

Phase II Trial of FOLFOX6, Bevacizumab, and Cetuximab in the First-line Treatment of Metastatic Colorectal Cancer

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Abstract: ***Purpose:*** To examine FOLFOX/bevacizumab/cetuximab in the first-line treatment of metastatic colorectal cancer (mCRC). ***Methods:*** ***Design:*** Randomized phase II trial aimed at achieving a 60% objective response rate (ORR). Due to frequent cetuximab-related hypersensitivity reactions the trial was amended to a single-arm design. ***Eligibility:*** Previously untreated mCRC, measurable disease, Eastern Cooperative Oncology Group performance status (ECOG-PS) 0–1. ***Treatment:*** Modified FOLFOX6 (oxaliplatin 85 mg/m², leucovorin 350 mg, and 5-fluorouracil 400 mg/m² bolus; 2.4 g/m² infusion, 46 h) day 1; bevacizumab 5 mg/kg on day 1; cetuximab 400 mg/m² on day 1, then 250 mg/m² on days 1 and 8, every 14 days (1 cycle) until progressive disease (PD); restaging occurred every 4 cycles. ***Results:*** With emerging negative progression-free survival (PFS) data from a similarly designed trial, this trial closed early. Enrollment (N=31) was from August 2005–June 2008. ***Patient characteristics:*** Median age was 55 years (29–78); 58% were male; 71% were ECOG-PS 0. Ten cycles (median) were completed (range 2–62). The ORR was 55% (95% confidence interval [CI], 36–73%); 11 patients (35%) had stable disease; 1 patient (3%) had PD; 2 patients (6%) were unevaluable. Median PFS was 9 months (95% CI, 8.3–15.2 months); median overall survival was 25.7 months (95% CI, 15.4–27.6 months). Grade 3/4 toxicities (>1 patient) included neutropenia (25%), rash (23%; grade 2 events, 45%), diarrhea (19%), fatigue (16%), pain (16%), anemia (13%), sensory neuropathy (13%), deep-vein thrombosis (10%), nausea (10%), pulmonary embolism (7%), anorexia (6%), and vomiting (6%). ***Conclusion:*** In this limited trial, it is unclear whether cetuximab contributed to FOLFOX/bevacizumab efficacy, although the response rate, PFS, and overall survival were high. The regimen was generally well-tolerated, with expected skin effects; thromboembolic rates should be assessed in larger analyses. Cetuximab's role in first-line mCRC treatment is likely best guided by K-RAS testing in future clinical trials.

Introduction

The treatment of metastatic colorectal cancer (mCRC) was advanced in 2004 with the accelerated approvals by the US Food and Drug Administration of bevacizumab (Avastin, Genentech) and cetuximab (Erbix, ImClone/Bristol-Myers Squibb). Bevacizumab, a monoclonal antibody against vascular endothelial growth factor (VEGF), was shown to improve survival when combined with chemotherapy in the first-line setting compared with chemotherapy alone.¹ Cetuximab, a monoclonal antibody to the epidermal growth factor receptor (EGFR), was shown to have clinical activity when used alone or in combination with chemotherapy in patients previously treated for advanced disease.² More recently, single-agent activity was demonstrated in patients with refractory disease with panitumumab (Vectibix, Amgen), a second monoclonal antibody to EGFR.³

Preclinical models have demonstrated that targeting VEGF and EGFR simultaneously may be a strategy to enhance tumor killing and minimize the development of resistance.^{4,5} Recently, this strategy has been studied in patients with unknown primary cancers and advanced non-small-cell lung cancer using bevacizumab and the oral EGFR tyrosine kinase inhibitor erlotinib (Tarceva, Genentech), which proved to be active and safe.

Bevacizumab and cetuximab have each proven to be active and safe when combined with infusional fluorouracil, leucovorin and oxaliplatin (FOLFOX) regimens.⁶⁻⁸ We sought to study the combination of these 2 agents when used with a modern first-line chemotherapy platform (modified FOLFOX6). Herein, we report the results from a phase II study of FOLFOX6, bevacizumab, and cetuximab administered as first-line treatment in patients with mCRC.

Patients and Methods

This trial was initiated in August 2005 within the Sarah Cannon Research Institute Oncology Research Consortium, a community-based research network.

Patients

Patients with histologically confirmed mCRC were enrolled. Patients could have received 1 prior chemotherapy regimen in the adjuvant setting more than 6 months prior to enrollment, but no prior therapy for metastatic disease. Patients had measurable disease per Response Evaluation Criteria in Solid Tumors version 1.0 (RECIST).⁹ Other eligibility criteria included age of 18 years or older; absence of active brain metastases; Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0–1 (ranging from normal to ambulatory, but restricted in strenuous activity); adequate organ function

(defined as absolute neutrophil count $\geq 1.5 \times 10^9/L$, platelet count $\geq 75 \times 10^9/L$, serum bilirubin $\leq 2.5 \times$ the upper limit of normal [ULN] and serum aspartate aminotransferase [AST] and alanine transaminase [ALT] $< 5 \times$ ULN, and serum creatinine ≤ 1.6 mg/dL).

Exclusion criteria included peripheral neuropathy higher than grade 1; major surgery within 4 weeks of treatment; major bleeding, hemoptysis, or coagulopathy; significant proteinuria; pregnancy or lactation; clinically significant cardiovascular disease; medically uncontrolled hypertension; and prior malignancy within 3 years, except nonmelanoma skin cancer and cervical carcinoma in situ. Patients on stable therapeutic anticoagulation were eligible. All patients provided written informed consent prior to enrollment.

Pretreatment Evaluation

Prior to treatment, patients were evaluated by history, physical exam, and laboratory testing, including magnesium, calcium, and potassium levels. Baseline tumor staging was performed using computed tomography (CT) scans of the chest and abdomen/pelvis.

Treatment Plan

This trial was originally designed as a randomized phase II trial of FOLFOX and bevacizumab with or without cetuximab. However, as discussed in greater detail below, an enrollment delay due to a high rate of cetuximab-related hypersensitivity reactions (HSRs) at the Nashville site led to the amendment of this study to a single-arm design of FOLFOX, bevacizumab, and cetuximab.

All patients received cetuximab: 400 mg/m² (first cycle only) administered intravenously (IV) on day 1 and 250 mg/m² IV on day 8 with all subsequent cycles 250 mg/m² IV on days 1 and 8. Day 1 cetuximab was immediately followed by bevacizumab 5 mg/kg IV, oxaliplatin 85 mg/m² IV, and 5-fluorouracil 400 mg/m² IV bolus, followed by 2,400 mg/m² administered as a continuous infusion over 46 hours via a pump (outpatient) and leucovorin 350 mg IV (modified FOLFOX6). Cycles were 14 days (Figure 1).

Patients were restaged with CT scans every 4 cycles (per RECIST v1.0). If there was no evidence of disease progression, patients received treatment until progressive disease or irreversible toxicity with restaging every 2 months. At physician discretion, oxaliplatin could be stopped after 12 cycles.

Dose modifications for FOLFOX, bevacizumab, and cetuximab were based on standard practice for these approved therapies. Once an agent was reduced, it could not be increased. No more than 2 dose reductions were allowed for fluorouracil/leucovorin, oxaliplatin, or cetuximab (bevacizumab could be held, but not reduced). In the case of unacceptable toxicity or intolerance to fluoro-

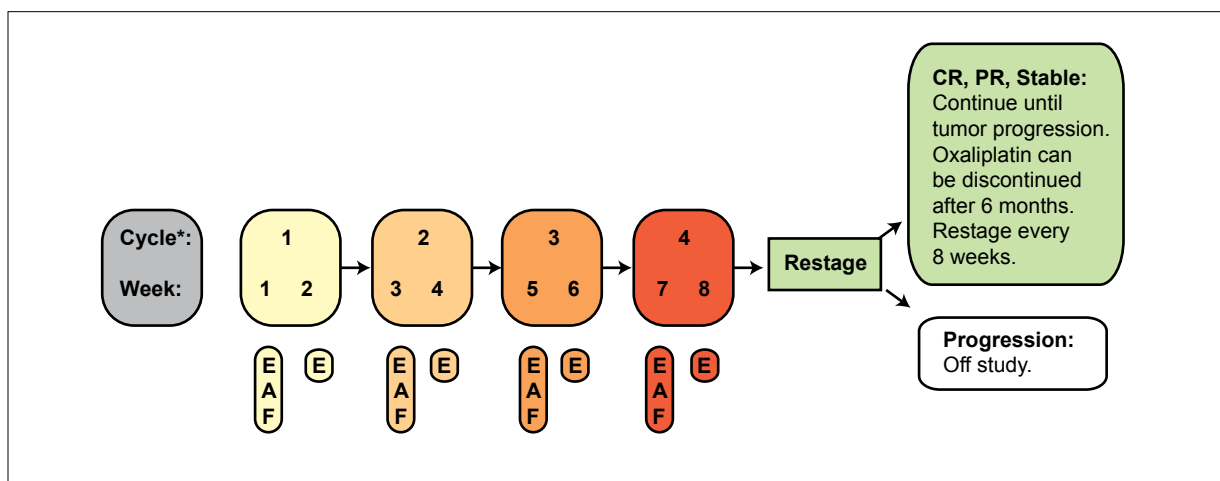


Figure 1. Study design.

*1 cycle=2 weeks.

Doses: Cetuximab (E): First Cycle: 400 mg/m² IV, day 1 and 250 mg/m² IV, day 8; all subsequent cycles: 250 mg/m² IV, days 1 and 8.

Bevacizumab (A): 5 mg/kg IV, day 1. Modified FOLFOX6 (F): 5-FU, 400 mg/m² IV bolus followed by 2,400 mg/m² IV, day 1; leucovorin, 350 mg as a 2-hour infusion prior to 5-FU, day 1; oxaliplatin, 85 mg/m² IV as a 2-hour infusion, day 1.

CR=complete response; PD=progressive disease; PR=partial response.

uracil/leucovorin, oxaliplatin, bevacizumab, or cetuximab, the agent responsible could be stopped and the patient could continue with the other study medication(s). However, bevacizumab had to be given in the presence of fluorouracil; and if FOLFOX was stopped, the patient had to come off study.

Cetuximab delays and dose reductions were made for grade 3/4 skin toxicity and other grade 3/4 toxicity attributable to cetuximab. Grade 1/2 cetuximab HSRs were managed with treatment interruptions and resumption of treatment at a slower infusion. Grade 3/4 HSRs were managed with treatment cessation, epinephrine, diphenhydramine, steroids, cimetidine, fluid, oxygen, supportive care as needed, and permanent discontinuation of cetuximab.

Toxicity assessments were made according to the Common Terminology Criteria for Adverse Events (CTCAE version 3.0) of the National Cancer Institute. Cytokines were not administered with the first course of treatment; however, prophylactic granulocyte colony-stimulating factor for patients experiencing febrile neutropenia was permitted at the discretion of the treating physician and was not to be a substitute for mandated dose reductions.

Initially, the only premedications administered to prevent HSRs included diphenhydramine 50 mg intravenously 30–60 minutes prior to cetuximab, dexamethasone 10–20 mg, and a 5-HT₃ serotonin receptor antagonist for oxaliplatin. However, as discussed below, the HSR premedication regimen was subsequently revised to include dexamethasone 20 mg administered orally 12 and 6 hours before cetuximab, diphenhydramine 50 mg IV

30–60 minutes prior to cetuximab, and cimetidine 300 mg (or equivalent H₂-blocker) IV 30–60 minutes prior to cetuximab.

This trial was approved by the institutional review boards of all participating institutions. The Sarah Cannon Research Institute designed and coordinated the trial and was responsible for all aspects of data collection and analysis. Cetuximab (Cancer Chemotherapy National Service Center code IMC-C225) was provided by Bristol-Myers Squibb. Commercially available forms of chemotherapy and bevacizumab were used.

Definition of Response

All patients were evaluated for response by RECIST v1.0 criteria. The final response category assigned represented the best response obtained during treatment.

Statistical Methods

The primary objective of the original randomized phase II study was to assess the overall response rate of each regimen. Secondary objectives were to assess progression-free survival (PFS), median overall survival (OS), and treatment-related toxicity. These objectives did not change when this trial was amended to a single-arm design after a prolonged suspension due to severe HSRs. The sample size was based on the assumption that this combination regimen would achieve a response rate of more than 60%. By contrast, a response rate of 45% or less would not justify further study. This trial employed a design based on a 2-stage MiniMax accrual plan. If at least 12 responses were seen in the first 26 evaluable patients, an additional

Table 1. Baseline Characteristics

Characteristic	Number of Patients (%) (N=31)
Age	Median, 55 years Range, 29–78 years
Sex	
Male	18 (58%)
Female	13 (42%)
ECOG Performance Status	
0	22 (71%)
1	9 (29%)
Metastatic Site	
Lymph nodes	4 (13%)
Liver	27 (87%)
Lung	10 (32%)
Location of Treatment Facility	
Nashville site	15 (48%)
Consortium sites	16 (52%)

25 evaluable patients would be treated. Fifty-one evaluable patients would be required to achieve this objective (alpha level 0.10 and power 0.8). It should be noted that the original alpha level in the randomized design was 0.05. Accounting for a 10% rate for nonevaluable patients, 57 patients were scheduled to be accrued.

An early stopping rule was present for toxicity. If, at the time of the interim efficacy analysis in the first stage, it was found that more than 30% of patients experienced grade 4 hematologic or nonhematologic toxicity or grade 3 or 4 hepatic toxicity, accrual would be terminated. After an unplanned safety analysis for HSRs due to cetuximab, patients were enrolled in increments of 10. If additional grade 3/4 HSRs occurred in more than 1 patient per 10 patients accrued, the trial would be halted.

Overall response rate (ORR) was defined as the proportion of treated patients who were deemed to have a complete or partial response after completing 2 months of treatment. PFS was defined as the interval between the start date of treatment and the date of occurrence of progressive disease or death. OS was measured from the date of first treatment until the date of death from any cause. Toxicity was evaluated in all patients who received at least 1 dose of therapy. If there was intolerable toxicity or discontinuation of treatment secondary to toxicity, the patient was considered assessable, but was classified as a treatment failure. If other cancer therapy was initiated before progressive disease occurred, the patient was censored on the date on which the other therapy began. If a patient was lost to follow-up, the patient was censored on the date of last contact. Survival curves were constructed using the method of Kaplan and Meier.¹⁰

Results

Patient Characteristics

The planned enrollment was for 70 patients. However, in June 2008, data were emerging from a similarly designed randomized prospective trial using capecitabine, oxaliplatin, and bevacizumab with or without cetuximab (CAIRO2), which showed a negative PFS in the cetuximab-treated cohort.¹¹ Thus, enrollment in our trial was stopped at 31 patients, who were enrolled from August 2005 to June 2008. Fifty-two percent were from Tennessee, and 48% from Ohio, Kentucky, and Mississippi. Baseline characteristics for all patients are described in Table 1. The median age was 55 years (range, 29–78 years). Eighteen (58%) patients were male and 13 patients were female. ECOG PS was 0 in 22 (71%) patients and 1 in 9 (29%) patients. Metastatic sites included liver (87%), lung (32%), and lymph nodes (13%). Thirteen (42%) patients had 2 or more metastatic sites. Six (19%) patients had received prior adjuvant chemotherapy.

Treatment Received

The median follow-up is 20 months (range, 11–43 months). Fourteen (45%) patients completed 12 cycles of chemotherapy, bevacizumab, and cetuximab (median 12, range 2–62 cycles). Nine (29%) patients received more than 12 cycles of treatment. Two (6%) patients were not evaluable for a response due to treatment-related diarrhea (1 patient), and physician discretion to come off study (1 patient); both are included in the efficacy analysis. Four (13%) patients completed all planned therapy. The remaining patients stopped therapy because of progressive disease (32%), toxicity (19%), other illness (7%), physician preference (10%), patient compliance or request (16%), or death (3%).

Response

All 31 patients are included in the response analysis (Table 2). A complete response was seen in 1 (3%) patient, and partial responses in 16 (52%) patients, for an ORR of 55% (95% confidence interval [CI], 36–73%). Eleven (35%) patients had stable disease, and 1 (3%) patient had progressive disease.

Progression-Free Survival and Overall Survival

The median PFS was 9 months (95% CI, 8.3–15.2 months; Figure 2). The median OS was 25.7 months (95% CI, 15.4–27.6 months; Figure 3). Three-year OS was 13% (95% CI, 2–33%).

Treatment-Related Toxicity

Treatment-related toxicity is summarized in Table 3. In general, the regimen was well tolerated with expected skin effects. The most common (>3%) grade 3/4 tox-

Table 2. Response Rates (N=31)

Response	Number (%)
Complete	1 (3%)
Partial	16 (52%)
Stable disease	11 (35%)
Progression	1 (3%)
Not evaluable*	2 (6%)

*Not evaluable due to treatment-related toxicity (1 patient); off study due to physician discretion (1 patient).

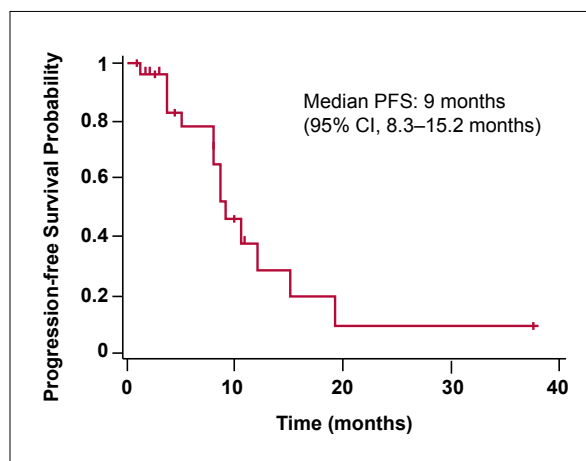
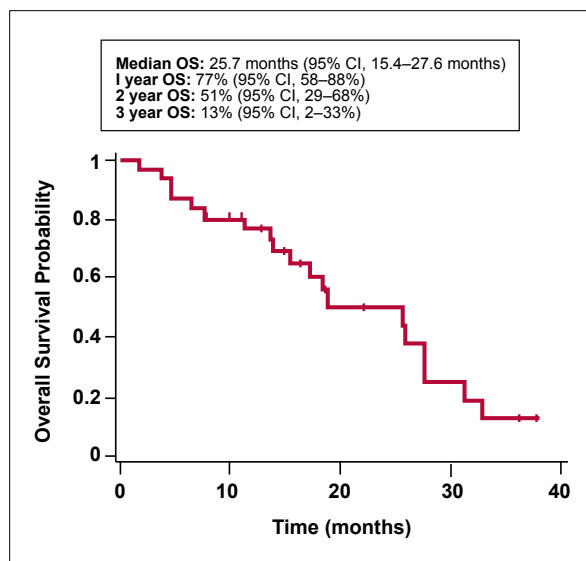
iciencies were anemia (13%), neutropenia (25%), anorexia (6%), diarrhea (19%), fatigue (16%), nausea (10%), vomiting (6%), pain (16%), rash (23%; grade 2 events, 45%), deep venous thrombosis (10%), pulmonary embolism (7%), and sensory neuropathy (13%). All other grade 3/4 hematologic and nonhematologic toxicities were uncommon (limited to ≤ 1 patient). There were no treatment-related deaths, bowel perforations, or significant bleeding events.

Two grade 3 HSRs occurred at our Nashville site in the first month of opening this trial. These events coincided with other severe HSRs occurring at this site in another cetuximab trial and in patients treated off-study, necessitating cetuximab-trial suspensions. This trial was suspended until May 2006, when it reopened at all sites with a revised premedication schedule and staggered enrollment (see Methods). However, the Nashville site was closed to further accrual after 1 additional severe HSR (grade 4) was observed in August 2006, for a total severe HSR rate of 20% in Nashville. Subsequently, 1 additional severe HSR (grade 3) occurred at our Mississippi site. There were no grade 2 HSRs. At the time of this report, 11 (36%) patients are alive. Fifteen patients (48%) received subsequent therapy.

Discussion

The treatment options for patients with mCRC have expanded over the last decade. In addition to the wider adoption of infusional fluorouracil with oxaliplatin or irinotecan, the newest agents, bevacizumab, cetuximab, and most recently, panitumumab, are now considered standard for patients with advanced disease. Median survival has shifted from 16 months to 20+ months.

Combining modern therapies without overlapping toxicities is a potential strategy to enhance treatment efficacy without jeopardizing safety. Bevacizumab and cetuximab exert their anticancer effects in 2 distinct tumor growth pathways targeting VEGF and EGFR,

**Figure 2.** Progression-free survival (PFS).**Figure 3.** Overall survival (OS).

respectively. Preclinical and clinical data suggest that this strategy may have merit.^{4,5,12,13} Indeed, multikinase drugs like vandetanib (AstraZeneca) are in development to simultaneously target these pathways.¹⁴

Our trial was originally designed as a randomized study; however, a prolonged enrollment delay due to a high rate of cetuximab-related severe HSRs in Nashville led to amending this to a single-arm design of FOLFOX, bevacizumab, and cetuximab. The 20% severe HSR rate in Nashville was alarming and led to the closing of enrollment at this site. The reasons for this high HSR rate are not clear, but this has been reported by other regional centers as well.¹⁵ Pooled data from these centers suggest that

Table 3. Grade 3/4 Toxicity in More Than 1 (3%) Patient

Toxicity	Number of Pts (%), N=31	
	Grade 3	Grade 4
Anemia	0	4 (13%)
Leukopenia	4 (13%)	0
Neutropenia	6 (19%)	2 (6%)
Anorexia	3 (10%)	0
Diarrhea	5 (16%)	1 (3%)
Fatigue	4 (13%)	0
Hypersensitivity reaction (no grade 2 events)	3 (10%)	1 (3%)
Nausea	4 (13%)	0
Vomiting	2 (6%)	0
Pain	3 (10%)	2 (6%)
Rash*	7 (23%)	0
Deep vein thrombosis	2 (6%)	0
Sensory neuropathy	4 (13%)	0
Pulmonary embolism	0	2 (7%)

*Grade 2 rash occurred in 12 (45%) patients.

preexisting immunoglobulin E antibodies to cetuximab may account for this excessive HSR rate.¹⁶

Our trial demonstrated that the combination of FOLFOX, bevacizumab, and cetuximab was associated with a moderately high response rate, PFS, and OS. These outcomes are encouraging, but the trial design limits our ability to discern what benefit cetuximab contributes. As well, the small size of the trial causes the confidence intervals associated with these outcomes to be broad, meaning that this regimen could potentially be inferior to other standard first-line regimens. Indeed, a recent randomized trial of chemotherapy and bevacizumab with or without panitumumab was closed early after a finding of inferior efficacy with panitumumab (median PFS, 10.0 and 11.4 months for the panitumumab and control arms, respectively; HR, 1.27; 95% CI, 1.06–1.52; median OS, 19.4 and 24.5 months, respectively).¹⁷ Additionally, as previously discussed, in a randomized phase III trial of capecitabine/oxaliplatin and bevacizumab with or without cetuximab, the median PFS was 10.7 months in the cetuximab arm compared with 9.8 months in the control group ($P=.019$; HR, 1.22), necessitating early trial closure.¹¹

In our trial, this regimen was associated with relatively limited severe toxicity. Rash and diarrhea were expected toxicities, which did not appear to be increased over rates observed in other infusional fluorouracil/oxaliplatin and cetuximab trials.^{6,8} The observed

thromboembolic events were limited to a small number of patients, but were noticeable when put in context with other published experience with combination therapy in the first-line setting. In the randomized IFL/bevacizumab trial by Hurwitz and colleagues, thromboembolic events occurred in 19.4% of patients treated with bevacizumab compared with 16.2% in the placebo group.¹ In the recent randomized trial of chemotherapy and bevacizumab plus or minus panitumumab, panitumumab treatment was associated with a slightly higher rate of pulmonary emboli than in the control group (6% vs 4%), in addition to other excess toxicity in the form of diarrhea, infections, and skin toxicity.¹⁷

Conclusion

This single-arm trial demonstrated that FOLFOX6, bevacizumab, and cetuximab could be administered safely as a first-line regimen for patients with mCRC. The response rate, PFS, and OS outcomes were encouraging, but this trial was limited in its role in assessing the impact of cetuximab to standard FOLFOX and bevacizumab therapy. Two large randomized trials of oxaliplatin/bevacizumab-based regimens have demonstrated inferior outcomes for patients when monoclonal antibodies to EGFR are added to treatment. It is possible that selecting patients by K-RAS status might help identify a subset of patients who benefit from combined targeted therapy.¹⁸

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(Continued on page 498)

(Spigel et al, continued from page 485)

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