

5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5).

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The application of the ESMO-Magnitude of Clinical Benefit Scale (ESMO-MCBS) 13 to the field of ABC (P Shimon, personal communication) shows that the quality of clinical research has improved over the last decade and that better therapies have been developed, providing hope that a substantial improvement in the median OS of ABC patients might soon be seen. However, some clinically relevant questions are still unanswered and may be difficult to address through traditional

clinical trials, such as the best sequence of therapies for each individual patient. The application of computer analytics to big data and real-world data is one of the potential ways forward. In-depth discussion must take place regarding the impact of this 'new' level of evidence (LoE) in current treatment guidelines and their integration with clinical trial data.

The 5th International Consensus Conference for Advanced Breast Cancer (ABC 5) took place in Lisbon, Portugal, on 14th-16th November 2019, bringing together 1500 participants from 94 countries worldwide, including health professionals, patient advocates and journalists. Since its first edition in 2011, the main goal of the ABC conference has been the development of high-quality international consensus guidelines for the management of ABC. These guidelines are based on available evidence and on expert opinion when evidence is lacking. They represent the best management options for ABC patients globally, assuming accessibility to all available therapies. Adaptation of these guidelines is often needed in settings where access to care is suboptimal.

The ABC 5 guidelines are jointly developed by ESO and ESMO, and have been endorsed by several international oncology organisations, such as the European Society of Breast Cancer Specialists (EUSOMA), European Society for Radiotherapy and Oncology (ESTRO), European Society of Gynaecological Oncology (ESGO), Union for International Cancer Control (UICC), Senologic International Society (SIS)/International School of Senology (ISS), Federación Latino-Americana de Mastología (FLAM), European Oncology Nursing Society (EONS), European Society of Surgical Oncology (ESSO), Arbeitsgemeinschaft Gynäkologische Onkologie e.V. (AGO) and the International Society of Geriatric Oncology (SIOG), and have official representation from the American Society of Clinical Oncology (ASCO). The ABC 5 conference was also organised under the auspices of the Organisation of European Cancer Institutes (OECI) and with the support of the Breast Cancer Research Foundation (BCRF), Susan G. Komen and the ABC Global Alliance.

This manuscript summarises the guidelines developed at ABC 5, each of which are accompanied by the LoE, grade of recommendation (GoR), percentage of consensus reached at the conference and supporting references. In addition, the ESMO-MCBS version 1.1 13 (v1.1) was used to calculate scores for new therapies/indications approved by the European Medicines Agency (EMA) since the last ABC guidelines, as well as a few new therapies that have been scored but are still under EMA evaluation (<https://www.esmo.org/Guidelines/ESMO-MCBS>). A table with these scores is included (see supplementary Table S1 , available at <https://doi.org/10.1016/j.annonc.2020.09.010>).

Before the ABC 5 conference, preliminary recommendation statements on the management of ABC were prepared based on available published data and following the ESMO guidelines methodology (see <http://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology>). These recommendations were circulated to all 44 panel members by e-mail for comments and corrections on content and wording. A final set of recommendations was presented, discussed and voted upon during the consensus session of ABC 5. All panel members were instructed to vote on all questions, and any members with a potential conflict of interest or who did not feel comfortable answering the question (e.g. due to lack of expertise in a particular field) were instructed to vote 'abstain'. Additional changes in the wording of statements were made during the session. As some important studies were presented a few weeks later at the 2019 San Antonio Breast Cancer Symposium, particularly for new anti-HER2 therapies, three additional statements were developed after the ABC 5 conference, circulated for revision and voted by all panel members. Statements related to the management of side-effects and difficult symptoms, included under the supportive and palliative care section, were not voted on during the consensus session, but were discussed and unanimously agreed by e-mail, and are therefore considered to have 100% consensus agreement. Previous ABC recommendations that did not require update or only minor changes were not re-voted but were reviewed by all panel members by e-mail and remain valid. To provide a full overview of all ABC guidelines currently approved, this manuscript includes a list of all recommendations per subject, highlighting those that were discussed, voted and approved in ABC 5. However, this manuscript only describes the evidence for newly developed or updated guidelines. We refer the reader to the manuscripts of previous ABC guidelines for the detailed

explanation of guidelines not updated/added during ABC 5.

Supplementary Table S2 , available <https://doi.org/10.1016/j.annonc.2020.09.010> , describes the LoE and GoR system used, 14 as per ESMO guidelines methodology.

Supplementary Figures , available at <https://doi.org/10.1016/j.annonc.2020.09.010> , feature updated ABC diagnostic and treatment algorithms.

Slides with all ABC guideline statements are available online at <http://www.abc-lisbon.org/> and <http://www.esmo.org/guidelines/breast-cancer/consensus-recommendations-advanced-breast-cancer-abc-5> . Section I ABC definitions

ABC, advanced breast cancer; AI, aromatase inhibitor; consensus, percentage of panel members in agreement with the statement; ChT, chemotherapy; ET, endocrine therapy; GoR, grade of recommendation; HER2, human epidermal growth factor receptor 2; LHRH, luteinising hormone-releasing hormone; LoE, level of evidence; n/a, not applicable; OFA, ovarian function ablation; OFS, ovarian function suppression; PD, disease progression; q4w, every 4 weeks; RT, radiotherapy; ULN, upper limit of normal.

Given the aim of standardising definitions and homogenising the use of certain medical terms, ABC has provided several definitions throughout the years. At ABC 5, the definition of visceral crisis was revisited, with some examples added (i.e. liver and lung visceral crisis) to better clarify the definition and avoid any misunderstanding between the mere existence of visceral metastases and the presence of visceral crisis. This situation is estimated to occur in only around 10%-15% of first-line ABC cases and requires the use of the most rapidly efficacious therapy, which is not necessarily chemotherapy (ChT) in all situations.

A more subjective and difficult to define situation is 'impending visceral crisis', where the criteria for visceral crisis are not yet met but, without rapidly efficacious measures, it is foreseen to happen. An example is a situation where more than 70% of the liver is occupied by metastases, the liver enzymes are substantially altered but bilirubin is still normal. In this type of situation, we also recommend the use of the most rapidly efficacious therapy. Section II General guidelines

Open communication between patients and their cancer care teams as a primary goal.

Educating patients about treatment options and supportive care, through development and dissemination of evidence-based information in a clear, culturally appropriate form.

Encouraging patients to be proactive in their care and to share decision making with their healthcare providers.

Empowering patients to develop the capability of improving their own QoL within their cancer experience.

Always taking into account patient preferences, values and needs as essential to optimal cancer care.

Patients should have easy access to well-designed clinical studies since these are crucial for further improvement in the management of ABC.

Have access to the most up-to-date treatments and innovative therapies at accessible breast units/centres.

Be treated in specialist breast units/centres/services (SBUs) by a specialised multidisciplinary team including specialised side-effects management and a nurse experienced in the treatment of ABC.

Survivorship issues and palliative care should be addressed and offered at an early stage.

A quality assurance programme covering the entire breast cancer pathway from screening and diagnosis to treatment, rehabilitation, follow-up and palliative care, including services and support for ABC patients and their caregivers, should be implemented by SBUs.

ABC, advanced breast cancer; ASCO, American Society of Clinical Oncology; consensus, percentage of panel members in agreement with the statement; CTCAE, Common Terminology Criteria for Adverse Events; EMA, European Medicines Agency; EORTC, European Organisation for Research and Treatment of Cancer; ESMO-MCBS, European Society for Medical Oncology Magnitude of Clinical Benefit Scale; FACT, Functional Assessment of Cancer Therapy; FDA, Food and Drug Administration; GoR, grade of recommendation; LoE, level of evidence; MBC, metastatic breast cancer; PRO, patient-reported outcome; PROM, patient-reported outcome measure; QoL, quality of life.

Fortunately, these last few years have seen the development and approval of several new therapies for ABC, some with an impact on OS. Consequently, some ABC patients can live many years with their disease under control or in complete remission. Since the usual methods for systemic imaging of metastatic disease do not provide good imaging of the breast, the panel believes that breast imaging is an option to consider in the surveillance follow-up of these patients. Additionally, and importantly, if at any time locoregional relapse or progression is suspected, breast imaging must be carried out.

At ABC 5, several discussions took place regarding how best to provide information regarding prognosis and length of life to ABC patients. Conversations about prognosis, priorities and end-of-life care are vitally important for those affected by advanced cancer and should be part of routine care. 15 Information about prognosis and likely survival time with and without different anticancer treatments is important to enable fully informed and educated decision making by patients. It also helps patients to plan for the future, arrange finances and work, maximise time with loved ones, plan special events and prepare for death. Misunderstandings about prognosis are common 16 , 17 , 18 and are associated with increased exposure to futile treatments. 19 , 20 , 21 , 22 Most patients want considerably more information than many healthcare professionals expect, but the type and amount of information sought should be clarified. 23 There are some significant cultural variations, in particular the involvement of the family in filtering information, which can make disclosure about prognosis and survival especially challenging. 24 Although some physicians may avoid discussing prognosis for fear of upsetting the patient or destroying hope, there is no evidence that increased information about prognosis with sensitive communication is harmful to patients, or that it increases anxiety or distress. 25 , 26 , 27 , 28 , 29 , 30 For patients wanting quantitative information on life expectancy, providing ranges for worst-case, typical and best-case scenarios is more helpful and conveys more hope than providing a single point estimate of median survival. 31 Ranges for survival scenarios are also more accurate than a single point estimate of expected survival. 16 , 32 , 33 Oncologists should offer prognostic information to all patients with ABC, allowing patients to determine the type and extent of information required. The patient's needs for prognostic information are likely to fluctuate over time, and as their disease progresses, so it is important for oncologists to repeatedly determine the information required throughout the illness from diagnosis to death. Oncologists also need guidance and communication skills training on how to handle these difficult discussions, as there is evidence that some oncologists are overly optimistic about survival benefits from anticancer treatments while others are unduly nihilistic about the benefits of good quality supportive care. 34 Section III Assessment and treatment general guidelines

ABC, advanced breast cancer; ChT, chemotherapy; CM, cyclophosphamide/methotrexate; consensus, percentage of panel members in agreement with the statement; DFI, disease-free

interval; ESMO-MCBS, European Society for Medical Oncology Magnitude of Clinical Benefit Scale; ET, endocrine therapy; GoR, grade of recommendation; HER2, human epidermal growth factor 2; HR, hormone receptor; LoE, level of evidence; MBC, metastatic breast cancer; OS, overall survival; PD, disease progression; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PS, performance status; QoL, quality of life; TNBC, triple-negative breast cancer.

Germline BRCA status, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) for estrogen receptor (ER)-positive ABC and programmed death-ligand 1 (PD-L1) for triple-negative ABC were included as important factors to take into consideration when making treatment decisions. Details about how to evaluate these factors and their clinical implications are discussed in the respective sections of the guidelines.

The statement about the use of bevacizumab was rewritten but consensus was still not achieved. In the discussion, it became clear that the main reasons for this lack of consensus were the withdrawal of approval by the Food and Drug Administration (FDA), rendering it an unavailable option in the United States, and the fact that for many panellists, bevacizumab should not be considered a treatment option. The available data show that bevacizumab combined with ChT as first-line therapy for ABC provides a moderate benefit in progression-free survival (PFS) and no benefit in OS. The ESMO-MCBS v1.1 score for bevacizumab is two. 35 Some experts believe it can be a good option for situations of extensive cutaneous inflammatory disease due to its potential antiangiogenic effect. Section IV ER-positive/HER2-negative (luminal-like) ABC

Palbociclib + AI first line: efficacy score: 3 (PFS); no improved QoL; ESMO-MCBS v1.1 score: 3

Abemaciclib + AI first line: efficacy score: 3 (PFS); no QoL reported; ESMO-MCBS v1.1 score: 3

Ribociclib + AI first line postmenopausal: efficacy score: 3 (PFS); no improved QoL; ESMO-MCBS v1.1 score: 3

Ribociclib + ET first line premenopausal: efficacy score: 4 (PFS & OS); QoL improved; ESMO-MCBS v1.1 score: 5

Palbociclib + fulvestrant second line: efficacy score: 3 (PFS & OS); improved QoL; ESMO-MCBS v1.1 score: 4

Ribociclib + fulvestrant first, second line: efficacy score: 4 (PFS & OS); no improvement in QoL; ESMO-MCBS v1.1 score: 4

Abemaciclib + fulvestrant second line: efficacy score: 4 (PFS & OS); no QoL benefit; ESMO-MCBS v1.1 score: 4

ABC, advanced breast cancer; AE, adverse event; AI, aromatase inhibitor; CDK, cyclin-dependent kinase; ChT, chemotherapy; consensus, percentage of panel members in agreement with the statement; ER, estrogen receptor; ESMO-MCBS, European Society for Medical Oncology Magnitude of Clinical Benefit Scale; ET, endocrine therapy; GoR, grade of recommendation; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; LHRH, luteinising hormone-releasing hormone; LoE, level of evidence; mTOR, mammalian target of rapamycin; n/a, not applicable; NSAI, non-steroidal aromatase inhibitor; OFS, ovarian function suppression; OFA, ovarian function ablation; OS, overall survival; PD, progressive disease; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PFS, progression-free survival; QoL, quality of life; SAI, steroidal aromatase inhibitor.

The last 2 years have seen the establishment of cyclin-dependent kinase (CDK)4/6 inhibitors combined with endocrine therapy (ET) as the standard of care for ER-positive/HER2-negative ABC

in view of the OS benefit seen in several trials, 36 , 37 , 38 , 39 , 40 , 41 , 42 both in the first- and second-line settings, substantial PFS benefit and good toxicity profile. 36 , 37 , 38 , 39 , 40 , 41 , 42 , 43 , 44 , 45 , 46 , 47 , 48 , 49 , 50 , 51 , 52 , 53 , 54 , 55 , 56 , 57 These agents can be combined with an aromatase inhibitor (AI) or fulvestrant, and are effective in de novo or recurrent ABC, in first or second line, in cases of primary or secondary resistance, in postmenopausal and premenopausal women (the latter with ovarian function suppression/ablation), and in men (preferably with a luteinising hormone-releasing hormone agonist). Of note, the combination of tamoxifen and ribociclib led to increased cardiotoxicity (arrhythmia) and should be avoided. 36 Notwithstanding these results, the panel acknowledges that there is a small group of patients who can be treated with ET alone; although clear identification of these patients is not possible at this time, factors such as limited burden of metastatic disease and features of less aggressive biology [i.e. very long disease-free interval (DFI)] can help with this identification. There are currently no biomarkers to enable accurate identification of these patients. The ESMO-MCBS scores provided are based on available data at the time of publication of this manuscript. These scores may change in the future, with new data being published, and updates will be provided on the ESMO website.

The SOLAR-1 phase III, randomised, placebo-controlled trial evaluated the role of alpelisib, an oral inhibitor of the phosphoinositide 3-kinase alpha (PI3K α) isoform, in combination with fulvestrant, for postmenopausal women and men who had previously been treated with an AI. 58 In the PIK3CA -mutated cohort, alpelisib provided a PFS benefit of 11.0 months versus 5.7 months [hazard ratio (HR) for progression or death: 0.65; 95% confidence interval (CI) 0.50-0.85, $P < 0.001$]. OS data are not yet available. Toxicity was substantially increased in the alpelisib arm, especially hyperglycaemia, rash, gastrointestinal (GI) complaints (nausea, vomiting, loss of appetite, mucositis, diarrhoea) and fatigue, which lead to dose reductions/interruptions in around 70% of patients and discontinuations in 25%. Alpelisib, in combination with fulvestrant, was EMA-approved for use in this setting in July 2020. The ESMO-MCBS for alpelisib in combination with fulvestrant was established at three because this scoring system does not consider the percentages of dose alterations and/or discontinuations as a marker of important toxicity, which in the opinion of the ABC panel, is a shortcoming of the v1.1 of the scale (scheduled to be changed in the upcoming version 1.2 of the ESMO-MCBS). In view of the balance between efficacy and toxicity, it is crucial to carefully select patients who may be candidates for this treatment, considering the inclusion/exclusion criteria in SOLAR-1 and comorbidities, especially pre-existing diabetes and baseline HbA1c levels. It is also recommended that patients take non-sedating antihistamines to prevent rash at the start of therapy 59 , 60 ; these can be discontinued after 4 weeks as the risk of rash is primarily in the first 2 weeks of therapy. The ABC panel considers alpelisib a treatment option for patients with ER-positive/HER2-negative PIK3CA -mutated ABC, but in view of the higher benefit provided by CDK4/6 inhibitors, alpelisib plus ET should be used after CDK4/6 plus ET. Only 20 patients (6%) in SOLAR-1 had been previously exposed to a CDK4/6 inhibitor. However, this is a common issue in oncology, where standards of care might change during the course of a trial. Furthermore, the large phase II BYLieve trial has shown efficacy of alpelisib after CDK4/6 inhibitor use. 60 Based on all of the available data, the ABC panel acknowledges that no data exist to determine the best sequence of therapies for this ABC subtype but believes that the most adequate sequence, in settings where availability of all drugs exist, is the use of a CDK4/6 inhibitor plus ET as first line, followed by alpelisib plus ET in patients with PIK3CA -mutated tumours or everolimus plus ET in patients with PIK3CA -wild type or unknown tumours. Section V HER2-positive ABC

ABC, advanced breast cancer; ChT, chemotherapy; CM, cyclophosphamide and methotrexate; consensus, percentage of panel members in agreement with the statement; DFI, disease-free interval; ESMO-MCBS, European Society for Medical Oncology Magnitude of Clinical Benefit Scale; ET, endocrine therapy; GoR, grade of recommendation; HER2, human epidermal growth factor receptor 2; LoE, level of evidence; MBC, metastatic breast cancer; n/a, not applicable; OS, overall survival; PFS, progression-free survival; T-DM1, trastuzumab emtansine.

After years of relatively limited progress in the management of advanced HER2-positive breast cancer, the last year has enriched our armamentarium of drugs effective in this ABC subtype. A number of new representatives of the most relevant classes of drugs—monoclonal antibodies,

antibody-drug conjugates (ADCs) and tyrosine kinase inhibitors (TKIs)—have demonstrated activity superior to previously-available options in patients pretreated with standard first- and second-line treatments.

Tucatinib, a highly selective inhibitor of the HER2 tyrosine kinase, used in combination with capecitabine and trastuzumab in a population of ABC patients pretreated with trastuzumab, pertuzumab and trastuzumab emtansine (T-DM1), demonstrated improvement of PFS (median 7.8 months versus 5.6 months, HR 0.54; 95% CI 0.42-0.71, $P < 0.001$) and OS (median 21.9 months versus 17.4 months, HR 0.66; 95% CI 0.50-0.88; $P = 0.005$) compared with patients treated with capecitabine/trastuzumab/placebo. 62 This was achieved at the expense of increased toxicity, mostly diarrhoea and elevated aminotransferase levels of grade ≥ 3 , but did not lead to frequent treatment discontinuation. Importantly, a reduction in the risk of CNS progression or death by 69% was observed in patients with stable brain metastases, while a confirmed objective response rate of 47% and a reduced risk of death by 51% were observed in patients with active brain metastases. 63

Trastuzumab deruxtecan (DS-8201), an ADC composed of trastuzumab, a cleavable tetrapeptide-based linker and a cytotoxic topoisomerase I inhibitor, demonstrated a response rate of 60.6% (95% CI 53.4-68.0) and an unprecedented median PFS of 16.4 months (95% CI 12.7—not reached) in a phase II study of heavily pretreated patients (median six lines, range 2-27 lines, including trastuzumab and T-DM1). 64 Trastuzumab deruxtecan was associated with a 13.6% risk of interstitial lung disease (ILD)/pneumonitis, fatal in 2.2% of cases, which needed appropriate and rapid diagnosis and treatment. For the safe utilisation of this compound in clinical practice (i.e. outside clinical trials), active surveillance and education regarding the signs and symptoms, for both patients and healthcare professionals, are crucial to enable rapid diagnosis and management. Confirmatory results from phase III studies are eagerly awaited and needed to accurately determine the role of this very promising drug in the HER2-positive ABC setting.

Both tucatinib and trastuzumab deruxtecan are FDA-approved and await evaluation by the EMA.

Another two agents which demonstrated formally positive (although clinically of questionable value) trial results in pretreated HER2-positive ABC patients are margetuximab (a monoclonal antibody) and neratinib. Margetuximab resulted in only a 0.9-month PFS prolongation (HR 0.76; 95% CI 0.59-0.98, $P = 0.033$) compared with trastuzumab (both combined with ChT of physician's choice), no OS benefit and a good toxicity profile. 65 The potential role of CD16A genotype as a predictor of anti-HER2 antibody efficacy was explored and initial results were encouraging and deserve further evaluation. Margetuximab is currently under evaluation by the FDA and EMA and is not yet approved for use in ABC.

Neratinib provided a small reduction in the risk of disease progression of 24% (95% CI 0.63-0.93; $P = 0.006$, medians not provided), a marginal difference in PFS and no impact on OS (co-primary end point) compared with lapatinib (both in combination with capecitabine), at the cost of increased toxicity. 66 Furthermore, the NALA study has a severe limitation of not having a comparator arm with trastuzumab plus capecitabine, which was previously shown to provide superior OS to lapatinib plus capecitabine in the first- and second-line settings. 67 As of October 2020, neratinib in combination with capecitabine is FDA-approved for pretreated metastatic HER2-positive breast cancer, but is still under evaluation by the EMA in this setting.

It is especially important to emphasise that there are no comparative data between these four new anti-HER2 agents and that the question regarding the optimal sequence of treatments after trastuzumab, pertuzumab and T-DM1 is currently unknown. Section VI Triple-negative ABC

ABC, advanced breast cancer; AR, androgen receptor; ChT, chemotherapy; consensus, percentage of panel members in agreement with the statement; ESMO-MCBS, European Society for Medical Oncology Magnitude of Clinical Benefit Scale; GoR, grade of recommendation; HER2,

human epidermal growth factor receptor 2; LoE, level of evidence; n/a, not applicable; PD-L1, programmed death-ligand 1; T-DM1, trastuzumab emtansine; TNBC, triple-negative breast cancer.

For PD-L1 testing, see precision medicine statements.

Recent years have brought about the beginning of a significant change in the approach to triple-negative ABC with the recognition that both clinically and molecularly this is not one but many diseases. For most patients, ChT remains the only available non-investigational systemic treatment option for non- BRCA -mutated triple-negative ABC, with no specific recommendations regarding types of agents, with the possible exception of platinum compounds for patients with BRCA -mutated triple-negative ABC. However, immunotherapy has emerged as an option in the first-line setting for those with PD-L1 $\geq 1\%$ in immune cells. IMpassion-130 is a phase III randomised, placebo-controlled trial that compared atezolizumab and nab-paclitaxel with nab-paclitaxel alone. 68 The study had co-primary end points of PFS and OS in the intention-to-treat (ITT) population and had a hierarchal design that allowed for evaluation of OS in the PD-L1-positive population if the OS in the ITT population was significantly improved from the addition of atezolizumab. In the ITT population, atezolizumab provided a benefit in PFS of 7.2 versus 5.5 months with a HR of 0.8 (95% CI 0.69-0.92, $P = 0.002$). In the PD-L1 positive group, atezolizumab provided a PFS benefit of 7.5 versus 5 months with a HR of 0.62 (95% CI 0.49-0.78, $P < 0.001$). In the ITT population, there was no significant benefit in OS with the addition of atezolizumab; median OS was 21.3 months versus 17.6 months (HR 0.84; 95% CI 0.69-1.02, $P = 0.08$). However, despite the hierarchal statistical design that precluded an OS analysis in the PD-L1-positive population if the OS in the ITT population was not significant, an analysis was conducted and presented, and showed an OS of 25 months versus 15.1 months favouring the atezolizumab arm. Based on these data, atezolizumab in combination with nab-paclitaxel was approved and may be considered an option in the first-line setting for de novo advanced/metastatic disease or disease that has developed at least 12 months after completion of (neo)adjuvant ChT in tumours that have PD-L1 expression $\geq 1\%$ based on staining of the immune cells using the companion test of SP142 PD-L1 immunohistochemical assay (Ventana Medical Systems). 68 Recently, these data were updated showing a PFS difference of 2.5 months and an OS difference of 7 months in the PD-L1-positive population. 69 More recently, at ASCO 2020 virtual meeting, data from the KEYNOTE-355 trial was presented. KEYNOTE-355 was a randomised double-blind, phase III trial evaluating the role of pembrolizumab plus ChT for previously untreated triple-negative ABC, which showed an improvement in PFS with the addition of pembrolizumab (9.7 versus 5.6 months; HR 0.65; CI 0.49-0.86, $P = 0.0012$) for PD-L1-positive (combined positive score ≥ 10), triple-negative ABC. 70

Checkpoint inhibitor monotherapy in later lines for triple-negative ABC is not recommended due to low response rates, as seen in the KEYNOTE-199 trial. 71 In patients with triple-negative ABC and a germline BRCA mutation, a poly-adenosine diphosphate ribose polymerase (PARP) inhibitor is a preferred treatment option (please refer to section on hereditary ABC). In the small proportion of patients with both PD-L1-positive disease and BRCA1/2 mutations, the selection of immunotherapy or a PARP inhibitor for first-line treatment remains an area of debate.

No further data to support antiandrogen therapy for triple-negative ABC with expression of the androgen receptor has been published since ABC 4 and therefore it cannot be recommended for routine clinical use outside a clinical trial.

Sacituzumab govitecan-hziy has demonstrated promising activity in advanced lines for triple-negative ABC in a phase I/II study of 108 patients who had received a range of 2-10 prior treatments for metastatic disease. 72 The overall response rate was 33.3% (95% CI 24.6-43.1), with a median duration of response of 7.7 months (95% CI 4.9-10.8). Of the patients with a response to sacituzumab govitecan-hziy, 55.6% maintained their response for ≥ 6 months and 16.7% maintained their response for ≥ 12 months. Based on these preliminary results, the FDA has granted accelerated approval. However, phase III results are needed to confirm efficacy and establish the role of this agent in the management of triple-negative ABC. Section VII Hereditary ABC

ABC, advanced breast cancer; CDK, cyclin-dependent kinase; ChT, chemotherapy; consensus, percentage of panel members in agreement with the statement; ESMO-MCBS, European Society for Medical Oncology Magnitude of Clinical Benefit Scale; ET, endocrine therapy; GoR, grade of recommendation; HER2, human epidermal growth factor receptor 2; LoE, level of evidence; MBC, metastatic breast cancer; n/a, not applicable; OS, overall survival; PARPi, poly-adenosine diphosphate ribose polymerase inhibitor; PFS, progression-free survival; QoL, quality of life.

For ABC patients, results from germline genetic testing for a mutation in BRCA1/2 have therapeutic implications and should therefore be discussed with the patient and carried out as early as possible. Genetic testing should be guided by national/international guidelines, 73 should be proposed to all male breast cancer patients and may also be considered for all patients with triple-negative disease. Genes to be tested depend on personal and family history. However, at present, only germline mutations in BRCA1/2 have any clinical utility and therapeutic impact. Although BRCA1/2 are the most frequently mutated genes, testing for other additional moderate- to high-penetrance genes may be considered, if deemed appropriate by the geneticist/genetic counsellor, but it must be clarified to the patient that, at present, a mutation in another moderate- to high-penetrance gene has limited clinical implications in the setting of ABC—this is an area of research with several ongoing clinical trials and emerging phase II data suggesting a benefit of PARP inhibitors (PARPis) in patients with germline PALB2 mutations. 74

Since ABC 4, further data from the OlympiAD study suggested an OS benefit for olaparib when given in the first-line setting, with a median OS of 22.6 versus 14.7 months (HR 0.51; 95% CI 0.29-0.90, $P = 0.02$) in a subgroup analysis of predefined stratification subgroups, 75 lending further support to existing data for a PFS benefit with olaparib in the ITT population of the study. 76

The EMBRACA study 77 had a similar design to the OlympiAD study, comparing talazoparib with ChT monotherapy per physician's choice (capecitabine, eribulin, vinorelbine or gemcitabine). Most patients had not received prior platinum-based therapy. At a median follow-up of 11.2 months, PFS was longer in the talazoparib arm (8.6 versus 5.6 months, HR 0.54; 95% CI 0.41-0.71, $P < 0.0001$). Recently, at the American Association for Cancer Research (AACR) 2020 virtual meeting, an update was presented and no benefit was demonstrated in OS. 78 However, it is worth noting that nearly 60% of patients in the control arm went on to receive a PARP inhibitor or platinum agent. At the ESMO 2019 annual meeting, data was presented from the BROCADE3 study—the first phase III study in ABC comparing the addition of a PARPi (veliparib) to a platinum-containing regimen (paclitaxel and carboplatin) for germline BRCA -mutated ABC. 79 The study demonstrated a PFS benefit favouring the veliparib arm, with a median PFS of 14.5 versus 12.6 months (HR 0.71; 95% CI 0.57-0.88, $P = 0.002$) and a suggestion of sustained response at 2 and 3 years favouring the arm that was receiving maintenance veliparib but at the expense of significant toxicity. Peer-reviewed publication of the data is awaited, and further data are needed before this combination can be recommended for germline BRCA -mutated ABC.

Further studies are also needed to clarify the value of PARPis in platinum-resistant disease, as well as their value compared with platinum compounds. Section VIII Precision medicine

ABC, advanced breast cancer; consensus, percentage of panel members in agreement with the statement; ctDNA, circulating tumour DNA; ER, estrogen receptor; ET, endocrine therapy; GoR, grade of recommendation; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; LoE, level of evidence; MMR-D, mismatch repair deficiency; MSI-H, microsatellite instability-high; NGS, next-generation sequencing; NTRK, neurotrophic receptor tyrosine kinase; PD, disease progression; PD-1, programmed cell death protein 1; PgR, progesterone receptor; PI3K, phosphoinositide 3-kinase; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; TRKi, tropomyosin receptor kinase inhibitor.

Circulating DNA assays assess cell-free tumour DNA qualitatively and quantitatively for molecular alterations in a non-invasive fashion from a simple blood sample. Different technologies are available from single-gene assay by quantitative polymerase chain reaction (qPCR) to whole genome sequencing by next-generation sequencing (NGS). 80 , 81 Standardisation is a critical point, especially for NGS-based analysis. There is insufficient evidence of clinical validity and utility for the majority of circulating tumour DNA (ctDNA) assays in advanced cancer. 82 Thus, ctDNA assessment is not recommended for demonstration of disease progression in ABC. However, for single biomarkers using targeted assays, ctDNA assessment is an option for the detection of PIK3CA mutations for selection of patients eligible for alpelisib.

The progress of precision medicine has helped to describe around 40 recurrent driver alterations in breast cancer. ESMO has recently developed a scale for clinical actionability of molecular targets (ESCAT) to interpret the targetability of genomic alterations in the context of clinical practice. 83 The aim is to help clinicians to prioritise treatment after NGS results. The tool ranks genomic alterations in tiers, based on the strength of their clinical validation (from I to V and X). ERBB2 amplification, germline deleterious BRCA 1 and 2 mutations and PIK3CA mutations are all classified as tier IA. The majority of PIK3CA mutations affect hot spots i.e. the three most frequent in exons 9 and 20 (exon 9: E542K, E545K, helicase domain; exon 20: H1047R, kinase domain). They are present in up to 40% of metastatic luminal breast cancer. The mutations activate the alpha isoform of PI3K and drive oncogenicity. There were three sub-analyses of the SOLAR-1 trial 58 which showed that the benefit seen with alpelisib was independent of the type of PIK3CA test, i.e. tissue biopsy from the primary or the metastasis, liquid or tissue biopsy, NGS or targeted PCR test. 84 , 85 , 86 If treatment with the PI3K inhibitor, alpelisib, is available, patients should be tested for PIK3CA mutation (in exons 9 and 20) in tissue (metastasis or primary) and/or by ctDNA testing in blood. Patients who do not have an available archival tissue sample and have an uninformative result using the liquid biopsy test could consider undergoing a new biopsy for PIK3CA mutation testing.

Acquisition of ESR1 mutations, frequent in ABC patients previously treated by AIs (20%-40%), is one of the mechanisms of resistance to hormonal therapies. The consequence is a ligand-independent, constitutive activity of ER. To assess the impact of the presence of ESR1 mutations in plasma samples of ABC patients, the post hoc prospective-retrospective analysis of the SOFEA trial failed to demonstrate a statistically significant impact of ESR1 mutations on response to AI versus fulvestrant (interaction test between the two regimens $P = 0.07$). The analysis of the PALOMA-3 trial showed that the presence of plasma ESR1 mutations had no impact on response to palbociclib (interaction test between the two regimens $P = 0.74$). 87 Despite promising preclinical data and statistical trends, the ESCAT scale for ESR1 mutations is tier II. 83 Therefore, ESR1 mutation status assessment is not ready for routine clinical use and is not recommended, either for demonstration of disease progression or selection of hormonal treatment (such as a switch from AI to fulvestrant).

Increased counts of tumour-infiltrating lymphocytes (TILs) are prognostic for survival in triple-negative breast cancer (TNBC), making this disease a potential target for immunotherapy. 88 Based on the results of the IMpassion-130 trial, 68 atezolizumab was approved with the Ventana PD-L1 (SP142) assay as a companion diagnostic immunohistochemistry (IHC) assay. Therefore, PD-L1 status should be tested in cases of first-line triple-negative ABC if treatment with immune checkpoint inhibitors is available. Several IHC assays are available to assess PD-L1 status. 89 SP263 (Ventana) and 22-C3 (Dako), both of which are widely used in pathology laboratories for other tumour types, have been evaluated for their clinical validity in the context of the IMpassion-130 trial but failed to reproduce SP142 clinical validity. 90 Thus, PD-L1 status by SP142 is the companion test for the use of atezolizumab in combination with a taxane for first-line therapy in triple-negative ABC, with a cut-off of 1% positive staining on immune cells. It is critical for medical oncologists and pathologists to know the available assays and their relevance to the therapeutic options in order to develop a workflow for IHC testing.

Tumours with staining of ER <1% and progesterone receptor (PgR) <1% and with HER2-negative results by IHC and/or in situ hybridisation are defined as TNBC. 91 Patients with a low (1%-10%) expression of hormone receptors and HER2-negative account for 2%-3% of breast cancers. They may share morphological (high grade, poor differentiation) 92 and biological features 93 , 94 with TNBC and experience a similarly poor survival. 95 , 96 A meta-analysis assessing the survival benefit of ET for ER-low (<10%) primary breast cancer showed lower endocrine responsiveness compared with ER-positive tumours [odds ratio (OR) 0.52, P = 0.034]. 97 Recently, the ASCO-College of American Pathologists (CAP) guidelines acknowledged that patients with tumours between 1% and 10% of ER staining represent a new reporting category, stipulating the lack of data concerning benefit from ET and the proximity to ER-negative breast cancer of this patient group. 98 We recommend that this strategy is also adopted for ABC patients with a low ER-positive status.

Section IX Specific sites of metastases

ABC, advanced breast cancer; ChT, chemotherapy; consensus, percentage of panel members in agreement with the statement; CPG, Clinical Practice Guideline; CSF, cerebrospinal fluid; DFI, disease-free interval; ER, estrogen receptor; ESMO, European Society for Medical Oncology; ET, endocrine therapy; GoR, grade of recommendation; HER2, human epidermal growth factor receptor 2; LMD, leptomeningeal disease; LoE, level of evidence; MRI, magnetic resonance imaging; OS, overall survival; PS, performance status; QoL, quality of life; RCT, randomised controlled trial; RT, radiotherapy; WBRT, whole-brain radiotherapy.

The ABC panel decided to endorse the ESMO Clinical Practice Guideline (CPG) related to the use of bone-targeted agents (bisphosphonate, denosumab), which replace all previous statements regarding this subject. 99

Leptomeningeal disease (LMD) is a rare complication of breast cancer with a 5% incidence rate. LMD carries a poor prognosis, with a median OS of approximately 4 weeks which can be prolonged to a few months in some patients with aggressive multimodal treatment. 100 Its diagnosis is based on clinical evaluation, cerebrospinal magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) analysis. The European Association of Neuro-Oncology (EANO) and ESMO have proposed classifying LMD using two major criteria: presence (type I) or not (type II) of positive CSF and neuroimaging findings. 101 The same authors have proposed defining the therapeutic plan based on the presentation of the disease [nodular (A) or linear (B) or mixed (C) meningeal involvement, positive CSF cytology, presence or not of extracerebral disease, etc.] and taking into account the patient's life expectancy. 102 Available active treatment options are RT, intra-CSF therapy and systemic therapy. The choice of treatment should always involve multidisciplinary discussion. Currently, there is no accepted standard of care for breast cancer LMD and recommendations are essentially expert opinion-based. The EANO-ESMO CPG recommends considering focal RT for circumscribed, notably symptomatic lesions, and whole-brain RT (WBRT) for extensive nodular or symptomatic linear LMD. 101 The use of intrathecal therapy is controversial. It is recommended in cases where tumour cells are present in the CSF; it is optional in cases of linear metastatic meningeal disease. 100 , 101 , 102 This strategy is not recommended in patients with obstructive hydrocephalus (RT can be used to restore CSF flow and successful restoration should be checked before the use of any intrathecal treatment) or in patients with nodular meningeal metastases only. Three agents are commonly used for intrathecal treatment of LMD: methotrexate, cytarabine (including liposomal cytarabine) or thioTEPA. 100 , 101 , 102 Their use can cause a spectrum of toxicities ranging from myelosuppression to neurotoxicity. Methotrexate is the most commonly used agent. Neurotoxicity is increased with the use of methotrexate and RT and this combination is not recommended. Other agents, such as trastuzumab for HER2-positive disease, are under evaluation. Intrathecal therapy can be considered in cases where systemic disease is stable. However, two prospective trials have shown that the addition of intrathecal to systemic therapy has no OS or QoL advantage. 102 Retrospective data suggest some activity of different agents used systemically. 100 , 101 , 102

Section X Specific populations

No new statements for this section were developed at ABC 5.

ABC, advanced breast cancer; AI, aromatase inhibitor; consensus, percentage of panel members in agreement with the statement; ER, estrogen receptor; ET, endocrine therapy; GoR, grade of recommendation; LHRH, luteinising hormone-releasing hormone; LoE, level of evidence.

No new statements for this section were developed at ABC 5.

ABC, advanced breast cancer; BCS, breast-conserving surgery; ChT, chemotherapy; consensus, percentage of panel members in agreement with the statement; ChT, chemotherapy; CT, computed tomography; ER, estrogen receptor; ET, endocrine therapy; GoR, grade of recommendation; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; LABC, locally advanced breast cancer; LoE, level of evidence; pCR, pathological complete response; PET, positron emission tomography; PgR, progesterone receptor; PS, performance status; QoL, quality of life; RT, radiotherapy; SLNB, sentinel lymph node biopsy.

For the purpose of these recommendations, LABC means inoperable, non-metastatic locally advanced breast cancer.

For postmenopausal symptoms in general: mind-body interventions, physical training and CBT are effective non-pharmacological treatment options.

For hot flushes: venlafaxine, oxybutynin, gabapentin, clonidine and acupuncture are available options.

ABC, advanced breast cancer; CBT, cognitive behavioural therapy; CDK, cyclin-dependent kinase; ChT, chemotherapy; CIPN, chemotherapy-induced peripheral neuropathy; consensus, percentage of panel members in agreement with the statement; ER, estrogen receptor; ESMO, European Society for Medical Oncology; GoR, grade of recommendation; HFS, hand and foot syndrome; LoE, level of evidence; MASCC, Multinational Association of Supportive Care in Cancer; mTOR, mammalian target of rapamycin; n/a, not applicable; NIP, non-infectious pneumonitis; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PROM, patient-reported outcome measure; q.i.d., four times a day; QoL, quality of life; RT, radiotherapy.

Recent data on cannabidiol for medical use has not yet substantiated claims indicating that it is effective in cancer pain management to the same level as morphine 109 and more research is needed. 110

Many therapies for ABC are associated with estrogen deprivation and patients often suffer from menopausal symptoms such as hot flushes, night sweats, sleep disturbances, fatigue, arthralgia, cognitive impairment, depression and vaginal dryness, as well as impaired sexual functioning (e.g. loss of sexual desire, dyspareunia). Hormone replacement therapy is contraindicated due to the endocrine character of the disease and should not be used to treat complaints. Nevertheless, the final decision belongs to the patient, after adequate information, since in some cases these symptoms are impacting significantly on QoL. 111 , 112 For menopausal symptoms in general, mind-body interventions, physical training and cognitive behavioural therapy should be recommended as effective non-pharmacological treatment options. 113 , 114 , 115 , 116 , 117 To control hot flushes, valid alternatives are venlafaxine, oxybutynin, gabapentin and clonidine. 118 , 119 , 120 , 121 Sleep disturbances may be treated with melatonin. 122 , 123 There is no convincing evidence that phytotherapeutic drugs may improve menopausal symptoms. Possible drug interactions must be considered.

Sexuality is an experience on many levels and is not confined to the act of intercourse. ABC patients frequently experience impaired sexual health and need specific attention. A recent retrospective study showed that breast cancer patients are more affected than patients with ovarian cancer or healthy controls: decreased or no interest in sexual activity was frequently reported with a significant association to less satisfaction and more discomfort (dyspareunia); however, the lack of

desire was not associated with global health status, QoL or the ability to experience orgasms; estrogen deprivation (gonadotropin-releasing hormone agonists, AIs) seemed to have more impact than tamoxifen. 124

Dyspareunia is often caused by vaginal dryness. The first choice for treating vaginal dryness and soreness are hormone-free lubricants (e.g. water-based gel, hyaluronic acid gel). 125 , 126 , 127 If hormone-free measures are not effective, low-dose estriol-containing vaginal medication may be used. 128 , 129 , 130 , 131 , 132 The value of local testosterone application and of invasive measures like vaginal laser or hyaluronic acid injections is still unclear. 133 , 134 , 135 In summary, gynaecological and sexual symptoms are important challenges for most ABC patients. In particular, even in an anonymous setting, patients are often too shy to report their problems regarding impaired sexual life. Therefore, active verbalisation of gynaecological and sexual symptoms in an adequate and trustful atmosphere is a mandatory part of follow-up visits. Openly addressing misconceptions and sexual challenges after treatment, as well as educating patients, have been shown to improve QoL. When life expectancy is limited, physical contact, affection, emotional communication and comfort are particularly important. Standardised instruments (questionnaires) may help to assess the grade of impairment. 136 , 137 , 138 , 139 , 140 At first recurrence, one out of four patients is younger than 50 years old and premenopausal. Therefore, issues of fertility and contraception must be discussed, and for the latter, only hormone-free contraceptives can be recommended. 141

Section XIII Integrative medicine

Physical exercise/sport (equivalent to 3-5 hours of moderate walking per week) improves QoL, cardiorespiratory fitness, physical performance and fatigue, and it may also improve DFS and OS.

MBSR programmes, hypnosis and yoga may improve QoL and fatigue, and help reduce anxiety, distress and some side-effects of anticancer therapies.

Acupuncture may help against ChT-induced nausea and vomiting, fatigue and hot flushes.

Drugs outside the approved indication (e.g. methadone)

Orthomolecular substances (selenium, zinc, etc.)

High-dose vitamins (vitamin C, D, E, carotenoids, etc.)

No new statements for this section were developed at ABC 5.

ABC, advanced breast cancer; ChT, chemotherapy; CIM, complementary and integrative medicine; consensus, percentage of panel members in agreement with the statement; DFS, disease-free survival; GoR, grade of recommendation; LoE, level of evidence; MBSR, mindfulness-based stress reduction; n/a, not applicable; OS, overall survival; QoL, quality of life.

ABC guidelines provide a useful tool for the management of ABC in clinical practice. Each guideline has an associated LoE, GoR and percentage of consensus. Additionally, v1.1 of the ESMO-MCBS 13 was applied to drugs approved by the EMA after 2016. As usual, if additional new agents are approved by the EMA before the next ABC Consensus Conference, the ESMO-MCBS will be applied and the result will be made available as an e-update to the present guidelines.

We acknowledge that in many areas of the world, some of these guidelines may not be implemented due to the existence of disparities in access. It is the mission of the ABC Global Alliance 142 to fight for better outcomes for all ABC patients around the world. For this goal to be achieved, efforts must continue not only in research but also in public policy to ensure equal access to multidisciplinary, specialised care, including anticancer, palliative and end-of-life care, and full implementation of these guidelines. We emphasise again that reimbursement rules in all countries should be patient-centred and be an incentive to, not work against, the clinical implementation of

high-quality international guidelines. Clinical trials and consequent approval and reimbursement must not continue to exclude certain groups of patients, such as premenopausal women and men, which keep seeing their treatment options reduced in many countries.

At a time when the world is facing the COVID-19 pandemic, the ABC community must unite to maintain or increase the resources needed to face the ever-rising cancer 'epidemic', which is responsible for 18.1 million new cases and 9.6 million deaths annually worldwide, with half a million deaths annually due to ABC. 12

Cardoso F. Costa A. Norton L. ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2) *Breast* 23 5 2014 489 502 25244983 10.1016/j.breast.2014.08.009 2
Cardoso F. Costa A. Norton L. ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2) *Ann Oncol* 25 10 2014 1871 1888 25234545 10.1093/annonc/mdu385 PMC4176456 3 Cardoso F. Spence D. Mertz S. Global analysis of advanced/metastatic breast cancer: decade report (2005-2015) *Breast* 39 2018 131 138 29679849 10.1016/j.breast.2018.03.002 4 Howlader N. Noone A.M. Krapcho M. SEER Cancer Statistics Review, 1975-2013, National Cancer Institute. Based on November 2015 SEER Data Submission 2016 SEER Bethesda, MD Available at https://seer.cancer.gov/archive/csr/1975_2013/ 5 Sundquist M. Brudin L. Tejler G. Improved survival in metastatic breast cancer 1985-2016 *Breast* 31 2017 46 50 27810699 10.1016/j.breast.2016.10.005 6 Kobayashi K. Ito Y. Matsuura M. Impact of immunohistological subtypes on the long-term prognosis of patients with metastatic breast cancer *Surg Today* 46 7 2016 821 826 26467559 10.1007/s00595-015-1252-x 7 Fietz T. Tesch H. Rauh J. Palliative systemic therapy and overall survival of 1,395 patients with advanced breast cancer—results from the prospective German TMK cohort study *Breast* 34 2017 122 130 28586735 10.1016/j.breast.2017.05.014 8 Gobbi E. Ezzalfani M. Dieras V. Time trends of overall survival among metastatic breast cancer patients in the real-life ESME cohort *Eur J Cancer* 96 2018 17 24 29660596 10.1016/j.ejca.2018.03.015 9 Deluche E. Antoine A. Bachelot T. Contemporary outcomes of metastatic breast cancer among 22,000 women from the multicentre ESME cohort 2008-2016 *Eur J Cancer* 129 2020 60 70 32135312 10.1016/j.ejca.2020.01.016 10 Malmgren J.A. Mayer M. Atwood M.K. Differential presentation and survival of de novo and recurrent metastatic breast cancer over time: 1990-2010 *Breast Cancer Res Treat* 167 2 2018 579 590 29039120 10.1007/s10549-017-4529-5 PMC5790843 11 Breast Cancer Foundation NZ "I'm still here". Insights into living—and dying—with advanced breast cancer in New Zealand. Breast Cancer Foundation NZ Available at <https://www.breastcancerfoundation.org.nz/what-we-do/advocacy/abcinnz> 12 Bray F. Ferlay J. Soerjomataram I. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries *CA Cancer J Clin* 68 6 2018 394 424 30207593 10.3322/caac.21492 13 Cherny N.I. Dafni U. Bogaerts J. ESMO-magnitude of clinical benefit scale version 1.1 *Ann Oncol* 28 10 2017 2340 2366 28945867 10.1093/annonc/mdx310 14 Dykewicz C.A. Summary of the guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients *Clin Infect Dis* 33 2 2001 139 144 (adapted from: Gross PA, Barrett TL, Dellinger EP, et al. Purpose of quality standards for infectious diseases. *Clin Infect Dis* . 1994;1918:1421) 11418871 10.1086/321805 15 Mack J.W. Weeks J.C. Wright A.A. End-of-life discussions, goal attainment, and distress at the end of life: predictors and outcomes of receipt of care consistent with preferences *J Clin Oncol* 28 7 2010 1203 1208 20124172 10.1200/JCO.2009.25.4672 PMC2834470 16 Smith-Uffen M.E.S. Johnson S.B. Martin A.J. Estimating survival in advanced cancer: a comparison of estimates made by oncologists and patients *Support Care Cancer* 28 7 2020 3399 3407 31781946 10.1007/s00520-019-05158-5 17 Hagerty R.G. Butow P.N. Ellis P.M. Communicating prognosis in cancer care: a systematic review of the literature *Ann Oncol* 16 7 2005 1005 1053 15939716 10.1093/annonc/mdi211 18 Fried T.R. Bradley E.H. O'Leary J. Prognosis communication in serious illness: perceptions of older patients, caregivers, and clinicians *J Am Geriatr Soc* 51 10 2003 1398 1403 14511159 10.1046/j.1532-5415.2003.51457.x 19 Mack J.W. Cronin A. Keating N.L. Associations between end-of-life discussion characteristics and care received near death: a prospective cohort study *J Clin Oncol* 30 35 2012 4387 4395 23150700 10.1200/JCO.2012.43.6055 PMC3675701 20 Wright A.A. Zhang B. Ray A. Associations between end-of-life discussions, patient mental health, medical

care near death, and caregiver bereavement adjustment JAMA 300 14 2008 1665 1673 18840840 10.1001/jama.300.14.1665 PMC2853806 21 Weeks J.C. Cook E.F. O'Day S.J. Relationship between cancer patients' predictions of prognosis and their treatment preferences JAMA 279 21 1998 1709 1714 9624023 10.1001/jama.279.21.1709 22 Pronzato P. Bertelli G. Losardo P. What do advanced cancer patients know of their disease? A report from Italy Support Care Cancer 2 4 1994 242 244 7522106 10.1007/BF00365729 23 Jenkins V. Fallowfield L. Saul J. Information needs of patients with cancer: results from a large study in UK cancer centres Br J Cancer 84 1 2001 48 51 11139312 10.1054/bjoc.2000.1573 PMC2363610 24 Arraras J.I. Greimel E. Chie W.C. Cross-cultural differences in information disclosure evaluated through the EORTC questionnaires Psychooncology 22 2 2013 268 275 22052786 10.1002/pon.2088 25 Fallowfield L.J. Jenkins V.A. Beveridge H.A. Truth may hurt but deceit hurts more: communication in palliative care Palliat Med 16 4 2002 297 303 12132542 10.1191/0269216302pm575oa 26 Barnett M.M. Does it hurt to know the worst?—psychological morbidity, information preferences and understanding of prognosis in patients with advanced cancer Psychooncology 15 1 2006 44 55 15750997 10.1002/pon.921 27 Enzinger A.C. Zhang B. Schrag D. Outcomes of prognostic disclosure: associations with prognostic understanding, distress, and relationship with physician among patients with advanced cancer J Clin Oncol 33 32 2015 3809 3816 26438121 10.1200/JCO.2015.61.9239 PMC4737862 28 Gattellari M. Voigt K.J. Butow P.N. When the treatment goal is not cure: are cancer patients equipped to make informed decisions? J Clin Oncol 20 2 2002 503 513 11786580 10.1200/JCO.2002.20.2.503 29 Hagerty R.G. Butow P.N. Ellis P.M. Communicating with realism and hope: incurable cancer patients' views on the disclosure of prognosis J Clin Oncol 23 6 2005 1278 1288 15718326 10.1200/JCO.2005.11.138 30 Smith T.J. Dow L.A. Virago E. Giving honest information to patients with advanced cancer maintains hope Oncology (Williston Park) 24 6 2010 521 525 20568593 31 Kiely B.E. McCaughan G. Christodoulou S. Using scenarios to explain life expectancy in advanced cancer: attitudes of people with a cancer experience Support Care Cancer 21 2 2013 369 376 22717918 10.1007/s00520-012-1526-4 32 Stockler M.R. Tattersall M.H. Boyer M.J. Disarming the guarded prognosis: predicting survival in newly referred patients with incurable cancer Br J Cancer 94 2 2006 208 212 16404420 10.1038/sj.bjc.6602908 PMC2361107 33 Kiely B.E. Martin A.J. Tattersall M.H. The median informs the message: accuracy of individualized scenarios for survival time based on oncologists' estimates J Clin Oncol 31 28 2013 3565 3571 24002504 10.1200/JCO.2012.44.7821 34 Fallowfield L.J. Catt S.L. May S.F. Therapeutic aims of drugs offering only progression-free survival are misunderstood by patients, and oncologists may be overly optimistic about likely benefits Support Care Cancer 25 1 2017 237 244 27619389 10.1007/s00520-016-3408-7 35 Hey S.P. Gyawali B. D'Andrea E. A systematic review and meta-analysis of bevacizumab in first-line metastatic breast cancer: lessons for research and regulatory enterprises J Natl Cancer Inst 112 4 2020 335 342 31651981 10.1093/jnci/djz211 PMC7156929 36 Im S.A. Lu Y.S. Bardia A. Overall survival with ribociclib plus endocrine therapy in breast cancer N Engl J Med 381 4 2019 307 316 31166679 10.1056/NEJMoa1903765 37 Slamon D.J. Neven P. Chia S. Overall survival with ribociclib plus fulvestrant in advanced breast cancer N Engl J Med 382 6 2020 514 524 31826360 10.1056/NEJMoa1911149 38 Slamon D.J. Neven P. Chia S. Phase III randomized study of ribociclib and fulvestrant in hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer: MONALEESA-3 J Clin Oncol 36 24 2018 2465 2472 29860922 10.1200/JCO.2018.78.9909 39 Sledge G.W. Jr. Toi M. Neven P. The effect of abemaciclib plus fulvestrant on overall survival in hormone receptor-positive, erbb2-negative breast cancer that progressed on endocrine therapy-MONARCH 2: a randomized clinical trial JAMA Oncol 6 1 2019 116 124 10.1001/jamaoncol.2019.4782 PMC6777264 31563959 40 Sledge G.W. Jr. Toi M. Neven P. MONARCH 2: abemaciclib in combination with fulvestrant in women with HR+/HER2- advanced breast cancer who had progressed while receiving endocrine therapy J Clin Oncol 35 25 2017 2875 2884 28580882 10.1200/JCO.2017.73.7585 41 Tripathy D. Im S.A. Colleoni M. Ribociclib plus endocrine therapy for premenopausal women with hormone-receptor-positive, advanced breast cancer (MONALEESA-7): a randomised phase 3 trial Lancet Oncol 19 7 2018 904 915 29804902 10.1016/S1470-2045(18)30292-4 42 Tripathy D. Sohn J. Im S.-A. Abstract GS2-05: first-line ribociclib vs placebo with goserelin and tamoxifen or a non-steroidal aromatase inhibitor in premenopausal women with hormone receptor-positive, HER2-negative advanced breast cancer: results from the randomized phase III MONALEESA-7 trial Cancer Res 78 4 Supplement 2018 GS2-05 43 Finn R.S. Martin M. Rugo H.S. Palbociclib and letrozole in advanced breast cancer N Engl J Med 375 20 2016 1925 1936 27959613

10.1056/NEJMoa1607303 44 Hortobagyi G.N. Stemmer S.M. Burris H.A. Ribociclib as first-line therapy for HR-positive, advanced breast cancer *N Engl J Med* 375 18 2016 1738 1748 27717303

10.1056/NEJMoa1609709 45 Rugo H.S. Finn R.S. Diéras V. Palbociclib plus letrozole as first-line therapy in estrogen receptor-positive/human epidermal growth factor receptor 2-negative advanced breast cancer with extended follow-up *Breast Cancer Res Treat* 174 3 2019 719 729 30632023

10.1007/s10549-018-05125-4 PMC6438948 46 di Leo A. Toi M. Campone M. MONARCH 3: abemaciclib as initial therapy for patients with HR+/HER2- advanced breast cancer *Ann Oncol* 28 suppl 5 2017 v605 v649 47 Hortobagyi G.N. Stemmer S.M. Burris H.A. Updated results from MONALEESA-2, a phase 3 trial of first-line ribociclib + letrozole in hormone receptor-positive (HR+), HER2-negative (HER2-), advanced breast cancer (ABC) *J Clin Oncol* 35 15_suppl 2017 1038 48 Cristofanilli M. Turner N.C. Bondarenko I. Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial *Lancet Oncol* 17 4 2016 425 439 26947331

10.1016/S1470-2045(15)00613-0 49 Goetz M.P. Toi M. Campone M. MONARCH 3: abemaciclib as initial therapy for advanced breast cancer *J Clin Oncol* 35 32 2017 3638 3646 28968163

10.1200/JCO.2017.75.6155 50 Harbeck N. Iyer S. Bhattacharyya H. Impact of disease progression status on time to deterioration of patient reported health related quality of life in first line ER+ HER2-advanced/metastatic breast cancer patients in the PALOMA-2 study *Breast* 36 2017 S43 51 Johnston S. Martin M. Di Leo A. MONARCH 3 final PFS: a randomized study of abemaciclib as initial therapy for advanced breast cancer *NPJ Breast Cancer* 5 2019 5 30675515

10.1038/s41523-018-0097-z PMC6336880 52 Rugo H.S. Diéras V. Gelmon K.A. Impact of palbociclib plus letrozole on patient-reported health-related quality of life: results from the PALOMA-2 trial *Ann Oncol* 29 4 2018 888 894 29360932 10.1093/annonc/mdy012 PMC5913649

53 Verma S. O'Shaughnessy J. Burris H.A. Health-related quality of life (HRQoL) of postmenopausal women with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) advanced breast cancer (ABC) treated with ribociclib + letrozole: results from MONALEESA-2 *J Clin Oncol* 35 15_suppl 2017 1020 54 Harbeck N. Iyer S. Turner N. Quality of life with palbociclib plus fulvestrant in previously treated hormone receptor-positive, HER2-negative metastatic breast cancer: patient-reported outcomes from the PALOMA-3 trial *Ann Oncol* 27 6 2016 1047 1054 27029704 10.1093/annonc/mdw139 PMC4880065 55 Kaufman P.A. Toi M. Neven P. Health-related quality of life in MONARCH 2: abemaciclib plus fulvestrant in hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy *Oncologist* 25 2 2020 e243 e251 32043763 10.1634/theoncologist.2019-0551 PMC7011625 56 Turner N.C. Slamon D.J. Ro J. Overall survival with palbociclib and fulvestrant in advanced breast cancer *N Engl J Med* 379 20 2018 1926 1936 30345905 10.1056/NEJMoa1810527 57 Verma S. Bartlett C.H. Schnell P. Palbociclib in combination with fulvestrant in women with hormone receptor-positive/HER2-negative advanced metastatic breast cancer: detailed safety analysis from a multicenter, randomized, placebo-controlled, phase III study (PALOMA-3) *Oncologist* 21 10 2016 1165 1175 27368881 10.1634/theoncologist.2016-0097 PMC5061543 58 André F. Ciruelos E. Rubovszky G. Alpelisib for PIK3CA-mutated, hormone receptor-positive advanced breast cancer *N Engl J Med* 380 20 2019 1929 1940 31091374 10.1056/NEJMoa1813904 59 Nunnery S.E. Mayer I.A. Management of toxicity to isoform α -specific PI3K inhibitors *Ann Oncol* 30 suppl 10 2019 x21 x26 10.1093/annonc/mdz440 31928691 60 Rugo H.S. Lerebours F. Ciruelos E. Alpelisib (ALP) + fulvestrant (FUL) in patients (pts) with PIK3CA -mutated (mut) hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) advanced breast cancer (ABC) previously treated with cyclin-dependent kinase 4/6 inhibitor (CDKi) + aromatase inhibitor (AI): BYLieve study results *J Clin Oncol* 38 15_suppl 2020 1006 61 Cardoso F. Senkus E. Costa A. 4th ESO-ESMO International Consensus Guidelines for advanced breast cancer (ABC 4) *Ann Oncol* 29 8 2018 1634 1657 30032243 10.1093/annonc/mdy192 PMC7360146 62 Murthy R.K. Loi S. Okines A. Tucatinib, trastuzumab, and capecitabine for HER2-positive metastatic breast cancer *N Engl J Med* 382 7 2020 597 609 31825569 10.1056/NEJMoa1914609 63 Lin N.U. Borges V. Anders C. Intracranial efficacy and survival with tucatinib plus trastuzumab and capecitabine for previously treated HER2-positive breast cancer with brain metastases in the HER2CLIMB trial *J Clin Oncol* 38 23 2020 2610 2619 32468955 10.1200/JCO.20.00775 PMC7403000 64 Modi S. Saura C. Yamashita T. Trastuzumab deruxtecan in previously treated HER2-positive breast cancer *N Engl J Med* 382 7 2020 610 621 31825192 10.1056/NEJMoa1914510 PMC7458671 65 Rugo H.S. Im

S.-A. Wright G.L.S. SOPHIA primary analysis: a phase 3 (P3) study of margetuximab (M) + chemotherapy (C) versus trastuzumab (T) + C in patients (pts) with HER2+ metastatic (met) breast cancer (MBC) after prior anti-HER2 therapies (Tx) J Clin Oncol 37 15_suppl 2019 1000 66 Saura C. Oliveira M. Feng Y.-H. Neratinib + capecitabine versus lapatinib + capecitabine in patients with HER2+ metastatic breast cancer previously treated with ≥ 2 HER2-directed regimens: findings from the multinational, randomized, phase III NALA trial J Clin Oncol 37 15_suppl 2019 1002 67 Pivot X. Manikhas A. ■urawski B. CEREBEL (EGF111438): a phase III, randomized, open-label study of lapatinib plus capecitabine versus trastuzumab plus capecitabine in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer J Clin Oncol 33 14 2015 1564 1573 25605838 10.1200/JCO.2014.57.1794 68 Schmid P. Adams S. Rugo H.S. Atezolizumab and nab-paclitaxel in advanced triple-negative breast cancer N Engl J Med 379 22 2018 2108 2121 30345906 10.1056/NEJMoa1809615 69 Schmid P. Rugo H.S. Adams S. Atezolizumab plus nab-paclitaxel as first-line treatment for unresectable, locally advanced or metastatic triple-negative breast cancer (IMpassion130): updated efficacy results from a randomised, double-blind, placebo-controlled, phase 3 trial Lancet Oncol 21 1 2020 44 59 31786121 10.1016/S1470-2045(19)30689-8 70 Cortes J. Cescon D.W. Rugo H.S. KEYNOTE-355: randomized, double-blind, phase III study of pembrolizumab + chemotherapy versus placebo + chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer J Clin Oncol 38 15_suppl 2020 1000 10.1016/S0140-6736(20)32531-9 33278935 71 Cortés J. Lipatov O. Im S. KEYNOTE-119: phase 3 study of pembrolizumab (pembro) versus single-agent chemotherapy (chemo) for metastatic triple-negative breast cancer (mTNBC) Ann Oncol 30 suppl 5 2019 v851 v934 72 Bardia A. Mayer I.A. Vahdat L.T. Sacituzumab govitecan-hziy in refractory metastatic triple-negative breast cancer N Engl J Med 380 8 2019 741 751 30786188 10.1056/NEJMoa1814213 73 Paluch-Shimon S. Cardoso F. Sessa C. Prevention and screening in BRCA mutation carriers and other breast/ovarian hereditary cancer syndromes: ESMO Clinical Practice Guidelines for cancer prevention and screening Ann Oncol 27 suppl 5 2016 v103 v110 27664246 10.1093/annonc/mdw327 74 Tung N.M. Robson M.E. Ventz S. TBCRC 048: a phase II study of olaparib monotherapy in metastatic breast cancer patients with germline or somatic mutations in DNA damage response (DDR) pathway genes (olaparib expanded) J Clin Oncol 38 15_suppl 2020 1002 10.1200/JCO.20.02151 33119476 75 Robson M.E. Tung N. Conte P. OlympiAD final overall survival and tolerability results: olaparib versus chemotherapy treatment of physician's choice in patients with a germline BRCA mutation and HER2-negative metastatic breast cancer Ann Oncol 30 4 2019 558 566 30689707 10.1093/annonc/mdz012 PMC6503629 76 Robson M. Im S.A. Senkus E. Olaparib for metastatic breast cancer in patients with a germline BRCA mutation N Engl J Med 377 6 2017 523 533 28578601 10.1056/NEJMoa1706450 77 Litton J.K. Rugo H.S. Ettl J. Talazoparib in patients with advanced breast cancer and a germline BRCA mutation N Engl J Med 379 8 2018 753 763 30110579 10.1056/NEJMoa1802905 PMC10600918 78 Litton JK, Hurvitz SA, Mina LA, et al. Talazoparib in germline BRCA1/2-mutated HER2-negative advanced breast cancer: final overall survival results from randomized phase 3 EMBRACA trial. AACR virtual annual meeting. 27-28 April 2020. Abstract CT071. 10.1016/j.annonc.2020.08.2098 PMC10649377 32828825 79 Dieras V.C. Han H.S. Kaufman B. Phase 3 study of veliparib with carboplatin and paclitaxel in HER2-negative advanced/metastatic gBRCA-associated breast cancer Ann Oncol 30 suppl 5 2019 v851 v934 80 Diaz L.A. Jr. Bardelli A. Liquid biopsies: genotyping circulating tumor DNA J Clin Oncol 32 6 2014 579 586 24449238 10.1200/JCO.2012.45.2011 PMC4820760 81 Alimirzaie S. Bagherzadeh M. Akbari M.R. Liquid biopsy in breast cancer: a comprehensive review Clin Genet 95 6 2019 643 660 30671931 10.1111/cge.13514 82 Merker J.D. Oxnard G.R. Compton C. Circulating tumor DNA analysis in patients with cancer: American Society of Clinical Oncology and College of American Pathologists joint review J Clin Oncol 36 16 2018 1631 1641 29504847 10.1200/JCO.2017.76.8671 83 Condorelli R. Mosele F. Verret B. Genomic alterations in breast cancer: level of evidence for actionability according to ESMO Scale for Clinical Actionability of molecular Targets (ESCAT) Ann Oncol 30 3 2019 365 373 30715161 10.1093/annonc/mdz036 84 Rugo H.S. Mayer I. Conte P. Abstract CT142: prevalence of PIK3CA mutations in patients with hormone receptor-positive, human epidermal growth factor-2-negative advanced breast cancer from the SOLAR-1 trial Cancer Res 79 13 Supplement 2019 CT142 85 Juric D. Ciruelos E. Rubovszky G. Abstract GS3-08: Alpelisib + fulvestrant for advanced breast cancer: subgroup analyses from the phase III SOLAR-1 trial Cancer Res 79 4 Supplement 2019 GS3-08 86 Juric D. Andre F. Singer C.F. Abstract P4-10-04: clinical outcomes of alpelisib in

hormone receptor-positive, human epidermal growth factor receptor-2-negative advanced breast cancer by next-generation sequencing-detected PIK3CA alteration status and phosphatase and tensin homolog loss: biomarker analysis from the SOLAR-1 study *Cancer Res* 80 4 Supplement 2020 P4-10-04 87 Fribbens C. O'Leary B. Kilburn L. Plasma ESR1 mutations and the treatment of estrogen receptor-positive advanced breast cancer *J Clin Oncol* 34 25 2016 2961 2968 27269946 10.1200/JCO.2016.67.3061 88 Harbeck N. Penault-Llorca F. Cortes J. Breast cancer *Nat Rev Dis Primers* 5 1 2019 66 31548545 10.1038/s41572-019-0111-2 89 Adam J. Le Stang N. Rouquette I. Multicenter harmonization study for PD-L1 IHC testing in non-small-cell lung cancer *Ann Oncol* 29 4 2018 953 958 29351573 10.1093/annonc/mdy014 90 Rugo H.S. Loi S. Adams S. Performance of PD-L1 immunohistochemistry (IHC) assays in unresectable locally advanced or metastatic triple-negative breast cancer (mTNBC): post-hoc analysis of IMpassion130 *Ann Oncol* 30 suppl 5 2019 v851 v934 91 Wolff A.C. Hammond M.E.H. Allison K.H. Human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline focused update *J Clin Oncol* 36 20 2018 2105 2122 29846122 10.1200/JCO.2018.77.8738 92 Gloyeske N.C. Dabbs D.J. Bhargava R. Low ER+ breast cancer: is this a distinct group? *Am J Clin Pathol* 141 5 2014 697 701 24713741 10.1309/AJCP34CYSATWFDQP 93 Deyarmin B. Kane J.L. Valente A.L. Effect of ASCO/CAP guidelines for determining ER status on molecular subtype *Ann Surg Oncol* 20 1 2013 87 93 22875649 10.1245/s10434-012-2588-8 94 Iwamoto T. Booser D. Valero V. Estrogen receptor (ER) mRNA and ER-related gene expression in breast cancers that are 1% to 10% ER-positive by immunohistochemistry *J Clin Oncol* 30 7 2012 729 734 22291085 10.1200/JCO.2011.36.2574 95 Balduzzi A. Bagnardi V. Rotmensz N. Survival outcomes in breast cancer patients with low estrogen/progesterone receptor expression *Clin Breast Cancer* 14 4 2014 258 264 24325948 10.1016/j.clbc.2013.10.019 96 Yi M. Huo L. Koenig K.B. Which threshold for ER positivity? a retrospective study based on 9639 patients *Ann Oncol* 25 5 2014 1004 1011 24562447 10.1093/annonc/mdu053 PMC3999801 97 Chen T. Zhang N. Moran M.S. Borderline ER-positive primary breast cancer gains no significant survival benefit from endocrine therapy: a systematic review and meta-analysis *Clin Breast Cancer* 18 1 2018 1 8 28712925 10.1016/j.clbc.2017.06.005 98 Allison K.H. Hammond M.E.H. Dowsett M. Estrogen and progesterone receptor testing in breast cancer: ASCO/CAP Guideline update *J Clin Oncol* 38 12 2020 1346 1366 31928404 10.1200/JCO.19.02309 99 Coleman R. Hadji P. Body J-J. Bone health in cancer: ESMO Clinical Practice Guidelines *Ann Oncol* 31 12 2020 1650 1663 32801018 10.1016/j.annonc.2020.07.019 100 Franzoi M.A. Hortobagyi G.N. Leptomeningeal carcinomatosis in patients with breast cancer *Crit Rev Oncol Hematol* 135 2019 85 94 30819451 10.1016/j.critrevonc.2019.01.020 101 Le Rhun E. Weller M. Brandsma D. EANO-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up of patients with leptomeningeal metastasis from solid tumours *Ann Oncol* 28 suppl 4 2017 iv84 iv99 28881917 10.1093/annonc/mdx221 102 Le Rhun E. Preusser M. van den Bent M. How we treat patients with leptomeningeal metastases *ESMO Open* 4 suppl 2 2019 e000507 31231573 10.1136/esmoopen-2019-000507 PMC6555600 103 Roila F. Molassiotis A. Herrstedt J. 2016 MASCC and ESMO guideline update for the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting and of nausea and vomiting in advanced cancer patients *Ann Oncol* 27 suppl 5 2016 v119 v133 27664248 10.1093/annonc/mdw270 104 Cardoso F. Costa A. Norton L. 1st International consensus guidelines for advanced breast cancer (ABC 1) *Breast* 21 3 2012 242 252 22425534 10.1016/j.breast.2012.03.003 105 Knaul F.M. Farmer P.E. Krakauer E.L. Alleviating the access abyss in palliative care and pain relief—an imperative of universal health coverage: the Lancet Commission report *Lancet* 391 10128 2018 1391 1454 29032993 10.1016/S0140-6736(17)32513-8 106 Fallon M. Giusti R. Aielli F. Management of cancer pain in adult patients: ESMO Clinical Practice Guidelines *Ann Oncol* 29 suppl 4 2018 iv166 iv191 30052758 10.1093/annonc/mdy152 107 Jones M.R. Viswanath O. Peck J. A brief history of the opioid epidemic and strategies for pain medicine *Pain Ther* 7 1 2018 13 21 29691801 10.1007/s40122-018-0097-6 PMC5993682 108 Page R. Blanchard E. Opioids and cancer pain: patients' needs and access challenges *J Oncol Pract* 15 5 2019 229 231 31013181 10.1200/JOP.19.00081 109 Cannabis and cannabinoids *Med Lett Drugs Ther* 61 1585 2019 179 182 31770357 110 Alves P. Amaral C. Teixeira N. Cannabis sativa: much more beyond $\Delta(9)$ -tetrahydrocannabinol *Pharmacol Res* 157 2020 104822 32335286 10.1016/j.phrs.2020.104822 111 Holmberg L. Iversen O.E. Rudenstam C.M. Increased risk of recurrence after hormone replacement therapy in breast cancer survivors *J Natl Cancer Inst* 100 7

2008 475 482 18364505 10.1093/jnci/djn058 112 Fahlén M. Fornander T. Johansson H. Hormone replacement therapy after breast cancer: 10 year follow up of the Stockholm randomised trial *Eur J Cancer* 49 1 2013 52 59 22892060 10.1016/j.ejca.2012.07.003 113 Duijts S.F. van Beurden M. Oldenburg H.S. Efficacy of cognitive behavioral therapy and physical exercise in alleviating treatment-induced menopausal symptoms in patients with breast cancer: results of a randomized, controlled, multicenter trial *J Clin Oncol* 30 33 2012 4124 4133 23045575 10.1200/JCO.2012.41.8525 114 Mann E. Smith M.J. Hellier J. Cognitive behavioural treatment for women who have menopausal symptoms after breast cancer treatment (MENOS 1): a randomised controlled trial *Lancet Oncol* 13 3 2012 309 318 22340966 10.1016/S1470-2045(11)70364-3 PMC3314999 115 Stefanopoulou E. Grunfeld E.A. Mind-body interventions for vasomotor symptoms in healthy menopausal women and breast cancer survivors. A systematic review *J Psychosom Obstet Gynaecol* 38 3 2017 210 225 27832718 10.1080/0167482X.2016.1235147 116 Lahart I.M. Metsios G.S. Nevill A.M. Physical activity for women with breast cancer after adjuvant therapy *Cochrane Database Syst Rev* 1 1 2018 Cd011292 29376559 10.1002/14651858.CD011292.pub2 PMC6491330 117 Hartman S.J. Nelson S.H. Myers E. Randomized controlled trial of increasing physical activity on objectively measured and self-reported cognitive functioning among breast cancer survivors: the memory & motion study *Cancer* 124 1 2018 192 202 28926676 10.1002/cncr.30987 PMC5735009 118 Ramaswami R. Villarreal M.D. Pitta D.M. Venlafaxine in management of hot flashes in women with breast cancer: a systematic review and meta-analysis *Breast Cancer Res Treat* 152 2 2015 231 237 26067931 10.1007/s10549-015-3465-5 119 Johns C. Seav S.M. Dominick S.A. Informing hot flash treatment decisions for breast cancer survivors: a systematic review of randomized trials comparing active interventions *Breast Cancer Res Treat* 156 3 2016 415 426 27015968 10.1007/s10549-016-3765-4 PMC4838539 120 Shan D. Zou L. Liu X. Efficacy and safety of gabapentin and pregabalin in patients with vasomotor symptoms: a systematic review and meta-analysis *Am J Obstet Gynecol* 222 6 2020 564 579.e12 31870736 10.1016/j.ajog.2019.12.011 121 Leon-Ferre R.A. Novotny P.J. Wolfe E.G. Oxybutynin vs placebo for hot flashes in women with or without breast cancer: a randomized, double-blind clinical trial (ACCRU SC-1603) *JNCI Cancer Spectr* 4 1 2020 pkz088 32337497 10.1093/jncics/pkz088 PMC7050158 122 Chen W.Y. Giobbie-Hurder A. Gantman K. A randomized, placebo-controlled trial of melatonin on breast cancer survivors: impact on sleep, mood, and hot flashes *Breast Cancer Res Treat* 145 2 2014 381 388 24718775 10.1007/s10549-014-2944-4 PMC4060962 123 Innominato P.F. Lim A.S. Palesh O. The effect of melatonin on sleep and quality of life in patients with advanced breast cancer *Support Care Cancer* 24 3 2016 1097 1105 26260726 10.1007/s00520-015-2883-6 124 Mayer S. Iborra S. Grimm D. Sexual activity and quality of life in patients after treatment for breast and ovarian cancer *Arch Gynecol Obstet* 299 1 2019 191 201 30386993 10.1007/s00404-018-4922-2 125 Stute P. Is vaginal hyaluronic acid as effective as vaginal estriol for vaginal dryness relief? *Arch Gynecol Obstet* 288 6 2013 1199 1201 24178484 10.1007/s00404-013-3068-5 126 Serati M. Bogani G. Di Dedda M.C. A comparison between vaginal estrogen and vaginal hyaluronic for the treatment of dyspareunia in women using hormonal contraceptive *Eur J Obstet Gynecol Reprod Biol* 191 2015 48 50 26070127 10.1016/j.ejogrb.2015.05.026 127 Origoni M. Cimmino C. Carminati G. Postmenopausal vulvovaginal atrophy (VVA) is positively improved by topical hyaluronic acid application. A prospective, observational study *Eur Rev Med Pharmacol Sci* 20 20 2016 4190 4195 27831658 128 Donders G. Bellen G. Neven P. Effect of ultra-low-dose estriol and lactobacilli vaginal tablets (Gynoflor®) on inflammatory and infectious markers of the vaginal ecosystem in postmenopausal women with breast cancer on aromatase inhibitors *Eur J Clin Microbiol Infect Dis* 34 10 2015 2023 2028 26223323 10.1007/s10096-015-2447-1 PMC4565868 129 Buchholz S. Mögele M. Lintermans A. Vaginal estriol-lactobacilli combination and quality of life in endocrine-treated breast cancer *Climacteric* 18 2 2015 252 259 25427450 10.3109/13697137.2014.991301 130 Mazzarello S. Hutton B. Ibrahim M.F.K. Management of urogenital atrophy in breast cancer patients: a systematic review of available evidence from randomized trials *Breast Cancer Res Treat* 152 1 2015 1 8 26003182 10.1007/s10549-015-3434-z 131 Caruso S. Cianci S. Amore F.F. Quality of life and sexual function of naturally postmenopausal women on an ultralow-concentration estriol vaginal gel *Menopause* 23 1 2016 47 54 26079974 10.1097/GME.0000000000000485 132 American College of Obstetricians and Gynecologists' Committee on Gynecologic Practice Farrell R. ACOG Committee opinion no. 659: the use of vaginal estrogen in women with a history of estrogen-dependent breast cancer *Obstet Gynecol* 127 3 2016 e93 e96 26901334

10.1097/AOG.0000000000001351 133 Melisko M.E. Goldman M.E. Hwang J. Vaginal testosterone cream vs estradiol vaginal ring for vaginal dryness or decreased libido in women receiving aromatase inhibitors for early-stage breast cancer: a randomized clinical trial JAMA Oncol 3 3 2017 313 319 27832260 10.1001/jamaoncol.2016.3904 134 Hersant B. SidAhmed-Mezi M. Belkacemi Y. Efficacy of injecting platelet concentrate combined with hyaluronic acid for the treatment of vulvovaginal atrophy in postmenopausal women with history of breast cancer: a phase 2 pilot study Menopause 25 10 2018 1124 1130 29738415 10.1097/GME.0000000000001122 135 Romero-Otero J. Lauterbach R. Aversa A. Laser-based devices for female genitourinary indications: position statements from the European Society for Sexual Medicine (ESSM) J Sex Med 17 5 2020 841 848 32201147 10.1016/j.jsxm.2020.02.013 136 Bartula I. Sherman K.A. The Female Sexual Functioning Index (FSFI): evaluation of acceptability, reliability, and validity in women with breast cancer Support Care Cancer 23 9 2015 2633 2641 25669965 10.1007/s00520-015-2623-y 137 Mancha R.G. Muñoz M. de la Cruz-Merino L. Development and validation of a sexual relations satisfaction scale in patients with breast cancer - "SEXSAT-Q" Health Qual Life Outcomes 17 1 2019 143 31420041 10.1186/s12955-019-1197-7 PMC6698031 138 Reese J.B. Sorice K.A. Zimmaro L.A. Communication about sexual health in breast cancer: what can we learn from patients' self-report and clinic dialogue? Patient Educ Couns 103 9 2020 1821 1829 32349896 10.1016/j.pec.2020.03.029 PMC7423724 139 Dai Y. Cook O.Y. Yeganeh L. Patient-reported barriers and facilitators to seeking and accessing support in gynecologic and breast cancer survivors with sexual problems: a systematic review of qualitative and quantitative studies J Sex Med 17 7 2020 1326 1358 32331967 10.1016/j.jsxm.2020.03.004 140 Atkins L. Fallowfield L.J. Fallowfield's sexual activity questionnaire in women with without and at risk of cancer Menopause Int 13 3 2007 103 109 17785035 10.1258/175404507781605578 141 Gompel A. Ramirez I. Bitzer J. Contraception in cancer survivors - an expert review Part I. Breast and gynaecological cancers Eur J Contracept Reprod Health Care 24 3 2019 167 174 31033361 10.1080/13625187.2019.1602721 142 ABC Global Alliance ABC Global Charter 2018. ABC Global Alliance Available at <https://www.abcgloballiance.org/wp-content/uploads/2018/06/ABC-Global-Charter-Booklet-June-2018-Final.pdf> Supplementary data Supplementary File

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