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Specific Immunotherapy in Advanced Cervical-Uterine Cancer Using Humanized Monoclonal Antibody Nimotuzumab and CIMAvax-EGF® Therapeutic Vaccine

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Abstract

Cervical uterine cancer represents the fourth most common malignant neoplasm worldwide in the female sex in terms of incidence, principally from epithelial origen. The high expression of EGFR in this tumor leads to the search for therapeutic alternatives. An Expanded Access Clinical Program was carried out in parallel groups, randomized, multicenter and prospective study, to evaluate the survival of patients with advanced cervical carcinoma, without therapeutic alternative, who would be treated with the therapeutic vaccine CIMAvax-EGF®, the humanized mAb nimotuzumab or the combination of both products, which targeted EGF and EGFR respectively. The patients were included between 2008 and 2010 with a more than five years follow-up. The results show that the serious adverse events related to the experimental treatments were 0.9%; 1.1% and 2.6% and a median ITT survival of 9.1, 23.5, and 16.3 months for CIMAvax-EGF®, nimotuzumab and the combination of both, respectively. Thus fulfilling the hypothesis of safety and efficacy proposed in the investigation was achieved. The three therapeutic regimens achieved overall survival rates greater than 35% at 60 months, encouraging

results for advanced uterine cervical cancer. A phase III clinical trial is proposed to consolidate these results in a greater number of patients with nimotuzumab as study drug.

Keywords

CIMAvax-EGF®, Nimotuzumab, Survival, Safety, Advanced Cervical Cancer

1. Introduction

Cervical uterine cancer represents the fourth malignant neoplasm with the highest incidence in the world in women with 569,847 in 2018. It is also reported as the fourth cause of death from cancer in this sex, being Latin America and the Caribbean a health problem public, with a mortality rate of 7.1/100,000 inhabitants, which is the third in the world [1].

These neoplasms predominantly had epithelial origin, with overexpressing the Epidermal Growth Factor Receptor (EGFR) in a high percentage [2] [3] [4]. The high expression of EGFR in this type of patients leads to the search for therapeutic alternatives against this therapeutic target. Although there are reports of some studies with anti EGFR monoclonal antibodies (mAbs) in this indication, in advanced stages, the results have not been as expected.

The humanized mAb nimotuzumab directed against EGFR has been demonstrated a therapeutic efficacy, with increased survival in patients with persistent, recurrent or advanced-stage cervical cancer used as monotherapy [5] [6]. On the other hand, the CIMAvax EGE vaccine has shown therapeutic efficacy in patients with non-small cell lung tumors (NSCLC) [7], due to its capacity to develop anti EGF antibodies able to reduce circulating EGF concentrations by increasing the antibody titer in treated patients.

The use of both products in the treatment of epithelial uterine cervical cancer using them as monotherapy or in a combination of both could become a therapeutic alternative in advanced disease patients.

2. Material and Method

A clinical study classified as Expanded Access Clinical Program (EACP), randomized (by ASAL randomized software 1.2 for windows), multicenter, prospective were conducted, in five hospitals, to evaluate the survival of patients with advanced cervical carcinoma without any therapeutic alternative. The patients, that received the therapeutic cancer vaccine CIMAVAX-EGF®, the mAb humanized nimotuzumab or the combination of both were enrolled in three groups, used a random numbers list from April 4th, 2008 to May 17th, 2010. Patients with a diagnosis confirmed by cyto-histological techniques as persistent, recurrent or advanced cervical cancer, who had received all available lines of treatment for its tumor, were taken into account as inclusion criteria, any subject with oncospecific treatment in the moment of inclusion, who gave their in-

formed consent, with an ECOG ≤ 3. Patients who were receiving another product under investigation, who had previously received the products under evaluation, with decompensated chronic diseases or general status > 3, were excluded. The classification of adverse events was according to the common toxicity criteria (CTC) of the National Cancer Institute od United State of America, version 3.0 [8].

The hypothesis of the study was proposed taking into account the safety and efficacy profile of the treatments. Success was considered if less than 20.0% of the patients in the treated groups developed related serious adverse events (SAE) and if the patients reach an overall survival advantage of at least three months (after two years of follow-up), with respect to conventional therapy (which at the time of initiation of the study was not longer than seven months).

2.1. Research Products

CIMAvax-EGF® vaccine: It is the result of the emulsion of the chemical conjugate of 1 mg of recombinant human EGF (EGF hu-rec) P64k protein from Neisseria Meningitides (P64k rec) with the adjuvant Montanide ISA 51. It was administered intramuscularly, 4 mg of the vaccine per dose, at four immunization points, two higher and two lower. The treatment was planning in two stages: induction with vaccine administration every 14 days, 5 times and Maintenance every 28 days for at less two years.

Nimotuzumab (CIMAher®): Is ahumanized monoclonal antibody, IgG1 subclass. It was administered intravenously, 200 mg per dose over 1 hour. Treatment divided into two stages: Induction stage once a week for 12 consecutive weeks and maintenance stage once every 14 days.

Nimotuzumaband CIMAvax-EGF® vaccine combination: was administered in schedules and doses similar to the two previous groups, on different days to identify the toxicity associated with each type of treatment.

In all cases, treatment continued beyond progression of the disease, until the appearance of unmanageable toxicity or the worsening of the general condition of the patient ECOG > 3.11.

2.2. Safety

All randomized patients were evaluable after receiving at least one dose. For the toxicity analysis, the adverse events (AE) presented by the patients in each of the treatment groups were compared according CTCAE version 3 [8].

2.3. Statistics

The sample size calculation used binomial distribution for pilot clinical trial of translational therapies, which allows obtaining a value from which an upper limit of toxicity can be estimated [9]. A range of number of patients per treatment group of 44 - 49 was established by statistical criterion according to power, assuming that 80% would be used (49 patients per treatment group taking into

account 10% additional). By presetting a maximum tolerable toxicity limit (20.0%), the sample size can be determined to take into account type I error = 0.05 and a maximum tolerable toxicity ratio = 0.20. To answer the efficacy hypothesis A bilateral hypothesis assuming type I error alpha = 0.05, type II error beta = 0.2, a difference of three months of survival related to the most frequent reference value in the literature reported in the year that the investigation begins (NCCN. 2009, QRTaround 6 months) [10].

3. Results and Discussion

The EGFR receptor and its ligands have been a widely studied therapeutic target in tumors of epithelial origin and it is associated as a poor prognostic factor in this disease [11].

In Cuba, in 2008, given the low availability of therapeutic options in the second line of treatment in advanced cervical cancer (recurrent, persistent or metastatic), the use of therapies directed against the available therapeutic EGF-EGFR target was proposed.

In this Expanded Access Clinical Program (EACP), 180 patients with a diagnosis of carcinoma of the cervix of epithelial origin, refractory to all previous therapies due to advanced disease, were included in an expanded clinical study (EACP) distributed in three groups of patients. Randomized 75 patients in the nimotuzumab group, 59 inCIMAvax-EGF® vaccine and 46 in the combination of both products. 74.4% of the patients were included with an acceptable general state (ECOG 0-1). Squamous cell carcinoma was the predominant histological type (54.4%). A significant association was observed for the histological subtypes in the three groups analyzed according to the estimate by the X^2 test, with a higher proportion of Adenocarcinoma (ADC) in the group treated with the CIMAvax-EGF® vaccine. The rest of the variables were balanced.

Of 1018 AEs described, 45.7% were related to treatment and of which 12.3% were classified as serious (**Figure 1**). Related SAE were 0.9; 1.1% and 2.6% for CIMAvax-EGF®, nimotuzumab and the combination respectively, a proportion lower than the established in the working hypothesis. Therapeutics were well tolerated and proved the possibility to be used as prolonged therapy, beyond progression even when two of them were administered in the same patient as combination therapy. Similar reports have been found in the clinical trials concluded with nimotuzumab and the CIMAvax EGF® vaccine in other cancer indications, where they have been applied in monotherapy modality or in combination with chemo radiotherapy, for prolonged periods such as head and neck [12] and high-grade glioblastomas of malignancy [13] among others [14]. In a multicenter study in persistent, recurrent, or metastatic cervical cancer by Cetina *et al*. used nimotuzumab combined with chemotherapy was shown to be well tolerated [5]. The present study, in which added Cimavax egf vaccine into the treatment scheme of nimotuzumab, the toxicity of the treatments was similar.

Survival rates were up to 5 years. ITT and PP analysis was not statistical different however, it is remarkable that for the three therapeutic regimens, overall

Category by Adverse Events					
Adverse Events	CIMAvax/EGF n = 351 n (%)	Nimotuzumab n = 354 n (%)	Combination n = 313 n (%)	Total n = 1018 n (%)	p-value
Treatment-related AE	195 (55.6)	83 (23.4)	187 (59.7)	465 (45.7)	0.00001
EA grade 3-4	33 (9.4)	61 (17.2)	27 (8.6)	121 (11.9)	0.0006
Grade 3-4 AE related to treatment	0 (0)	4 (1.1)	5 (1.6)	9 (0.9)	0.0745
Serious EA	21 (5.9)	71 (20.1)	33 (10.5)	125 (12.3)	0.00001
Serious treatment-related AE	3 (0.9)	4 (1.1)	8 (2.6)	15 (1.5)	0.1542

CIMAvax EGF Vaccine	DEFINITIVE	PROBABLE	POSSIBLE	Total
	# (%)	# (%)	# (%)	# (%)
Asthenia	0 (0.0)	1 (100)	0 (0.0)	1 (33.3)
Pain	1 (100)	0 (0.0)	0 (0.0)	1 (33.3)
Skin rash	0 (0.0)	0 (0.0)	1 (100)	1 (33.3)
Total	1 (100)	1 (100)	1 (100)	3 (100)

Nimotuzumab AcM	DEFINITIVE	PROBABLE	POSSIBLE	Total
	# (%)	# (%)	# (%)	# (%)
Asthenia	0 (0.0)	1 (100)	0 (0.0)	1 (25.0)
Cough	0 (0.0)	0 (0.0)	1 (50.0)	1 (25.0)
Skin rash	1 (100)	0 (0.0)	1 (50.0)	2 (50.0)
Total	1 (100)	1 (100)	2 (100)	4 (100)

Combination CIMAvaxEGF Vaccine/nimotuzumab AcM	DEFINITIVE	PROBABLE	POSSIBLE	Total
	# (%)	# (%)	# (%)	# (%)
Cellulite	0 (0.0)	0 (0.0)	1 (25.0)	1 (12.5)
Dyspnoea	0 (0.0)	1 (50.0)	0 (0.0)	1 (12.5)
Pain	2 (100.0)	1 (50.0)	1 (25.0)	4 (50.0)
Bleeding	0 (0.0)	0 (0.0)	1 (25.0)	1 (12.5)
Cough	0 (0.0)	0 (0.0)	1 (25.0)	1 (12.5)
Total	2 (100)	2 (100)	4 (100)	8 (100.0%)

Figure 1. Total AE reported in the expanded clinical use program.

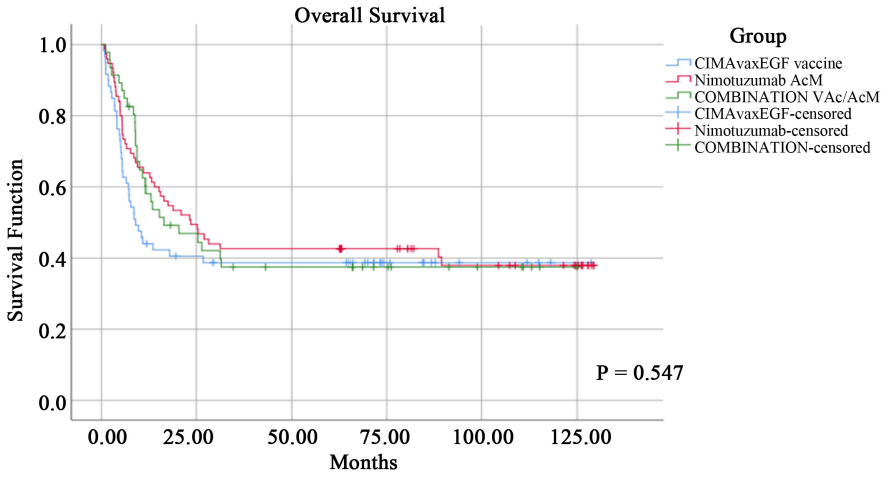
survival was higher than those established for the working hypothesis (three months more than survival reported in 2008, which was 6.2 months) [10]. **Figure 2** and **Figure 3** describe ITT and PP survival respectively, in it, a trend of benefic can be observed in patients who receiving nimotuzumab (23.55 and 31.14 months respectively).

Although CIMAvax-EGF® vaccine showed numerically lower survival, it was not significant. In this group, a greater number of ADCs from endocervix (32%) were included, made a difference between the treatment groups (p = 0.049). Previously reports showed that this histological variant has a worse response to chemotherapy or radiotherapy treatments in comparison with tumors of epithelial origin variants [14] [15].

Research in cancer treatment has focused on applying treatments that prolong the control of the disease with an adequate quality of life [16] [17]. The survival rate in this study, at 60 months, was greater than 35% in all treatment groups, unexpected survival for this type of patients (**Figure 2** and **Figure 3**). Since 2014, long-term surviving patients have been reported in the Cuban population treated with CIMAvax-EGF® vaccine in lung cancer [18]. The patients included in this study have a similar behavior to lung cancer refer patients as long term survival (between 37.4% - 42.7% for the ITT analysis and 39.7% - 50% for PP, **Figure 2** and **Figure 3**) [19].

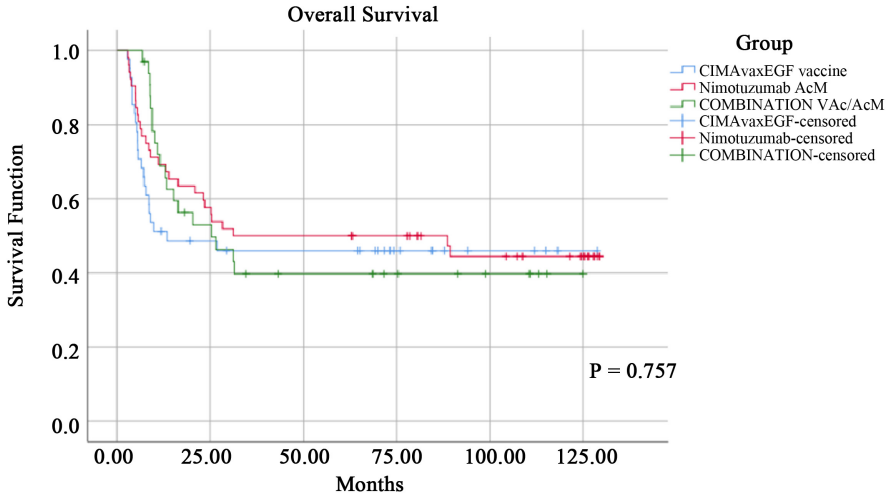
A therapeutic benefit was observed in patients with ECOG I and previous RT/CT treatment in the group of patients that received the vaccine CIMAVAX-EGF®, while patients treated with the humanized Mab were benefited when age was over 50 years, ECOG 2 and histological diagnosis of squamous cell carcinoma. These parameters become as a predictive variable, which may influence the appropriate selection of patients to be treated (predictive variables).

Nimotuzumab mAb, whose first therapeutic approach was related to passive



Patients	Mean (months)	Median (months)	Survival rate (months) %				
			6 m	12 m	24 m	36 m	60
CIMAVax EGF® n = 59 cen = 23	53.7 (38.4-38.4)	9.1 (5.1-13.0)	62.7	44.1	40.5	38.7	38.7
Nimotuzumab n = 75 cen = 30	59.5 (46.3-72.5)	23.6 (12.3-34.7)	73.3	54.0	49.3	42.7	42.7
Combination n = 46 cen = 18	54.5 (38.1-70.4)	16.4 (0.4-32.3)	87.0	58.0	46.8	37.4	37.4

Figure 2. Intent to treat (ITT) overall survival analysis.



Patients	Mean (months)	Median (months)	Survival rate (months) %				
			6 m	12 m	24 m	36 m	60 m
CIMAVax EGF® n = 59 cen = 23	63.1 (44.4-81.8)	13.54 (-)	70.7	51.2	48.7	46.0	46.0
Nimotuzumab n = 75 cen = 30	68.5 (52.7-84.1)	31.15 (0.0-108.1)	80.8	69.2	57.7	50.0	50.0
Combination n = 46 cen = 18	58.9 (39.9-77.8)	25.4 (5.9-44.8)	97.0	68.0	53.0	39.7	39.7

Figure 3. Per Protocol (PP) overall survival analysis.

therapy [12], can directly inhibit tumor growth once it blocks EGF receptor on the cell surface. It inhibits signaling transduction to the nucleus to avoid cell

proliferation is achieves in less time than the effect of CIMAvax-EGF® vaccine, which requires from two to six weeks to induce antibody response against naive EGF, and thus induce indirectly inhibition of EGFR activation (**Figure 4**).

Although cervical cancer does not have a high mutation rate in the EGFR signaling chain [20], there are reports of clinical studies that used treatments with intracellular tyrosine kinase inhibitors (TKIs) of the EGFR chain such as sunitinib, imatinib and temsirolimus. These studies do not show evidence of clinical benefit in advanced stages diseases [21]. On the other hand, several authors have reported the use of mAb against this receptor, such as cetuximab [22], matuzumab [23] and panitumomab [24], with modest results that did not exceed the expectation of the international medical community in comparison with established therapy for this stage of the disease.

A multicenter, open-label, prospective, randomized, phase II clinical trial was conducted in patients with advanced or recurrent cervical cancer, without treatment or after having failed prior chemotherapy (n = 108). In it was comparing carboplatin plus paclitaxel (standard) versus carboplatin plus paclitaxel plus cetuximab therapy and showed that the addition of cetuximab to carboplatin

Study or Subgroup	Log (Hazard ratio)	SE	CIMAvax Total	Nimotuzumab Total	Hazard Ratio IV, Fixed, 95% CI
1.1.1 Global Overall	0.215	0.278	59	75	1.24 [0.72, 22.14]
1.1.2 age					
<50	0.513	0.511	41	72	1.67 [0.61, 4.55]
≥50	0.063	0.379	48	45	1.07 [0.51, 2.24
Not available Age	0.241	1.274	11	10	1.27 [0.10, 15.46]
1.1.3 Race					
Black	-1.119	0.348	2	9	0.33 [0.17, 0.65]
Caucasian	0.301	0.372	43	44	1.35 [0.65, 2.80]
Half-blood	0.712	1.122	7	11	2.04 [0.23, 18.38]
Not available race	0.191	0.885	7	11	1.21 [0.21, 6.86]
1.1.4 Background					
Non	0.159	0.321	38	58	1.17 [0.62, 2.20]
Yes	0.392	0.611	21	17	1.48 [0.45, 4.90]
1.1.5 ECOG					
0	0.169	0.713	9	19	1.18 [0.29, 4.79]
1	-0.081	0.273	32	37	0.92 [0.54, 1.57]
2	1.766	0.283	9	3	5.85 [3.36, 10.18]
Not available ECOG	0.722	1.881	9	11	2.06 [0.05, 82.16]
1.1.6 Histological Type					
Adenocarcinoma	0.191	0.707	16	6	1.21 [0.30, 4.84]
Not available histological	-0.302	0.511	9	15	0.74 [0.27, 2.01]
Other histological	-0.806	0.355	5	10	0.45 [0.22, 0.90]
Squamous carcinoma	0.481	0.487	29	44	1.62 [0.62, 4.20]
1.1.7 Stage					
I	-1.057	0.364	5	6	0.35 [0.17, 0.71]
II	-0.024	0.381	21	20	0.98 [0.46, 2.06]
III	-0.261	0.226	19	33	0.77 [0.49, 1.20]
IV	-1.024	0.086	39	38	0.36 [0.30, 0.43]
Not available stage	0.391	1.046	10	13	1.48 [0.19, 11.49]
1.1.8 Previous Treatment					
Chemotherapy	-0.055	0.522	0	3	0.95 [0.34, 2.63]
Chemo radiotherapy	-0.977	0.224	42	45	0.38 [0.24, 0.58]
No treatment	0.023	0.783	10	13	1.02 [0.22, 4.75]
Radiotherapy	-0.327	0.327	7	14	0.72 [0.24, 0.19]
Surgery	0.144	0.144	13	10	1.15 [0.05, 28.57]

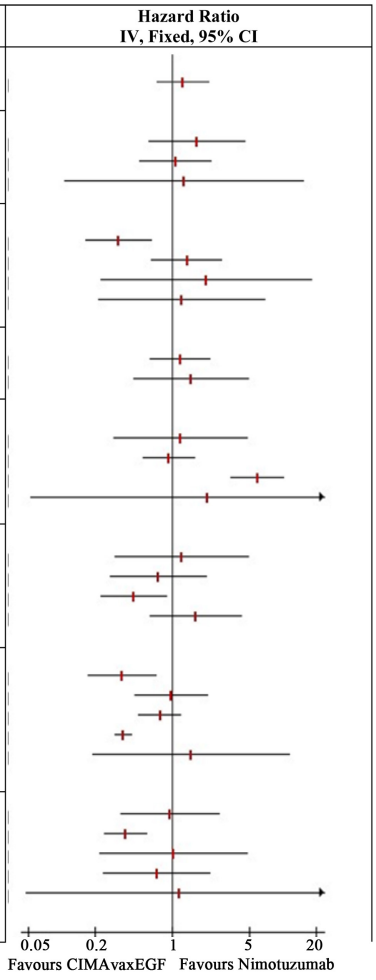


Figure 4. Predictive variables to treatment response for nimotuzumab and CIMAvax-EGF® vaccine groups.

and paclitaxel were feasible but not more effective than chemotherapy alone. For this reason, cetuximab not proceed to phase III. In this study, chimeric mAb caused grade ≥ 3 skin toxicities and induced delay in up to two consecutive infusions. The dose reductions were permanent [25]. Current treatment recommendations for persistent, recurrent or metastatic cervical cancer indicate as adequate the carboplatin/paclitaxel or cisplatin/paclitaxel chemotherapy regimen in 253 where the reported survival ranges from 18.3 months to 17.5 months respectively, being more is beneficial in terms of tolerance [26] [27].

The addition of Bevacizumab to this chemotherapy showed an increase in survival and progression-free survival to figures of 17.0 and 8.2 months, respectively, without a deterioration in quality of life despite the adverse reactions reported for this anti VEGFR mAb [28]. Despite being the only mAb reported to date as approved for the indication of cervical cancer in advanced stages, its cost makes it difficult to spread it to all patients who need it, in addition, not all tumors show high expression of this receptor [29].

The increased survival and long-term duration of responses in patients treated with nimotuzumab, after a few doses (at least 6), suggested the blockade of EGFR signaling transduction and the inhibition of tumor cells proliferation, but it was not the only mechanisms of action underlying the efficacy of this antibody. [30] Mazorra *et al*. demonstrated that sera from patients treated with nimotuzumab, were capable of triggering effector mechanisms such as inhibition of the cell proliferation, ADCC and CDC (*in vitro* studies), probably due to the presence of specific antibodies against tumor cells promoted for the nimotuzumab action. It is able to trigger the antigenic presentation process that led immunogenic cell death in this assay [31]. We suggest it as a mechanism, which favors the control of the disease and with it, increases the overall survival of the patients.

There is evidence of high expression of HB-EGF and autocrine activation of the same in cervical tumor cells, making it the predominant mechanism of activation of EGFR receptors in this type of tumor [32]. Although EGF expression is associated with macrophages, CCL2 and GM-CSF expression, and macrophage numbers are associated with M-CSFR and CCR2 expression, macrophages do not appear to be the predominant source of HB-EGF activation. Since the relative amount of HB-EGF measured in the epithelial compartment was on average four times higher than the relative amount of HB-EGF in the stromal compartment. These results suggest that, in cervical cancer the main source of tumor cell activation is HB-EGF [32] and for its CIMAVax EGF vaccine is less effective along but in combination with nimotuzumab, any way may become in alternative to treat advanced cervical cancer too.

4. Conclusion

CIMAvax-EGF® therapeutic vaccine, nimotuzumab and the combination of both in the treatment of cervical uterine tumors of epithelial origin in advanced stages

of the disease have an acceptable safety profile and are well tolerated even in prolonged periods. The severe AE with a causal relationship did not exceed 3% in any of the schemes. The three therapeutic regimens achieved global survival rates at 60 months higher than 35% in all cases, unprecedented in the literature to date, proposing the design of a phase III clinical trial to consolidate these results using nimotuzumab.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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