

Phase II Randomized Study of ISIS 3521 and ISIS 5132 in Patients with Locally Advanced or Metastatic Colorectal Cancer: A National Cancer Institute of Canada Clinical Trials Group Study¹

M. Christine Cripps,² Alvaro T. Figueredo, Amit M. Oza, Marianne J. Taylor, Anthony L. Fields, John T. Holmlund, Lynn W. McIntosh, Richard S. Geary, and Elizabeth A. Eisenhauer

Ottawa Regional Cancer Centre, Ottawa, Ontario, K1H 8L6 Canada [M. C. C.]; Hamilton Regional Cancer Centre, Hamilton, Ontario, Canada [A. L. F.]; Princess Margaret Hospital, Toronto, Ontario, Canada [A. M. O.]; London Regional Cancer Centre, London, Ontario Canada [M. J. T.]; Cross Cancer Institute, Edmonton, Alberta, Canada [A. T. F.]; Isis Pharmaceuticals, Carlsbad, California [J. T. H., R. S. G.]; and National Cancer Institute of Canada, Clinical Trials Group, Kingston, Ontario, K7L 3N6 Canada [L. W. M., E. A. E.]

ABSTRACT

Background: Because treatment of metastatic colon cancer is noncurative, new treatments are needed. This trial evaluated the antitumor effects of two targeted anticancer agents: (a) ISIS 3521, an antisense inhibitor of the protein kinase C α ; and (b) ISIS 5132, an antisense inhibitor of c-raf kinase in patients untreated previously with recurrent or metastatic colorectal carcinoma.

Patients and Methods: All patients had colorectal adenocarcinoma with measurable disease and no prior chemotherapy for metastatic disease. Patients were randomized to receive either ISIS 3521 or ISIS 5132 at a dose of 2 mg/kg/day as a continuous i.v. infusion 21 of 28 days. Cycles were repeated as long as progression was not seen, and doses of both agents were modified according to toxic effects. A two-arm study design was used with each study arm considered independently. Steady-state blood levels of both antisense molecules were measured on days 8, 15, and 22 of the first cycle of therapy.

Results: Thirty-seven eligible patients were enrolled, and 32 were evaluable for response (17 receiving ISIS 3521 and 15 receiving ISIS 5132). No responses were noted. Four

of the patients receiving ISIS 3521 had stable disease, and 5 patients receiving ISIS 5132 were stable.

Conclusion: Neither ISIS 5132 nor ISIS 3521 given in the dose and schedule studied induced objective responses in untreated colorectal cancer patients.

INTRODUCTION

In 1999, colorectal cancer accounted for an estimated 17,000 cases and 6,500 deaths in Canada and was the third leading cause of cancer death in men and women (1). Although highly curable when diagnosed early, ~45% of patients will eventually die of metastatic disease (2).

The standard treatment for metastatic colorectal cancer has historically been 5-FU and folinic acid (Mayo Regimen), but a recent trial adding CPT-11 has demonstrated a modest increase in survival (3). Given the limited survival advantage and the toxicity of the treatment, there is a need to identify more active or less toxic systemic agents. The purpose of this study was to evaluate two new antisense oligonucleotides targeting PKC- α ³ (ISIS 3521) and c-raf kinase (ISIS 5132) in untreated patients with advanced colorectal cancer in a noncomparative randomized Phase II design.

The molecular target for antisense oligonucleotides is the mRNA, which codes for a specific protein. On hybridizing to the mRNA coding for a specific protein, antisense oligonucleotides reduce or inhibit the protein expression of a protein. Both ISIS 3521 and ISIS 5132 are antisense phosphorothioate oligodeoxynucleotides that hybridize to the 3' untranslated region of the human PKC- α or c-raf kinase mRNA, respectively.

PKC- α (an abundant isozyme of PKC) is universally expressed throughout tissues and is found in many transformed cell lines (4, 5). There is also considerable evidence implicating PKC in the abnormal proliferation, which occurs during tumor promotion and carcinogenesis (6). Evidence from human malignancies also suggests that PKC plays an important role in the growth or progression of some tumors (4). Thus, PKC- α is an attractive target for antitumor drug (7).

Raf kinases serve as central regulators of mitogenic signaling pathways by connecting upstream growth factor-mediated tyrosine kinase stimulation with downstream activation of serine threonine kinases (8). There is substantial evidence to support the direct role of raf kinases in the development and maintenance of human malignancies; it is central to the mitogen-activated protein kinase signaling cascade (8) and is a downstream effector of ras protein function. Because ras mutations

Received 9/4/01; revised 3/7/02; accepted 3/18/02.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

¹ Supported by Grants from the National Cancer Institute of Canada and Isis Pharmaceuticals.

² To whom requests for reprints should be addressed, at Ottawa Regional Cancer Centre, 501 Smyth Road, Ottawa, Ontario, K1H 8L6 Canada. Phone: 613-737-7700, extension 6762; Fax: 613-247-3511; E-mail: Christine.Cripps@orcc.on.ca.

³ The abbreviation used is: PKC, protein kinase C.

are present in a high proportion of human cancers, including colorectal cancers (9), novel therapies directed against *raf* kinase may prove useful in the treatment of *ras*-dependent tumors (10–13).

Experimental antitumor activity was demonstrated for ISIS 3521 and 5132 in several *in vivo* model systems. Decrease in the targeted protein expression was noted with both drugs after incubation in A549 carcinoma cells *in vitro*. The IC_{50} for ISIS 3521 was ~ 100 nM and, for ISIS 5132, ~ 50 – 100 nM in this assay system. Preclinical data suggested prolonged administration of oligonucleotide resulted in superior efficacy, thus Phase I trials of both drugs were carried out with both 21-day infusion and 2 h three times weekly infusion schedules (14–17).

In the Phase I trials, evidence of antitumor activity was observed with both drugs. Nemunaitis *et al.* (14) reported complete responses in 2 patients with low-grade non-Hodgkin's lymphoma, who received ISIS 3521 by 2-h infusion thrice weekly. Yuen *et al.* (15) reported a partial response in ovarian cancer after treatment with ISIS 3521 by 21-day infusion. In the trials of ISIS 5132, although objective responses of measurable disease were not observed, O'Dwyer *et al.* (16) reported prolonged stable disease in patients with colon and renal carcinoma and reduction of *c-raf*-mRNA in the peripheral blood mononuclear cells of the majority of patients studied after thrice weekly 2-h infusion.

Both drugs were well tolerated in both schedules. The 21-day infusion schedule was chosen for further study to ensure more continuous tumor exposure to drug; it was also more convenient for patients because it required only once weekly clinic visits (rather than three times a week). The maximum tolerated dose of ISIS 5132 given by continuous infusion was not reached at 4 mg/kg/day. For ISIS 3521, fatigue and thrombocytopenia were observed at 3 mg/kg/day. The recommended Phase II dose for both drugs was 2 mg/kg/day. The steady-state plasma concentrations of full-length oligonucleotide observed at this dose level were comparable with the *in vitro* IC_{50} s of both drugs for mRNA expression, protein expression, and proliferation.

This randomized noncomparative Phase II trial was done to determine tolerability and quantitative efficacy of ISIS 3521 and ISIS 5132 in patients with locally advanced or metastatic colorectal cancer.

PATIENTS AND METHODS

Patients with histologically proven metastatic or recurrent colorectal cancer with bidimensionally measurable disease were eligible for this study. No prior systemic chemotherapy for metastatic or recurrent disease could have been given. Adjuvant chemotherapy was permitted but must have been completed ≥ 12 months before study entry. Patients had to have an Eastern Cooperative Oncology Group performance status of 0 or 1 and a life expectancy of ≥ 12 weeks. Patients must have been ≥ 18 years of age, and there was no upper age limit. Additional eligibility criteria included absolute granulocytes $\geq 1.5 \times 10^9$ /liter, platelets 100×10^9 /liter, serum creatinine $\leq 2 \times$ upper limit, a bilirubin of ≤ 2 times the upper normal limit, < 5 times the upper limit of normal, and a normal prothrombin time (or international normalized ratio) and partial thrombin time. Pa-

tients may have had radiation therapy but must have recovered from acute toxic effects before registration. At a minimum, one measurable lesion had to have been $\geq 2 \times 2$ cm on computed tomography scan or $\geq 1 \times 1$ cm on chest X-ray or physical exam. Initially, patient entry was restricted to those with relatively nonbulky disease (largest lesion ≤ 40 cm²) because there was a theoretical concern that these agents might take some time to have an effect on tumor mass and might be preceded by temporary increases in tumor size. If this consideration was true, then patients with bulky metastatic disease might not tolerate a period of growth before shrinkage. However, later in the trial, this requirement was eliminated, because it reduced substantially the number of eligible patients, and we felt that, if the drugs were to be useful, it was best tested in a more widely representative population of metastatic disease patients.

Informed consent was obtained from all patients before the start of treatment, and the study was approved by the Research Ethics Board at each participating institution.

The patients were evaluated at baseline by physical examination, computed tomography scans, and chest X-rays (and other X-rays as clinically indicated). Patients were then randomized to receive either ISIS 3521 or ISIS 5132.

Therapy consisted of either ISIS 3521 or ISIS 5132 at a dose of 2 mg/kg/day as a continuous i.v. infusion for 21 days. This was repeated every 4 weeks. A central line or a peripherally inserted central venous catheter was used for administration of the assigned drug. Evaluation of response was performed every two cycles with the repetition of all initially positive radiology.

A complete response was defined as disappearance of all clinical and radiological evidence of tumor determined by two observations not < 4 weeks apart. The patients must also have been free of all tumor-related symptoms. Partial response was defined as a $\geq 50\%$ decrease in the overall sum of the products of measurable lesions determined by two observations not < 4 weeks apart. No simultaneous increase in the size of any lesion or the appearance of any new lesion may have occurred, or the appearance of any new lesions may have occurred. Stable disease was defined as disease less than a partial response that is $< 50\%$ decrease in the overall sum of the products of measurable lesions or progression less than progressive disease documented to be present for ≥ 6 weeks after the start of therapy. Progressive disease was defined as an unequivocal increase of $\geq 25\%$ in the overall sum of the products of measurable lesions as compared with baseline. The appearance of new lesions constituted progressive disease. Response duration was measured from the time the measurement criteria were first met until disease progression was documented.

Toxicity was assessed before every course of therapy and graded using the National Cancer Institute of Canada Clinical Trials Group Expanded Common Toxicity Criteria. Doses were reduced for hematologic and nonhematologic toxic effects. The dose of the next cycle was decreased by 50% if either nadir granulocytes were $< 0.5 \times 10^9$ /liter, the patient experienced febrile neutropenia, or if the platelet count was $< 25 \times 10^9$ /liter. Nadir blood values had only to be achieved on one occasion for the dose reduction rules to come into play. Treatment was discontinued if there was no recovery of counts by 2 weeks' time. Grade 4 nausea and vomiting, despite antiemetic therapy,

and grade 3 major organ toxicity required a dose reduction of 50% for the next cycle.

Blood sampling to determine plasma levels of ISIS 3521 and ISIS 5132 was done predose and on days 8, 15, and 22 5–10 min before the pump was stopped in cycles 1 and 3. An aliquot of plasma (100 μ l) for each sample was spiked with a known concentration of internal standard (T_{27} , a 27-mer phosphorothioate oligodeoxythymidine) and extracted using solid phase extraction and analyzed by capillary electrophoresis (18). Extracted samples were analyzed by capillary gel electrophoresis using a Beckman capillary electrophoresis instrument (Beckman Instruments, Irvine, CA) with UV detection at 260 nm. The limit of quantitation for this assay is \sim 0.10 μ g/ml in plasma.

The sample size for each arm of the trial was based on a Fleming two-stage design using a null and alternate hypothesis of \leq 5 and \geq 20%, respectively. Fifteen evaluable patients were to be recruited to each arm, and responses were assessed. Randomization would continue to 30 evaluable patients in each arm if at least one objective response was seen in both arms. If only one arm had response(s) observed, the other would close, and accrual was to continue only in the arm with activity. If neither arm had at least one objective response, the trial was to close.

RESULTS

From March 11, 1998 to September 29, 1999, 38 patients were randomized with 19 to each arm. One patient cancelled (withdrew consent before starting treatment); thus, 37 patients (19 on ISIS 3521 and 18 on ISIS 5132) were evaluable for nonhematological and hematological toxicity. Five patients could not be evaluated for response. One had a major dosing error receiving only 1/7th of the planned dose. Two patients received only 1 week of treatment before withdrawing consent, and 2 patients did not have repeat radiological tests to reassess response. Patient characteristics of the 37 treated patients are listed in Table 1. Liver was the predominant site of metastatic disease (28 patients). Fourteen patients had one site of disease, 10 had two sites of disease, and 5 patients had three sites. Eight patients had 4 sites of disease. Fourteen patients had prior adjuvant chemotherapy, and 13 patients had prior radiotherapy.

Response. Four of the 17 evaluable patients treated with ISIS 3521 had stable disease (median duration of 3.4 months), and five of the 15 evaluable patients treated with ISIS 5132 had stable disease (median duration of 3.5 months). There were no complete or partial responses (response rate 0% in both arms with 95% confidence intervals of 0–16.2% and 0–18.1%, respectively, for ISIS 3521 and ISIS 5132, respectively). Thus, the trial was closed to accrual at the end of the first stage in both arms. All remaining patients had disease progression.

Toxicity. Toxicity was graded according to National Cancer Institute of Canada Clinical Trials Group Expanded Common Toxicity Criteria. In general, both agents were well tolerated. Toxic effects are shown in Table 2. There were no grade 4 or 5 toxic effects in either arm. The only episode of grade 3 hematologic toxicity was a single patient receiving ISIS 5132 with grade 3 thrombocytopenia. The most common non-hematologic toxicities were lethargy, anorexia, nausea, and vomiting. There were also 15 patients who had transient eleva-

Table 1 Patient characteristics

	ISIS 3521 <i>n</i> = 19	ISIS 5132 <i>n</i> = 18	All patients <i>n</i> = 37
Median age (years and range)	59 (36–82)	63 (47–79)	62 (36–82)
	No. patients		
Sex			
Female	7	6	13
Male	12	12	24
Performance status (ECOG) ¹			
0	6	11	17
1	13	7	20
Prior therapy			
Adjuvant chemotherapy	9	5	14
Radiotherapy	9	4	13
Sites of disease			
Abdomen	1	2	3
Ascites	3	3	6
Bone	1	1	2
Colon	0	3	3
Liver	14	14	28
Lung	3	8	11
Nodes	5	9	14
Pelvis	2	4	6
Rectum	1	0	1
Skin	0	2	2
Spleen	1	1	2
S.C. soft tissue	0	2	2
Other	1	0	1
No. of sites of disease			
1	11	3	14
2	4	6	10
3	2	3	5
4	2	6	8

¹ ECOG, Eastern Cooperative Oncology Group.

tions of liver enzymes while receiving therapy. Fourteen were grade 1 or 2, and none were clinically significant. In some cases, these changes were attributable to worsening of pre-existing liver metastases, but 2 of 9 patients who had no evidence of liver metastases at baseline exhibited grade 1 elevation of aspartate aminotransferase attributed to the antisense therapy. Both of these patients were receiving ISIS 5132. Frequent monitoring of partial thromboplastin time and international normalized ratio while on study showed no evidence of meaningful changes in these parameters.

Pharmacokinetics. The mean steady-state blood levels from those patients who underwent plasma sampling on days 8, 15, and 22 are summarized in Table 3. Overall, \sim 55–70% of oligonucleotides was in the intact, 20-mer form. The remainder had undergone some degradation to shorter length oligonucleotide. The overall mean steady-state concentration of ISIS 3521 was 0.892 μ g/ml (130 nM) and of ISIS 5132 was 0.783 μ g/ml (116 nM).

DISCUSSION

Neither ISIS 3521 nor ISIS 5132 demonstrated evidence of clinical activity as assessed by objective response in this population of metastatic colorectal cancer patients untreated previously. Although it can be argued that with noncytotoxic agents, stable disease, rather than objective response, might be the more likely beneficial clinical outcome, only 9 patients in both arms

Table 2 Hematologic and nonhematologic toxic effects: worst by patient

Toxicity	ISIS 3512 (n = 19)					ISIS 5132 (n = 18)				
	Gr 1	2	3	4	Total	Gr 1	2	3	4	Total
Fatigue	6	7			13	6	6	1		13
Anorexia	3	1	1		5	2	2			4
Nausea	2		2		4	4	1			5
Vomiting	2	1			3	1				1
Stomatitis	2	1			3	2				2
Diarrhea	1				1	2				2
Infection					0		1			1
Altered mood	1	1			2					0
Granulocytes					0					0
Hemoglobin	9	4			13	6	4			10
Platelets	4	1			5	4		1		5
Creatinine	2				2	3				3
AST (all pts)	5	2			7	5	2	1		8
AST (pts without liver metastases, n = 9)					0	2				2

^a Nonhematologic effects included are those possible, probably, or definitely drug related.

Table 3 Summary of plasma concentrations of ISIS 3521 and ISIS 5132

ISIS drug	Sample day	No. patients	Parent plasma concentration (µg/ml) ^a	Total plasma concentration (µg/ml)	% Intact ^b
3521	8	9	0.880 ± 0.670	1.200 ± 0.855	68.01 ± 14.85
	15	6	0.546 ± 0.316	0.789 ± 0.526	60.50 ± 7.75
	22	11	1.250 ± 1.809	1.433 ± 1.746	55.43 ± 3.95
	Css ^c		0.892 ± 0.352	1.141 ± 0.326	
5132	8	6	0.642 ± 0.520	0.870 ± 0.853	70.31 ± 11.31
	15	6	1.142 ± 1.461	1.256 ± 1.483	61.49
	22	9	0.565 ± 0.442	0.782 ± 0.775	70.60 ± 6.47
	Css		0.783 ± 0.313	0.969 ± 0.252	

^a 1 µg/ml = 142.86 nM.

^b Not all patients could be analysed for % intact.

^c Average concentration of days 8, 15, and 22.

(28%) had stable disease of a relatively brief duration (median 3.4 months). Thus, it is unlikely that treatment with the *c-ras* kinase antisense or the PKC- α antisense has meaningful clinical activity in this disease.

There are several potential explanations for this lack of efficacy. It is possible that with the dose and/or schedule used, there were insufficient tumor concentrations of the antisense agents achieved to effectively inhibit target protein production. Although the mean steady-state plasma levels for both agents were above their respective IC₅₀s for inhibition of mRNA expression, these levels may not have been achieved in the target tissue. Assays of tumor levels of drug might have been helpful in determining this, but serial tumor measures were not thought to be feasible when the trial was designed. It could be also argued that the 2-h, three-times-a-week schedule might have been better suited for Phase II evaluation because higher peak concentrations of drug can be achieved with a short infusion. However, all preclinical evidence suggested that continuous exposure to antisense was desirable, so the rationale for the 21-day infusion seems sound. Secondly, it is possible that adequate levels were in fact achieved, and either the targets themselves are not important in this malignancy or other intracellular events pre-

vented the drugs from inhibiting protein production in an effective manner.

A number of other Phase II trials with these agents are under way, but as yet, none have been published. In addition, a Phase I/II trial in non-small cell lung cancer of ISIS 3521 in combination with carboplatin and paclitaxel has been reported recently (19). Investigators found no evidence of additive toxicity when the antisense was combined with chemotherapy, and the regimen was promising with respect to measures of efficacy (response rates, time to progression, and survival). These results have led to a large randomized trial of this combination regimen *versus* paclitaxel + carboplatin in patients with advanced non-small cell lung cancer.

Other small inhibitors of the same molecular targets are undergoing evaluation at this time, and these studies may help determine whether these targets are relevant in colorectal cancer. However, based on our results, we feel that additional single agent studies with ISIS 3521 and ISIS 5132 at this dose and schedule in this population are not warranted. In fact, the results of the randomized combination study referred to above will be very important, not only in determining the role of the particular antisense molecule, but in contributing to our more general

understanding of how such targeted therapies might be best deployed.

ACKNOWLEDGMENTS

We are grateful for the support of the National Cancer Institute Canada and Isis Pharmaceuticals, the editorial review by Dr. Elizabeth Eisenhauer, and the assistance in the preparation of the manuscript by Doris Potenza. We also thank the following investigators who, in addition to the authors, contributed to this study: Dr. Malcolm Moore, Princess Margaret Hospital, Toronto, Ontario, Canada; Drs. Anthony Fields and Laurie Wood, Cross Cancer Institute, Edmonton, Alberta, Canada; and Dr. Rakesh Goel, Ottawa Regional Cancer Centre, Ottawa, Ontario, Canada.

REFERENCES

- Canadian Cancer Statistics 2000. National Cancer Institute of Canada, Statistics. Canada.
- Cohen, A. M., Minsky, B. D., and Schilsky, R. L. Colon cancer. *In*: V. T. DeVita, Jr., S. Hellman, and S. A. Rosenberg (eds.), *Cancer: Principles & Practice of Oncology*, Ed. 4, p. 92. Philadelphia: J. B. Lippincott Co., 1993.
- Saltz, L. B., Cox, J. V., Blanke, C., Rosen, L. S., Fehrenbacher, L., Moore, M. J., Maroun, J. A., Ackland, S. P., Locker, P. K., Pirota, N., Elfring, G. L., and Miller, L. L. Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. Irinotecan Study Group. *N. Engl. J. Med.*, *343*: 905–914, 2000.
- Basu, A. The potential of protein kinase C as a target for anticancer treatment. *Pharmacol. Ther.*, *59*: 257–280, 1993.
- Gescher, A. Towards selective pharmacological modulation of protein kinase C: opportunities for the development of novel antineoplastic agents. *Br. J. Cancer*, *66*: 10–19, 1992.
- Yuspa, S. H. The pathogenesis of squamous cell carcinoma: lessons learned from studies of skin carcinogenesis—thirty-third G. H. A. Clowes Memorial Award Lecture. *Cancer Res.*, *54*: 1178–1189, 1994.
- Dean, N. M., McKay, R., Condor, T. O., and Bennett, C. F. Inhibition of protein kinase C: α expression in human A-549 by antisense oligonucleotides inhibits induction of intracellular adhesion molecule 1 (ICAM-1) mRNA by phorbol ester. *J. Biol. Chem.*, *269*: 16416–16424, 1994.
- Daum, G., Eisenmann-Toppe, I., Fries, H-W., Toppnair, J., and Rapp, U. R. The ins and outs of raf kinases. *TIPS*, *19*: 474, 1994.
- Hamilton, S. Molecular genetics of colorectal carcinoma. *Cancer (Phila.)*, *70* (Suppl.): 1216–1221, 1992.
- Zhang, X-F., Settleman, J., Kyriakis, J. M., Takeuchi-Suzuki, E., Elledge, S. J., Marshall, M. S., Bruder, J. T., Rapp, U. R., and Avruch, J. Normal and oncogenic p^{21ras} proteins bind to the animoterminal domain of *c-raf*-1. *Nature (Lond.)*, *364*: 308–313, 1993.
- Bos, J. L. Ras oncogenes in human cancer: a review. *Cancer Res.*, *49*: 4682, 1989.
- Rapp, U. R., Cleveland, J. L., Bonner, T. I., and Storm, S. M. The raf oncogenes. *In*: E. P. Reddy, A. M. Skalka, and T. Curran (eds.), *The Oncogene Handbook*, p. 213. Amsterdam: Elsevier Science Publishers, B. V., 1988.
- Stanton, V. P., Jr., and Cooper, G. M. Activation of human raf transforming genes by deletion of normal animo-terminal coding sequences. *Mol. Cell. Biol.*, *7*: 1171, 1987.
- Nemunatis, J., Holmlund, J. T., Kravynak, M., Richards, D., Bruce, J., Ognoskie, N., Kwok, T. J., Geary, R., Dorr, A., Von Hoff, D. D., and Eckhardt, S. G. Phase I evaluation of ISIS 3521 (ISI 641A), an antisense oligodeoxynucleotide to protein kinase C- α in patients with advanced cancer. *J. Clin. Oncol.*, *17*: 3586–3595, 1999.
- Yuen, A. R., Halsey, J., Fisher, G. A., Holmlund, J. T., Geary, R. S., Kwok, T. J., Dorr, A., and Siki, B. I. Phase I study of an antisense oligonucleotide to protein kinase C- α (ISIS 3521/ISI 641A) in patients with cancer. *Clin. Cancer Res.*, *5*: 3357–3363, 1999.
- Stevenson, J. P., Yao, K-S., Gallagher, M., Friedland, D., Mitchell, E. P., Cassella, A., Monia, B., Yu, R., Holmlund, J., Dean, N., Dorr, F. A., Geary, R., and O'Dwyer, P. J. Phase I clinical/pharmacokinetic and pharmacodynamic trial of the *c-raf*-kinase antisense oligonucleotide ISIS 5132 (CGP 69846A). *J. Clin. Oncol.*, *17*: 2227–2236, 1999.
- Cunningham, C. C., Holmlund, J. T., Schiller, J. H., Geary, R. S., Kwok, T. J., Dorr, A., and Nemunaitis, J. A phase I trial of *c-raf* kinase antisense oligonucleotide ISIS 5132 administered as a continuous intravenous infusion in patients with advanced cancer. *Clin. Cancer Res.*, *6*: 1626–1631, 2000.
- Leeds, J. M., Graham, M. J., Truong, L., and Cummins, L. L. Quantitation of phosphorothioate oligonucleotides in human plasma. *Anal. Biochem.*, *235*: 36–43, 1996.
- Yuen, A., Halsey, J., Fisher, G., Advani, R., Moore, M., Saleh, M., Ritch, P., Harker, G., Ahmed, F., Jones, C., Polikoff, J., Keiser, W., Kwok, T., Holmlund, J., Dorr, A., and Siki, B. I. Phase I/II trial of ISIS 3521, an antisense inhibitor of PKC α , with carboplatin and paclitaxel in non-small cell lung cancer. *Proc. Am. Soc. Clin. Oncol.*, *20*: 309a, 2001.

Clinical Cancer Research

Phase II Randomized Study of ISIS 3521 and ISIS 5132 in Patients with Locally Advanced or Metastatic Colorectal Cancer: A National Cancer Institute of Canada Clinical Trials Group Study

M. Christine Cripps, Alvaro T. Figueredo, Amit M. Oza, et al.

Clin Cancer Res 2002;8:2188-2192.

Updated version Access the most recent version of this article at:
<http://clincancerres.aacrjournals.org/content/8/7/2188>

Cited articles This article cites 16 articles, 8 of which you can access for free at:
<http://clincancerres.aacrjournals.org/content/8/7/2188.full#ref-list-1>

Citing articles This article has been cited by 10 HighWire-hosted articles. Access the articles at:
<http://clincancerres.aacrjournals.org/content/8/7/2188.full#related-urls>

E-mail alerts [Sign up to receive free email-alerts](#) related to this article or journal.

Reprints and Subscriptions To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions To request permission to re-use all or part of this article, use this link
<http://clincancerres.aacrjournals.org/content/8/7/2188>.
Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.