International Research Journal of Oncology

Volume 7, Issue 2, Page 186-198, 2024; Article no.IRJO.121450

Tucatinib: A Breakthrough in Advanced Breast Cancer Therapy

Siddhi Parab [a*], Aanchal Gvalani [a], Priyanka Das [a], Sunaina Anand [a] and Anish Desai [a]

[a] Department of Medical Affairs, IntelliMed Healthcare Solutions Pvt Ltd, Mumbai, India.

Authors' contributions

This work was carried out in collaboration among all authors. Author SP collected the data under the supervision of authors AG, PD, SA, and AD. Author SP wrote the first draft, which was reviewed by all the authors. All authors read and approved the final manuscript.

Article Information

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/121450

Minireview Article

Received: 11/06/2024
Accepted: 14/08/2024
Published: 22/08/2024

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 inhibits HER2 signalling through its intracellular tyrosine kinase domain, disrupting critical pathways such as PI3K/AKT and MAPK. The HER2CLIMB trial (N=612) showed that combining tucatinib with trastuzumab and capecitabine significantly improved progression-free survival (PFS) (9.9 vs. 4.2 months, 95% CI) and overall survival (OS) (21.6 vs. 12.5 months, 95% CI) compared to placebo, with notable efficacy in reducing brain metastases. The most common adverse events associated with tucatinib were diarrhoea [331 (81.9%)], palmar-plantar erythrodysesthesia [264 (65.3%)], nausea [264 (65.3%)], and vomiting [152 (37.6%)]. Despite these, the overall safety profile was manageable and tolerable. Current NCCN, ASCO, and ESMO guidelines endorse tucatinib for patients with HER2-positive MBC who have progressed through prior HER2-targeted therapies. Ongoing clinical trials investigate tucatinib's efficacy with

**Corresponding author: E-mail: siddhi.parab@intellimed.org;*

Cite as: *Parab, Siddhi, Aanchal Gvalani, Priyanka Das, Sunaina Anand, and Anish Desai. 2024. "Tucatinib: A Breakthrough in Advanced Breast Cancer Therapy". International Research Journal of Oncology 7 (2):186-98. https://journalirjo.com/index.php/IRJO/article/view/159.*

other agents to overcome resistance mechanisms and enhance treatment outcomes. Future research should optimise combination therapies, manage long-term side effects, and identify 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"[1]. "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" [2]. "Breast cancer is the most common cancer in India, accounting for 28.2% of all female cancers" [3]. "A recent SURVCAN-3 study [4] published in 2023 found that the 3-year median survival for breast cancer across countries was 84%, whereas, in India, it was 68%" [5].

"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 (PFS) and overall survival (OS)" [6]. 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 tumour burden and central nervous system (CNS) involvement [7]. These treatments often prolong relapse-free survival when used as adjuvants, although accessibility to these drugs can be limited by cost and availability [8]. From the patient's perspective, while traditional treatments have been effective, newer drugs, specifically designed to penetrate the CNS and target HER2-positive tumours, 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" [1]. "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" [9].

"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" [1,10]. "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" [11].

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 signalling pathways that regulate cell growth and survival [12]. 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 signalling 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) [12–15].

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 signalling with potentially fewer side effects, improving the drug's therapeutic index [16,17]. 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 signalling pathway, tucatinib disrupts critical processes involved in cancer cell survival and proliferation, offering a potent treatment option for patients with HER2-positive cancers.[18]

2.2 Synergistic Effects with Other Therapies

Tucatinib's inhibition of the HER2 signalling pathway not only directly impedes cancer cell proliferation but exhibits synergistic effects when combined with other therapies, enhancing overall treatment efficacy [19]. 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 signalling [20]. Furthermore, when used alongside chemotherapy agents such as capecitabine, tucatinib enhances the cytotoxic effects of chemotherapy on cancer cells. This multi-pronged approach maximises 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 [19,21].

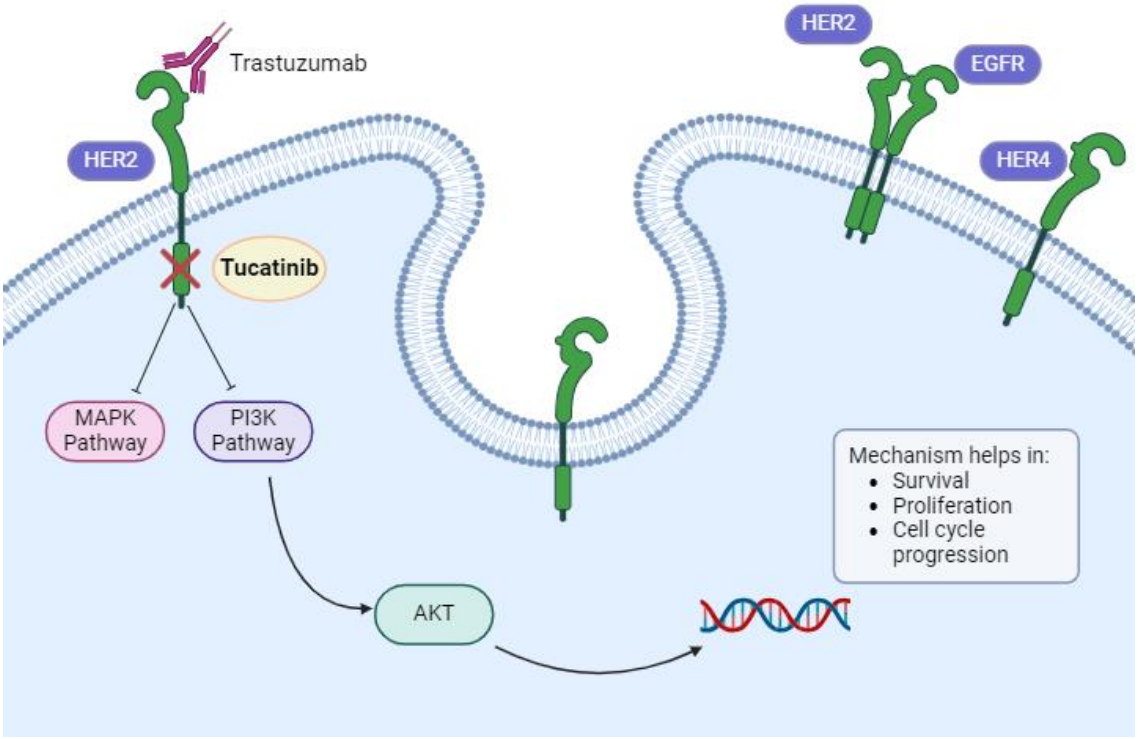

Fig. 1. Mechanism of tucatinib with trastuzumab by inhibiting HER2 signalling pathway
Abbreviations: AKT, Protein kinase B; EGFR, epidermal growth factor receptor; HER2, Human epidermal growth factor receptor 2; PI3K, Phosphoinositide 3-kinases

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. [22]	International, randomised, 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^2)] vs placebo +Combination for 21 days	PFS rate (At 1 year): Tucatinib-combination group: 33.1%; Placebo-combination group: 12.3% (95% CI, 0.42 to 0.71; P<0.001) Median duration of PFS: 7.8 months (95% CI, 7.5 to 9.6) and 5.6 months (95% CI, 4.2 to 7.1), respectively OS rate (At2-years): Tucatinib-combination group: 44.9%; Placebo-combination group: 26.6% (95% CI, 0.50 to 0.88; P=0.005) Median duration of OS: 21.9 months (95% CI, 18.3 to 31.0) and 17.4 months (95% CI, 13.6 to 19.9), respectively. ORR: 40.6% (95% CI, 35.3 to 46.0) vs. 22.8% (95% CI, 16.7 to 29.8) (P<0.001) respectively.	**Tucatinib and combination resulted in better PFS and OS outcomes than a placebo.**
NU Lin et al. HER2CLIMB trial [23]	International, multicenter, randomised, double-blind, placebo-controlled clinical trial	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 sc every 3 weeks) and capecitabine (1000 mg/m2 orally BID on days 1-14 of each 3-week	Median PFS Tucatinib-combination group: 9.9 months (95% CI, 8.4-11.7 months Placebo-combination group: 4.2 months (95% CI, 3.6-5.7 months Median OS (9.1 months):	**Tucatinib, in combination with trastuzumab and capecitabine, was associated with a 61.4% reduction in the risk of CNS-PFS, improved OS and**

Trial	Study design	Sample size, Study population	Intervention, dose, frequency	Results	Inference
			cycle).	Tucatinib-combination group vs. placebo-combination group: 21.6 vs. 12.5months; 95% CI, 18.1-28.5 vs. 11.2-16.9 Duration of intracranial response: Tucatinib-combination group: 8.6 months (95% CI, 5.5-10.3 months) Placebo-combination group: 3.0 months (95% CI, 3.0-10.3 months) ORR-IC: 47.3% vs 20.0%	**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 receptor 2-positive metastatic breast cancer; PFS, progression-free survival; ORR-IC, intracranial objective response rate; OS, overall survival

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. [22]	International, randomised, 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^2)] vs placebo +Combination for 21 days	Common adverse events (Grade 3 or higher) in tucatinib combination vs placebo: Diarrhea (12.9% and 8.6%), PPE syndrome, elevations in ALT (5.4% and 0.5%) and AST (4.5% and 0.5%) levels, nausea, fatigue, and vomiting	**Safety events of note included diarrhoea that was managed with short courses of antidiarrheal agents and transient, reversible elevations in liver enzyme levels**
G Curigliano et al. [23] (HER2CLIMB-Final	Randomised, double-blind, placebo-	N=612, patients with pretreated	Tucatinib (300 mg orally BID) or placebo (orally	Adverse events in grade 1 or 2 [N(%)]: diarrhoea	**The Tucatinib combination was well**

Trial	Study design	Sample size, Study population	Intervention, dose, frequency	Results	Inference
analysis)	controlled trial	HER2D MBC with and without BMs	BID), both in combination with trastuzumab (6 mg/kg iv or sc every 3 weeks) and capecitabine (1000 mg/m2 orally BID on days 1-14 of each 3-week cycle).	[331 (81.9)], PPE syndrome [264 (65.3)], nausea [264 (65.3)], fatigue [264 (65.3)], and vomiting [152 (37.6)] Adverse events most common in grade 3[N(%)]: PPE syndrome [57 (14.1)], diarrhoea [53 (13.1)], elevations in ALT [23 (5.7)] and AST [19 (4.7)], and fatigue [22 (5.4)]	**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

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—a clinical trial conducted by RK Murthy et al. [22] In the HER2CLIMB trial by NU Lin et al., patients received either tucatinib or placebo in combination with trastuzumab and capecitabine. The addition of tucatinib to trastuzumab and capecitabine led to improved PFS and OS compared to the addition of a placebo [23], a subgroup analysis demonstrated that tucatinib combined with trastuzumab and capecitabine enhanced OS 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).

4. SAFETY PROFILE

4.1 Common Adverse Events

In a clinical trial conducted by RK Murthy et al. [22], the most frequent adverse events in patients receiving the tucatinib combination were diarrhoea, palmar-plantar erythrodysesthesia syndrome, nausea, fatigue, and vomiting. Similarly, the HER2CLIMB analysis [23] indicated that the tucatinib combination was well tolerated, with a low discontinuation rate due to adverse events (Table 2).

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 [24]. Key concerns include potential cardiotoxicity, given the history of heart-related issues with other HER2-targeted therapies, necessitating regular cardiac monitoring [25]. Hepatotoxicity is another significant risk, warranting frequent liver function tests to detect and manage any liver damage promptly [26]. Gastrointestinal toxicity, particularly severe diarrhoea, 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 favourable risk-benefit balance over extended treatment periods [27].

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 [1,28]. 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 [29]. 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 [9].

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 [30] or in combination with trastuzumab in HER2-positive breast cancer xenograft models [31]. 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 diarrhoea, nausea, and palmar-plantar erythrodysesthesia [22]. Furthermore, the phase 3 HER2CLIMB trial [23] 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) [32-35], T-DXd (NCT04539938 and NCT04538742) [36,37], and CDK4/6 inhibitors (NCT03054363) [38] in patients with HER2-positive breast cancer (Table 4).

Table 3. Guidelines and recommendations for breast cancer

Guidelines	Recommendation
National Comprehensive Cancer Network (NCCN) [39]	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.
American Society of Clinical Oncology (ASCO) [40]	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
European Society for Medical Oncology(ESMO)[41]	A combination of tucatinib with trastuzumab and capecitabine displayed promising antitumor activity in patients with HER2-positive MBC, including those with BMs
National Institute for Health and Care Excellence (NICE) [42]	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; HER2 positive; Human epidermal growth factor receptor 2-positive; MBC, metastatic breast cancer

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	[32-35]
	T-DXd	NCT04539938, NCT04538742	HER2+ breast cancer	[36,37]
	CDK4/6is	NCT03054363	HER2+ breast cancer	[38]

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 [43]. Despite advancements in treatment modalities, the heterogeneity of the disease often leads to therapeutic challenges, particularly in cases of metastatic or recurrent breast cancer [44]. 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 [45]. The pivotal HER2CLIMB trial showcased the significant clinical benefits of tucatinib when combined with trastuzumab and capecitabine. Tucatinib substantially improved PFS, OS, 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 [23].

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 [16,46]. Tucatinib's favourable 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 minimise treatment-related toxicities [47].

As precision medicine continues to evolve, identifying predictive biomarkers to guide patient selection and optimise treatment strategies with tucatinib remains a crucial area of investigation [48]. Biomarker-driven approaches hold the potential to identify patient subgroups most likely to benefit from tucatinib-based therapies, enabling personalised treatment decisions and maximising therapeutic outcomes [49]. 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 [16,50].

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 diarrhoea 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 [51].

9. CONCLUSION

Tucatinib represents a promising advancement in the treatment of HER2-positive breast cancer, including patients with brain metastases. It has demonstrated 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 maximise 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.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of manuscripts.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Tucatinib (Tukysa): CADTH reimbursement review: Therapeutic area: Advanced or metastatic breast cancer. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2022.
   Available:http://www.ncbi.nlm.nih.gov/books/NBK595371/
2. Breast cancer.;
   Available:https://www.who.int/news-room/fact-sheets/detail/breast-cancer
3. Sathishkumar K, Chaturvedi M, Das P, Stephen S, Mathur P. Cancer incidence estimates for 2022 and projection for 2025: Result from national cancer registry programme, India. Indian J Med Res. 2022;156(4–5):598–607.
   Available:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10231735/
4. Swaminathan R. Cancer survival in countries in transition, with a focus on selected Asian countries. In: Vaccarella S, Lortet-Tieulent J, Saracci R, Conway DI, Straif K, Wild CP, editors. Reducing social inequalities in cancer: Evidence and priorities for research. Lyon (FR): International Agency for Research on Cancer; 2019.
   Available:http://www.ncbi.nlm.nih.gov/books/NBK566195/

5. Soerjomataram I, Cabasag C, Bardot A, Fidler-Benaoudia MM, Miranda-Filho A, Ferlay J, et al. Cancer survival in Africa, central and south America, and Asia (SURVCAN-3): A population-based benchmarking study in 32 countries. Lancet Oncol. 2023;24(1):22–32.

6. Bredin P, Walshe JM, Denduluri N. Systemic therapy for metastatic HER2-positive breast cancer. Semin Oncol. 2020;47(5):259–69.

7. Chakrabarti K, Swartz LK, Gill A, Fang F, Kidwell KM, Morikawa A. Development of CNS metastases in breast cancer patients treated with curative intent: A case–control study. CNS Oncol. 2020;9(3):CNS61.
Available:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7546155/

8. Ocran Mattila P, Ahmad R, Hasan SS, Babar ZUD. Availability, affordability, access, and pricing of anti-cancer medicines in low- and middle-income countries: A systematic review of literature. Front Public Health. 2021;9:628744.
Available:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8120029/

9. Gennari A, André F, Barrios CH, Cortés J, de Azambuja E, De Michele A, et al. ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. Ann Oncol 2021;32(12):1475–95.

10. Shah M, Wedam S, Cheng J, Fiero MH, Xia H, Li F, et al. FDA approval summary: Tucatinib for the treatment of patients with advanced or metastatic HER2-positive breast cancer. Clinical Cancer Research. 2021;27(5):1220–6.
Available:https://aacrjournals.org/clincancerres/article/27/5/1220/83630/FDA-Approval-Summary-Tucatinib-for-the-Treatment

11. Gupta R, Gupta S, Antonios B, Ghimire B, Jindal V, Deol J, et al. Therapeutic landscape of advanced HER2-positive breast cancer in 2022. Med Oncol. 2022;39(12):258.

12. Olson D, Taylor J, Willis K, Hensley K, Allred S, Zaval M, et al. HER2-selective and reversible tyrosine kinase inhibitor tucatinib potentiates the activity of T-DM1 in preclinical models of HER2-positive Breast Cancer. Cancer Res Commun. 2023;3(9):1927–39.
Available:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10519189/

13. Kulukian A, Lee P, Taylor J, Rosler R, de Vries P, Watson D, et al. Preclinical activity of HER2-selective tyrosine kinase inhibitor tucatinib as a single agent or in combination with trastuzumab or docetaxel in solid tumor models. Molecular Cancer Therapeutics. 2020;19(4):976–87.
Available:https://doi.org/10.1158/1535-7163.MCT-19-0873

14. Loibl S, Gianni L. HER2-positive breast cancer. Lancet. 2017;389(10087):2415–29.

15. Kumar R, Goel H, Solanki R, Rawat L, Tabasum S, Tanwar P, et al. Recent developments in receptor tyrosine kinase inhibitors: A promising mainstay in targeted cancer therapy. Medicine in Drug Discovery. 2024;23:100195.
Available:https://www.sciencedirect.com/science/article/pii/S2590098624000204

16. Swain SM, Shastry M, Hamilton E. Targeting HER2-positive breast cancer: Advances and future directions. Nat Rev Drug Discov. 2023;22(2):101–26.
Available:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9640784/

17. Yang X, Wu D, Yuan S. Tyrosine kinase inhibitors in the combination therapy of HER2 positive breast cancer. Technol Cancer Res Treat. 2020;19:1533033820962140.
Available:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7592330/

18. Garcia-Alvarez A, Papakonstantinou A, Oliveira M. Brain metastases in HER2-positive breast cancer: Current and novel treatment strategies. Cancers (Basel). 2021;13(12):2927.
Available:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8230933/

19. Sirhan Z, Thyagarajan A, Sahu RP. The efficacy of tucatinib-based therapeutic approaches for HER2-positive breast cancer. Mil Med Res. 2022;9:39.
Available:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9277867/

20. Kreutzfeldt J, Rozeboom B, Dey N, De P. The trastuzumab era: Current and upcoming targeted HER2+ breast cancer therapies. Am J Cancer Res. 2020;10(4):1045–67.
Available:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7191090/

21. Wilkinson L, Gathani T. Understanding breast cancer as a global health concern. Br J Radiol. 2022;95(1130):20211033.

Available:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8822551/

22. Tucatinib, Trastuzumab, Capecitabine for HER2-positive metastatic breast cancer. New England Journal of Medicine;
Available:https://www.nejm.org/doi/full/10.1056/NEJMoa1914609
23. Tucatinib vs Placebo, Both in combination with trastuzumab and capecitabine, for previously treated ERBB2 (HER2)-positive metastatic breast cancer in patients with brain metastases: Updated exploratory analysis of the HER2CLIMB randomized clinical trial. Neurology. JAMA Oncology. JAMA Network;
Available:https://jamanetwork.com/journals/jamaoncology/fullarticle/2799133
24. IJMS | Free Full-Text | Molecular targeting of the human epidermal growth factor receptor-2 (HER2) genes across various cancers;
Available:https://www.mdpi.com/1422-0067/25/2/1064
25. Dent SF, Morse A, Burnette S, Guha A, Moore H. Cardiovascular toxicity of novel HER2-targeted therapies in the treatment of breast cancer. Curr Oncol Rep. 2021;23(11):128.
26. Viganò M, La Milia M, Grassini MV, Pugliese N, De Giorgio M, Fagiuoli S. Hepatotoxicity of small molecule protein kinase inhibitors for cancer. Cancers (Basel). 2023;15(6):1766.
Available:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10046041/
27. Tucatinib. In: LiverTox: Clinical and Research Information on Drug-Induced Liver Injury. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012.
Available:http://www.ncbi.nlm.nih.gov/books/NBK595112/
28. Schettini F, Conte B, Buono G, De Placido P, Parola S, Griguolo G, et al. T-DM1 versus pertuzumab, trastuzumab and a taxane as first-line therapy of early-relapsed HER2-positive metastatic breast cancer: an Italian multicenter observational study. ESMO Open. 2021;6(2):100099.
Available:https://www.sciencedirect.com/science/article/pii/S2059702921000569
29. Gion M, Trapani D, Cortés A, Valenza C, Lin N, Cortés J, et al. Systemic therapy for HER2-Positive metastatic breast cancer: Moving into a new era. American society of clinical oncology educational book. 2022;(42):82–92.
Available:https://ascopubs.org/doi/10.1200/EDBK_351222
30. Kulukian A, Lee P, Taylor J, Rosler R, De Vries P, Watson D, et al. Preclinical activity of HER2-selective tyrosine kinase inhibitor tucatinib as a single agent or in combination with trastuzumab or docetaxel in solid tumor models. Mol Cancer Ther. 2020;19(4):976–87.
31. O'Brien NA, Huang HKT, McDermott MSJ, Madrid AM, Luo T, Ayala R, et al. Tucatinib has selective activity in HER2-positive cancers and significant combined activity with approved and novel breast cancer-targeted therapies. Mol Cancer Ther. 2022;21(5):751–61.
32. Alliance for Clinical Trials in Oncology. The CompassHER2 Trials (Comprehensive Use of pathologic response assessment to optimize therapy in HER2-positive breast Cancer) CompassHER2 residual disease (RD), a Double-Blinded, Phase III Randomized Trial of T-DM1 Compared With T-DM1 and Tucatinib. clinicaltrials.gov; 2024.
Available:https://clinicaltrials.gov/study/NCT04457596
33. Seagen Inc. Randomized, double-blind, phase 3 study of tucatinib or placebo in combination with ado-trastuzumab emtansine (T-DM1) for subjects with unresectable locally-advanced or metastatic HER2+ breast cancer (HER2CLIMB-02). clinicaltrials.gov; 2024.
Available:https://clinicaltrials.gov/study/NCT03975647
34. Seagen Inc. A Phase 1b, Open-label study to assess the safety and tolerability of tucatinib (ONT-380) combined with ado-trastuzumab emtansine (Trastuzumab Emtansine; T-DM1). clinicaltrials.gov; 2020.
Available:https://clinicaltrials.gov/study/NCT01983501
35. Anders C. Secondary BRain metastases prevention after isolated intracranial progression on trastuzumab/pertuzumab or T-DM1 in patients with advanced human epidermal growth factor receptor 2+ brEast cancer with the addition of tucatinib. clinicaltrials.gov; 2024.
Available:
https://clinicaltrials.gov/study/NCT05323955

36. Seagen Inc. A Single Arm, Open label phase 2 study of tucatinib in combination with trastuzumab deruxtecan in subjects with previously treated unresectable locally-advanced or metastatic HER2+ Breast Cancer. clinicaltrials.gov; 2024.
Available:https://clinicaltrials.gov/study/NCT04539938

37. AstraZeneca. A Phase 1b/2 multicentre, open-label, modular, dose-finding and dose-expansion study to explore the safety, tolerability, and anti-tumour activity of trastuzumab deruxtecan (T-DXd) in combination with other anti-cancer agents in patients with HER2-positive metastatic breast cancer (DESTINY-Breast07). clinicaltrials.gov; 2024.
Available:https://clinicaltrials.gov/study/NCT04538742

38. University of Colorado, Denver. Phase IB/II open-label single arm study to evaluate safety and efficacy of tucatinib in combination with palbociclib and letrozole in subjects with hormone receptor positive and HER2-positive metastatic breast cancer. clinicaltrials.gov; 2023.
Available:https://clinicaltrials.gov/study/NCT03054363

39. Modi, et al. Trastuzumab deruxtecan in previously treated HER2-.pdf; 2020.
Available:https://www2.tri-kobe.org/nccn/guideline/breast/english/breast.pdf

40. Management of advanced human epidermal growth factor receptor 2–positive breast cancer and brain metastases: ASCO Guideline Update. Journal of Clinical Oncology.;
Available:https://ascopubs.org/doi/10.1200/JCO.22.00520

41. Corti C, Criscitiello C. Tucatinib approval by EMA expands options for HER2-positive locally advanced or metastatic breast cancer. ESMO Open. 2021;6(2).
Available:https://www.esmoopen.com/article/S2059-7029(21)00019-3/fulltext

42. NICE. The national institute for health and care excellence.;
Available:https://www.nice.org.uk/

43. Arnold M, Morgan E, Rumgay H, Mafra A, Singh D, Laversanne M, et al. Current and future burden of breast cancer: Global statistics for 2020 and 2040. Breast. 2022;66:15–23.
Available:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9465273/

44. Feng Y, Spezia M, Huang S, Yuan C, Zeng Z, Zhang L, et al. Breast cancer development and progression: Risk factors, cancer stem cells, signaling pathways, genomics, and molecular pathogenesis. Genes Dis. 2018;5(2):77–106.
Available:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6147049/

45. Carlino F, Solinas C, Orditura M, Bisceglia MD, Pellegrino B, Diana A. Editorial: Heterogeneity in breast cancer: clinical and therapeutic implications. Front Oncol. 2024;14:1321654.
Available:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10926019/

46. Conte P, Ciruelos E, Curigliano G, De Laurentiis M, Del Mastro L, Gennari A, et al. Positioning of tucatinib in the new clinical scenario of HER2-positive metastatic breast cancer: An Italian and Spanish consensus paper. Breast. 2024;76:103742.
Available:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC11134910/

47. Mercogliano MF, Bruni S, Mauro FL, Schillaci R. Emerging targeted therapies for HER2-positive breast cancer. Cancers. 2023;15(7):1987.
Available:https://www.mdpi.com/2072-6694/15/7/1987

48. Subhan MA, Parveen F, Shah H, Yalamarty SSK, Ataide JA, Torchilin VP. Recent advances with precision medicine treatment for breast cancer including triple-negative sub-type. Cancers (Basel). 2023;15(8):2204.
Available:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10137302/

49. Miglietta F, Dieci MV, Griguolo G, Guarneri V. Neoadjuvant approach as a platform for treatment personalization: Focus on HER2-positive and triple-negative breast cancer. Cancer Treatment Reviews. 2021;98:102222.
Available:https://www.sciencedirect.com/science/article/pii/S0305737221000700

50. Lei Z, Tian Q, Teng Q, Wurpel JND, Zeng L, Pan Y, et al. Understanding and targeting resistance mechanisms in cancer. MedComm. 2020. 2023;4(3):e265.

Available:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10203373/

51. Clinical Review. In: Tucatinib (Tukysa): CADTH Reimbursement Review: Therapeutic Area: Advanced or metastatic breast cancer. Canadian Agency for Drugs and Technologies in Health; 2022.
Available:https://www.ncbi.nlm.nih.gov/books/NBK595370/

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of the publisher and/or the editor(s). This publisher and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.

© Copyright (2024): Author(s). The licensee is the journal publisher. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle5.com/review-history/121450