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"Positioning of tucatinib in the new clinical scenario of HER2-positive metastatic breast cancer: An Italian and Spanish consensus paper"

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ABSTRACT

Introduction: Advancements in monoclonal antibodies, tyrosine kinase inhibitors, and antibody drug conjugates (ADCs) have notably enhanced outcomes for metastatic HER2-positive breast cancer patients. Despite the expanding treatment options and clinical complexities, determining the optimal sequence of HER2-targeted therapies remains partly uncertain, influenced by various factors.

Methods: To refine HER2-positive metastatic breast cancer management, particularly regarding tucatinib's position, a Steering Committee of leading oncologists in breast cancer care devised a panel of statements via a Delphi approach, focusing on five key topics: general clinical management, therapeutic approaches for patients with HER2-positive breast cancer and brain metastases, treatment sequence, and tucatinib's safety and efficacy.

Results: A total of 29 statements were deliberated, with strong consensus achieved for most. However, no consensus emerged regarding the management of brain progression alongside stable extracranial disease: 48 % advocated for switching to tucatinib, while 53 % favored a stereotactic brain radiotherapy (SBRT) approach if feasible.

Conclusion: The unanimous consensus attained in this Delphi panel, particularly regarding tucatinib's efficacy and safety, underscores oncologists' recognition of its clinical significance based on existing trial data. These findings align closely with current literature, shedding light on areas necessitating further investigation, not thoroughly explored in prior studies. Moreover, the results underscore the scarcity of data on managing brain

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progression alongside stable extracranial disease, emphasizing the imperative for dedicated research to address these gaps and yield definitive insights.

1. Introduction

Breast cancer remains a significant global health challenge, with an estimate of 374,800 women diagnosed in Europe in 2022, and 95,800 deaths attributable to this disease in the same year [1].

The identification of specific molecular subtypes has revolutionized the approach to its diagnosis and treatment, in both early and metastatic setting. Among these subtypes, human epidermal growth factor receptor 2 (HER2)-positive breast cancer represents a distinct entity characterized by aggressive behavior and poor prognosis, and approximately one-third of HER2-positive BC patients present with or develop regional or distant metastatic disease [2,3]. Over the years, the advent of monoclonal antibodies, tyrosine Kinase inhibitors, and antibody drug conjugates (ADCs) has significantly improved outcomes for metastatic HER2-positive breast cancer patients [4].

The efficacy of dual HER2 blockade regimen, marked by a median progression free survival (PFS) of 18.7 months and a median overall survival (OS) of 57.1 months, underscores the initial success in restraining the disease [5]. However, the current landscape compels to address the unmet challenges arising in the wake of disease progression. Particularly, the threat of brain metastases emerges as a critical concern, necessitating a move towards more tailored interventions [6–8].

The most effective sequence of HER2-targeted therapies remains partially uncertain, influenced by several factors such as prior treatments in the early and metastatic setting, the duration of the relapse-free interval from adjuvant treatments, tumor burden and central nervous system (CNS) involvement, patient's perspectives, and the accessibility of drugs in each specific country [3,9].

The DESTINY Breast-03 trial has established trastuzumab deruxtecan (T-DXd) as the new standard for second-line treatment in metastatic HER2-positive breast cancer, reporting a clinical significant survival benefit as compared to trastuzumab entamsine (T-DM1) [10]. Nevertheless, there exists a subset of patients and clinical scenarios where its role is less defined, characterized by the presence of active brain metastases [11,12]. Further refinements are warranted to delineate the optimal management across diverse patient profiles.

Tucatinib, a small molecule tyrosine kinase inhibitor, has added a new option to the therapeutic landscape for HER2-positive metastatic breast cancer [13]. It is highly selective for the kinase domain of HER2 with minimal inhibition of HER, that contributes to a lower incidence and severity of diarrhea and rash than that typically associated with dual HER2/EGFR inhibitors [14]. The pivotal HER2-CLIMB trial evaluated tucatinib vs. placebo, both in combination with trastuzumab and capecitabine, in 612 HER2-positive metastatic breast cancer previously treated with trastuzumab, pertuzumab, and T-DM1. The trial demonstrated a benefit in PFS and OS that remained consistent across all predefined subgroups, including patients with brain metastases, who represented 48 % of the population [15].

Considering the continuous evolution in terms of treatment options and the complexity of clinical scenarios in clinical practice, it becomes crucial to define what is the best management of patients with pretreated HER2-positive disease, particularly with reference to areas of uncertainty that have not been comprehensively represented in clinical trials.

Within this context, a collaborative effort between Italian and Spanish experts in breast cancer aimed to establish a consensus paper to elucidate the role of tucatinib within the treatment of HER2-positive metastatic breast cancer, and potential synergies with existing therapeutic modalities.

Through a review of existing literature, clinical trials, and real-world evidence, this consensus paper offers a detailed view on how to handle specific clinical situations in treatment plans and its possible effects on outcomes for HER2-positive metastatic breast cancer patients.

2. Materials and methods

The Delphi method is a survey technique that uses responses to a standardized questionnaire developed by a panel of experts to facilitate the convergence of opinions or the achievement of a common opinion in areas where scientific evidence is scarce or needed [16,17]. The Delphi method involves the repeated administration of questionnaires, where each statement can be evaluated through a 5-point Likert scale, with a score from 1 to 5.

- 1, strongly disagree;
- 2, disagree;
- 3, agree;
- 4, more than agree;
- 5, strongly agree.

Results are expressed as a percentage of respondents who scored each item as 1 or 2 (disagreement) or as 3, 4, or 5 (agreement). A positive consensus is reached if the percentage of agreement is greater than 66 %. No consensus is reached, when the sum of the responses for a negative consensus (1 and 2) or a positive consensus (3, 4, and 5) is <66 %.

In September 2023 a Steering Committee composed by 6 Italian and 5 Spanish Oncologists leading experts in breast cancer care met to discuss the main areas of interest and, after reviewing the published literature on tucatinib, they identified five major topics: a) general clinical management of HER2-positive disease, b) therapeutic approaches to patients with brain metastases, c) treatment sequence, d) safety and e) efficacy of tucatinib. Each topic was subdivided in a variable number of statements corresponding to items where greater need of clarification and debate existed. The Board was also asked to identify 2 colleagues for each board member who served as external impartial validators and judged clarity and readability of the statements. After, these statements were surveyed via an online platform, between October and November 2023, to 80 panelists, who met the following profile: Italian/Spanish Oncologists working in Hospital or clinic, with at least 1 year of experience in breast cancer care with tucatinib or at least 3 patients being treated with the drug. The vote was anonymous, and no compensation was given to any of the identified voters. The study does not report on or involve the use of any animal or human data or tissue, and does not contain data from any individual person, so there was no need for ethics approval nor prior approval of the study protocol. All experts involved in the Delphi survey were informed of the study's objectives and the possibility of publishing the results in a peer-reviewed article. The participation was voluntary. They expressed their consent to participate in the survey after logging into the secure online survey platform via credentials, by actively clicking on the appropriate box. Using the Delphi method, the answers were analyzed aiming to acquire the rate of agreement and disagreement with the statements.

3. Results

Eighty panelists were identified from the following countries: Italy (n = 47, 58,75 %) and Spain (n = 33, 41,25 %). For both countries the majority of the participants worked in the Northern regions.

Age distribution was: 12 (20 %) ≤ 40 years old, 38 (62 %) between 40 and 60 years old, and 11 (16 %) > 60 years old. Clinical experience was: 9 (15 %) ≤ 10 years, 23 (38 %) between 11 and 20 years, 17 (28 %)

between 21 and 30 years, 11 (18 %) between 31 and 40 years, and 1 (1 %) more than 40 years.

Overall, 29 statements were discussed, pertaining to a) general clinical management of HER2-positive disease, b) therapeutic approaches to patients with brain metastases, c) treatment sequence, d) safety and e) efficacy of tucatinib.

a. Clinical management strategies for HER2-positive metastatic breast cancer patients

Statement #1	1	2	3	4	5	TOT
1.1 - HER2-status should be evaluated at the time of relapse	3	3	17	18	39	80
	8%		93%			100%
1.2 - A relapsed tumor that is HER2-negative, but the primary tumor diagnosed years ago was HER2+, should be treated as HER2-negative from now on	5	17	26	22	10	80
	28%		73%			100%
1.3 - After progression on T-DXd, it is appropriate to use a drug with different mechanism of action (Tucatinib)	1	0	9	34	36	80
	1%		99%			100%
1.4 - After progression on T-DXd, it is appropriate to use another weaker ADC (T-DM1)	2	55	19	3	1	80
	71%		29%			100%
1.5 - Other biomarkers (eg, HER2 levels, HER2 mRNA or pam50) should be further explored to optimize treatment sequencies	0	12	33	22	13	80
	15%		85%			100%

Ninety-nine percent (99 %) of the panelists considered Tucatinib the appropriate treatment after progression on T-DXd, citing its different mechanism of action. Although opinions were less convergent (71 %), T-DM1 was not deemed a proper option in this scenario. The panel advocates for exploring additional biomarkers (e.g., HER2 levels, HER2 mRNA, or PAM50) to refine treatment sequences, emphasizing a personalized, biomarker-driven approach to optimization (agreement level 85 %).

b. Brain metastasis management in HER2-positive breast cancer

Statement #2	1	2	3	4	5	TOT
2.1 - To date, there are no biomarkers, or well-defined and established predictive factors, regarding the likelihood of developing brain metastases in HER2-positive breast cancer	0	0	34	34	12	80
	0%		100%			100%
2.2 - In the metastatic disease, as drugs with intracranial efficacy are currently available, it is important to screen for the presence of brain metastases, even asymptomatic ones, to intercept and then treat intracranial tumour involvement early	1	13	27	27	12	80
	18%		83%			100%
2.3 - In the case of only intracranial progression during anti-HER2 treatment, in addition to locoregional treatment (if indicated), the systemic therapy should be changed	8	46	16	8	2	80
	68%		33%			100%
2.4 - Tucatinib has the most robust data from the registration trial regarding treatment efficacy of patients with active brain metastases	1	1	24	30	24	80
	3%		98%			100%
2.5 - In the presence of brain lesions treatable with SBRT and stable extracranic disease, change anti-HER2 therapy to tucatinib is appropriate in postponing the need for locoregional treatment, rather than using stereotactic radiotherapy ab initio without changing the systemic therapy (as per the ESMO guidelines)	2	36	17	19	6	80
	48%		53%			100%
2.6 - In the presence of brain lesions having an indication for treatment using whole brain radiotherapy (> 10 lesions + negative prognostic factors), change anti-HER2 therapy to tucatinib is appropriate in postponing the need for locoregional treatment	0	13	24	32	11	80
	16%		84%			100%
2.7 - The pharmacological characteristics (PK/PD) of tucatinib support the potential of preventing/postponing the occurrence of brain metastases, highlighted by the post-hoc data from the HER2CLIMB study	0	8	29	34	9	80
	10%		90%			100%

In addressing the challenges of clinical management in HER2-positive metastatic breast cancer, the expert panel reached a consensus on key principles. There was a unanimous call for evaluating status of HER2 at metastatic site (agreement level 93 %), ensuring treatment alignment with the evolving disease profile. The panelists' opinions on treating previously HER2-positive breast cancer as HER2-negative were less convergent, although consensus was reached (73 %).

The panelists unanimously agreed that currently, there are no biomarkers useful for identifying a subgroup of patients with an increased likelihood of developing brain metastases within HER2-positive breast cancer patients. A broad consensus was also achieved on asymptomatic screening for brain involvement, aiming for early detection and

treatment (83 %), especially considering the use of drugs with intracranial activity.

No consensus emerged regarding the management of brain progression and stable extracranial disease: 48 % of the panelists voted for switching to Tucatinib, while 53 % disagreed, preferring a stereotactic brain radiotherapy (SBRT) approach if feasible. However, 84 % of the voters agreed that switching to Tucatinib is the most appropriate approach in cases of brain lesions suitable only for whole-brain radiotherapy.

Tucatinib is considered the molecule with the most robust data from prospective randomized trials regarding its efficacy in patients with active brain metastases; 90 % of voters believed that Tucatinib may potentially prevent and/or postpone the occurrence of brain metastasis due to its pharmacological features.

c. Sequence Strategies in HER2-positive metastatic breast cancer

The interval from the end of (neo)adjuvant treatment to the first recurrence was confirmed to play a relevant role in the choice of first-line treatment, with 98 % agreement. Furthermore, 98 % of the voters believed that the optimal treatment sequence in the metastatic setting is pertuzumab + trastuzumab - > T-DXd - > trastuzumab + tucatininib + capecitabine. However, 86 % considered a Tucatinib-based regimen as the standard option in the presence of active brain metastasis.

Although consensus was obtained, the panelists' opinions on the role of Tucatinib in the first-line for patients relapsed after pertuzumab and T-DXd in the early setting were less convergent (68 % disagree vs. 33 % agree). Disagreement was also reached (70 %) on the possible treatment options of T-DM1 or tucatinib + trastuzumab and capecitabine after progression on the first line with dual blockade, leaving T-DXd for further lines.

Statement #3	1	2	3	4	5	TOT
3.1 - The time interval from the end of (neo)adjuvant therapy to the first recurrence may influence the choice of therapy in the first-line metastatic setting	0	2	28	33	17	80
	3%		98%			100%
3.2 - Currently, from a sequencing perspective, the standard of treatment in the metastatic setting is: taxane/trastuzumab/pertuzumab -> T-Dxd -> trastuzumab/tucatinib/capecitabine	0	2	22	30	26	80
	3%		98%			100%
3.3 - In the case of patients having already been treated with trastuzumab/ pertuzumab and TDM-1 in the early setting, tucatinib might be a first-line option in the metastatic setting	2	52	20	5	1	80
	68%		33%			100%
3.4 - In the presence of active brain metastases in the second-line metastatic setting, the standard of treatment is trastuzumab/tucatinib/capecitabine	0	11	38	22	9	80
	14%		86%			100%
3.5 - Although no efficacy data are currently available for T-DM1 post T- DXd, this therapeutic strategy is still a possible treatment option in clinical practice in this setting	0	21	45	14	0	80
	26%		74%			100%
3.6 - In the absence of randomised head-to-head clinical trials, good Real World Evidence (RWE) data are useful to design the sequence strategy	0	4	34	34	8	80
	5%		95%			100%
3.7 - There are patients progressing to taxane+trastuzumab+pertuzumab in the first-line who could be treated with either T-DM1 or tucatinib/trastuzumab/capecitabine, leaving TDXd for later lines	8	48	22	2	0	80
	70%		30%			100%

d. Tolerability/Safety

Statement #4	1	2	3	4	5	TOT
4.1 - When choosing a treatment regimen in the metastatic setting, it is also important to consider tolerability data which is linked to the attrition rate of each treatment strategy.	1	1	22	39	17	80
	3%		98%			100%
4.2 - Treatment discontinuation due to the toxicity of the trastuzumab/capecitabine/tucatinib regimen is low also in real-word patients	1	3	38	36	2	80
	5%		95%			100%
4.3 - In the case of typical toxicity during a trastuzumab/capecitabine/tucatinib regimen (hand-foot syndrome, diarrhoea), the first strategy for managing these events is the dose reduction/suspension of capecitabine or its use with a metronomic regimen.	1	4	42	29	4	80
	6%		94%			100%
4.4 - Safety profile of a given regimen including dose reductions, drug discontinuations and supportive care needed to maintain treatment, in addition to efficacy data should be considered when selecting a new line of treatment	0	0	33	35	12	80
	0%		100%			100%

High agreement was reached with the statement highlighting the relevance of considering the tolerability of a drug (agreement level 98 %), as well as the safety profile when selecting a new line of treatment in the metastatic setting (agreement level 100 %). Regarding tucatinib, nearly all the panelists agree on the low treatment discontinuation due to toxicity in a real-word setting (95 %); moreover, 94 % of the panelists agreed that reduction or holding of the capecitabine is the first measure to adopt in case of typical toxicity emerged during the treatment with trastuzumab capecitabine and tucatinib.

e. Efficacy

Statement #5	1	2	3	4	5	TOT
5.1 - Data from the HER2CLIMB trial make the triple combination with tucatinib the standard of treatment in third-line metastatic therapy	0	4	27	28	21	80
	5%		95%			100%
5.2 - Data from the HER2CLIMB trial make the triple combination with tucatinib the preferred second-line treatment in the presence of active brain metastases	0	14	35	23	8	80
	18%		83%			100%
5.3 - To date, the HER2CLIMB study is the only trial that required 100% prior treatment with pertuzumab and T-DM1)	0	2	32	24	22	80
	3%		98%			100%
5.4 - HER2CLIMB efficacy results remain valid after the introduction of T-DXd in second-line, but more RWE of tucatinib/trastuzumab/cape after T-DXd are desirable	0	2	33	36	9	80
	3%		98%			100%
5.5 - RWE and/or single arm trials will help physicians make decisions about the best sequencing treatment strategy	0	5	22	39	14	80
	6%		94%			100%
5.6 - In metastatic HER2+ breast cancer, OS benefit is the main driver to chose therapy	1	5	34	30	10	80
	8%		93%			100%

There was almost unanimous consensus on the efficacy of Tucatinib, in combination with trastuzumab and capecitabine, in the third line after prior treatment with pertuzumab and an ADC (T-DM1 or T-DXd). The use of Tucatinib in the second line in patients with active brain metastases reached a relatively weak agreement (83 %), reflecting the grey zone of the best regimen for this selected population. Agreement was also reached on the usefulness of data derived from Real-World Evidence (RWE), as well as considering the Overall Survival (OS) benefit as the main driver (94 % and 93 %, respectively), to define the best sequencing treatment strategy for HER2-positive metastatic breast cancer patients.

4. Discussion

This consensus paper highlights relevant topics regarding the management of HER2-positive metastatic breast cancer, especially on the positioning of tucatinib in the current landscape, addressed by a Delphi approach to measure the rate of agreement and disagreement across a Scientific Board including Italian and Spanish opinion leaders in breast cancer care, and a Panel of 80 oncologists, with the aim of developing a consensus built on evidence-based expert opinion and common clinical practice.

The Panel was generally aligned on aspects related to the characterization of relapsed disease in the context of HER2-positive breast cancer. It emphasized the importance of reassessing HER2-status at the time of relapse, recognizing the dynamic nature of the disease. Additionally, if a tumor, previously diagnosed as HER2-positive, relapses as HER2-negative, the consensus was to treat it as such moving forward. It is fair to consider that current evolutions in the definition of HER2 low disease and the resulting therapeutic possibilities call for the need to follow the evolutionary dynamism of tumor biology to ensure the most targeted treatment possible. In this context fits the agreement about the usefulness of developing new biomarkers to optimize treatment sequences and overcome or prevent resistance mechanisms within the same class drugs.

In February 2021, the EMA approved tucatinib in combination with trastuzumab and capecitabine for the treatment of adult patients with locally advanced or metastatic HER2-positive breast cancer based on the results of the HER2CLIMB study. The inclusion criteria included previous treatment with trastuzumab, pertuzumab, and T-DM1 in any settings, making the entire enrolled population already exposed to standard I- and II-line treatment for that era. The median PFS was 7.6 months for the tucatinib combination group vs. 4.9 months for the placebo combination group (HR 0.57, 95 % CI 0.47–0.70, $p < 0.00001$), while OS duration in the tucatinib combination group reached 24.7 months vs. 19.2 months observed in the placebo combination group, with an HR for death of 0.73 (95 % CI 0.59–0.90, p 0.004).

More recently, the second line treatment of metastatic HER2-positive breast cancer has been revolutionized by the advent of T-DXd. Efficacy and position of this drug in the therapeutic sequence after first line chemotherapy plus trastuzumab and pertuzumab have been firmly established by the DESTINYBreast-03 trial, that demonstrated a remarkable increase in median PFS (28.8 vs. 6.8 months, HR 0.33, 95 % CI 0.26–0.43) and a significant advantage in OS (HR 0.64, 95 % CI 0.47–0.87) as compared to T-DM1. According to international guidelines and as acknowledged by the Panel, T-DXd is indisputably the preferred therapeutic option after disease progression to dual HER2 blockade including pertuzumab, received either in the early or metastatic setting.

To date, there are no data derived from prospective trials considering a sequence of therapy including T-DXd and tucatinib. However, the Panel agreed that the option of tucatinib in combination with trastuzumab and capecitabine can be considered in patients who progress after treatment with T-DXd. This statement is mainly supported by real-world and retrospective evidences, that show significant efficacy of tucatinib for patients with HER2-positive metastatic breast cancer previously exposed to T-DXd, including heavily pretreated patients and with brain metastases [18,19].

According to European Society for Medical oncology (ESMO) guidelines, tucatinib has sparked interest in its potential role in the evolving clinical scenario, being the preferred third line therapy for HER2-positive disease [12].

The management of patients with brain metastases deserves an ad-hoc discussion. Brain metastasis occurs in up to 50 % of with HER2-positive tumors; this incidence has increased over time, mainly due to improved systemic treatment and prolonged survival. While HER2-positive disease has a better prognosis compared to other subtypes, the overall prognosis of patients with brain metastases remains unfavorable, underscoring the need for more effective systemic treatment options [20].

The CNS poses challenges for drug delivery, especially high molecular weight drugs like monoclonal antibodies. To address this, TKIs designed for HER2 offer promise for treating HER2-positive metastatic breast cancer with brain metastases. HER2CLIMB is the pivotal randomized trial that uniquely allows enrollment of patients with active brain metastases. 48 % of the patients in the HER2CLIMB study had brain metastases at baseline, of which 60 % untreated or progressing after previous local treatment [15]. Within this specific sub-population of the study, tucatinib prolonged median OS by 9.1 months as compared to placebo (21.6 vs. 12.5 months), as well as median CNS-PFS (9.9 vs 4.2 months). Median OS and CNS-PFS were significantly longer also in patients with active brain metastases. The HR for the risk of occurrence of new brain lesions as first site of progression was 0.55 (95 % CI 0.36–0.85) with the tucatinib combination than with placebo [21].

Overall, the Panel agreed on the key role of tucatinib in the specific clinical scenario of treating a patient with active brain lesions. For these evidence, ESMO guidelines place this compound as a potential second-line option when brain is the predominant site of disease progression, and suggest such a combination in the case of relapse after first-line therapy if the patient has active brain metastases not eligible for local treatment with radiotherapy [12]. Also ASCO guidelines recommended that tucatinib capecitabine and trastuzumab may be offered to patients with HER2-positive metastatic breast cancer who have brain metastases and whose disease has progressed on at least one previous HER2-directed therapy in order to delay local treatment until there is an evidence of intracranial progression [11].

The conflicting results obtained in this Delphi panel regarding the management of brain progression and stable extracranial disease reflect the uncertainty emerging from this clinical scenario.

For patients whose systemic disease is not progressive at the time of brain metastasis diagnosis, systemic therapy should not be switched from their current HER2-targeted therapy regimen, according to ASCO guidelines [11]. Yet, the presence of a drug with efficacy both within the brain and beyond could profoundly transform the multidisciplinary care of patients with HER2-positive metastatic breast cancer and brain metastases. Implementing a personalized treatment strategy that involve surgery, radiotherapy, and systemic treatments based on individual patient characteristics has the potential to enhance prognosis and quality of life [8].

HER2-CLIMB02 was a randomized trial conducted on 460 patients with or without baseline BM (including stable, progressing, or untreated BM not requiring local therapy) treated with tucatinib or placebo in combination with T-DM-1: of note, around 23 % of patients had treated stable, progressing, or untreated brain metastases not requiring immediate local therapy.

At San Antonio Breast Cancer Symposium 2023 results of the primary analysis were showed, reporting a significant improvement in mPFS with the addition of Tucatinib in the whole population (9.5 vs 7.4 months, HR 0.76; P = 0.0163) and in patients with brain involvement (7.8 vs 5.7 months, HR 0.64, 95 % CI 0.46–0.89). This is the second randomized study including patients with brain metastases demonstrating that a tucatinib-containing regimen may be useful to delay disease progression in HER2-positive metastatic breast cancer, reinforces the role of tucatinib in this setting (possible adding flexibility in terms of combination partner) [22].

Moreover, ongoing trials, such as CompassHER2 RD trial (NCT04457596) and HER2CLIMB-05 (NCT05132582), will help to clarify the role of adding Tucatinib, in addition to standard treatment, to prevent or delay brain metastases in both the early and advanced setting.

The safety of Tucatinib was acknowledged by all panelists, in agreement with what had emerged from prospective clinical trials and real-word data [15,23].

In the HER2-CLIMB, combination of tucatinib with capecitabine was well-tolerated, with low rate of discontinuation to adverse events (5.7 %): rates of grade≥3 diarrhea and palmar-plantar erythrodysesthesia syndrome were similar, and may be also related to capecitabine; elevated liver enzymes were higher in patients treated with tucatinib, but were transient and reversible [24].

The rate of AEs were similar in a real-world setting with a lower rate of severe adverse events, although a higher rate of hepatotoxicity (13 % of grade≥3); in this study higher occurrence of drug interactions associated with tucatinib was observed, and it is imperative to reassess concurrent medications for necessary adjustments in therapy and vigilant monitoring [23].

Conclusions provided in this report trough a Delphi method are based on the opinions of a panel of 80 European oncologist highly specialized in breast cancer care and with broad experience with the use of tucatinib.

The results obtained in this survey on the optimal position of tucatinib in the therapeutic algorithm of HER2-positive metastatic breast cancer may serve as a general reference for a more rational approach, as well as a strong base to develop the appropriate treatment sequence in this population, also considering the number of new compounds available for this population.

The consensus reached in this Delphi study provides an overview on the role of tucatinib in the clinical practice of 80 European breast cancer specialists.

The substantial consensus reached on certain topics, particularly regarding efficacy and safety, mirrors oncologists' awareness of the clinical significance of tucatinib as derived from available trials.

The results obtained closely align with findings of available literature, offering a compelling snapshot of issues that have yet to be thoroughly explored by prior studies. Additionally, the results underscore the scarcity of data concerning the management of brain progression with stable extracranial disease, emphasizing the need for dedicated studies to address these gaps and arrive at conclusive insights.

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CRediT authorship contribution statement

Pierfranco Conte: Conceptualization, Supervision, Validation, Writing – review & editing. **Eva Ciruelos:** Writing – review & editing, Conceptualization, Supervision, Validation. **Giuseppe Curigliano:** Conceptualization, Supervision, Validation, Writing – review & editing. **Michelino De Laurentiis:** Conceptualization, Supervision, Validation, Writing – review & editing. **Lucia Del Mastro:** Conceptualization, Supervision, Validation, Writing – review & editing. **Alessandra Gennari:** Supervision, Validation, Writing – review & editing, Conceptualization. **Antonio Llombart:** Conceptualization, Supervision, Validation, Writing – review & editing. **Miguel Martìn:** Conceptualization, Supervision, Validation, Writing – review & editing. **Francesca Poggio:** Conceptualization, Data curation, Visualization, Writing – original draft, Methodology. **Aleix Prat:** Conceptualization, Supervision, Validation, Writing – review & editing. **Fabio Puglisi:** Conceptualization, Supervision, Validation, Writing – review & editing. **Cristina Saura:** Conceptualization, Supervision, Validation, Writing – review & editing.

Declaration of competing interest

PC: Consulting or Advisory Role: Daiichi Sankyo/Lilly, Reveal

Genomics, Gilead Sciences; Speakers' Bureau: Roche/Genentech, Novartis, AstraZeneca, Lilly, BMS; Research Funding: Merck KGaA (Inst); Patents, Royalties, Other Intellectual Property: HER2Dx patent; Expert Testimony: AstraZeneca.

EC: reports consulting fees from Novartis, Lilly, Pfizer, Roche, AstraZeneca, and Daiichi Sankyo; speaker's bureau from Lilly, Pfizer, AstraZeneca, and Daiichi Sankyo; and travel and accommodations from Pfizer and Roche.

GC: received honoraria for speaker's engagement: Roche, Seattle Genetics, Novartis, Lilly, Pfizer, Foundation Medicine, NanoString, Samsung, Celltrion, BMS, MSD; Honoraria for providing consultancy: Roche, Seattle Genetics, NanoString; Honoraria for participating in Advisory Board: Roche, Lilly, Pfizer, Foundation Medi-cine, Samsung, Celltrion, Mylan; Honoraria for writing engagement: Novartis, BMS; Honoraria for participation in Ellipsis Scientific Affairs Group; Institutional research funding for conducting phase I and II clinical trials: Pfizer, Roche, Novartis, Sanofi, Celgene, Servier, Orion, AstraZeneca, Seattle Genetics, AbbVie, Tesaro, BMS, Merck Serono, Merck Sharp Dome, Janssen-Cilag, Philogen, Bayer, Medivation, MedI- mmune

MDL: advisory boards, activities as a speaker, travel grants, consultancy: Eli Lilly, Novartis, Seagen, Takeda, Roche, Daiichi Sankyo, Tomalab, Gilead, Genetic, Menarini, Sophos, AstraZeneca, Pfizer, Sanofi, Ipsen, Pierre Fabre, GSK. AG: research funding to the Institution: AstraZeneca, Pfizer, Janssen, Roche, MSD, Daichii-Sankyo, GSK/Tesaro, HiFiBio, Merck, Boehringer-Ingelheim, Exelixis, Bayer, Incyte, Bayer, Aileron; travel, accommodation, expenses: Gentili.

LDM: advisory role for Agendia, Amgen, AstraZeneca, Collage SpA, Daiichi Sankyo, Eli Lilly, Exact Sciences, Gilead, GSK, Havas Life, Pfizer, Pierre Fabre, Roche, Seagen Int, Stemline Menarini and Uvet; personal fees as an invited speaker for Accademia Nazionale Medicina, Andromeda E20, Aristea, Delphi international, Editree, Eli Lilly, Ipsen, Meeting SrL, MSD, Novartis, Over Srl, Prex Srl, Symposia and Vyvamed Srl; personal fees for writing engagements for Edizioni Minerva Medica, Pensiero Scientifico Editore and Roche; personal consultancy fees from Eli Lilly, Gilead, Kardo Srl and Sharing Progress in Cancer Care (SPCC)—Switzerland; personal fees for author slide kits from Forum service and Think2it; personal fees for interviews from Infomedica Srl and Think2it; institutional funding as a local PI from AstraZeneca, Daiichi Sankyo, Eli Lilly, Gilead, Novartis, Novella Clinical, Roche and Seagen; institutional funding as a national coordinating PI from Roche; institutional research grant from Pfizer; and non-remunerated product samples from FoundationOne.

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MM: Honoraria: Roche/Genentech, Lilly, Pfizer, Novartis, Pierre Fabre, Seagen; Consulting or Advisory Role: Roche/Genentech, Novartis, Pfizer, Lilly, AstraZeneca, Daiichi-Sankyo; Speakers' Bureau: Lilly/ImClone, Lilly/ImClone, Roche/Genentech, Pierre Fabre; Research Funding: Novartis (Inst), Roche (Inst), Puma Biotechnology (Inst); Travel, Accommodations, Expenses: Daiichi-Sankyo; Other Relationship: Roche, Novartis.

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References

[1] https://ecis.jrc.ec.europa.eu/pdf/Breast_cancer_2022-Oct_2023.pdf [n.d].
[2] Nader-Marta G, Martins-Branco D, De Azambuja E. How we treat patients with metastatic HER2-positive breast cancer. ESMO Open 2022;7:100343. https://doi.org/10.1016/j.esmoop.2021.100343.
[3] Martínez-Sáez O, Prat A. Current and future management of HER2-positive metastatic breast cancer. JCO Oncol. Pract. 2021;17:594–604. https://doi.org/10.1200/OP.21.00172.
[4] Di Maio M, Bighin C, Schettini F, Ruelle T, Marandino L, Fabi A, et al. Evolving treatments and outcomes in HER2-Positive metastatic breast cancer: data from the GIM14/BIOMETA study. Breast. Edinb. Scotl. 2023;72:103583. https://doi.org/10.1016/j.breast.2023.103583.
[5] Swain SM, Miles D, Kim S-B, Im Y-H, Im S-A, Semiglazov V, et al. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA): end-of-study results from a double-blind, randomised, placebo-controlled, phase 3 study. Lancet Oncol 2020;21:519–30. https://doi.org/10.1016/S1470-2045(19)30863-0.
[6] Darlix A, Louvel G, Fraisse J, Jacot W, Brain E, Debled M, et al. Impact of breast cancer molecular subtypes on the incidence, kinetics and prognosis of central nervous system metastases in a large multicentre real-life cohort. Br J Cancer 2019;121:991–1000. https://doi.org/10.1038/s41416-019-0619-y.
[7] Pestalozzi BC, Holmes E, De Azambuja E, Metzger-Filho O, Hogge L, Scullion M, et al. CNS relapses in patients with HER2-positive early breast cancer who have and have not received adjuvant trastuzumab: a retrospective substudy of the HERA trial (BIG 1-01). Lancet Oncol 2013;14:244–8. https://doi.org/10.1016/S1470-2045(13)70017-2.
[8] Müller V, Bartsch R, Lin NU, Montemurro F, Pegram MD, Tolaney SM. Epidemiology, clinical outcomes, and unmet needs of patients with human epidermal growth factor receptor 2-positive breast cancer and brain metastases: a systematic literature review. Cancer Treat Rev 2023;115:102527. https://doi.org/10.1016/j.ctrv.2023.102527.
[9] Simmons C, Rayson D, Joy AA, Henning J-W, Lemieux J, McArthur H, et al. Current and future landscape of targeted therapy in HER2-positive advanced breast cancer: redrawing the lines. Ther. Adv. Med. Oncol. 2022;14:175883592110666. https://doi.org/10.1177/17588359211066677.
[10] Hurvitz SA, Hegg R, Chung W-P, Im S-A, Jacot W, Ganju V, et al. Trastuzumab deruxtecan versus trastuzumab emtansine in patients with HER2-positive metastatic breast cancer: updated results from DESTINY-Breast03, a randomised, open-label, phase 3 trial. Lancet 2023;401:105–17. https://doi.org/10.1016/S0140-6736(22)02420-5.
[11] Ramakrishna N, Anders CK, Lin NU, Morikawa A, Temin S, Chandarlapaty S, et al. Management of advanced human epidermal growth factor receptor 2–positive breast cancer and brain metastases: ASCO guideline update. J Clin Oncol 2022;40:2636–55. https://doi.org/10.1200/JCO.22.00520.
[12] Gennari A, André F, Barrios CH, Cortés J, De Azambuja E, DeMichele A, et al. ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. Ann Oncol 2021;32:1475–95. https://doi.org/10.1016/j.annonc.2021.09.019.
[13] Criscitiello C, Corti C, De Laurentiis M, Bianchini G, Pistilli B, Cinieri S, et al. Tucatinib's journey from clinical development to clinical practice: new horizons for HER2-positive metastatic disease and promising prospects for brain metastatic

spread. Cancer Treat Rev 2023;120:102618. https://doi.org/10.1016/j.ctrv.2023.102618.
[14] Moulder SL, Borges VF, Baetz T, Mcspadden T, Fernetich G, Murthy RK, et al. Phase I study of ONT-380, a HER2 inhibitor, in patients with her2+-advanced solid tumors, with an expansion cohort in HER2+ metastatic breast cancer (MBC). Clin Cancer Res 2017;23:3529–36. https://doi.org/10.1158/1078-0432.CCR-16-1496.
[15] Curigliano G, Mueller V, Borges V, Hamilton E, Hurvitz S, Loi S, et al. Tucatinib versus placebo added to trastuzumab and capecitabine for patients with pretreated HER2+ metastatic breast cancer with and without brain metastases (HER2CLIMB): final overall survival analysis. Ann Oncol 2022;33:321–9. https://doi.org/10.1016/j.annonc.2021.12.005.
[16] Giannarou Lefkothea, Zervas Efthimios. Using Delphi technique to build consensus in practice. International Journal of Business Science & Applied Management (IJBSAM), ISSN 1753-0296, International Journal of Business Science & Applied Management, s.l. 2014;9(2):65–82. n.d.
[17] Walker A, Selfe J. The Delphi method: a useful tool for the allied health researcher. Br. J. Ther. Rehabil. 1996;3:677–81. https://doi.org/10.12968/bjtr.1996.3.12.14731.
[18] Frenel J-S, Zeghondy J, Guerin C, Mailliez A, Volant E, Poumeaud F, et al. Efficacy of tucatinib+trastuzumab+capecitabine (TTC) after trastuzumab-deruxtecan (T-DXd) exposure in Her2-positive metastatic breast cancer: a French multicentre retrospective study. J Clin Oncol 2023;41:1014. https://doi.org/10.1200/JCO.2023.41.16_suppl.1014. 1014.
[19] Anders CK, Neuberger E, Schwartz NR, Bartley K, Hsu L-I, Wong G, et al. Real-world patient characteristics and treatment patterns associated with tucatinib therapy in patients with HER2+ metastatic breast cancer. J Clin Oncol 2023;41:1051. https://doi.org/10.1200/JCO.2023.41.16_suppl.1051. 1051.
[20] Nader-Marta G, Martins-Branco D, Agostinetto E, Bruzzone M, Ceppi M, Danielli L, et al. Efficacy of tyrosine kinase inhibitors for the treatment of patients with HER2-positive breast cancer with brain metastases: a systematic review and meta-analysis. ESMO Open 2022;7:100501. https://doi.org/10.1016/j.esmoop.2022.100501.
[21] Lin NU, Murthy RK, Abramson V, Anders C, Bachelot T, Bedard PL, et al. 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. JAMA Oncol 2023;9:197. https://doi.org/10.1001/jamaoncol.2022.5610.
[22] Hurvitz SA, Loi S, O'Shaughnessy J, et al. HER2CLIMB-02: primary analysis of a randomized, double-blind phase 3 trial of tucatinib and trastuzumab emtansine for previously treated HER2-positive metastatic breast cancer. Abstract presented at: 2023 San Antonio Breast Cancer Symposium; December 5-9. 2023. San Antonio, TX. Abstract GS01-10. n.d.
[23] Moore H, Anders C, Sammons SL, Erkanli A, Parish A, DiCola C. Abstract P4-01-10: evaluating the safety of tucatinib in combination with trastuzumab and capecitabine for human epidermal growth factor 2 (HER2)-positive metastatic breast cancer in a real-world setting. Cancer Res 2023;83:P4. https://doi.org/10.1158/1538-7445.SABCS22-P4-01-10. 01-10-P4-01–10.
[24] Okines AFC, Paplomata E, Wahl TA, Wright GLS, Sutherland S, Jakobsen E, et al. Management of adverse events in patients with HER2+ metastatic breast cancer treated with tucatinib, trastuzumab, and capecitabine (HER2CLIMB). J Clin Oncol 2020;38:1043. https://doi.org/10.1200/JCO.2020.38.15_suppl.1043. 1043.