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Brief Research Report

Real-world efficacy of tucatinib in Danish human epidermal growth factor receptor 2-positive metastatic breast cancer

Laurits Sebastian Dahl[1], Ann Søegaard Knoop[2], Maj-Britt Jensen[1], Eva Harder[3], Jeanette Dupont Rønlev[4] & Tobias Berg[1, 2]

1) Danish Breast Cancer Group (DBCG), Department of Oncology, Copenhagen University Hospital – Rigshospitalet, 2) Department of Oncology, Copenhagen University Hospital – Rigshospitalet, 3) Department of Oncology, Copenhagen University Hospital – Herlev Hospital, 4) Department of Oncology, Odense University Hospital, Denmark

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ABSTRACT

INTRODUCTION. Tucatinib in combination with trastuzumab and capecitabine is approved for the treatment of metastatic human epidermal growth factor receptor 2 (HER2) positive breast cancer in third-line and later based on the results of the HER2CLIMB trial. In this short report, we evaluate the extent and efficacy of tucatinib treatment among Danish patients.

METHODS. This is a retrospective study that includes all known Danish patients who initiated tucatinib prior to June 1, 2024. We utilised the nationwide clinical database of the Danish Breast Cancer.

RESULTS. In total, 38 patients were treated. Nineteen (50%) of the patients had central nervous system (CNS) metastases, and 21 (55%) had visceral disease. Median progression-free survival was 8.7 months (95% CI: 6.2; 13.3) and median overall survival was 22.4 months (95% CI: 13.1; N/A). Nine patients exhibited a performance status of 2-3 (n = 5) or uncontrollable CNS metastases (n = 4), not meeting the inclusion criteria applied in the HER2CLIMB trial.

CONCLUSIONS. Our results align with data presented from the HER2CLIMB trial. Considerably fewer patients than initially expected have been treated in Denmark.

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Metastatic breast cancer is the leading cause of cancer-related death among women globally [1]. Dramatic advancements in breast cancer survival have been made over the past three decades,

attributed to more widespread screening and the continuous evolution of adjuvant therapy [2]. However, 5% of patients present with metastatic breast cancer, and 10-35% develop metastatic disease within ten years, depending on initial stage and histopathological profile. At this point, the disease is considered incurable and treatment is given with a palliative intent [3, 4]. This concerns around 1,000 patients in Denmark annually.

Metastatic breast cancer overexpresses human epidermal growth factor receptor 2 (HER2) in approximately 20% of cases [5]. While the HER2-positive subtype is aggressive, targeted antibody-based therapies have shown potential to extend overall survival to 60 months or more [6-8]. Brain metastases are a common complication within this subtype and are associated with a poorer prognosis [9].

Tucatinib, a tyrosine kinase inhibitor, was approved for use in Denmark in March 2022 in combination with trastuzumab (a HER2-targeted antibody) and capecitabine (a chemotherapeutic agent) [10]. The HER2CLIMB trial randomised patients in a 2:1 ratio to receive tucatinib or placebo in combination with trastuzumab and capecitabine. The included patients had received extensive previous treatment with a median of three prior lines of treatment, and at least one line of trastuzumab, pertuzumab and trastuzumab-emtasine at any point in the metastatic setting. The HER2CLIMB trial demonstrated a progression-free survival (PFS) of 7.8 months (95% CI: 7.5; 9.6) in the tucatinib-treated group compared to 5.8 months (95% CI: 4.2; 7.1) in the placebo group [11]. Overall survival (OS) was similarly improved, achieving 21.9 months (95% CI: 18.3; 31.0) versus 17.4 months (95% CI: 13.6; 19.9). All patients in the trial had an Eastern Cooperative Oncology Group performance status (PS) score of 0 or 1. Additionally, patients with active brain metastases were eligible for randomisation unless they required urgent cerebral intervention or had ongoing use of corticosteroids equivalent to ≥ 15 mg/day of prednisolone.

In relation to their recommendation, the Danish Medicines Council (DMC) requested a report on patient characteristics, length of treatment, time to progression and survival from Danish practice after two years, after which the DMC would reconsider their recommendation. At the time of their recommendation, the DMC expected that 71 patients would initiate tucatinib treatment annually. This work is based on the report submitted to the DMC where we aim to evaluate the extent of tucatinib treatment, characterise the patients receiving the medication and evaluate efficacy.

Methods

This is a retrospective, non-interventional cohort study utilising the nationwide database of the Danish Breast Cancer Group. To ensure completeness of data, each department of oncology in Denmark provided a list of all patients treated with tucatinib at the respective centres. Data were extracted on all patients treated with tucatinib before 1 June 2024, regardless of treatment duration.

Data were extracted on age, date of diagnosis, date of progression and death, PS, metastatic sites and treatment, including initiation and discontinuation dates. Chart review identified uncontrollable central nervous system (CNS) metastases (> 15 mg prednisolone /day).

The primary endpoint was PFS, defined as time from initiation of tucatinib treatment to progression, death of any cause or end of follow-up. The secondary endpoint was OS, defined as time from initiation of tucatinib treatment to death of any cause or end of follow-up. PFS and OS were calculated for all patients and for the sub-population meeting the DMC recommendation. The Kaplan-Meier method was used to estimate survival outcomes, which are presented with medians and 95% CI. Median potential follow-up was estimated using the inverse Kaplan-Meier method and presented with 95% CI. All data analyses were conducted in R version 4.3.2.

Trial registration: Approved by the Capital Regions Research Overview (P-2024-175774) and the Centre for Health Research (R-24065900).

Results

In total, 38 patients were treated with tucatinib. Most patients were in good PS (PS 0-1), but five patients had PS > 1, eight patients had unknown PS, and another four patients had uncontrollable CNS metastases. Half the patients had CNS metastases, and a majority had visceral disease. Most patients had ≥ 3 metastatic sites, and the median number of prior lines of metastatic treatment was three (**Table 1**).

TABLE 1 Patient characteristics at initiation of tucatinib (N = 38).

Age, yrs	
Median (range)	60 (37-82)
Performance status, n (%)	
0	15 (39)
1	10 (26)
2	3 (7.9)
3	2 (5.)
Unknown	8 (21)
Metastases, n (%)	
Bone	21 (55)
Lung	15 (39)
Liver	13 (34)
CNS	19 (50)
Visceral disease	21 (55)
Bone only	2 (5.3)
Uncontrollable CNS	4 (11)
Metastatic sites, n (%)	
1	8 (21)
2	9 (24)
≥ 3	21 (55)
Treatment lines prior to tucatinib, n (%)	
Median	3
0	1 (2.6)
1	6 (16)
2	4 (11)
3	16 (42)
4	6 (16)
6	2 (5.3)
7	2 (5.3)
8	1 (2.6)
Select previous metastatic treatment, n (%)[a]	
Trastuzumab	34 (89)
Pertuzumab	32 (84)
Trastuzumab emtansine	31 (8)
Vinorelbine	29 (76)
Trastuzumab deruxtecan	4 (11)
Taxan	10 (27)

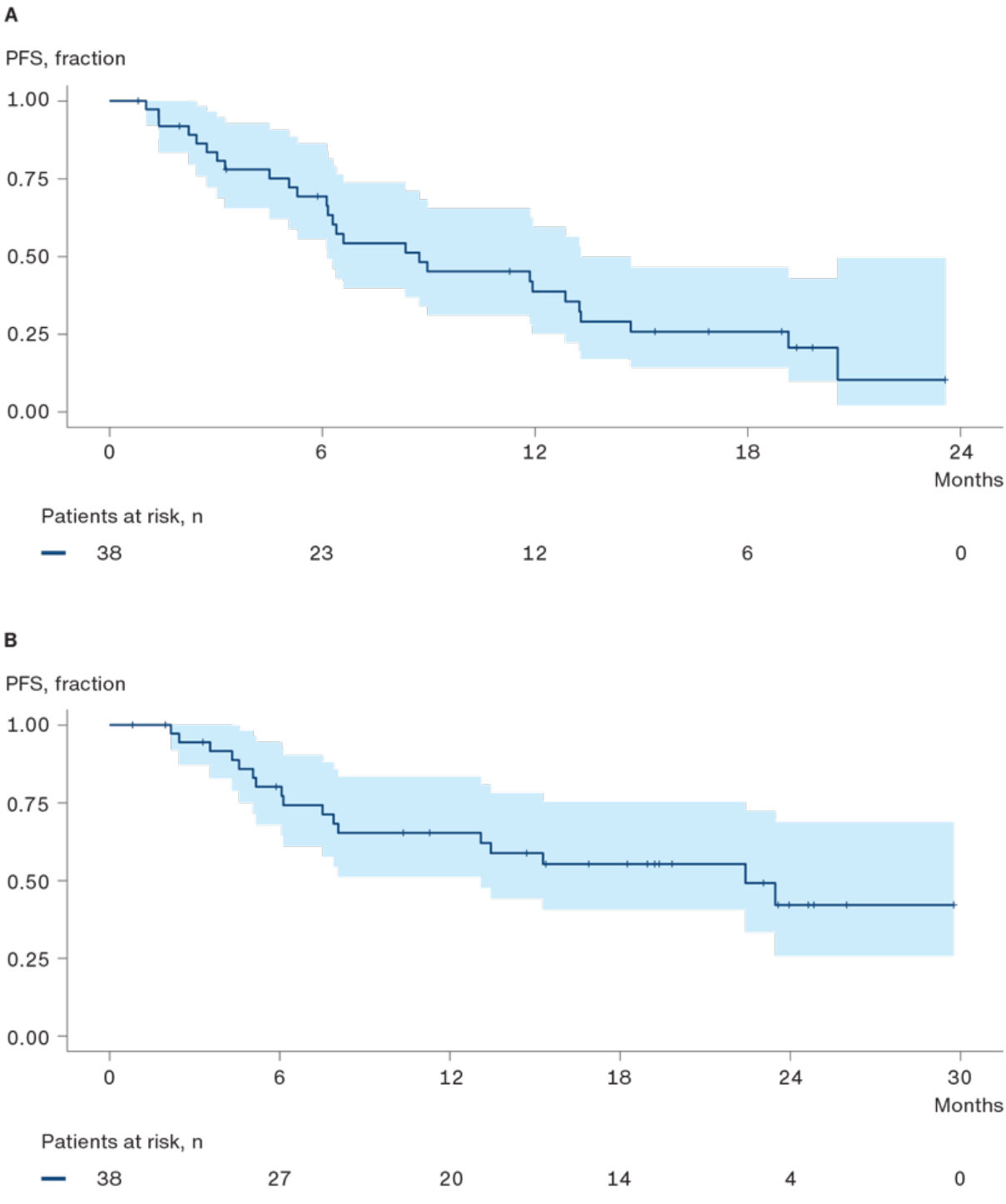
CNS = central nervous system.
a) Displays select treatments and is not exhaustive.

Survival

Among the 38 patients, 24 (63%) progressed and three (8%) died as their first event after initiating tucatinib treatment. Median PFS was 8.7 months (95% CI: 6.2; 13.3) (**Figure 1** A). Seventeen patients (44%) died within the study period, and the median OS was 22.4 months (95% CI: 13.1; N/A) (Figure 1

B). Estimated median follow-up was 19.4 months (95% CI: 16.9; N/A) for PFS and 19.4 months (95% CI: 18.3; 24.6) for OS. No difference was observed in PFS or OS when we excluded the nine patients who were not treated in pursuance of the DMC recommendation.

FIGURE 1 **A**. Median progression-free survival (PFS): 8.7 (95% CI: 6.2; 13.3) months. **B**. Median overall survival: 22.4 (95% CI: 13.1; -) months.



Discussion

Our survival results are consistent with those reported in the HER2CLIMB trial. The PFS result demonstrates efficacy of similar magnitude, and OS likewise appears to align with HER2CLIMB. However, our estimates carry considerable uncertainty due to the limited sample size. It is important to consider the clinical characteristics of our patient cohort. While baseline characteristics were largely comparable, nine patients in our cohort would have been excluded from the original study due to PS 2-3 or uncontrollable brain metastases. These features strengthen the indication that tucatinib performs as expected in a broader real-world population.

A central limitation of this study was the small sample size. As a population-based study, it is subject to the risk of data inaccuracies, and the possibility of missing data cannot be ruled out. Nevertheless, the strength of population-based studies lies in their ability to more accurately reflect real-world clinical outcomes.

The limited number of patients (19 patients/yr versus the expected 71 patients/yr) is likely a result of the timing of the approval of tucatinib. Concurrent with its recommendation for use in Denmark, the DESTINY-Breast 03 study was published in March 2022, leading to the approval of the HER2-targeted antibody-drug conjugate trastuzumab deruxtecan (T-DXd) in January 2023 [7, 12]. The approval of T-DXd has likely influenced treatment choices and shifted priorities, contributing to the small number of patients treated with tucatinib. However, an increase in tucatinib use is likely in the future as it remains a treatment option upon T-DXd progression.

Recommendations from the DMC are often conditional. This means that continued use depends on whether national efficacy data collected over 2-3 years align with the results that supported its recommendation for general use. This process allows clinicians and health authorities to determine if treatments provide benefits like those seen in their original studies and to ensure that treatments are administered as indicated.

However, a limitation arises when fewer patients than expected are treated with a drug, as observed currently and previously [13]. Furthermore, if a real-world study reports significantly poorer results than the original randomised trial, the differences in methodological power between the two should be considered [14].

Conclusions

Our survival data align with the efficacy presented in the HER2CLIMB trial. The small sample size can be attributed to the approval of competing therapies. At present, Danish data support the continued use of tucatinib in heavily pre-treated HER2-positive metastatic breast cancer.

Correspondence *Laurits Sebastian Dahl.* E-mail: laurits.sebastian.dahl.03@regionh.dk

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Conflicts of interest ASK reports financial support from or interest in AstraZeneca, Novartis, Pfizer, Seattle Genetics, Merck, Eli Lilly, Roche, Seagen, Gilead, Daiichi Sankyo, MSD. MBJ reports financial support from or interest in Novartis. EH reports financial support from or interest in Novartis, AstraZeneca, MSD, Daiichi Saknyo, Pfizer, Gilead. TB reports financial support from or interest in Pfizer, AstraZeneca, Novartis, Samsung Bioepis, Seattle Genetics, Merck, Eli Lilly and Daiichi Sankyo. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. These are available together with the article at ugeskriftet.dk/dmj

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REFERENCES

1. Benson JR, Jatoi I. The global breast cancer burden. Future Oncol. 2012;8(6):697-702. https://doi.org/10.2217/fon.12.61
2. Berry DA, Cronin KA, Plevritis SK, et al. Effect of screening and adjuvant therapy on mortality from breast cancer. N Engl J Med. 2005;353(17):1784-92. https://doi.org/10.1056/NEJMoa050518
3. Pan H, Gray R, Braybrooke J, et al. 20-year risks of breast-cancer recurrence after stopping endocrine therapy at 5 years. N Engl J Med. 2017;377(19):1836-46. https://doi.org/10.1056/NEJMoa1701830
4. Daily K, Douglas E, Romitti PA, Thomas A. Epidemiology of de novo metastatic breast cancer. Clin Breast Cancer. 2021;21(4):302-8. https://doi.org/10.1016/j.clbc.2021.01.017
5. Owens MA, Horten BC, Da Silva MM. HER2 amplification ratios by fluorescence in situ hybridization and correlation with immunohistochemistry in a cohort of 6556 breast cancer tissues. Clin Breast Cancer. 2004;5(1):63-9. https://doi.org/10.3816/CBC.2004.n.011
6. Swain SM, Baselga J, Kim SB, et al. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. N Engl J Med. 2015;372(8):724-34. https://doi.org/10.1056/NEJMoa1413513
7. Cortés J, Hurvitz SA, Im SA, et al. Trastuzumab deruxtecan versus trastuzumab emtansine in HER2-positive metastatic breast cancer: long-term survival analysis of the DESTINY-Breast03 trial. Nat Med. 2024;30(8):2208-15. https://doi.org/10.1038/s41591-024-03021-7
8. Slamon DJ, Godolphin W, Jones LA, et al. Studies of the HER-2/neu proto-oncogene in human breast and ovarian cancer. Science. 1989;244(4905):707-12. https://doi.org/10.1126/science.2470152
9. Bendell JC, Domchek SM, Burstein HJ, et al. Central nervous system metastases in women who receive trastuzumab-based therapy for metastatic breast carcinoma. Cancer. 2003;97(12):2972-7. https://doi.org/10.1002/cncr.11436
10. Medicinrådet. Tucatinib (Tukysa) i kombination med trastuzumab og capecitabin. https://medicinraadet.dk/anbefalinger-og-vejledninger/laegemidler-og-indikationsudvidelser/t/tucatinib-tukysa-i-komb-med-trastuzumab-og-capecitabin-metastatisk-her2-positiv-brystkraeft (25 Jan 2024)
11. Murthy RK, Loi S, Okines A, et al. Tucatinib, trastuzumab, and capecitabine for HER2-positive metastatic breast cancer. N Engl J Med. 2020;382(7):597-609. https://doi.org/10.1056/NEJMoa1914609
12. Medicinrådet. Trastuzumab deruxtecan (Enhertu). https://medicinraadet.dk/anbefalinger-og-vejledninger/laegemidler-og-indikationsudvidelser/t/trastuzumab-deruxtecan-enhertu-brystkraeft (26 Jan

2023)

13. Garly R, Knoop A, Jensen MB, et al. Atezolizumab and nab-paclitaxel for advanced breast cancer in Danish real-world patients. Dan Med J. 2023;70(9):A01230034
14. Hansen RG, Berg T, Knoop AS. Betingede anbefalinger fra Medicinrådet. Ugeskr Læger. 18 Mar 2024

