Advanced Breast Cancer

AGO Recommendations 2022 – Focus on ABC6 Consensus

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ABC6-Konsens im Fokus der AGO-Empfehlungen 2022

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ABSTRACT

Over the past few years, there have been many developments in the treatment of advanced breast cancer; these have been incorporated into national and international treatment guidelines, resulting in an improved prognosis for these patients. The 6th International Consensus Conference for Advanced Breast Cancer (ABC6) was held in November 2021. The aim is to standardize the treatment of advanced breast cancer based on a high level of evidence, and to make new treatment options accessible to all patients. In this article we discuss the ABC6 consensus in the context of German treatment guidelines, and compare it with clinical practice in Germany. The authors refer to the current recommendations of the Breast Cancer Working Group for Gynecological Oncology (AGO Mamma) published in March 2022. The AGO Breast Cancer Guidelines are updated annually. Since discrepancies between national and international guidelines can occur due to country-specific regulations, this is a useful comparison to make.

The German authors refer to the voting results of the ABC6 panelists from 6 November 2021.

ZUSAMMENFASSUNG

In der Behandlung des fortgeschrittenen Mammakarzinoms gab es in den letzten Jahren zahlreiche Fortschritte, die in internationale und nationale Therapieempfehlungen eingeflossen sind und dazu beigetragen haben, die Prognose der Patient*innen zu verbessern. Im November 2021 tagte die 6. „Internationale Konsensuskonferenz zum fortgeschrittenen Mammakarzinom“ (ABC6: 6th International Consensus Conference for Advanced Breast Cancer). Ziel ist es, die Behandlung des fortgeschrittenen Mammakarzinoms weltweit auf hohem Evidenzlevel zu standardisieren und neue Therapieoptionen allen Patient*innen zugänglich zu machen. Im vorliegenden Manuskript geht es darum, den ABC6-Konsensus vor dem Hintergrund der deutschen Therapieempfehlungen zu diskutieren und mit dem klinischen Vorgehen in Deutschland abzugleichen. Die Autoren beziehen sich auf die aktuellen Empfehlungen der Arbeitsgemeinschaft gynäkologische Onkologie, Kommission Mamma (AGO Mamma) vom März 2022. Die Empfehlungen der AGO Mamma werden jährlich aktualisiert. Ein solcher Abgleich erscheint sinnvoll, da aufgrund länderspezifischer Besonderheiten Abweichungen zwischen internationalen und nationalen Empfehlungen bestehen können. Die deutschen Autoren beziehen sich auf die Abstimmungsergebnisse der ABC6-Panelisten vom 06. November 2021.

Introduction

National and international treatment recommendations form the basis for implementing new treatment options in everyday clinical practice and optimizing therapeutic procedures based on a high level of evidence. The 6th International Consensus Conference for Advanced Breast Cancer (ABC6) has set itself the goal of improving diagnosis and treatment of inoperable locally advanced (LABC) and metastatic breast cancer (MBC), and making it accessible to all patients across countries.

The first ABC consensus conference (ABC1) met in November 2011 in Lisbon (Portugal), where it has been held every two years since then. In November 2021, the sixth ABC consensus conference (ABC6) took place, which was held as a virtual event for the first time due to the pandemic. The consensus is developed by a panel of international experts, including the two German breast cancer experts, Nadia Harbeck from Munich and Christoph Thomssen from Halle (Saale), as well as patient representative Renate Haidinger (Breast Cancer Germany e. V.), who is also the Director of the General Assembly of the ABC Global Alliance Congress. Patient representative Eva Schumacher-Wulf from Germany gave the keynote lecture during the ABC6 Consenus session.

ABC6 consensus and recommendations of the AGO Mamma

In Germany, the Breast Cancer Working Group for Gynecological Oncology (AGO Mamma) updates its treatment recommendations each year based on the current data. In this article, the authors discuss the ABC6 consensus with respect to the current AGO recommendations [1, 2]. The authors refer to the discussion questions and voting results of the ABC6 panelists during the plenary session held on 6 November 2021. Voting results from previous years (ABC1–5) that were not discussed at the ABC6 consensus continue to be valid. The grading system used in the ABC6 consensus is based on the treatment recommendations of ESMO (European Society of Medical Oncology) (▶ **Table 1**) [3].

▶ **Table 1** Level of Evidence Grading System for the ABC consensus [3].

Level of evidence	
I	Evidence from at least one large-scale, randomized controlled trial of high methodological quality (low potential for bias), or a meta-analysis of homogeneous randomized studies that have been completed and validated.
II	Small-scale randomized studies or large-scale randomized studies in which bias cannot be excluded (low level of methodological quality), or a meta-analysis based on such studies or based on a heterogenous collection of studies
III	Prospective cohort studies
IV	Retrospective cohort studies or case control studies
V	Studies with no control group, case reports, expert opinions
Grade of recommendation	
A	Strong evidence of efficacy with substantial clinical benefit, strongly recommended
B	Strong to medium evidence of efficacy but only limited clinical benefit, generally recommended
C	Insufficient evidence of efficacy, or else the therapeutic benefit does not outweigh the risks or disadvantages (side effects, costs, etc.), recommended as optional
D	Moderate evidence against efficacy or for a poor outcome, not generally recommended
E	Moderate evidence against efficacy or for a poor outcome, not recommended at all

Inoperable Locally Advanced Breast Cancer (LABC)

The treatment of inoperable locally advanced breast cancer (LABC) is usually multimodal [1, 2]. With regard to treatment planning, there was no discrepancy between the AGO recommendations [1, 2] and the ABC6 consensus: at least one biopsy must

be performed *before* starting treatment in order to determine histology and biomarkers (HR and HER2 status, grading, PD-L1 status, and Ki67) (LoE/GoR: I/A) (ABC6 majority vote: 95.7%). Staging includes a full medical history with physical examination, laboratory analysis, and imaging of thorax, abdomen, and skeletal system (ABC6 majority vote: 100%).

In contrast to the situation in Germany, the ABC6 panelists consider PET-CT (positron emission tomography with computed tomography) to be the preferred imaging procedure for inoperable, invasive LABC (ABC6 majority vote: 76.1%). In Germany [4, 5] PET-CT is not part of routine clinical practice, although it may be useful in individual cases [1, 2].

Systemic treatment for inoperable HR+/HER2− LABC

For the treatment of invasive inoperable LABC, the ABC6 panelists focused on systemic treatment of the various subtypes of breast cancer. In cases of hormone receptor-positive/HER2-negative (HR+/HER2−) LABC, the ABC6 panelists (majority vote: 95.6%) confirm endocrine-based treatment with a CDK4/6 inhibitor or anthracycline/taxane-based chemotherapy as the treatment of first choice (LoE/GoR: I/A). The decision in favor of endocrine-based treatment or chemotherapy should be based on tumor characteristics (grading, biomarker expression, tumor burden) and the patient's condition (general condition, disease-related symptoms, comorbidities, wishes/preferences) (LoE/GoR: expert opinion/A) (majority vote: 88.9%).

According to AGO Mamma, endocrine-based treatment with a CDK4/6 inhibitor is standard for HR+/HER2− ABC and is therefore generally preferable. Anthracycline/taxane-based chemotherapy (M0 in staging) is primarily favored when the focus is improving local control and achieving secondary operability. It is also indicated in cases of imminent organ failure [1, 2].

Systemic treatment of inoperable locally advanced TNBC

The ABC6 consensus (majority vote: 82.6%) recommends anthracycline/taxane-based chemotherapy for locally advanced inoperable triple negative breast cancer (TNBC) (LoE/GoR: I/A). If there is evidence of germ line mutation in the breast cancer genes 1 + 2 *(gBRCA [breast cancer] 1/2)*, the use of platinum in combination with a taxane is the preferred (but not the only) option (majority vote: 73.3%) (LoE/GoR: I/A).

At the time of the ABC6 consensus, pembrolizumab was only approved in Europe for locally recurring, inoperable TNBC, or for the metastatic situation with evidence of PD-L1 positivity (PD-L1 CPS ≥ 10), and with a treatment-free interval of at least six months (TFI ≥ 6 months). Bearing in mind the expected approval in the (post)neoadjuvant setting, the ABC6 panelists already advocated – analogous to the Keynote(KN)522 study [6] – the use of pembrolizumab (in addition to chemotherapy) regardless of PD-L1 expression for patients with inoperable locally advanced TNBC as soon as the expanded approval has been granted (majority vote: 89.0%).

According to AGO [1, 2], anthracycline/taxane-based chemotherapy is the "backbone" therapy in TNBC. Combination partners are – depending on the individual situation – a checkpoint inhibitor (CPI) and/or carboplatin. In line with the KN522 study [6], AGO recommends the neoadjuvant and subsequent post-neoadjuvant use of pembrolizumab in combination with chemotherapy in stage cT2 or cN+ [1, 2]. The absolute benefit for event-free survival (EFS) is + 7.7%; patients without pathological complete remission (non-pCR) had an absolute increase in EFS of + 10.6% compared with chemotherapy alone [1, 6]. That's why AGO Mamma highly recommends pembrolizumab in the post-neoadjuvant setting with "double plus" for "non-pCR" patients [1, 2]. In the meantime the approval has been granted by the european authorities.

Inoperable HER2+ LABC

In the case of inoperable HER2+ LABC, taxane-based chemotherapy is indicated in addition to anti-HER2 therapy in order to increase the chance of achieving pathological complete remission (pCR) (ABC6 majority vote: 95.6%). In accordance with AGO Mamma [1, 2], the ABC6 panelists recommend dual antibody blockade with trastuzumab and pertuzumab as the optimal anti-HER2 therapy (LoE/GoR: I/A). On the other hand, only a good half of the ABC6 panelists (54.3%) endorsed the addition of an anthracycline (LoE/GoR: I/B), whereas one third was against (32.6%). If an anthracycline is used, it should be added sequentially (LoE/GoR: I/A) (majority vote: 87.0%).

The AGO also recommends the sequential anthracycline use in addition to a taxane [1, 2]. Additional anthracycline may be useful for patients with four or more positive lymph nodes, and/or if there is curative intent. The German experts consider the TCbHP regimen (six cycles of docetaxel/carboplatin plus trastuzumab/pertuzumab) [7] to be an effective anthracycline-free alternative which is an option especially when anthracyclines are contraindicated.

For patients with inoperable HER2+ LABC (either inflammatory or noninflammatory) who are being treated with curative intent and are in complete remission (pCR) following adequate preoperative systemic therapy and appropriate locoregional interventions, the ABC6 consensus (majority vote: 91.3%) recommends adjuvant anti-HER2 therapy, ideally with trastuzumab/pertuzumab, for one year (LoE/GoR: I/A). For non-pCR patients (HER2+ LABC), the ABC6 panelists (majority vote: 87.0%) recommend switching to trastuzumab emtansine in the post-neoadjuvant setting (T-DM1; over 14 cycles) (LoE/GoR: I/A). This is in line with the recommendation of the AGO Mamma [1, 2].

BRCA germ line *(gBRCA)* mutation in inoperable LABC

According to the ABC6 consensus, patients initially presenting with inoperable *gBRCA*-mutated LABC with axillary lymph node involvement (cN > 1), who respond well to preoperative systemic therapy, should receive adjuvant treatment with olaparib for one year (majority vote: 80.4%) (LoE/GoR: I/A). The German experts agree, and add that this should apply regardless of the patient's hormone receptor status [8]. The AGO Mamma recommends adjuvant olaparib in addition to adjuvant standard endocrine therapy regardless of menopausal status in patients with germ line mutations in the *BRCA1/2* genes either for non-pCR patients with TNBC, or for non-pCR patients with hormone receptor-positive (HR+) breast cancer and CPS-EG ≥ 3 or pN2a tumor having under-

gone primary surgery [1, 2]. This is in line with the inclusion criteria of the OlympiA study [8].

Therapeutic approach in Oligometastatic Breast Cancer

According to the ABC6 consensus (majority vote: 87%), oligometastatic breast cancer is defined as a maximum of five metastases in the same organ and may potentially be treated curatively with local measures. Since the diagnosis of oligometastatic breast cancer also depends on the sensitivity of the imaging procedures, the ABC6 panelists recommend appropriate clinical studies to validate the sensitivity of the imaging procedures with regard to this question (LoE: expert opinion/NA).

According to the ABC6 consensus, a multimodal approach with "potentially curative" intention should be attempted for individual patients with oligometastatic ABC. This includes, for example, patients with a low tumor burden and high sensitivity to systemic therapy. The patients must also be able to be treated locally. In such cases, systemic therapy should be started, supplemented by locoregional measures (LoE/GoR: expert opinion/B) (ABC6 majority vote: 95.7%).

German expert opinion agrees with this. In the case of a potentially curative situation, according to AGO, surgical treatment [9, 10] and/or stereotactic ablative radiotherapy (SABR) [10] may be useful in addition to systemic therapy. The systemic therapy should then be started postoperatively [1, 2].

According to the ABC6 consensus, the value of SABR is unclear. Data from the randomized Phase II study SABR-COMET indicate a survival benefit [10]. Therefore, the use of SABR to treat oligometastases may be considered in individual cases (LoE/GoR: II/B) (majority vote: 87.0%). German experts require the use of SABR to be discussed in a tumor board. Further sites of metastases must be excluded. Also, from the German expert opinion, response to systemic therapy is mandatory for the indication of SABR.

Metastases in the contralateral axilla

Lymph node involvement in the contralateral axilla (without evidence of tumor in the contralateral breast) is classified by the ABC6 panelists (majority vote: 84.8%) as metastatic disease (stage IV). If, on the other hand, metachronous lymph node metastases appear in the contralateral axilla following local treatment of the ipsilateral axilla in early breast cancer (alone or simultaneously with an ipsilateral "in-breast" recurrence), this is considered by the ABC6 consensus to be a case of regional metastases. With a multidisciplinary approach, these patients have a chance of long-term survival, and possibly even cure (LoE: expert opinion/NA).

German physicians agree with this expert opinion. The AGO Mamma has also endorsed this statement [1, 11]. In these situations, however, the German experts require extended diagnostics, including PET-CT and MRI (breast MRI). The aim is to reliably exclude contralateral breast cancer and other tumor manifestations. The tumor biology should also be taken into account. Since there is no standard procedure for the situation described here, these patients should be discussed in an interdisciplinary tumor board.

Focus on Biopsy of Metastases

In line with the AGO Mamma [1], the ABC6 panelists (majority vote: 97.8%) require biological markers, especially estrogen receptor (ER) and HER2 status, to be determined in metastases at least once, provided that this is clinically feasible (LoE/GoR: I/A).

Importance of the progesterone receptor

The progesterone receptor (PR) serves primarily to distinguish TNBC from luminal carcinoma. If a patient is PR-positive but negative for both ER and HER2, according to the ABC6 consensus (majority vote: 82.2%), the therapy options that have been validated for triple negative ABC apply (LoE/GoR: expert opinion/B). Since this constellation is very rare, it should be discussed with the pathologist. A quality-assured immunohistochemical examination must be carried out, because this is essential for an appropriate treatment decision (majority vote: 82.2%).

In this situation, the German experts recommend that the patient's hormone receptor (HR) status should be determined once again [12]. If PR expression > 10% is confirmed, endocrine-based therapy should be startet. If PR expression is not confirmed or is < 10%, therapy should be performed as for triple negative ABC.

Discrepancies in relation to the primary tumor

If the results for the metastases differ from those of the primary tumor, according to the ABC6 consensus (majority vote: 80.0%), endocrine therapy or anti-HER2 therapy should be done if at least one metastasis biopsy has shown a positive status for ER or HER2. However, the various treatment options must be discussed with the patient (majority vote: 95.7). The German experts recommend having different samples from the primary tumor and the metastases re-analyzed by the same pathology institute. This should be done with full use of all of the immunohistochemical methods. If the differing test results are confirmed, the treatment strategy should be based on the clinically leading metastasis [expert opinion].

Systemic Treatment of ABC

The choice of systemic therapy depends on various factors. Besides the preliminary therapy – its efficacy, its side effects, and the disease-free interval in the adjuvant setting – these factors include the aggressiveness of the disease, the location of the metastases, comorbidities, the patient's preferences, and the estimated life expectancy. Predictive factors must also be taken into account. Besides the HR and HER2 status, according to AGO, PD-L1 and *gBRCA* status must be determined, as well as somatic BRCA (sBRCA) and *PALB (partner and localizer for BRCA) 2* status. In addition, AGO recommends PIK3CA (phosphatidylinositol-4,5-bisphosphate3-kinase catalytic subunit alpha) testing, and possibly testing for MSI (microsatellite instability), NTRK (neurotrophic tyrosine receptor kinase) gene fusions, and ESR1 mutations (mutations in the estrogen receptor) [1, 2].

Hormone Receptor-Positive HER2-Negative (HR+/HER2−) ABC

As a basis for the ABC6 consensus on HR+/HER2− ABC, the ABC6 panelists, in agreement with AGO [1], defined the term "endocrine resistance" as follows: primary endocrine resistance is considered if metastasis occurs within two years after adjuvant endocrine therapy (ET), or, in advanced cancer, if progression occurs within six months under first-line endocrine therapy. If primary resistance has been excluded, secondary endocrine resistance can be assumed (LoE: expert opinion/NA). Since the development of endocrine resistance is a continuum, the definitions stated above serve primarily as guidance for clinical studies; they cannot always be transferred to everyday clinical practice (ABC6 majority vote: 96%).

Endocrine-based combination confirmed as standard

The ABC6 panelists confirmed endocrine-based therapy with a CDK4/6 inhibitor as standard first-line treatment for ER+/HER2− ABC. This is justified by the substantial survival benefit compared with endocrine monotherapy. In a direct comparison with chemotherapy, the endocrine-based combination was not inferior (majority vote: 95.7%) (LoE/GoR: I/A) [13, 14].

This is in line with the recommendation of the AGO Mamma [1, 2]. From the German experts' opinion, endocrine-based therapy can also be considered in cases of suspected endocrine resistance. In the case of partial resistance, for example, the relapse pattern also plays a role in the treatment decision.

Use of Alpelisib in PIK3CA-mutated ABC

If a PIK3CA mutation is detected, the phosphatidylinositol-3-kinase *(PI3K)* inhibitor Alpelisib (plus fulvestrant) is an effective treatment option for HR+/HER2− ABC [15] (ABC6 majority vote: 95.6%). According to the ABC6 panelists, patients should meet the criteria for the SOLAR-1 pivotal study. These include prior treatment with an aromatase inhibitor (AI), normal HbA_{1c} levels, and *no* pre-existing diabetes mellitus (LoE/GoR: I/A). Alpelisib also seems to be effictive after CDK4/6 inhibition. This is indicated by the nonrandomized cohort study BYLieve [16]. The ABC6 panelists therefore see a second-line option in the combination of Alpelisib/ET (fulvestrant or AI) if a PIK3CA mutation is detected (ABC6 majority vote: 93.3%; LoE/GoR: I/B).

The German expert group agrees with this. Given evidence of a PIK3CA mutation, AGO recommends the combination of alpelisib/fulvestrant as a "possible" option for postmenopausal patients with HR+/HER2− metastatic breast cancer [1, 2].

Significance of ESR1 mutation status

If ESR1 mutations leading to clinical progression develop during treatment with an AI (± targeted substance), according to the ABC6 consensus, AI should not be used in the subsequent line of therapy (LoE/GoR: II/B) (majority vote: 84.4%). However, if an ESR1 mutation is detected, the ongoing therapy should only be changed if there is documented evidence of clinical disease progression. Therefore, according to the ABC6 consensus, determination of ESR1 status is currently not mandatory for providing adequate treatment to patients with ER+/HER2− ABC (LoE/GoR: II/D) (majority vote: 84.8%).

This is in line with clinical practice in Germany: if ESR1 mutation is detected, this reduces the probability of responding to endocrine therapy, but it does not rule out a possible response – also because fulvestrant is generally used in second-line endocrine therapy. The fact that the patient's endocrine sensitivity may possibly be reduced also applies in the case of endocrine-based treatment [17]. According to AGO, ESR1 mutation can be a predictive factor for treatment response. The committee recommends making use of ESR1 mutation testing as a predictive marker in individual cases [1, 2].

Treatment of HER2-Positive ABC

For HER2-positive ABC, anti-HER2 therapy with trastuzumab/pertuzumab is considered the standard first-line option, and is used in addition to chemotherapy [1, 2]. According to AGO, this applies without restrictions to patients with primary metastases as well as after adjuvant anti-HER2 therapy with trastuzumab and a treatment-free interval (TFI) ≥ 6 months. In the case of rapid progression (TFI < 6 months), the antibody drug conjugate (ADC) trastuzumab deruxtecan (T-DXd) may be an option for first-line treatment [1, 2].

Treatment sequencing in later lines

After first-line treatment with trastuzumab/pertuzumab-based systemic therapy, the ABC6 panelists (majority vote: 89.1%) and the AGO Mamma both recommend T-DXd as the new standard second-line treatment for HER2-positive (HER2+) ABC. This is based on DESTINY-Breast03 study [18] in which T-DXd showed a substantial PFS benefit (HR 0.28) and indications of an overall survival (OS) advantage in direct comparison with T-DM1, the former standard second-line treatment. [18]. According to the ABC6 consensus (majority vote: 89.1%), if T-DXd is unavailable or contraindicated, T-DM1 remains a preferred second-line treatment for HER2+ ABC.

The tyrosine kinase inhibitor tucatinib, approved in combination with trastuzumab/capecitabin, is recommended by the ABC6 panelists (majority vote: 91.3%) as a third-line treatment for HER2+ metastatic breast cancer (MBC), in accordance with the recommendation of the AGO Mamma (LoE/GoR: I/A) [1, 2]. In direct comparison with trastuzumab/capecitabin (without tucatinib), this triple combination significantly lengthened the median PFS and the median OS of MBC patients who had been pretreated with pertuzumab/trastuzumab and T-DM1 [19]. The study cohort also included patients with stable or active brain metastases. From the German expert opinion, the triple combination with tucatinib may also be an option for patients with active brain metastases, even before T-DXd [20].

If T-DXd has not yet been used, according to the ABC6 consensus, it may also be a preferred treatment option beyond the second line of treatment. This also applies to intensively pretreated patients with HER2+ ABC (majority vote: 84.8%) (LoE/GoR: II/A) and is in line with the recommendation of AGO [1, 2]. In the pivotal study DESTINYBreast01 [21], patients had undergone a median of six prior therapies.

With regard to T-DXd, the German experts also refer to the international phase IIIb/IV study DESTINYBreast12 (NCT04739761), in which pretreated ABC patients with and without brain metastases are included, and encourage participation in the trial. For more information, go to https://www.uniklinikum-dresden.de/de/das-klinikum/kliniken-polikliniken-institute/gyn/forschung/klinische-studien/mammastudien

Proactive management of side effects for T-DXd and tucatinib

For both T-DXd and the triple combination tucatinib/capecitabin/trastuzumab, the ABC6 panelists recommend proactive management of side effects. For T-DXd, the focus is on the pulmonary toxicity associated with this drug – especially interstitial lung disease (ILD) (LoE/GoR: I/A). The German experts point out that the ILD rate in the DESTINYBreast03 study [18] was significantly lower than in the DESTINYBreast01 study [21], which can be attributed to early detection of symptoms and better management of side effects.

According to the ABC6 panelists, special attention must be paid to diarrhea for the triple combination with tucatinib. The toxicity is triggered by an overlapping spectrum of side effects with capecitabine, which is why loperamide should be proactively prescribed.

Treatment of Triple Negative ABC

Value of immunotherapy

For patients with PD-L1-positive (PD-L1+) triple negative ABC, according to the ABC6 consensus, a combination therapy with checkpoint inhibitors (CPI) plus chemotherapy is the preferred first-line treatment in the majority of these patients. This also applies for patients with triple negative ABC who have had a recurrence within 6 to 12 months under (neo)adjuvant chemotherapy. The ABC6 panelists recommend both pembrolizumab (plus taxane or carboplatin/gemcitabin) (LoE/GoR: I/A) and atezolizumab (plus nab-paclitaxel) (LoE/GoR: II/B). Based on the current data, there is a higher level of evidence for pembrolizumab.

This is in line with the recommendation of the AGO Mamma [1, 2]. In Germany, both CPIs (plus the appropriate chemotherapy) are approved as first-line treatment for triple negative MBC. For PD-L1-positive patients with triple negative ABC, the first-line use of both CPIs is recommended regardless of whether there is evidence of a germ line mutation in *BRCA1/2* or *PALB2*. Based on the available data, the AGO Mamma gave pembrolizumab (plus chemotherapy) a strong recommendation in patients with a PD-L1 CPS (combined positive score) ≥ 10 and a TFI ≥ 6 months (LoE GR AGO 1b B ++). Atezolizumab plus nab-paclitaxel also is recommended, with a slightly lower recommendation grade, only a single "plus" recommendation in patients with a PD-L1 IC ≥ 1% and a TFI ≥ 12 months (1b B +) [1, 2]. The German experts further recommend taking prior (neo)adjuvant therapy into account when making the treatment decision.

It should be noted that different methods are used to determine PD-L1-positive status for the use of pembrolizumab or atezolizumab (ABC6 majority vote: 88.9%). For first-line use of pembrolizumab (plus chemotherapy), PD-L1 status is determined using the CPS, which measures the percentage of PD-L1-positive cells, including lymphocytes and macrophages. For first-line use of atezolizumab (plus nab-paclitaxel), the SP142 antibody assay (Ventana) has been validated as a companion diagnostic test. PD-L1-positive status for the use of atezolizumab is measured on the immune cells (IC) [1, 2].

This is in line with the recommendation of the AGO Mamma [1, 2]. However, in Germany there is no mandatory companion diagnostic test. Regardless of the assay or test system used, quality assurance must be guaranteed.

Sacituzumab govitecan – the first ADC for triple negative ABC

Since November 2021, the ADC sacituzumab govitecan (SG) has been approved in Europe for the treatment of advanced TNBC in patients with at least two prior systemic therapies, of which at least one for advanced disease (https://www.ema.europa.eu/en/medicines/human/EPAR/trodelvy). The ABC6 panelists (majority vote: 95.7%) consider SG to be the preferred treatment option for this patient group. In the ASCENT pivotal study [22], SG not only significantly prolonged the median PFS, but also the median OS regardless of previous therapy. The AGO Mamma highly recommends SG for the approved indication [1, 2]. That makes SG the preferred option in Germany for the second line treatment in patients with advanced TNBC, regardless of their PD-L1 status or germ line mutations in the *BRCA1/2* or *PALB2* gene.

When using SG, proactive management is important. According to the ABC6 consensus, the focus is on gastrointestinal symptoms such as diarrhea, nausea, and vomiting (LoE/GoR: I/A). From the German expert opinion, neutropenia must also be considered. However, primary prophylactic G-CSF use is only recommended in patients at increased risk, e.g., patients with febrile neutropenia during previous therapy. Diarrhea may also occur time-delayed, which is why patients should be closely monitored during the first few weeks, according to the German experts.

Focus on Hereditary Breast Cancer

Value of panel testing

According to the ABC6 consensus (majority vote: 93.3%), the only robust data currently available that are relevant for treatment decisions, i.e., whether to use a PARP inhibitor, relate to *gBRCA1/2* mutations (LoE/GoR: I/A). The testing of other risk genes may be considered in individual cases, for example, if the result is important for other family members. In this case, it must be explained to the patient that panel testing generally does not have any clinical consequences if other genes then *BRCA1* and *2* and *PALB2* are involved (ABC6 majority vote: 89.1%) (LoE/GoR: expert opinion/C).

German expert opinion agrees with this. Every patient with HER2-negative MBC should be tested for *BRCA1/2* status, regardless of family history or HR status. The AGO Mamma strongly recommends for *gBRCA1/2* testing in HER2-negative MBC patients as a predictor for treatment response. In case of *PALB2* mutations there is a therapeutic benefit from the use of a PARP inhibitor.

AGO recommends *gPALB2* testing and testing for a somatic BRCA1/2 mutation as an option in individual cases [1, 2].

Indication for PARP inhibition

With reference to a Phase II study with olaparib [23], the ABC6 consensus (majority vote: 93.3) favors using a PARP inhibitor even if there is evidence of a somatic *BRCA1/2* mutation *(sBRCA1/2)* or a germ line mutation in PALB2 *(gPALB2)*. However, it is important to explain the implications to the patient (LoE/GoR: II/B). The ABC6 panelists made no statement regarding the use of talazoparib.

This approach is approved by German experts, based on the AGO recommendations [1]. In the case of detected *gPALB2* or *sBRCA1/2* mutations, the AGO Mamma considers the use of olaparib to be an option in individual cases. However, the approval of olaparib is currently linked to germ line mutations. The same applies for talazoparib. For patients with evidence of a *gBRCA1/2* mutation, the AGO Mamma strongly recommends talazoparib and olaparib (1b A ++ in both cases) [1, 2].

PARP inhibition versus platinum in ER− ABC

For hereditary ABC, there are currently no studies that compared monotherapy with a PARP inhibitor with the use of platinum. For this reason, it is also unclear whether PARP inhibitors are still effective after platinum pretreatment (ABC6 majority vote: 89.1). According to AGO Mamma, early use of a PARP inhibitor should be favored in triple negative ABC patients [1, 2]. Stratified analyses indicate that the first-line use of a PARP inhibitor is more effective than first-line treatment with platinum [24, 25]. Moreover, in Germany, carboplatin is already commonly used in the neoadjuvant setting.

PARP inhibition or immunotherapy?

In triple negative PD-L1+ and *gBRCA*-associated ABC, combined chemotherapy/immunotherapy is in competition with PARP inhibition as first-line treatment. In this case, too, there is a lack of data on the optimal therapy sequence. The ABC6 panelists (majority vote: 91.3 %) favor first-line use of immunotherapy/chemotherapy, as this has been demonstrated to have significant benefits for OS [26, 27] (LoE/GoR: expert opinion/B). The German experts agree in principle, but point out that the constellation of PD-L1+ *gBRCA*-mutated ABC is very rare, occurring in less than 10 % of TNBC patients.

The AGO Mamma gives a “double plus” recommendation for both PARP inhibition and immunotherapy/chemotherapy with pembrolizumab (TFI ≥ 6 months). In case of progression both options are respectively recommended as second-line treatment. Chemotherapy/immunotherapy with atezolizumab (for both first- and second-line treatment) is given only a single “plus” recommendation due to the somewhat poorer data available [1, 2].

PARP inhibition in ER+ ABC?

With *gBRCA*-mutated ER+ ABC, both PARP inhibition and endocrine-based combination therapy with a CDK4/6 inhibitor are options for first-line treatment. According to the ABC6 consensus (majority vote: 93.5 %), first-line use of endocrine-based combination therapy with a CDK4/6 inhibitor should be the preferred option, to be used *before* PARP inhibition. This is based on the significant benefit for OS that has been seen with first-line use of CDK4/6 inhibitors compared to endocrine monotherapy in ER+/HER2− ABC (LoE/GoR: expert opinion/A).

From the German expert opinion, this sequence makes sense because treatment with a PARP inhibitor cannot be started until the results of *gBRCA* testing have been obtained. If endocrine-based therapy with a CDK4/6 inhibitor is used first, there is time to wait for the test result to use it in the second-line treatment, without losing treatment time. The AGO Mamma also recommends this approach [1, 2].

Adequate Treatment of Brain Metastases

Breast cancer is the second most common cause of CNS metastases. Due to constant improvements in treatment and the associated longer survival times the incidence of brain metastases is increasing [1, 2]. Despite this development, according to both the ABC6 consensus (majority vote: 84.8 %) and the AGO Mamma, there is no need to perform routine cerebral imaging in asymptomatic patients with ABC, regardless of the breast cancer subtype (LoE/GoR: II/D). The AGO Mamma recommends that patients with brain metastases should be discussed by an interdisciplinary tumor review board [1, 2].

However, the German experts had differing opinions with regard to the voting results of the ABC6 panelists. They agreed that for every patient an individual risk/benefit assessment should be considered and discussed with the patient. Moreover, even if there is currently no evidence that early intervention results in longer survival or better quality of life for asymptomatic patients with brain metastases, the possibility of this being true in individual cases cannot be ruled out. The course of the disease also depends on the tumor burden in the brain, the localization of the metastases, and which treatment options are available in the (individual) situation. Moreover, in individual cases, there may be increased risk of a cerebral event. For this reason, supplementary imaging performed in addition to staging may be of benefit in individual cases [28].

Treating brain metastases in HER2+ ABC

If patients with HER2+ ABC and stable extracranial disease develop brain metastases that are able to be stereotactically irradiated, the German experts and the ABC6 consensus agree to continue the patient’s ongoing systemic treatment without any change (majority vote: 88.9 %) (LoE/GoR: I/D). This is also in line with the recommendation of the AGO Mamma (2c C +) [1, 2].

For relapsed patients with HER2+ ABC and with metastasis localized only in the brain that can be stereotactically irradiated, there is *no* indication for additional chemotherapy according to the ABC6 consensus (majority vote: 82.6 %) (LoE/GoR: I/D). If anti-HER2 therapy with trastuzumab was ended before the relapse, it should be restarted (ABC6 majority vote: 87.0 %) (LoE/GoR: II/B).

German expert opinion agrees because these patients are at high risk of extracranial metastasis. Considering the palliative care situation, additional anti-HER2 therapy with trastuzumab is recommended, as it is considerably better tolerated than chemo-

therapy. In the case of extracranial progression, chemotherapy should be added to anti-HER2 therapy.

Systemic treatment of HER2+ brain metastases?

In the case of *active* brain metastases, according to the ABC6 consensus (majority vote: 91.1%), treatment with tucatinib plus trastuzumab/capecitabin is a new alternative to local therapy. This triple combination is currently the best available treatment option for patients with HER2+ ABC and progressive brain metastases as driver of disease progression after local treatment (majority vote: 91.1%) (LoE/GoR: I/A).

The tucatinib pivotal study HER2CLIMB did not cover the situation of locally treatable brain metastasis [19]. Therefore, from a German expert opinion, in the case of active brain metastases, the treatment options should be discussed by an interdisciplinary tumor review board. Nevertheless, the German experts consider the initially purely systemic treatment with tucatinib/trastuzumab/capecitabin to be an option. The AGO rates the tucatinib combination as a "possible" option (2b B +) in patients with active stable brain metastases [1, 2].

Referring to the prospective single-arm KAMILLA study [29], the ABC6 consensus (majority vote: 79.5%) also sees T-DM1 as a treatment option in the case of *active* brain metastases (LoE/GoR: II/A). The German experts comment that, in contrast to the HER2-CLIMB study [19], only patients with *stable and treatable* brain metastases were included in the KAMILLA study. The AGO Mamma only recommends T-DM1 for individual cases of brain metastasis (2b B +/−); however, T-DXd may be a a possible option for asymptomatic patients with *stable* brain metastases who are *not* receiving corticosteroids or anticonvulsants (2b B +) [1, 2].

Peritoneal Carcinosis and Ascites

Patients with peritoneal carcinosis and ascites have a particularly poor prognosis and considerably impaired quality of life. According to the ABC6 consensus, palliative interventions must be initiated at an early stage. In addition, an appropriately trained palliative care team should be consulted (LoE/GoR: I/A) (ABC6 majority vote: 95.6%).

Since peritoneal carcinosis is often difficult to visualize radiologically, the treating physician must keep an eye out for typical complaints. These include abdominal pain, nausea, anorexia, cachexia, increased waist circumference, obstipation, and fatigue. For adequate management, the ABC6 panelists refer to the ESMO (European Society of Medical Oncology) guidelines [20]. From the German expert opinion, a sampling laparoscopy should also be performed for histological confirmation. This also serves to exclude the possibility of ovarian cancer. With regard to management of ascites, the German experts refer to the guideline of the German Association for Palliative and Supportive Medicine [30, 31].

Advanced Breast Cancer in Men

The recommendations of the ABC6 consensus on treating advanced breast cancer in men are in line with those of the AGO Mamma [1, 2]: the ABC6 panelists voted unanimously in favor of offering men with ABC the same genetic testing and counselling as women in the corresponding situations (LoE/GoR: II/A). According to the ABC6 consensus, men with ER+ ABC must be offered the same treatment options as those available to women. These include targeted drugs such as CDK4/6, mTOR, and PIK3CA inhibitors (LoE/GoR: II/A) (ABC6 majority vote: 95.6%). The AGO Mamma recommends that men with breast cancer should be treated in certified breast centers [1, 2].

Considering Supportive and Palliative Treatment

Addressing treatment-related cognitive impairment

Cancer and treatment-related cognitive impairment (CRCI) is described in up to 75% of patients [1, 2]. Often, these impairments cannot be substantiated based on objective findings, such as imaging. According to the ABC6 consensus, neuropsychological test methods and structural changes in the brain that can be captured on imaging are often only of limited informative value. Such cases are most likely multifactorial events. For this reason, cerebral imaging is only recommended to exclude or prove brain metastases (LoE: I/A) (majority vote: 97.8%). According to the ABC6 consensus, cognitive impairment as a possible consequence of oncological treatment should be discussed actively with the patient and routinely monitored (LoE: II/A) (majority vote: 91.1%).

German expert opinion agrees. The German experts recommend increased awareness of treatment-associated complaints and impairments, which also include cognitive impairments. According to the AGO Mamma, it may be possible to improve cognitive functions through behavioral therapy and the use of methylphenidate [1, 2].

Supporting oncological treatment through physical activity

Exercise and moderate sport have been recommended for a number of years as a supportive measure for oncological treatment. They can also help with cancer and treatment-related cognitive impairments. According to the ABC6 consensus, moderate physical activity is recommended, for example 150–300 minutes per week, or 75 minutes per week of higher intensity exercise (LOE: II/A).

AGO also recommends exercise as a supplementary measure to support a more favorable prognosis. However, the German experts point out the differing levels of physical condition among patients, and therefore warn against setting strict standards as to the duration and intensity of physical activity. Patients are recommended to get regular exercise; however, this needs to be adapted to the individual in questions [1, 2].

Informing patients about unfavorable factors

According to the ABC6 consensus (100%), patients should be informed about factors that can have an unfavorable influence on the disease and can be modified. These include, for example, certain medications, emotional stress, pain, fatigue, sleep disorders, alcohol consumption, or vitamin B deficiency. For patients who

report a considerable impairment of their quality of life, the ABC6 panelists recommend a neuropsychological assessment and cognitive rehabilitation measures (LoE: III/A) (ABC6 majority vote: 95.6%). The German experts agree [1,2].

Interdisciplinary approach for interstitial lung disease

Interstitial lung disease (ILD) is a rare but serious complication of many oncology drugs and may require the expertise of a pulmonologist. Prompt diagnosis through computed tomography and early intervention are important. These recommendations are in line with those of the AGO Mamma. According to AGO Mamma, treatment should be guided by the severity and the noxious agents triggering the condition [1,2]. Reference is also made to the prescribing information for the drug.

In the case of Grade 2 symptomatic ILD, the ABC6 panelists (majority vote: 84.4%) recommend pausing the treatment as a general principle. In addition, systemic steroids are indicated. Once the complaints have subsided, the cancer therapy can be resumed at a reduced dosage. With ILD grade 3 or higher, the treatment must be stopped.

A special case here, according to the ABC6 consensus, is T-DXd-induced ILD. In this case, special precautions are required (majority vote: 84.4%). With asymptomatic lung changes visible on x-ray, treatment with T-DXd must be stopped, and the patient must be given systemic steroids (≥ 0.5 mg/kg BW prednisone or equivalent). If the changes regress within 28 days, T-DXd therapy can be resumed at the full dosage. If recovery takes longer (over 28 days), the T-DXd dose should be reduced by one dose level. In the case of grade 2 ILD, systemic steroids must be administered immediately (≥ 1 mg/kg prednisone or equivalent); at the same time, T-Dxd therapy must be stopped immediately and permanently. It is important that the steroids are tapered off gradually over at least four weeks (LoE/GoR: IA).

When is it helpful to reduce the dose?

According to the ABC6 consensus, the optimal dose for a particular medication is part of the clinical development of cancer medication (majority vote: 95.7%). However, there are indications that the maximum tolerated dose (MTD) may not be required for successful treatment in all patients [32]. In addition, the feasibility of the treatment, the therapeutic goal, and the patient's quality of life play a role in determining the dosage (LoE/GoR: expert opinion/NA). Accordingly, deviations from standard doses may be useful, or even necessary.

The German experts object that a validated treatment regimen should not be arbitrarily modified without a clear rationale. In principle, drug therapy should be started at the approved dosage. It may make sense in individual cases to adjust the dose according to side effects [32].

Strengthening and supporting care staff

All of the ABC6 panelists (100%) made the argument that people involved in nursing and caring for ABC patients need more support in their work, more appreciation, and psychological support if necessary. This applies equally for professional nurses and caregivers as well as for their families. This also includes protection against discrimination in the workplace, and adjusting the work flexibly according to the care situation. Information and tools required for adequate care must be accessible to all caregivers and patients (LoE: expert opinion/NA).

From the German point of view, providing support for nursing care staff is an urgent social and political challenge. The demands of the ABC6 consensus must be supported and implemented without limitation. In addition, according to the recommendation of AGO, all patients with an incurable cancer must be offered palliative care. This applies irrespective of whether or not they are receiving cancer-specific treatment. The AGO Mamma calls for palliative care specialists to be integrated in the oncological decision-making process, for example in the context of an interdisciplinary tumor review board [1,2].

Perspectives and Outlook

Once again, the ABC6 conference was a platform for intensive debate about the latest developments in advanced and metastatic breast cancer. As with previous ABC conferences, the collaboration between physicians and patient representatives from all corners of the Earth was hugely significant. For the latter, it was an opportunity to present their wishes and concerns, and discuss them directly with breast cancer experts. Also, through this interactive exchange, the ABC consensus makes an important contribution towards standardizing and optimizing the treatment of advanced breast cancer on the international, worldwide level. The next ABC7 consensus conference will be held in Lisbon on 9–11 November 2023.

ABC6 PANELISTS

1. Fatima Cardoso, PT (chair)
2. Eric P. Winer, US (honorary chair)
3. Larry Norton, US (honorary chair)
4. Alberto Costa, CH/IT (honorary chair, ESO educational rep.)
5. Renate Haidinger, DE (co-chair, patient advocate)
6. Nagi S. El Saghir, LB (scientific committee)
7. Alexandru Eniu, CH (scientific committee)
8. Shani Paluch-Shimon, IL (scientific committee)
9. Frédérique Penault-Llorca, FR (scientific committee, Nice St. Paul)
10. Hope S. Rugo, US (scientific committee)
11. Theresa Wiseman, UK (nurse, EONS, scientific committee)
12. Joseph Gligorov, FR (Nice/St. Paul French guidelines)
13. Ann Partridge, US (ASCO)
14. Mariana Chavez MacGregor, US (ASCO)
15. William Gradishar, US (NCCN)
16. Nadia Harbeck, DE (AGO, German guidelines)
17. Christoph Thomssen, DE (AGO, German guidelines)
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