HER2+ BREAST CANCER TREATMENT LANDSCAPE*[1-8]

<table>
<tr><th>NEOADJUVANT</th><th>ADJUVANT</th><th>1L</th><th>2L</th><th>3L+</th></tr>
<tr>
<td rowspan="2">Pertuzumab
Indicated for use in combination with trastuzumab and chemotherapy for the neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer (either greater than 2 cm in diameter or node-positive) as part of a complete treatment regimen for early breast cancer.</td>
<td>Pertuzumab
Indicated for use in combination with trastuzumab and chemotherapy for the adjuvant treatment of patients with HER2-positive early breast cancer at high risk of recurrence.</td>
<td>Pertuzumab
Indicated for use in combination with trastuzumab and docetaxel for the treatment of patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease.</td>
<td colspan="2">TUKYSA
Indicated in combination with trastuzumab and capecitabine for treatment of adult patients with advanced unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases, who have received one or more prior anti-HER2-based regimens in the metastatic setting.</td>
</tr>
<tr>
<td>Trastuzumab emtansine
As a single agent, is indicated for the adjuvant treatment of patients with HER2-positive early breast cancer who have residual invasive disease after neoadjuvant taxane and trastuzumab-based treatment.</td>
<td>Trastuzumab emtansine
As a single agent, is indicated for the treatment of patients with HER2-positive, metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination. Patients should have either:
• Received prior therapy for metastatic disease, or
• Developed disease recurrence during or within six months of completing adjuvant therapy</td>
<td colspan="2">Trastuzumab emtansine
As a single agent, is indicated for the treatment of patients with HER2-positive, metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination. Patients should have either:
• Received prior therapy for metastatic disease, or
• Developed disease recurrence during or within six months of completing adjuvant therapy</td>
</tr>
<tr>
<td colspan="2" rowspan="2">Trastuzumab
Indicated for adjuvant treatment of HER2 overexpressing node positive or node negative (ER/PR negative or with one high-risk feature) breast cancer:
• As part of a treatment regimen containing doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel
• As part of a treatment regimen with docetaxel and carboplatin
• As a single agent following multi-modality anthracycline-based therapy</td>
<td>Neratinib
As a single agent is indicated for the extended adjuvant treatment of adult patients with early-stage HER2-positive breast cancer, to follow adjuvant trastuzumab-based therapy.</td>
<td colspan="2">Margetuximab-cmkb
Indicated, in combination with chemotherapy, for the treatment of adult patients with metastatic HER2-positive breast cancer who have received two or more prior anti-HER2 regimens, at least one of which was for metastatic disease.</td>
</tr>
<tr>
<td colspan="2" rowspan="2">Fam-trastuzumab deruxtecan-nxki
Indicated for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens in the metastatic setting.†

Lapatinib
Indicated in combination with capecitabine for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress HER2 and who have received prior therapy including an anthracycline, a taxane, and trastuzumab.‡

Neratinib
In combination with capecitabine is indicated for the treatment of adult patients with advanced or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens in the metastatic setting.</td>
</tr>
<tr>
<td colspan="3">Trastuzumab
• In combination with paclitaxel for the first-line treatment of HER2-overexpressing metastatic breast cancer
• As a single agent for treatment of HER2-overexpressing breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease</td>
</tr>
</table>

*This table is not intended to compare the indications or clinical efficacy and safety of the listed products. This list does not include information about dosing or administration of the products. For a complete description of these products, please refer to the full Prescribing Information for each.
†This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.
‡Limitations of Use: Patients should have disease progression on trastuzumab prior to initiation of treatment with lapatinib in combination with capecitabine.

Important Safety Information

Warnings and Precautions

- **Diarrhea:** TUKYSA can cause severe diarrhea including dehydration, hypotension, acute kidney injury, and death. In HER2CLIMB, 81% of patients who received TUKYSA experienced diarrhea, including 12% with Grade 3 and 0.5% with Grade 4. Both patients who developed Grade 4 diarrhea subsequently died, with diarrhea as a contributor to death. Median time to onset of the first episode of diarrhea was 12 days and the median time to resolution was 8 days. Diarrhea led to TUKYSA dose reductions in 6% of patients and TUKYSA discontinuation in 1% of patients. Prophylactic use of antidiarrheal treatment was not required on HER2CLIMB.

Please see additional Important Safety Information and the full Prescribing Information.

Important Safety Information (cont'd)

Warnings and Precautions (cont'd)

If diarrhea occurs, administer antidiarrheal treatment as clinically indicated. Perform diagnostic tests as clinically indicated to exclude other causes of diarrhea. Based on the severity of the diarrhea, interrupt dose, then dose reduce or permanently discontinue TUKYSA.

- **Hepatotoxicity:** TUKYSA can cause severe hepatotoxicity. In HER2CLIMB, 8% of patients who received TUKYSA had an ALT increase >5 × ULN, 6% had an AST increase >5 × ULN, and 1.5% had a bilirubin increase >3 × ULN (Grade ≥3). Hepatotoxicity led to TUKYSA dose reductions in 8% of patients and TUKYSA discontinuation in 1.5% of patients.

  Monitor ALT, AST, and bilirubin prior to starting TUKYSA, every 3 weeks during treatment, and as clinically indicated. Based on the severity of hepatotoxicity, interrupt dose, then dose reduce or permanently discontinue TUKYSA.

- **Embryo-Fetal Toxicity:** TUKYSA can cause fetal harm. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential, and male patients with female partners of reproductive potential, to use effective contraception during TUKYSA treatment and for at least 1 week after the last dose.

Adverse Reactions

Serious adverse reactions occurred in 26% of patients who received TUKYSA; those occurring in ≥2% of patients were diarrhea (4%), vomiting (2.5%), nausea (2%), abdominal pain (2%), and seizure (2%). Fatal adverse reactions occurred in 2% of patients who received TUKYSA including sudden death, sepsis, dehydration, and cardiogenic shock.

Adverse reactions led to treatment discontinuation in 6% of patients who received TUKYSA; those occurring in ≥1% of patients were hepatotoxicity (1.5%) and diarrhea (1%). Adverse reactions led to dose reduction in 21% of patients who received TUKYSA; those occurring in ≥2% of patients were hepatotoxicity (8%) and diarrhea (6%).

The most common adverse reactions in patients who received TUKYSA (≥20%) were diarrhea, palmar-plantar erythrodysesthesia, nausea, fatigue, hepatotoxicity, vomiting, stomatitis, decreased appetite, abdominal pain, headache, anemia, and rash.

Lab Abnormalities

In HER2CLIMB, Grade ≥3 laboratory abnormalities reported in ≥5% of patients who received TUKYSA were decreased phosphate, increased ALT, decreased potassium, and increased AST.

The mean increase in serum creatinine was 32% within the first 21 days of treatment with TUKYSA. The serum creatinine increases persisted throughout treatment and were reversible upon treatment completion. Consider alternative markers of renal function if persistent elevations in serum creatinine are observed.

Drug Interactions

- **Strong CYP3A/Moderate CYP2C8 Inducers:** Concomitant use may decrease TUKYSA activity. Avoid concomitant use of TUKYSA.
- **Strong or Moderate CYP2C8 Inhibitors:** Concomitant use of TUKYSA with a strong CYP2C8 inhibitor may increase the risk of TUKYSA toxicity; avoid concomitant use. Increase monitoring for TUKYSA toxicity with moderate CYP2C8 inhibitors.
- **CYP3A Substrates:** Concomitant use may increase the toxicity associated with a CYP3A substrate. Avoid concomitant use of TUKYSA where minimal concentration changes may lead to serious or life-threatening toxicities. If concomitant use is unavoidable, decrease the CYP3A substrate dosage.
- **P-gp Substrates:** Concomitant use may increase the toxicity associated with a P-gp substrate. Consider reducing the dosage of P-gp substrates where minimal concentration changes may lead to serious or life-threatening toxicity.

Use in Specific Populations

- **Lactation:** Advise women not to breastfeed while taking TUKYSA and for at least 1 week after the last dose.
- **Renal Impairment:** Use of TUKYSA in combination with capecitabine and trastuzumab is not recommended in patients with severe renal impairment (CLcr < 30 mL/min), because capecitabine is contraindicated in patients with severe renal impairment.
- **Hepatic Impairment:** Reduce the dose of TUKYSA for patients with severe (Child-Pugh C) hepatic impairment.

Please see the full Prescribing Information.

References:
1. TUKYSA [Prescribing Information]. Bothell, WA: Seattle Genetics, Inc. April 2020. **2.** Ado-trastuzumab emtansine [Prescribing Information]. South San Francisco, CA: Genentech, Inc. 2020. **3.** Fam-trastuzumab deruxtecan-nxki [Prescribing Information]. Basking Ridge, NJ: Daiichi Sankyo, Inc. 2021. **4.** Lapatinib [Prescribing Information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation. 2021. **5.** Neratinib [Prescribing Information]. Los Angeles, CA: Puma Biotechnology, Inc. 2020. **6.** Pertuzumab [Prescribing Information]. South San Francisco, CA: Genentech, Inc. 2020. **7.** Trastuzumab [Prescribing Information]. South San Francisco, CA: Genentech, Inc. 2021. **8.** Margetuximab-cmkb [Prescribing Information]. Rockville, MD: MacroGenics, Inc. 2020.

Seagen®

TUKYSA®
tucatinib
50 mg | 150 mg tablets