Tucatinib (Tukysa®) with trastuzumab and capecitabine for the treatment of HER2-positive locally advanced or metastatic breast cancer

General information [1]

Drug description	Indication
Tucatinib is an antineoplastic protein kinase inhibitor which inhibits HER2 kinase. This leads to inhibition of downstream cell signalling and cell proliferation and induces death in HER2-driven tumour cells.	Tucatinib is indicated 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 2 prior anti-HER2 treatment regimens.

Current treatment [2]

- The second line treatment of advanced HER2-positive breast cancer includes:
  - Trastuzumab emtansine is recommended, as an option for treating HER2-positive, unresectable, locally advanced or metastatic breast cancer in adults who previously received trastuzumab and a taxane, separately or in combination. Patients should have either received prior therapy for locally advanced or metastatic disease or developed disease recurrence during or within 6 months of completing adjuvant therapy.
- The third line treatment of advanced HER2-positive breast cancer includes:
  - Eribulin for treating locally advanced or metastatic breast cancer after 2 or more chemotherapy regimens.

Regulatory status

EMA [2]

Approval status for this indication: On 10 December 2020, the CHMP adopted a positive opinion, recommending the granting of a marketing authorisation for Tukysa®.

UPDATE: Date of issue of marketing authorisation valid throughout the European Union: 11/02/2021

The full indication is:

- Tukysa® is indicated 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 2 prior anti-HER2 treatment regimens.

Other indications: none

✓ Medicine under additional monitoring

FDA [3]

Approval status for this indication: On 17 April 2020, the FDA approved Tukysa® in combination with trastuzumab and capecitabine, for adult patients with 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.

Other indications: none

✓ **Orphan drug**,
✓ **Fast track**, and
✓ **Breakthrough therapy designation**

Costs

84 Tukysa® tablets 150 mg = € 6,498.00 (ex-factory price) [4]
HER2CLIMB trial patients of the tucatinib-combination group received tucatinib at a dose of 300 mg orally twice daily [5].

Study characteristics [5-8]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
HER2CLIMB NCT02614794	Total trial population: n=612 Primary endpoint-population: n=480	tucatinib (300 mg orally twice daily) in combination with trastuzumab (6 mg/kg of body weight IV once every 21 days, with an initial loading dose of 8 mg/kg; subcutaneous administration was allowed) and capecitabine (1000 mg/m² of BSA orally twice daily on days 1 to 14 of each 21-day cycle)	Placebo (orally twice daily) in combination with trastuzumab (6 mg/kg of body weight IV once every 21 days, with an initial loading dose of 8 mg/kg; subcutaneous administration was allowed) and capecitabine (1000 mg/m² of BSA orally twice daily on days 1 to 14 of each 21-day cycle)	PFS among the first 480 patients who underwent randomization	international, randomized, double-blind, phase II trial	HER2	Seattle Genetics	Link

Efficacy (I vs. C)	Safety (I vs. C)
Efficacy in the primary endpoint population **Estimated PFS at 1 year**: 33.1% (95% CI 26.6-39.7) vs. 12.3% (95% CI, 6.0-20.9) **Median duration of PFS** was 7.8 months (95% CI, 7.5-9.6) vs. 5.6 months (95% CI, 4.2-7.1) **Risk of disease progression or death,** as assessed by means of BICR in the primary endpoint analysis population: 46% lower I vs. C, HR 0.54 (95% CI, 0.42-0.71; p<0.001) **Efficacy in the total trial population** **Estimated OS at 2 years**: 44.9% (95% CI, 36.6-52.8) vs. 26.6% (95% CI, 15.7-38.7) **Median duration of OS**: 21.9 months (95% CI, 18.3-31.0) vs. 17.4 months (95% CI, 13.6-19.9) **Risk of death** was 34% lower in I than in C, HR 0.66 (95% CI, 0.50-0.88; p=0.005) **Estimated PFS at 1 year among the patients with brain metastases:** 24.9% (95% CI, 16.5-34.3) vs. 0% **Median duration of PFS**: 7.6 months (95% CI, 6.2-9.5) vs. 5.4 months (95% CI, 4.1-5.7) **Risk of disease progression or death** was 52% lower in I than in C, HR 0.48 (95% CI, 0.34-0.69, p<0.001) **Risk of disease progression or death in a pre-specified analysis involving the patients without brain metastases**: 43% lower in I than in C, HR 0.57 (95% CI, 0.41-0.80) **Confirmed objective response** among the 511 patients with measurable disease at baseline (as assessed by means of BICR): 40.6% (95% CI, 35.3-46.0) vs. 22.8% (95% CI, 16.7-29.8; p<0.001), CR=0.9% vs. 1.2%; PR=39.7% vs. 21.6% HRQoL analysis [9]: ❖ In HER2CLIMB, data from 217 patients on the tucatinib arm and 113 patients on the placebo arm were available for HRQoL analyses. ❖ In all 5 EQ-5D-5L domains, most patients in both arms reported only slight or no problems. ❖ Reported moderate, severe, or extreme problems were low and similar between treatment arms. ❖ No clinically meaningful differences in HRQoL were observed between treatment arms. ❖ Mean EQ-5D-5L VAS scores were similar between treatment arms and stable throughout duration of therapy. ❖ Decline on EQ-5D-5L domains and VAS scores were not seen while patients were on therapy. ❖ In conclusion, QoL in patients treated with tucatinib + trastuzumab + capecitabin was maintained throughout the treatment period which was longer compared to patients receiving only trastuzumab + capecitabine.	**Grade ≥3 AEs**: n=223/404 (55.2%) vs. n=96/197 (48.7%) **Death[1]:** n=6/404 (1.5%) vs. n=5/197 (2.5%) **Discontinuation[2]:** n=23/404 (5.7%) vs. n=6/197 (3.0%)

ESMO-MCBS version 1.1

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	2a	>12m ≤24m	OS: +4.5 m	HR 0.66 (0.50-0.88)	HR≤0.70 AND gain ≥3-<5 m	3	-	ND	-	3
Adapted	NC	2a	>12m ≤24m	OS: +4.5 m	HR 0.66 (0.50-0.88)	HR≤0.70 AND gain ≥3-<5 m	3	+6.5% grade ≥3 AEs, +2.7% discontinuation	ND	-	3

Risk of bias (study level)

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
yes	unclear	yes	unclear[3]	yes[4]	unclear

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Abbreviations: AE=adverse event, AJ=adjustment, BICR= blinded independent central review, C=comparator, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CR=complete response, EMA=European Medicines Agency,ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, HER2=human epidermal growth factor receptor 2,

[1] Death due to AE(s); I: cardiac arrest, cardiac failure, dehydration, multiple organ dysfunction syndrome, sepsis, and septic shock in 1 patient each; C: cardiac arrest, multiple-organ dysfunction syndrome, myocardial infarction, sepsis, and systemic inflammatory response syndrome in 1 patient each.
[2] Discontinuation due to AE(s)
[3] HRQoL not reported; HER2CLIMB trial is ongoing until 05/2022
[4] The steering committee and representatives of the sponsor designed the trial. The authors wrote the manuscript with the assistance of a medical writer funded by the sponsor.

HR=hazard ratio, HRQoL=health-related quality of life, I=intervention, Int.=intention, m=months, MG=median gain, n=number of patients, NA=not available, ND=no difference, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, PR=partial response, HRQoL=health-related quality of life, SAE=serious adverse event, ST=standard treatment, VAS=visual analog scale

References:

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