Cymraza	fully human monoclonal antibody directed against the extracellular domain of VEGFR-2 which blocks the interaction between VEGF A, C, D and VEGFR-2	8 mg/kg q2w IV as single agent or in combination with weekly paclitaxel Approved for metastatic gastric cancer not approved for breast cancer		Hypertension, arterial and venous thromboembolic events, hemorrhage, gastrointestinal perforations and fistulae, impaired wound healing, infusion reactions, reversible posterior leukoencephalopathy syndrome (RPLS), clinical deterioration of liver Child-Pugh B or C liver cirrhosis. May cause fetal harm

These highlights do not include all the information needed to use the respective drugs safely and effectively. See full prescribing information for all information needed to use these agents safely. We do not take responsibility for the correctness of the content

5.5 months (range 2.3–13.7 months) with an overall survival of 10.2 months. Bevacizumab was well tolerated; the main side effects were headache, nausea and vomiting, hypertension, minor bleeding (epistaxis), venous thromboembolic events, and proteinuria. The dose-limiting toxicity was headache associated with nausea and vomiting. This was neither caused by hypertension nor by brain metastases.

Several phase III trials have subsequently investigated the efficacy of bevacizumab in combination with chemotherapy. The pivotal open-label randomized phase III trial, ECOG 2100, demonstrated that the addition of bevacizumab to paclitaxel increased median PFS from 5.9 to 11.8 months (HR 0.6, $p < 0.001$) and doubled the response rates (25.2 % vs. 49.2 %, $p < 0.001$) in first-line unselected metastatic breast cancer. However, there was no significant improvement in OS [220, 221].

In 2008, the FDA granted accelerated approval for bevacizumab to be used in combination with first-line paclitaxel for metastatic HER2-negative breast cancer, based on these results. Approval by the EMA followed in 2009.

Consistent with E2100, all of the phase III trials in the first-line setting (AVADO, Ribbon-1) as well as in later lines (Ribbon-2), demonstrated significantly improved overall response rates as well as progression-free survival, even if at a considerably lower level, but failed to provide evidence that bevacizumab in combination with first-line chemotherapy prolongs overall survival [123, 222–224]. The efficacy of bevacizumab in addition to weekly paclitaxel could further be confirmed by identical results observed for the combination in the TURANDOT study (PFS 11 months, ORR 44 %) and CALGB 40502 study (PFS 10.6 months) [225, 226].

Subsequently, a pooled analysis of the three randomized phase III first-line trials including 2447 patients also failed to demonstrate any indication of an overall survival benefit from bevacizumab [227]. Triple-negative breast cancer is associated with a significantly higher expression and more frequent amplification of VEGF-A [228–230]. This has led to the hypothesis of a specifically higher activity of antiangiogenic agents in TNBC. Yet, neither of the individual trials nor the combined analyses found a sign of a more pronounced or even OS benefit from bevacizumab in triple-negative MBC. The combined analysis included 621 patients with TNBC from these trials and confirmed the increased ORR (42 % vs. 23 %) and PFS (8.1 vs. 5.4 months; HR 0.63; $p < 0.0001$), however, without a trend for an improved OS (18.9 vs. 17.5 months; HR 0.96; ns) [227].

In November 2011, the FDA revoked its accelerated approval for bevacizumab for the treatment of breast cancer based on the findings from the confirmatory trials. Thus, bevacizumab is no longer approved for the treatment of

metastatic breast cancer in the US. Other indications remained untouched from this decision. In contrast, bevacizumab remains approved in the EU by the EMA for first-line treatment of HER2-negative metastatic breast cancer in combination with paclitaxel and capecitabine.

The role of bevacizumab in early breast cancer has also been investigated in several phase II and III trials. Data from neoadjuvant trials provide evidence for a moderate improvement of pCR rates from the addition of bevacizumab to anthracycline- and taxane-based neoadjuvant chemotherapy. In the German neoadjuvant GeparQuinto trial (n = 1948), adding bevacizumab significantly improved pCR rates (ypT0/is ypN0) from 16.5 to 20.5 % (p = 0.03). This effect was completely driven by patients with TNBC (27.9 vs. 39.3 %, p = 0.003) [231]. In GeparQuinto, bevacizumab was only given during the neoadjuvant treatment phase. Thus, effects of longer adjuvant bevacizumab maintenance could not be investigated. The trial reported no trends for improved survival (DFS and OS), neither in the overall study population nor in the TNBC subgroup [232]. At the same time, the NSABP B40 phase III trial reported a numerical but insignificant increase of pCR by the addition of bevacizumab, from 23 to 27.9 % (p = 0.08) [233]. In contrast to GeparQuinto, a significant difference in pCR rates was observed within the HR-positive subgroup (11.1 % vs. 16.8 %, p = 0.03). Recently, a randomized neoadjuvant trial exclusively conducted in triple-negative disease, the CALGB 40603 (Alliance) trial (n = 443), reported a marginal increase in pCR (ypT0/is ypN0) from 44 to 52 % (p = 0.057) for patients randomized to bevacizumab [116]. Thus, data from the neoadjuvant trials remain inconclusive.

It is still a matter of debate how far pCR rates can be regarded a surrogate for survival and moreover, how large the increment in pCR rates has to be in order to translate into a survival benefit. Thus, data from adjuvant trials have to be regarded as more informative in this respect. To date, two large adjuvant randomized phase III trials have reported survival data in addition to the neoadjuvant NSABP B40 in which patients received adjuvant bevacizumab maintenance therapy [234]. BEATRICE (n = 2591) exclusively included patients with triple-negative disease. The trial randomized patients to standard adjuvant chemotherapy in combination with or without bevacizumab, followed by maintenance bevacizumab until completion of 12 months or observation [235]. After a median follow-up of 32 months, there was no significant difference in invasive DFS (iDFS), the primary endpoint. 3-year iDFS was 82.7 in the observation arm versus 83.7 % in patients randomized to receive bevacizumab (HR 0.87, p = 0.18). Based on the number of events in this triple-negative population a signal of efficacy could have been expected if there was any clinically meaningful difference, despite the relatively short follow-up. The second large randomized phase III trial investigating the adjuvant role of bevacizumab, the ECOG 5103 trial (n = 4950), also included HR-positive patients. Patients either received standard chemotherapy consisting of AC followed by weekly paclitaxel alone or in combination with bevacizumab concomitantly to the chemotherapy only or for an additional maintenance phase [236]. There was no significant difference in iDFS between the chemotherapy-only arm and the bevacizumab maintenance arm. 5-year iDFs was 77 % for chemotherapy-only and 80 % for patients receiving bevacizumab maintenance (HR 0.87, p = 0.17). 5-year OS rates were identical between the two arms (90 %). In patients with triple-negative disease, there seemed to be a trend for a better iDFS in patients receiving bevacizumab (HR 0.77, 95 % CI 0.58–1.03). In NSABP B40, which also included patients with HR-positive disease, bevacizumab led to a significant improvement in OS (HR 0.68, p = 0.004). The effect, however, was more pronounced in the HR-positive subset. Thus, the data on bevacizumab in the adjuvant setting are inconsistent and bevacizumab does not play a role in the treatment of primary breast cancer.

To date, there is no clinically useful validated predictive biomarker for the benefit of bevacizumab, precluding the possibility to define a subgroup of patients with clearer benefit from bevacizumab and possibly an OS improvement. Retrospective analyses of several prospective trials have suggested that plasma VEGF-A levels might provide such a biomarker for patient selection. The prospective MERIDIAN trial (NCT01663727) was designed to validate the predictive value of plasma VEGF-A. Patients were randomized to paclitaxel plus either placebo or bevacizumab as first-line therapy, stratified by baseline plasma VEGF-A. The trial confirmed the well-recognized PFS benefit from bevacizumab (HR 0.68, p = 0.0007) but failed to demonstrate any meaning of pVEGF-A as a predictive biomarker. There was no differential benefit from bevacizumab comparing the pVEGF-A high versus low group. The results have only been presented in abstract form at the ESMO meeting 2015 [237].

Due to the only modest benefit associated with bevacizumab, the ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2) state that this is only an option in selected cases for first- (and second-) line therapy [2]. This might apply, e.g., to situations in which a fast response is of importance (e.g., heavy disease burden, visceral crisis) and in which combination chemotherapy regimens might otherwise be considered.

The most important bevacizumab-associated side effects are hypertension, proteinuria, thromboembolic events, bleeding, surgery and wound healing complications, bowel perforations, fistulae and reversible posterior leukoencephalopathy syndrome (RPLS) as a very rare but serious complication. Bevacizumab has also been suspected to increase the risk of osteonecrosis of the jaw when combined with bisphosphonates and also to increase the risk of symptomatic congestive heart failure.

20.2.2.2 Antiangiogenic Tyrosine Kinase Inhibitors (TKIs) and Other Agents, Sorafenib, Sunitinib

In addition to monoclonal antibodies, a series of tyrosine kinase inhibitors (TKIs) against pro-angiogenic kinases like VEGF- and PDGF-receptors has been developed, including Sunitinib, Sorafenib and Pazopanib. As a result of the increased off-target effects of these TKIs, combination with chemotherapeutic agents has proven difficult. Their efficacy as monotherapy in MBC is limited with ORRs ranging from 0 to 11 % [238–241]. Sunitinib and Sorafenib have been developed in phase IIb/III programs.

Sunitinib (SUTENT®)

Sunitinib is an oral multi-targeted antiangiogenic tyrosine kinase inhibitor (TKI). It inhibits vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), stem cell factor receptor (KIT), and colony-stimulating factor-1 receptor (CSF1R). Currently, it is approved in the US and EU as a single agent for the treatment of gastrointestinal stromal tumors (GIST), advanced renal cell carcinoma (RCC) and pancreatic neuroendocrine tumors (pNET). Sunitinib demonstrated an overall response rate of 11 % in a single-arm phase II trial in patients with metastatic breast cancer who were pretreated with anthracycline and taxane [242]. It has been extensively investigated in a series of phase III clinical trials, but failed to prove any benefit both as monotherapy and in combination with chemotherapy. However, it caused considerable additional toxicity [238, 243–245]. Further development of sunitinib in breast cancer has been discontinued.

Sorafenib (NEXAVAR®)

Sorafenib is an oral inhibitor of multiple tyrosine kinases, currently indicated for hepatocellular carcinoma, advanced renal cell carcinoma, and differentiated thyroid carcinoma. It inhibits RAF kinases, c-KIT, and Flt-3, VEGFR-2 as well as PDGFR-β and has antiproliferative as well as antiangiogenic effects, targeting both tumor and endothelial cells [246, 247]. It has been hypothesized that this broader spectrum of activity might help bypass some of the resistance mechanisms observed with bevacizumab which prevent greater efficacy of the anti-VEGF-mAB. Sorafenib demonstrated activity in a phase IIb study in combination with either capecitabine or gemcitabine in patients who had received prior therapy with bevacizumab, though accompanied by a high rate of palmar-plantar erythema (45 % grade 3) [248, 249]. However, in the confirmatory placebo-controlled phase III trial, sorafenib, when combined with capecitabine, failed to improve PFS (HR 0.97, $p = 0.46$) or OS (HR 1.19, $p = 0–93$), but expectedly caused extensive toxicities [250]. Other randomized trials investigating the combination of sorafenib and docetaxel also failed to demonstrate efficacy of sorafenib in chemotherapy combinations [251, 252]. Based on the available data, further investigations of the role of sorafenib in breast cancer do not seem warranted.

Several other antiangiogenic multi-tyrosine kinase inhibitors, like pazopanib (VOTRIENT®) and cediranib, have been investigated in breast cancer [253–256]. In the light of their modest activity but considerable toxicity none of these antiangiogenic TKIs will play a role in the treatment of MBC.

20.2.2.3 Aflibercept, VEGF-Trap (ZALTRAP®)

Aflibercept (VEGF-Trap) is a fully human soluble VEGF receptor fusion protein with a unique mechanism of action. It is a potent inhibitor of angiogenesis that binds to VEGF-A with higher affinity than monoclonal antibodies. It blocks all VEGF-A and -B isoforms plus placental growth factor (PIGF), another pro-angiogenic factor involved in tumor angiogenesis. VEGF-Trap exerts its antiangiogenic effects through regression of tumor vasculature, remodeling, or normalization of surviving vasculature and inhibition of new tumor vessel growth. VEGF-Trap has a relatively long half-life of approximately 2 weeks. Based on a significant prolongation of OS in a randomized phase III trial, it has been approved in combination with FOLFIRI for the treatment of metastatic colorectal cancer (mCRC) after prior therapy with oxaliplatin [257, 258]. The North Central Cancer Treatment Group (NCCTG) N0573 2-stage phase II trial explored the efficacy of single agent aflibercept in metastatic breast cancer after prior therapy with anthracyclines and taxanes and could only demonstrate minor activity with an overall response rate of 4.8 % and a median PFS of 2.4 months. As the trial did not meet its primary efficacy goals, the study was terminated after the inclusion of 21 patients [259]. Toxicity was as expected for an anti-VEGF therapy. There is currently no further development of aflibercept in breast cancer.

20.2.2.4 Ramucirumab (CYRAMZA®)

Ramucirumab is a fully human monoclonal antibody directed against the extracellular domain of VEGFR-2 which blocks the interaction between VEGF and VEGFR-2. It has demonstrated improvements in OS in metastatic gastric cancer and advanced non-small-cell lung cancer [260, 261]. Ramucirumab is currently approved for the treatment of metastatic gastric cancer. In breast cancer, ramucirumab has been investigated in a large randomized phase III trial (TRIO-012; $n = 1144$) in the first-line setting. Patients were randomly assigned to either docetaxel plus placebo or ramucirumab. The addition of ramucirumab did not lead to a meaningful improvement of clinical outcome (PFS: HR 0.88, $p = 0.08$; OS HR 1.01, $p = 0.92$) [262]. There are

currently no ongoing trials for the clinical development of ramucirumab in breast cancer.

20.2.2.5 Trebananib (AMG386)

Apart from VEGF and its receptors, a second key regulatory pathway, the angiopoetin axis, is involved in the induction and regulation of tumor angiogenesis. Angiopoetin-1 and Angiopoetin-2 (Ang-1, Ang-2) regulate the vasculature by binding to their proprietary receptor tyrosine kinase tie-2. Vascular remodeling is regulated by the balance between Ang-1 and Ang-2. Ang-1, predominantly secreted by vascular smooth muscle cell and pericytes, leads to vessel normalization, whereas Ang-2 increases vessel destabilization and endothelial cell migration [263–266]. Although both pathways, VEGF/VEGFR and angiopoetin/Tie-2, are distinct, they interact and blocking both pathways simultaneously may lead to a more complete control of tumor growth than blocking just one. Trebananib is a novel recombinant peptide-Fc fusion protein (peptibody) selectively targeting the interaction of Ang1 and Ang2 with the Tie2 receptor. In preclinical studies, the combination of bevacizumab and trebananib showed enhanced antitumor activity compared to each drug alone. In a randomized phase III trial (TRINOVA-1, $n = 919$) in recurrent ovarian cancer, trebananib (15 mg/kg) demonstrated activity when added to weekly paclitaxel with a significantly prolonged median PFS (HR 0.66, $p < 0.0001$). At the interim analysis there was no significant difference in overall survival [267]. Generalized or localized edema as well as pleural effusions and ascites account for the most striking toxicity specifically associated with trebananib. In breast cancer, the efficacy of trebananib was investigated in a large randomized phase II trial. Patients with metastatic, HER2-negative breast cancer received weekly paclitaxel in combination with bevacizumab plus two different doses of trebananib or in combination with either bevacizumab or trebananib alone. The trial was unable to demonstrate a significant prolongation of PFS from the addition of trebananib to paclitaxel and bevacizumab [268].

20.2.3 Endocrine Therapy (ET)

About 60–80 % of breast cancers are hormone receptor (HR) positive. The concept of endocrine therapy in the treatment of breast cancer was already introduced in 1896 when George Beatson reported surgical removal of the ovaries (now known as the major source of estrogen) could benefit women with inoperable breast cancer. However, at that time neither estrogens nor their receptors and functions were known. See Table 20.8 for a summary of antihormonal agents and targeted agents used in combination with endocrine therapy.

20.2.3.1 Selective Estrogen Receptor Modulators (SERMs), Tamoxifen

Selective estrogen receptor modulators (SERMs), in contrast to complete estrogen receptor (ER) antagonists, exert differential tissue selective, mixed agonist–antagonist effects. These tissue selective effects vary between the different members of the class. Upon dimerization, estrogen receptors are translocated into the cell nucleus and exert most of their function as transcription factors. Further, nongenomic functions of ER have been described but are not very well understood yet.

Most SERMs exhibit anti-estrogenic effects on breast tissue and some members of this class of drugs have proven to be effective chemopreventive agents against breast cancer. However, several SERMs, e.g., tamoxifen exhibit agonistic activity in the endometrium, which in the case of tamoxifen leads to a significantly (two- to threefold) increased risk of endometrial cancer, which has been observed in many trials. In contrast, raloxifen does not seem to have any relevant stimulatory effects on the endometrium. In addition, SERMs generally exhibit tissue selective agonist activity on the bone, which in the case of raloxifen, has been clinically exploited to prevent and treat osteoporosis [269]. These tissue selective agonistic activities are not observed with therapies purely leading to estrogen deprivation like aromatase inhibitors (AIs), which explains their detrimental effects on bone mineral density but unchanged risk of endometrial cancer. Although not fully understood, most of the tissue-specific antagonist–agonist activity of SERMs is explained by three interactive mechanisms: differential expression of ERα and ERβ in different target tissues, a differential conformational change upon ligand binding and differential expression and binding of ER co-regulatory proteins.

Tamoxifen

Tamoxifen has been the most commonly used drug for the treatment of breast cancer for decades. It is currently used for the treatment of HR-positive advanced and early breast cancer irrespective of stage and menopausal status. Tamoxifen is the standard endocrine treatment for male breast cancer as well.

Tamoxifen itself is considered a prodrug with relatively weak affinity for ER and is subject to extensive metabolism. For the conversion of tamoxifen into its clinically active metabolites 4-hydroxy-tamoxifen and endoxifen (4-hydroxy-*N*-desmethyltamoxifen), the cytochrome P450 enzyme CYP2D6 in the liver is the rate limiting step. The active metabolites have a 30–100-fold greater affinity for ER and endoxifen is regarded as the most clinically active metabolite. CYP2D6 is a highly polymorphic gene, and it

has been suggested that patients carrying variants with lower enzymatic activity (poor metabolizers) might derive less benefit from tamoxifen. Endoxifen blood levels do vary according to CYP2D6 genotype and are influenced by the concomitant use of CYP2D6 inhibitors like paroxetine. In addition, some retrospective studies have demonstrated reduced clinical activity of tamoxifen in poor metabolizers [270–274]. However, several subsequent clinical investigations have produced conflicting results [275]. A retrospective analysis of CYP2D6 variants in two large randomized phase III trials of adjuvant endocrine therapy (BIG 1-98 and ATAC) failed to provide any evidence of a predictive role of CYP2D6 genetic testing with regards to benefit from tamoxifen [276, 277]. Therefore, currently there is no role of CYP2D6 testing to tailor endocrine therapy for breast cancer.

Tamoxifen first reported activity as an endocrine therapy option for the treatment of breast cancer in 1971 with a response rate of 22 % [278]. Of note, early trials have not been conducted exclusively in HR-positive patients but in unselected populations [279]. Compared to other endocrine treatment options available at the time, tamoxifen had a favorable toxicity profile. Subsequent trials have confirmed the clinical activity of tamoxifen in metastatic breast cancer and a meta-analysis including more than 5000 patients from clinical trials demonstrated a response rate of 30–34 % with an additional 19 % of patients achieving a stable disease for more than six months [279, 280]. Higher doses than 20 mg per day did not provide improved efficacy [281–283].

Tamoxifen was first approved by the FDA in 1977 and subsequently also in Europe for the treatment of advanced breast cancer and later for the treatment of early breast cancer for both pre- and postmenopausal women as well. According to the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis, 5-years of adjuvant tamoxifen reduces breast cancer mortality by about a third (HR 0.68, $p < 0.00001$), largely independent of age, progesterone receptor (PR) status and use of chemotherapy. 5-years of tamoxifen were significantly more effective in reducing the risk of recurrence and breast cancer deaths than 1–2 years of tamoxifen. In ER-positive disease the annual breast cancer mortality rates are similar during years 0–4 and 5–15 as is the proportional risk reduction by tamoxifen during these years. As a result of this carry-over effect the cumulative risk reduction is more than twice as big after 15 years as at year 5 [283, 284]. Recently, two large randomized phase III trials, ATTOM and ATLAS, have demonstrated a significant benefit from 10 years of tamoxifen compared to 5 years. The absolute reduction of breast cancer mortality seen in these trials 15 years after starting adjuvant endocrine therapy was about 3 % and deaths from endometrial cancer or pulmonary embolism were significantly increased. Thus, the expected gain in the individual patient has to be weighed against the risk of potentially fatal adverse events [285, 286].

In the US, tamoxifen has also been approved for women with DCIS to reduce the risk of invasive cancer in later life and as a prophylaxis for women at high risk for breast cancer based on results from the NSABP B24 and the NSABP P1 trial [283, 287–289].

Tamoxifen is a well tolerated and accepted drug; however, there are some side effects, which may interfere with compliance and some which are potentially fatal. Adverse events include hot flashes, vaginal discharge, vaginal dryness, pruritus vulvae, headaches, dizziness, mood alterations/depression, hair thinning and/or partial hair loss, fluid retention/edema, visual disturbances (e.g., cataracts, corneal disturbances, and retinopathy), elevation of liver enzymes, elevation of triglyceride levels, hypercalcemia and loss of appetite. The potentially dangerous side effects of tamoxifen include deep vein thrombosis, pulmonary embolism, and endometrial cancer. The risk of endometrial cancer is increased by a factor of 2–7 and is explained by the tissue-specific agonistic effect of tamoxifen on the endometrium. These cancers occur almost exclusively in postmenopausal women and become clinically evident by postmenopausal bleeding. Serial ultrasound scans for the detection of endometrial thickening is not helpful, as many patients develop subendometrial edema, induced by tamoxifen, which cannot be discriminated from malignant growth.

20.2.3.2 Aromatase Inhibitors

Whereas in premenopausal women, estrogen is mostly produced by the ovaries, in the postmenopausal setting estrogen synthesis mainly occurs in peripheral tissues through the conversion of androgens produced in the adrenal gland into estrogen by an enzyme called aromatase. This can effectively and specifically be inhibited by third-generation aromatase inhibitors (AIs). There are three third-generation aromatase inhibitors in clinical use for the treatment of breast cancer today, namely: anastrozol, exemestane, and letrozol. In contrast to nonsteroidal AIs (letrozole and anastrozol), exemestane, a steroidal AI, covalently binds to the enzyme leading to an irreversible inhibition. Third-generation AIs, the most potent and specific as well as least toxic AIs, can reduce serum estrogen levels by more than 95 % [290].

Several randomized phase III trials have investigated the efficacy of the three AIs compared to tamoxifen in the first-line treatment of HR-positive advanced breast cancer in postmenopausal women. At the time, the trials were conducted and only a minority of patients in these trials had received prior adjuvant endocrine therapy (14–19 %) [291–293]. In all of these trials AIs compared favorably to tamoxifen with objective response rates (ORR) from 30 to 46 % and time to progression (TTP) ranging from 9.4 to 10.7 months. In addition, aromatase inhibitors have also

demonstrated clinical activity after the failure of tamoxifen [294]. In turn, letrozol, anastrozole, and exemestane have been approved for the treatment of HR-positive metastatic breast cancer in postmenopausal women and have largely replaced tamoxifen as the first-line therapy. Whereas steroidal and nonsteroidal aromatase inhibitors seem not to be completely cross-resistant, there is no evidence to suggest that any of these agents are superior to the others [295, 296].

The role of aromatase inhibitors in the adjuvant setting has been investigated in a series of phase III trials pursuing several strategies, including upfront aromatase inhibitors, switching to an AI after 2–3 years of tamoxifen or extended therapy with an AI after completion of 5 years of tamoxifen. All of these trials demonstrate a superiority of AIs over tamoxifen alone in the adjuvant treatment of postmenopausal HR-positive breast cancer [297–302]. BIG 1-98 directly compared 5 years of letrozole to 5 years of tamoxifen and demonstrated a significant overall survival advantage for letrozole at an 8-year follow-up, both for the ITT population and an analysis adjusting for crossover (IPCW) [IIT: HR 0.87; $p = 0.048$; IPCW: HR 0.79; $p = 0.0006$] [299].

In a large patient-level meta-analysis from the EBCTCG including 31920 women from 9 randomized trials, patients treated with 5 years of an aromatase inhibitor compared to 5 years of tamoxifen had a significantly improved DFS (HR 0.8; $p < 0.0001$) and OS (HR 0.89; $p = 0.1$), with absolute 10-year gains of 3.6 % for DFS and 2.7 % for OS. In contrast, 5 years of an AI were only marginally better in terms of DFS (RR 0.9; $p = 0.045$—absolute difference 0.7 %) but not OS (RR 0.96; $p = 0.45$) if compared to tamoxifen for 2–3 years followed by an AI. The sequencing strategy, however, was significantly more effective compared to 5 years of tamoxifen (DFS RR 0.82; $p = 0.0001$ and OS RR 0.82; $p = 0.0002$) [303]. There is no evidence to suggest superiority of one AI over the others in the adjuvant therapy. Based on the available data, it is generally recommended in international guidelines (e.g., NCCN, ASCO, AGO, St. Gallen), that adjuvant endocrine therapy for postmenopausal women should include an AI (if tolerated) [54, 304–306]. However, the optimal sequence and duration remains elusive.

It is also a widely accepted concept that giving an AI upfront to high-risk patients (e.g., with axillary lymph node involvement) might be beneficial. However, switching to tamoxifen after 2–3 years of AI can be considered in case of intolerability since there was no statistically significant difference in DFS among patients who received 5 years of AI compared to 2–3 years of AI followed by tamoxifen [307]. This concept is mainly supported by results from BIG 1-98, which has also investigated an inverse sequence of letrozole followed by tamoxifen.

As more than half of breast cancer recurrences occur more than 5 years after the initial diagnosis and after completion of tamoxifen, several trials have investigated the strategy of extended endocrine therapy with AIs (MA.17, ABCSG 6a, NSABP B33) [308–311]. All of these trials have shown a reduction of breast cancer recurrence (HR 0.60–0.68). MA.17, the largest of these trials, comparing 5 years of letrozole to placebo after completion of 5 years of tamoxifen, also provided evidence for an OS benefit in node-positive patients (HR 0.61, $p = 0.04$) [308, 309, 312].

Aromatase inhibitors are generally well tolerated. Their toxicity profile substantially differs from tamoxifen. In contrast to tamoxifen AIs are not associated with an increased risk of endometrial cancer and venous thromboembolic events. Instead, they lead to a more pronounced bone loss and a higher rate of fractures as well as musculoskeletal symptoms like arthralgias and osteoarthritis. Musculoskeletal symptoms are estimated to occur in up to 50 % of patients and lead to a treatment discontinuation in 20 % [313]. Further common side effects are vasomotor symptoms (hot flushes), increased sweating, depression, edema, increases in cholesterol levels, and an increased risk of cardiac ischemic events (myocardial infarction, angina). It is advisable to monitor bone mineral density regularly in women who take AIs [307].

In premenopausal women the inhibition of the aromatase does not significantly decrease the production and the amount of circulating estrogen, but the initial slight decrease in estrogen levels activates the hypothalamus and pituitary axis to increase gonadotropin secretion, which in turn increases the FSH and LH levels. Aromatase inhibitors are contraindicated for premenopausal women.

20.2.3.3 Fulvestrant—Selective Estrogen Receptor Downregulator (SERD)

Fulvestrant is a selective estrogen receptor downregulator (SERD), which are directed against estrogen receptors and exert purely antagonistic effects. Fulvestrant is the only representative of the class of drugs currently in clinical use. It competitively binds to estrogen receptors with a binding affinity 100 times greater than that of tamoxifen [314]. Upon binding, it blocks ER dimerization and DNA binding, inhibits nuclear uptake, and increases the turnover and degradation of ER leading to inhibition of estrogen signaling.

Clinically, fulvestrant was first developed at a dose of 250 mg given as a monthly intramuscular injection. Fulvestrant$_{250}$ was shown to be equally effective as anastrozole in patients who had progressed on endocrine therapy (mostly tamoxifen) [294]. Based on these results, fulvestrant received approval as a further option for HR-positive advanced breast cancer by the FDA in 2002 and in Europe in 2004 for the treatment of hormone receptor-positive metastatic breast cancer in postmenopausal women with disease progression following anti-estrogen therapy.

A randomized neoadjuvant phase trial (NEWEST) pointed to a greater biologic activity of fulvestrant at a dose of

500 mg compared to 250 mg, including a significantly higher reduction of Ki67 labeling index [315]. This and further data prompted several trials to investigate the clinical efficacy of this higher dose.

The FIRST trial, a randomized phase II trial, compared fulvestrant$_{500}$ to anastrozole as first-line therapy for metastatic breast cancer. Although there was no difference in clinical benefit rate (primary end point) or response, the TTP was significantly longer in the fulvestrant arm (23.5 vs. 13.1 months; HR 0.66; $p = 0.01$) as well as overall survival (54.1 vs. 48.4 months; HR 0.7; $p = 0.04$) [316, 317]. Results of the ongoing confirmatory phase III FALCON trial are expected in 2016 (NCT01602380). A press release in may 2016 announced that the FALCON trial met its primary end point by significantly increasing PFS. The CONFIRM trial (phase III) randomized patients with HR-positive metastatic breast cancer, who experienced progression after prior endocrine therapy with tamoxifen or an AI to either fulvestrant 500 mg q4w or 250 mg q4w. Patients treated with 500 mg of fulvestrant had significantly longer PFS (6.5 vs. 5.5 months; HR 0.81; $p = 0.0006$) as well as OS (26.4 vs. 22.3 months; HR 0.81; $p = 0.016$) [318, 319].

Fulvestrant has a similar tolerability profile as anastrozole and AIs, but with a significantly lower incident of musculoskeletal symptoms like arthralgia. Like the AIs, fulvestrant lacks the increased risk of endometrial cancer and thromboembolism observed with tamoxifen, because it is void of any estrogenic effects. In current clinical trials, fulvestrant has turned into a preferred endocrine combination partner due to its efficacy and tolerability.

20.2.3.4 Combination of Endocrine Therapies

As the currently available endocrine drugs have different modes of actions and are partially noncross-resistant, several trials set out to investigate combinations of endocrine therapies to improve efficacy of ET. However, conflicting results have been reported from the comparison of the combination of fulvestrant (250 mg) with anastrozole versus anastrozole as a single agent. The FACT trial demonstrated no advantage from the combination, whereas the SWOG S0226 trial showed a benefit in terms of TTP and OS [320, 321]. Furthermore, the SoFEA trial provided similar efficacy for the combination of fulvestrant and anastrozole compared with fulvestrant or exemestane alone as second-line endocrine therapy. Therefore, until there is further evidence, combinations of endocrine therapies should not be adopted into routine clinical practice [296, 322].

20.2.3.5 Gonadotropin-Releasing Hormone (GnRH) Analogs

Synthetic GnRH or luteinizing hormone (LHRH) analogs differ from native GnRH by a 100–200-fold stronger binding affinity to GnRH receptors on pituitary gonadotroph cells. Synthetic GnRH/LHRH analogs lead to an initial intense release of stored luteinizing hormone (LH) and follicle-stimulating hormone (FSH) called flare-up effect, resulting in a transient raise in serum estradiol in women. A prolonged application of these agents, as opposed to the pulsatile secretion that occurs naturally, however, leads to a desensitization of gonadotropin producing cells caused by downregulation of GnRH/LHRH receptors and a dysregulation of intracellular signaling [323]. This leads to an inhibition of LH/FSH secretion and ultimately the production of estradiol. GnRH/LHRH analogs are administered as depot injections. In contrast, GnRH/LHRH antagonists, which are not in clinical use against breast cancer, inhibit gonadotropin secretion by direct competitive receptor blockade without receptor downregulation.

After the first description of this therapeutic principle by Beatson in 1896[324], ovarian ablation, either by means of oophorectomy or radioablation remained the gold standard for the treatment of premenopausal patients with advanced breast cancer for decades. Subsequently, GNRH/LHRH analogs have demonstrated similar efficacy, providing an alternative. In early trials, tamoxifen has demonstrated comparable efficacy to ovarian ablation [325, 326]. Later trials as well as a meta-analysis proved that the combination of tamoxifen and GnRH/LHRH analogs was superior than either agent alone in terms of PFS and OS [327, 328]. Hence, the combination of tamoxifen with ovarian ablation is the standard recommended by current international guidelines (ABC2 consensus; National Comprehensive Cancer Network [NCCN], Guidelines, breast cancer, version 1.2016; AGO, v2016.1) [2, 305, 306]. After progression on or after tamoxifen and with an indication for further endocrine therapy, it is currently recommended for pre- and perimenopausal patients to be treated by ovarian ablation (either by GnRH-A or through surgical oophorectomy) and then treated as if they were postmenopausal [2, 296, 305].

Data on the adjuvant use of GnRH analogs are more inconclusive. Adding tamoxifen to goserelin after six cycles of CAF as adjuvant treatment of breast cancer in premenopausal women significantly improves DFS [329].

However, for many years, evidence from randomized trials to demonstrate benefit from the addition of goserelin to tamoxifen in the adjuvant setting was lacking and a patient-level meta-analysis provided only very limited information [330]. Recently, data from a randomized phase III trial (SOFT) demonstrated that the addition of ovarian ablation (by means of GnRH analogs, radioablation or oophorectomy) did not significantly improve DFS in the overall study population [331]. However, a subgroup analysis showed that for women at sufficient risk of recurrence to warrant adjuvant chemotherapy, ovarian function suppression improved outcomes but at the cost of tolerability [331]. Based on these data, the use of GnRH analogs in the adjuvant endocrine treatment of premenopausal patients remains

an option for selected individual patients after weighing risk of recurrence, expected benefit, tolerability and QoL [332].

Side effects include hot flushes, sweating, emotional lability, depression, anxiety, loss of bone mineral density, dizziness, headache, arthralgia, musculoskeletal symptoms, amenorrhea, seborrhea, decreased libido, vaginitis, dyspareunia, breast atrophy, peripheral edema, weight gain and tiredness.

Currently, goserelin (Zoladex®) is the only agent approved for the palliative treatment of advanced breast cancer in pre- and perimenopausal women in the US as well as Europe. In addition, leuprorelin has received approval for metastatic breast cancer in Europe. Several additional GnRH/LHRH analogs are available for the treatment of advanced prostate cancer. Based on their mode of action there is no rationale for the use of GNRH analog in postmenopausal patients. GnRH/LHRH analogs are also used for several gynecologic diseases as well as in assisted reproduction.

20.2.3.6 Further Targeted Agents Used in Combination with Endocrine Therapies

Some patients with HR-positive MBC show primary resistance to endocrine therapy and the remaining patients will ultimately develop secondary resistance and progress. Furthermore, since most patients today receive adjuvant endocrine therapy, some even for an extended duration of 10 years, patients we treat in the first-line setting today, differ substantially from those included in the large phase III trials on AIs and fulvestrant in first-line, which included predominantly ET naïve patients. They are likely to develop endocrine resistance more quickly. Endocrine resistance therefore presents a major clinical problem.

A huge effort has been undertaken to target mechanisms of endocrine resistance such as the PIK3CA/AKT/mTOR pathway, the cell cycle machinery, and the cross talk between HR and growth factor receptor signaling by combining endocrine therapies with novel targeted agents to restore endocrine sensitivity. With everolimus, an mTORC1 inhibitor, and palbociclib, a cdk4/6 inhibitor, two such agents have received approval and document the progress made.

mTOR and PIK3CA Inhibitors

Preclinical studies provide evidence that growth factor receptor signaling pathways, particularly those that converge on phosphatidylinositol 3-kinase (PI3K) and mitogen-activated protein kinase (MAPK/ERK), are involved in resistance to endocrine therapy [333, 334]. PI3K is the most frequently altered pathway in breast cancer. PI3K activation, experimentally, is associated with de novo and acquired endocrine resistance and blocking the pathway can restore endocrine sensitivity. Based on this rational several agents blocking the PI3K-Akt-mTOR at different levels have been developed and are in clinical testing.

Everolimus (Afinitor)

Everolimus is an oral mTOR inhibitor targeting mTORC1, one of the two mTOR complexes (mTORC1 & 2). Based on results from the randomized, double-blind phase III BOLERO-2 trial (n = 724), everolimus has been approved for the treatment of postmenopausal women with HR-positive MBC in combination with exemestane after failure of a nonsteroidal AI. In BOLERO-2, patients randomized to the combination of exemestane and everolimus had a significantly longer PFS (6.9 vs. 2.8 months; HR 0.43; $p < 0.001$) [335]. However, OS was not significantly improved (31.0 vs. 26.6 months; HR, 0.89; $p = 0.1426$) [336]. Supporting data come from a randomized phase II trial (TAMRAD), comparing tamoxifen plus everolimus to tamoxifen alone, providing a significant improvement in time to progression (TTP) from 4.5 to 8.6 months (HR 0.54) [337].

However, the toxicity profile of everolimus can be challenging. In BOLERO-2, the rate of grade 3/4 adverse events was significantly higher in patients receiving everolimus compared to placebo (55 % vs. 33 %) as was the proportion of patients who discontinued treatment due to adverse events (29 % vs. 5 %) [336]. Side effects of everolimus include stomatitis and oral ulcerations, noninfectious pneumonitis, increased risk of infections, hyperglycemia, elevation of blood lipid levels, elevation of liver enzymes, renal failure, hematologic toxicity including anemia, neutropenia, lymphopenia, thrombopenia, impaired wound healing, rash, fatigue and gastrointestinal disturbances amongst others. Patients should avoid live vaccines and close contact to those who have received live vaccines.

Ongoing translational research has been trying to investigate predictive biomarkers, however, thus far has failed to do so. For example, activating PIK3CA mutations, major candidates, at least if tested mainly on primary tumor tissue did not provide any predictive information [338].

PIK3CA Inhibitors

Alterations in PIK3CA are the most frequent molecular alterations in HR-positive breast cancer and are identified in 45 and 29 % of luminal A and B tumors, respectively [296]. However, the role of PIK3CA mutations in luminal breast cancers is complex and still not entirely understood. Their implications might in fact play distinctive roles in early versus advanced breast cancer. In primary breast cancer the presence of PIK3CA mutations is consistently associated with good prognosis luminal A-like breast cancers (lower grade, less lymph node involvement, and progesterone receptor positivity) [339]. In advanced ER-positive breast

cancers selected by primary endocrine therapy, PIK3CA mutations may behave as a mechanism of endocrine resistance that merits combined therapy [340]. In fact, in vitro, the combination of estrogen deprivation and PI3K inhibition acts synergistically [341]. PI3K therefore constitutes an attractive target in combination with endocrine therapy in breast cancer.

Several PI3K inhibitors are currently in clinical development programs, ranging from unspecific pan-PI3K inhibitors (e.g., buparlisib) to modern third generation, α isoform specific PIK3CA inhibitors (e.g., alpelisib, taselisib), sparing off-target effects, and as hoped, unnecessary toxicity. Most activation mutations affect hot spot regions within PIK3CA [342].

First clinical data have emerged from randomized trials. In a randomized phase II trial (FERGI), pictilisib, a pan-PI3K inhibitor, when added to fulvestrant, was associated with a nonsignificant PFS improvement from 5.1 to 6.6 months (HR 0.74; $p = 0.095$). PIK3CA mutation status did not predict outcome [343]. The BELLE-2 trial, a randomized, double-blind, placebo-controlled phase III trial, randomized postmenopausal patients who progressed after or on an AI, to fulvestrant plus either placebo or buparlisib (BKM120), a pan-Class I PI3K inhibitor, that targets all four PI3K isoforms. The trial met its primary endpoint by increasing PFS in the full study population by 1.9 months from 5.0 to 6.9 months (HR 0.78; $p < 0.001$). PI3K activation, determined by PI3K mutations (mostly in the primary tumor) and PTEN loss, did not predict PFS benefit from buparlisib, a coprimary endpoint in the trial. However, PIC3CA mutations determined in circulating tumor DNA (ctDNA) at the time of entering the trial was a significant predictive factor for activity of buparlisib. In patients with PIC3CA ctDNA mutations there was a PFS improvement from 3.2 to 7.0 months (HR 0.58; $p < 0.001$), whereas in patients without ctDNA PIK3CA mutations there was no difference in PFS by treatment (6.8 months in both arms) [344]. Buparlisib was associated with considerable toxicities and grade 3/4 AEs were significantly more frequent with buparlisib (77.3 % vs. 32 %). The safety profile was mainly characterized by elevation of liver enzymes, rash, hyperglycemia, and mood disorders like depression and anxiety [344]. The PFS benefit in the ITT population is modest at best. The ctDNA PIK3CA mutant subgroup may derive a clinically meaningful benefit, if this predictive biomarker is validated. Future will tell if this will outweigh the toxicity associated with this pan-PI3K class I inhibitor. It is likely, however, that clinical development will move to another class of PI3K inhibitors.

There is hope that PI3Kα-selective inhibitors might offer an improved therapeutic index, with greater activity and less toxicity. Alpelisib (BYL719) and Taselisib (GDC0032) are examples of this class of drugs. Currently, large randomized phase III trials investigating their role are ongoing and will provide more definitive answers concerning the future of PIK3CA inhibitors in HR+ breast cancer (SOLAR [Alpelisib], NCT02437318; SANDPIPER [Taselisib], NCT02340221).

Palbociclib (Ibrance™) and Cdk4/6 Inhibitors

Translational research points to a profound deregulation of the cyclin D1/CDK4/6/retinoblastoma (Rb) pathway in HR-positive breast cancer, with frequent cyclin D1 amplifications, gains in CDK4 and overexpression of Rb [345, 346]. The activation of CDK4/6 by cyclin D leads to Rb phosphorylation and progression of the cell cycle into S phase and is associated with resistance to endocrine therapy [296, 347]. In vitro studies showed that luminal ER-positive cell lines (including those, which are HER2 amplified) were most sensitive to palbociclib, an orally active, highly selective inhibitor of the cyclin D kinases (CDK)4 and CDK6, whereas non-luminal/basal-like cell lines were most resistant. Palbociclib preclinically demonstrates synergy with endocrine therapies [348]. These observations served as a rationale to develop palbociclib primarily in HR+ breast cancer. In the randomized phase II PALOMA-1 trial, palbociclib in combination with letrozole as first-line therapy for HR+ MBC in postmenopausal patients, significantly improved PFS from 10.2 to 20.2 months in comparison to letrozole alone (HR 0.48; $p = 0.0004$) [349]. Based on these results, the FDA granted palbociclib in combination with letrozole in the first-line setting accelerated approval in 2015. Approval for Europe by the EMA is currently outstanding, but is expected in 2016. Subsequently, data from the randomized, double-blind, placebo-controlled phase III trial (PALOMA-3) confirmed the activity. In contrast to PALOMA-1, PALOMA-3 recruited patients with advanced HR-positive, HER2-negative breast cancer who had relapsed or progressed during prior endocrine therapy. Patients were randomized to fulvestrant in combination with either palbociclib or placebo. The median progression-free survival was increased from 3.8 months in the placebo arm to 9.2 months with palbociclib (HR 0.42; $P < 0.001$) [350]. Palbociclib is very well tolerated, with a rate of treatment discontinuation due to AEs of only 2.6 %. Hematologic toxicities, predominantly neutropenia and lymphopenia, make up for the most frequent grade 3/4 toxicities. However, despite the rate of grade 3/4 neutropenia of 62 % febrile neutropenia was a rare event in PALOMA-3 (0.6 %) and was not different when compared to the placebo arm [350]. Other common side effects of palbociclib are leukopenia, anemia, thrombopenia, fatigue, hair loss, and stomatitis. Based on these results the FDA has extended the indication of palbociclib to the combination with fulvestrant in women progressing after or on prior endocrine therapy. Very recently, data from PALOMA-1 where

confirmed by the registrational PALOMA-2 phase III trial combining letrozol and palbociclib in the first-line setting.

Due to a favorable toxicity profile compared to everolimus in daily clinical practice, palbociclib is often used in earlier lines. Apart from palbociclib, two further cdk4/6 inhibitors, ribociclib (LEE011), and abamaciclib (LY2853219), are being investigated in phase III clinical trials (MONALEESA-2; MONARCH-2). In addition, large randomized phase III trials are currently recruiting patients with HR-positive primary breast cancer to investigate the role of palbociclib in the post-neoadjuvant (PENELOPE–NCT01864746) and adjuvant setting (PALLAS–NCT02513394).

20.2.4 PARP-Inhibitors

Homologous recombination (HR) represents an important error-free DNA repair mechanism for double strand breaks. HR uses the homologous sequence of the sister chromatid which is used to precisely repair the double strand break. The BRCA1 and BRCA2 genes are important components of the HR machinery. In *BRCA*-associated tumors, the nonmutated *BRCA1/2* allele is inactivated. In turn, these tumors accumulate double strand breaks and are characterized by genomic instability. The inhibition of base excision repair in such cells leads to the accumulation of double strand breaks during replication, which cannot be repaired accurately due to the HR deficiency. Poly-(Adenosine-Diphosphate)-Ribose-Polymerase (PARP) is an enzyme centrally involved in base excision repair (BER). Inhibiting PARP in HR deficient cells leads to specific synthetic lethality [351].

Phenotypic similarities between basal-like subtype and *BRCA*-associated breast cancers have lead to the strategy to select patients for PARP-inhibition by their TNBC phenotype. An alternative strategy is to restrict the development of PARP inhibitors to *BRCA*-associated breast cancer types. Currently several PARP inhibitor such as Olaparib, Veliparib, Rucaparib, Niraparib, Talazoparib (BMN673) and others are undergoing clinical development. Olaparib was the first PARP inhibitor to be granted regulatory approval of recurrent high-grade serous ovarian cancer by the FDA and the EMEA. Olaparib was first developed in a single-arm phase II study recruiting patients with *BRCA*-associated breast cancer in two consecutive cohorts treated with 100 mg bid and 400 mg bid, respectively. This trial demonstrated a promising dose-dependent ORR of 22 % (100 mg bid) and 41 % (400 mg bid) with a median PFS of 5.7 months for the higher dose [352]. Similar results were observed for *BRCA*-associated ovarian cancer [353].

Gelmon et al. studied the efficacy of Olaparib in unselected TNBC. However, they were unable to demonstrate any confirmed responses among 26 patients included which was in contrast to the efficacy observed in ovarian cancer in the same trial [354]. A recent study including several *BRCA*-associated solid tumors demonstrated a discouraging ORR of only 12.9 % with a PFS of only 3.7 months in the 62 *BRCA*-associated breast cancers included. The ORR seemed to be higher in breast cancer patients without prior platinum chemotherapy (20 % vs. 9.5 %). However, again results were more promising in the ovarian cancer cohort. Overall, these data suggest that PARP-inhibition at least by Olaparib is more effective in (BRCA associated) ovarian cancer than in *BRCA* associated breast cancer.

As part of the I-Spy 2 trial the combination of Carboplatin and Veliparib added to weekly Paclitaxel and followed by Doxorubicin/Cyclophosphamide led to a doubling of the pCR rate in the triple-negative study population from 26 to 52 %. Trial statistics predict a probability of 90 % of success for this combination in a phase III trial [355]. Currently several PARP inhibitors are in clinical development for breast cancer in the adjuvant, neoadjuvant, and metastatic setting. Table 20.10 summarizes current phase III trials investigating PARP inhibitors in breast cancer. Olaparib is usually well tolerated, with moderate side effects including, nausea, vomiting as well as anorexia and fatigue. Of more concern are long-term adverse events which include increased rates of treatment-associated MDS and AML especially when these drugs are used in the adjuvant setting.

20.2.5 Bone-Targeted Agents

Breast cancer patients are at risk of several skeletal complications, including treatment-induced bone loss leading to osteoporosis and an increased fracture risk. In addition, the majority of patients with advanced breast cancer will develop bone metastases, which can lead to pain, dysfunction, fractures and hypercalcemia as an oncologic emergency. Bone-targeted agents are used to prevent or treat these conditions. In addition, there is data suggesting potential role of bone-targeted agents in the adjuvant setting to prevent recurrences and decrease mortality (Table 20.11).

20.2.5.1 Bisphosphonates

Bisphosphonates (BPs) are synthetic analogs of naturally occurring pyrophosphates of the bone matrix. They are subdivided into nonnitrogenous and nitrogenous (amino) bisphosphonates, which differ partly in their mode of action by which they inhibit osteoclasts and in their capacity to inhibit bone absorption [356, 357]. Bisphosphonates are clinically used for the treatment of osteoporosis, osteitis deformans (Paget's disease of the bone), bone metastases, malignancy-associated hypercalcemia and multiple myeloma.

Table 20.10 Current Phase III trials of PARP inhibitors in breast cancer (modified after [110])

Sponsor	ClinicalTrial.gov Identifier	Trial	Treatment	Population	Biomarker
Abbvie	NCT02032277	Brightness	Carboplatin-based NAC + Veliparib/Palcebo	Triple-negative early breast cancer	–
AstraZeneca	NCT02032823	OlympiA	Maintainance Olaparib/Placebo	HER2-early breast cancer	BRCA1/2 mutation
AstraZeneca	NCT02000622	OlympiaD	Olaparib versus Physician's choice	Advanced/metastatic HER2-breast cancer	BRCA1/2 mutation
Abbvie	NCT02163694	Brocade	Carboplatin/Paclitaxel plus Veliparib/Placebo	Advanced/metastatic HER2-breast cancer	BRCA1/2 mutation
Tesaro	NCT01905592	BRAVO	Niraparib versus Physician's choice	Advanced/metastatic HER2-breast cancer	BRCA1/2 mutation
BioMarin	NCT01945775	EMBRACA	Talazoparib versus Physician's choice	Advanced/metastatic HER2-breast cancer	BRCA1/2 mutation

Source Marmé and Schneeweiss [392]. Epub 2015 Jun 24. Copyright © 2015 Karger Publishers, Basel, Switzerland
Abbreviations: *NAC* neoadjuvant chemotherapy

Table 20.11 Bone-targeted agents

Agent	Trade name® (selection)	Mode of action	Dosing	Interactions	Selected adverse events and precautions
Zoledronate	Zometa®	Inhibition of osteoclasts	4 mg q4w (q3w) IV	Absorption reduced if taken together with calcium, Mg, Fe containing substances or antacids	Acute phase reactions with flu-like symptoms and musculoskeletal pain, electrolyte disturbances including hypocalcemia, hypophosphatemia, hypomagnesenemia, renal failure, edema, osteonecrosis of the jaw and atypical femoral fractures. Stomach pain, dyspepsia, inflammation and erosions of the esophagus and diarrhea predominantly for oral BPs Precaution sufficient hydration! Substitution of vitamin D and calcium p.o. according to specific label Can cause fetal harm.
Ibandronate	Bondronate®		6 mg q4w (q3w) IV or 50 mg daily p.o.		
Clodronate	Bonefos®		1,600 mg daily p.o.		
Pamidronate	Aredia®		90 mg q4w (q3w) i.v.		
Denosumab	Xgeva® Prolia® (for the treatment and prevention of osteoporosis only)	Fully human monoclonal IgG2-anti-RANKL antibody	Xgeva: 120 mg s. c. q4w Prolia: 60 mg s.c. q6 m	None	Osteonecrosis of the jaw, hypocalcemia (severe and fatal cases reported), hypophosphatemia, acute phase reactions, atypical fractures, fatigue/asthenia Supplementation of calcium and vitamin D required to prevent severe hypocalcemia Can cause fetal harm

These highlights do not include all the information needed to use the respective drugs safely and effectively. See full prescribing information for all information needed to use these agents safely. We do not take responsibility for the correctness of the content

Nonnitrogenous Bisphosphonates

BPs are taken up by osteoclasts via endocytosis and then further metabolized to compounds that replace the terminal pyrophosphate moiety of adenosine triphosphate (ATP), forming a nonfunctional molecule that competes with ATP in the cellular energy metabolism. Accumulation of these metabolites inhibits the absorption capacity and induces apoptosis by inhibiting ATP-dependent enzymes. This leads to an overall decrease in bone absorption [356, 357].

Nitrogenous Bisphosphonates (Amino-bisphosphonates)

Second- and third-generation, nitrogen-containing BPs, furthermore block farnesyl diphosphate (FPP) synthase, a key

enzyme of the mevalonate pathway. Loss of FPP synthesis and its metabolites prevents posttranslational modifications of small GTPases (Ras, Rab, Rho, and Rac), which are crucial in the regulation of various processes important for osteoclast function. The disruption of the mevalonate pathway leads to the accumulation of isopentenyl pyrophosphate (IPP) in osteoclasts, which is converted to a cytotoxic ATP analog [356]. The potency of amino-BPs, e.g., zoledronic acid, in preclinical experiments is substantially higher than that of first generation bisphosphonates like clodronate (Table 20.12) [358].

The clinical activity of BPs to prevent so-called skeletal-related events (SREs) in patients with bone metastases, defined as pathological fractures, hypercalcemia, spinal cord compression, or the need for surgical intervention or radiotherapy has been demonstrated in several phase III trials as well as a meta-analysis [359–366]. They are also effective in reducing bone pain and improving global quality of life [359, 362]. In a randomized phase III trial comparing zoledronic acid (ZA) to placebo, ZA significantly delayed the time-to-first-SRE and reduced the overall rate of SRE by 41 % (HR 0.59, $p = 0.019$) compared with placebo [359].

In keeping with preclincal data, zoledronic acid has demonstrated the highest efficacy in reducing the risk of skeletal complications when compared to other BPs [367–370]. It is the most commonly used BP in the oncologic setting, however, risk of related adverse events like osteonecrosis of the jaw (ONJ) might also be higher compared to less potent BPs.

Zoledronate, clodronate, ibandronate, and pamidronate are approved for the therapy of (bone-) metastasized breast cancer, whereas alendronate is only approved for osteoporosis in postmenopausal women. Recommended agents for the use in the United States are zoledronate (4 mg IV every 3–4 weeks) and pamidronate (90 mg IV every 3–4 weeks) as indicated by the National Comprehensive Cancer Network guideline, breast cancer version 1.2016. In addition to zoledronate and pamidronate, ibandronate and clodronate are recommended for the treatment of bone metastases in Europe.

According to its label, zoledronate is administered as a 4 mg intravenous infusion every 3–4 weeks with concomitant substitution of calcium and vitamin D. Recent evidence suggests that prolonging dosing intervals to 12 weeks after a year of 3–4 weekly dosing does not compromise efficacy, but might have fewer side effects [356, 371].

The toxicity profile of bisphosphonates is favorable, with the most frequent side effects being acute phase reactions, manifesting as fever, chills and mylagias. They can be observed in up to 55 % of patients [372] and usually occur within 24 h of the first infusions and are short lived. Antipyretics and anti-inflammatory drugs can successfully alleviate symptoms. Not all BPs are associated with the same frequency of acute phase reactions. Zoledronate has a higher tendency compared to other BPs. Furthermore, two infrequent but serious adverse events are of major concern: renal toxicity and osteonecrosis of the jaw (ONJ). ONJ is a rare but severe event, which is reported in approximately 1.3 % of patients treated with zoledronate in randomized trials as therapy for bone metastases [373]. The risk for developing ONJ is considerably higher during intravenous amino-bisphosphonate therapy than in patients on oral BPs. Most affected patients present with specific risk factors like poor oral hygiene, history of dental extractions, preexisting dental or paradontal disease, use of dental appliances, radiotherapy, and concomitant administration of antiangiogenic agents [373]. Prior to the start of IV BP therapy, patients should be referred to a dentist or dental surgeon for an examination. If required, dental surgical procedures should ideally be completed before the start of the treatment and if dental extractions become necessary during BP therapy, special measures have to be taken. Other risk factors for ONJ are corticosteroid use, diabetes mellitus, smoking, as well as the potency of the bisphosphonate and the duration of use. Patient education about these serious side effects is crucial.

Table 20.12 Summary of different classes of bisphosphonates and their relative potencies

Nonnitrogenous bisphosphonates		Potency in relation to etidronate [358]
First generation	Etidronate	1
	Clodronate	10
	Tiludronate	10
Nitrogen-containing bisphosphonates		
Second generation	Pamidronate	100
	Neridronate	100
	Alendronate	500
	Ibandronate	1000
Third generation	Risedronate	2000
	Zoledronate	10,000

Renal toxicity is a further major concern with (IV) BPs. Increased creatinine levels from baseline are seen in about 10 % of patients under BP therapy. The rates vary between the individual BPs. Monitoring of serum creatinine levels and creatinine clearance is crucial during IV BP therapy and additional nephrotoxic drugs should be avoided if possible. Of note, patients with metastatic cancer are at risk of kidney failure as a result of numerous predisposing factors like frequent administration of contrast media, analgesics, and last but not least nephrotoxic cytotoxic agents. The use of denosumab for this indication avoids this problem. Further side effects include edema and electrolyte imbalances, including hypophosphatemia, hypocalcemia and hypomagnesemia, and atypical fractures. Prophylactic substitution of vitamin D and calcium is therefore recommended during BP therapy [372]. Oral administration of BPs like ibandronate or clodronate can also provoke dyspepsia and gastroesophageal irritation as well as diarrhea [356].

20.2.5.2 Rank Ligand (RANKL) Inhibitors

Denosumab

Denosumab is a fully human monoclonal IgG2 antibody that specifically targets a ligand known as RANKL (Receptor Activator of NF-κB Ligand), which is a key mediator of osteoclast formation, function, and survival. RANKL is naturally expressed by osteoblasts and counterbalanced by osteoprotegrin, its natural inhibitor to keep bone turnover in balance. Tumor cells within the bone can secrete cytokines (e.g., TNF, IL-1, TGF-β) which stimulate the expression and secretion of RANKL in osteoblast. Upon binding to its receptor (RANK), which is expressed on immature osteoclasts, RANKL leads to osteoclast differentiation, activation, and survival, thereby inducing bone absorption. Denosumab mimics the endogenous function of osteoprotegrin to prevent bone resorption.

The clinical activity of denosumab to prevent SREs has been evaluated in three phase III registrational trials, with identical study design, comparing denosumab (120 mg s.c. q28d) to IV zoledronate, the most potent BP in clinical use, in patients with bone metastases. In the phase III trial, investigating the use of denosumab in breast cancer metastasized to the bone (n = 2046), denosumab was superior to zoledronic acid and significantly delayed the time-to-first SRE (HR 0.82; p = 0.01), the primary endpoint, as well as the time-to-first and subsequent SRE (RR 0.77, p = 0.001) [374]. Consistent results were reported for patients with bone metastases from solid tumors in the other trials. However, denosumab did not show superiority in patients with multiple myeloma [375–377]. An integrated analysis demonstrated that denosumab was also significantly superior in preventing bone pain and improving quality of life [377, 378].

Denosumab 120 mg s.c., q28d (XGeva®) has been approved for the prevention of SRE in patients with bone metastases from solid tumors by the FDA in 2010 and the EMA for Europe in 2011.

Based on a large randomized phase III trial, denosumab 60 mg s.c. (Prolia®) given every 6 months, in the US is also indicated to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer [379]. In addition, in the US as well as in Europe, denosumab 60 mg s.c. given every 6 months has received approval for the treatment of postmenopausal women with osteoporosis at high risk for fracture. In a large randozimed phase III trial, denosumab reduced the risk of new vertebral fractures by 68 % (RR 0.32; $p < 0.001$) [380].

As denosumab can induce severe and potentially life-threatening hypocalcemia, supplementation of calcium and vitamin D is essential, as is the monitoring of serum calcium levels and the education about associated signs and symptoms. Other relevant adverse effects include ONJ, which occurred in 1.8 % of patients within the phase III trials in patients with bone metastases, acute phase reactions, fatigue/asthenia, hypophosphatemia, and nausea. Atypical fractures of the femur neck are further rare events.

20.2.5.3 Adjuvant Use of Bone-Targeted Agents

Adjuvant Bisphosphonates

In addition to their ability to inhibit bone resorption in bone metastases, preclinical data from animal models and early clinical data suggested that bisphosphonates might also play a role in preventing bone metastases [381]. As a consequence, bisphosphonates have been investigated as adjuvant therapies for early breast cancer. Several adjuvant trials have reported improved bone metastases-free, disease-free, and overall survival for oral clodronate and intravenous zoledronic acid [382, 383]. However, other trials failed to demonstrate similar benefits from adjuvant bisphosphonates [384–386]. Prespecified and exploratory subgroup analyses in these trials suggested that benefits are restricted to postmenopausal or older patients [387].

Finally, a large individual patient data-based meta-analysis carried out by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG), including 18766 patients treated within 26 clinical trials addressed the question of the role of adjuvant bisphosphonate therapy. In this meta-analysis significant effects on recurrences, distant recurrences, bone metastases, and breast cancer mortality were observed but proved to be small and of borderline significance in the overall population. However, among the 11,767 postmenopausal patients within these trials, a highly statistically significant reduction in recurrences (RR 0.86,

$p = 0.002$), distant recurrences (0.82, $p = 0.0003$), bone recurrences (0.72, $p = 0.0002$) and breast cancer mortality (0.82, $p = 0.002$) was observed, whereas mortality from other causes was unchanged. Further subgroup analysis did not demonstrate a differential effect by type or schedule of bisphosphonate, duration of therapy, and hormone receptor status [388]. In contrast, no benefit from adjuvant bisphosphonates was seen in premenopausal patients.

Although possible explanations, why this effect is only seen in postmenopausal women remain hypothetical, there is some preclinical data from mouse models that support the validity of this observation. In a mouse model, zoledronate only inhibited the formation of bone metastases in ovariectomized animals [389].

The data on adjuvant bisphosphonates are controversially perceived and discussed amongst experts, due to the conflicting results of the individual trials. The current 2016 version of the American National Comprehensive Cancer Network (NCCN) guidelines does not give a statement regarding the use of BPs in the adjuvant setting, whereas the most recent (2016) yearly updated treatment guideline by the "Arbeitsgemeinschaft Gynäkologische Onkologie" (AGO) recommends the use of adjuvant BPs in postmenopausal patients. Finally, the Panel of the 2015 St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer was divided on this question, with a small majority supporting the adjuvant use of BPs in postmenopausal patients and only a minority supporting their use in premenopausal patients receiving LHRH plus tamoxifen.

Adjuvant Denosumab

Recently, a randomized, placebo-controlled phase III trial (ABCSG-18, NCT00556374), investigating the role of adjuvant denosumab (60 mg s.c. q6 m) reported data on the prevention of clinical bone fractures during adjuvant aromatase inhibitor therapy, its primary endpoint. The addition of denosumab led to a 50 % relative reduction in clinical fractures [390]. The substantial difference in the primary endpoint led the independent data monitoring committee to recommend that patients should be offered unblinding and cross over to denosumab in case they received placebo. As a result, a time-driven, "premature" DFS analysis (secondary endpoint) was recommended and performed. The results of the DFS analysis were presented at the San Antonio Breast Cancer Symposium in December 2015. The intention to treat analysis showed a borderline significant improvement in DFS (HR 0.816, $p = 0.051$), which reached significance in a sensitivity analysis, censoring at crossover (HR 0.81, $p = 0.042$) as well as in a subgroup analysis of patients with a tumor size larger than 2 cm (HR 0.66, $p = 0.017$) [391]. Due to the limitations mentioned above, the adjuvant use of denosumab 60 mg s.c. q6 m, cannot be recommended, as yet. It does, however, represent a valuable treatment option to prevent fractures and bone loss in patients at risk. For a general recommendation of denosumab as adjuvant therapy in breast cancer, results from the randomized, placebo-controlled phase III D-Care trial (NCT01077154) have to be awaited. This trial investigates the efficacy of denosumab (given at higher doses of 120 mg s.c.) to reduce recurrences in patients with early breast cancer at high risk of recurrence.

Until further data are available, recommendations for individual patients have to be made on an individual basis, taking into account, bone mineral density, the risk of fractures, adjuvant therapy, menopausal status, risk of recurrence as well as potential adverse effects of bisphosphonates and denosumab.

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