Tucatinib

10:00 • ANTINEOPLASTIC AGENTS

- Tucatinib, a highly selective, reversible tyrosine kinase inhibitor of human epidermal growth factor receptor type 2 (HER2), is an antineoplastic agent.

USES

● *Breast Cancer*

Combination Therapy with Trastuzumab and Capecitabine

Tucatinib is used in combination with trastuzumab and capecitabine for the treatment of human epidermal growth factor receptor type 2 (HER2)-positive unresectable, locally advanced, or metastatic breast cancer in adults, including those with brain metastases, who have previously received at least one anti-HER2-based regimen in the metastatic setting. The drug has been designated an orphan drug by the FDA for use in the treatment of breast cancer that has metastasized to the brain.

The current indication for tucatinib is based principally on the results of a randomized, double-blind, placebo-controlled phase 2 study (HER2CLIMB) in adults with HER2-positive, unresectable, locally advanced, or metastatic breast cancer (with or without brain metastases) previously treated with trastuzumab, pertuzumab, or ado-trastuzumab emastine (separately or in combination) in the neoadjuvant, adjuvant, or metastatic setting. In this study, 612 patients were randomized (stratified by presence or history of brain metastases, Eastern Cooperative Oncology Group [ECOG] performance status, and geographic region) in a 2:1 ratio to receive either tucatinib 300 mg orally twice daily in combination with trastuzumab (8 mg/kg IV initially, followed by either 6 mg/kg IV or 600 mg by subcutaneous injection on day 1 of each 21-day cycle) and capecitabine (1 g/m^2 orally twice daily on days 1–14 of each 21-day cycle) or placebo in combination with trastuzumab and capecitabine. Treatment was continued until disease progression or unacceptable toxicity occurred. The primary measure of efficacy was progression-free survival (as assessed by a blinded independent central review committee) according to Response Evaluation Criteria in Solid Tumors (RECIST v1.1). In the primary efficacy population (consisting of the initial 480 patients randomized in the study), the median age of patients was 54 years; 73% of the patients were White, 99% were female, 51% had an ECOG performance status of 1, 60% had estrogen and/or progesterone receptor-positive disease, and 74% had visceral metastases. Approximately one-half (48%) of patients had active brain metastases or a history of brain metastases; 23% of these patients had untreated brain metastases, 40% had previously treated but stable brain metastases, and 37% had previously treated but radiographically progressing brain metastases. Patients had received a median of 4 prior systemic therapies or a median of 3 prior systemic therapies in the metastatic setting; all patients had previously received trastuzumab and ado-trastuzumab emtansine and all but 2 patients had previously received pertuzumab. This study excluded patients with leptomeningeal disease.

In the primary efficacy population, patients receiving tucatinib in combination with trastuzumab and capecitabine had a longer median progression-free survival than those receiving the placebo combination regimen (7.8 versus 5.6 months). In the total patient population, median overall survival also was prolonged in patients receiving the tucatinib combination regimen compared with those receiving the placebo regimen (21.9 versus 17.4 months). Among the patients with a history or presence of parenchymal brain metastases at baseline, median progression-free survival in patients receiving the tucatinib or placebo combination regimen was 7.6 or 5.4 months, respectively. Among patients with measurable disease, patients receiving the tucatinib combination regimen also had higher objective response rates compared with those receiving the placebo combination regimen (40.6% versus 22.8%); complete response was achieved in 0.9 or 1.2% of patients receiving these respective treatments. At the time of analysis, the median duration of response was 8.3 months in patients receiving the tucatinib combination regimen and 6.3 months in those receiving the placebo combination regimen. Exploratory analyses of the cohort of patients with a history or presence of brain metastases at baseline also suggested prolonged progression-free survival (9.9 versus 4.2 months) and overall survival (18.1 versus 12 months) and higher rates of objective response (47.3 versus 20%) in patients receiving the tucatinib combination regimen compared with those receiving the placebo combination regimen.

DOSAGE AND ADMINISTRATION

● *General*

Pretreatment Screening

- Serum ALT, AST, and bilirubin concentrations.
- Verify pregnancy status in females of reproductive potential.

Patient Monitoring

- Serum ALT, AST, and bilirubin concentrations every 3 weeks during therapy, and as clinically indicated.

Premedication and Prophylaxis

- Prophylactic use of antidiarrheal agents not required in HER2CLIMB study.

● *Administration*

Tucatinib is administered orally twice daily (approximately every 12 hours), at the same time each day, without regard to meals. Tucatinib tablets should be swallowed intact and should not be chewed, crushed, broken, cracked, or split.

If a dose of tucatinib is missed or vomited, the next dose should be taken at the regularly scheduled time.

● *Dosage*

Breast Cancer

For use in combination with trastuzumab and capecitabine for the treatment of HER2-positive unresectable, locally advanced, or metastatic breast cancer, the recommended adult dosage of tucatinib is 300 mg twice daily. Therapy should be continued until disease progression or unacceptable toxicity occurs.

Clinicians should consult the manufacturers' labelings or published protocols for information on the dosage, method of administration, and administration sequence of other antineoplastic agents used in combination regimens.

Tucatinib and capecitabine may be administered at the same time. In the HER2CLIMB study, capecitabine 1 g/m^2 twice daily was administered within 30 minutes after a meal on days 1–14 and trastuzumab 8 mg/kg IV initially, followed by either 6 mg/kg IV or 600 mg by subcutaneous injection was administered on day 1 of each 21-day cycle.

Dosage Modification for Toxicity

If adverse reactions occur during tucatinib therapy, temporary interruption of therapy, dosage reduction, and/or permanent discontinuance of the drug may be necessary. If dosage reduction is required, the dosage of tucatinib should be reduced as described in Table 1.

TABLE 1. Dosage Reduction for Tucatinib Toxicity

Dose Reduction Level	Dosage Reduction after Recovery from Toxicity (Initial Dosage = 300 mg twice daily)
First	Restart at 250 mg twice daily
Second	Restart at 200 mg twice daily
Third	Restart at 150 mg twice daily
Fourth	Permanently discontinue tucatinib

Table 2 indicates the recommended dosage modification (i.e., temporary interruption of therapy, dosage reduction, discontinuance of therapy) for adverse effects according to severity.

TABLE 2. Dosage Modification for Tucatinib Toxicity

Adverse Reaction and Severity	Modification
Diarrhea	
Grade 3	Initiate appropriate medical therapy and withhold tucatinib therapy; when diarrhea improves to grade 1 or less, resume at same dosage If grade 3 diarrhea occurs despite appropriate antidiarrheal therapy, intensify medical therapy and withhold tucatinib therapy; when diarrhea improves to grade 1 or less, resume at next lower dosage (see Table 1)
Grade 4	Permanently discontinue therapy
Hepatic Toxicity	
Grade 2 elevations of serum bilirubin concentrations	Withhold therapy; when toxicity improves to grade 1 or less, resume at same dosage
Grade 3 elevations of serum ALT or AST concentrations	Withhold therapy; when toxicity improves to grade 1 or less, resume at next lower dosage (see Table 1)
Grade 3 elevations of serum bilirubin concentrations	Withhold therapy; when toxicity improves to grade 1 or less, resume at next lower dosage (see Table 1)
Grade 4 elevations of serum ALT, AST, or bilirubin concentrations	Permanently discontinue therapy
Elevations of serum ALT or AST >3 times the upper limit of normal (ULN) with concomitant elevations in serum bilirubin concentrations >2 times the ULN	Permanently discontinue therapy
Other Toxicity	
Grade 3	Withhold therapy; when toxicity improves to grade 1 or less, resume at next lower dosage (see Table 1)
Grade 4	Permanently discontinue therapy

Concomitant Use of Drugs Affecting Hepatic Microsomal Enzymes

Concomitant use of tucatinib with potent inhibitors of cytochrome P-450 (CYP) isoenzyme 2C8 should be avoided. If concomitant use cannot be avoided, the manufacturer recommends reducing the dosage of tucatinib to 100 mg twice daily. If concomitant use of the potent CYP2C8 inhibitor is discontinued, the tucatinib dosage should be returned (after 3 elimination half-lives of the CYP2C8 inhibitor) to the dosage used prior to initiation of the CYP2C8 inhibitor.

● *Special Populations*

Hepatic Impairment

For patients with severe hepatic impairment (Child-Pugh class C), the manufacturer recommends a tucatinib dosage of 200 mg twice daily.

No dosage adjustment is necessary in patients with mild or moderate hepatic impairment (Child-Pugh class A or B).

Renal Impairment

No dosage adjustment is necessary in patients with mild or moderate renal impairment (creatinine clearance 30–89 mL/minute using Cockcroft-Gault formula).

Because capecitabine is contraindicated in patients with severe renal impairment (creatinine clearance less than 30 mL/minute using Cockcroft-Gault formula), combination therapy with tucatinib, capecitabine, and trastuzumab is not recommended in such patients.

Geriatric Patients

The manufacturer makes no specific dosage recommendations for geriatric patients. No overall differences in efficacy were observed between geriatric patients and younger adults; however, incidence of serious adverse reactions (e.g., diarrhea, vomiting, nausea) may be higher in patients 65 years of age or older.

CAUTIONS

● *Contraindications*

None.

● *Warnings/Precautions*

Combination Therapy

When tucatinib is used in combination with capecitabine and trastuzumab, the usual cautions, precautions, and contraindications associated with capecitabine and trastuzumab must be considered in addition to those associated with tucatinib. For further information regarding warnings and precautions associated with capecitabine or trastuzumab, see Cautions in Capecitabine 10:00 and also see Cautions: Precautions and Contraindications, in Trastuzumab 10:00.

Diarrhea

Severe diarrhea associated with dehydration, hypotension, acute kidney injury, and death has been reported in patients receiving tucatinib. In the HER2CLIMB study, diarrhea was reported in 81% of patients receiving tucatinib and was grade 3 or 4 in severity in 12 or 0.5% of patients, respectively. Death secondary to grade 4 diarrhea occurred in both patients who developed grade 4 diarrhea. The median time to initial onset of diarrhea was 12 days and the median time to resolution was 8 days. Dosage reduction or discontinuance of tucatinib therapy was necessary because of diarrhea in 6 or 1% of patients, respectively. In the HER2CLIMB study, antidiarrheal prophylaxis was not required.

Antidiarrheal therapy should be administered as clinically indicated if diarrhea occurs during tucatinib therapy. Diagnostic tests should be performed as clinically indicated to exclude other causes of diarrhea. Temporary interruption, dosage reduction, or permanent discontinuance of tucatinib may be necessary depending on the severity of the diarrhea. (See Dosage Modification for Toxicity under Dosage and Administration.)

Hepatic Toxicity

Severe hepatotoxicity has been reported in patients receiving tucatinib. In the HER2CLIMB study, elevations in ALT or AST concentration exceeding 5 times the upper limit of normal (ULN) occurred in 8 or 6% of patients receiving tucatinib, respectively. Elevations in serum bilirubin concentration exceeding 3 times the ULN occurred in 1.5% of tucatinib-treated patients. Dosage reduction or discontinuance of tucatinib therapy was necessary because of hepatotoxicity in 8 or 1.5% of patients, respectively.

Liver function tests (i.e., ALT, AST, bilirubin concentrations) should be evaluated prior to initiation of therapy, every 3 weeks thereafter, and as clinically indicated. Temporary interruption, dosage reduction, or permanent discontinuance of tucatinib may be necessary depending on the severity of hepatotoxicity. (See Dosage Modification for Toxicity under Dosage and Administration.)

Fetal/Neonatal Morbidity and Mortality

There are no adequate and well-controlled studies of tucatinib in pregnant women; however, based on its mechanism of action and animal findings, tucatinib may cause fetal harm. Embryofetal toxicity (e.g., increased fetal resorption, abortion, decreased fetal weight) and teratogenicity (e.g., skeletal, visceral, external malformations) have been demonstrated in pregnant animals receiving tucatinib at exposure levels 1.3 times or more the human exposure at the recommended dosage.

Pregnancy should be avoided during tucatinib therapy. The manufacturer states that a pregnancy test should be performed prior to initiation of tucatinib therapy in females of reproductive potential and that such women should be advised to use effective contraceptive methods while receiving tucatinib therapy and for at least 1 week after the last dose of the drug. In addition, men with such female partners should use effective contraceptive methods while receiving

tucatinib and for at least 1 week after the last dose of the drug. Patients should be apprised of the potential hazard to the fetus if tucatinib is used during pregnancy.

Impairment of Fertility

Results of animal studies suggest that tucatinib may impair male and female fertility.

Specific Populations

Pregnancy

Tucatinib may cause fetal harm if administered to pregnant women based on its mechanism of action and animal findings. (See Fetal/Neonatal Morbidity and Mortality under Cautions.)

Lactation

It is not known whether tucatinib or its metabolites are distributed into human milk. The effects of the drug on breast-fed infants or on the production of milk also are unknown.

Because of the potential for serious adverse reactions to tucatinib in breast-fed infants, women should be advised not to breast-feed while receiving the drug and for at least 1 week after the last dose.

Pediatric Use

Safety and efficacy of tucatinib have not been established in pediatric patients.

Geriatric Use

In the HER2CLIMB study, 26% of patients receiving tucatinib were 65 years of age or older, while 2.5% were 75 years of age or older. No overall differences in efficacy were observed between geriatric patients and younger adults. Patients 65 years of age or older had a higher incidence of serious adverse reactions (e.g., diarrhea, vomiting, nausea) compared with younger adults (34 or 24%, respectively).

Hepatic Impairment

Following administration of a single 300-mg dose of tucatinib, area under the plasma concentration-time curve (AUC) of tucatinib in individuals with mild or moderate hepatic impairment (Child-Pugh class A or B) was similar to that in individuals with normal hepatic function, but was increased by 1.6-fold in those with severe hepatic impairment (Child-Pugh class C); therefore, the manufacturer recommends a tucatinib dosage of 200 mg twice daily in patients with severe hepatic impairment.

Renal Impairment

In a population pharmacokinetic analysis, mild or moderate renal impairment did not have clinically important effects on the pharmacokinetics of tucatinib; no dosage adjustment is necessary in patients with mild or moderate renal impairment.

The pharmacokinetic profile of tucatinib has not been established in patients with severe renal impairment.

● *Common Adverse Effects*

Adverse effects reported in at least 20% of patients receiving tucatinib include diarrhea, palmar-plantar erythrodysesthesia, nausea, fatigue, hepatotoxicity, vomiting, stomatitis, decreased appetite, abdominal pain, headache, anemia, and rash.

Tucatinib has been shown to increase serum creatinine concentrations. Tucatinib decreases tubular secretion of creatinine by inhibiting renal organic cation transporter (OCT) 2 and multidrug and toxin extrusion transporter (MATE) 1. In the HER2CLIMB study, the mean increase in serum creatinine was 32% within the initial 21 days of tucatinib therapy. Elevated concentrations of serum creatinine persisted during therapy and reversed following discontinuance of therapy. The manufacturer states that assessment of alternative markers for renal function may be necessary if elevated serum creatinine concentrations persist.

DRUG INTERACTIONS

Tucatinib is metabolized principally by cytochrome P-450 (CYP) isoenzyme 2C8 and, to a lesser extent, by CYP3A. In vitro, tucatinib demonstrates reversible inhibition of CYP isoenzymes 2C8 and 3A, and time-dependent inhibition of CYP3A. In vitro, the drug is not an inhibitor of CYP isoenzymes 1A2, 2B6, 2C9, 2C19, and 2D6, or uridine diphosphate-glucuronosyltransferase (UGT) 1A1.

In vitro studies indicate that tucatinib is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), but is not a substrate of organic anion transporter (OAT) 1, OAT3, organic cation transporter (OCT) 1, OCT3, organic anion transporting polypeptide (OATP) 1B1, OATP1B3, multidrug and toxin extrusion (MATE) 1, MATE2K, or bile salt export pump (BSEP).

● *Drugs Affecting Hepatic Microsomal Enzymes*

Inhibitors of CYP2C8

Concomitant use of tucatinib with potent inhibitors of CYP2C8 may result in increased systemic exposure to tucatinib and an increased incidence of adverse effects. Concomitant administration of the potent CYP2C8 inhibitor gemfibrozil (600 mg twice daily) with tucatinib (single 300-mg dose) increased the area under the concentration-time curve (AUC) and peak plasma concentration of tucatinib by 3- and 1.6-fold, respectively.

Concomitant use of tucatinib with potent inhibitors of CYP2C8 should be avoided. If concomitant use of a potent CYP2C8 inhibitor cannot be avoided, the manufacturer recommends reducing the dosage of tucatinib to 100 mg twice daily. If concomitant use of the potent CYP2C8 inhibitor is discontinued, the tucatinib dosage should be returned (after 3 elimination half-lives of the CYP2C8 inhibitor) to the dosage used prior to initiation of the CYP2C8 inhibitor.

If concomitant therapy with a moderate CYP2C8 inhibitor is required, patients should be monitored closely for signs of tucatinib toxicity.

Inducers of CYP3A or 2C8

Concomitant use of tucatinib with potent CYP3A or moderate CYP2C8 inducers may result in decreased systemic exposure to tucatinib and reduced tucatinib efficacy. Concomitant administration of the potent CYP3A and moderate CYP2C8 inducer rifampin (600 mg once daily) with tucatinib (single 300-mg dose) decreased AUC and peak plasma concentration of tucatinib by 48 and 37%, respectively.

Concomitant use of tucatinib with potent CYP3A or moderate CYP2C8 inducers should be avoided.

Inhibitors of CYP3A

When the potent CYP3A inhibitor itraconazole (200 mg twice daily) was administered concomitantly with tucatinib (single 300-mg dose), both AUC and peak plasma concentration of tucatinib increased by 1.3-fold.

● *Drugs Metabolized by Hepatic Microsomal Enzymes*

Substrates of CYP3A

Concomitant use of tucatinib with CYP3A substrates may result in increased systemic exposure to the CYP3A substrate and increased incidence of adverse effects of the substrate drug. When the CYP3A substrate midazolam (single 2-mg dose) was administered concomitantly with tucatinib (300 mg twice daily), AUC and peak plasma concentration of midazolam increased 5.7- and 3-fold, respectively.

Concomitant use of tucatinib with CYP3A substrates that have a narrow therapeutic index should be avoided. If concomitant use of CYP3A substrates that have a narrow therapeutic index cannot be avoided, the dosage of the CYP3A substrate should be adjusted as appropriate.

● *Drugs Affected by Transport Systems*

Substrates of P-gp

Concomitant use of tucatinib with P-gp substrates may result in increased systemic exposure of the P-gp substrate and increased incidence of adverse effects of the substrate drug. When the P-gp substrate digoxin (single 0.5-mg dose) was administered concomitantly with tucatinib (300 mg twice daily), AUC and peak plasma concentrations of digoxin increased 1.5- and 2.4-fold, respectively.

If concomitant use of P-gp substrates that have a narrow therapeutic index is required, the dosage of the P-gp substrate should be adjusted as appropriate.

Substrates of MATE1, MATE2K, and OCT2

When a single 850-mg dose of metformin hydrochloride (a substrate of MATE1, MATE2K, and OCT2) was administered concomitantly with tucatinib (300 mg twice daily for 7 days), AUC and peak plasma concentrations of metformin increased 1.4- and 1.1-fold, respectively. Tucatinib reduced the renal clearance of metformin without any effect on glomerular filtration rate (GFR).

● *Omeprazole*

Concomitant administration of tucatinib and the proton-pump inhibitor omeprazole did not affect the pharmacokinetics of tucatinib.

● *Tolbutamide*

Concomitant administration of tucatinib and tolbutamide (sensitive CYP2C9 substrate) did not have a clinically important effect on the pharmacokinetics of tucatinib.

DESCRIPTION

Tucatinib, a highly selective, reversible tyrosine kinase inhibitor of human epidermal growth factor receptor type 2 (HER2), is an antineoplastic agent. In vitro, the drug has been shown to inhibit phosphorylation of HER2 and HER3 resulting in inhibition of downstream signaling of the mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K/Akt) pathways. In vivo, tucatinib has demonstrated inhibition of cellular proliferation of HER2-expressing tumors. The combination of tucatinib with trastuzumab demonstrated increased antitumor activity compared with either drug alone.

In cell-based assays, tucatinib has demonstrated 500-fold greater selectivity for HER2 than for epidermal growth factor receptor (EGFR), thereby potentially reducing the incidence of adverse effects associated with EGFR inhibition, such as adverse GI and dermatologic effects.

Area under the serum concentration-time curve (AUC) and peak plasma concentrations of tucatinib are dose proportional over a dosage range of 50–300 mg. Following oral administration of tucatinib, peak plasma concentrations of the drug are achieved in a median of 2 hours. With twice-daily administration, steady-state concentrations of the drug are achieved in approximately 4 days and the accumulation based on AUC or peak plasma concentration is 1.7- or 1.5-fold, respectively. Administration of tucatinib (single 300-mg dose) with a high-fat meal decreased the rate of absorption (time to peak concentrations delayed by 2.5 hours) and increased the mean AUC by 1.5-fold, but did not substantially affect peak plasma concentration; however, these changes are not considered clinically meaningful. Tucatinib is 97.1% bound to plasma proteins at clinically relevant concentrations. Tucatinib is metabolized principally by cytochrome P-450 (CYP) isoenzyme 2C8 and, to a lesser extent, by CYP3A. Following oral administration of a single radiolabeled dose of tucatinib, approximately 86% of the radioactivity was recovered in feces (16% of the dose as unchanged drug) and 4.1% was recovered in urine. The mean elimination half-life of tucatinib is approximately 8.5 hours. Systemic exposure of tucatinib is not affected by age, serum albumin concentration (2.5–5.2 g/dL), body weight (41–138 kg), and race (White, Black, or Asian).

ADVICE TO PATIENTS

- Advise the patient to read the FDA-approved patient labeling (Patient Information).
- Inform patients that tucatinib has been associated with severe diarrhea. Instruct patients on how to manage diarrhea and to inform their healthcare provider immediately if there is any change in bowel patterns.
- Inform patients that tucatinib has been associated with severe hepatotoxicity and that they should report signs and symptoms of liver dysfunction to their healthcare provider immediately.
- Inform pregnant women and females of reproductive potential of the risk to a fetus. Advise women to inform their healthcare provider of a known or suspected pregnancy.
- Advise females of reproductive potential to use effective contraception during treatment with tucatinib and for at least 1 week after the last dose.
- Advise male patients with female partners of reproductive potential to use effective contraception during treatment with tucatinib and for at least 1 week after the last dose.
- Advise women not to breast-feed during treatment with tucatinib and for at least 1 week after the last dose.
- Advise males and females of reproductive potential that tucatinib may impair fertility.
- Inform clinicians of existing or contemplated concomitant therapy, including prescription and OTC drugs and dietary or herbal supplements, as well as any concomitant illnesses.
- Inform patients of other important precautionary information. (See Cautions.)

Overview® (see Users Guide). For additional information on this drug until a more detailed monograph is developed and published, the manufacturer's labeling should be consulted. It is *essential* that the manufacturer's labeling be consulted for more detailed information on usual cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and acute toxicity. For further information on the handling of antineoplastic agents, see the ASHP Guidelines on Handling Hazardous Drugs at http://www.ahfsdruginformation.com.

PREPARATIONS

Tucatinib is available only from a designated specialty pharmacy. The manufacturer should be contacted for additional information.

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Tucatinib

Oral		
Tablets, film-coated	50 mg	**Tukysa®**, Seattle Genetics
	150 mg	**Tukysa®**, Seattle Genetics

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