

Breast Cancer (Recurrent or Metastatic) Treatment Regimens

Clinical Trials: The NCCN recommends cancer patient participation in clinical trials as the gold standard for treatment.

Cancer therapy selection, dosing, administration, and the management of related adverse events can be a complex process that should be handled by an experienced healthcare team. Clinicians must choose and verify treatment options based on the individual patient; drug dose modifications and supportive care interventions should be administered accordingly. The cancer treatment regimens below may include both U.S. Food and Drug Administration-approved and unapproved indications/regimens. These regimens are only provided to supplement the latest treatment strategies.

These Guidelines are a work in progress that may be refined as often as new significant data becomes available. The National Comprehensive Cancer Network Guidelines[®] are a consensus statement of its authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult any NCCN Guidelines[®] is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The NCCN makes no warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way.

Note: All recommendations are category 2A unless otherwise indicated.

► Systemic Therapy for ER- and/or PR-Positive Recurrent or Stage IV (M1) Disease^{1,a}

REGIMEN	DOSING
HER2-Negative and Postmenopausal or Premenopausal Receiving Ovarian Ablation or Suppression^{2-6,b}	
Preferred Regimens: First-Line Therapy	
Abemaciclib + Anastrozole (Category 1) ^{7,9,c}	Days 1-28: Abemaciclib 150mg orally twice daily Days 1-28: Anastrozole 1mg orally once daily. Repeat cycle every 4 weeks.
Abemaciclib + Exemestane (Category 1) ^{7,8,10,c}	Days 1-28: Abemaciclib 150mg orally twice daily Days 1-28: Exemestane 25mg orally once daily. Repeat cycle every 4 weeks.
Abemaciclib + Fulvestrant (Category 1) ^{8,11,12,c}	Days 1-28: Abemaciclib 150mg orally twice daily Day 1 and 15: Fulvestrant 500mg IM. Administer one 4-week cycle, followed by: Days 1-28: Abemaciclib 150mg orally twice daily Day 1: Fulvestrant 500mg IM. Repeat cycle every 4 weeks.
Abemaciclib + Letrozole (Category 1) ^{7,8,13,c}	Days 1-28: Abemaciclib 150mg orally twice daily Days 1-28: Letrozole 2.5mg orally once daily Repeat cycle every 4 weeks.
Anastrozole ^{9,12}	Days 1-28: Anastrozole 1mg once orally. Repeat cycle every 4 weeks.
Exemestane ^{10,13-15}	Days 1-28: Exemestane 25mg orally once daily. Repeat cycle every 4 weeks.
Fulvestrant (Category 1) ^{16,17}	Days 1,15: Fulvestrant 500mg IM. Administer for one 28-day cycle, followed by: Day 1: Fulvestrant 500mg IM. Repeat cycle every 4 weeks.
Fulvestrant + Anastrozole (Category 1) ^{9,16,18}	Days 1,15: Fulvestrant 500mg IM Days 1-28: Anastrozole 1mg orally. Administer for one 28-day cycle, followed by: Day 1: Fulvestrant 500mg IM Days 1-28: Anastrozole 1mg orally. Repeat cycle every 4 weeks.
Fulvestrant + Letrozole (Category 1) ^{15,18,19}	Days 1,15: Fulvestrant 500mg IM Days 1-28: Letrozole 2.5mg orally. Administer for one 28-day cycle, followed by: Day 1: Fulvestrant 500mg IM Days 1-28: Letrozole 2.5mg orally. Repeat cycle every 4 weeks.
Letrozole ^{10-19,22}	Days 1-28: Letrozole 2.5mg orally once daily. Repeat cycle every 4 weeks.
Palbociclib + Anastrozole (Category 1) ^{9,23,24,c}	Days 1-21: Palbociclib 125mg orally once daily Days 1-28: Anastrozole 1mg orally once daily. Repeat cycle every 4 weeks.

continued

Breast Cancer (Recurrent or Metastatic) Treatment Regimens

► Systemic Therapy for ER- and/or PR-Positive Recurrent or Stage IV (M1) Disease^{1,a} (continued)

REGIMEN	DOSING
HER2-Negative and Postmenopausal or Premenopausal Receiving Ovarian Ablation or Suppression ^{2-6,b} (continued)	
Preferred Regimens: First-Line Therapy (continued)	
Palbociclib + Exemestane (Category 1) ^{13,23,24,c}	Days 1-21: Palbociclib 125mg orally once daily Days 1-28: Exemestane 25mg orally once daily. Repeat cycle every 4 weeks.
Palbociclib + Fulvestrant (Category 1) ^{15,23,25,c}	Days 1-21: Palbociclib 125mg orally once daily Days 1,15: Fulvestrant 500mg IM daily. Administer for one 28-day cycle, followed by: Days 1-21: Palbociclib 125mg orally once daily Day 1: Fulvestrant 500mg IM. Repeat cycle every 4 weeks.
Palbociclib + Letrozole (Category 1) ^{19,23,24,c}	Days 1-21: Palbociclib 125mg orally once daily Days 1-28: Letrozole 2.5mg orally once daily. Repeat cycle every 4 weeks.
Ribociclib + Anastrozole (Category 1) ^{9,26,27,c}	Days 1-21: Ribociclib 600mg orally once daily Days 1-28: Anastrozole 1mg orally once daily. Repeat cycle every 4 weeks.
Ribociclib + Exemestane (Category 1) ^{13,26,27,c}	Days 1-21: Ribociclib 600mg orally once daily Days 1-28: Exemestane 25mg orally once daily. Repeat cycle every 4 weeks.
Ribociclib + Fulvestrant (Category 1) ^{16,27,28,c}	Days 1-21: Ribociclib 600mg orally once daily Days 1,15: Fulvestrant 500mg IM. Administer one 4-week cycle, followed by: Days 1-21: Ribociclib 600mg orally once daily Day 1: Fulvestrant 500mg IM. Repeat cycle every 4 weeks.
Ribociclib + Letrozole (Category 1) ^{19,26,27,c}	Day 1-21: Ribociclib 600mg orally once daily Days 1-28: Letrozole 2.5mg orally once daily. Repeat cycle every 4 weeks.
Tamoxifen ²⁹⁻³¹	Day 1-28: Tamoxifen 20mg orally once daily. Repeat cycle every 4 weeks.
Toremifene ³²	Days 1-28: Toremifene 60mg orally once daily. Repeat cycle every 4 weeks.
Preferred Regimens: Second- and Subsequent-Line Therapy	
Abemaciclib + Fulvestrant (if CDK4/6 inhibitor not previously used; Category 1) ^{8,16,33,34,c}	Days 1-28: Abemaciclib 150mg orally twice daily Days 1,15: Fulvestrant 500mg IM. Administer one 4-week cycle, followed by: Days 1-28: Abemaciclib 150mg orally twice daily Day 1: Fulvestrant 500mg IM. Repeat cycle every 4 weeks.
Alpelisib + Fulvestrant (<i>PIK3CA</i> mutation; Category 1) ^{16,35,36,d}	Days 1-28: Alpelisib 300mg orally once daily Days 1,15: Fulvestrant 500mg IM. Administer for one 4-week cycle, followed by: Days 1-28: Alpelisib 300mg orally once daily Day 1: Fulvestrant 500mg IM. Repeat cycle every 4 weeks.
Anastrozole ^{9,12}	Days 1-28: Anastrozole 1mg once orally. Repeat cycle every 4 weeks.
Everolimus + Exemestane ^{13,37,38,c}	Days 1-28: Everolimus 10mg orally once daily Days 1-28: Exemestane 25mg orally once daily. Repeat cycle every 4 weeks.

continued

Breast Cancer (Recurrent or Metastatic) Treatment Regimens

► Systemic Therapy for ER- and/or PR-Positive Recurrent or Stage IV (M1) Disease^{1,a} (continued)

REGIMEN	DOSING
HER2-Negative and Postmenopausal or Premenopausal Receiving Ovarian Ablation or Suppression^{2-6,b} (continued)	
Preferred Regimens: Second- and Subsequent-Line Therapy (continued)	
Everolimus + Fulvestrant ^{13,17,37,38,c}	Days 1-28: Everolimus 10mg orally once daily Days 1,15: Fulvestrant 500mg IM. Administer for one 28-day cycle, followed by: Days 1-28: Everolimus 10mg orally once daily Day 1: Fulvestrant 500mg IM. Repeat cycle every 4 weeks.
Everolimus + Tamoxifen ^{29,37,38,c}	Days 1-28: Everolimus 10mg orally once daily Days 1-28: Tamoxifen 20mg orally once daily. Repeat cycle every 4 weeks.
Exemestane ^{10,13-15}	Days 1-28: Exemestane 25mg orally once daily. Repeat cycle every 4 weeks.
Fulvestrant ^{16,17}	Days 1,15: Fulvestrant 500mg IM. Administer for one 28-day cycle, followed by: Day 1: Fulvestrant 500mg IM. Repeat cycle every 4 weeks.
Letrozole ^{10,19,22}	Days 1-28: Letrozole 2.5mg orally once daily. Repeat cycle every 4 weeks.
Palbociclib + Fulvestrant (if CDK4/6 inhibitor not previously used; Category 1) ^{16,24,25,c}	Days 1-21: Palbociclib 125mg orally once daily Days 1,15: Fulvestrant 500mg IM daily. Administer for one 28-day cycle, followed by: Days 1-21: Palbociclib 125mg orally once daily Day 1: Fulvestrant 500mg IM. Repeat cycle every 4 weeks.
Ribociclib + Fulvestrant (if CDK4/6 inhibitor not previously used; Category 1) ^{16,27,28,c}	Days 1-21: Ribociclib 600mg orally once daily Days 1-15: Fulvestrant 500mg IM. Administer one 4-week cycle, followed by: Days 1-21: Ribociclib 600mg orally once daily Day 1: Fulvestrant 500mg IM. Repeat cycle every 4 weeks.
Tamoxifen ²⁹⁻³¹	Day 1-28: Tamoxifen 20mg orally once daily. Repeat cycle every 4 weeks.
Toremifene ³²	Days 1-28: Toremifene 60mg orally once daily. Repeat cycle every 4 weeks.
Useful in Certain Circumstances	
Abemaciclib ^{8,34}	Days 1-28: Abemaciclib 200mg orally twice daily. Repeat cycle every 4 weeks.
Ethinyl Estradiol ^{8,39}	Days 1-28: Estradiol 10mg orally three times daily. Repeat cycle every 4 weeks.
Fluoxymesterone ^{40,41}	Days 1-28: Fluoxymesterone 10mg orally twice daily. Repeat cycle every 4 weeks.
Megestrol Acetate ^{42,43}	Days 1-28: Megestrol 40mg orally four times daily. Repeat cycle every 4 weeks.
HER2-Positive and Postmenopausal or Premenopausal Receiving Ovarian Ablation or Suppression^{b,e,f}	
Anastrozole ^{9,10}	Days 1-28: Anastrozole 1mg orally once daily. Repeat cycle every 4 weeks.
Anastrozole + Lapatinib ^{9,44,45}	Days 1-28: Anastrozole 1mg orally once daily Days 1-28: Lapatinib 1,500mg orally once daily. Repeat cycle every 4 weeks.

continued

Breast Cancer (Recurrent or Metastatic) Treatment Regimens

► Systemic Therapy for ER- and/or PR-Positive Recurrent or Stage IV (M1) Disease^{1,a} (continued)

REGIMEN	DOSING
HER2-Positive Postmenopausal or Premenopausal Receiving Ovarian Ablation or Suppression^{e,f} (continued)	
Anastrozole + Lapatinib + Trastuzumab ^{9,44,46}	<p>Days 1-28: Anastrozole 1mg orally once daily Days 1-28: Lapatinib 1,000mg orally once daily cycled every 4 weeks, with: Day 1: Trastuzumab 4mg/kg IV over 90 minutes on week 1, then 2mg/kg IV over 30 minutes starting week 2 cycled weekly.</p> <p>OR</p> <p>Days 1-28: Anastrozole 1mg orally once daily Days 1-28: Lapatinib 1,000mg orally once daily cycled every 4 weeks, with: Day 1: Trastuzumab 8mg/kg IV over 90 minutes on cycle 1, then 6mg/kg IV over 30 minutes starting with cycle 2 cycled every 3 weeks.</p>
Anastrozole + Trastuzumab ^{9,46,47}	<p>Days 1-21: Anastrozole 1mg orally once daily Day 1: Trastuzumab 8mg/kg IV over 90 minutes on cycle 1, then 6mg/kg IV over 30 minutes starting with cycle 2. Repeat cycle every 3 weeks.</p>
Exemestane ^{10,13}	<p>Days 1-28: Exemestane 25mg orally once daily. Repeat cycle every 4 weeks.</p>
Exemestane + Lapatinib ^{10,44}	<p>Days 1-28: Exemestane 25mg orally once daily Days 1-28: Lapatinib 1,500mg orally once daily. Repeat cycle every 4 weeks.</p>
Exemestane + Lapatinib + Trastuzumab ^{10,44,46}	<p>Days 1-28: Exemestane 25mg orally once daily Days 1-28: Lapatinib 1,000mg orally once daily cycled every 4 weeks, with: Day 1: Trastuzumab 4mg/m² IV over 90 minutes on week 1, then 2mg/m² IV over 30 minutes starting week 2 cycled weekly.</p> <p>OR</p> <p>Days 1-28: Exemestane 25mg orally once daily Days 1-28: Lapatinib 1,000mg orally once daily cycled every 4 weeks, with: Day 1: Trastuzumab 8mg/kg IV over 90 minutes on cycle 1, then 6mg/m² IV starting with cycle 2 cycled every 3 weeks.</p>
Exemestane + Trastuzumab ^{10,46,47}	<p>Days 1-28: Exemestane 25mg orally once daily cycled every 4 weeks, with: Day 1: Trastuzumab 4mg/kg IV over 90 minutes on week 1, then 2mg/kg IV starting week 2 cycled weekly.</p> <p>OR</p> <p>Days 1-28: Exemestane 25mg orally once daily cycled every 4 weeks, with: Day 1: Trastuzumab 8mg/kg IV over 90 minutes on cycle 1, then 6mg/m² IV starting with cycle 2 cycled every 3 weeks.</p>
Fulvestrant ^{16,17}	<p>Days 1,15: Fulvestrant 500mg IM. Administer for one 28-day cycle, followed by: Day 1: Fulvestrant 500mg IM. Repeat cycle every 4 weeks.</p>
Fulvestrant + Trastuzumab ^{16,46,48,49}	<p>Days 1,15: Fulvestrant 500mg IM on cycle 1, followed by: Day 1: Fulvestrant 500mg IM starting with cycle 2 cycled every 4 weeks, with: Day 1: Trastuzumab 4mg/kg IV over 90 minutes on week 1, then 2mg/m² IV starting week 2 cycled weekly.</p> <p>OR</p> <p>Days 1,15: Fulvestrant 500mg IM on cycle 1, followed by: Day 1: Fulvestrant 500mg IM starting with cycle 2 cycled every 4 weeks, with: Day 1: Trastuzumab 8mg/kg IV 90 minutes on cycle 1, then 6mg/m² IV over 30 minutes starting with cycle 2 cycled every 3 weeks.</p>
Letrozole ^{19-22,50}	<p>Days 1-28: Letrozole 2.5mg orally once daily. Repeat cycle every 4 weeks.</p>
Letrozole + Lapatinib ^{19,45,51}	<p>Days 1-28: Lapatinib 1,500mg orally once daily Days 1-28: Letrozole 2.5mg orally once daily. Repeat cycle every 4 weeks.</p>
Letrozole + Lapatinib + Trastuzumab ^{19,44,46}	<p>Days 1-28: Letrozole 2.5mg orally once daily Days 1-28: Lapatinib 1,000mg orally once daily cycled every 4 weeks, with: Day 1: Trastuzumab 4mg/kg IV over 90 minutes on week 1, then 2mg/m² IV starting week 2 cycled weekly.</p> <p>OR</p> <p>Days 1-28: Letrozole 2.5mg orally once daily Days 1-28: Lapatinib 1,000mg orally once daily cycled every 4 weeks, with: Day 1: Trastuzumab 8mg/kg IV 90 minutes on cycle 1, then 6mg/m² IV over 30 minutes starting with cycle 2 cycled every 3 weeks.</p>

continued

Breast Cancer (Recurrent or Metastatic) Treatment Regimens

► Systemic Therapy for ER- and/or PR-Positive Recurrent or Stage IV (M1) Disease^{1,a} (continued)

REGIMEN	DOSING
HER2-Positive Postmenopausal or Premenopausal Receiving Ovarian Ablation or Suppression^{e,f} (continued)	
Letrozole + Trastuzumab ^{19,46,47}	<p>Days 1-28: Letrozole 2.5mg orally once daily cycled every 4 weeks, with: Day 1: Trastuzumab 4mg/kg IV over 90 minutes on week 1, then 2mg/kg IV over 30 minutes starting with week 2 cycled weekly.</p> <p>OR</p> <p>Days 1-28: Letrozole 2.5mg orally once daily cycled every 4 weeks, with: Day 1: Trastuzumab 8mg/kg IV over 90 minutes on cycle 1, then 6mg/kg over 30 minutes starting with cycle 2 cycled every 3 weeks.</p>
Tamoxifen ^{29,31,52}	<p>Day 1-28: Tamoxifen 20mg orally once daily. Repeat cycle every 4 weeks.</p>
Tamoxifen + Trastuzumab ^{29,46,47}	<p>Days 1-28: Tamoxifen 20mg orally once daily cycled every 4 weeks, with: Day 1: Trastuzumab 4mg/kg IV over 90 minutes on week 1, then 2mg/kg IV over 30 minutes starting with week 2 cycled weekly.</p> <p>OR</p> <p>Days 1-28: Tamoxifen 20mg orally once daily cycled every 4 weeks, with: Day 1: Trastuzumab 8mg/kg IV over 90 minutes on cycle 1, then 6mg/kg over 30 minutes starting with cycle 2 cycled every 3 weeks.</p>

► Chemotherapy Regimens For Recurrent or Stage IV (M1) Disease^{1,a,g,h}

HER2-Negative	
Preferred Regimens	
Capecitabine ^{53,54}	<p>Days 1-14: Capecitabine 1,000-1,250mg/m² orally twice daily. Repeat cycle every 3 weeks.</p>
Carboplatin (triple-negative breast cancer [TNBC] and germline <i>BRCA1/2</i> mutation) ⁵⁵	<p>Day 1: Carboplatin AUC 6 IV over 30 minutes. Repeat cycle every 3 or 4 weeks.</p>
Cisplatin (TNBC and germline <i>BRCA1/2</i> mutation) ⁵⁶	<p>Day 1: Cisplatin 75mg/m² IV over 60 minutes. Repeat cycle every 3 weeks.</p>
Doxorubicin ⁵⁷⁻⁶⁰	<p>Day 1: Doxorubicin 60-75mg/m² IV push. Repeat cycle every 3 weeks.</p> <p>OR</p> <p>Day 1: Doxorubicin 20mg/m² IV push. Repeat cycle weekly.</p>
Eribulin ^{61,62}	<p>Days 1,8: Eribulin 1.4mg/m² IV push. Repeat cycle every 3 weeks.</p>
Gemcitabine ⁶³	<p>Days 1,8,15: Gemcitabine 800-1,200mg/m² IV over 30 minutes. Repeat cycle every 4 weeks.</p>
Liposomal Doxorubicin ^{64,65}	<p>Day 1: Liposomal Doxorubicin 40-50mg/m² IV. Repeat cycle every 4 weeks.</p>
Paclitaxel ^{66,67}	<p>Day 1: Paclitaxel 175mg/m² IV over 3 hours. Repeat cycle every 3 weeks.</p> <p>OR</p> <p>Day 1: Paclitaxel 80mg/m² IV over 60 minutes. Repeat cycle weekly.</p>
Vinorelbine ⁶⁸	<p>Day 1: Vinorelbine 25mg/m² over 5-10 minutes. Repeat cycle weekly.</p>
Other Recommended Regimens	
Albumin-Bound Paclitaxel ⁶⁹⁻⁷¹	<p>Day 1: Albumin-bound paclitaxel 260mg/m² IV over 30 minutes. Repeat cycle every 3 weeks.</p> <p>OR</p> <p>Days 1,8,15: Albumin-bound paclitaxel 100mg/m² IV over 30 minutes. Repeat cycle every 4 weeks.</p> <p>OR</p> <p>Days 1,8,15: Albumin-bound paclitaxel 125mg/m² IV over 30 minutes. Repeat cycle every 4 weeks.</p>

continued

Breast Cancer (Recurrent or Metastatic) Treatment Regimens

► Chemotherapy Regimens For Recurrent or Stage IV (M1) Disease^{1,a,g,h} (continued)

REGIMEN	DOSING
HER2-Negative (continued)	
Other Recommended Regimens (continued)	
Cyclophosphamide ⁷²	Days 1-21: Cyclophosphamide 50mg orally once daily. Repeat cycle every 4 weeks.
Docetaxel ^{73,74}	Day 1: Docetaxel 60-100mg/m ² IV over 60 minutes. Repeat cycle every 3 weeks. OR Days 1,8,15,22,29,36: Docetaxel 35mg/m ² IV over 60 minutes. Repeat cycle every 8 weeks (6 weeks on- followed by 2 weeks off-treatment)
Epirubicin ⁷⁵	Day 1: Epirubicin 60-90 mg/m ² IV push. Repeat cycle every 3 weeks.
Ixabepilone ^{76,77}	Day 1: Ixabepilone 40mg/m ² (max 88mg) IV over 3 hours. Repeat cycle every 3 weeks.
Useful in Certain Circumstances	
AC ⁷⁸	Day 1: Doxorubicin 60mg/m ² IV push Day 1: Cyclophosphamide 600mg/m ² IV over 30 minutes. Repeat cycle every 3 weeks.
Carboplatin + Albumin-Bound Paclitaxel ^{69,79}	Days 1,8: Albumin-Bound Paclitaxel 125mg/m ² IV over 30 minutes Days 1,8: Carboplatin AUC 2 IV over 30 minutes. Repeat cycle every 3 weeks.
Carboplatin + Paclitaxel ^{80,81}	Day 1: Paclitaxel 175-200mg/m ² IV over 3 hours, followed by: Day 1: Carboplatin AUC 6 IV over 30 minutes. Repeat cycle every 3 weeks. OR Days 1,8,15: Paclitaxel 100mg/m ² IV over 60 minutes, followed by: Days 1,8,15: Carboplatin AUC 2 IV over 30 minutes. Repeat cycle every 4 weeks.
CMF ⁸²⁻⁸⁴	Days 1-14: Cyclophosphamide 100mg/m ² orally once daily Days 1,8: Methotrexate 40mg/m ² IV push Days 1,8: Fluorouracil 600mg/m ² IV push. Repeat every 4 weeks.
Docetaxel + Capecitabine ⁸⁵	Day 1: Docetaxel 75 mg/m ² IV over 60 minutes Days 1-14: Capecitabine 950-1.250mg/m ² orally twice daily. Repeat cycle every 3 weeks.
EC ^{86,87}	Day 1: Epirubicin 100mg/m ² IV push Day 1: Cyclophosphamide 830mg/m ² IV over 30 minutes. Repeat cycle every 3 weeks.
Gemcitabine + Carboplatin ⁸⁸	Days 1,8: Gemcitabine 1,000mg/m ² IV over 30 minutes Days 1,8: Carboplatin AUC 2 IV over 30 minutes. Repeat cycle every 3 weeks.
GT ⁸⁹	Day 1: Paclitaxel 175mg/m ² IV over 3 hours, followed by: Days 1,8: Gemcitabine 1,250mg/m ² IV over 30 minutes. Repeat cycle every 3 weeks.
Paclitaxel + Bevacizumab ^{90,91}	Days 1,8,15: Paclitaxel 90mg/m ² IV over 60 minutes Days 1,15: Bevacizumab 10mg/kg IV. Repeat cycle every 4 weeks.
HER2-Positiveⁱ	
Preferred Regimens	
Pertuzumab + Trastuzumab + Docetaxel (Category 1) ^{46,92-94,j}	Day 1: Pertuzumab 840mg IV over 60 minutes on cycle 1, then 420mg IV over 30 minutes starting with cycle 2 Day 1: Trastuzumab 8mg/kg IV over 90 minutes on cycle 1, then 6mg/kg IV over 30 minutes starting with cycle 2, followed by: Day 1: Docetaxel 75mg/kg IV over 60 minutes on cycle 1, then 75-100mg/m ² over 60 minutes starting with cycle 2. Repeat cycle every 3 weeks.

continued

Breast Cancer (Recurrent or Metastatic) Treatment Regimens

►Chemotherapy Regimens For Recurrent or Stage IV (M1) Disease^{1,a,g,h} (continued)

REGIMEN	DOSING
HER2-Positive ¹ (continued)	
Preferred Regimens (continued)	
Pertuzumab + Trastuzumab + Paclitaxel ^{46,92,95}	<p>Day 1: Pertuzumab 840mg IV over 60 minutes on cycle 1, then 420mg IV over 30 minutes starting with cycle 2 Day 1: Trastuzumab 8mg/kg IV over 90 minutes on cycle 1, then 6mg/kg IV over 30 minutes starting with cycle 2 Days 1,8,15: Paclitaxel 80mg/kg IV over 60 minutes. Repeat cycle every 3 weeks.</p> <p>OR</p> <p>Day 1: Pertuzumab 840mg IV over 60 minutes on cycle 1, then 420mg IV over 30 minutes starting with cycle 2 Day 1: Trastuzumab 4mg/kg IV over 90 minutes on cycle 1, followed by: Days 8,15: Trastuzumab 2mg/kg IV over 30 minutes on cycle 1, followed by: Days 1,8,15: Trastuzumab 2mg/kg IV over 30 minutes starting with cycle 2 Days 1,8,15: Paclitaxel 80mg/kg IV over 60 minutes. Repeat cycle every 3 weeks.</p> <p>OR</p> <p>Day 1: Pertuzumab 840mg IV over 60 minutes on cycle 1, then 420mg IV over 30 minutes starting with cycle 2 Day 1: Trastuzumab 8mg/kg IV over 90 minutes on cycle 1, then 6mg/kg IV over 30 minutes starting with cycle 2 Day 1: Paclitaxel 175mg/m² IV over 3 hours. Repeat cycle every 3 weeks.</p> <p>OR</p> <p>Day 1: Pertuzumab 840mg IV over 60 minutes on cycle 1, then 420mg IV over 30 minutes starting with cycle 2 Day 1: Trastuzumab 4mg/kg IV over 90 minutes on cycle 1, followed by: Days 8,15: Trastuzumab 2mg/kg IV over 30 minutes on cycle 1, followed by: Days 1,8,15: Trastuzumab 2mg/kg IV over 30 minutes starting with cycle 2 Day 1: Paclitaxel 175mg/m² IV over 3 hours. Repeat cycle every 3 weeks.</p>
Other Recommended Regimens	
Ado-Trastuzumab Emtansine (T-DM1; Category 1) ⁹⁶⁻⁹⁸	<p>Day 1: Ado-trastuzumab emtansine 3.6mg/kg IV over 90 minutes on cycle 1, followed by: Day 1: Ado-trastuzumab emtansine 3.6mg/kg over 30 minutes beginning with cycle 2. Repeat cycle every 3 weeks.</p>
Fam-Trastuzumab Deruxtecan-nxki ^{99,100,k}	<p>Day 1: Fam-Trastuzumab Deruxtecan-nxki 5.4mg/kg IV. Repeat cycle every 3 weeks.</p>
Lapatinib + Capecitabine ^{48,54,101}	<p>Days 1-21: Lapatinib 1,250mg orally once daily Days 1-14: Capecitabine 1,000mg/m² orally twice daily. Repeat cycle every 3 weeks.</p>
Neratinib + Capecitabine ^{102,103}	<p>Days 1-21: Neratinib 240mg orally Days 1-14: Capecitabine 750mg/m² orally twice daily. Repeat cycle every 3 weeks.</p>
Trastuzumab + Albumin-bound Paclitaxel ^{46,69-71,104,j}	<p>Day 1: Albumin-bound Paclitaxel 260mg/m² IV over 30 minutes cycled every 3 weeks, with: Day 1: Trastuzumab 4mg/kg IV over 90 minutes on week 1, then 2mg/kg IV over 30 minutes starting week 2 cycled weekly.</p> <p>OR</p> <p>Day 1: Albumin-bound Paclitaxel 260mg/m² IV over 30 minutes. Day 1: Trastuzumab 8mg/kg IV over 90 minutes on cycle 1, then 6mg/kg IV over 30 minutes starting with cycle 2 cycled every 3 weeks.</p> <p>OR</p> <p>Days 1,8,15: Albumin-bound Paclitaxel 100 or 125mg/m² cycled every 4 weeks, with: Day 1: Trastuzumab 4mg/kg IV over 30 minutes on week 1, then 2mg/kg IV over 30 minutes starting week 2 cycled weekly.</p> <p>OR</p> <p>Days 1,8,15: Albumin-bound Paclitaxel 100 or 125 mg/m² IV over 30 minutes cycled every 4 weeks, with: Day 1: Trastuzumab 8mg/kg IV over 90 minutes of cycle 1, then 6mg/kg IV over 30 minutes starting with cycle 2 cycled every 3 weeks.</p>
Trastuzumab + Capecitabine ^{46,54,105,106}	<p>Days 1-14: Capecitabine 1,000-1,250mg/m² orally twice daily cycled every 3 weeks, with: Day 1: Trastuzumab 4mg/kg IV over 90 minutes on week 1, then 2mg/kg IV over 30 minutes starting week 2 cycled every week.</p> <p>OR</p> <p>Days 1-14: Capecitabine 1,000-1,250mg/m² orally twice daily Day 1: Trastuzumab 8mg/kg IV over 90 minutes, then 6mg/kg IV over 30 minutes cycled every 3 weeks.</p>

continued

Breast Cancer (Recurrent or Metastatic) Treatment Regimens

►Chemotherapy Regimens For Recurrent or Stage IV (M1) Disease^{1,a,g,h} (continued)

REGIMEN	DOSING
HER2-Positive ⁱ (continued)	
Other Recommended Regimens (continued)	
Trastuzumab + Carboplatin ^{46,55,104,j}	<p>Day 1: Carboplatin AUC 6 IV over 30 minutes cycled every 3 or 4 weeks, with: Day 1: Trastuzumab 4mg/kg IV over 90 minutes on week 1, then 2mg/kg IV over 30 minutes starting week 2 cycled weekly.</p> <p>OR</p> <p>Day 1: Carboplatin AUC 6 IV over 30 minutes cycled every 3 or 4 weeks, with: Day 1: Trastuzumab 8mg/kg IV over 90 minutes on cycle 1, then 6mg/kg IV starting with cycle 2 cycled every 3 weeks.</p>
Trastuzumab + Cisplatin ^{46,56,104,j}	<p>Day 1: Cisplatin 75mg/m² IV over 60 minutes cycled every 3 weeks, with: Day 1: Trastuzumab 4mg/kg IV 90 minutes on week 1, then 2mg/kg IV over 30 minutes starting week 2 cycled weekly.</p> <p>OR</p> <p>Day 1: Cisplatin 75mg/m² IV over 60 minutes. Day 1: Trastuzumab 8mg/kg IV over 90 minutes, then 6mg/kg IV over 30 minutes cycled every 3 weeks.</p>
Trastuzumab + Cyclophosphamide ^{46,72,104}	<p>Days 1-21: Cyclophosphamide 50mg orally once daily cycled every 4 weeks, with: Day 1: Trastuzumab 4mg/kg IV over 90 minutes on week 1, then 2mg/kg IV over 30 minutes starting week 2 cycled weekly.</p> <p>OR</p> <p>Days 1-21: Cyclophosphamide 50mg orally once daily cycled every 4 weeks, with: Day 1: Trastuzumab 8mg/kg IV over 90 minutes on cycle 1, then 6mg/kg IV over 30 minutes starting with cycle 2 cycled every 3 weeks.</p>
Trastuzumab + Docetaxel ^{46,107,108,j}	<p>Day 1: Docetaxel 80-100mg/m² IV over 60 minutes cycled every 3 weeks, with: Day 1: Trastuzumab 4mg/kg IV over 90 minutes on week 1, then 2mg/m² IV over 30 minutes starting week 2 cycled weekly.</p> <p>OR</p> <p>Day 1: Docetaxel 80-100 mg/m² IV over 60 minutes. Day 1: Trastuzumab 8mg/kg IV over 90 minutes with cycle 1, then 6mg/kg IV over 30 minutes starting with cycle 2 cycled every 3 weeks.</p> <p>OR</p> <p>Days 1,8,15: Docetaxel 35mg/m² IV over 60 minutes cycled every 4 weeks, with: Day 1: Trastuzumab 4mg/kg IV over 90 minutes on week 1, then 2mg/kg IV over 30 minutes starting week 2 cycled weekly.</p> <p>OR</p> <p>Days 1,8,15: Docetaxel 35mg/m² IV over 60 minutes cycled every 4 weeks, with: Day 1: Trastuzumab 8mg/kg IV over 90 minutes on cycle 1, then 6mg/kg IV over 30 minutes starting with cycle 2 cycled every 3 weeks.</p>
Trastuzumab + Eribulin ^{46,61,62,104,j}	<p>Days 1,8: Eribulin 1.4mg/m² IV push cycled every 3 weeks, with: Day 1: Trastuzumab 4mg/m² IV over 90 minutes on week 1, then 2mg/kg IV over 30 minutes starting week 2 cycled weekly.</p> <p>OR</p> <p>Days 1,8: Eribulin 1.4mg/m² IV push. Day 1: Trastuzumab 8mg/kg IV over 90 minutes on cycle 1, then 6mg/kg IV over 30 minutes starting with cycle 2 cycled every 3 weeks.</p>
Trastuzumab + Gemcitabine ^{46,63,104,j}	<p>Days 1,8,15: Gemcitabine 800-1,200mg/m² IV over 30 minutes cycled every 4 weeks, with: Day 1: Trastuzumab 4mg/kg IV over 90 minutes on week 1, then 2mg/kg IV over 30 minutes starting week 2 cycled weekly.</p> <p>OR</p> <p>Days 1,8,15: Gemcitabine 800-1,200mg/m² IV over 30 minutes cycled every 4 weeks, with: Day 1: Trastuzumab 8mg/kg IV over 90 minutes on cycle 1, then 6mg/kg IV over 30 minutes starting with cycle 2 cycled every 3 weeks.</p>
Trastuzumab + Ixabepilone ^{46,76,77,104,j}	<p>Day 1: Ixabepilone 40mg/m² (maximum 88mg) IV over 3 hours cycled every 3 weeks, with: Day 1: Trastuzumab 4mg/kg IV over 90 minutes on week 1, then 2mg/kg IV over 30 minutes starting week 2 cycled weekly.</p> <p>OR</p> <p>Day 1: Ixabepilone 40mg/m² (maximum 88mg) IV over 3 hours cycled every 3 weeks, with: Day 1: Trastuzumab 8mg/kg IV over 90 minutes on cycle 1, then 6mg/kg IV over 30 minutes starting with cycle 2 cycled every 3 weeks.</p>
Trastuzumab + Lapatinib (without cytotoxic therapy) ^{45,46,109}	<p>Days 1-21: Lapatinib 1,000mg orally once daily cycled every 3 weeks, with: Day 1: Trastuzumab 4mg/kg IV over 90 minutes on week 1, then 2mg/kg IV over 30 minutes starting week 2 cycled weekly.</p> <p>OR</p> <p>Days 1-21: Lapatinib 1,000mg orally once daily, with: Day 1: Trastuzumab 8mg/kg IV over 90 minutes on cycle 1, then 6mg/kg IV over 30 minutes starting with cycle 2 cycled every 3 weeks.</p>

continued

Breast Cancer (Recurrent or Metastatic) Treatment Regimens

► Chemotherapy Regimens For Recurrent or Stage IV (M1) Disease^{1,a,g,h} (continued)

REGIMEN	DOSING
HER2-Positive ^l (continued)	
Other Recommended Regimens (continued)	
Trastuzumab + Paclitaxel ^{46,104,110,111,j}	<p>Day 1: Paclitaxel 80-90mg/m² IV over 60 minutes</p> <p>Day 1: Trastuzumab 4mg/kg IV over 90 minutes on week 1, then 2mg/kg IV over 30 minutes starting week 2 cycled weekly.</p> <p>OR</p> <p>Day 1: Paclitaxel 80-90mg/m² IV over 60 minutes cycled weekly, with:</p> <p>Day 1: Trastuzumab 8mg/kg IV over 90 minutes on cycle 1, then 6 mg/kg IV over 30 minutes starting with cycle 2 cycled every 3 weeks.</p> <p>OR</p> <p>Day 1: Paclitaxel 175mg/m² IV over 3 hours cycled every 3 weeks, with:</p> <p>Day 1: Trastuzumab 4mg/kg IV over 90 minutes on week 1, then 2mg/kg IV over 30 minutes starting week 2 cycled weekly.</p> <p>OR</p> <p>Day 1: Paclitaxel 175mg/m² IV over 3 hours</p> <p>Day 1: Trastuzumab 8mg/kg IV over 90 minutes on cycle 1, then 6mg/kg IV over 30 minutes starting with cycle 2 cycled every 3 weeks.</p>
Trastuzumab + Paclitaxel + Carboplatin ^{46,111-113}	<p>Day 1: Paclitaxel 175mg/m² IV over 3 hours, followed by:</p> <p>Day 1: Carboplatin AUC 6 IV over 30 minutes cycled every 3 weeks, with:</p> <p>Day 1: Trastuzumab 4mg/kg IV on week 1, then 2mg/kg over 30 minutes starting with week 2 cycled weekly.</p> <p>OR</p> <p>Day 1: Paclitaxel 175mg/m² IV over 3 hours, followed by:</p> <p>Day 1: Carboplatin AUC 6 IV over 30 minutes, with:</p> <p>Day 1: Trastuzumab 8mg/kg IV over 90 minutes on cycle 1, then 6mg/kg IV starting with cycle 2 cycled every 3 weeks.</p> <p>OR</p> <p>Days 1,8,15: Paclitaxel 80mg/m² IV over 60 minutes, followed by:</p> <p>Days 1,8,15: Carboplatin AUC 2 IV over 30 minutes cycled every 4 weeks, with:</p> <p>Day 1: Trastuzumab 4mg/kg IV on week 1, then 2mg/kg over 30 minutes starting with week 2 cycled weekly.</p> <p>OR</p> <p>Days 1,8,15: Paclitaxel 80mg/m² IV over 60 minutes, followed by:</p> <p>Days 1,8,15: Carboplatin AUC 2 IV over 30 minutes cycled every 4 weeks, with:</p> <p>Day 1: Trastuzumab 8mg/kg IV over 90 minutes on cycle 1, then 6mg/kg IV starting with cycle 2 cycled every 3 weeks.</p>
Trastuzumab + Vinorelbine ^{46,114,j}	<p>Day 1: Vinorelbine 25mg/m² IV over 5-10 minutes, with:</p> <p>Day 1: Trastuzumab 4mg/kg over 90 minutes on week 1, then 2mg/kg over 30 minutes starting with week 2 cycled weekly.</p> <p>OR</p> <p>Day 1: Vinorelbine 25mg/m² IV over 5-10 minutes cycled weekly, with:</p> <p>Day 1: Trastuzumab 8mg/kg IV over 90 minutes on cycle 1, then 6mg/kg IV over 30 minutes starting with cycle 2 cycled every 3 weeks.</p>

► Additional Targeted Therapies and Associated Biomarker Testing for Recurrent or Stage IV (M1) Disease^{1,a}

Preferred Regimens	
Atezolizumab + Albumin-Bound Paclitaxel (PD-L1 expression 1% or higher on tumor-infiltrating immune cells) ^{69,115,116}	<p>Days 1,15: Atezolizumab 840mg IV over 60 minutes, followed by:</p> <p>Days 1,8,15: Albumin-bound Paclitaxel 100mg/m² IV.</p> <p>Repeat cycle every 4 weeks.</p>
Olaparib (germline <i>BRCA1/2</i> mutation; Category 1) ^{117,118,i}	<p>Days 1-28: Olaparib 300mg orally twice daily.</p> <p>Repeat cycle every 4 weeks.</p>
Talazoparib (germline <i>BRCA1/2</i> mutation) (Category 1) ^{119,120}	<p>Days 1-28: Talazoparib 1mg orally once daily.</p> <p>Repeat cycle every 4 weeks.</p>
Preferred Regimens: Second-Line Therapy	
Alpelisib + Fulvestrant (for Hormone-receptor positive, HER2-negative disease; <i>PIK3CA</i> mutation; Category 1) ^{16,35,36,d}	<p>Days 1-28: Alpelisib 300mg orally once daily</p> <p>Days 1,15: Fulvestrant 500mg IM.</p> <p>Administer for one 4-week cycle, followed by:</p> <p>Days 1-28: Alpelisib 300mg orally once daily</p> <p>Day 1: Fulvestrant 500mg IM.</p> <p>Repeat cycle every 4 weeks.</p>

continued

Breast Cancer (Recurrent or Metastatic) Treatment Regimens

► Additional Targeted Therapies and Associated Biomarker Testing for Recurrent or Stage IV (M1) Disease^{1,a} (continued)

REGIMEN	DOSING
HER2-Positive ¹ (continued)	
Useful Under Certain Circumstances	
Entrectinib (<i>NTRK</i> gene fusion) ^{121,122,m}	Days 1-28: Entrectinib 600mg orally once daily. Repeat cycle every 4 weeks.
Larotrectinib (<i>NTRK</i> gene fusion) ^{123,124,m}	Days 1-28: Larotrectinib 100mg orally twice daily. Repeat cycle every 4 weeks.
Pembrolizumab (MSI-H/dMMR) ^{125-127,n}	Day 1: Pembrolizumab 200mg IV over 30 minutes. Repeat cycle every 3 weeks.

- The selection, dosing, and administration of anti-cancer agents and the management of associated toxicities are complex. Modifications of drug and schedule and initiation of supportive care interventions are often necessary because of expected toxicities and individual patient variability, prior treatment, and comorbidity. The optimal delivery of anti-cancer agents therefore requires a health care delivery team experienced in the use of anti-cancer agents and the management of associated toxicities in patients with cancer.
- Ovarian suppression for premenopausal women with hormone receptor-positive disease: Day 1: Goserelin 3.6mg subcutaneous every 4 weeks until endocrine therapy is completed or no longer required or Day 1: Leuprolide 3.75mg IM every 4 weeks until endocrine therapy is completed or no longer required.
- If there is disease progression while on CDK4/6 inhibitor therapy, there are no data to support an additional line of therapy with another CDK4/6-containing regimen. Likewise, if there is disease progression while on an everolimus-containing regimen, there are no data to support an additional line of therapy with another everolimus-containing regimen.
- Indicated after progression on prior endocrine therapy and prior chemotherapy in the metastatic setting.
- Trastuzumab and hyaluronidase-oyk injection (Day 1: Trastuzumab and hyaluronidase-oyk 600mg subcutaneous over 2-5 minutes every 3 weeks) for subcutaneous use may be substituted for trastuzumab.^{128,129} Do not substitute trastuzumab and hyaluronidase-oyk for or with ado-trastuzumab emtansine or fam-trastuzumab deruxtecan-nxki. An FDA-approved biosimilar is an appropriate substitute for trastuzumab.
- If treatment was initiated with chemotherapy and trastuzumab + pertuzumab, and the chemotherapy was stopped, endocrine therapy may be added to the trastuzumab + pertuzumab.
- Albumin-bound paclitaxel may be substituted for paclitaxel or docetaxel due to medical necessity (ie, hypersensitivity reaction). If substituted for weekly paclitaxel or docetaxel, then the weekly dose of nab-paclitaxel shown not exceed 125mg/m².
- Sequential single agents are preferred, but chemotherapy combinations may be used in select patients with high tumor burden, rapidly progressive disease, and visceral crisis.
- Trastuzumab given in combination with an anthracycline is associated with significant cardiac toxicity. Concurrent use of trastuzumab and pertuzumab with an anthracycline should be avoided.
- Patients previously treated with chemotherapy plus trastuzumab in the absence of pertuzumab in the metastatic setting may be considered for one line of therapy including both trastuzumab and pertuzumab in combination with or without cytotoxic therapy (such as vinorelbine or taxane). Further research is needed to determine the ideal sequencing strategy for anti-HER2 therapy.
- Fam-Trastuzumab Deruxtecan-nxki is indicated following two or more lines of prior HER2-targeted therapy in the metastatic setting. This agent is contraindicated for patients with pneumonitis or interstitial lung disease (ILD).
- There is also a capsule formulation available. However, do not substitute the capsules for the tablets on a mg-per-mg basis due to differences in dosing and bioavailability
- Larotrectinib and entrectinib are indicated for the treatment of solid tumors that have an *NTRK* gene fusion without a known acquired resistance mutation and have no satisfactory alternative treatments or that have progressed following treatment.
- Pembrolizumab is indicated for the treatment of patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options.

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Breast Cancer (Recurrent or Metastatic) Treatment Regimens

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