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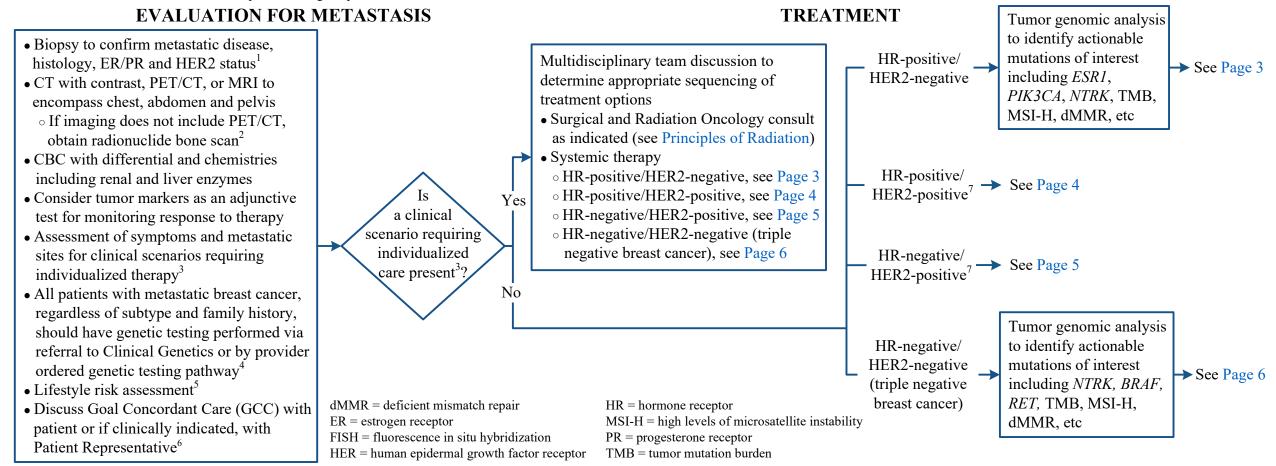
ECOG = Eastern Cooperative Oncology Group HER = human epidermal growth factor receptor HR = hormone receptor Page 1 of 17

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Note: Consider Clinical Trials as treatment options for eligible patients.



Note: Patients with bone metastases and life expectancy > 12 weeks should receive a bisphosphonate if creatinine clearance \geq 30 mL/minute or denosumab after dental evaluation, in addition to other anti-cancer therapy.

¹ For patients eligible for systemic therapy and/or clinical trials, molecular testing on tumor biopsy should be done at initial recurrence or next line of therapy for both standard of care options (including rarer aberrations that may qualify for agnostic treatments, *e.g., NTRK, BRAF, RET,* TMB, MSI-H, dMMR) or eligibility for clinical trials. While tumor testing may be more sensitive for mutational burden, *ESR1* mutations are more easily detected on liquid biopsy.

² If bone scan shows substantial lesions in weight-bearing areas that are not included in the CTs, then additional views are indicated to rule out impending fractures

³See Appendix A

⁴See Genetic Counseling algorithm

⁵ See Physical Activity, Nutrition, and Tobacco Cessation Treatment algorithms; ongoing reassessment of lifestyle risks should be a part of routine clinical practice

⁶ GCC should be initiated by the Primary Oncologist. If Primary Oncologist is unavailable, Primary Team/Attending Physician to initiate GCC discussion and notify Primary Oncologist. Patients, or if clinically indicated, the Patient Representative should be informed of therapeutic and/or palliative options. GCC discussion should be consistent, timely, and re-evaluated as clinically indicated. The Advance Care Planning (ACP) note should be used to document GCC discussion. Refer to GCC home page (for internal use only).

⁷HER2-positive by either immunohistochemistry 3+ or FISH, (HER2/CEP17 ratio ≥ 2)

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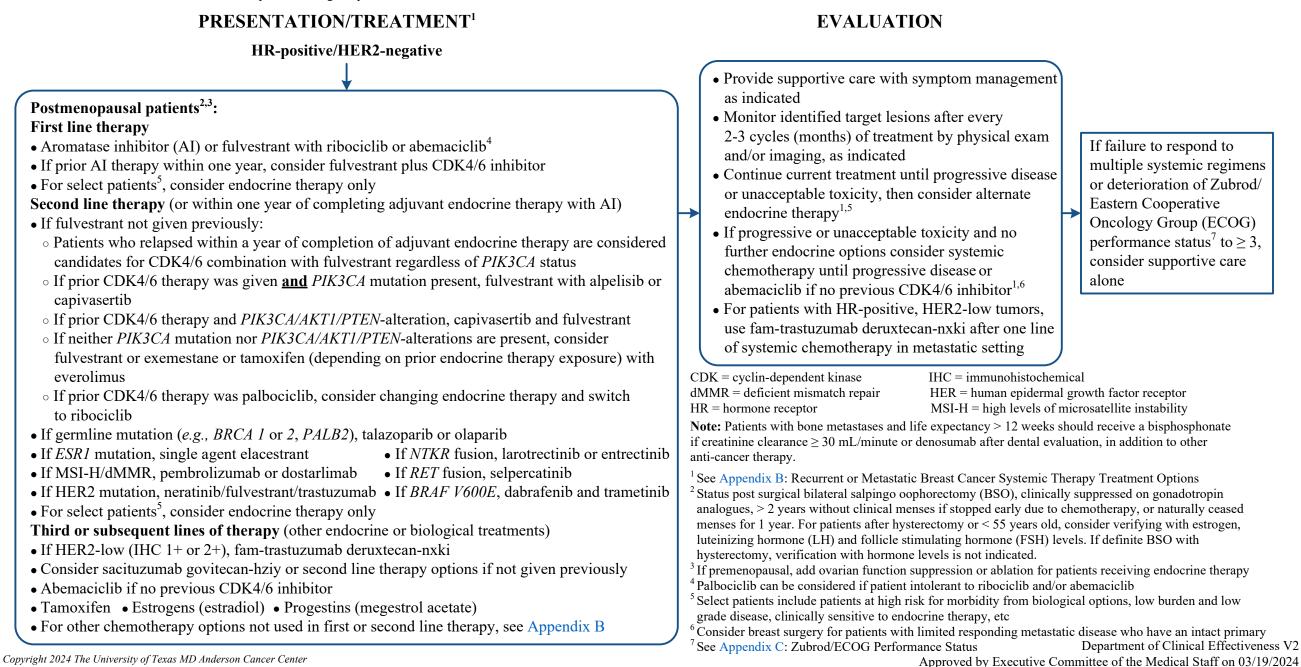
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PRESENTATION **TREATMENT¹** Postmenopausal patients^{3,4}: First line therapy⁵ • If no prior trastuzumab⁶ or > 6 months since adjuvant trastuzumab: • Docetaxel or paclitaxel plus trastuzumab and pertuzumab⁷ • For select patients, aromatase-inhibitor (AI) with trastuzumab or lapatinib or trastuzumab plus lapatinib indicated • If ≤ 6 months from adjuvant trastuzumab or if prior (neo) adjuvant pertuzumab: • Fam-trastuzumab deruxtecan-nxki or consider alternate HER2 directed therapies Second line therapy⁵ • Fam-trastuzumab deruxtecan-nxki if not previously given HR-positive/ Third or subsequent lines of therapy^{5,8} HER2-positive² • Ado-trastuzumab emtansine, if not previously given • Tucatinib plus trastuzumab and capecitabine • Capecitabine plus lapatinib or trastuzumab • Neratinib plus capecitabine • Margetuximab-cmkb plus chemotherapy (capecitabine, vinorelbine, gemcitabine or eribulin) • Trastuzumab plus a taxane, with or without carboplatin • Trastuzumab plus lapatinib • Trastuzumab plus chemotherapy (vinorelbine, gemcitabine, capecitabine or eribulin) • Trastuzumab plus pertuzumab (if pertuzumab not previously given) indicated • Other endocrine therapy not previously used (tamoxifen, estrogens, progestins or androgens)

EVALUATION

• Provide supportive care with symptom management as indicated • Monitor identified target lesions after every 2-3 cycles (months) of treatment by physical exam and/or imaging, as If failure to respond to multiple anti-HER2 Continue current treatment until therapies and/or progressive disease or unacceptable endocrine systemic toxicity, then consider alternate regimens or anti-HER2 therapy (with or without deterioration of Zubrod/ endocrine therapy) 1,8,9 Eastern Cooperative • If progressive or unacceptable toxicity **Oncology** Group and no other anti-HER2 therapy or (ECOG) performance endocrine options are available, consider status¹⁰ to > 3, consider chemotherapy or other systemic therapy supportive care alone until progressive disease^{1,9} • Monitor neurological symptoms and if suspicious, obtain central nervous system (CNS) imaging as clinically

> HER = human epidermal growth factor receptor HR = hormone receptor

Note: Patients with bone metastases and life expectancy > 12 weeks should receive a bisphosphonate if creatinine clearance \geq 30 mL/minute or denosumab after dental evaluation, in addition to other anti-cancer therapy. ¹ See Appendix B: Recurrent or Metastatic Breast Cancer Systemic Therapy Treatment Options

- ⁹ Consider breast surgery for patients with limited responding metastatic disease who have an intact primary
- ¹⁰ See Appendix C: Zubrod/ECOG Performance Status

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² HER2-positive by either immunohistochemistry 3+ or fluorescence in situ hybridization (FISH), (HER2/CEP17 ratio \geq 2)

³ Status post surgical bilateral salpingo oophorectomy (BSO), clinically suppressed on gonadotropin analogues, > 2 years without clinical menses if stopped early due to chemotherapy, or naturally ceased menses for 1 year. For patients

after hysterectomy or < 55 years old, consider verifying with estrogen, luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels. If definite BSO with hysterectomy, verification with hormone levels is not indicated.

⁴ If premenopausal, add ovarian function suppression or ablation for patients receiving endocrine therapy

⁵ In patients with central nervous system metastases, tucatinib-containing regimens are preferred

⁶Obtain cardiac evaluation at baseline and as clinically indicated

⁷After 4-6 months with no progression or unacceptable toxicity, chemotherapy may be discontinued with continuation of trastuzumab and pertuzumab with endocrine therapy

⁸ Endocrine therapy may be used for maintenance of response if toxicity prompts discontinuation of anti-HER2 therapy. Endocrine therapy alone may also be used for third and subsequent lines therapy, although anti-HER2 regimens are preferred.

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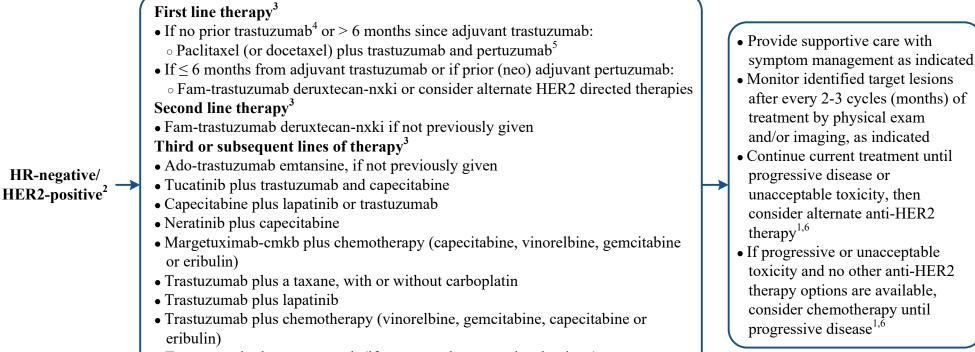
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Note: Consider Clinical Trials as treatment options for eligible patients.

PRESENTATION

TREATMENT¹

EVALUATION



• Trastuzumab plus pertuzumab (if pertuzumab not previously given)

FISH = fluorescence in situ hybridization

HER = human epidermal growth factor receptor

HR = hormone receptor

Note: Patients with bone metastases and life expectancy > 12 weeks should receive a bisphosphonate if creatinine clearance \geq 30 mL/minute or denosumab after dental evaluation, in addition to other anti-cancer therapy.

¹See Appendix B: Recurrent or Metastatic Breast Cancer Systemic Therapy Treatment Options

² HER2-positive by either immunohistochemistry 3+ or FISH, (HER2/CEP17 ratio \geq 2)

- ³ In patients with central nervous system metastases, tucatinib-containing regimens are preferred
- ⁴Obtain cardiac evaluation at baseline and as clinically indicated
- ⁵After 4-6 months with no progression or unacceptable toxicity, chemotherapy may be discontinued with continuation of trastuzumab and pertuzumab
- ⁶Consider breast surgery for patients with limited responding metastatic disease who have an intact primary

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If failure to respond to multiple anti-HER2 therapies or deterioration of Zubrod/Eastern Cooperative Oncology Group (ECOG) performance status⁷ to \geq 3, consider supportive care alone

⁷See Appendix C: Zubrod/ECOG Performance Status

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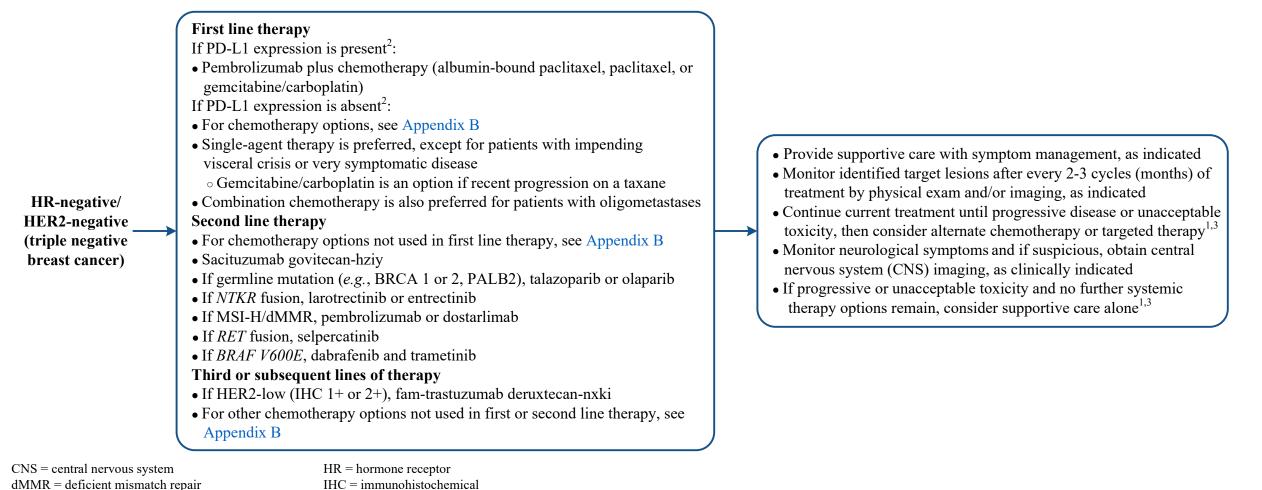
Note: Consider Clinical Trials as treatment options for eligible patients.

PRESENTATION

TREATMENT¹

EVALUATION

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Note: Patients with bone metastases and life expectancy > 12 weeks should receive a bisphosphonate if creatinine clearance ≥ 30 mL/minute or denosumab after dental evaluation, in addition to other anti-cancer therapy

¹See Appendix B: Recurrent or Metastatic Breast Cancer Systemic Therapy Treatment Options

² PD-L1 expression is evaluated with PD-L1 IHC (immunohistochemical assay) 22C3 and considered to be present if Combined Positive Score (CPS) is ≥ 10

MSI-H = high levels of microsatellite instability

³Consider breast surgery for patients with limited responding metastatic disease who have an intact primary

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HER = human epidermal growth factor receptor

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APPENDIX A: Clinical Scenarios Requiring Individualized Therapy

- Oligometastasis¹ or Stage IV NED²
- Brain metastases (refer to Brain Metastases Management algorithm)
- Leptomeningeal disease (refer to Leptomeningeal Metastases algorithm)
- Choroid metastases
- Cord compression (refer to Spinal Cord Compression Management in Cancer Patients algorithm)
- Plexopathy/radiculopathy
- Extensive local-regional disease
- Pathologic fracture
- Impending pathologic fracture
- Pleural effusion³ (refer to Management of Malignant Pleural Effusion Adult algorithm)
- Pericardial effusion³
- Superior vena cava syndrome
- Biliary obstruction
- Ureteral obstruction
- Pregnancy⁴
- de novo M1 inflammatory breast cancer (refer to Breast Cancer Inflammatory (IBC) algorithm)

NED = no evidence of disease

¹Oligometastases includes selected patients with up to 5 metastatic lesions in the same or different organ sites. These patients may be considered for definitive treatment with curative intent.

² Stage IV NED is considered to include patients with up to 5 metastatic lesions in the same or different organ sites who have been treated with surgical or other ablative therapy. These patients

- may be considered for definitive treatment with curative intent.
- ³ If patient is symptomatic, a multidisciplinary team discussion is required

⁴ Refer to Management of Pregnant Patients with Cancer Policy (#CLN0582)

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APPENDIX B: Recurrent or Metastatic Breast Cancer Systemic Therapy Treatment Options

Chemotherapy				
Preferred single agents: Anthracyclines • Doxorubicin • Pegylated liposomal doxorubicin	Taxanes • Paclitaxel • Albumin-bound paclitaxel	Anti-metabolites Capecitabine Gemcitabine 	Other microtubule inhibitors • Vinorelbine • Eribulin	Other single agents: • Carboplatin • Sacituzumab govitecan-hziy
Other single agents: • Cyclophosphamide • Cisplatin	EpirubicinIxabepilone	• Docetaxel • Mitomycin C		
Combination chemotherapy regimer • FAC/CAF (cyclophosphamide, doxor • FEC (fluorouracil, epirubicin, and cyclophospham • AC (doxorubicin and cyclophospham	rubicin, and fluorouracil)• Hclophosphamide)• C	EC (epirubicin and cyc CMF (cyclophosphami Gemcitabine and carbo	de, methotrexate, and fluorouracil)	Docetaxel and capecitabineGemcitabine and paclitaxel
HER2 Based Therapies				
First-line regimens for HER2-positiv • Pertuzumab plus trastuzumab plus pa • Pertuzumab plus trastuzumab plus do	clitaxel	umab naïve disease or	those who recurred > 6 months after	r adjuvant trastuzumab)
Other options (not considered prefer • Trastuzumab with docetaxel • Trastuzumab with paclitaxel with or v	• Trastu	zumab with vinorelbin zumab with capecitabi	1 1	tuzumab (if pertuzumab not previously given
Regimens for trastuzumab-exposed • Fam-trastuzumab deruxtecan-nxki • Ado-trastuzumab emtansine • Tucatinib plus trastuzumab plus cape • Trastuzumab plus lapatinib without c • Trastuzumab plus chemotherapy (cap	citabine ytotoxic therapy	ne or eribulin)	 Lapatinib plus capecit Trastuzumab plus cap Neratinib plus capecit Margetuximab-cmkb gemcitabine or eribuli 	ecitabine cabine plus chemotherapy (capecitabine, vinorelbine

ER = estrogen receptor PR = progesterone receptor

Continued on next page

¹Dose-dense AC is not indicated for treatment of metastatic breast cancer

² After maximal benefit achieved with chemotherapy, consider continuous anti-HER2 therapy alone, if ER or PR positive, in combination with appropriate endocrine therapy (does not apply to ado-trastuzumab emtansine)

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APPENDIX B: Recurrent or Metastatic Breast Cancer Systemic Therapy Treatment Options - continued

Endocrine Based Therapies		
 Aromatase inhibitors (AI) AI with or without CDK 4/6 inhibitor (abemaciclib or ribociclib) Anastrozole Letrozole Exemestane Exemestane, fulvestrant, or tamoxifen with everolimus Tamoxifen Elacestrant 	 Fulvestrant Fulvestrant with alpelisib for <i>PIK3CA</i> mutation Fulvestrant with capivasertib for <i>PIK3CA/AKT1/PTEN</i>-alterations Fulvestrant with or without CDK 4/6 inhibitor (abemaciclib, palbociclib, or ribocic Fulvestrant with AI Abemaciclib single agent Progestin (megestrol acetate) Estrogen (estradiol) 	
Other Therapies		
 With PD-L1 expression: Pembrolizumab plus chemotherapy (albumin-b). If <i>NTKR</i> fusion, larotrenctinib or entrectinib If <i>RET</i> fusion, selpercatinib If <i>BRAF V600E</i>, dabrafenib, and trametinib If MSI-H/dMMR, pembrolizumab, or dostarlimab BRCA-positive directed therapies:	bound paclitaxel, paclitaxel, or gemcitabine and carboplatin)	
TalazoparibOlaparib		
Molecularly targeted agents along with <i>NTRK</i> fusion-directed: • Larotrectinib and Entrectinib		
Total Mutation Burden-High (TMB-H: ≥ 10 muts/mb/dMMR positiv • Pembrolizumab	re):	
Bone-directed therapies: • Pamidronate disodium • Zoledronic acid • Denosumab• Strontium-89 • Samarium Sm 153 lexidronam		

CDK = cyclin-dependent kinase MSI-H = high levels of microsatellite instability dMMR = deficient mismatch repair

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APPENDIX C: Zubrod/ECOG Performance Status

Description	Scale
Fully active, able to carry on all pre-disease performance without restriction	0
Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (<i>e.g.</i> , light house work, office)	1
Ambulatory and capable of self care but unable to perform any work activities; up and about $> 50\%$ of waking hours	2
Capable of only limited self care, confined to bed or chair $> 50\%$ of waking hours	3
Completely disabled, cannot carry on any self care, totally confined to bed or chair	4
Dead	5

ECOG = Eastern Cooperative Oncology Group

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PRINCIPLES OF BREAST ONCOLOGIC SURGERY

Stage IV disease

- Traditionally, surgical management of the primary and regional nodes are not recommended in the setting of stage IV disease
- In patients with oligometastatic disease and excellent response to systemic therapy locoregional therapy may be considered in carefully selected patients evaluated by the multidisciplinary team
- Given data indicating no survival benefit for surgery in patients with metastatic disease, surgery within the context of a clinical trial would be appropriate
- Radiation therapy and/or palliative mastectomy may be considered in patients with advanced local progression, symptomatic fungating and/or bleeding tumors not responsive to systemic therapy

PRINCIPLES OF RADIATION

Oligometastatic Disease

- For patients with oligometastatic disease who have undergone definitive surgery, conventional treatment with whole breast or chest wall and undissected draining lymphatics, to include the internal mammary nodes (IMN), supraclavicular (SCV), and level III axilla is recommended. Include level I/II axilla if axillary lymph node dissection (ALND) not performed.
- Enrollment in a trial for randomization to treatment is recommended for treatment of the oligometastatic disease site, (*e.g.*, bone, lung, liver). Off trial, patients being considered for definitive treatment should be discussed both in a multidisciplinary setting and within the radiation oncology service
- Additional treatment of the oligometastatic disease site, (*e.g.*, bone, lung, liver) with radiation therapy or enrollment in a trial for randomization to treatment is also recommended. Trial radiation doses may be reasonable for patients being considered for definitive treatment off trial.
- Consultation to other radiation services based on oligometastatic disease site may be warranted as follows:
 - \circ Brain with < 10 metastatic lesions: Central nervous system (CNS) Radiation Oncology¹
- Spine with limited (1-2) vertebral body involvement: CNS Radiation Oncology for stereotactic treatment
- Skull base: Head and Neck Radiation Oncology
- Lung metastases: Thoracic Radiation Oncology
- \circ Liver metastases: Gastrointestinal Radiation Oncology
- \circ Limited bone metastases: Breast Radiation Oncology

Widely Metastatic Disease

- Consultation to other radiation services for non-oligometastatic disease should be considered for the following:
 - \circ Brain with ≥ 10 metastatic lesions or diffuse spine disease: Breast Radiation Oncology¹
 - Leptomeningeal disease (LMD): CNS Radiation Oncology¹
 - o Diffuse bone disease, including spine or bone disease causing pain or at risk of fracture: Radiation Oncology Bone Metastatic Clinic or Breast Radiation Oncology
 - \circ Bleeding and/or painful and/or fungating primary mass: Breast Radiation Oncology

¹Patients who are not candidates for radiation, or in select highly chemo/biotherapy-sensitive cases, treatment with systemic bio-chemotherapy regimens used for non-CNS metastatic disease can be considered

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DEVELOPMENT CREDITS

This practice algorithm is based on majority expert opinion of the Breast Center providers at the University of Texas MD Anderson Cancer Center. It was developed using a multidisciplinary approach that included input from the following:

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