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ORIGINAL REPORT

Randomized Phase III Trial of Single-Agent Pemetrexed Versus Carboplatin and Pemetrexed in Patients With Advanced Non–Small-Cell Lung Cancer and Eastern Cooperative Oncology Group Performance Status of 2

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ABSTRACT

Purpose
To compare single-agent pemetrexed (P) versus the combination of carboplatin and pemetrexed (CP) in first-line therapy for patients with advanced non–small-cell lung cancer (NSCLC) with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 2.

Patients and Methods
In a multicenter phase III randomized trial, patients with advanced NSCLC, ECOG PS of 2, any histology at first and later amended to nonsquamous only, no prior chemotherapy, and adequate organ function were randomly assigned to P alone (500 mg/m^2) or CP (area under the curve of 5 and 500 mg/m^2, respectively) administered every 3 weeks for a total of four cycles. The primary end point was overall survival (OS).

Results
A total of 205 eligible patients were enrolled from eight centers in Brazil and one in the United States from April 2008 to July 2011. The response rates were 10.3% for P and 23.8% for CP ($P = .032$). In the intent-to-treat population, the median PFS was 2.8 months for P and 5.8 months for CP (hazard ratio [HR], 0.46; 95% CI, 0.35 to 0.63; $P < .001$), and the median OS was 5.3 months for P and 9.3 months for CP (HR, 0.62; 95% CI, 0.46 to 0.83; $P = .001$). One-year survival rates were 21.9% and 40.1%, respectively. Similar results were seen when patients with squamous disease were excluded from the analysis. Anemia (grade 3, 3.9%; grade 4, 11.7%) and neutropenia (grade 3, 1%; grade 4, 6.8%) were more frequent with CP. There were four treatment-related deaths in the CP arm.

Conclusion
Combination chemotherapy with CP significantly improves survival in patients with advanced NSCLC and ECOG PS of 2.

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INTRODUCTION

Patients with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 2 account for a significant percentage of patients with advanced non–small-cell lung cancer (NSCLC), and their management in clinical practice tends to be inconsistent, given the lack of rigorous randomized data. Despite some evidence to the contrary, including the prospective subset analysis of the Cancer and Leukemia Group B (CALGB) trial[1] and a recent trial comparing carboplatin and paclitaxel with erlotinib,[2] both of which showed superior survival with combination chemotherapy, current guidelines are equivocal with respect to the optimal therapy for patients with advanced NSCLC and an ECOG PS of 2.[3]

We conducted a prospective randomized phase III trial to compare single-agent pemetrexed versus the combination of carboplatin and pemetrexed in the first-line management of patients with advanced NSCLC with an ECOG PS of 2. At the time the trial was designed, the combination of pemetrexed with carboplatin was emerging as a promising option in

the treatment of advanced NSCLC[4] and was felt to be particularly suitable for this population because of its favorable toxicity profile.

PATIENTS AND METHODS

Eligibility

Patients with cytologic or histologic confirmation of stages IIIB (malignant effusion) and IV NSCLC by the sixth edition of the American Joint Committee on Cancer manual were eligible if they had measurable disease and an ECOG PS of 2. Initially, patients with all histologic subtypes were eligible. A protocol amendment was implemented to exclude patients with squamous cell histology in May 2009, when 14 such patients had been enrolled. Prior chemotherapy was not allowed. Patients with locally advanced disease amenable to combined-modality therapy were not eligible. Prior irradiation was allowed, and toxicities had to be resolved before study entry. Patients with brain metastases were eligible if neurologically stable and no longer receiving corticosteroids after appropriate therapy. Adequate organ function was required, including glomerular filtration rate $\geq$ 45 mL/min. Patients with concurrent active malignancies, except in situ carcinoma of the cervix and basal cell carcinoma of the skin, were not eligible. Approval by the institutional review board at each participating institution was required. All patients signed informed consent.

Treatment Plan

Patients were randomly assigned to pemetrexed 500 mg/m^2 alone or the combination of carboplatin at an area under the curve of 5 and pemetrexed 500 mg/m^2, both administered intravenously on day 1 every 21 days for up to four cycles. All patients received premedications with dexamethasone, vitamin B12, and folic acid according to the pemetrexed label. Maintenance therapy was not allowed. Patients who progressed during or after protocol treatment were treated at their physicians' discretion. Random assignment was performed by an independent provider not involved in the study and stratified by stage (IIIB v IV), weight loss ($\geq$ 5% v < 5%), and age ($\geq$ 70 v < 70 years). Toxicity was assessed every cycle using the Common Terminology Criteria for Adverse Events (version 3.0). Dose reductions of chemotherapy were made according to prespecified guidelines based on episodes of febrile neutropenia, grade 4 thrombocytopenia and/or bleeding, and any grade 3 or 4 nonhematologic toxicity except nausea/emesis. Treatment delays of up to 3 weeks were allowed. Any patient who required a dose reduction continued to receive a reduced dose for the remainder of the study. Administration of myeloid growth factors was permitted only for febrile neutropenia and was not a substitute for appropriate dose reductions. Erythropoiesis stimulating factors were permitted. The need for palliative irradiation was considered as indicative of progression, and such patients were discontinued from the study. Response was assessed by imaging studies every two cycles and evaluated by RECIST.

Statistical Analysis

The primary objective was to compare overall survival (OS) between the two treatment arms. Secondary end points included response rate, progression-free survival (PFS), and toxicity. Response and progression were evaluated in this study using RECIST criteria, which take into account changes in only the largest diameter of the tumor lesions. PFS was measured from the date of first treatment dose to either the date the patient was first recorded as having disease progression or the date of death if the patient died as a result of any cause before progression. OS was measured from the date of first treatment dose to the date of death or the last date the patient was known to be alive, in which case the patient was censored as of that date. The study was designed with 80% power and a two-sided type I error of 0.05, assuming that pemetrexed plus carboplatin would result in a median survival of at least 4.3 months and pemetrexed alone would result in a median survival of at least 2.9 months (hazard ratio [HR], 0.674), which required a total of 208 eligible patients, who were enrolled over 22 months. A planned interim analysis was carried out after 46 events, and no major safety or efficacy concerns were raised at that point. All survival distributions were calculated using the Kaplan-Meier method and compared by the log-rank test. Cox regression analyzes were used to calculate HRs. Exploratory subgroup analyzes were performed based on age, histology, and smoking status. Associations among dichotomized data were examined using the χ^2 and Fisher's exact tests. Monitoring at all participating institutions in Brazil were conducted at regular intervals to review source documents and compliance with protocol requirements.

RESULTS

Baseline Characteristics

A total of 217 patients were randomly assigned between April 2008 and July 2011 to P (n = 109) or CP (n = 108; Fig 1). Twelve

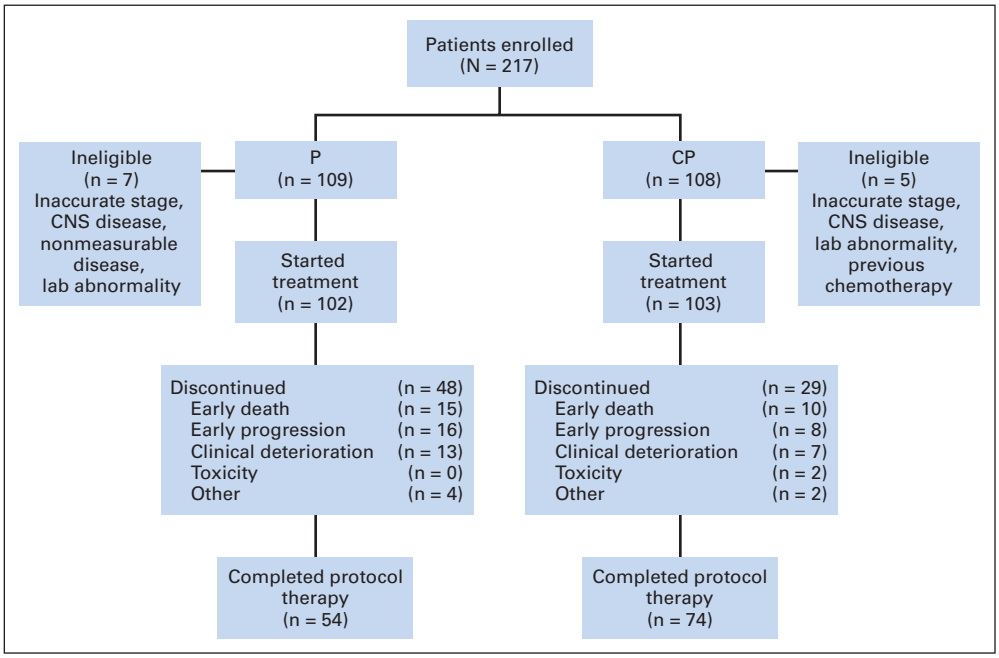

Fig 1. CONSORT diagram showing patient registration, treatment arm assignments, and exclusions. CP, combination of carboplatin and pemetrexed; P, pemetrexed.

Table 1. Baseline Demographic and Clinical Characteristics of Randomly Assigned Patients

Characteristic	P (n = 102) No.	P (n = 102) %	CP (n = 103) No.	CP (n = 103) %	P
Age, years					
Median	65		65		.92*
Range	40-86		41-90		
≥ 70	36	35.3	38	36.9	.81†
Sex					.53†
Male	60	58.8	65	63.1	
Female	42	41.2	38	36.9	
Disease stage					.77†
IIIB	5	4.9	6	5.8	
IV	97	95.1	97	94.2	
Weight loss ≥ 5%	55	53.9	60	58.3	.53†
Histology					.11‡
Adenocarcinoma	82	80.4	85	82.5	
Squamous cell	11	10.8	3	2.9	
Unknown	5	4.9	5	4.9	
Smoking status					.38†
Current	11	10.8	18	17.3	
Former	68	66.7	63	60.2	
Never	23	22.5	23	22.5	
Comorbidities					
Hypertension	46	45.1	46	44.7	.95†
COPD	18	17.6	12	11.7	.23†
Diabetes mellitus	8	7.8	13	12.6	.26†

NOTE. There were no significant differences between arms.
Abbreviations: COPD, chronic obstructive pulmonary disease; CP, combination of carboplatin and pemetrexed; P, pemetrexed.
*Student test.
†χ^2 test.
‡Fisher's exact test.

patients—seven in the P arm and five in the CP arm—were deemed ineligible because of stage IIIB disease without a malignant pleural effusion (n = 4), uncontrolled CNS disease (n = 2), nonmeasurable disease (n = 1), glomerular filtration rate < 45 mL/min (n = 2), transaminases > 5× the upper limit of normal range (n = 2), and prior chemotherapy. Of the 205 eligible patients, 102 were assigned to P and 103 to CP. There were no major differences in patient characteristics between the two arms (Table 1). Approximately 95% of patients had stage IV disease, and 35% were age ≥ 70 years. Slightly more than half of the patients experienced ≥ 5% weight loss. Smoking history was similar between the arms. There were more patients with squamous cell carcinoma in the P arm (10.8%) than in the CP arm (2.9%), and histology was unknown in 4.9% and 4.9% of patients in each arm, respectively. The prevalence of comorbidities was low in both arms except for hypertension.

Patient Disposition and Drug Exposure

Although the median number of cycles was four in both arms, only 53.9% of patients in the P arm completed the prescribed four cycles compared with 70.9% in the CP arm ($P = .012$). Principal reasons for discontinuation in the P and CP arms included early death (14.7% *v* 9.7%), early progression (15.7% *v* 7.8%), clinical deterioration (12.7% *v* 6.8%), toxicity (0% *v* 1.9%), and others (4% *v* 2%), respectively. As expected, therapy delays (20.6% *v* 44.7%) and dose reductions (2.9% *v* 3.9%) were more common in the combination arm. Approximately 35% percent of patients in both arms received second-line therapy (Table 2). A higher percentage of patients in the single-agent arm received platinum-based therapy, whereas a higher percentage in the combination arm received docetaxel as second line.

Table 2. Second-Line Therapy

Therapy	P No.	P %	CP No.	CP %
Any	36	35.3	36	35.0
Platinum based	25	69.4	14	38.9
Erlotinib	3	8.3	3	8.3
Docetaxel	3	8.3	10	27.8
Pemetrexed	1	2.8	3	8.3
NR	4	11.1	4	11.1
Other*	0	0.0	2	5.6

Abbreviations: CP, combination of carboplatin and pemetrexed; NR, not reported; P, pemetrexed.
*Gemcitabine and vinorelbine.

Toxicity

Hematologic toxicity was mild. The frequency of grades 3 and 4 anemia (3.9% *v* 11.7%), neutropenia (1.0% *v* 6.8%), and thrombocytopenia (0% *v* 1.0%) was higher in the combination arm (Table 3). However, the incidence of febrile neutropenia (2.9% *v* 1.0%) was similar between the two treatment arms ($P = .37$). Grades 3 and 4 nonhematologic toxicities were conspicuously low in both arms. Dyspnea was more frequent in the P arm, most likely as a manifestation of disease rather than treatment toxicity. There were four documented treatment-related deaths in the combination arm (3.9%) as a result of renal failure, sepsis, pneumonia, and thrombocytopenia.

Efficacy

The median follow-up was 27.5 months (95% CI, 20.5 to 34.5). Best response could not be determined in 34.4% and 23.3% of patients in the P and CP arms, respectively, primarily because of lack of confirmation by RECIST (Table 4). The most common specific reasons were clinical deterioration (11.7% and 7.7%, respectively) and premature death (14.7% and 9.7%, respectively). Among evaluable patients,

Table 3. Toxicity

Grade 3 or 4 Toxicity	P (n = 102) No.	P (n = 102) %	CP (n = 103) No.	CP (n = 103) %	P
Anemia	4	3.9	12	11.7	.07*
Thrombocytopenia	0	0.0	1	1.0	1.00*
Neutropenia	1	1.0	7	6.8	.06*
Febrile neutropenia	3	2.9	1	1.0	.37*
Nausea/emesis	1	1.0	5	4.9	.21*
Diarrhea	2	2.0	1	1.0	.62*
Dyspnea	11	10.8	6	5.8	.19†
Grade 5 event‡	0	0.0	4	3.9	.12*

Abbreviations: CP, combination of carboplatin and pemetrexed; P, pemetrexed
*Fisher's exact test.
†χ^2 test.
‡Renal failure, sepsis, pneumonia, and thrombocytopenia.

Table 4. Efficacy Outcomes

Outcome	P (n = 102)	CP (n = 103)	*P*
ORR, %	10.5	24	.032*
PFS			< .001†
Median, months	2.8	5.8	
Range, months	2.5-3.2	4.7-6.9	
1 year, %	2	17	
OS			.001†
Median, months	5.3	9.3	
Range, months	4.1-6.5	7.2-11.2	
1 year, %	21.9	40.1	

Abbreviations: CP, combination of carboplatin and pemetrexed; ORR, overall response rate; OS, overall survival; P, pemetrexed; PFS, progression-free survival.

*χ^2 test; percentages were calculated based on 67 and 79 evaluable patients in P and CP arms, respectively; ORR in all randomly assigned patients was 6.9% in P arm and 18.4% in CP arm; evaluable patients only.

†Log-rank test.

objective response rates were 10.5% in the P arm (seven of 67) and 24% in the CP arm (19 of 79; $P = .032$). Among all randomly assigned patients, the respective figures were 6.9% (seven of 102) and 18.4% (19 of 103 patients). In the P arm, 31.4% of patients progressed at the time of first assessment compared with 11.7% of patients in the CP arm. Median PFS was 2.8 months (95% CI, 2.5 to 3.2 months) for patients treated with P and 5.8 months (95% CI, 4.7 to 6.9 months) for patients treated with CP (HR, 0.46; 95% CI, 0.35 to 0.63; $P < .001$). The 6- and 12-month PFS rates were 18.4% and 2% versus 48.9% and 17%, respectively (Fig 2A). Median survival times were 5.3 (95% CI, 4.1 to 6.5 months) and 9.3 months (95% CI, 7.4 to 11.2 months), respectively; the 6- and 12-month survival rates were 44.9% and 21.9% in the P arm and 66.8% and 40.1% in the CP arm, respectively (Fig 2B). The OS distributions were statistically significant in favor of the combination arm (HR, 0.62; 95% CI, 0.46 to 0.83; $P = .001$).

A subsequent analysis was performed excluding patients with squamous cell carcinoma (n = 14) and unknown histology (n = 10). The HRs for PFS (HR, 0.46; 95% CI, 0.33 to 0.63; $P < .001$) and OS (HR, 0.65; 95% CI 0.47 to 0.89; $P = .007$) were similar to those of the intent-to-treat population, confirming the superiority of the combination regimen in a pure pemetrexed-eligible population. A repeat analysis excluding only patients with squamous cell disease showed similar results. In the subset of elderly patients (P arm, n = 36; CP arm, n = 38), median survival times were 5.3 and 9.9 months, respectively (HR, 0.49; 95% CI, 0.29 to 0.82; $P = .006$) compared with 5.9 and 2.8 months in younger patients (HR, 0.49; 95% CI, 0.34 to 0.70; $P < .001$); in the subset of never-smokers (P arm, n = 23; CP arm, n = 23), median survival times were 4.2 and 9.4 months, respectively (HR, 0.54; 95% CI, 0.28 to 1.05; $P = .069$) compared with 5.6 and 8.8 months in active/former smokers (HR, 0.65; 95% CI, 0.46 to 0.90; $P = .01$). When analyzed by enrollment, the median survival of patients enrolled at the highest enrolling center (n = 119) was 7.9 compared with 5.8 months for the other sites (HR, 1.00; 95% CI, 0.74 to 1.3; $P = .991$). Lastly, an exploratory analysis by number of comorbidities, based on information extracted from medical records, showed no significant difference in median survival in the group with no comorbidities (n = 64; 6.9 months), one comorbidity (n = 89; 6.3 months), and ≥ one comorbidities (n = 62; 8.2 months).

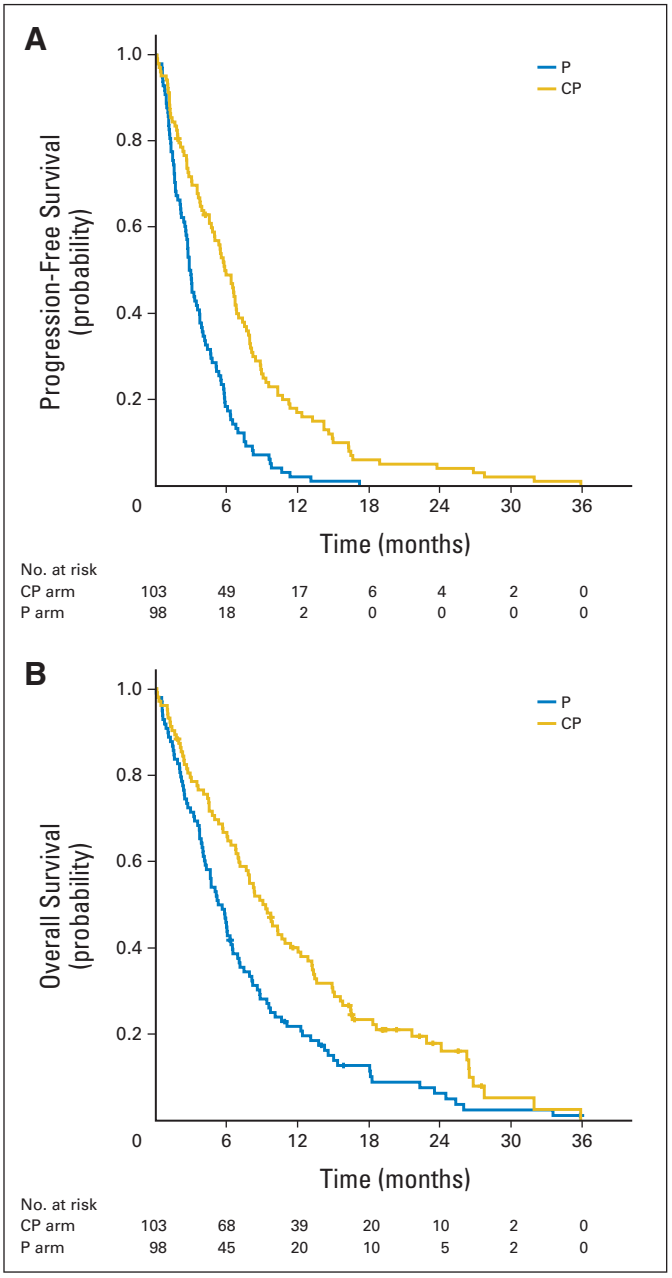

Fig 2. (A) Progression-free and (B) overall survival for patients randomly assigned to pemetrexed (P) or combination of carboplatin and pemetrexed (CP).

DISCUSSION

The question of single-agent versus combination chemotherapy in patients with advanced NSCLC and an ECOG PS of 2 has persisted unanswered for more than a decade. Although concerns about safety and benefit are appropriate,[5] the advent of better supportive care, along with more effective and tolerable carboplatin-based doublets, has allowed us to revisit this question in a more modern light. In particular, we wanted to address practice patterns in which patients with ECOG PS of 2 are treated with inferior regimens, which leads to worse outcomes and, in a circular argument, reinforces the view that treatment is indeed of limited benefit in these patients.

To our knowledge, our study is the first to demonstrate that combination chemotherapy conclusively improves survival compared with single-agent therapy in patients with ECOG PS of 2. Although we cannot rule out the possibility that the study population may not have been representative of the average ECOG PS 2 population, we do not believe that patient selection accounted for our results. First, at the main center in Brazil—Instituto Nacional de Cancer—where > 60% of patients were enrolled, two independent investigators had to agree on the ECOG PS 2 assignment before the patient was enrolled. Second, in a trial conducted in the United States, in which patients with ECOG PS of 2 were randomly assigned to either erlotinib or carboplatin plus paclitaxel,[2] the median survival for patients treated with the combination was 9.7 months, similar to the median survival of 9.3 months observed in our trial. On the other hand, our results are disproportionate to those of the Cancer and Leukemia Group B trial, in which the median survival of the PS 2 subset (99 of 561 patients) was 2.4 months in the single-agent arm and 4.7 months in the combination arm. In addition to patient selection, it is possible that patients enrolled onto a trial limited to those with an ECOG PS of 2 may have slightly better PS than patients enrolled onto trials permitting ECOG PS of 0 to 2, allowing investigators to make a better distinction between the two subsets.

The secondary end points of response rate and PFS were also significantly improved with combination chemotherapy. Furthermore, toxicity was low and manageable, except for four treatment-related deaths in the combination arm. Although this rate is higher than anticipated for patients with an ECOG PS of 0 to 1 treated with a carboplatin doublet, it is not unexpected and underscores the need for close vigilance of patients with an ECOG PS of 2. For example, in the trial by Quoix et al,[6] which compared single-agent versus combination chemotherapy in elderly patients with advanced NSCLC, the treatment mortality rate was similar at 4.4% in the combination arm.

Because of the use of pemetrexed, our study was almost entirely restricted to patients with nonsquamous cell histology. However, we believe the benefits of combination over single-agent chemotherapy are not limited to pemetrexed-based regimens or to patients with nonsquamous histology. The taxane-based combinations used in the trials we have cited corroborate the same principle and expand the pool of patients with an ECOG PS of 2 who are candidates for combination chemotherapy.

Our study did not collect comorbidity data uniformly, but we did not observe a major difference in outcome based on presence or number of comorbidities. Hence, although it is tempting to conclude that patients with an ECOG PS of 2 primarily on the basis of comorbidities fare differently than those affected mainly by disease burden, we cannot substantiate that claim based on our data. We suggest that future trials among patients with an ECOG PS of 2 use a formal comorbidity analysis as a stratification factor to further elucidate this issue.

In summary, our study provides strong evidence that combination chemotherapy is superior to single-agent therapy in all relevant clinical end points. Our results suggest it should be offered to patients with an ECOG PS of 2.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. 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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