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Tucatinib (breast cancer) –

Addendum to Commission A21-26[1]

Addendum

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List of abbreviations

Abbreviation	Meaning
AE	adverse event
CTCAE	Common Terminology Criteria for Adverse Events
EQ-5D	European Quality of Life Questionnaire – 5 Dimensions
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HER2	human epidermal growth factor 2
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MMRM	mixed effect model repeated measurement
PT	preferred term
RCT	randomized controlled trial
SAE	serious adverse events
SOC	system organ class
VAS	visual analogue scale

1 Background

On 27 July 2021, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A21-26 (Tucatinib – Benefit assessment according to § 35a Social Code Book V) [1].

In its dossier [2], the pharmaceutical company (hereinafter "company") presented the HER2CLIMB study for the direct comparison of tucatinib + trastuzumab + capecitabine versus placebo + trastuzumab + capecitabine. The HER2CLIMB study does not allow a comparison with the G-BA's appropriate comparator therapy and was therefore not used for the benefit assessment.

The G-BA commissioned IQWiG with assessing both the HER2CLIMB study and the analyses submitted by the company in the commenting procedure [3], taking into account the information in the dossier.

The responsibility for the present assessment and the assessment result lies exclusively with IQWiG. The assessment is sent to the G-BA. The G-BA decides on the added benefit.

2 Assessment

Below, the HER2CLIMB study [4-8] is assessed. The HER2CLIMB study is a randomized controlled trial (RCT) comparing tucatinib + trastuzumab + capecitabine versus placebo + trastuzumab + capecitabine in adult patients with human epidermal growth factor 2 (HER2) positive, locally advanced or metastatic breast cancer who previously received at least 2 anti-HER2 therapy regimens.

2.1 Study and patient characteristics

Data on study, intervention, and patient characteristics as well as on the planned duration of follow-up observation, the course of the study, and subsequent therapies are presented in dossier assessment A21-26 [1].

Data cut-off dates

A total of 4 data cut-offs are available for the HER2CLIMB study:

- 1st data cut-off 4 September 2019: analysis of the primary outcome of progression-free survival predefined in the study protocol
- 2nd data cut-off 8 November 2019: unplanned analysis of safety outcomes upon request by the European Medicines Agency
- 3rd data cut-off 29 May 2020: unplanned analysis of safety outcomes upon request by the European Medicines Agency
- 4th data cut-off 8 February 2021: final analysis of overall survival after about 361 events as predefined in the statistical analysis plan

For the assessment of the HER2CLIMB study, only the 1st data cut-off on 4 September 2019 was used since complete analyses were available only for this data cut-off. Analyses for the 2nd data-cut off on 8 November 2019 are not presented in the company's dossier. For the 3rd data cut-off on 29 May 2020, the company's dossier presents analyses only of adverse events (AEs). The analyses on the 4th data cut-off on 8 February 2021, which the company submitted with its comment, lack results on total rates of AEs without progression events, specific AEs, subgroup analyses on AEs as well as Kaplan-Meier curves for time-to-event analyses.

2.2 Results

Outcomes included

The following patient-relevant outcomes were to be included in the assessment:

- Mortality
  - Overall survival
- Morbidity
  - Health status recorded with the visual analogue scale (VAS) of the European Quality of Life Questionnaire – 5 Dimensions (EQ-5D)
- Side effects
  - SAEs
  - Severe AEs (operationalized as Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)
  - Discontinuation due to AEs (discontinuation of at least 1 drug component)
  - Further specific AEs, if any

Table 1 shows the outcomes of the HER2CLIMB study for which data were available.

Table 1: Matrix of outcomes – RCT, direct comparison: tucatinib + trastuzumab + capecitabine vs. placebo + trastuzumab + capecitabine

Study	Outcomes						
	Overall survival	Health status (EQ-5D VAS)	Health-related quality of life	SAEs	Severe AEs[a]	Discontinuation due to AEs	Specific AEs[a, b]
HER2CLIMB	Yes	No[c]	No[d]	Yes	Yes	Yes	Yes

a. Severe AEs are operationalized as CTCAE grade ≥ 3.
b. The following events are considered (MedDRA coding): "gastrointestinal disorders" (SOC, AEs), "diarrhoea" (PT, AEs), "alanine aminotransferase increased" (PT, severe AEs), "aspartate aminotransferase increased" (PT, severe AEs), and "dyspnoea" (PT, severe AEs).
c. No usable data available; see Section 2.2 of this addendum for the reasoning.
d. Outcome not recorded.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life Questionnaire – 5 Dimensions; MedDRA: Medical Dictionary for Regulatory Activities; PT: preferred term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: system organ class; VAS: visual analogue scale

- Health status (EQ-5D VAS): In the HER2CLIMB study, the EQ-5D instrument was surveyed only starting from version 7 of the study protocol (30 August 2017). At that point, about half of the study's patients had already been included. The analyses presented by the company on the outcome of health status (EQ-5D VAS) therefore cover only patients included in the study under protocol version 7 or later. These analyses comprise 217 patients in the intervention arm (52.9%) and 112 patients in the comparator arm (55.4%) Since absence from the analyses is based only on the time of study inclusion rather than other observed values, this exclusion of patients who joined the HER2CLIMB study prior to protocol version 7 generally does not bias results. Presumably, the populations randomized before protocol version 7 do not materially differ from those randomized from version 7 onward. The results for the outcome of health status are therefore transferable to the entire study population and are generally relevant for the assessment.

  For the outcome of health status, the company submitted responder analyses for time to initial deterioration by ≥ 7 or ≥ 10 points (scale range EQ-5D VAS: 0 to 100 points). However, these analyses were not used. As discussed in the IQWiG General Methods [9,10], a response criterion should be predefined to cover at least 15% of the range of an instrument's scale (for post hoc analyses, exactly 15% of the range of the scale) in order to reflect with sufficient certainty a change that is perceivable for patients. The results for the submitted responder analyses are presented as supplementary information in Appendix C. In addition, the company presented a mixed effect model repeated measurement (MMRM) analysis. This analysis was also disregarded because it lacked relevant information on methods. For instance, the documents fail to show how many patients were included for calculating the effect estimator or how the analysis dealt with the visit after treatment discontinuation. Irrespective of the described ambiguities, the MMRM analysis submitted by the company did not show any statistically significant difference between treatment groups (mean difference: -0.5; 95% CI: [-3.1; 2.1]).

Risk of bias and certainty of results

The risk of bias across outcomes was rated as low for the HER2CLIMB study. For the results of the outcome of all-cause mortality, the risk of bias is rated as low. Except for the outcome of treatment discontinuation due to AEs, all side effects outcomes have a high risk of bias of results due to differing treatment and follow-up durations with potentially informative censoring. While the risk of bias for the outcome of discontinuation due to AEs is low, the certainty of results is limited for this outcome. Premature treatment discontinuation for reasons other than AEs represents a competing event for the outcome of interest, discontinuation due to AEs. This means that while AEs that would have led to treatment discontinuation might occur after discontinuation for other reasons, it is no longer possible to survey the criterion of "discontinuation" for them. It is impossible to estimate how many AEs are affected by this issue. Therefore, the certainty of results of all side effects outcomes is limited.

Results

Table 2 summarizes the results of the comparison of tucatinib + trastuzumab + capecitabine versus placebo + trastuzumab + capecitabine in adult patients with HER2-positive, locally advanced or metastatic breast cancer who previously received at least 2 anti-HER2 therapy regimens.

Kaplan-Meier curves relating to the event-time analyses are found in Appendix A. Tables on common AEs, serious adverse events (SAEs), severe AEs (CTCAE grade ≥ 3), and discontinuation due to AEs are presented in Appendix B.

Table 2: Results (mortality, AEs) – RCT, direct comparison: tucatinib + trastuzumab + capecitabine vs. placebo + trastuzumab + capecitabine (multipage table)

Study **Outcome category** **Outcome**	**Tucatinib + trastuzumab + capecitabine**		**Placebo + trastuzumab + capecitabine**		**Tucatinib + trastuzumab + capecitabine vs. Placebo + trastuzumab + capecitabine**
	N	**Median time to event in months/days [95% CI]** **Patients with event n (%)**	**N**	**Median time to event in months [95% CI]** **Patients with event n (%)**	**HR [95% CI]; p-value[a]**
HER2CLIMB[b]					
Mortality					
Overall survival	410	21.9 [18.3; 31.0] 130 (31.7)	202	17.4 [13.6; 19.9] 85 (42.1)	0.66 [0.50; 0.88]; 0.005
Morbidity	No usable data[c]				
Health-related quality of life	No outcomes surveyed in this category				
Side effects					
AEs (supplementary information)[d]	404	0.13 [0.13; 0.16][e] 401 (99.3)	197	0.26 [0.20; 0.33][e] 191 (97.0)	–
SAEs[d]	404	30.94 [21.39; NC][e] 104 (25.7)	197	NR [11.04; NC][e] 53 (26.9)	0.81 [0.58; 1.14]; 0.232
Severe AEs[d, f]	404	4.80 [3.55; 7.98][e] 223 (55.2)	197	9.03 [4.14; 10.45][e] 96 (48.7)	1.10 [0.87; 1.41]; 0.427
Discontinuation due to AEs[g]	404	NR 45 (11.1)	197	18.20 [16.26; NC][e] 19 (9.6)	0.95 [0.55; 1.64]; 0.846
Gastrointestinal disorders (SOC, AEs)	404	0.23 [0.20; 0.26][e] 382 (94.6)	197	0.49 [0.43; 0.72][e] 162 (82.2)	1.91 [1.57; 2.31]; < 0.001
Diarrhoea (PT, AEs)	404	0.49 [0.43; 0.53][e] 327 (80.9)	197	3.48 [2.14; 6.01][e] 105 (53.3)	2.39 [1.92; 2.99]; < 0.001
Alanine aminotransferase increased (PT, severe AEs[f])	404	NR 22 (5.4)	197	NR 1 (0.5)	10.62 [1.43; 78.79]; 0.021[h]
Aspartate aminotransferase increased (PT, severe AEs[f])	404	NR 18 (4.5)	197	NR 1 (0.5)	8.81 [1.18; 65.94]; 0.034[h]
Dyspnoea (PT, severe AEs[f])	404	NR 7 (1.7)	197	NR 10 (5.1)	0.31 [0.12; 0.83]; 0.019[h]

Table 2: Results (mortality, AEs) – RCT, direct comparison: tucatinib + trastuzumab + capecitabine vs. placebo + trastuzumab + capecitabine (multipage table)

Study Outcome category Outcome	Tucatinib + trastuzumab + capecitabine		Placebo + trastuzumab + capecitabine		Tucatinib + trastuzumab + capecitabine vs. Placebo + trastuzumab + capecitabine
	N	Median time to event in months/days [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[a]

a. HR and CI: Cox proportional hazards model; p-value: log rank test; each stratified by brain metastases at study start (yes vs. no), ECOG-PS (0 vs. 1), and region (North America vs. rest of the world).
b. First data cut-off (4/09/2019).
c. See Section 2.2 of this addendum for the reasoning.
d. AEs excluding the events the company deemed to be due to progression of the underlying condition (not included are the PTs "cancer pain", "tumour pain", "malignant pleural effusion", and "tumour thrombosis" from the SOC "neoplasms benign, malignant, and unspecified [incl. cysts and polyps]").
e. IQWiG calculation.
f. Operationalized as CTCAE grade ≥ 3.
g. Discontinuation of ≥ 1 drug component(s).
h. Without stratification factors.

CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; HR: hazard ratio; n: number of patients with (at least 1) event; N: number of analysed patients; NC: not calculable; NR: not reached; PT: preferred term; RCT: randomized controlled trial; SOC: system organ class

Mortality

Overall survival

For the outcome of overall survival, a statistically significant difference in favour of tucatinib + trastuzumab + capecitabine versus placebo + trastuzumab + capecitabine was found.

Health-related quality of life

The HER2CLIMB study did not survey health-related quality of life. This results in no advantage or disadvantage of tucatinib + trastuzumab + capecitabine versus placebo + trastuzumab + capecitabine.

Side effects

SAEs, severe AEs (CTCAE grade ≥ 3), discontinuation due to AEs (discontinuation of at least 1 drug component)

No statistically significant difference between tucatinib + trastuzumab + capecitabine versus placebo + trastuzumab + capecitabine was found for any of the outcomes of SAEs, severe AEs (CTCAE ≥ grade 3), or discontinuation due to AEs.

Specific AEs

For each of the outcomes of gastrointestinal disorders (system organ class [SOC], AEs) and its component outcome of diarrhoea (preferred term [PT], AEs) as well as for the outcomes of alanine aminotransferase increased (PT, severe AEs [CTCAE grade ≥ 3]), and aspartate aminotransferase increased (PT, severe AEs [CTCAE grade ≥ 3]), there is a statistically significant difference to the disadvantage of tucatinib + trastuzumab + capecitabine in comparison with placebo + trastuzumab + capecitabine.

For the outcome of dyspnoea (PT, severe AEs [CTCAE grade ≥ 3]), a statistically significant difference in favour of tucatinib + trastuzumab + capecitabine versus placebo + trastuzumab + capecitabine was found.

2.2.1 Subgroups and other effect modifiers

For this assessment, the following potential effect modifiers were taken into account:

- Age (< 65 vs. ≥ 65 years)
- Brain metastases at baseline (yes versus no)

Interaction tests were performed whenever at least 10 patients per subgroup were included in the analysis. For binary data, there must also be 10 events in at least 1 subgroup.

Only results showing an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are presented only if there is a statistically significant and relevant effect in at least one subgroup.

Side effects

Specific AEs

For the outcomes of gastrointestinal disorders (SOC, AEs) as well as its component outcome of diarrhoea (PT, AEs), a statistically significant effect modification by the attribute of age was found (< 65 years versus ≥ 65 years). However, both age groups show a disadvantage of tucatinib + trastuzumab + capecitabine versus placebo + trastuzumab + capecitabine. Despite a statistically significant interaction, the presentation of isolated subgroup results was therefore foregone.

2.3 Summary

In summary, the HER2CLIMB study furnishes the following results for tucatinib + trastuzumab + capecitabine versus placebo + trastuzumab + capecitabine:

- Advantages in the outcomes of overall survival and dyspnoea (PT, AE)
- Disadvantages in the outcomes of gastrointestinal disorders (SOC, AEs) and its component outcome of diarrhoea (PT, AEs) as well as alanine aminotransferase increased

(PT, severe AEs [CTCAE grade ≥ 3]) and aspartate aminotransferase increased (PT, severe AEs [CTCAE grade ≥ 3])

The G-BA decides on the added benefit.

3 References

The list of references contains citations by the company which may lack some bibliographic information.

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Appendix A – Kaplan-Meier curves

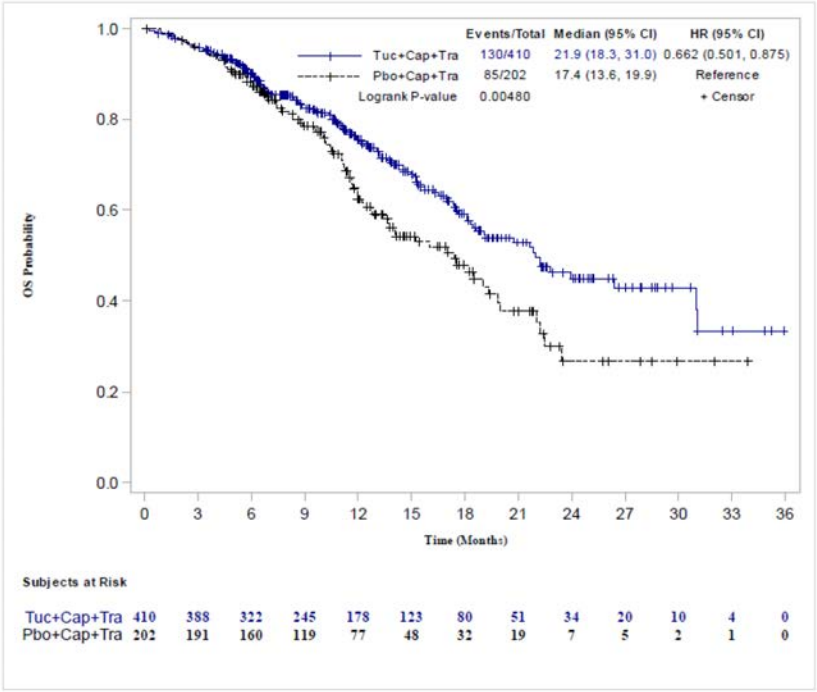

Figure 1: Kaplan-Meier curves on the outcome of overall survival in the HER2CLIMB study (1st data cut-off of 4 September 2019)

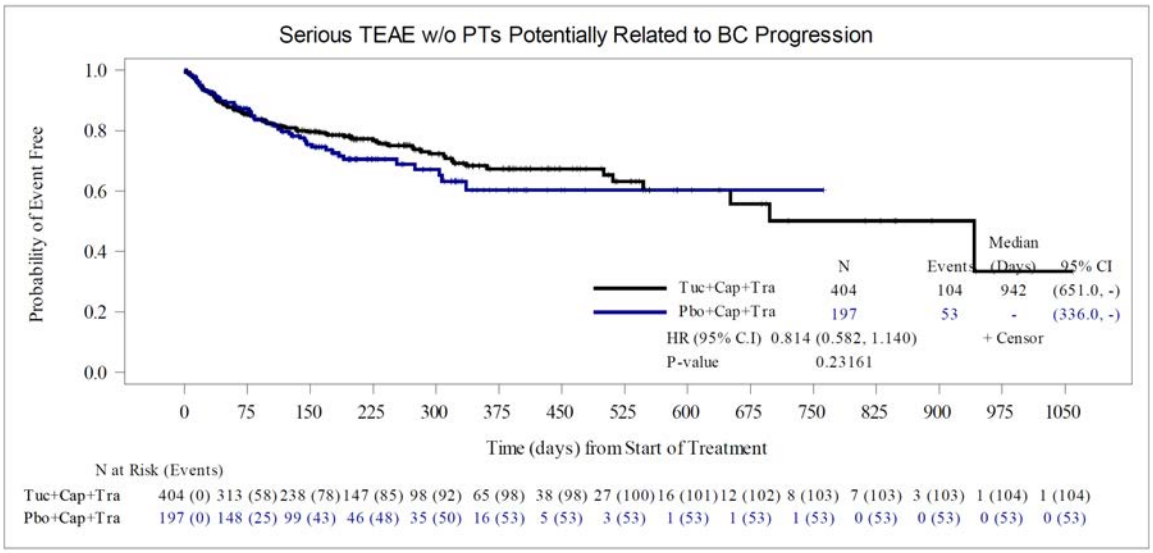

Figure 2: Kaplan-Meier curves on the outcome of SAEs (without progression events) in the HER2CLIMB study (1st data cut-off of 4 September 2019)

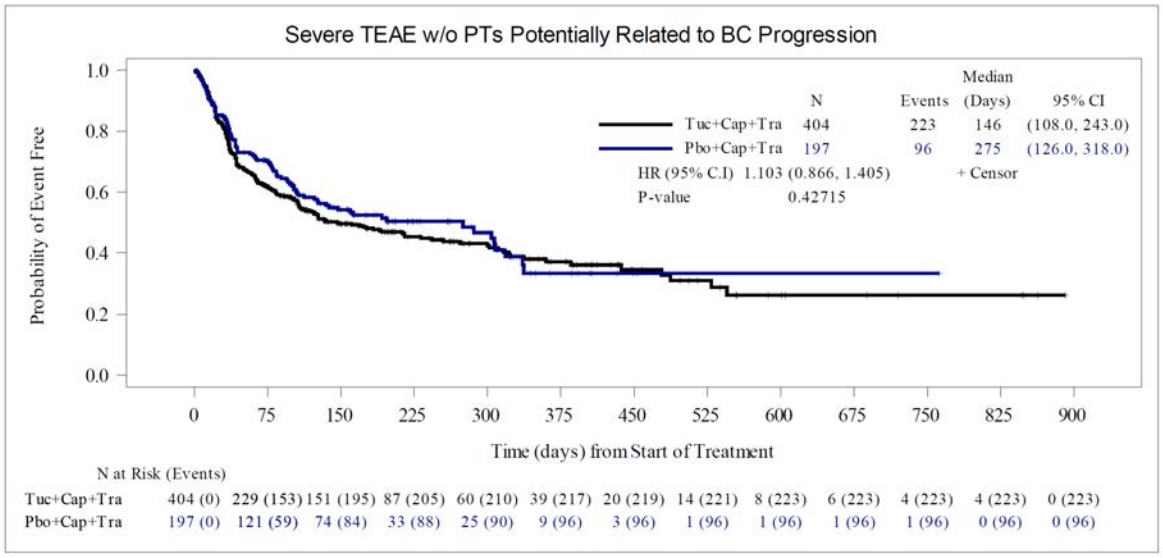

Figure 3: Kaplan-Meier curves on the outcome of severe AEs (CTCAE grade ≥ 3 [without progression events]) in the HER2CLIMB study (1st data cut-off of 4 September 2019)

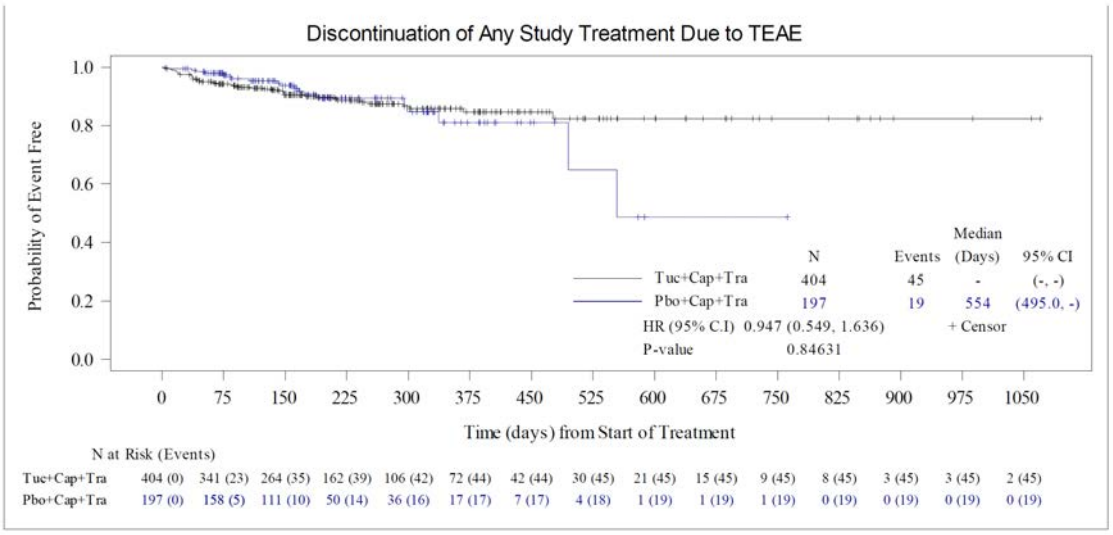

Figure 4: Kaplan-Meier curves on the outcome of discontinuation due to AEs (≥ 1 drug component) in the HER2CLIMB study (1st data cut-off of 4 September 2019)

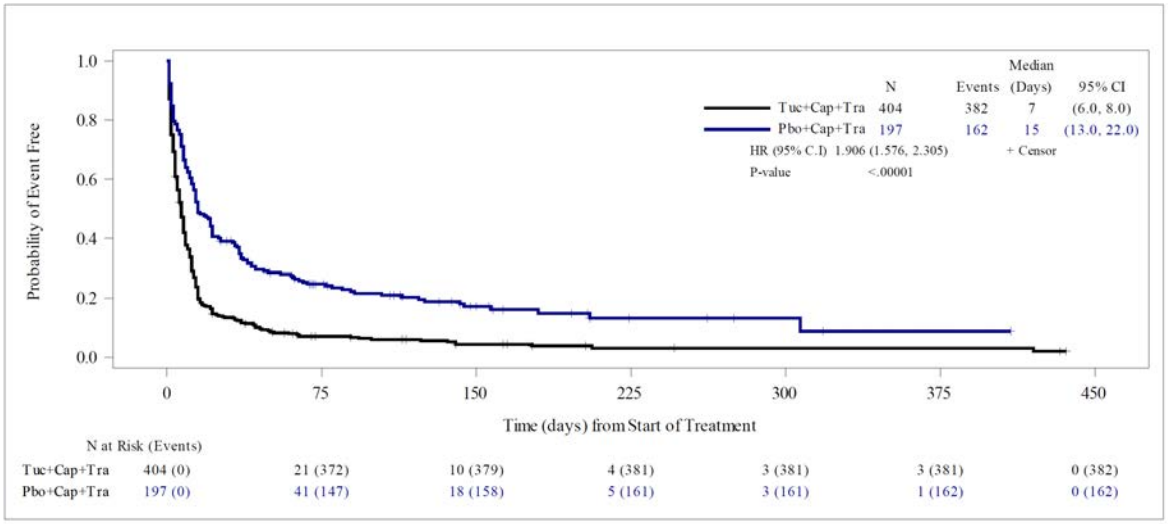

Figure 5: Kaplan-Meier curves on the outcome of gastrointestinal disorders (SOC) in the HER2CLIMB study (1st data cut-off of 4 September 2019)

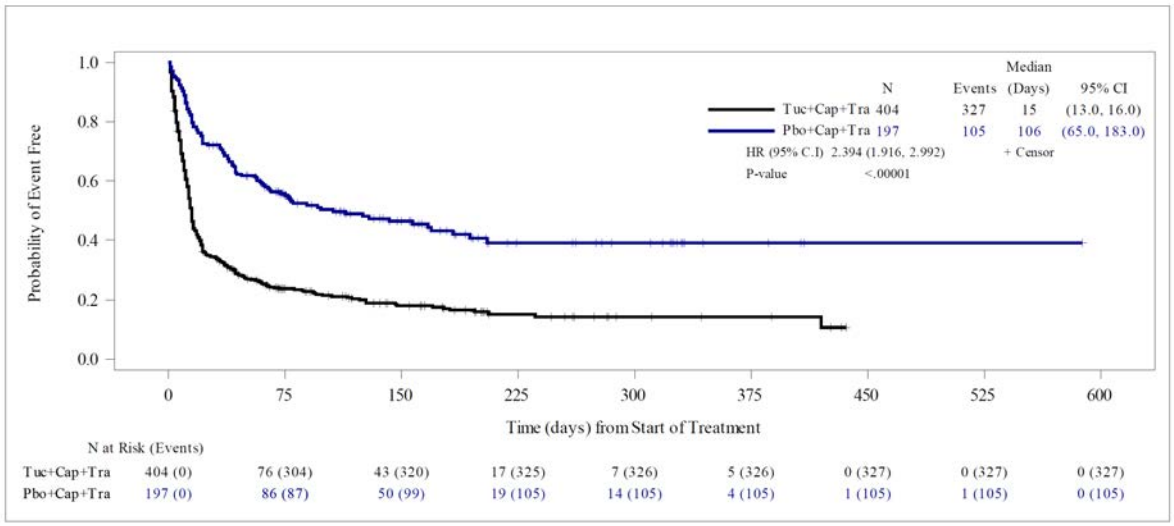

Figure 6: Kaplan-Meier curves on the outcome of diarrhoea (PT) in the HER2CLIMB study (1st data cut-off of 4 September 2019)

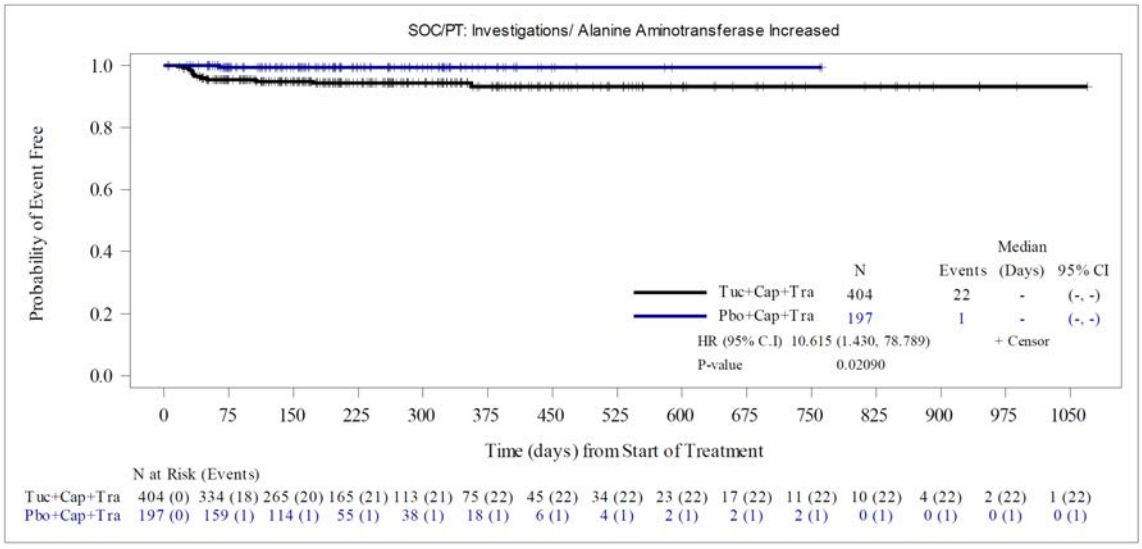

Figure 7: Kaplan-Meier curves on the outcome of alanine aminotransferase increased (PT, CTCAE grade ≥ 3) in the HER2CLIMB study (1st data cut-off of 4 September 2019)

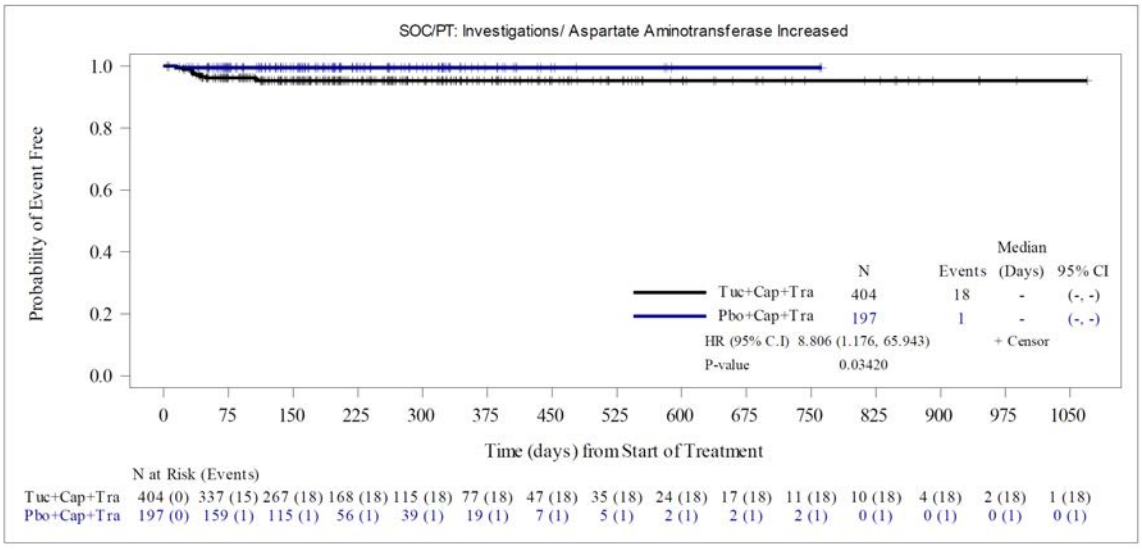

Figure 8: Kaplan-Meier curves on the outcome of aspartate aminotransferase increased (PT, CTCAE grade ≥ 3) in the HER2CLIMB study (1st data cut-off of 4 September 2019)

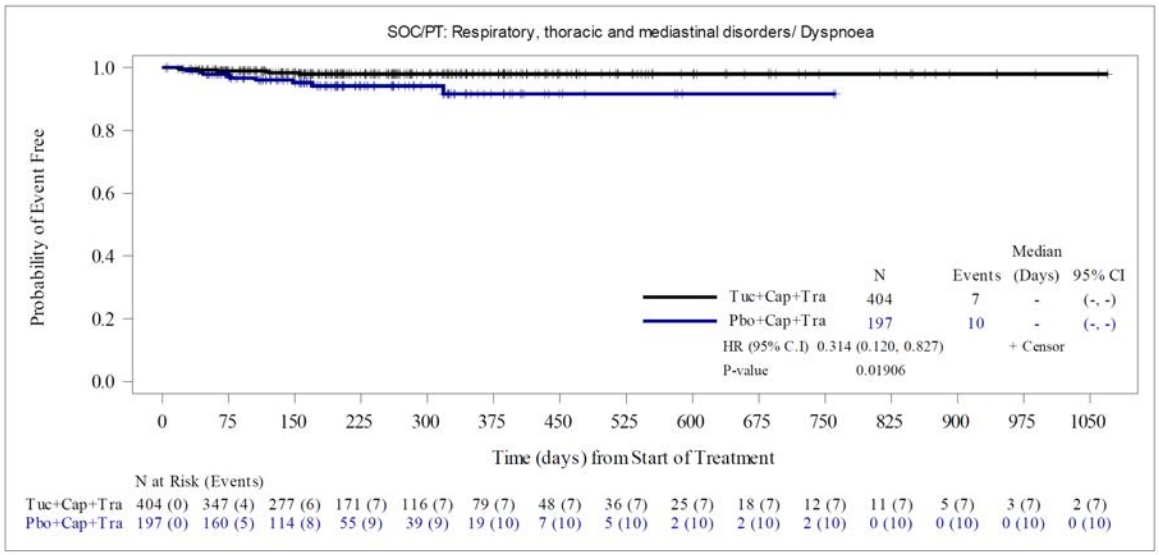

Figure 9: Kaplan-Meier curves on the outcome of dyspnoea (PT, CTCAE grade ≥ 3) in the HER2CLIMB study (1st data cut-off of 4 September 2019)

Appendix B Results on side effects

Regarding the total rates of AEs, SAEs, and severe AE (CTCAE grade ≥ 3), the tables below present events for SOCs and PTs as per Medical Dictionary for Regulatory Activities (MedDRA), each on the basis of the following criteria:

- Total rate of AEs (any severity): events which occurred in at least 10% of patients in 1 study arm
- Total rates of severe AEs (CTCAE grade ≥ 3) and SAEs: events which occurred in at least 5% of patients in 1 study arm
- Additionally, for all events of any severity: events which occurred in at least 10 patients and in at least 1% of patients in 1 study arm

For the outcome of discontinuation due to AEs, all events (SOCs/PTs) which led to discontinuation are presented.

Table 3: Common AEs[a] – RCT, direct comparison: tucatinib + trastuzumab + capecitabine vs. placebo + trastuzumab + capecitabine (multipage table)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Tucatinib + trastuzumab + capecitabine N = 404**	**Placebo + trastuzumab + capecitabine N = 197**
HER2CLIMB[c]		
Total rate of AEs[d]	401 (99.3)	191 (97.0)
Gastrointestinal disorders	382 (94.6)	162 (82.2)
Diarrhoea	327 (80.9)	105 (53.3)
Nausea	236 (58.4)	86 (43.7)
Vomiting	145 (35.9)	50 (25.4)
Stomatitis	103 (25.5)	28 (14.2)
Abdominal pain	59 (14.6)	31 (15.7)
Constipation	59 (14.6)	39 (19.8)
Dyspepsia	43 (10.6)	19 (9.6)
Upper abdominal pain	29 (7.2)	18 (9.1)
Gastro-oesophageal reflux disease	23 (5.7)	6 (3.0)
Abdominal distension	22 (5.4)	9 (4.6)
Dry mouth	21 (5.2)	5 (2.5)
Flatulence	15 (3.7)	6 (3.0)
Haemorrhoids	11 (2.7)	1 (0.5)
Mouth ulcers	10 (2.5)	4 (2.0)
Diseases of the skin and subcutaneous tissue	306 (75.7)	142 (72.1)
Palmar-plantar erythrodysaesthesia syndrome	256 (63.4)	104 (52.8)
Dry skin	38 (9.4)	18 (9.1)
Skin hyperpigmentation	34 (8.4)	11 (5.6)
Maculopapular rash	27 (6.7)	10 (5.1)
Pruritus	23 (5.7)	12 (6.1)
Alopecia	19 (4.7)	7 (3.6)
Onychomadesis	17 (4.2)	4 (2.0)
Acneiform dermatitis	12 (3.0)	3 (1.5)
Onychoclasis	11 (2.7)	6 (3.0)
Rash	11 (2.7)	7 (3.6)
Erythema	10 (2.5)	5 (2.5)
General disorders and administration site conditions	252 (62.4)	120 (60.9)
Fatigue	182 (45.0)	85 (43.1)
Peripheral oedema	42 (10.4)	20 (10.2)
Asthenia	29 (7.2)	15 (7.6)
Fever	21 (5.2)	8 (4.1)
Chills	16 (4.0)	9 (4.6)
Influenza-like illness	16 (4.0)	5 (2.5)
Non-cardiac chest pain	15 (3.7)	3 (1.5)
Investigations	241 (59.7)	71 (36.0)

Table 3: Common AEs[a] – RCT, direct comparison: tucatinib + trastuzumab + capecitabine vs. placebo + trastuzumab + capecitabine (multipage table)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Tucatinib + trastuzumab + capecitabine N = 404**	**Placebo + trastuzumab + capecitabine N = 197**
Aspartate aminotransferase increased	86 (21.3)	22 (11.2)
Alanine aminotransferase increased	81 (20.0)	13 (6.6)
Blood bilirubin increased	75 (18.6)	20 (10.2)
Blood creatinine increased	56 (13.9)	3 (1.5)
Weight decreased	54 (13.4)	11 (5.6)
Blood alkaline phosphatase increased	25 (6.2)	6 (3.0)
Low platelet count	19 (4.7)	5 (2.5)
Decreased neutrophil count	18 (4.5)	5 (2.5)
Decreased leukocyte count	18 (4.5)	10 (5.1)
Decreased platelet count	11 (2.7)	7 (3.6)
Infections and infestations	206 (51.0)	80 (40.6)
Urinary tract infection	43 (10.6)	15 (7.6)
Upper respiratory tract infection	38 (9.4)	15 (7.6)
Nasopharyngitis	20 (5.0)	12 (6.1)
Paronychia	20 (5.0)	3 (1.5)
Nail infection	13 (3.2)	3 (1.5)
Sinusitis	13 (3.2)	6 (3.0)
Localized infection	11 (2.7)	2 (1.0)
Oral herpes	11 (2.7)	3 (1.5)
Metabolic and nutritional disorders	204 (50.5)	71 (36.0)
Decreased appetite	100 (24.8)	39 (19.8)
Hypokalaemia	64 (15.8)	24 (12.2)
Hypomagnesaemia	35 (8.7)	9 (4.6)
Dehydration	31 (7.7)	10 (5.1)
Hypophosphataemia	25 (6.2)	10 (5.1)
Hyperglycaemia	23 (5.7)	3 (1.5)
Hyponatraemia	16 (4.0)	6 (3.0)
Hypocalcaemia	13 (3.2)	8 (4.1)
Nervous system disorders	191 (47.3)	86 (43.7)
Headache	87 (21.5)	40 (20.3)
Peripheral sensory neuropathy	47 (11.6)	12 (6.1)
Dizziness	45 (11.1)	27 (13.7)
Dysgeusia	30 (7.4)	5 (2.5)
Paraesthesia	20 (5.0)	8 (4.1)
Seizure	11 (2.7)	2 (1.0)

Table 3: Common AEs[a] – RCT, direct comparison: tucatinib + trastuzumab + capecitabine vs. placebo + trastuzumab + capecitabine (multipage table)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Tucatinib + trastuzumab + capecitabine N = 404**	**Placebo + trastuzumab + capecitabine N = 197**
Musculoskeletal and connective tissue disorders	183 (45.3)	67 (34.0)
Arthralgia	59 (14.6)	9 (4.6)
Back pain	45 (11.1)	23 (11.7)
Pain in the extremities	42 (10.4)	17 (8.6)
Muscular spasms	38 (9.4)	5 (2.5)
Myalgia	26 (6.4)	9 (4.6)
Muscular weakness	17 (4.2)	7 (3.6)
Musculoskeletal pain	17 (4.2)	7 (3.6)
Bone pain	16 (4.0)	3 (1.5)
Musculoskeletal chest pain	15 (3.7)	7 (3.6)
Neck pain	11 (2.7)	3 (1.5)
Respiratory, thoracic, and mediastinal disorders	171 (42.3)	73 (37.1)
Cough	57 (14.1)	23 (11.7)
Dyspnoea	48 (11.9)	23 (11.7)
Epistaxis	47 (11.6)	10 (5.1)
Oropharyngeal pain	25 (6.2)	8 (4.1)
Rhinorrhoea	21 (5.2)	5 (2.5)
Nasal congestion	16 (4.0)	6 (3.0)
Pulmonary embolism	13 (3.2)	5 (2.5)
Pleural effusion	10 (2.5)	11 (5.6)
Disorders of the blood and lymphatic system	119 (29.5)	48 (24.4)
Anaemia	80 (19.8)	23 (11.7)
Neutropenia	32 (7.9)	17 (8.6)
Thrombocytopenia	25 (6.2)	11 (5.6)
Leukopoenia	10 (2.5)	7 (3.6)
Injury, poisoning, and procedural complications	70 (17.3)	27 (13.7)
Fall	24 (5.9)	8 (4.1)
Psychiatric disorders	69 (17.1)	37 (18.8)
Insomnia	33 (8.2)	17 (8.6)
Depression	17 (4.2)	1 (0.5)
Anxiety	10 (2.5)	9 (4.6)
Eye disorders	65 (16.1)	31 (15.7)
Dry eye	22 (5.4)	9 (4.6)
Blurred vision	13 (3.2)	8 (4.1)
Increased tear secretion	12 (3.0)	5 (2.5)

Table 3: Common AEs[a] – RCT, direct comparison: tucatinib + trastuzumab + capecitabine vs. placebo + trastuzumab + capecitabine (multipage table)

Study	**Patients with event n (%)**	
SOC[b] PT[b]	**Tucatinib + trastuzumab + capecitabine N = 404**	**Placebo + trastuzumab + capecitabine N = 197**
Vascular disease	64 (15.8)	21 (10.7)
Hypertension	18 (4.5)	9 (4.6)
Hot flash	17 (4.2)	6 (3.0)
Hypotension	10 (2.5)	1 (0.5)
Hepatobiliary disorders	41 (10.1)	12 (6.1)
Hyperbilirubinaemia	26 (6.4)	8 (4.1)
Renal and urinary disorders	40 (9.9)	9 (4.6)
Reproductive system and breast disorders	30 (7.4)	11 (5.6)
Heart disease	24 (5.9)	15 (7.6)
Disorders of the ear and labyrinth	21 (5.2)	12 (6.1)
Immune system disorders	12 (3.0)	6 (3.0)
Benign, malignant, and unspecified neoplasms (incl. cysts and polyps)	11 (2.7)	4 (2.0)

a. Events which occurred in ≥ 10 patients in at least 1 study arm.
b. MedDRA version 22.0; SOC and PT terminology adopted unmodified from Module 4 A.
c. First data cut-off (4/09/2019).
d. AEs including events that the company deemed to be due to progression of the underlying disease.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least 1 event; N: number of analysed patients; PT: preferred term; RCT: randomized controlled trial; SOC: system organ class

Table 4: Common AEs[a] – RCT, direct comparison: tucatinib + trastuzumab + capecitabine vs. placebo + trastuzumab + capecitabine

Study	**Patients with event n (%)**	
SOC[b] PT[b]	**Tucatinib + trastuzumab + capecitabine N = 404**	**Placebo + trastuzumab + capecitabine N = 197**
HER2CLIMB[c]		
Total rate of SAEs[d]	104 (25.7)	53 (26.9)
Gastrointestinal disorders	30 (7.4)	14 (7.1)
Diarrhoea	16 (4.0)	7 (3.6)
Vomiting	10 (2.5)	5 (2.5)
Infections and infestations	21 (5.2)	11 (5.6)
Respiratory, thoracic, and mediastinal disorders	19 (4.7)	15 (7.6)
Nervous system disorders	16 (4.0)	10 (5.1)
Metabolic and nutritional disorders	11 (2.7)	5 (2.5)

a. Events which occurred in ≥ 10 patients in at least 1 study arm.
b. MedDRA version 22.0; SOC and PT terminology adopted unmodified from Module 4 A.
c. First data cut-off (4/09/2019).
d. AEs including events that the company deemed to be due to progression of the underlying disease.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least 1 event; N: number of analysed patients; PT: preferred term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: system organ class

Table 5: Common severe AEs[a] (CTCAE grade ≥ 3) – RCT, direct comparison: tucatinib + trastuzumab + capecitabine vs. placebo + trastuzumab + capecitabine

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Tucatinib + trastuzumab + capecitabine N = 404**	**Placebo + trastuzumab + capecitabine N = 197**
HER2CLIMB[c]		
Total rate of severe AEs (CTCAE grade ≥3)[d]	223 (55.2)	96 (48.7)
Gastrointestinal disorders	86 (21.3)	28 (14.2)
Diarrhoea	52 (12.9)	17 (8.6)
Nausea	15 (3.7)	6 (3.0)
Vomiting	12 (3.0)	7 (3.6)
Stomatitis	10 (2.5)	1 (0.5)
Diseases of the skin and subcutaneous tissue	56 (13.9)	19 (9.6)
Palmar-plantar erythrodysaesthesia syndrome	53 (13.1)	18 (9.1)
Investigations	46 (11.4)	8 (4.1)
Alanine aminotransferase increased	22 (5.4)	1 (0.5)
Aspartate aminotransferase increased	18 (4.5)	1 (0.5)
Metabolic and nutritional disorders	41 (10.1)	17 (8.6)
Hypokalaemia	13 (3.2)	10 (5.1)
Hypophosphataemia	11 (2.7)	4 (2.0)
General disorders and administration site conditions	27 (6.7)	17 (8.6)
Fatigue	19 (4.7)	8 (4.1)
Respiratory, thoracic, and mediastinal disorders	27 (6.7)	17 (8.6)
Pulmonary embolism	13 (3.2)	4 (2.0)
Dyspnoea	7 (1.7)	10 (5.1)
Disorders of the blood and lymphatic system	26 (6.4)	19 (9.6)
Anaemia	15 (3.7)	5 (2.5)
Infections and infestations	24 (5.9)	14 (7.1)
Nervous system disorders	20 (5.0)	11 (5.6)
Musculoskeletal and connective tissue disorders	16 (4.0)	13 (6.6)
Vascular disease	14 (3.5)	6 (3.0)

a. Events which occurred in ≥ 10 patients in at least 1 study arm.
b. MedDRA version 22.0; SOC and PT terminology adopted unmodified from Module 4 A.
c. First data cut-off (4/09/2019).
d. AEs including events that the company deemed to be due to progression of the underlying disease.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least 1 event; N: number of analysed patients; PT: preferred term; RCT: randomized controlled trial; SOC: system organ class

Table 6: Discontinuation due to AEs – RCT, direct comparison: tucatinib + trastuzumab + capecitabine vs. placebo + trastuzumab + capecitabine (multipage table)

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**Tucatinib + trastuzumab + capecitabine N = 404**	**Placebo + trastuzumab + capecitabine N = 197**
HER2CLIMB[b]		
Total rate of discontinuation due to AEs	45 (11.1)	19 (9.6)
Gastrointestinal disorders	13 (3.2)	2 (1.0)
Diarrhoea	8 (2.0)	2 (1.0)
Vomiting	4 (1.0)	0 (0)
Nausea	3 (0.7)	0 (0)
Gastritis	1 (0.2)	0 (0)
Gastrointestinal pain	1 (0.2)	0 (0)
Oral pain	1 (0.2)	0 (0)
Stomatitis	1 (0.2)	0 (0)
Diseases of the skin and subcutaneous tissue	12 (3.0)	5 (2.5)
Palmar-plantar erythrodysaesthesia syndrome	9 (2.2)	4 (2.0)
Dermatomyositis	1 (0.2)	0 (0)
Maculopapular rash	1 (0.2)	0 (0)
Urticaria	1 (0.2)	0 (0)
Dry skin	0 (0)	1 (0.5)
Investigations	8 (2.0)	3 (1.5)
Alanine aminotransferase increased	5 (1.2)	1 (0.5)
Aspartate aminotransferase increased	3 (0.7)	1 (0.5)
Blood bilirubin increased	3 (0.7)	2 (1.0)
Reduced ejection fraction	1 (0.2)	0 (0)
Neutrophil count decreased	1 (0.2)	0 (0)
Leukocyte count decreased	1 (0.2)	0 (0)
Infections and infestations	5 (1.2)	1 (0.5)
Sepsis	2 (0.5)	1 (0.5)
Nail bed infection	1 (0.2)	0 (0)
Oesophageal candidiasis	1 (0.2)	0 (0)
Oral candidiasis	1 (0.2)	0 (0)
Septic shock	1 (0.2)	0 (0)
Respiratory, thoracic, and mediastinal disorders	4 (1.0)	0 (0)
Respiratory failure	2 (0.5)	0 (0)
Acute respiratory failure	1 (0.2)	0 (0)
Suffocation	1 (0.2)	0 (0)
Pleural effusion	1 (0.2)	0 (0)

Table 6: Discontinuation due to AEs – RCT, direct comparison: tucatinib + trastuzumab + capecitabine vs. placebo + trastuzumab + capecitabine (multipage table)

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**Tucatinib + trastuzumab + capecitabine N = 404**	**Placebo + trastuzumab + capecitabine N = 197**
Metabolic and nutritional disorders	4 (1.0)	1 (0.5)
Dehydration	3 (0.7)	0 (0)
Decreased appetite	1 (0.2)	1 (0.5)
Hypophosphataemia	1 (0.2)	0 (0)
General disorders and administration site conditions	3 (0.7)	4 (2.0)
Fatigue	2 (0.5)	3 (1.5)
Fever	1 (0.2)	0 (0)
Malaise	0 (0)	1 (0.5)
Multiorgan dysfunction syndrome	0 (0)	1 (0.5)
Hepatobiliary disorders	3 (0.7)	1 (0.5)
Hyperbilirubinaemia	2 (0.5)	1 (0.5)
Hepatotoxicity	1 (0.2)	0 (0)
Musculoskeletal and connective tissue disorders	3 (0.7)	0 (0)
Muscular weakness	2 (0.5)	0 (0)
Bone pain	1 (0.2)	0 (0)
Disorders of the blood and lymphatic system	2 (0.5)	3 (1.5)
Neutropenia	2 (0.5)	0 (0)
Haemolytic anaemia	0 (0)	1 (0.5)
Thrombocytopenia	0 (0)	2 (1.0)
Heart disease	2 (0.5)	1 (0.5)
Cardiac arrest	1 (0.2)	0 (0)
Heart failure	1 (0.2)	1 (0.5)
Nervous system disorders	2 (0.5)	0 (0)
Dizziness	1 (0.2)	0 (0)
Peripheral motor neuropathy	1 (0.2)	0 (0)
Eye disorders	1 (0.2)	0 (0)
Optic neuropathy	1 (0.2)	0 (0)
Benign, malignant, and unspecified neoplasms (incl. cysts and polyps)	1 (0.2)	0 (0)
Pyogenic granuloma	1 (0.2)	0 (0)
Psychiatric disorders	1 (0.2)	0 (0)
Depressed mood	1 (0.2)	0 (0)

a. MedDRA version 22.0; SOC and PT terminology adopted unmodified from Module 4 A.
b. First data cut-off (4/09/2019).
AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least 1 event; N: number of analysed patients; PT: preferred term; RCT: randomized controlled trial; SOC: system organ class

Appendix C Results on health status (EQ-5D VAS, supplementary presentation)

Table 7: Results (morbidity, supplementary presentation) – RCT, direct comparison: tucatinib + trastuzumab + capecitabine vs. placebo + trastuzumab + capecitabine

Study Outcome category Outcome	Tucatinib + trastuzumab + capecitabine		Placebo + trastuzumab + capecitabine		Tucatinib + trastuzumab + capecitabine vs. Placebo + trastuzumab + capecitabine
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[a]
HER2CLIMB[b]					
Morbidity					
Health status (EQ-5D VAS)[c, d]					
≥ 7 points	217	NR [7.6; NC] 73 (33.6)	112	5.8 [4.3; NC] 42 (37.5)	0.81 [0.55; 1.18]; 0.261
≥ 10 points	217	NR [7.7; NC] 71 (32.7)	112	6.7 [4.3; NC] 40 (35.7)	0.82 [0.56; 1.21]; 0.313

a. Effect estimate and CI: Cox model stratified by brain metastases at baseline (yes vs. no), ECOG-PS (0 vs. 1), and region (North America vs. rest of the world). p value: log rank test; each stratified by brain metastases at baseline (yes vs. no), ECOG-PS (0 vs. 1), and region (North America vs. rest of the world).
b. First data cut-off (4/09/2019).
c. Data on EQ-5D VAS are available only for 52.9% of patients in the intervention arm and 55.4% of patients in the comparator arm (for the justification, see Section 2.2 of the present addendum).
d. Operationalized as time to first deterioration.

CI: confidence interval; EQ-5D: European Quality of Life Questionnaire – 5 Dimensions; HR: hazard ratio; n: number of patients with (at least 1) event; N: number of analysed patients; NC: not calculable; ND: no data; NR: not reached; RCT: randomized controlled trial; VAS: visual analogue scale

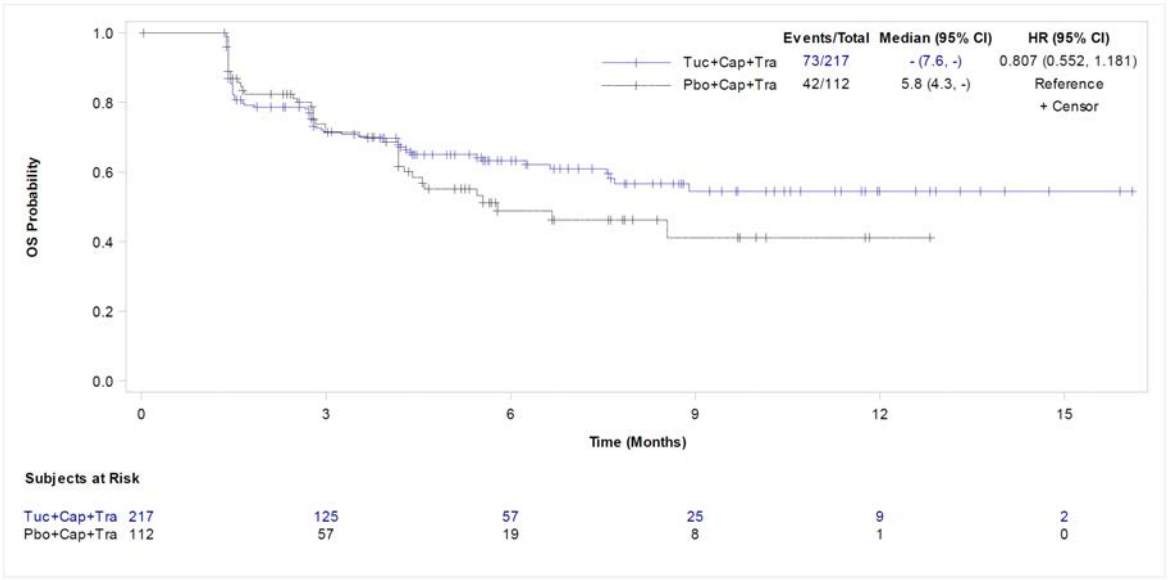

Figure 10: Kaplan-Meier curves at the time point EQ-5D VAS (time to first deterioration by ≥ 7 points) in the HER2CLIMB study (first data cut-off of 4/09/2019)

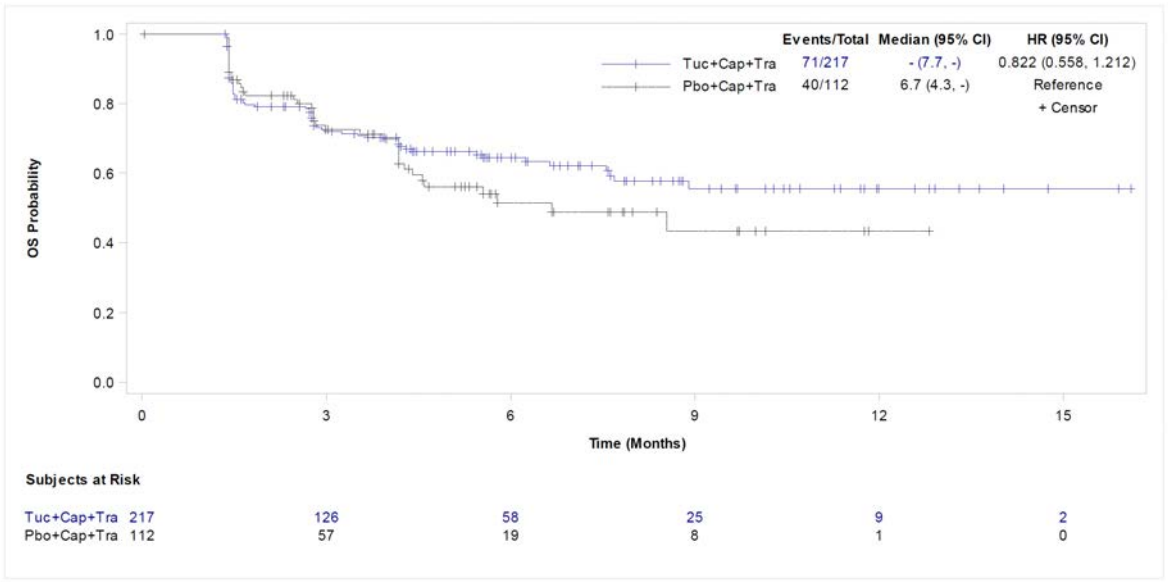

Figure 11: Kaplan-Meier curves at the time point EQ-5D VAS (time to first deterioration by ≥ 10 points) in the HER2CLIMB study (first data cut-off of 4/09/2019)