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Updated survival outcomes with ivosidenib in patients with previously treated IDH1-mutated intrahepatic-cholangiocarcinoma: an Italian real-world experience

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Abstract

Background: The results of the phase III ClarIDHy trial led to the FDA approval of ivosidenib as a therapeutic option for patients with locally advanced or metastatic cholangiocarcinoma (CCA) harboring isocitrate dehydrogenase 1 (IDH1) mutations. We recently published the first data on the use of ivosidenib in a real-world setting.

Objective: Here we report the updated survival results of 11 patients with locally advanced or metastatic IDH1-mutated CCA who received ivosidenib in clinical practice.

Patients and methods: Patients treated with ivosidenib as second- and third-line treatments for advanced CCA have been collected with the aim to evaluate the survival outcomes. A molecular study has been performed by next generation sequencing essay.

Results: Overall, 11 patients were included. After a median follow-up of 13.7 months, median progression-free survival from the start of treatment with ivosidenib was 4.4 months (95% CI: 2.0–5.8), whereas median overall survival was 15 months (95% CI: 6.6–15.0) regardless of treatment line. Disease control rate was 63%, with two patients achieving a partial response (18%). Eighteen percent of patients experienced at least one treatment-related adverse events (AEs), but no grade ⩾3 was reported. The most frequently observed grade 2 AEs were prolonged QT interval and hypomagnesemia. A molecular profiling was performed on 8 out of 11 patients, highlighting TP53, BAP1, CDKN2A, and CDKN2B as the most common co-altered genes in these patients.

Conclusion: The present update confirms the results of our previous real-world experience on the use of ivosidenib in IDH1-mutated CCA. Real-world evidence on larger numbers of patients is needed to confirm our findings.

Keywords: cholangiocarcinoma, IDH1 mutation, ivosidenib, next generation sequencing, target therapy

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Introduction

Advanced cholangiocarcinoma (CCA) is as an aggressive disease characterized by dismal prognosis and scarce treatment options.[1,2] For more than 10 years the combination of cisplatin plus gemcitabine was the only approved therapeutic option for patients affected by this heterogeneous disease, with median overall survival (OS) less than 1 year.[3,4] Recently, the addition of the anti-programmed cell death ligand 1 durvalumab to the chemotherapy backbone has demonstrated to confer a survival benefit in terms of both OS and

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progression-free survival (PFS), thus becoming the new standard of care for all patients affected by CCA.[5] Interestingly, the last years have seen the emergence of interesting new data on the genomic and molecular profile of CCA, highlighting a significant heterogeneity within this group of malignancies. In particular, a number of potentially targetable genomic alterations have been recognized in a significant proportion of patients with CCA, including mutations of isocitrate dehydrogenase 1 (IDH1), which have been detected in around 13% of patients with intrahepatic CCA.[1–4] The randomized placebo-controlled phase III ClarIDHy trial tested the IDH1-inhibitor ivosidenib in patients with previously treated unresectable (locally advanced or metastatic) CCA carrying IDH1 mutation. Ivosidenib was demonstrated to confer a survival benefit in terms of PFS [2.7 months (95% CI: 1.6–4.2) *versus* 1.4 months [(95% CI: 1.4–1.6); HR: 0.37, 95% CI: 0.25–0.54; $p < 0.0001$] and OS [10.3 months (95% CI: 7.8–12.4) *versus* 5.1 months (95% CI: 3.8–7.6); HR: 0.49, 95% CI: 0.34–0.70, $p < 0.001$ in the crossover adjusted analysis] compared to placebo, thus receiving the approval by the United States Food and Drug Administration (FDA) in this setting.[6,7] Moreover, a recently published real-world experience from our research group highlighted the negative prognostic role of IDH1 mutation in patients with advanced CCA who progressed on first-line therapy and who did not receive ivosidenib as subsequent anticancer treatment.[8] The authors concluded that the poor survival outcomes of patients with IDH1-mutated CCA receiving chemotherapy and/or best supportive care should provide a further input toward the investigation of IDH1 inhibitors in this group of patients. Moving from these premises, we recently published the first real-word Italian experience of the use of ivosidenib in patients with advanced CCA carrying IDH1 mutation, confirming the favorable outcome and good safety profile of this recently FDA-approved drug in a real-world context.[9] In the present work we reported the updated survival results of the first worldwide real-world experience of use of ivosidenib in previously treated patients with advanced CCA.

Materials and methods

Accrual and procedures

Patients treated from May 2021 to April 2022 with ivosidenib for locally advanced or metastatic CCA carrying the IDH1 mutation from six Italian institutions were included in this study. Clinical, pathological, and molecular data were prospectively collected at the single institutions, pooled in a common dataset, and retrospectively analyzed. Ivosidenib was administered at the standard dose of 500 mg once daily in continuous 28-day cycles in the frame of a named patient use program. Tumor samples were included on formalin-fixed, paraffin-embedded sections from surgical specimen or, when not available, from biopsy specimens. A full histopathologic review by an expert biliopancreatic pathologist was performed for each patient's sample. All patients included in the cohort were tested for IDH1 status at baseline. Moreover, a genomic analysis of the primary tumors was performed by a next generation sequencing (NGS)-platform, in order to define the mutational status of all the 324 genes included in the FoundationOne assay.

Patients provided informed consent for treatment with ivosidenib, not yet approved in Italy, while the consent for the retrospective analyses was waived.

The study was approved by the Ethics Committees at each participating institution and was conformed to the ethical guidelines of the 1975 Declaration of Helsinki. The informed consensus on use was 113/INT/2021.

Statistical analysis

The analysis aimed to investigate the survival outcomes in terms of PFS and OS of patients with advanced CCA carrying IDH1 mutation and receiving ivosidenib after progression on at least one previous systemic treatment.

OS was defined as the time from the beginning of treatment with ivosidenib to death from any cause. PFS was defined as the time from the beginning of treatment with ivosidenib to disease progression or death. OS and PFS were estimated by the Kaplan-Meier method. Median follow-up was calculated through the reverse Kaplan-Meier method. Treatment response was evaluated by computed tomography and categorized as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD) by local review according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1.[10]

Objective response rate (ORR) was defined as the rate of CR and PR under treatment with

ivosidenib; disease control rate (DCR) was defined as the rate of CR and PR plus the rate of SD under treatment with ivosidenib.

In addition, we evaluated the survival outcomes according to the genomic and molecular profile revealed by the NGS analysis and applied to clinical practice through the easy-to-use algorithm we built in the previous clustering analysis performed by our research group.[11]

Finally, a safety analysis was conducted on all patients who received at least one dose of treatment, and adverse events (AEs) were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0.[12] Treatment interruptions and/or dose reductions were allowed to manage AEs.

A p value <0.05 was considered statistically significant. MedCalc package (MedCalc® version 16.8.4) was used for statistical analysis.

Results

Patient characteristics

Overall, 11 patients were included in our cohort of patients who received ivosidenib for locally advanced (5/11, 45%) or metastatic (6/11, 55%) IDH1-mutated CCA between May 26, 2021, and November 24, 2022, at six Italian institutions. Slightly more patients were women (54%) with median age of 57 years (range: 38–76). At baseline, 63% of the patients presented with Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 0, and 45% of the patients underwent primary tumor resection at diagnosis. All the patients received chemotherapy as first-line treatment: 73% of the patients received cisplatin plus gemcitabine, whereas 27% received other chemotherapy regimens, including gemcitabine monotherapy, gemcitabine plus oxaliplatin plus nab-paclitaxel, and 5-fluorouracil plus irinotecan. Overall, two patients (18%) received ivosidenib as second-line treatment, seven patients (64%) as third-line treatment, and two patients (18%) as fourth-line treatment.

Adequate tissue samples were available for 8 out of 11 patients (73%) to perform a complete NGS analysis by FoundationOne essay. R132C missense mutation was the most prevalent IDH1 missense mutation observed in the cohort (56%). Three patients carried R100Q, R132G, and R132S IDH1 mutations, respectively. Beyond the IDH1 mutation, additional somatic mutations were found in all patients with a molecular profile. In the order of frequency, 3 out of 8 patients (37.5%) presented BAP1 mutation; 2 out of 8 patients (25%) presented CDKN2A/CDKN2B loss; 2 out of 8 patients (25%) KRAS/NRAS mutation; and 2 out of 8 patients (25%) TP53 mutation; 1 out of 8 patients (12.5%) presented genomic alterations of ARID1A; 1 out of 8 patients (12.5%) presented PBRM1; 1 out of 8 patients (12.5%) presented PI3KCA; and 1 out of 8 patients (12.5%) presented MTAP (Figure 1). Few patients presented more than one genomic alteration of interest: 1 out of 8 patients presented both BAP1 and NRAS mutations; 1 out of 8 patients presented both ARID1A mutation and CDKN2A/2B loss; 1 out of 8 patients presented both PBRM1 and TP53 mutation; 1 out of 8 patients presented both BAP1 mutation and FGFR2 translocation; and finally, 1 out of 8 patients presented both KRAS mutation and CDKN2A/2B loss.

The complete baseline clinico-pathological characteristics are reported in Tables 1 and 2.

Survival outcomes

Median follow-up was 13.7 months (95% CI: 7.3–16.5). At the data cutoff, six patients (55%) had died. Survival outcomes for each patient are showed in Table 2.

In previous first-line treatment, median PFS was 5.8 months (95% CI: 2.5–34.3). DCR was 55%, with all six patients achieving SD with no objective response. Forty-five percent of the patients experienced PD as best response to the first-line treatment.

All patients received ivosidenib after progression to at least one previous line of systemic therapy. In particular, two patients (18%) received ivosidenib as second-line treatment, seven patients (64%) as third line, and two patients (18%) as fourth line. At the data cutoff, eight patients (73%) showed PD, while three patients (27%) were still receiving ivosidenib treatment.

Overall, median OS from the start of ivosidenib was 15 months (95% CI: 6.6–15.0) regardless of treatment line, while median PFS was 4.4 months (95% CI: 2.0–5.8) (Figure 2).

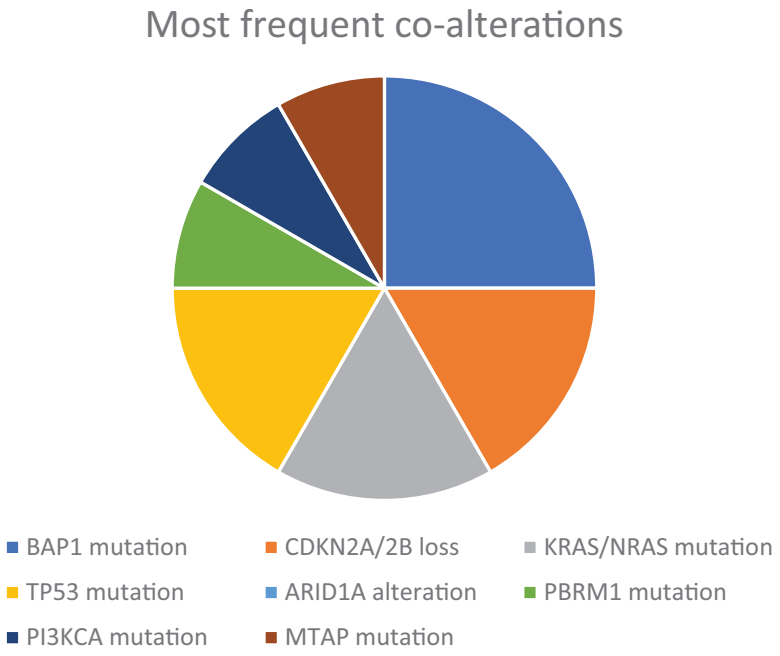

Figure 1. Most frequent co-alterations in the sample.

Regardless of treatment line, DCR was 63%; in particular, two patients (18%) experienced PR, five patients (45%) SD, and four patients (37%) PD as best response to ivosidenib. Clinical outcomes for each patient are showed in Table 2.

In addition, we characterized our patients from a molecular and genomic point of view according to the three genomic clusters revealed by our previous clustering analysis on IDH1-mutated CCA,[10] through the clinical application of an easy-to use algorithm. We identified three patients (37.5%) in cluster 1, three patients in cluster 2 (37.5%), and two patients (25%) in cluster 3. The survival analysis according to the genomic clustering classification showed median PFS not reached for patients in cluster 2 *versus* median PFS of 4.3 months (95% CI: 0.9–5.8) for patients in cluster 1 and cluster 3, without reaching a statistical significance (HR: 3.3, 95% CI: 0.64–17.35, $p = 0.1519$).

Safety profile

All patients included in the study started treatment with ivosidenib at the standard dose of 500 mg orally once per day. Two patients (18%) experienced treatment-related AEs (TRAEs), which were all graded 2. In particular, one grade 2 prolonged QT interval on electrocardiogram and one grade 2 hypomagnesemia, both without subjective symptoms. Treatment interruption followed by dose reduction to 250 mg/day has been required in one patient due to TRAEs (prolonged QT).

Discussion

The present work reports the updated survival results of a cohort of patients with advanced IDH1-mutated CCA who received ivosidenib after at least one previous systemic treatment line. In our previous work, including eight patients treated with ivosidenib for advanced IDH1-mutated CCA we reported promising survival results. In the current work we report the updated survival outcomes of the same patients after a longer and more adequate follow-up, and we added two more patients to our cohort. Interestingly, the promising results suggested by our previous work have been confirmed in the present one: median OS, which was not reached in the previous work, has been updated after a more adequate follow-up, now reaching 15 months. This is remarkable result, mainly considering the results of the phase III ClarIDHy trial, which showed a median OS of 10.3 months with ivosidenib, significantly longer compared to the OS experienced by patients receiving placebo in the crossover adjusted analysis.[7] By a direct and unappropriated comparison, we could speculate that the better OS reported in our study could be explained by the small sample size and the

Table 1. Patients' characteristics.

Characteristics at the start of ivosidenib	*N* = 11 (%)
Sex	
Men	4 (46)
Women	7 (54)
Age (years)	
Mean ± SD	57 ± 11
Range	38–76
Extent of disease	
Locoregional	5 (45)
Metastatic	6 (55)
Primary tumor resected	
Yes	5 (45)
No	3 (27.5)
NA	3 (27.5)
ECOG PS	
0	7 (63)
1	1 (9)
NA	3 (28)
First-line chemotherapy	
Cisplatin-gemcitabine	8 (73)
Other	3 (27)
Previous systemic lines (*N*)	
1	2 (18)
2	7 (64)
3	2 (18)
CA 19-9 concentration	
Mean	47.9
Range	(12–123)

CA: carbohydrate antigen.

small follow-up time. Nevertheless, we know that a direct comparison between the results of a large randomized trial and a real-world experience reporting the survival outcomes of 11 patients treated in clinical practice could not be done, but some considerations can be made. Advanced CCAs are heterogeneous malignancies with a dismal prognosis and scarce therapeutic options.[1,2] In Europe, the only approved treatment for patients with advanced CCA who progressed on a previous line of chemotherapy and without actionable mutations is the doublet of fluoropyrimidine and platinum compounds, which reached a median OS of 6.2 months in the ABC-06 trial, regardless of the primary tumor site and the molecular profile.[13] No standard third-line therapy has already been established for patients with advanced CCA without actionable mutations, but case series and retrospective investigations reported unsatisfactory OS of approximately 5 months.[14] Moreover, a negative prognostic value of IDH1 mutation in patients with advanced CCA who progressed on first-line treatment was highlighted in a large retrospective study.[9] Patients carrying IDH1 mutation receiving a further treatment after progression on cisplatin plus gemcitabine showed a median OS of 8.2 months compared to 14.1 months for patients with IDH1 wild-type tumors, thus making the definition of better therapeutic strategies for this subgroup of patients an urgent unmet need. Given these premises, the observed median OS of 15 months for patients with IDH1-mutated tumors receiving ivosidenib after progression on at least one systemic treatment seems particularly promising and deserve further investigations. Moreover, our analysis showed a median PFS of 4.4 months, thus confirming the results we showed in our previous report.[9] In the ClarIDHy trial,[6,7] median PFS was of 2.7 months, but differences in terms of timepoints for tumor assessment have to be taken into consideration, besides the significative divergences in terms of study design and sample size. Our analysis showed promising results also in terms of ORR and DCR. In fact, ORR was 18% and DCR was 63%, which were substantially consistent with our previous real-world report (ORR: 25%, DCR: 62.5%). Concerning the safety profile, our results support the good tolerability of ivosidenib, as shown in the ClarIDHy trial.[6,7] Indeed, our study reported a low rate of AEs, with no reported grade ⩾3 AEs. Interestingly, no events of diarrhea, nausea or fatigue were reported, which on the contrary were reported as the most common AEs in the ClarIDHy trial. Further real-world data on larger numbers of patients are needed to confirm the good tolerability of ivosidenib in this setting and to better evaluate the incidence of the most

Table 2. Patients' Outcomes and genetic alterations.

Patient ID	Extent of disease	Setting	Best response	Progressed disease under ivosidenib	PFS (months)	OS (months)	IDH1 mutation	Concomitant genetic alterations
1	M	III L	PD	Yes	3.7	8.8	R132C	PIK3CA, TP53
2	M	III L	PD	Yes	3.3	6.6	R132C	BAP1, NRAS
3	LA	III L	SD	No	11.1	11.1	R132C	BAP1, RAD21
4	LA	III L	SD	Yes	4.3	8.6	R132C	ARID1A, NOTCH, NTRK1, CDKN2A/2B, BRCA1
5	M	II L	SD	Yes	5.8	15.0	R100Q	PBRM1, TP53, EGFR, EPHB1, AXIN1
6	LA	II L	SD	Yes	4.4	10.2	R132C	PSM2
7	M	III L	PR	Yes	5.8	10.7	NA	NA
8	M	III L	PR	No	16.45	16.45	NA	NA
9	LA	IV L	SD	No	13.7	13.7	R132G	FGFR2, BAP1
10	LA	III L	PD	Yes	2.0	7.3	R132C	NA
11	M	IV L	PD	Yes	0.92	1.88	R132S	MTAP, CDKN2A/2B, KRAS, PDGFR

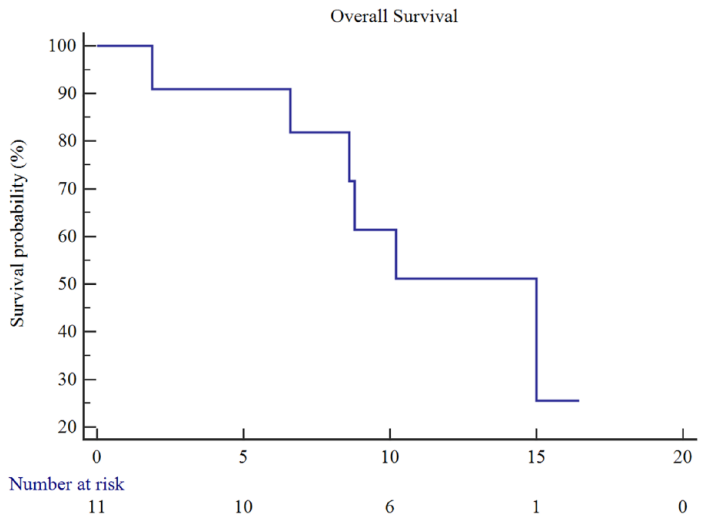

Figure 2. Kaplan-Meier curve of overall survival.

common AEs reported in the registration trial. Another point deserving attention concerns the molecular and genomic profile. In our study, 8 out of 11 patients underwent extensive molecular profiling through a large NGS panel which included the evaluation of 324 genes. Thus, several significant co-mutations were detected, including mutations of BAP1, KRAS/NRAS, TP53, ARID1A, PBRM1, PI3KCA, and MTAP. With the limitation of a comparison between real-world data on a small sample of patients and results from a randomized controlled trial, our results are consistent with the molecular data reported in the ClarIDHy trial.[6,7] In addition, most common molecular alterations reported in our analysis are consistent with the results from previous retrospective studies,[11,15–20] thus reinforcing the knowledge about the molecular profile of CCA. Finally, we applied our previously defined algorithm in order to classify patients in three clusters defined accordingly to our previous clustering analysis, with the aim to test the prognostic role that we previously highlighted. Interestingly, this analysis confirms the results achieved in our previous real-world experience, showing a tendence toward a better PFS for patients included in cluster 2 compared to those included in cluster 1 and 3, even if without statistical significance. According to our previous analysis, cluster 1 was mainly characterized by mutations in KRAS/NRAS pathway and in genes involved in the cell cycle and apoptosis; cluster 2 was characterized by alterations mainly in genes involved in chromatin modification, DNA damage control systems and PI3K; finally, cluster 3

was identified by the presence of TP53 mutations.[11] The survival benefit for patients in cluster 2 highlighted in the clustering analysis and confirmed in the present work could be related to the selection of negative molecular features in cluster 1 and cluster 3, since both KRAS/NRAS mutations and TP53 mutations have been previously showed to have a negative prognostic impact in patients with CCA.[19,21] Despite the undoubted value of the present small-size validation of our previous results from the clustering analysis, the present data could not be considered as conclusive, due to the small sample size which makes further investigations mandatory. Further molecular and genomic investigations on patients with IDH1-mutated CCA should be performed in clinical practice, and a larger use of NGS platforms able to study the status of a significative number of genes should become standard of care.

The present work accounts a number of limitations. First, it is a retrospective investigation conducted on a small sample of patients, thus a selection bias could not be excluded due to the nature of the study. Moreover, the small sample size itself amplifies the selection bias, and no direct and adequate comparison with other results from prospective trials and/or retrospective works conducted on large sample size could be performed. Second, several clinico-pathological features, as well as data about subsequent anticancer therapies are lacking, and their possible impact on survival outcomes could not be measured. Despite the overmentioned limits, to the best of our knowledge, the present report constitutes the first real-world experience of the use of ivosidenib in patients with advanced IDH1-mutated CCA. Real-world data on larger samples are mandatory in order to confirm the promising results showed in our analysis, as well as to better define the molecular profile of these patients. A deeper knowledge of the molecular profile could highlight prognostic and predictive factors of response to treatment as well as mechanisms of resistance to ivosidenib, thus opening the way for new research in this field and filling an important clinical gap for this group of patients with a dismal prognosis.

Conclusion

In conclusion, the present update confirms the results of our previous real-world experience on the use of ivosidenib in IDH1-mutated CCA. Real-world evidence on larger numbers of patients is needed to confirm our findings. Moreover, a deeper knowledge about the molecular and genomic profile would help to understand possible resistance mechanisms, which could underlie, thus suggesting possible new therapeutic strategies for this setting of patients.

Declarations

Ethics approval and consent to participate

Institutional Review Board Statement: The Ethical Review Board of each Institutional Hospital approved the present study. This study was performed in line with the principles of the Declaration of Helsinki. Informed Consent Statement: Written informed consent for treatment was obtained for all patients.

Ethics approval and consent to participate

Ethics Statement: The study was conducted in accordance with the Declaration of Helsinki and the protocol was approved by the Ethics Committee of each institution involved in the project. Under the condition of retrospective archival tissue collection and patients' data anonymization, our study was exempted from the acquisition of informed consent from patients by the institutional review board.

Consent for publication

Yes (113/INT/2021).

Author contribution(s)

Margherita Rimini: Conceptualization; Data curation; Formal analysis; Methodology; Resources; Software; Supervision; Validation; Writing – original draft.

Valentina Burgio: Conceptualization; Writing – review & editing.

Lorenzo Antonuzzo: Conceptualization; Writing – review & editing.

Lorenza Rimassa: Conceptualization; Data curation; Investigation; Methodology; Writing – review & editing.

Ester Oneda: Conceptualization; Writing – review & editing.

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Stefano Cascinu: Writing – review & editing.

Andrea Casadei-Gardini: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Writing – original draft; Writing – review & editing.

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Availability of data and materials
Data available on request from the authors.

Availability of data and materials
The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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