

Phase III Trial of Fludarabine Plus Cyclophosphamide Compared With Fludarabine for Patients With Previously Untreated Chronic Lymphocytic Leukemia: US Intergroup Trial E2997

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ABSTRACT

Purpose

The combination of fludarabine and cyclophosphamide is an effective regimen for patients with chronic lymphocytic leukemia (CLL). However, it may be accompanied by increased toxicity compared with fludarabine alone. E2997 is a phase III randomized Intergroup trial comparing fludarabine and cyclophosphamide (FC arm) versus fludarabine (F arm) alone in patients receiving their first chemotherapy regimen for CLL.

Patients and Methods

Symptomatic, previously untreated patients with CLL were randomly assigned to receive either fludarabine 25 mg/m² intravenously (IV) days 1 through 5 or cyclophosphamide 600 mg/m² IV day 1 and fludarabine 20 mg/m² IV days 1 through 5. These cycles were repeated every 28 days for a maximum of six cycles.

Results

A total of 278 patients were randomly assigned in this Intergroup study. Treatment with fludarabine and cyclophosphamide was associated with a significantly higher complete response (CR) rate (23.4% v 4.6%; $P < .001$) and a higher overall response (OR) rate (74.3% v 59.5%, $P = .013$) than treatment with fludarabine as a single agent. Progression-free survival (PFS) was also superior in patients treated with fludarabine and cyclophosphamide than those treated with fludarabine (31.6 v 19.2 months, $P < .0001$). Fludarabine and cyclophosphamide caused additional hematologic toxicity, including more severe thrombocytopenia ($P = .046$), but it did not increase the number of severe infections ($P = .812$).

Conclusion

Fludarabine and cyclophosphamide produced an increase in OR and CR, and it improved PFS in patients with previously untreated CLL compared with fludarabine alone and was not associated with an increase in infectious toxicity.

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INTRODUCTION

Although progress has been made in developing treatments able to induce complete response (CR) in patients with chronic lymphocytic leukemia (CLL), most patients will relapse and ultimately die with their disease. More effective therapies are needed. The purine analog fludarabine is the most active single agent in the treatment of CLL, with CR rates of 20% observed in large cooperative group trials.^{1,2} The alkylating agent cyclophosphamide is also active against CLL and has been widely used in combination chemotherapy regimens.³⁻⁵

In vitro studies indicate that fludarabine may enhance the effect of cyclophosphamide by inhibiting repair of the interstrand cross-links produced by the alkylating agent.^{5,6} A number of different regimens combining these two agents have now been investigated, including a phase II study of fludarabine and cyclophosphamide (FC arm) conducted by the Eastern Cooperative Oncology Group (ECOG, Philadelphia, PA) in patients with previously untreated CLL.⁷⁻¹⁰ Forty-two percent of patients achieved a CR. Despite concerns from previous studies using combination regimens with fludarabine or other nucleoside analogs,^{11,12}

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the toxicity of this regimen was acceptable. Based on these promising results, a US Intergroup trial was initiated in 1999 to evaluate the combination of fludarabine and cyclophosphamide compared with single-agent fludarabine in patients with previously untreated CLL.

PATIENTS AND METHODS

Study Design

E2997 was a randomized, multicenter phase III study initiated by ECOG and later amended to include Cancer and Leukemia Group B (CALGB, Chicago, IL) and Southwest Oncology Group. Institutional review board approval was obtained at all participating institutions.

Patients 18 years or older with a diagnosis of progressive CLL using National Cancer Institute (NCI, Bethesda, MD) criteria,¹³ who had not previously been treated with chemotherapy, were eligible. Serum creatinine could not exceed 2 mg/dL. Patients with serum creatinine greater than 1.5 mg/dL were required to have creatinine clearance of at least 40 mL/min. Patients with a second malignancy other than basal cell carcinoma of the skin (unless treated with curative intent more than 2 years from study entry), an active infection, a performance status (PS) of more than 2, or total bilirubin greater than 2 mg/dL (unless secondary to CLL) were excluded. Patients with evidence of autoimmune hemolytic anemia or thrombocytopenia or a history of steroid treatment for these disorders were also excluded, as were pregnant or lactating women. All patients provided written informed consent. The diagnosis was confirmed by central review of a peripheral blood smear. Peripheral blood specimens were received in ECOG's leukemia reference laboratory from 257 (92%) of 278 patients registered to E2997. Specimens contained between 32% and 99% leukemic lymphocytes (median 82% of WBCs). By multiparameter flow cytometry, all patients were diagnosed as B-cell CLL, with 97% demonstrating the classical CD5+ immunophenotype.

Treatment

Patients randomly assigned to combination chemotherapy received 600 mg/m² intravenously (IV) cyclophosphamide on day 1 of a 28-day cycle and fludarabine at 20 mg/m² IV every day on days 1 through 5 of the 28-day cycle (FC arm). Patients randomly assigned to single-agent therapy received fludarabine at 25 mg/m² IV every day on days 1 through 5 of the 28-day cycle (F arm). Treatment was given for a maximum of six cycles. To receive scheduled therapy, the hemoglobin had to be at least 10 g/dL, and platelets had to be at least 75,000/ μ L, or within 10% of the pretreatment baseline. (Maximum baselines reflected in such calculations were to be 13 g/dL and 100,000/ μ L.) Fludarabine was reduced in the first cycle for impaired renal function in each arm (Table 1).

Dose modifications for cycles 2 and beyond were mandated for both fludarabine and cyclophosphamide in patients randomly assigned to the FC arm. Dose modifications were specified in the protocol based on nadir platelet or hemoglobin, grade 2 or higher gastrointestinal toxicity (except nausea and vomiting without sufficient prophylaxis), infection, grade 2 and 3 genitourinary toxicity, and other grade 3 toxicity. Patients who experienced grade 3 or higher fludarabine-related pneumonitis or grade 4 cardiac toxicity, or who developed autoimmune hemolytic anemia, autoimmune thrombocytopenia, or other autoimmune disorders were to discontinue protocol treatment. Par-

allel dose modifications were mandated for patients assigned to the F arm. All dose modifications were presented as a percentage of the full dose, which permitted parallel adjustments of fludarabine on both arms, even though the daily dose was different.

Patients randomly assigned to combination chemotherapy with fludarabine and cyclophosphamide were to receive prophylaxis against herpes zoster and filgrastim (granulocyte colony-stimulating factor, 5 μ g/kg/d, subcutaneously), with a recommended start of day 8 of a cycle. Patients randomly assigned to the F arm were not mandated to receive growth factor support.

All patients were to receive *Pneumocystis carinii* prophylaxis and allopurinol for 7 days, beginning 1 day before initiation of chemotherapy. Treatment with corticosteroids, including use as an antiemetic, was prohibited.

Patients were to be treated to maximal response or until there was no evidence of residual disease as detected by flow cytometry. Patients with progressive disease after receiving two or more cycles of therapy were to discontinue protocol treatment.

Monitoring

Baseline investigations included tumor measurement by physical examination, PS assessment, full laboratory parameters, and a CBC. Bone marrow aspirates and biopsy were taken, and immunophenotyping of bone marrow by flow cytometry was carried out. The CBC was repeated weekly. Tumor measurement was repeated after every second cycle. Follow-up examinations were carried out every 3 months for the first year and every 6 months thereafter.

End Points and Statistical Considerations

The primary end point of this randomized phase III trial was the comparison of efficacy based on the rate of CR in each of the randomized treatment arms. Response was evaluated according to NCI Working Group criteria.¹³ The study was designed to detect an increase in the CR rate from 25% on fludarabine alone to 45% on fludarabine and cyclophosphamide, with 90% power and overall one-sided type I error of .025.

Stepwise logistic regression models were used to identify clinical factors associated with the achievement of CR, overall response (OR), and progression-free survival (PFS). Additional modeling investigated the behavior of ordered categorical factors and other factors of interest. These factors included Rai stage, sex, race (white v nonwhite), decade of age, PS, splenomegaly, hepatomegaly, time from initial diagnosis, and elevated lactate dehydrogenase (LDH). Wald test *P* values are reported for the individual factors in the resulting models.

RESULTS

Patient Characteristics

Of the 278 patients enrolled onto this study, 70% were male. The median age was 61 years (33 to 86 years). Median time from initial diagnosis to study entry was 13.2 months. Patients commonly presented with splenomegaly (63%) and/or lymphadenopathy (87%). Table 2 and Table 3 present further details on patient characteristics at study entry by randomized treatment arm.

Treatment

Of the 264 patients with data on reason for ending study therapy, 178 (67.4%) completed their treatment per protocol. Fifteen patients (5.7%) discontinued protocol treatment because of progressive disease (four on the FC arm and 11 on the F arm). Thirty-eight patients (14.4%) experienced toxicity that resulted in the termination of study therapy (23 on FC and 15 on F). Two patients (0.8%), both on F, died during treatment. Five patients (1.9%) withdrew consent or refused further therapy (three on FC and two on F). One patient on F (0.4%) received nonprotocol therapy. In addition, 24 patients terminated study therapy before the completion of treatment for other reasons (9.1%), 12 on FC, and 12 on F. One hundred sixty-nine patients

Table 1. Dose Reduction for Impaired Renal Function

Creatinine Clearance (mL/min)	Fludarabine Dose (mg/m ²)	
	Arm A	Arm B
71-above	20	25
61-70	14	17.5
51-60	12	15
40-50	10	12.5
0-39	Not eligible	Not eligible

Table 2. Patient Characteristics at Enrollment (n = 278)

Characteristic	FC (n = 141)	Fludarabine (n = 137)	Total (n = 278)
Median age, years	61	61	61
Range	39 to 86	33 to 83	33 to 86
Male, No.	99	96	195
%	70	70	70
Median leukocyte count, 10 ⁹ /L	31.3	42.8	37.0
Range	0.3 to 429	1.7 to 525.6	0.3 to 525.6
Median hemoglobin, g/L	11.0	11.5	11.3
Range	4.4 to 16.2	4.7 to 15.4	4.4 to 16.2
Median platelet count, 10 ⁹ /L	139	154	146
Range	21 to 616	16 to 452	16 to 616
ECOG performance status			
0	64	67	131
%	45	49	47
1	56	47	103
%	40	34	37
2	19	20	39
%	13	15	14
Median time from diagnosis, months	11.5	16.2	13.2
Range	0 to 150	0 to 240	0 to 240
Rai stage, baseline			
0	4	3	7
%	3	2	3
1	37	33	70
%	26	24	25
2	35	41	76
%	25	30	27
3	30	31	61
%	21	22	22
4	33	27	60
%	23	20	22
Unknown	2	2	4
Splenomegaly	1	1	1
Yes	83	90	173
%	59	66	62
No	55	45	100
%	39	33	36
Unknown	3	2	5
%	2	1	2
Lymphadenopathy			
Yes	121	118	239
%	86	86	86
No	17	17	34
%	12	12	12
Unknown	3	2	5
%	2	1	2

NOTE. Three patients on FC reported prior splenectomy.
Abbreviations: FC, fludarabine and cyclophosphamide; ECOG, Eastern Cooperative Oncology Group.

Table 3. Baseline Characteristics FISH Category

Characteristic	FC (n = 122)	Fludarabine (n = 113)	Total (n = 235)
17p	10	9	19
11q	24	16	40
6q	7	1	8
t(12)	21	27	48
Normal	17	20	37
13q	43	38	81
IgH	0	2	2

Abbreviations: FISH, fluorescent in situ hybridization; FC, fludarabine and cyclophosphamide; IgH, immunoglobulin heavy chain.

a documented partial response (PR). Overall response (OR) rates, defined as CR plus PR, were 74.3% on FC and 59.5% on F (Fisher's exact test $P = .013$).

Stepwise logistic regression identified that only random assignment to the FC arm ($P < .0001$) and enrollment onto the study with Rai stage 0 or 1 disease ($P = .0001$) were associated with an increased odds of achieving CR. The estimated OR associated with treatment with fludarabine and cyclophosphamide is 6.93 (95% CI, 2.72 to 17.62); the estimated OR associated with treatment for Rai stage 0 or 1 disease is 4.29 (95% CI, 2.03 to 9.08).

Additional modeling investigated the effect of time from initial diagnosis to study entry and decade of age and found no statistically significant associations with the odds of achieving a CR. Achievement of an overall objective response, defined as CR or PR, was modeled in a parallel fashion to that described previously. The regression procedure identified only treatment arm as having a significant impact on the odds of achieving a response to therapy. The OR associated with treatment on the FC arm of the study is 1.905 (95% CI, 1.131 to 3.206; $P = .015$). There were no statistically significant associations with time from diagnosis to initiation of treatment.

Progression-Free Survival

At the time of this report, 129 patients have reported either progression or death in the absence of progression. Of these, 54 events have occurred in patients treated with fludarabine and

Table 4. Response Rates According to Treatment Arms As Defined by NCI Criteria

Response Type	FC	Fludarabine
Complete response	32	6
%	23.4	4.6
Partial response	69	72
%	50.4	54.6
Stable disease	20	31
%	14.6	23.5
Progression	6	9
%	4.4	6.8
Unassessable	9	13
%	6.6	9.9
No response data	1	1
%	0.7	0.8

Abbreviations: NCI, National Cancer Institute; FC, fludarabine and cyclophosphamide.

received the full six cycles of therapy. Of these, 83 patients were randomly assigned to the FC arm and 86 were randomly assigned to the F arm.

Response

Table 4 presents response data available for 267 of the 278 randomly assigned patients. The CR rate for patients assigned to the FC arm was 23.4%, compared with 4.6% for patients assigned to the F arm (Fisher's exact test, $P = .000007$). A total of 69 (50.4%) of 137 patients on FC and 72 (54.5%) of 132 patients on F achieved

cyclophosphamide, and 75 in patients treated with fludarabine ($P = .0001$ by the log-rank test). Median progression-free survival (PFS) on fludarabine and cyclophosphamide is currently estimated at 31.6 months, compared with 19.2 months on fludarabine (Fig 1).

Prognostic Factor Analysis

Stepwise proportional hazards regression models were investigated to identify factors associated with improved PFS. This procedure identified randomized treatment arm (FC), more than 3 years from diagnosis to study entry, presence of splenomegaly at study entry, and PS 2 at study entry for inclusion. Random assignment to the FC arm was associated with a hazard ratio (HR) of 0.513 ($P = .0003$), and diagnosis of more than 3 years before study entry was associated with a HR of 0.650 ($P = .035$). Each of these factors was associated with an improved PFS. Splenomegaly (HR 1.990; $P = .0007$) and PS 2 (HR = 1.591; $P = .43$) were associated with a shorter PFS. Please see Grever et al¹⁴ for a full description of prognostic factors in this trial.

Survival

With only 55 deaths to date among patients enrolled in this study, it is not unexpected that the randomized treatment arms do not differ at this time (log-rank test, $P = .69$). Of the patients who died, 29 were randomly assigned to the FC arm and 26 to the F arm. Two-year overall survival is currently estimated as 79% for patients randomly assigned to FC and 80% for patients randomly assigned to F. Median follow-up is 2 years among the 223 censored patients.

Toxicity

Fifty percent of patients on the FC arm experienced grade 3 or higher nonhematologic toxicities, compared with 33% of patients on the F arm ($P = .007$). The difference in the toxicity was restricted to the incidence of grade 3 toxicities—40% on FC compared with 25% on F. There was no difference in rates of infection ($P = .812$). Table 5 presents the percentages of patients experiencing grade 3 or higher toxicities on this study.

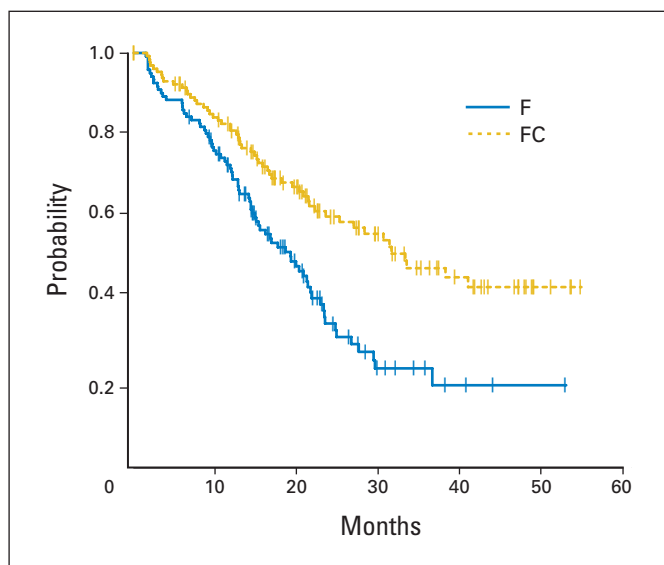


Fig 1. Progression-free survival by treatment arm. Using the Kaplan-Meier method, the progression-free survival duration was computed from random assignment until documented progression of disease or death without progression. F, fludarabine-alone arm; FC, fludarabine plus cyclophosphamide arm.

Table 5. Grade 3 or Higher Treatment-Related Toxicity According to Arm of Study

Toxicity Type	Treatment Arm					
	FC (n = 136)			Fludarabine (n = 132)		
	Grade (%)			Grade (%)		
	3	4	5	3	4	5
Hematologic						
CD4	27	7	—	17	5	—
Hemoglobin	17	13	—	14	6	—
Leukocytes	42	29	—	36	6	—
Lymphopenia	89	—	—	57	—	—
Neutrophils	23	46	—	28	35	—
Platelets	24	4	—	15	1	—
Nonhematologic						
Allergic reaction	2	—	—	2	—	—
Fatigue	4	1	—	2	2	—
Rash/desquamation	6	1	—	5	1	—
Alkaline phosphatase	3	—	—	1	—	—
Bilirubin	2	1	—	1	2	—
AST	4	1	—	3	—	—
ALT	4	1	—	2	—	—
Febrile neutropenia	5	—	—	5	—	—
Infection with grade 3 or 4 neutropenia	7	1	1	8	2	1
Infection without neutropenia	9	—	—	3	—	—
Pneumonitis/pulmonary infiltrates	3	—	—	1	1	1
Dyspnea	4	1	—	3	—	—
Worst degree	40	9	1	25	6	2

NOTE. Only toxicities with > 2% incidence are displayed. Abbreviation: FC, fludarabine and cyclophosphamide.

More hematologic toxicity was noted in patients randomly assigned to the FC arm. Despite the mandate to use myeloid growth factors, increased grade 3 and 4 leukopenia was seen on the FC arm ($P < .00001$). Among the 136 FC patients, 128 (94%) reported receiving filgrastim. Among the 133 F patients, 30 (23%) reported receiving filgrastim. Patients on the FC arm also experienced worse anemia ($P = .032$) and thrombocytopenia ($P = .046$). There was no difference in autoimmune hemolytic anemia between the two arms.

Second Malignancies

At the time of this analysis, 22 second malignancies had been reported, 11 in each arm. These included two cases of hematologic malignancies (one unspecified lymphoma and one Hodgkin's disease), five lung cancers, and nine nonmelanoma skin cancers.

DISCUSSION

The results of this randomized phase III Intergroup study demonstrate that the fludarabine and cyclophosphamide regimen yields improved CR, OR, and PFS compared with fludarabine alone. As yet, no survival advantage has been seen, which is expected given the long survival of many patients with CLL.

Logistic regression models found no significant associations with the odds of achieving a CR but did find that requiring therapy after 3 years from diagnosis was associated with a superior PFS. This finding is consistent with the popular clinical notion that the longer a patient

doesn't require therapy, the better that patient will do. While it might be tempting to reserve fludarabine and cyclophosphamide only for patients who had progressed within the first 3 years from diagnosis, this approach is not supported by the results of this study. All patients benefited from receiving fludarabine and cyclophosphamide no matter how much time elapsed from diagnosis to requiring therapy.

In this phase III Intergroup trial, lower OR and CR rates were observed compared with those reported in the two phase II trials conducted in ECOG and elsewhere in which CR rates of 42% and 47% were seen.^{7,10} While the difference in results when therapies are moved from phase II to III trials is well-known, it is important to keep this in mind when comparing these results to phase II results of other therapies, regardless of the setting or size of the trial. The results of this trial are consistent with the findings of the German CLL Study Group (GCLLSG) phase III trial, comparing fludarabine to a 3-day regimen of fludarabine and cyclophosphamide in younger patients with CLL.¹⁵ Although the GCLLSG study had a higher OR rate in the combination arm, the CR rate of 24% and the difference between the CR rate in the FC (24%) and F (7%) arms is very similar to the results of this study. Both studies also found a highly significant difference in PFS in favor of FC. There are differences compared with the results of the GCLLSG study in terms of partial responses and hematologic toxicity. The partial response rate is lower on the current study on both the F and FC arms. However, it should be noted the OR rate on the F arm is very similar to other studies such as the last North American Intergroup Trial (NAIT) (59.2% v 63%) as was the incidence of grade 3 to 4 thrombocytopenia (16% v 13%). The CR rate of fludarabine in both this study and the GCLLSG are lower than was seen in the previous NAIT trial.

It is not clear why the response rate and toxicity of the control arm vary from one study to another. While the GCLLSG study was restricted to patients younger than 65 years, most of the prognostic factors are similar to E2997 in terms of baseline clinical characteristics. It is possible that there is some unrecognized variation in the application of the response criteria or unknown prognostic factor. We believe this highlights the importance of randomized trials with an emphasis on the analysis of the difference between the two arms. The results of this trial built on the NAIT trial findings, in which fludarabine was found to have superior response rates and PFS than that of chlorambucil.¹¹

While alkylating agents and nucleoside analogs are the two most active classes of drugs in the treatment of CLL, the development of combination regimens have been hampered because of a concern for excessive toxicity. For instance, the previous NAIT study found that the combination of fludarabine and chlorambucil was excessively toxic.¹¹ In low-grade lymphoma, an arm of a cooperative group trial combining fludarabine with cyclophosphamide was closed early because of excessive toxicity.¹⁶ Fortunately, patients on the combination arm of this trial did not experience excessive toxicity. Although more patients on the FC arm withdrew early because of excessive toxicity, these withdrawals were offset by a nearly equivalent number of patients who did not complete the therapy because of progressive CLL in the F arm. This balance between increased efficacy and toxicity, which has not been seen in some other trials, is likely a result of the dose of cyclophosphamide that was chosen, which is 40% less than the dose used in low-grade lymphoma, and supportive care.

In initial phase II studies, filgrastim was administered with fludarabine and cyclophosphamide given the significant neutropenia seen with previous combination studies with fludarabine. This regi-

men has never been studied without filgrastim. While there is more grade 4 neutropenia with fludarabine and cyclophosphamide than fludarabine, it is very possible that there would be even more toxicity if filgrastim was not used. Until safety studies are conducted that demonstrate the safety of fludarabine and cyclophosphamide without filgrastim, we continue to recommend filgrastim with this fludarabine and cyclophosphamide regimen in most patients.

In summary, the results of this study demonstrate that fludarabine and cyclophosphamide yields improved CR, OR, and PFS compared with fludarabine in patients with previously untreated CLL, and it was well-tolerated in this patient population. Certainly, there is precedence for combination therapies being more effective in the treatment of malignant diseases. Numerous other therapies are being developed for the initial treatment of patients with CLL. Most prominently, rituximab is being added to fludarabine-containing regimens. A phase II cooperative group study of fludarabine and rituximab produced results similar to the phase II results of FC, highlighting the need for comparative trials.¹⁷ The results of the fludarabine, cyclophosphamide, and rituximab regimen are very encouraging with phase II CR rate reported to be 70% in previously untreated patients with this disease.¹⁸ Optimization of the actual drugs, doses, and schedules of administration should be pursued expediently to establish the standard to be used in future attempts to improve outcome in this disease.

Careful assessment of variations in patient populations will be necessary to determine if explanations can be found for differences in complete remission rates that have been reported between various trials. While these differences may relate to sample size and population characteristics, there also may be differences in the prognostic biomarkers between the respective studies. The extraordinary agreement of the results between this clinical trial and the GCLLSG clinical studies provides assurance that CR rates still need to be markedly improved with either arm. The need for verification of encouraging preliminary results from phase II trials requires a continued commitment to registering patients on controlled clinical trials.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author or immediate family members indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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