

## Minireview Article

### Tucatinib: A Breakthrough in Advanced Breast Cancer Therapy

#### ABSTRACT

Tucatinib is a highly selective tyrosine kinase inhibitor targeting the HER2 protein, representing a significant advancement in treating HER2-positive metastatic breast cancer (MBC), including cases with brain metastases. This review assesses the efficacy and safety of tucatinib in combination with trastuzumab and capecitabine. Tucatinib acts by inhibiting HER2 signaling through its intracellular tyrosine kinase domain, disrupting critical pathways such as PI3K/AKT and MAPK, which are essential for tumor cell proliferation and survival. The HER2CLIMB trial demonstrated that tucatinib, when combined with trastuzumab and capecitabine, significantly improves progression-free survival and overall survival compared to placebo, with notable efficacy in reducing brain metastases. Common adverse events associated with tucatinib include diarrhea, palmar-plantar erythrodysesthesia, and nausea, though the overall safety profile is generally manageable. Current guidelines from NCCN, ASCO, and ESMO endorse tucatinib for patients with HER2-positive MBC who have progressed through prior HER2-targeted therapies. Ongoing clinical trials are investigating tucatinib's efficacy in combination with other agents to overcome resistance mechanisms and further enhance treatment outcomes. Future research should focus on optimizing combination therapies, managing long-term side effects, and identifying predictive biomarkers to refine patient selection and treatment strategies. This review underscores tucatinib's pivotal role in advancing the management of HER2-positive MBC and highlights the need for continued exploration in this therapeutic area.

**Keywords:** *Tucatinib, HER2-positive breast cancer, metastatic breast cancer, tyrosine kinase inhibitor*

#### 1. INTRODUCTION

Breast cancer is the most frequently diagnosed cancer and the most frequent cause of cancer-related deaths in women worldwide. Human epidermal growth factor receptor 2 (HER2) positivity may account for 15% to 20% of breast cancers. Some estimates suggest that up to 30% of patients with HER2-positive breast cancer will develop metastases in the brain.<sup>[1]</sup> According to the World Health Organization, in 2022, there were 2.3 million women diagnosed with breast cancer worldwide, and the disease resulted in around 670,000 fatalities.<sup>[2]</sup> Breast cancer is the most common cancer in India, accounting for 28.2% of all female cancers.<sup>[3]</sup> A recent SURVCAN-3 study<sup>[4]</sup> published in 2023 found that the 3-year median survival for breast cancer across countries was 84%, whereas, in India, it was 68%.<sup>[5]</sup>

In breast cancer, the molecular subtype might influence the therapeutic approach and the expected clinical outcomes. The HER2, an oncogene for tumorigenesis, is overexpressed in 15–20% of invasive breast cancer; before the availability of anti-HER2 drugs, HER2-positive breast cancer was associated with an increased risk of visceral metastasis and worse outcomes such as shorted progression-free survival and overall survival.<sup>[6]</sup> In the last decades, several anti-HER2 treatments have been approved as first- and second-line treatments, associated with significant improvements in the prognosis of patients with advanced HER2+ disease. Prior treatments for early and metastatic breast cancer, such as chemotherapy, hormone therapy, and HER2-targeted therapies, have significantly impacted tumor burden and central nervous system (CNS) involvement.<sup>[7]</sup> These treatments often prolong relapse-free survival when used as adjuvants, although accessibility to these drugs can be limited by cost and availability.<sup>[8]</sup> From the patient's perspective, while traditional treatments have been effective, newer drugs, specifically designed to penetrate the CNS and target HER2-positive tumors, offer a promising alternative with potentially better outcomes and quality of life.

Currently, available therapies for patients with HER2-positive metastatic breast cancer (MBC) include taxane chemotherapy, trastuzumab, and pertuzumab in the first line, and trastuzumab emtansine (T-DM1) in the second line.<sup>[1]</sup> More recently, the therapeutic armamentarium has been increased, and new effective therapies are available as treatment options for patients with HER2+ breast cancer who had no benefit from previous therapies. According to ESMO guidelines, several factors, such as the type of prior second-line therapy, patient characteristics, and benefit-risk profile of drugs, must be considered when choosing the best option for these patients. Specifically, tucatinib plus trastuzumab, capecitabine, and TDM-1 are the two treatment options recommended as third-line therapies in HER2+ BC patients with two failed treatment lines.<sup>[9]</sup>

Tucatinib is a tyrosine kinase inhibitor (TKI) of the HER2 protein. Inhibition of the HER2 protein limits the growth of cancer cells. Tucatinib, in combination with trastuzumab and capecitabine, was approved by the FDA (in April 2020) for the treatment of patients with locally advanced or HER2-positive MBC, including patients with brain metastases, who have received prior therapy with trastuzumab, pertuzumab, and T-DM1, separately or in combination. The recommended dose of tucatinib is 300 mg orally twice daily, along with trastuzumab and capecitabine.<sup>[1]</sup> Conversely, to other TKIs, the high selectivity of this drug for HER2 and lower selectivity for epidermal growth factor receptor (EGFR) results in fewer side effects related to EGFR inhibition.<sup>[10]</sup>

This drug review aims to study the efficacy and safety of tucatinib in combination with trastuzumab and capecitabine in patients with locally advanced or HER2-positive MBC, including patients with brain metastases.

## **2. MECHANISM OF ACTION OF TUCATINIB**

### **2.1 Inhibition of HER2 signaling pathway**

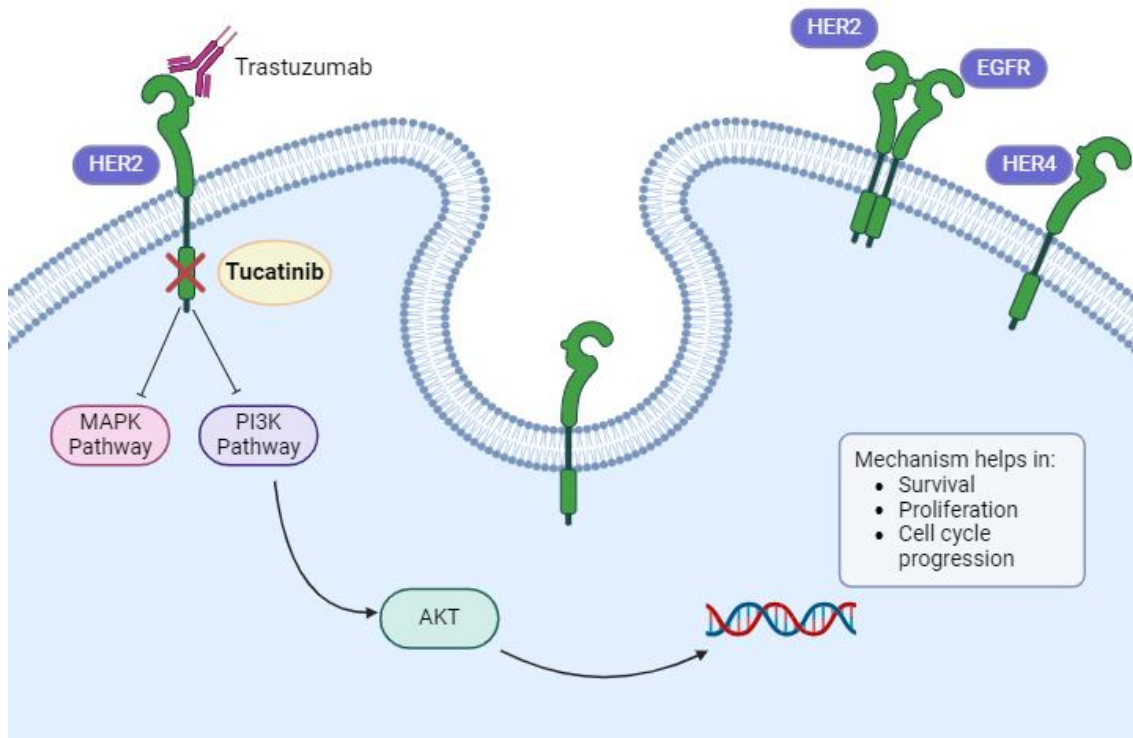
Tucatinib is a highly selective TKI designed to target the HER2 protein, which is overexpressed in certain types of cancer, particularly breast cancer. The HER2 receptor is a critical component of the cell signaling pathways that regulate cell growth and survival.<sup>[11]</sup> By binding specifically to the intracellular tyrosine kinase domain of the HER2 receptor, tucatinib inhibits the autophosphorylation of the receptor. This inhibition prevents the activation of key downstream signaling pathways, notably the PI3K/AKT and MAPK pathways, which are essential for cell proliferation and survival. By disrupting these pathways, tucatinib effectively halts the proliferation of cancer cells and induces apoptosis, thereby exerting its therapeutic effects (Fig. 1).<sup>[12]</sup>

The specificity of tucatinib for the HER2 receptor is particularly advantageous, as it reduces the likelihood of off-target effects commonly seen with less selective TKIs. This high selectivity allows for a more effective inhibition of HER2 signaling with potentially fewer side effects, improving the drug's therapeutic index.<sup>[13]</sup> Additionally, tucatinib's ability to cross the blood-brain barrier addresses the challenge of brain metastases in HER2-positive breast cancer, a common site of disease progression. By targeting and inhibiting the HER2 signaling pathway, tucatinib disrupts critical processes involved in cancer cell survival and proliferation, offering a potent treatment option for patients with HER2-positive cancers.<sup>[14]</sup>

### **2.2 Synergistic effects with other therapies**

Tucatinib's inhibition of the HER2 signaling pathway not only directly impedes cancer cell proliferation but exhibits synergistic effects when combined with other therapies, enhancing overall treatment efficacy.<sup>[15]</sup> For instance, combining tucatinib with trastuzumab, a monoclonal antibody that targets the extracellular domain of HER2, results in a dual blockade of the receptor, both externally and internally, leading to a more comprehensive inhibition of HER2 signaling.<sup>[16]</sup> Furthermore, when used alongside chemotherapy agents such as capecitabine, tucatinib enhances the cytotoxic effects of chemotherapy on cancer cells. This multi-pronged approach maximizes the disruption of cancer cell growth and survival mechanisms and helps overcome resistance mechanisms that might develop with monotherapy. Such synergistic combinations have been shown to significantly improve clinical outcomes in patients with HER2-positive breast cancer, including those with advanced or metastatic disease.<sup>[15]</sup>

**Fig 1:** Mechanism of tucatinib with trastuzumab by inhibiting HER2 signaling pathway



Abbreviations: AKT, Protein kinase B; EGFR, epidermal growth factor receptor; HER2, Human epidermal growth factor receptor 2; PI3K, Phosphoinositide 3-kinases.

### 3. CLINICAL EFFICACY OF TUCATINIB

Patients with HER2-positive MBC who have experienced disease progression after treatment with multiple HER2-targeted therapies face limited options. Tucatinib, an investigational oral medication, is a highly selective inhibitor of the HER2 tyrosine kinase. In a clinical trial conducted by RK Murthy et al.<sup>[17]</sup>, patients received either tucatinib or placebo in combination with trastuzumab and capecitabine. The addition of tucatinib to trastuzumab and capecitabine led to improved progression-free survival and overall survival compared to the addition of a placebo. In the HER2CLIMB trial by NU Lin et al.<sup>[18]</sup>, a subgroup analysis demonstrated that tucatinib combined with trastuzumab and capecitabine enhanced overall survival and reduced the risk of new brain lesions. These findings underscore the significance of this treatment regimen for patients with ERBB2-positive MBC, including those with brain metastases (Table 1).

**Table 1:** Clinical efficacy of Tucatinib in combination therapy

| Trial                            | Study design                                  | Sample size, Study population                         | Intervention, dose, frequency  | Results   | Inference  |
|----------------------------------|---|---|--|---|--|
| RK Murthy et al. <sup>[17]</sup> | International, randomized, double-blind trial | N=480, Patients with HER2-positive MBC, Age ≥18 years | Tucatinib (300 mg orally BID +[trastuzumab(6 mg/kg)&capecitabine (1000 mg/m <sup>2</sup> )]vs placebo +Combination for 21 days | <b>Progression-free survival rate(At 1 year):</b> Tucatinib-combination group: 33.1%; Placebo-combination group: 12.3% (95% CI, 0.42 to | Tucatinib and combination resulted in better progression-free survival and overall survival outcomes |

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|  |   |   |   | <p>0.71; P&lt;0.001)</p> <p><b>Median duration of progression-free survival:</b>7.8 months (95% CI, 7.5 to 9.6) and 5.6 months (95% CI, 4.2 to 7.1), respectively</p> <p><b>Overall survival rate (At2-years):</b> Tucatinib-combination group:44.9%; Placebo-combination group: 26.6%(95% CI, 0.50 to 0.88; P=0.005)</p> <p><b>Median duration of overall survival:</b>21.9 months (95% CI, 18.3 to 31.0) and 17.4 months (95% CI, 13.6 to 19.9), respectively.</p> <p>ORR: 40.6% (95% CI, 35.3 to 46.0) vs. 22.8% (95% CI, 16.7 to 29.8) (P&lt;0.001) respectively.</p> | than a placebo.   |
| NU Lin et al. HER2CLIM B trial <sup>[18]</sup> | International , multicenter, randomized, double-blind, placebo-controlled | N=612, patients with ERBB2-positive MBC, including those with BMs | Tucatinib (300 mg orally BID) or placebo (orally BID), both in combination with trastuzumab (6 mg/kg iv or scelevery 3 weeks) and capecitabine(1000 | <p><b>Median OS (9.1 months):</b></p> <p>Tucatinib-combination group vs. placebo-combination group:21.6 vs.</p>   | Tucatinib, in combination with trastuzumab and capecitabine , improved OS and |

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|  | clinical trial |  | mg/m <sup>2</sup> orally BID on days 1-14 of each 3-week cycle). | 12.5months; 95% CI, 18.1-28.5 vs. 11.2-16.9<br><br><b><u>Duration of intracranial response:</u></b><br><br>Tucatinib-combination group:8.6 months (95% CI, 5.5-10.3 months)<br><br>Placebo-combination group:3.0 months (95% CI, 3.0-10.3 months)<br><br><b><u>ORR-IC:47.3% vs 20.0%</u></b> | ORR-IC while reducing the risk of developing new brain lesions. |
|--|----------------|--|--|--|---|

Abbreviations: BID, twice daily; BM, brain metastases; CI, confidence interval; HER2-positive MBC, Human epidermal growth factor 2-positive metastatic breast cancer; ORR-IC, intracranial objective response rate; OS, overall survival.

#### 4. SAFETY PROFILE

##### 4.1 Common adverse events

In a clinical trial conducted by RK Murthy et al.<sup>[17]</sup>, the most frequent adverse events in patients receiving the tucatinib combination were diarrhea, palmar-plantar erythrodysesthesia syndrome, nausea, fatigue, and vomiting. Similarly, the HER2CLIMB analysis<sup>[18]</sup> indicated that the tucatinib combination was well tolerated, with a low discontinuation rate due to adverse events (Table 2).

**Table 2:** Safety profile of Tucatinib in combination therapy

| Trial                            | Study design                                  | Sample size, Study population                         | Intervention, dose, frequency   | Results   | Inference  |
|----------------------------------|---|---|---|---|--|
| RK Murthy et al. <sup>[17]</sup> | International, randomized, double-blind trial | N=480, Patients with HER2-positive MBC, Age ≥18 years | Tucatinib (300 mg orally BID + [trastuzumab (6 mg/kg) & capecitabine (1000 mg/m <sup>2</sup> )] vs placebo +Combination | <b><u>Common adverse events (Grade 3 or higher) in tucatinib combination vs placebo:</u></b> Diarrhea (12.9% and 8.6%), PPE syndrome, elevations in ALT (5.4% and 0.5%) and AST | Safety events of note included diarrhea that was managed with short courses of antidiarrheal agents and transient, |

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|  |  |  | for 21 days  | (4.5% and 0.5%) levels, nausea, fatigue, and vomiting  | reversible elevations in liver enzyme levels   |
| G Curigliano et al. <sup>[18]</sup> (HER2CLIMB-Final analysis) | Randomized, double-blind, placebo-controlled trial | N=612, patients with pretreated HER2D MBC with and without BMs | Tucatinib (300 mg orally BID) or placebo (orally BID), both in combination with trastuzumab (6 mg/kg iv or sc every 3 weeks) and capecitabine (1000 mg/m <sup>2</sup> orally BID on days 1-14 of each 3-week cycle). | <b>Adverse events ingrade 1 or 2 [N(%)]:</b> diarrhea[331 (81.9)], PPE syndrome [264 (65.3)], nausea [264 (65.3)], fatigue [264 (65.3)], and vomiting [152 (37.6)]<br><b>Adverse events most common in grade 3[N(%)]:</b> PPE syndrome [57 (14.1)], diarrhea[53 (13.1)], elevations in ALT [23 (5.7)] and AST [19 (4.7)], and fatigue [22 (5.4)] | The Tucatinib combination was well tolerated, with a low discontinuation rate due to adverse events. |

Abbreviations: ALT, alanine aminotransferase;AST, aspartate aminotransferase; BID, twice daily;BM, brain metastases; HER2-positive MBC, Human epidermal growth factor receptor 2-positive metastatic breast cancer; PPE, palmar-plantar erythrodysesthesia.

## 5. LONG-TERM SAFETY CONSIDERATIONS

Long-term safety considerations for tucatinib are critical due to its chronic administration in a population often receiving multiple therapies. Key concerns include potential cardiotoxicity, given the history of heart-related issues with other HER2-targeted therapies, necessitating regular cardiac monitoring.<sup>[19]</sup> Hepatotoxicity is another significant risk, warranting frequent liver function tests to detect and manage any liver damage promptly.<sup>[20]</sup> Gastrointestinal toxicity, particularly severe diarrhea, must be vigilantly monitored and managed to prevent dehydration and other complications. Additionally, the risk of drug interactions and the impact on patients with pre-existing conditions or those taking concomitant medications should be continuously evaluated to ensure a favorable risk-benefit balance over extended treatment periods.<sup>[21]</sup>

## 6. TUCATINIB: PLACE IN THERAPY

### 6.1 Guideline Recommendations

Treatment options for patients diagnosed with HER2-positive metastatic breast cancer typically involve a combination of taxane chemotherapy, trastuzumab, and pertuzumab in the initial line of therapy, followed by trastuzumab emtansine (T-DM1) as a second-line treatment.<sup>[1]</sup> More recently, the therapeutic armamentarium has been increased, and new effective therapies are available as treatment options for patients with HER2+ breast cancer who had no benefit from previous therapies. According to ESMO guidelines, several factors, such as the type of prior second-line therapy, patient characteristics, and benefit-risk profile of drugs, must be considered when choosing the best option for these patients. Specifically, tucatinib plus trastuzumab, capecitabine, and TDM-1 are the two treatment options recommended as third-line therapies in HER2+ BC patients with two failed treatment lines.<sup>[9]</sup>

**Table 3:** Guidelines and recommendations for breast cancer

| Guidelines  | Recommendation  |
|---|---|
| <b>National Comprehensive Cancer Network (NCCN)</b> <sup>[22]</sup>             | Tucatinib+ trastuzumab+ capecitabine (category 1) is a recommended regimen for HER-2 positive disease, with the following footnote: For adult patients with advanced unresectable or HER-2 MBC, including patients with brain metastases who have received one or more lines of prior HER-2 targeted therapy in the metastatic setting. |
| <b>American Society of Clinical Oncology (ASCO)</b> <sup>[23]</sup>             | Tucatinib capecitabine and trastuzumab may be offered to patients with HER2-positive MBC who have brain metastases and whose disease has progressed on at least one previous HER2-directed therapy to delay local treatment until there is evidence of intracranial progression   |
| <b>European Society for Medical Oncology(ESMO)</b> <sup>[24]</sup>              | A combination of tucatinib with trastuzumab and capecitabine displayed promising antitumor activity in patients with HER2-positive MBC, including those with BMs  |
| <b>National Institute for Health and Care Excellence (NICE)</b> <sup>[25]</sup> | Tucatinib is an option for treating HER2-positive breast cancer that has spread in people who have already tried 2 or more anti-HER2 treatments.  |

Abbreviations: BM, brain metastases; HER2positive, Human epidermal growth factor receptor 2-positive; MBC, metastatic breast cancer.

## 7. EMERGING COMBINATION STRATEGIES

Tucatinib is a selective HER2 TKI that, due to its reduced inhibition of EGFR, has demonstrated antitumor activity in preclinical models of breast and gastric cancers when used alone<sup>[26]</sup> or in combination with trastuzumab in HER2-positive breast cancer xenograft models.<sup>[27]</sup> These promising preclinical results led to a phase 1 clinical trial (HER2CLIMB and NCT02614794) to evaluate tucatinib in combination with trastuzumab and capecitabine. This combination exhibited significant antitumor effects in patients with MBC, with the main adverse events reported being diarrhea, nausea, and palmar-plantar erythrodysesthesia.<sup>[17]</sup> Furthermore, the phase 3 HER2CLIMB trial<sup>[18]</sup> demonstrated that tucatinib effectively reduced brain metastases, leading to its approval by the FDA as the first TKI for treating brain metastases. Given these encouraging outcomes, multiple clinical trials are now investigating tucatinib in combination with T-DM1 (NCT04457596, NCT03975647, NCT01983501, and NCT05323955)<sup>[28-31]</sup>, T-DXd (NCT04539938 and NCT04538742)<sup>[32,33]</sup>, and CDK4/6 inhibitors (NCT03054363)<sup>[34]</sup> in patients with HER2-positive breast cancer (Table 4).

**Table 4:** Current ongoing clinical trials of Tucatinib in HER2+ breast cancer

| Description  | In Combination with | Clinical Trial Identifier                          | Population          | Reference          |
|--|---------------------|--|---------------------|--------------------|
| Selective and reversible HER2 inhibitor with minimal inhibition of EGFR/HER1 | T-DM1               | NCT04457596, NCT03975647, NCT01983501, NCT05323955 | HER2+ breast cancer | <sup>[28-31]</sup> |
|  | T-DXd               | NCT04539938, NCT04538742                           | HER2+ breast cancer | <sup>[32,33]</sup> |
|  | CDK4/6is            | NCT03054363  | HER2+ breast cancer | <sup>[34]</sup>    |

Abbreviations: CDK4/6is, cyclin-dependent kinase 4 inhibitors; HER2, human epidermal growth factor receptor 2; T-DM1, trastuzumab-emtansine; T-DXd, trastuzumab-deruxtecan.

## 8. FUTURE RESEARCH DIRECTIONS AND UNMET NEEDS OF TUCATINIB IN BREAST CANCER

Breast cancer remains one of the most prevalent and formidable malignancies affecting women globally.<sup>[35]</sup> Despite advancements in treatment modalities, the heterogeneity of the disease often leads to therapeutic challenges, particularly in cases of metastatic or recurrent breast cancer. In this context, the emergence of novel targeted therapies such as tucatinib presents a promising avenue for improving patient outcomes and addressing unmet medical needs.<sup>[36]</sup> The pivotal HER2CLIMB trial showcased the significant clinical benefits of tucatinib when combined with trastuzumab and capecitabine, which substantially improved progression-free survival, overall survival, and quality of life compared to standard therapy alone. These findings underscore the potential of tucatinib to redefine the treatment landscape for HER2-positive MBC, offering a much-needed option for patients who have progressed on prior lines of therapy.<sup>[18]</sup>

Looking ahead, the future perspective of tucatinib in breast cancer appears promising on several fronts. While tucatinib's initial approval was focused on HER2-positive MBC, ongoing research efforts are exploring its utility in other settings, including early-stage HER2-positive breast cancer and central nervous system metastases.<sup>[13]</sup> Tucatinib's favorable safety profile and synergistic mechanisms of action make it an attractive candidate for combination therapies. Preclinical and clinical studies evaluate tucatinib in combination with other targeted agents, immunotherapies, and chemotherapy agents to enhance treatment efficacy, overcome resistance mechanisms, and minimize treatment-related toxicities.<sup>[37]</sup>

As precision medicine continues to evolve, identifying predictive biomarkers to guide patient selection and optimize treatment strategies with tucatinib remains a crucial area of investigation.<sup>[38]</sup> Biomarker-driven approaches hold the potential to identify patient subgroups most likely to benefit from tucatinib-based therapies, enabling personalized treatment decisions and maximizing therapeutic outcomes. Despite the initial success of tucatinib, acquired resistance remains a significant challenge in the clinical management of HER2-positive breast cancer. Understanding the molecular mechanisms underlying resistance to tucatinib and developing rational strategies to overcome resistance represent critical research focus areas, such as prolonging treatment responses and improving long-term patient outcomes.<sup>[13]</sup>

Tucatinib therapy, while effective for HER2-positive metastatic breast cancer, has several limitations and unmet needs. These include the development of resistance mechanisms, the need for improved management of side effects like diarrhea and liver toxicity, limited accessibility and affordability for patients, and insufficient data on its efficacy across diverse patient populations. Additionally, there is a need for further research on optimal combination therapies to enhance their effectiveness and extend patient survival.<sup>[39]</sup>

## CONCLUSION

Tucatinib represents a promising advancement in the treatment of HER2-positive breast cancer, including patients with brain metastases, demonstrating significant improvements in clinical outcomes and quality of life. Ongoing research and innovative approaches will likely expand its utility across various settings and patient populations. Ensuring global access to tucatinib is essential to maximize its impact on public health. Through continued research, innovation, and advocacy, tucatinib has the potential to transform breast cancer treatment and significantly benefit patients worldwide.

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