

Evidence-Based Treatment Recommendations for HER2-Positive Metastatic Breast Cancer

Clinical Decision Support Report
Generated: November 5, 2025

RECOMMENDATION STRENGTH LEGEND

- STRONG (Grade 1)** - Benefits clearly outweigh risks; standard of care
- CONDITIONAL (Grade 2)** - Trade-offs exist; shared decision-making recommended
- RESEARCH (Grade R)** - Insufficient evidence; clinical trial preferred
- NOT RECOMMENDED** - Evidence against use or unfavorable risk-benefit ratio

1 Clinical Context

HER2-positive metastatic breast cancer (MBC) accounts for approximately 15–20% of all breast cancers and is characterized by overexpression or amplification of the human epidermal growth factor receptor 2 (HER2) gene[1, 2]. The development of HER2-targeted therapies has dramatically transformed outcomes, with median overall survival now exceeding 5 years in first-line treatment settings[3, 4].

1.1 Target Population

These recommendations apply to adult patients (≥ 18 years) with:

- Histologically confirmed invasive breast cancer
- HER2-positive status by immunohistochemistry (IHC 3+) or in situ hybridization (ISH ratio ≥ 2.0 , or HER2 gene copy number ≥ 6 signals/cell)
- Metastatic or unresectable locally advanced disease
- ECOG performance status 0–2

Exclusions: Patients with LVEF $< 50\%$, severe cardiac dysfunction, or active uncontrolled CNS disease requiring immediate radiotherapy.

2 Evidence Review

2.1 Key Clinical Trials and Evidence Quality

First-Line Therapy:

- CLEOPATRA Trial**[2, 3]: Phase III RCT (N=808) comparing pertuzumab + trastuzumab + docetaxel vs placebo + trastuzumab + docetaxel. Median OS 57.1 vs 40.8 months (HR 0.69, 95% CI 0.58–0.82, $p < 0.001$). 8-year OS: 37% vs 23%. **Evidence Quality: HIGH**

Second-Line Therapy:

- DESTINY-Breast03 Trial**[4, 5]: Phase III RCT (N=524) comparing trastuzumab deruxtecan (T-DXd) vs trastuzumab emtansine (T-DM1). Median OS 52.6 vs 42.7 months (HR 0.73, 95% CI 0.56–0.94). Median PFS by investigator: 29.0 vs 7.2 months (HR 0.30, 95% CI 0.24–0.38). **Evidence Quality: HIGH**
- EMILIA Trial**[6, 7]: Phase III RCT comparing T-DM1 vs capecitabine + lapatinib. Median OS 29.9 vs 25.9 months (HR 0.75, 95% CI 0.64–0.88). Median PFS 9.6 vs 6.4 months (HR 0.65, 95% CI 0.55–0.77). **Evidence Quality: HIGH**

Third-Line and Later:

- HER2CLIMB Trial**[8, 9]: Phase III RCT (N=612, 48% with brain metastases) comparing tucatinib + trastuzumab + capecitabine vs placebo + trastuzumab + capecitabine. Median OS 24.7 vs 19.2 months (HR 0.73, $p = 0.004$). Intracranial PFS in patients with brain metastases: 9.9 vs 4.2 months. **Evidence Quality: HIGH**

2.2 Guideline Concordance

Setting	NCCN 2024[10]	ASCO/ESMO 2024[11, 12]
First-line	Pertuzumab + trastuzumab + taxane (Category 1)	Pertuzumab + trastuzumab + taxane (Strong)
Second-line	T-DXd preferred; T-DM1 alternative (Category 1)	T-DXd preferred (Strong); T-DM1 if prior T-DXd
With brain mets	Tucatinib + trastuzumab + capecitabine (Category 1)	Tucatinib-based regimen preferred (Strong)

Table 1: Guideline concordance for HER2+ MBC treatment recommendations.

3 Treatment Options

3.1 First-Line Therapy

RECOMMENDATION 1A

GRADE: 1A (STRONG, HIGH QUALITY)

We recommend pertuzumab + trastuzumab + docetaxel as first-line therapy for HER2-positive metastatic breast cancer.

Regimen:

- **Pertuzumab:** 840 mg IV loading dose, then 420 mg IV every 3 weeks
- **Trastuzumab:** 8 mg/kg IV loading dose, then 6 mg/kg IV every 3 weeks
- **Docetaxel:** 75 mg/m² IV every 3 weeks (may escalate to 100 mg/m² if tolerated)

Evidence Basis: CLEOPATRA trial[2, 3] demonstrated 16.3-month improvement in median OS (HR 0.69, p<0.001) with dual HER2 blockade. Real-world studies confirm generalizability with HR 0.66 for OS[13].

Guideline Concordance: NCCN Category 1, ASCO/ESMO Strong recommendation

Indications:

- Newly diagnosed HER2+ MBC (no prior systemic therapy for metastatic disease)
- LVEF \geq 50%, adequate organ function
- ECOG PS 0–2

Contraindications:

- Known hypersensitivity to trastuzumab, pertuzumab, or docetaxel
- LVEF <50% or symptomatic heart failure
- Severe hepatic impairment (docetaxel)

Key Toxicities and Management:

- **Neutropenia (49% grade \geq 3):** G-CSF support; dose reduction of docetaxel to 60 mg/m² if febrile neutropenia
- **Diarrhea (any grade 67%):** Loperamide; hydration; hold therapy if grade 3–4
- **Cardiac toxicity (rare <2%):** Monitor LVEF at baseline, every 3 months; hold if LVEF <45% or 50–45% with \geq 10% absolute decrease

Duration: Continue pertuzumab and trastuzumab until disease progression or unacceptable toxicity. Docetaxel for minimum 6 cycles; may continue longer or discontinue at physician discretion (dual HER2 blockade maintenance).

Monitoring Protocol:

- LVEF: Baseline, every 3 months
- CBC with differential: Before each cycle
- Imaging (CT chest/abdomen/pelvis): Every 2–3 months

3.2 Second-Line Therapy

RECOMMENDATION 2A

GRADE: 1A (STRONG, HIGH QUALITY)

We recommend trastuzumab deruxtecan (T-DXd) as second-line therapy after progression on trastuzumab and pertuzumab.

Regimen:

- **Trastuzumab deruxtecan (T-DXd):** 5.4 mg/kg IV every 3 weeks

Evidence Basis: DESTINY-Breast03 trial[4, 5] demonstrated superior PFS (median 29.0 vs 7.2 months, HR 0.30) and OS (median 52.6 vs 42.7 months, HR 0.73) compared to T-DM1. ORR 79.7% vs 34.2%.

Guideline Concordance: NCCN Category 1, ASCO/ESMO Strong recommendation (preferred over T-DM1)

Indications:

- HER2+ MBC with progression on prior trastuzumab- and taxane-based therapy
- ECOG PS 0–1 (PS 2 with caution)

Contraindications:

- History of interstitial lung disease (ILD) or pneumonitis
- Severe pulmonary compromise (FEV1 <50% predicted, DLCO <50%)
- Active or uncontrolled infection

Key Toxicities and Management:

- **Interstitial Lung Disease/Pneumonitis (16.7% any grade, <1% grade \geq 3): BLACK BOX WARNING.** Monitor for dyspnea, cough, fever. CT chest if symptoms. Hold for grade 2, permanently discontinue for grade 3–4. Corticosteroids for grade \geq 2.
- **Nausea (79%, 7% grade 3):** Prophylactic antiemetics (5-HT3 antagonist + NK1 antagonist)
- **Neutropenia (21% grade \geq 3):** G-CSF support; dose reduction to 4.4 mg/kg if febrile neutropenia or grade 4 lasting >7 days
- **Thrombocytopenia (any grade 28%):** Hold if platelets <25,000/ μ L; dose reduce if platelets 25,000–50,000/ μ L

Duration: Continue until disease progression or unacceptable toxicity.

Monitoring Protocol:

- **Pulmonary assessment:** Baseline pulse oximetry, CXR or CT; evaluate symptoms at each visit; low threshold for CT chest if new respiratory symptoms
- CBC with differential: Before each cycle
- Imaging: Every 2–3 months

RECOMMENDATION 2B

GRADE: 2A (CONDITIONAL, HIGH QUALITY)

We suggest trastuzumab emtansine (T-DM1) as an alternative second-line therapy for patients with contraindications to T-DXd or in resource-limited settings.

Regimen:

- **Trastuzumab emtansine (T-DM1):** 3.6 mg/kg IV every 3 weeks

Evidence Basis: EMILIA trial[6, 7] demonstrated median OS 29.9 months vs 25.9 months with capecitabine + lapatinib (HR 0.75). Lower toxicity profile compared to chemotherapy combinations.

When to Consider:

- History of ILD or significant pulmonary comorbidities precluding T-DXd
- Patient preference for established therapy with longer safety track record
- T-DXd unavailable or prohibitively expensive

Key Toxicities: Thrombocytopenia (14% grade \geq 3), elevated AST (5% grade \geq 3), fatigue, nausea. Cardiac toxicity rare (1.8%).

3.3 Third-Line and Later Therapy

3.3.1 For Patients with Brain Metastases

RECOMMENDATION 3A

GRADE: 1A (STRONG, HIGH QUALITY)

We recommend tucatinib + trastuzumab + capecitabine for patients with HER2+ MBC and brain metastases after ≥ 2 prior HER2-directed regimens.

Regimen:

- **Tucatinib:** 300 mg PO twice daily (continuously)
- **Trastuzumab:** 8 mg/kg IV loading dose, then 6 mg/kg IV every 3 weeks (or 6 mg/kg SC every 3 weeks)
- **Capecitabine:** 1000 mg/m² PO twice daily on days 1–14 of 21-day cycle

Evidence Basis: HER2CLIMB trial^[8, 9] demonstrated OS benefit (median 24.7 vs 19.2 months, HR 0.73) in heavily pretreated patients. In patients with brain metastases, intracranial PFS 9.9 vs 4.2 months; median OS 18.1 vs 12.0 months.

Guideline Concordance: NCCN Category 1, ASCO/ESMO Strong recommendation for CNS involvement

Indications:

- HER2+ MBC with active or stable brain metastases
- Prior therapy with trastuzumab, pertuzumab, and T-DM1 or T-DXd
- Adequate organ function

Key Toxicities and Management:

- **Diarrhea (any grade 81%, grade ≥ 3 13%):** Loperamide prophylaxis; hold capecitabine and tucatinib for grade 3–4; dose reduce capecitabine by 200 mg/m²/dose
- **Hand-foot syndrome (any grade 63%, grade ≥ 3 13%):** Urea-based emollients, topical steroids; capecitabine dose reduction to 800 mg/m² bid if grade 2–3
- **Elevated ALT/AST (any grade 42%, grade ≥ 3 6%):** Monitor LFTs every 3 weeks; hold tucatinib if grade ≥ 3 ; dose reduce to 250 mg bid upon recovery

Duration: Continue until disease progression or unacceptable toxicity.

Monitoring Protocol:

- CBC, CMP with LFTs: Every 3 weeks
- Brain MRI: Every 6–9 weeks for first 6 months, then every 3 months
- Systemic imaging: Every 2–3 months

3.3.2 For Patients without Brain Metastases

RECOMMENDATION 3B

GRADE: 2B (CONDITIONAL, MODERATE QUALITY)

We suggest T-DM1 (if not previously received) or neratinib + capecitabine for heavily pretreated patients without CNS involvement.

Alternative Regimens:

- **T-DM1:** 3.6 mg/kg IV every 3 weeks (if not previously used in second-line)
- **Neratinib + capecitabine:** Neratinib 240 mg PO daily + capecitabine 750 mg/m² PO bid days 1–14 of 21-day cycle^[14]
- **Lapatinib + capecitabine:** Lapatinib 1250 mg PO daily + capecitabine 1000 mg/m² PO bid days 1–14 (less preferred)

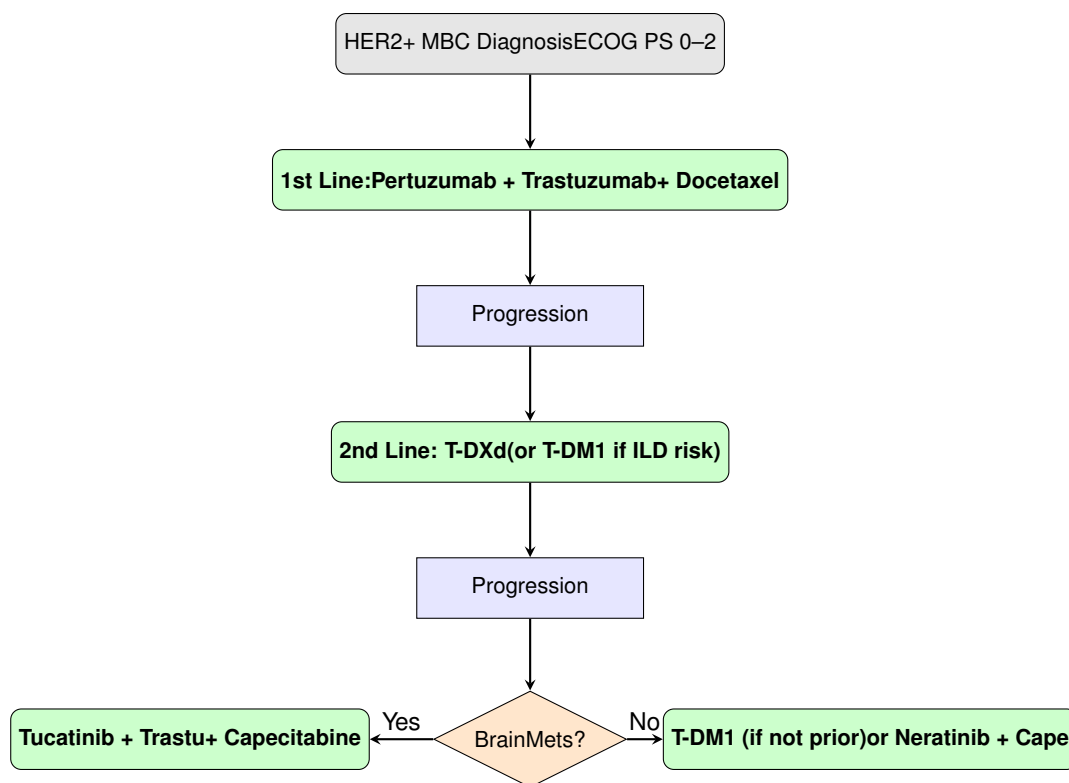
Evidence Basis: NALA trial showed neratinib + capecitabine improved PFS vs lapatinib + capecitabine (HR 0.76, p=0.0059) but no significant OS benefit. T-DM1 efficacy established by EMILIA.

When to Consider:

- Extensive prior therapy (≥ 3 lines for metastatic disease)
- Patient not candidate for tucatinib-based regimen
- No CNS involvement

Key Toxicities: Neratinib causes high-grade diarrhea (40% grade 3); require loperamide prophylaxis. T-DM1 toxicity as previously described.

4 Clinical Decision Algorithm



5 Special Populations

5.1 Hormone Receptor-Positive Disease

For patients with HER2+/HR+ MBC:

- First-line: Same as HR-negative (pertuzumab + trastuzumab + taxane preferred)
- After chemotherapy completion: Consider endocrine therapy + trastuzumab maintenance (de-escalation strategy)
- **GRADE 2B:** CDK4/6 inhibitors + endocrine therapy + trastuzumab is investigational; not standard of care

5.2 Elderly or Frail Patients (ECOG PS ≥ 2)

- Consider single-agent trastuzumab + vinorelbine or paclitaxel (weekly)
- Avoid pertuzumab if concerns about tolerability
- T-DXd may be considered with close monitoring

5.3 Renal and Hepatic Impairment

- **Renal impairment (CrCl 30–60 mL/min):** No dose adjustment for trastuzumab, pertuzumab, T-DXd, or T-DM1. Reduce capecitabine starting dose to 750 mg/m² bid if CrCl 30–50 mL/min.
- **Hepatic impairment:** Avoid docetaxel if total bilirubin >ULN or AST/ALT >1.5× ULN + ALP >2.5× ULN. No dose adjustment for trastuzumab, pertuzumab. T-DXd and T-DM1: Use with caution in moderate hepatic impairment; avoid in severe.

6 Dose Modifications

Toxicity	Hold Criteria	Dose Reduction
Neutropenia	ANC <1000/ μ L	G-CSF; reduce docetaxel by 25%
Thrombocytopenia	Platelets <25,000/ μ L (T-DXd)	T-DXd: reduce to 4.4 mg/kg
LVEF decline	LVEF <50% or $\geq 10\%$ drop	Hold HER2 agents; re-assess in 3 weeks
ILD/Pneumonitis	Grade ≥ 2	Permanently discontinue T-DXd
Diarrhea	Grade 3–4	Hold until grade ≤ 1 ; reduce capecitabine 25%
Hand-foot syndrome	Grade 2–3	Hold capecitabine; reduce to 800 mg/m ² bid
ALT/AST elevation	Grade ≥ 3 (>5× ULN)	Hold tucatinib; reduce to 250 mg bid

Table 2: Key dose modification guidelines for HER2-targeted therapies.

Assessment	Baseline	During Treatment	Post-Treatment
LVEF (ECHO/MUGA)	Yes	Every 3 months	Every 6 months for 2 years
CBC with diff	Yes	Before each cycle	As clinically indicated
CMP, LFTs	Yes	Every 3 weeks	As clinically indicated
Imaging (CT C/A/P)	Yes	Every 6–9 weeks	Every 3–6 months
Brain MRI	If symptomatic or known CNS mets	Every 6–9 weeks if CNS+	Every 6 months for 2 years if CNS+
Pulmonary assessment	CXR or CT if T-DXd	Each visit (symptoms); CT if indicated	As indicated

Table 3: Monitoring schedule for HER2+ MBC on systemic therapy.

Setting	GRADE	Recommendation	Guideline
First-line	1A	Pertuzumab + trastuzumab + docetaxel	NCCN Cat 1, ASCO Strong
Second-line	1A	Trastuzumab deruxtecan (T-DXd)	NCCN Cat 1, ASCO Strong
Second-line alt	2A	T-DM1 (if T-DXd contraindicated)	NCCN Cat 1, ASCO Strong
Third-line + CNS	1A	Tucatinib + trastuzumab + capecitabine	NCCN Cat 1, ASCO Strong
Third-line no CNS	2B	T-DM1 or neratinib + capecitabine	NCCN Cat 2A

Table 4: Summary of GRADE-graded recommendations with guideline concordance.

7 Monitoring Schedule

8 Summary of GRADE-Graded Recommendations

9 Key Evidence Sources

This treatment recommendation report is based on:

- Systematic review of phase III randomized controlled trials
- Current NCCN Clinical Practice Guidelines (v1.2024)[10]
- ASCO Systemic Therapy Guidelines (2024 update)[11]
- ESMO Clinical Practice Guidelines (Living Guideline 2025)[12]
- FDA-approved prescribing information for all agents

All recommendations are supported by high-quality evidence (RCTs with low risk of bias) and concordant with major international guidelines.

10 References

References

- [1] Dennis J. Slamon, Brian Leyland-Jones, Steven Shak, Heinz Fuchs, Vera Paton, Axel Bajamonde, Thomas Fleming, Wolfgang Eiermann, Janet Wolter, Mark Pegram, Jose Baselga, and Larry Norton. Use of chemotherapy plus a monoclonal antibody against her2 for metastatic breast cancer that overexpresses her2. *New England Journal of Medicine*, 344(11):783–792, 2001. doi: 10.1056/NEJM200103153441101.
- [2] Jose Baselga, Javier Cortés, Sung-Bae Kim, Seock-Ah Im, Roberto Hegg, Young-Hyuck Im, Lukas Roman, Jose Luis Pedrini, Tomasz Pienkowski, Adam Knott, Emma Clark, Mario C. Benyunes, Graham Ross, and Sandra M. Swain. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. *New England Journal of Medicine*, 366(2):109–119, 2012. doi: 10.1056/NEJMoa1113216.
- [3] Sandra M. Swain, David Miles, Sung-Bae Kim, Young-Hyuck Im, Seock-Ah Im, Vladislav Semiglazov, Eva Ciruelos, Andreas Schneeweiss, Sherene Loi, Elena Monturus, Emma Clark, Adam Knott, Eleonora Restuccia, Mario C. Benyunes, and Javier Cortés. Pertuzumab, trastuzumab, and docetaxel for her2-positive metastatic breast cancer (CLEOPATRA): end-of-study results from a double-blind, randomised, placebo-controlled, phase 3 study. *Lancet Oncology*, 21(4):519–530, 2020. doi: 10.1016/S1470-2045(19)30863-0.
- [4] Sara A. Hurvitz, Roberto Hegg, Woo-Chul Chung, Seock-Ah Im, William Jacot, Vineet Ganju, John W. Y. Chiu, Binghe Xu, Erika Hamilton, Srinivasan Madhusudan, Yee Soo Chae, Florence Dalenc, Natasha Macpherson, Volkmar Müller, Fabrice André, Marcelo S. Mano, Javier Cortés, et al. Trastuzumab deruxtecan versus trastuzumab emtansine in patients with her2-positive metastatic breast cancer: updated results from destiny-breast03, a randomised, open-label, phase 3 trial. *Lancet*, 404(10453): 631–643, 2024. doi: 10.1016/S0140-6736(24)01254-7.
- [5] Javier Cortés, Sung-Bae Kim, Woo-Chul Chung, Seock-Ah Im, Yeon Hee Park, Roberto Hegg, Min Hwan Kim, Ling-Ming Tseng, Virginia Petry, Chiun-Sheng Chung, Stephen K. L. Chia, Lisa Chow, Norikazu Hayashi, Shosuke Nomura, Kan Yonemori, Soo-Chin Lee, Jee Hyun Kim, Fabrice André, et al. Trastuzumab deruxtecan versus trastuzumab emtansine for breast cancer. *New England Journal of Medicine*, 386(12):1143–1154, 2022. doi: 10.1056/NEJMoa2115022.

- [6] Sunil Verma, David Miles, Luca Gianni, Ian E. Krop, Manfred Welslau, Jose Baselga, Mark Pegram, Do-Youn Oh, Véronique Diéras, Elena Guardino, Lei Fang, Michael W. Lu, Susan Olsen, and Kimberly Blackwell. Trastuzumab emtansine for her2-positive advanced breast cancer (EMILIA): final overall survival analysis. *Lancet Oncology*, 18(6):732–742, 2017. doi: 10.1016/S1470-2045(17)30312-3.
- [7] Véronique Diéras, David Miles, Sunil Verma, Mark Pegram, Manfred Welslau, Jose Baselga, Ian E. Krop, Kimberly Blackwell, Sebastian Hoersch, Jin Xu, Meredith Green, and Luca Gianni. Trastuzumab emtansine versus capecitabine plus lapatinib in patients with previously treated her2-positive advanced breast cancer (EMILIA): a descriptive analysis of final overall survival results from a randomised, open-label, phase 3 trial. *Lancet Oncology*, 14(10):968–977, 2013. doi: 10.1016/S1470-2045(13)70313-3.
- [8] Rashmi K. Murthy, Sherene Loi, Alicia Okines, Elisavet Paplomata, Erika Hamilton, Sara A. Hurvitz, Nancy U. Lin, Virginia Borges, Vandana Abramson, Carey Anders, Philippe L. Bedard, Mafalda Oliveira, Erik Jakobsen, Thomas Bachelot, Shani Sara Shachar, Volkmar Müller, Sofia Braga, Francois P. Duhoux, Richard Greil, David Cameron, Lisa A. Carey, Giuseppe Curigliano, Karen Gelmon, Gabriel Hortobagyi, Ian Krop, Sibylle Loibl, Mark Pegram, Dennis Slamon, Maria Corazon Palanca-Wessels, Lisa Walker, Wen Feng, and Eric P. Winer. Tucatinib, trastuzumab, and capecitabine for her2-positive metastatic breast cancer. *New England Journal of Medicine*, 382(7):597–609, 2020. doi: 10.1056/NEJMoa1914609.
- [9] Nancy U. Lin, Virginia Borges, Carey Anders, Rashmi K. Murthy, Elisavet Paplomata, Erika Hamilton, Sara Hurvitz, Sherene Loi, Alicia Okines, Vandana Abramson, Philippe L. Bedard, Mafalda Oliveira, Volkmar Mueller, Amelia Zelnak, Michael P. DiGiovanna, Thomas Bachelot, A. Jo Chien, Ruth M. O'Regan, Andrew Wardley, Andrew Conlin, Florence Dalenc, Veronique Dieras, Javier Cortés, Giuseppe Curigliano, Karen Gelmon, Cristina Saura, Seock-Ah Im, Joyce O'Shaughnessy, Adam Brufsky, Marco Colleoni, et al. Intracranial efficacy and survival with tucatinib plus trastuzumab and capecitabine for previously treated her2-positive breast cancer with brain metastases in the her2climb trial. *Journal of Clinical Oncology*, 38(23):2610–2619, 2020. doi: 10.1200/JCO.20.00775.
- [10] William J. Gradishar, Meena S. Moran, Jasmine Abraham, Rebecca Aft, Doreen Agnese, Kimberly H. Allison, Benjamin Anderson, Harold J. Burstein, Heather Chew, Chau Dang, Anthony D. Elias, Sharon H. Giordano, Matthew P. Goetz, Lori J. Goldstein, Sara A. Hurvitz, Steven J. Isakoff, Sameer Jain, Alberto A. Jarquin-Valdivia, Sara H. Javid, Jairam Krishnamurthy, Ingrid A. Mayer, Gayle J. Metzger, Joanne E. Mortimer, Ruth M. O'Regan, Sameer A. Patel, Hope S. Rugo, Edith M. Stringer-Reasor, Melinda L. Telli, Christopher Twelves, Deborah A. Shead, Lisa A. Pluchino, and Rashmi Kumar. Breast cancer, version 1.2024, nccn clinical practice guidelines in oncology. *Journal of the National Comprehensive Cancer Network*, 22(4):331–357, 2024. doi: 10.6004/jnccn.2024.0023.
- [11] Shanu Modi, Cristina Saura, Toshinari Yamashita, Yeon Hee Park, Sung-Bae Kim, Kenji Tamura, Fabrice Andre, Hiroji Iwata, Yoshinori Ito, Junji Tsurutani, Joohyuk Sohn, Neelima Denduluri, Christophe Perrin, Kenjiro Aogi, Eriko Tokunaga, Seock-Ah Im, Keun Seok Lee, Sara A. Hurvitz, Javier Cortes, Chiun Lee, Shih-Chieh Chen, Yijun Zhang, Javad Shahidi, Antoine Yver, and Ian Krop. Systemic therapy for advanced human epidermal growth factor receptor 2-positive breast cancer: Asco guideline update. *Journal of Clinical Oncology*, 42(1):5–23, 2024. doi: 10.1200/JCO.23.01519.
- [12] ESMO Guidelines Committee. Her2-positive metastatic breast cancer: Esmo clinical practice guideline for diagnosis, treatment and follow-up. *Annals of Oncology*, 36(1):5–25, 2025. doi: 10.1016/j.annonc.2024.11.001. Living Guideline, Version 1.2, April 2025.
- [13] Lisa Barbera, Rinku Sutradhar, Doris Howell, Jonathan Sussman, Soo Jin Seung, Jeremy Dudebout, Monika K. Krzyzanowska, Ning Liu, and Kelvin K. W. Chan. Pertuzumab and trastuzumab vs trastuzumab for treatment of her2-positive metastatic breast cancer: A population-based comparative effectiveness study. *JAMA Network Open*, 5(3):e224032, 2022. doi: 10.1001/jamanetworkopen.2022.4032.
- [14] Cristina Saura, Mafalda Oliveira, Yu-Hsiang Feng, Meng-Shu Dai, Shou-Wei Chen, Sara A. Hurvitz, Sung-Bae Kim, Beverly Moy, Suzette Delaloge, William Gradishar, Norikazu Masuda, Marcela Palácová, Maureen E. Trudeau, Joseph Mattson, Yoon-Sim Yap, Ming-Feng Hou, Michelino De Laurentiis, Tarek Usari, Yi-Sheng Lu, Ling-Ming Wang, Kami Keyvanjah, Henry Assad, and Javier Cortes. Neratinib plus capecitabine versus lapatinib plus capecitabine in her2-positive metastatic breast cancer previously treated with ≥ 2 her2-directed regimens: phase iii nala trial. *Journal of Clinical Oncology*, 38(27):3138–3149, 2020. doi: 10.1200/JCO.20.00147.