Summary Report of Benefit-Risk Assessment

TUKYSA FILM-COATED TABLETS 50 MG AND 150 MG

NEW DRUG APPLICATION

Active Ingredient(s)	Tucatinib
Product Registrant	Nyprax Pharma Pte. Ltd.
Product Registration Number	SIN15942P, SIN15943P
Application Route	Full evaluation
Date of Approval	19 May 2020

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A INTRODUCTION

TUKYSA is indicated in combination with trastuzumab and capecitabine for treatment of patients with locally 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.

The active substance, tucatinib, is an oral tyrosine kinase inhibitor (TKI) that targets the human epidermal growth factor receptor 2 (HER2).

Tukysa is available as film-coated tablets containing 50 mg and 150 mg of tucatinib. Other ingredients in the tablet core are copovidone, crospovidone, sodium chloride, potassium chloride, sodium bicarbonate, colloidal silicon dioxide, magnesium stearate and microcrystalline cellulose. Ingredients in the film coating include polyvinyl alcohol, titanium dioxide, macrogol/polyethylene glycol, talc and yellow iron oxide non-irradiated.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, Tucatinib, is manufactured at [redacted]. The drug product, Tucatinib Film Coated Tablets, is manufactured at Corden Pharma GmbH, Plankstadt, Germany.

Drug substance:

Adequate controls have been presented for the starting materials, intermediates and reagents. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate.

The characterisation of the drug substance and its impurities are in accordance with ICH guidelines. Potential and actual impurities, including potentially genotoxic impurities are adequately controlled.

The drug substance specifications are established in accordance with ICH Q6A and the impurity limits are considered appropriately qualified. The analytical methods used have been adequately described and non-compendial methods are appropriately validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing was presented.

The stability data presented for [redacted] were adequate to support the approved storage condition and re-test period. The packaging is [redacted] within a [redacted]. The drug substance is approved for storage at [redacted] with a re-test period of [redacted] months.

Drug product:

The tablet is manufactured using a spray drying/compression approach, followed by film-coating. The process is considered to be a standard process.

All manufacturing sites involved are compliant with Good Manufacturing Practice (GMP). Proper development and validation studies were conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications are established in accordance with ICH Q6A and impurity limits are considered adequately qualified. The analytical methods used have been adequately described and non-compendial methods were appropriately validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing was presented.

The stability data submitted were adequate to support the approved shelf-life of 24 months when stored at or below 30ºC. The container closure system is an aluminium/aluminium blister pack of 8 tablets/blister for the 50 mg strength and 4 tablets/blister for the 150 mg strength.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of tucatinib in combination with trastuzumab and capecitabine for the treatment of patients with locally advanced unresectable or metastatic HER2-positive breast cancer was based primarily on data from one pivotal study, HER2CLIMB (ONT-308-206). The HER2CLIMB study was a Phase II, randomised, double-blind study of tucatinib in combination with trastuzumab and capecitabine in patients with locally advanced unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases, who were previously treated with trastuzumab, pertuzumab, and trastuzumab emtansine (T-DM1) in any setting.

Patients were randomised in a 2:1 ratio to receive tucatinib 300 mg orally twice daily (BID) or placebo, in combination with trastuzumab and capecitabine. Patients received treatment administered in cycles of 21 days each. Capecitabine was given at 1000 mg/m^2 orally BID on Days 1 to 14 of each 21-day cycle. Trastuzumab was given as a loading dose of 8 mg/kg intravenous (IV) followed by 6 mg/kg once every 21 days (or as 600 mg of trastuzumab given subcutaneously once every 3 weeks). Patients continued treatment until disease progression or unacceptable toxicity.

The primary efficacy endpoint was progression-free survival (PFS) assessed by blinded independent central review (BICR) per RECIST 1.1 in the first 480 randomised patients (ITT-PFS population). The key secondary endpoints were overall survival (OS) in all randomised patients (ITT-OS population), PFS assessed by BICR ($PFS_{BrainMets}$) in patients with brain metastases at baseline ($PFS_{BrainMets}$ population) and confirmed objective response rate (ORR) assessed by BICR.

A total of 612 patients were randomised into the study – 410 patients in the tucatinib arm and 202 patients in the placebo arm. The median duration of exposure to tucatinib/placebo in the ITT-PFS population was 7.3 months (range <0.1 to 35.1 months) in the tucatinib arm and 4.4 months (range <0.1 to 24.0 months) in the placebo arm.

The patient demographics and baseline disease characteristics were well-balanced between the treatment arms. The median age was 54.0 years (range 22 to 82 years), and 116 patients (19.0%) were ≥65 years of age. The majority of patients were female (99.2%) and 5 patients (0.8%) were male. The majority of patients were White (72.5%) and 23 patients (3.8%) were Asian. Approximately half (291 patients, 47.5%) had a presence or history of brain metastases

at baseline; of these, 40.2% had treated and stable brain metastases, 37.1% had treated but progressing brain metastases and 22.7% had untreated brain metastases. Patients had a median of 4 (range 2 to 17) prior lines of systemic therapy, with 3 (range 1 to 14) of these prior lines in the metastatic setting. Patients were required to have received prior therapy with trastuzumab, pertuzumab and T-DM1. Overall, 100% of patients had prior trastuzumab, 99.7% had prior pertuzumab and 100% had prior T-DM1.

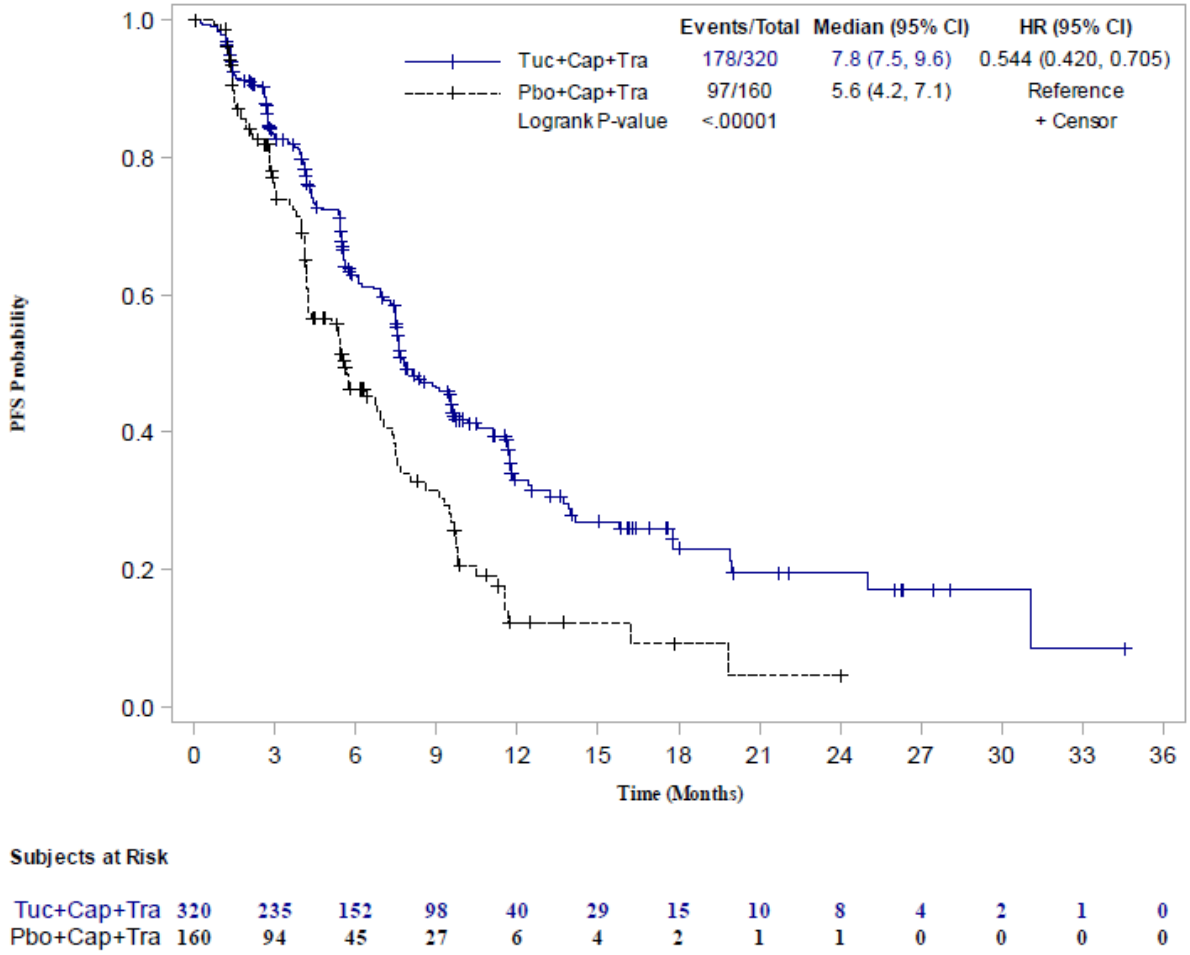
Summary of key efficacy results

	Tucatinib	Placebo
Primary endpoint		
PFS per BICR (ITT-PFS), n	320	160
PFS events, n (%)	178 (55.6%)	97 (60.6%)
Median PFS (months) (95% CI)	7.8 (7.5, 9.6)	5.6 (4.2, 7.1)
Stratified HR (95% CI)	0.544 (0.420, 0.705)	
Stratified log-rank p-value	<0.00001	
Key secondary endpoints		
OS (ITT-OS), n	410	202
OS events, n (%)	130 (31.7%)	85 (42.1%)
Median OS (months) (95% CI)	21.9 (18.3, 31.0)	17.4 (13.6, 19.9)
Stratified HR (95% CI)	0.662 (0.501, 0.875)	
Stratified log-rank p-value	0.00480[a]	
$PFS_{BrainMets}$ ($ITT\text{-}PFS_{BrainMets}$), n	198	93
PFS events, n (%)	106 (53.5%)	51 (54.8%)
Median PFS (months) (95% CI)	7.6 (6.2, 9.5)	5.4 (4.1, 5.7)
Stratified HR (95% CI)	0.483 (0.339, 0.689)	
Stratified log-rank p-value	<0.00001[b]	
ORR per BICR (ITT-OS), n		
Confirmed ORR, % (95% CI)	40.6 (35.3, 46.0)	22.8 (16.7, 29.8)
Stratified CMH p-value	0.00008	

[a] Statistically significant after adjustment for multiplicity. The threshold for statistical significance is 0.0074.
[b] Statistically significant after adjustment for multiplicity. The threshold for statistical significance is 0.0080.

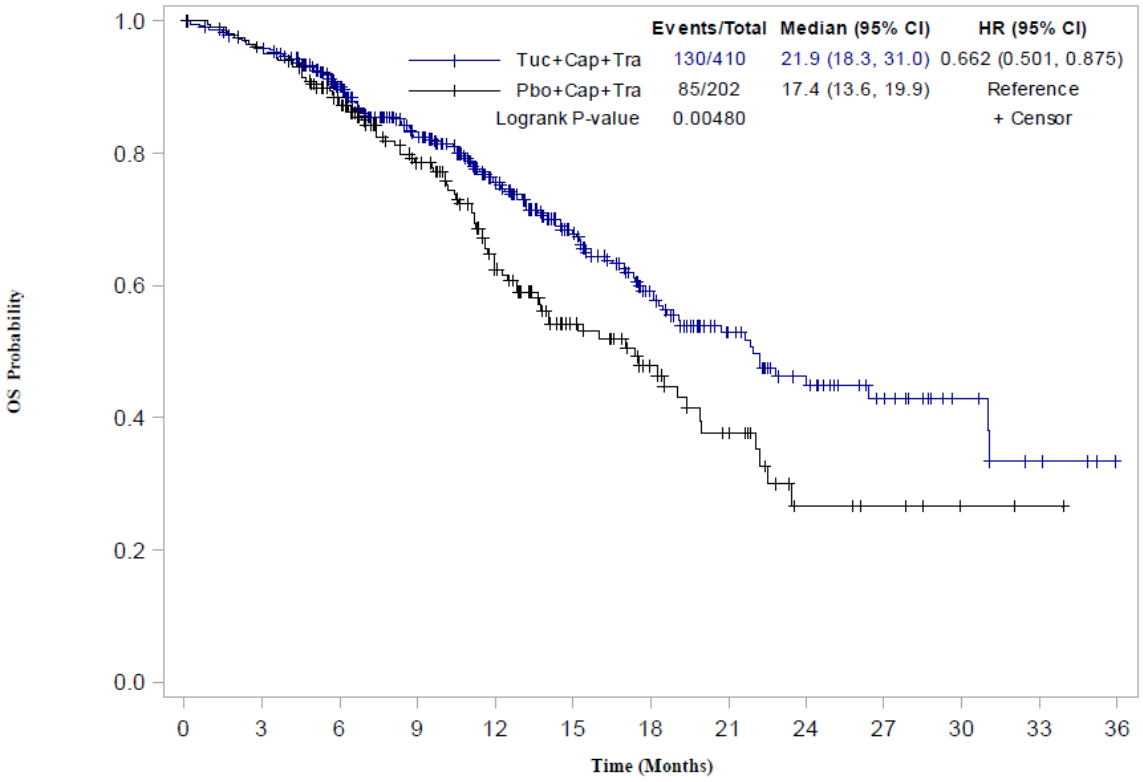
Treatment with tucatinib resulted in an increase in PFS of 2.2 months over the placebo arm. The median PFS assessed by BICR was 7.8 months (95% CI 7.5, 9.6) in the tucatinib arm and 5.6 months (95% CI 4.2, 7.1) in the placebo arm (hazard ratio [HR] 0.544; 95% CI 0.420, 0.705; p<0.00001). The results of various sensitivity analyses for PFS per BICR showed consistent outcomes supporting the primary analysis, with HRs ranging from 0.54 to 0.56 and median differences ranging from 2.2 to 2.3 months, demonstrating the robustness of the PFS results. The PFS per investigator yielded a median PFS difference of 3.2 months (median PFS 7.5 vs 4.3 months; HR 0.561; 95% CI 0.447, 0.703; p<0.00001), further supporting the robustness of the results. Pre-specified subgroup analyses demonstrated consistent PFS benefit in all subgroups analysed, including hormone receptor status (estrogen receptor [ER] and/or progesterone receptor [PR] positive, ER and PR negative), presence or history of brain metastases at baseline (yes, no), ECOG performance status (0, 1), age (≥65 years, <65 years), race (White, non-white), and region (North America, rest of world).

Kaplan-Meier curves of PFS per BICR (ITT-PFS population)



The key secondary endpoint, OS, showed a statistically significant and clinically meaningful improvement of 4.5 months for the tucatinib combination compared to control. The median OS was 21.9 months (95% CI 18.3, 31.0) in the tucatinib arm and 17.4 months (95% CI 13.6, 19.9) in the placebo arm (HR 0.662; 95% CI 0.501, 0.875; p=0.00480). The subgroup analyses of OS showed consistent benefit with hazard ratios favouring the tucatinib arm in all pre-specified subgroups analysed.

Kaplan Meier curves of OS (ITT-OS population)



Subjects at Risk

Tuc+Cap+Tra	410	388	322	245	178	123	80	51	34	20	10	4	0
Pbo+Cap+Tra	202	191	160	119	77	48	32	19	7	5	2	1	0

The key secondary endpoint, PFS per BICR in patients with brain metastases ($PFS_{BrainMets}$), showed statistically significant benefits in this subpopulation, with a HR of 0.483 (95% CI 0.339, 0.689; p<0.00001), and a median $PFS_{BrainMets}$ of 7.6 months (95% CI 6.2, 9.5) in the tucatinib arm and 5.4 months (95% CI 4.1, 5.7) in the placebo arm.

The confirmed ORR per BICR was statistically significantly higher in the tucatinib arm (40.6% [95% CI 35.3, 46.0]) compared to the placebo arm (22.8% [95% CI 16.7, 29.8]) (p=0.00008). The confirmed ORR per investigator was consistent with the analysis per BICR. ORR per investigator was 40.9% (95% CI 35.8, 46.2) in the tucatinib arm compared to 21.4% (95% CI 15.5, 28.3) in the placebo arm (p=0.00001).

Overall, the HER2CLIMB study met its primary endpoint and all key secondary endpoints. The results adequately supported the efficacy of tucatinib in combination with trastuzumab and capecitabine for the intended population of patients with HER2-positive breast cancer, including patients with brain metastases.

D ASSESSMENT OF CLINICAL SAFETY

The safety data supporting the use of tucatinib in combination with trastuzumab and capecitabine in patients with previously treated, locally advanced unresectable or metastatic

HER2-positive breast cancer comprised a total of 601 patients (404 patients in the tucatinib arm and 197 patients in the placebo arm) enrolled in the HER2CLIMB study who had received at least one dose of study treatment. In the HER2CLIMB study, patients in the tucatinib arm had a longer median duration of exposure to tucatinib (5.8 months) compared to that in the placebo arm (4.4 months). The median duration of exposure to capecitabine and trastuzumab were also longer in the tucatinib arm (5.7 months and 6.0 months, respectively) compared to the placebo arm (4.4 months and 4.6 months, respectively).

Overview of safety profile (HER2CLIMB study)

	Tucatinib (N=404)	**Placebo (N=197)**
Any AE	401 (99.3%)	191 (97.0%)
Any treatment-related AE Tucatinib/placebo-related	392 (97.0%) 343 (84.9%)	180 (91.4%) 144 (73.1%)
Grade ≥3 AE	223 (55.2%)	96 (48.7%)
Treatment-related Grade ≥3 AE Tucatinib/placebo-related	173 (42.8%) 111 (27.5%)	60 (30.5%) 32 (16.2%)
SAE	104 (25.7%)	53 (26.9%)
Treatment-related SAE Tucatinib/placebo-related	44 (10.9%) 28 (6.9%)	13 (6.6%) 11 (5.6%)
AE leading to death	8 (2.0%)	6 (3.0%)
Treatment-related AE leading to death Tucatinib/placebo-related	3 (0.7%) 2 (0.5%)	1 (0.5%) 1 (0.5%)
Treatment discontinuation due to AE Discontinued tucatinib/placebo Discontinued capecitabine Discontinued trastuzumab	45 (11.1%) 23 (5.7%) 41 (10.1%) 18 (4.5%)	19 (9.6%) 6 (3.0%) 18 (9.1%) 5 (2.5%)
Treatment-discontinuation due to treatment-related AE Tucatinib/placebo-related	16 (4.0%) 13 (3.2%)	5 (2.5%) 5 (2.5%)

The most commonly reported treatment-emergent adverse events (AEs) with higher incidences in the tucatinib arm compared to the placebo arm were diarrhoea (80.9% vs 53.3%), palmar-plantar erythrodysaesthesia (PPE) syndrome (63.4% vs 52.8%), nausea (58.4% vs 43.7%), vomiting (35.9% vs 25.4%), decreased appetite (24.8% vs 19.8%), stomatitis (25.5% vs 14.2%), aspartate aminotransferase (AST) increased (21.3% vs 11.2%), alanine aminotransferase (ALT) increased (20.0% vs 6.6%), anaemia (19.8% vs 11.7%), blood bilirubin increased (18.6% vs 10.2%), arthralgia (14.6% vs 4.6%), weight decreased (13.4% vs 5.6%), blood creatinine increased (13.9% vs 1.5%), epistaxis (11.6% vs 5.1%), peripheral sensory neuropathy (11.6% vs 6.1%), and muscle spasms (9.4% vs 2.5%).

The most commonly reported tucatinib/placebo-related AEs with higher incidences in the tucatinib arm compared to the placebo arm were diarrhoea (55.2% vs 29.9%), nausea (39.9% vs 20.8%), vomiting (21.5% vs 11.2%), AST increased (16.3% vs 6.6%), ALT increased (15.3% vs 4.6%), decreased appetite (14.9% vs 6.6%), blood bilirubin increased (12.4% vs 6.6%), and blood creatinine increased (5.2% vs 0.5%).

The most commonly reported Grade ≥3 AEs on the tucatinib and placebo arms were PPE syndrome (13.1% vs 9.1%), diarrhoea (12.9% vs 8.6%), ALT increased (5.4% vs 0.5%), fatigue (4.7% vs 4.1%), and AST increased (4.5% vs 0.5%). The incidence of serious AEs (SAEs) were comparable between treatment arms (25.7% in the tucatinib arm vs 26.9% in the placebo arm). The most commonly reported SAEs were diarrhoea (4.0% vs 3.6%), vomiting (2.5% vs 2.5%), and nausea (2.0% vs 1.5%).

The incidence of AEs leading to tucatinib or placebo discontinuation was low (5.7% in the tucatinib arm vs 3.0% in the placebo arm). The most common events were diarrhoea (1.0% vs

0.5%), ALT increased (1.0% vs 0.5%), AST increased (0.7% vs 0.5%), blood bilirubin increased (0.7% vs 0.5%), and vomiting (0.7% vs 0%). The incidences of dose interruptions (53.5% vs 40.6%) and dose reductions (20.8% vs 10.7%) were numerically higher in the tucatinib arm compared to the placebo arm. The majority of these were due to gastrointestinal-related events (diarrhoea, vomiting and nausea) and elevated liver function tests (increased ALT, AST and blood bilirubin). The number and incidence of deaths due to AEs were balanced between the treatment arms (2% in the tucatinib arm vs 3% in the placebo arm). The AEs leading to death were mostly related to cardiovascular or infection events occurring in both treatment arms.

The most notable safety concerns with tucatinib were hepatotoxicity and diarrhoea, which have been described in the warnings and precautions section in the approved package insert. Hepatotoxicity events were primarily liver function test abnormalities (AST/ALT/bilirubin increases), which were observed at a higher incidence with tucatinib compared to placebo (39.4% vs 22.8%). The majority of these events were Grades 1 or 2 in severity, and appeared to be transient, asymptomatic, reversible and manageable with dose interruptions and modifications. Five patients in the tucatinib integrated safety population were identified to meet Hy's law laboratory criteria (AST/ALT >3xULN, and concurrent bilirubin >2xULN and ALP <1.5xULN), but these cases had other plausible alternative aetiologies and were not considered to be true Hy's law cases. The potential for tucatinib to cause severe drug-induced liver injury will be further monitored through post-marketing surveillance.

Gastrointestinal events, in particular diarrhoea (80.9% in the tucatinib arm vs 53.3% in the placebo arm), were the most frequent AEs associated with tucatinib treatment. The majority of diarrhoea events were Grade 1 (43.3% vs 32.0%) or Grade 2 (24.8% vs 12.7%) in severity. Grade ≥3 diarrhoea occurred in 12.9% and 8.6% of patients, respectively. There were two patients, both in the tucatinib arm, who reported Grade 4 diarrhoea. One of the 2 patients died from dehydration, the other from multiple organ dysfunction syndrome. In both patients, diarrhoea was ongoing at the time of death. Both patients had suspected infection concurrent with the diarrhoea event. Diarrhoea events could generally be managed with dose modifications and treatment with antidiarrheal medication.

Overall, tucatinib in combination with trastuzumab and capecitabine presented an acceptable safety profile for the intended population given the disease setting. Appropriate warnings and precautions have been put in place in the package insert to address the identified safety risks.

E ASSESSMENT OF BENEFIT-RISK PROFILE

Advanced breast cancer is a serious and life-threatening condition. HER2-positive breast cancer comprises 15-30% of all breast cancers, and is associated with poor prognosis, tends to be more aggressive and more likely to recur. After progression on first- and second-line therapies with trastuzumab, pertuzumab and trastuzumab emtansine (T-DM1), treatment options are limited and there is currently no accepted standard of care. There is an unmet medical need for more effective therapies in patients with HER2-positive advanced breast cancer.

Patients with advanced breast cancer and brain metastases particularly have worse prognosis, and current treatment options are limited to either surgical resection, radiosurgery and/or whole brain radiotherapy. There is currently no systemic treatment that has shown improved survival benefit in these patients with brain metastases.

Tucatinib in combination with trastuzumab and capecitabine had been shown to provide treatment benefit in terms of a statistically significant PFS prolongation of 2.2 months for the tucatinib combination with trastuzumab and capecitabine compared to the control arm receiving placebo with trastuzumab and capecitabine (median PFS per BICR: 7.8 vs 5.6 months; HR 0.544; 95% CI 0.420, 0.705; p<0.00001). More importantly, OS was shown to be statistically significantly and clinically meaningfully prolonged by 4.5 months for the tucatinib combination compared to control (median OS: 21.9 vs 17.4 months; HR 0.662; 95% CI 0.501, 0.875; p=0.00480). In addition, treatment benefits of tucatinib in patients with brain metastases were demonstrated in terms of the key secondary endpoint, PFS per BICR in patients with baseline brain metastases (7.6 vs 5.4 months; HR 0.483; 95% CI 0.339, 0.689), and supported by subgroup analyses of PFS per BICR and OS showing consistent outcomes in both patients with and without brain metastases.

The safety profile of tucatinib in combination with trastuzumab and capecitabine was considered acceptable relative to the benefits. The most notable safety concerns with tucatinib were hepatotoxicity and diarrhoea, which have been adequately addressed in the local package insert via the provision of relevant warnings and precautions, as well as dose adjustment recommendations in the event of toxicities.

Overall, the benefit-risk profile of tucatinib in combination with trastuzumab and capecitabine in the treatment of patients with locally 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 was considered favourable.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk balance of Tukysa for the treatment of patients with locally 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 was deemed favourable and approval of the product registration was granted on 19 May 2020.

APPROVED PACKAGE INSERT AT REGISTRATION

TUKYSA® (tucatinib) Film-Coated Tablets: 50 mg and 150 mg

1 INDICATIONS AND USAGE

TUKYSA is indicated in combination with trastuzumab and capecitabine for treatment of patients with locally 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.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dose of TUKYSA is 300 mg (two 150 mg tablets) taken orally twice daily continuously in combination with trastuzumab and capecitabine, at doses described in Table 1. Refer to the Full Prescribing Information for co-administered trastuzumab and capecitabine for additional information.

Table 1: Recommended dosing

Treatment	Dose	Treatment Days	Timing Relative to Food Intake
TUKYSA	300 mg orally twice daily	Continuously	Take with or without a meal
Capecitabine	1000 mg/m^2 orally twice daily	Days 1 to 14 every 21 days	Take within 30 minutes after a meal
Trastuzumab			Not applicable
Intravenous dosing			
Initial dose	8 mg/kg intravenously	Day 1	
Subsequent doses	6 mg/kg intravenously	Every 21 days	
OR			
Subcutaneous dosing	600 mg subcutaneously	Every 21 days	

Treatment with TUKYSA should be continued until disease progression or unacceptable toxicity.

TUKYSA tablets should be swallowed whole. Tablets should not be chewed, crushed, or split prior to swallowing.

TUKYSA should be taken approximately 12 hours apart, at the same time every day, with or without a meal. TUKYSA may be taken at the same time with capecitabine. In the case of a missed dose, the next dose should be taken at the regularly scheduled time.

2.2 Dose Modifications

Dose Modifications for Adverse Reactions

The recommended TUKYSA dose modifications for patients with adverse reactions are provided in Tables 2 to 5. Refer to the Full Prescribing Information for co-administered trastuzumab and capecitabine for dose modifications for toxicities suspected to be caused by those therapies.

Table 2: TUKYSA Dose Reduction Schedule

Dose Level	TUKYSA Dose
Recommended starting 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[1]

1. Do not dose below 150 mg twice daily. Permanently discontinue TUKYSA in patients unable to tolerate 150 mg orally twice daily.

Table 3: TUKYSA Dose Modifications – Hepatotoxicity

Liver Function Abnormalities[1]	TUKYSA Dose Modification
Grade 2 bilirubin (>1.5 to 3 × ULN)	Hold TUKYSA until recovery to ≤ Grade 1, then resume TUKYSA at the same dose level.
Grade 3 elevation of ALT or AST (> 5 – ≤ 20 x ULN) OR Grade 3 elevation of bilirubin (> 3 – ≤ 10 x ULN)	Hold TUKYSA until severity ≤ Grade 1. Then resume TUKYSA at the next lower dose level.
Grade 4 elevation of ALT or AST (> 20 x ULN) OR Grade 4 elevation of bilirubin (> 10 x ULN)	Permanently discontinue TUKYSA.
ALT or AST > 3 x ULN AND Bilirubin > 2 x ULN	Permanently discontinue TUKYSA.

ULN: upper limit of normal; ALT: alanine aminotransferase; AST: aspartate aminotransferase
1. Grading per CTCAE v4.03

Table 4: TUKYSA Dose Modifications – Diarrhea

Diarrhea	TUKYSA Dosage Modification
Grade 3 without anti-diarrheal treatment	Initiate or intensify appropriate medical therapy. Hold TUKYSA until recovery to ≤ Grade 1, then resume TUKYSA at the same dose level.
Grade 3 with anti-diarrheal treatment	Initiate or intensify appropriate medical therapy. Hold TUKYSA until recovery to ≤ Grade 1, then resume TUKYSA at the next lower dose level.
Grade 4	Permanently discontinue TUKYSA.

Table 5: TUKYSA Dose Modifications for Other Adverse Reactions

General Adverse Reactions[1]	TUKYSA Dose Modification
Grade 3	Hold TUKYSA until severity ≤ Grade 1. Then resume

	TUKYSA at the next lower dose level.
Grade 4	Permanently discontinue TUKYSA.

1. Grading per CTCAE v4.03

Dosage Modifications for Severe Hepatic Impairment

For patients with severe hepatic impairment (Child-Pugh C), reduce the recommended dosage to 200 mg orally twice daily *[see Use in Specific Populations (8.7), Clinical Pharmacology (12.3)]*.

Dosage Modifications for Concomitant Use with Strong CYP2C8 Inhibitors

Avoid concomitant use of strong CYP2C8 inhibitors with TUKYSA. If concomitant use with a strong CYP2C8 inhibitor cannot be avoided, reduce the recommended dosage to 100 mg orally twice daily. After discontinuation of the strong CYP2C8 inhibitor for 3 elimination half-lives, resume the TUKYSA dose that was taken prior to initiating the inhibitor [*see Drug Interactions (7.2), Clinical Pharmacology (12.3)*].

3 DOSAGE FORMS AND STRENGTHS

50 mg tablets: round, yellow, film-coated, debossed with “TUC” on one side and “50” on the other side.

150 mg tablets: oval-shaped, yellow, film-coated, debossed with “TUC” on one side and “150” on the other side.

4 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients contained in TUKYSA.

5 WARNINGS AND PRECAUTIONS

5.1 Hepatotoxicity

Hepatotoxicity has been reported during treatment with TUKYSA [*see Adverse Reactions (6.1)*]. The median time to onset of any grade increased ALT, AST, or bilirubin was 36 days; 84% of events resolved, with a median time to resolution of 22 days.

Monitor ALT, AST, and bilirubin prior to initiation of treatment and every three weeks thereafter or as clinically indicated. Based on the severity of the adverse reaction, interrupt dose, then dose reduce or permanently discontinue TUKYSA [*see Dosage and Administration (2.2)*].

5.2 Diarrhea

Diarrhea, including severe events resulting in dehydration, hypotension, acute kidney injury, and death, has been reported during treatment with TUKYSA [*see Adverse Reactions (6.1)*]. The median time to onset of any grade diarrhea was 12 days; 80% of diarrhea events resolved, with a median time to resolution of 8 days. Prophylactic use of antidiarrheals was not required. Antidiarrheals were used in less than half of treatment cycles where diarrhea events were reported. The median duration of antidiarrheal use was 3 days per cycle.

If diarrhea occurs, administer antidiarrheals as clinically indicated. Based on the severity of the diarrhea, interrupt dose, then dose reduce or permanently discontinue TUKYSA [*see Dosage and Administration (2.2)*]. Perform diagnostic tests as clinically indicated to exclude other causes of diarrhea.

5.3 Embryo-Fetal Toxicity

Based on findings from animal studies and its mechanism of action, TUKYSA may cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of tucatinib to pregnant rats and rabbits during organogenesis caused embryo-fetal mortality, reduced fetal weight and fetal abnormalities at maternal exposures ≥ 1.3 times the human exposure (AUC) at the recommended dose.

TUKYSA should not be used during pregnancy. If TUKYSA is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patients must be advised of the potential risk to the fetus. Advise females of reproductive potential to use effective contraception during treatment and for at least 1 week after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment and for at least 1 week after the last dose of TUKYSA [*see Use in Specific Populations (8.1, 8.3)*].

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Hepatotoxicity [*see Warnings and Precautions (5.1)*]
- Diarrhea [*see Warnings and Precautions (5.2)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

HER2CLIMB

The data described in this section reflect exposure to TUKYSA in combination with trastuzumab and capecitabine from HER2CLIMB, a randomized, double-blind, placebo-controlled, active comparator, global trial in patients with locally advanced unresectable or metastatic HER2-positive breast cancer, who received at least one dose of study drug.

The median duration of exposure to TUKYSA was 5.8 months (range, <0.1, 35.1).

Serious adverse events occurred in 26% of patients treated with TUKYSA compared to 27% of patients treated with placebo + trastuzumab + capecitabine (control arm). The most common serious adverse reactions (≥2%) in patients treated with TUKYSA were diarrhea (4%), vomiting (2%), and nausea (2%).

Adverse events leading to treatment discontinuation occurred in 6% of patients treated with TUKYSA compared to 3% of patients in the control arm; the most common adverse reactions leading to treatment discontinuation of TUKYSA were diarrhea (1%) and ALT increased (1%). Adverse events leading to dose reduction occurred in 21% of patients treated with TUKYSA compared to 11% of patients in the control arm; the most common adverse reactions leading to dose reduction of TUKYSA were diarrhea (6%), ALT increased (5%), and AST increased (4%).

Table 6 summarizes the any grade, Grade ≥3 adverse reactions reported in patients in HER2CLIMB.

Table 6: Adverse Reactions (≥10%) in Patients Who Received TUKYSA and with a Difference Between Arms of ≥ 5% Compared to Placebo in HER2CLIMB (All Grades)

	TUKYSA + Trastuzumab + Capecitabine N = 404			Placebo + Trastuzumab + Capecitabine N = 197		
SOC Preferred Term	All Grade %	Grade 3 %	Grade 4 %	All Grade %	Grade 3 %	Grade 4 %
Gastrointestinal disorders						
Diarrhea	81	12	0.5	53	9	0
Nausea	58	3.7	0	44	3	0
Vomiting	36	3	0	25	3.6	0
Stomatitis[1]	32	2.5	0	21	0.5	0
Skin and subcutaneous tissue disorders						
Palmar-plantar erythrodysesthesia syndrome	63	13	0	53	9	0
Rash[2]	20	0.7	0	15	0.5	0
Hepatobiliary disorders						
Hepatotoxicity[3]	42	9	0.2	24	3.6	0
Metabolism and nutrition disorders						
Decreased appetite	25	0.5	0	20	0	0
Blood and lymphatic system disorders						
Anemia[4]	21	3.7	0	13	2.5	0
Musculoskeletal and connective tissue disorders						
Arthralgia	15	0.5	0	4.6	0.5	0
Investigations						
Creatinine increased[5]	14	0	0	1.5	0	0
Weight decreased	13	1	0	6	0.5	0
Nervous System Disorders						
Peripheral neuropathy[6]	13	0.5	0	7	1	0
Respiratory, thoracic and mediastinal disorders						
Epistaxis	12	0	0	5	0	0

1. Stomatitis includes stomatitis, oropharyngeal pain, oropharyngeal discomfort, mouth ulceration, oral pain, lip ulceration, glossodynia, tongue blistering, lip blister, oral dysesthesia, tongue ulceration, and aphthous ulcer
2. Rash includes rash maculo-papular, rash, dermatitis acneiform, erythema, rash macular, rash papular, rash pustular, rash pruritic, rash erythematous, skin exfoliation, urticaria, dermatitis allergic, palmar erythema, plantar erythema, skin toxicity, and dermatitis
3. Hepatotoxicity includes hyperbilirubinemia, blood bilirubin increased, bilirubin conjugated increased, alanine aminotransferase increased, transaminases increased, hepatotoxicity, aspartate aminotransferase increased, liver function test increased, liver injury, and hepatocellular injury

4. Anemia includes anemia, hemoglobin decreased, and normocytic anemia
5. Due to inhibition of renal tubular transport of creatinine without affecting glomerular function
6. Peripheral neuropathy includes peripheral sensory neuropathy, neuropathy peripheral, peripheral motor neuropathy, and peripheral sensorimotor neuropathy

Table 7: Laboratory Abnormalities (≥20%) Worsening from Baseline in Patients Who Received TUKYSA and with a Difference of ≥5% Compared to Placebo in HER2CLIMB

	TUKYSA + Trastuzumab +Capecitabine[1]		Placebo + Trastuzumab +Capecitabine[1]	
	All Grades %	Grades ≥3 %	All Grades %	Grades ≥3 %
Hematology				
Decreased hemoglobin	59	3.3	51	1.5
Chemistry				
Decreased phosphate	57	8	45	7
Increased bilirubin	47	1.5	30	3.1
Increased ALT	46	8	27	0.5
Increased AST	43	6	25	1
Decreased magnesium	40	0.8	25	0.5
Decreased potassium [2]	36	6	31	5
Increased creatinine [3]	33	0	6	0
Decreased sodium [4]	28	2.5	23	2
Increased alkaline phosphatase	26	0.5	17	0

1. The denominator used to calculate the rate varied from 351 to 400 in the TUKYSA arm and 173 to 197 in the control arm based on the number of patients with a baseline value and at least one post-treatment value. Grading was based on NCI-CTCAE v.4.03 for laboratory abnormalities, except for increased creatinine which only includes patients with a creatinine increase based on the upper limit of normal definition for grade 1 events (NCI CTCAE v5.0).
2. Laboratory criteria for Grade 1 is identical to laboratory criteria for Grade 2.
3. Due to inhibition of renal tubular transport of creatinine without affecting glomerular function.
4. There is no definition for Grade 2 in CTCAE v.4.03.

Description of selected adverse reactions

Creatinine Increased

Increased serum creatinine was observed in 14% of patients treated with TUKYSA due to inhibition of renal tubular transport of creatinine without affecting glomerular function. In clinical studies, increases in serum creatinine (30% mean increase) occurred within the first 21 days of treatment with TUKYSA, remained elevated but stable throughout treatment and were reversible upon treatment discontinuation. Alternative markers such as BUN, cystatin C, or calculated GFR, which are not based on creatinine, may be considered to determine whether renal function is impaired.

7 DRUG INTERACTIONS

7.1 Effects of Other Drugs on TUKYSA

Table 8 includes drug interactions that affect the pharmacokinetics of tucatinib.

Table 8: Drug Interactions that Affect TUKYSA

Strong CYP3A or moderate CYP2C8 Inducers	
Clinical Impact	Concomitant use with a strong CYP3A or moderate CYP2C8 inducer decreases tucatinib AUC [see Clinical Pharmacology (12.3)] which may reduce TUKYSA efficacy.
Prevention or Management	Avoid concomitant use of TUKYSA with a strong CYP3A or moderate CYP2C8 inducer.
Strong or moderate CYP2C8 Inhibitors	
Clinical Impact	Concomitant use with a strong CYP2C8 inhibitor increases tucatinib AUC [*see Clinical Pharmacology (12.3)*] which may increase the risk of TUKYSA toxicity.
Prevention or Management	Avoid concomitant use of TUKYSA with strong CYP2C8 inhibitors. If concomitant use with a strong CYP2C8 inhibitor cannot be avoided, reduce the recommended dosage to 100 mg orally twice daily. After discontinuation of the strong CYP2C8 inhibitor for 3 elimination half-lives, resume the TUKYSA dose that was taken prior to initiating the inhibitor. Increase monitoring for TUKYSA toxicity with moderate CYP2C8 inhibitors.

7.2 Effects of TUKYSA on Other Drugs

Table 9 summarizes the effect of TUKYSA on other drugs.

Table 9: TUKYSA Drug Interactions that Affect Other Drugs

CYP3A Substrates	
Clinical Impact	Concomitant use with CYP3A substrates may increase the plasma concentrations of CYP3A substrates [*see Clinical Pharmacology (12.3)*]. Increased plasma concentrations of CYP3A substrates may lead to increased toxicity of the CYP3A substrates.
Prevention or Management	Avoid concomitant use of TUKYSA with CYP3A substrates, where minimal concentration changes may lead to serious or life-threatening toxicities. If concomitant use is unavoidable, decrease the CYP3A substrate dosage in accordance with approved product labeling.
P-glycoprotein (P-gp) Substrates	

Clinical Impact	Concomitant use with P-gp substrates may increase the plasma concentrations of P-gp substrates. Concomitant use with digoxin, a P-gp substrate, increased digoxin concentrations [*see Clinical Pharmacology (12.3)*]. Increased concentrations of digoxin may lead to increased risk of adverse reactions, including cardiac toxicity.
Prevention or Management	P-gp substrates where minimal concentration changes may lead to serious or life-threatening toxicities should be used with caution when coadministered with TUKYSA. Decrease the P-gp substrate dosage in accordance with approved product labelling.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

TUKYSA is used in combination with trastuzumab and capecitabine. Refer to the Full Prescribing Information of trastuzumab and capecitabine for pregnancy information.

There are no available human data on TUKYSA use in pregnant women to inform a drug-associated risk of adverse developmental outcomes. TUKYSA may cause fetal harm based upon findings from animal studies and the drug's mechanism of action *[see Clinical Pharmacology (12.1)]*. In animal studies, administration of TUKYSA to pregnant rats and rabbits during organogenesis resulted in embryo-fetal mortality, reduced fetal weight and fetal abnormalities at maternal exposures ≥ 1.3 times the human exposure (AUC) at the recommended dose *[see Animal Data]*. Pregnant women and female patients of childbearing potential treated with TUKYSA should be advised of the potential risk to the fetus.

TUKYSA should not be used during pregnancy. If TUKYSA is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient must be advised of the potential risk to the fetus.

Animal Data

In pilot embryo-fetal development studies, pregnant rats and rabbits received oral doses of tucatinib up to 150 mg/kg/day during the period of organogenesis.

In rats, oral administration of tucatinib resulted in maternal toxicity (body weight loss, reduced body weight gain, low food consumption) at doses ≥ 90 mg/kg/day. Fetal effects included reduced number of live fetuses, decreased fetal weight, and fetal abnormalities (increase in skeletal variations, incomplete ossification) at ≥ 90 mg/kg/day (approximately 3.5 times the human exposure at the recommended dose based on AUC).

In rabbits, oral administration of tucatinib resulted in increased resorptions, decreased percentages of live fetuses, and skeletal, visceral, and external malformations in fetuses at doses ≥ 90 mg/kg/day (1.3 times the human exposure at the recommended dose based on AUC). Fetal abnormalities included domed head, brain dilation, incomplete ossification of frontal and parietal bones, and a hole in the parietal bone.

8.2 Lactation

Risk Summary

No data are available regarding the presence of tucatinib or its metabolites in human or animal milk or its effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in a breastfed child from TUKYSA, advise lactating women not to breastfeed while taking TUKYSA and for at least 1 week after the last dose.

TUKYSA is used in combination with trastuzumab and capecitabine. Refer to the Full Prescribing Information of trastuzumab and capecitabine for lactation information.

8.3 Females and Males of Reproductive Potential

TUKYSA can cause fetal harm when administered to a pregnant woman. TUKYSA is used in combination with trastuzumab and capecitabine. Refer to the Full Prescribing Information of trastuzumab and capecitabine for contraception and infertility information.

Pregnancy testing

Verify the pregnancy status of females of reproductive potential prior to initiating treatment with TUKYSA.

Contraception

Females

Advise patients of risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TUKYSA and for at least 1 week after the last dose [*see Use in Specific Populations (8.1)*].

Males

Advise males with female partners of reproductive potential to use effective contraception during treatment with TUKYSA and for at least 1 week after the last dose of TUKYSA.

Infertility

No fertility studies in women or men have been conducted.

Based on findings from animal studies, TUKYSA may impair fertility in females of reproductive potential [*see Nonclinical Toxicology (13.1)*].

8.4 Pediatric Use

Safety and effectiveness of TUKYSA in pediatric patients have not been established.

8.5 Geriatric Use

In HER2CLIMB, 82 patients who received TUKYSA were ≥65 years, of whom 8 patients were ≥75 years. The incidence of serious adverse reactions in those receiving TUKYSA was 34% in patients ≥65 years compared to 24% in patients <65 years. The most frequent serious adverse reactions in patients who received TUKYSA and ≥65 years were diarrhea (9%), vomiting (6%), and nausea (5%). There were no observed overall differences in the effectiveness of TUKYSA in patients ≥65 years compared to younger patients. There were too few patients ≥75 years to assess differences in effectiveness or safety.

8.6 Renal Impairment

No dose adjustment is recommended for patients with mild or moderate renal impairment (creatinine clearance [CLcr] 30 to 89 mL/min). No dose recommendation is available for patients with severe renal impairment.

8.7 Hepatic Impairment

Tucatinib exposure is increased in patients with severe hepatic impairment (Child-Pugh C). Reduce the dose of TUKYSA for patients with severe (Child-Pugh C) hepatic impairment [see Dosage and Administration (2.2), Clinical Pharmacology (12.3)].

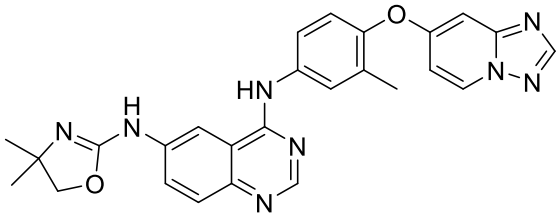
No dose adjustment for TUKYSA is required for patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment.

10 OVERDOSAGE

There is no known antidote for overdosage with TUKYSA. In case of overdosage, the patient should be closely monitored for adverse reactions, and supportive treatment should be administered as appropriate.

11 DESCRIPTION

Tucatinib is a small molecule inhibitor of the receptor tyrosine kinase human epidermal growth factor receptor 2 protein (HER2). The chemical name is (N4-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-N6-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)quinazoline-4,6-diamine. The molecular formula is $C_{26}H_{24}N_8O_2$ and the molecular weight is 480.52 g/mol. The chemical structure is as follows:



TUKYSA (tucatinib) is supplied as 50 mg and 150 mg film-coated tablets for oral administration and contain the following inactive ingredients:

Tablet core: copovidone, crospovidone, sodium chloride, potassium chloride, sodium bicarbonate, colloidal silicon dioxide, magnesium stearate, and microcrystalline cellulose.

Coating: yellow film coat: polyvinyl alcohol, titanium dioxide, macrogol/polyethylene glycol, talc, and yellow iron oxide non-irradiated.

Each TUKYSA 50 mg tablet contains 10.10 mg (0.258 mEq) potassium and 9.21 mg (0.401 mEq) sodium.

Each TUKYSA 150 mg tablet contains 30.29 mg (0.775 mEq) potassium and 27.64 mg (1.202 mEq) sodium.

Pharmacotherapeutic group: Antineoplastic agent, protein kinase inhibitor

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

HER2 gene amplification in tumor cells results in over-expression of the HER2 protein and drives formation of HER2 homodimers and HER2/HER3 heterodimers, which leads to constitutive activation of downstream signaling cascades, increased cell proliferation, and metastasis.

Tucatinib is a tyrosine kinase inhibitor of HER2. In cellular signaling assays, tucatinib is >1000-fold more selective for HER2 compared to epidermal growth factor receptor. In vitro, tucatinib inhibits phosphorylation of HER2 and HER3, resulting in inhibition of downstream cell signaling and cell proliferation, and induces death in HER2 driven tumor cells. In vivo, tucatinib inhibits the growth of HER2 driven tumors and the combination of tucatinib and trastuzumab showed enhanced anti-tumor activity in vitro and in vivo compared to either drug alone. In an intracranial mouse tumor model, tucatinib demonstrated increased distribution to tumor tissue compared with brain parenchyma and resulted in increased survival.

12.2 Pharmacodynamics

Cardiac Electrophysiology

Multiple doses of TUKYSA 300 mg BID did not have an effect on the QTc interval in a TQT study in healthy subjects.

12.3 Pharmacokinetics

Plasma tucatinib exposure (AUC_{inf} and C_{max}) demonstrated dose proportional increases at oral doses from 50 to 300 mg (0.17 to 1 times the recommended dose). Tucatinib exhibited 1.7-fold accumulation for AUC and 1.5-fold accumulation for C_{max} following administration of 300 mg tucatinib twice daily for 14 days. Time to steady state was approximately 4 days.

Absorption

Following a single tucatinib oral dose of 300 mg, the median time to peak plasma concentration was approximately 2.0 hours (range 1.0 to 4.0 hours).

Effects of Food

Following administration of a single dose of tucatinib in 11 subjects after a high-fat meal (approximately 58% fat, 26% carbohydrate, and 16% protein), the mean AUC_{inf} increased by 1.5-fold, the T_{max} shifted from 1.5 hours to 4.0 hours, and C_{max} was unaltered. The effect of food on the PK of tucatinib was not clinically meaningful, thus TUKYSA may be administered without regard to food.

Distribution

The apparent volume of distribution of tucatinib was approximately 1670 L. The plasma protein binding was 97.1% at clinically relevant concentrations.

Elimination

Following a single oral dose of 300 mg, tucatinib is cleared from plasma with a mean half-life of approximately 8.7 hours and apparent clearance of 148 L/h.

Metabolism

Tucatinib is metabolized primarily by CYP2C8 and to a lesser extent via CYP3A.

Excretion

Tucatinib is predominantly eliminated by the hepatobiliary route and is not appreciably renally eliminated. Following a single oral dose of 300 mg [14C]-tucatinib, approximately 85.8% of the total radiolabeled dose was recovered in feces (15.9% of the administered dose as unchanged tucatinib) and 4.1% in urine with an overall total recovery of 89.9% within 312 hours post-dose. In plasma, approximately 75.6% of the plasma radioactivity was unchanged, 19% was attributed to identified metabolites, and approximately 5% was unassigned.

Specific Populations

Age (< 65 years (n =211); ≥ 65 years (n = 27)), albumin (25 to 52 g/L), creatinine clearance ([CLcr] 60 to 89 mL/min (n = 89) CLcr 30 to 59 mL/min (n=5)), body weight (41 to 138 kg), and race (White (n=168), Black (n=53), or Asian (n=10)) did not have a clinically meaningful effect on tucatinib exposure.

Renal Impairment

No clinically significant differences in the pharmacokinetics of tucatinib were observed in patients with mild to moderate renal impairment (creatinine clearance: 30 to 89 mL/min by Cockcroft-Gault). The effect of severe renal impairment (creatinine clearance: < 30 mL/min) on the pharmacokinetics of tucatinib is unknown.

Hepatic Impairment

Mild (Child-Pugh A), moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment had no clinically relevant effect on tucatinib exposure. Tucatinib AUC0-INF was increased by 1.6 fold in subjects with severe (Child-Pugh C) hepatic impairment compared to subjects with normal hepatic function.

Drug Interaction Studies

Clinically Significant Interactions with TUKYSA

Table 10: Effect of Other Drugs on TUKYSA

Concomitant Drug (Dose)	**TUKYSA Dose**	**Ratio (90% CI) of Exposure Measures of Tucatinib Combination/No combination**	
		C_{max}	**AUC**
CYP3A Inhibition Itraconazole (200 mg BID)	300 mg single dose	1.32 (1.23, 1.42)	1.34 (1.26, 1.43)
CYP3A/2C8 Induction Rifampin (600 mg once daily)		0.63 (0.53, 0.75)	0.52 (0.45, 0.60)

CYP2C8 Inhibition Gemfibrozil (600 mg BID)		1.62 (1.47, 1.79)	3.04 (2.66, 3.46)

Table 11: Effect of TUKYSA on Other Drugs

Concomitant Drug (Dose)	TUKYSA Dose	Ratio (90% CI) of Exposure Measures of Tucatinib Combination/No combination	
		C_{max}	AUC
Repaglinide (CYP2C8) (0.5 mg single dose)	300 mg twice daily	1.69 (1.37, 2.10)	1.69 (1.51, 1.90)
Midazolam (CYP3A) (2 mg single dose)		3.01 (2.63, 3.45)	5.74 (5.05, 6.53)
Digoxin (P-gp) (0.5 mg single dose)		2.35 (1.90, 2.90)	1.46 (1.29, 1.66)
Metformin (MATE1/2-K)1 (850 mg single dose)		1.08 (0.95, 1.23)	1.39 (1.25, 1.54)

1. Tucatinib reduced the renal clearance of metformin without any effect on glomerular filtration rate (GFR) as measured by iohexol clearance and serum cystatin C.

Drugs without Clinically Significant Interactions with TUKYSA

No clinically significant drug interactions have been observed when TUKYSA is combined with omeprazole (a proton pump inhibitor) or tolbutamide (a sensitive CYP2C9 substrate).

In Vitro Studies

Tucatinib is a substrate of CYP2C8 and CYP3A.

Tucatinib is a reversible inhibitor of CYP2C8 and CYP3A and a time-dependent inhibitor of CYP3A, at clinically relevant concentrations.

Tucatinib has low potential to inhibit CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and UGT1A1 at clinically relevant concentrations.

Tucatinib is a substrate of P-gp and BCRP. Tucatinib is not a substrate of OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, MATE2-K, and BSEP.

Tucatinib inhibits MATE1/MATE2-K-mediated transport of metformin and OCT2/MATE1-mediated transport of creatinine. The observed serum creatinine increase in clinical studies with tucatinib is due to inhibition of tubular secretion of creatinine via OCT2 and MATE1.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with tucatinib.

Tucatinib was not mutagenic in an in vitro bacterial reverse mutation (Ames) assay. Tucatinib was not clastogenic in either an in vitro chromosome aberration assay or an in vivo mouse bone marrow micronucleus assay.

Fertility studies in animals have not been conducted. In repeat-dose toxicity studies up to 13 weeks duration, decreased corpora lutea/corpus luteum cyst, increased interstitial cells of the ovary, atrophy of the uterus, and mucification of the vagina were observed in female rats at doses ≥ 6 mg/kg/day (approximately 0.1 times the human exposure at the recommended dose based on AUC). Atrophy and edema of the testes and oligospermia/germ cell debris in the epididymides were observed in male rats at ≥ 120 mg/kg/day (approximately 13 times the human exposure at the recommended dose based on AUC).

14 CLINICAL STUDIES

14.1 HER2-Positive Metastatic Breast Cancer

The efficacy of TUKYSA in combination with trastuzumab and capecitabine was evaluated in a randomized, double-blind, placebo-controlled, active comparator, global trial (HER2CLIMB, NCT02614794). Patients enrolled had locally advanced unresectable or metastatic HER2-positive breast cancer, with or without brain metastases, and had prior treatment with trastuzumab, pertuzumab, and ado-trastuzumab emtansine (T-DM1) separately or in combination, in the neoadjuvant, adjuvant or metastatic setting. HER2 overexpression or amplification was confirmed by central laboratory analysis.

Patients with brain metastases were eligible to enroll provided they were neurologically stable and did not require immediate radiation or surgery. Patients who required immediate local intervention could receive local therapy and be subsequently enrolled. The study included patients with untreated brain metastases and patients with treated brain metastases that were either stable or progressing since last treatment. The trial excluded patients with leptomeningeal disease.

A total of 612 patients were randomized 2:1 to receive TUKYSA in combination with trastuzumab and capecitabine (N=410) or placebo in combination with trastuzumab and capecitabine (N=202). Randomization was stratified by the presence or history of brain metastases (yes vs. no), Eastern Cooperative Oncology Group (ECOG) performance status (0 vs. 1), and region (U.S., Canada, or rest of world).

Patient demographics and baseline disease characteristics were balanced between treatment arms. The median age was 54 years (range, 22 to 82); 116 (19%) patients were age 65 or older. The majority were white (73%) and female (99%), and 51% had an ECOG performance status of 1. Four percent of patients were Asian. Most patients (99.5%) had metastatic disease. Sixty percent had estrogen and/or progesterone receptor-positive disease. Forty-eight percent of patients had a presence or history of brain metastases; of these, 23% had untreated brain metastases, 40% had treated but stable brain metastases, and 37% had treated but radiographically progressing brain metastases. Seventy-four percent of patients had visceral metastases, 49% of patients had lung metastases, 35% had liver metastases, and 14% had skin metastases. Patients had a median of 4 (range, 2 to 17) prior lines of systemic therapy and a median of 3 (range, 1 to 14) prior lines of systemic therapy in the metastatic setting.

TUKYSA or placebo, 300 mg orally twice per day, was administered until disease progression or unacceptable toxicity. Trastuzumab was administered intravenously as a loading dose of 8 mg/kg on Day 1 of Cycle 1, followed by a maintenance dose of 6 mg/kg on Day 1 of each subsequent 21-day cycle. An alternate dosing option for trastuzumab was a fixed dose of 600 mg administered subcutaneously on Day 1 of each 21-day cycle. Capecitabine, 1000 mg/m^2 orally twice per day, was administered on Days 1 through 14 of each 21-day cycle.

The primary endpoint was progression-free survival (PFS) by blinded independent central review (BICR) in the first 480 randomized patients. The median duration of exposure to TUKYSA was 7.3 months (range <0.1, 35.1) for patients on the TUKYSA + trastuzumab + capecitabine arm compared to 4.4 months (range <0.1, 24.0) of

placebo for patients on the placebo + trastuzumab + capecitabine arm. Similar differences in exposure to trastuzumab and capecitabine were observed.

Secondary endpoints were evaluated in all randomized patients (N=612) and included overall survival (OS), PFS among patients with a history or presence of brain metastases ($PFS_{BrainMets}$), and confirmed objective response rate (ORR).

Efficacy results are summarized in Tables 12 to 15 and Figures 1 to 3.

Efficacy results were consistent across all patient subgroups including hormone receptor status, presence or history of brain metastases, ECOG status, region, and age.

Table 12: PFS per BICR

PFS[1,2]	**TUKYSA + Trastuzumab + Capecitabine** **N=320**	**Placebo + Trastuzumab + Capecitabine** **N=160**
Number of events (%)	178 (56)	97 (61)
Hazard ratio (95% CI)[3]	0.54 (0.42, 0.71)	
P-value[4]	<0.00001	
Median (months) (95% CI)	7.8 (7.5, 9.6)	5.6 (4.2, 7.1)
6 month PFS (%) (95% CI)	62.9 (56.9, 68.4)	46.3 (37.2, 54.9)
12 month PFS (%) (95% CI)	33.1 (26.6, 39.7)	12.3 (6.0, 20.9)

BICR=blinded independent central review; CI=confidence interval; PFS=progression-free survival.

1. Primary PFS analysis conducted in first 480 randomized patients. PFS based on Kaplan-Meier analyses.
2. PFS as determined by the investigator was consistent with PFS as assessed by BICR.
3. Hazard ratio and 95% confidence intervals are based on stratified Cox proportional hazards regression model controlling for stratification factors (presence or history of brain metastases, ECOG status, and region of world)
4. Two-sided p-value based on re-randomization procedure (Rosenberger and Lachin 2002) controlling for stratification factors

Figure 1: PFS per BICR

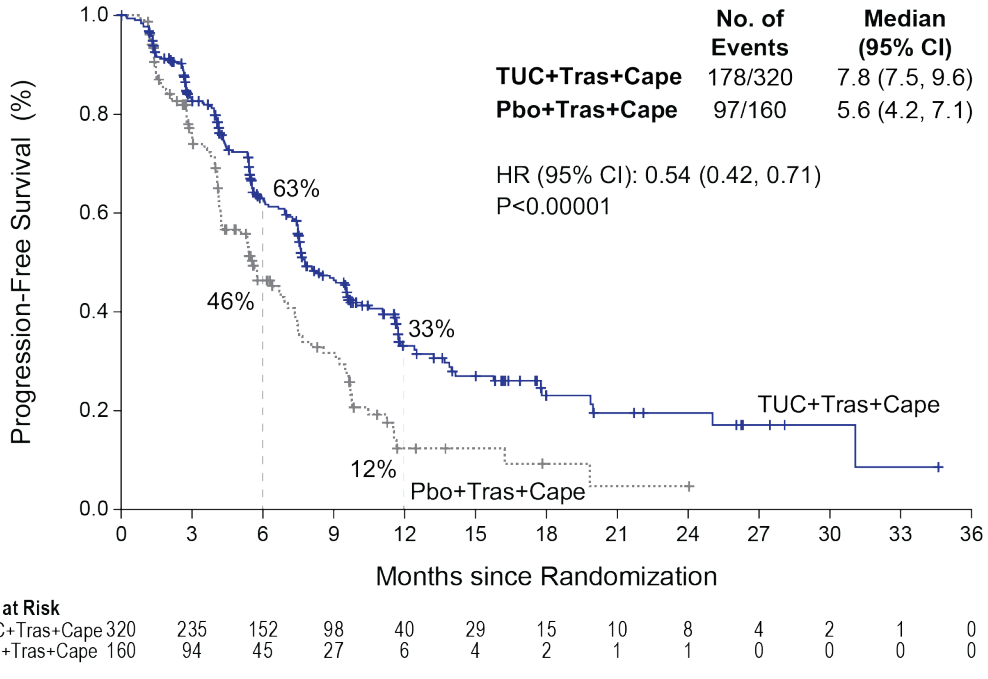


Table 13: Overall Survival

OS	TUKYSA + Trastuzumab + Capecitabine	Placebo + Trastuzumab + Capecitabine
	N=410	**N=202**
Number of deaths, n (%)	130 (32)	85 (42)
Hazard ratio (95% CI)[1]	0.66 (0.50, 0.88)	
P-value[2]	0.00480	
Median OS, months (95% CI)	21.9 (18.3, 31.0)	17.4 (13.6, 19.9)
12 month OS (%) [95% CI]	75.5 (70.4, 79.9)	62.4 (54.1, 69.5)
24 month OS (%) [95% CI]	44.9 (36.6, 52.8)	26.6 (15.7, 38.7)

1. Hazard ratio and 95% confidence intervals are based on stratified Cox proportional hazards regression model controlling for stratification factors (presence or history of brain metastases, ECOG status, and region of world)
2. Two-sided p-value based on re-randomization procedure (Rosenberger and Lachin 2002) controlling for stratification factors, compared with the allocated alpha of 0.0074 for this interim analysis (with 60% of the planned number of events for final analysis)

Figure 2: Overall Survival

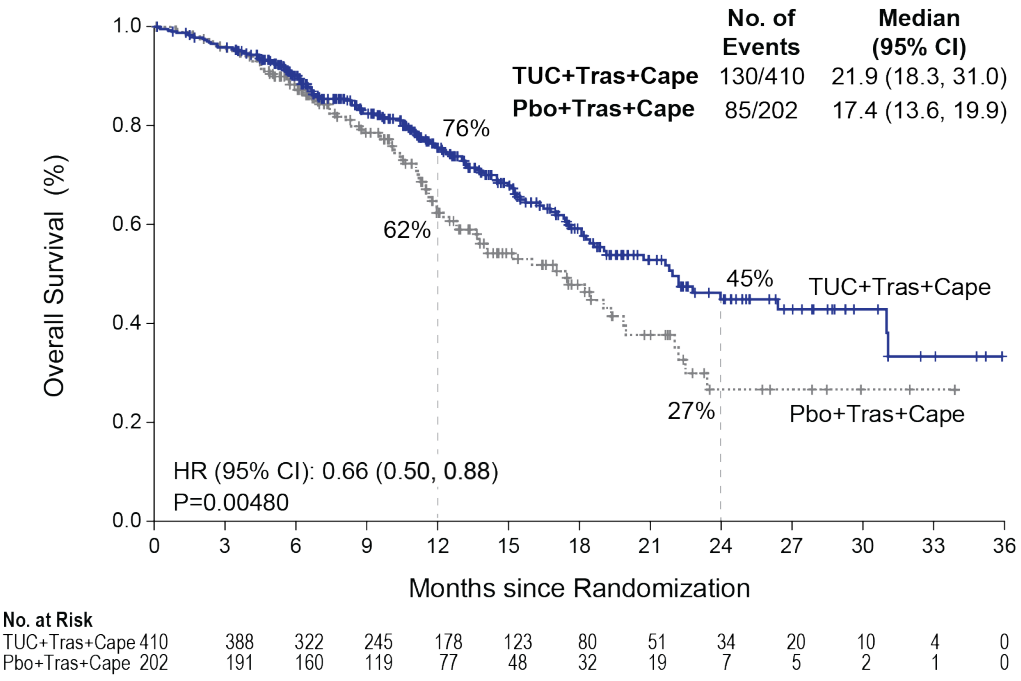


Table 14: PFS per BICR in Patients with Brain Metastases

$PFS_{BrainMets}$[1]	TUKYSA + Trastuzumab + Capecitabine	Placebo + Trastuzumab + Capecitabine
	N=198	N=93
Number of events (%)	106 (53.5)	51 (54.8)
Hazard ratio (95% CI)[2]	0.48 (0.34, 0.69)	
P-value[3]	<0.00001	
Median (months) (95% CI)	7.6 (6.2, 9.5)	5.4 (4.1, 5.7)
6 month PFS (%) (95% CI)	60.4 (52.4, 67.5)	33.9 (21.0, 47.2)
12 month PFS (%) (95% CI)	24.9 (16.5, 34.3)	-

1. Analysis includes patients with history or presence of parenchymal brain metastases at baseline, including target and non-target lesions. Does not include patients with dural lesions only.
2. Hazard ratio and 95% confidence intervals are based on stratified Cox proportional hazards regression model controlling for stratification factors (ECOG status and region of world)
3. Two-sided p-value based on re-randomization procedure (Rosenberger and Lachin 2002) controlling for stratification factors, compared with the allocated alpha of 0.0080 for this interim analysis (with 71% of the planned number of events for final analysis)

Figure 3: PFS per BICR in Patients with Brain Metastases

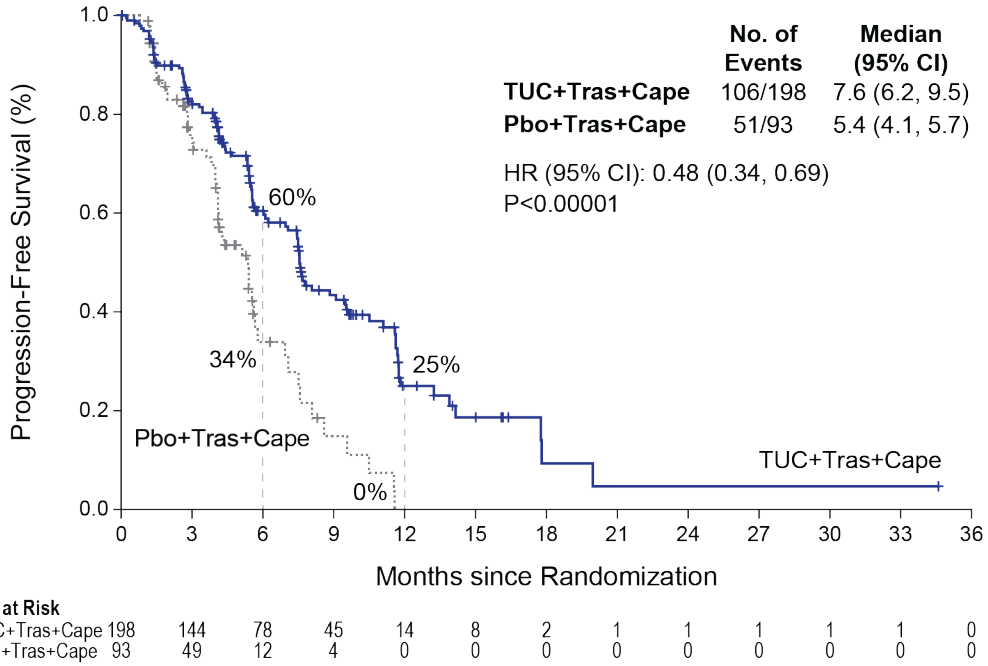


Table 15: Confirmed ORR and DOR per BICR

ORR for Patients with Measurable Disease	TUKYSA + Trastuzumab + Capecitabine	Placebo + Trastuzumab + Capecitabine
	N=340	N=171
ORR (95% CI)[1]	40.6 (35.3, 46.0)	22.8 (16.7, 29.8)
P-value[2]	0.00008	
CR (%)	3 (0.9)	2 (1.2)
PR (%)	135 (39.7)	37 (21.6)
DOR		
Median DOR in months (95% CI)[3]	8.3 (6.2, 9.7)	6.3 (5.8, 8.9)

CR=complete response; ORR=objective response rate, patients with complete or partial response; PR=partial response; DOR=duration of response

1. Two-sided 95% exact confidence interval, computed using the Clopper-Pearson method (1934)
2. Cochran-Mantel-Haenszel test controlling for stratification factors (presence or history of brain metastases, ECOG status, and region of world)
3. Calculated using the complementary log-log transformation method (Collett, 1994)

Health-related quality of life (HRQoL) was assessed as a secondary endpoint in HER2CLIMB using the EQ-5D-5L questionnaire for the measurement of overall health status. The addition of tucatinib to a regimen of trastuzumab and capecitabine maintained HRQoL over the course of the study and was similar to the active control arm.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

TUKYSA 50 mg tablets are supplied as yellow, film-coated, round tablets containing 50 mg of tucatinib. Each tablet is debossed with “TUC” on one side and “50” on the other side.

TUKYSA 150 mg tablets are supplied as yellow, film-coated, oval-shaped tablets containing 150 mg of tucatinib. Each tablet is debossed with “TUC” on one side and “150” on the other side.

150 mg blister presentation:

4 tablets per blister and 21 blisters per carton

50 mg blister presentation:

8 tablets per blister and 11 blisters per carton

oPA/ALU/PVC blisters, sealed with aluminum foil.

Store at 30°C or below.

17 PATIENT COUNSELING INFORMATION

Hepatotoxicity

- Inform patients that TUKYSA has been associated with hepatotoxicity and that they should report signs and symptoms of liver dysfunction to their healthcare provider immediately [*see Warnings and Precautions (5.1)*].

Diarrhea

- Inform patients that TUKYSA has been associated with diarrhea. Instruct patients on how to manage diarrhea and to inform their healthcare provider immediately if there is any change in bowel patterns [*see Warnings and Precautions (5.2)*].

Embryo-fetal Toxicity

- Instruct patients to notify their healthcare provider immediately in the event of a pregnancy or if pregnancy is suspected during TUKYSA treatment. Inform female patients of the risk to a fetus and potential loss of the pregnancy *[see Use in Specific Populations (8.1)]*.
- Advise female patients and male patients with female partners of reproductive potential to use effective contraception during treatment with TUKYSA and for at least 1 week after the last dose of TUKYSA *[see Use in Specific Populations (8.3)]*.
- Advise women not to breastfeed during treatment with TUKYSA and for at least 1 week after the last dose *[see Use in Specific Populations (8.2)]*.

SeattleGenetics™

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DATE OF REVISION: DD MONTH YEAR