

HER2+ MBC Treatment Algorithm:

Strategies for 2nd-Line Therapy and Beyond

HER2 MBC TREATMENT ALGORITHM

CNS Metastases Absent

FIRST-LINE THERAPY[a]

1. **PREFERRED** — Taxane + trastuzumab + pertuzumab [CLEOPATRA] [NCCN Category 1]

   Pertuzumab + trastuzumab + paclitaxel

[a]DESTINY-Breast03 interim data suggest T-DXd + pertuzumab may become first-line; adjust subsequent therapy accordingly.

SECOND-LINE THERAPY

2. **PREFERRED** — T-DXd [NCCN category 1]

   T–DXd > T–DM1 for PFS/OS; monitor for ILD

THIRD-LINE THERAPY

3. **PREFERRED** — Taxane + trastuzumab + pertuzumab [HER2CLIMB] [NCCN category 1]

   Ado-trastuzumab emtansine

FOURTH-LINE THERAPY (optimal sequence not known)

4. Trastuzumab + docetaxel or vinorelbine
   Trastuzumab + paclitaxel ± carboplatin
   Capecitabine + trastuzumab or lapatinib
   Trastuzumab + lapatinib (without cytotoxic therapy)
   Trastuzumab + other chemotherapy agents
   Neratinib + capecitabine
   Margetuximab-cmkb + chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine)
   Abemaciclib in combination with fulvestrant and trastuzumab [for HR+ only] [NCCN Category 2B]
   Targeted therapy and emerging biomarker options

CNS Metastases Present

BRAIN METASTASIS (PARENCHYMAL)

When was the CNS metastasis identified?

1 Baseline (at diagnosis)

Symptomatic/large/eloquent	Asymptomatic/low-burden/ stable extracranial
Local therapy first (neurosurgical resection followed by SRS to cavity) or SRS alone	Consider CNS-active systemic therapy (tucatinib triplet or T-DXd) to delay RT, with close MRI follow-up
Proceed to systemic therapy selection: First-line [preferred] Pertuzumab + trastuzumab + taxane (CLEOPATRA regimen), regardless of CNS involvement	For asymptomatic BM, HER2CLIMB showed tucatinib triplet delayed new BM (IC–PFS 9.9 vs 4.2 mo) T-DXd also active (DESTINY-Breast12: mPFS 17.3 mo with BM)

2 After CNS progression on systemic therapy

If extracranial disease controlled	If high extracranial burden
Limited progression: Add focal RT, continue current systemic	Choose systemic with strongest extracranial control (T-DXd if ADC-eligible, tucatinib triplet if not)
Multiple progression: Consider switch to CNS-active systemic (tucatinib triplet or T-DXd)	

BEST PRACTICE:

- Avoid/delay WBRT when possible to limit neurocognitive toxicity
- Coordinate with radiation oncology on whether to pause systemic therapy during RT

LEPTOMENINGEAL METASTASES

Minimally symptomatic, good PS	Highly symptomatic/nodular or refractory LMs
• Favor systemic therapy first (tucatinib triplet or T–DXd), as both have LM–activity signals (TBCRC049; DEBBRAH) • Consider intrathecal therapy • Choose by extracranial burden, toxicity profile, route (PO+IV vs IV), and patient preference	• Consider RT (including proton craniospinal in select cases) • Intrathecal therapy generally deferred

Clinical trials strongly encouraged when applicable and available.

PATIENT- AND DISEASE-SPECIFIC FACTORS INFLUENCING TREATMENT SELECTION

DISEASE PATTERN

- **CNS-only progression:** After local therapy (if needed), reasonable to switch to CNS-active systemic (tucatinib triplet or T-DXd)
- **CNS + high extracranial burden (eg, liver):** Lean toward agent with strong systemic control (eg, T-DXd) or use tucatinib triplet if ADC-ineligible/after ADC. Discuss options with patient to guide final choice
- **T-DXd preferred for high systemic burden** (DESTINY-Breast03: mPFS 22.4 mo in non-BM cohort)

TOXICITY AND COMORBIDITIES

- **Pulmonary risk/ILD:** Prior or active ILD may favor alternatives to T-DXd
- **Gastrointestinal sensitivity:** History of diarrhea may favor T-DXd over tucatinib + capecitabine
- **Cytopenias/marrow reserve:** Low counts may favor non-capecitabine regimens
- **Cardiac history:** Rare with modern HER2-targeted regimens, but pre-existing dysfunction may require closer monitoring or low-risk options

PRIOR THERAPY/EXPOSURE

- Tucatinib triplet remains a key option for tucatinib-naive patients; typically later-line after T-DXd if no CNS disease
- May be used earlier in active CNS metastases

LOGISTICS AND PATIENT PREFERENCES

- PO+IV (tucatinib triplet) vs IV–only (T–DXd); infusion access; travel; and how often follow-up visits, labs, and imaging will be needed

TREATMENT MONITORING AND TRIGGERS TO CHANGE THERAPY

Deferring RT with systemic therapy:

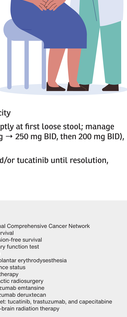
- MRI brain every 6–8 weeks early, then space out if stable
- Add focal RT for oligoprogression
- Escalate if symptoms appear

On T–DXd:

- Screen for cough, dyspnea, fever; CT chest/PFTs if suspected
  - Baseline PFTs recommended if pulmonary comorbidities exist; repeat at ILD suspicion
- Permanently stop for grade ≥2 ILD; manage with steroids
- Grade 1 interruption ± steroids, rechallenge possible if resolved (ASCO 2025: 27% recurrence risk, median 211 days to recurrence)

On tucatinib triplet:

- Monitor for diarrhea, PPE, anemia, and hepatotoxicity
- For diarrhea, initiate antidiarrheal treatment promptly at first loose stool; manage with treatment interruption, dose reduction (300 mg → 250 mg BID, then 200 mg BID), or discontinuation per prescribing information
- For PPE or anemia, hold or reduce capecitabine and/or tucatinib until resolution, then resume at reduced doses as tolerated



Abbreviations

ADC: antibody-drug conjugate
ASCO: American Society of Clinical Oncology
BID: twice daily
BM: brain metastases
CNS: central nervous system
CT: computed tomography
HER2: human epidermal growth factor receptor 2
HR: hormone receptor
IC-PFS: intracranial progression-free survival
ILD: interstitial lung disease
IV: intravenous
LM: leptomeningeal metastases
MBC: metastatic breast cancer
mPFS: median progression-free survival
MRI: magnetic resonance imaging
NCCN: National Comprehensive Cancer Network
OS: overall survival
PFS: progression-free survival
PFT: pulmonary function test
PO: by mouth
PPE: palmar-plantar erythrodysesthesia
PS: performance status
RT: radiation therapy
SRS: stereotactic radiosurgery
T-DM1: trastuzumab emtansine
T-DXd: trastuzumab deruxtecan
Tucatinib triplet: tucatinib, trastuzumab, and capecitabine
WBRT: whole-brain radiation therapy

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