Targeted Therapy of HER2-Negative Breast Cancer

Florian Schütz  Christoph Domschke  Andreas Schneeweiss

University Hospital Heidelberg, Breast Unit, National Center for Tumor Diseases, Heidelberg, Germany

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Summary
Personalized and targeted treatments are the most discussed topics in oncology. However, how much personalized medicine is standard of care nowadays and how much is part of our hope for a better future? So far, only a few targeted therapies are available in daily practice for the treatment of human epidermal growth factor receptor 2 (HER2)-negative breast cancer. And even for these few targeted agents – besides those targeting the estrogen receptor (ER) for endocrine treatment – thus far, predictive factors are missing. There are many new drugs and strategies under evaluation but, unfortunately, they are being developed without any cross-comparison. What drug will we choose for which patient in the future? Without answering this question oncologists will not be able to individualize treatment. Predictive factors for every new splendid drug are eagerly needed before it comes to an approval.

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Introduction
In breast cancer, important steps have been made towards the targeted treatment of patients according to their breast cancer subtype defined by the expression of hormone receptors and the human epidermal growth factor receptor 2 (HER2). Hereby, the expression of HER2 seems to be the strongest single stimulus for breast cancer proliferation. Furthermore, the expression of HER2 is associated with poor clinical prognosis. HER2-targeted treatment, however, has led to an enormous improvement in breast cancer prognosis if patients in the pre-trastuzumab area are compared with those treated with trastuzumab [1]. Also in tumors without HER2 overexpression, Cosseti et al. [1] have found a substantial improvement in both disease-free and overall survival. The reason for this may be found in the introduction of new cytotoxic agents (e.g., taxanes or eribulin), the optimized use of established cytotoxic agents (e.g., liposomal formulations of anthracyclines or solvent-free formulations of taxanes), and in the development of combined treatment approaches to delay or circumvent resistance (e.g., combining endocrine treatment with a mammalian target of rapamycin (mTOR) inhibitor).

Personalized treatment of selective tumors, however, will be the key note of oncology [2]. Although many gene signatures of specific pathways or central mechanisms like immunogenic features have been found, so far, there is no trial showing a benefit for patients when they are treated according to their molecular subtype, probably due to the enormous intra- and intertumoral heterogeneity [3, 4].

Here, we discuss the current standards and recent advances in systemic targeted treatment options in HER2-negative breast cancer. In the absence of HER2 overexpression, breast cancer can be divided into 2 groups: the estrogen receptor (ER)-negative and progesterone receptor (PgR)-negative group (so-called triple-negative breast cancer (TNBC)) and the ER/PgR-positive group (so-called luminal-like breast cancer).

Triple-Negative Breast Cancer
TNBC is a heterogeneous disease. In fact, the signaling pathways responsible for cell growth and proliferation are quite different between specific subtypes of TNBC. Therefore, it is difficult to name therapies that are directed against specific tumor characteristics [5].

Primary non-metastatic TNBC should be treated with chemotherapy regimens that are usually used in the highly proliferative luminal B-like subtype [6, 7]. However, it has been shown in both the neoadjuvant and the metastatic setting that bevacizumab (BEV), an antibody targeting the vascular endothelial growth fac-
tor (VEGF), has some benefits in TNBC. Angiogenesis is important to supply all parts of highly proliferative and fast growing tumors. VEGF blockade leads to a reduction in tumor vascularization. In the neoadjuvant GeparQuinto trial, when BEV was added to a standard chemotherapy in HER2-negative primary breast cancer patients, it significantly increased the rate of pathological complete response [8]. Overall survival, however, was not improved by the addition of BEV to neoadjuvant chemotherapy [9]. Therefore, the addition of BEV to standard neoadjuvant chemotherapy cannot be recommended.

In metastatic breast cancer, BEV is able to prolong progression-free survival but not overall survival in combination with taxane-based chemotherapy or capcitabine [7, 10]. Therefore, it is approved for the first-line treatment of HER2-negative metastatic breast cancer in combination with a taxane or capcitabine [11, 12]. In the second line, the addition of BEV to chemotherapy also prolongs progression-free survival but not overall survival in HER2-negative breast cancer [13]. Despite extensive translational research efforts, a predictive marker for patients who will benefit from the addition of BEV has so far not emerged [14].

The combination of BEV plus an endocrine therapy with letrozole compared to letrozole alone in postmenopausal metastatic breast cancer patients has failed to improve progression-free survival in the LEA trial [15]. Recently, however, the first results of the phase III Cancer and Leukemia Group B (CALGB) trial 40503 have been presented. This trial showed a significant improvement in progression-free survival with the addition of BEV to letrozole as compared to letrozole alone as first-line treatment in 352 postmenopausal metastatic breast cancer patients (hazard ratio (HR) 0.75, 95% confidence interval (CI) 0.59–0.96; p = 0.016) [16]. It would be of great interest to pool these trial populations to answer the question whether BEV in combination with endocrine treatment could be of benefit for some patients. Economic topics, however, may arise, e.g. by questioning if 4 more months of progression-free survival are worth the higher costs and additional adverse events associated with BEV.

Despite the fact that molecular subtyping is able to dissect TNBC in several biologically different subtypes (basal-like, BRCA-like, luminal androgen receptor (LAR)-like, claudin-low and -high subtypes, and others), up to now, we do not draw many consequences from this information [17]. Thus far, the first results of the phase III Cancer and Leukemia Group B (CALGB) trial 40503 have been presented. This trial showed a significant improvement in progression-free survival with the addition of BEV to letrozole as compared to letrozole alone as first-line treatment in 352 postmenopausal metastatic breast cancer patients (hazard ratio (HR) 0.75, 95% confidence interval (CI) 0.59–0.96; p = 0.016) [16]. It would be of great interest to pool these trial populations to answer the question whether BEV in combination with endocrine treatment could be of benefit for some patients. Economic topics, however, may arise, e.g. by questioning if 4 more months of progression-free survival are worth the higher costs and additional adverse events associated with BEV.

TNBC and Germline BRCA Mutation

Fasching et al. [18] have shown that tumors with BRCA1 or BRCA2 mutations have a higher sensitivity to chemotherapy in general. Higher rates of pathological complete response are more common in mutation carriers. Some trials have shown positive effects for the addition of carboplatin to standard neoadjuvant chemotherapy in TNBC [19, 20]. In the GeparSixto trial, the addition of carboplatin to an anthracycline/taxane-based neoadjuvant chemotherapy improved the pathological complete response rate from 36.9% to 53.2%. Recently, on behalf of the GeparSixto study group, von Minckwitz et al. [21] presented that, after a median follow-up of 35 months, this improvement in the pathological complete response rate translates into an improved 3-year disease-free survival (85.1% vs. 76.1%, HR 0.56, 95% CI 0.33–0.96; p = 0.0350). Interestingly, patients with wild-type BRCA status seem to benefit more from the addition of carboplatin than patients with germline BRCA mutation. As a consequence, independent from the BRCA status, the addition of carboplatin to standard neoadjuvant chemotherapy should be discussed in patients with high-risk TNBC.

HER2-Negative, Hormone Receptor-Positive Breast Cancer

Endocrine therapy is the oldest targeted treatment in breast cancer. Its benefit regarding the 10-year breast cancer mortality has been estimated recently for postmenopausal breast cancer patients with hormone receptor-positive tumors to be 12.1% for 5-year adjuvant treatment with tamoxifen (TAM) and 14.2% for 5-year adjuvant treatment with aromatase inhibitors (AIs). A comparison of these 2 endocrine treatments has favored the use of an AI in postmenopausal patients (10-year breast cancer mortality TAM vs. AI, response rate (RR) 0.85, 95% CI 0.75–0.96; 2p = 0.009) [22]. In premenopausal patients, the standard of treatment remains as the 5- to 10-year adjuvant treatment with TAM [3]. However, especially in very young patients or those with high risk of recurrence, additional suppression of the ovarian function, e.g., by gonadotropin-releasing hormone (GnRH) analogs may be of further benefit [23].

Endocrine Resistance in HER2-Negative, Hormone Receptor-Positive Breast Cancer

Unfortunately, some patients with ER/PgR-positive breast cancer relapse despite adequate adjuvant endocrine therapy. Several mechanisms of primary and secondary resistance to endocrine treatment have been described: loss of ERα [24], mutations of ER genes [25], or modulation of co-regulators. There are multiple interactions between ERs, growth factors, different kinase signaling pathways like the epidermal growth factor receptor (EGFR), insulin-like growth factor receptor (IGFR), mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK), and phosphatidylinositol 3-kinase (PI3K) pathways. In particular, the PI3K pathway seems to play an important role in developing secondary endocrine resistance as it promotes cellular proliferation and anti-apoptotic responses [26]. A major downstream effector in the PI3K pathway is the mTOR protein. Activation of the PI3K/Akt/mTOR pathway phosphorylates the ER, resulting in hormone-independent activation [27]. Everolimus (EVE) is an oral mTOR inhibitor that may overcome endocrine resistance when it is given additionally to an endocrine agent. In the BOLERO-2 trial, EVE plus exemestan was superior in disease-free survival in comparison to exemestan alone in patients with advanced breast cancer who...
were treated previously with anastrozole or letrozole (event-free survival 11.0 vs. 4.1 months, HR 0.38, 95% CI 0.31–0.48; p < 0.0001). However, there was no benefit in overall survival. Furthermore, a high number of patients developed side toxicities like stomatitis (about 60%), abacterial pneumonitis, and infections.

**Promising Approaches for the Future**

**Anti-Androgenic Treatment in LAR-Positive TNBC**

The androgen receptor (AR) is expressed in up to one-third of the TNBCs. The AR is most abundant in the LAR molecular subtype of TNBC [28]. Enzalutamide, an AR inhibitor that impairs nuclear localization of the AR, was used to elucidate the role of the AR in preclinical models of ER-positive and -negative breast cancer. AR inhibition significantly reduced baseline proliferation, anchorage-independent growth, migration, and invasion and increased apoptosis in TNBC in vitro and in vivo [29]. Enzalutamide is a promising targeted therapy for multiple molecular subtypes of AR-positive TNBC.

**PARP Inhibitors in BRCA Mutation Carriers**

Recently olaparib, an inhibitor of poly(ADP-ribose) polymerase (PARP), has been approved for the treatment of high-grade serous recurrent ovarian cancer as maintenance treatment following response to a carboplatin-containing therapy [30]. PARP is an enzymatic complex that helps to repair DNA single-chain damage. If DNA double-strand breaks are induced, e.g. by platinum salts, and the main repair mechanism of double-strand breaks called homologous recombination is disturbed, e.g. by BRCA mutation, the DNA double-strand break repair machinery mainly depends on PARP. By additionally blocking PARP (synthetic lethality), double-strand breaks can no longer be repaired effectively and apoptosis is induced.

Iniparib, which initially was thought to act via PARP inhibition, showed substantial improvement in progression-free survival when used in addition to carboplatin and gemcitabine in a phase II trial in metastatic breast cancer [31]. In the following phase III trial, however, no significant benefit was observed regarding progression-free or overall survival. In addition, in the meantime, iniparib is no longer viewed as a PARP inhibitor due to preclinical data.

Nevertheless, it is justified to test PARP inhibitors in TNBC tumors, especially in those with BRCA mutation [32]. Olaparib is now tested in 2 randomized phase III trials, examining its effect in the neoadjuvant (NeoOlympia) and the adjuvant setting (Olympia). Velparib, another PARP inhibitor, is also tested in standard neoadjuvant chemotherapy in a randomized phase III study (Brightness). Further trials in the metastatic setting are active.

**CDK4/6 Inhibitors in Endocrine-Resistant Tumors**

Several subtypes of cyclin D kinases (CDK) are involved in cell cycle control. A CDK inhibitor can induce cell cycle arrest especially in highly proliferating cancer cells, leading to apoptosis. CDK4 and CDK6 are responsible for cell cycle progression from the G1 to the S phase [33]. Palbociclib is an inhibitor of CDK4 and CDK6 and can overcome endocrine resistance in hormone receptor-positive breast cancer.

The phase II PALOMA-1 study has led to an accelerated approval by the Food and Drug Administration (FDA). In this trial, palbociclib in combination with letrozole as compared to letrozole alone significantly prolongs progression-free survival in patients with hormone receptor-positive metastatic breast cancer (20.2 vs. 10.2 months, HR 0.488, 95% CI 0.319–0.748) [34].

Recently, first results of the PALOMA-3 study have been presented [35]. PALOMA-3 is a randomized phase III trial in ER-positive HER2-negative metastatic breast cancer with 2 arms: palbociclib plus fulvestrant and fulvestrant alone. Both pre- and postmenopausal patients with endocrine resistance were included in the trial. There was a significant benefit in progression-free survival (9.2 vs. 3.8 months, HR 0.422, 95% CI 0.318–0.560; p < 0.000001). An approval of this new class of drugs is anticipated in the European Union in late 2016.

**Checkpoint Inhibitors in TNBC**

Immune checkpoints like programmed cell death-1 (PD-1) with its ligand PD-L1 seem to play an important role in immune escape of a defined group of solid cancers [36]. By the expression of PD-L1, tumor cells can activate PD-1 on T cells, which leads to an inactivation of effector T cells and a clinically relevant immune escape. Antibody-related blockade of PD-1 by the specific antibody pembrolizumab has led to an inactivation of the immune escape and an activation of effector T cell-mediated tumor rejection. This has been shown first in a phase III trial in malignant melanoma [37].

In a phase II trial in TNBC, pembrolizumab has shown reduced efficacy in comparison to malignant melanoma. Approximately 20% of the patients responded to treatment with this checkpoint inhibitor. However, if a clinical response was initiated, the duration of response was quite impressive. A phase III trial is still ongoing.

Although no classic parameter has been found to predict response to immune checkpoint inhibitors, an immunological gene expression profile has been identified in malignant melanoma that may identify patients who will respond better to immunological treatment [38]. Whether this gene expression profile could also be used in breast cancer is part of further research.

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