

Update Breast Cancer 2024 Part 1 – Expert Opinion on Advanced Breast Cancer

Update Mammakarzinom 2024 Teil 1 – Expertenmeinungen zu Brustkrebs in fortgeschrittenen Krankheitsstadien




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ABSTRACT

Clinical evidence is interpreted based on clinical studies and personal experience which can lead to different interpretations of data. This makes the opinions issued by panels of experts such as the Advanced Breast Cancer Panel which convened in November 2023 for the seventh time (ABC7) particularly important. At the conference, current issues around advanced breast cancer were evaluated by an international team of experts.

In 2023 the data on CDK4/6 inhibitors was so extensive that the answers to questions about the sequencing of therapy and the potential use of chemotherapy as an alternative therapy were relatively clear. Moreover, data on antibody drug conjugates which provides a good overview of their uses is available for all molecular subtypes.

Some therapeutic settings, including patients with brain metastases or leptomeningeal disease, older patients, locally advanced breast cancer and visceral crises, continue to be particularly important and were discussed in structured sessions. The scientific context of some of the topics discussed at ABC7 is presented and assessed here.

ZUSAMMENFASSUNG

Klinische Evidenz wird auf Basis klinischer Studien und der persönlichen Erfahrung interpretiert. Dies kann in einer unterschiedlichen Deutung der Datenlage resultieren. Vor diesem Hintergrund sind Expertenpanels wie das Advanced Breast Cancer Panel, das im November 2023 zum 7. Mal zusammengekommen ist (ABC7), von besonderer Bedeutung. Aktuelle Themen werden von einem internationalen Expertenteam bewertet.

Im Jahr 2023 scheint sich die Datenlage zu den CDK4/6-Inhibitoren so verdichtet zu haben, dass Fragen zur Sequenz und zu einer möglichen Chemotherapie als Alternative relativ klar beantwortet werden können. Des Weiteren sind für alle molekularen Subtypen Daten zu Antikörper-Wirkstoff-Konjugaten vorhanden, sodass ein gutes Bild über deren Einsatz entstanden ist. Einige Therapiesituationen sind nach wie vor von besonderer Bedeutung und sind strukturiert diskutiert worden, wie zum Beispiel Hirnmetastasen und leptomeningeale Erkrankung, ältere Patientinnen, das lokal fortgeschrittene Mammakarzinom und die viszerale Krise. Im Rahmen dieser Arbeit werden einige der diskutierten Themen im wissenschaftlichen Kontext dargestellt und bewertet.

Background

The Advanced Breast Cancer Conference in Lisbon (ABC7 held in 2023) focuses on the treatment of patients with advanced breast cancer. Following two days consisting mainly of overview presentations of the most important thematic areas, the third day consisted of a panel voting on key issues affecting the treatment of patients with advanced breast cancer. The majority of questions voted on during the conference and the relevant answers together with an assessment by the ABC7 panelists (ABC7 panelists; Supplement Table S1, online) are presented here (Supplement Table S2, online). In addition, a few selected topics have been placed in a scientific context to provide more differentiated background information about the questions.

Expansion of the Therapeutic Spectrum

After the human genome was decoded and with a growing understanding of intracellular signal transduction pathways, a number of studies were carried out in the last 20 years on patients with advanced breast cancer which lastingly changed clinical practice and treatment standards. Most of the innovations relate to signaling pathways, which have also been found to be connected to the pathogenesis and progression of breast cancer, e.g., inhibition of the PI3K/Akt-kinase pathway or utilization of the mechanisms of immune checkpoint inhibitors. Many of the discoveries were a direct consequence of systematically putting the newly obtained knowledge about the human genome to good use. Other developments have led to the development of new classes of drugs such as antibody drug conjugates (ADC), PROTACS (proteolysis-targeting chimeras) and radioligand therapeutics. While the use of PROTACS and radioligand therapeutics to treat breast cancer is

still in clinical development, several ADCs have already been approved for the treatment of advanced breast cancer.

The introduction of antibody drug conjugates

The ADC trastuzumab emtansine was introduced more than 10 years ago to treat patients with advanced HER2-positive breast cancer after the EMILIA trial showed that it offered superior results over the tyrosine kinase inhibitor lapatinib in combination with capecitabine, both with regards to progression-free survival (PFS) and overall survival (OS) [1, 2]. The introduction of new linker technology and other substances has led to the development of new ADCs such as trastuzumab deruxtecan (T-DXd). This new ADC did not just significantly improve the prognosis of HER2-positive disease [3] but also the prognosis of breast cancer in some patients with hormone receptor (HR)-positive/HER2-negative (HER2_{low} population) and triple-negative (TNBC) breast cancer [4]. Moreover, the mechanism of action was also elucidated for sacituzumab govitecan, which targets Trop2 (trophoblast cell surface antigen 2) [5, 6]. Sacituzumab govitecan improves both the PFS and the OS of patients with HR-positive/HER2-negative breast cancer and of TNBC patients. Accordingly, these therapies now hold a major position in the therapeutic landscape.

Immune therapies

Immune therapies differ from previous therapeutic approaches in that they change the tumor's micro-environment and mainly modify the interactions between the tumor cell and immune cells. The Keynote-355 trial was able to show that first-line therapy with pembrolizumab offered a benefit in terms of a better PFS and OS for patients with TNBC [7, 8]. To assess the therapeutic effect, patients were investigated for PD-L1 expression (combined positive score; CPS). The effects of pembrolizumab were only significantly detectable if expression was confirmed with a score of more than 10. The Impassion130 trial showed similar results for atezolizumab, even though OS analysis did not achieve formal statistical significance [9–11], and the results of the Impassion131 trial could not be confirmed [12]. It should be noted here that a different score must be used for the indication for treatment with atezolizumab (PD-L1 positive immune cells; IC score).

Overcoming endocrine resistance

The possibility of reducing the risk of progression or death for a certain period of time for a relevant percentage of HR+/HER2- patients is one of the big developments of recent years. The better understanding of the precise mechanisms of endocrine signaling pathways has translated into targeted therapies which modify these signaling pathways to achieve tumor control. Several drugs have been tested in clinical trials, including CDK4/6 inhibitors [13, 14], the Akt inhibitor capivasertib [15] and the PI3K inhibitor inavolisib [16], and have been found to improve overall survival (ribociclib and abemaciclib) or have shown very promising trends with regards to overall survival (capivasertib and inavolisib).

State of knowledge on homologous recombination as an approach for therapy options

The introduction of PARP (poly [ADP-ribose] polymerase) inhibitors [17–22] represents a remarkable milestone in the treatment

of patients with breast cancer. Following the discovery of the *BRCA1* and *BRCA2* genes, increased our understanding of the relevance of homologous recombination in the pathogenesis and progression of breast cancer. More recently, the importance of these genes is also being discussed in connection with possible endocrine resistance. An alternative explanation for reduced endocrine sensitivity in tumors with homologous recombination deficiency (HRD) could be that HR-positive tumors should be classified as a basal subtype and therefore endocrine therapy will not have the desired effect.

The voting in Lisbon at ABC7 took account of these more recent developments. Some of the facts are presented in more detail below.

Treatment of Patients with Advanced HR-positive, HER2-negative (HR+/HER2-) breast cancer

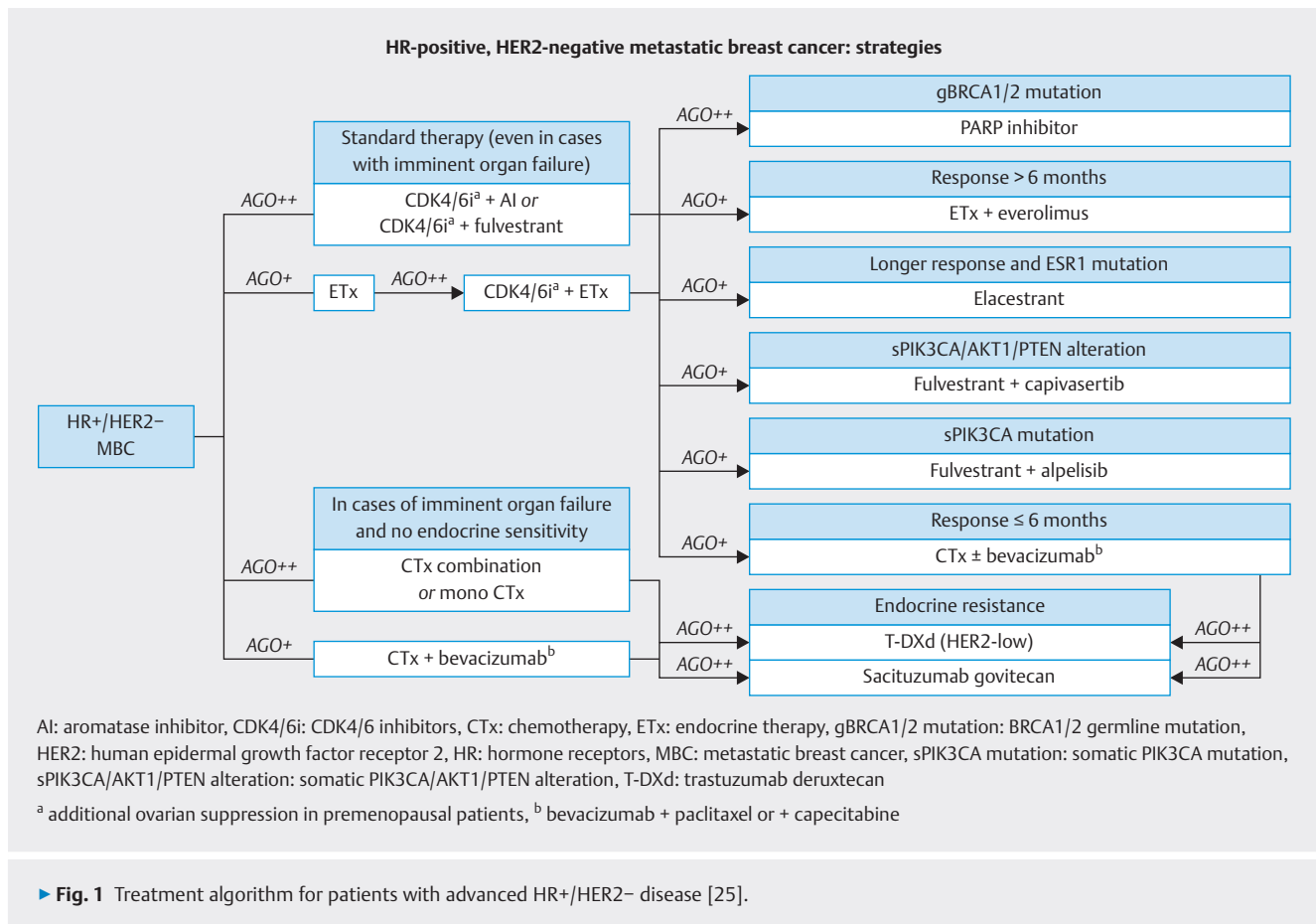
Now that treatment with CDK4/6 inhibitors has become the therapy standard for first-line treatment [23, 24], questions now mainly focus on the best therapy sequence.

- Which **exceptional** patients should not receive a CDK4/6 inhibitor as first-line therapy? The focus was on the specific issue of how patients in visceral crisis who require urgent treatment should be treated.
- Which **therapy sequence** is best if a CDK4/6 inhibitor is administered as part of first-line therapy? With effective follow-up therapies (elacestrant, everolimus, alpelisib, PARP inhibitors, trastuzumab deruxtecan, sacituzumab govitecan) the question is what is the most effective therapy sequence. At the moment, the majority of patients undergoing second-line therapy still receive chemotherapy [24]. Could the new endocrine therapies change this approach and what is the significance of ADCs? ► **Fig. 1** shows possible therapy sequences as assessed in national therapy recommendations (<https://www.ago-online.de/leitlinien-empfehlungen/leitlinien-empfehlungen/kommission-mamma>, [25]).

Chemotherapy – now the exception for first-line therapy of HR+/HER2+ ABC (advanced breast cancer) patients?

One therapeutic situation which comes up regularly when discussing whether chemotherapy is necessary is visceral crisis and/or constellations where remission is urgently needed (**Question 43** to **Question 46**). Up to now, the guidelines considered chemotherapy to be one of the standard options in this setting [26]. However, the presentation of the results from the phase II RIGHT Choice trial has changed the data by showing that endocrine-based therapy can also be a valid option as a first-line therapy for patients in urgent need of remission (**Question 3**).

In the RIGHT Choice trial, the first-line therapy group also included patients with advanced HR+/HER2- breast cancer who had symptomatic visceral metastasis, were in visceral crisis, showed rapid disease progression, or had strong symptoms of non-visceral disease [27]. The patients were randomized either



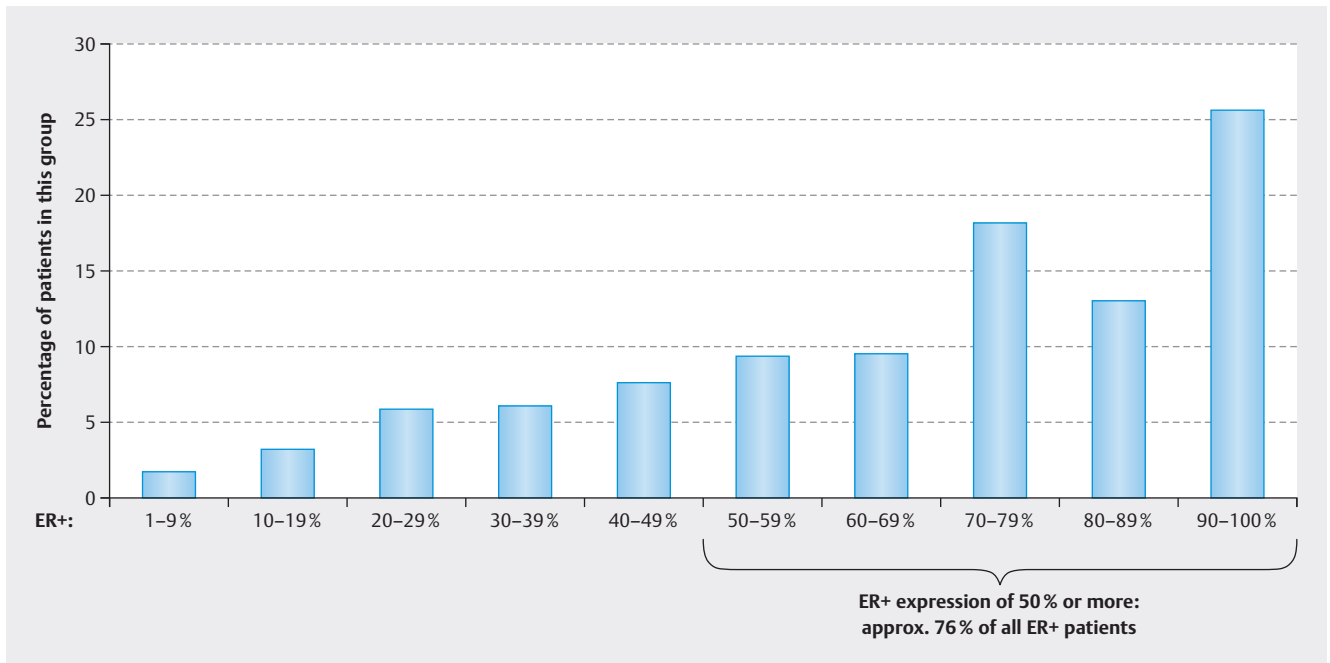
to therapy with ribociclib + letrozole (\pm goserelin) or to combination chemotherapy consisting of one of the following chemotherapies: docetaxel + capecitabine, paclitaxel + gemcitabine or capecitabine + vinorelbine. The primary study endpoint was PFS. Median PFS in the ribociclib arm was 24.0 months and therefore better than in the chemotherapy arm (12.3 months; HR = 0.54; 95% CI: 0.36–0.79; $p = 0.007$) [27].

A recently updated analysis of the study noted that the percentage of patients with high ER (estrogen receptor) expression was relatively high. In the study, 79–91% of patients had an ER expression of 50% or more. It is possible that this reflects the normal distribution of ER expression. In a cohort from the USA, immunohistochemistry showed that 76% of ER-positive patients had an expression of 50% or more (► **Fig. 2**) [28]. Another anomaly of the RIGHT Choice trial was the young age of the patients. The median patient age in the study was 43 to 45 years [29], whereas usually the mean age of HR+/HER2- patients with metastatic disease is 57–58 years when patients receive chemotherapy as their first-line treatment and about 61.5 years when they are treated with a CDK4/6 inhibitor [23, 30–32]. The question that arises here is to what extent can the data of the RIGHT Choice trial be transferred to older patient populations. However, because of the clinical benefit of not carrying out chemotherapy, more than 95% of the ABC7 panelists voted to transpose the results also to postmenopausal patients and men (**Question 3**).

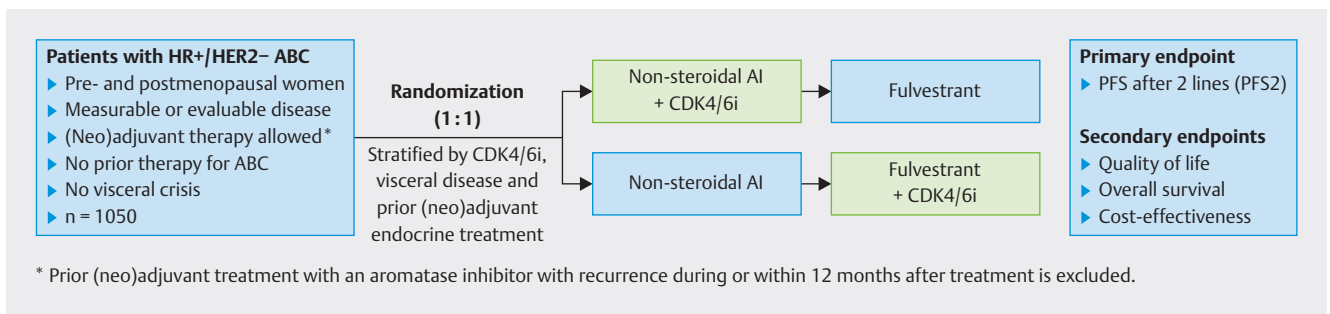
Optimization of CDK4/6 inhibitor use in different therapy lines

Even though the therapeutic standard now includes the use of CDK4/6 inhibitors as part of first-line therapy, some studies have focussed on later therapy lines and cohorts with higher levels of endocrine resistance (e.g., Monaleesa-3, Monarch-2 and Paloma 3 studies). In these therapeutic settings the addition of CDK4/6 inhibitors was found to be associated with good tumor control. Many treating physicians are of the opinion that it is important to have a therapy that is still effective for advanced lines of therapy. This is the context of the SONIA trial [33]. The SONIA trial was a randomized study which compared use of the CDK4/6 inhibitor palbociclib in the first and the second line of therapy (► **Fig. 3**). No differences were found with regards to OS.

Since the vast majority of the participants in the SONIA study were treated with palbociclib and the Paloma-2 trial also found no difference in OS when it compared letrozole with palbociclib + letrozole [34], the interpretation of the data is difficult and transferring the results of the SONIA trial is problematic. This was also reflected by the voting results of the ABC7 panelists. More than 93% viewed the inclusion of a CDK4/6 inhibitor into first-line therapy as the standard but were of the opinion that endocrine monotherapy was useful in exceptional situations (e.g., low tumor burden and problems with the availability of CDK4/6 inhibitors) (**Question 4**).



► **Fig. 2** Distribution of ER expression in a cohort of breast cancer patients (Fig. is based on data from: Ma et al. 2013 [28]).



* Prior (neo)adjuvant treatment with an aromatase inhibitor with recurrence during or within 12 months after treatment is excluded.

► **Fig. 3** Study design of SONIA trial (data from [33]). PFS: progression-free survival; ABC: advanced breast cancer.

Limited data on treatment beyond progression with CDK4/6 inhibitors

With combination therapies, the question always arises whether continuation of the therapy could be useful once disease has progressed if slight changes are then made to the therapy. Two phase II studies have been carried out for CDK4/6 inhibitors and data are available: the MAINTAIN trial [35] randomized patients with disease progression despite CDK4/6 inhibitor therapy 1:1 (n = 119) either into a therapy arm with ribociclib and an amended endocrine therapy (ET; continuation of CDK4/6 inhibitor therapy under ribociclib or switch to ribociclib) or a therapy arm consisting of monotherapy with ET alone. Continuation of the CDK4/6 inhibitor therapy was associated with longer median PFS (HR = 0.57; 95% CI: 0.39–0.95). The PACE trial addressed a similar question [36]. The PACE trial also included patients with disease progression under CDK4/6 inhibitor therapy. The patients were randomized into therapy with a) fulvestrant, b) fulvestrant + palbociclib, or c) fulvestrant + palbociclib + avelumab. When the 55 fulvestrant pa-

tients were compared with the 111 fulvestrant + palbociclib patients, no difference was found with regards to median PFS. The median PFS was similarly short for both arms with 4.8 and 4.6 months, respectively.

Given these data, more than 90% of ABC7 panelists considered therapy “beyond progression” to be unsuitable for clinical practice and recommended that such therapies should only be carried out in the context of clinical trials (Question 7).

Elacestrant on the way to standard clinical practice?

With the new oral selective estrogen receptor degraders (SERDs), a number of new substances (elacestrant, giredestrant, imlunestrant, camizestrant, vepdegestrant) are currently undergoing clinical testing. Elacestrant has already been approved by the EMA (European Medicines Agency) and the FDA (U.S. Food and Drug Administration) for the treatment of patients with previously treated metastatic disease whose tumors have a missense mutation in the *ESR1* gene, which codes for the estrogen receptor α .

The approval of elacestrant is based on the EMERALD trial [37]. The improvement in the median PFS in the EMERALD trial was only marginally significant for the total trial population. The median PFS was extended from 1.9 months to 2.8 months in the total population (HR = 0.70; 95% CI: 0.55–0.88) [37]. A bigger difference between the randomization arms was seen in the subgroup of patients with a tumor with *ESR1* mutation (HR = 0.55; 95% CI: 0.39–0.77), while in the group of patients without *ESR1* mutation the HR was 0.86 (95% CI: 0.63–1.19) [37]. The analysis found no OS benefit. Given these data, the vote by the ABC7 panel on whether elacestrant should be recommended for routine clinical use was divided. 51% of panelists were unable to make this recommendation whereas 44% were in favor (**Question 10**); nevertheless, the use of elacestrant was supported by more than 81% of panelists as a therapeutic option to treat tumors with *ESR1* mutations as a second or third line of treatment (**Question 11**).

Capivasertib and other endocrine therapies as linkers between early and late therapy lines

The AKT kinase inhibitor capivasertib has already been approved in the USA for patients with disease progression after prior endocrine therapy to treat tumors with a mutation in *PIK3CA*, *AKT1* or *PTEN*. In the CAPITELLO-291 trial, capivasertib in combination with fulvestrant improved the median PFS of patients with a mutation in these genes from 3.1 months to 7.3 months (HR = 0.50; 95% CI: 0.38–0.65, $p < 0.0001$). The OS analysis also showed a promising improvement with a hazard ratio of 0.74 (95% CI: 0.56–0.98) [15]. The majority of patients had previously been treated with a CDK4/6 inhibitor. This approach could therefore become the standard therapy for this therapeutic setting. Other therapies which can be administered in this setting are chemotherapies, alpelisib, everolimus with endocrine therapy or the above-mentioned elacestrant in the presence of an *ESR1* mutation.

Establishing effective endocrine or endocrine-based therapies after CDK4/6 inhibitor therapy which could then be used in clinical practice would constitute significant progress in the treatment of HR+/HER2- patients, as traditional chemotherapies are currently still the most commonly used therapies in this setting [24]. The current indication still requires the administration of chemotherapy before one of the effective ADCs trastuzumab deruxtecan or sacituzumab govitecan can be administered. The Destiny-Breast06 trial could change this situation [38]. The data of this study have not yet been published but their publication is expected in the near future. In the study trastuzumab deruxtecan are administered after two previous endocrine therapies. If this change is implemented, the most common therapy sequence would be CDK4/6i (CDK4/6inhibitor) → other endocrine-based therapy → ADC.

Antibody drug conjugates have arrived in clinical practice

With sacituzumab govitecan for patients with HR+/HER2- breast cancer or TNBC and trastuzumab deruxtecan for patients with HER2-positive and HER2-low-expressing tumors, two very effective ADCs are available to treat patients with advanced breast cancer. The administration of T-DXd is currently tied to the presence of HER2 expression (expression should be at least in the HER2-low

range). In this context, 97.6% of participating ABC7 panelists proposed (**Question 2**) that pathologists should provide a detailed assessment of the patient's HER2 status using the following categories:

- HER2-zero/null
- HER2-low: 1+ or 2+/ISH (in situ hybridization) not-amplified
- HER2-positive (ISH amplified or HER2 3+)

Although ADCs are associated with a higher incidence of side effects (hematological toxicity, nausea and vomiting, alopecia) and cases with interstitial lung disease (ILD) and fatal outcomes have been reported for T-DXd, the benefits with regards to OS were considered so significant that almost all of the panelists described sacituzumab govitecan and T-DXd as the preferred therapy option in the respective therapeutic setting (**Question 12** and **Question 13**). The panel was also of the opinion that the administration of trastuzumab deruxtecan in HR-pos/HER2-low disease before initiating treatment with sacituzumab govitecan was the better therapy sequence even though the data on sequencing is limited (**Question 14**). The Destiny-Breast04 trial with T-DXd investigated patients in earlier therapy lines (after endocrine therapy and one to two chemotherapies) [39], and the Tropics-02 trial [5] investigated the effect of sacituzumab govitecan in patients who had received at least two chemotherapies. Therapeutic monitoring is particularly important with regards to T-DXd. The ABC7 panelists were agreed that patients being treated with T-DXd should have a high-resolution CT scan for early detection of interstitial lung disease every six to eight weeks (**Question 13**). If the CT scan detects asymptomatic ILD, treatment with T-DXd must be paused until this side effect has been fully resolved.

Other ADCs are already in the pipeline, for example, datopotamab deruxtecan (Dato-DXd) which targets Trop-2 in a similar fashion to sacituzumab govitecan and has the same payload as T-DXd. In a randomized study, HR+/HER2- patients with advanced breast cancer who had previously undergone one or two chemotherapies were analyzed to see whether Dato-DXd or chemotherapy was more effective [40]. The median PFS in this population with significant prior treatment was extended from 4.9 months to 6.9 months (HR = 0.63; 95% CI: 0.52–0.76), OS data are still pending [40]. The drug has not yet been approved and therefore currently does not play a role in the planning of therapy sequences.

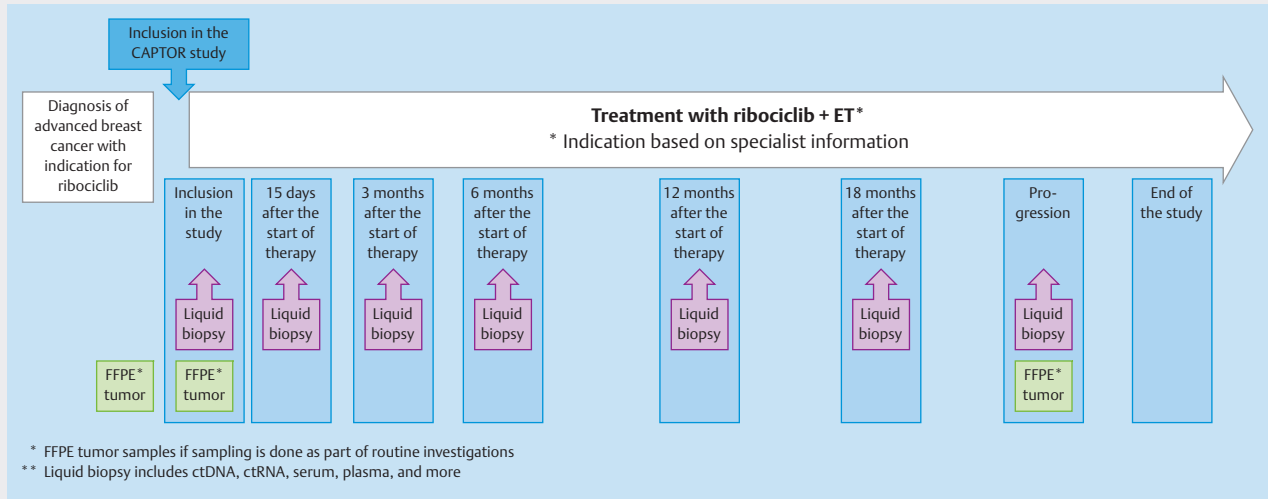
Outlook for patients with HR+/HER2- advanced breast cancer

As the understanding of the resistance mechanisms in patients with advanced breast cancer has increased, more and more substances are being tested which are either being added to existing therapies or administered sequentially and offer additional benefits to patients. One example of this is the PI3K inhibitor inavolisib. The INAVO120 trial compared a combination of palbociclib, fulvestrant and inavolisib with a combination of palbociclib and fulvestrant. The combination with inavolisib showed a PFS benefit (HR = 0.43; 95% CI: 0.32–0.59). Even though the change in OS was not formally statistically significant, the HR for the comparison was very promising (HR = 0.64; 95% CI: 0.43–0.97), the substance also appears to have a comparatively favorable side effect profile [16]. This agent is also not yet available for use in routine clinical practice.

Study design and study objectives

- ▶ N = 2000 patients with advanced breast cancer and an indication for ribociclib
- ▶ Liquid biopsy at the start of the study and sequentially over the course of the study
- ▶ FFPE tumor samples if sampling is done as part of routine investigations
- ▶ Collection of all digitally available information (histological, radiological images...)

- ▶ Co-primary study endpoints: PFS and OS rates after 12 months
- ▶ Secondary study endpoints: PFS, OS, quality of life, tolerability
- ▶ Exploratory study endpoints: genome-wide biomarker detection and validation



Germline DNA: HR genes, genome-wide SNPs

ctDNA changes over time to monitor disease

ctDNA for molecular tumor characterization

ctDNA for molecular tumor characterization

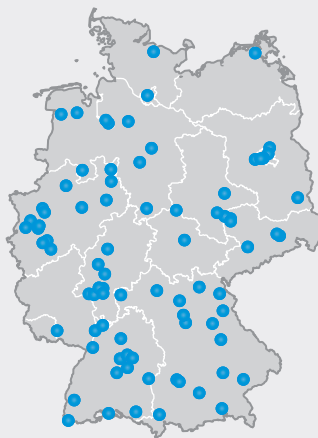
Leukocyte RNA for immunological characterization

Leukocyte RNA for immunological characterization

FFPE for spatial multiomics

FFPE for spatial multiomics

Participating centers



Involved study groups/professional associations

- ▶ AGO-B Breast Study Group
- ▶ Gynecological oncology working group (AGO)
- ▶ German Society of Senology

▶ **Fig. 4** Study design of the CAPTOR-BC trial (from [13]).

Some study programs are actively looking to understand endocrine resistance better during or after standard first-line therapy. The largest such program in Germany is the CAPTOR-BC trial [13]. More than 100 study centers across Germany have enrolled patients in the study who receive standard treatment with ribociclib and endocrine therapy as their first line of therapy. The effectivity and resistance mechanisms are being analyzed as part of an extensive translational study program (► Fig. 4).

Treatment of Patients with Advanced HER2-positive Breast Cancer

Since the introduction of T-DXd [3] and tucatinib [41], there have been no new therapies which have changed routine clinical treatment of patients with HER2-positive breast cancer. As these drugs are increasingly being administered in clinical practice, interest has focused on special therapeutic situations such as the treatment of brain metastases, a common occurrence with HER2-positive disease.

In the HER2CLIMB study, analysis of treatment of brain metastases was already planned in advance. A total of 291 patients with brain metastases were enrolled in the 2:1 randomized study, and were randomized either to the arm receiving tucatinib, capecitabine and trastuzumab or the arm treated with trastuzumab and capecitabine [42]. Median CNS (central nervous system)-related PFS improved with a hazard ratio of 0.32 (95% CI: 0.22–0.48) and OS improved with a hazard ratio of 0.58 (95% CI: 0.40–0.85). There was also a significant difference with regards to response to treatment between the two arms. In the tucatinib arm, 47.3% of patients achieved remission (41.8% had partial remission [PR] and 5.5% had complete remission [CR]), while this was only the case for 20% of patients in the arm without tucatinib (15% PR and 5% CR).

Recently, the results of patients with CNS involvement who were included in the DESTINY-Breast01–03 studies were presented [43]. As part of these trials, a total of 231 patients with brain metastases were treated with either T-DXd or chemotherapy. The rate of remission for both active and stable brain metastases was about 45% [43] (about 29% of cases had partial remission and 16% had complete remission).

Based on this data the overwhelming majority of ABC7 panelists considered T-DXd to be a therapeutic option for patients with brain metastases (Question 29).

Treatment of Patients with Advanced Triple-negative Breast Cancer (TNBC)

What is the right therapy sequence for patients with triple-negative disease

Prior to the introduction of immune checkpoint inhibitors (cases with PD-L1 positivity in the first line of therapy), PARP inhibitors (cases with germline mutation in *BRCA1/2*) and the ADCs T-DXd and sacituzumab govitecan, the therapy landscape for patients with advanced triple-negative disease consisted of a sequence of

chemotherapies. The fact that specialists are now discussing the optimal therapy sequence is the result of a number of positive studies carried out in recent years. Based on the currently available evidence, the introduction of ADCs in particular has raised a number of questions.

The ASCENT trial demonstrated a benefit from sacituzumab govitecan for patients who had a median of three previous chemotherapies. The benefit was evident not just for PFS but also for OS [6]. With 468 triple-negative disease patients in the trial, the randomized ASCENT trial is creating the basis for a high level of evidence. The Destiny-Breast04 trial also included a cohort of TNBC patients with HER2-low expression [39]. These patients had had a median of three previous therapies. A benefit with regards to PFS and OS was also evident for this small subpopulation of 68 patients [39].

This raises the question of what the most beneficial sequence is. Most of the ABC7 panelists were of the opinion that the data showed that sacituzumab govitecan should be administered first when treating TNBC patients with HER2-low expression (Question 15).

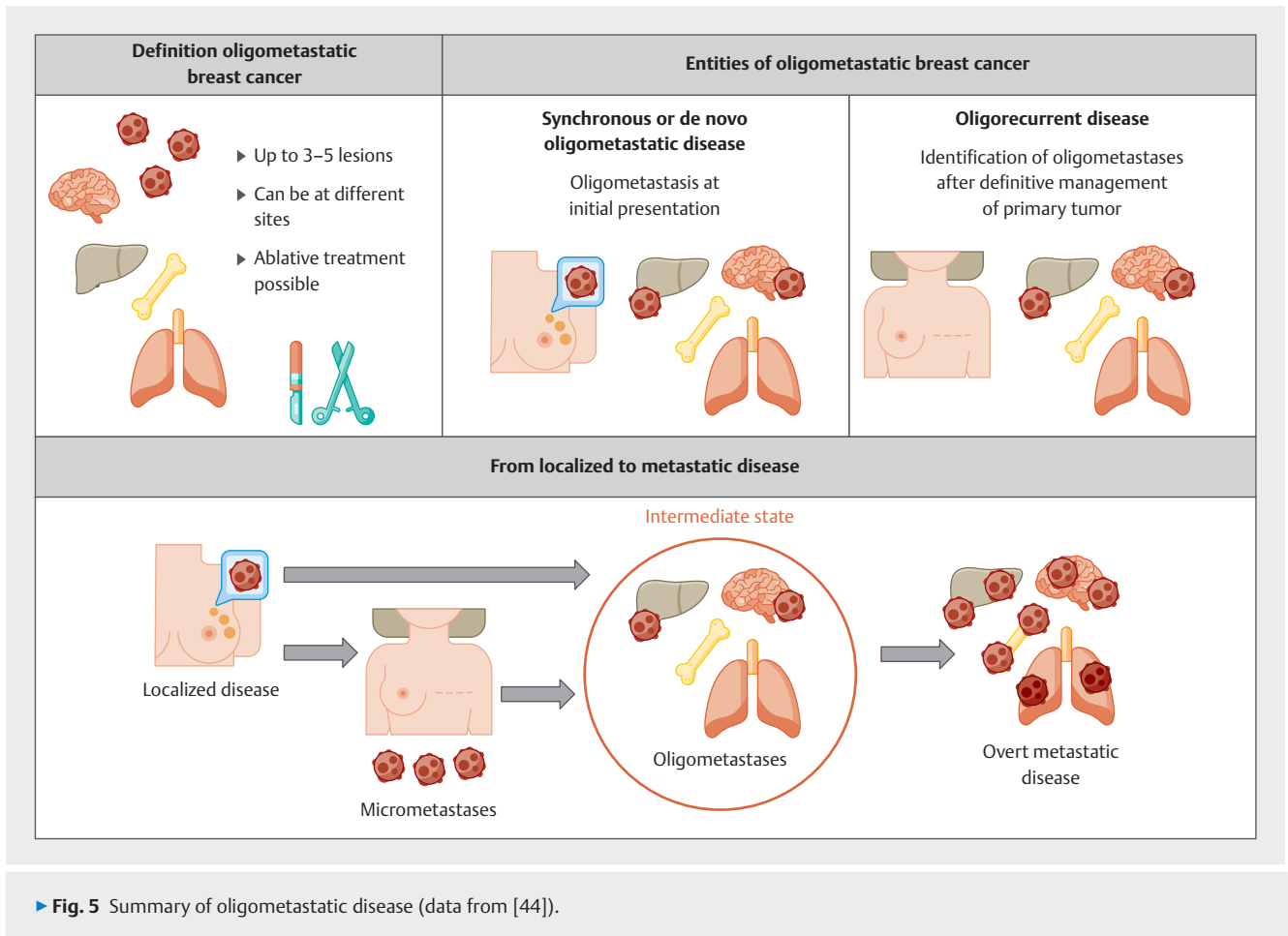
Special Therapy Situations

Oligometastasized disease

One issue which has preoccupied patients and treating physicians for decades is oligometastatic disease. The hypothesis that oligometastatic disease should be treated differently from manifest metastatic disease is based on the idea that if the number of metastases and the localizations of disease are limited, treatment in addition to standard systemic therapies could consist of local therapeutic procedures to treat the metastases. The background to this is the still speculative assumption that oligometastatic patients could be candidates for long-term remission or even cure. It is important to ensure that systemic therapies are not replaced by localized procedures. Most studies consider between three and five localized metastases as the maximum number to be still be termed oligometastatic disease. ► Fig. 5 provides an overview of the term and the concept of oligometastasis [44]. The evidence for local ablative procedures in this patient group is not high. There are two randomized studies, the NRG-BR002 and the SABR-COMET study, which have looked at this issue in recent years.

The SABR-COMET study included cancer patients with between one and up to five metastases [45]. All of the metastases had to be treatable with stereotactic radiotherapy. A total of 99 patients were included in the study and randomized 2:1 to receive either stereotactic intervention or conventional palliative radiotherapy. A standard systemic therapy was administered in parallel. Eighteen patients with breast cancer participated in the study, of whom four in the stereotactic treatment arm survived for more than five years [45].

The NRG-BR002 trial is a study which specifically focused on breast cancer patients [46]. This study enrolled patients with between one and four metastases who had controlled disease under first-line therapy. The 125 breast cancer patients were randomized 1:1 to stereotactic radiotherapy and/or surgical resection with continuation of systemic therapy or systemic therapy alone



according to standard. This study was unable to show a benefit for local therapies with regards to PFS or OS [46].

Given these limited data, the overwhelming majority of the ABC7 panelists rejected localized treatment of metastases as a standard therapy (**Question 17**).

Removal of the primary tumor

A similar question arose in connection with resection of a primary tumor when disease has already metastasized. Of all the patients who present with metastasis, this situation (de-novo metastatic setting) occurs in about 50% of HER2-positive patients, 22% of triple-negative and 36% of HR+/HER2- patients [47]. It is well established with a high level of evidence that surgery of a primary tumor does not improve prognosis [54]. However, the use of this approach may be guided by patient preference and nursing aspects, meaning that, although prognosis will not improve, surgery may still be considered. Most of the panelists agreed (**Question 18**).

Other special therapeutic situations

Other special therapeutic situations discussed at the conference were locally advanced inoperable breast cancer (**Question 36** to **Question 42**), visceral crisis (**Question 43** to **Question 46**) and therapy of patients with HIV infection (**Question 22** to **Question 24**).

Other Topics

In addition to therapeutic situations, the internal and external circumstances which affect treatment and/or can affect the well-being of patients are also important. Some of these situations were also raised and discussed.

In recent years, wars have broken out in various crisis regions across the world which significantly negatively affect general medical care. This does not just apply to acute disease but also to chronic diseases such as advanced breast cancer [48]. All panelists were agreed that therapies can be adjusted to specific special situations and that colleagues in the respective crisis regions need to be supported (**Question 19**).

Severe psychiatric disorders pose a particular challenge when treating patients. Some therapies have to be adapted accordingly. It is especially important to be aware of drug interactions [49]. Management of the therapies of patients with advanced breast cancer and additional comorbidities such as mental disorders should be planned proactively and carried out by an interdisciplinary team (**Question 21**).

Pregnant women with advanced breast cancer continue to present very specific challenges. Some questions focused on this issue (**Question 30** to **Question 35**). While pregnancy during ongoing breast cancer therapy should be avoided with the appropri-

ate contraception, the most common constellation for this group of patients is a new diagnosis of breast cancer in women who are already pregnant. Breast cancer tends to be in a more advanced stage of disease in these women compared to non-pregnant women [50–53] and is an interdisciplinary challenge. The Expert Consensus Statements of the ESMO (European Society for Medical Oncology) [55] and the International Advisory Board of Cancer in Pregnancy (www.ab-cip.org) are relevant in this context.

Outlook

In recent years, therapies have been developed for all breast cancer subtypes (TNBC, HER2+, HR+/HER2-) which have led to an OS benefit for patients. Some of these therapies are accompanied by higher clinically relevant toxicity. As the longer survival times are accompanied by relevant toxicity profiles, the issue of maintaining patients' quality of life has become particularly important. Some of the questions on this issue were also discussed (**Question 27** and **Question 28**). For example, it was proposed that measuring quality of life using patient-reported outcome tools could become part of routine clinical practice. This can be done using both classic paper-based methods and digital forms of data collection. It could help to move this important aspect more center stage during interactions between medical staff and patients. The conference participants also raised issues which require more research. These include treatment holidays and the therapeutic management of patients in long-term remission. Although there is not a lot of evidence from studies, pausing treatment is considered appropriate in certain cases although the situation requires a case-by-case decision. How long such treatment holidays can be and in which situations they are appropriate still needs to be defined and investigated further (**Question 25** and **Question 26**).

Irrespective of this, it can be stated that some of the therapies introduced in recent years are very effective and have contributed to an improvement in palliative treatment. To what extent the OS benefits will lead to lower overall mortality as a consequence of the therapeutic improvements for this group of patients still remains to be seen.

Supplement

- **Supplement Tab. S1:** Panelists of ABC7 conference.
- **Supplement Tab. S2:** Questions voted on by the ABC7 panelists. Because voting was done live, the list does not claim to be complete. The questions have been numbered to match the text of this article. The numbering was not specified during the ABC7 conference.

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Conflict of Interest

B. A. received honoraria and travel grants from AstraZeneca, Gilead, Genomic Health, Roche, Novartis, GSK, Stemline, Lilly, MSD, Eisai, Tesaro, Daiichi Sankyo and Pfizer.

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T. N. F. has participated on advisory boards for Amgen, Daiichi Sankyo, Novartis, Pfizer, and Roche and has received honoraria for lectures from Amgen, Celgene, Daiichi Sankyo, Roche, Novartis and Pfizer.

A. D. H. received speaker and consultancy honoraria from AstraZeneca, Genomic Health, Roche, Novartis, Celgene, Lilly, MSD, Eisai, Teva, Tesaro, Daiichi Sankyo, Hexal and Pfizer.

M. H. has no conflict of interest.

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