

# Docetaxel, Cisplatin, and 5-Fluorouracil-Based Induction Chemotherapy in Patients with Locally Advanced Squamous Cell Carcinoma of the Head and Neck

*The Dana Farber Cancer Institute Experience*

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**BACKGROUND.** The authors conducted a series of four Phase I–II trials of high-dose and intermediate-dose docetaxel, cisplatin, and 5-fluorouracil (TPF)-based induction chemotherapy for patients with advanced squamous cell carcinoma of the head and neck (SCCHN). The chemotherapy regimens and response rates for each trial were published previously. In the current analysis, the authors report the data on long-term survival, patterns of failure, and morbidity among the patients who were treated at their institution.

**METHODS.** A total of 101 patients with previously untreated, locally advanced, curable SCCHN were entered onto the studies. Overall, 68 patients (67%) had N2–N3 disease, and 86 patients (85%) had Stage IV disease. Patients were treated with combinations of TPF with or without leucovorin. Cycles were repeated every 21–28 days for a total of 3 cycles followed by hyperfractionated radiotherapy.

**RESULTS.** After a median follow-up of 49 months, 65 patients (64%) remain alive with no evidence of disease (NED), and 3 patients remain alive with disease, for an overall survival rate of 67% (68 patients). Twenty-six patients had locoregional recurrences (LRR), and 5 patients had both LRR and distant metastasis (DM). Only five patients had DM as the sole site of failure. Four patients underwent salvage surgery at the primary site and remain alive with NED. Excluding 17 patients with nasopharyngeal carcinoma, of 84 patients, 55 patients remain alive with NED (65%). Notably, 43 of 84 patients (51%) had oropharyngeal primary tumors, and 30 of those patients remain alive with NED (70%). Significant morbidity was low, with two treatment-related deaths. All but two of the surviving patients are able to swallow and had their feeding tubes removed.

**CONCLUSIONS.** These data suggest that docetaxel adds incrementally to the efficacy of cisplatin and fluorouracil. Local-regional failures continue to be the major impediment to cure in these patients. Given the increase in local-regional dose intensity with chemoradiation, sequential treatment plans that integrate induction chemotherapy and chemoradiotherapy seem to be the logical next step. *Cancer* 2003;97:412–8. © 2003 American Cancer Society.

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**KEYWORDS:** head and neck carcinoma, induction chemotherapy, docetaxel, cisplatin, 5-fluorouracil, hyperfractionated radiotherapy.

**P**atients with locally advanced squamous cell carcinoma of the head and neck (SCCHN) usually are managed by surgery and radiation or by a combination of chemotherapy, radiotherapy, and

selected surgery.<sup>1</sup> Although patients with early-stage disease (Stage I and II) often are cured by radiotherapy or surgery alone, patients with more advanced disease (Stage III and IV, M0) frequently require a multimodality approach to obtain the best results. Despite advances in our understanding of the biology of this disease, improvements in surgical and radiation therapy techniques, and the additional impact of chemotherapy and combined-modality approaches, long-term survival in patients with locally advanced disease, measured as 2-year and 3-year overall survival (OS) and progression free survival, has remained < 50% in randomized trials.<sup>2-5</sup>

Combination chemotherapy with cisplatin and fluorouracil (PF) is the most commonly used induction regimen in the treatment of patients with locally advanced SCCHN. The original PF chemotherapy regimen results in major response rates of 60–90% and complete responses (CRs) in the range of 20–50%.<sup>3,4,6</sup> PF is an effective alternative to surgery in patients with carcinoma of the larynx and hypopharynx who are treated for organ preservation.<sup>2-5</sup> Induction chemotherapy with PF also has shown improved survival in patients with both unresectable and resectable disease when chemotherapy was followed by standard fractionated radiotherapy and when postradiation surgery for lymph node disease was included in the treatment.<sup>2,6</sup> It should be noted, however, that this is not a generally accepted approach and does not represent the standard of care. Unlike trials for patients with unresectable disease, randomized trials for organ preservation have recruited limited numbers of patients with advanced N2 and N3 lymph node disease.<sup>3,4</sup> Patients who present with advanced lymph node disease have fewer CRs to induction chemotherapy and chemoradiotherapy and are at high risk of developing distant metastasis (DM) if they survive their local-regional disease. Despite the high overall response rates with PF induction chemotherapy, the moderate CR rates at the primary site and the poor CR rate in patients with extensive lymph node disease are disappointing and are associated with low survival rates, particularly in trials that recruit patients with advanced stage disease.

These results have stimulated intensive investigations of new agents and combinations in an attempt to improve the complete clinical response rates and the primary site pathologic response rates achieved with induction chemotherapy. Docetaxel is an effective agent in the treatment of patients with SCCHN. It has produced response rates of 21–42% as a single agent in patients with locally advanced, recurrent, and/or metastatic disease.<sup>7-9</sup> The most significant toxicity is febrile neutropenia. Neuropathy, which is a major side

effect of cisplatin, is minimal with docetaxel. Differences in the mechanisms of action and the relatively nonoverlapping toxicities of taxanes (particularly docetaxel), compared with PF and PF-related combination therapy, have prompted investigators to examine the combination of these agents with PF-based regimens to increase the response rates and cure rates in patients with advanced SCCHN who are treated with curative intent.

We performed four consecutive trials between December, 1994 and December, 1998 to evaluate combinations of docetaxel (T) and PF (TPF) in the treatment of patients with locally advanced SCCHN. TPF with leucovorin (TPFL) or without leucovorin was given as induction chemotherapy in a standardized format followed, in all trials, by hyperfractionated radiation therapy. The preliminary results and early survival data have been published.<sup>10-13</sup> In the current analysis, we collected and reviewed the data on long-term survival, patterns of failure, and morbidity of the patients who were treated at the Dana Farber Cancer Institute (DFCI) on all four trials. The trials were entitled TPFL-5, TPFL-4, OP-TPFL, and TPF. TPF was a multi-institutional study in which the DFCI participated. Fourteen DFCI patients from that trial were included in this summary. The other three trials were conducted in the DFCI, and all patients are presented.

## MATERIALS AND METHODS

Patients with locally advanced, nonmetastatic SCCHN were enrolled in institutional review board (IRB)-approved Phase I–II studies of induction chemotherapy followed by definitive radiation therapy. All patients signed IRB-approved consents prior to enrollment. The entry criteria are described in the initial reports of the trials. In brief, patients with American Joint Committee on Cancer (AJCC) Stage III or IV SCCHN, with the exception of patients who had T1N1 disease or exophytic T3N0 lesions, were eligible. The TPF study also excluded patients who had tumors of the nasopharynx, nasal cavity, paranasal sinuses, and unknown primaries. Patients who had received previous chemotherapy were excluded, and patients who had undergone definitive surgery or who had received any prior radiotherapy for SCCHN were excluded. Patients were treated with three cycles of induction chemotherapy with TPF with or without leucovorin followed by hyperfractionated radiotherapy (Table 1).

For the four studies, standard toxicity assessment and dose modifications were applied, as detailed in corresponding publications.<sup>10-13</sup> Response assessment was performed after induction chemotherapy, preferably in association with an examination under anesthesia (EUA) and biopsy, and was repeated 4–6

**TABLE 1**  
Summary of the TPFL-5, TPFL-4, OP-TPFL, and TPF Study Parameters

Variable	Regimen			
	TPFL-5	TPFL-4	OP-TPFL	TPF
Study phase	Phase I-II	Phase II	Phase I-II	Phase II
Docetaxel (mg/m <sup>2</sup> )	25-60 (d1)	60 (d1)	60-90 (d1)	75 (d1)
Cisplatin (mg/m <sup>2</sup> /day)	25 IVCI (d1-d5)	31.25 IVCI (d1-d4)	100 bolus (d1)	75-100 IVCI (d1)
5-FU (mg/m <sup>2</sup> IVCI)	700 (d2-d5)	700 (d1-d4)	700 (d1-d4)	1000 (d1-d4)
Leucovorin (mg/m <sup>2</sup> IVCI)	500 (d1-d5)	500 (d1-d4)	500 (d1-d4)	None
G-CSF	Yes	Yes	Yes	No
Antibiotics	Yes	Yes	Yes	Yes
Postinduction radiotherapy	BID	BID	BID	BID

TPF: docetaxel, cisplatin, and 5-fluorouracil; TPFL: TPF plus leucovorin; OP-TPFL: outpatient TPFL regimen; d: day; IVCI: intravenous, continuous infusion; G-CSF: granulocyte-colony stimulating factor; BID: twice daily.

weeks after radiation therapy. Response assessment for the TPFL5, TPFL4, and OP-TPFL trials included a clinical response assessment. Response assessment for TPF was based on clinical and radiologic assessments. All patients had gastrostomy tubes placed prior to starting radiation therapy. Patients with N3 neck disease underwent planned neck dissections regardless of the response in the neck. Patients with N1-N2 lymph node disease underwent neck dissection after radiation therapy only if evidence remained of persistent disease on physical examination and/or imaging studies after the induction chemotherapy phase. TPFL-5 and TPFL-4 were administered in the hospital, whereas OP-TPFL and TPF were given as outpatient regimens. The chemotherapy regimens, ancillary medications, and response monitoring for each trial have been described previously<sup>10-13</sup> and are summarized in Table 1.

Definitive radiation therapy, which was administered 5 days per week in 2 fractions of 1.2 grays (Gy) separated by 6 hours, was delivered to the primary tumor site and neck. The total dose to the primary tumor site was between 72 Gy and 74 Gy. Neck lymph nodes received between 66 Gy and 70 Gy.

## RESULTS

Between December 1994 and December 1998, a total of 101 patients were enrolled in the 4 studies. Primary sites for all four studies were as follows: the larynx in 17 patients (17%), the hypopharynx in 4 patients (4%), the oropharynx in 43 patients (43%), the oral cavity in 12 patients (12%), the nasopharynx in 17 patients (17%), the maxillary sinus in 2 patients (2%), and unknown primary tumors in 6 patients (6%) (Table 2). The tumor-lymph node staging of all patients is listed in Table 3. There were 86 patients (85%) with Stage IV disease and 15 patients (15%) with Stage III disease.

**TABLE 2**  
Primary Tumor Site

Site	Regimen				Total
	TPFL-5	TPFL-4	OP-TPFL	TPF	
Number	23	30	34	14	101
Larynx	2	7	5	3	17
Hypopharynx	2	1	—	1	4
Oropharynx	12	9	15	7	43
Oral cavity	2	2	5	3	12
Nasopharynx	4	7	6	—	17
Max. sinus	—	2	—	—	2
Unknown	1	2	3	—	6

TPF: docetaxel, cisplatin, and 5-fluorouracil; TPFL: TPF plus leucovorin; OP-TPFL: outpatient TPFL regimen; Max. sinus: maxillary sinus.

**TABLE 3**  
Primary Tumor and Lymph Node Staging

Lymph node status	Primary tumor status				
	TX	T1	T2	T3	T4
N0	0	0	0	12	10
N1	0	0	0	3	8
N2	1	5	9	14	16
N3	5	2	6	3	7

N2 and N3 lymph node disease was present in 68 patients (67%). Forty-one patients (40%) had T4 primary tumors, and 32 patients (31%) had T3 primary tumors. None of the patients were lost to follow-up. Survival data and toxicity data were collected as of November, 2001. The median follow-up was 49 months. Response data for the individual studies have been reported previously. Individual study data for

survival, patterns of failure, and morbidity are described below.

#### TPFL-5

Twenty-three patients were enrolled in the TPFL-5 trial. After a median follow-up of 68 months (range, 60–84 months), 16 patients (70%) remained alive with no evidence of disease (NED). Two patients are alive with disease (both with nasopharyngeal carcinoma [NPC]) for an OS rate of 78% (18 of 23 patients). Five patients had local-regional recurrences (LRRs), and one patient had both LRR and DM. The disease free survival (DFS) was 73% (16 of 22 patients), with 1 patient who died from an unknown cause. Nine patients underwent surgery on the neck, with eight planned surgeries and one surgery that was performed for salvage and was not successful. None of the patients underwent salvage surgery at the primary site. None of the patients had DM as the sole site of recurrence. One patient had a second primary tumor (floor of mouth). All patients who remained alive at the time of this writing had their gastrostomy tubes removed.

#### TPFL-4

Thirty patients were enrolled in the TPFL-4 trial. After a median follow-up of 51 months (range, 46–58 months), 17 patients (57%) remained alive with NED, and 1 patient remained alive with disease (NPC), for an OS rate of 60% (18 of 30 patients). Ten patients developed LRR, and 3 patients developed LRR and DM. Three patients developed DM as the sole site of recurrence (two in the lungs and one in the liver/bone). One patient had a second primary tumor (prostate carcinoma) and remained alive with NED. Three patients underwent salvage surgeries on the primary tumor and remained alive with NED at the time of this writing. Eight patients underwent neck dissections: three were planned and five were for salvage; of those five patients, one remained alive with NED at the time of this writing. All patients who remained alive at the time of this writing had their gastrostomy tubes removed. One patient died during induction from sepsis. The DFS rate for the whole group was 43% (13 of 30 patients).

#### OP-TPFL

Thirty-four patients were enrolled in the OP-TPFL trial. After a median follow-up of 38 months (range, 31–48 months), 21 patients (62%) remained alive, all with NED (OS), at the time of this writing. Twenty patients have been disease free continuously, and 2 patients died of intercurrent illnesses, for a DFS rate of 63% (20 of 32 patients). One patient underwent primary salvage surgery and remained alive with NED.

Ten patients developed LRR, and one patient developed both LRR and DM. Two patients had DM as the sole site of recurrence (one patient developed DM to bone, and one patient developed DM to the brain). No second primary tumors were identified. Thirteen patients underwent planned neck dissections. All but one of the patients who remained alive at the time of this writing had their gastrostomy tubes removed.

#### TPF

Fourteen patients from the multiinstitutional TPF trial were enrolled at the DFCI. After a median follow-up of 40 months (range, 36–45 months), 11 patients (78%) remained alive with NED (OS). One patient developed an LRR, and three patients developed second primary tumors (one patient with colon carcinoma, one patient with carcinoma of the tongue, and one patient with lung carcinoma). Four patients underwent planned neck dissections. One patient died during laryngectomy for radiation-induced laryngeal disease at 23 months with NED. One patient remained dependant on a feeding tube. Eleven patients (78%) remained alive at 3 years, and 11 of 13 patients remained continuously disease free for > 3 years, for a DFS rate of 85%: One patient died from complications of therapy (included), and 1 patient died from a second carcinoma of the lung (censored).

#### OS and Pattern of Failure for Docetaxel Regimens

A total of 101 patients were enrolled in the 4 trials (Table 4). The median follow-up was 49 months (range, 31–84 months). A total of 65 patients (64%) remained alive with NED at the time of this writing, and 3 patients remained alive with disease (all NPC). OS is shown in Figure 1 in a Kaplan–Meier plot. Twenty-six patients developed LRR, and 5 patients developed both LRR and DM. Five patients (5%) developed DM as the sole site of recurrence. Thirty-four patients underwent neck dissection (27 planned and 7 as salvage). Two of the seven patients who underwent salvage surgery remained alive with NED at the time of this writing, and four of seven patients underwent salvage surgery at the primary site.

Excluding 17 patients with NPC, a tumor type that differs in its biology compared with the more common forms of SCCHN, there was a total of 84 patients. Of these 84 patients, 55 patients remained alive with NED (65%) at the time of this writing. Notably, 43 of 84 patients (51%) had oropharyngeal primary tumors, and 30 of those patients remained alive with NED (70%).

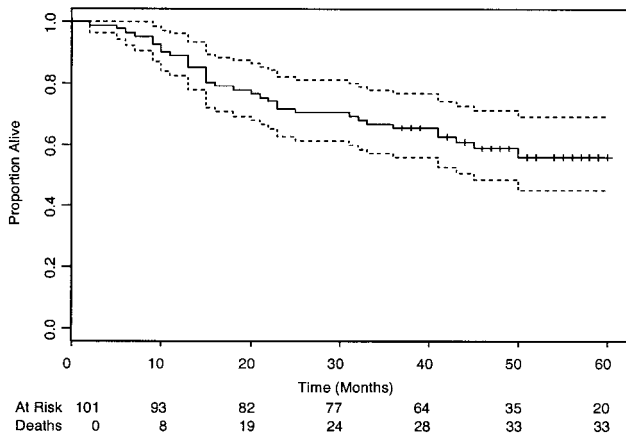
There were a total of 7 recurrences among the 101 patients at > 2 years: 1 patient with NPC and 6 patients with non-NPC (three of those were at > 3 years).

**TABLE 4**  
Summary of Data on the Four Studies

Variable	Regimen				Total
	TPF	OP-TPFL	TPFL-4	TPFL-5	
No.	14	34	30	23	101
Follow-up (months)					
Median	40	38	51	68	49
Range	36–45	31–48	46–58	60–84	31–84
LRR	1	10	10	5	26
DM	0	2	3	0	5
LR failure and DM	0	1	3	1	5
Total DM	0	3	6	1	10
Neck dissection					
Planned	4	13	3	7	27
Salvage	0	0	5 (1 NED)	2 (1 NED)	7 (2 NED)
Salvage primary/NED <sup>a</sup>	0	1	3	0	4
Second primary	3 (1 SCCHN)	0	1 (prostate)	1 (SCCHN)	5
Treatment deaths	1 (late)	0	1	0	2
Alive NED (%)	11 (78)	21 (61)	17 (56)	16 (70)	65 (64)
Alive with disease	0	0	1	2	3
Total alive (%)	11 (78)	21 (61)	18 (60)	18 (78)	68 (67)

TPF: docetaxel, cisplatin, and 5-fluorouracil; TPFL: TPF plus leucovorin; LRR: local-regional recurrence; LR: local-regional; DM: distant metastases; NED: no evidence of disease; SCCHN: squamous cell carcinoma of the head and neck;

<sup>a</sup>Patients who were salvaged at the primary site with surgery, currently with NED.



**FIGURE 1.** Kaplan–Meier overall survival curve for the entire study population.

All the non-NPC late recurrences were local-regional in nature (Table 5).

**NPC Data**

There were 17 patients with NPC: Ten patients (58%) were alive with NED at the time of this writing. Two patients died of LRR (12%), and five patients developed DM (29%), two of whom remained alive at the time of this writing. NPC may occur late, although only one patient had a late recurrence in our series: That patient developed a lung metastasis after being

**TABLE 5**  
Late Recurrences

Tumor type	Recurrences > 2 yrs		
	Local-regional	DM	Total
NPC	0	1	1
Non-NPC	6	0	6
Total	6	1	7

NPC: nasopharyngeal carcinoma; DM: distant metastases.

alive with NED for 43 months. All other local recurrences and DM appeared at < 12 months. Notably, instances of DM were rare among the patients with non-NPC (5 of 84 patients; 6%).

**Second Primary Tumors**

There were five second primary tumors (5%): two SCCHNs, one patient developed Duke Stage A colon carcinoma, one patient had prostate carcinoma, and one patient had lung carcinoma. Both second primary tumors in the head and neck area occurred > 3 years after the original tumor and at a site > 3 cm from the original primary site. One second primary tumor was associated with dysplastic changes, and both patients underwent successful surgery. Both patients were free of active disease at the time of this writing.

## DISCUSSION

In the current study, we have reported on the combined long-term follow-up of four studies in which a taxane, docetaxel, was added to an induction regimen of PF or PFL. The response rates to each induction chemotherapy regimen (i.e., prior to starting radiation therapy) were described previously and were > 90% in all 4 trials.<sup>10-13</sup> All patients had locally advanced, potentially curable SCCHN. The data shown in this summary indicate an excellent long-term survival rate in these patients. Indeed, survival with no active disease for the entire 101 patients and for the 84 patients with non-NPC was 64% and 65%, respectively. This was achieved after a median follow-up > 4 years (49 months). The greatest risk of recurrence was local regional, in that 31 patients (30%) had local-regional recurrences: Five of those patients had DM at the same time. Five patients (5%) had DM as the sole site of failure. Late failures, at > 3 years, have been rare, representing 3% of patients (3 of 101 patients) and 8% of failures (3 of 36 failures). The rate of second primaries in the head and neck area was relatively low at 2% (2 patients).

Significant morbidity in our trials was low, with one patient dying from sepsis and another patient dying during laryngectomy for delayed radionecrosis. All but two of the surviving patients were able to swallow again and had their feeding tubes removed.

The use of chemotherapy in patients with SCCHN continues to stir much controversy whether it is used in an induction fashion or concomitant with radiation therapy. A concise review of the role of chemotherapy in these tumors is warranted here.

Induction chemotherapy has been investigated extensively in patients with carcinoma of the head and neck.<sup>2-4,6</sup> Induction chemotherapy allows the delivery of high doses of chemotherapy with full systemic exposure; toxicity usually is transient, and an intermediate assessment of response is possible. When the treating physicians have an intermediate assessment of response, the selection of further combination chemoradiotherapy and surgery can be moderated based on the expected prognosis and toxicity. Subsequent chemoradiotherapy and limited surgery may be selected to increase the level of functional organ preservation in appropriate prognostic groups.

The two most cited trials of induction chemotherapy for organ preservation are the Veterans Administration laryngeal carcinoma study and a study by the European Organization for Research and Treatment of Cancer. Both were Phase III, randomized trials. Those two studies showed clearly that induction chemotherapy yielded survival rates comparable to the rates

achieved with up-front surgery and allowed for organ preservation in substantial numbers of patients with resectable disease who were randomized to the chemotherapy arm. In another study published by Domenge et al.<sup>2</sup> for the French Groupe d'Etude des Tumeurs de la Tete et du Cou, patients who were randomized to induction chemotherapy followed by locoregional treatment had a significantly better median OS compared with patients who were treated with the same locoregional treatment without induction therapy (5.1 years vs. 3.3 years). The Studio trial<sup>6</sup> explored the use of induction chemotherapy in a broader population of patients and stratified them into resectable and unresectable groups. In that trial, patients in the unresectable group who received chemotherapy had almost two-fold better OS and DFS rates. Patients in the resectable group underwent surgery prior to radiation therapy, which may have reduced the impact of induction chemotherapy for the group.

Chemoradiotherapy is another widely used approach for treating patients with locally advanced head and neck carcinoma. In a recently reported, Phase III larynx-preservation trial (R91-11) that compared radiation therapy versus chemoradiation therapy versus induction chemotherapy, there was no difference in OS between the three groups.<sup>14</sup> The rate of larynx preservation was best in the concomitant arm.

The trial published by Calais et al. in 1999 reported a 3-year OS rate in patients with oropharynx carcinoma who received concomitant chemoradiation of 51%.<sup>5</sup> This was reduced further to 30% after 5 years.<sup>15</sup> That trial showed a clear advantage of concomitant chemoradiation compared with radiation alone and has been adopted widely in the treatment of these patients. Many consider that it represents a standard of care.

In all of our reported trials, we used a twice-daily, fractionated radiotherapy plan. Although the optimal fractionation schedule for curative radiotherapy continues to be controversial, in a recently reported Phase III trial, hyperfractionation, like what was used in the current trials, and accelerated fractionation with concomitant boost were more efficacious compared with standard fractionation.<sup>16</sup> It is noteworthy that acute side effects were increased with these regimens. The best way to combine these modalities with chemotherapy is an area of active research, and it is important to emphasize that long-term toxicity is a major concern.

Given the increase in local-regional dose intensity with concomitant chemoradiation therapy and the difficulty of administering postradiotherapy adjuvant chemotherapy, sequential treatment plans that inte-

grate induction chemotherapy and chemoradiotherapy may seem a logical and reasonable evolution in therapy for patients with locally advanced disease. Induction chemotherapy followed by chemoradiotherapy would be expected to increase local-regional control and the control of DM. Several different sequential programs currently are under investigation in an effort to improve local-regional control in these patients. One Phase III study is comparing induction TPF with induction PF, and both treatments are followed by concomitant chemoradiation therapy with weekly, single-agent carboplatin.<sup>17,18</sup> The moderated chemoradiation therapy combined with a full dose of induction chemotherapy in this regimen is intended to achieve better local-regional control and to reduce the local and long-term side effects associated with pure chemoradiotherapy while providing the full benefit of high-dose, systemic induction chemotherapy. Other regimens combine different induction schemas with more intense chemoradiotherapy.<sup>19,20</sup>

In conclusion, TPF-based induction chemotherapy was tolerated well by patients with newly diagnosed head and neck carcinoma, and the response rates were excellent. Survival trends were encouraging, with few instances of second primary tumors or DM. However, we understand the limitation of the current data from these Phase I–II trials with patients who were treated at a single institution. Only a Phase III, randomized trial will establish whether this regimen represents a new standard of care.

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