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# Impact of Tucatinib on Health-Related Quality of Life in Patients with HER2+ Metastatic Breast Cancer with Brain Metastases

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## Background

- Disease progression in metastatic breast cancer (MBC) can negatively impact quality of life (QoL).[1]
- For patients with HER2+ MBC previously treated with trastuzumab, pertuzumab, and trastuzumab emtansine (T-DM1), no single regimen is considered the standard of care.[2,3]
- Up to 50% of patients with HER2+ MBC may develop brain metastases and effective and tolerable treatment options are needed.[4–7]
- Patients with HER2+ MBC and brain metastases have an increased likelihood to have reduced health-related quality of life (HRQoL) compared to patients without brain metastases.[8]
- Tucatinib is a highly selective oral tyrosine kinase inhibitor of HER2 with minimal inhibition of EGFR.[9]
- The pivotal HER2CLIMB trial compared tucatinib (TUC) or placebo (Pbo), in combination with trastuzumab (Tras) and capecitabine (Cape), in patients with HER2+ MBC, with and without brain metastases, previously treated with trastuzumab, pertuzumab, and T-DM1.[10]
  - Enrolled a large percentage of patients (48%; 291/612) with history or presence of brain metastases at baseline
  - The addition of tucatinib resulted in clinically meaningful and statistically significant improvements in overall survival (OS), progression-free survival (PFS), and objective response rate (ORR) in patients with HER2+ MBC and was well tolerated with a manageable safety profile.
  - Tucatinib was approved by the FDA for patients with HER2+ MBC, including patients with brain metastases, whose cancers have progressed on at least one prior anti-HER2 regimen in the metastatic setting.
- Here we present an evaluation of the impact of tucatinib on HRQoL in patients with brain metastases.

## Study Design

**Key Eligibility Criteria**
- HER2+ MBC
- Prior treatment with trastuzumab, pertuzumab, and T-DM1
- ECOG performance status 0 or 1
- Brain MRI at baseline

**48% of patients had brain metastases at baseline**
including previously untreated, treated stable, and treated and progressing

R* (2:1)

N=410: **Tucatinib** 300 mg PO BID + **Trastuzumab** 6 mg/kg Q3W, loading dose 8 mg/kg C1D1 + **Capecitabine** 1000 mg/m² PO BID Days 1–14; *21-day cycle*

N=202: **Placebo** + **Trastuzumab** 6 mg/kg Q3W, loading dose 8 mg/kg C1D1 + **Capecitabine** 1000 mg/m² PO BID Days 1–14; *21-day cycle*

*Stratification factors:
- Presence of brain metastases (yes/no)
- ECOG status (0 or 1)
- Region (US or Canada or rest of world)

https://clinicaltrials.gov/ct2/show/NCT02614794[10]

Patients with HRQoL data (N=331)
BM patients with HRQoL data (N=164)
Health-related quality of life assessments: Baseline, Cycle 3, Cycle 5, Cycle 7, Cycle 9, 30-day follow-up

## Methods

### Total Study Population
- 612 patients randomized 2:1 February 2016 to May 2019

### HRQoL with Brain Metastases Study Population
- Assessments initiated in August 2017
- HRQoL data were available from 331 of 612 patients, including 164 patients with brain metastases:
  - 107 patients in the tucatinib arm
  - 57 patients in the placebo arm

### HRQoL Assessments
- **Overall health status:** visual analog scale (VAS)
- **Time to deterioration of QoL:** defined as decrease of 7 points on VAS[11]
- **Change from baseline on individual patient-reported items**
  - Mobility, self-care, usual activities, pain/discomfort, and anxiety/depression
  - Each dimension has 5 levels: no, slight, moderate, severe, or extreme problems

## HER2CLIMB Primary Analysis Results[10]

- The HER2CLIMB trial met all primary and alpha-controlled secondary endpoints at the first interim analysis.
- Benefit was observed in patients with and without brain metastases.
- Median duration of exposure: Tucatinib 7.3 months (<0.1–35.1), Placebo 4.4 months (<0.1– 24.0).

| PFS by BICR N=480* | Overall Survival N=612 | PFS by BICR in patients with brain metastases N=291 |
|---|---|---|
| Hazard Ratio: 0.54 | Hazard Ratio: 0.66 | Hazard Ratio: 0.48 |
| 95% CI: 0.42 to 0.71, P<0.001 | 95% CI: 0.50 to 0.88, P=0.005 | 95% CI: 0.34 to 0.69, P<0.001 |
| **Risk of progression or death was reduced by 46%** | **Risk of death was reduced by 34%** | **Risk of progression or death was reduced by 52%** |

PFS: progression-free survival; BICR: blinded independent central review
*The primary endpoint of PFS was assessed in the first 480 patients enrolled.

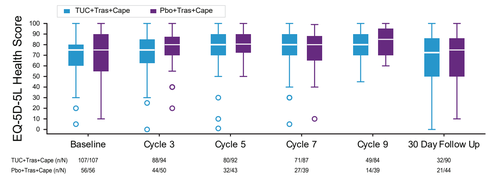
## Baseline Patient Characteristics

- Baseline characteristics were consistent between the total population, including total brain metastases population, and HRQoL brain metastases population.

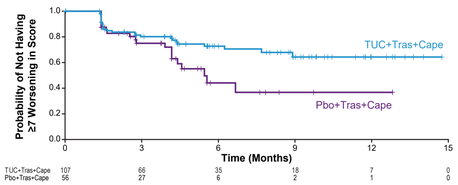
| | | Total Study Population | | Brain Metastases Population | | HRQoL Population with Brain Metastases | |
|---|---|---|---|---|---|---|---|
| | | TUC+Tras+Cape (N=410) | Pbo+Tras+Cape (N=202) | TUC+Tras+Cape (n=198) | Pbo+Tras+Cape (n=93) | TUC+Tras+Cape (n=107) | Pbo+Tras+Cape (n=57) |
| Age in years, median (range) | | 55.0 (22, 80) | 54.0 (25, 82) | 53 (22, 75) | 52 (25, 75) | 54 (22, 75) | 52 (25, 75) |
| Female, n (%) | | 407 (99.3) | 200 (99.0) | 197 (99.5) | 92 (98.9) | 107 (100) | 56 (98.2) |
| ECOG PS, n (%) | 0 | 204 (49.8) | 94 (46.5) | 92 (46.5) | 38 (40.9) | 51 (47.7) | 22 (38.6) |
| | 1 | 206 (50.2) | 108 (53.5) | 106 (53.5) | 55 (59.1) | 56 (52.3) | 35 (61.4) |
| Stage IV at initial diagnosis, n (%) | | 143 (34.9) | 77 (38.1) | 77 (38.9) | 39 (41.9) | 42 (39.3) | 25 (43.9) |
| Hormone Receptor Status, n (%) | ER and/or PR positive | 243 (59.3) | 127 (62.9) | 107 (54.0) | 59 (63.4) | 64 (59.8) | 34 (59.6) |
| | ER and PR negative | 161 (39.3) | 75 (37.1) | 88 (44.4) | 34 (36.6) | 41 (38.3) | 23 (40.4) |
| Prior lines of therapy, median (range) | Overall | 4 (2, 14) | 4 (2, 17) | 4 (2, 11) | 3 (2, 17) | 4 (2, 11) | 3 (2, 12) |
| | Metastatic setting | 3 (1, 14) | 3 (1, 13) | 2 (1, 11) | 3 (1, 13) | 2 (1, 11) | 3 (1, 11) |
| Presence/history of brain metastases, n (%) | | 198 (48.3) | 93 (46) | 198 (100) | 93 (100) | 107 (100) | 57 (100) |

## Overall HRQoL in HRQoL Population with Brain Metastases

- HRQoL was maintained throughout treatment and was not noticeably different between treatment arms.




## Time to Worsening (≥7 points) in EQ-5D-5L Health Score in HRQoL Population with Brain Metastases

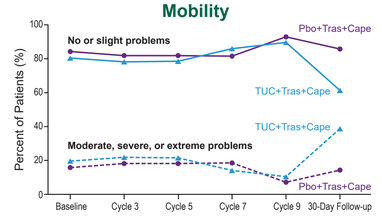


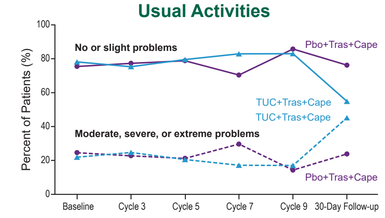

| | Events/Total | HR (95% CI) | Median (95% CI) |
|---|---|---|---|
| TUC+Tras+Cape | 26/107 | 0.51 | – (–, –) |
| Pbo+Tras+Cape | 20/56 | (0.28, 0.93) | 5.5 months (4.2, –) |

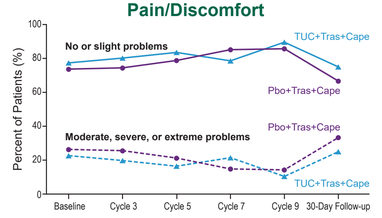
- Addition of tucatinib significantly delayed time to worsening of EQ-5D-5L Health Score.
  - Compared to the placebo arm, patients on the tucatinib arm had a 49% reduction in the risk of deterioration

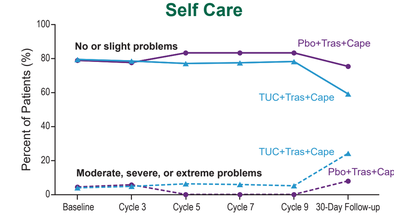
## EQ-5D-5L Subscale Responses at Baseline and Up to 30 Days Follow-Up in HRQoL Population with Brain Metastases

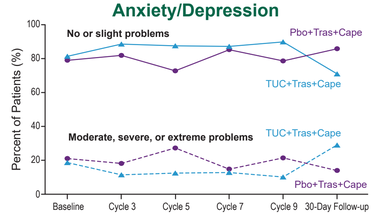
- There was no noticeable change in the categories throughout the course of treatment.
- Mobility, usual activities, pain/discomfort, and self-care worsened after treatment discontinuation.




## Conclusions

- In HER2+ MBC patients with brain metastases, tucatinib in combination with trastuzumab and capecitabine demonstrates significantly longer and clinically meaningful time to deterioration of HRQoL.
- Patients, including those with brain metastases, treated with tucatinib, trastuzumab, and capecitabine maintain HRQoL throughout the treatment period, which was longer compared to patients treated with only trastuzumab and capecitabine.[10]
- These results, together with the HER2CLIMB primary analysis and the HRQoL analysis in the total population, demonstrate that this regimen improves PFS and OS, and maintains QoL in all patients, including those with brain metastases.

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