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CLINICAL INVESTIGATION **Rectum**

PREOPERATIVE HYPERFRACTIONATED ACCELERATED RADIOTHERAPY (HART) AND CONCOMITANT CPT-11 IN LOCALLY ADVANCED RECTAL CARCINOMA: A PHASE I STUDY

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Purpose: Patients with locally advanced rectal carcinoma are at risk for both local recurrence and distant metastases. We demonstrated the efficacy of preoperative hyperfractionated accelerated radiotherapy (HART). In this Phase I trial, we aimed at introducing chemotherapy early in the treatment course with both intrinsic antitumor activity and a radiosensitizer effect.

Methods and Materials: Twenty-eight patients (19 males; median age 63, range 28–75) with advanced rectal carcinoma (cT3: 24; cT4: 4; cN+: 12; M1: 5) were enrolled, including 8 patients treated at the maximally tolerated dose. Escalating doses of CPT-11 (30–105 mg/m^2/week) were given on Days 1, 8, and 15, and concomitant HART (41.6 Gy, 1.6 Gy bid × 13 days) started on Day 8. Surgery was to be performed within 1 week after the end of radiochemotherapy.

Results: Twenty-six patients completed all preoperative radiochemotherapy as scheduled; all patients underwent surgery. Dose-limiting toxicity was diarrhea Grade 3 occurring at dose level 6 (105 mg/m^2). Hematotoxicity was mild, with only 1 patient experiencing Grade 3 neutropenia. Postoperative complications (30 days) occurred in 7 patients, with an anastomotic leak rate of 22%.

Conclusions: The recommended Phase II dose of CPT-11 in this setting is 90 mg/m^2/week. Further Phase II exploration at this dose is warranted. © 2003 Elsevier Inc.

Preoperative radiochemotherapy, CPT-11, Hyperfractionated radiotherapy, Rectal cancer.

INTRODUCTION

Colorectal carcinoma is commonly referred to as a single disease, although adenocarcinoma of the rectum is a distinct entity, with particular biologic and genetic features and clinical behavior (1). Both local recurrences and distant metastases are common in rectal carcinoma (2). The risk of local recurrence is dependent on penetration into the bowel wall and clearance of the surgical margins. Its particular anatomic structure, with lack of peritoneal cover and narrow adjacent structures, makes a complete surgical clearance difficult. For locally advanced rectal carcinoma, a combined modality approach has been the standard of care for more than a decade (3); improved local control and overall survival has been shown in several randomized trials (4–8). The Swedish Rectal Cancer Trial (SRCT) showed that preoperative accelerated radiotherapy (5 × 5 Gy) significantly prolonged survival, compared with surgery alone (8). Nevertheless, at 5 years, only 58% of patients were alive with preoperative treatment, and distant metastases were a common cause of failure in 40% of patients.

With standard surgery alone, local recurrences occur in up to 30% of patients, with more optimal surgery recurrence rates of about 15% reported (9, 10). With newer surgical techniques and total mesorectal excision (TME), local recurrence rates as low as 5–8% were reported at a median follow-up of only 2 years (11). However, these excellent results were achieved by specially trained surgeons at high-volume centers. This large randomized study demonstrated a decrease in local recurrence rate from 8% to 2% with the addition of preoperative accelerated radiotherapy (11).

We previously established preoperative hyperfractionated and accelerated radiotherapy, followed by immediate surgery for patients with advanced rectal cancer (12, 13). In the mid 1990s, new cytotoxic agents with demonstrated activity against colorectal cancer became available. Irinotecan (CPT-11), a camptothecin derivative and topoisomerase-I inhibitor, is an active single agent against colorectal cancer

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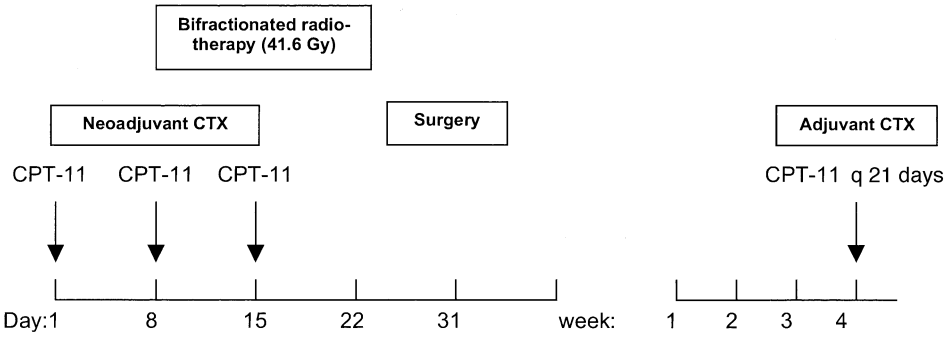

Fig. 1. Design of the trial. Preoperative hyperfractionated radiotherapy: Days 8–24; preoperative chemotherapy (CTX) with CPT-11: Days 1, 8, and 15; surgery (SX) immediately after end of radiation: Days 25–30; and adjuvant chemotherapy with CPT-11 × four cycles every 21 days.

and has exquisite radiosensitizing properties (14). The introduction of chemotherapy early in the disease course, when tumor burden is low and the vascular bed is intact, may theoretically be an additional advantage, improving local control and eliminating micrometastatic disease. Few clinical studies have evaluated concomitant administration of CPT-11 and radiation in rectal cancer (15–17). We thus initiated a Phase I trial, introducing escalating doses of weekly CPT-11 with concomitant hyperfractionated accelerated radiotherapy.

METHODS AND MATERIALS

Eligibility and staging

Patients ages 18–75 years with a World Health Organization (WHO) performance status of 0–2 and histologically confirmed adenocarcinoma of the rectum International Union Against Cancer (UICC) Stage II–IV (cT3, cT4) were eligible for this study.

Patients with metastatic disease were eligible when the control of the distant disease was judged to be of lesser importance than the goal of obtaining optimal local control. Other eligibility criteria included adequate hematologic reserve (white cell blood count $\geq$3 G/L, hemoglobin $\geq$100 g/L, platelet count $\geq$100 G/L), and adequate hepatic and renal function (serum creatinine $<$135 μmol/L, serum bilirubin $<$20 mmol/L, transaminases and alkaline phosphatase $<$1.5 times the upper limit of normal). No prior chemotherapy or radiotherapy was allowed. All patients gave written informed consent, and the protocol was approved by the local Ethics Committee. Prior malignant disease, serious psychiatric disorders, chronic diarrhea, uncontrolled heart failure or angina pectoris, myocardial infarction during the last year, uncontrolled hypertension, and pregnancy or lactation were exclusion criteria. Pretreatment disease evaluation included physical examination, transrectal ultrasonography, and computer tomography (CT) of the chest, abdomen, and pelvis.

Study design and treatment plan

This study was designed as a Phase I trial, with escalating doses of preoperative CPT-11 and concomitant hyperfractionated radiotherapy in patients with advanced rectal cancer (Fig. 1). Six escalating dose levels of weekly CPT-11 were explored: 30, 45, 60, 75, 90, and 105 mg/m^2, in cohorts of 3–6 patients. CPT-11 was administered as a 30–90 min infusion on Days 1, 8, and 15. No CPT-11 administration was planned on Day 22 to avoid compromising the subsequent surgery as a result of potential hematotoxicity. Hyperfractionated radiotherapy began on Day 8 and continued through Day 24 twice daily (bid, with a 6-h interval between fractions, Monday to Friday), for a total of 41.6 Gy (26 × 1.6 Gy). Patients were irradiated with a linear accelerator with a minimal accelerating potential of 6 MV (Varian Clinac 2100 or Philips Linac 75-5). The dose prescription was at the intersection of the fields (four-field technique). The homogeneity was within 5% of the dose prescribed at the isocenter. The field margins were defined according to a "standard field," as described by Gunderson (18). The upper limit was located at the L5-S1 interspace. The lower limit was decided according to the localization of the primary tumor. For low-located tumors within a range of 5 cm from the anal margin, this latter was included in the treatment volume. For lesions located higher than 5 cm, the exclusion of the anal margin was checked by *in vivo* dosimetry using thermoluminescent dosimetry (TLD). Corrections of the lower limit were done if required.

Surgery was to be performed within 1 week after the end of irradiation. Most patients were operated on by the team of gastrointestinal surgeons at the University Hospital Lausanne; 9 patients underwent surgery in one of the affiliated local hospitals.

Adjuvant chemotherapy with single-agent CPT-11 for four cycles every 21 days was planned to start 3–6 weeks after surgery. Because of prior irradiation of the pelvis and the fear of increased bone marrow toxicity, the initial dose of adjuvant CPT-11 was reduced to 250 mg/m^2, to then be escalated to 300 mg/m^2 and then to the standard 350 mg/m^2 in cycles 2 and 3 in the absence of severe myelosuppression.

Patients had a physical examination, a complete blood count, and blood chemistry at least once per week during treatment. All toxicity was scored according to the National Cancer Institute Common Toxicity Criteria, version 2.0

Table 1. Patient and treatment characteristics (n = 28)

Age, y	
Median	63
Range	28–75
Gender: male/female	19/9
Performance status (ECOG)	
Median	0
Range	0–2
Neoadjuvant therapy	
Total no. of CPT-11 administrations	83
No. patients who completed radiotherapy (41.6 Gy)	27
Surgery	
Low anterior resection	18
Abdominoperineal resection	10
Delay last day of radiotherapy until surgery	
Median	5
Range	1–11

(19). Special attention was drawn to perioperative and 30-day postoperative complications, in particular anastomotic leakage, wound healing impairment, pelvic abscess or other severe infections, and perioperative mortality.

The primary study end point was to assess feasibility and toxicity and to determine the maximally tolerated dose (MTD) of weekly CPT-11 and concomitant HART. Dose-limiting toxicity (DLT) was defined as hematologic Grade 4 toxicity of >7 days' duration, or neutropenic fever requiring hospitalization or any other ≥Grade 3 nonhematologic toxicity. At least 3 patients were to be treated per dose level; if DLT was observed in more than 1 patient, a total of 6 patients had to be treated at that dose level. If 2 or more patients at a given dose level developed DLT, the maximally tolerated dose would be defined as the dose level below DLT. Dose escalation was allowed when all patients of a given dose level were discharged from the hospital after surgery. After reaching DLT, additional patients were treated at the recommended Phase II dose.

RESULTS

Patient characteristics

Between December 1998 and October 2001, 28 patients with rectal adenocarcinoma clinical Stage II, III, and IV were enrolled in this Phase I trial. All patients were evaluated for toxicity and survival. Patient characteristics are summarized in Table 1. There were 19 men and 9 women with a median age of 60 years (range 28–75 years). The initial clinical tumor stage was T3 in 24 patients and T4 in 4 patients (Table 2). Lymph node involvement was suspected in 12 patients by CT scan or transrectal ultrasound; in 1 patient the node status could not be assessed. Five patients had distant metastases at diagnosis.

Preoperative treatment

All patients but two received the preoperative radiochemotherapy as planned. One did not receive the third dose of CPT-11 (DL 5) because of neutropenia Grade 2, and 1 patient missed the last fraction of radiotherapy (1.6 Gy)

Table 2. Clinical and pathologic TNM stages (n = 28)

T/N stage	cN0	cN+	cNx
Clinical stages			
cT1			
cT2			
cT3*	13	11	
cT4	2	1	1
Pathologic stage	pN0	pN1	pN2
pT1			
pT2	3	5	
pT3	10	4	3
pT4	1		2

* Five patients M1.

because of nonhematologic toxicity Grade 3 (diarrhea and abdominal cramping). In the other 26 patients, no dose reductions of CPT-11 or interruption or delay of radiotherapy were necessary. After 1 patient had developed severe toxicity in dose level 4 (75 mg/m^2), 3 additional patients were included at this dose level with no further event of severe toxicity.

Hematotoxicity was minor, and only 1 patient developed Grade 3 neutropenia and neutropenic fever (Table 3). Neutropenia Grade 1 or 2 was observed in 6 patients. Grade 1 or 2 anemia was present in 6 patients, 2 of whom already had a low hemoglobin level at the time of inclusion.

Diarrhea was an expected toxicity: mild to moderate diarrhea was observed in most patients but easily controllable with loperamide. Six patients developed Grade 3 diarrhea. Both patients treated at dose level 6 (105 mg/m^2) experienced severe diarrhea that was considered DLT (Table 4). The recommended dose level (RDL) was thus defined at 90 mg/m^2, and an additional 8 patients were treated at this dose level. Of a total of 11 patients treated at the RDL, Grade 3 diarrhea occurred in 2 patients (18%). Other occasional toxicities observed were abdominal cramping, dysuria and urinary tract infection, and asthenia.

Quality of life was not formally assessed in this Phase I study. When using the WHO performance status (PS) as a surrogate for quality of life, one third of the patients had no deterioration of the PS. Most of the patients experienced mild asthenia with deterioration of the PS from 0 to 1. Three patients had a PS of 2 before surgery, and a PS 3 before surgery was noted in the two patients with Grade 3 diarrhea.

Table 3. Hematologic toxicity, all dose levels (n = 28)

Toxicity	Grade 1/2	Grade 3
Leucopenia	16	0
Neutropenia	6	1*
Anemia	6†	0
Thrombocytopenia	0	0

* Febrile neutropenia.

† Two patients already had grade 1 anemia before treatment started.

Table 4. Nonhematologic Grade 3 toxicity

Dose level	1	2	3	4	5	6	7
Dose (mg/m^2)	30	45	60	75	90	105	90
No. of patients	$n = 3$	$n = 3$	$n = 3$	$n = 6$	$n = 3$	$n = 2$	$n = 8$
Toxicity (No. of patients)							
Diarrhea	0	1	0	1*	0	2	2
Infection	0	0	1†	1*	0	0	0
Abdominal cramping	0	0	0	0	0	0	1
Nausea/vomiting	0	0	0	0	0	0	0
Proctitis	0	0	0	0	0	0	0
Dysuria	0	0	0	0	0	0	1
Asthenia	0	0	0	0	0	0	2

Note: One patient could experience more than one side effect. No grade 4 toxicity occurred.

* One patient with febrile neutropenia with diarrhea Grade 3 requiring hospitalization and intravenous antibiotics and hydratation.

† Urinary infection without neutropenia, requiring intravenous antibiotics.

Surgery and postoperative complications

The median time from the end of radiotherapy to surgery was 5 days, with a range of 1–11 days. Twenty-five patients proceeded to the planned surgery within 1 week. Surgery was to include TME. Sphincter-preserving low anterior resection (LAR) was performed in 18 patients and 6 patients received a temporary protective ileostomy. In 10 patients, a low rectal tumor abdominoperineal resection (APR) with permanent colostomy was necessary. Of the four clinical stage T4 tumors, none required resection of the adjacent, presumably infiltrated organ. It remains unclear whether this is a true effect of the prior radiochemotherapy or rather a reflection of the inherent difficulties in preoperative clinical staging.

Major complications within the 30 postoperative days were observed in 7 patients and are listed by dose level in Table 5. Anastomotic leak occurred in 3 patients: 1 experienced sepsis, and 2 patients experienced pelvic abscess (in one as a consequence of the anastomotic leak). Another patient experienced intraoperative sepsis. A 71-year-old patient with hypertensive heart disease and previous aortic valve replacement died 3 weeks after surgery (APR) of acute myocardial infarction associated with pneumonia and abdominal wound dehiscence. Furthermore, one patient developed an anastomotic leak 3 months after surgery together with pelvic infection. The anastomotic leak rate, including this late complication, is 22% (4 of 18 patients with LAR).

Minor surgical toxicity was essentially observed in patients treated with APR: prolonged perineal wound healing or local infection of perineal scar was observed in all patients having an APR. Nevertheless, the wound healing of the perineal scar lasted longer than 4 months in 1 patient.

Other complications observed were deep venous thrombosis (1), arterial hypertension Grade 3 (1), and postoperative hypovolemic shock resulting from bleeding of a gastric ulcer (1). One patient needed immediate postoperative intensive care because of pulmonary atelectasia that occurred during surgery.

Most of the patients (18) were able to undergo sphincter-preserving surgery. It is of note that 5 patients with a very distal tumor of $\leq$4 cm from the anal verge underwent sphincter preservation. Four of those patients had negative surgical margins and did not develop local recurrence at a median follow-up of 23 months.

All surgical specimens were reviewed by the same pathologist (H.B.). Of the 28 evaluated specimens, 22 patients

Table 5. Postoperative complications per dose level (30 days) ($n = 28$)

DL	mg/m^2	No. patients	Toxicity, no. of patients	Time onset	Ileostomy
1	30	3	0		
2	45	3	0		
3	60	3	1 anastomotic leak	2 weeks	no
			1 pelvic abscess	3 weeks	no
4	75	6	0		
5	90	3	0		
6	105	2	1 anastomotic leak + sepsis	1 week	no
			1 anastomotic leak + pelvic abscess	2 weeks	yes
5	90	8	1 sepsis + prolonged abdominal wound healing + sterile presacral collection	Postoperative 4 weeks†	yes
			1 prolonged perineal wound healing over 4 months		APR
			1 death	3 weeks	APR

Abbreviations: DL = dose level; APR = abdominoperineal resection.

Table 6. Radial tumor clearance ($n = 28$)

Distance of tumor from radial resection margin	Number of patients
>0.5 cm	18
>1 mm	3
1 mm	1
<1 mm	2
Positive radial resection margins	6

(79%) had a negative radial margin, and in 2 of them the clearance (distance between the tumor and the radial margin) was <1 mm (Table 6). Positive radial margin involvement was seen in 6 patients.

Downstaging between the initial clinical T-stage and the postoperative pathologic stage was observed in 10 patients. The T-stage remained unchanged in 16 patients and a higher T-stage was reported in 2 (Table 7). UICC stage distribution differs between clinical and pathologic stage because of more accurate detection of nodal involvement in the surgical specimen. Of the 12 patients with presumed radiologic nodal involvement, only 6 had pathologically confirmed lymph node metastases at surgery (Table 2).

Adjuvant chemotherapy

Twenty-one patients (75%) received the planned postoperative, adjuvant chemotherapy with single-agent CPT-11. No adjuvant chemotherapy was given to 7 patients for the following reasons: two deaths (metastatic progression, myocardial infarct), prolonged perineal wound healing (1 patient), postoperative infectious complications (2 patients), and patient refusal (2 patients). Dose escalation to the standard 350 mg/m^2 was possible without severe toxicity in 16 of 21 patients (76%) despite prior pelvic irradiation. Overall, toxicity and tolerance of adjuvant treatment was as expected for single agent CPT-11.

Follow-up

Median follow-up is 2 years. Twenty-one patients are alive and 18 have no evidence of disease. Local recurrence occurred in 2 patients at 12 and 24 months after inclusion. One of these had positive surgical radial margins and simultaneously had distant metastases at the time of recurrence. Three initially M0 patients developed distant metastases. Two patients developed a second malignancy: one renal cancer and one head-and-neck carcinoma.

Table 7. T downstaging ($n = 28$)

Tumor stage	No. of patients
Tumor downstaged	10
cT4–pT3	2
cT4–pT2	1
cT3–pT2	7
Identical T stage	16
cT3–pT3	15
cT4–pT4	1
Tumor upstaging	2
cT3–pT4	2

DISCUSSION

Despite new surgical techniques and multimodality therapy with radiochemotherapy, the prognosis of patients with locally advanced rectal cancer remains inferior to comparable stages of colon cancer.

Our protocol integrates both radiotherapy and chemotherapy early in the treatment of this disease, with the aim of reaching the best locoregional control and to prevent systemic relapse. CPT-11 is a camptothecin derivative with specific inhibition of the topoisomerase-I enzyme. It has demonstrated activity against metastatic colorectal cancer both as a single agent after 5-FU failures and in combination with 5-FU as a first-line treatment (20). *In vitro,* the cytotoxicity of irradiation against cancer cells is enhanced by concurrent administration of CPT-11 (14). In the presence of topoisomerase-I inhibitors, a lower radiation dose is required to reach a similar cytotoxic effect. However, this effect is only observed when cells are exposed to the drug before or during irradiation, but not after irradiation (14). The mechanism of radiosensitization can be explained through a DNA repair inhibition by camptothecin derivatives (21). Another theory suggests that single-strand DNA breaks induced by topoisomerase-I inhibitors lead to sublethal damage for the tumor cell, and that additional radiation-induced DNA damage may convert this into lethal DNA damage. Extrapolating from the *in vitro* experiences, clinical radiochemotherapy regimens have been developed essentially in head-and-neck, esophageal, and non–small-cell lung cancers (22–25).

In this Phase I trial, we have shown that the addition of weekly CPT-11 to preoperative hyperfractionated accelerated radiotherapy for patients with locally advanced rectal cancer is feasible. The weekly dose was escalated from 30 mg/m^2 to 105 mg/m^2. Acute diarrhea is the known DLT for both CPT-11 chemotherapy and intestinal radiation therapy. Expectedly acute diarrhea has been the DLT in this combined modality treatment.

5-Fluorouracil has been frequently used concomitantly with preoperative or postoperative radiotherapy for rectal cancer. With this type of regimen, severe diarrhea is observed in 11–23% of patients, but dermatitis and mucositis are more frequently associated with this treatment. In particular, hematologic toxicity Grade 3 and 4 is reported in 10–18% of the patients (26–28).

Minsky *et al.* reported on a Phase I trial of radiochemotherapy in which CPT-11 was administered daily before standard fractionated radiotherapy. At a total dose of 65 mg/m^2 per week (13 mg/m^2/day) for 6 weeks, severe diarrhea was the DLT (16). Weekly CPT-11 and continuous infusion 5-FU with concomitant standard fractionated radiotherapy has been evaluated in another Phase I trial in rectal cancer (17). A subsequent Phase II trial reported a rather high acute toxicity rate; 28% of patients suffered

from Grade 3 diarrhea, 20% from severe mucositis, and approximately 10% of the patients had Grade 3 abdominal cramping (15). The 18% Grade 3 diarrhea incidence at the recommended Phase II dose in our trial compares favorably with other reports and allows us to administer a systemically active dose of irinotecan with concomitant radiotherapy.

A particular concern of any preoperative therapy is the potential increase in surgical morbidity. Details of perioperative and postoperative complications are frequently not reported in many trials. In a recent publication, a single institution reported a 30-day postoperative complication rate as high as 38% in patients treated with preoperative radiochemotherapy (29). In our trial, we observed a 25% postoperative complication rate. Surgery including TME has an incidence of anastomotic dehiscence of approximately 16% (30). In a recent Dutch multicenter trial, the anastomotic leak rate (AL rate) was 13–15% with and without preoperative irradiation (31). Our AL rate of 22% (within 30 days: 17%) is comparable, though rather high. It has been shown that the confection of a protective ileostomy may reduce the risk of an anastomotic leakage to approximately 5% (26). In our trial, there was no difference in AL rate between patients with and without protective ileostomy. Nevertheless, because the combination of accelerated radiotherapy and CPT-11 may prolong postoperative anastomotic healing, we suggest that protective ileostomy should be considered in these patients.

Effective preoperative treatment may allow for tumor downstaging and thus eventually allow for sphincter-preserving surgery. The design of our study demands surgery be performed within 4 weeks of treatment start and within 1 week from the end of irradiation. Because of the immediate surgery, the full effect of the neoadjuvant treatment, which thus underestimates the true downstaging capacity of this regimen, may not be appreciated. However, we favor a short interval between radiotherapy and surgery according to the regimen used in the SRCT (8), because this may facilitate surgery before the development of radiation-induced fibrosis. The potential risk of accelerated repopulation of tumor cells after the end of irradiation is also less with a short interval. Early surgical intervention will still provide an optimal treatment for a subgroup of patients with potentially resistant tumors.

The best way of integrating chemotherapy and radiotherapy to surgery as well as the type of cytostatic to use is currently the subject of several investigations. Three randomized Phase III trials have been designed, comparing preoperative radiochemotherapy with postoperative adjuvant therapy. Two studies had to close prematurely because of lack of accrual (Radiation Therapy Oncology Group 94-01 and National Surgical Adjuvant Breast and Bowel Project R-03). The German Intergroup Trial is the only ongoing trial (32).

The European Organization for Research and Treatment of Cancer trial 22921 investigates the role of preoperative chemotherapy when combined with preoperative radiotherapy as well as the role of adjuvant chemotherapy after combined preoperative treatment. The recently published Dutch study underlines that, with TME and a short course of preoperative radiotherapy, the local failure rate can be decreased significantly (11).

In our proposed regimen, we integrated an active chemotherapy agent with concomitant preoperative accelerated radiotherapy. This may allow improved local and distant control of advanced rectal cancer and facilitate sphincter-preserving surgery. Further Phase II exploration of this regimen at a dose of 90 mg/m^2 is warranted.

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