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CLINICAL TRIAL REPORT

Does the Dose of Standard Adjuvant Chemotherapy Affect the Triple-negative Breast Cancer Benefit from Extended Capecitabine Metronomic Therapy? An Exploratory Analysis of the SYSUCC-001 Trial

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Purpose: Results from studies of extended capecitabine after the standard adjuvant chemotherapy in early stage triple-negative breast cancer (TNBC) were inconsistent, and only low-dose capecitabine from the SYSUCC-001 trial improved disease-free survival (DFS). Adjustment of the conventional adjuvant chemotherapy doses affect the prognosis and may affect the efficacy of subsequent

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treatments. This study investigated whether the survival benefit of the SYSUCC-001 trial was affected by dose adjustment of the standard adjuvant chemotherapy or not.

Patients and Methods: We reviewed the adjuvant chemotherapy regimens before the extended capecitabine in the SYSUCC-001 trial. Patients were classified into "consistent" (standard acceptable dose) and "inconsistent" (doses lower than acceptable dose) dose based on the minimum acceptable dose range in the landmark clinical trials. Cox proportional hazards model was used to investigate the impact of dose on the survival outcomes.

Results: All 434 patients in SYSUCC-001 trial were enrolled in this study. Most of patients administered the anthracycline-taxane regimen accounted for 88.94%. Among patients in the "inconsistent" dose, 60.8% and 47% received lower doses of anthracycline and taxane separately. In the observation group, the "inconsistent" dose of anthracycline and taxane did not affect DFS compared with the "consistent" dose. Moreover, in the capecitabine group, the "inconsistent" anthracycline dose did not affect DFS compared with the "consistent" dose. However, patients with "consistent" taxane doses benefited significantly from extended capecitabine (P=0.014). The sufficient dose of adjuvant taxane had a positive effect of extended capecitabine (hazard ratio [HR] 2.04; 95% confidence interval [CI] 1.02 to 4.06).

Conclusion: This study found the dose reduction of adjuvant taxane might negatively impact the efficacy of capecitabine. Therefore, the reduction of anthracycline dose over paclitaxel should be given priority during conventional adjuvant chemotherapy, if patients need dose reduction and plan for extended capecitabine.

Keywords: adjuvant chemotherapy, capecitabine, SYSUCC-001, triple-negative breast cancer, TNBC

Introduction

Triple-negative breast cancer (TNBC) exhibits high aggressiveness, poor prognosis, and extensive visceral metastases. Systemic chemotherapy based on taxane and/or anthracycline combinations has been the mainstream therapeutic option for early stage TNBC patients.[1] However, even if early stage TNBC patients receive the standard adjuvant chemotherapy, their prognosis is not very satisfactory, with a 5-year disease-free survival (DFS) accounts for 70%.[2–4] Several trials have shown that early stage TNBC patients could benefit from conventional adjuvant chemotherapy regimen combined with capecitabine.[5,6] In addition, whether prolonged chemotherapy will improve the DFS of early stage TNBC patients remains an interesting research question. Clinical trials, such as CREATE-X,[7] GEICAM-CIBOMA,[8] and SYSUCC-001,[9] investigated the efficacy of extended capecitabine after neo/adjuvant chemotherapy. Of note, GEICAM-CIBOMA and SYSUCC-001 trials enrolled only early stage TNBC patients, but these two trials reported conflicting results. GEICAM-CIBOMA trial did not demonstrate statistically survival benefit from extended capecitabine. By contrast, the SYSUCC-001 trial showed that low-dose capecitabine maintenance therapy for 1 year significantly improved 5-year DFS and was highly cost-effective.[10]

The low-dose capecitabine in the metronomic fashion may inhibit angiogenesis and immune escape to prevent metastasis and recurrence[11] that might explain the different results between the GEICAM-CIBOMA and SYSUCC-001 studies. However, there might be other reasons, such as duration of capecitabine or the previous adjuvant chemotherapy regimen. Whether the dose of standard adjuvant chemotherapy affecting the benefit from capecitabine maintenance therapy has not been studied.

Many trials investigated which type, or dose of chemotherapy could improve the DFS of TNBC patients.[12] Overall survival rate for those patients receiving high-dose chemotherapy was higher than for patients in a dose-dense regimen.[13] In addition, higher dose of taxane associated with a significant improvement in median time to progression.[14] In contrast, a reduction of the anthracycline dose was associated with higher mortality risk and significantly decreased 5-year absolute survival in all molecular subtypes.[15]

The regimen and dose in standard adjuvant chemotherapy were different in clinical trials of adjuvant capecitabine.[7–9] The CREATE-X trial found that theTNBC subgroup who had completed neoadjuvant chemotherapy but had residual invasive tumor identified on surgical pathology could derive greater benefit from the addition of capecitabine. However, the GEICAM-CIBOMA trial failed to demonstrate that adding capecitabine to standard adjuvant chemotherapy improved DFS or overall survival. We found that the minimum acceptable dose regimens for chemotherapy per protocol in the European GEICAM-CIBOMA trial was higher than the dose in the Asian CREATE-X trial. Moreover, the anthracycline-taxane regimen administrated accounted for 67% in the GEICAM-CIBOMA trial, but 89% in the SYSUCC-001 trial. This difference might explain the conflicting results of the GEICAM-CIBOMA and SYSUCC-001 trials. Hence, our

study investigated the effect of the previous dose or regimen of conventional adjuvant chemotherapy on the survival outcome of extended capecitabine in the SYSUCC-001 study. It is an ad hoc analysis of SYSUCC-001 trial.

The standard adjuvant chemotherapy regimen in SYSUCC-001 trial was reviewed and classified according to the chemotherapeutic doses as "consistent" (the doses within the range of the acceptable regimens for chemotherapy for participation in previous trials) or "inconsistent" (the doses lower than the minimum acceptable regimens for chemotherapy for participation in previous trials) based on the acceptable dose range in the landmark clinical trials (Table 1).[16–21] The regimens and consistency of adjuvant chemotherapy were analyzed the relationship with the prognosis of TNBC patients in the SYSUCC-001 trial.

Materials and Methods

Patient Eligibility

The major inclusion and exclusion criteria were described in Wang et al,[9] who compared the efficacy and adverse events of 1-year low-dose capecitabine (650 mg/m^2, bid) maintenance with observation following standard adjuvant treatment in patients with early stage TNBC in the SYSUCC-001 trial. The participants were women who had pathologically confirmed invasive breast ductal carcinoma that was hormone receptor negative (<1% positive cells by immunohistochemistry staining) and ERBB2 negative, and the stage is T1b–3N0–3M0. The trial excluded inflammatory or bilateral breast cancer; a history of invasive breast cancer or other malignancies; receipt of other biologic agents or immunotherapy; lactation or pregnancy; or severe coexisting illness. The present study was approved by the Ethics Committee of Sun Yat-sen University, and the requirement of obtaining written informed consent from the patients was waived owing to the retrospective nature of the study. Patients' medical data were handled confidentially, and the study followed the Declaration of Helsinki.

Chemotherapy Treatment and Classification of Variables

This trial enrolled 434 TNBC patients at stages II–III, as the SYSUCC-001 trial defined. Eligible patients were randomly assigned in a 1:1 ratio to receive either low-dose capecitabine maintenance or observation. All patients had completed conventional adjuvant chemotherapy, including A/EC, A/EC-T, TA/E, CMF, FA/EC, FA/EC-T, TA/EC, and TC regimens (A, doxorubicin; E, epirubicin; C, cyclophosphamide; T, paclitaxel [P] or docetaxel [D]; M, methotrexate; F, 5-fluorouracil). CMF was classified as a non-anthracycline-taxane regimen. A/EC and FA/EC was classified as anthracycline regimen. TC was taxane regimen. The anthracycline-taxane regimen was TA/E, FA/EC-T, A/EC-T and TA/EC.

In addition, the dose of anthracycline and taxane was reviewed and classified according to the acceptable dose ranges in the landmark clinical trials that described in Table 1. Therefore, patients were stratified into "consistent" or "inconsistent" groups according to their actual therapeutic anthracycline and taxane doses as mentioned before. There were four groups of patients which were taxane (consistent or inconsistent) and anthracycline (consistent or inconsistent).

Table 1 Minimum Acceptable Regimens for Chemotherapy for Participation in Previous Trials

Type of Regimen	Regimens
Anthracyclines (A or E combined with C, with or without F) without taxanes, taxanes combined with C[16,17]	Initial minimum permitted dose of E is from 75 to 100 mg/m^2, and the dose of A is 50 mg/m^2. The dose for EC is 90 mg/m^2, and that for FEC/CEF is 90–100 mg/m^2 (administered every 21 days). The dose for D is 75 mg/m^2
Anthracyclines (with or without C and/or F) and taxanes administered sequentially[17–20]	Initial minimum dose for injection of A is 60 mg/m^2 (50 mg/m^2 is also accepted for A in regimens of FAC). The dose for E is 90 mg/m^2 (75 mg/m^2 is also accepted for E in regimens such as FEC). The dose for P is 175 mg/m^2 (75 mg/m^2 or 100 mg/m^2 every 7 days for 8 doses; or 80 mg/m^2 every 7 days for 12 doses). The dose for D is 100 mg/m^2 or 75 mg/m^2
Anthracyclines are administered (with or without C) together with taxanes[20,21]	Initial minimum dose for injection of A is 50 mg/m^2. The dose for E is 75 mg/m^2. The dose for P is 135 mg/m^2. The dose for D is 60 mg/m^2 or 75 mg/m^2

Notes: A, doxorubicin; E, epirubicin; C, cyclophosphamide; T, Paclitaxel (P) or docetaxel (D); M, methotrexate; F, 5-fluorouracil.

Patient Follow-up and Endpoints

Follow-up information was obtained from the outpatient electronic records at all 13 Chinese study sites in the SYSUCC-001 study and by telephone interviews. Patients were assessed every 3 months during the first 1–2 years, then every 6 months until 5 years, and thereafter annually (median follow-up 61 months, interquartile range: 44–82 months). The evaluation mainly included routine hematological and laboratory examinations, menstrual status, breast and abdominal ultrasonography or computed tomography. Chest X-rays and bone scans were performed yearly.

The primary endpoint of this study was DFS until March 2020, which was defined as the time from the date of randomization to the first occurrence of the following events: local relapse, distant metastasis, contralateral breast cancer, or death from any cause.

Statistical Analysis

The differences of the baseline characteristics between capecitabine and observation group were analyzed using *t*-test on continuous variables and chi-square/Fisher's exact test on category variables. Cox proportional hazards models were used to investigate the impact of dose on the survival outcome of early stage TNBC patients in SYSUCC-001 trial. Hazard ratios (HRs) and the 95% confidence intervals (CIs) were estimated in both univariate and multivariate analyses in each group. Subgroup analyses were conducted according to prognostic factors, including anthracycline and taxane doses. The consistency of the treatment effects was evaluated using an unadjusted Cox proportional hazard model, with interaction analysis. In addition, 95%CIs of the median survival time were calculated using the Simon method.

A two-tailed *P*-value <0.5 was considered statistically significant. All statistical analyses were conducted using R software version 4.0.1 (Vanderbilt University, Nashville, TN, USA).

Results

Patients' Characteristics

From April 2010 to December 2016, the SYSUCC-001 trial enrolled 434 patients who completed the full analysis set. Baseline characteristics of the standard adjuvant chemotherapy are reported in Table 2. The anthracycline-taxane regimen

Table 2 Baseline Characteristics of the SYSUCC-001 Trial

Variables	Capecitabine Group (N=221), n (%)	Observation Group (N=213), n (%)	P-value*
Neo/adjuvant chemotherapy regimens			0.839
Non-anthracycline-taxane	2 (0.9)	1 (0.5)	
Anthracycline	1 (0.5)	2 (0.9)	
Taxane	20 (9.0)	22 (10.3)	
Anthracyclines-taxane	198 (89.6)	188 (88.3)	
Neo/adjuvant chemotherapy dose			
Anthracycline dose			0.141
Consistent	57 (25.8)	69 (32.4)	
Inconsistent	142 (64.3)	122 (57.3)	
NA	22 (10.0)	22 (10.3)	
Taxane dose			>0.99
Consistent	113 (51.1)	110 (51.6)	
Inconsistent	104 (47.1)	100 (46.9)	
NA	4 (1.8)	3 (1.4)	

Note: *Ignoring missing values.
Abbreviation: NA, non-anthracycline or non-taxane.

was the most common regimen accounted for 88.94% of patients which was 89.6% and 88.3% in the capecitabine and observation groups respectively. Only 29.1% and 51.35% of patients received the "consistent" doses of anthracycline and taxane, respectively, according to acceptable dose ranges in the landmark clinical trials. In the capecitabine group, 25.8% and 51.1% of patients received "consistent" dose of anthracycline and taxane respectively. In the observation group, 32.4% and 51.6% of patients received "consistent" dose of anthracycline and taxane respectively. There was no difference in either regimens or dose between the capecitabine and observation groups in the SYSUCC-001 trial.

Primary Endpoint

In the observation group, the "inconsistent" dose of anthracycline-taxane did not affect DFS compared with the "consistent" dose of chemotherapy by using the multivariate analysis. In addition, the "inconsistent" anthracycline dose did not affect DFS compared with the "consistent" dose in capecitabine group. However, patients with "inconsistent" taxane dose negatively affected survival outcome from extended capecitabine by using the multivariate analysis (HR 2.04; 95%CI: 1.02–4.06) (Table 3). Interactive analysis showed that the patients who received "consistent" dose of taxane benefited from extended capecitabine treatment (P=0.014) (Table 4).

Moreover, the cumulative hazard of capecitabine with "consistent" taxane doses was the lowest in the four groups (Figure 1), which suggested that the benefit from extended capecitabine depended on adequate taxane dose.

Table 3 Subgroup Analysis of DSM in Capecitabine Group and Observation Group According to Doses

Variables	Capecitabine Group (N=221)				Observation Group (N=213)			
	N	DSM (%)	HR[a]	HR[b]	N	DSM (%)	HR[a]	HR[b]
Anthracycline dose								
Consistent	57	15 (36.2)	Ref	Ref	69	23 (33.3)	Ref	Ref
Inconsistent	142	20 (14.1)	0.51 (0.26–1.0)	0.65 (0.32–1.33)	122	27 (22.1)	0.67 (0.38–1.16)	0.66 (0.37–1.20)
Taxane dose								
Consistent	113	15 (13.3)	Ref	Ref	110	35 (31.8)	Ref	Ref
Inconsistent	104	23 (22.1)	1.75 (0.91–3.35)	2.04 (1.02–4.06)	100	21 (21.0)	0.60 (0.35–1.04)	0.73 (0.42–1.29)

Notes: [a]Univariate analysis; [b]Multivariate analysis corrected for other baseline information.
Abbreviation: DSM, disease-specific mortality; HR, hazard ratio.

Table 4 Interactive Analysis of DSM in Capecitabine Group and Observation Group According to Regimen Dose Standard

Subgroup	DSM No./total No.		HR (95%CI)	P interaction
	Capecitabine	Observation		
Anthracycline dose				
Consistent	15/57	23/69	0.80 (0.42–1.53)	0.552
Inconsistent	20/142	27/122	0.62 (0.35–1.10)	
NA	3/22	6/22		
Taxane dose				
Consistent	15/113	35/110	0.38 (0.21–0.70)	0.014*
Inconsistent	23/104	21/100	1.09 (0.61–1.98)	
NA	0/4	0/3		

(*Continued*)

Table 4 (Continued).

Subgroup	DSM No./total No.		HR (95%CI)	P interaction
	Capecitabine	Observation		
Anthracycline-taxane dose				
Consistent	7/27	12/27	0.54 (0.21–1.37)	0.693
Inconsistent	28/170	38/162	0.69 (0.42–1.12)	
NA	3/24	6/24		

Note: *P<0.05.
Abbreviations: DSM, disease-specific mortality; CI, confidence interval; NA, non-anthracycline or non-taxane.

Discussion

The standard treatment of early stage TNBC patients bases on adjuvant and neoadjuvant chemotherapy.[22] Adjuvant anthracycline-taxane is recommended as the preferred regimen for early stage TNBC patients,[23,24] and extended capecitabine after neo/adjuvant chemotherapy has proved to be survival benefit.[25] The National Comprehensive Cancer Network (NCCN) 2023 version 1[26] breast cancer guidelines recommend adjuvant capecitabine under two conditions. First, the patients who does not achieve pathology complete response from neoadjuvant chemotherapy,

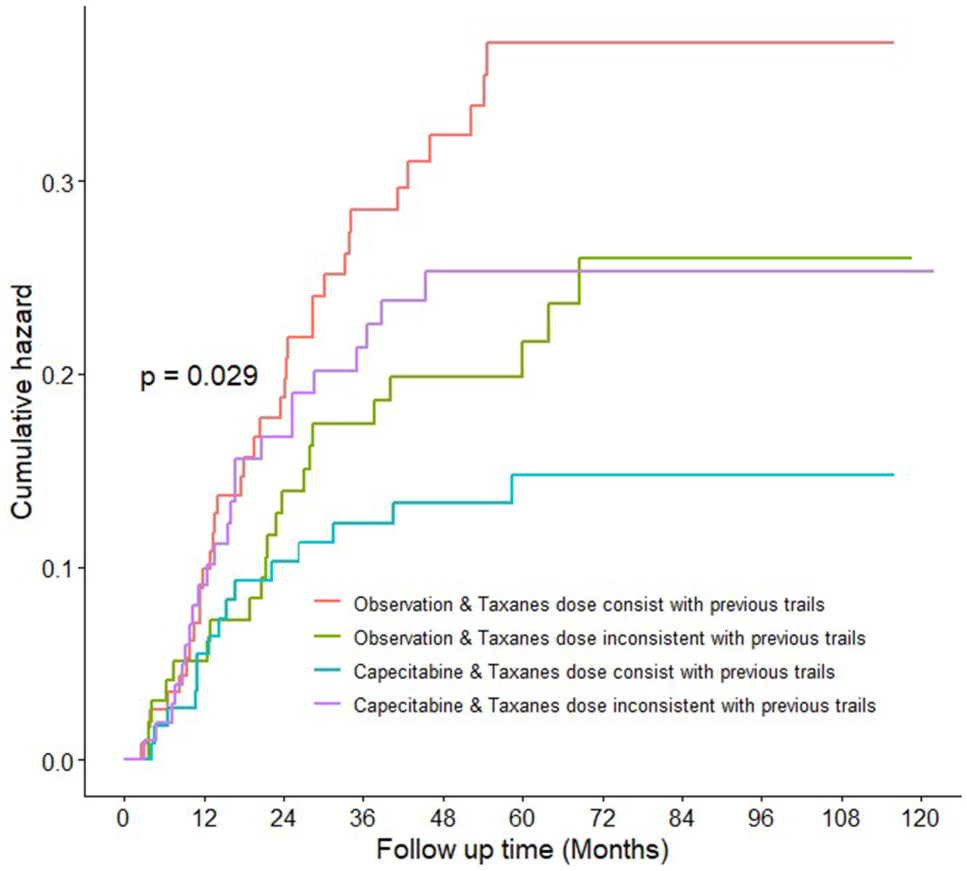

Figure 1 Cumulative hazard divided by taxane dose in the capecitabine group and observation group. Median observation for all curves was 61 months (interquartile range, 44–82 months). Cumulative hazards were estimated using Kaplan–Meier analysis and compared using log rank tests. Hazard ratios with 95% confidence intervals were estimated using a Cox proportional hazards model.

according to the results of the CREATE-X trial.[7] Second, the maintenance therapy for 1-year low dose capecitabine following standard adjuvant treatment, according to the result of the SYSUCC-001 trial.[9]

However, the results of capecitabine maintenance therapy in the SYSUCC-001 trial and GEICAM-CIBOMA trials[8] were different. There was no study that have focused on either the regimen or the doses in the standard adjuvant chemotherapy of these trials.

In our study, the anthracycline-taxane chemotherapy was the most common regimen in both the capecitabine and observation groups as recommend in the international guideline. The type of conventional adjuvant chemotherapy regimen did not affect survival benefit of extended capecitabine in the SYSUCC-001 trial.

Regarding to doses of chemotherapy, the previous research demonstrated that the dose of antitumor drugs was associated with therapeutic effects.[27] Furthermore, a reduction in the dose of anthracycline or taxane affected the prognosis of breast cancer patients,[14,15] but whether it would impact the effect of extended capecitabine treatment was unknown.

There were different standard adjuvant chemotherapy regimens and dose intensities, including the "inconsistent" dose chemotherapy between the SYSUCC-001 study with other previous trials. More than 60% patients received the "inconsistent" dose of anthracyclines, and 47% of patients received the "inconsistent" dose of taxane in the SYSUCC-001 trial. Interestingly, when the "consistent" dose of taxane was used in adjuvant chemotherapy, capecitabine further improved the DFS of early stage TNBC patients. Further researches to investigate why the "consistent" dose of taxane but not of anthracyclines might affect the benefit from capecitabine maintenance treatment were warranted.

Regarding to the conflicting results of the GEICAM-CIBOMA and SYSUCC-001 trials, there were several differences between these studies including the racial/ethnic backgrounds of patients, dose and duration of capecitabine administration. Metronomic chemotherapy can overcome drug resistance through inhibiting tumor neovascularization, restoring the anticancer immune response, and inducing tumor dormancy.[11] In addition, prolonged treatment might also reduce the recurrence.[9] The research of dose intensities of conventional adjuvant chemotherapy in the GEICAM-CIBOMA trial would be informative. Noteworthy, in a meta-analysis of the GEICAM-CIBOMA and SYSUCC-001 trials, capecitabine maintenance significantly improved DFS in early stage TNBC patients who received adjuvant standard chemotherapy.[28]

Moreover, the KEYNOTE-522 clinical trial estimated event-free survival at 36 months was improved 7.7% in the pembrolizumab–chemotherapy group compared to the placebo–chemotherapy group.[29] The data from the KEYNOTE-522, IMpassion031, I-SPY2 and GeparNuevo trials showed that the addition of immunotherapy to chemotherapy provides statistically significant benefits in EFS and OS.[30] These studies showed that immunotherapy or platinum may play an important role in the treatment of TNBC. They not only improve the PCR, but also provide benefits in long-term survival. The change of the previous treatments will also affect the benefits from extended capecitabine treatment.

As a retrospective ad hoc analysis, there are many inevitable biases in subgroups that are separated by the type of adjuvant standard chemotherapy regimen or doses, and small numbers of events. In addition, the SYSUCC-001 trial did not include patients receiving neo/adjuvant platinum or a programmed cell death protein 1/programmed cell death ligand 1 (PD-1/PD-L1) inhibitor. Cancer treatment evolves rapidly, more and more personalized and targeted therapies are developing quickly, further randomized controlled studies or real-world data would validate and replenish the results of our study.

Conclusion

In summary, this study confirmed the survival benefit of the extended low-dose capecitabine for 1 year in early stage TNBC patients regardless of types of standard adjuvant chemotherapy regimen or dose of anthracycline. More importantly, the dose reduction of adjuvant taxane might negatively impact the efficacy of capecitabine. Our results further supported the addition of capecitabine to the standard dose of paclitaxel for early stage TNBC patients. Therefore, our results can also give the suggestion that the reduction of anthracycline dose over paclitaxel should be given priority during conventional adjuvant chemotherapy if patients need dose reduction and plan for extended capecitabine.

Abbreviations

TNBC, triple-negative breast cancer; DFS, disease-free survival; HR, hazard ratio; CI, confidence interval; A, doxorubicin; E, epirubicin; C, cyclophosphamide; T, paclitaxel (P) or docetaxel (D); M, methotrexate; F, 5-fluorouracil;

NCCN, National Comprehensive Cancer Network; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Declarations

The present study was approved by the Ethics Committee of Sun Yat-sen University, and the requirement of obtaining written informed consent from the patients was waived owing to the retrospective nature of the study. Patients' medical data were handled confidentially, and the study followed the Declaration of Helsinki.

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Author Contributions

All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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