ASCO Guidelines

Metastatic Breast Cancer: ASCO Resource Stratified Guideline

Summary of Recommendations by Resource Setting

First-Line Systemic Metastatic Breast Cancer Treatment

HR-Positive, HER2-Negative

	Basic	Limited	Enhanced
1.1.1 HR-positive, HER2-negative: Post-menopausal	*Tamoxifen*, palliative,[a] and best supportive care should be provided Surgery and *tamoxifen* when patient presents with certain symptoms	Sequential hormonal therapy[1] AIs only if OA/OS is available	Sequential hormonal therapy[1]
1.1.2 HR-positive, HER2-negative with immediately life-threatening disease or in those with rapid visceral recurrence on adjuvant hormone therapy	*Tamoxifen* Palliative[a] and best supportive care	Single-agent chemotherapy Combination regimens may be offered for symptomatic or immediately-life threatening disease	Single-agent chemotherapy Combination regimens may be offered for symptomatic or immediately-life threatening disease
1.1.3 HR-positive, HER2-negative with immediately life-threatening disease without prior adjuvant hormone therapy	*Tamoxifen* Palliative[a] and best supportive care	Single-agent chemotherapy Combination regimens may be offered for symptomatic or immediately-life threatening disease	Single-agent chemotherapy Combination regimens may be offered for symptomatic or immediately-life threatening disease for which time may allow only for one potential chance for therapy
1.1.4 HR-positive, HER2-negative; Post-menopausal without prior adjuvant hormone therapy	*Tamoxifen*	*Tamoxifen* (nonsteroidal AI if available) Sequential hormone therapy[2]	A nonsteroidal AI and a ***CDK4/6 inhibitor***
1.1.5 HR-positive, HER2-negative; Pre-menopausal	*Tamoxifen* Bilateral oophorectomy	*Tamoxifen* or alternate hormone therapy Surgical options, *e.g.* bilateral oophorectomy; other options: OA/OS Sequential hormone therapy if AI[b]	Ovarian suppression or ablation in combination with hormonal therapy (or if without exposure to prior hormone therapy, *tamoxifen* alone or ovarian suppression alone or ablation alone). Sequential hormone therapy
1.1.6 HR-positive, HER2-negative: postmenopausal Pre-menopausal with treatment-naïve	*Tamoxifen*	*Tamoxifen* or AI Nonsteroidal if available for postmenopausal *Tamoxifen* with OA/OS if available for premenopausal or AI with OA/OS If male patients, then with a gonadotropin-releasing analog	Nonsteroidal AI and a ***CDK4/6 inhibitor*** combined with ovarian function suppression (if male patients, then with a gonadotropin-releasing hormone analog)
1.1.7 HR-positive: recurrence within one year of completing adjuvant AI therapy	*Tamoxifen*	Alternative hormonal treatment (*tamoxifen*, SAI[b] ***fulvestrant***)	***Fulvestrant*** and a ***CDK4/6 inhibitor***
1.1.8 HR-positive: recurrence ≥ 12 months of completing adjuvant therapy	*Tamoxifen*	May reuse specific hormone agent	AI[b] + ***CDK4/6 inhibitor*** May reuse specific hormonal agent
1.1.9 Male breast cancer	*Tamoxifen*	*Tamoxifen* or (combined hormone blockage NSAI with LHRH analog	Hormonal therapy (A nonsteroidal AI and a ***CDK4/6 inhibitor*** [with a gonadotropin-releasing hormone analog])

HER2-Positive

	Basic	Limited	Enhanced
1.2.1 HER2-positive (see below for additional options for HR-positive and HER2-positive)	Palliative[a] and best supportive care	Chemotherapy, option include *anthracyclines* (note: doxorubicin on EML), *once weekly paclitaxel, docetaxel, carboplatin* *Capecitabine*	HER2-targeted therapy combined with chemotherapy. Options include: *trastuzumab*, ***pertuzumab***, and a taxane If ***pertuzumab*** not available, then chemotherapy and *trastuzumab* If taxane not available, then vinorelbine or platinum
1.2.2 HER2-positive, HR-positive (In special circumstances such as low disease burden, the presence of co-morbidities [contraindications to HER2-targeted therapy such as congestive heart failure], and/or the presence of a long disease-free interval)	Single-agent hormone therapy (*tamoxifen*) Hormonal therapy with ovarian ablation	Single-agent chemotherapy with *anthracyclines, one weekly paclitaxel, docetaxel, carboplatin, CMF (cyclophosphamide, methotrexate, flurouracil)* Hormonal therapy alone (if AI[c] and tamoxifen available)	HER2-targeted therapy (*trastuzumab* + ***pertuzumab***) with chemotherapy or hormonal therapy plus HER2-targeted therapy or hormonal therapy alone (latter in special circumstances. Clinicians should recommend HER2-targeted therapy-based combinations for first-line treatment, except for highly selected patients with ER-positive or PgR-positive and HER2-positive disease for whom clinicians may use endocrine therapy alone In special circumstances, such as low disease burden, the presence of co-morbidities (contraindications to HER2-targeted therapy such as congestive heart failure), and/or the presence of a long disease free-interval, clinicians may offer first-line endocrine therapy alone

Triple-Negative

	Basic	Limited	Enhanced
1.3.1 Triple-negative without known PD-L1	Palliative[a] and best supportive care	Single-agent chemotherapy	Single-agent chemotherapy rather than combination chemotherapy
1.3.2 Triple-negative without known PD-L1 and with symptomatic or immediately life-threatening disease	Palliative[a] and best supportive care	Single-agent chemotherapy Combination chemotherapy if possible	Single-agent chemotherapy Combination chemotherapy if possible
1.3.3 Triple-negative with known PD-L1 and no contraindications	Palliative[a] and best supportive care (PD-L1 testing not available)	Single-agent chemotherapy	Addition of immune checkpoint inhibitor to chemotherapy (***atezolizumab*** plus ***nab-paclitaxel*** or ***pembrolizumab*** plus chemotherapy) as first-line therapy

BRCA Mutations

(note: the recommendations for patients with HR-positive, HER2-positive, and triple-negative breast cancer are also options for patients when PARPi are not available)

	Basic	Limited	Enhanced
1.4.1.a *BRCA1/2* mutations (HR-positive)	*Tamoxifen* – if ER-positive, then see ER-positive recommendations and/or HER2-positive, see HER2-positive recommendations Palliative[a] and best supportive care	*Tamoxifen* with OA AI with OA Single-agent chemotherapy rather than combination chemotherapy	***PARPi*** Single-agent chemotherapy rather than combination chemotherapy
1.4.1.b *BRCA1/2* mutations, HR-negative, HER2-negative	Palliative[a] and best supportive care	Single-agent chemotherapy	***PARPi***[c]/Chemotherapy
1.4.2 HR-positive, HER2-negative, *BRCA1/2* mutations (no longer benefiting from endocrine therapy)	Palliative[a] and best supportive care	Single-agent chemotherapy, combination regimens may be offered for symptomatic or immediately life-threatening disease, especially *carboplatin* as first option	***PARPi*** (in the first- through third-line setting rather than chemotherapy), if not available, then: Single-agent chemotherapy, combination regimens may be offered for symptomatic or immediately life-threatening disease

Notes.

Italics = medications on EML (not universally available in low-income and lower-middle-income countries (<50%)). ***Italics, bold*** = not on EML.

(1) In Basic settings, the recommendations presume that neither chemotherapy nor targeted therapy or molecular testing are available.

(2) Per the "Palliative Care in the Global Setting: ASCO Resource-Stratified Guideline" recommendations, there should be a coordinated system where the palliative care needs of patients and families are identified and met at all levels, in collaboration with the team providing oncology care. The health care system should have trained personnel who are licensed to prescribe, deliver, and dispense opioids at all levels. Distance communication should be instituted at the national or regional level through oncology centers (or other tertiary care centers) to support those providing oncology care to patients in lower-resource areas.

(3) General: palliative care needs should be addressed for all patients with cancer at presentation using appropriate screening, especially when disease-modifying interventions are not available.

[a] Palliative care may or may not include radiation therapy for symptom control.

[b] Patients who are premenopausal: can only receive aromatase inhibitors if accompanied by ovarian ablation or ovarian suppression.

[c] Patients eligible for *PARPi* if they previously received chemotherapy for neoadjuvant, adjuvant, or metastatic disease.

Abbreviations.

AI, aromatase inhibitor; CMF, cyclophosphamide, methotrexate, fluorouracil; EML, Essential Medicines List; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; LHRH, luteinizing hormone-releasing hormone; NSAI, nonsteroidal aromatase inhibitor; OA, ovarian ablation; OS, ovarian suppression; PARPi, poly(ADP-ribose) polymerase inhibitor; PgR, progesterone receptor; SAI, steroidal aromatase inhibitor

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Summary of Recommendations by Resource Setting

Second-Line Systemic Metastatic Breast Cancer Treatment

HR-Positive, HER2-Negative

	Basic	Limited	Enhanced
2.1.1 HR-positive, HER2-negative, no longer benefiting from endocrine therapy	Palliative[a] and best supportive care	Single-agent chemotherapy, combination regimens may be offered for symptomatic or immediately life-threatening disease	Single-agent chemotherapy, combination regimens may be offered for symptomatic or immediately life-threatening disease
2.1.2 HR-positive, HER2-negative Post-menopausal MBC progressing on prior treatment with nonsteroidal AIs, either before or after treatment with fulvestrant	*Tamoxifen* if previously not used	*Tamoxifen* Or single-agent chemotherapy, combination regimens may be offered for symptomatic or immediately-life threatening disease	***Exemestane*** and ***everolimus***
2.1.3 Postmenopausal women, and male patients, with HR-positive, HER2-negative, *PIK3CA* mutation, ABC, or MBC following prior endocrine therapy including an AI, with or without a CDK4/6 inhibitor	Palliative[a] and best supportive care	*Tamoxifen* Or single-agent chemotherapy, combination regimens may be offered for symptomatic or immediately-life threatening disease (Careful screening for and management of common toxicities are required)	***Alpelisib*** in combination with endocrine therapy in combination with ***fulvestrant*** (Careful screening for and management of common toxicities are required)
2.1.4 Postmenopausal women with HR-positive, HER2-negative, without PIK3CA mutation, MBC following prior endocrine therapy including an AI, with or without a CDK4/6 inhibitor	Palliative[a] and best supportive care	*Tamoxifen* Or single-agent chemotherapy, combination regimens may be offered for symptomatic or immediately-life threatening disease	Endocrine therapy, AI, or ***fulvestrant*** ± ***everolimus***
2.1.5 HR-positive, HER2-negative with recurrence on prior hormone therapy with or without targeted therapy with immediately life-threatening disease or in those with rapid visceral recurrence on adjuvant endocrine therapy	Hormone therapy Palliative[a] and best supportive care	Single-agent chemotherapy, combination regimens may be offered for symptomatic or immediately-life threatening disease	Hormone therapy with or without targeted therapy or single-agent chemotherapy
2.1.6 HR-positive, HER2-negative, with germline *BRCA1/2* mutation no longer benefiting from hormone therapy	Palliative[a] and best supportive care	Single-agent chemotherapy, combination regimens may be offered for symptomatic or immediately-life threatening disease, especially *carboplatin* as first option	***PARPi*** Single-agent chemotherapy, combination regimens may be offered for symptomatic or immediately-life threatening disease, especially carboplatin as first option

HER2-Positive

	Basic	Limited	Enhanced
2.2.1 HER2-positive	Palliative[a] and best supportive care (HER2 testing likely not available)	Chemotherapy (*anthracyclines, docetaxel, once weekly paclitaxel, carboplatin, CMF)* *Capecitabine* *Capecitabine* + ***lapatinib*** *Trastuzumab* with second-line therapy	(1) ***Trastuzumab deruxtecan*** (if 1 not available, then 2) (2) ***Trastuzumab emtansine*** (if 2 not available, then 3) (3) *Capecitabine* + ***lapatinib*** (if 3 not available, then 4) (4) *Trastuzumab* with second-line chemotherapy
2.2.2 HER2-positive, received HER2-targeted therapy and chemotherapy in first-line	(Total mastectomy for ipsilateral in-breast recurrence if single bone metastasis only) If no medical treatment available, and no pathology, for palliative reasons, including local control, primary surgery in patients who are symptomatic when systemic anti-HER2 therapy is not available	Chemotherapy with *anthracyclines, docetaxel, once weekly paclitaxel,* and *carboplatin, CMF* *Capecitabine* Hormonal therapy alone	(1) ***Trastuzumab deruxtecan*** (if 1 not available, then 2) (2) ***Trastuzumab emtansine*** (if 2 not available, then 3) (3) *Capecitabine* + ***lapatinib*** (if 3 not available, then 4) (4) *Trastuzumab* with second-line chemotherapy
2.2.3 HER2-positive, if a patient finished trastuzumab-based adjuvant treatment ≤ 12 months before recurrence	Palliative[a] and best supportive care	Chemotherapy (*anthracyclines, docetaxel, carboplatin, CMF, capecitabine*)	(1) ***Trastuzumab deruxtecan*** (if 1 not available, then 2) (2) ***Trastuzumab emtansine*** (if 2 not available, then 3) (3) *Capecitabine* + ***lapatinib*** (if 3 not available, then 4) (4) *Trastuzumab* with second-line chemotherapy
2.2.4 HER2-positive, if a patient finished trastuzumab-based adjuvant treatment > 12 months before recurrence	Palliative[a] and best supportive care	Chemotherapy (*anthracyclines, once weekly paclitaxel, docetaxel, carboplatin*)	HER2-targeted therapy combined with chemotherapy *Trastuzumab,* ***pertuzumab***, and a taxane If ***pertuzumab*** not available, then chemotherapy and trastuzumab. If taxane not available, then ***vinorelbine***, platinum

Triple-Negative

	Basic	Limited	Enhanced
2.3.1 Triple-negative with known PD-L1 and no contraindications	Palliative[a] and best supportive care	Single-agent chemotherapy; start with sequencing taxane or platinum; may offer metronomic chemotherapy for disease control	Single-agent chemotherapy rather than combination chemotherapy; start with sequencing taxane or platinum; may offer metronomic chemotherapy for disease control

Notes.
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(2) Per the "Palliative Care in the Global Setting: ASCO Resource-Stratified Guideline" recommendations, there should be a coordinated system where the palliative care needs of patients and families are identified and met at all levels, in collaboration with the team providing oncology care. The health care system should have trained personnel who are licensed to prescribe, deliver, and dispense opioids at all levels. Distance communication should be instituted at the national or regional level through oncology centers (or other tertiary care centers) to support those providing oncology care to patients in lower-resource areas.
(3) General: palliative care needs should be addressed for all patients with cancer at presentation using appropriate screening, especially when disease-modifying interventions are not available.

[a] Palliative care may or may not include radiation therapy for symptom control.

Abbreviations.
ABC, advanced breast cancer, AI, aromatase inhibitor CMF, cyclophosphamide, methotrexate, fluorouracil; EML, Essential Medicines List; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; MBC, metastatic breast cancer; NA, not available; PARPi, poly(ADP-ribose) polymerase inhibitor

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Third-Line and Beyond Metastatic Breast Cancer Treatment

Triple-Negative

	Basic	Limited	Enhanced
3.1.1 Triple-negative	Palliative[a] and best supportive care	Palliative[a] and best supportive care	Single-agent chemotherapy rather than combination chemotherapy
3.1.2 Triple-negative with germline *BRCA1/2* mutations (previously been treated with chemotherapy in the neoadjuvant, adjuvant, or metastatic setting)	Palliative[a] and best supportive care	***PARPi*** (for those with known mutation status)	***PARPi*** (for those with known mutation status)

HR-Positive, *BRCA* mutation

	Basic	Limited	Enhanced
3.2.1 HR-positive, germline *BRCA1/2* mutation	Palliative[a] and best supportive care	***PARPi*** (for those with known mutation status)	***PARPi*** (for those with known mutation status) Single-agent chemotherapy rather than combination chemotherapy

HER2-Positive

	Basic	Limited	Enhanced
3.3.1 HER2-positive	Palliative[a] and best supportive care	Chemotherapy	***Trastuzumab emtansine***
3.3.2 HER2-positive, HR-positive	Palliative[a] and best supportive care	Hormonal therapy	*Trastuzumab* + hormonal therapy
3.3.3 Patient is receiving HER2-targeted therapy and chemotherapy combinations (timing, duration, scheduling)	Not relevant	If a patient is receiving HER2-targeted therapy and chemotherapy combinations, the chemotherapy should continue for approximately 4-6 months (or longer) and/or to the time of maximal response, depending on toxicity and in the absence of progression. When chemotherapy is stopped, clinicians should continue the HER2-targeted therapy; no further change in the regimen is needed until the time of progression or unacceptable toxicities.	If a patient is receiving HER2-targeted therapy and chemotherapy combinations, the chemotherapy should continue for approximately 4-6 months (or longer) and/or to the time of maximal response, depending on toxicity and in the absence of progression. When chemotherapy is stopped, clinicians should continue the HER2-targeted therapy; no further change in the regimen is needed until the time of progression or unacceptable toxicities.

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(3) General: palliative care needs should be addressed for all patients with cancer at presentation using appropriate screening, especially when disease-modifying interventions are not available.

[a] Palliative care may or may not include radiation therapy for symptom control.

Abbreviations.
EML, Essential Medicines List; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; PARPi, poly(ADP-ribose) polymerase inhibitor

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Summary of Recommendations by Resource Setting

Third-Line Options in the Maximal Setting

HER2-Positive Breast Cancer

Recommendation	Strength
If a patient's HER2-positive advanced breast cancer has progressed during or after second line or greater HER2-targeted treatment and the patient has already received ***pertuzumab*** and ***TDxd***, (if a patient has not received pertuzumab, ***pertuzumab***)	-
If a patient has not received T-DM1 in second-line, ***T-DM1*** regimen	Strong
Tucatinib combined with trastuzumab and *capecitabine*	Strong
Trastuzumab deruxtecan	Strong
Neratinib combined with *capecitabine*	Weak
Lapatinib and trastuzumab	Weak
Lapatinib and *capecitabine*	Weak
Other combinations of chemotherapy and trastuzumab	Weak
Margetuximab plus chemotherapy	Weak
If a patient has not received pertuzumab, ***pertuzumab***	Weak
Hormonal therapy (in patients with ER-positive and/or PgR-positive disease	Weak
Abemaciclib combined with trastuzumab and ***fulvestrant***	Weak

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Source.
ASCO 2022 guideline

Abbreviations.
EML, Essential Medicines List; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; PgR, progesterone receptor; TDxd, trastuzumab deruxtecan; T-DM1, trastuzumab emstansine