

## Discussion of ABC7 Consensus and German Recommendations

### ABC7-Konsens – diskutiert vor dem Hintergrund deutscher Empfehlungen



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**ABSTRACT**

The rationale behind the “International Consensus Conference for Advanced Breast Cancer” (ABC) is to standardize the treatment of patients with advanced or metastatic breast cancer worldwide using an evidence-based approach. The aim is also to ensure that patients in all countries receive adequate treatment based on current treatment recommendations and standards. The 7th International Consensus Conference on Advanced Breast Cancer (ABC7) took place from November 9 to 12, 2023 in Lisbon/Portugal. ABC7 focused on metastatic disease as well as on locally advanced and inflammatory breast cancer. Special topics included the treatment of oligometastatic patients, leptomeningeal disease, treatment of brain metastases, and pregnant women with ABC. As in previous years, patient advocates from all over the world participated in the consensus conference and were involved in decision making.

**ZUSAMMENFASSUNG**

Ziel der „Internationalen Konsenskonferenz zum fortgeschrittenen Mammakarzinom“ (International Consensus Conference for Advanced Breast Cancer [ABC]) ist es, die Behandlung der Patientinnen mit fortgeschrittenem bzw. metastasiertem Mammakarzinom auf evidenzbasierter Grundlage weltweit zu standardisieren und sicherzustellen, dass in allen Ländern eine adäquate Behandlung mit Zugang zu den aktuellen Therapieempfehlungen und -standards ermöglicht wird. Die mittlerweile 7. „Internationale Konsenskonferenz zum fortgeschrittenen Mammakarzinom“ (ABC7) fand vom 9.–12. November 2023 in Lissabon/Portugal statt. ABC7 fokussierte neben der metastasierten Erkrankung auch auf das lokal fortgeschrittene und das inflammatorische Mammakarzinom. Spezielle Themen waren unter anderem die Behandlung oligometastasierter Patientinnen, die leptomeningeale Erkrankung, die Behandlung von Hirnmetastasen sowie von schwangeren Patientinnen mit fortgeschrittenem Mammakarzinom. Wie schon in den vergangenen Jahren nahmen auch Patientenvertreterinnen aus der ganzen Welt an der Konferenz teil und waren an der Konsensfindung beteiligt.

**Introduction**

The International Consensus Conference on the Diagnosis and Treatment of Advanced Breast Cancer (ABC: Advanced Breast Cancer) has been taken place in Lisbon/Portugal since November 2011. The rationale of the ABC consensus conferences is to discuss new developments and study results and develop a consensus on diagnostic and therapeutic procedures for clinical practice. The focus is on patients with locally advanced, not primarily operable breast cancer and patients with inflammatory or metastatic disease. The aim is to standardize diagnosis and treatment worldwide using an evidence-based approach. All patients with breast cancer should get access to new therapies.

The 7th Consensus Conference (ABC7) was held on November 9–12, 2023. The international panel consisted of 44 participants also including patient advocates (see box). There were three participants from Germany on the panel: Professor Nadia Harbeck, Munich; Professor Volkmar Müller, Hamburg, and the patient advocate Eva Schumacher-Wulf, who co-chaired the voting during consensus sessions.

**Discussion of ABC7 Consensus from a German perspective**

The discussion presented here refers to the voting results of the ABC conference on-site and reviews them in the context of German recommendations, in particular the recommendations of the (German) Breast Commission of the Gynecological Oncology Working Group (AGO Mamma), which are updated every year [1]. In this manuscript, the German experts have focused on topics which are relevant for clinical practice in Germany. Recommendations issued at ABC consensus conferences in previous

years which were not discussed again at the ABC7 conference remain valid and are also not discussed here. ► **Table 1** shows the grading system on which the ABC7 consensus is based [2].

► **Table 1** Grading system for the ABC7 consensus [2].

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.

## Locally Advanced/Inflammatory Breast Cancer (LABC/IBC)

According to the ABC7 panel, locally advanced breast cancer (LABC) is defined as inoperable, non-metastatic, locally advanced disease. The ABC7 panel defines inflammatory breast cancer (IBC) as a clinical-pathological diagnosis made by a multiprofessional group of experts (T4d or stage IV if metastases are present). The following criteria must be present for a diagnosis of IBC:

1. Early evidence of erythema, edema and/or orange peel skin and/or warm breast tissue with/without palpable tumor tissue,
2. A short history of disease (< 6 months),
3. Erythema must cover a least one third of the breast,
4. Confirmation of an invasive carcinoma by a pathologist.

Skin ulcerations are rare with IBC. A punch biopsy of the skin may confirm the diagnosis (Level of Evidence/Grading [LoE/GR]: I/A; ABC majority vote: 95.4%).

### Diagnosis and staging

According to the ABC7 panel, biopsy is a standard diagnostic tool and important for deciding on the appropriate treatment strategy as the biopsy results are used to determine the histological subtype, grading and the expression of biomarkers. In case of an inoperable LABC or IBC (both M0), the hormone receptor status (ER/PR), HER2 status, *Ki67* value and germline *BRCA1/2* status (*gBRCA1/2*) must be determined. After confirmation of metastatic IBC, PD-L1 status must be additionally determined if it is triple-negative breast cancer (TNBC), while *PIK3CA* status must be additionally determined in ER+/HER2- IBC. Determination of the *Ki67* is not necessary (LoE/GR: I/A; ABC majority vote: 88.6%).

According to the German recommendations, only ER/PR status, HER2 status and *Ki67* are of therapeutic relevance for inoperable LABC/IBC (each: M0). In the metastatic setting, the German experts recommend to determine additionally *gBRCA* status in patients with HER2-negative (HER2-) IBC, PD-L1 expression should additionally be determined for TNBC, and *ESR1* and *PIK3CA* mutation status should be determined in estrogen receptor-positive/HER2-negative (ER+/HER2-) IBC as soon as disease progression occurs after endocrine-based treatment with a CDK4/6 inhibitor [1]. Determination of *ESR1* mutation should be based on circulating DNA in the blood (liquid biopsy).

There is a high risk of metastasis in LABC and IBC. Before starting systemic therapy, comprehensive staging including complete histology, physical examination and laboratory tests plus imaging (thorax, abdomen, skeleton) are mandatory (LoE/GR: I/A, 100%). For non-lobular invasive breast cancer, the ABC7 panel recommends PET-CT *instead of* CT scan and bone scintigraphy. CT scan and bone scintigraphy *or* whole-body MRI are preferred for most lobular breast carcinomas (LoE/GR: II/A; ABC majority vote: 95.2%).

A PET-CT is not recommended in the German guidelines. It is not financially feasible as there is no reimbursement. From a medical point of view, however, the German experts support its use, as almost 20% more metastases are detected with PET-CT [3–5]. It is currently not clear, however, whether this translates into a

better prognosis. From a German perspective, it is important that differentiation between stage III and stage IV influences the choice and duration of therapy. In stage III, which has a potentially curative chance, the duration of therapy is limited in contrast to stage IV.

### Therapy for HR+ LABC/IBC

Primary systemic treatment options for HR+ LABC (M0) are anthracycline and taxane-based chemotherapy or endocrine-based therapy, for example, with a CDK4/6 inhibitor (LoE/GR: I/A). The choice of therapy is based on tumor characteristics and the patient's preference (LoE/GR: expert opinion/A). If anthracycline- and taxane-based chemotherapy is used as primary treatment for patients with inoperable HR+ IBC without distant metastases, the ABC7 panel recommends further postoperative treatment with endocrine-based therapy plus a CDK4/6 inhibitor (LoE/GR: I/A; ABC majority vote: 95.2%). These opinions correspond to the recommendations of AGO Mamma [1].

### Therapy for triple-negative LABC/IBC

There is also agreement with the AGO recommendation [1] for patients with inoperable triple-negative LABC/IBC. Primary therapy consists of anthracycline/taxane-based chemotherapy (LoE/GR: I/A) with pembrolizumab in patients without metastases. This is standard irrespective of PD-L1 status [6]. In patients with metastatic TNBC, the addition of pembrolizumab is only indicated for patients who are PD-L1-positive (CPS  $\geq 10$ ) [7] (LoE/GR: I/A; ABC majority vote: 93.0%).

### Therapy for HER2-positive LABC/IBC

As primary systemic therapy for patients with inoperable HER2-positive (HER2+) LABC/IBC, the ABC7 panel recommends integrating an anthracycline in addition to anti-HER2-targeted therapy (double blockade) plus taxane-based chemotherapy (LoE/GR: I/B; ABC majority vote: 62.7% with 32.5% rejection). Of note is: there was not yet a majority in favor of this approach at the ABC6 consensus conference. The German opinion is that anthracyclines represent an option for these patients. Anthracycline/taxane-based chemotherapy plus anti-HER2-targeted therapy is an equivalent option to the TCHP regimen (taxane/platinum plus double blockade) over six cycles [1].

### Therapy for LABC/IBC with *gBRCA1/2* mutation

It is currently unknown how to integrate the PARP inhibitor olaparib optimally into postoperative treatment with capecitabine or pembrolizumab for patients with inoperable triple-negative LABC/IBC and confirmed *gBRCA1/2* mutation. Safety data in the metastatic setting indicate that a combination of olaparib/pembrolizumab could be an option (LoE/GR: III/B) [8,9]. The ABC panel supports this approach with a majority vote (79.5%) for patients with inoperable LABC/IBC and *gBRCA1/2* mutation. The German experts agree with this approach for M0 patients with LABC/IBC and *gBRCA1/2* mutation who have no pathological complete remission (non-pCR) after systemic therapy with pembrolizumab plus olaparib (administered simultaneously or sequentially).

The situation is analogous for initially inoperable ER+/HER2- LABC/IBC with *gBRCA1/2* mutation. The question here is whether

postoperative olaparib can be administered in addition to abemaciclib. The simultaneous application of both drugs is not possible for safety reasons due to side-effects. According to the ABC7 panel, there could be an option during the postoperative treatment, with olaparib followed by abemaciclib (LoE/GR: III/B; ABC majority vote: 68.2%; rejected by: 14.6%). From a German perspective, the evidence for this sequence is currently low. Nevertheless, it is basically conceivable.

## General Statements on HR+/HER2- Advanced Breast Cancer (ABC)

### Endocrine resistance

The ABC7 panel confirmed that the definitions of primary and secondary (acquired) endocrine resistance also apply to endocrine-based therapy with a CDK4/6 inhibitor and do not merely refer to endocrine therapy (ET). In terms of content, the definitions are unchanged and correspond to the recommendation issued by AGO Mamma [1]. From a German perspective, it is important that the development of endocrine resistance is a continuum. The definitions primarily play a role for the inclusion criteria in clinical trials and are less important in clinical practice (ABC majority vote: 95.4%). The German experts emphasize that the course of the disease is crucial in clinical practice [1].

### CDK4/6 inhibition is the standard first-line approach even for aggressive disease

The ABC panel confirmed that endocrine-based therapy with a CDK4/6 inhibitor is the standard first-line therapy, also for the majority of patients with HR+/HER2- ABC and clinically aggressive disease (LoE/GR: I/A) as well as for postmenopausal patients and for men with breast cancer. The prerequisite is that they meet the disease characteristics of the RIGHT Choice trial [10] (LoE/GR: expert opinion/B; ABC majority vote: 95.4%).

The RIGHT Choice trial [10] compared endocrine-based first-line therapy with ribociclib/aromatase inhibitors (AI) in pre- and perimenopausal patients with clinically aggressive HR+/HER2- ABC ( $\pm$  visceral crisis) with combination chemotherapy (taxane/capecitabine or capecitabine/vinorelbine). Clinically aggressive disease (without visceral crisis) was defined as symptomatic visceral metastases, rapid disease progression, impending visceral crisis, and significant non-visceral symptoms including a serum bilirubin level of  $< 1.5$  mg/dl. Patients with clinically aggressive disease (and no visceral crisis) who received endocrine-based first-line therapy lived a median of twelve months longer without progression compared to patients who received combination chemotherapy (HR 0.42) [10].

For patients with a visceral crisis, the efficacy of endocrine-based therapy is comparable to that of chemotherapy but overall tolerance is better [10]. According to the ABC panel, endocrine-based therapy with a CDK4/6 inhibitor is potentially the better therapeutic option, even in patients with visceral crisis, and should be preferred to chemotherapy (LoE: II/B; ABC majority vote: 95.4%).

The German experts agree with both votes. What remains unclear from a German perspective is to what extent the results can be transferred to patients with low ER expression, for example, an ER expression of  $\leq 20\%$  [1].

### HR+/HER2-low ABC

The German experts agree [1] that for patients with HR+ ABC and low HER2 expression (HER2-low), the HER2 score should be specified in accordance with the updated ASCO/CAP recommendation of 2023 [11]. Consequently, it is important to differentiate immunohistochemically between IHC0, IHC1+, IHC2+ (amplified or not) and IHC3+. The pathology report should differentiate between HER2-zero (IHC0), HER2-low (IHC1+ or IHC2+ not amplified) and HER2+ (ISH 2+ amplified or HER2 3+) (LoE/GR: expert opinion/A; ABC majority vote: 97.6%). This is relevant with regards to trastuzumab deruxtecan (T-DXd) and sacituzumab govitecan for HR+/HER2-low ABC. There was no ABC panel vote on HR+ ABC with HER2-ultra-low. The results of the Destiny Breast (DB) 06 trial (<https://clinicaltrials.gov/study/NCT04494425>) have to be awaited.

## Treatment of ER+/HER2- ABC

### Use of CDK4/6 inhibitors

Given the findings of the SONIA trial [12], the ABC7 panel considers endocrine monotherapy to be an acceptable alternative for some patients with ER+/HER2- ABC; this includes patients with low tumor burden, a long disease-free interval (DFI) and patients who prefer endocrine monotherapy (ABC majority vote: 93.1%). Notwithstanding the above, the standard first-line treatment remains endocrine-based therapy with a CDK4/6 inhibitor.

The SONIA trial addressed the question whether patients with ER+/HER2- ABC should receive endocrine-based therapy with a CDK4/6 inhibitor (90% of patients received palbociclib) as first or second-line treatment. No statistically significant differences in efficacy were found after a median follow-up of more than 37 months. According to the ABC7 panel, it is unclear whether first-line therapy with ribociclib and abemaciclib would have achieved the same results. It is also not clear how many patients in the monotherapy arm did not receive second-line therapy.

In Germany, endocrine monotherapy is also a first-line option for selected patients with ER+/HER2- ABC. The standard treatment, however, is endocrine-based therapy with a CDK4/6 inhibitor. In contrast to the ABC7 panel, AGO Mamma evaluated the evidence of the available CDK4/6 inhibitors individually, based on PFS and overall survival (OS) data [1].

### Maintenance therapy after first-line chemotherapy

There are currently almost no data which support endocrine-based maintenance therapy with a CDK4/6 inhibitor after first-line chemotherapy for ER+/HER2- ABC [13]. Nevertheless, 75.0% of ABC7 panelists consider not just endocrine monotherapy but also endocrine-based therapy as a potential maintenance therapy after first-line chemotherapy. In another vote, 39.5% were *in favor of* endocrine monotherapy as maintenance therapy and 41.8% were opposed to it. In Germany, first-line chemotherapy is rarely used

for ER+/HER2- ABC. AGO Mamma recommends endocrine monotherapy for subsequent maintenance therapy [1].

One question which has been repeatedly discussed is whether patients with progression under endocrine-based first-line therapy with a CDK4/6 inhibitor may receive endocrine-based therapy with a CDK4/6 inhibitor as second-line therapy (TbP: treatment beyond progression). The majority of the ABC7 panel rejected TbP outside clinical trials (LoE/GR: expert opinion/D; ABC majority vote: 90.6%).

The German experts point out that TbP may be an option in this situation. In the MAINTAIN trial [14], a switch of CDK4/6 inhibitor *plus* a change of endocrine therapy showed superior results in terms of median PFS compared to the control arm with endocrine monotherapy (+ placebo) (HR 0.57;  $p = 0.006$ ). But irrespective of this, there are numerous further treatment options which may be an alternative after endocrine-based first-line therapy. Such options include elacestrant in patients with confirmed *ESR1* mutation, alpelisib/fulvestrant for patients with confirmed *PIK3CA* mutation and everolimus plus endocrine therapy or fulvestrant monotherapy [1]. The *ESR1* mutation should be determined by circulating DNA in the blood from the so-called liquid biopsy.

### Oral SERDs: importance of elacestrant

Elacestrant is the first oral SERD (selective estrogen receptor degrader) approved in Europe to treat ER+/HER2- ABC with *ESR1* mutation. For these patients, elacestrant is a new option for second-line and/or third-line therapy in the metastatic setting (ABC majority vote: 81.3%). This corresponds to the recommendation of AGO Mamma [1].

The approval is based on the randomized phase III EMERALD trial [15, 16] in patients who had 1–2 previous endocrine therapies including endocrine-based therapy with a CDK4/6 inhibitor. Patients with *ESR1* mutation who are pretreated with a CDK4/6 inhibitor for more than twelve months were found to benefit slightly more than patients with a shorter prior CDK4/6 inhibitor therapy [17]. *ESR1* mutation should be determined by circulating DNA in the blood, so-called liquid biopsy.

### Importance of capivasertib

In November 2023, the combination of capivasertib/fulvestrant was approved in the USA to treat patients with endocrine-resistant ER+/HER2- ABC and *PI3K/PTEN/AKT* alterations. The approval is independent of menopausal status (+ GnRH in premenopausal women) and is also a new therapeutic option for men with ER+/HER2- ABC (LoE/GR: I/B). As this combination had not yet been approved at the time of the ABC7 consensus conference, it was not voted on during the conference.

Approval is based on the randomized phase III CAPitello-291 trial [18] in patients with ER+/HER2- ABC who had been pretreated with multiple systemic therapies (incl. 1–2 previous endocrine therapies; 70% were treated with a CDK4/6 inhibitor). Compared to monotherapy with fulvestrant (+ placebo), a median PFS benefit was reported for capivasertib/fulvestrant, both in the general population and in the subgroup of patients with altered *PI3K/PTEN/AKT* signaling pathway (~ 41%) ( $p < 0.001$  respectively). The OS data were not yet mature. All patients either developed recur-

rence or progression within twelve months after adjuvant AI therapy or under AI therapy in the metastatic setting [18].

For clinical use in Germany, capivasertib must receive its European approval from the EMA (European Medicine Agency). Currently, it is not clear whether approval will be linked to biomarkers (altered *PI3K/PTEN/AKT* signaling pathway).

### Sacituzumab govitecan for ER+/HER2-ABC

In agreement with the recommendations of AGO Mamma [1], the ABC7 panel confirmed the anti-TROP 2-targeting ADC sacituzumab govitecan (SG) as a new therapeutic option for patients with ER+/HER2- ABC who had had multiple previous treatments (LoE/GR: I/B; ABC majority vote: 95.3%). In the randomized phase III TROPiCS02 trial which served as the approval study [19, 20], SG achieved a statistically significant median PFS benefit (HR 0.66;  $p = 0.0003$ ) in patients with ER+/HER2- ABC who had been intensively pretreated (60% had metastatic disease and had received several chemotherapies) [19] and was already showing a significant OS benefit [20]. Both HER2-zero and HER2-low patients benefited from this approach. Proactive management of side effects including informing patients in detail about side effects is necessary because of the increased risk of gastrointestinal problems, particularly diarrhea and nausea/vomiting. The German experts point out that SG can be administered with proactive management of side effects.

### T-DXd for ER+/HER2-low ABC

The ABC7 panel recommends T-DXd as the preferred treatment for patients with endocrine-resistant ER+/HER2-low ABC who have had 1–2 previous chemotherapies for metastatic disease. The panel mentioned the DB04 trial [21] which showed a clear median PFS benefit (HR 0.51;  $p < 0.001$ ) and longer OS (HR 0.64;  $p = 0.003$ ) for T-DXd compared to chemotherapy alone (TPC: treatment of physician's choice). The ABC7 panel also recommends proactive management of side effects for T-DXd. Attention must focus on the risk of interstitial lung disease (ILD) and/or pneumonitis as well as gastrointestinal toxicities, meaning that a computed tomography (CT) scan should be carried out every 6–8 weeks. Prophylactic interventions against nausea/vomiting are additionally recommended (LoE/GR: I/A; ABC vote: 100%).

In principle, the German experts agree with this. From a German perspective, however, routine chest CT scan every 6–8 weeks is not mandatory. Imaging should be done based on the patient's symptoms. It is important to pay attention to early symptoms such as shortness of breath, which may be early signs of ILD. The patient must be informed accordingly. Interdisciplinary cooperation with the respective medical specialists should already start with early symptoms; if the patient reports shortness of breath, a thoracic CT scan should be performed and a pulmonologist should be consulted additionally. Early interdisciplinary cooperation may be crucial to avoid discontinuing treatment. In addition, it is important to consider the requirements of the most recent medicinal product information.



## Discussion on sequence of ADCs

T-DXd and SG are two ADCs approved for patients with ER+/HER2-low ABC and several pretreatments. Based on the trial data of the two ADCs and the respective study populations [20,21], the ABC7 panel recommends administering T-DXd before patients receive SG (LoE/GR: expert opinion/B; ABC majority vote: 95.3%). In TROPiCS02 patients had more lines of pretreatment than those in the DB04 trial [21]. This is reflected in the approval for both ADCs. From a German perspective, the vote of the ABC7 panel is reasonable and corresponds to the recommendations of AGO Mamma [1].

## Triple-negative/HER2-low ABC

The approval of T-DXd for HER2-low ABC is independent of hormone receptor and also includes triple-negative HER2-low ABC. It should be noted, however, that only 11.3% of patients had a negative hormone receptor status in the approval study DB04 [21]. This subgroup had a similar benefit from T-DXd as the overall population (PFS: HR 0.46; OS: HR 0.48). According to the ABC panel, T-DXd is also an effective therapeutic option as second-line therapy or beyond for patients with triple-negative HER2-low ABC in the metastatic setting. Regarding the management of side effects, the same recommendations apply as for ER+/HER2- ABC (LoE/GR: I/B; ABC majority vote: 88.6%). The German experts refer readers to the statements for ER+/HER2- ABC.

Based on the data for triple negative HER2-low ABC, the ABC7 panel recommends – in contrast to ER+/HER2- ABC – the reverse sequence, i.e. SG should be used before T-DXd. The evidence for T-DXd for triple-negative HER2-low ABC is lower than for SG because of the small subgroup in the DB04 trial [21]. In the randomized phase III ASCENT trial [22], SG showed significant benefits in patients with advanced or metastatic TNBC (PFS: HR 0.41;  $p < 0.001$ . OS: HR 0.48;  $p < 0.001$ ) compared to chemotherapy alone (TPC). The German experts agree with the ABC7 vote, which corresponds to the recommendations of AGO Mamma [1]. They add, however, that a reverse ADC sequence could also be justified based on an individual management of side effects and patient's preferences.

## T-DXd for Brain Metastasis

Treatment options for patients with ABC and brain metastases (BM) has been expanded by the use of new drugs such as T-DXd. According to the ABC7 panel, T-DXd is a therapeutic option for patients with HER2+ ABC and either locally pretreated or locally non-pretreated BM (LoE/GR: II/B; ABC majority vote: 97.7%). This is based on data from the DB01, 02 and 03 trials [23–25] as well as an explorative pooled analysis of the three trials which focused on the efficacy of T-DXd for active BM [26].

The German experts agree with the ABC panel vote but note that the pooled data analysis on the use of T-DXd for active BM [26] was explorative. The evidence is less robust than evidence from a randomized trial such as HER2Climb with tucatinib/capecitabine/trastuzumab [27]. It is important to be aware of this for treatment decision for active BM.

## Oligometastatic Disease

There is a consensus that routine local ablation is not justifiable in ABC patients with extracranial asymptomatic oligometastases. The ABC7 panel discussed the value of stereotactic brain radiation (SBRT) or stereotactic ablative brain radiotherapy (SABR) in these patients and considered the contradictory results from different studies. The randomized phase II NRG-BR002 trial [28] found no efficacy benefits, whereas the significantly smaller randomized phase II SABR-COMET trial [29] SBRT/SABR showed an OS benefit in patients with well controlled primary tumors (HR 0.47;  $p = 0.006$ ).

The ABC7 panel rejected ablation of asymptomatic extracranial oligometastases outside clinical trials with a clear majority vote (LoE/GR: II/D; ABC majority vote: 97.6%). The German view is that the ablation of extracranial asymptomatic oligometastases is only an option in individual cases and the decision should be taken by a multidisciplinary team. The most important question in this context is whether the therapy should/must be continued postoperatively with curative or palliative intent. One problem is that it is difficult to carry out prospective randomized trials to obtain more evidence on this issue.

## Resection of the Primary Tumor Only by Individual Decision

In patients with de novo metastatic breast cancer (stage IV), the primary tumor is usually *not* resected as this is not associated with an OS benefit [1]. Exceptions are possible if this would improve the patient's quality of life. According to the ABC7 consensus, the patient's preference plays a decisive role and must be taken into account (LoE/GR: I/C [70%]).

According to the ABC7 panel, examples of the indication for resection of the primary tumor would be symptomatic primary tumor (palliation), progression of the primary tumor with well-controlled metastatic disease, or complete remission of metastases (no evidence of disease) but evidence of tumor tissue in the primary tumor (ABC majority vote: 97.6%). The procedure corresponds to clinical practice in Germany [1].

## Is Treatment Interruption an Option for Long-term Responders?

For ABC patients with well-controlled disease and long-term response to therapy, the ABC7 panel is open to the option of a longer treatment interruption (treatment holiday) if requested by the patient (LoE/GR: IV/B; ABC majority vote: 97.7%). In individual cases, this may also apply to patients with long-lasting complete remission. The approach should be discussed in detail with the patient. Therapy must be continued if progression occurs (LoE/GR: expert opinion/B; ABC majority vote: 97.7%).

There are no robust data supporting longer therapy interruptions in either situation. The standard in Germany is to administer effective drugs to patients with metastatic disease as long as possible and for as long as the patient's quality of life is good. The pa-

tient should be managed accordingly [1]. Longer therapy interruptions like treatment holiday should therefore not be initiated proactively. However, interruptions can be justified in the context of the patient's quality of life and her preferences. One alternative proposed by the German experts is to reduce the intensity of therapy (de-escalation strategy), for example by omitting the CDK4/6 inhibitor or temporarily pausing its administration during endocrine-based therapy. With chemotherapy there is the option to stop it for a short period of time, for example because the patient is going on holiday.

## Treatment of Visceral Crisis

A visceral crisis is an exclusion criterion in many clinical trials. Available data are therefore limited and the therapeutic evidence is low. According to the ABC7 panel, a visceral crisis is no contra-indication in ER+/HER2- ABC for endocrine-based therapy with a CDK4/6 inhibitor. Endocrine-based therapy should potentially even be preferred to primary chemotherapy. It is important that patients with HER2+ ABC who develop a visceral crisis are given anti-HER2 targeted therapy additionally (LoE: II/A; ABC majority vote 95.4%). The German experts agree [1].

### Visceral crisis due to hepatic metastasis

If a hepatic visceral crisis develops due to extensive hepatic metastasis, the therapeutic options are very limited because of the significantly impaired hepatic function. In this situation the ABC7 panel recommends a weekly therapeutic regimen with reduced doses (LoE/GR: IV/B; ABC majority vote: 92.8%). The German experts add that a hepatic visceral crisis is defined as a bilirubin level > 1.5 mg/dl [30] and that particular caution is required when the bilirubin level is > 2 mg/dl. Affected patients should not receive any medications which are metabolized in the liver. Therapeutic options include capecitabine and platinum, as they can usually be administered without reducing the dose.

### Visceral crisis from bone marrow infiltration

For patients with bone marrow infiltration, the ABC7 panel recommends weekly administration of paclitaxel (LoE: IV/B) or capecitabine (LoE: IV/B) and an endocrine-based therapy with a CDK4/6 inhibitor for patients with ER+/HER2- ABC (LoE: IV/B; ABC majority vote: 86.0%). The German experts agree [1].

## Prompt Recording of Health-related Quality of Life

Attention must be paid in clinical practice to disease-related symptoms and therapy-related side effects reported by patients (PRO = patient-reported outcome). To ensure that this is done, the ABC7 panel proposes the use of evidence-based measurement tools which are easy to apply in routine clinical practice and easy to handle for patients, for example, through user-friendly online platforms which can be accessed using a tablet or cell phone. Regular systematic monitoring ensures prompt communication with patients. Side effects can be recorded and treated more quickly (LoE/GR: I/B).

This important statement is very welcome. In Germany, this topic has already been taken up with the decision of the insurance companies to cover the cost for digital healthcare applications (DiGa: Digitale Gesundheitsapplikation) to provide the use and prescription of quality-assured apps as part of routine care (more information is available at: <https://diga.bfarm.de/de/verzeichnis>). Nevertheless, such apps cannot and should not replace physician-patient discussion but may be used additionally.

### Standardized measurement tools should be used

It is agreed that standardized tools are also necessary to collect data about patients' health-related quality of life. Carrying out an assessment with only the CTCAE (Common Terminology Criteria for Adverse Events) scale is no longer up to date (for more information: [https://ctep.cancer.gov/protocoldevelopment/electronic\\_applications/ctc.htm](https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm)). Specific modules or subscales, for example, from EORTC (European Organization on Research and Treatment of Cancer) questionnaires may offer alternatives. For realistic results, the methodology, the time of data collection, and the handling of missing data must be defined (LoE/GR: expert opinion/A; ABC majority vote: 97.7%).

## Contraception and Pregnancy in ABC Patients

The ABC7 panel recommends that all ABC patients of childbearing age, irrespective of their breast cancer subtype, should be counselled about the options for and necessity of non-hormonal contraceptive interventions and made aware of the risks and problems when carrying a pregnancy while receiving oncologic treatment (LoE/GR: II/A; ABC majority vote: 93.0%). Particular attention must be given to ABC patients receiving treatment without ovarian function suppression (OFS) or ablation (OFA), as some therapies have a slight gonadotoxic effect and do not induce menopause (LoE/GR: II/A; ABC majority vote: 100%). The German experts add that the patient must be informed that oral hormonal contraception is contraindicated during oncologic therapy.

### Pregnant patients to receive extensive information and counselling

With a clear majority vote (97.5%), the ABC7 panel emphasizes that the treatment and care of pregnant patients with ABC requires a multidisciplinary approach and an appropriate team of experts (LoE/GR: expert opinion/A). All treatment decisions must be in accordance with the wishes of the patient and, if necessary, those of her partner. The patient and her partner must be informed extensively about the complex situation and therapeutic options and know about the potential effects concerning life of the patient (mother) and the health of the fetus (LoE/GR: expert opinion/A). This is already standard of care in Germany.

### Imaging during pregnancy

According to the ABC7 panel, the preferred imaging procedure for staging is whole-body diffusion-weighted magnetic resonance imaging (DW-MRI) (LoE/GR: expert opinion/B; ABC majority vote: 77.2%). From the German perspective, it is important to consider whether staging could be dispensed with. Alternative options in early pregnancy are thoracic CT scan and ultrasonography of the

upper abdomen. MRI is becoming increasingly relevant in clinical practice for patients in long-term remission. No contrast agents must be used during pregnancy.

### Chemotherapy during pregnancy is basically safe

The ABC7 panel has confirmed that chemotherapy is currently the only systemic therapy which is safe to administer in the 2nd/3rd trimester of pregnancy (LoE/GR: II/A). The situation is particularly difficult for patients with HER2+ ABC as anti-HER2 targeted therapies are contraindicated during pregnancy (LoE/GR: expert opinion/A; ABC majority vote: 95.2%). The German experts add that no targeted therapies and no immunotherapy must be administered during pregnancy.

### Discussion regarding pregnancy termination

There was a lot of discussion on whether termination of pregnancy may be an option under certain circumstances and should be made available to patients who request it (LoE/GR: expert opinion/A). A clear majority (95.3%) of the ABC7 panel voted in favor.

The German experts commented the ABC statement as follows: the patient (mother) must receive comprehensive information during a multidisciplinary discussion. Alternatives to terminate the pregnancy should be discussed. If there is no danger to the life of the mother and/or child, there is a good chance to maintain the pregnancy until the fetal organs are sufficiently mature and the child can be delivered. During this period, the disease should be controlled with chemotherapy. If the patient (mother) wishes to terminate the pregnancy, this is legally possible in Germany as the abortion is medically indicated.

### ABC patients with HIV

There is very little data available on the treatment of ABC patients with HIV. It is important to be aware that these patients have a poorer prognosis and a higher risk of more side effects from oncologic treatment than patients without HIV. The German experts agree with all statements by the ABC7 panelists concerning therapy of ABC patients with HIV:

Oncologists and HIV specialists should work together as an interdisciplinary team (LoE/GR: expert opinion/A). Well-controlled HIV disease (no detectable viral load) is generally no exclusion criterion for participating in clinical trials (LoE/GR: expert opinion/A). The ABC7 consensus recommendations apply to ABC patients both with and without HIV.

Before starting oncologic treatment, ABC patients with HIV should be carefully examined for other morbidities with increased incidence due to HIV, and treatment should be initiated if necessary (LoE/GR: expert opinion/B). For myelotoxic chemotherapy, primary G-CSF prophylaxis is recommended (LoE/GR: expert opinion/A).

There are currently no data on the use of CDK4/6 inhibitors for patients with ER+ ABC and HIV (LoE/GR: expert opinion/NA). Safety data suggest that immune checkpoint inhibitors are a potential treatment option (LoE/GR: IV/B). Most cytotoxic drugs are safe if there is no detectable viral load and the CD4+ T-cell count is  $\geq 200/\mu\text{l}$  under modern anti-retroviral therapy (ART) (LoE/GR: expert opinion/B).

HIV treatment must be continued simultaneously to oncologic treatment (LoE/GR: expert opinion/A). If the patient has not previously received ART, oncological treatment should be delayed if possible and initiated two weeks after beginning ART (LoE/GR: expert opinion/B). Potential drug interactions must be checked. If clinically relevant interactions occur, the viral load must be monitored closely. This also applies to the CD4+ T-cell count if medications are associated with a higher risk of lymphocytopenia, (LoE/GR: expert opinion/B).

### Treatment of Older ABC Patients

The statements of the ABC7 panel on the treatment of older ABC patients correspond to the recommendations of AGO Mamma and to clinical practice in Germany [1]. It is self-evident that older patients should be involved in the decision-making process about their treatment and their preferences must be taken into account (LoE/GR: expert opinion/A). Older patients must also be offered the opportunity to participate in clinical trials (LoE/GR: expert opinion/A; ABC majority vote: 100%).

Special attention must be paid to potential drug interactions in older patients as they often take more medications (polypharmacy) than younger patients (LoE/GR: I/A; ABC majority vote: 100%). The German experts wish to add that older patients must also be asked about any over-the-counter medications and nutritional supplements they may be taking.

The ABC7 panel recommends following the EUSOMA-SIOG guidelines for the management of older ABC patients [31]. It is particularly worth noting that other therapy schedules, dose reductions, or stepwise dose escalation (until reaching the standard recommended dose) may be required in older patients to reduce adverse events (LoE/GR: expert opinion/A; ABC majority vote: 77.2%).

### Geriatric assessment desirable

The German experts support the ABC7 majority vote (90.4%) about carrying out a geriatric assessment in older patients when deciding on the appropriate therapy. The ABC7 panel recommends initial use of the G8 questionnaire as a geriatric screening tool. If the scores are low, a more detailed geriatric assessment should follow (LoE/GR: I/A). This approach is still not commonly used in Germany. The G8 questionnaire consists of eight questions and can be easily integrated into clinical practice [32, 33]; it is one of several available tools.

### Elderly patients with ER+/HER2- ABC

Endocrine-based therapy with a CDK4/6 inhibitor is also the standard first-line treatment for the majority of elderly patients with ER+/HER2- ABC (LoE/GR: II/A). Real-world data suggest that this also applies to elderly patients in poor (unfit) performance status [34–38] (LoE/GR: III/B; ABC majority vote: 93.0%).

When treating unfit ABC patients, the ABC7 panel recommends initially administering lower doses of the CDK4/6 inhibitor even though evidence-based data are lacking (LoE/GR: expert opinion/B; ABC majority vote: 90.6%). The German experts disagree. The evidence-based standard dose should initially be given even in older patients and dose reductions should be the excep-



tion. If necessary, treatment may be switched to endocrine monotherapy [1].

### Elderly patients with HER2+ ABC

Unless there are no absolute contraindications, older patients with HER2+ ABC should receive anti-HER2 targeted therapy just like younger patients (LoE/GR: I/A; ABC majority vote: 100%). For the new anti-HER2-targeting agents which are potentially associated with a higher risk of side effects, the ABC7 panel recommends starting with a lower dose if necessary and adjusting the dose under careful monitoring, depending on how well the patient tolerates it (LoE/GR: expert opinion/A; ABC majority vote: 83.7%). The German experts agree. They add that for combination regimens such as tucatinib/capecitabine/trastuzumab, the alternative is to only reduce the dose of the combination partner (capecitabine).

## Leptomeningeal Disease

There is no accepted standard for the treatment of patients with ABC and leptomeningeal disease (LMD).

### Diagnosis of LMD

If possible, these patients should be included in clinical trials, specifically in trials evaluating therapies to treat CNS metastases (LoE/GR: expert opinion/A). The treatment decision must be discussed by an interdisciplinary team which also considers the patient's prognosis. It is also important to have a detailed discussion with the patient and her carers (LoE/GR: expert opinion/A). To assess the full extent of disease, the ABC7 panel recommends an MRI of the full length of the spine using gadolinium-containing contrast agents (LoE/GR: expert opinion/A; ABC majority vote: 100%).

The German experts add that if there is a suspicion of LMD, clinical symptoms, imaging and examination of the cerebrospinal fluid are the mainstays of diagnosis. If two of the three results are positive, the diagnosis is confirmed. Imaging alone is not adequate for a diagnosis as false-positive findings cannot be excluded. Nevertheless, if LMD is suspected, imaging should always include an MRI of the neuraxis.

### Therapeutic options for LMD

According to the ABC7 panel, focal irradiation (brain or craniospinal) is an option for circumscribed symptomatic lesions (LoE/GR: III/B). However, whole-brain radiation therapy (WBRT) is recommended for extensive nodular lesions or symptomatic linear LMD (LoE/GR: III/B; ABC majority vote: 97.7%).

From a German perspective, interdisciplinary coordination in treatment decisions is necessary. The decision for irradiation, especially WBRT, must be carefully weighed; on the one hand the poor prognosis of patients with LMD must be taken into account and on the other hand it must be acknowledged that there are also other therapeutic options such as systemic therapy. From a German perspective, systemic therapy with new drugs is preferable to WBRT for extensive lesions. This particularly applies to HER2 + ABC with LMD.

### Shunt placement

The German experts are very cautious about placing a shunt in the situations described above. Nevertheless, placement of a ventriculoperitoneal shunt is an option in cases with elevated intracranial pressure or symptomatic hydrocephalus as these are acute situations. The German experts agree with the ABC7 panel (LoE/GR: expert opinion/B). Here again, the treatment decisions should be done during interdisciplinary discussions.

### Is intrathecal chemotherapy an option?

Intrathecal chemotherapy does not prolong overall survival, does not improve patients' quality of life and is associated with significant toxicity. Nevertheless, it can be a therapeutic option to alleviate symptoms of disease in individual cases with stable systemic disease (LoE/GR: III/C).

In contrast to historical data, studies with small numbers found that intrathecal administration of trastuzumab was relatively effective. In individual cases, the ABC7 panel considers it an option to treat ABC patients with HER2+ LMD (LoE/GR: III/B). From a German perspective, intrathecal trastuzumab should be administered cautiously and only to selected patients with HER2+ LMD as new systemic therapies with proven efficacy are now available to treat these patients, for example, T-DXd or tucatinib/capecitabine. Efficacy data are also available for capecitabine monotherapy (LoE/GR V/B).

## Conclusion and Outlook

Once again the ABC7 consensus conference has provided a platform for intensive discussions on the latest diagnostic and therapeutic developments for the treatment of advanced and metastatic breast cancer. As in previous years, on-site discussions between physicians and patient advocates as well as between patient advocates from different countries have proved to be very valuable. The next ABC8 consensus conference will be held in Lisbon on November 6–8, 2025.

## ABC7 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, *not present*)
5. Eva Schumacher-Wulf, DE (co-chair, patient advocate)
6. Sandra Ximena Franco Millan, CO (scientific committee)
7. Karen Gelmon, CA (scientific committee)
8. Joseph Gligorov, FR (scientific committee)
9. Volkmar Mueller, DE (scientific committee)
10. Birgitte V. Offersen, DK (scientific committee)
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