



SEOM-GEICAM-SOLTI clinical guidelines in advanced breast cancer (UPDATE 2025)

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Received: 5 October 2025 / Accepted: 7 October 2025 / Published online: 3 November 2025
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Abstract

Advanced breast cancer represents a challenge for patients and physicians due to its dynamic genomic changes, which are associated with resistance to treatments. The main goals of treatment in advanced breast cancer are to improve patient quality of life and to increase patient survival. This is achieved using the most appropriate sequence of treatments based on knowledge of the natural history of the disease. In these guidelines (updated in 2025), we summarize current evidence and available therapies for the medical management of advanced breast cancer.

Keywords Advanced breast cancer · Anti-HER2 therapy · Endocrine therapy · Guidelines · Metastatic breast cancer

Introduction

Breast cancer is a major public health issue, both due to high incidence and prevalence and to substantial morbidity and mortality [1]. Although breast cancer is one of the most

treatment-sensitive solid tumors, advanced breast cancer (ABC) is very rarely curable. Treatment for ABC is therefore usually palliative, with the main aims being to improve the patient's quality of life (QoL) and to prolong survival [2].

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As understanding of tumor biology has increased, researchers are increasingly focused on identifying more specific and better-tolerated therapies. The resulting emergence of new endocrine and cytotoxic targeted therapies, along with improved regimens, has changed the natural history of ABC [3].

The aim of the guidelines presented in this article is to summarize current evidence and provide evidence-based recommendations for the management of ABC in clinical practice. As the regulatory status of new drugs is subject to change, all therapies for which robust evidence of activity has been demonstrated in clinical trials are included, regardless of the Spanish approval status at the time of publication.

Methodology

These Spanish Society of Medical Oncology (Sociedad Española de Oncología Médica; SEOM) guidelines have been developed based on the consensus of ten medical oncologists specializing in breast cancer who are part of the Spanish Breast Cancer Research Group (Grupo Español de Investigación en Cáncer de Mama; GEICAM) and the Spanish Collaborative Group for the Study, Treatment and Other Experimental Strategies in Solid Tumors (Grupo Español de Estudio, Tratamiento y Otras Estrategias Experimentales en Tumores Sólidos; SOLTI) cooperative groups. The Infectious Diseases Society of America-United States (US) Public Health Service Grading System for Ranking Recommendations in Clinical Guidelines was used to assign the level of evidence and the grade of recommendation to each of the consensus statements in this treatment guideline (Table 1) [4].

The recommendations in these guidelines have been updated to reflect the results of clinical trials released since publication of the previous guidelines [5] and the current standard of care. The updated recommendations are provided in Table 2, and the changes made versus the recommendations in the previous version of the guidelines are shown in Table 3.

Pathology and molecular biology

At the time of a first diagnosis of ABC (newly diagnosed or relapsed), a tumor biopsy is necessary to determine estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) status [6] [I, A].

HER2-low breast cancers (defined as immunohistochemically 1 + or 2 + and lack of *HER2* gene amplification measured by in situ hybridization) should be identified, as they may derive benefit from targeted therapies.

In patients with metastatic triple-negative breast cancer (TNBC), programmed death-ligand 1 (PD-L1) status should be determined [I, A] by immunohistochemistry, to decide if therapy with immune checkpoint inhibitors should be incorporated into first-line treatment [7].

In HER2-negative ABC, germline *BRCA1/2* mutation (gBRCAm) status should be determined [I, A], as treatment with poly-ADP ribose polymerase (PARP) inhibitors could be indicated [8]. Somatic sequencing [II, A] cannot substitute gBRCAm testing [9].

In ER- and/or PR-positive HER2-negative ABC patients, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (*PIK3CA*) mutations should be assessed [I, A], so that the use of *PIK3CA* inhibitors can be considered [10]. Beyond *PIK3CA* mutations, other genetic alterations that

Table 1 Strength of recommendation and quality of evidence score [4]

Category, grade	Definition
<i>Strength of recommendation</i>	
A	Strong evidence for efficacy with a substantial clinical benefit; strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit; generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc.); optional
D	Moderate evidence against efficacy or for adverse outcome; generally not recommended
E	Strong evidence against efficacy or for adverse outcome; never recommended
<i>Quality of evidence</i>	
I	Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity
II	Evidence from small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Evidence from prospective cohort studies
IV	Evidence from retrospective cohort studies or case–control studies
V	Evidence from studies without control group, case reports, or expert opinions

Table 2 SEOM clinical practice guidelines for advanced breast cancer (2025): summary of recommendations

Recommendation	Category, grade
Diagnosis and initial work-up	
<i>Pathology and molecular biology</i>	
At the time of ABC diagnosis (newly diagnosed or relapsed disease), a tumor biopsy should be taken for immunohistochemical determination of ER, PR, and HER2 status	I, A
In cases of metastatic triple-negative breast cancer, PD-L1 status should be determined by immunohistochemistry, to guide the appropriateness of immune checkpoint inhibitors as part of first-line treatment	I, A
In HER2-negative ABC, gBRCAm status should be determined to clarify the appropriateness of PARP inhibitor therapy	I, A
Somatic sequencing cannot substitute for gBRCAm testing	II, A
In ER- and/or PR-positive HER2-negative ABC, <i>PIK3CA</i> mutations should be assessed to guide use of <i>PIK3CA</i> inhibitors	I, A
Other genetic alterations that can activate the PI3K/AKT pathway, such as mutations of <i>AKT1</i> or <i>PTEN</i> , should be considered	I, B
<i>ESR1</i> status should be assessed	I, A
HER2-ultralow category (immunohistochemistry score > 0 but < 1 +) may be evaluated in ER-positive ABC that shows minimal HER2 protein expression	I, B
Assessment of MSI-high status could be considered if therapy with pembrolizumab is available	I, C
Assessment of NTRK fusions/translocations may be performed since their presence is associated with high efficacy of NTRK inhibitors, irrespective of primary tumor type	I, C
Next-generation sequencing and circulating tumor DNA genomic profiling tests could be considered	III, B
<i>Other methods of disease assessment</i>	
Staging of metastatic disease should include thoracic and abdominal CT and a bone scan	II, A
¹⁸ F-FDG-PET-CT may be used instead of CT and bone scan	II, B
While tumor marker assessment may be useful, changes in treatment lines should not be based solely on increases in these markers	II, C
Central nervous system screening in asymptomatic patients is not routinely recommended	V, C
A biopsy of new metastatic disease or recurrence should be performed whenever possible, since there may be discordance in ER, PR and HER2 status between the primary tumor and metastatic tumors	II, A
HR-positive/HER2-negative ABC	
Sequential ETs, as monotherapy or combined with targeted therapies, are the preferred choice as initial treatment for HR-positive/HER2-negative ABC	I, A
Pre- and perimenopausal women should undergo ovarian function suppression or ablation, and be treated as postmenopausal women	I, A
Concomitant chemotherapy and ET is not recommended	II, D
<i>First-line treatment</i>	
ET in combination with CDK4/6i is standard-of-care for first- or second-line treatment of HR-positive/HER2-negative ABC	I, A
CDK4/6i treatment should be initiated as soon as possible after diagnosis	II, C
ET monotherapy should be reserved for patients with comorbidities preventing the use of a CDK4/6i, in which case, both AIs and fulvestrant are suitable options	I, A
The combination of ET with CDK4/6i can be considered after clinical stabilization or chemotherapy discontinuation	III, D
<i>Second-line treatment</i>	
In patients progressing on AI or within the first year after completion of adjuvant ET, treatment with CDK4/6i and fulvestrant is recommended	I, A
It is reasonable to assess <i>ESR1</i> mutation status to help guide the choice of second-line ET	II, B
It is also reasonable to assess activation of the PI3K-AKT pathway to guide the choice of second-line ET	I, A
Alpelisib is approved by the European Medicines Agency for patients progressing on ET monotherapy	I, B
Everolimus in combination with AI or fulvestrant is also an option, although the PFS benefit of this combination could have been overestimated (due to the large amount of censored data in the clinical trials)	I, B
In cases of acquired <i>ESR1</i> mutations during first-line treatment with AI plus a CDK4/6i, elacestrant monotherapy has demonstrated superiority over fulvestrant monotherapy and, therefore, represents an appropriate second-line ET option in this population	I, A
<i>Chemotherapy</i>	
Chemotherapy remains a cornerstone in the treatment of advanced HR-positive/HER2-negative breast cancer when ET options have been exhausted	I, A
Sequential chemotherapy monotherapies are generally preferred; however, in selected cases, particularly where there is a high tumor burden or when a rapid response is needed, combination treatment may be indicated	II, A

Table 2 (continued)

Recommendation	Category, grade
Taxanes and anthracyclines should be considered in patients who have not received them in the neo/adjuvant setting	I, A
<i>Antibody–drug conjugates</i>	
Trastuzumab deruxtecan (T-DXd) has emerged as the most effective option for patients with ET-exhausted tumors, both as an immediate first-line treatment in HR-positive/HER2-low or HER2-ultralow tumors, and as a second-line option in HER2-low disease	I, A
<i>PARP inhibitors</i>	
In patients with HR-positive/HER2-negative tumors harboring gBRCAm, a PARP inhibitor should be considered after first-line ET plus CDK4/6i	I, C
<i>HR-negative/HER2-negative ABC</i>	
Patients with PD-L1–positive tumors may benefit, in particular, from checkpoint inhibitor-based combinations and, therefore, PD-L1 status should be tested before first-line treatment is initiated	I, A
Patients with metastatic TNBC who may be considered for PARP inhibitor treatment should undergo testing for germline <i>BRCA1</i> and <i>BRCA2</i> pathogenic or likely pathogenic mutations	I, B
Other biomarkers, such as tumor mutational burden, deficient-mismatch repair/microsatellite instability-high and NTRK fusions, could be tested for in patients who are candidates for pembrolizumab or TRK inhibitors, respectively	III, B
<i>First-line treatment</i>	
<i>PD-L1-positive metastatic TNBC</i>	
Due to conflicting clinical trial results, use of atezolizumab in combination with chemotherapy as first-line treatment for PD-L1–positive TNBC is limited	II, A
Pembrolizumab, in combination with chemotherapy, is considered standard-of-care as first-line treatment for PD-L1–positive TNBC	I, A
<i>PD-L1-negative germline BRCA wild-type metastatic TNBC</i>	
Sequential use of single-agent chemotherapy is the preferred approach, with combination therapies reserved for patients with aggressive, symptomatic, or life-threatening disease	I, A
Chemotherapy (with the exception of conventional anthracyclines) should be administered until disease progression or unacceptable toxicity	I, B
In chemotherapy-naïve patients, taxanes or anthracyclines are the preferred first-line treatment	I, A
Docetaxel should be also considered an option irrespective of gBRCAm status and previous exposure to anthracyclines and/or taxanes	I, A
Bevacizumab (combined with taxanes or capecitabine) may be considered for patients with visceral crisis or high symptomatic disease	I, C
Maintenance therapy with bevacizumab plus capecitabine after induction first-line treatment with bevacizumab plus docetaxel may be considered for selected cases	I, C
<i>Second-line and subsequent treatment</i>	
Capecitabine, eribulin, carboplatin, gemcitabine, and vinorelbine monotherapies are options in patients pretreated with anthracyclines and taxanes	I, A
Sacituzumab govitecan should be considered the preferred treatment after anthracyclines and taxanes	I, A
T-DXd may also be an option in this setting	I, B
<i>HER2-positive ABC</i>	
For patients with metastatic HER2-positive breast cancer, anti-HER2-directed therapy should be included in the treatment regimen	I, A
<i>First-line therapy</i>	
<i>Newly diagnosed metastatic disease</i>	
Trastuzumab and pertuzumab in combination with taxanes is associated with improvement in PFS, ORR, and OS versus chemotherapy alone	I, A
Vinorelbine, instead of taxanes, can be offered to patients with contraindications to taxanes	III, C
In postmenopausal patients with HR-positive/HER2-positive tumors, the combination of AIs and an anti-HER2 agent (trastuzumab or lapatinib) should be limited to low-risk or unfit patients	II, B
<i>Disease relapse after neo/adjuvant treatment</i>	
For patients who progress during or within 6 months of adjuvant treatment, T-DXd is the preferred option	I, A
For patients who progress ≥ 6 months after the completion of adjuvant therapy, the most accepted recommendation is trastuzumab plus pertuzumab in combination with a taxane, rather than other agents	I, A
<i>Second-line therapy</i>	

Table 2 (continued)

Recommendation	Category, grade
Evidence suggests there is benefit in continuing with second-line anti-HER2 therapy after progression during or following first-line treatment with trastuzumab	I, A
T-DXd is the preferred second-line option for patients who experience disease progression following a trastuzumab-containing regimen	I, A
<i>Third-line and further therapy</i>	
Patients who have been treated with two or more lines of anti-HER2 therapy may benefit from a third or further line of such treatment	I, A
Tucatinib-trastuzumab-capecitabine may be a good option for patients previously treated with T-DM1 and/or T-DXd	II, B
Lapatinib plus trastuzumab may be useful in patients progressing on trastuzumab, particularly those with HR-negative disease	II, B
For patients who experience disease progression following a trastuzumab-containing regimen in the metastatic setting, options include T-DXd (preferred regimen), T-DM1, continuation of trastuzumab with a different chemotherapy partner, tucatinib-trastuzumab-capecitabine or a tyrosine kinase-based combination, and anti-HER2 agents plus ET in HR-positive/HER2-positive breast cancer	I, B
The optimal number of lines of anti-HER2 therapy for metastatic breast cancer is currently unknown, although available data suggest benefits are maintained in the third line and beyond	II, B
<i>Genetic testing and BRCA-associated disease</i>	
Germline testing indications include patients with metastatic HER2-negative disease who had previously been treated with an anthracycline and a taxane in the (neo)adjuvant or metastatic setting	I, A
Somatic testing indications include patients with metastatic HER2-negative disease who had previously been treated with an anthracycline and a taxane in the (neo)adjuvant or metastatic setting	II, A
Patients with HR-positive ABC who have experienced disease progression during or after one prior line of ET and who are no longer candidates for further ET, due to endocrine resistance or exhaustion, should be considered for palliative chemotherapy	I, A
In platinum-naïve patients with gBRCAm TNBC, platinum chemotherapy should be preferred to taxanes	I, A
Patients with HR-positive gBRCAm advanced disease should receive first-line ET with CDK4/6i and consider PARP inhibitor beyond progression	I, A
<i>CNS metastases</i>	
Routine CNS disease screening is not recommended in the absence of signs/symptoms	III, C
<i>Local therapy</i>	
Surgical resection remains the first option in patients with single or limited brain metastases, to relieve intracranial pressure or to assist with histology/biomarkers/molecular profiling	II, A
Stereotactic radiosurgery is now the primary treatment for patients with single or limited brain metastasis (≤ 10 lesions)	I, A
Whole brain radiation therapy may be considered for patients with > 10 metastases and poor performance status	II, B
Hippocampus-sparing radiation therapy is a preferred strategy to decrease neurocognitive impairment	II, B
<i>Systemic therapy in HER2-positive patients</i>	
In patients with new brain metastases and controlled systemic disease, local therapy with the same anti-HER2 regimen can be considered	II, B
In patients with new brain metastases who have progressive systemic disease, HER2-targeted therapy should be provided according to the algorithms for treatment of HER2-positive ABC	I, B
Tucatinib-trastuzumab-capecitabine is the preferred regimen, particularly among patients with oligosymptomatic and limited disease, and for patients who prefer to defer radiation	II, B
T-DXd may also be considered, particularly if systemic progression is a clinical issue	II, C
<i>Systemic therapy in HER2-negative patients</i>	
Classical chemotherapy agents (such as capecitabine, methotrexate, carboplatin, etoposide, vinorelbine, and gemcitabine) have shown limited therapeutic benefit	II, B
Bevacizumab can improve CNS response and may be an option, particularly in TNBC	III, C
Abemaciclib and ribociclib penetrate the blood–brain barrier and have shown intracranial activity in small early trials	II, C
New agents, including immune checkpoint inhibitors, PARP inhibitors, and drug conjugates, are being evaluated in clinical trials for potential intracranial efficacy	III, C
<i>Oligometastatic breast cancer</i>	
Given the likelihood of limited tumor burden, patients may benefit from locoregional therapies, including surgical excision, radiofrequency, and stereotactic body radiotherapy	II, B
Selected patients may be offered a multimodal approach with curative intent, including local therapy to all known metastases, if it can be safely accomplished and a multidisciplinary team is involved	III, C

Table 2 (continued)

Recommendation	Category, grade
<i>Male breast cancer</i>	
AIs (concurrently to gonadotropin-releasing hormone analogs or orchidectomy) or fulvestrant are recommended as front-line, except in cases of visceral crisis or rapidly progressive disease	III, B
The management of other subtypes or late lines of advanced disease should follow that of female patients (PIK3CA or mTOR inhibitors, HER2-targeted therapy, immunotherapy, and PARP inhibitors)	III, B
<i>Supportive and palliative care</i>	
In addition to receiving the best antineoplastic treatment along with the appropriate measures to avoid therapy-associated toxicity, patients should be offered optimal symptom control, and psychological, social, and spiritual support	[II, A]

ABC advanced breast cancer, *AIs* aromatase inhibitors, *ATK* activating receptor tyrosine kinases, *ATK1* AKT serine/threonine kinase 1, *CDK4/6i* cyclin-dependent kinase 4/6 inhibitors, *CT* computed tomography, *ER* estrogen receptor, *ESR1* estrogen receptor 1, *ET* endocrine therapy, ¹⁸*F-FDG* 2-deoxy-2-[fluorine-18] fluoro-D-glucose, *gBRCAm* germline *BRCA1/2* mutation, *HER2* human epidermal growth factor receptor 2, *HR* hormone receptor, *MSI* microsatellite instability, *mTOR* mammalian target of rapamycin, *NTRK* neurotrophic tyrosine receptor kinase, *ORR* objective response rate, *OS* overall survival, *PARP* poly-ADP ribose polymerase, *PD-L1* programmed death-ligand 1, *PET* positron emission tomography, *PFS* progression-free survival, *PIK3CA* phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha, *PI3K* phosphoinositide 3-kinase, *PR* progesterone receptor, *PTEN* phosphatase and tensin homolog, *T-DM1* trastuzumab emtansine, *T-DXd* trastuzumab derux-*tecan*, *TNBC* triple-negative breast cancer

can activate the phosphoinositide 3-kinase (PI3K)/activating receptor tyrosine kinases (AKT) pathway, such as those of AKT serine/threonine kinase 1 (*AKT1*) or phosphatase and tensin homolog (*PTEN*) genes, should be considered [11] [I, B]. In addition, estrogen receptor 1 (*ESR1*) gene status should be assessed, so that the use of an oral selective estrogen receptor degrader (SERD) can be considered [12] [I, A].

HER2-ultralow category may be evaluated in ER-positive ABC that shows minimal HER2 protein expression [13] [I, B]. This category is specifically defined by an immunohistochemistry score > 0 but < 1 + [14]. Tumors in this category exhibit faint or barely perceptible HER2 expression, which remains below the threshold typically used to classify HER2-low tumors.

Assessment of microsatellite instability (MSI-high), an infrequent biomarker [15] [I, C] could be considered if therapy with pembrolizumab is available. Other infrequently assessed biomarkers that might also be tested are the neurotrophic tyrosine receptor kinase (NTRK) fusions/translocations [16] [I, C], since their presence is associated with high efficacy of NTRK inhibitors, irrespective of the type of primary tumor (agnostic indication) [17].

Next-generation sequencing (NGS) and circulating tumor DNA (ctDNA) genomic profiling tests could be considered to assist in identifying actionable alterations, such as *PIK3CA*, *ESR1*, *BRCA1/2*, and *HER2* mutations, MSI-high status, elevated tumor mutational burden, and NTRK fusions/translocations [18] [III, B].

General statement: image and disease assessment guidelines

Systemic therapy is the standard-of-care for ABC, but locoregional therapies may be included if clinically indicated for optimal management; referral to the supportive care team should be also considered as soon as possible [19]. In elderly patients, a comprehensive geriatric assessment is highly recommended [20]. Genetic counseling and cardio-oncology evaluation should also be considered as part of the multidisciplinary approach for patients with ABC [21, 22].

Staging of metastatic disease should include thoracic and abdominal computed tomography (CT) and a bone scan [23] [II, A]. 2-Deoxy-2-[fluorine-18] fluoro-D-glucose (¹⁸F-FDG) positron emission tomography (PET)-CT may be used instead of CT and bone scan [24] [II, B].

Tumor marker assessment may be useful, but changes in treatment lines should not be performed solely on findings of increases in these markers [II, C].

Central nervous system (CNS) screening in asymptomatic patients is not routinely recommended [23] [V, C].

A biopsy of new metastatic disease or recurrence should be performed whenever possible, since discordance in ER, PR, and HER2 status between the primary tumor and metastatic tumors may occur [25] [II, A].

HR-positive/HER2-negative ABC

General statements

Sequential endocrine therapies (ET), as monotherapy or combined with targeted therapies, are the preferred choice

Table 3 Summary of changes made in the 2025 guidelines

2022 recommendation	New or changed 2025 recommendation
<i>Methodology</i> (Table 1)	
Strength of recommendation A–E; Quality of evidence graded I–III	The definitions of the strength of recommendation and quality evidence have been reworded, and two further lower levels of quality of evidence (IV [evidence from retrospective cohort studies or case–control studies] and V [evidence from studies without control group, case reports, or expert opinions]) have been added
<i>Pathology and molecular biology</i>	
N/A	Beyond <i>PIK3Ca</i> mutations, other genetic alterations that can activate the PI3K/AKT pathway, such as <i>AKT1</i> or <i>PTEN</i> genes, should be considered [I, B]
N/A	<i>ESR1</i> gene status should also be assessed so that the use of an oral SERD can be considered [I, A]
N/A	HER2-ultralow category may be evaluated in ER-positive ABC that shows minimal HER2 protein expression [I, B]. This category is specifically defined by an immunohistochemistry score > 0 but < 1 + . Tumors in this category exhibit faint or barely perceptible HER2 expression, which remains below the threshold typically used to classify HER2-low tumors
According to the ESCAT guidelines that include high number of level II alterations, tumor multigene NGS and ctDNA genomic profiling tests are still not routinely recommended, although they should be offered to MBC patients if it may change treatment or enable their inclusion in clinical trials [V, B]	NGS and ctDNA genomic profiling tests could be considered to assist in identifying actionable alterations, such as <i>PIK3CA</i> , <i>ESR1</i> , <i>BRCA1/2</i> , and <i>HER2</i> mutations, MSI-high status, elevated tumor mutational burden, and NTRK fusions/translocations [III, B]
<i>General statement: image and disease assessment guidelines</i>	
Biopsy of novel metastatic disease or recurrence should be performed whenever possible, since discordances in ER, PR and HER2-status between primary and metastatic tumors may occur [I, B]. In case of discordances, there are no specific recommendations on which of the results should be taken into account, but the use of endocrine therapy or anti-HER2 therapy should be considered if there has been an ER/PR or HER2 positive biopsy at any time [III, C]	A biopsy of new metastatic disease or recurrence should be performed whenever possible, since discordance in ER, PR, and HER2-status between the primary tumor and metastatic tumors may occur [II, A]
<i>HR-positive/HER2-negative ABC</i>	
<i>First-line treatment</i>	
Ribociclib or abemaciclib with fulvestrant may be an adequate option for first-line treatment [I, A], based on the MONALEESA-3 and MONARCH-2 studies [I, A]	Recommendation removed
The potential benefit of fulvestrant combined with CDK4/6i compared to AI was assessed in combination with palbociclib in the PARSI-FAL trial, in which fulvestrant–palbociclib failed to be superior, and also to be non-inferior in PFS compared to letrozole–palbociclib [II, C]	Recommendation removed
<i>Second-line treatment</i>	
N/A	It is reasonable to assess <i>ESR1</i> mutation status [II, B] or activation of the PI3K-AKT pathway [I, A] to help guide the choice of second-line ET
N/A	In cases of acquired <i>ESR1</i> mutations during first-line treatment with AI plus a CDK4/6i, elacestrant monotherapy has demonstrated superiority over fulvestrant monotherapy and, therefore, represents an appropriate second-line ET option in this population [I, A]
<i>Chemotherapy</i>	
N/A	Sequential chemotherapy monotherapies are generally preferred. However, in selected cases, particularly where there is a high tumor burden or when a rapid response is needed, combination treatment may be indicated [I, A]
N/A	Taxanes and anthracyclines should be considered in patients who have not received them in the neo/adjuvant setting [I, A]
<i>Bevacizumab</i>	

Table 3 (continued)

2022 recommendation	New or changed 2025 recommendation
Treatment with bevacizumab plus chemotherapy as the first chemotherapy line may be considered in selected patients due to PFS benefit, although a significant benefit in OS has not been demonstrated [I, C]	Recommendation removed
<i>Antibody–drug conjugates</i>	
N/A	T-DXd has emerged as the most effective option for patients with ET-exhausted tumors, both as an immediate first-line treatment in HR-positive/HER2-low or HER2-ultralow tumors, and as a second-line option in HER2-low disease [I, A]
<i>HR-negative/HER2-negative ABC</i>	
<i>First-line treatment; PD-L1–negative gBRCA wild-type metastatic TNBC</i>	
Taxanes or anthracyclines are the preferred first-line treatment in chemotherapy-naïve patients with late recurrences (> 1 year) after completing neo/adjuvant anthracyclines and/or taxanes [I, A]	Recommendation removed
<i>HER2-positive ABC</i>	
<i>First-line therapy; disease relapse after neo/adjuvant treatment</i>	
N/A	For patients who progress ≥ 6 months after the completion of adjuvant therapy, the most accepted recommendation is trastuzumab plus pertuzumab in combination with a taxane, rather than other agents [I, A]
<i>Third-line and further therapy</i>	
N/A	For patients who experience disease progression following a trastuzumab-containing regimen in the metastatic setting, options include T-DXd (preferred regimen), trastuzumab emtansine, continuation of trastuzumab with a different chemotherapy partner, tucatinib-trastuzumab-capecitabine, or a tyrosine kinase-based combination, and anti-HER2 agents plus ET in HR-positive/HER2-positive breast cancer [I, B]
<i>Genetic testing and BRCA-associated disease</i>	
N/A	Patients with HR-positive ABC who have experienced disease progression during or after one prior line of ET and who are no longer candidates for further ET, due to endocrine resistance or exhaustion, should be considered for palliative chemotherapy [I, A]
<i>CNS metastases</i>	
N/A	Routine CNS disease screening is not recommended currently in absence of signs/symptoms [III, C]
<i>Local therapy</i>	
SRS is generally preferred for patients with oligometastatic disease and for lesions not surgically accessible [I, A]. It may also be considered for patients with a higher number of brain metastasis after complete resection [II, A]. SRS has become an important strategy to improve local control with few side effects	SRS is now the primary treatment for patients with single or a limited number of brain metastasis (≤ 10 lesions) [I, A]. Postoperative SRS is an alternative to whole brain radiation therapy for patients who undergo resection of brain metastases, with a reduced risk of neurocognitive decline; however, preoperative SRS might be favored given the lower risks of radiation necrosis and leptomeningeal disease
Whole brain radiation therapy may be considered for patients with numerous brain metastases and poor performance status [II, B]; hippocampus avoidance are strategies to decrease neurocognitive impairment should be considered	Whole brain radiation therapy may be considered for patients with numerous brain metastases (> 10) and poor performance status [II, B]; hippocampus-sparing radiation therapy is a preferred strategy to decrease neurocognitive impairment [II, B]
<i>Systemic therapy in HER2-negative patients</i>	
New agents including immune checkpoint inhibitors, PARPi, and drug conjugates are being evaluated in clinical trials for potential intracranial efficacy	New agents including immune checkpoint inhibitors, PARPi, and drug conjugates are being evaluated in clinical trials for potential intracranial efficacy [III,C]
<i>Oligometastatic breast cancer</i>	

Table 3 (continued)

2022 recommendation	New or changed 2025 recommendation
The standard-of-care for oligometastatic disease in breast cancer is the use of systemic therapy, but given the likelihood of limited tumor burden, it may benefit from a radical approach with the addition of locoregional treatments to all sites of the disease for long-term disease control and eventually cure. Local treatment strategies include surgical excision, radiofrequency, and SBRT	The standard-of-care for oligometastatic disease in breast cancer is systemic therapy, but given the likelihood of limited tumor burden, patients may benefit from the use of locoregional therapies, including surgical excision, radiofrequency, and SBRT [II, B]
N/A	Selected patients may be offered a multimodal approach with curative intent, including local therapy to all known metastases, if it can be safely accomplished and a multidisciplinary team is involved [III, C]
<i>Supportive and palliative care</i>	
N/A	In addition to receiving the best antineoplastic treatment along with the appropriate measures to avoid therapy-associated toxicity, patients should be offered optimal symptom control, and psychological, social, and spiritual support [II, A]

ABC advanced breast cancer, AI aromatase inhibitor, AKT activating receptor tyrosine kinases, AKT1 AKT serine/threonine kinase 1, CDK4/6i cyclin-dependent kinase 4/6 inhibitor, CNS central nervous system, ctDNA circulating tumor DNA, ER estrogen receptor, ESCAT ESMO Scale for Clinical Actionability of molecular Targets, ESR1 estrogen receptor 1, ET endocrine therapy, gBRCA germline BRCA1/2, HER2 human epidermal growth factor receptor 2, HR hormone receptor, MBC metastatic breast cancer, MSI microsatellite instability, N/A not applicable (recommendation not provided in the previous version of the guidelines), NGS next-generation sequencing, NTRK neurotrophic tyrosine receptor kinase, OS overall survival, PARPi poly-ADP ribose polymerase inhibitors, PFS progression-free survival, PI3K phosphoinositide 3-kinase, PR progesterone receptor, PTEN phosphatase and tensin homolog, SERD selective estrogen receptor degrader, SBRT stereotactic body radiotherapy, SRS stereotactic radiosurgery, T-DXd trastuzumab deruxtecan

as initial treatment for hormone receptor (HR)-positive/HER2-negative ABC [I, A] (Fig. 1). Front-line chemotherapy should only be considered for visceral crisis (Fig. 2), defined as life-threatening disease at risk of imminent organ failure and for which a rapid response is needed [23]. Pre- and perimenopausal women should undergo ovarian function suppression or ablation and be treated as postmenopausal women [I, A].

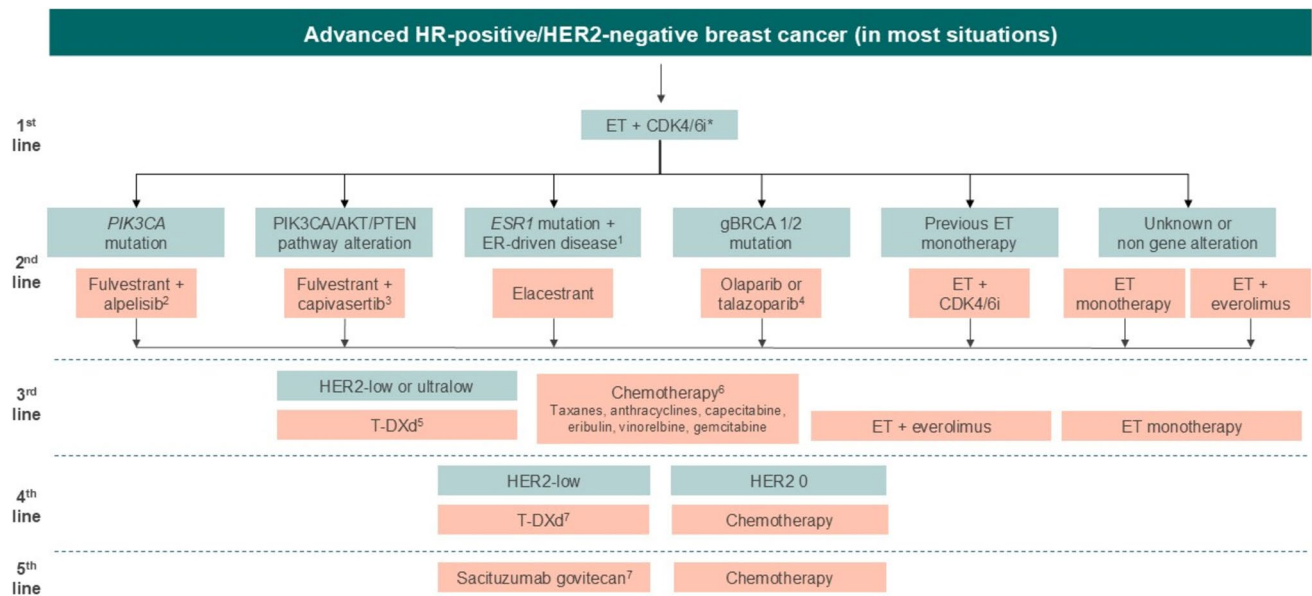
First-line treatment is considered for patients with no prior ET or for those who progress at least 12 months after completing adjuvant treatment (endocrine-sensitive scenario). Primary endocrine resistance, defined as recurrence within the first 2 years of adjuvant ET or progressing in the first 6 months of ET in the advanced setting, can occur [23]. Secondary resistance has been defined as disease recurrence after at least 2 years of adjuvant ET and within a year from its completion, or progression after at least 6 months of ET in the advanced setting [23].

First-line treatment

ET in combination with cyclin-dependent kinase (CDK)4/6 inhibitors (CDK4/6i) has become the standard-of-care for the first- or second-line treatment of HR-positive/HER2-negative ABC [I, A]. All three approved CDK4/6i (palbociclib, ribociclib, and abemaciclib) have demonstrated an improvement in progression-free survival (PFS) as first-line. Ribociclib was demonstrated to significantly improve overall survival (OS) in the first-line setting in the MONALEESA-2,

3, and 7 trials [26–28]: MONALEESA-7 was conducted exclusively in premenopausal women [27], while MONALEESA-3 also included hormone-resistant patients [28]. An OS benefit with abemaciclib was demonstrated in hormone-refractory patients in the MONARCH-2 trial [29], while palbociclib failed to show significant improvement in OS in patients with tumors sensitive or resistant to ET [30]. No randomized study has compared the different CDK4/6i, so indirect comparisons across trials should be cautiously considered, particularly because populations are not completely interchangeable. Although no trial has assessed the preference of first- versus second-line CDK4/6i treatment, the general recommendation is to use them as soon as possible after diagnosis [II, C].

ET monotherapy should be reserved for patients with comorbidities preventing the use of a CDK4/6i. In these patients, both aromatase inhibitors (AI) and fulvestrant are suitable options [I, A]. There is scarce evidence for maintenance therapy with CDK4/6i after chemotherapy and, thus, in general, maintenance therapy should be carried out with ET monotherapy [31]. Hence, it seems reasonable to consider this combination after clinical stabilization or chemotherapy discontinuation due to toxicity for the few cases (e.g., visceral crisis) in whom chemotherapy has been delivered first [III, D].



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Fig. 1 Treatment algorithm for advanced HR-positive/HER2-negative breast cancer in most situations. *Inavolisib in combination with palbociclib+ET has been approved by the US FDA, but not by the EMA, in first-line line for patients HR-positive/HER2-negative tumors with *PIK3CA*^{mut}. ¹ER-driven disease may be defined in patients achieving at least 12 months of progression-free survival with first-line ET+CDK4/6i. ²Currently approved for patients progressing after endocrine monotherapy. ³EMA approved but pending approval by health authorities in Spain. ⁴EMA approved but not approved by health authorities in Spain. ⁵Pending EMA approval. ⁶The preferred sequence of chemotherapies is currently unknown.

Second-line treatment

In patients progressing on AI or within the first year after completion of adjuvant ET, treatment with CDK4/6i and fulvestrant is recommended [28, 32] [I, A].

PIK3CA mutations are found in approximately 40% of patients with ABC, while additional activation of this signaling pathway may result from *AKT* mutations or *PTEN* loss of function [33]. In addition, approximately 40% of patients with HR-positive ABC who have been previously treated with AIs acquire *ESR1* mutations [34]. For this reason, it is reasonable to assess *ESR1* mutation status [II, B] or activation of the PI3K–AKT pathway [I, A] to help guide the choice of second-line ET.

For patients who experience disease progression during adjuvant ET and whose tumors harbor a *PIK3CA* mutation, the addition of inavolisib to first-line treatment with fulvestrant and palbociclib represents the most reasonable option,

Previous treatments, comorbidities, and patient's preferences should be taken into account. ⁷EMA approved. *AKT* AKT serine/threonine kinase, *CDK4/6i* cyclin-dependent kinase 4/6 inhibitor, *EMA* European Medicines Agency, *ER* estrogen receptor, *ESR1* estrogen receptor 1, *ET* endocrine therapy, *gBRCA* germline BRCA, *HER2* human epidermal growth factor receptor 2, *HR* hormone receptor, *PIK3CA* phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha, *PTEN* phosphatase and tensin homolog, *T-DXd* trastuzumab emtansine, *T-DXd* trastuzumab deruxetecan, *US FDA* United States Food and Drug Administration

in light of current evidence demonstrating improvements in PFS and OS [35]. In patients with tumors exhibiting activation of the PI3K–AKT signaling pathway who have progressed after first-line treatment with an AI with or without a CDK4/6i, the combination of capivasertib and fulvestrant has been shown to significantly improve PFS compared with fulvestrant alone, and should therefore be considered in this setting [36].

Alpelisib in combination with fulvestrant demonstrated an improvement in PFS in patients with *PIK3CA* mutations and a non-significant benefit in OS [10]; a very small proportion of these patients had received CDK4/6i. As a result, alpelisib is now approved by the European Medicines Agency (EMA) for patients progressing on ET monotherapy [37] [I, B]. Everolimus in combination with AI or fulvestrant is also an option for second-line treatment [38, 39] [I, B]. However, the PFS benefit of the latter could have been overestimated due to a high level of censored data in the clinical trials [I, B]. Of note, these

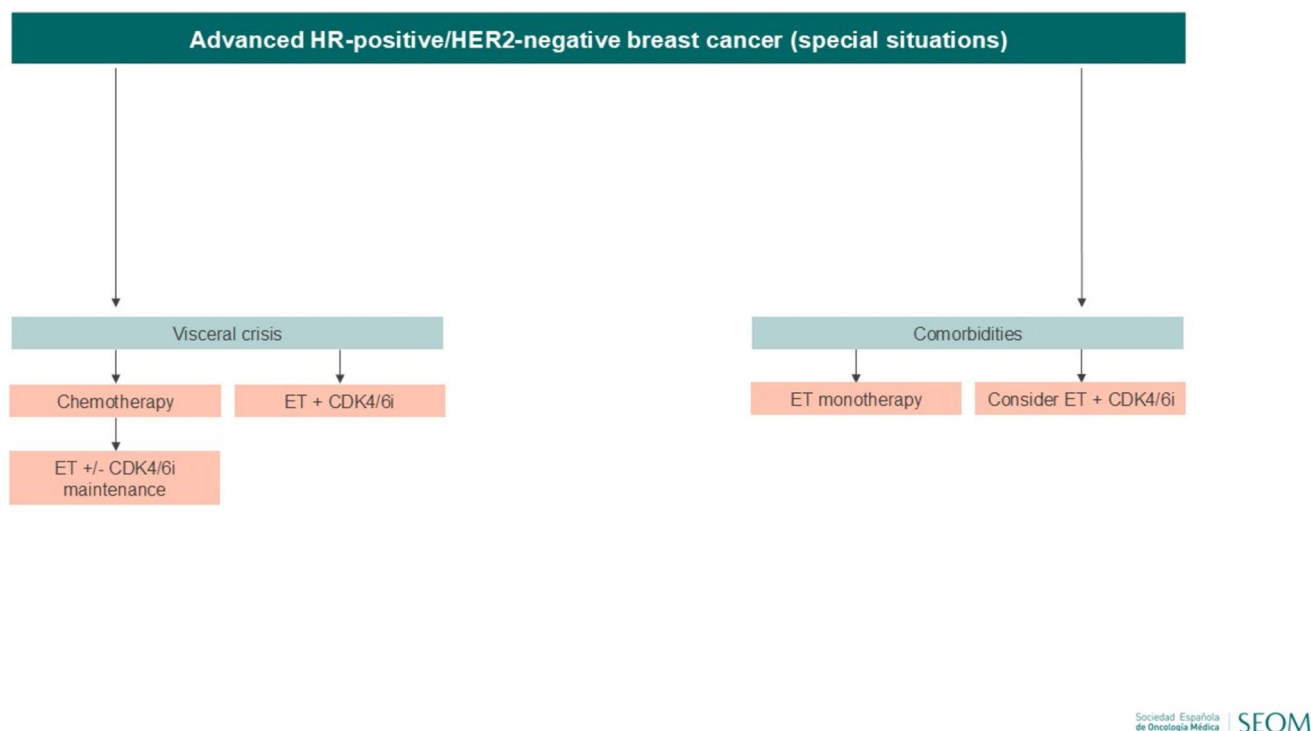


Fig. 2 Treatment algorithm for advanced HR-positive/HER2-negative breast cancer in special situations. *CDK4/6i* cyclin-dependent kinase 4/6 inhibitor, *ET* endocrine therapy, *HER2* human epidermal growth factor receptor 2, *HR* hormone receptor

two combinations were tested before the use of CDK4/6i, so efficacy data after CDK4/6i are limited.

In cases of acquired *ESR1* mutations during first-line treatment with AI plus a CDK4/6i, elacestrant monotherapy has demonstrated superiority over fulvestrant monotherapy and, therefore, represents an appropriate second-line ET option in this population [I, A]. The benefit of elacestrant appears to be more pronounced in patients who have shown prior sensitivity to first-line ET, typically defined as PFS greater than 12 months [40].

Chemotherapy

Chemotherapy remains a cornerstone in the treatment of HR-positive/HER2-negative ABC when ET options have been exhausted [I, A]. However, antibody–drug conjugates (ADCs) are beginning to displace chemotherapy, even being positioned as the preferred option following ET in certain clinical scenarios, which are described further below.

The selection of chemotherapy regimen is based on patient characteristics, previous treatments, expected toxicities, and patient preferences. Sequential chemotherapy monotherapies are generally preferred. However, in selected cases, particularly where there is a high tumor burden or when a rapid response is needed, combination treatment may be indicated [II, A]. Taxanes and anthracyclines should be

considered in patients who have not received them in the neo/adjuvant setting [I, A].

Capecitabine is an option frequently used in early ABC treatment lines due to its oral availability and favorable toxicity profile [41]; before starting such treatment, and to avoid severe, even lethal, toxicities, an assessment of a potential dihydropyrimidine dehydrogenase (DPD) deficiency by genotyping *DPYD* gene polymorphisms is recommended [38, 42].

Other chemotherapy agents useful in this metastatic setting are eribulin, vinorelbine, gemcitabine, carboplatin, and others. In this setting, eribulin has been shown to provide an OS benefit [42, 43].

Antibody–drug conjugates

Trastuzumab deruxtecan (T-DXd) has emerged as the most effective option for patients with ET-exhausted tumors, both as an immediate first-line treatment in HR-positive/HER2-low or HER2-ultralow tumors, and as a second-line option in HER2-low disease [I, A]. The use of T-DXd in the first- or second-line setting should be carefully considered by the physician and the patient, based on the individual characteristics of the disease [44, 45].

In addition, a phase 3 trial comparing sacituzumab govitecan versus therapy per physician's choice (TPC) in an

HR-positive/HER2-negative population as a late-line treatment showed a significant improvement in PFS and OS [46].

Datopotamab deruxtecan is another ADC that has also demonstrated efficacy in terms of PFS in this clinical setting [47].

PARP inhibitors

Both olaparib and talazoparib have shown superiority in terms of PFS to single-agent TPC in phase 3 studies that included patients with HER2-negative tumors harboring gBRCAm [48, 49]. Benefit was observed irrespective of HR status. However, another study found that talazoparib did not significantly improve OS compared with chemotherapy in patients with gBRCA1/2-mutated HER2-negative disease [50]. In the HR-positive setting, for this specific population, treatment with a PARP inhibitor should be considered after first-line ET plus CDK4/6i [I, C].

HR-negative/HER2-negative ABC

TNBC is clinically defined by the lack of ER, PR and HER2 expression. It accounts for nearly 15% of all breast

cancers and is associated with worse prognosis than other subtypes [48, 51].

Patients with PD-L1-positive tumors may benefit more from checkpoint inhibitor-based combinations than patients with other tumor types and, therefore, PD-L1 should be tested before first-line treatment is initiated [I, A]. Patients with metastatic TNBC who may be considered for treatment with a PARP inhibitor should undergo testing for germline *BRCA1* and *BRCA2* pathogenic or likely pathogenic mutations [I, B]. Other biomarkers, such as tumor mutational burden or deficient-mismatch repair/MSI-high, could be assessed in patients who are candidates for pembrolizumab, while NTRK fusions may be evaluated in those eligible for tyrosine receptor kinase inhibitors [III, B].

First-line treatment

The choice of first-line treatment should be guided by the expression of PD-L1 and gBRCAm analysis (Fig. 3).

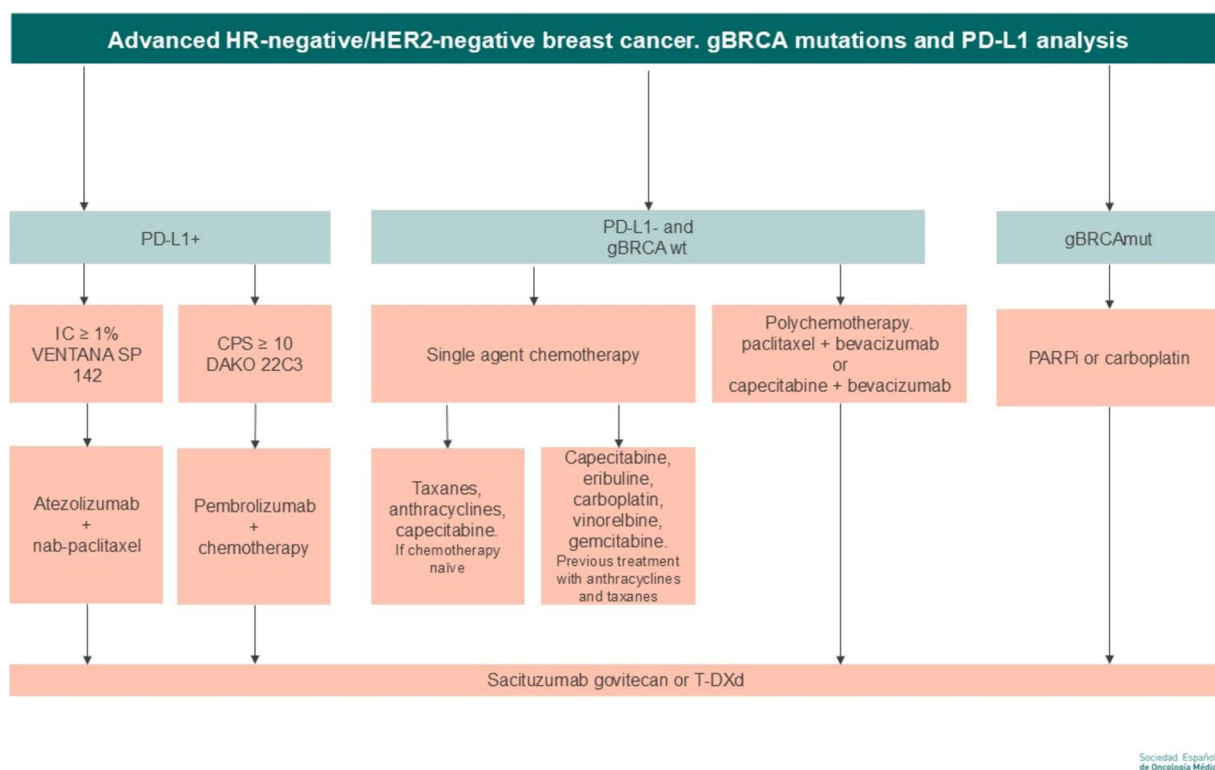


Fig. 3 Algorithm for the treatment of advanced triple-negative breast cancer. CPS combined positive score, gBRCA germline *BRCA*, HER2 human epidermal growth factor receptor 2, HR hormone receptor,

IC tumor-infiltrating immune cells, *mut* mutated, *PARPi* poly-ADP ribose polymerase inhibitors, *PD-L1* programmed death-ligand 1, *T-DXd* trastuzumab deruxtecan, *wt* wild type

PD-L1-positive metastatic TNBC

The addition of a checkpoint inhibitor to standard chemotherapy has been evaluated in several phase 3 clinical trials. Atezolizumab, in combination with chemotherapy as first-line treatment for patients with PD-L1-positive TNBC, showed conflicting results in two clinical trials (IMpassion130 and IMpassion131) [52, 53]. As a result, its use in clinical practice is now limited [II, A].

Pembrolizumab, in combination with chemotherapy as first-line treatment for patients with PD-L1-positive TNBC, has demonstrated significant improvements in PFS and OS [54, 55]. Therefore, it is considered the standard-of-care in this setting [I, A].

PD-L1-negative gBRCAm metastatic TNBC

For the management of this type of ABC, see the sections on genetic testing and BRCA-associated disease.

PD-L1-negative gBRCA wild-type metastatic TNBC

The choice of cytotoxic agent is influenced by several factors (previous exposure, disease-free interval, comorbidities) and must be considered individually. Although polychemotherapy provides higher rates of objective response and longer time to progression, it is associated with higher toxicity and the OS benefit is small [54, 56]. Therefore, sequential use of single-agent chemotherapy is preferred; hence, combination therapies should be reserved for patients with aggressive, symptomatic, or life-threatening disease [I, A]. Longer chemotherapy duration is associated with higher efficacy, as well as an increased risk of toxicity [56, 57]. Therefore, with the exception of conventional anthracyclines, chemotherapy should be administered until disease progression or unacceptable toxicity [I, B].

In chemotherapy-naïve patients, taxanes or anthracyclines are the preferred first-line treatment [I, A]. The TNT trial showed similar efficacy of carboplatin compared with docetaxel, and docetaxel should be also considered an option irrespective of gBRCAm status and previous exposure to anthracyclines and/or taxanes [58] [I, A]. Bevacizumab improves PFS and objective response rate (ORR) but not OS when combined with taxanes or capecitabine in HER2-negative ABC patients and may be considered for patients with visceral crisis or high symptomatic disease [59] [I, C]. Maintenance therapy with bevacizumab plus capecitabine after induction first-line treatment with bevacizumab plus docetaxel improves PFS and OS for HER2-negative ABC patients compared with bevacizumab alone and may be considered for selected cases [60] [I, C].

Second-line and subsequent treatment

Capecitabine, eribulin, carboplatin, gemcitabine, and vinorelbine are effective as monotherapies in patients pretreated with anthracyclines and taxanes [61–64] [I, A]. Due to the lack of high-quality comparative data, the most efficacious sequencing of chemotherapy agents in the treatment of ABC has yet to be defined. The treatment decision should be individualized considering different toxicity profiles, previous exposure, and patient preferences.

Sacituzumab govitecan (SG), an ADC composed of a Trop-2 antibody coupled to an SN-38 payload, significantly improved median PFS and OS compared with TPC [64, 65]. Based on these results, SG should be considered the preferred treatment after anthracyclines and taxanes [I, A]. Although supported by less evidence, treatment with T-DXd may also be an option in this setting [44] [I, B].

HER2-positive ABC

A high level of HER2 overexpression, as determined by either 3+ staining by immunohistochemistry for the HER2 protein or evidence of *HER2* gene amplification by fluorescence in situ hybridization (FISH ratio ≥ 2.0 or HER2 copy number ≥ 6.0), is a strong predictive factor for sensitivity to HER2-targeted agents, and these criteria should be used to select patients for these drugs [66]. For patients with metastatic HER2-positive breast cancer, anti-HER2-directed therapy should be included in the treatment regimen [66] [I, A]. Figure 4 shows the recommended first-line treatment algorithm for patients with HER2-positive ABC.

First-line therapy

Newly diagnosed metastatic disease

First-line treatment with trastuzumab and pertuzumab in combination with taxanes is associated with improvement in PFS, ORR, and OS versus chemotherapy alone (CLEOPATRA trial) [67] [I, A]. In patients with contraindications to taxanes, vinorelbine may be considered as an alternative option [68] [III, C].

In postmenopausal patients with HR-positive/HER2-positive tumors, the combination of AIs and an anti-HER2 agent (trastuzumab or lapatinib) has been shown to increase PFS and ORR but not OS versus ET alone [69–71]. Overall, the efficacy with these combinations seems inferior to that reached with chemotherapy plus anti-HER therapy and their use should be limited to low-risk or unfit patients [II, B].

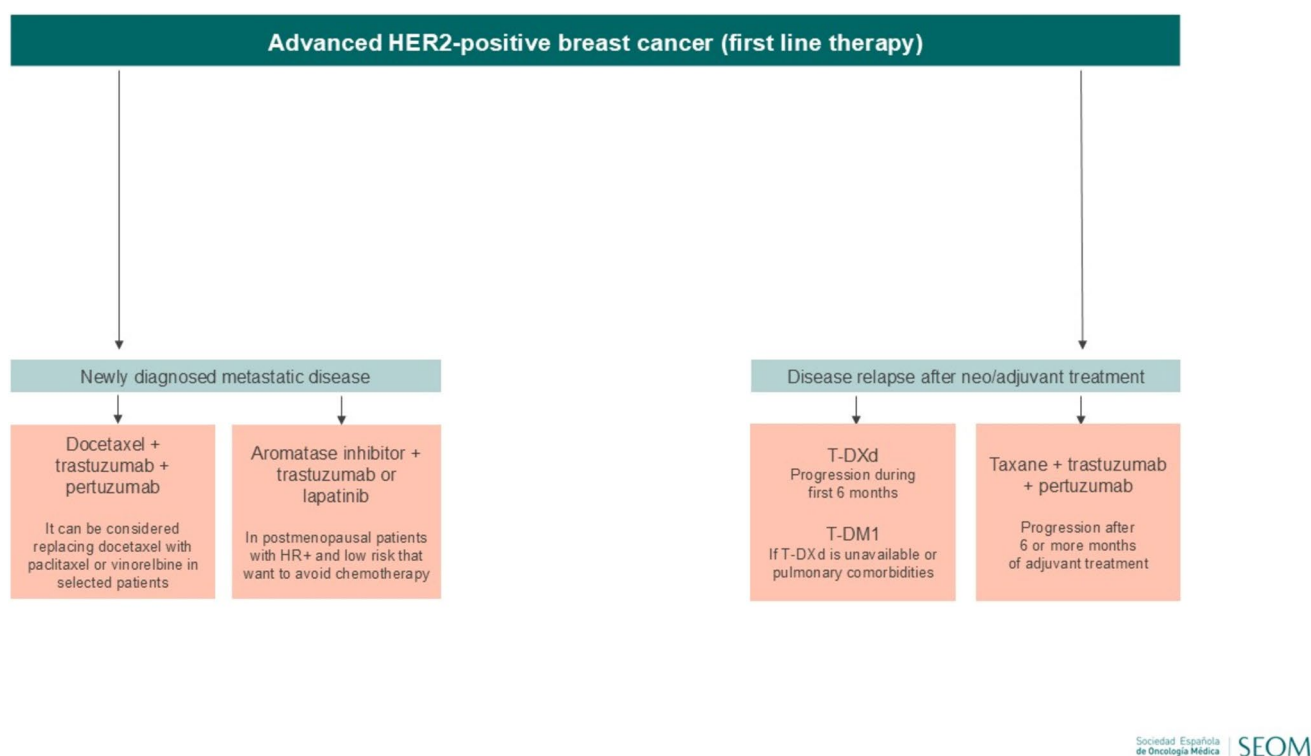


Fig. 4 Algorithm for first-line treatment of advanced HER2-positive breast cancer. *HER2* human epidermal growth factor receptor 2, *HR* hormone receptor, *T-DM1* trastuzumab emtansine, *T-DXd* trastuzumab deruxitecan

Disease relapse after neo/adjuvant treatment

For patients who progress during or within 6 months of adjuvant treatment, there is limited scientific evidence on the best treatment option [72]. In the phase 3 Destiny-Breast03 trial [73, 74], which included patients with progression on a trastuzumab- and taxane-containing regimen, median PFS and OS were significantly superior with T-DXd versus trastuzumab emtansine (T-DM1) and the benefit was observed in all the subgroups analyzed. For patients who progress during or within 6 months of adjuvant treatment, T-DXd is the preferred option [I, A].

For patients who progress ≥ 6 months after the completion of adjuvant therapy, the most accepted recommendation is trastuzumab plus pertuzumab in combination with a taxane, rather than other agents [I, A].

Second-line therapy

Several studies have shown that there is benefit in continuing with second-line anti-HER2 therapy after progression during or following first-line treatment with trastuzumab [I, A]. Based on the Destiny-Breast03 trial, for patients who experience disease progression following a trastuzumab-containing regimen, T-DXd is the preferred second-line option [73] [I, A].

Third-line and further therapy

Patients with advanced HER2-positive breast cancer who have been treated with two or more lines of anti-HER2 therapy may benefit from a third or further line of such treatment [I, A]. The choice is often based on prior treatments, patient preference, prior toxicities, and drug availability. In a randomized trial that included heavily pretreated patients (median of four prior lines of therapy, but no prior T-DXd), PFS and OS rates were superior in patients receiving tucatinib–trastuzumab–capecitabine to those in patients receiving capecitabine–trastuzumab only [75]. Therefore, tucatinib–trastuzumab–capecitabine may be a good option for patients previously treated with T-DM1 and/or T-DXd [II, B].

The combination of lapatinib plus trastuzumab in patients progressing on trastuzumab showed a higher PFS and OS versus lapatinib alone. The benefit was more notable in the subgroup of patients with HR-negative disease [76] [II, B].

For patients who experience disease progression following a trastuzumab-containing regimen in the metastatic setting, options include T-DXd (preferred regimen), T-DM1, continuation of trastuzumab with a different chemotherapy partner, tucatinib–trastuzumab–capecitabine, or a tyrosine kinase-based combination, and anti-HER2 agents plus ET in HR-positive/HER2-positive breast cancer [I, B].

The optimal number of lines of anti-HER2 therapy for ABC is currently unknown, although available data suggest that benefits are maintained in the third line and beyond [II, B].

Genetic testing and BRCA-associated disease

BRCA1 and *BRCA2* are high-penetrance cancer susceptibility genes involved in homologous recombination DNA repair that are mutated in 5% of unselected patients with breast cancer [77]. In addition to cancer family history and personal criteria related to early onset or phenotype, testing criteria for *BRCA1* and *BRCA2* genes have been expanded over time to optimize identification of patients who might benefit from active therapies that create DNA double-strand breaks or stalled replication forks, such as the platinum salts or PARP inhibitors. Therefore, updated germline [I, A] and somatic [II, A] testing indications include patients with metastatic HER2-negative disease who had previously been treated with an anthracycline and a taxane in the (neo)adjuvant or metastatic setting. Patients with BRCA-mutated HR-positive ABC who have experienced disease progression during or after one prior line of ET and who are no longer candidates for further ET, due to endocrine resistance or exhaustion, should be considered for palliative chemotherapy [I, A].

In platinum-naïve patients with gBRCAm TNBC, platinum chemotherapy is preferred to taxanes, based on the results of the phase 3 TNT trial, which compared first-line carboplatin to docetaxel [58] [I, A]. Unlike the unselected population, in which no difference between arms was observed, gBRCAm carriers had a greater ORR and median PFS with carboplatin. However, no OS benefit was seen [58].

In addition, two PARP inhibitors have been evaluated in two phase 3 trials, OlympiA and EMBRACA, in which patients were randomized to olaparib or talazoparib, respectively, versus TPC [48, 49, 78, 79]. In both studies, patients who received olaparib or talazoparib had longer PFS, higher ORR, and better QoL in first-to-third-lines than those receiving single-agent TPC. These trials failed to show a statistically significant improvement in OS.

Patients with HR-positive gBRCAm advanced disease should receive first-line ET with CDK4/6i and consider PARP inhibitor beyond progression [I, A].

HER2-low ABC

More than half of breast cancers historically categorized as HER2-negative express low levels of HER2 (ERBB2), defined as immunohistochemically 1+ or 2+ and a lack of

HER2 gene amplification measured by in situ hybridization [80]. However, these HER2-low tumors are heterogeneous, and include both HR-positive and HR-negative breast cancers that may vary in prognosis and response to systemic treatments [81].

In one study in which nearly 90% of participants had HR-positive tumors, T-DXd significantly improved PFS and OS compared with TPC among patients with HER2-low metastatic breast cancer, regardless of HR status [44]. This highlights the clinical relevance of the HER2-low patient population and supports the importance of implementing reproducible and sensitive assays to measure HER2-low expression, as the reproducibility of HER2-low pathological analysis may be suboptimal.

CNS metastases

The incidence of brain metastases in ABC has increased in recent decades, mainly because of the improved survival of these patients [82]. More than one-third of HER2-positive breast cancer patients, one-third of patients with metastatic TNBC, and 15% of patients with HR-positive/HER2-negative ABC will develop brain metastases [49, 83]. Progression into the CNS is still a therapeutic challenge, due to the negative impact on QoL and survival [83, 84].

Early detection by magnetic resonance imaging and treatment of CNS lesions may improve QoL, management, and perhaps survival in women with ABC, especially those with HER2-positive or triple-negative subtypes [82]. Several clinical trials are being carried out to address this issue [78, 84]. However, routine CNS disease screening is not recommended currently in the absence of signs/symptoms [III, C].

The landscape of the treatment of brain metastases in patients with breast cancer has changed in recent years with an increasing use of systemic therapy and focal stereotactic radiosurgery (SRS), which has led to a decrease in surgery and whole brain radiotherapy [82]. In all patients, a multidisciplinary approach is essential for optimal management.

Local therapy

Surgical resection remains the first option for single or a limited number brain metastases, to relieve intracranial pressure or to obtain histology/biomarkers/molecular profiling [78, 79] [II, A]. SRS is now the primary treatment for patients with single or a limited number of brain metastasis (≤ 10 lesions) [I, A]. Postoperative SRS is an alternative to whole brain radiation therapy for patients who undergo resection of brain metastases, with a reduced risk of neurocognitive

decline; however, preoperative SRS might be favored given the lower risks of radiation necrosis and leptomeningeal disease [85].

Whole brain radiation therapy may be considered for patients with numerous brain metastases (> 10) and poor performance status [II, B]; hippocampus-sparing radiation therapy is a preferred strategy to decrease neurocognitive impairment [II, B].

Systemic therapy in HER2-positive patients

A number of anti-HER2 agents have shown intracranial activity, even in heavily pretreated patients [79, 86].

In patients who have new brain metastases and controlled systemic disease, maintenance systemic therapy using the same anti-HER2 regimen can be considered [II, B]. In those with new brain metastases who have progressive systemic disease, HER2-targeted therapy should be provided according to the algorithms for the treatment of HER2-positive ABC [I, B].

Tucatinib–trastuzumab–capecitabine is the preferred regimen, particularly among patients with oligosymptomatic and limited disease, and for those who prefer to defer radiation [II, B]. T-DXd may also be considered, particularly if systemic progression is a clinical issue [II, C].

Systemic therapy in HER2-negative patients

Classical chemotherapy agents, such as capecitabine, methotrexate, carboplatin, etoposide, vinorelbine, and gemcitabine, have been used in this scenario with limited therapeutic benefit [86, 87] [II, B]. Bevacizumab can improve CNS response and may be an option, particularly in TNBC [87, 88] [III, C]. The CDK4/6i abemaciclib and ribociclib penetrate the blood–brain barrier and have shown intracranial activity in small early trials [89, 90] [II, C].

New agents, including immune checkpoint inhibitors, PARP inhibitors, and drug conjugates, are being evaluated in clinical trials for potential intracranial efficacy [III, C].

Oligometastatic breast cancer

Oligometastatic breast cancer is defined as a low-burden disease with ≤ 5 lesions, and represents up to 10% of the patients with ABC [91]. The distinction between oligo- and widely-metastatic disease is increasingly recognized because of treatment and survival implications [88, 92].

The standard-of-care for oligometastatic disease in breast cancer is systemic therapy, but given the likelihood

of limited tumor burden, patients may benefit from the use of locoregional therapies, including surgical excision, radiofrequency, and stereotactic body radiotherapy (SBRT) [II, B]. A meta-analysis of oligometastatic breast cancer patients treated by SBRT I indicated that this treatment offered local control of 97% at 1 year and 90% at 2 years [93]. However, the analysis and comparison of local control at the treated bone lesion between different series are complicated by the heterogeneity of populations and treatments.

The optimal management of oligometastatic breast cancer remains unclear due to the scarcity and heterogeneity of existing data. However, selected patients with oligometastatic disease may be offered a multimodal approach with curative intent, including local therapy to all known metastases, if it can be safely accomplished and a multidisciplinary team is involved [III, C].

Male breast cancer

Male breast cancer accounts for about 1% of all breast cancers [94]. However, its incidence can be higher among males with either genetic disorders or germline mutations in cancer susceptibility genes (*BRCA2*, *CHEK2*, *ATM*, and *PALB2*) regardless of family history [95]. While most males are diagnosed at early stages, diagnostic delays explain a higher rate of de novo metastatic disease (32%) compared with the female population [94]. In addition, male patients with breast cancer have a worse overall prognosis than their female counterparts [94].

Management recommendations are mostly extrapolated from either retrospective studies or clinical trials including large number of females. Since luminal B-like/HER2-negative invasive ductal carcinoma is the most frequent subtype occurring in males, both AIs (concurrently to gonadotropin-releasing hormone analogs or orchiectomy) or fulvestrant should be recommended as front-line, except in cases of visceral crisis or rapidly progressive disease [III, B]. Recent real-world data suggest similar PFS benefit and favorable safety profile of CDK4/6i combined with AIs or fulvestrant in males compared with females [96]. While prospective international data and clinical trials have included newly diagnosed male cases, data remain limited [97]. However, it is reasonable to follow similar approaches to management of other subtypes or late lines of advanced disease (i.e., with PIK3CA or mammalian target of rapamycin [mTOR] inhibitors, HER2-targeted therapy, immunotherapy, and PARP inhibitors) to those used in female patients [98] [III, B].

Supportive and palliative care

ABC is an incurable disease, with a median OS ranging from 1.5 to more than 5 years, depending on subtype [99]. In addition to receiving the best antineoplastic treatment along with the appropriate measures to avoid therapy-associated toxicity, patients should be offered optimal symptom control, and psychological, social, and spiritual support [II, A]. Regarding symptom control, antiresorptive agents (zoledronic acid or denosumab) should be considered in the presence of bone metastases to prevent skeletal-related events and as co-adjuvant drugs for pain control [100]. Optimization of oral care should be implemented to minimize the risk of osteonecrosis of the jaw [101].

Palliative care (PC) is an approach that improves the QoL of patients with breast cancer and their caregivers, through prevention, early identification, and treatment of physical, psychosocial, and spiritual issues [102]. PC should start early in the course of disease, while patients are receiving curative treatment, and multidisciplinary and collaborative approaches should be integrated in the PC. Patients followed up concurrently by PC specialists and a medical oncologist reported better QoL and less depression, received less chemotherapy, and achieved longer OS than those who were treated under a traditional care model [98, 103].

Future directions

Currently, several questions regarding the management of ABC remain unanswered. This is the case, for example, for NGS panel tests or liquid biopsy, which have shown clinical utility for the detection of actionable mutations (*PIK3CA* mutations, *ERBB2* amplification, and *gBRCAm*) [104] but are not yet integrated in routine practice or are on hold until full approval/reimbursement of the therapies for which such molecular alterations apply. In addition, the development of accurate predictive biomarkers of benefit with currently available or future treatments is mandatory, as well as identification of the best techniques to assess biomarkers.

Regarding novel treatments for HR-positive/HER2-negative patients, several ETs are in different stages of development, especially for patients with mutations in *ESR1*, acting in different ways on the ER. Other agents designed to overcome endocrine resistance are also being developed (AKT inhibitors, fibroblast growth factor inhibitors, and aurora kinase A inhibitors). For ER-negative/HER2-negative ABC, different strategies are being investigated, such as PARP inhibitors, AKT inhibitors, mitogen-activated protein kinase inhibitors, or combining checkpoint inhibitors with other immunotherapy or targeted agents.

In the development of anti-HER2 therapy, efforts are focused on novel tyrosine kinase inhibitors, ADCs, bispecific antibodies, immunotherapy, and agents that inhibit HER2 protein production or induce its destruction. It is also necessary to establish the optimal sequencing of all these therapies and whether the combination of some of these agents could improve outcomes in patients with ABC.

Acknowledgements The authors thank Sara López-Tarruella and Alvaro Rodríguez-Lescure for their review and validation of the levels of evidence and grades of recommendation in this guideline. The authors also thank Marie Cheeseman who provided editorial assistance in updating the guideline on behalf of Springer Health+.

Author contributions The Spanish Society of Medical Oncology (SEOM) was responsible for the article conception. All authors are equally responsible for this work; all authors performed the literature search and data analysis, drafted and/or critically revised the manuscript, and approved the final version.

Funding This work was funded by the Spanish Society of Medical Oncology (SEOM).

Data availability Data sharing is not applicable to this article as no datasets were generated or analyzed.

Declarations

Conflict of interest Jose Angel Garcia-Saenz has received speaker fees and has attended an advisory board for Novartis, Lilly, Daiichi Sankyo, and Gilead; has attended an advisory board for AstraZeneca, Pierre Fabre, and Eisai; has received a grant from Seagen; has received speaker fees from Roche, Asofarma, and Exact Sciences; and has received a grant and has attended an advisory board for Stemline Menarini. Isabel Blancas Lopez-Barajas has received speaker fees and grants and has attended an advisory board for Roche, Lilly, and AstraZeneca; has received speaker fees and has attended an advisory board for Novartis, Celgene, Eisai, Pierre Fabre, BMS, Daiichi Sankyo, Grünenthal, Seagen, and Veracyte; and has received a grant from Agendia. Isabel Echavarria has received speaker fees and has attended an advisory board for Lilly; has received speaker fees from Pfizer, Novartis, Roche, and Pierre Fabre; and has attended an advisory board for AstraZeneca. Mireia Margeli Vila has attended an advisory board for Gilead, Lilly, Pierre Fabre, Daiichi Sankyo, and Eisai; has received a grant from Pfizer; and has received speaker fees from Pierre Fabre. Fernando Moreno Antón has received speaker fees, grants, and other fees and has attended an advisory board for Pfizer; has attended an advisory board for Novartis, Daiichi Sankyo, and AstraZeneca; and has received other fees from MSD, Pierre Fabre, Gilead, Seagen, and Roche. Sonia Pernas has received speaker fees and non-financial support and has attended an advisory board for AstraZeneca and Daiichi Sankyo; has received grants and has attended an advisory board for Roche; has received speaker fees and non-financial support from Lilly and Novartis; has attended an advisory board for Pierre Fabre and Seagen; has received non-financial support Gilead; has received non-financial support and has attended an advisory board for Pfizer; and has received speaker fees from Eisai. Meritxell Bellet Ezquerria has received speaker fees from Pfizer, Lilly, and Novartis; has attended an advisory board for Pfizer, Lilly, Novartis, and Stemline Menarini; and has received travel expenses from Pfizer. Carmen Hinojo Gonzalez, Teresa Ramon y Cajal, and Nuria Ribelles declare that they have no conflicts of interest.

Ethics approval and informed consent Not applicable. The manuscript does not contain clinical studies or patient data.

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