Efficacy and Safety of Zanubrutinib in Japanese Patients With B-Cell Malignancies

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Abstract 30055

COI disclosure

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■ This study has been approved by the local IRB.

Background

- Zanubrutinib is a potent, selective, irreversible, next-generation BTK inhibitor designed to maximize BTK occupancy and minimize off-target kinase inhibition and associated AEs[1]
- Zanubrutinib is approved globally for the treatment of B-cell malignancies in adults[2-4]
- BGB-3111-111 (NCT04172246) is an ongoing, multicenter, open-label phase 1/2 study to assess the safety and efficacy of zanubrutinib in Japanese patients with mature B-cell malignancies
- An IRC-based efficacy assessment is key to confirm the reliability of the study and support regulatory approval from agencies

Here, we present the IRC-assessed efficacy of zanubrutinib in Japanese patients and report concordance with the investigator-based assessment in the BGB-3111-111 study from the 2022 DCO

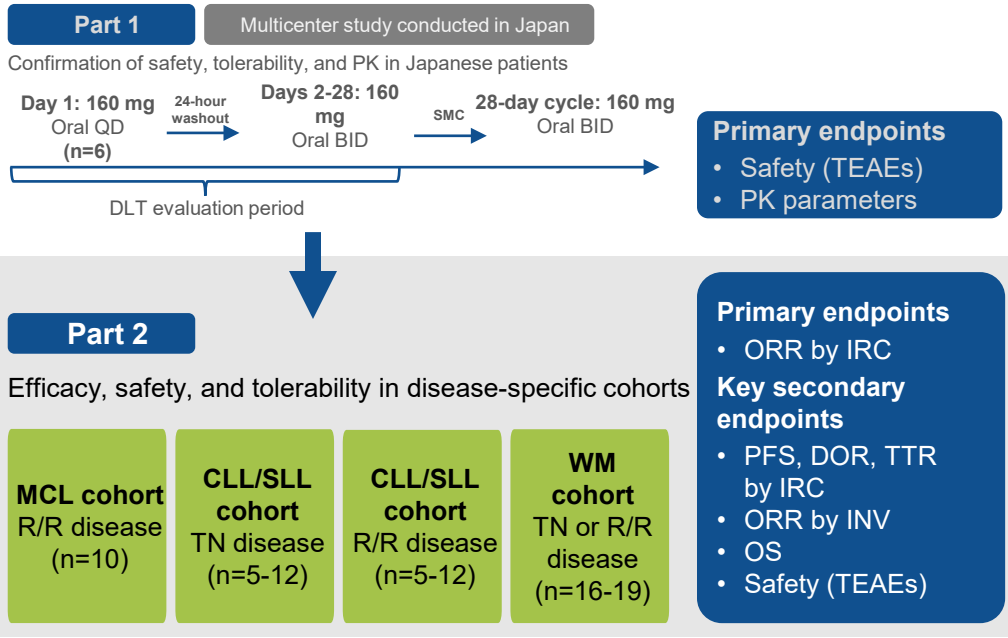
AE, adverse event; BTK, Bruton tyrosine kinase; DCO, data cut-off; IRC, independent review committee.

1. Guo Y, et al. *J Med Chem*. 2019;62(17):7923-7940; 2. Brukinsa. Package insert. BeiGene USA, Inc; 2023;
3. Brukinsa. Product monograph. Beigene Switzerland GmbH; 2021; 4. Gale RP. *Chin Med J (Engl)*. 2022;135(8):883-886.

Study design

Key eligibility criteria

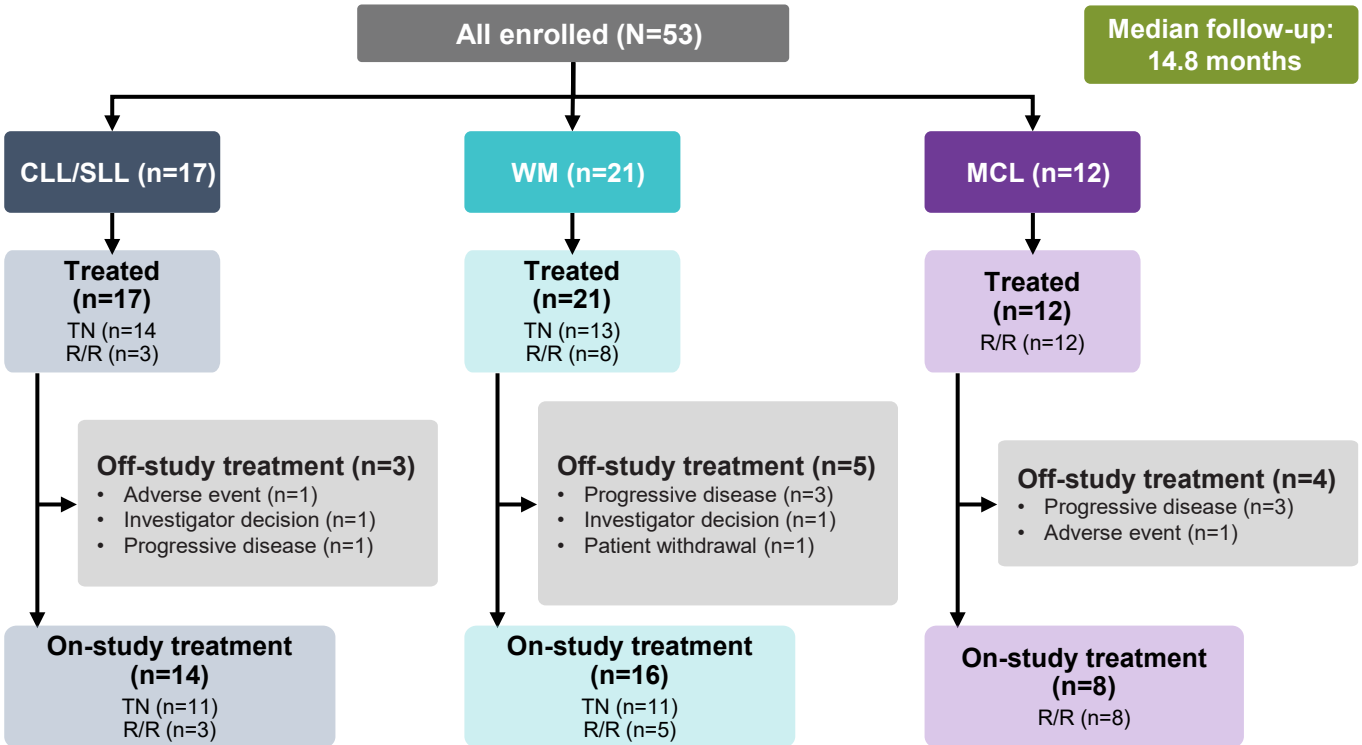
- Japanese
- Age ≥20 years
- ECOG PS of 0-2
- Confirmed diagnosis of mature B-cell neoplasms (CLL/SLL, MCL, FL, MZL, or WM)
- Measurable disease[a]
- No prior systemic chemotherapy or radiation therapy within 2 weeks prior to first dose of zanubrutinib
- No prior alloSCT or therapy with B-cell receptor inhibitor or BCL2 inhibitor



alloSCT, allogeneic stem cell transplant; BCL2, B-cell lymphoma 2; BID, twice daily; DLT, dose-limiting toxicity; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; INV, investigator; IRC, independent review committee; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; QD, once daily; R/R, relapsed or refractory; SMC, safety monitoring committee; TEAE, treatment-emergent adverse event; TN, treatment naive; TTR, time to response; WM, Waldenström macroglobulinemia.

[a] MCL, WM, MZL, and FL only

Patient disposition



Data cutoff date: 10 May 2022

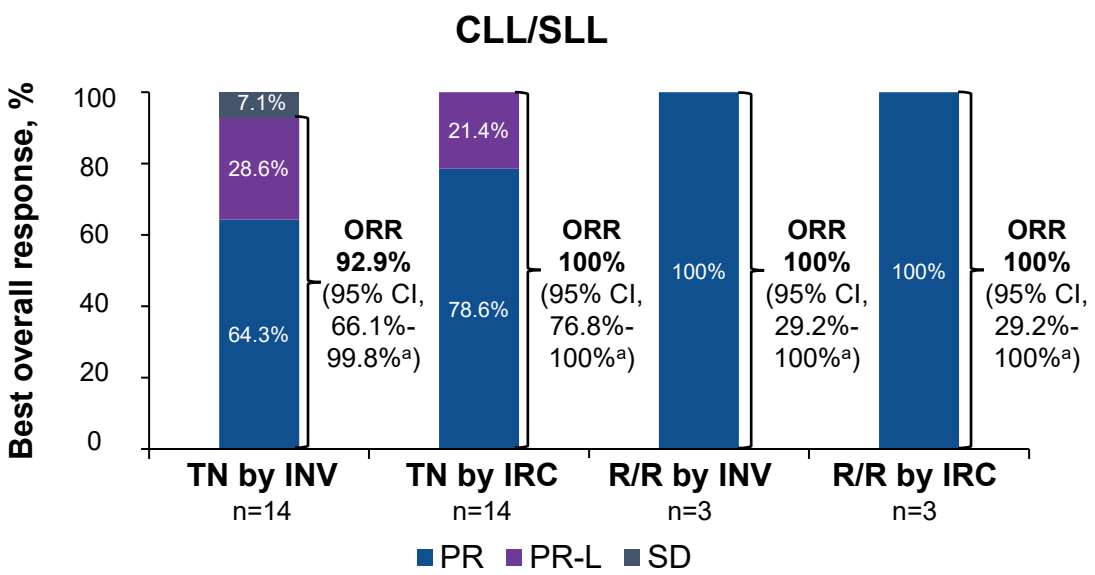
CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; MCL, mantle cell lymphoma; R/R, relapsed or refractory; TN, treatment naive; WM, Waldenström macroglobulinemia.

Baseline characteristics

Characteristics	CLL/SLL (n=17)		WM (n=21)		R/R MCL (n=12)	Total (N=53)
	TN (n=14)	R/R (n=3)	TN (n=13)	R/R (n=8)		
Age, median (range), years	67.5 (38-77)	76.0 (72-77)	71.0 (37-83)	67.5 (61-78)	74.5 (58-84)	71.0 (37-84)
<65 years, n (%)	6 (42.9)	0	3 (23.1)	2 (25.0)	1 (8.3)	13 (24.5)
≥65 years, n (%)	8 (57.1)	3 (100)	10 (76.9)	6 (75.0)	11 (91.7)	40 (75.5)
Sex, n (%)						
Male	10 (71.4)	2 (66.7)	6 (46.2)	5 (62.5)	10 (83.3)	36 (67.9)
Female	4 (28.6)	1 (33.3)	7 (53.8)	3 (37.5)	2 (16.7)	17 (32.1)
ECOG PS, n (%)						
0	12 (85.7)	3 (100)	10 (76.9)	5 (62.5)	9 (75.0)	42 (79.2)
1	2 (14.3)	0	3 (23.1)	3 (37.5)	3 (25.0)	11 (20.8)
No. of prior lines of therapy in patients with R/R disease, median (range)	–	2.0 (1-2)	–	3.5 (1-8)	1.0 (1-2)	2.0 (1-8)

CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; MCL, mantle cell lymphoma; R/R, relapsed or refractory; TN, treatment naive; WM, Waldenström macroglobulinemia.

Patients with CLL/SLL had an ORR of >90%

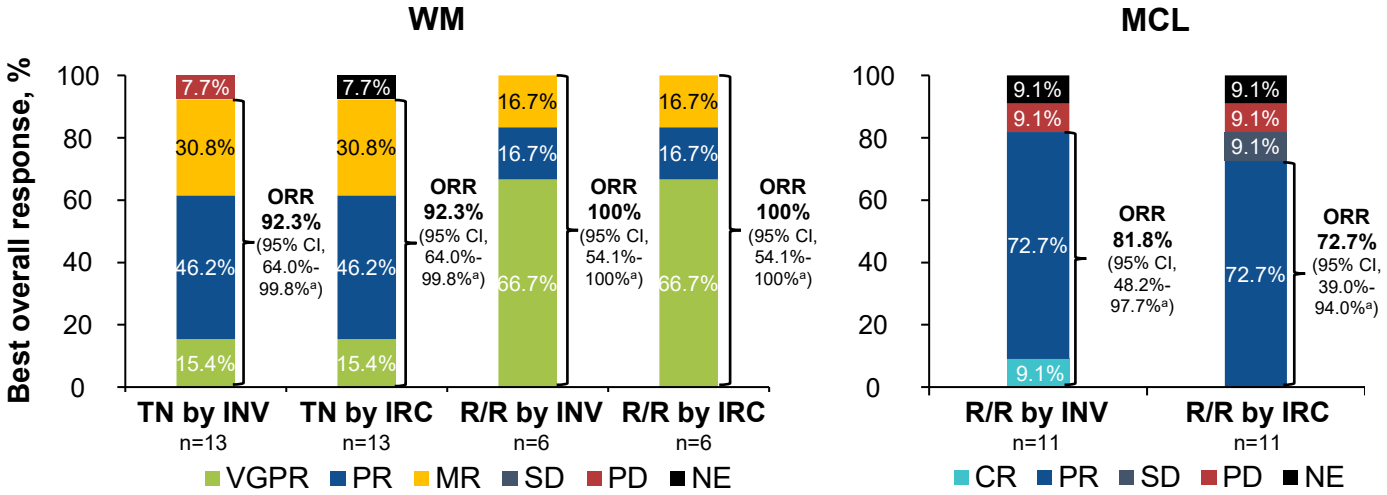


- The proportion of patients with CLL/SLL who had a consistent assessment of overall response by IRC and INV was >90%

CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; INV, investigator; IRC, independent review committee; ORR, overall response rate; PR, partial response; PR-L, partial response with lymphocytosis; R/R, relapsed or refractory; SD, stable disease; TN, treatment naive.

[a] Estimated using the Clopper-Pearson method.

Patients with WM had an ORR of >90%

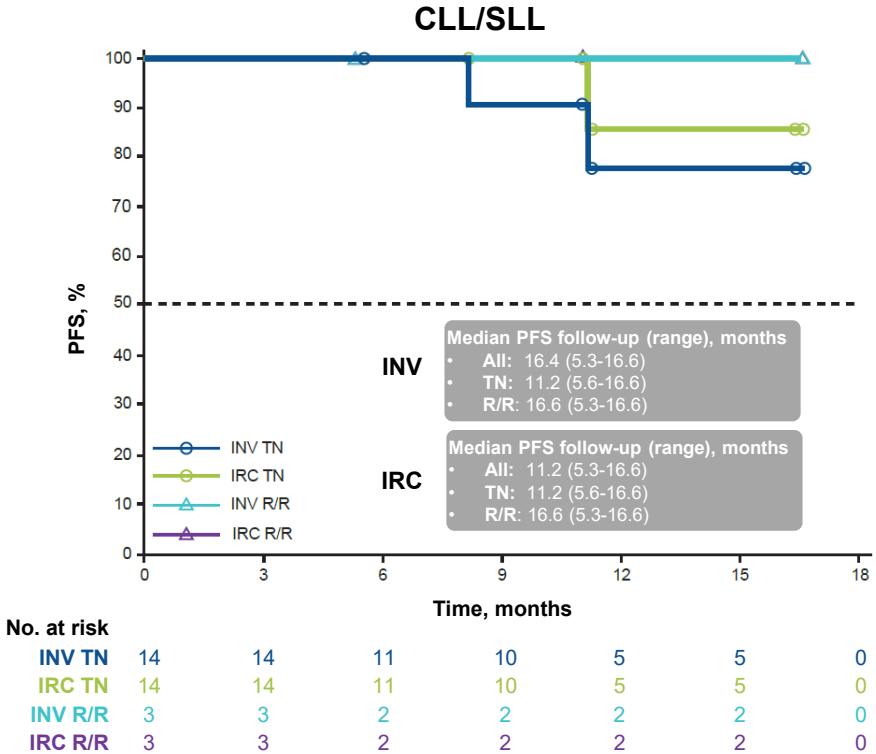


- The proportion of patients with WM and R/R MCL who had a consistent assessment of overall response by IRC and INV was >90%

CR, complete response; INV, investigator; IRC, independent review committee; MCL, mantle cell lymphoma; MR, minor response; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; R/R, relapsed or refractory; SD, stable disease; TN, treatment naive; VGPR, very good partial response; WM, Waldenström macroglobulinemia.

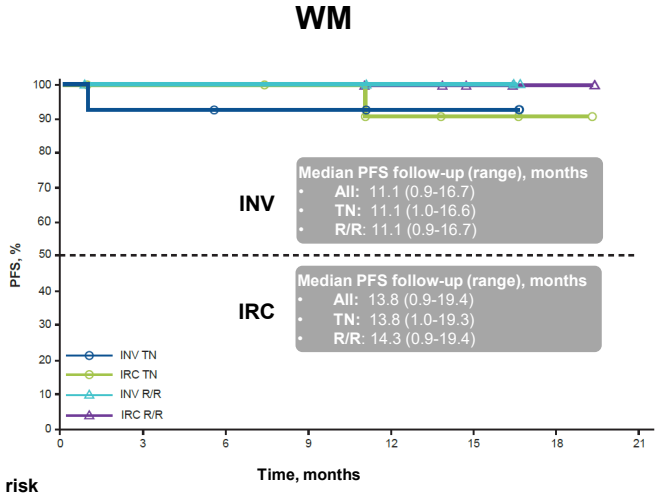
[a] Estimated using the Clopper-Pearson method.

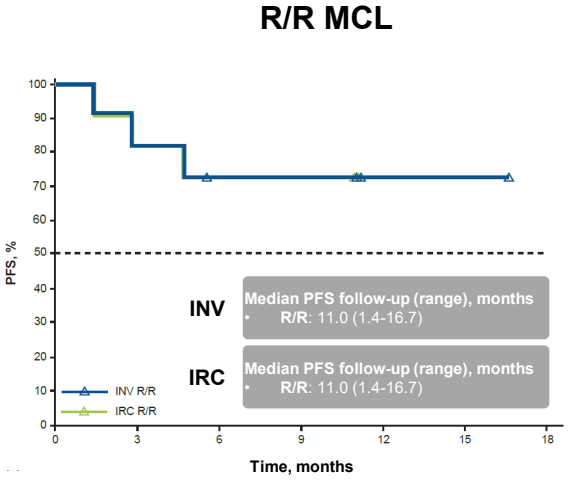
50% PFS was not reached in the CLL/SLL group



CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; INV, investigator; IRC, independent review committee; PFS, progression-free survival; R/R, relapsed or refractory; TN, treatment naive.

50% PFS was not reached in the WM or MCL groups





No. at risk

INV TN	13	12	11	11	4	4	0	0
IRC TN	13	12	12	11	7	4	1	0
INV R/R	6	5	5	5	2	2	0	0
IRC R/R	6	5	5	5	4	2	1	0

INV R/R	11	9	5	5	2	2	0	
IRC R/R	11	9	5	5	2	2	0	

MCL, mantle cell lymphoma; INV, investigator; IRC, independent review committee; PFS, progression-free survival; R/R, relapsed or refractory; TN, treatment naive; WM, Waldenström macroglobulinemia.

Safety results were similar to previously published data[1-4]

Most Common TEAEs (Incidence ≥10% of Total Patients)[a]

n (%)	CLL/SLL (n=19)		WM (n=21)		R/R MCL (n=12)		Total (N=55)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
≥1 TEAE	18 (94.7)	8 (42.1)	20 (95.2)	8 (38.1)	12 (100)	8 (66.7)	53 (96.4)	26 (47.3)
Platelet count decreased	3 (15.8)	3 (15.8)	4 (19.0)	2 (9.5)	2 (16.7)	0	10 (18.2)	5 (9.1)
Pyrexia	3 (15.8)	0	3 (14.3)	0	3 (25.0)	0	10 (18.2)	0
COVID-19	5 (26.3)	0	2 (9.5)	0	1 (8.3)	1 (8.3)	8 (14.5)	1 (1.8)
Neutrophil count decreased	3 (15.8)	3 (15.8)	3 (14.3)	3 (14.3)	1 (8.3)	0	7 (12.7)	6 (10.9)
Anemia	4 (21.1)	0	2 (9.5)	1 (4.8)	0	0	6 (10.9)	1 (1.8)
Arthralgia	0	0	5 (23.8)	0	1 (8.3)	0	6 (10.9)	0
Back pain	1 (5.3)	0	2 (9.5)	0	3 (25.0)	0	6 (10.9)	0
Constipation	4 (21.1)	0	1 (4.8)	0	0	0	6 (10.9)	0
Nasopharyngitis	2 (10.5)	0	4 (19.0)	0	0	0	6 (10.9)	0
Purpura	2 (10.5)	0	4 (19.0)	0	0	0	6 (10.9)	0

[a] Median study follow-up time of 26.7 months (Data cutoff date: 10 May 2023)

CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; MCL, mantle cell lymphoma; R/R, relapsed or refractory; TEAE, treatment-emergent adverse event; WM, Waldenström macroglobulinemia.

1. Tam CS, et al. *Lancet Oncol*. 2022;23(8):1031-1043; 2. Brown JR. *N Engl J Med*. 2023;388(4):319-332; 3. Tam CS, et al. *Blood*. 2020;136(18):2038-2050; 4. Dimopoulos MA, et al. *J Clin Oncol*. 2023;JCO2202830.

Rates of atrial fibrillation/flutter were low and similar to results from global studies[1-4]

TEAEs of Special Interest[a]

n (%)	CLL/SLL (n=19)	WM (n=21)	R/R MCL (n=12)	Total (N=55)
Any TEAE of special interest	16 (84.2)	17 (81.0)	10 (83.3)	44 (80.0)
Infections	13 (68.4)	11 (52.4)	5 (41.7)	30 (54.5)
Hemorrhage	8 (42.1)	11 (52.4)	5 (41.7)	25 (45.5)
Thrombocytopenia	3 (15.8)	4 (19.0)	3 (25.0)	11 (20.0)
Neutropenia	4 (21.1)	4 (19.0)	2 (16.7)	10 (18.2)
Anemia	4 (21.1)	2 (9.5)	0	6 (10.9)
Second primary malignancies	3 (15.8)	1 (4.8)	1 (8.3)	6 (10.9)
Hypertension	0	3 (14.3)	2 (16.7)	5 (9.1)
Atrial fibrillation and flutter	1 (5.3)	1 (4.8)	0	2 (3.6)

- TLS was not reported in any patients

[a] Median study follow-up time of 26.7 months (Data cutoff date: 10 May 2023)

CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; MCL, mantle cell lymphoma; R/R, relapsed or refractory; TEAE, treatment-emergent adverse event; TLS, tumor lysis syndrome; WM, Waldenström macroglobulinemia.

1. Tam CS, et al. *Lancet Oncol*. 2022;23(8):1031-1043; 2. Brown JR. *N Engl J Med*. 2023;388(4):319-332; 3. Tam CS, et al. *Blood*. 2020;136(18):2038-2050; 4. Dimopoulos MA, et al. *J Clin Oncol*. 2023;JCO2202830.

Conclusions

- Zanubrutinib had high ORRs by IRC in Japanese patients in the ongoing BGB-3111-111 study
- The concordance rate between IRC-assessed and INV-assessed ORR was high
- Further follow-up (DCO 10 May 2023, N=55) did not show any new safety signals, and results were comparable to those from global studies
- High concordance rates between IRC and INV support the reliability of efficacy results of the BGB-3111-111 study and further supports zanubrutinib as an efficacious and safe BTKi for Japanese patients with CLL/SLL, WM, or R/R MCL

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