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Efficacy and Safety of Trastuzumab Biosimilar (CT-P6) Compared With Reference Trastuzumab in Patients With HER2-positive Advanced Gastric Cancer

A Retrospective Analysis

Joo-Hwan Park, MD, Ja Hyun Yeo, MD,* Young Saing Kim, MD, PhD,* Inkeun Park, MD, PhD,* Hee Kyung Ahn, MD,* Eun Kyung Cho, MD, PhD,* Dong Bok Shin, MD, PhD,* Jun-Young Yang, MD,† Hyung-Sik Kim, MD, PhD,‡ Woon Kee Lee, MD, PhD,† and Sun Jin Sym, MD, PhD**

Objectives: Treatment with trastuzumab and chemotherapy significantly improves the outcome in patients with human epidermal growth factor receptor 2 (HER2)-positive advanced gastric cancer (AGC). CT-P6 (trastuzumab-pkrb; Herzuma) is a trastuzumab biosimilar approved for the treatment of HER2-positive gastric cancer. In this study, we aimed to compare the efficacy and safety of CT-P6 and reference trastuzumab as first-line treatment for HER2-positive AGC.

Materials and Methods: The medical records of 102 patients with HER2-positive AGC treated with first-line trastuzumab-based chemotherapy were retrospectively reviewed. These patients were treated with either reference trastuzumab (n = 72) or a biosimilar (n = 30). Treatment outcomes, such as objective response rate, progression-free survival (PFS), and overall survival (OS), were compared between the reference and biosimilar groups.

Results: The objective response rate of both groups (52.8% and 56.8% in the reference and biosimilar groups, respectively) were comparable ($P = 0.72$). No statistically significant difference was observed with the reference versus biosimilar trastuzumab for PFS (median PFS, 6.9 vs. 5.4 mo; $P = 0.98$) or OS (median OS, 12.3 mo vs. not reached; $P = 0.42$). Safety profiles were similar between the 2 groups.

Conclusions: Biosimilar trastuzumab showed equivalent outcome to reference trastuzumab, with similar adverse events. Biosimilar trastuzumab can suitably and safely replace trastuzumab as a reference for the treatment of HER2-positive AGC.

Key Words: gastric cancer, trastuzumab, biosimilar, CT-P6

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Although the incidence of gastric cancer (GC) is steadily declining, GC remains an important cancer worldwide that accounted for over 1 million new cases in 2020, ranking fifth for incidence and fourth for mortality globally.[1] Since complete surgical resection is the only potentially curative treatment for GC, early diagnosis is essential in GC to ensure a good prognosis. However, GC is often at an advanced stage at the time of diagnosis. At advanced stages, GC can be treated with palliative chemotherapy but can rarely be cured.[2] Cytotoxic chemotherapy remains the backbone of palliative treatment, with a median overall survival (OS) of less than a year. Platinum-based and fluoropyrimidine-based combination therapy is the preferred first-line treatment for advanced gastric cancer (AGC).[3]

Human epidermal growth factor receptor 2 (HER2) plays a central role in the pathogenesis of several human cancers.[4] HER2 is also overexpressed or amplified in 20% to 25% of gastric and gastroesophageal junction cancer.[5] In the Trastuzumab for Gastric Cancer (ToGA) trial, the addition of the HER2-targeting monoclonal antibody trastuzumab to platinum-fluoropyrimidine chemotherapy in HER2-positive AGC improved response rates, progression-free survival (PFS), and OS compared with chemotherapy alone.[6] Median OS was 13.8 months for patients assigned to trastuzumab plus chemotherapy arm compared with 11.1 months in the chemotherapy group (hazard ratio = 0.74; 95% confidence interval [CI]: 0.60-0.91; $P = 0.0046$). Trastuzumab, in combination with platinum-based chemotherapy, is the standard of care as frontline therapy for HER2-positive AGC.

A biosimilar is a biological product that is highly similar to the reference product and has no clinically meaningful differences in terms of the safety, purity, and potency of the product.[7–9] CT-P6 (Herzuma; Celltrion Inc., Incheon, South Korea), a trastuzumab biosimilar, has equivalent pharmacokinetics to the reference trastuzumab in healthy subjects.[10] CT-P6 was approved for the treatment of patients with HER2-positive early-stage breast cancer based on the results of a phase 3 trial.[11] The use of CT-P6 has also been extrapolated to the treatment of metastatic breast cancer and metastatic GC. The approval of trastuzumab biosimilars may provide more patients with access to trastuzumab in clinical practice.

Although trastuzumab biosimilars are of growing importance in AGC, no studies have directly compared the efficacy and safety between the trastuzumab biosimilar CT-P6 and reference trastuzumab in patients with AGC. Herein, we investigated whether the reference trastuzumab and its biosimilar are interchangeable and compared the efficacy and side effects of these molecules in treating patients with HER2-positive AGC.

MATERIALS AND METHODS

Patient Selection Criteria

One hundred two patients with HER2 overexpression or *HER2*-amplified AGC who received first-line trastuzumab-based chemotherapy between February 2011 and December 2020 at the Gachon University Gil Medical Center, Republic of Korea, were

From the *Division of Medical Oncology, Departments of Internal Medicine; †Surgery; and ‡Radiology, Gachon University Gil Medical Center, Incheon, Republic of Korea.

W.K.L. and S.J.S. are co-correspondence author.

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Correspondence: Sun Jin Sym, MD, PhD, Division of Medical Oncology, Department of Internal Medicine, Gachon University Gil Medical Center, 21, Namdong-daero 774 beon-gil, Namdong-gu, Incheon 21565, Republic of Korea. E-mail: sympson@gilhospital.com.

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retrospectively reviewed. The selection criteria for this study were as follows: at least 18 years of age; histologically confirmed gastric adenocarcinoma with distant metastases or recurrent disease; documented HER2 overexpression by immunohistochemistry and/or *HER2* gene amplification by silver in situ hybridization; no previous chemotherapy except adjuvant chemotherapy completed at least 6 months before enrollment; an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 2; adequate organ function; no serious clinical complications. This retrospective study was reviewed and approved by the Institutional Review Board of Gachon University Gil Medical Center (Incheon, Republic of Korea).

Treatment Methods

All patients received trastuzumab in combination with fluoropyrimidine/platinum chemotherapy. Trastuzumab was administered by intravenous infusion at a loading dose of 8 mg/kg on day 1 of the first cycle, followed by 6 mg/kg doses every 3 weeks. Since the biosimilar of trastuzumab (CT-P6; Celltrion Inc.) was approved for AGC, physicians decided whether patients receive a biosimilar or reference trastuzumab, called Herceptin (Genentech, San Francisco, CA). Dose reductions of chemotherapy, including the initial dose, and treatment delays, were decided at each physician's discretion according to the patient's general condition, organ function, and the severity of hematological and nonhematological toxicities. Treatment was repeated until disease progression, unacceptable toxicity, or patient refusal. When a maximal clinical benefit was obtained, the treatment was stopped after 8 cycles, according to the investigator's decision.

TABLE 1. Patient Baseline Demographics and Disease Characteristics

	n (%)		
Characteristics	**Reference Trastuzumab (N = 72)**	**Biosimilar Trastuzumab (N = 30)**	***P***
Age, median (range) (y)	63 (28-86)	66 (28-83)	0.216
Sex			
Male	59 (81.9)	29 (96.7)	0.060
ECOG performance status			0.043
0	21 (29.2)	2 (6.7)	
1	39 (54.2)	22 (73.3)	
2	12 (16.7)	6 (20)	
Previous gastrectomy	19 (26.4)	10 (33.3)	0.479
Primary site			0.147
EG junction	4 (5.6)	2 (6.7)	
Cardia	4 (5.6)	0 (0)	
Body	41 (56.9)	12 (40)	
Antrum	23 (31.9)	16 (53.3)	
Disease status			0.437
Initially metastatic	55 (76.4)	25 (83.3)	
Recurrent	17 (23.6)	5 (16.7)	
No. metastatic sites			0.639
1	30 (41.7)	11 (36.7)	
≥2	42 (58.3)	19 (63.3)	
Histologic grade			0.218
Well-differentiated/ moderately differentiated	36 (50)	19 (63.3)	
Poorly differentiated/ signet ring cell	36 (50)	11 (36.7)	
HER2 status			0.858
IHC 3+	37 (51.4)	16 (53.3)	
IHC 2+ and ISH-positive	35 (48.6)	14 (46.7)	
LVEF at baseline, median (range)	66 (30-83)	60 (50-74)	0.070
Chemotherapy backbone			1.000
XP	69 (95.8)	30 (100)	
FP	2 (2.8)	0 (0)	
XELOX	1 (1.4)	0 (0)	

ECOG indicates Eastern Cooperative Oncology Group; EG, esophagogastric; FP, fluorouracil+cisplatin; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; LVEF, left ventricular ejection fraction; XELOX, capecitabine+oxaliplatin; XP, capecitabine+cisplatin.

Assessment of Efficacy and Toxicity

Tumor response was evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1.[12] Objective response rate (ORR) was defined as the proportion of confirmed complete response (CR) or partial response at the best response. Disease control rate was defined as the percentage of confirmed CR, partial response, or stable disease at the best response. Adverse events were assessed using the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. PFS was measured from the date of initial treatment to the date of disease progression, death from any cause, or the last follow-up visit. OS was defined as the time from the first day of treatment until either the time of death from any cause or the last follow-up visit.

Statistical Analysis

Clinical variables were compared between groups using an independent *t* test or Pearson χ^2 test, as appropriate. Tumor response to chemotherapy was compared across treatments using the Pearson χ^2 test. The PFS and OS were estimated using the Kaplan-Meier method, and the significant differences between these curves were determined using the log-rank test. All statistical analyses were conducted using the R software (version 3.6.3), an open-source statistical software program. Statistical significance was set at *P*-value <0.05.

TABLE 2. Treatment Delivery and Objective Responses

	n (%)		
	Reference Trastuzumab (N = 72)	**Biosimilar Trastuzumab (N = 30)**	***P***
Treatment delivery, median (range)			
Total cycles	6 (1-19)	5 (1-26)	0.834
No. chemotherapy cycles	6 (1-13)	5 (1-9)	0.557
Conversion surgery	15 (16.3)	3 (10.0)	0.557
Best overall response			
CR	2 (2.8)	0 (0)	
PR	36 (50)	17 (56.7)	
SD	12 (16.7)	5 (16.7)	
PD	5 (6.9)	1 (3.3)	
NE	17 (23.6)	7 (23.3)	
ORR	38 (52.8)	17 (56.7)	0.720
DCR	50 (69.4)	22 (73.3)	0.695

CR indicates complete response; DCR, disease control rate; NE, not evaluated; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

RESULTS

Patient Characteristics

From February 2011 to December 2020, 30 patients received biosimilar trastuzumab (CT-P6) in combination with platinum-based chemotherapy (biosimilar group), whereas 72 patients received reference trastuzumab with platinum-based chemotherapy (reference group). The baseline characteristics of the patients are summarized in Table 1. The backgrounds of the patients were not significantly different, excluding ECOG PS. Patients in the reference group had better PS than those in the biosimilar group.

Treatment Exposure and Tumor Response

The number of chemotherapy cycles was not significantly different between the 2 groups: median of 6 cycles (range: 1 to 19) in the reference group and 5 cycles (range: 1 to 26) in the biosimilar group. Tumor responses are shown in Table 2. Only 2 patients achieved a confirmed CR in the reference group, and no patients achieved CR in the biosimilar group. The ORR of the 2 groups was not significantly different (52.8% in the reference group vs. 56.7% in the biosimilar group, respectively; $P = 0.720$). The disease control rates of the reference and biosimilar were 69.4% and 73.3%, respectively ($P = 0.695$).

Survival

The median follow-up time for PFS was 48.0 months in the reference group and 7.2 months in the biosimilar group. After the median follow-up period, 81 patients (64/70 patients [91.4%] in the reference group and 17/32 patients [53.1%] in the biosimilar group) had progressed or died. The survival curves are shown in Figure 1. The median PFS was 6.9 months

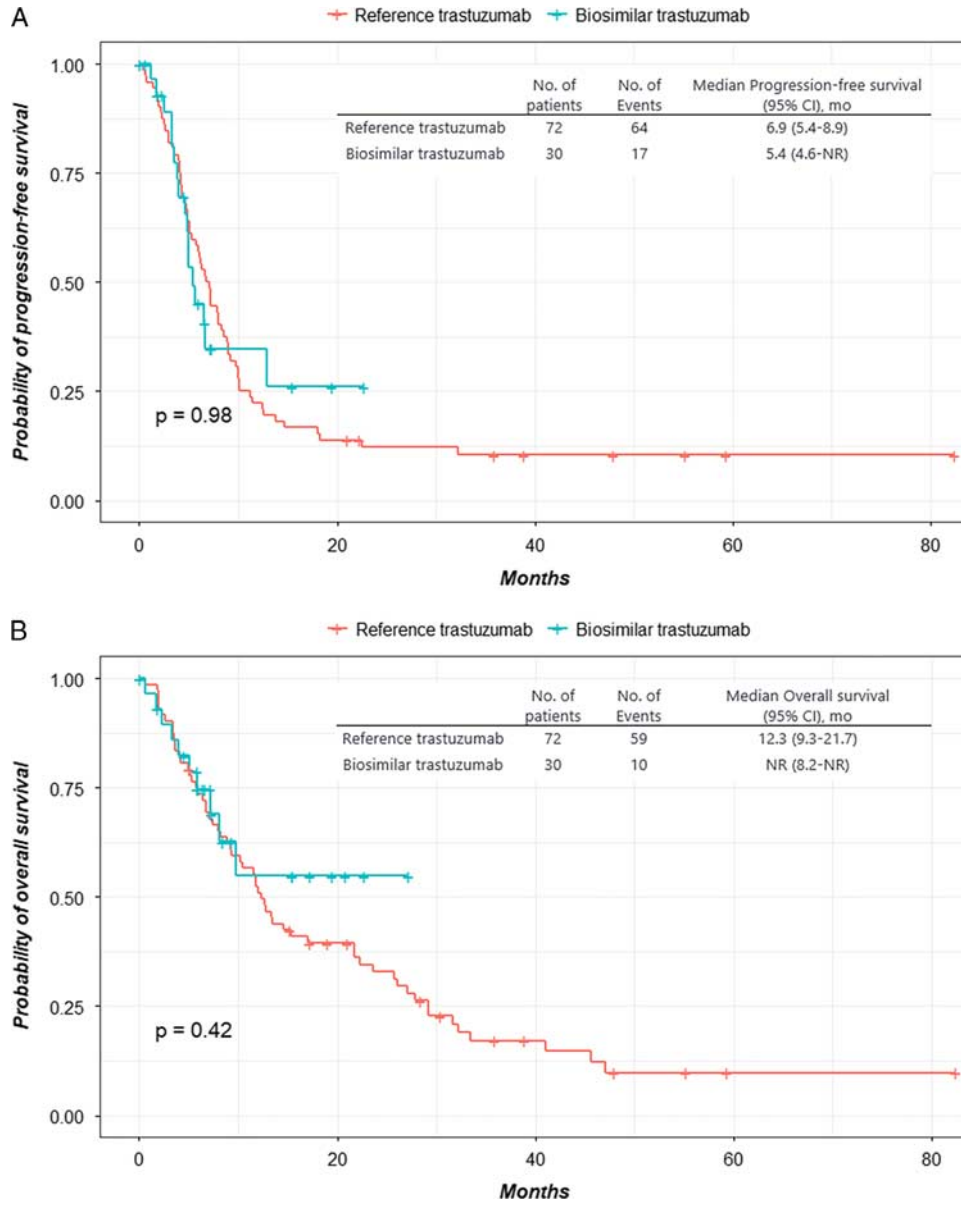

FIGURE 1. The Kaplan-Meier curves for progression-free survival (A) and overall survival (B) for patients taking reference trastuzumab versus trastuzumab biosimilar (CT-P6). CI indicates confidence interval; NR, not reported. full color online

TABLE 3. Adverse Events in Patients With Advanced Gastric Cancer After Treatment With Reference and Biosimilar Trastuzumab

	n (%)			
	Reference Trastuzumab (N = 72)		Biosimilar Trastuzumab (N = 30)	
Adverse Event	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Hematological				
Anemia	65 (90.3)	13 (18.1)	30 (100)	12 (40)
Leukopenia	37 (51.4)	6 (8.3)	21 (70)	5 (16.7)
Neutropenia	40 (55.6)	15 (20.8)	21 (70)	11 (36.7)
Thrombocytopenia	35 (48.6)	4 (5.6)	18 (60)	3 (10)
Febrile neutropenia	6 (8.3)	6 (8.3)	4 (13.3)	4 (13.3)
Nonhematological				
Fatigue	24 (33.3)	0 (0)	8 (26.7)	0 (0)
Anorexia	35 (48.6)	0 (0)	12 (40)	0 (0)
Nausea	25 (34.7)	1 (1.4)	9 (30)	0 (0)
Vomiting	17 (23.6)	4 (5.6)	6 (20)	0 (0)
Diarrhea	10 (13.9)	0 (0)	8 (26.7)	0 (0)
Constipation	4 (5.6)	0 (0)	2 (6.7)	0 (0)
Stomatitis	16 (22.2)	3 (4.2)	5 (16.7)	1 (3.3)
Hand-foot syndrome	12 (16.7)	0 (0)	0 (0)	0 (0)
CIPN	9 (12.5)	1 (1.4)	1 (3.3)	0 (0)
Heart failure	9 (12.5)	0 (0)	3 (10)	0 (0)
Increased serum creatinine	5 (6.9)	1 (1.4)	6 (20)	0 (0)
Increased AST or ALT	2 (2.8)	0 (0)	1 (3.3)	0 (0)
Hyperbilirubinemia	1 (1.4)	0 (0)	0 (0)	0 (0)

ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; CIPN, chemotherapy-induced peripheral neuropathy.

(95% CI, 5.4-8.9) in the reference group and 5.4 months (95% CI, 4.6-could not be calculated) in the biosimilar group ($P = 0.98$). The median OS was 12.3 months (95% CI, 9.3-21.7) in the reference group and was not reached (95% CI, 8.2-lower limit could not be calculated) in the biosimilar group ($P = 0.42$). There was no difference in the outcomes between the 2 groups.

Safety

The hematological and nonhematological adverse events are listed in Table 3. The proportion of patients reporting at least 1 adverse event and grade 3 or worse treatment-related adverse events were similar between the 2 groups. The most frequent adverse events in both groups were hematological toxicities, such as anemia, leukopenia, neutropenia, and thrombocytopenia. Heart failure was reported in 9 patients in the reference group (12.5%) and 3 patients in the biosimilar group (10.0%). However, no grade 3 or 4 heart failure was reported. Of these patients, trastuzumab was discontinued in only 1 patient in the biosimilar group because of a confirmed decrease in left ventricular ejection fraction (LVEF). The LVEF measurements are presented in Table 4. Of the 102 patients who received trastuzumab-based chemotherapy, only 27 patients (37.5%) in the reference group and 12 patients (40.0%) in the biosimilar had both baseline and posttreatment LVEF measurements recorded using the echocardiogram. Six patients (22.2%) in the reference group and 2 patients (16.7%) in the biosimilar group showed a $\geq 10\%$ decrease in LVEF. Among these patients, 1 patient (3.7%) in the reference group and 1 patient (8.3%) in the biosimilar group showed a $\geq 10\%$ decrease in LVEF and final LVEF that decreased to or below 50%.

TABLE 4. Change in Left Ventricular Ejection Fraction From Baseline During Trastuzumab-based Chemotherapy

	n (%)	
	Reference Trastuzumab (N = 27)	Biosimilar Trastuzumab (N = 12)
No decrease	7 (25.9)	4 (33.3)
Decrease of <10 points from baseline	14 (51.9)	6 (50.0)
Decrease of ≥ 10 points from baseline	6 (22.2)	2 (16.7)
< 50 points and decrease of ≥ 10 points from baseline	1 (3.7)	1 (8.3)

DISCUSSION

The results of this study demonstrated similar clinical efficacy and safety between the biosimilar trastuzumab and its reference product in patients with HER2-positive AGC. To the best of our knowledge, this study is the first to directly compare the efficacy and safety of trastuzumab biosimilar to reference trastuzumab in patients with AGC. The ORRs of both groups were comparable (52.8% in the reference group and 56.7% in the biosimilar group). Furthermore, no statistically significant difference was observed in the survival outcomes between the 2 molecules. Although the patients in the biosimilar group had worse PS than those in the reference group, comparable efficacies were demonstrated between the 2 drugs in this study. Furthermore, biosimilar trastuzumab was well tolerated and demonstrated similar safety profiles compared with reference trastuzumab.

Compared with chemotherapy alone, treatment with trastuzumab in combination with chemotherapy significantly improved OS among patients with HER2-positive AGC.[6] However, targeted cancer drugs such as trastuzumab are relatively more expensive compared with other chemotherapy drugs. Despite its clinical benefits, this high price can represent a substantial barrier to trastuzumab treatment, especially in a financially constrained environment.[13] Since the price of biosimilars is generally lower than that of the reference products, the cost saved by switching patients to biosimilars could enable improved access to these clinically effective drugs.

Several trastuzumab biosimilar candidates have been developed in recent years. The US Food and Drug Administration (FDA) has approved 5 trastuzumab biosimilars: trastuzumab-anns, trastuzumab-dkst, trastuzumab-dttb, trastuzumab-pkrb, and trastuzumab-qyyp.[14] CT-P6 (trastuzumab-pkrb), produced by the South Korean Biotechnology Company Celltrion, has demonstrated comparable pharmacodynamics and efficacy to trastuzumab in clinical trials.[10,11,15,16] Trastuzumab biosimilars have been studied only in patients with breast cancer, and extrapolation has been granted from early breast cancer to metastatic breast cancer and metastatic GC. Extrapolation is an established regulatory principle that refers to the approval of a biosimilar for use in an indication held by the reference product, not directly studied in a comparative clinical trial with a biosimilar.[17] Although some controversy exists regarding this topic, this concept is critical to the goals of an abbreviated pathway—improving access and options at a

potentially lower cost. Thus, the use of biosimilars for the treatment of patients with HER2-positive AGC could be considered an effective way to provide budgetary savings and increase patient access to biological medicines.

Recently, a phase Ib/II study (PANTHERA trial) has shown that biosimilar trastuzumab (CT-P6) is effective in patients with HER2-positive AGC when used in combination with pembrolizumab and chemotherapy.[18] These findings also have implications for reducing the costs of care by using biosimilars. The use of biosimilar trastuzumab is expected to increase in both clinical practice and clinical trials. However, no studies have directly compared the efficacy and safety of trastuzumab biosimilar to reference trastuzumab in patients with AGC. Therefore, the results of this study highlighting the efficacy and safety between the 2 drugs will guide future clinical trials.

There are several limitations to the current study. First, this was a retrospective analysis based on chart review. A retrospective study could provide important insights into the actual clinical use of biosimilar trastuzumab. However, due to reliance upon electronic medical records, if adverse events were not recorded, it was assumed that they did not occur. Second, this study included a small population (n = 122) from a single institution. Third, since follow-up echocardiography was not routinely performed after trastuzumab treatment, it was difficult to accurately compare the cardiovascular safety between the 2 drugs. Echocardiography was performed to assess cardiac function when heart failure was clinically suspected. We might have missed patients who had no symptoms of heart failure but had decreased cardiac function. In our study, follow-up echocardiography was performed for only 12 patients (40%) in the biosimilar group and 27 patients (37.5%) in the reference group. Therefore, larger prospective studies are needed to confirm our findings.

The findings of this retrospective study demonstrated that biosimilar trastuzumab (CT-P6) is as efficacious as reference trastuzumab in terms of response rates, PFS and OS with comparable toxicity. in patients with HER2-positive AGC. The results of this study will help investigators in planning clinical studies in patients treated with biosimilar trastuzumab. Further prospective studies with large numbers of patients are, however, needed to validate these results.

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