

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	
Abemaciclib + Anastrozole (Category 1) ^{7,9,c,d}	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,d}	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,d}	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,d}	Days 1-28: Abemaciclib 150mg orally twice daily Days 1-28: Letrozole 2.5mg orally once daily Repeat cycle every 4 weeks.
Anastrozole ^{9,13-17}	Days 1-28: Anastrozole 1mg once orally. Repeat cycle every 4 weeks.
Everolimus + Exemestane ^{10,18,19,d}	Days 1-28: Everolimus 10mg orally once daily Days 1-28: Exemestane 25mg orally once daily. Repeat cycle every 4 weeks.
Everolimus + Fulvestrant ^{12,18-20,d}	Days 1-28: Everolimus 10mg orally once daily Days 1 and 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 ^{18,19,21,d}	Days 1-28: Everolimus 10mg orally once daily Days 1-28: Tamoxifen 20mg orally once daily. Repeat cycle every 4 weeks.
Exemestane ^{10,14,22,23}	Days 1-28: Exemestane 25mg orally once daily. Repeat cycle every 4 weeks.
Fulvestrant (Category 1) ^{12,20}	Days 1 and 15: Fulvestrant 500mg IM. Administer for one 28-day cycle, followed by: Day 1: Fulvestrant 500mg IM. Repeat cycle every 4 weeks.
Fulvestrant + Alpelisib (for PIK3CA-mutated tumors) (Category 1) ^{12,24,25,e}	Days 1-28: Alpelisib 300mg orally once daily Days 1 and 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.

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 (continued)	
Letrozole ^{13-15,26,27}	Days 1-28: Letrozole 2.5mg orally once daily. Repeat cycle every 4 weeks.
Palbociclib + Anastrozole (Category 1) ^{9,28,29,c}	Days 1-21: Palbociclib 125mg orally once daily Days 1-28: Anastrozole 1mg orally once daily. Repeat cycle every 4 weeks.
Palbociclib + Exemestane (Category 1) ^{10,28,29,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) ^{12,29,30,c}	Days 1-21: Palbociclib 125mg orally once daily Days 1 and 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) ^{13,28,29,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) ^{9,31,32,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) ^{10,31,32,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) ^{12,32,33,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) ^{13,31,32,c}	Day 1-21: Ribociclib 600mg orally once daily Days 1-28: Letrozole 2.5mg orally once daily. Repeat cycle every 4 weeks.
Tamoxifen ^{21,34,35}	Day 1-28: Tamoxifen 20mg orally once daily. Repeat cycle every 4 weeks.
Toremifene ³⁶	Days 1-28: Toremifene 60mg orally once daily. Repeat cycle every 4 weeks.
Useful in Certain Circumstances	
Abemaciclib ^{8,37,d,f}	Days 1-28: Abemaciclib 200mg orally twice daily. Repeat cycle every 4 weeks.
Estradiol ³⁸	Days 1-28: Estradiol 10mg orally three times daily. Repeat cycle every 4 weeks.
Fluoxymesterone ^{39,40}	Days 1-28: Fluoxymesterone 10mg orally twice daily. Repeat cycle every 4 weeks.
Megestrol ^{41,42}	Days 1-28: Megestrol 40mg orally four times daily. Repeat cycle every 4 weeks.
Ribociclib + Tamoxifen (Category 1) ^{21,32,43}	Days 1-21: Ribociclib 600mg orally once daily Days 1-28: Tamoxifen 20mg 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 and Postmenopausal^{4,4-46,g,h}	
Anastrozole ^{9,14}	Days 1-28: Anastrozole 1mg orally once daily. Repeat cycle every 4 weeks.
Anastrozole + Lapatinib ^{9,47,48}	Days 1-28: Anastrozole 1mg orally once daily Days 1-28: Lapatinib 1,500mg orally once daily. Repeat cycle every 4 weeks.
Anastrozole + Lapatinib + Trastuzumab ^{9,47-49}	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. OR 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.
Anastrozole + Trastuzumab ^{9,49,50}	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.
Exemestane ^{10,14}	Days 1-28: Exemestane 25mg orally once daily. Repeat cycle every 4 weeks.
Exemestane + Lapatinib ^{10,47,48}	Days 1-28: Exemestane 25mg orally once daily Days 1-28: Lapatinib 1,500mg orally once daily. Repeat cycle every 4 weeks.
Exemestane + Lapatinib + Trastuzumab ^{10,47-49}	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/m ² IV over 90 minutes on week 1, then 2mg/m ² IV over 30 minutes starting week 2 cycled weekly. OR 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/m ² IV starting with cycle 2 cycled every 3 weeks.
Exemestane + Trastuzumab ^{10,49,50}	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. OR 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/m ² IV starting with cycle 2 cycled every 3 weeks.
Fulvestrant ^{12,20}	Days 1 and 15: Fulvestrant 500mg IM. Administer for one 28-day cycle, followed by: Day 1: Fulvestrant 500mg IM. Repeat cycle every 4 weeks.
Fulvestrant + Trastuzumab ^{12,49,51,52}	Days 1 and 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/m ² IV starting week 2 cycled weekly. OR Days 1 and 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/m ² IV over 30 minutes starting with cycle 2 cycled every 3 weeks.
Letrozole ^{13,15,26,27,53}	Days 1-28: Letrozole 2.5mg orally once daily. Repeat cycle every 4 weeks.
Letrozole + Lapatinib ^{13,48,54}	Days 1-28: Lapatinib 1,500mg orally once daily Days 1-28: Letrozole 2.5mg 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 and Postmenopausal^{44-46,g,h} (continued)	
Letrozole + Lapatinib + Trastuzumab ^{13,47-49}	<p>Days 1-28: Letrozole 2.5mg orally once daily</p> <p>Days 1-28: Lapatinib 1,000mg orally once daily cycled every 4 weeks, with:</p> <p>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</p> <p>Days 1-28: Lapatinib 1,000mg orally once daily cycled every 4 weeks, with:</p> <p>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 + Trastuzumab ^{13,49,50}	<p>Days 1-28: Letrozole 2.5mg orally once daily cycled every 4 weeks, with:</p> <p>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:</p> <p>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 ^{21,35,55}	<p>Day 1-28: Tamoxifen 20mg orally once daily.</p> <p>Repeat cycle every 4 weeks.</p>
Tamoxifen + Trastuzumab ^{21,49,50}	<p>Days 1-28: Tamoxifen 20mg orally once daily cycled every 4 weeks, with:</p> <p>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:</p> <p>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,i}

HER2-Negative	
Preferred Regimens	
Atezolizumab + Albumin-Bound Paclitaxel (PD-L1-positive triple-negative breast cancer) ⁵⁶⁻⁵⁸	<p>Days 1 and 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>
Capecitabine ^{59,60}	<p>Days 1-14: Capecitabine 1,000-1,250mg/m² orally twice daily.</p> <p>Repeat cycle every 3 weeks.</p>
Carboplatin (triple-negative breast cancer and <i>BRCA1/2</i> mutation) ⁶¹	<p>Day 1: Carboplatin AUC 6 IV over 30 minutes.</p> <p>Repeat cycle every 3 or 4 weeks.</p>
Cisplatin (triple-negative breast cancer and <i>BRCA1/2</i> mutation) ⁶²	<p>Day 1: Cisplatin 75mg/m² IV over 60 minutes.</p> <p>Repeat cycle every 3 weeks.</p>
Doxorubicin ⁶³⁻⁶⁶	<p>Day 1: Doxorubicin 60-75mg/m² IV push.</p> <p>Repeat cycle every 3 weeks.</p> <p>OR</p> <p>Day 1: Doxorubicin 20mg/m² IV push.</p> <p>Repeat cycle weekly.</p>
Eribulin ^{67,68}	<p>Days 1 and 8: Eribulin 1.4mg/m² IV push.</p> <p>Repeat cycle every 3 weeks.</p>
Gemcitabine ⁶⁹	<p>Days 1,8,15: Gemcitabine 800-1,200mg/m² IV over 30 minutes.</p> <p>Repeat cycle every 4 weeks.</p>
Liposomal Doxorubicin ^{70,71}	<p>Day 1: Liposomal Doxorubicin 40-50mg/m² IV.</p> <p>Repeat cycle every 4 weeks.</p>
Olaparib (germline <i>BRCA1/2</i> mutation) (Category 1) ^{72,73,k}	<p>Days 1-28: Olaparib 300mg orally twice daily.</p> <p>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,i} (continued)

REGIMEN	DOSING
HER2-Negative (continued)	
Preferred Regimens (continued)	
Paclitaxel ^{74,75}	Day 1: Paclitaxel 175mg/m ² IV over 3 hours. Repeat cycle every 3 weeks. OR Day 1: Paclitaxel 80mg/m ² IV over 60 minutes. Repeat cycle weekly.
Talazoparib (germline <i>BRCA1/2</i> mutation) (Category 1) ^{76,77}	Days 1-28: Talazoparib 1mg orally once daily. Repeat cycle every 4 weeks.
Vinorelbine ⁷⁸	Day 1: Vinorelbine 25mg/m ² over 5-10 minutes. Repeat cycle weekly.
Other Recommended Regimensⁱ	
Albumin-Bound Paclitaxel ^{58,79,80}	Day 1: Albumin-bound paclitaxel 260mg/m ² IV over 30 minutes. Repeat cycle every 3 weeks. OR Days 1,8,15: Albumin-bound paclitaxel 100mg/m ² IV over 30 minutes. Repeat cycle every 4 weeks. OR Days 1,8,15: Albumin-bound paclitaxel 125mg/m ² IV over 30 minutes. Repeat cycle every 4 weeks.
Cyclophosphamide ⁸¹	Days 1-21: Cyclophosphamide 50mg orally once daily. Repeat cycle every 4 weeks.
Docetaxel ^{82,83}	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 ⁸⁴	Day 1: Epirubicin 60-90 mg/m ² IV push. Repeat cycle every 3 weeks.
Ixabepilone ^{85,86}	Day 1: Ixabepilone 40mg/m ² (max 88mg) IV over 3 hours. Repeat cycle every 3 weeks.
Useful in Certain Circumstances^j	
AC ⁸⁷	Day 1: Doxorubicin 60mg/m ² IV push Day 1: Cyclophosphamide 600mg/m ² IV over 30 minutes. Repeat cycle every 3 weeks.
CMF ⁸⁸⁻⁹⁰	Days 1-14: Cyclophosphamide 100mg/m ² orally once daily Days 1 and 8: Methotrexate 40mg/m ² IV push Days 1 and 8: Fluorouracil 600mg/m ² IV push. Repeat every 4 weeks.
Docetaxel + Capecitabine ⁹¹	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 ^{92,93}	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 ⁹⁴	Days 1 and 8: Gemcitabine 1,000mg/m ² IV over 30 minutes Days 1 and 8: Carboplatin AUC 2 IV over 30 minutes. Repeat cycle every 3 weeks.
GT (Gemcitabine + Paclitaxel) ⁹⁵⁻	Day 1: Paclitaxel 175mg/m ² IV over 3 hours, followed by: Days 1 and 8: Gemcitabine 1,250mg/m ² IV over 30 minutes. Repeat cycle every 3 weeks.
Paclitaxel + Bevacizumab ^{96,97}	Days 1,8,15: Paclitaxel 90mg/m ² IV over 60 minutes Days 1 and 15: Bevacizumab 10mg/kg IV. Repeat cycle every 4 weeks.

continued

Breast Cancer (Recurrent or Metastatic) Treatment Regimens

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

REGIMEN	DOSING
HER2-Positive^{44-46,g,l,m}	
Preferred Regimens	
Pertuzumab + Trastuzumab ^{49,98,99,m}	<p>Day 1: Pertuzumab 840mg IV over 60 minutes on cycle 1, then 420mg IV over 30 minutes starting with cycle 2</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. 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</p> <p>Day 1: Trastuzumab 4mg/kg IV over 90 minutes on cycle 1, followed by:</p> <p>Days 8 and 15: Trastuzumab 2mg/kg IV over 30 minutes on cycle 1, followed by:</p> <p>Days 1,8,15: Trastuzumab 2mg/kg IV over 30 minutes starting with cycle 2. Repeat cycle every 3 weeks.</p>
Pertuzumab + Trastuzumab + Docetaxel (Category 1) ^{49,98,100}	<p>Day 1: Pertuzumab 840mg IV over 60 minutes on cycle 1, then 420mg IV over 30 minutes starting with cycle 2</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, followed by:</p> <p>Day 1: Docetaxel 75mg/kg IV over 60 minutes on cycle 1, then 75-100mg/m² over 60 minutes starting with cycle 2. Repeat cycle every 3 weeks.</p>
Pertuzumab + Trastuzumab + Paclitaxel ^{49,98,101}	<p>Day 1: Pertuzumab 840mg IV over 60 minutes on cycle 1, then 420mg IV over 30 minutes starting with cycle 2</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</p> <p>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</p> <p>Day 1: Trastuzumab 4mg/kg IV over 90 minutes on cycle 1, followed by:</p> <p>Days 8 and 15: Trastuzumab 2mg/kg IV over 30 minutes on cycle 1, followed by:</p> <p>Days 1,8,15: Trastuzumab 2mg/kg IV over 30 minutes starting with cycle 2</p> <p>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</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</p> <p>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</p> <p>Day 1: Trastuzumab 4mg/kg IV over 90 minutes on cycle 1, followed by:</p> <p>Days 8 and 15: Trastuzumab 2mg/kg IV over 30 minutes on cycle 1, followed by:</p> <p>Days 1,8,15: Trastuzumab 2mg/kg IV over 30 minutes starting with cycle 2</p> <p>Day 1: Paclitaxel 175mg/m² IV over 3 hours. Repeat cycle every 3 weeks.</p>
Other Recommended Regimens	
Ado-trastuzumab emtansine (Category 1) ¹⁰²⁻¹⁰⁴	<p>Day 1: Ado-trastuzumab emtansine 3.6mg/kg IV over 90 minutes on cycle 1, followed by:</p> <p>Day 1: Ado-trastuzumab emtansine 3.6mg/kg over 30 minutes beginning with cycle 2. Repeat cycle every 3 weeks.</p>
Lapatinib + Capecitabine ^{48,60,105}	<p>Days 1-21: Lapatinib 1,250mg orally once daily</p> <p>Days 1-14: Capecitabine 1,000mg/m² orally twice daily. Repeat cycle every 3 weeks.</p>
Trastuzumab + Albumin-bound Paclitaxel ^{49,58,79,80,106}	<p>Day 1: Albumin-bound Paclitaxel 260mg/m² IV over 30 minutes 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: Albumin-bound Paclitaxel 260mg/m² IV over 30 minutes.</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. Repeat cycle every 3 weeks.</p> <p>OR</p> <p>Days 1,8,15: Albumin-bound Paclitaxel 100 or 125mg/m² cycled every 4 weeks, with:</p> <p>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:</p> <p>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>

continued

Breast Cancer (Recurrent or Metastatic) Treatment Regimens

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

REGIMEN	DOSING
HER2-Positive ^{g,l,m} (continued)	
Other Recommended Regimens (continued)	
Trastuzumab + Capecitabine ^{49,60,107,198}	<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. Repeat cycle every 3 weeks.</p>
Trastuzumab + Carboplatin ^{49,61,106}	<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 ^{49,62,106}	<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. Repeat cycle every 3 weeks.</p>
Trastuzumab + Cyclophosphamide ^{49,106,109}	<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 ^{49,110,111}	<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. Repeat cycle 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 ^{49,67,68,106}	<p>Days 1 and 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 and 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. Repeat cycle every 3 weeks.</p>
Trastuzumab + Gemcitabine ^{49,69,106}	<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 ^{49,85,86,106}	<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. Repeat cycle every 3 weeks.</p>

continued

Breast Cancer (Recurrent or Metastatic) Treatment Regimens

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

REGIMEN	DOSING
HER2-Positive ^{g,i,m} (continued)	
Other Recommended Regimens (continued)	
Trastuzumab + Lapatinib (without cytotoxic therapy) ^{48,49,112}	<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 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>
Trastuzumab + Paclitaxel ^{49,106,113,114}	<p>Day 1: Paclitaxel 80-90mg/m² IV over 60 minutes Day 1: Trastuzumab 4mg/kg IV over 90 minutes on week 1, then 2mg/kg IV over 30 minutes starting week 2. Repeat cycle weekly.</p> <p>OR</p> <p>Day 1: Paclitaxel 80-90mg/m² IV over 60 minutes cycled weekly, 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> <p>OR</p> <p>Day 1: Paclitaxel 175mg/m² 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: Paclitaxel 175mg/m² IV over 3 hours 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>
Trastuzumab + Paclitaxel + Carboplatin ^{49,114-116}	<p>Day 1: Paclitaxel 175mg/m² IV over 3 hours, followed by: Day 1: Carboplatin AUC 6 IV over 30 minutes cycled every 3 weeks, with: 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: Day 1: Carboplatin AUC 6 IV over 30 minutes, with: Day 1: Trastuzumab 8mg/kg IV over 90 minutes on cycle 1, then 6mg/kg IV starting with cycle 2. Repeat cycle every 3 weeks.</p> <p>OR</p> <p>Days 1,8,15: Paclitaxel 80mg/m² IV over 60 minutes, followed by: Days 1,8,15: Carboplatin AUC 2 IV over 30 minutes cycled every 4 weeks, with: 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: Days 1,8,15: Carboplatin AUC 2 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 starting with cycle 2 cycled every 3 weeks.</p>
Trastuzumab + Vinorelbine ^{49,117,118}	<p>Day 1: Vinorelbine 25mg/m² IV over 5-10 minutes Day 1: Trastuzumab 4mg/kg over 90 minutes on week 1, then 2mg/kg over 30 minutes starting with week 2. Repeat cycle weekly.</p> <p>OR</p> <p>Day 1: Vinorelbine 25mg/m² IV over 5-10 minutes cycled weekly, 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> <p>OR</p> <p>Days 1 and 8: Vinorelbine 30-35 mg/m² IV over 5-10 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>Days 1 and 8: Vinorelbine 30-35 mg/m² IV over 5-10 minutes 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>

a. 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.

b. 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.

continued

Breast Cancer (Recurrent or Metastatic) Treatment Regimens

- c. CDK4/6 inhibitor (abemaciclib, palbociclib, or ribociclib) in combination with an aromatase inhibitor (anastrozole, letrozole, or exemestane) or fulvestrant may be considered as a treatment option for first-line therapy for women who are postmenopausal or premenopausal (receiving ovarian suppression or ablation with an LHRH agonist) with hormone-receptor positive, HER2-negative metastatic breast cancer. Fulvestrant has been combined with CDK4/6 inhibitors (ie, palbociclib, ribociclib) in the first-line setting in two randomized trials.
- d. If there is disease progression while in 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.
- e. The safety of alpelisib in patients with Type I or uncontrolled Type II diabetes has not been established.
- f. Indicated after progression on prior endocrine therapy and prior chemotherapy in the metastatic setting.
- g. Trastuzumab and hyaluronidase-oysk injection (Day 1: Trastuzumab and hyaluronidase-oysk 600mg subcutaneous over 2-5 minutes every 3 weeks) for subcutaneous use may be substituted for trastuzumab. Do not substitute trastuzumab and hyaluronidase-oysk for or with ado-trastuzumab emtansine.
- h. If treatment was initiated with chemotherapy and trastuzumab + pertuzumab, and the chemotherapy was stopped, endocrine therapy may be added to the trastuzumab + pertuzumab.
- i. 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.
- j. Sequential single agents are preferred, but chemotherapy combinations may be used in select patients with high tumor burden, rapidly progressive disease, and visceral crisis.
- k. 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.
- l. 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.
- m. 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.

References

1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer V2.2019. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed August 14, 2019.
2. Moore HC, Unger JM, Phillips KA, et al. Goserelin for ovarian protection during breast-cancer adjuvant chemotherapy. *N Engl J Med*. 2015;372:923-932.
3. Hackshaw A, Houghton J, et al. Adjuvant goserelin in pre-menopausal patients with early breast cancer: Results from the ZIPP study. *Eur J Cancer*. 2006;42:895-904.
4. Goserelin (Zoladex) [package insert]. Lake Forest, IL: TerSera Therapeutics LLC; 2017.
5. Leuprolide (Lupron) [package insert]. North Chicago, IL: AbbVie, Inc.; 2018.
6. Klijn JG, Blamey RW, Boccardo F, et al. Combined tamoxifen and luteinizing hormone-releasing hormone (LHRH) agonist versus LHRH agonist alone in premenopausal advanced breast cancer: a meta-analysis of four randomized trials. *J Clin Oncol*. 2001;19:343-353.
7. Goetz MP, Toi M, Campone M et al. MONARCH 3: Abemaciclib as initial therapy for advanced breast cancer. *J Clin Oncol*. 2017;35:3638-3646.
8. Abemaciclib (Verzenio) [package insert]. Indianapolis, IN: Lilly USA, LLC; 2019.
9. Anastrozole (Arimidex) [package insert]. Baudette, IL: Ani Pharmaceuticals Inc.; 2018.
10. Exemestane (Aromasin) [package insert]. New York, NY: Pfizer Pharmaceutical Co.; 2018.
11. Sledge GW Jr, Toi M, Neven P, et al. MONARCH 2: Abemaciclib in Combination With Fulvestrant in Women With HR+/HER2- Advanced Breast Cancer Who Had Progressed While Receiving Endocrine Therapy. *J Clin Oncol*. 2017;35:2875-2884.
12. Fulvestrant (Faslodex) [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2019.
13. Letrozole (Femara) [package insert]. East Hanover, NJ: Novartis Pharmaceutical Corp.; 2017.
14. Ellis MJ, Suman VJ, Hoog J, et al. Randomized phase II neoadjuvant comparison between letrozole, anastrozole, and exemestane for postmenopausal women with estrogen receptor-rich stage 2 to 3 breast cancer: clinical and biomarker outcomes and predictive value of the baseline PAM50-based intrinsic subtype--ACOSOG Z1031. *J Clin Oncol*. 2011;29:2342-2349.
15. Torrisi R, Bagnardi V, Rotmensz N, et al. Letrozole plus GnRH analogue as pre-operative and adjuvant therapy in premenopausal women with ER positive locally advanced breast cancer. *Breast Cancer Res Treat*. 2011;126:431-441.
16. Howell A, Cuzick J, Baum M, et al. Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. *Lancet*. 2005;365:60-62.
17. Bergh J, Jönsson PE, Lidbrink EK, et al. FACT: an open-label randomized phase III study of fulvestrant and anastrozole in combination compared with anastrozole alone as first-line therapy for patients with receptor-positive postmenopausal breast cancer. *J Clin Oncol*. 2012;30:1919-1925.
18. Baselga J, Campone M, Piccart M, et al. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. *N Engl J Med*. 2012;366:520-529.
19. Everolimus (Afinitor) [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corp.; 2019.
20. Di Leo A, Jerusalem G, Petruzelka L, et al. Final overall survival: fulvestrant 500 mg vs 250 mg in the randomized CONFIRM trial. *J Natl Cancer Inst*. 2014;106(1):djt337.
21. Tamoxifen (Nolvadex) [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2004.
22. Pagani O, Regan MM, Walley BA, et al. Adjuvant exemestane with ovarian suppression in premenopausal breast cancer. *N Engl J Med*. 2014;371:107-118.
23. Paridaens RJ, Dirix LY, Beex LV, et al. Phase III study comparing exemestane with tamoxifen as first-line hormonal treatment of metastatic breast cancer in postmenopausal women: the European Organisation for Research and Treatment of Cancer Breast Cancer Cooperative Group. *J Clin Oncol*. 2008;26:4883-4890.
24. André F, Ciruelos E, Rubovszky G, et al. Alpelisib for PIK3CA-mutated, hormone receptor-positive advanced breast cancer. *N Engl J Med*. 2019;380:1929-1940.
25. Alpelisib (Piqray) [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corp.; 2019.
26. Goss PE, Ingle JN, Martino S, et al. Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: updated findings from NCIC CTG MA.17. *J Natl Cancer Inst*. 2005;97:1262-1271.
27. Dombrowsky P, Smith I, Falskø G, et al. Letrozole, a new oral aromatase inhibitor for advanced breast cancer: double-blind randomized trial showing a dose effect and improved efficacy and tolerability compared with megestrol acetate. *J Clin Oncol*. 1998;16:453-461.
28. Finn RS, Crown JP, Lang I, et al. The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study. *Lancet Oncol*. 2015;16:25-35.
29. Palbociclib (Ibrance) [package insert]. New York, NY: Pfizer Labs; 2019.
30. Turner NC, Ro J, André F, et al. Palbociclib in hormone-receptor-positive advanced breast cancer. *N Engl J Med*. 2015;373:209-219.
31. Hortobagyi GN, Stemmer SM, Burris HA, et al. Ribociclib as first-line therapy for HR-positive, advanced breast cancer. *N Engl J Med*. 2016;375:1738-1748.
32. Ribociclib (Kisqali) [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corp.; 2018.
33. Slamon DJ, Neven P, Chia S, et al. Phase III randomized study of ribociclib and fulvestrant in hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer: MONALEESA-3. *J Clin Oncol*. 2018;36:2465-2472.
34. Davies C, Pan H, Godwin J, et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. *Lancet*. 2013;381:805-816.
35. Burstein HJ, Lacchetti C, Griggs JJ. Adjuvant endocrine therapy for women with hormone receptor-positive breast cancer: American Society of Clinical Oncology clinical practice guideline update on ovarian suppression summary. *J Oncol Pract*. 2016;12:390-393.
36. International Breast Cancer Study Group, Pagani O, Gelber S, et al. Toremifene and tamoxifen are equally effective for early-stage breast cancer: first results of International Breast Cancer Study Group Trials 12-93 and 14-93. *Ann Oncol*. 2004;15:1749-1759.

continued

Breast Cancer (Recurrent or Metastatic) Treatment Regimens

References (continued)

37. Dickler MN, Tolaney SM, Rugo HS, et al. MONARCH 1, A phase II study of abemaciclib, a CDK4 and CDK6 inhibitor, as a single agent, in patients with refractory HR+/HER2- metastatic breast cancer. *Clin Cancer Res*. 2017;23:5218-5224.
38. Anderson GL, Chlebowski RT, Aragaki AK, et al. Conjugated equine oestrogen and breast cancer incidence and mortality in postmenopausal women with hysterectomy: extended follow-up of the Women's Health Initiative randomised placebo-controlled trial. *Lancet Oncol*. 2012;13:476-486.
39. Ingle JN, Suman VJ, Mailliard JA, et al. Randomized trial of tamoxifen alone or combined with fluoxymesterone as adjuvant therapy in postmenopausal women with resected estrogen receptor positive breast cancer. North Central Cancer Treatment Group Trial 89-30-52. *Breast Cancer Res Treat*. 2006;98:217-222.
40. Fluoxymesterone (Androxy). [package insert]. Morristown, NJ: Upsher-Smith Laboratories Inc.; 2014.
41. Buzdar A, Douma J, Davidson N, et al. Phase III, multicenter, double-blind, randomized study of letrozole, an aromatase inhibitor, for advanced breast cancer versus megestrol acetate. *J Clin Oncol*. 2001;19:3357-3366.
42. Megestrol acetate (Megace) [package insert]. Princeton, NJ: Bristol-Myers Squibb, Co.; 2016.
43. Tripathy D, Im SA, Colleoni M, et al. Ribociclib plus endocrine therapy for premenopausal women with hormone-receptor-positive, advanced breast cancer (MONALEESA-7): a randomised phase 3 trial. *Lancet Oncol*. 2018;19:904-915.
44. Jackisch C, Hegg R, Stroyakovskiy D, et al. HannahH phase III randomised study: Association of total pathological complete response with event-free survival in HER2-positive early breast cancer treated with neoadjuvant-adjuvant trastuzumab after 2 years of treatment-free follow-up. *Eur J Cancer*. 2016;62:62-75.
45. Gligorov J, Ataseven B, Verrill M, et al. Safety and tolerability of subcutaneous trastuzumab for the adjuvant treatment of human epidermal growth factor receptor 2-positive early breast cancer: SafeHer phase III study's primary analysis of 2573 patients. *Eur J Cancer*. 2017;82:237-246.
46. Trastuzumab hyaluronidase-oysk (Herceptin Hylecta) [package insert]. South San Francisco, CA: Genentech, Inc. 2019.
47. Johnston SRD, Hegg R, Im SA, et al. Phase III, randomized study of dual human epidermal growth factor receptor 2 (HER2) blockade with lapatinib plus trastuzumab in combination with an aromatase inhibitor in postmenopausal women with HER2-positive, hormone receptor-positive metastatic breast cancer: ALTERNATIVE. *J Clin Oncol*. 2018;36:741-748.
48. Lapatinib (Tykerb) [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corp.; 2018.
49. Trastuzumab (Herceptin) [package insert]. South San Francisco, CA: Genentech, Inc.; 2018.
50. Kaufman B, Mackey JR, Clemens MR, et al. Trastuzumab plus anastrozole versus anastrozole alone for the treatment of postmenopausal women with human epidermal growth factor receptor 2-positive, hormone receptor-positive metastatic breast cancer: results from the randomized phase III TAnDEM study. *J Clin Oncol*. 2009;27:5529-5537.
51. Pietras R, Marquez D, Chen H-W, et al. Improved antitumor therapy with Herceptin and Faslodex for dual targeting of HER-2 and estrogen receptor signaling pathways in human breast cancers with overexpression of HER-2/neu gene. *Breast Cancer Res Treat*. 2003;82:S12-S13.
52. Robertson JF. Fulvestrant (Faslodex) -- how to make a good drug better. *Oncologist*. 2007;12:774-784.
53. Ellis MJ, Ma C. Letrozole in the neoadjuvant setting: the P024 trial. *Breast Cancer Res Treat*. 2007;105 Suppl 1:33-43.
54. Johnston S, Phippen J Jr, Pivov X, et al. Lapatinib combined with letrozole versus letrozole and placebo as first-line therapy for postmenopausal hormone receptor-positive metastatic breast cancer. *J Clin Oncol*. 2009;27:5538-5546.
55. Davies C, Pan H, Godwin J, et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. *Lancet*. 2013;381:805-816.
56. Schmid P, Adams S, Rugo HS, et al. Atezolizumab and nab-paclitaxel in advanced triple-negative breast cancer. *N Engl J Med*. 2018;379:2108-2121.
57. Atezolizumab (Tecentriq) [package insert]. South San Francisco, CA: Genentech, Inc.; 2019.
58. Albumin-bound paclitaxel (Abraxane) [package insert]. Summit, NJ: Celgene Corp.; 2018.
59. Bajetta E, Procopio G, Celio L, et al. Safety and efficacy of two different doses of capecitabine in the treatment of advanced breast cancer in older women. *J Clin Oncol*. 2005;23:2155-2161.
60. Capecitabine (Xeloda) [package insert]. South San Francisco, CA: Genentech, Inc.; 2015.
61. Isakoff SJ, Goss PE, Mayer EL, et al. A multicenter phase II study of cisplatin or carboplatin for metastatic triple-negative breast cancer and evaluation of p63/p73 as a biomarker of response [abstract]. *J Clin Oncol*. 29 (15_suppl_abstr TBCRC009).
62. Silver DP, Richardson AL, Eklund AC, et al. Efficacy of neoadjuvant cisplatin in triple-negative breast cancer. *J Clin Oncol*. 2010;28:1145-1153.
63. Gasparini G, Dal Fior S, Panizzoni GA, et al. Weekly epirubicin versus doxorubicin as second line therapy in advanced breast cancer. A randomized clinical trial. *Am J Clin Oncol*. 1991;14:38-44.
64. Gundersen S, Kvinnsland S, Klepp O, et al. Weekly adriamycin versus VAC in advanced breast cancer. A randomized trial. *Eur J Cancer Clin Oncol*. 1986;22:1431-1434.
65. Chan S, Friedrichs K, Noel D, et al. Prospective randomized trial of docetaxel versus doxorubicin in patients with metastatic breast cancer. *J Clin Oncol*. 1999;17:2341-2354.
66. Hortobagyi GN, Yap HY, Kau SW, et al. A comparative study of doxorubicin and epirubicin in patients with metastatic breast cancer. *Am J Clin Oncol*. 1989;12:57-62.
67. Eribulin (Halaven) [package insert]. Woodcliff Lake, NJ: Eisai Inc.; 2017.
68. Cortes J, O'Shaughnessy J, Loesch D, et al. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study. *Lancet*. 2011;377:914-923.
69. Seidman AD. Gemcitabine as single-agent therapy in the management of advanced breast cancer. *Oncology (Williston Park)*. 2001;15(2 Suppl 3):11-14.
70. O'Brien ME, Wigler N, Inbar M, et al. Reduced cardiotoxicity and comparable efficacy in a phase III trial of pegylated liposomal doxorubicin HCl (CAELYX/Doxil) versus conventional doxorubicin for first-line treatment of metastatic breast cancer. *Ann Oncol*. 2004;15:440-449.
71. Doxorubicin hydrochloride liposome injection (Doxil) [package insert]. Horsham, PA: Janssen Products LP; 2017.
72. Olaparib (Lynparza) [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2019.
73. Robson M, Im SA, Senkus E, et al. Olaparib for metastatic breast cancer in patients with a germline BRCA mutation. *N Engl J Med*. 2017;377:523-533.
74. Seidman AD, Tiersten A, Hudis C, et al. Phase II trial of paclitaxel by 3-hour infusion as initial and salvage chemotherapy for metastatic breast cancer. *J Clin Oncol*. 1995;13:2575-2581.
75. Perez EA, Vogel CL, Irwin DH, et al. Multicenter phase II trial of weekly paclitaxel in women with metastatic breast cancer. *J Clin Oncol*. 2001;19:4216-4223.
76. Litton JK, Rugo HS, Ettl J, et al. Talazoparib in patients with advanced breast cancer and a germline BRCA mutation. *N Engl J Med*. 2018;379:753-763.
77. Talazoparib (Talzenna) [package insert]. New York, NY: Pfizer Labs; 2018.
78. Zelek L, Barthier S, Riofrio M, et al. Weekly vinorelbine is an effective palliative regimen after failure with anthracyclines and taxanes in metastatic breast carcinoma. *Cancer*. 2001;92:2267-2272.
79. Gradishar WJ, Tjulandina S, Davidson N, et al. Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer. *J Clin Oncol*. 2005;23:7794-7803.
80. Gradishar WJ, Krasnojn D, Cheporov S, et al. Significantly longer progression-free survival with nab-paclitaxel compared with docetaxel as first-line therapy for metastatic breast cancer. *J Clin Oncol*. 2009;27:3611-3619.
81. Licchetta A, Correale P, Migali C, et al. Oral metronomic chemo-hormonal-therapy of metastatic breast cancer with cyclophosphamide and megestrol acetate. *J Chemother*. 2010;22:201-204.
82. Burris HA 3rd. Single-agent docetaxel (Taxotere) in randomized phase III trials. *Semin Oncol*. 1999;26(3 Suppl 9):1-6.
83. Rivera E, Mejia JA, Arun BK, et al. Phase 3 study comparing the use of docetaxel on an every-3-week versus weekly schedule in the treatment of metastatic breast cancer. *Cancer*. 2008;112:1455-1461.
84. Bastholt L, Dalmark M, Gjedde SB, et al. Dose-response relationship of epirubicin in the treatment of postmenopausal patients with metastatic breast cancer: a randomized study of epirubicin at four different dose levels performed by the Danish Breast Cancer Cooperative Group. *J Clin Oncol*. 1996;14:1146-1155.

continued

Breast Cancer (Recurrent or Metastatic) Treatment Regimens

References (continued)

85. Perez EA, Lerzo G, Pivot X, et al. Efficacy and safety of ixabepilone (BMS-247550) in a phase II study of patients with advanced breast cancer resistant to an anthracycline, a taxane, and capecitabine. *J Clin Oncol*. 2007;25:3407-3414.
86. Ixabepilone (Ixempra) [package insert]. Princeton, NJ: R-Pharm US LLC; 2016.
87. Fisher B, Brown AM, Dimitrov NV, et al. Two months of doxorubicin-cyclophosphamide with and without interval reinduction therapy compared with 6 months of cyclophosphamide, methotrexate, and fluorouracil in positive-node breast cancer patients with tamoxifen-nonresponsive tumors: results from the National Surgical Adjuvant Breast and Bowel Project B-15. *J Clin Oncol*. 1990;8:1483-1496.
88. Goldhirsch A, Colleoni M, Coates AS, et al. Adding adjuvant CMF chemotherapy to either radiotherapy or tamoxifen: are all CMFs alike? The International Breast Cancer Study Group (IBCSG). *Ann Oncol*. 1998;9:489-493.
89. Bonadonna G, Brusamolino E, Valagussa P, et al. Combination chemotherapy as an adjuvant treatment in operable breast cancer. *N Engl J Med*. 1976;294:405-410.
90. Bonadonna G, Valagussa P, Moliterni A, et al. Adjuvant cyclophosphamide, methotrexate, and fluorouracil in node-positive breast cancer: the results of 20 years of follow-up. *N Engl J Med*. 1995;332:901-906.
91. O'Shaughnessy J, Miles D, Vukelja S, et al. Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: phase III trial results. *J Clin Oncol*. 2002;20:2812-2823.
92. Piccart MJ, Di Leo A, Beauduin M, et al. Phase III trial comparing two dose levels of epirubicin combined with cyclophosphamide with cyclophosphamide, methotrexate, and fluorouracil in node-positive breast cancer. *J Clin Oncol*. 2001;19(3):3103-3110.
93. Langley RE, Carmichael J, Jones AL, et al. Phase III trial of epirubicin plus paclitaxel compared with epirubicin plus cyclophosphamide as first-line chemotherapy for metastatic breast cancer: United Kingdom National Cancer Research Institute trial AB01. *J Clin Oncol*. 2005;23:8322-8330.
94. O'Shaughnessy J, Osborne C, Pippen JE, et al. Iniparib plus chemotherapy in metastatic triple-negative breast cancer. *N Engl J Med*. 2011;364:205-214.
95. Albain KS, Nag SM, Calderillo-Ruiz G, et al. Gemcitabine plus Paclitaxel versus Paclitaxel monotherapy in patients with metastatic breast cancer and prior anthracycline treatment. *J Clin Oncol*. 2008;26:3950-3957.
96. Miller K, Wang M, Gralow J, et al. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. *N Engl J Med*. 2007;357:2666-2676.
97. Avastin (Bevacizumab) [package insert]. South San Francisco, CA: Genentech, Inc.; 2019.
98. Pertuzumab (Perjeta) [package insert]. South San Francisco, CA: Genentech, Inc.; 2018.
99. Baselga J, Gelmon KA, Verma S, et al. Phase II trial of pertuzumab and trastuzumab in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer that progressed during prior trastuzumab therapy. *J Clin Oncol*. 2010;28:1138-1144.
100. Baselga J, Cortés J, Kim SB, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. *N Engl J Med*. 2012;366:109-119.
101. Datko F, D'Andrea G, M Dickler M, et al. Phase II study of pertuzumab, trastuzumab, and weekly paclitaxel in patients with metastatic HER2-overexpressing metastatic breast cancer. [abstract]. *Cancer Res*. 2012;72(suppl_24): abstr P5-18-20).
102. Verma S, Miles D, Gianni L, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. *N Engl J Med*. 2012;367:1783-1791.
103. von Minckwitz G, Huang CS, Mano MS, et al. Trastuzumab emtansine for residual invasive HER2-positive breast cancer. *N Engl J Med*. 2019;380:617-628.
104. Ado-trastuzumab emtansine (Kadcyla) [package insert]. South San Francisco, CA: Genentech, Inc.; 2018.
105. Geyer CE, Forster J, Lindquist D, et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. *N Engl J Med*. 2006;355:2733-2743.
106. Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med*. 2001;344:783-792.
107. von Minckwitz G, du Bois A, Schmidt M, et al. Trastuzumab beyond progression in human epidermal growth factor receptor 2-positive advanced breast cancer: a German Breast Group 26/Breast International Group 03-05 Study. *J Clin Oncol*. 2009;27:1999-2006.
108. Bartsch R, Wenzel C, Altorjai G, et al. Capecitabine and trastuzumab in heavily pretreated metastatic breast cancer. *J Clin Oncol*. 2007;25:3853-3858.
109. Licchetta A, Correale P, Migali C, et al. Oral metronomic chemo-hormonal-therapy of metastatic breast cancer with cyclophosphamide and megestrol acetate. *J Chemother*. 2010;22:201-204.
110. Marty M, Cognetti F, Maraninchi D, et al. Randomized phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer administered as first-line treatment: the M77001 study group. *J Clin Oncol*. 2005;23:4265-4274.
111. Esteva FJ, Valero V, Booser D, et al. Phase II study of weekly docetaxel and trastuzumab for patients with HER-2-overexpressing metastatic breast cancer. *J Clin Oncol*. 2002;20:1800-1808.
112. Blackwell KL, Burstein HJ, Storniolo AM, et al. Randomized study of Lapatinib alone or in combination with trastuzumab in women with ErbB2-positive, trastuzumab-refractory metastatic breast cancer. *J Clin Oncol*. 2010;28:1124-1130.
113. Seidman AD, Fornier MN, Esteva FJ, et al. Weekly trastuzumab and paclitaxel therapy for metastatic breast cancer with analysis of efficacy by HER2 immunophenotype and gene amplification. *J Clin Oncol*. 2001;19:2587-2595.
114. Leyland-Jones B, Gelmon K, Ayoub JP, et al. Pharmacokinetics, safety, and efficacy of trastuzumab administered every three weeks in combination with paclitaxel. *J Clin Oncol*. 2003;21:3965-3971.
115. Perez EA. Carboplatin in combination therapy for metastatic breast cancer. *Oncologist*. 2004;9:518-527.
116. Robert N, Leyland-Jones B, Asmar L, et al. Randomized phase III study of trastuzumab, paclitaxel, and carboplatin compared with trastuzumab and paclitaxel in women with HER-2-overexpressing metastatic breast cancer. *J Clin Oncol*. 2006;24:2786-2792.
117. Burstein HJ, Keshaviah A, Baron AD, et al. Trastuzumab plus vinorelbine or taxane chemotherapy for HER2-overexpressing metastatic breast cancer: the trastuzumab and vinorelbine or taxane study. *Cancer*. 2007;110:965-972.
118. Andersson M, Lidbrink E, Bjerre K, et al. Phase III randomized study comparing docetaxel plus trastuzumab with vinorelbine plus trastuzumab as first-line therapy of metastatic or locally advanced human epidermal growth factor receptor 2-positive breast cancer: the HERNATA study. *J Clin Oncol*. 2011;29:264-271.

(Revised 8/2019) © 2019 by Haymarket Media, Inc.