Current Medical Treatment of Patients with Non-Colorectal Liver Metastases: Primary Tumor Breast Cancer

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Summary

Background: (Metastatic) breast cancer is a heterogeneous entity in which every disease subtype requires an individualized systemic treatment approach. **Methods:** We reviewed the currently available data regarding systemic therapy of breast cancer and present a review of historical and current treatment approaches, with the publications cited covering a time span from 1896 to the last ASCO 2015. **Results:** Systemic therapy of metastatic breast cancer may include chemotherapy, endocrine therapy, and targeted therapies (e.g. antibody-based approaches). Based on the patient's breast cancer subtype, these agents may be employed alone or in combination. Therefore, characterization of the phenotype of the disease is necessary and may include biopsy of the metastatic site. Novel therapeutic approaches include immunologic therapies as well as PARP, PI3K and CDK 4/6 inhibitors, which are currently under investigation in clinical trials. **Conclusion:** Systemic therapy of metastatic breast cancer requires complex and individualized treatment approaches that are best offered in an interdisciplinary setting.

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Introduction: Breast Cancer – a Heterogeneous Entity

Rather than being a homogeneous entity, breast cancer is increasingly recognized to consist of several molecular subtypes that differ significantly with regard to both tumor biology and clinical behavior.

Currently, three different subtypes are relevant:

- Luminal breast cancer: This subtype is HR(hormone receptor)-positive; however, significant differences with regard to response to endocrine therapy may be observed. Whereas luminal A breast cancer is commonly highly endocrine sensitive and slowly proliferating, luminal B breast cancer is less endocrine sensitive and comes with a higher proliferation rate which results in a less favorable prognosis.
- HER2-positive breast cancer: This subtype is characterized by an overexpression/amplification of HER2/neu which results in an increased chance of response against HER2-targeted agents such as trastuzumab, pertuzumab, and lapatinib. However, it is increasingly recognized that HER2-positive/HR-positive breast cancer and HER2-positive/HR-negative breast cancer are significantly biologically different.
- Triple-negative breast cancer (TNBC): This subtype is defined by a lack of HR expression (i.e. expression of estrogen receptor (ER) and progesterone receptor (PR)) as well as a lack of overexpression/amplification of the HER2/neu oncogene. Consequently, endocrine treatment and HER2-targeted agents are not indicated and chemotherapy remains the most important agent of choice in all disease settings. Overall, this breast cancer subtype has an unfavorable prognosis with high rates of recurrence and rapid progression in advanced disease stages. The prognosis of patients with TNBC, however, is highly dependent on their response against chemotherapy: If patients respond well to chemotherapy, prognosis may be very favorable [1].

Breast Cancer Subtyping in the Metastatic Setting

It is well known that both HR expression and HER2/neu status may vary during the development of metastatic disease. Pooled relative discordance rates between primary tumors and metastatic disease for ER, PR, and HER2 status of 20% (95% confidence interval (CI) 16–35%), 33% (95% CI 29–38%), and 8% (95% CI 6–10%), respectively, have been reported [2]. Discordance in receptor expression status may be a result of many biological and technical phenomena. Some of these phenomena constitute of:

- tumor heterogeneity;
- change in receptor status as a result of (targeted) treatment;
- technical issues (fixation schedules, decalcification protocols);
- tumor microenvironment.

Since it is highly important that the molecular subtype of the metastatic entity is well identified, examiners are encouraged to biopsy the metastatic site whenever possible in order to immunohistochemically stain the tumor tissue and to determine the receptor status of the metastasis.

To date, however, there are several open questions with regard to molecular subtyping of metastatic breast cancer:

- (1) Breast cancer (and metastatic breast cancer in particular) is known to be highly heterogeneous. Therefore, metastatic sites in a given patient may very well represent distinct molecular entities and thus respond differentially to a given therapy. As a result, the optimal number of biopsies is not defined and may very well not be achieved in a clinical setting.
- (2) There is no evidence-based recommendation yet as to how to react to a 'loss' of a given therapeutic target (such as loss of HR or HER2/neu overexpression) – particularly if endocrine therapy is considered as a maintenance option after induction chemotherapy.

Endocrine Therapy

In hormone-sensitive metastatic breast cancer, endocrine therapy is the therapy of choice [3]. Only in cases of an acutely life-threatening disease progression chemotherapy should be chosen in ER-positive HER2-negative disease. In contrast, if no such indication exists, endocrine therapy should be preferred. The agents used in endocrine therapy are described in the following paragraphs, with the data cited covering a time span from the first publication on the efficacy of an oophorectomy in 1896 to the latest data presented at the American Society of Clinical Oncology (ASCO) meeting 2015.

Selective Estrogen Receptor Modulators

In the early 1970s, the first data about the efficacy of tamoxifen, a selective ER modulator, in metastatic breast cancer were published [4, 5]. With response rates between 16 and 56% and a superior toxicity profile compared to the former standard, i.e. high-dose estrogen [6], tamoxifen was established as the therapy of choice for metastatic breast cancer [7–12]. Although the median

time to progression (TTP) with tamoxifen is only about 6 months, the response is robust with patients responding for 12–18 months, in rare cases even years. However, a comparison between tamoxifen and the former standard, diethylstilbestrol – a high-dose estrogen therapy –, showed an inferiority of tamoxifen concerning overall survival (OS) [13]. The main reason for establishing tamoxifen as the new standard over 40 years ago was its superior toxicity profile. Tamoxifen still is a valid option in endocrine therapy of metastatic breast cancer but has become an agent for higher lines of therapy over the years.

Aromatase Inhibitors

Aromatase inhibitors have replaced tamoxifen in the first line of endocrine therapy for metastatic breast cancer. Unlike tamoxifen, their mechanism of action is not aiming at the ER on the surface of the tumor cell directly, but is suppressing the production of estrogen in the periphery in postmenopausal women. Their response rates and TTP are superior to tamoxifen whereas their toxicity profile is comparable [14].

The first studies on aromatase inhibitors compared them in the second line after tamoxifen therapy to the former second-line standard megestrol or medroxyprogesterone acetate [15, 16]. In several studies, a significant benefit for OS could be shown for anastrozole [17, 18], as well as a significantly longer time to treatment failure and a significantly higher response rate for letrozole [19]. The only steroidal aromatase inhibitor (exemestane) proved to provide a significant benefit concerning TTP, time to treatment failure, and OS [20, 21]. The toxicity profiles of all three aromatase inhibitors were superior compared to megestrol or medroxyprogesterone.

In the first-line setting, aromatase inhibitors were superior compared to tamoxifen. Whereas the results concerning anastrozole were contradictory – in one study no significant superiority to tamoxifen could be seen [22], while another investigation published at the same time showed a better progression-free survival (PFS) and clinical benefit rate [23] –, letrozole and exemestane proved to have a significantly better effect on response rate, clinical benefit rate, and PFS [24–26].

These data led to the establishment of aromatase inhibitors as a first-line standard. Although there are competitors on the horizon, aromatase inhibitors still represent a mainstay in the endocrine therapy of metastatic breast cancer in postmenopausal women.

Selective Estrogen Receptor Downregulators

Another option in the endocrine treatment of metastatic breast cancer is the selective ER downregulator fulvestrant. Unlike tamoxifen, it is completely lacking the partial estrogen agonism that may be a reason for treatment failures and definitely is the reason for the elevated risk for endometrial cancer in postmenopausal women treated with tamoxifen [27]. A direct comparison with anastrozole in higher lines of therapy resulted in a proof of non-inferiority [28], whereas the comparison with tamoxifen in the first line showed no superiority of fulvestrant. In the overall population of this study, which included patients with unknown receptor sta-

tus, fulvestrant even showed a trend for inferiority; however, in the patients with proven hormone sensitivity no differences were seen [14]. Further investigations on fulvestrant focused on the dosage and resulted in a change of the standard dose from 250 to 500 mg [29]. This finally led to a proof of superiority for anastrozole in the first-line setting in a phase II study [30]. The ongoing phase III trial FALCON, comparing fulvestrant and anastrozole in the first line, will hopefully answer the question of where fulvestrant will find its place in the endocrine treatment cascade of metastatic breast cancer.

Luteinizing Hormone Agonists

For many years the endocrine therapy of choice for premenopausal women suffering from metastatic breast cancer was oophorectomy [8, 31]. Since the development of tamoxifen researchers have tried to establish an alternative to surgery by comparing the drug with the operation in premenopausal patients, thus trying to spare patients the risks of surgery and the psychological trauma of the oophorectomy [32]. Although tamoxifen seems to have a comparable effect as ovarian suppression, the published results failed to prove equal efficacy, mainly for methodological reasons [9, 33]. One of the main caveats of tamoxifen in premenopausal patients with intact ovaries is its ability to cause high peaks of estrogen levels with unknown – possibly damaging – effects on the course of the disease. The development of luteinizing hormone agonists as agents leading to an ovarian suppression offered a way out of this dilemma. Whereas the first use of the new agents was mainly led by the idea of replacing surgery [34], the strategy of combining ovarian suppression with tamoxifen was the next and logical step. This was based on the idea of ovarian suppression leading to an artificial menopause, thus making it possible to apply the known benefits of tamoxifen for postmenopausal patients to the premenopausal setting. A large meta-analysis showed significant benefits for response rates, progression-free interval, and OS [35] for the combination of luteinizing hormone agonists and tamoxifen and implemented this therapy as the standard for premenopausal patients.

Chemotherapy and Targeted Agents for Metastatic Breast Cancer

Indication for Chemotherapy in Metastatic Breast Cancer

Overall, an indication for chemotherapy in metastatic breast cancer may be seen in three situations:

- HR-positive/HER2-negative breast cancer unsuitable for endocrine intervention alone due to (i) resistance to endocrine interventions or (ii) rapid (life-threatening) disease progression and high need for remission;
- TNBC as there are yet no relevant targets suitable for targeted therapy outside of clinical trials;
- HER2-positive metastatic breast cancer (because chemotherapy is part of the majority of several HER2-targeted treatment regimens).

Monochemotherapy versus Polychemotherapy

If chemotherapy is indicated, monotherapy is usually applied. Although polychemotherapy has been shown to increase response rates and even prolong PFS rates compared to monochemotherapy, this may be counterbalanced by an increased rate of (severe) toxicities. Therefore, combination chemotherapy in metastatic breast cancer (i.e. combination of taxanes with either anthracyclines or antimetabolites) should be restricted to cases with severe symptoms and high need for remission.

Choice of Agents

In some cases (such as in HER2-targeted therapy), certain chemotherapy agents (such as docetaxel with pertuzumab/trastuzumab or capecitabine with lapatinib) may be selected based upon licensing issues or as an evidence-based approach focusing on efficacy in certain combination regimens. In other cases, the selection of chemotherapy agents is less strict. Since taxanes and anthracyclines are considered to represent the most efficacious agents in breast cancer chemotherapy, these agents should be used before other agents are selected unless (i) there are contraindications or (ii) these agents have already been used in earlier disease stages.

Overall, factors that assist in choosing the optimal combination chemotherapy agent are:

- ER/PR, HER2; combination with biologicals;
- previous treatments (and their toxicities);
- recurrence-free interval following adjuvant therapy;
- aggressiveness of disease, localization of metastases;
- estimated survival time;
- concurrent diseases (including organ function);
- expectations/preference of patient [36].

Agents that may be used are:

- Taxanes (paclitaxel/docetaxel/nab-paclitaxel);
- anthracyclines (epirubicin/doxorubicin/(PEG-)liposomal doxorubicin);
- platinum (carboplatin/cisplatin);
- vinorelbine;
- capecitabine;
- eribulin;
- gemcitabine.

Although the optimal duration of chemotherapy is still and repeatedly a matter of debate, there is consensus that the duration of a given chemotherapy regimen should be restricted to the patient's therapeutic index (i.e. therapeutic efficacy vs. therapeutic toxicity) remaining positive [37].

There is yet limited evidence as to whether certain breast cancer molecular subtypes derive a particular benefit from specific chemotherapy agents, and evidence is even more limited in metastatic disease. However, there is accumulating evidence which supports a particular role for platinum salts among patients with hereditary breast cancer (i.e. those harboring a BRCA mutation). For a long time, evidence was limited to data from retrospective analyses. However, this has changed since the publication of the results from the British TNT (Triple Negative Trial) study. In this study, patients with either TNBC or metastatic breast cancer with a muta-

tion in BRCA1 or BRCA 2 were randomized to either taxane monotherapy (docetaxel 100 mg/m² q3w, 6 cycles) or carboplatin (AUC6, q3w, 6 cycles) [38]. Analysis of the primary study endpoint (response rate following 3–6 cycles) showed a significant difference in favor of the therapy with platinum salts among patients with hereditary breast cancer (response rates for carboplatin vs. docetaxel 68 vs. 33%, respectively; $p = 0.03$). For patients with metastatic non-hereditary breast cancer no significant association was observed (28 vs. 37%, $p = 0.16$). Therefore, the German Gynecological Oncology Group (Arbeitsgemeinschaft Gynäkologische Onkologie (AGO)) has recommended the preference of platinum salts (i.e. carboplatin) to taxanes (i.e. docetaxel) among patients with metastatic breast cancer carrying a BRCA1 or BRCA2 mutation.

Use of Antiangiogenic Therapy

The most prominent antiangiogenic agent in oncology is bevacizumab, which represents a humanized monoclonal immunoglobulin G antibody against the vascular endothelial growth factor. In Germany, bevacizumab is licensed for use in patients with HER2-negative metastatic breast cancer as part of first-line therapy in combination with either paclitaxel or capecitabine. Of note, in a direct comparison of both treatment regimens, the paclitaxel combination seems to be slightly more efficacious compared to bevacizumab/capecitabine (TURANDOT trial, median PFS 11.0 vs. 8.1 months) [39].

The use of bevacizumab in breast cancer, however, is still a matter of debate both in Germany and internationally, given that across all trials the addition of bevacizumab to chemotherapy has improved PFS rates but no OS endpoints: for instance, in the pivotal ECOG 2100 study which led to the approval of bevacizumab, median PFS was 11.8 vs. 5.9 months for the first-line use of paclitaxel with and without bevacizumab, respectively [40]. Similar rates have been shown for capecitabine (RIBBON-1, 8.6 vs. 5.7 months) [41]. In contrast, even in meta-analyses of these trials, the hazard ratio (HR) for OS in association with the use of bevacizumab was 0.95 (95% CI: 0.85–1.06) [42]. In fact, the efficacy data regarding bevacizumab has triggered an intense debate as to which efficacy endpoint has the most value among patients with metastatic breast cancer.

Nevertheless, bevacizumab is not only licensed in both combinations in first-line therapy but is also recommended for use in this setting as part of German national treatment recommendations [43].

Chemotherapy with HER2-Targeted Agents

For a long time, the prognosis of patients with HER2-positive breast cancer was considered to be the most unfavorable among all subtypes of breast cancer. The development of the monoclonal HER2-targeted antibody trastuzumab, however, has changed this perception dramatically [44]. HER2-positive disease, despite usually representing a fast proliferating, highly aggressive entity, is currently regarded to represent one of the subtypes with the largest number of highly efficacious treatment options. Therefore, rather than being an unfavorable prognostic factor, HER2 is nowadays re-

garded as a favorable predictive parameter since it represents the prerequisite for an increasing number of highly active HER2-targeted agents.

HER2-Targeted Antibodies and Antibody-Drug Conjugates

The first antibody that was developed against the HER2/neu receptor is the monoclonal antibody trastuzumab. Trastuzumab is a humanized monoclonal antibody targeted against the extracellular domain of the HER2 receptor. Due to the use of trastuzumab in combination with monotherapy, significant improvements in OS have been demonstrated [45]. Nowadays, trastuzumab is regarded as the first agent in the era of molecularly targeted agents in breast cancer and thus as a forerunner to a paradigm shift in the treatment of the disease.

Recently, the development of another HER2-targeted monoclonal antibody has improved the efficacy of trastuzumab even further. Pertuzumab is a monoclonal antibody directed against the HER2/HER3 dimerization domain of the HER2 receptor. If patients are treated with trastuzumab and pertuzumab in combination with docetaxel as part of a first-line chemotherapy regimen, OS rates of as high as 56.5 months may be reached [46]. Therefore, this regimen is considered as today's first-line chemotherapy standard regimen for patients with HER2-positive metastatic breast cancer.

Antibody-drug conjugates (ADC) offer another treatment option for patients with HER2-positive breast cancer. Trastuzumab-emtansine (TDM-1) is a highly effective antibody-drug conjugate of the cytotoxic DM1 and trastuzumab. After internalization of the ADC the cytotoxin is released and targets the tumor cell from the inside. The use of TDM-1 may also increase both PFS and OS rates. In the pivotal EMILIA study, which eventually served as a registration study for TDM-1 in metastatic HER2-positive breast cancer, OS rates for TDM-1 compared to capecitabine/lapatinib were 30.9 vs. 25.1 months [47]. TDM-1 is licensed for use in patients with HER2-positive metastatic breast cancer either as part of a second-line treatment regimen or in case of fast progression (<6 months) after a trastuzumab-based treatment regimen in the curative setting.

Small Molecules Targeting HER2 Signaling

Apart from HER2-directed antibodies, HER2 signaling may also be abrogated by the use of small molecules. Lapatinib was the second HER2-targeted agent which was registered for HER2-positive metastatic breast cancer in combination with capecitabine, and is a small molecule targeting both HER1/EGFR and HER2. Registration was based upon the results of a randomized study showing a PFS benefit of approximately 4 months for the combination of capecitabine/lapatinib versus capecitabine alone (HR 0.34, $p < 0.001$) [48]. However, since both pertuzumab/trastuzumab and TDM1 have demonstrated an OS benefit, lapatinib is largely recognized as a treatment option for later-line therapy. In addition to lapatinib/capecitabine, lapatinib is also registered for the treatment of HER2-positive/HR-positive breast cancer in combination with letrozole [49] as well as for patients with HER2-positive/HR-negative breast cancer in combination with trastuzumab [50].

Fig. 1. PI3K pathway.

Fig. 2. mTOR pathway.

Neratinib is a novel member of the family of HER2-targeted agents. The small molecule irreversibly targets HER1, HER2, and HER4 and has not been licensed yet for the treatment of breast cancer. The agent, however, demonstrated significant efficacy in an adjuvant study presented at the recent meeting 2015 [51] and is currently under investigation in several trials, including a head-to-head combination of capecitabine and neratinib versus capecitabine and lapatinib (NALA, NCT01808573).

Novel Agents for the Treatment of Metastatic Breast Cancer

PI3K/mTOR Inhibitors in Hormone Receptor-Positive Breast Cancer

The phosphoinositide 3-kinase (PI3K)/activated protein kinase (AKT)/mammalian target of rapamycin (mTOR) (fig. 1, 2) pathway plays an important role in cell growth, survival and proliferation. It is also a central part of signal transduction for cell metabolism [52]. The pathway is activated by growth factors, leading to a phosphorylation of PI3K. One of the inhibitors of the PI3K/AKT/mTOR pathway is phosphatase and tensin homolog (PTEN), a tumor suppressor gene that inhibits the activation of AKT. As in many other tumors, this pathway is activated in breast cancer. This happens either because of mutations in PTEN, PIK3CA, or AKT or

because of amplifications or mutations of receptor tyrosine kinases such as HER2. Since there is an intensive crosstalk between the signaling of the estrogen receptor and PI3K, the PI3K/AKT/mTOR pathway is considered to play a major role in the development of endocrine resistance [53]. In the last years, several targeted therapies inhibiting the pathway have been developed in order to find a way to overcome endocrine resistance in combination with fulvestrant or aromatase inhibitors. Table 1 summarizes the results of the most important studies on PI3K and mTOR inhibition in hormone-sensitive metastatic breast cancer. Whereas the development of therapies targeting PI3K is still in the stage of clinical studies, the combination of the mTOR inhibitor everolimus with the steroidal aromatase inhibitor exemestane is already a standard therapy after the failure of a non-steroidal aromatase inhibitor such as anastrozole or letrozole. If the patient has not received a non-steroidal aromatase inhibitor in the adjuvant setting, the therapy with everolimus and exemestane is used in second or higher lines, whereas patients who have been treated with anastrozole or letrozole during the course of the adjuvant therapy may receive the combination of an mTOR inhibitor and a steroidal aromatase inhibitor as a first-line therapy option at the time of generalization of the disease.

PI3K/mTOR Inhibitors in HER2-Positive Breast Cancer

There is an increasingly solid body of evidence that alterations of the PI3K/AKT/mTOR pathway in addition to mediating endocrine resistance may also be involved in mediating resistance against HER2-targeted agents in HER2-positive breast cancer. Several analyses including one meta-analysis demonstrate that alterations in PI3K signaling, such as alterations of PIK3CA, may confer resistance against dual blockade with trastuzumab and lapatinib (i.e. decrease rates of pathological remission in neoadjuvant therapy regimens) and may even be associated with adverse survival, particularly in HER2-positive/HR-positive subtypes [54].

The BOLERO-1 and BOLERO-3 studies evaluated mTOR inhibition by means of everolimus in HER2-positive breast cancer in combination with trastuzumab among patients with HER2-positive metastatic breast cancer. In a translational analysis using patient samples from these studies, Slamon et al. [55] evaluated whether there was an association between alteration in the PI3K/mTOR cascade and efficacy of everolimus in reversing trastuzumab resistance. In fact, PI3K mutations as well as other PI3K pathway alterations led to an increased everolimus efficacy [55].

These analyses demonstrate that PI3K targeting may hold the promise of not only reversing endocrine resistance (i.e. through the use of everolimus in combination with exemestane) but also of reversing resistance against HER2-targeted agents in certain HER2-positive subtypes. The latter indication, however, needs to be studied more intensely before its translation into clinical practice outside of clinical trials.

CDK 4/6 Inhibitors

Dysregulation of the cell cycle is a major characteristic of cancer. The family of cyclin-dependent kinases (CDK) is an important factor in the regulation of the cell cycle. CDK 4 and 6 as well as

Table 1. Results for the use of mTOR and PI3K inhibitors in hormone-sensitive metastatic breast cancer (modified from [64])

Substance	Inhibition	Phase	N	Combination partners	Clinical benefit
Everolimus (BOLERO-2)	mTOR	III	724	exemestane	PFS: 10.6 vs. 4.1 months [65]
Tamoxifen (TAMRAD)	mTOR	II	111	tamoxifen	TTP: 8.6 vs. 4.5 months [66]
Ridaforolimus	mTOR	II / random.	80	dalotuzumab / exemestane	PFS not significant ^a HR 1.18; 80%-CI: 0.8–1.72; (p = 0.565) [67]
BKM120 (Burparlisib)	PI3K class I (pan)	Ib	51	letrozole	clinical benefit rate: 31% [68]
BKM120 (Burparlisib)	PI3K class I (pan)	I	31	fulvestrant	evidence for antitumor activity [69]
GDC 0941 (Pictilisip) / FERG1 trial	PI3K class I (pan)	II / random.	168	fulvestrant	PFS: 6.6 vs. 5.1 months [70] ^b more benefit for ER-/PR-positive tumors
BYL719	PI3K selective (class I, α)	I	64	fulvestrant stratified for PI3K mutations	evidence for antitumor activity [71] ^c
BYL719	PI3K selective (class I, α)	I	14	letrozol or exemestane	evidence for antitumor activity [72]

^a23.3 weeks (with ridaforolimus) vs. 31.9 weeks.

^bNot statistically significant; PIK3CA mutations were not predictive for response.

^cPartial remissions were only seen in patients with PIK3CA mutations.

PFS = Progression-free survival; TTP = time to progression; HR = hazard ratio; ER = estrogen receptor; PR = progesterone receptor.

cyclin D are responsible for the transition from G1 phase to S phase through phosphorylation of retinoblastoma and thus are crucial for the cell cycle (fig. 3) [56]. Three agents serving as inhibitors of CDK 4/6 activity are currently undergoing intensive development in metastatic breast cancer: palbociclib, ribociclib (LEE011), and abemaciclib. Palbociclib is the agent immediately awaiting approval. In 2009, the inhibitory effect of palbociclib on ER-positive breast cancer cells was demonstrated in vitro [57]. This fueled the further development of the substance in the setting of advanced ER-positive breast cancer. A phase II study (PALOMA-1) comparing letrozole plus palbociclib in the first-line therapy for metastatic or advanced disease resulted in a prolongation of the PFS from 10.2 to 20.2 months and led to an accelerated approval of palbociclib in combination with letrozole as first-line endocrine therapy by the Food and Drug Administration (FDA). A phase III trial (PALOMA-2) has recently completed accrual [58]. For patients after failure of endocrine therapy, data from a phase III trial are already available (PALOMA-3): Here, the investigators chose fulvestrant as an endocrine combination partner for palbociclib and as the competitor in the control arm. In the combination arm, patients had a median PFS of 9.2 months, which proved to be significantly superior to the 3.8 months in the control arm [59]. After these promising results and the approval by the FDA, final approval in Europe is awaited for the end of 2015, probably at first for first-line therapy in combination with letrozole.

The available data for abemaciclib and ribociclib (LEE011) also show clinical efficacy and no unexpected warning signs [60, 61]. Table 2 presents the current study portfolio for CDK 4/6 inhibition in metastatic breast cancer.

The CDK 4/6 inhibitors are one of the most promising innovations in the management of breast cancer in the past few years and are expected to change the course of endocrine therapy.

Immune Oncology

Numerous analyses have shown that tumor cell-immune cell interaction plays an important role in breast cancer in general and in triple-negative disease in particular. For instance, translational analyses of patients with TNBC show that these patients derive an increased benefit from neoadjuvant chemotherapy if their tumor presents with a strong lymphocytic infiltrate.

Consequently, immunologicals are currently under intensive investigation in several malignant entities including breast cancer. These agents act through an alteration of the tumor cell-immune system interaction, which eventually leads to a demasking of the tumor cell and allows for the immune system to recognize and attack the tumor cell. The efficacy of these types of agents does therefore strongly depend on the mutational frequency of the tumor type. The most promising results yet have been published in the

Table 2. Active studies with CDK 4/6 inhibitors in metastatic breast cancer

Agent	Phase	Regimen	Patients (planned enrollment, N)
Palbociclib (PD0332991)	phase 3 (PALOMA-2) (NCT01740427);	palbociclib + LET vs. LET + PBO	ER+, HER2– MBC (450)
	phase 2 (INGE-B) (Eudract 2015-001603-32)	palbociclib + LET vs. letrozole	ER+, HER2– MBC without previous endocrine treatment for MBC (120)
LEE011	phase 3 (MONALEESA-2) (NCT01958021);	LEE011 + LET vs. LET + PBO	ER+, HER2– MBC without previous treatment for MBC (500)
	phase 1/2 (NCT01857193);	LEE011 + EVE + EXE	ER+, HER2– MBC or LABC resistant towards LET or ANA (185)
	phase 1/2 (NCT01872260)	LEE011 + BYL719 + LET	ER+ MBC or LABC (130)
Abemaciclib (LY2835219)	phase 3 (MONARCH-2) NCT02107703	abemaciclib + FUL vs. FUL	ER+, HER2– MBC (no previous endocrine therapy or progression on previous therapy with AI or TAM) (550)
MBC = Metastatic breast cancer; LET = letrozole; PBO = placebo; FUL = fulvestrant; ANA = anastrozole; EVE = everolimus; AI = aromatase inhibitor; TAM = tamoxifen; EXE = exemestane; LABC = locally advanced breast cancer.			

context of malignant melanoma. However, both the high mutational frequency and the need to develop novel therapeutic concepts other than chemotherapy have fostered the development of immune oncology also in the TNBC subtype. Of particular interest as a target in TNBC is the programmed cell death protein 1 (PD-1) and its two ligands PD-L1 and PD-L2. All three proteins may be inactivated by the use of humanized antibodies in order to inactivate their interaction. At the San Antonio Breast Cancer Symposium (SABCS) 2014, results of a phase I clinical trial were presented which analyzed the efficacy and safety of pembrolizumab (Keytruda) among patients with TNBC. Among 27 patients, one case of complete remission, four cases of partial remission, and seven cases of stable disease were assessed. No significant safety signals were recorded [62].

PARP Inhibition

The enzyme poly(ADP-ribose) polymerase (PARP) is involved in a large number of intracellular processes. One of the most significant functions is the repair of DNA damage. Inhibition of PARP in tumor cells may inhibit their capacity to repair DNA

damage resulting from both radiation and cytotoxic therapy [63]. This aspect is of particular interest in patients with (triple-negative) breast cancer harboring a BRCA mutation, since these tumors already suffer from an impaired DNA damage capacity.

The mechanism of action of PARP inhibitor is often referred to as synthetic lethality, which describes a combined effect of i) inhibition of BRCA function through a genetic/somatic mutation and ii) iatrogenic inhibition of the compensatory role of PARP through application of PARP inhibitors.

Several PARP inhibitors are currently under intensive investigation among all stages of TNBC and/or hereditary (i.e. BRCA-associated) breast cancer.

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