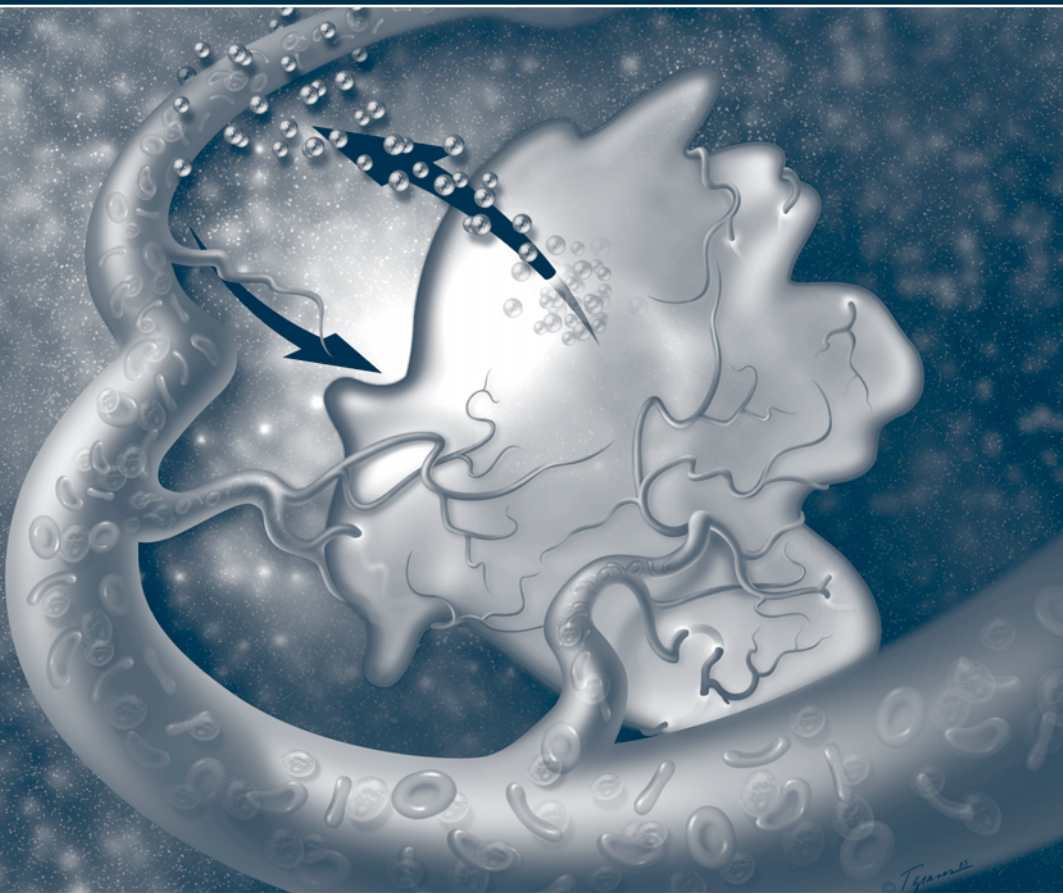


ANTI-ANGIOGENIC THERAPY IN ONCOLOGY



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STATEMENT OF NEED

Every cancer begins as a tiny cluster of abnormal cells. This stage of tumor growth can last from months to years, eventually producing proteins known as angiogenic growth factors. These are released into nearby tissues and stimulate new blood vessels to sprout vigorously from existing healthy blood vessels and into the tumor. Anti-angiogenic therapy is a new form of cancer treatment using drugs called “angiogenesis inhibitors,” which specifically halt new blood vessel growth, stabilize the patient, and in some cases, shrink tumors. Such therapy may be applied to a variety of tumor types, including colorectal, renal, non-small cell lung, prostate, breast, and pancreatic. A better understanding of these novel agents is critical for clinicians to improve the care of patients with cancer.

TARGET AUDIENCE

This activity is designed for oncologists.

ACTIVITY GOAL

The goal of this activity is to provide oncologists with medical information, which should aid them in delivering better care to their patients.

LEARNING OBJECTIVES

After completing this module, the reader should be better able to:

1. Discuss the efficacy of gemcitabine in the treatment of pancreatic cancer
2. Explain the role of angiogenesis in pancreatic cancer
3. Assess the new studies that combine gemcitabine and targeted therapies with other agents in treating pancreatic cancer

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ISSUE 6: Clinical Updates in Pancreatic Cancer

INTRODUCTION – THE STATISTICS OF PANCREATIC CANCER

Pancreatic cancer is one of the most incurable and lethal human cancers. This year, an estimated 33,730 new cases of pancreatic adenocarcinoma will occur in the United States.¹ Of these, approximately 32,300 will ultimately succumb to the disease. Over 95% of all patients diagnosed with pancreatic cancer will fall victim to their malignancy within 5 years of diagnosis.¹ The death rate from this cancer has decreased in men since the 1970s, while it has plateaued in women after peaking between 1975 and 1984.¹ Currently, pancreatic cancer ranks tenth among new cases of cancer in both men and women; however, it ranks fourth in mortality.¹

Risk factors for pancreatic cancer include cigarette and cigar smoking. Incidence rates are more than 2-fold greater in smokers than nonsmokers.¹ Risk also appears to be linked to obesity, high-fat diets, cirrhosis, physical inactivity, chronic pancreatitis, and diabetes. Recent findings suggest that smoking and alcohol work together to cause pancreatic adenocarcinomas.² The tobacco-specific nitrosamine, NNK (4-[methylnitrosamino]-1-[3-pyridyl]-1-butanone), induces pancreatic ductal adenocarcinomas in laboratory rodents. It has also been found that ethanol enhances the NNK-induced proliferation of pancreatic

ductal cells via signaling. Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) may inhibit this response. Such findings suggest a possible mechanism for pancreatic cancer that may be alcohol- and/or smoking-related.

Surgery, radiotherapy, and chemotherapy are treatment options that may extend survival or can be palliative, but they seldom result in a cure. Clinical trials with several targeted agents may offer improved survival and should be considered as treatment options.¹ This issue of the newsletter will focus on the latest therapies and regimens that are being used in the treatment of advanced pancreatic cancer.

ANGIOGENESIS AND PANCREATIC CANCER

Angiogenesis is the biological process by which blood vessels are formed and often accompanies the growth of malignant tissue.³ Vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF),⁴ and platelet-derived growth factor (PDGF)⁵ are important determinants of angiogenesis in human cancers and are therefore a focus for therapeutic intervention.

Expression of VEGF receptors has been shown in pancreatic cancer cells.^{6,7} Positive correlations have been drawn between strong cellular expression of VEGF and greater microvessel density, liver metastasis, and poor survival.⁷ Recently, VEGF-targeted agents, including an anti-VEGF monoclonal antibody, bevacizumab, have been found to be effective in impeding the growth and spread of pancreatic cancer in animal models.^{8,9}

THE ROLE OF GEMCITABINE

Gemcitabine is used as palliative therapy in patients with advanced pancreatic cancer. This treatment can reduce pain and improve quality of life.¹⁰ Prior to the introduction of gemcitabine, 5-fluorouracil (5-FU) had been used with limited success, substantial excessive toxicities, and low response rates.^{11,12} However, 2 pivotal trials showed a significantly increased response to gemcitabine over 5-FU, including in patients refractory to 5-FU.^{13,14} Good tolerability and a low incidence of adverse events are distinct advantages of

TABLE 1

Principles of Chemotherapy in Pancreatic Adenocarcinoma¹⁵

- Use systemic therapy in the adjuvant setting and in the management of locally advanced unresectable and metastatic disease
- Discuss the goals of systemic therapy with patients prior to start of therapy
- Closely monitor patients undergoing chemotherapy
- Standard first-line therapy for patients with metastatic disease is gemcitabine at 1000 mg/m² over 30 minutes, weekly for 3 weeks every 28 days.
 - Consider gemcitabine or gemcitabine-based combination therapy without radiotherapy as an alternative to 5-FU-based chemoradiation for patients with locally advanced, unresectable disease, or as adjuvant therapy
 - Substitute fixed-dose-rate gemcitabine at 10 mg/m²/minute for standard infusion of gemcitabine over 30 minutes
- Gemcitabine combinations have shown a favorable or potentially favorable impact on time to progression or survival (overall or 1-year):
 - Gemcitabine + cisplatin¹⁶
 - Gemcitabine + erlotinib¹⁷
 - Gemcitabine + capecitabine¹⁸
 - Gemcitabine + cetuximab¹⁹
 - Gemcitabine + bevacizumab⁹
- Other options include capecitabine (1000 mg/m² PO twice daily, days 1-14 every 21 days)¹⁵ or 5-FU plus oxaliplatin³⁷

TABLE 2

Preliminary Results of a Phase 2 Trial of Fixed-dose Rate Infusion of Gemcitabine, Low-dose Cisplatin, and Bevacizumab in 35 Patients with Advanced Pancreatic Cancer²⁷

EFFICACY PARAMETERS	RESULTS
Objective response (unconfirmed) PR CR	8 (21.0%) 7 (18.4%) 1 (2.6%)
SD	19 (50.0%; includes 2 minor responses)
Disease control (CR + PR + SD)	27 (71.0%)
CA19-9 decline (>50%) [n=24]	13 (58.3%)
Median overall survival Estimated 1-yr survival	7.5 months 37%
TTP	5.8 months

CR = complete response; PR = partial response; SD = stable disease; TTP = time to progression.

single-agent gemcitabine and enable its integration into combination regimens.

Gemcitabine remains the mainstay of treatment for advanced pancreatic cancer [Table 1].¹⁵ Randomized phase 2 data suggest that improvement in 1- and 2-year survival may be realized by administering gemcitabine at a fixed-dose rate (FDR) infusion.²⁰ While combination therapy may be an improvement, no significant, clinically meaningful survival benefit has been observed when gemcitabine was combined with bolus or infusional 5-FU, capecitabine, metalloproteinase inhibitors, or the farnesyl transferase inhibitor tipifarnib.²¹ Ongoing randomized trials are presently investigating gemcitabine-based combination regimens involving bevacizumab, the platinum, capecitabine, the TKIs, irinotecan, docetaxel and other therapies.

SENDING BEVACIZUMAB INTO THE FRAY

Bevacizumab is a recombinant, humanized, anti-VEGF monoclonal antibody that inhibits angiogenesis. VEGF is a key regulator of physiological angiogenesis during embryogenesis, skeletal growth, and reproductive functions.²² VEGF has also been implicated in pathological angiogenesis associated with tumors, including renal cell carcinomas. VEGF inhibition is being evaluated as a strategy for the prevention of angiogenesis and vascular leakage in malignant tissue and represents one possible strategy for improving survival in patients with advanced pancreatic cancer.²²

Promising results have been demonstrated using the combination of standard-infusion

gemcitabine and bevacizumab in advanced pancreatic cancer. In one study, gemcitabine was given on days 1, 8, and 15 every 28 days, while bevacizumab was administered after the chemotherapy on days 1 and 15. At 26 months of follow-up, the results showed a median progression-free survival (PFS) of 5.4 months and a median overall survival (OS) of 8.8 months.⁹ The 6-month survival rate was 77%. Pretreatment VEGF levels did not correlate with outcome, suggesting other, as yet unknown, pathways by which the combination of drugs may work. Grade 3 and 4 toxicities included hypertension (19%), thrombosis (13%), visceral perforation (8%), and bleeding (2%).

Gemcitabine plus capecitabine has shown improved PFS compared

with gemcitabine alone in patients naive to chemotherapy who had unresectable or metastatic pancreatic carcinoma.²³ A recent phase 3 study suggested that pancreatic carcinoma patients demonstrated better overall survival with gemcitabine plus capecitabine compared to gemcitabine alone.¹⁸ In that study, patients were randomized to gemcitabine weekly for 7 weeks, followed by a 1-week rest, and then weekly gemcitabine for 3 out of 4 weeks (n=266), or to gemcitabine for 3 of 4 weeks and capecitabine for 21 of 28 days. At the time of the interim analysis, 70% of the patients had died. However, the combination showed a marginally improved OS over the single agent ($P=.026$); median survival was 7.4 and 6 months, respectively; 1-year survival rates were 26% and 19%. The objective response (OR) rates were 7% (0 complete responses [CR], 19 partial responses [PR]) for the single agent and 14% (3 CR, 35 PR) for the combination ($P=.008$). Except for the more frequent development of neutropenia in the combination group (17% vs 11%), the toxicity profiles were essentially identical. Given the potential of this combination, and the fact that pancreatic carcinomas have an angiogenic nature, the next logical step would be to evaluate gemcitabine plus capecitabine in combination with bevacizumab.

GEMCITABINE/BEVACIZUMAB-BASED STUDIES

A phase 2 study of gemcitabine (days 1 and 8 of a 21-day cycle), bevacizumab (every 21 days), and capecitabine (twice daily for

TABLE 3

Tumor Response in a Phase 3 Trial of Erlotinib + Gemcitabine vs Gemcitabine in Patients With Advanced Pancreatic Cancer¹⁷

	ERLOTINIB % (N=268)	PLACEBO % (N=262)
CR	0.4	1.1
PR	8.2	6.9
SD	48.9	41.2
CR+PR+SD	57.8	49.2
PD	22.4	26.3
NOT EVALUABLE	20.1	24.4

CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease

14 days) is being conducted in advanced pancreatic patients with an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1.²⁴ In this study, 22% of patients experienced PR; the median PFS was 4.4 months, and median OS was 8.9 months. This study is ongoing and accruing more patients for evaluation of safety of the combination.

Platinum compounds are also being combined with gemcitabine and bevacizumab in this patient population. The addition of platinum appeared to significantly improve PFS and response rate. One pooled analysis analyzed the results of 503 advanced pancreatic cancer patients who had received gemcitabine as monotherapy or a combination of gemcitabine with a platinum analog.²⁵ The results suggest that a gemcitabine-platinum regimen produces modest improvements in overall survival (median OS = 8.3 vs 6.7 months; $P=.031$) and progression-free survival (PFS = 5.5 vs 3.5 months; $P=.003$).²⁵

A pooled analysis of 3682 pancreatic cancer patients in 12 phase-3 trials that looked at single-agent gemcitabine, along with platinum-containing and fluoropyrimidine-containing gemcitabine combinations, showed that the addition of platinum to the regimen improved PFS ($P<.0001$) and overall response rate ($P=.001$), compared to gemcitabine monotherapy, better than the fluoropyrimidine regimens.²⁶ Thus, research is advancing toward more platinum-gemcitabine regimens, especially in the treatment of younger and fitter advanced pancreatic cancer patients.

A phase 2 study of gemcitabine given at

FDR infusion, bevacizumab, and low-dose cisplatin (20 mg/m²), all administered on days 1 and 15 of a 28-day cycle is in progress.²⁷ The results from the first 35 patients, presented in **Table 2**, demonstrated the safety and modest efficacy of the combination of FDR gemcitabine, low-dose cisplatin, and bevacizumab.²⁷ In this study, CA19-9, an oncofetal antigen expressed by several different cancers but particularly prevalent in gastrointestinal carcinomas, was used as a marker to determine prognosis and tumor recurrence. One multivariate analysis showed that the response of CA19-9 was the strongest independent predictor of survival ($P<.001$).²⁸ More than 50% of patients in this study experienced a 50% or greater drop in CA19-9 levels.²⁷ Overall, rates of disease control and CA19-9 response are encouraging, suggesting this combination warrants additional study.

A phase 2 study of gemcitabine, bevacizumab, and oxaliplatin²⁹ is currently enrolling patients with previously untreated metastatic disease. The object of this study is to determine the 6-month survival of patients and the toxicity of this triple regimen. A total of 83 patients will receive gemcitabine and bevacizumab on days 1 and 15 and oxaliplatin on days 2 and 16. An interim analysis is expected in the upcoming months.

EGFR AS A TARGET IN PANCREATIC CANCER THERAPY

Pancreatic adenocarcinomas and dysplasias frequently overexpress receptor tyrosine kinases, such as EGFR.³⁰ In one analysis of 12 human pancreatic cell lines, 100% expressed EGFR.³⁰ Cytoplasmic EGFR expression in human pancreatic cancer, particularly in the progression of pancreatic ductal adenocarcinoma, is associated with metastases ($P<.01$), as well as poor prognosis.^{31,32}

This clinical picture may be related to enhancement of angiogenesis via the increased production of proangiogenic molecules. Indeed, blocking EGFR via the oral administration of a novel EGFR TKI, PKI166, has been shown to decrease VEGF expression and increase apoptosis of tumor-associated endothelial cells in pancreatic cancer xenografts.³³ When the TKI (PKI166) was given with gemcitabine, the volume of tumor cells was reduced by 85%.

Erlotinib, another oral EGFR TKI, when combined with gemcitabine, boosted gemcitabine-induced apoptosis in pancreatic cancer xenografts in the murine model,

thereby setting the stage for human clinical trials using the erlotinib-gemcitabine regimen.³⁴

A phase 3 trial showed that erlotinib (100 mg/day) modestly prolonged survival when combined with gemcitabine (1000 mg/m² weekly) compared to gemcitabine alone.¹⁷ Tumor responses are shown in **Table 3**. The 1-year survival rates favored the combination regimen: 24% versus 17%; PFS was also significantly improved in the gemcitabine-erlotinib group ($P=.003$). Based on these results, the FDA approved the use of erlotinib when combined with gemcitabine chemotherapy for the treatment of advanced pancreatic cancer in patients who have not received previous chemotherapy.³⁵ A phase 2 trial showed that bevacizumab and gemcitabine plus erlotinib or cetuximab, an alternative EGFR TKI, were active in advanced pancreatic cancer.³⁶ The erlotinib and cetuximab arms had comparable

median PFS (3.6/3.6 months) and 6-month survival rates (38%/41%), with more grade 3 or 4 thrombocytopenia and anemia occurring in the erlotinib arm and more rash, deep venous thrombosis, and pulmonary emboli in the cetuximab arm. This study is expected to generate additional data.

CONCLUSIONS

Treatment of pancreatic cancer appears to be improved when targeted therapies are added to gemcitabine, the mainstay of pharmacotherapy for this devastating disease. Blocking VEGF-induced angiogenesis, as well as EGFR and other growth factors, may lead to prolonged survival especially for those patients with advanced disease. Research continues in the development of still more potent and direct therapeutic regimens to treat this aggressive malignancy. ■

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EVALUATION

1. How well did the activity meet the identified Statement of Need?
2. How would you rate your satisfaction with this activity?
3. How well did this activity help you meet the following objectives?
 - a. Discuss the efficacy of gemcitabine in the treatment of pancreatic cancer
 - b. Explain the role of angiogenesis in pancreatic cancer
 - c. Assess the new studies that combine gemcitabine and targeted therapies with other agents in treating pancreatic cancer.
4. Evaluate whether the activity was free from commercial bias.
5. Assess the degree to which this activity is helpful in your practice.
6. How would you rate the objectivity, balance, and scientific rigor of this activity?
7. How does this activity rate in comparison to other activities that you have participated in?

Send other comments to
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Anti-angiogenic Therapy in Oncology POSTTEST

1. Of those who receive a diagnosis of pancreatic cancer today, how many will likely still be alive after 5 years?
 - A. <5%
 - B. 10%
 - C. 25%
 - D. >50%
2. Recent findings suggest that which 2 risk factors work together to cause pancreatic adenocarcinomas?
 - A. Smoking and diabetes
 - B. Diabetes and alcohol use
 - C. Alcohol use and smoking
 - D. Obesity and smoking
3. Which of the following is not an important determinant of angiogenesis in human cancers?
 - A. VEGF
 - B. PDGF
 - C. bFGF
 - D. EGF
4. Which drug is the mainstay of treatment for pancreatic cancer?
 - A. 5-FU
 - B. Gemcitabine
 - C. Cisplatin
 - D. Bevacizumab
5. Which of the following is a recombinant humanized, anti-VEGF monoclonal antibody that inhibits angiogenesis?
 - A. Erlotinib
 - B. Cetuximab
 - C. Bevacizumab
 - D. Oxaliplatin
6. What is true about gemcitabine plus capecitabine compared to gemcitabine alone in pancreatic cancer patients?
 - A. No difference in overall survival
 - B. More neutropenia in the combination group
 - C. No difference in response rates
 - D. More overall toxicity in the combination group
7. An analysis of phase 3 patients with pancreatic cancer showed that the addition of which agent class improved progression-free survival and overall response rate compared to gemcitabine monotherapy?
 - A. Platinums
 - B. Fluoropyrimidines
 - C. EGFR TKIs
 - D. None of the above
8. One multivariate analysis showed that the oncofetal antigen CA19-9 was the strongest independent predictor of survival in pancreatic cancer.
 - A. True
 - B. False
9. Cytoplasmic EGFR expression in pancreatic cancer is associated with:
 - A. Metastatic disease
 - B. Favorable prognosis
 - C. Fewer toxicities
 - D. All of the above
10. Based on the results of a phase 3 study, the FDA approved the use of which agent combined with gemcitabine for the treatment of advanced pancreatic cancer in treatment-naïve patients?
 - A. Erlotinib
 - B. Cetuximab
 - C. Cisplatin
 - D. Bevacizumab

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POSTTEST

- | | |
|--|---|
| 1. <input type="checkbox"/> a. <input type="checkbox"/> b. <input type="checkbox"/> c. <input type="checkbox"/> d. | 6. <input type="checkbox"/> a. <input type="checkbox"/> b. <input type="checkbox"/> c. <input type="checkbox"/> d. |
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| 3. <input type="checkbox"/> a. <input type="checkbox"/> b. <input type="checkbox"/> c. <input type="checkbox"/> d. | 8. <input type="checkbox"/> a. <input type="checkbox"/> b. |
| 4. <input type="checkbox"/> a. <input type="checkbox"/> b. <input type="checkbox"/> c. <input type="checkbox"/> d. | 9. <input type="checkbox"/> a. <input type="checkbox"/> b. <input type="checkbox"/> c. <input type="checkbox"/> d. |
| 5. <input type="checkbox"/> a. <input type="checkbox"/> b. <input type="checkbox"/> c. <input type="checkbox"/> d. | 10. <input type="checkbox"/> a. <input type="checkbox"/> b. <input type="checkbox"/> c. <input type="checkbox"/> d. |

EVALUATION

	<i>Poor</i>	<i>Satisfactory</i>	<i>Good</i>	<i>Very Good</i>	<i>Excellent</i>
1.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3a.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3b.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3c.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Last Name: |_____| First Name: |_____|
(please print)

Degree: MD DO Other Please specify: _____

Address: _____

City: _____ State: _____ Zip: _____

Phone: _____ Fax: _____ E-mail: _____

Actual Time Spent on Activity: _____

Comments: _____

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