Cancerworld

Making sense of recent progress in advanced breast cancer

Anna Wagstaff / 6 March 2024

Every two years breast cancer specialists and patient advocates gather at the Advanced Breast Cancer (ABC) International Consensus Conference to discuss challenges and uncertainties in treatment and care of people with advanced breast cancer, to explore how evidence, knowledge and understanding has changed since the previous conference, and to update the international consensus ABC guidelines.

For many participants this gathering is somewhat of a highlight of the crowded breast cancer conference calendar for a number of reasons. It was the first cancer conference – and remains one of the few – to focus exclusively on improving standards of care for patients with advanced disease. Its launch challenged the then-dominant narrative that this group of patients were effectively beyond help, and affirmed that their quality of life and survival matters and can benefit enormously from investing in research and developing evidence-based guidelines for treatment and care. Recognition of the value of the expertise and insights contributed by the advocacy and patient participants – a signature of ABC conferences – also makes for unusually inclusive and patient-centred discussions.

This biennial gathering is becoming increasingly important as clinicians have to work out the best ways to use a steady stream of new therapies, including antibody–drug conjugates (ADCs), and

agents aimed at novel targets.

Built into the structure and approach of the conference is a recognition that the quality of treatment is only one among many factors that determine how cancer impacts on the life of the patient and their family. The equal weight that is given to the different aspects reflects the priorities of the patient community to an extent that is still unusual within cancer conferences. A linked global advocacy organisation, the ABC Global Alliance, acts as a transmission system to help ensure that the recommendations don't remain on paper only, but are lobbied for across the world to improve the lives of people living with advanced cancer.

The clinical picture: what we learned in the past two years

In terms of the changing clinical picture, looking back over the new evidence published since ABC6, the conference organisers picked out key findings to inform discussions of treatment options.

Evolution in defining subtypes and biomarkers

'HER2-low' breast cancers. Many breast cancers previously classified as HER2-negative are now classified as HER2-low, with important implications for treatment strategies. This is not a new subtype, but rather a new biomarker for targeted therapies. Breast tumours are classified as HER2-low on the basis of an immunohistochemistry test result of IHC1+ or IHC2+ (with a negative FISH test). The new information since ABC6 clarified some issues around sampling location, pretreatment and stability.

To be classified as HER2-low, it is enough to have the presence of HER2-low status in at least one sample, be it in the primary tumour or a metastatic lesion and in any line setting.

HER2 status can be very unstable, with HER-low status being particularly unstable, especially during disease progression, so it is advisable to reassess.

All of this has important implications for the detail required in pathology: it is no longer sufficient to classify a tumour as HER2+ or HER2– the pathology report must include details of the IHC and FISH test results used.

A more precise definition of endocrine sensitivity/resistance. ABC7 revisited the classification of endocrine sensitivity/resistance, primarily to make it easier to interpret the results of clinical trials, by ensuring every trial uses the same definition. The proposal is for four categories: endocrine naïve, primary endocrine resistance, secondary or acquired endocrine resistance and endocrine insensitivity.

Endocrine naïve covers disease that has never been treated with endocrine therapy, so the sensitivity to endocrine therapy is unknown.

Primary endocrine resistance keeps its existing definition – i.e. where there is relapse during the first two years of adjuvant endocrine therapy or progressive disease within six months of first-line therapy in the advanced disease setting.

Secondary/acquired endocrine resistance relates to resistance acquired outside the parameters that define primary resistance (relapse in the adjuvant setting after two years, progression in first-line therapy after six months, progression after any duration of second or later line endocrine-based therapy or a known ESR1 mutation).

Endocrine insensitivity – which is more of a clinically-oriented definition – applies to situations where further lines of endocrine therapy would be deemed inappropriate, for instance if disease progression had occurred within two months of the latest line of endocrine therapy, or there are no further good options of endocrine-based therapies to offer.

Definitions of primary and secondary/acquired resistance stand independent of resistance to any targeted agents, such as CDK4/6, PI3K, MTOR or AKT inhibitors, that may used alongside the endocrine therapy. This is because emerging evidence shows none of the mechanisms of resistance to these inhibitors, aside from ESR1 mutation, affect the choice of endocrine agent.

Oligometastatic disease: implications of emerging evidence. Evidence regarding the benefit local treatment of metastases in the oligometastatic setting has advanced somewhat since ABC6. Treatment recommendations were revised on the basis of the findings of a new trial, and the definition of oligometastatic disease was tightened up.

Oligometastatic disease is defined as low volume disease with a limited number and size of metastatic lesions (generally no more than five), which can be located in different organs, but are all potentially amenable for local treatment. ABC7 recommended that the definition only applies when the metastatic lesions are located in solid sites; it does not apply, for instance, in the case of pleural effusion, ascites and leptomeningeal disease.

In terms of treatment recommendations, the US NRG-BR002 phase II trial, which compared standard care to local treatment of metastatic lesions in oligometastatic breast cancer found no significant benefit of adding local treatment of the metastasis in either overall or progression free survival. These results ran counter to the results of the COMET trial – a smaller phase II trial that had included only 18 breast cancer patients – which had been reported at ABC6.

An upside to those results, however, was that outcomes in the 'standard treatment' arm were much better than had been anticipated. "Maybe we are indeed improving a lot on the efficacy of systemic therapies," concluded Fatima Cardoso, the founder and Chair of the ABC International Consensus Guidelines Conferences.

On the basis of the current evidence, the consensus was therefore that, with the exception of brain metastases, routine ablation of oligometastases is not recommended for routine clinical practice. It can, however, be discussed in selected cases, always within a multidisciplinary tumour board and

being clear with the patient that there is no evidence that it will improve survival.. Treatment of oligometastatic disease should always start with systemic therapy.

Drug protocols: what's changed since ABC6?

Some new drugs have come on the market since ABC6, together with new evidence for how best to use existing treatments, particularly for patients with hormone-dependent advanced breast cancer – mostly HER2-negative or HER2-low. It was the task of the ABC7 consensus panel to try to interpret what the new information and new options mean in their entirety for the standard of care – at least in settings where patients have access to these expensive drugs.

Trastuzumab deruxtecan in HER2-low. One clear recommendation was in favour of using trastuzumab deruxtecan in patients with hormone-positive HER2-low disease. This ADC, which links the topoisomerase I inhibitor deruxtecan to the monoclonal antibody trastuzumab, and targets HER2 receptors, was approved by the US regulators in 2022. The results of the DESTINY Breast-04 trial, comparing this treatment with physicians choice of chemotherapy in patients who had already received two previous lines of chemotherapy, showed an overall survival benefit of 6.3 months. The ABC7 consensus panel flagged up the potentially fatal side effect of pneumonitis associated with this treatment. The strong consensus was that, while this toxicity points to the need for careful monitoring, the impressive survival benefit makes it an important option for the vast majority of this patient population.

Sacituzumab govitecan for triple negative disease. The panel also reviewed the results for the ADC sacituzumab govitecan, a Trop-2-directed antibody linked with a topoisomerase inhibitor approved in 2023 for treating triple negative advanced breast cancer – a subtype where progress has been particularly difficult. Results from the TROPiCS-02 phase III trial, done in a very heavily pretreated patient population, showed an overall survival benefit of 3.2 months.

On the basis of current evidence on the relative survival benefit, the panel recommended that trastuzumab deruxtecan should be given in an earlier line than sacituzumab govitecan.

Datopotamab deruxtecan – a third ADC awaiting approval. The increasing importance of ADCs in the hormone-responsive, HER-negative metastatic breast cancer setting was underlined by the inclusion of a third example, datopotamab deruxtecan, to the therapies discussed at ABC7. This ADC, which links the topoisomerase I inhibitor deruxtecan to a monoclonal antibody targeting TROP-2, reported positive early results for its phase III TOPION Breast01 trial at the ESMO congress in October 2023. The ABC7 consensus panel opted to wait for the overall survival results before considering recommending its use in routine clinical practice, in view of its toxicity profile, small benefit for progression free survival, and the availability of other treatment options.

Capivasertib – an AKT inhibitor for breast cancer. Another new drug in this space is capivasertib, a first-in-class AKT inhibitor that was approved by the US drug regulator, FDA, in November 2023, for the treatment of hormone-dependent HER2-negative disease with one or more PIK3CA/AKT1/PTEN-alterations. In the CAPitello trial the capivasertib arm showed an extension of progression free survival of 3.6 months in the unselected patient population and 4.2 months in the "AKT pathway-altered population". It also showed a better toxicity profile than previously approved PIK3CA inhibitors, such as alpelisib.

The ABC7 consensus panel recommended capivasertib could be an option, particularly in patients whose tumours harbour alterations of the AKT pathway. Given the many options now open to this patient population – endocrine therapy at the forefront, CDK4/6 inhibitors, the mTOR inhibitor everolimus, PI3K inhibitors and also ADCs and chemotherapy – together with the paucity of relevant

biomarkers, the consensus panel flagged up the need to determine the best sequence of options for each individual patient.

A SERD for advanced breast cancer. Also under review by the ABC7 consensus panel was a novel selective oestrogen receptor downregulator, elacestrant, approved by the FDA in January 2023 for treatment of hormone-dependent HER2-negative metastatic breast cancer, with ESR1 mutation, that has progressed after at least one prior line of hormonal therapy. The phase III EMERALD trial showed only a small PFS benefit of 1.9 months, which did not convince everyone on the consensus panel.

The recommendation was that it should be considered an option, particularly for patients who had been on a CDK4/6 inhibitor for more than six months, which would indicate a more sensitive disease.

Use of CDK4/6 inhibitors. CDK4/6 inhibitors (palbociclib, ribociclib and abemaciclib) have been approved for the treatment of patients with hormone-dependent HER2-negative advanced breast cancer for many years now.

The results of the phase III SONIA trial offered new information on the question of whether progression free or overall survival could be improved in this group of patients by using CDK4/6 inhibitors as a second-line treatment, rather than current practice of using it upfront alongside hormonal therapy.

The findings showed a non-significant difference for PFS and overall survival. A note of caution was raised, however, that palbociclib, used in that trial, may not be the most effective of the three CDK4/6 inhibitors. In view of the totally of data and the never before seen survival benefit in the 1st line setting, the overwhelming consensus at ABC7 recommended continuing to give CDK4/6 in the first line. However, the results of the SONIA trial provide a rationale to use hormonal treatments alone as first line in certain specific circumstances, such as low volume of disease or a very long disease-free interval, also taking into account patient preferences and access issues.

The panel also recommended against continuing with CDK4/6 treatment after disease progression, on the basis of the current evidence, except within a clinical trial.

The ‘no drug’ option – short breaks and longer cessation of treatment

While clinicians and patients alike will always welcome having access to additional options and lines of treatment, the benefits of taking time off from treatment is something many patients yearn for – not just because of the side effects, but because of the way that their cancer and treatment can come to dominate their lives.

ABC7 therefore also took a discussion on the evidence around the benefits and risks associated with treatment breaks, and even treatment cessation, to help inform discussions when clinicians are asked by their patients about how risky that could be.

The broad recommendation here was: yes, it is fine to plan a short break in treatment, with careful supervision. The risk is lowest in people who have been responding to the treatment for a long time and have controlled disease.

Stopping treatment for longer can be considered a safe recommendation only in situations of very long-term complete remissions. ‘A few years’ was the general consensus, regarding the duration of complete remission that could be considered safe before stopping, but the panel was unable to agree on a more precise cut-off point. There was, however, agreement on the overall approach to issues of breaks and cessations: treating the whole patients means accepting the need to balance following

the optimal treatment schedules for the disease against other priorities in a patient's life – things they need or want to do – which they may feel requires more 'time off' from treatment.

That issue is set to increase in importance as treatments hopefully continue to extend the years of life that people diagnosed with breast cancer can expect. The ABC conferences are the perfect place to develop that discussion.

The full consensus recommendations from ABC7 will be published on the Guidelines page of the ABC conferences website

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