NCPE Assessment

Technical Summary

Tucatinib (Tukysa®)

HTA ID: 22058

September 2025

Applicant: Pfizer Ireland

Tucatinib (Tukysa®), in combination with trastuzumab and capecitabine, for the treatment of adult patients with HER2-positive locally advanced or metastatic breast cancer who have received at least two prior anti-HER2 treatment regimens.

NCPE
National Centre for Pharmacoeconomics, Ireland

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of tucatinib (Tukysa®).

Following assessment of the Applicant's submission, the NCPE recommends that tucatinib (Tukysa®) not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments.*

The Health Service Executive (HSE) asked the NCPE to carry out an evaluation of the Applicant's (Pfizer Ireland) Health Technology Assessment of tucatinib (Tukysa®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes comparative clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

Summary

In March 2024, Pfizer Ireland submitted a dossier which investigated the comparative clinical effectiveness, cost-effectiveness and budget impact of tucatinib (Tukysa®) in combination with trastuzumab and capecitabine (Tuc+tras+cap) for the treatment of adult patients with HER2-positive locally advanced or metastatic breast cancer (mBC) who have received at least two prior anti-HER2 treatment regimens. Pfizer Ireland is seeking reimbursement on the High-Tech Drug Arrangement.

Tucatinib is a reversible, potent and selective tyrosine kinase inhibitor of HER2. The recommended dose of tucatinib is 300 mg orally twice daily, in combination with trastuzumab (loading does of 8 mg/kg intravenously day 1 of cycle 1, followed by a maintenance dose of 6 mg/kg (intravenously) or 600mg (subcutaneously) on day 1 of every 21-day cycle thereafter) and capecitabine orally (1,000 mg/m^2 of body-surface area twice daily on days 1 to 14 of every 21-day cycle). Treatment with tucatinib should be continued until disease progression or unacceptable toxicity.

The product licence for tucatinib permits treatment following at least two prior anti-HER2 treatment regimens. The line of therapy is not specified in the product licence. The European Society of Medical Oncology (ESMO) guidelines recommend the use of Tuc+tras+cap or trastuzumab deruxtecan for patients with active brain metastases (BM) in the second-line (2L) setting, or in patients with evidence of fast progression, where a local intervention is not indicated. Tuc+tras+cap, trastuzumab deruxtecan, or trastuzumab emtansine (T-DM1) are recommended at third-line (3L), based on prior treatment received, toxicity profile, or patient characteristics. The National Cancer Comprehensive Cancer Network (NCCN) guidelines, recommend Tuc+tras+cap as the preferred 3L treatment in patients with systemic and central nervous system progression (i.e, including BM), and note that Tuc+tras+cap may be used in 2L. The NCCN guidelines recommend trastuzumab deruxtecan in 2L and T-DM1 in 3L. The Applicant's cost-effectiveness analysis considered Tuc+tras+cap in the 3L HER2-positive mBC setting only. The Applicant considered T-DM1, trastuzumab plus capecitabine (Tras+cap), trastuzumab plus single agent chemotherapy (vinorelbine or lapatinib; herein "Tras+doublets"), lapatinib plus capecitabine (Lap+cap), and neratinib as

relevant comparators in the 3L setting. Clinical Opinion obtained by Review Group indicated that T-DM1 was the most commonly reported comparator to Tuc+tras+cap in the 3L setting. The Review Group requested that the Applicant update their submission to consider the full licensed population, inclusive of patients treated at 2L, however this was not provided by the Applicant. This is a key limitation of the submission.

1. Comparative effectiveness of tucatinib

The efficacy and safety data for tucatinib is from the completed Phase 2 international, randomized, double-blind trial, HER2CLIMB, which evaluated Tuc+tras+cap versus placebo combined with trastuzumab and capecitabine (Pbo+tras+cap) in participants with HER2-positive mBC in the 2L and later setting. Participants were randomly assigned, in a 2:1 ratio, to tucatinib (n=410) (300 mg orally twice daily throughout the treatment period) or placebo (n=202) (orally twice daily). All participants also received trastuzumab (loading does of 8 mg/kg intravenously on day 1 of cycle 1, followed by maintenance of 6 mg/kg on day 1 of every 21-day cycle thereafter, and capecitabine (1,000 mg/m^2 orally twice daily on days 1 to 14 of each 21-day cycle). Subcutaneous administration of trastuzumab was also permitted, at a fixed dose of 600 mg, without a loading dose. At the end of the double-blind phase of the study, participants were unblinded to their treatment assignment, wherein participants initially randomised to Pbo+tras+cap could cross over to Tuc+tras+cap. The first patient cross-over occurred in February 2020.

Approximately 48% of participants had a presence or history of BM at baseline; of these, 23% had untreated BM, 40% had treated but stable BM, and 37% had treated but radiographically progressing BM. All participants had prior treatment with trastuzumab, pertuzumab and T-DM1, which was standard of care at the time of trial design. The median and mean number of prior systemic therapies were both four (range: 2 to 17). The Review Group note that the treatment landscape for HER2-positive mBC has changed since the completion of HER2CLIMB.

Due to amendments to the trial protocol, there were several analyses sets and data cut-offs (DCOs). The primary endpoint was progression free survival (PFS) in the primary analysis population (the first 480 randomised participants (Tuc+tras+cap: n=320; Pbo+tras+cap:

n=160)). In the primary analysis (DCO: September 2019), Tuc+tras+cap was associated with a significantly longer median PFS of 7.8 months, relative to 5.6 months with Pbo+tras+cap (Hazard Ratio (HR): 0.54 (95% CI 0.42 to 0.71)). The median PFS in participants with BM at baseline (a key secondary outcome in the primary analysis population) was 7.6 months with Tuc+tras+cap versus 5.4 months in the placebo arm (HR: 0.48 (95% CI 0.34 to 0.69)). Overall survival (OS) was assessed as a key secondary endpoint in the full trial population (n=612) at the February 2021 DCO. Tuc+tras+cap was associated with a significantly longer median OS of 24.7 months, compared to 19.2 months in the Pbo+tras+cap arm (HR: 0.73 (95% CI: 0.59 to 0.90). In total, 13% of participants in the Pbo+tras+cap arm crossed over to Tuc+tras+cap. Sensitivity analyses indicated that HRs adjusted for crossover were consistent with the HR from the unadjusted analysis.

Health related quality of life (HRQoL) was analysed as a secondary outcome measured using the EQ-5D-5L visual analogue scale (VAS). The HRQoL data had a high missing rate at baseline. No clinically meaningful differences in HRQoL or significant difference in time to deterioration of HRQoL was observed between the two treatment arms during study treatment. In the subpopulation of patients with stable or active BM at baseline, the time to deterioration of HRQoL was longer in the Tuc+tras+cap arm, relative to Pbo+tras+cap HR: 0.51 (0.28 to 0.93).

The Review Group consider that trastuzumab deruxtecan is a relevant comparator in the 2L setting in line with international clinical guidelines. However, an indirect treatment comparison was not implemented by the Applicant to investigate the relative efficacy of Tuc+tras+cap versus trastuzumab deruxtecan. This is a limitation of this submission. The Applicant investigated the relative efficacy (OS and PFS) of Tuc+tras+cap versus comparators relevant to the 3L setting only. Studies included in the Applicant's network meta-analyses (NMA) were conducted in the 2L or later line setting due to a paucity of data when including only 3L or later line setting. Comparators in the NMA included T-DM1, Tras+doublets, Lap+cap, and neratinib. The Tras+doublets could not be connected to the evidence network due a paucity of data. The Applicant assumed equal efficacy of Tras+cap and the Tras+doublets. The Review Group requested that the Applicant provide an NMA with BM as an effect modifier (BM is associated with poorer prognosis). The Applicant declined, citing a

paucity of data. The Review Group consider this a major limitation of the submission. Overall, the NMA indicate that Tuc+tras+cap is associated with improved outcomes (OS and PFS) versus all comparators investigated (Tras+cap, Trast+doublet, neratinib, Lap+cap) except T-DM1. There is substantial heterogeneity between the studies included in the networks. This may result in biased effect estimates. The NMA outputs should be interpreted with caution.

Safety of tucatinib

The safety population, in HER2CLIMB, included all participants who received at least one dose of assigned treatment (n=601); final analysis DCO September 2022. Median treatment duration was 7.4 months (range: 0.1 to 59.4) with tucatinib and 4.4 months (range: 0.1 to 26.9) with placebo. Treatment emergent adverse events (TEAEs), that occurred in the blinded phase, led to the discontinuation in 5.7% and 3.6% of participants in the Tuc+tras+cap and Pbo+tras+cap arms respectively. Grade ≥3 TEAEs which occurred in greater than 5% of participants in the Tuc+tras+cap arm were palmar-plantar erythrodysesthesis syndrome (14% versus 9%), diarrhoea (13% versus 9%), elevated liver enzymes (ALT 6% versus 0.5%; AST 5% versus 0.5%), fatigue (6% versus 4%) and dyspnoea (2% versus 5%) in the Tuc+tras+cap and Pbo+tras+cap arms, respectively.

2. Cost effectiveness of tucatinib

Methods

A cost effectiveness model (CEM) (a four-state cohort-based partitioned survival model) was implemented to assess the cost-effectiveness of Tuc+tras+cap in comparison with the comparators of interest (Tras+cap, Tras+doublet, neratinib, Lap+cap and T-DM1) in the 3L setting. The four health states were informed by PFS, central nervous system-PFS, and OS data from the overall population of HER2CLIMB trial. All patients enter the model in the Progression-Free health state and receive either Tuc+tras+cap, Tras+cap, Trast+doublet, neratinib, Lap+cap and T-DM1. During each model cycle, patients may transition to the Progressed Disease (without CNS progression) health state, or the Progressed Disease (with CNS progression) health state or to the Death health state. Patients may transition from Progressed Disease (without CNS progression) to Progressed Disease (with CNS progression) or Death. Patients in Progressed Disease (with CNS progression) may transition to Death.

There is a lack of robust data to support the assumptions made by the Applicant regarding CNS progression and the CNS disutility estimates. These assumptions were used to inform the 'Progressed disease (with CNS progression)' health state. Therefore, a three-state model (removing the 'Progressed disease (with CNS progression)' health state) instead was implemented in the NCPE-adjusted base case. Utility data were sourced from the HER2CLIMB trial. There is an unquantifiable risk of bias associated with health state utilities implemented in the CEM, due to the high rate of missing utility data in the HER2CLIMB trial.

Results

The Review Group made several changes to the Applicant base case including updating the relative dose intensity of treatments, updating certain cost data and aligning the proportion of patients, who are assumed to receive subsequent treatments, to clinical opinion obtained by the Review Group. Results, of the resultant Applicant's base case, are presented in Table 1.

Table 1: Applicant base case incremental cost-effectiveness results (pairwise ICERs) [a, b, c]

Treatments	Total costs (€)	Total QALYs	Tuc+tras+cap vs		
			Incremental costs (€)	Incremental QALYs	Pairwise ICER (€/QALY)
Tuc+tras+cap	155,382	1.89	-	-	-
T-DM1	102,871	1.79	52,511	0.10	535,883
Tras+cap	64,789	1.43	90,593	0.46	197,461
Tras+doublets	71,358	1.43	84,024	0.46	183,144
Lap+cap	62,612	1.31	92,770	0.59	158,108
Neratinib	72,058	1.08	83,323	0.81	102,798

Tuc+tras+cap: Tucatinib, trastuzumab and capecitabine; **T-DM1**: trastuzumab emtansine; **Tras+cap:** Trastuzumab and capecitabine; **Lap+cap:** Lapatinib and capecitabine; **ICER:** incremental cost-effectiveness ratio; **PAS:** Patient Access Scheme**; QALY:** quality-adjusted life year

[a] Corresponding probabilistic ICERs s: vs T-DM1 (€659,943/QALY), vs Tras+cap (€190,239/QALY), vs Tras+doublet (€179,266/QALY), vs Lap+cap (€156,329/QALY), vs neratinib (€101,734/QALY).

[b] CIC PAS not included in this table

Total costs and QALYs presented are discounted (4%).

[C] Figures in the table are rounded; calculations may not be directly replicable.

The Review Group identified a number of further limitations in the Applicant's base case. Changes implemented in the NCPE adjusted base case included the choice of OS and PFS extrapolation curves, and the use of a three-state partitioned survival model (removing the

'Progressed disease (with CNS progression)' health state). The NCPE adjusted base case is presented in Table 2.

Table 2: NCPE adjusted base case incremental cost-effectiveness results[a, b, c]

Treatments	Total costs (€)	Total QALYs	Tuc+tras+cap vs		
			Incremental costs (€)	Incremental QALYs	Pairwise ICER (€/QALY)
Tuc+tras+cap	151,367	1.76	-	-	-
T-DM1	98,970	1.72	52,396	0.04	1,329,703
Tras+cap	60,650	1.40	90,717	0.36	253,882
Tras+doublet	67,220	1.40	84,146	0.36	235,494
Lap+cap	59,230	1.28	92,137	0.47	195,672
Neratinib	69,266	1.08	82,100	0.67	121,637

Tuc+tras+cap: Tucatinib, trastuzumab and capecitabine; **T-DM1**: trastuzumab emtansine; **Tras+cap:** Trastuzumab and capecitabine; **Lap+cap:** Lapatinib and capecitabine; **ICER:** incremental cost-effectiveness ratio; **PAS:** Patient Access Scheme**; PCT:** Physician's Choice of Treatment; **QALY:** quality-adjusted life year

[a] Corresponding probabilistic ICER using 5,000 iterations vs T-DM1 is €2,223,488/QALY. The corresponding probabilistic ICER using 1,000 simulations vs Tras+cap is €251,287/QALY, vs Tras+doublet is €233,250/QALY, vs Lap+cap is €199,974/QALY and vs neratinib is €121,635/QALY.

[b] CIC PAS not included in this table

Total costs and QALYs presented are discounted (4%).

[C] Figures in the table are rounded; calculations may not be directly replicable.

The Applicant and the NCPE adjusted base case probabilistic results are stable and similar to the deterministic results for all comparators except for T-DM1. The incremental QALY gain associated with Tuc+tras+cap versus T-DM1 is marginal, thus the ICER is unstable; it is very sensitive to minor changes in incremental costs.

Sensitivity analysis

A Price-ICER analysis was conducted to estimate the reductions in the price to wholesaler (PtW) of Tucatinib (expressed as a total rebate on the PtW) which would be required for Tuc+tras+cap to be considered cost effective. Analyses were conducted using the NCPE-adjusted base case. Price reductions from 72% to 97% would be required to achieve cost effectiveness at the €45,000 per QALY threshold versus all comparators excluding Tras+cap. It is not possible to achieve cost effectiveness versus Tras+cap at the €45,000 per QALY threshold. Given the marginal incremental QALY gain associated with Tuc+tras+cap versus T-DM1, the Price-ICER analysis for this comparison should be interpreted with caution.

3. Budget impact of tucatinib

The price-to-wholesaler of tucatinib 300mg tablets (88 tablets per pack) is €4,841. The estimated cost per patient, per year of treatment, with Tuc+tras+cap is €103,697 (including VAT). The Applicant estimates that there will be 107 patients with HER2-positive locally advanced or mBC who have received at least two prior anti-HER2 treatment regimens in the 3L setting. This number is potentially underestimated. The Applicant's budget impact analysis considered the use of tucatinib in the 3L HER2-positive mBC setting only. This is not reflective of licensed indication or international guidelines. The proportion of eligible patients expected to receive treatment with Tuc+tras+cap in the 3L setting was informed by clinical opinion obtained by the Applicant (11 patients in Year One, increasing to 34 patients in Year Five). There is considerable uncertainty associated with the Applicant's budget impact estimates. The Review Group made several amendments to the Applicant's budget impact estimates including an assumption of a relative dose intensity of 100% and corrections to the dosing for trastuzumab. Based on the NCPE-adjusted base case assumptions, the cumulative five-year gross and net drug budget impact (including VAT) of Tuc+tras+cap were €11.47 million and €7.43 million respectively. These estimates pertain to use in the 3L setting only.

4. Patient Organisation Submission

No patient organisation submissions were received during the course of the assessment.

5. Conclusion

The NCPE recommends that tucatinib not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments*.

*This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013