Table 1. **SYSTEMIC THERAPY FOR PATIENTS WITH ADVANCED HER2-POSITIVE BREAST CANCER SUMMARY OF RECOMMENDATIONS TABLE**

<table>
<thead>
<tr>
<th>Clinical Question</th>
<th>Recommendation</th>
<th>Evidence Rating</th>
</tr>
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</table>
| What is the optimal treatment for patients with HER2-positive advanced breast cancer? For patients with HER2-positive advanced breast cancer, is HER2-targeted therapy recommended for all in the first-line setting? | Clinicians should recommend HER2-targeted therapy-based combinations for first-line treatment, except for highly selected patients with estrogen receptor-positive (ER+) or progesterone receptor-positive (PgR+) and HER2-positive disease for whom clinicians may use endocrine therapy alone. | Type: Evidence-based  
Evidence Quality: High  
Strength of Recommendation: Strong |
| What is the optimal treatment for patients with HER2-positive advanced breast cancer? Is HER2-targeted therapy recommended for all in the second-line setting? | If a patient’s HER2-positive advanced breast cancer has progressed during or after first-line HER2-targeted therapy, clinicians should recommend second-line HER2-targeted therapy-based treatment. | Type: Evidence-based  
Evidence Quality: High  
Strength of Recommendation: Strong |
| What is the optimal treatment for patients with HER2-positive advanced breast cancer? Is HER2-targeted therapy recommended for all in the third-line setting and beyond? | If a patient’s HER2-positive advanced breast cancer has progressed during or after second-line or greater HER2-targeted treatment, clinicians should recommend third-line or greater-line HER2-targeted therapy-based treatment. | Type: Evidence-based  
Evidence Quality: Intermediate  
Strength of Recommendation: Moderate |
## SYSTEMIC THERAPY FOR PATIENTS WITH ADVANCED HER2-POSITIVE BREAST CANCER SUMMARY OF RECOMMENDATIONS TABLE

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| Which HER2-targeted therapy (trastuzumab, lapatinib, pertuzumab, or TDM-1) ± chemotherapy should be offered? | Clinicians should recommend the combination of trastuzumab, pertuzumab, and a taxane for first-line treatment, unless the patient has a contraindication to taxanes. | Type: Evidence-based  
Evidence Quality: High  
Strength of Recommendation: Strong |
| What is the specific recommended regimen in first-line?                             | If a patient’s HER2-positive advanced breast cancer has progressed during or after first-line HER2-targeted therapy, clinicians should recommend T-DM1 as a second-line line treatment. | Type: Evidence-based  
Evidence Quality: High  
Strength of Recommendation: Strong |
| Which HER2-targeted therapy (trastuzumab, lapatinib, pertuzumab, or TDM-1) ± chemotherapy should be offered? | If a patient’s HER2-positive advanced breast cancer has progressed during or after second-line or greater HER2-targeted therapy, but she has not received TDM-1, clinicians should offer TDM-1. | Type: Evidence-based  
Evidence Quality: High  
Strength of Recommendation: Strong |
| What is the specific recommended regimen in third-line and beyond?                  | If a patient’s HER2-positive advanced breast cancer has progressed during or after second-line or greater HER2-targeted treatment, but she has not received pertuzumab, clinicians may offer pertuzumab. | Type: Informal consensus  
Evidence Quality: Insufficient  
Strength of Recommendation: Weak |
### Summary of Recommendations Table

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<tr>
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<tr>
<td>If a patient’s HER2-positive advanced breast cancer has progressed during or after second-line or greater HER2-targeted treatment and she has already received pertuzumab and TDM-1, clinicians should recommend third–line or greater HER2-targeted therapy-based treatment. Options include lapatinib and capecitabine, as well as other combinations of chemotherapy and trastuzumab, lapatinib and trastuzumab, or hormonal therapy (in patients with ER+ and/or PgR+ disease). There is insufficient evidence to recommend one regimen over another.</td>
<td>Type: Informal consensus Evidence Quality: Insufficient Strength of Recommendation: Weak</td>
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<tr>
<td>What are the optimal timing, dose, schedule, and duration of treatment?</td>
<td>If a patient is receiving HER2-targeted therapy and chemotherapy combinations, the chemotherapy should continue for approximately 4-6 months (or longer) and/or to the time of maximal response, depending on toxicity and in the absence of progression. When chemotherapy is stopped, clinicians should continue the HER2-targeted therapy; no further change in the regimen is needed until the time of progression or unacceptable toxicities.</td>
<td>Type: Evidence-based Evidence Quality: Intermediate Strength of Recommendation: Moderate</td>
</tr>
<tr>
<td>How should any previous HER2 adjuvant therapy influence treatment for patients with a recurrence ≤ 12 months after adjuvant treatment?</td>
<td>If a patient finished trastuzumab-based adjuvant treatment ≤12 months prior to recurrence, clinicians should follow the second-line HER2-targeted therapy-based treatment recommendations.</td>
<td>Type: Evidence-based Evidence Quality: Intermediate Strength of Recommendation: Moderate</td>
</tr>
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# SYSTEMIC THERAPY FOR PATIENTS WITH ADVANCED HER2-POSITIVE BREAST CANCER SUMMARY OF RECOMMENDATIONS TABLE

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| How should any previous HER2 adjuvant therapy influence treatment for patients with a recurrence > 12 months after adjuvant treatment? | If a patient finished trastuzumab-based adjuvant treatment >12 months prior to recurrence, clinicians should follow the first-line HER2-targeted therapy-based treatment recommendations. | Type: Evidence-based  
Evidence Quality: High  
Strength of Recommendation: Strong |
| What is the most appropriate first-line therapy for patients with HER2-positive/ ER+/PgR+-advanced breast cancer? | If a patient’s cancer is hormone receptor-positive and HER2-positive, clinicians may recommend either:  
HER2-targeted therapy plus chemotherapy  
Endocrine therapy plus trastuzumab or lapatinib (in selected cases)  
Endocrine therapy alone (in selected cases) | Type: Evidence-based  
Evidence Quality: High  
Strength of Recommendation: Strong  
Type: Evidence-based  
Evidence Quality: High  
Strength of Recommendation: Moderate  
Type: Evidence-based  
Evidence Quality: Intermediate  
Strength of Recommendation: Weak |
| If a clinician plans to offer endocrine therapy at some point during a woman’s treatment, what is the appropriate sequencing? | If the patient has started with a HER2-positive targeted therapy and chemotherapy combination, clinicians may add endocrine therapy to the HER2-targeted therapy when chemotherapy ends and/or when the cancer progresses. | Type: Informal consensus  
Evidence Quality: Insufficient  
Strength of Recommendation: Weak |
| Can clinicians offer first-line endocrine therapy? If so, should it always be in combination with HER2-targeted therapy? | In special circumstances, such as low disease burden, the presence of co-morbidities (contradictions to HER2-targeted therapy such as congestive heart failure), and/or the presence of a long disease free-interval, clinicians may offer first-line endocrine therapy alone. | Type: Informal consensus  
Evidence Quality: Intermediate  
Strength of Recommendation: Weak |

Qualifying Statement: Although the clinician may discuss using endocrine therapy with or without HER2-targeted, the majority of patients will still receive chemotherapy plus HER2-targeted therapy.
Table 2.

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<tr>
<td><strong>What is the appropriate course of treatments for patients with HER2-positive advanced breast cancer and brain metastases?</strong></td>
<td>If a patient has a favorable prognosis for survival and a single brain metastasis, he/she should be evaluated by an experienced neurosurgeon for discussion of the option of surgical resection, particularly if the metastasis is &gt;3-4 cm and/or if there is evidence of symptomatic mass effect.</td>
<td>Type: Formal Consensus</td>
</tr>
<tr>
<td></td>
<td>If a patient has a favorable prognosis and a single brain metastasis of less than &lt; 3-4 cm without symptomatic mass effect, clinicians may offer either SRS or surgical resection, depending upon the location and surgical accessibility of the tumor, need for tissue diagnosis, and other considerations such as medical risk factors for surgery, and patient preference.</td>
<td>Evidence Quality: Intermediate</td>
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<tr>
<td></td>
<td>If these patients choose to undergo SRS, clinicians may discuss the options of adding WBRT to SRS versus SRS alone.</td>
<td>Recommendation Strength: Weak</td>
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<td></td>
<td>For most patients with brain metastases who undergo surgical resection, clinicians should recommend postoperative radiotherapy to the resection bed to reduce the risk of local recurrence.</td>
<td>Type: Formal Consensus</td>
</tr>
<tr>
<td></td>
<td>If a patient has a favorable prognosis and a single brain metastasis of greater than 3-4 cm which is deemed unresectable and unsuitable for SRS, clinicians may discuss the options of WBRT or fractionated stereotactic radiotherapy (FRST).</td>
<td>Evidence Quality: Intermediate</td>
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<td>Recommendation Strength: Weak</td>
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<tr>
<td><strong>Does the approach to local therapy of brain metastases differ in patients with HER2-positive breast cancer? (single brain metastasis, favorable prognosis)</strong></td>
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## DISEASE MANAGEMENT FOR PATIENTS WITH ADVANCED HER2-POSITIVE BREAST CANCER AND BRAIN METASTASES

### SUMMARY OF RECOMMENDATIONS TABLE

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| **What is the appropriate course of treatments for patients with HER2-positive advanced breast cancer and brain metastases?** | After treatment, serial imaging every 2-4 months may be used to monitor for local and distant brain failure. In a patient who presents with limited metastases suitable for SRS, clinicians may discuss SRS with or without WBRT. In a patient with lesions that are unresectable and unsuitable for SRS, clinicians may recommend WBRT and may discuss SRS following WBRT | Type: Formal Consensus  
Evidence Quality: Low  
Recommendation Strength: Weak  
Type: Formal Consensus  
Evidence Quality: Intermediate  
Recommendation Strength: Weak  
Type: Formal Consensus  
Evidence Quality: Low  
Recommendation Strength: Weak                                                                 |
| **Does the approach to local therapy of brain metastases differ in patients with HER2-positive breast cancer? (limited metastases [2-4 metastases] and favorable prognosis)** | If a patient has a favorable prognosis and presents with multiple, but limited metastases (2-4), treatment options depend on the size, resectability, and mass effect of the lesions. In a patient who has a large (>3-4 cm) lesion associated with symptomatic mass effect, clinicians may discuss surgical resection of the larger lesion, if the lesion is deemed resectable. The remaining lesions may be treated with SRS with or without WBRT. | Type: Formal Consensus  
Evidence Quality: Intermediate  
Recommendation Strength: Weak  
Type: Formal Consensus  
Evidence Quality: Intermediate  
Recommendation Strength: Weak  
Type: Formal Consensus  
Evidence Quality: Low  
Recommendation Strength: Weak |
| Clinical Question                                                                 | Recommendation                                                                                                                                                                                                                                                                                                                                                     | Evidence Rating                                                                                     |
|---------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| What is the appropriate course of treatments for patients with HER2-positive advanced breast cancer and brain metastases? | If a patient has symptomatic leptomeingeal metastases (specifically in the brain), clinicians may recommend WBRT. The management of leptomeingeal metastases is complex and recommendations regarding intrathecal therapy or systemic therapy for leptomeingeal metastases are outside the scope of these practice guidelines.                                                                 | Type: Formal Consensus  
Evidence Quality: Low  
Recommendation Strength: Moderate |
| Does the approach to local therapy of brain metastases differ in patients with HER2-positive breast cancer? (diffuse disease/extensive metastases) | If a patient has a more favorable prognosis and presents with many diffuse/brain metastases (≥5 metastases), clinicians may recommend WBRT. Patients with favorable prognoses are those with good performance status and effective systemic therapy options. The criteria may include KPS ≥70, age, controlled extracranial disease, and/or if good salvage systemic therapy options for extracranial disease are available. | Type: Formal Consensus  
Evidence Quality: Low  
Recommendation Strength: Weak |
| What is the appropriate course of treatments for patients with HER2-positive advanced breast cancer and brain metastases? | If a patient has brain metastases) and a poor prognosis, clinicians should discuss the options of best supportive care and/or palliative care, which may or may not include radiation therapy, on a case-by-case basis.                                                                 | Type: Formal Consensus  
Evidence Quality: Low  
Recommendation Strength: Weak |
| Does the approach to local therapy of brain metastases differ in patients with HER2-positive breast cancer? (patients with poor prognosis) | For a patient with symptomatic brain metastases and poor prognosis, WBRT may be offered if there is a reasonable expectation of symptomatic improvement which outweighs the acute and subacute treatment-related toxicities including fatigue and decline in neurocognitive function.                                                                 | Type: Formal Consensus  
Evidence Quality: Low  
Recommendation Strength: Weak |
# DISEASE MANAGEMENT FOR PATIENTS WITH ADVANCED HER2-POSITIVE BREAST CANCER AND BRAIN METASTASES

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| What is the appropriate course of treatments for patients with HER2-positive advanced breast cancer and brain metastases? Does the approach to local therapy of brain metastases differ in patients with HER2-positive breast cancer? (patients with progressive intracranial metastases despite initial therapy) | If a patient has progressive intracranial metastases, treatment options will depend on the patient’s prior therapies, burden of disease, performance status, and overall prognosis. | Type: Formal Consensus  
Evidence Quality: Low  
Recommendation Strength: Moderate |
| What is the appropriate course of treatments for patients with HER2-positive advanced breast cancer and brain metastases? Does the approach to local therapy of brain metastases differ in patients with HER2-positive breast cancer? (brain recurrence and radiation; limited recurrence) | For a patient with a favorable prognosis and limited recurrence that follows treatment with WBRT, clinicians may discuss SRS, surgery, a trial of systemic therapy, or enrollment onto a clinical trial.  
For a patient with a favorable prognosis and limited recurrence that follows treatment with SRS, clinicians may discuss repeat SRS, surgery, WBRT, a trial of systemic therapy, or enrollment onto a clinical trial. | Type: Formal Consensus  
Evidence Quality: Low  
Recommendation Strength: Moderate |
| What is the appropriate course of treatments for patients with HER2-positive advanced breast cancer and brain metastases? Does the approach to local therapy of brain metastases differ in patients with HER2-positive breast cancer? (brain recurrence and radiation; diffuse recurrence) | If a patient has diffuse recurrence that follows treatment with WBRT, clinicians may discuss palliative options such as repeat reduced dose WBRT, a trial of systemic therapy, enrollment onto a clinical trial, or best supportive care. | Type: Formal Consensus  
Evidence Quality: Low  
Recommendation Strength: Weak |
|                                                                                  | If a patient has diffuse recurrence that follows treatment with SRS, clinicians may discuss palliative options such as WBRT, a trial of systemic therapy, enrollment onto a clinical trial, or best supportive care. | Type: Formal Consensus  
Evidence Quality: Low  
Recommendation Strength: Moderate |
### DISEASE MANAGEMENT FOR PATIENTS WITH ADVANCED HER2-POSITIVE BREAST CANCER AND BRAIN METASTASES
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| How should systemic therapy be managed in patients with HER2-positive brain metastases (including how to manage systemic therapy when the brain is the only site of progression versus when progression is in both the brain and elsewhere)? *(Brain recurrence and Systemic therapy)* | For a patient who receives standard surgical or radiotherapy-based approaches to treat brain metastases and are receiving anti-HER2 based therapy and whose systemic disease is not progressive at the time of brain metastasis diagnosis, clinicians should not switch the systemic therapy. For a patient who receives standard surgical and/or radiotherapy-based approaches to treatment of brain metastases and whose systemic disease is progressive at the time of brain metastasis diagnosis, clinicians should offer HER2-targeted therapy according to the algorithms for treatment of HER2-positive metastatic breast cancer. | Type: Formal Consensus  
Evidence Quality: Low  
Recommendation Strength: Moderate  
Type: Formal Consensus  
Evidence Quality: Intermediate  
Recommendation Strength: Moderate |
| Is there a role for systemic therapy specifically to treat brain metastases in HER2-positive breast cancer? *(systemic treatment for brain metastases)* | If a patient has asymptomatic, low volume brain metastases and has not received radiation therapy, clinicians may discuss upfront therapy with lapatinib and capecitabine as an option. Clinicians should discuss the most recent data and inform patients that radiation therapy in this setting is still the primary option. If a patient develops intracranial disease progression following WBRT or SRS, including one who is not a candidate for re-irradiation, clinicians may discuss offering systemic therapy as an alternative, using a regimen with some evidence of activity in the setting of CNS disease. | Type: Formal Consensus  
Evidence Quality: Low  
Recommendation Strength: Weak  
Type: Formal Consensus  
Evidence Quality: Low  
Recommendation Strength: Weak |
### Clinical Question
Should patients with HER2-positive breast cancer be screened for development of brain metastases? *(screening)*

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| If a patient does not have a known history of or symptoms of brain metastases, clinicians should not perform routine surveillance with brain MRI. | Type: Formal Consensus  
Evidence Quality: Low  
Recommendation Strength: Weak |
| Clinicians should have a low threshold to perform diagnostic brain MRI testing in the setting of any neurologic symptoms suggestive of brain involvement, such as new onset headaches, unexplained nausea/vomiting, or change in motor/sensory function. | Type: Formal Consensus  
Evidence Quality: Low  
Recommendation Strength: Strong |