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Clinical Trial Results

Docetaxel, Oxaliplatin, and 5-Fluorouracil (DOF) in Metastatic and Unresectable Gastric/Gastroesophageal Junction Adenocarcinoma: A Phase II Study with Long-Term Follow-Up

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Trial Information

- **ClinicalTrials.gov Identifier:** NCT00711243
- **Sponsor**: Sanofi-Aventis
- **Principal Investigator**: Mary F. Mulcahy
- **IRB Approved**: Yes

Lessons Learned

- Adding docetaxel to the modified FOLFOX7 backbone (DOF) is a feasible three-drug combination therapy for advanced gastric cancer with high activity, providing evidence that leucovorin is not necessary in this setting.
- The DOF regimen represents an alternative to the FLOT (5-FU 2,600 mg/m^2 as 24-hour infusion with leucovorin 200 mg/m^2, oxaliplatin 85 mg/m^2, and docetaxel 50 mg/m^2) regimen that can be considered in select patients with advanced gastric cancer and is a potential choice in the curative setting.

Abstract

Background. The combination of docetaxel, cisplatin, and 5-fluorouracil (5-FU) demonstrates high response rates in advanced gastric cancer, albeit with increased toxicity. Given the efficacy of platinum-taxane-fluoropyrimidine regimens, this phase II study evaluated the efficacy and toxicity of docetaxel, oxaliplatin, and 5-FU (DOF) for the treatment of metastatic or unresectable gastric or gastroesophageal junction (GEJ) adenocarcinoma.

Methods. Patients with metastatic or unresectable gastric or GEJ adenocarcinoma with no prior therapy for metastatic disease received docetaxel 50 mg/m^2 on day 1, oxaliplatin 85 mg/m^2 on day 1, and 5-FU 2,400 mg/m^2 continuous intravenous infusion over 46 hours; cycles were repeated every 2 weeks. The primary endpoint was overall response rate (ORR).

Results. Forty-four patients were enrolled. Assessment of treatment response and toxicity was feasible in 41 and 43 patients, respectively. ORR was 73.2% (68.3% partial response; 4.9% complete response). Therapy was discontinued for progressive disease in 53%, toxicity in 26%, and death on treatment in 16%. Two patients underwent surgical resection. Thirty-three patients (76.7%) received at least seven cycles (7–34). Grade 3–4 toxicities occurred in 31 patients (72.1%), including neutropenia (23.3%), neurologic (20.9%), and diarrhea (14.0%). Median overall survival was 10.3 months.

Conclusion. DOF demonstrates a high response rate, expected safety profile, and prolonged survival and remains an option for select patients with unresectable or metastatic gastric or GEJ adenocarcinoma. ***The Oncologist*** 2019;24:1039–e642

Discussion

Docetaxel, cisplatin, and 5-FU (DCF) demonstrated improved ORR and overall survival (OS) in advanced gastric cancer compared with cisplatin and 5-FU alone, which led to its U.S. Food and Drug Administration approval in 2006. This regimen was associated with significant toxicity, with few patients able to tolerate this regimen for more than four cycles. Oxaliplatin is a

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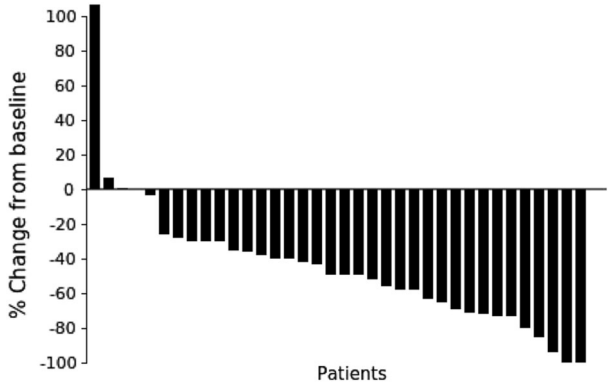


Figure 1. Waterfall plot showing best overall response (percentage change in tumor burden in patients with available measurements by RECIST criteria).

less toxic alternative to cisplatin in this setting. In 2008 when this trial began, 5-FU, oxaliplatin, and docetaxel had not been evaluated as a therapeutic regimen for this disease. In light of the superiority of DCF for response and survival, but its poor tolerance, it was postulated that an oxaliplatin-based regimen would be more tolerable. Based on a phase I lead-in, docetaxel 50 mg/m^2 was added to the modified FOLFOX7 backbone, and leucovorin was omitted (DOF).

This single-arm phase II study of DOF demonstrated an ORR of 73.2%, with 28 partial responses, two complete responses, and a median OS of 10.3 months. The median number of cycles was 11 (2–34), with 33 patients (76.7%) receiving 7 or more cycles. Despite 11 patients (25.6%) coming off treatment because of adverse events, the median number of cycles among these patients was eight (range, 5–18), with cumulative sensory neuropathy as the most common toxicity leading to discontinuation. These results compare favorably with other modified triplet regimens that have been subsequently published, such as modified DCF, docetaxel with 5-FU and carboplatin, epirubicin with oxaliplatin and 5-FU, and TEF (docetaxel, oxaliplatin, and 5-FU; Fig. 1).

The FLOT regimen (5-FU 2,600 mg/m^2 as 24-hour infusion with leucovorin 200 mg/m^2, oxaliplatin 85 mg/m^2, and docetaxel 50 mg/m^2) given biweekly has generated renewed enthusiasm in the curative setting for locally advanced gastric cancer. In the metastatic setting, FLOT demonstrated an ORR of 57.7% with a median OS of 11.1 months. A subsequent randomized trial of FLOT versus ECF or ECX (epirubicin, cisplatin, and 5-FU or capecitabine) in the perioperative setting demonstrated improved progression-free survival (30 versus 18 months; hazard ratio [HR], 0.75; p = .004) and OS (50 versus 35 months; HR 0.77; p = .012). In comparison with FLOT, DOF demonstrates similar rates of neutropenia and leukopenia, with lower rates of grade 3–4 infections but higher rates of grade 3–4 neuropathy.

These results show that adding docetaxel to the modified FOLFOX7 backbone permits delivery for a prolonged treatment duration and maintains high activity suggested by the high ORR, and they provide evidence that leucovorin is not necessary in this setting. Our long-term follow-up and mature survival suggests that DOF represents an alternative to FLOT in select patients with advanced gastric cancer and is a potential choice in the curative setting.

Trial Information	
Disease	Gastric cancer
Stage of Disease/Treatment	Metastatic/advanced
Prior Therapy	None
Type of Study – 1	Phase II
Type of Study – 2	Single arm
Primary Endpoint	Overall response rate
Secondary Endpoint	Toxicity
Additional Details of Endpoints or Study Design	
A Simon's optimal two-stage phase II trial design was used. A response rate of 20% or less was considered of insufficient activity to warrant further study. A response rate of 40% or greater will be worthy of further study. First, 13 subjects were to be enrolled, and if three or fewer responses were observed, then the study was to be stopped and the treatment would be declared of low interest. If at least four or more responses were observed, additional subjects were to be entered for a total of 43 treated. If 12 or fewer responses were observed, the treatment would be declared of insufficient activity. If 13 or more responses were observed, the treatment would be considered to have sufficient activity to proceed to further study. Overall survival is also reported.	
Investigator's Analysis	Active and should be pursued further

Drug Information	
Drug 1	
Generic/Working Name	Docetaxel
Trade Name	Taxotere
Drug Class	Microtubule-targeting agent
Dose	50 milligrams (mg) per squared meter (m^2)
Route	IV
Schedule of Administration	Patients received docetaxel 50 mg/m^2 on day 1 of a 14-day cycle, repeated every 2 weeks.

Drug 2	
Generic/Working Name	Oxaliplatin
Trade Name	Eloxatin
Drug Class	Platinum compound
Dose	85 milligrams (mg) per squared meter (m^2)
Route	IV
Schedule of Administration	Patients received oxaliplatin 85 mg/m^2 on day 1 of a 14-day cycle, repeated every 2 weeks.
Drug 3	
Generic/Working Name	5-Fluorouracil
Trade Name	Adrucil
Drug Class	Antimetabolite
Dose	2,400 milligrams (mg) per squared meter (m^2)
Route	Continuous intravenous infusion
Schedule of Administration	Patients received 5-fluorouracil 2,400 mg/m^2 continuous infusion over 46 hours on day 1 of a 14-day cycle, repeated every 2 weeks.

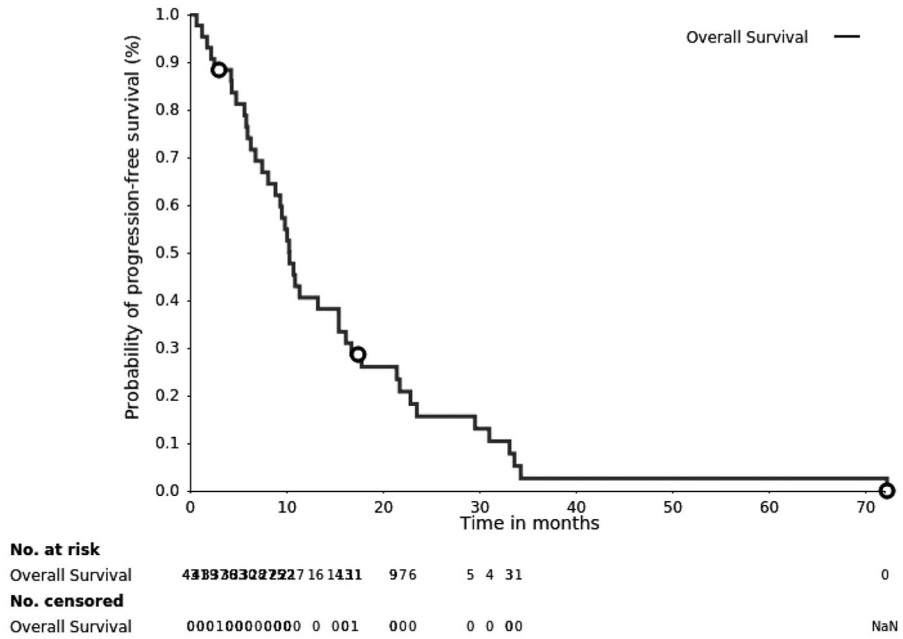
Patient Characteristics

Number of Patients, Male	30
Number of Patients, Female	14
Age	Median (range): 59 years (25–78 years)
Performance Status: ECOG	0 — 12 1 — 32 2 — 3 — Unknown —
Cancer Types or Histologic Subtypes	Gastric, 28 Gastroesophageal junction, 12 Esophageal, 3 Not recorded, 1

Primary Assessment Method

Title	Overall Response Rate
Number of Patients Enrolled	44
Number of Patients Evaluable for Toxicity	43
Number of Patients Evaluated for Efficacy	41
Evaluation Method	RECIST 1.0
Response Assessment CR	*n* = 2 (5%)
Response Assessment PR	*n* = 28 (68%)
Response Assessment SD	*n* = 9 (22%)
Response Assessment PD	*n* = 2 (2%)
(Median) Duration Assessments OS	10.3 months
Title	Overall Survival
Number of Patients Enrolled	44
Number of Patients Evaluated for Efficacy	43
(Median) Duration Assessments OS	10.3 months; confidence interval, 8.1–15.4

Kaplan-Meier Time Units, Months					
Time of scheduled assessment and/or time of event	No. progressed (or deaths)	No. censored	Percent at start of evaluation period	Kaplan-Meier %	No. at next evaluation/ No. at risk
0	0	0	100.00	100.00	43
0.6899	1	0	100.00	97.67	42
1.2485	1	0	97.67	95.35	41
1.7741	1	0	95.35	93.02	40
2.2012	1	0	93.02	90.70	39
2.5298	1	0	90.70	88.37	38
3.0226	0	1	88.37	88.37	37
4.2710	1	0	88.37	85.98	36
4.3368	1	0	85.98	83.60	35
4.7967	1	0	83.60	81.21	34
5.6509	1	0	81.21	78.82	33
5.8480	1	0	78.82	76.43	32
5.9795	1	0	76.43	74.04	31
6.3080	1	0	74.04	71.65	30
6.8008	1	0	71.65	69.26	29
7.4908	1	0	69.26	66.88	28
8.1150	1	0	66.88	64.49	27
8.8706	1	0	64.49	62.10	26
9.3634	1	0	62.10	59.71	25
9.5277	1	0	59.71	57.32	24
9.8563	1	0	57.32	54.93	23
10.0862	1	0	54.93	52.55	22
10.2834	1	0	52.55	50.16	21
10.3162	1	0	50.16	47.77	20
10.7433	1	0	47.77	45.38	19
10.9076	1	0	45.38	42.99	18
11.3676	1	0	42.99	40.60	17
13.2731	1	0	40.60	38.21	16
15.4415	2	0	38.21	33.44	14
16.1643	1	0	33.44	31.05	13
16.7556	1	0	31.05	28.66	12
17.4456	0	1	28.66	28.66	11
17.8070	1	0	28.66	26.06	10
21.4538	1	0	26.06	23.45	9
21.7495	1	0	23.45	20.84	8
22.8665	1	0	20.84	18.24	7
23.5236	1	0	18.24	15.63	6
29.5688	1	0	15.63	13.03	5
31.0472	1	0	13.03	10.42	4
33.1499	1	0	10.42	7.82	3
33.6427	1	0	7.82	5.21	2
34.2998	1	0	5.21	2.61	1
72.2793	1	0	2.61	0.00	0



Kaplan-Meier plot evaluating overall survival. Of note, two patients, for whom the date of death was not know, were censored for the last date known to be alive.

Adverse Events

Toxicity	Grade 1, (%)	Grade 2, (%)	Grade 3, (%)	Grade 4, (%)	Grade 5, (%)	Total, (%)
Fatigue	33	42	9	0		84
White blood cell decreased	16	35	16	5		72
Nausea	47	21	5	0		72
Peripheral sensory neuropathy	42	12	21	0		74
Anemia	40	23	5	2		70
Neutrophil count decreased	21	9	14	9		53
Diarrhea	26	12	14	0		51
Vomiting	37	7	7	0		51
Lymphocyte count decreased	7	14	14	0		35
Mucositis oral	16	7	9	0		33
Platelet count decreased	23	2	2	2		30
Anorexia	21	7	2	0		30
Constipation	19	5	0	0		23
AST	9	5	2	0		16
Weight loss	12	0	2	0		14
Alopecia	12	2	0	0		14
Skin	12	2	0	0		14
Taste alteration (dysgeusia)	9	5	0	0		14
Dyspnea (shortness of breath)	14	0	0	0		14
Dehydration	2	2	7	0		12
Pain	2	5	2	2		12
Hemorrhage, bleeding	9	2	0	0		12
Infection	0	2	5	2	2	12
Allergy	5	0	2	2		9
Fever	7	0	2	0		9
Rash	0	5	2	0		7
Hyperglycemia	5	0	2	0		7

Hypotension	0	2	2	0		5
Neuro-motor	0	5	0	0		5
Nail change	0	5	0	0		5
Edema	2	2	0	0		5
Abdominal distension	2	7	0	0		9
Thrombosis, thrombus, embolism	0	0	2	0		2
Muscle weakness	0	0	2	0		2
Flatus	2	0	0	0		2
Abd cramping	0	2	0	0		2
Hemorrhage, bleeding – GI bleed	0	0	0	0	2	2
Dysphagia	2	0	0	0		2
Alk phos	2	0	0	0		2
Hypoalb	2	0	0	0		2
Colitis	0	2	0	0		2
Foot syndrome	0	2	0	0		2
Hiccups	2	0	0	0		2
Headache	2	0	0	0		2
Ascites	0	2	0	0		2
Vision change	2	0	0	0		2
Back pain	2	0	0	0		2
Hyponatremia	2	0	0	0		2
Neuropsych	2	0	0	0		2
Urinary retention	2	0	0	0		2
Cardiac ischemia, infarction	0	0	0	0	2	2

Frequency of patients with adverse events by Common Terminology Criteria for Adverse Events, version 3.0.
Abbreviations: ANC, absolute neutrophil count; AST, aspartate aminotransferase; GI, gastrointestinal; NC/NA, no change from baseline/no adverse event.

Serious Adverse Events

Name	Grade	Attribution
Myocardial Infarction	5	Unlikely
Neutropenic sepsis	5	Definite
Gastrointestinal bleed	5	Unrelated
Gastrointestinal bleed	5	Unrelated
Disease progression	5	Unrelated
Disease progression	5	Unrelated
Disease progression	5	Unrelated

There were seven deaths on study. One patient died of a myocardial infarction after cycle 3, thought to be unrelated to treatment, and one patient died of neutropenic sepsis after cycle 2, which was thought to be treatment related. Three deaths were due to disease progression. Two patients died of hemorrhage because of disease.

Assessment, Analysis, and Discussion

Completion	Study completed
Investigator's Assessment	Active and should be pursued further

Gastric cancer remains a major cause of morbidity and mortality, with over 27,000 new cases and over 11,000 deaths expected in the U.S. in 2019 [1]. Patients with localized disease are treated with a combination of chemotherapy, radiation, and surgery [2], whereas patients with advanced disease are predominantly treated with chemotherapy [3] with the addition of trastuzumab in the setting of human epidermal growth factor-2 (HER2) overexpression [4]. Both two-drug and three-drug chemotherapy combinations have been investigated, with three-drug chemotherapy combinations predominantly limited by toxicity [2].

Chemotherapeutic agents with activity in gastric cancer include taxanes, platinums, and fluoropyrimidines. Docetaxel, cisplatin, and 5-fluorouracil (5-FU) (DCF) demonstrated improved

overall response rate (ORR) and overall survival (OS) compared with cisplatin and 5-FU [5], which led to U.S. Food and Drug Administration approval in 2006 [2]. This regimen was associated with significant toxicity with few patients able to tolerate for more than four cycles [5]. In 2008 when this trial began, 5-FU, oxaliplatin, and docetaxel had not been evaluated as a therapeutic regimen for this disease. Oxaliplatin is a less toxic alternative to cisplatin in this setting, with fewer cytopenias, less renal toxicity, decreased alopecia, and fewer thromboembolic events. In light of the DCF trial's superiority for response and survival but poor tolerance, it was postulated that an oxaliplatin-based regimen would be more tolerable.

The FOLFOX backbone, which includes a continuous intravenous (IV) infusion of 5-FU on days 1–2 with oxaliplatin on day 1 every 14 days, is commonly used in several gastrointestinal malignancies such as colorectal cancer [2, 6]. Although leucovorin is routinely added to this regimen to enhance the effect of 5-FU by inhibiting thymidylate synthase, leucovorin modulation of 5-FU activity was demonstrated in colon cancers; the use in gastric cancer has been by extrapolation. When this trial was designed, a modified FOLFOX backbone was administered with the addition of docetaxel. As this was the first clinical trial prospectively evaluating this novel triplet combination therapy, the phase II study was preceded by a phase I lead-in to determine the maximally tolerated dose of docetaxel in combination with the FOLFOX backbone, which was determined to be 50 mg/m^2 [7].

In this prospective, phase II, single-arm, multicenter study, we report long-term follow-up from the earliest trial to demonstrate efficacy and safety profile of DOF (docetaxel, oxaliplatin, and 5-FU) in gastric cancer. Overall, our study demonstrated an overall response rate of 73.2%, with 28 partial responses and 2 complete responses. Our cohort demonstrated a median OS of 10.3 months. This compares favorably with historical controls of triplet platinum-taxane-fluoropyrimidine regimens [5, 8–11].

The DCF regimen demonstrated an ORR of 37% with 69% of patients experiencing grade 3 or higher toxicity [5]. Despite a similar grade 3–4 toxicity rate in our trial compared with DCF, these were predominantly sensorineural and hematologic toxicities. Since the completion of this trial, other strategies to preserve efficacy while reducing toxicity of triplet regimens have been employed. These have included dose modification of DCF [10], replacement of cisplatin with carboplatin [11], and replacement of cisplatin with oxaliplatin [8]. Our response rate compares favorably with these modified triplet regimens that have been subsequently published. The modified DCF regimen reported an ORR of 49% [10]; docetaxel, 5-FU, and carboplatin reported an ORR of 66.7% [11]; and epirubicin, oxaliplatin, and 5-FU reported an ORR of 42.4% [12]. The TEF regimen (docetaxel, oxaliplatin, and 5-FU) reported an ORR of 46.6% [8].

In comparison, DOF offered a manageable toxicity profile that permitted treatment administration for an extended duration. The median number of cycles was 11 (range, 2–34), and 33 patients (76.7%) received 7 or more cycles. Although in our trial 11 patients (25.6%) came off treatment because of adverse events, the median number of cycles in these patients was 8 (range, 5–18), and the most common toxicity leading to discontinuation was cumulative sensory neuropathy.

Recently, the FLOT regimen (5-FU 2,600 mg/m^2 as a 24-hour infusion with leucovorin 200 mg/m^2, oxaliplatin 85 mg/m^2, and docetaxel 50 mg/m^2) given biweekly has generated renewed enthusiasm in the curative setting for locally advanced gastric and gastroesophageal junction (GEJ) cancer [13]. In a phase II trial evaluating this regimen in the metastatic setting in 54 patients, an ORR of 57.7% was noted with a median progression-free survival (PFS) of 5.2 months and OS of 11.1 months [14]. Most frequent grade 3–4 toxicities were neutropenia, leukopenia, diarrhea, and fatigue. A phase II randomized trial of FLOT versus ECF or ECX (epirubicin, cisplatin, and 5-FU or capecitabine) in the perioperative setting demonstrated improved R0 resection rates (84% vs. 77%; p = .011), downstaging (≤pT1 25% vs. 15%; p = .001), PFS (30 vs. 18 months with hazard ratio [HR] 0.75; p = .004), and OS (50 vs. 35 months with HR 0.77; p = .012) [13]. In comparison, our DOF regimen demonstrated similar rates of neutropenia and leukopenia, lower rates of grade 3–4 infections, and higher rates of grade 3–4 neuropathy. Overall, our regimen in which the 5-FU component is administered as 2,400 mg/m^2 over a 46-hour continuous IV infusion demonstrates a tolerable toxicity profile while maintaining high activity suggested by the high ORR in our population.

There are important limitations to this study. This is an older study that accrued between 2006 and 2008. Since that time, there has been a trend toward using two-drug rather than three-drug regimens for the treatment of advanced gastric cancer [2]. As this was a single-arm study, cross-trial comparisons should be taken with caution. We did not collect histologic and molecular data such as histopathologic subtype, HER2 expression, or molecular subtype. Despite these limitations, these data contribute important toxicity and efficacy data of the DOF regimen in the first line setting in advanced gastric cancer.

In conclusion, our study with long-term follow-up and mature survival contributes to the growing body of literature regarding the activity of docetaxel, oxaliplatin, and 5-FU in the treatment of gastric and GEJ adenocarcinoma. Our results suggest that leucovorin is not necessary in this setting and that DOF represents an alternative to FLOT in select patients with advanced gastric cancer and is a potential choice in the curative setting.

Acknowledgments

This clinical trial was supported by a grant from Sanofi-Aventis and was presented in part at the 2009 Gastrointestinal Cancers Symposium, San Francisco, CA (poster presentation).

Disclosures

Howard S. Hochster: Amgen, Bayer, Genentech (C/A); Theresa Ryan, **Veena Shankaran:** Proteus, Taiho (C/A), Bayer, AstraZeneca, Bristol-Myers Squibb, Merck, EMD Serono, Astellas (RF); **Devalingam Mahalingam:** Bristol-Meyers Squibb, Bayer, EMD Serono (C/A), Merck, Oncolytics (RF), Amgen, Bristol-Myers Squibb, Bayer, EMD Serono, Genentech, Eisai (H); Blake Jones Law Firm LLC (ET); **Al B. Benson III:** Bristol-Myers Squibb, Guardant Health, Eli Lilly & Company, Exelixis, Purdue Pharma, Inventive Health Inc., Axio, Genentech, Bayer, Merck, Rafael Pharmaceuticals, Astellas, Terumo, Taiho, Thera Bionic, LSK, Axio (C/A), Acerta, Celgene, Advanced Accelerator Applications, Novartis, Infinity Pharmaceuticals, Merck Sharp & Dohme, Taiho Pharmaceutical, Bristol-Myers Squibb, Medimmune/AstraZeneca, Xencor, PreECOG, Astellas, Amgen, ECOG-ACRIN (RF).

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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