Tucatinib (Tukysa®)

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What is tucatinib?
Tucatinib is an oral small-molecule tyrosine kinase inhibitor (TKI) that targets human epidermal growth factor receptor 2 (HER2). It targets the HER2 kinase domain intracellularly. In vitro it inhibits HER2 and HER3 phosphorylation, thus inhibiting downstream MAPK and AKT signaling and cell proliferation of HER2-positive cells.

What is this approved for?
Tucatinib is approved in combination with trastuzumab and capecitabine for treatment of advanced unresectable or metastatic HER2-positive breast cancer in patients who have received at least one prior HER2-targeted therapy in the metastatic setting. It is approved for treatment of unresectable or metastatic HER2-positive breast cancer based on results from the HER2CLIMB study (N Engl J Med 2020;382:597-609). This international, double-blind, controlled trial randomized patients 2:1 to treatment with tucatinib 300 mg by mouth twice daily continuously (n=410) and capecitabine 1,000 mg/m² by mouth twice daily with or without food, approximately 12 hours apart at the same time as capecitabine.

How do you administer this drug?
Tucatinib is administered as a 300 mg dose of 2 x 150 mg tablets taken by mouth twice daily with or without food, approximately 12 hours apart at the consistent times each day. Tablets should be swallowed whole and not crushed. Tucatinib may be administered at the same time as capecitabine.

Are there any premedications needed for tucatinib?
No premedications are required for tucatinib. Evaluation of common adverse effects does demonstrate a moderate-high risk of chemotherapy-induced nausea and vomiting. Addition of appropriate antiemetics for prevention of nausea and vomiting is recommended.

How do I adjust the dose in the setting of renal or hepatic insufficiency?
There are no recommended dose adjustments for renal impairment, due to lack of patients of these populations in the primary literature. The tucatinib/capecitabine/trastuzumab combination is not recommended in patients with creatinine clearance <30 mL/min according to capecitabine prescribing information.

At treatment initiation, there are no recommended dose adjustments for Child-Pugh class A or B hepatic impairment. Patients with Child-Pugh class C hepatic impairment at baseline should begin therapy at 200 mg twice daily rather than 300 mg. See table below for dosing recommendations in case of hepatotoxicity occurring during treatment.

**Hepatotoxicity Severity**

| Grade 2 hyperbilirubinemia (>1.5-3x ULN) | Hold until ≤ grade 1, then resume at same dose level |
| Grade 3 AST or ALT elevation (>5-20x ULN) or grade 3 hyperbilirubinemia (>3-10x ULN) | Hold until ≤ grade 1, then resume at next lower dose level |
| Grade 4 AST or ALT elevation (>20x ULN) or grade 4 hyperbilirubinemia (>10x ULN) | Permanently discontinue |
| ALT or AST >3x ULN and bilirubin >2x ULN | Permanently discontinue |

**Tucatinib Dose Reduction Levels**

| Initial dose | 300 mg twice daily |
| First dose reduction | 250 mg twice daily |
| Second dose reduction | 200 mg twice daily |
| Third dose reduction | 150 mg twice daily |

**ULN** = upper limit of normal

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Sweet potatoes are also quite healthy, to my delight. They are high in Vitamins B6, C, and D, and contain goodly amounts of iron, magnesium, and potassium. They are loaded with beta carotene, with its presumed chemopreventive effects. Presumed, because Vitamin A failed to prevent carcinogenesis in several randomized controlled trials. But I still give sweet potatoes an “A” for effort.

Pumpkin pie for dessert also gets high marks in my book. Pumpkins are a great source of fiber, better than whole wheat bread. They contain the antioxidants lutein and zeaxanthin, which a Google search assures me may prevent cataracts. I have early cataracts, so I will be sure to eat an extra slice of pie. Like sweet potatoes, they are high in vitamin A (though I probably have enough of that already), as well as riboflavin and folate. But pumpkin pies are pretty fatty, so maybe just one slice after all.

Mashed potatoes, as far as I can tell, are somewhat of a wash. The recently reported NIH-AARP study, which recruited over 566,000 participants and followed them for over 15 years, reported no excess in cancer or cardiac mortality for high potato consumption. The American Diabetes Association considers potatoes an appropriate food for diabetics, as their starches are broken down more slowly than the simple sugars found in so many foods.

I could go on and on, depending on which side dishes you like. Overall, though, Thanksgiving dinner seems pretty healthy, assuming you don’t drown in calories. Maybe even good for you from a chemoprevention standpoint. Especially the cranberries. But in this year of COVID-19, the health effects of Thanksgiving dinner are something more than cranberries and pumpkin pie.

Let me end with Abraham Lincoln, that great man who, in addition to saving the Union and ending slavery, issued the 1863 presidential proclamation that established Thanksgiving as an American holiday. Lincoln’s proclamation noted the horrors of war through which the United States was passing, but also reminded his fellow citizens of all they had to be thankful for: “the country, rejoicing in the consciousness of augmented strength and vigor, is permitted to expect continuance of years with large increase of freedom.”

His proclamation concluded with these lovely words, which I’ll quote in full: “I do therefore invite my fellow citizens in every part of the United States, and also those who are at sea and those who are sojourning in foreign lands, to set apart and observe the last Thursday of November next, as a day of Thanksgiving and Praise to our beneficent Father who dwelleth in the Heavens. And I recommend to them that while offering up the ascriptions justly due to Him for such singular deliverances and blessings, they do also, with humble confidence for our national perverseness and disobedience, commend to His tender care all those who have become widows, orphans, mourners or sufferers in the lamentable civil strife in which we are unavoidably engaged, and fervently implore the interposition of the Almighty Hand to heal the wounds of the nation and to restore it as soon as may be consistent with the Divine purposes to the full enjoyment of peace, harmony, tranquility and Union.”

To which I can only add my own “Amen.” Let those of us who give care, for those who have become widows, orphans, mourners, or sufferers. And let me wish all of you peace, harmony, tranquility, and Union, and our world continuance of years with a large increase of freedom. We, like Lincoln’s America, certainly need all of these. Some thoughts are for the ages. 

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**PHARMACY FORUM**

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**What are the common side effects (> or =10%)?**

The following side effects are reported for the combination of tucatinib with trastuzumab and capecitabine:

- Dermatologic: rash (20%), palmar-plantar erythrodysesthesia (63%)
- Gastrointestinal: diarrhea (81%), nausea (58%), vomiting (36%), reduced appetite (25%), constipation (15%), abdominal pain (15%), stomatitis (32%)
- Increased lab values: phosphorus (57%), magnesium (40%), potassium (16%), sodium (28%)
- Increased lab values: aspartate aminotransferase (AST) (21%), alanine aminotransferase (ALT) (20%), bilirubin (19%), creatinine (14-33%)
- Hepatic: hepatotoxicity (42%)
- Hematologic: anemia (21%)
- Nervous System: headache (22%), peripheral neuropathy (13%), dizziness (11%)
- Neuromuscular & Skeletal: arthralgia (15%)
- Respiratory: cough (14%), epistaxis (12%), dyspnea (12%)
- Other: weight loss (13%), urinary tract infection (11%), peripheral edema (10%)

**What are the uncommon side effects (less than 10%)?**

Seizures are an uncommon side effect, occurring in approximately 2 percent of patients.

**Are there any important drug interactions?**

Tucatinib is a major substrate of CYP2C8, and a minor substrate of CYP3A4. Use with strong CYP3A4 or moderate CYP2C8 inducers will decrease tucatinib concentration and effectiveness and should be avoided. Use with strong CYP2C8 inhibitors will increase risk of toxicities with tucatinib and should be avoided. If the combination with a strong CYP2C8 inhibitor is unavoidable, reduce tucatinib to 100 mg twice daily. Tucatinib is also a reversible inhibitor of CYP2C8 and CYP3A4 and may increase concentrations of drugs metabolized via these pathways.

**What should my patients know about tucatinib?**

- Important counseling points for patients include education on diarrhea, PPE, anemia, stomatitis and good oral hygiene practices, and appropriate use of antiemetic agents for nausea and vomiting.
- Patients of child-bearing age should also be educated on use of effective contraception throughout treatment and for at least 1 week after the last dose due to risk of fetal harm.

**What else should I know about tucatinib?**

There is a boxed warning for severe diarrhea (grade 3-4), which occurred in 12.9 percent of patients receiving tucatinib in the HER2CLIMB trial (~12% grade 3), and led to dose reductions in 6 percent and discontinuation in 1 percent of patients. Median time to onset of diarrhea was 12 days and median time to resolution was 8 days. Use of as-needed anti-diarrheal agents is recommended as appropriate. Specific dose adjustments and hold parameters for diarrhea are available in the prescribing information.

There is also a boxed warning for hepatotoxicity, which led to dose reduction in 8 percent and discontinuation in 1.5 percent of patients on tucatinib in HER2CLIMB. See hepatic dose adjustment recommendations above for management.

**What useful links are available regarding tucatinib?**

- FDA Approval Announcement: https://bit.ly/33uo5Xc

**Any ongoing clinical trials related to tucatinib?**

Trials are ongoing for use of tucatinib in combination with other agents such as palbociclib, letrozole, ado-trastuzumab emtansine, and trastuzumab deruxtecan for HER2-positive breast cancer. There are also ongoing studies of tucatinib in combination with trastuzumab deruxtecan in HER2-positive gastrointestinal cancers. More information is available about these clinical trials at https://clinicaltrials.gov.