Trifluridine-tipiracil in previously treated patients with oestrogen receptor-positive, HER2-negative metastatic breast cancer (BOOG 2019-01 TIBET trial): a single-arm, multicentre, phase 2 trial

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Summary

Background Effective later-line chemotherapy treatment options are scarce for patients with metastatic breast cancer (MBC). Trifluridine-tipiracil has shown survival benefit in heavily pre-treated patients with metastatic colorectal and in gastric cancer refractory to a fluoropyrimidine. This study aimed to investigate the efficacy of trifluridine-tipiracil in a Western population of previously treated patients with oestrogen receptor (ER+), HER2– MBC to facilitate further optimization of this treatment strategy.

Methods Adult patients at least 18 years old diagnosed with hormone receptor positive, HER2– receptor negative MBC with a performance status of 0 or 1 who have been treated with capecitabine in the metastatic setting and up to two other lines of chemotherapy, including a taxane, were enrolled in this single-arm, multicentre, phase 2 study in the Netherlands. The participants received trifluridine-tipiracil 35 mg/m^2 orally twice a day on days 1–5 and days 8–12 during a 28-day cycle until disease progression, unacceptable toxicity, or withdrawal of consent. The primary endpoint was the disease control rate (DCR) at 8 weeks, defined as the percentage of patients that had stable disease, partial response or complete response according to RECIST 1.1, in all patients that received at least one dose of trifluridine-tipiracil and met the key eligibility criteria defined *a priori*. Secondary endpoints included progression-free survival (PFS), overall survival (OS), safety, and quality of life and were performed in all patients that received at least one dose of trifluridine-tipiracil. The primary endpoint was considered met, justifying further research of this treatment regimen, if the lower boundary of the 80% confidence interval (CI) exceeded 30%. The study was registered within ClinicalTrials.gov (NCT04489173) and is closed for inclusion.

Findings Fifty female patients were enrolled from September 2020 to July 2023, with a median of 3 (IQR, 2–3) previous endocrine therapy lines and 2 (IQR, 2–3) chemotherapy lines for MBC. The DCR rate at 8 weeks was 64.0% (n = 32, 95% CI: 50.1–75.9%; 80% CI: 55.0–72.1%), thereby meeting the primary endpoint of this study. At data cutoff (January 8, 2024), the median follow-up time was 18.2 months (IQR, 13.1–25.1 months). The median PFS was 5.4 months (95% CI: 2.0–7.2 months) and the median OS 14.0 months (95% CI: 8.8–17.8 months). The safety profile of trifluridine-tipiracil aligned with expected toxicities and included leukopenia (n = 36, 69%), neutropenia (n = 43, 83%), and fatigue (n = 43, 83%). The most common grade 3–4 AEs were primarily haematological

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disorders and included neutropenia (n = 38, 73%), leukopenia (n = 15, 29%) and anaemia (n = 6, 12%). The most common SAEs (any grade) with a possible relationship with trifluridine-tipiracil included anaemia (n = 2) and vomiting (n = 2). No treatment-related deaths occurred. Quality of life scores remained stable throughout the treatment.

Interpretation Trifluridine-tipiracil demonstrated promising efficacy in heavily pre-treated patients with MBC, despite prior exposure to a fluoropyrimidine. Clinically, this suggests that trifluridine-tipiracil holds potential as a viable oral later-line treatment option with a manageable toxicity profile while maintaining quality of life. Preparations for a phase 3 trial are underway.

Funding Servier, France.

Keywords: Trifluridine-tipiracil; Metastatic breast cancer; Chemotherapy; Treatment

Research in context

Evidence before this study

We performed a PubMed search until July 1, 2024, using the terms ("trifluridine" OR "trifluridine-tipiracil" OR "TAS-102") AND "Breast". We identified one prospective study, a single-arm phase 2 trial conducted in Asia, which demonstrated promising antitumour activity of trifluridine-tipiracil in metastatic breast cancer patients. However, this study did not focus on patients with oestrogen receptor (ER+) and HER2-negative (HER2–) disease, nor did it require prior fluoropyrimidine treatment. Furthermore, the study's results may not be generalizable to non-Asian populations due to potential genetic and environmental differences that can influence treatment outcomes.

Added value of this study

This single-arm, phase 2 study showed that trifluridine-tipiracil is effective in a Western population of patients with ER+, HER2– metastatic breast cancer who had previously been treated with multiple lines of chemotherapy, including a taxane and capecitabine. Importantly, the effect of trifluridine-tipiracil was observed irrespective of the prior treatment duration with fluoropyrimidines. This study met its primary endpoint, demonstrating significant disease control. To our knowledge, this is the first trial to investigate trifluridine-tipiracil in such a targeted patient population in the Western context. The safety profile was manageable, and quality of life remained stable throughout the treatment period.

Implications of all the available evidence

These findings highlight the potential of trifluridine-tipiracil as a valuable later-line treatment option for ER+, HER2– metastatic breast cancer patients. With several treatment options available for later-line therapy, the ease of oral administration, minimal hospital visits, and the absence of alopecia and cardiotoxicity associated with trifluridine-tipiracil further underscore its potential as a viable treatment choice for metastatic breast cancer. Future research should focus on larger, randomized trials to confirm these findings and explore long-term outcomes.

Introduction

Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer-related deaths among women worldwide.[1] Approximately 75% of the cases are oestrogen-receptor positive (ER+) and human epidermal growth factor receptor 2-negative (HER2–).[2] The primary treatments for these patients consist of endocrine-based therapies, often combined with targeted agents such as cyclin-dependent kinase (CDK) 4/6 inhibitors.[3–5] Most patients eventually develop resistance to endocrine therapy that leads to progressive disease, making the use of systemic chemotherapy necessary.[6]

Anthracycline- or taxane-based regimens are usually considered as first-line chemotherapy for the treatment of metastatic breast cancer (MBC).[7] However, for patients who have been exposed to anthracyclines or taxanes in the (neo-)adjuvant setting, the median progression-free survival (PFS) of these first-line palliative chemotherapy regimens is typically 6–8 months.[8] International consensus guidelines recommend that in patients pretreated with an anthracycline and a taxane, single-agent capecitabine, vinorelbine, or eribulin are the preferred choices.[9] Among these options, capecitabine has shown substantial antitumour activity with a median PFS of 6.0–7.9 months and an overall response rate of 20–30%.[10] Within later-line therapies, the available treatment options are scarce and all exhibit a poor response rate with PFS ranging between 2 and 5 months.[11,12] This emphasizes the critical need for more effective and alternative later-line treatment options.

Trifluridine-tipiracil (also known as TAS-102) is an oral antitumour agent and consists of the active cytotoxic

component trifluridine, a nucleic acid analogue, and tipiracil, a thymidine phosphorylase inhibitor that prevents rapid degradation of trifluridine.[13,14] Unlike capecitabine, that requires activation to fluorouracil, trifluridine directly incorporates into DNA, leading to inhibition of DNA synthesis and subsequent tumour cell death.[15,16] Tipiracil's inhibition of thymidine phosphorylase also enhances the bioavailability of trifluridine, prolonging its antitumour activity.[13] In preclinical studies, trifluridine-tipiracil exhibited antitumour activity against cell lines resistant to fluorouracil, suggesting a potential to overcome resistance mechanisms associated with standard fluoropyrimidines.[17,18] Furthermore, thymidine phosphorylase is known to be overexpressed in various tumour types, including MBC, potentially amplifying the efficacy of trifluridine-tipiracil in this context.[19] It has been shown to significantly prolong survival in heavily pre-treated patients with metastatic colorectal and gastric cancer.[20,21] Therefore, it may be anticipated that patients with ER+, HER2– MBC who are refractory to capecitabine may have benefit from trifluridine-tipiracil treatment. Furthermore, unlike capecitabine, trifluridine-tipiracil does not cause hand-foot syndrome and is not dependent on dihydropyrimidine dehydrogenase (DPD) enzyme activity for its catabolism, while it also retains the convenience of oral administration.[20,21] In this study, we therefore evaluated the anti-tumour effect of trifluridine-tipiracil in terms of response rate in a population of ER+, HER2– MBC, previously treated with two or three lines of chemotherapy, including both a taxane and capecitabine.

Methods

Study design and participants

This trial was an single-arm, multicentre phase 2 study (BOOG 2019-01 TIBET) conducted in 10 hospitals in the Netherlands (Appendix: Supplementary Table S1) and within the Dutch Breast Cancer Research Group (BOOG). Adult women aged at least 18 years with a pathologically proven diagnosis of MBC were eligible if they had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–1, oestrogen-receptor positive (ER positive, at least 10%) and/or progesterone-receptor positive (PR, at least 10%) disease, and HER2 negative disease (HER2 positivity was defined as immunohistochemistry 3+ staining or in situ hybridization positive). Patients had to have been treated with capecitabine in the metastatic setting and up to two other lines of chemotherapy, including a taxane, which could have been administered either in the (neo)adjuvant or metastatic setting. Moreover, evaluable disease as defined per the Response Criteria in Solid Tumours (RECIST; version 1.1) and radiologically progressive disease before study entry were required.[22] Patients had to have adequate functions for bone marrow, liver and kidneys. The life expectancy had to be at least 12 weeks and only patients with toxicities grade ≤1 from previous therapies were eligible, except alopecia or other toxicities not considered a contraindication for trifluridine-tipiracil at investigator's discretion.

Patients were excluded if they had previously received trifluridine-tipiracil; radiotherapy within four weeks prior to enrolment; involvement of the central nervous system; 30% or more marrow-baring bone previously irradiated; other primary tumours within the last 5 years (except for adequately controlled basal cell carcinoma or carcinoma in situ of the cervix); the presence of a concomitant clinically significant medical condition that contraindicates the use of an investigational drug; an intolerance to lactose, as lactose is a component of the trifluridine-tipiracil tablet; or inability or constrained capacity to adhere to the study protocol. The study was registered within ClinicalTrials.gov (NCT04489173).

Procedures

Patients were treated with 35 mg/m^2 trifluridine-tipiracil taken orally twice a day (i.e., 70 mg/m^2 per day). Trifluridine-tipiracil was administered on day 1 through 5 and on day 8 through 12 during a 28-day cycle. As trifluridine-tipiracil is available in 15 mg and 20 mg tablets, dosages were rounded to the nearest feasible multiple of these strengths. Treatment was continued until disease progression, unacceptable toxicity, or withdrawal of consent. Dose reductions or interruptions were permitted to manage toxicities according to the discretion of the investigator. Dose reductions were performed in 5 mg/m^2 (total 10 mg/m^2 daily) steps to a minimum dose of 20 mg/m^2 (i.e., 40 mg/m^2/day) and dose interruptions were permitted for up to a maximum delay of 28 days. Patients requiring dose reductions below the minimum dose were discontinued from study treatment. All patients received antiemetic prophylaxis (i.e., metoclopramide on demand).

Response evaluation with a CT scan was performed every 8 weeks after start of treatment according to RECIST 1.1. In case of response at 16 weeks, imaging had to be repeated 4 weeks later to confirm the ongoing response. Safety evaluations were performed at baseline, two weeks after start of treatment and at the beginning of every next cycle. This included assessment of adverse events (AEs), physical examination, vital signs, and laboratory tests. Safety assessment was performed up to 30 days after the last dose of trifluridine-tipiracil. AEs and laboratory tests were graded according to the National Cancer Institute–Common Toxicity Criteria for Adverse Events (NCT-CTCAE, version 4.03). Quality of life was assessed at baseline and after 8, 16, 24, and 32 weeks using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30).

Outcomes

The primary endpoint was the disease control rate (DCR; stable disease, partial response or complete response according to RECIST 1.1) at 8 weeks, chosen to better reflect the treatment's ability to delay disease progression and maintain clinical benefit in heavily pretreated patients with advanced disease. This endpoint was adapted from previous studies with trifluridine-tipiracil in patients with metastatic colorectal and gastric cancer.[23–26] The secondary endpoints included PFS (time between study inclusion and disease progression or death of any cause), DCR rate at 16, 24 and 32 weeks, best overall response, safety and quality of life. Overall survival (OS; time between study inclusion and death) was included as an exploratory endpoint.

Statistical analysis

Given an optimal Simon two-stage design with P0 = 0.30 and P1 = 0.50 for the DCR rate at 8 weeks, a type I error (alpha) of 0.10 and type II error (beta) of 0.10, 46 patients were required. To account for potential drop-out for analysis of the primary endpoint, 50 eligible patients were planned to be enrolled. An interim analysis was performed after 22 patients, which justified further investigation (i.e., >7 patients were progression-free at 8 weeks). A Data Safety & Monitoring Committee was installed for this study and involved in the interim analysis.

The primary endpoint was assessed in the eligible population that included patients who received at least one dose of trifluridine-tipiracil and met the key eligibility criteria defined *a priori*. In case of no radiological evaluation due to early death or noncompliance with treatment within the first 8 weeks, a patient was included in the analysis and denoted as 'not evaluable', and classified as a failure for the primary endpoint. The frequency and percentage of patients free of progression at 8 weeks is given together with the 80% and 95% confidence intervals (CI), where the lower boundary of the 80% CI should be higher than 30% to justify further research of this treatment regimen. All patients who received at least one dose of trifluridine-tipiracil were used for the safety data analysis. Descriptive statistics were used to summarize efficacy, safety and quality of life data. Patient numbers, medians, and interquartile ranges (IQR) summarized continuous data, while categorical data were represented by the number and percentage of patients in each category. For the quality of life analysis, scores were calculated within each functional domain of the EORTC QLQ-C30 questionnaire. Changes in the median scores of overall health status were assessed using the Wilcoxon signed-rank test between baseline and 16 weeks, and between baseline and 32 weeks. For the remaining functional domains, changes were tested between baseline and 16 weeks only, also using the Wilcoxon signed-rank test. Statistical significance was set at $p < 0.05$. For PFS and OS, patients in whom the event was not observed, were censored at the date of last follow-up. For PFS, patients who stopped treatment due to toxicity or on patient request, were censored at last treatment date. However, if a patient passed away shortly after treatment discontinuation, this was considered an event, and time till death was then used in the analysis.

PFS and OS were analysed by means of the Kaplan–Meier method. The effect of duration of pretreatment with capecitabine (<18 weeks versus ≥18 weeks) was studied by means of the log-rank test. SAP version 1.0 and Stata version 17 were used for statistical analyses.

Ethics

This study was performed in accordance to the Declaration of Helsinki and the protocol was approved by medical ethics review committee Erasmus MC (MEC-2019-0468). Written informed consent was obtained from all patients.

Role of funding source

This work was supported by Servier by providing trifluridine-tipiracil and funds for this study. The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Patients and disease characteristics

From September 2020 to July 2023, 54 female patients were enrolled in the study. Of these, 52 received trifluridine-tipiracil (safety population), and 50 of these 52 patients were evaluable for the primary endpoint (eligible population). One patient did not meet the inclusion criteria due to insufficient creatinine clearance at baseline, and another patient did not receive a taxane as a previous treatment, and therefore these patients were excluded (Fig. 1). The median age was 60 years (IQR, 55–69), with the majority of patients having an ECOG PS of 1 (n = 35, 70%), and a median of 2 (IQR, 2–3) previous lines of chemotherapy and 3 (IQR, 2–3) previous lines of endocrine therapy, given in the metastatic setting (Table 1).

Study treatment

A total of 302 treatment cycles were administered, with a median duration of 5 (IQR, 2–9) treatment cycles per patient, and 29 patients (58%) received 4 cycles or more. Among the 52 treated patients, 28 (54%) experienced a dose reduction, and 40 (77%) encountered a dose delay during the course of treatment. Most patients required one dose reduction (n = 19, 37%), while 5 (10%) patients had two dose reductions and 4 (8%) patients had three dose reductions during treatment. Haematological AEs were the primary cause for both dose reductions and delays.

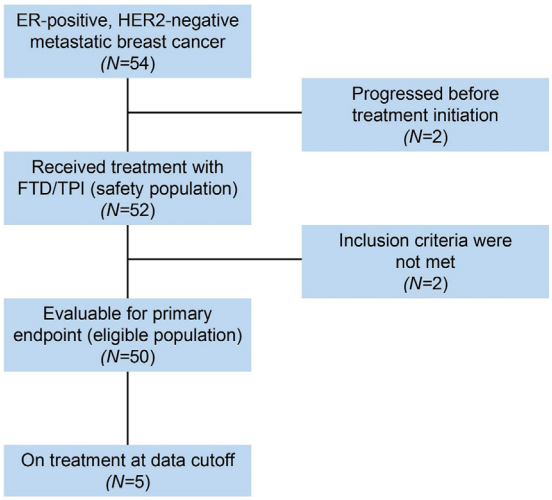

Fig. 1: **CONSORT Flow chart of participants.** Fifty-four patients were recruited to this study between September 2020 and July 2023 from 10 hospitals in the Netherlands. Fifty-two patients received treatment with trifluridine-tipiracil, two patients progressed before treatment initiation. Fifty patients were evaluable for the primary endpoint, two patients did not meet the inclusion criteria. The creatinine clearance criteria was not met for one patient at baseline, and one patient did not receive a taxane as previous treatment. Five patients were still on treatment with trifluridine-tipiracil at the date of data cutoff (Jan 8, 2024). Abbreviations: ER, estrogen receptor; FTD/TPI, trifluridine-tipiracil.

Response

At data cutoff (January 8, 2024), the median follow-up time for patients alive was 18.2 months (IQR, 8.1–32.4 months, range 13.1–25.1 months). Out of 50 eligible patients, 64.0% (n = 32, 95% CI, 50.1–75.9%, 80% CI, 55.0–72.1%) were progression-free at 8 weeks (Table 2), thereby meeting the primary endpoint of this study. Most patients (n = 28, 56%) had stable disease as per RECIST v1.1 at 8 weeks. The DCR rates at 16, 24 and 32 weeks were 50.0% (n = 25, 95% CI, 36.6–63.4%), 38.0% (n = 19, 95% CI, 25.8–51.9%), and 30.0% (n = 15, 95% CI, 19.0–43.8%), respectively. In the majority of the patients, stable disease (n = 25, 50%) was the best overall response according to RECIST v1.1. Best response for other patients were complete response (n = 1, 2%), partial response (n = 6, 12%), progressive disease (n = 13, 26%), and not evaluable in 10% (n = 5) of patients, respectively. The first measurement of complete response in that specific patient was observed after 24 weeks.

The median PFS in the eligible population was 5.4 months (95% CI, 2.0–7.2; Fig. 2A). Five patients were still receiving treatment with trifluridine-tipiracil at the time of the data cutoff. The median PFS did not differ between the groups based on prior treatment time on capecitabine (<18 weeks pretreatment on capecitabine:

Variable	Eligible population (N = 50)
Sex, No. (%)	
Female	50 (100%)
Age, years, median (IQR)	60 (55–69)
BMI, kg/m^2, median (IQR)	25 (22–31)
ECOG performance status, No. (%)	
0	15 (30%)
1	35 (70%)
ER status[a], No. (%)	
Negative	0 (0%)
Positive	46 (92%)
Not done	4 (8%)
PR status[a], No. (%)	
Negative	18 (36%)
Positive	27 (54%)
Not done	5 (10%)
Metastatic sites at baseline, median (IQR)	3 (2–4)
Metastatic sites, No. (%)	
Bone	41 (82%)
Liver	35 (70%)
Lymph nodes	23 (46%)
Lung	19 (38%)
Pleural effusion	13 (26%)
Peritoneal	8 (16%)
Soft tissue	10 (20%)
Skin	3 (6%)
Brain	0 (0%)
Previous endocrine lines in metastatic setting, median (IQR)	3 (2–3)
Previous endocrine treatment lines in metastatic setting, No. (%)	
Aromatase inhibitor	33 (66%)
Aromatase inhibitor and CDK4/6-inhibitor	15 (30%)
Everolimus and exemestane	5 (10%)
Fulvestrant	12 (24%)
Fulvestrant and CDK4/6-inhibitor	29 (58%)
Tamoxifen	15 (30%)
Other	6 (12%)
Previous chemotherapy lines in metastatic setting, median (IQR)	2 (2–3)
Previous chemotherapy treatment lines in metastatic setting, No. (%)	
Anthracyclines (doxorubicin or epirubicin)	7 (14%)
Capecitabine	50 (100%)
Taxanes	36 (72%)
Tegafur/gimeracil/oteracil	4 (8%)
Vinorelbine	1 (2%)
Other	7 (14%)
Previous radiotherapy for metastatic disease, No. (%)	31 (62%)

BMI, body mass index; ECOG, eastern cooperative oncology group; ER, estrogen receptor; IQR, interquartile range; No, number; PR, progesterone receptor.
[a]More than 10% receptor-positive staining was considered as positive.

Table 1: **Patient characteristics.**

Response rates	Eligible population (N = 50)
RECIST 1.1 responses at 8 weeks	
Complete response	0 (0%)
Partial response	4 (8%)
Stable disease	28 (56%)
Progressive disease	13 (26%)
Not evaluable[a]	5 (10%)
DCR rate at 8 weeks, % (80% CI)[b]	64.0% (55.0–72.1)
DCR rate at 8 weeks, % (95% CI)	64.0% (50.1–75.9)
DCR rate at 16 weeks, % (95% CI)	50.0% (36.6–63.4)
DCR rate at 24 weeks, % (95% CI)	38.0% (25.8–51.9)
DCR rate at 32 weeks. % (95% CI)	30.0% (19.0–43.8)
Best overall response (according to RECIST 1.1)	
Complete response	1 (2%)
Partial response	6 (12%)
Stable disease	25 (50%)
Progressive disease	13 (26%)
Not evaluable[a]	5 (10%)
Progression-free survival	
Progression-free survival events, *N* (%)	40 (80%)
Median progression-free survival, months (95% CI)	5.4 (2.0–7.2)
Overall survival	
Deaths, *N* (%)	34 (68%)
Median overall survival, months (95% CI)	14.0 (8.8–17.8)

CI, Confidence interval; DCR, Disease control rate; RECIST, Response Evaluation Criteria in Solid Tumours, PFS, Progression-free survival. [a]Five patients were not evaluable because they had no radiological assessment during treatment due to early death (*n* = 2), discontinuation due to treatment-related toxicity (*n* = 2), symptomatic deterioration because of disease progression (*n* = 1). [b]The primary endpoint consisted of the DCR rate with the 80% CI, where the lower boundary of the 80% CI had to be higher than 30% to justify further research.

Table 2: **Overall efficacy of trifluridine-tipiracil treatment by investigator assessment.**

median PFS 6.8 months, ≥18 weeks pretreatment on capecitabine: median PFS 5.3 months, p = 0.62). Eight (6%) patients had a progression-free time interval of more than 12 month.

With 34 of 50 patients deceased, median OS was 14.0 months (95% CI, 8.8–17.8; Fig. 2B) in the eligible population. Half of the patients (*n* = 25) received subsequent systemic treatment after trifluridine-tipiracil (Appendix: Supplementary Table S2). Paclitaxel (*n* = 11), eribulin (*n* = 7), and vinorelbine (*n* = 3) were the most commonly used drugs.

Safety

All 52 treated patients were eligible for safety evaluation (Table 3). Fatigue (*n* = 43, 83%), neutropenia (*n* = 43, 83%) and leukopenia (*n* = 36, 69%) were the most commonly reported all-grade AEs and laboratory abnormalities, reporting the worst toxicity of each AE for each patient. The most common grade 3–4 AEs were primarily haematological disorders and included neutropenia (*n* = 38, 73%), leukopenia (*n* = 15, 29%) and anaemia (*n* = 6, 12%). Two cases of grade 3 febrile neutropenia were reported, with one necessitating a dose reduction.

Serious AEs (SAEs) occurred in 17 (33%) of all patients. Three grade 5 SAEs were registered: stroke, hepatic failure due to hepatogenic metastases and one patient undergoing palliative sedation on patients' request. None of these events were deemed to have a possible relationship with the treatment. The most common SAEs (any grade) with a possible relationship with trifluridine-tipiracil included anaemia (*n* = 2) and vomiting (*n* = 2).

Quality of life

Fig. 3 shows the mean and median scores of the functioning scales and the overall health score based on the QLQ-C30 parameters. No relevant deterioration or improvement of the median overall health status up to 32 weeks was observed since start treatment (baseline = 66.7, IQR = 50.0–83.3; 32 weeks = 66.7, IQR = 33.3–75.0, p = 0.20; Fig. 3A). Across the six functional domains, median scores remained stable or showed only minor variations over time. For a detailed post-protocol analysis of individual-level changes, including recalculated baseline values for patients with follow-up data at 16 or 32 weeks, please refer to the Supplementary material (Appendix; pg. 2). Fatigue was associated with the highest symptom burden, but scores remained stable during course of treatment (Appendix; Supplementary Fig. S1). The mean scores on the symptom scales revealed that the rate of nausea, appetite loss and constipation increased during treatment, whereas the burden of pain decreased.

Discussion

In this study, 64% (*n* = 32, 80% CI, 55–72%) of the 50 eligible patients remained progression-free at 8 weeks, meeting the primary endpoint. The prespecified criteria required the lower boundary of the 80% CI to be higher than 30% to justify further research of trifluridine-tipiracil. These findings indicate that trifluridine-tipiracil may offer a meaningful clinical benefit for heavily pretreated patients with ER+, HER2– metastatic breast cancer, demonstrating potential as a viable oral treatment option with relatively mild side-effects, and therefore preserving quality of life.

Despite recent advances in the current treatment landscape for MBC, including the introduction of CDK4/6 inhibitors combined with endocrine therapy as the standard-of-care in first- or second-line treatment for ER-positive, HER2-negative MBC, significant heterogeneity exists in later treatment lines, which are usually associated with only modest survival benefit.[27,28] The efficacy of trifluridine-tipiracil in our study, with a median PFS of 5.4 months and a median OS of 14.0

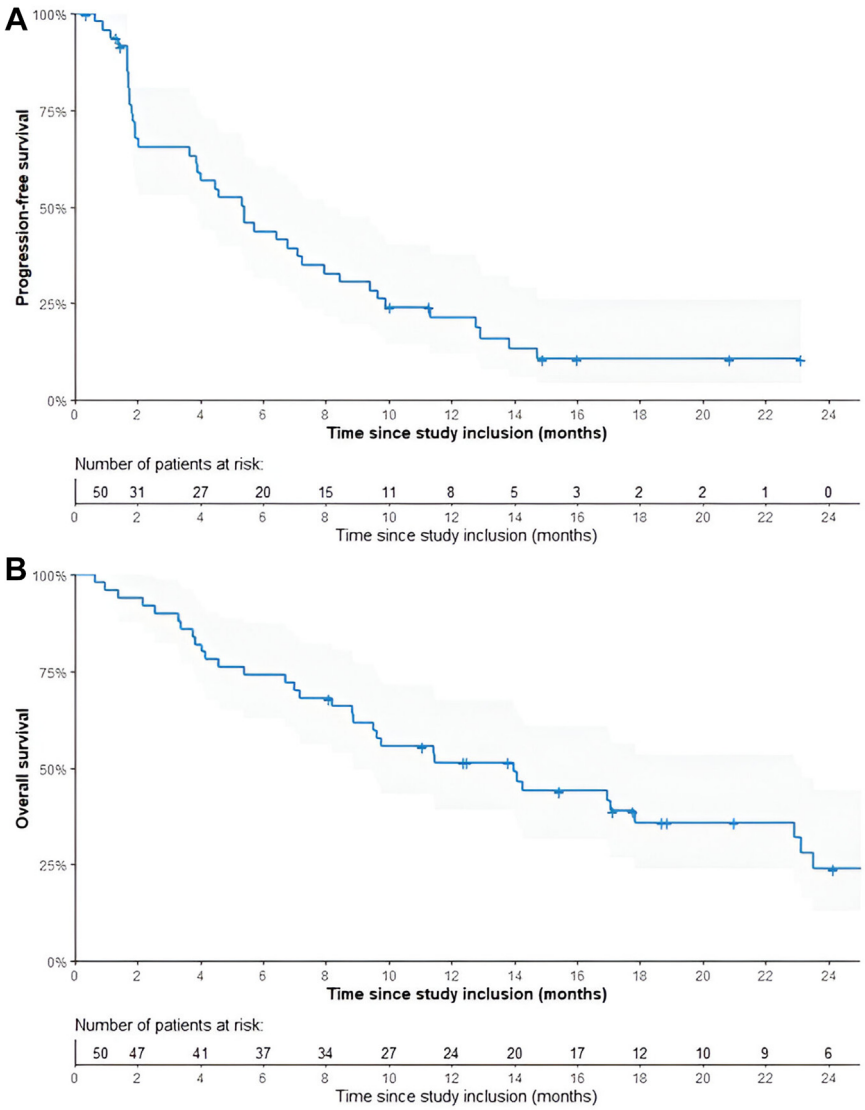

Fig. 2: **Efficacy of trifluridine-tipiracil.** Progression-free (A) and overall (B) survival in the eligible population (*N* = 50) according to the Kaplan–Meier method. The grey area represents the 95% confidence interval for the survival curve. The numbers in the table correspond to the number of patients at risk at each time interval since study inclusion.

months, is at least comparable with classic chemotherapy options such as eribulin and vinorelbine. Eribulin, based on several prospective studies (including the phase 3 EMBRACE trial), has shown a median PFS ranging from 2.8 to 4.1 months and a median OS ranging from 13.1–15.9 months in pretreated MBC patients.[29–32] Vinorelbine has demonstrated median PFS and OS ranging from 2.8 to 4.0 months and 12.5 to 16.4 months, respectively.[32,33] While other chemotherapeutic regimens, such as ixabepilone or metronomic schedules as CMF (cyclophosphamide, methotrexate, and fluorouracil) or oral methotrexate and cyclophosphamide, have been investigated in later-line settings, these are used less commonly in clinical practice due to limited efficacy and tolerability concerns. Eribulin and vinorelbine remain the most relevant comparators for assessing later-line chemotherapy options in MBC.[7,34–37] Although direct comparisons with these other chemotherapy options are hampered by differences in trial designs, the response rates observed with trifluridine-tipiracil are encouraging, particularly as these responses are independent of prior exposure time to a fluoropyrimidine. Additionally, in recent years, trastuzumab-deruxtecan has demonstrated a survival advantage with a median PFS of 9.9 months and a median OS of 23.4 months in previously treated patients with HER2-low MBC,

Adverse event	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Fatigue	43 (83%)	23 (44%)	16 (31%)	4 (8%)	0 (0%)	0 (0%)
Neutropenia	43 (83%)	1 (2%)	4 (8%)	22 (42%)	16 (31%)	0 (0%)
Leucopenia	36 (69%)	5 (10%)	16 (31%)	13 (25%)	2 (4%)	0 (0%)
Anaemia	35 (67%)	17 (33%)	12 (23%)	5 (10%)	1 (2%)	0 (0%)
Nausea	31 (60%)	16 (31%)	14 (27%)	1 (2%)	0 (0%)	0 (0%)
AST increased	29 (56%)	26 (50%)	3 (6%)	0 (0%)	0 (0%)	0 (0%)
AP increased	26 (56%)	16 (31%)	10 (19%)	0 (0%)	0 (0%)	0 (0%)
Diarrhea	21 (40%)	10 (19%)	9 (17%)	2 (4%)	0 (0%)	0 (0%)
GGT increased	20 (38%)	7 (13%)	10 (19%)	2 (4%)	1 (2%)	0 (0%)
ALT increased	19 (37%)	15 (29%)	4 (8%)	0 (0%)	0 (0%)	0 (0%)
Hypoalbuminemia	17 (33%)	10 (19%)	7 (13%)	0 (0%)	0 (0%)	0 (0%)
Anorexia	15 (29%)	8 (15%)	7 (13%)	0 (0%)	0 (0%)	0 (0%)
Vomiting	14 (27%)	5 (10%)	8 (15%)	1 (2%)	0 (0%)	0 (0%)
Constipation	12 (23%)	5 (10%)	7 (13%)	0 (0%)	0 (0%)	0 (0%)
Thrombocytopenia	12 (23%)	9 (17%)	0 (0%)	1 (2%)	2 (4%)	0 (0%)
Hyperglycemia	11 (21%)	8 (15%)	3 (6%)	0 (0%)	0 (0%)	0 (0%)

Data are n (%) of patients. AEs occur in ≥20% patients included. AEs are graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03. AE, adverse event; ALT, Alanine aminotransferase; AP, Alkaline phosphatase; AST, Aspartate aminotransferase.

Table 3: **Adverse events in the safety population (*N* = 52).**

thereby further influencing treatment choices.[38] Alongside response rates, treatment decisions and sequences will also be influenced by factors such as toxicity profiles, financial costs, and preferences regarding the administrative route and treatment scheduling.

To the best of our knowledge, this is the first prospective study investigating the use trifluridine-tipiracil in a Western population of patients with MBC. A recent phase 2 study conducted in Asia also demonstrated promising antitumour activity with a median PFS of 8.1 months and a median OS of 20.6 months.[39] However, important differences are that our study included only patients with ER+ and HER2– negative disease and required prior fluoropyrimidine treatment, in contrast to the Asian study, thus hindering direct comparison. In the subgroup of patients with prior exposure to fluoropyrimidine therapy, the median PFS was 5.7 months and the median OS was 18.0 months, comparable to the PFS and OS rates in this study. Moreover, geographical variations can significantly impact treatment outcomes due to genetic and

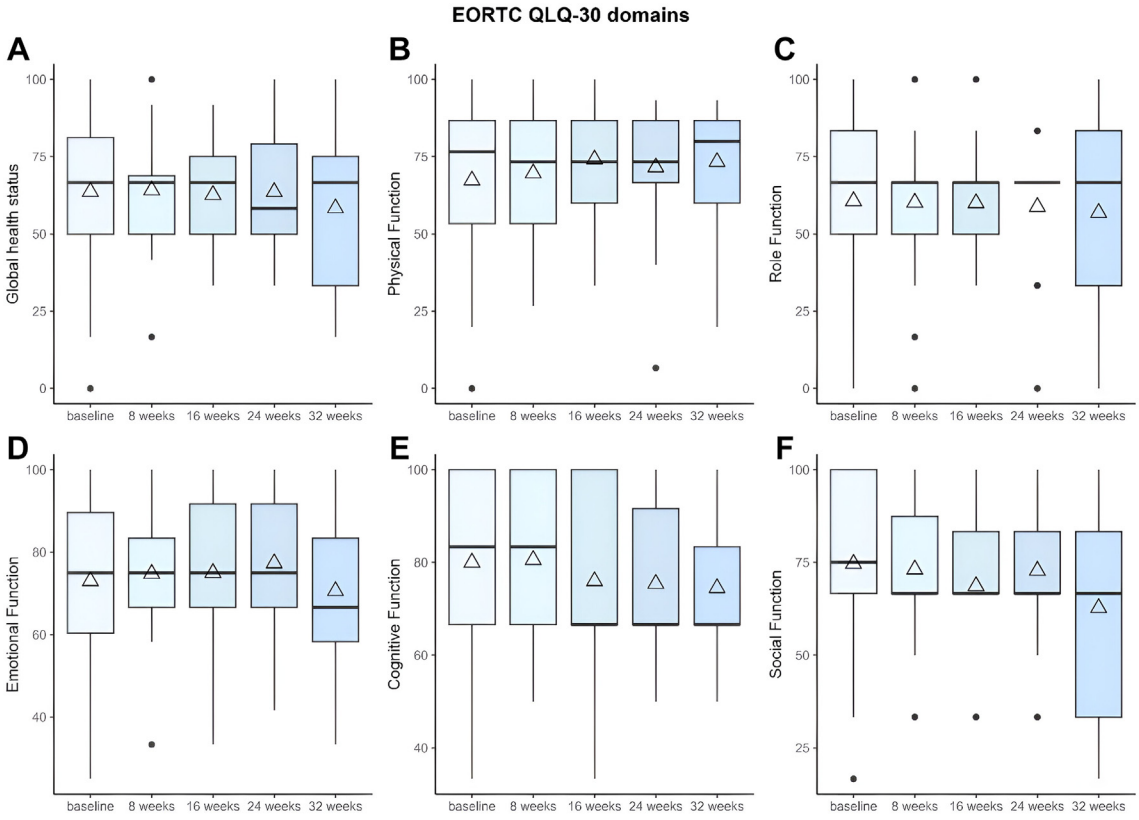

Fig. 3: **EORTC QLQ-C30 overall health score and functioning scales.** The global health status (A) and the five functional domains (B–F) assessed using the EORTC QLQ-30 questionnaires. Box plots display the median (horizontal line within the box), interquartile range (IQR; box boundaries represent the 25th and 75th percentiles), and whiskers (extending to the smallest and largest values within 1.5 × IQR). Points outside this range are shown as outliers (dots). Triangles represent the mean values. Sample sizes at each timepoint: baseline (*n* = 48), 8 weeks (*n* = 36), 16 weeks (*n* = 25), 24 weeks (*n* = 19), and 32 weeks (*n* = 17).

environmental factors. Also, genetic variations in *TYMS* (coding for the enzyme thymidylate synthase) and *DPYD* (coding for the enzyme dihydropyrimidine dehydrogenase) can influence the safety and efficacy profiles of fluoropyrimidine therapy, as highlighted by higher rates of adverse events during capecitabine treatment in Western populations compared to Asian populations.[40,41] Therefore, studying trifluridine-tipiracil in diverse populations is important to confirm the generalizability of the results.

The observed adverse events were in line with the known treatment profile of trifluridine-tipiracil.[20,21] Trifluridine-tipiracil was mainly associated with haematological toxicity, which was generally manageable with dose reductions or interruptions. Febrile neutropenia occurred in only two patients and resolved without the need for interventions as hospital-admission or introducing granulocyte colony-stimulating factor. Common adverse events associated with fluoropyrimidine use, such as hand-foot syndrome and grade 3–4 stomatitis, were not observed during this study. The manageable toxicity profile of trifluridine-tipiracil, including the absence of peripheral neuropathy and alopecia commonly associated with eribuline and vinorelbine, is particularly important as these toxicities can impair patient adherence and negatively affect quality of life. A relatively high incidence of hyperglycaemia (n = 11, 21%) was noted –all being only grade 1 or 2– and did not result in the initiation of new anti-diabetic medication or hospitalization. Hyperglycaemia was not observed in the phase 3 trials of trifluridine-tipiracil in colorectal cancer and gastric cancer, suggesting that this effect may not be directly related to trifluridine-tipiracil itself.[20,21] Therefore, the hyperglycaemia observed in our study may be incidental or related to the testing conditions rather than a class effect of trifluridine-tipiracil.

In this study, the use of trifluridine-tipiracil was supported by the maintenance of quality of life during treatment. These data are important for guiding informed decision-making regarding trifluridine-tipiracil, particularly given the heavily pre-treated status of this patient population. With several treatment options available for later-line treatment, the ease of oral administration, minimal hospital visits, and the absence of alopecia and cardiotoxicity associated with trifluridine-tipiracil further underscore its potential as a treatment choice for MBC.

Nonetheless, limitations of this study include the typical single-arm phase 2 design of the study, hampering a direct comparison to other agents. Moreover, although data on specific chemotherapy agents administered in the (neo)adjuvant setting were checked prior to inclusion to ensure eligibility, they were not systematically collected in the electronic case report forms. As such, we are only able to present baseline characteristics related to treatments in the metastatic setting. Additionally, the inclusion time of the study was delayed with almost a year due to the COVID-19 pandemic. However, it is important to note that no patients died due to COVID-19 during the study, and there was no evidence to suggest that the pandemic had any direct impact on patient outcomes. Moreover, a limitation of this study is the potential for healthy subject bias in the quality of life assessments, as patients in poorer health or with disease progression were less likely to complete follow-up questionnaires. This bias may have resulted in an overestimation of quality of life stability over time.

Despite these limitations, the findings of this study suggest that trifluridine-tipiracil offers a potential disease control benefit in heavily pretreated patients with ER-positive, HER2-negative MBC. To further explore the added value of trifluridine-tipiracil in pretreated metastatic breast cancer patients, a phase 3 trial will be carried out to randomize patients between trifluridine-tipiracil and other treatment options, with OS as the primary endpoint. Preparations are underway to initiate this trial.

In summary, the findings from this single-arm phase 2 study suggest that trifluridine-tipiracil exhibits promising activity in patients with heavily pretreated MBC, while maintaining quality of life and demonstrating manageable toxicity.

Contributors

SvdB, RB, and MB designed this study and wrote the protocol. NG, RM, MdB, MvB, JH, BV, MvR, LK, LH, KB, PN, SvdB, RB, and MB recruited patients and collected data. NG, RM, EOdH, RB, and MB did the statistical analysis. NG, RM, SvdB, EOdH, RB and MB verified all study data and wrote the initial manuscript. All authors reviewed and revised the manuscript, approved the final version of the manuscript, and had full access to all the data reported in the study and had final responsibility for the decision to submit the manuscript for publication.

Data sharing statement

The study protocol is available in the Appendix. Specific data requests by academic researchers who provide a methodologically sound proposal will be considered by the Dutch Breast Cancer Research Group (BOOG).

Declaration of interests

RM reports institutional grants for investigator-initiated trials from Astellas, Bayer, Boehringer-Ingelheim, Cristal Therapeutics, Deuter Oncology, Echo Pharmaceuticals, Nordic Pharma, Novartis, Pamgene, Pfizer, Roche, Sanofi, and Servier. SvdB reports institutional grants from Servier. All remaining authors have declared no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.103065.

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