

# ABC3 Consensus Commented from the Perspective of the German Guidelines\*

## Third International Consensus Conference for Advanced Breast Cancer (ABC3), Lisbon, 07. 11. 2015

ABC3-Konsensus vor dem Hintergrund deutscher Leitlinien kommentiert

Dritte Internationale Konsensuskonferenz zum fortgeschrittenen Mammakarzinom (ABC3), Lissabon, 07. 11. 2015

### Authors

M. Untch<sup>1</sup>, D. Augustin<sup>2</sup>, J. Ettl<sup>3</sup>, R. Haidinger<sup>4</sup>, N. Harbeck<sup>5</sup>, H.-J. Lück<sup>6</sup>, D. Lüftner<sup>7</sup>, F. Marmé<sup>8</sup>, L. Müller<sup>9</sup>, F. Overkamp<sup>10</sup>, E. Ruckhäberle<sup>11</sup>, M. Thill<sup>12</sup>, C. Thomssen<sup>13</sup>, R. Wuerstein<sup>14</sup>, N. Marschner<sup>15</sup>

### Affiliations

The affiliations are listed at the end of the article.

### Key words

- ABC3 Consensus
- Metastatic breast cancer
- System therapy
- Guidelines

### Schlüsselwörter

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### Correspondence

**Prof. Michael Untch**  
 HELIOS Klinikum Berlin-Buch  
 Klinik für Gynäkologie und Geburtshilfe, Interdisziplinäres Brustzentrum  
 Schwanebecker Chaussee 50  
 13125 Berlin  
[michael.untch@helios-kliniken.de](mailto:michael.untch@helios-kliniken.de)

### Abstract

The Third International Consensus Conference for Advanced Breast Cancer ABC3 on the diagnosis and treatment of advanced breast cancer was held in Lisbon from 5 to 7 November 2015. This year the focus was the treatment of metastatic breast cancer (stage IV) – including the patient perspectives. Important topics were questions relating to quality of life, the care for long-term survivors as well as the management of disease-related symptoms and treatment-based side effects. The use of standardised tools to assess individual treatment success and the benefits of new substances were important points for discussion. The diagnosis and treatment of inoperable locally advanced breast cancer were discussed two years ago during the ABC2 consensus [1]. A working group of German breast cancer experts commented on the results of the ABC panelists, paying particular attention to the German guidelines (AGO, S3, DGHO) on the diagnosis and treatment of breast cancer [2–5] in Germany.

### Zusammenfassung

Vom 05. bis 07. November 2015 fand in Lissabon die 3. internationale Konsensuskonferenz ABC3 (Advanced Breast Cancer Third Consensus) zu Diagnostik und Behandlung des fortgeschrittenen Mammakarzinoms statt. Der inhaltliche Schwerpunkt lag dieses Jahr auf der Behandlung des metastasierten Mammakarzinoms (Stadium IV) – u.a. unter besonderer Berücksichtigung der Perspektive der Patientinnen. Im Rahmen der Konsensusdiskussion wurde daher auch über Fragestellungen zur Lebensqualität, der Betreuung Langzeitüberlebender sowie des Umgangs mit erkrankungsbedingten Symptomen und therapiebedingten Nebenwirkungen abgestimmt. Neben den klassischen medizinischen Fragestellungen waren der Einsatz standardisierter Instrumente zur Bewertung des individuellen Therapieerfolgs sowie die Nutzenbewertung neuer Substanzen wichtige Diskussionspunkte. Diagnostik und Therapie des inoperablen lokal fortgeschrittenen Mammakarzinoms waren vor 2 Jahren anlässlich des ABC2-Konsensus diskutiert worden [1]. Eine Arbeitsgruppe deutscher Brustkrebsexperten hat die Abstimmungsergebnisse der ABC-Panelisten unter besonderer Berücksichtigung der deutschen Leitlinien (AGO, S3, DGHO) zu Diagnostik und Therapie des Mammakarzinoms [2–5] für den Therapiealltag in Deutschland kommentiert.

\* The present manuscript (modified version) is a cross-section of opinions from the point of view of German breast cancer experts. The first publication was in "Breast Care" 01/2016 (Thomssen C, Augustin D, Ettl J et al., ABC3-Consensus: assessment by a German group of experts. DOI: 10.1159/000443515). The official ABC3 consensus will be published under the authorship of the ABC3 panelists.

## Introduction

The aim of the ABC consensus on advanced and metastatic breast cancer (ABC = Advanced Breast Cancer) is to standardise the treatment situation for patients with locally advanced or metastatic breast cancer. The organiser of the ABC consensus conference is the European School of Oncology (ESO) in cooperation and coordination with various international specialist societies: ESMO (European Society of Medical Oncology), EUSOMA (European Society of Mastology), FLAM (Federacion Latino-Americana de Mastologia) and SIS (Senologic International Society). The ABC3 consensus is also supported by the Breast Cancer Research Foundation (BCRF) and the Susan G. Komen Breast Cancer Foundation.

This year's ABC3 consensus focussed on metastatic breast cancer (stage IV). Particular attention was paid to the patients' perspective. Corresponding questions – treatment objective, quality of life, care for long-term survivors, management of illness-related symptoms and treatment-based side effects – were part of the consensus discussion. The diagnosis and treatment of inoperable locally advanced breast cancer (stage IIIB) were already the focus of the ABC2 consensus conference in Lisbon in November 2013 [1].

The ABC3 panel consisted of 45 experts from 23 countries, including Prof. Dr. med. Nadia Harbeck, Munich, and Prof. Dr. med. Christoph Thomssen, Halle/Saale, two representatives from Germany and six patient representatives/nursing staff. The statements were commented by the panelists with “yes” (agreement), “no” (rejection) or “abstention”. As the consensus statements are based on the opinions of experts from various specialist fields who come from countries with different healthcare systems and resources, the German experts try to integrate the panelist views into everyday clinical practice in Germany.

The statements from the consensus conference discussed in this publication represent the discussion during the symposium in Lisbon (7 November 2015). The official publication of the ABC3 consensus statements will be published later this year (expected: Cardoso F et al. *The Breast* 2016; *Annals of Oncology* 2016).

## Metastatic Breast Cancer: General Statements

### Clinical benefit assessment of medications

To support physicians in assessing the efficacy of medication in tumour therapy, the ESMO and the American Society of Clinical Oncology (ASCO) have developed standardised tools for the objective benefits assessment of new therapies, the ESMO Magnitude of Clinical Benefit Scale (ESMO-MCBS) [6] and the ASCO Value Framework [7]. The major criteria are the extension of overall survival or progression-free survival and quality of life and/or toxicity. Medications are divided into those with a high, median or low clinical benefit. Almost 90% of the ABC3 panelists (87.5%) welcome the new scales in order to ensure, particularly in countries with limited resources, that medications are used and paid for if they have a high benefit (LoE: expert opinion).

The German expert group also welcomes these scales. The ESMO-MCBS, in particular, appears to be a reasonable additional approach focus on the importance of the study end points “overall survival” versus “progression-free survival” in the discussion. From a German viewpoint the ASCO scale, by contrast, puts a very strong emphasis on the cost aspect. In Germany, both scales have no significance for the specific treatment decision, accord-

ing to an explicit statement by the German experts. This is made by the physician on an individual basis together with the patient.

### Importance of telemedicine

ABC3 panelists (92.8%) and German experts see telemedicine as an important approach to care for patients who live in some distance from oncologic centres, such as in rural or sparsely populated areas. The prerequisite for this is that the use of corresponding information and communication technologies is ensured (LoE: expert opinion). However, the refunding of this important collaboration is not yet covered in Germany.

### Integration of “patient-reported outcome measures”

A significant majority of the ABC3 panelists (87.1%) support the routine use of validated tools in everyday clinical practice to record the side effects of oncologic treatment and disease-related symptoms. These PROMs (patient-reported outcome measures) should be easy to use in everyday clinical practice. This also includes simple application, for instance via mobile telephones. The systematic monitoring in this way facilitates communication between the patient and the treatment team and enables earlier intervention via supportive measures, which means increased quality of life for the patients (LoE: IC). The German experts fundamentally welcome the routine use of these tools. However, additional resources are required for documentation and evaluation.

### Care for long-term survivors

As patients with advanced and metastatic breast cancer are surviving longer due to improved treatment options, new challenges are expected. The ABC3 panelists (95%) and the German experts emphasise that the treatment strategy – taking into account treatment side effects, quality of life, treatment preferences and the patient's current life plan – need to be regularly adapted to the status of the disease. Particular attention should be paid for patient needs when planning treatment (LoE: expert opinion).

The German experts add that the scientific evaluation of this topic is required in treatment research. Until now, there are only a small number of “lighthouse projects” in Germany, such as the Deutsche Stiftung für junge Erwachsene mit Krebs (German Foundation for Young Adults with Cancer) [8].

All ABC3 panelists (100%) and the German experts agree that the patient's desire to work during treatment has to be taken into account when planning the treatment: The flexibility required for this must be granted at the workplace and working patients must also be guaranteed continuous treatment (LoE: expert opinion). According to the German experts, this must also be suitably accepted and implemented in society and in the workplace.

### Focus on patients with stable disease

Over 80% of the ABC3 panelists (82%) consider that an oncoplastic breast reconstruction can be offered to patients who are in a stable situation of their disease (LoE: expert opinion). From a German viewpoint, oncoplastic breast reconstruction for metastatic patients should be managed restrictively and only be discussed at the patient's request. The prerequisite is stabilization of the disease for a prolonged time period during systemic treatment with low proliferation and a longer life expectancy.

The ABC3 panelists did not agree whether imaging of the breast should be performed in patients with advanced disease who are stable over a longer period of time if there is suspicion of locore-

gional progression. A good half of the ABC3 panelists (52.5%) voted for and the rest were (47.5%) against (LoE: expert opinion). In Germany, patients with metastatic disease undergo regular *physical* examinations. No regular imaging of the breast is indicated from a German viewpoint for patients without symptoms or without suspicious findings. An imaging should only be required if there is suspicion of locoregional progression and if the findings of the imaging may have clinical consequences.

### Significance of a metastasis biopsy

According to ABC3 panelists (97.6%) and the German expert group, a biopsy of metastatic lesions should be performed if easily accessible. This is not only important for histological reasons, but also to confirm the diagnosis of the primary tumour. A metastasis biopsy is particularly recommended for the first metastasis (LoE: 1 B). Where clinically feasible, biological markers, particularly the hormone receptor (HR) and HER2 status in the metastatic setting should be re-evaluated at least once (LoE: 1 B). Technical difficulties within the tissue examination due to the metastasis localisation (for instance, bones) should be discussed with the pathologist in advance.

In case of discordant results the German group of experts also recommended serial tissue biopsies to further analyse the course of the disease. Besides punch biopsy the fine needle aspiration cytology is another valid technical option (for instance, FISH from cytology). A metastasis biopsy is also sensible from a German viewpoint in the event of unexpected non-response.

### Resection of the primary tumour

The resection of the primary tumour for de novo stage IV breast cancer patients does not usually extend the survival time. According to the ABC3 vote (~70%), possible exceptions are patients with bone only disease (LoE: 1 B). Nonetheless, the breast tumour removal can be considered on an individual basis for selected patients, particularly to improve quality of life (LoE: 2 B). The approach is currently being investigated further in prospective clinical studies.

From a German viewpoint, the decision must be made on an individual basis together with the patient and at her explicit request as no prolongation of survival time has yet been demonstrated. The patient's disease should also have been stable over a prolonged period under systemic treatment and the patient should have a longer life expectancy. If the patient decides to have surgery, this should be performed with clear margins. In general no axillary surgery is needed. The resection of the primary tumour is contraindicated for patients with poor response to systemic therapy and with "high-risk" metastasis.

### Using the opportunity of long-term survival

The German expert group agrees with the ABC3 panelists (90.6%) that there is a small percentage of patients who have a chance of long-term survival despite advanced disease. These are usually patients with oligometastatic disease who have achieved complete clinical remission under systemic treatment. This group of patients should be treated with a multimodal approach, including locoregional treatments with curative intention (LoE: expert opinion). A prospective clinical study is recommended for the further validation of this approach.

## HER2-positive Metastatic Breast Cancer



Patients with HER2-positive advanced or metastatic breast cancer should be offered an anti-HER2-therapy early in the first-line treatment – except in the presence of contraindications (LoE: 1 A).

### Focus: ER+/HER2+ metastatic illness

The German group of experts and the ABC3 panelists (72.0%) agree that an anti-HER2-therapy is indicated for patients with HER2+ advanced breast cancer *regardless* of the HR status. This also applies to the rare case that endocrine therapy is preferred over chemotherapy.

According to the ABC3 panelists, there have not yet been any studies in which the first-line treatment with an endocrine plus anti-HER2-drug was compared with chemotherapy plus anti-HER2-drug (LoE: 1 A). The indirect comparison is in favour of chemotherapy as no survival benefits have been shown for the combination of endocrine plus anti-HER2 treatment to date – unlike first-line treatment with chemotherapy plus anti-HER2 drugs [9].

From a German viewpoint, endocrine therapy should only be used very restrictively in the first-line setting. Outside of clinical studies, there is primarily only an indication for the aforementioned patients where chemotherapy cannot be used or is rejected by the patient [2]. In Germany, chemotherapy plus dual HER2 blockade – regardless of the HR status – is the standard for first-line treatment for patients with HER2-positive metastatic breast cancer. At present, the DETECT V study (CHEVENDO) is underway to compare endocrine therapy with chemotherapy, each in combination with dual HER2 blockade.

However, the majority of the ABC3 panelists (79.4%) and the German expert group see endocrine therapy as an option for maintenance treatment after the end of chemotherapy. However, this approach has not yet been investigated in randomised clinical studies (LoE: 1 C).

### Progression after first-line treatment

The ABC3 panelists (90.6%) and the German expert group recommend the continuation of anti-HER2 treatment beyond progression to the first-line treatment – in addition to cytostatic or endocrine therapy (LoE: 1 B). The German experts emphasise that the treatment of patients with HER2-positive breast cancer should always include an anti-HER2 component.

It is currently unclear how long patients with metastatic HER2-positive breast cancer require anti-HER2 treatment. The further treatment across various lines is recommended both by the ABC3 panelists (92.8%) and by the German experts. The anti-HER2 treatment should thus also be maintained for patients in long-term remission as long as the therapeutic index is positive. A discontinuation of the anti-HER2 therapy after several years of stable complete remission may be an option for some patients in case that treatment can be re-started at any time in case of progression (LoE: expert opinion). However, the German experts recommend, in line with the current AGO guidelines [2], not discontinuing the anti-HER2 treatment with a positive therapeutic index as re-induction is not always successful.

Agreement exists between all ABC3 panelists (100%) and the German expert group that patients who have received anti-HER2 treatment as part of (neo)adjuvant treatment should not be excluded from clinical studies in the metastatic setting.

### Dual HER2 blockade with trastuzumab/pertuzumab

The ABC3 panelists (95.4%) and the German experts agree that the combination of trastuzumab plus chemotherapy is superior to the combination of chemotherapy plus lapatinib for the first-line treatment of HER2-positive metastatic disease with regard to progression-free and overall survival. This is true regardless of whether or not the patient has received (neo)adjuvant pre-treatment with trastuzumab (disease-free interval [DFS] > 12 months) (LoE: 1 A).

The German experts add that dual HER2 blockade with trastuzumab/pertuzumab plus taxane is standard for the first-line treatment of HER2-positive metastatic breast cancer [2,9]. The duration of DFS – the period of time between the end of the (neo)adjuvant anti-HER2 therapy and the occurrence of metastasis – plays no role for the treatment decision (dual anti-HER2 treatment).

The majority of the ABC3 panelists (85.7%) also considered dual HER2 blockade with trastuzumab/pertuzumab plus taxane to be a first-line standard, although specifically for patients *without* anti-HER2 pre-treatment. For the first-line treatment of metastatic patients *with* (neo)adjuvant anti-HER2 pre-treatment, 75.6% of the ABC3 panelists recommend dual HER2 blockade as an “important option”. The ABC3 panelists refer to the fact that in the CLEOPATRA study, in which dual HER2 blockade plus docetaxel achieved a significant and clear survival benefit ( $p < 0.001$ ) compared with trastuzumab plus docetaxel in the final assessment [9] (LoE: 1 A), the majority of patients were not pre-treated with an anti-HER2 therapy. The magnitude of benefit was similar in the patients who had previous (neo)adjuvant anti-HER2 treatment (LoE: 1 A) [9].

In the AGO guideline [2], dual HER2 blockade plus taxane is recommended as *the* first-line standard in both situations as dual anti-HER2 blockade achieved the same relative risk reduction, regardless of whether or not patients received (neo)adjuvant pre-treatment with trastuzumab.

Despite insufficient data, the German experts recommend dual HER2 blockade as first-line option even in the case of rapid progression after (neo)adjuvant pre-treatment within twelve months (DFS < 12 months). An evidence-based alternative is treatment with T-DM1.

### Pertuzumab in later lines of treatment?

The German expert group agrees with the majority of the ABC3 panelists (86.0%) that, in the absence of data, there is currently no indication to continue treating patients with HER2-positive breast cancer and progression during or beyond the first-line treatment with trastuzumab/pertuzumab plus chemotherapy (no “pertuzumab beyond progression”). The use of pertuzumab/trastuzumab plus chemotherapy beyond the first-line treatment is, however, an option for patients who have not received dual HER2 blockade in the first-line setting (LoE: 2 C). This majority vote of the ABC3 panelists (75.6%) is supported by the German experts.

### Anti-HER2 second-line treatment

Almost 90% of the ABC3 panelists (88.0%) agree that beyond trastuzumab-based first-line treatment trastuzumab emtansine (T-DM1) is currently the most effective option for second-line treatment [10,11] [LoE 1 A]. The German expert group recommends second-line treatment with T-DM1 for patients with HER2+ metastatic breast cancer following pre-treatment with trastuzumab and taxane [2].

For patients with progression during trastuzumab-based treatment the majority of the ABC3 panelists (83.7%) also consider the combination trastuzumab/lapatinib (without chemotherapy) as treatment option for some patients (LoE: 1 B). However, there are currently no data on the use of this combination for patients with progression during pertuzumab/trastuzumab or T-DM1. From a German viewpoint the combination trastuzumab/lapatinib is recommended mainly for the HR-negative, HER2-positive metastatic disease. However, the combination in the approval-relevant phase-III study [12] also achieved a median survival advantage compared with monotherapy with lapatinib i.e. regardless of the HR status.

### Therapy sequences and combination partners

If there are no contraindications, patients with HER2-positive metastatic breast cancer receive anti-HER2 treatment across all lines of treatment. An optimal therapy sequence for the anti-HER2 treatment with regard to cytotoxic combination partners cannot be determined because pre-treatment can differ and combinations are multiple. There was no consensus on therapy sequences.

However, a clear majority of the ABC3 panelists (86.0%) defined docetaxel and paclitaxel as the preferred combination partners for dual HER2 blockade with trastuzumab/pertuzumab. Optional combination partners are vinorelbine (LoE: 1 B) and nab-paclitaxel (LoE: 2 B). The German experts agree.

The ABC3 panelists (90.6%) and the German experts recommend trastuzumab-based therapy for the later lines of treatment of HER2-positive metastatic breast cancer. Besides taxanes, the possible combination partners are liposomal doxorubicin, eribulin, capecitabine, gemcitabine or metronomic chemotherapy. However, the German experts indicate that there are currently no data on a combination with gemcitabine or with metronomic chemotherapy. From the German viewpoint, a further combination partner is vinorelbine.

### HER2-negative Metastatic Breast Cancer



#### ER+/HER2- metastatic breast cancer

The ABC3 panelists (92.6%) and the German expert group agree that patients with HER2-negative (HER2-) metastatic breast cancer and positive oestrogen receptor status (ER+) should preferably receive endocrine therapy. This also applies in the presence of visceral disease – unless there is a potentially life-threatening situation (“visceral crisis”) or concern/proof of endocrine resistance.

#### Focus on post-menopausal patients

The ABC3 panelists (84.0%) recommend an aromatase inhibitor or tamoxifen or fulvestrant for the endocrine first-line treatment of post-menopausal patients. The definitive treatment decision is made depending on the adjuvant endocrine pre-treatment (type and duration) and the disease-free time after the end of adjuvant treatment (LoE: 1 A). From a German viewpoint, an aromatase inhibitor or fulvestrant (500 mg) should preferably be used in first-line treatment.

Endocrine combination therapy has no significant status in Germany. The German experts thus agree with the close absolute majority vote of the ABC3 panelists (53.4%) *not* to use a combined endocrine first-line treatment with a non-steroidal aromatase inhibitor plus fulvestrant for postmenopausal patients without

prior adjuvant endocrine treatment. The German experts refer to two randomised phase-III studies [13, 14]:

- ▶ In the SWOG study [13], however, first-line treatment consisting of a non-steroidal aromatase inhibitor plus fulvestrant (250 mg) showed a significant advantage for progression-free (PFS) and overall survival compared with monotherapy of an aromatase inhibitor. The subgroup analysis confirmed the advantage only for patients without adjuvant endocrine pre-treatment (with tamoxifen) and a very long DFS ( $\geq 10$  years).
- ▶ In the FACT study [14] with a very similar design, no advantage was seen for the combination.

The German experts also indicate that in Germany, most patients with ER+/HER2 negative breast cancer receive endocrine adjuvant pre-treatment. Furthermore, in the SWOG study [13] there was no control arm with fulvestrant (500 mg) monotherapy. It is thus difficult to assess the significance of the combination (non-steroidal aromatase inhibitor/fulvestrant 250). In addition, the benefit of the combination aromatase inhibitor/fulvestrant was low for the subgroup of patients pre-treated with tamoxifen.

The German experts agree with the majority vote (84.6%) of the ABC3 panelists that the combination of aromatase inhibitor plus the mTOR inhibitor everolimus is a valid option for postmenopausal patients with ER+/HER2-negative metastatic breast cancer with disease progression during treatment with a non-steroidal aromatase inhibitor. The combination offers the chance of a significant PFS benefit ( $p < 0.001$ ) plus a numeric median survival advantage of around five months [15]. However, there is also agreement that the treatment decision must be made on an individual basis in view of the increased toxicity induced by everolimus (LoE: 1 B).

### Significance of palbociclib

A potential new option for the first-line treatment of postmenopausal patients with ER+/HER2-negative metastatic breast cancer is the CDK4/6 inhibitor palbociclib, which showed an impressive PFS advantage in combination with the aromatase inhibitor letrozol compared with the aromatase inhibitor alone in a randomised phase-II study (HR 0.488;  $p = 0.0004$ ) [16]. About half (51.1%) of the ABC3 panelists pointed out that the phase-II data have to be confirmed in a phase-III study [17] before the combination of palbociclib/aromatase inhibitor can be recommended as a treatment option. Around 40% of the ABC3 panelists had the opinion that the phase-II data already justify clinical use.

However, beyond first-line treatment, a clear majority of the ABC3 panelists (85.7%) views the combination of palbociclib/fulvestrant as an option for *pre-, peri- and postmenopausal* patients with ER+/HER2 metastatic breast cancer. The panelists justify this with the significant PFS advantage seen in the interim analysis of the PALOMA3 study with a median of around five months (HR 0.422;  $p < 0.000001$ ) and a simultaneous improvement in quality of life for the patients [18]. Pre- and perimenopausal patients additionally require an LHRH-agonist (LoE: 1 B).

The German experts indicate that palbociclib has not yet been approved in Germany. The German and European approval of palbociclib is expected in 2016. Phase-III data with the combination palbociclib/aromatase inhibitor are also expected in 2016.

### Endocrine treatment sequences for post-menopausal patients

The optimum endocrine therapy sequence following endocrine first-line treatment cannot be defined as it depends on the respective pre-treatment. Possible treatment options according to

the ABC3 panelists (92.5%) are aromatase inhibitors, tamoxifen, fulvestrant/palbociclib, aromatase inhibitor/everolimus, tamoxifen/everolimus, fulvestrant alone, megestrol acetate and estradiol (LoE: 1 A).

In Germany, progestogens and estradiol are only used on an individual basis. The 500-mg dosage is to be observed for fulvestrant. From a German viewpoint, a well-tolerated chemotherapy can be an alternative to endocrine third-line therapy.

### Focus on pre-menopausal patients

According to the ABC3 panelists (93.0%), ovarian suppression and ablation in combination with an additional endocrine drug is the preferred treatment option for premenopausal patients with ER+/HER2-negative metastatic breast cancer who should receive endocrine therapy (LoE: 1 B). Ovarian ablation via laparoscopic bilateral oophorectomy guarantees adequate oestrogen suppression, including contraception, and prevents potential initial flare phenomena, which can occur under LHRH-agonists. In addition, it may also increase the chance of participating in a clinical study (LoE: expert opinion). Furthermore, from the viewpoint of the ABC3 panelists (90.6%), radiomenolysis is also an option in order to achieve lasting ovarian ablation.

The German expert group specifies that additional ovarian suppression is standard for premenopausal patients [19]. Permanent suppression of the ovaries using radiotherapy should only take place in case of contraindications against GnRH analogues and if a bilateral oophorectomy as endocrine ablation is significantly delayed.

As an additional endocrine therapy for premenopausal patients, 95.2% of the ABC3 panelists voted for the use of either an aromatase inhibitor or of tamoxifen – depending on the type and duration of the adjuvant endocrine pre-treatment. For pharmacological reasons, an aromatase inhibitor requires additional ovarian suppression or ablation (LoE: 1 B). This currently also applies to fulvestrant, which can also be an option in the view of the panelists (LoE: 1 C). The German experts agree in each case.

### Triple-negative advanced breast cancer

The ABC3 panelists (97.7%) and the German expert group agree that, in the absence of other data, the same chemotherapy recommendations apply for patients with advanced, non-BRCA-mutated triple-negative breast cancer (TNBC) as for patients with HER2-negative disease (LoE: 1 A). Regardless of the BRCA status, the ABC3 panelists (90.6%) assessed treatment with carboplatin as an important treatment option for TNBC patients who have received (neo)adjuvant pre-treatment with anthracyclines and taxanes. Carboplatin has a comparable efficacy to docetaxel with a more favourable side effect profile (LoE: 1 A). The German experts once again agree.

### Statements on Specific Problems



The German expert group agrees with each of the following statements by the majority of the ABC3 panelists:

- ▶ *Metronomic chemotherapy*: metronomically dosed chemotherapy can be a reasonable therapeutic approach for patients not requiring rapid tumor response (LoE: 1B). One well-investigated regimen is the combination of low-dose cyclophosphamide and methotrexate (CM) [20]. Capecitabine and oral vinorelbine are currently being evaluated for metronomic treatment strategies. The German experts add that metronomic chemo-

therapy strategies should be compared with conventionally dosed chemotherapy in randomised studies.

- ▶ **Re-induction of anthracyclines:** the re-induction of anthracyclines in the metastatic situation is an evidence-based option for patients with HER2-negative breast cancer who have received (neo)adjuvant pre-treatment with anthracyclines. The cumulative overall dose for anthracyclines and cardiac contraindications should be taken into account. Ideally, the patient should have been disease-free for at least one year after adjuvant treatment. The German experts add that weekly anthracyclines or pegylated liposomal formulations, may represent a valid option, even if the cumulative total dose is reached.
- ▶ **BRCA-mutated metastatic breast cancer:** platinum-based regimens are a preferred treatment option for metastatic patients with BRCA-mutated TNBC or endocrine-resistant breast cancer who are already pre-treated with anthracyclines and taxanes in the (neo)adjuvant or metastatic setting. In TNBC-patients without family history a BRCA germline testing should only be performed if this may result in clinical consequences.
- ▶ **Bone metastases:** antiresorptive substances such as bisphosphonates and denosumab are routinely recommended in patients with osseous metastatic lesions in addition to further oncological treatment (LoE: 1 A). According to the ABC3 vote, the 3-monthly administration of zoledronic acid is not inferior to the monthly standard dosage (LoE: 1 B). From the German viewpoint, a 3-monthly administration should only be considered when a stable situation is achieved after the monthly standard administration. If no contraindications exist, the additional supplementation with calcium and vitamin D should be recommended; for denosumab it is obligatory (LoE: 1 C).
- ▶ **Brain metastases with HER2-positive disease:** systemic treatment should not be changed in patients with HER2-positive breast cancer and brain metastases as long as the extracranial disease is stable (LoE: 1 C). If the brain metastasis is the only metastasis localisation, it is currently unclear whether chemotherapy applied in addition to local measures substantially improves the course of the disease. However, it is recommended to start anti-HER2 therapy (trastuzumab) again if this has been stopped in the meantime (LoE: 1 C).
- ▶ **“Next-generation sequencing”:** information gained from genome testing using NGS (“next-generation sequencing”) in order to detect potential molecular changes during therapy and disease progression has so far not been validated sufficiently to base clinical decisions on it. There is a lack of results from clinical studies that document an advantage for treatment decision based on NGS. This approach must still be classified as experimental.

## Definitions for Clinical Practice

### ▼ Oligometastatic disease

No consensus exists between the majority of the ABC3 panelists and the German experts for the definition of “oligometastatic breast cancer”. Indisputably this means a low metastatic tumour load and a limited number of metastatic lesions. However, according to the ABC3 vote, this means a maximum of five lesions not necessarily in the same organ. From a German viewpoint, oligometastasis is defined as limited metastasis in *one* organ. There is agreement that local measures are also an important potential treatment option for oligometastatic disease; the aim of treatment is a clinically complete remission.

## Multiple chronic conditions (MCCs)

All ABC3 panelists (100%) define patients with “multiple chronic conditions” (MCCs) as those with numerous (clinically relevant) comorbidities, such as cardiac diseases, limited kidney and/or liver function or an auto-immune disease. MCC patients require intensive support and special individual treatment concepts. General treatment recommendations for these patients are difficult to define (“difficult to account for all of the possible extrapolations to develop specific recommendations for care”).

## Supportive and Palliative Care

▼  
No formal consensus took place at the ABC3 conference with regard to supportive therapy and palliative treatment for patients with advanced breast cancer, so no comment is made from a German viewpoint.

## ABC3 – A Forum for Patient Initiatives

▼  
The representatives of international patient groups also met during the ABC3 conference. In total, 66 representatives from Europe, Asia, the Middle East, Africa, Australia, and North, South and Central America attended. They presented the results of their work at the plenary session at the ABC3 conference on 7 November 2015.

For the near future, four key objectives were defined:

- ▶ Establishment of an “ABC Global Advocate Community”. The aim is to establish a shared network to exchange experiences and discuss and implement mutual goals and strategies in a timely fashion.
- ▶ This is closely associated with an “alliance” of the regular dialogue between the patient groups, for instance via webinars. The focus should lie on treatment recommendations and aspects of quality of life.
- ▶ The information campaign for patients with metastatic breast cancer should be coordinated and improved worldwide. This also includes translating the ABC3 consensus into the respective national language.
- ▶ In the future, the representatives of patient groups also want to meet personally once a year to exchange experiences and share objectives.

In an emotional talk, Shirley A. Mertz, a patient representative from the USA, acknowledged the efforts of all physicians on behalf of the participating patient groups for their commitment to help patients. She also indicated how important this commitment is for each individual patient. Mertz: “Your work affects how long we live and the quality of life we have”.

## Summary and Outlook

▼  
The ABC consensus offered an informative discussion on the latest developments in advanced breast cancer. The next ABC4 consensus conference will take place from 9–11 November 2017 in Lisbon. The next “state-of-the-art meeting” of the AGO Mamma, with updated guidelines on the diagnosis and treatment of breast cancer takes place on 5th March 2016 in Frankfurt am Main.

## Comment

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## Conflicts of Interest

Michael Untch has no conflict of interest. Christoph Thomssen received honoraria from Amgen, AstraZeneca, Celgene, Genomic Health, NanoString, Novartis, Pfizer, Roche, Teva. Doris Augustin has no conflict of interest. Johannes Ettl received honoraria from Celgene, Eisai, GSK, Janssen, Novartis, Pfizer, Roche; research grant from Celgene; travel grant from Celgene, GSK, Novartis, Pfizer, Roche. Renate Haidinger has no conflict of interest. Hans-Joachim Lück received honoraria from Roche, Novartis, Eisai, Celgene. Diana Lüftner received honoraria from Roche, Amgen, Celgene, Novartis, Pfizer. Frederik Marmé received honoraria from Amgen, Pfizer, Novartis, Roche, AstraZeneca, Genomic Health, PharmaMar. Norbert Marschner has no conflict of interest. Lothar Müller has no conflict of interest. Friedrich Overkamp has no conflict of interest. Eugen Ruckhäberle received honoraria from Amgen, Celgene, Janssen-Cilag, Novartis, Pierre Fabre, Roche. Marc Thill received honoraria from Roche, Celgene, Novartis, Genomic Health, AstraZeneca, Teva, Myriad, Boehringer, Amgen, pfm Medical. Rachel Würstlein received honoraria from Celgene, Pfizer, Novartis, Roche, Eisai, AstraZeneca, Amgen, MSD, Pierre Fabre. Nadia Harbeck received honoraria from Celgene, Novartis, Pfizer, Roche.

## Affiliations

- <sup>1</sup> Klinik für Gynäkologie und Geburtshilfe, Interdisziplinäres Brustzentrum, HELIOS Klinikum Berlin-Buch, Berlin; *Writing Committee*
- <sup>2</sup> Mammazentrum Ostbayern, DONAUISAR Klinikum Deggendorf, Deggendorf
- <sup>3</sup> Frauenklinik und Poliklinik, Klinikum rechts der Isar, Technische Universität München, Munich
- <sup>4</sup> Brustkrebs Deutschland e. V. (*patient representative*)
- <sup>5</sup> Brustzentrum, Klinikum der Universität München, München; *Writing Committee, ABC Panel Member*
- <sup>6</sup> Gynäkologisch-Onkologische Praxis, Hannover
- <sup>7</sup> Medizinische Klinik mit Schwerpunkt Hämatologie, Onkologie und Tumorerkrankungen, Charité Berlin, Campus Benjamin Franklin, Berlin; *Writing Committee*
- <sup>8</sup> Sektion Gynäkologische Onkologie, Nationales Centrum für Tumorerkrankungen (NCT), Heidelberg
- <sup>9</sup> Onkologie UnterEms, Leer-Emden-Papenburg
- <sup>10</sup> Medizinischer Onkologe, OncoConsult.Hamburg GmbH, Hamburg
- <sup>11</sup> Frauenklinik, Universitätsklinikum Düsseldorf, Düsseldorf
- <sup>12</sup> Klinik für Gynäkologie und Geburtshilfe, Interdisziplinäres Brustzentrum, Agaplesion Markus Krankenhaus, Frankfurt am Main
- <sup>13</sup> Universitätsklinik und Poliklinik für Gynäkologie, Martin-Luther-Universität, Halle an der Saale; *Writing Committee, ABC Panel Member*
- <sup>14</sup> Brustzentrum, Klinikum der Universität München, Munich; *Writing Committee*
- <sup>15</sup> Gemeinschaftspraxis für interdisziplinäre Onkologie und Hämatologie, Freiburg; *Writing Committee*

## References

- 1 *Cardoso F, Costa A, Norton L et al.* ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2). *Breast* 2014; 23: 489–502
- 2 Online: [www.ago-online.de](http://www.ago-online.de); last access: 15.11.2015
- 3 *Liedtke C, Thill M, Hanf V et al.* AGO recommendations for diagnosis and treatment of patients with advanced and metastatic breast cancer: update 2015. *Breast Care (Basel)* 2015; 10: 199–205
- 4 Online: [www.awmf.org](http://www.awmf.org); last access: 15.11.2015
- 5 Online: [www.dgho.de/Onkopedia](http://www.dgho.de/Onkopedia); last access: 24.11.2015
- 6 *Cherny NI, Sullivan R, Dafni U et al.* A standardized, generic, validated approach to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies: the European society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS). *Ann Oncol* 2015; 26: 1547–1573
- 7 *Schnipper LE, Davidson NE, Wollins DS et al.* American Society of Clinical Oncology statement: a conceptual framework to assess the value of cancer treatment options. *J Clin Oncol* 2015; 33: 2563–2577
- 8 Online: [www.junge-erwachsene-mit-krebs.de](http://www.junge-erwachsene-mit-krebs.de); last access: 15.11.2015
- 9 *Swain S, Baselga J, Kim SB et al.* Pertuzumab, trastuzumab and docetaxel in HER2-positive metastatic breast cancer. *N Engl J Med* 2015; 372: 724–734
- 10 *Verma S, Miles D, Gianni L et al.* Trastuzumab emtansine for HER2-positive advanced breast cancer. *N Engl J Med* 2012; 367: 1783–1791
- 11 *Wildiers H, Kim SB, Gonzalez-Martin A et al.* T-DM1 for HER2-positive MBC: primary results from TH3RESA, a phase 3 study of T-DM1 vs. treatment of physician's choice. *Proc ECC-ESMO 2013*; LBA 15
- 12 *Blackwell KL, Burstein HJ, Storniolo AM et al.* Overall survival benefit with lapatinib in combination with trastuzumab for patients with human epidermal growth factor receptor 2-positive metastatic breast cancer: final results from the EGF104900 study. *J Clin Oncol* 2012; 30: 2585–2592
- 13 *Mehta RS, Barlow WE, Albain KS et al.* Combination anastrozole and fulvestrant in metastatic breast cancer. *N Engl J Med* 2012; 367: 435–444
- 14 *Bergh J, Jönsson PE, Lidbrink EK et al.* FACT: an open-label randomized phase III study of fulvestrant and anastrozole in combination compared with anastrozole alone as first-line therapy for patients with receptor-positive postmenopausal breast cancer. *J Clin Oncol* 2012; 30: 1919–1925
- 15 *Baselga J, Campone M, Piccart M et al.* Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. *N Engl J Med* 2012; 366: 520–529
- 16 *Finn RS, Crown JP, Lang I et al.* Final results of a randomized phase II study of PD 0332991, a cyclin-dependent kinase-4/6 inhibitor, in combination with letrozole vs. letrozole alone for first-line treatment of ER+/HER2- advanced breast cancer (PALOMA-1; TRIO-18). *AAO Annual Meeting 2014, San Diego/ZSA*, 06. April 2014, CT101
- 17 *ClinicalTrials.gov: NCT01740427.* A study of palbociclip + letrozole vs. letrozole for 1st line treatment of postmenopausal women with ER+/HER2- advanced breast cancer. Online: <https://clinicaltrials.gov>; last access: 15.11.2015
- 18 *Turner N, Ro J, Andre F et al.* Palbociclip in hormone-receptor-positive advanced breast cancer. *N Engl J Med* 2015; DOI: 10.1056/NEJMoa1505270; Online: <http://www.nejm.org/doi/full/10.1056/NEJMoa1505270>; last access: 30.11.2015
- 19 *Klijn JG, Blamey RW, Boccardo F et al.* Combined Hormone Agents Trialists' Group and the European Organization for Research and Treatment of Cancer. Combined tamoxifen and luteinizing hormone-releasing hormone (LHRH) agonist versus LHRH agonist alone in premenopausal advanced breast cancer: a meta-analysis of four randomized trials. *J Clin Oncol* 2001; 19: 343–353
- 20 *Curigliano G.* Phase I dose-finding study of the gamma secretase inhibitor PF-03084014 (PF-4014) in combination with docetaxel in patients with advanced triple-negative breast cancer. *JCO Proc ASCO* 2015; #1068

**ABC3 Consensus Panelists**

1. Fatima Cardoso, PT (chair)
2. Eric P. Winer, US (chair)
3. Alberto Costa, CH/IT (chair)
4. Larry Norton, US (chair)
5. Elzbieta Senkus-Konefka, PL (chair)
6. Doris Fenech, MT (advocate & nurse)
7. Musa Mayer, US (advocate)
8. Shirley A Mertz, US (advocate)
9. Dian C.J. Corneliusen-James, US (advocate)
10. Evi Papadopoulos, CY (advocate)
11. Lillie D. Shockney, US (nurse)
12. Matti S. Aapro, CH
13. Fabrice André, FR
14. Carlos H. Barrios, BR
15. Jonas Bergh, SE
16. Gouri S. Bhattacharyya, IN
17. Laura Biganzoli, IT
18. Maria João Cardoso, PT
19. Giuseppe Curigliano, IT
20. Véronique Dieras, FR
21. Nagi El Saghir, LB
22. Alex Eniu, RO
23. Lesley Fallowfield, UK
24. Patrick Flamen, BE
25. Prudence A. Francis, AU
26. Karen Gelmon, CA
27. Alessandra Gennari, IT
28. Nadia Harbeck, DE
29. Clifford A. Hudis, US
30. Bella Kaufman, IL
31. Ian E. Krop, US
32. Hanneke Meijer, NL
33. Shinji Ohno, JP
34. Olivia Pagani, CH
35. Fedro Peccatori, IT
36. Frédérique Penault-Llorca, FR
37. Martine J. Piccart, BE
38. Jean-Yves Pierga, FR
39. Hope S. Rugo, US
40. George W. Sledge, US
41. Sandra M. Swain, US
42. Christoph Thomssen, DE
43. Andrew Tutt, UK
44. Daniel A. Vorobiof, ZA
45. Binghe Xu, CN