Tucatinib Extends PFS in HER2-Positive Breast Cancer, No New Safety Signals

Written by The Life Science Feed Editorial Team · Published 28 June 2026 · Edited by Mara Voss

Managing HER2-positive metastatic breast cancer, particularly in pre-treated patients, remains a clinical challenge due to disease progression and the emergence of brain metastases. The availability of targeted therapies that can effectively control systemic disease while also addressing central nervous system involvement is critical for improving patient outcomes. Recent data on tucatinib, a highly selective HER2 tyrosine kinase inhibitor, indicate its capacity to extend progression-free survival without introducing new safety concerns, offering a valuable option for this patient population.

KEY TAKEAWAYS

- The Pivot: Tucatinib continues to demonstrate significant clinical benefit in HER2-positive metastatic breast cancer, particularly in patients with brain metastases.
- The Data: Tucatinib, in combination with trastuzumab and capecitabine, reduced the risk of disease progression or death by 46% (HR 0.54, 95% CI 0.42-0.71, pThe Action: Clinicians should consider tucatinib-based regimens for patients with HER2-positive metastatic breast cancer, especially those with active or previously treated brain metastases, given its established efficacy and manageable safety profile.

HER2-positive breast cancer constitutes approximately 15-20% of all breast cancer diagnoses and is characterized by aggressive disease biology and a higher propensity for metastatic spread, including to the brain. Historically, the prognosis for patients with HER2-positive metastatic breast cancer was poor, but the advent of HER2-targeted therapies, such as trastuzumab and pertuzumab, has significantly improved outcomes. Despite these advancements, many patients eventually experience disease progression, necessitating further lines of treatment. A particular challenge is the management of brain metastases, which occur in up to 50% of patients with HER2-positive metastatic breast cancer and are often associated with significant morbidity and mortality. The blood-brain barrier limits the penetration of many systemic therapies, making effective treatment of central nervous system (CNS) metastases difficult. Therefore, therapies capable of crossing the blood-brain barrier and demonstrating intracranial activity are of substantial clinical interest. Tucatinib is an orally available, highly selective tyrosine kinase inhibitor (TKI) that targets HER2. Its selectivity for HER2, with minimal off-target activity against epidermal growth factor receptor (EGFR), is hypothesized to contribute to a more favorable safety profile compared to less selective TKIs. Preclinical studies and early clinical trials indicated that tucatinib possesses CNS penetrance, suggesting its potential utility in treating brain metastases. This characteristic is particularly important given the unmet need for effective treatments in this specific patient subgroup. The clinical development of tucatinib has focused on evaluating its efficacy and safety in heavily pre-treated patients with HER2-positive metastatic breast cancer, including those with brain metastases, who have progressed on prior

HER2-targeted therapies. The rationale for combining tucatinib with other HER2-targeted agents, such as trastuzumab, and chemotherapy, such as capecitabine, is based on the principle of synergistic blockade of the HER2 pathway and complementary mechanisms of action to overcome resistance mechanisms and enhance anti-tumor activity.

The trial

The pivotal Phase II HER2CLIMB trial investigated tucatinib in combination with trastuzumab and capecitabine in patients with unresectable locally advanced or metastatic HER2-positive breast cancer who had previously received trastuzumab, pertuzumab, and trastuzumab emtansine (T-DM1). A notable aspect of the HER2CLIMB trial design was the inclusion of patients with active brain metastases, a population often excluded from other clinical trials due to concerns about safety and confounding factors. This inclusion was critical for directly assessing the intracranial activity of tucatinib. The trial randomized patients in a 2:1 ratio to receive either tucatinib (300 mg orally twice daily) or placebo, both in combination with trastuzumab (6 mg/kg intravenously every 3 weeks, with a loading dose of 8 mg/kg) and capecitabine (1000 mg/m2 orally twice daily on days 1-14 of a 21-day cycle). The primary endpoint was progression-free survival (PFS) as assessed by blinded independent central review. Key secondary endpoints included overall survival (OS), PFS in patients with brain metastases, objective response rate (ORR), and safety. The trial enrolled 612 patients across multiple international sites. The median follow-up for the primary analysis was 14.1 months.1

The primary analysis demonstrated a statistically significant improvement in PFS for patients treated with tucatinib, trastuzumab, and capecitabine compared to those receiving placebo, trastuzumab, and capecitabine. The median PFS was 7.8 months (95% CI 7.5-9.6) in the tucatinib arm versus 5.6 months (95% CI 4.7-6.8) in the placebo arm. This translated to a hazard ratio (HR) for progression or death of 0.54 (95% CI 0.42-0.71, P46% reduction in the risk of disease progression or death with tucatinib. The benefit was consistent across various subgroups, including those with and without brain metastases at baseline. For patients with brain metastases, the median PFS was 7.6 months (95% CI 6.2-9.5) in the tucatinib arm compared to 5.4 months (95% CI 4.1-5.7) in the placebo arm (HR 0.48, 95% CI 0.33-0.69, P1

Overall survival (OS) also showed a significant improvement with tucatinib. The median OS was 21.9 months (95% CI 18.3-31.0) in the tucatinib arm versus 17.4 months (95% CI 13.6-19.9) in the placebo arm (HR 0.73, 95% CI 0.59-0.90, P=.005). This represents a 27% reduction in the risk of death. The OS benefit was observed despite subsequent therapies received by some patients in the placebo arm, further highlighting the robust efficacy of tucatinib. The objective response rate (ORR) was also higher in the tucatinib arm, at 41% (95% CI 36-47) compared to 23% (95% CI 17-30) in the placebo arm (P1

Regarding safety, tucatinib demonstrated a manageable safety profile with no new or unexpected safety signals. The most common adverse events (AEs) of grade 3 or higher in the tucatinib arm included diarrhea (12.9% vs 1.4% in placebo), palmar-plantar erythrodysesthesia syndrome (12.7% vs 10.9%), and elevated aspartate aminotransferase (AST) (5.4% vs 0.5%) or alanine aminotransferase (ALT) (4.5% vs 0.5%). While diarrhea and liver enzyme elevations were more frequent with tucatinib, they were generally manageable with dose modifications or supportive care. Discontinuation rates due to adverse events were 5.7% in the tucatinib arm and 3.0% in the placebo arm. The safety profile was consistent with previous observations for tucatinib and other HER2 TKIs, but without the significant skin rash often associated with less selective EGFR/HER2 inhibitors. The low rate of serious adverse events and treatment discontinuations suggests that the benefits of tucatinib outweigh the risks for this patient population.1

Further analyses have consistently supported these initial findings. A long-term follow-up of the HER2CLIMB trial, presented at subsequent medical conferences, confirmed the sustained PFS and OS benefits with tucatinib. These updates reinforced the durability of response and the long-term tolerability of the regimen. The consistent efficacy observed across various subgroups, including those with different sites of metastases and varying numbers of prior lines of therapy, further strengthens the evidence for tucatinib's broad applicability in this setting. The data also provided additional insights into the management of specific adverse events, such as diarrhea, through proactive interventions and dose adjustments, allowing patients to remain on therapy for longer durations and maximize clinical benefit. The sustained benefit in patients with brain metastases, including those with active and progressing lesions, remains a cornerstone of tucatinib's clinical utility. The ability to control both systemic and CNS disease simultaneously is a significant advantage, potentially reducing the need for repeated local therapies for brain lesions and improving neurological outcomes. The trial's design, which included a substantial proportion of patients with brain metastases, provided robust evidence for tucatinib's intracranial activity, a feature not consistently demonstrated by all HER2-targeted agents. This aspect is particularly relevant for clinical practice, as brain metastases represent a major cause of morbidity and mortality in HER2-positive breast cancer. The data from HER2CLIMB have led to the incorporation of tucatinib into international treatment guidelines for HER2-positive metastatic breast cancer, particularly for patients with brain metastases or those who have progressed on multiple prior HER2-targeted regimens. The consistent safety profile, without new signals emerging with longer follow-up, provides reassurance regarding its long-term use. The overall evidence base for tucatinib, derived primarily from the HER2CLIMB study, positions it as an important therapeutic option for patients with advanced HER2-positive breast cancer, especially those with CNS involvement, who have exhausted other standard treatments. The sustained efficacy and manageable safety profile underscore its value in extending progression-free and overall survival in a challenging patient population.

CLINICAL IMPLICATIONS

The sustained efficacy and consistent safety profile of tucatinib, particularly its demonstrated intracranial activity, solidify its position as a critical component in the treatment armamentarium for HER2-positive metastatic breast cancer. For clinicians, this means a clear, evidence-based option for patients who have progressed on multiple prior HER2-targeted therapies, especially those with active or previously treated brain metastases. The data from HER2CLIMB are compelling enough to warrant its consideration early in the sequence of third-line or later treatments, given the significant improvements in both progression-free and overall survival. The ability to manage CNS disease effectively with a systemic agent reduces the reliance on repeated local therapies, potentially improving patient quality of life and reducing neurological complications. From an industry perspective, the success of tucatinib highlights the value of developing highly selective agents with specific pharmacokinetic properties, such as CNS penetrance. This targeted approach, avoiding broader EGFR inhibition, has translated into a more favorable safety profile compared to older generation TKIs, making it a more tolerable option for patients who are often heavily pre-treated. The continued investment in understanding resistance mechanisms and developing agents that can overcome them, as tucatinib appears to do, will be crucial for future drug development in oncology. The commercial success of tucatinib also underscores the market demand for therapies that address specific, high-unmet-need patient populations, such as those with brain metastases.

> For patients, the availability of tucatinib offers a tangible extension of progression-free and overall survival, coupled with a manageable side effect profile. The prospect of controlling both systemic disease and brain metastases with a single oral regimen can significantly impact their daily lives, potentially reducing hospital visits and the burden of treatment. While side effects like diarrhea and liver enzyme elevations require careful monitoring and proactive management, they are generally reversible and do not typically lead to treatment discontinuation. This balance of efficacy and tolerability is paramount for maintaining quality of life in a chronic, advanced disease setting, allowing patients to live longer with better disease control.

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