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Positive Quality Intervention: Tucatinib (Tukysa®) Management

Description: The purpose of this PQI is to highlight tucatinib and its usage and management in advanced unresectable or metastatic HER2-positive breast cancer who have received one or more prior anti-HER2-based regimens in the metastatic setting.

Background: Tucatinib is an oral tyrosine kinase inhibitor that is highly selective for HER2, a growth factor receptor over-expressed in various types of cancers.[1] Tucatinib binds to the HER2 protein, inhibiting its role in signaling pathways and ultimately the growth of HER2-expressing cells. Tucatinib, in combination with trastuzumab and capecitabine, was studied in the HER2CLIMB trial that enrolled patients with locally advanced unresectable or metastatic HER2 positive breast cancer previously treated with trastuzumab, pertuzumab, or trastuzumab emtansine. Patients received either tucatinib 300 mg orally twice daily or placebo in addition to trastuzumab and capecitabine.[2]

	Tucatinib Group	Placebo Group
PFS at 1 year	33.1%	12.3%
Median PFS duration	7.8 months	5.6 months
OS at 2 years	44.9%	26.6%
Median OS duration	21.9 months	17.4 months

Additionally, researchers analyzed the subgroup of patients with brain metastases and found significantly increased PFS with tucatinib in this patient population as well, reporting primary results of PFS at one year of 24.9% in the tucatinib group compared to 0% in the placebo group. An exploratory analysis in the HER2CLIMB trial of intracranial efficacy in patients with brain metastases who received tucatinib combination versus placebo group was presented at the 2020 ASCO Annual meeting. The authors found a 42% reduction in the risk of death, a 68% reduction in the risk of CNS disease progression or death, and an increase in intracranial response rate (47% vs. 20%) for patients who had active measurable intracranial lesions at baseline.[5]

PQI Process: Identify eligible HER2 positive patients as potential candidates for tucatinib; upon receiving a prescription for tucatinib

- Verify appropriate starting dose: 300 mg by mouth two times daily
- Confirm orders for capecitabine and trastuzumab
- Drug interactions: avoid concomitant strong CYP3A4 and CYP2C8 inhibitors and inducers
- When to adjust which agent
    - All side effects should be assessed for relationship to tucatinib, capecitabine, and/or trastuzumab
    - Liver function abnormalities: tucatinib dose should be adjusted
    - Renal function abnormalities: capecitabine dose should be adjusted
    - Left ventricular ejection fraction (LVEF):
        - Tucatinib should be held if $\geq$ 16% reduction from baseline, LVEF below limits of normal and $\geq$ 10% reduction from baseline, or LVEF < 40%
        - Trastuzumab should be held if $\geq$ 16% reduction from baseline, LVEF below limits of normal and $\geq$ 10% reduction from baseline
    - QTc prolongation: tucatinib dose should be adjusted, regardless of relationship to drug
    - **Trastuzumab Dose Adjustment:** Hold until Grade 0/1, if longer than 28 days repeat loading dose

Tucatinib Dose Adjustments

Dose Reduction	Recommended Dose	How to Supply
1st dose reduction	250 mg PO BID	One 150 mg tablet + two 50 mg tablets BID
2nd dose reduction	200 mg PO BID	One 150 mg tablet + one 50 mg tablet BID
3rd dose reduction	150 mg PO BID	One 150 mg tablet BID

Capecitabine Dose Adjustment

Grade	Action	Adjustment (% starting dose)
Grade 1	Maintain dose level	Maintain dose level
Grade 2 – 1st Appearance	Hold until Grade 0/1	100%
Grade 2 – 2nd Appearance	Hold until Grade 0/1	75%
Grade 2 – 3rd Appearance	Hold until Grade 0/1	50%
Grade 2 – 4th Appearance	Discontinue	-
Grade 3 – 1st Appearance	Hold until Grade 0/1	75%
Grade 3 – 2nd Appearance	Hold until Grade 0/1	50%
Grade 3 – 3rd Appearance	Discontinue	-
Grade 4	Hold until Grade 0/1 or discontinue	-

Patient-Centered Activities:

- Provide Oncology Chemotherapy Education (OCE) sheet
- Provide Tucatinib Patient Guided Resource
- Administration: can be taken with or without food at the same time twice each day and at the same time as the capecitabine in the regimen
- Counsel patient on common side effects
    - Diarrhea (80.9%)
        - Provide Oral Chemotherapy Education Supplemental Sheet
        - Reported to be manageable with short courses of antidiarrheals
        - Recommend antidiarrheal agents to have on hand when starting tucatinib
    - Palmar-plantar erythrodysaesthesia syndrome (63.4%)
        - See **Medication Induced Hand-Foot Syndrome** PQI and provide Oral Chemotherapy Education Supplemental Sheet
    - Nausea (58%), vomiting (35.9%)
        - See **Chemotherapy Induced Nausea and Vomiting** PQI, CINV Assessment Tool, and provide Oral Chemotherapy Education Supplemental Sheet
    - Fatigue (45%)
    - Increased liver transaminases (20%)
        - Reported to be transient and reversible
    - Stomatitis, headache, decreased appetite also reported
- Storage: store at room temperature in the original bottle; do not remove desiccant from bottle
    - Once the bottle is opened, medication should be used within 3 months
- Patient Assistance: NCODA Financial Assistance Tool

References:

1. English DP, Rogue DM, Santin AD. HER2 expression beyond breast cancer: therapeutic implications for gynecologic malignancies. *Mol Diagn Ther*. 2013;17(2):85-99.
2. Murthy RK, Loi S, Okines A, et al. Tucatinib, trastuzumab, and capecitabine for HER2-positive metastatic breast cancer. *NEJM*. 2020; 382:597-609.
3. Tucatinib (Tukysa) [package insert].
4. Tucatinib combination extends survival in HER2- positive metastatic breast cancer, including patients with brain metastases. The ASCO Post. Available at: https://www.ascopost.com/issues/january-25-2020/tucatinib-combination-extends-survival-in-her2-positive-metastatic-breast-cancer/. Published JAN 25, 2020.
5. Lin NU, Borges V, Anders C, 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. *JCO*. 2020, JCO2000775. doi: 10.1200/JCO.20.00775.