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ABC6 Consensus: Assessment by a Group of German Experts

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Keywords

Advanced breast cancer · Systemic therapy · Therapeutic sequence · Oligometastasis disease · Brain metastases · Supportive care

Abstract

Background: The first International Consensus Conference for Advanced Breast Cancer (ABC1) took place 10 years ago in November 2011. The rationale was – and still is – to standardize treatment of advanced breast cancer (ABC) based on the available evidence and to ensure that worldwide all breast cancer patients receive adequate treatment and access to new therapies. ***Rationale for the Manuscript:*** The 6th International Consensus Conference for ABC (ABC6) took place from November 4 to 6, 2021 and was the first in a purely online format, due to the COVID-19 pandemic. In the present manuscript, a working group of German breast cancer experts comments on the voting results of the ABC6 panelists regarding their applicability for routine clinical practice in Germany. ***Method:*** The ABC6 votes mainly include modified or new statements. With regard to all statements not modified for the ABC6 consensus, the German experts refer to the published paper of the ABC5 consensus. The German experts base their comments on the current recommendations of the Breast Committee of the Gynecological Oncology Working Group (Arbeitsgemeinschaft Gynäkologische Onkologie, AGO Mamma). ***Topics:*** ABC6 focused on new treatment options and their implications for clinical practice. Optimal therapy sequencing for example was one of the issues. To solve the challenge of a more individualized treatment, precision medicine is fundamental. Oligometastatic disease, brain metastases and adequate supportive and palliative care were also addressed. Of special interest was the treatment of inoperable locally advanced breast cancer, which was discussed as a separate topic. As in previous years, patient advocates from around the world were an integral part of the ABC6 conference and had a major input into the consensus.

Nadia Harbeck and Christoph Thomssen are ABC Panel Members. Renate Haidinger and Eva Schumacher-Wulf are patient advocates. Renate Haidinger is co-chair of Brustkrebs Deutschland [German Breast Cancer Association] e.V.

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Introduction

The International Consensus Conference for Advanced Breast Cancer (ABC) on diagnosis and treatment of advanced breast cancer started 10 years ago in November 2011 and has been taking place since then every 2 years in Lisbon, Portugal. The intention is to harmonize and standardize the treatment of patients with locally advanced or metastatic breast cancer worldwide and to make medically necessary therapies available to all patients. The recent sixth Consensus Conference (ABC6) was held from November 4 to 6, 2021 – due to the COVID-19 pandemic, for the first time as a virtual event.

This year, the panel consisted of 46 breast cancer experts, including patient advocates, one oncology nurse, and one psycho-oncologist (shown in the Appendix). As in previous years (ABC1–5), Nadia Harbeck, Munich, and Christoph Thomssen, Halle (Saale), two breast cancer experts from Germany, were ABC panel members together with the Director of the General Assembly of the ABC Global Alliance Congress, the German patient advocate Renate Haidinger (Brustkrebs Deutschland e.V.). The German patient advocate Eva Schumacher-Wulf presented the keynote lecture on patient advocates' most important concerns during the ABC6 Conference plenary session.

ABC6 Consensus Discussed from a German Perspective

In this "post-ABC6" publication, the ABC6 consensus voting is discussed with regard to the annually updated treatment recommendations of the "Breast" Committee of the Gynecological Oncology Working Group (AGO Mamma) [1, 2]. Potential subsequent modifications of the ABC6 consensus voting in the final publication cannot be anticipated. Of note, the ABC6 panelists voted on updated or new statements only. Earlier ABC1–5 statements remain valid. The grading system of the ABC6 consensus is based on the ESMO treatment guidelines [3, 4] (shown in Table 1).

Table 1. Level of evidence grading system used by ABC6 panelists [4]

Levels of evidence	
I	Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity
II	Small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case-control studies
V	Studies without control group, case reports, experts' opinions
Grades of recommendation	
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, …), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

Oligometastatic Breast Cancer

According to the ABC6 majority vote (87%), oligometastatic breast cancer is defined as metastatic disease with a maximum of five metastases, which do not have to be in the same organ but can be treated by means of local measures with potentially curative intent. The diagnosis of oligometastatic breast cancer also depends on the imaging used. The ABC6 panelists, therefore, recommend clinical studies to compare imaging techniques in this regard (Level of Evidence [LoE]: expert opinion/NA). The German experts agree.

Contralateral Axillary Metastases

According to the ABC6 panelists (majority vote: 84.8%), lymph node involvement in the contralateral axilla (without evidence of a tumor in the contralateral breast) is classified as metastatic disease (stage IV). Metachronous lymph node metastases in the contralateral axilla after local treatment of the ipsilateral axilla in early breast cancer (alone or at the same time as an ipsilateral "in-breast" relapse) are classified as regional metastases. With a multidisciplinary approach, these patients have the chance of long-term survival and even of cure (LoE: expert opinion/NA).

The German experts generally agree (expert opinion) but stipulate completion of the diagnostic process, including PET-CT and magnetic resonance imaging (MRI), to rule out contralateral breast cancer and further tumor manifestations. Tumor biology should also be considered. As there is no standard procedure, further management should therefore be discussed in the context of an interdisciplinary tumor board.

In individual cases, a multimodal approach with "potentially curative" intent may be an option for oligometastatic ABC. These are patients with oligometastases that are accessible to local therapy or patients with low tumor burden and high sensitivity to systemic therapy. In these (rare) cases, it is recommended to begin with systemic therapy; this may be supplemented by locoregional ther-

apy (LoE/GoR [Grade of Recommendation]: expert opinion/B) (ABC6 majority vote: 95.7%).

The role of stereotactic ablative radiotherapy (SABR) is not yet clear. Data from the randomized phase 2 SABR-COMET study suggest a benefit concerning overall survival [5]. SABR of the oligometastases can, therefore, be an option in individual cases (LoE/GoR: II/B) (majority vote: 87.0%). The German experts add that a presentation to the entity-specific tumor board, the exclusion of additional metastatic sites, and documented response to systemic therapy are prerequisites for the use of SABR.

Focus on Biopsies of Metastases

The German experts and the ABC6 panelists (majority vote: 97.8%) agree that metastases should be tested at least once for biological markers, particularly estrogen receptor (ER) status and HER2 status, if clinically feasible (LoE/GoR: I/A).

Significance of the Progesterone Receptor

The progesterone receptor (PR) is primarily used for identification of triple-negative breast cancer (TNBC). According to the ABC6 panelists (majority vote: 82.2%), therapies validated for triple-negative ABC are an option in the rare cases with a positive PR status but clearly negative ER and HER2 status (LoE/GoR: expert opinion/B). However, the results should be discussed with the pathologist since quality-assured immunohistochemistry (IHC) assessment is the basis of an appropriate treatment decision (majority vote: 82.2%). The German experts recommend retesting the hormone-receptor (HR) status in order to rule out a misidentification [6]. If PR expression >10% is confirmed with ER negative status, they recommend starting endocrine-based therapy. If PR expression is not confirmed or is <10%, the therapy should correspond to the treatment for triple-negative ABC [1, 2].

Deviation from the Primary Tumor

If the test results of the metastasis deviate from that of the primary tumor, the ABC6 panelists (majority vote: 80.0%) recommend endocrine-based or anti-HER2 therapy as soon as at least one metastatic biopsy has a positive ER or HER2 status. In case of a triple-negative primary tumor, for example, approved therapies for triple-negative disease as well as possibly those for ER+/HER2– or HER2+ ABC must be discussed with the patient (majority vote: 95.7%).

The German experts further recommend re-testing of the primary tissue and of the metastasis in the same pathological laboratory. If the deviating test results are confirmed by using the entire range of pathological methods, tumor heterogeneity must be considered for treatment decision. The therapeutic strategy should be guided by the clinically most relevant metastasis.

Estrogen Receptor-Positive, HER2-Negative (HR+/HER2–) ABC

The ABC6 panelists defined "endocrine resistance" as a basis for the ABC6 consensus concerning HR+/HER2– locally advanced or metastatic breast cancer. They also presented the updated assessment of endocrine-based therapy with a CDK4/6 inhibitor based on the ESMO-MCBS (ESMO Magnitude of Clinical Benefit Scale) [7, 8]. The German experts did not elaborate on ESMO-MCBS since this scale is primarily of political significance with the intention to facilitate access to new therapies worldwide. In Germany, the scale is still of minor importance [1, 2].

Definition of "Endocrine Resistance"

According to the ABC6 consensus, primary endocrine resistance exists if a relapse occurs within 2 years after adjuvant endocrine therapy (ET) or if progression occurs within 6 months during first-line ET in advanced cancer. If primary resistance is excluded, secondary endocrine resistance can be assumed (LoE: expert opinion/NA). The development of endocrine resistance is a continuum. These definitions are, therefore, primarily a guideline for clinical trials and not always applicable to the routine clinical practice (majority vote: 96%).

The German experts add that endocrine-based therapy is the preferable option when deciding between ET and chemotherapy. ET can also be considered when endocrine resistance is proven or suspected. In the case of partial resistance, for example, the relapse pattern also plays a role in the treatment decision.

Endocrine-Based Combination or Chemotherapy?

The ABC6 panelists confirm endocrine-based therapy with a CDK4/6 inhibitor as first-line standard for ER+/HER2– ABC, which achieves a substantial survival benefit compared to endocrine monotherapy. In direct comparison with chemotherapy, it is not inferior (majority vote: 95.7%) (LoE/GoR: I/A) [9, 10].

Alpelisib in PIK3CA-Mutated ABC

If a PIK3CA (phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha) mutation is detected, the phosphatidylinositol-3-kinase (PI3K) inhibitor alpelisib (plus fulvestrant) is an effective treatment option for patients with HR+/HER2– ABC [11] (majority vote: 95.6%). In accordance with the SOLAR-1 study, patients should have received prior treatment with an aromatase inhibi-

tor (AI), should have normal HbA1c levels, and should not have pre-existing diabetes mellitus (LoE/GoR: I/A). Data from the non-randomized cohort study BYLieve [12] suggest that alpelisib also works after CDK4/6 inhibition. If a PIK3CA mutation is detected, the ABC6 panelists (majority vote: 93.3%) and the German experts see the combination alpelisib/ET as a second-line option (fulvestrant or AI) (LoE/GoR: I/B).

ESR1 Mutation Status

ESR1 mutations may develop during treatment with an AI (±targeted drug) and cause therapy resistance. Therefore, therapy *without* an AI is recommended in the subsequent line of therapy if ESR1 mutations are detected (LoE/GoR: II/B) (ABC6 majority vote: 84.4%). An ongoing therapy, however, should only be changed if ESR1 mutations are accompanied by clinical progression. ESR1 testing is not an absolute requirement for adequate treatment of patients with ER+/HER2– ABC (LoE/GoR: II/D) (majority vote: 84.8%).

The German experts generally agree. From a German perspective, response to ET is less likely but not precluded if ESR1 mutations are detected. They may come up during adjuvant treatment already, and, moreover, in first-line therapy, a combination of AI plus CDK 4/6 inhibitor is already used, and second-line therapy is usually combined with fulvestrant. Endocrine sensitivity, however, may be lower. This also applies to endocrine-based therapy [13]. The AGO Mamma recommends testing for ESR1 mutations as a predictive marker in individual cases only [1, 2].

Treatment of HER2-Positive ABC

Therapy Sequence: T-DXd or T-DM1 as Second Line?

The ABC6 panelists (majority vote: 89.1%) and the German experts agree in recommending the antibody-drug conjugate (ADC) trastuzumab deruxtecan (T-DXd) as a new second-line standard for patients with HER2-positive (HER2+) ABC after first-line treatment with trastuzumab/pertuzumab-based systemic treatment. In direct comparison with the previous second-line standard, trastuzumab emtansine (T-DM1), T-DXd achieved a substantial PFS benefit (HR 0.28) with an initial trend for an overall survival benefit [14]. The German experts add that first-line use of T-DXd after (neo)adjuvant or post-neoadjuvant administration of trastuzumab/pertuzumab is at present not covered by the current regulatory approval in Germany because one out of two prior anti-HER2 therapies must have been administered in the metastatic setting.

Regardless, T-DXd is a preferred treatment option in later lines of therapy if the drug has not yet been administered in second line. This also applies to heavily pretreated patients with HER2+ ABC according to the ABC6 panelists (majority vote: 84.8%) (LoE/GoR: II/A). In the pivotal study DESTINYBreast01 trial [15], patients had a median of six prior therapies. If T-DXd is not available or contraindicated, the ABC6 panelists (majority vote: 89.1%) still recommend T-DM1 as the preferred second-line therapy for HER2+ ABC. Given the pulmonary toxicity, specifically interstitial lung disease (ILD) and pneumonitis, associated with T-DXd, the proactive side effect management is recommended (LoE/GoR: I/A).

The German experts agree with all the statements concerning T-DXd. The ESMO-MBC Guideline [16] was updated including the recent T-DXd data in October 2021. The AGO treatment algorithm will be updated in early 2022. The German experts argue that T-DXd is significantly more effective than T-DM1 [14, 15]. Of note is that the ILD rate in DESTINYBreast03 [14] was significantly lower than in DESTINYBreast01 [15], which can be explained by the early symptom recognition and better side effect management. The pulmonary toxicity is manageable and grade ≥3 was below 1% in DESTINYBreast03 [14]. Nevertheless, the German experts point out that in patients with preexisting pulmonary diseases, the potential lung toxicity of T-DXd should be taken into account when assessing benefits and risks. Broad access to T-DXd is offered by the international phase 3b/4 DESTINYBreast12 study (NCT04739761), in which pretreated ABC patients with and without brain metastases are enrolled. Further information: https://www.uniklinikum-dresden.de/de/das-klinikum/kliniken-polikliniken-institute/gyn/forschung/klinische-studien/mammastudien. Altogether, the lower the tumor burden is, the more carefully the risk-benefit ratio must be discussed with the patient.

Tucatinib in Combination with Trastuzumab/Capecitabine

The ABC6 panelists (majority vote: 91.3%) recommend the tyrosine kinase inhibitor tucatinib, which is approved in combination with trastuzumab/capecitabine as third-line therapy for HER2+ metastatic breast cancer (LoE/GoR: I/A). Compared to trastuzumab/capecitabine (without tucatinib), the three-drug combination significantly prolonged the median PFS and median OS of metastatic breast cancer patients pretreated with pertuzumab/trastuzumab and T-DM1 [17]. The study also included patients with stable or active brain metastases. As with T-DXd, proactive management of side effects is necessary, especially in the case of diarrhea.

The German experts point out that the toxicity is triggered by an overlapping side effect spectrum with capecitabine as part of the three-drug combination. Loperamide should be prescribed prophylactically. The Ger-

man experts confirm the third-line use of tucatinib/trastuzumab/capecitabine after a pertuzumab/trastuzumab-based first-line therapy and second-line treatment with T-DXd. According to the currently available data, the three-drug combination with tucatinib may also be an option before T-DXd in the case of active brain metastases [16].

Treatment of Triple-Negative ABC

Importance of Immunotherapy

According to the ABC6 consensus, combination therapy consisting of a checkpoint inhibitor (CPI) and chemotherapy is the preferred first-line therapy for the majority of patients with PD-L1 (programmed death-ligand 1)-positive (PD-L1+) triple-negative ABC. This also applies to TNBC patients who relapse within 6–12 months after (neo)adjuvant chemotherapy. Both pembrolizumab (plus a taxane or carboplatin/gemcitabine) (LoE/GoR: I/A) and atezolizumab (plus nab-paclitaxel) (LoE/GoR: II/B) received a clear majority vote.

The German experts agree. Since both CPIs (plus the respective chemotherapies) are approved in Germany as first-line therapy for triple-negative metastatic breast cancer, the decision of which combination to use must be made on an individual basis, considering the respective PD-L1 status as well as prior (neo)adjuvant therapy if applicable.

It should be noted that PD-L1 positivity is determined differently for the two CPIs. The German experts agree with the ABC6 panelists (majority vote: 88.9%) that the PD-L1 status for the first-line use of pembrolizumab (plus chemotherapy) should be determined using the CPS (combined positive score), which evaluates PD-L1+ tumor cells as well as immune cells. CPS ≥10 is required for pembrolizumab therapy. The SP142 antibody (Ventana) is validated as a companion test for first-line use of atezolizumab (plus nab-paclitaxel). PD-L1 positivity for the use of atezolizumab is determined on immune cells (IC) only with a cut-off of ≥1% of stained immune cells.

The German experts point out that there is no mandatory companion test in Germany. Regardless of the assay or test system used, quality assurance must be ensured, such as by means of the round robin tests performed by the German Pathology Society.

Sacituzumab Govitecan: First ADC for Triple-Negative ABC

With sacituzumab govitecan, the first ADC has become available for triple-negative ABC in November 2021. The marketing approval refers to patients who have had at least two prior therapies, at least one of which was for advanced disease (https://www.ema.europa.eu/en/medicines/human/EPAR/trodelvy). According to the ABC6 panelists (majority vote: 95.7%), the drug is the preferred treatment option for these patients. Despite intensive prior treatment, sacituzumab govitecan not only prolonged median PFS but also median OS in the pivotal ASCENT trial [18]. Proactive therapy management is important with a focus on gastrointestinal complications like diarrhea, nausea, and vomiting (LoE/GoR: I/A). The German experts agree. Patients should not be denied the chance for a significant OS benefit. Possible gastrointestinal complications can be treated or even avoided through proactive management (e.g., prophylactic administration of loperamide).

Hereditary Breast Cancer

Is Panel Testing Useful?

According to the ABC6 panelists (majority vote: 93.3%), robust data that are relevant to the treatment decision (use of a PARP [poly-ADP-ribose-polymerase] inhibitor) are currently only available for germline mutations in breast cancer genes 1 and 2 (*g*BRCA1/2) (LoE/GoR: I/A). Testing of other moderate- to high-risk genes may be considered in individual cases, such as the result is important for family members. Patients must be informed that panel testing generally has no clinical consequences for themselves (ABC6 majority vote: 89.1%) (LoE/GoR: expert opinion/C).

The German experts agree. Every patient with HER2-negative metastatic breast cancer should be tested for *g*BRCA 1/2 regardless of family history and HR status. In addition to *g*BRCA1/2, evidence of efficacy of a PARP inhibitor is also seen for PALB-2.

Use of PARP Inhibitors

Referencing a phase 2 study with olaparib [19], the ABC6 panelists (majority vote: 93.3%) also endorse the use of a PARP inhibitor if there is evidence of a somatic BRCA1/2 mutation or a germline mutation in PALB2. This is considered justifiable because no larger studies are to be expected for this indication. The patients would need to be informed accordingly (LoE/GoR: II/B). The German experts agree but emphasize that regulatory approval for olaparib is linked to BRCA1/2 germline mutations only.

PARP-Inhibition or Platinum?

Currently, there are no studies comparing PARP inhibitor monotherapy versus platinum in hereditary ABC. It is not clear whether PARP inhibitors are still effective after prior treatment with platinum (ABC6 majority vote: 89.1%). Early use of a PARP inhibitor is favored from a German perspective. Stratified analyses indicate that

first-line use of at least the PARP inhibitor Olaparib is more effective than first-line treatment with platinum [20, 21]. In addition, carboplatin is often already used in the neoadjuvant setting in Germany.

PARP Inhibitors in ER+ ABC?

In case of *g*BRCA-mutated ER+ ABC, the ABC6 panelists (majority vote: 93.5%) prefer first-line use of an endocrine-based combination therapy with a CDK4/6 inhibitor *prior* to use of a PARP inhibitor. The ABC6 panelists justify their vote by citing the significant overall survival benefit that has been achieved with first-line use of CDK4/6 inhibitors compared to endocrine monotherapy in ER+/HER2– ABC (LoE/GoR: expert opinion/A).

The German experts add that the results of *g*BRCA testing are mandatory to use a PARP inhibitor. Starting with an endocrine-based therapy plus CDK4/6 inhibitor, the test results can be awaited (no time loss in first line) and be used for second-line therapy.

PARP Inhibition or Immunotherapy?

Data on the optimal therapy sequence with a PARP inhibitor or a combination of CPI and chemotherapy are also missing for triple-negative PD-L1+ and *g*BRCA-associated ABC. The ABC6 panelists (majority vote: 91.3%) prefer the first-line use of immuno-/chemotherapy because significant OS benefits have been shown here [22, 23] (LoE/GoR: expert opinion/B). The German experts agree and point out that the constellation of a PD-L1+ *g*BRCA-mutated ABC is seen in less than 10% of TNBC patients.

Unresectable Locally Advanced Breast Cancer

In case of unresectable locally advanced breast cancer (LABC), adequate treatment planning requires at least *one* core biopsy *before* start of any therapy to assess histology and biomarkers (HR and HER2 status, grade, PD-L1 status, and Ki67) (LoE/GoR: I/A) (ABC6 majority vote: 95.7%). For patients with unresectable LABC, staging includes a complete medical history with physical examination, laboratory tests, and imaging of chest, abdomen, and skeletal system (ABC6 majority vote: 100%). This is consistent with the AGO recommendations [1, 2].

PET-CT is the preferred imaging method for unresectable, invasive LABC (ABC6 majority vote: 76.1%). In Germany, however, PET-CT is not common in clinical practice [24, 25], but may be useful in individual cases according to the AGO Mamma recommendation [1, 2].

Fundamental Statements on Treatment

Patients with unresectable LABC are usually treated with a multimodal approach. In this regard, the ABC6 panelists refer to the still valid ABC5 statements [26]. But there were new votes on systemic therapy for the various subtypes.

Systemic Therapy for Unresectable HR+/HER2– LABC

According to the ABC6 consensus (majority vote: 95.6%), anthracycline/taxane-based chemotherapy or endocrine-based treatment with a CDK4/6 inhibitor are therapy options for unresectable HR+ LABC (LoE/GoR: I/A). The treatment decision should be based on the tumor characteristics (grade, biomarker expression, tumor burden) and the patient's condition (performance status, disease-related symptoms, comorbidities, preferences) (LoE/GoR: expert opinion/A) (majority vote: 88.9%).

This is common practice in Germany. In cases of doubt, preference should be given to endocrine-based therapy with a CDK4/6 inhibitor. Anthracycline/taxane-based chemotherapy (stage M0) is favored for improving local control and achieving secondary operability.

Systemic Therapy for Unresectable Locally Advanced TNBC

For locally advanced unresectable TNBC, the ABC6 panelists (majority vote: 82.6%) recommend initial anthracycline/taxane-based chemotherapy (LoE/GoR: I/A). They endorse the use of platinum in combination with a taxane primarily (but not exclusively) in patients with *g*BRCA-associated cancer (majority vote: 73.3%) (LoE/GoR: I/A). If pembrolizumab is approved for locally advanced unresectable TNBC, the drug should be used in combination with chemotherapy, regardless of PD-L1 expression, as in the KN522 study [27] (majority vote: 89.0%).

From a German perspective, sequential anthracycline/taxane-based chemotherapy is the essential backbone to be combined with a CPI and/or carboplatin depending on the individual situation [1, 2]. The use of atezolizumab for unresectable LABC is covered by the approval of the European Medicines Agency (EMA): currently, pembrolizumab in combination with chemotherapy is approved for locally relapsed, inoperable, or metastatic TNBC, if PD-L1 positivity (CPS ≥10) has been detected. For LABC the data from KEYNOTE-522 study should be taken into consideration until official EMA approval is available [27].

Unresectable HER2+ LABC

It is agreed (ABC6 majority vote: 95.6%) that taxane-based chemotherapy is indicated as an add-on to anti-HER2 therapy for unresectable HER2+ LABC. The goal is to increase the chance of pathological complete remission (pCR). Dual antibody blockade with trastuzumab and pertuzumab is recommended as the optimal anti-

HER2 therapy (LoE/GoR: I/A). This is consistent with the AGO Mamma recommendations [1, 2].

Only slightly more than half of the ABC6 panelists (54.3%) recommend the adjuvant treatment with anthracyclines (LoE/GoR: I/B). One-third (32.6%) did not agree. Anthracyclines should be used sequentially to taxanes if necessary (LoE/GoR: I/A) (majority vote: 87.0%); only the taxanes should be combined with anti-HER2 antibodies. From a German perspective, the adjuvant sequential use of an anthracycline may be useful in patients with high tumor burden and/or in the case of curative intention. An effective anthracycline-free alternative is the TCHP regimen (docetaxel/carboplatin with trastuzumab/pertuzumab) [28].

The German experts and the ABC6 panelists (91.3%) agree that patients with unresectable HER2+ (inflammatory or non-inflammatory) LABC who are in complete remission after adequate preoperative systemic therapy and locoregional treatment and who are being treated with curative intent, need adjuvant anti-HER2 therapy for 1 year, ideally with trastuzumab/pertuzumab (LoE/GoR: I/A). For HER2+ LABC patients without complete remission, the ABC6 panelists (majority vote: 87.0%) recommend adjuvant treatment with trastuzumab emtansine (T-DM1) for 14 cycles (LoE/GoR: I/A). This is consistent with the AGO Mamma recommendations [1, 2].

Germline BRCA Mutations in Unresectable LABC

Adjuvant treatment with olaparib for 1 year is recommended for patients with unresectable *g*BRCA-mutated LBCA and initial presentation of axillary lymph node involvement (cN ≥1) if they responded well to the preoperative systemic therapy and the surgical outcome in the breast and axillary region is adequate (ABC6 majority vote: 80.4%) (LoE/GoR: I/A). Referencing the OlympiA study [29], the German experts emphasize that this applies regardless of ER status.

Focus on Brain Metastases

Regardless of the underlying breast cancer subtype, asymptomatic patients with ABC do not require routine brain imaging (LoE/GoR: II/D) (ABC6 majority vote: 84.8%).

The German experts have different opinions regarding this statement and advocate an individual risk-benefit assessment, which should be discussed with the patient. Currently, there is no evidence that asymptomatic patients with brain metastases live longer or benefit in terms of quality of life because of early detection and intervention. However, benefits cannot be ruled out in individual cases, and depend on the extent and location of the tumor burden in the brain and the available treatment options. However, since there may be an increased risk of cerebral adverse events, some of the German experts recommend brain imaging in addition to routine staging [30]. It is agreed that patients with cerebral metastases must be treated by specialized physicians and discussed in the interdisciplinary tumor board. In addition to systemic therapy, there are several local options that can be considered for the individual situation.

Brain Metastases in HER2+ ABC

The German experts agree with continuing the ongoing systemic therapy in case that patients with HER2+ ABC and stable extracranial disease develop brain metastases that can be treated by stereotactic radiation (ABC6 majority vote: 88.9%) (LoE/GoR: I/D).

According to the ABC6 consensus (majority vote: 82.6%), chemotherapy is *not* indicated for relapsed HER2+ ABC patients who have brain metastases as the only site of metastasis and are being treated with stereotactic radiation (LoE/GoR: I/D). If anti-HER2 therapy with trastuzumab was discontinued before the patient relapsed, it should be resumed (ABC6 majority vote: 87.0%) (LoE/GoR: II/B).

The German experts agree. Such patients are at high risk for developing extracranial metastasis. In view of the palliative situation, they recommend adjuvant anti-HER2 therapy with trastuzumab, which is significantly better tolerated than chemotherapy. In the event of extracranial progression, chemotherapy should be added to anti-HER2 therapy.

Systemic Treatment of HER2+ Brain Metastases?

According to the ABC6 panelists (majority vote: 91.1%), treatment with tucatinib plus trastuzumab/capecitabine may be a new therapeutic alternative to local therapy for patients with active brain metastases. Primarily, however, the combination of these three drugs is currently the best available treatment option for patients with HER2+ ABC and progressive brain metastases being the driver of disease progression after local therapy (majority vote: 91.1%) (LoE/GoR: I/A). The situation of locally treatable brain metastasis was not covered by the HER2CLIMB study, the pivotal trial for tucatinib [17]. The German experts, therefore, recommend discussing all treatment options for active brain metastases in the interdisciplinary tumor board, including tucatinib/trastuzumab/capecitabine.

Referencing the prospective one-arm KAMILLA study [31], the ABC6 panelists (majority vote: 79.5%) also see T-DM1 as a treatment option for active brain metastases (LoE/GoR: II/A). The German experts note that, unlike the HER2Climb study [17], the KAMILLA study only enrolled patients with treated and stable brain metastases.

Peritoneal Carcinomatosis and Ascites

Peritoneal carcinomatosis and ascites most frequently occur in cases of invasive lobular breast cancer. Due to the unfavorable prognosis and substantial impairment of quality of life in these patients, early palliative treatment is necessary. An appropriately trained palliative care team should be involved in a timely manner (LoE/GoR: I/A) (ABC6 majority vote: 95.6%).

Peritoneal carcinomatosis is often difficult to depict radiographically. Typical symptoms include abdominal pain, nausea, anorexia, cachexia, increased waist circumference, ascites, constipation, and fatigue. The ABC6 panelists reference the ESMO guidelines for adequate management [16]. The German experts also recommend laparoscopy for histological confirmation and to rule out ovarian cancer. With regard to the management of ascites, the German experts refer to the German Association for Palliative and Supportive Medicine guideline [32, 33].

Advanced Breast Cancer in Male

The ABC6 panelists (100%) recommend offering genetic testing to men with ABC, similar as to women (LoE/GoR: II/A). In the case of ER+ ABC, men are treated with the same therapy options that are available for women, including targeted substances like CDK4/6, mTOR, and PI3KCA inhibitors (LoE/GoR: II/A) (ABC6 majority vote: 95.6%). The German experts agree.

Supportive and Palliative Care

Treatment-Related Cognitive Impairment ("Onco-Brain")

Breast cancer patients frequently report cancer and treatment-related cognitive impairment even though evidence of this is not documented by imaging. One problem is that neuropsychological test methods and structural changes in the brain seen by imaging have only limited informative value. A multifactorial event is suspected. Cerebral imaging is, therefore, only recommended for ruling out or detecting brain metastases (LoE: III/NA) (ABC6 majority vote: 97.8%). Cognitive impairment as a possible consequence of oncological treatment should be actively addressed and routinely reviewed (LoE: II/A) (ABC6 majority vote: 91.1%). The German experts agree with increased attentiveness to treatment-related symptoms and limitations. Physicians should talk to patients about this and deepen the conversation, if necessary.

Adequate Support of Patients

Physical activity and moderate exercise can also help with tumor and treatment-related cognitive impairment. The ABC6 panelists recommend moderate physical activity for 150–300 min per week or more intense activity for 75 min per week (LOE: II/A). Given that the endurance of ABC patients varies, the German experts caution against strict guidelines for duration and intensity of physical activity. In general, patients should be advised to exercise regularly according to their own capabilities and preferences. [1, 2].

Patients should be informed about factors that could adversely affect the course of the disease and can be corrected, such as the taking of certain medications, emotional stress, pain, fatigue, sleep disorders, alcohol consumption, or vitamin B deficiency (ABC6 majority vote: 100%). Patients who report significant adverse effects on their quality of life should also be offered neuropsychological assessment and cognitive rehabilitation (LoE: III/A) (ABC6 majority vote: 95.6%).

Interstitial Lung Disease and Pneumonitis

Interstitial lung disease (ILD), also known as a specific form of pneumonitis, is a rare but serious complication associated with many oncological drugs and may require the expertise of a pulmonologist. Prompt diagnosis, by means of CT, and intervention are important. The German experts agree with the ABC6 panelists' recommendations:

- ILD not induced by T-DXd: In the case of symptomatic grade 2 ILD, treatment needs to be discontinued (majority vote: 84.4%). In addition, systemic steroids are indicated. If the symptoms have subsided, treatment can be continued at a reduced dose. Treatment must be discontinued in the case of grade 3 or higher ILD.
- ILD induced by T-DXd: In this case, special precautionary measures are necessary (ABC6 majority vote: 84.4%). With asymptomatic, but radiographically visible changes in the lung, treatment with T-DXd must be stopped and systemic steroids (≥0.5 mg/kg BW prednisone or equivalent) must be administered. If the changes resolve within 28 days, T-DXd therapy may be restarted at full dose. In the case of a later recovery (after more than 28 days), the T-DXd dose needs to be reduced by one dose level. In the case of grade 2 ILD, systemic steroids (≥1 mg/kg prednisone or equivalent) must be administered immediately and T-DXd therapy permanently discontinued. It is important to taper steroids slowly over a period of at least 4 weeks (LoE/GoR: IA).

Maximum or Minimum Dosing?

According to the ABC6 panelists (majority vote: 95.7%), optimal dosing of a drug needs to be part of the

clinical development of anti-cancer drugs. However, studies indicate that the maximum tolerated dose does not have to be used in all patients [34]. In addition, the dosing should consider feasibility of the therapy, treatment goals, and patient's quality of life (LoE/GoR: expert opinion/NA). The German experts caution against arbitrarily modifying validated treatment regimens. Drug therapy should be started with the approved dosing and may be de-escalated depending on the side effects [34].

Caring for "Long-Term Survivors"

The ABC6 panelists (100%) argued that all individuals employed in the care and nursing of ABC patients should receive more support in their work, more appreciation and, if necessary, more psychological support. This applies to professional nurses as well as family caregivers and also includes protection against discrimination in the workplace and enough flexibility to adapt work to the care situation. The information and tools necessary for adequate care must be accessible to all caregivers and patients (LoE: expert opinion/NA). The German experts fully agree. Providing support to caregivers is an urgent social and political challenge.

Conclusion and Future Directions

The ABC6 Conference once again was a platform for intensive discussions on the most recent developments in advanced and metastatic breast cancer. As in previous years, the cooperation with patient advocates from Europe, Asia, the Middle East, Africa, Australia, and North, South, and Central America who expressed their concerns and requests, was most important. That is also why the ABC consensus constitutes an important contribution in terms of standardizing the treatment of advanced breast cancer on an international level and optimizing treatment worldwide. The next ABC7 Consensus Conference is scheduled in Lisbon from November 9 to 11, 2023. With ABC6.5, a special on-site edition is planned for 2022 (November 11–12, 2022).

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Author Contributions

All authors contributed equally to the conception, writing, and proofreading.

Appendix

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resa 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) 18 – Birgitte V. Offersen, DK (ESTRO) 19 – Laura Biganzoli, IT (Eusoma) 20 – Maria João Cardoso, PT (Eusoma) 21 – Shirley A. Metz, US (patient advocate) 22 – Elizabeth Bergsten-Nordstrom, SE (patient advocate) 23 – Ranjit Kaur, MY (patient advocate) 24 – Ginny Mason, US (patient advocate) 25 – Lesley Fallowfield, UK (psycho-oncologist) 26 – Matti S. Aapro, CH 27 – Carlos H. Barrios, BR 28 – Jonas Bergh, SE 29 – Javier Cortés, ES 30 – Rebecca Dent, SG 31 – Prudence A. Francis, AU 32 – Karen Gelmon, CA 33 – Xichun Hu, CN 34 – Sung-Bae Kim, KR 35 – Smruti Koppikar, IN 36 – Frédéric E. Lecouvet, BE 37 – Silvia Neciosup, PE 38 – Shinji Ohno, JP 39 – Olivia Pagani, CH 40 – Aleix Prat, ES 41 – Elzbieta Senkus, PL 42 – George W. Sledge, US 43 – Sandra Swain, US 44 – Daniel A. Vorobiof, US 45 – Binghe Xu, CN 46 – Giuseppe Curigliano, IT

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