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IN BRIEF

A Second Indication for Tucatinib *(Tukysa)*

The oral kinase inhibitor tucatinib (*Tukysa* – Seagen) has received accelerated approval from the FDA for use in combination with trastuzumab *(Herceptin)* for treatment of adults with RAS wild-type human epidermal growth factor receptor 2 (HER2)-positive unresectable or metastatic colorectal cancer that has progressed following treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy regimens. Tucatinib was approved in 2020 for use in combination with trastuzumab and capecitabine (*Xeloda*, and generics) for treatment of adults with advanced unresectable or metastatic HER2-positive breast cancer, including those with brain metastases, who received at least one prior anti-HER2-based regimen for metastatic disease.[1]

MECHANISM OF ACTION — Tucatinib binds irreversibly to HER2 and other enzymes that promote cell growth, resulting in reduced signaling, cell cycle arrest, and apoptosis. Tucatinib penetrates the blood-brain barrier more effectively than anti-HER2 monoclonal antibodies, which may allow for more effective treatment of brain metastases.[2]

CLINICAL STUDIES — Accelerated approval of tucatinib was based on the results of an unpublished (summarized in the package insert), open-label trial (MOUNTAINEER) in 84 patients with HER2-positive, RAS wild-type, unresectable or metastatic colorectal cancer who received prior treatment with fluoropyrimidine, oxaliplatin, irinotecan, and an anti-vascular endothelial growth factor (VEGF) monoclonal antibody. Patients with mismatch repair deficiency (dMMR) or microsatellite instability-high (MSI-H) disease also had to receive prior treatment with an anti-programmed cell death protein-1 (PD-1) monoclonal antibody. Patients who received prior anti-HER2 therapy were excluded. All patients received tucatinib 300 mg twice daily with trastuzumab (8 mg/kg IV on day 1 of cycle 1, then 6 mg/kg on day 1 of each subsequent 21-day cycle) until disease progression or unacceptable toxicity occurred. The overall response rate (ORR) was 38%, of which 3% were complete responses. The median duration of response was 12.4 months and 81% of patients had a duration of response ≥6 months and 34% had a duration of response ≥12 months.

ADVERSE EFFECTS — The most common adverse effects (frequency ≥20%) of tucatinib in the MOUNTAINEER trial were diarrhea, fatigue, rash, nausea, abdominal pain, infusion-related reactions, and pyrexia. Severe hepatotoxicity can occur; transaminase and bilirubin levels should be monitored before starting tucatinib and every 3 weeks during treatment.

DRUG INTERACTIONS — Tucatinib is metabolized primarily by CYP2C8 and to a lesser extent by CYP3A. It should not be used concurrently with strong CYP3A inducers, moderate CYP2C8 inducers, or strong CYP2C8 inhibitors. If coadministration of a strong CYP2C8 inhibitor is necessary, the dosage of tucatinib should be reduced to 100 mg twice daily. Tucatinib is an inhibitor of CYP3A and P-glcoprotein (P-gp) and a substrate of P-gp; concurrent use of tucatinib with a P-gp or CYP3A substrate can increase serum concentrations of the substrate and possibly its toxicity.[3]

PREGNANCY AND LACTATION — In animal studies, tucatinib was associated with fetal death, decreased fetal weight, and fetal abnormalities at exposures 3.5 times the human exposure at the recommended dose. Women of reproductive potential and their male partners should use effective contraception during tucatinib treatment and for at least 1 week after

the last dose. There are no data on the presence of tucatinib in human breast milk or on its effect on the breastfed infant or milk production. Women should not breastfeed during treatment with tucatinib and for at least 1 week after the last dose.

DOSAGE, ADMINISTRATION, AND COST —Tucatinib is available in 50- and 150-mg tablets. The recommended dosage for the new indication is 300 mg taken every 12 hours in combination with trastuzumab until disease progression or unacceptable toxicity occurs. The tablets should be swallowed whole and not be crushed, chewed, or split. A missed dose should be skipped, and the next dose should be taken at its regularly scheduled time. The dosage should be reduced to 200 mg twice daily in those with severe hepatic impairment (Child-Pugh C). The labeling specifies a number of dosage adjustments that should be made if adverse effects occur. A 30-day supply of *Tukysa* costs $23,514.[4] ■

1. Two drugs for advanced HER2-positive breast cancer. Med Lett Drugs Ther 2020; 62:182.
2. R Duchnowska et al. Tyrosine kinase inhibitors for brain metastases in HER2-positive breast cancer. Cancer Treat Rev 2018; 67:71.
3. Inhibitors and inducers of CYP enzymes, P-glycoprotein, and other transporters. Med Lett Drugs Ther 2023 January 25 (epub). Available at: medicalletter.org/downloads/CYP_PGP_Tables.pdf
4. Approximate WAC. WAC = wholesaler acquisition cost or manufacturer's published price to wholesalers; WAC represents a published catalogue or list price and may not represent an actual transactional price. Source: AnalySource® Monthly. February 5, 2023. Reprinted with permission by First Databank, Inc. All rights reserved. ©2023. www.fdbhealth.com/policies/drug-pricing-policy.