Schedule-selective Biochemical Modulation of 5-Fluorouracil: A Phase II Study in Advanced Colorectal Cancer


Medical Oncology [A. F. S., C. A., A. P. G., A. M. M., L. M. T., E. A. B., R. R.], Surgical Oncology [S. B.], and Epidemiology [P. B.] Departments, Istituto Nazionale per la Ricerca sul Cancro, and Institute of Radiology, University of Genoa [G. A. R.], Viale Benedetto XV, 10 16132 Genova, Italy; Medical Oncology-Ospedali Galliera, Via Mura delle Cappuccine 14, 16100 Genova, Italy [S. M.]; and Memorial Sloan-Kettering Cancer Center, New York, New York 10021 [J. R. B.]

Abstract

Based on experimental findings suggesting that 5-fluorouracil (Fura) may have different mechanisms of action depending on the schedule of administration, we generated the hypothesis that biochemical modulation of this fluoropyrimidine should be schedule specific. We thus tested the activity of a hybrid regimen consisting of two biweekly cycles of Fura bolus (600 mg/m²) modulated by pretreatment (24-h interval) with methotrexate (200 mg/m²), alternating with a 3-week continuous infusion of Fura (200 mg/m²/day) modulated by low-dose (65)leucovorin (20 mg/m² bolus weekly).

Thirty-three consecutive patients with advanced measurable colorectal cancer and no prior therapy for metastatic disease entered the study from February 1992 to August 1993. They were treated with two biweekly cycles of Fura bolus (600 mg/m²) preceded by (24-h interval) methotrexate (200 mg/m²), alternating with a 3-week continuous infusion of Fura (200 mg/m²/day) modulated by low-dose (65)leucovorin (20 mg/m² bolus weekly). The median Eastern Cooperative Oncology Group performance status was 1; the liver was the only metastatic site in 17 patients. Treatment outcome was evaluated by computed tomographic scan in all patients, except for two.

Three complete and 13 partial responses were obtained among these 33 patients (response rate, 48%; 95% confidence limits, 31–66%). Performance status (Eastern Cooperative Oncology Group) influenced clinical response. The combined complete response and partial response rate was 69%, 33%, and 25% in patients with an Eastern Cooperative Oncology Group performance status of 0, 1, and 2, respectively ($\chi^2 = 4.8$, $P = 0.032$, two-tailed Mantel test for trend). After a median follow-up of 26 months, 10 patients are still alive. The median progression-free survival and overall survival were 9.5 and 20.2 months, respectively. No toxic deaths or grade 4 toxicity occurred. The incidence of grade 3 toxicity per patient in any cycle was: mucositis 6%, diarrhea 3%, and vomiting 3% for the bolus part and 21%, 3%, and 6%, respectively, for the continuous infusion part of the regimen. Hand-foot syndrome occurred in 27% of the patients treated with the continuous infusion regimen.

Introduction

While the Phase II clinical activity of novel agents such as the camptothecin analogue CPT-11 (1) and the new TS inhibitor ZD 1694 (2) are promising, the standard treatment of advanced colorectal cancer remains Fura. The response rate to this drug given as a weekly bolus is approximately 10–15%, and biochemical modulation of the fluoropyrimidine by MTX or LV is needed to reach a 20–30% response rate in this disease (3, 4). Initial enthusiastic reports of Fura modulation with phosphonoacetyl-l-aspartate (5) or IFN (6) have not been confirmed by subsequent studies (7, 8). The most widely used modulating agents therefore remain LV and MTX. Several randomized comparisons of either combination versus Fura alone were analyzed in two recent meta-analysis articles (3, 4). The objective tumor response rates to Fura alone obtained in the two analyses were 11% and 10% as compared to 23% in Fura + LV-treated patients ($P < 0.000001$) and 19% in patients receiving sequential MTX-Fura ($P < 0.0001$). Despite this enhanced activity, overall survival was not significantly different with Fura + LV as compared to Fura alone (11.5 versus 11.0 months, respectively). In addition, the small, although significant, survival advantage for MTX-Fura as compared to Fura alone (10.7 versus 9.1 months, respectively, $P = 0.0024$) indicates that the clinical benefit of these regimens is limited.

Both of these regimens have strong experimental rationales. In the presence of excess 5,10-methylenetetrahydrofolate, generated by LV, the Fura anabolite 5-fluoro(oxy)uridylate forms a more stable inhibitory complex with TS, thereby depleting thymidine triphosphate pools required for both DNA synthesis and repair. On the other hand, pretreatment of colon tumor cells with MTX has been shown to enhance the amount of fluorouridine triphosphate incorporated into RNA; this effect appears to be a consequence of the antifol-induced blockade of purine biosynthesis resulting in accumulation of phosphoribosyl-pyrophosphate, a substrate promoting the activation of FUra to fluorouridine triphosphate (9).

1 Supported by Grants CNR ACRO 94.01213.PF39, AIRC 1994, and CNR BTBS 93.01119.PF70 and grant CA 61586 from the USPHS.
2 To whom requests for reprints should be addressed.
3 American Cancer Society Professor.
4 The abbreviations used are: TS, thymidylate synthase; FUra, 5-fluorouracil; MTX, methotrexate; LV, 5-formyltetrahydrofolate; CI, continuous infusion; CT, computed tomographic; ECOG, Eastern Cooperative Oncology Group; CR, complete response; PR, partial response; PFS, progression-free survival; PS, performance status.
CI FUra represents another rational approach toward improving the activity of this drug in colorectal cancer. Pharmacokinetics, pharmacodynamics, and tumor cell kinetics support this administration schedule for FUra (10, 11).

This article describes a Phase II clinical study of a treatment protocol for advanced colorectal cancer patients based on a series of experimental findings: (a) repeated short-term exposures of human colon cancer cells to FUra in vitro produced resistance via an RNA-related mechanism, whereas resistance to long-term exposures to FUra was mediated by a DNA-directed mechanism (12); and (b) continuous exposure to FUra is cytotoxic to cells resistant to bolus FUra in the same in vitro model (13). These findings allowed us to suggest that FUra may be considered to have two different modes of action depending on its schedule of administration, and that it may be possible to selectively modulate each schedule biochemically. Enhancement of FUra cytotoxicity by LV may be maximal when the fluoropyrimidine is given for prolonged periods of time, as demonstrated in vitro (14), while channeling FUra into RNA using MTX may improve results when short-term, high-dose administration is used. The clinical results of a hybrid-alternating regimen based on this approach to biochemical modulation of FUra are presented.

Patients and Methods

Eligibility Criteria. Every patient with advanced colorectal cancer referred to the Istituto Tumori in Genoa between February 1992 and August 1993 was entered on this protocol if they satisfied all of the following requirements: (a) They had to have biopsy-proven relapsed or metastatic adenocarcinoma of the colon or rectum. (b) The disease had to be measurable. Appropriate radiological examinations (mostly CT scans) had to be obtained no longer than 1 month before the beginning of treatment to serve as a baseline for serial evaluation of the patient's disease status. (c) No prior chemotherapy for metastatic disease was allowed. Adjuvant chemotherapy was not an exclusion criterion provided that treatment was completed longer than 1 year before study entry. Radiation therapy was an exclusion criterion provided that treatment was completed no longer than 1 month before the beginning of treatment. (d) ECOG PS had to be 0, 1, or 2. Serum bilirubin and creatinine levels were required to be less than 3.0 and 1.8, respectively, and aspartate aminotransferase and glutamic-pyruvic transaminase less than four times the upper limits of normal. Granulocyte counts of greater than 1500/mm³ and platelet counts of greater than 100,000/mm³ were required.

Additional eligibility criteria included geographic accessibility, the absence of clinically relevant ascites, and the absence of other medical conditions clearly contraindicating the delivery of any chemotherapy.

This protocol was approved by the Ethical Committee of the Istituto Nazionale per la Ricerca sul Cancro. Only verbal informed consent was required. Before treatment patients were informed as to: (a) the presence of metastatic colorectal cancer; (b) the poor prognosis of their disease; and (c) the experimental nature of this treatment protocol. Upon study entry all patients were given a schedule of drug treatment along with written information about the anticipated toxicities.

![Design of drug regimen. One cycle = 8 weeks. In the first part of the cycle, patients were given MTX, 200 mg/m² i.v. diluted in 500 ml D₅W, infused in 1 h, day 1; FUra, 600 mg/m² i.v. bolus, day 2; and (6S)LV, 10 mg/m² p.o. every 6 h × 6, after FUra bolus (modified from Ref. 15). In the second part of the cycle, patients were given FUra, 200 mg/m²/day CI × 3 weeks, and (6S)LV, 20 mg/m² i.v. bolus every week (modified from Ref. 16).](image)

Treatment Plan. To test our hypothesis of schedule-dependent biochemical modulation of FUra, two well-studied regimens of biochemically modulated schedules were used sequentially. Sequential MTX and bolus FUra (15) were used alternately with CI FUra modulated by LV (16). Fig. 1 illustrates the regimen. One complete cycle of treatment consisted of two MTX → FUra bolus treatments given on days 1 and 2 and 15 and 16, followed by 3 weeks of CI FUra given from day 29 to day 49 modulated by weekly (6S)LV (active form of this coenzyme). After 1 week of rest, the second cycle was started on day 57. The entire duration of one cycle is thus 8 weeks.

CI FUra was administered through an implanted catheter and a venous Port-a-cath (Pharmacia) connected to a portable programmable external pump (CADD-1; Pharmacia). Toxicity was evaluated on days 15, 29, 36, 43, 50, and 57. Complete blood counts were obtained on the same days. Liver function tests, blood urea nitrogen, creatinine, and electrolytes were obtained monthly.

Dose modification criteria for the MTX → FUra regimen were as follows: no dose reduction for gastrointestinal grade I and II toxicity. For grade III diarrhea or mucositis, the treatment was delayed until recovery, and the doses of MTX and FUra of the next cycle were decreased by 50%. The dose was reduced by 50% also for a WBC count of <3000/mm³ or platelet count of <75,000/mm³ on the day of recovery. Treatment was discontinued in the case of grade IV toxicity. CI FUra was discontinued if mucositis and/or palmar-plantar dysesthesia/burning occurred. In the case of severe (grade III) mucositis, the infusion was resumed at a reduced FUra dose (50%). Toxicity is expressed according to WHO criteria.

The duration of treatment depended on outcome. Upon documentation of CR, two additional cycles were given (4 additional months of treatment). In the case of a PR, treatment was continued until two consecutive CT scans, obtained 2 months apart, failed to demonstrate further tumor shrinkage. At that point, chemotherapy was stopped, and the disease was monitored every 2 months. The same regimen was resumed upon documentation of tumor progression. In patients with disease stabilization, treatment was continued until evidence of progression was observed.

Response Evaluation. All patients received at least 2 months of therapy with adequate pretreatment and follow-up radiographic studies, and were thus considered assessable for response. Measurable tumor was defined as a tumor mass that could be clearly measured in two dimensions by imaging tech-
niques. A CR was defined as complete disappearance of all evidence of tumor and return of abnormal tests to normal levels for a minimum of 8 weeks. A PR was defined as a 50% or greater reduction in the sum of the products of the largest perpendicular diameters of all measured lesions in the absence of progression of any lesion or the appearance of any new lesion for at least 8 weeks. Stable disease was defined as too small a change in measurable disease to meet the requirements for PR or progression, without the appearance of new lesions for a period of at least 8 weeks, provided that there was no worsening of symptoms. Disease progression was defined as the development of new areas of malignant disease, or an increase by at least 25% in measurable disease, or a 25% increase in the size of the lesions over that attained at the best response.

An independent radiologist reviewed the CT scans of all patients. Indicator lesions were measured at each successive cycle. The baseline tumor areas and their variations at each successive evaluation were expressed in cm².

Dose Intensity. Delivered dose intensity for bolus FUra and for CI FUra was expressed in mg/m²/week.

Statistical Methods. The study was designed according to Simon's (17) minimax design. Setting P0 = 20% and P1 = 40%, the study should continue if at least four responses occurred among the first 18 patients. In the second stage, the regimen would be dropped if fewer than 10 responses among 33 patients were seen, whereas additional studies would be considered if more than 10 responses occurred (α error, 0.05; β error, 0.20). As 16 responses were seen in 33 patients, the study was stopped. The PFS was measured from the initiation of therapy until the date of disease progression as defined above. The probability of treatment failure and survival was calculated using the Kaplan-Meier method (18). The association between PS and the proportion of responses was assessed using the Mantel test for trend (19).

Results

Patient Characteristics. Between February 1992 and August 1993, 33 consecutive patients were accrued. Table 1 shows the characteristics of the 33 patients entered into this study. Only four patients had received prior adjuvant therapy: two received FUra-LV, one FUra-levamisol, and one unknown chemotherapy. Fifteen of 33 patients had cancer-related symptoms. Fifteen of 33 patients had cancer-related symptoms. The median time between diagnosis of metastatic disease and study entry was 1 (range, 0–16) month. Seventeen patients had liver metastases only, deemed inoperable by our surgeons. The median number of tumor lesions evaluated per patient was three. All patients were assessable for toxicity and response.

Treatment Outcome. Response was evaluated by CT scan in 31 patients, chest X-ray in 1 patient, and ultrasound in 1 patient with multiple liver metastases which were not evaluable by CT scan. Three CRs and 13 PRs were observed among the 33 patients. The overall response rate was 48% (exact 95% confidence interval, 31–66%). The time to achieve a PR or CR was 2 months (eight cases), 4 months (four cases), and 6 months (four cases). Although there were no patients who had tumor shrinkage qualifying for response longer than 6 months after the beginning of treatment, some patients showed continued tumor shrinkage (Fig. 2), and the median time to achieve the maximum clinical response among responding patients was 5 (range, 2–8) months. Fig. 2 also shows the baseline areas of the indicator lesions followed during the study. Our reviewer radiologist usually measured 2–10 lesions on the baseline CT scan films, but this number dropped substantially because not all of them were remeasurable in all of the follow-up films. Thus, in general, the baseline tumor area reported correlates with, but does not represent the total tumor bulk.

Three of the 16 responses were obtained in patients with two metastatic sites, the rest being liver only (12 patients), and lung only (1 patient). All three CRs were obtained in patients with multiple lesions in the liver as the only metastatic site. These responses lasted 6, 8, and 11 months. One of these patients underwent surgical exploration that revealed no residual disease in the liver, but a small nonresectable hylar metastatic lymph node was found. Another patient with near-complete response (97% tumor mass reduction after 10 months of treatment) was rendered disease-free upon hepatic resection of one residual tumor nodule, and is still disease-free 5 months after surgery.

Table 2 illustrates the influence of PS on the clinical response. The combined CR and PR rate was 69%, 33%, and 25% in patients with an ECOG PS of 0, 1, and 2, respectively (χ², 4.6, P = 0.032, two-tailed Mantel test for trend). Age and primary site did not appear to influence the overall clinical response. In patients younger than 60 years of age, one CR and five PRs were obtained (46%) compared to two CRs and eight PRs (50%) in patients over 60 years of age. Five of 9 rectal and 11 of 24 colon cancers responded. The median response duration was 6.5 (range, 2.6–13.6) months.

---

### Table 1 Patient characteristics (n = 33)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>63</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>41–81</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>17</td>
<td>51</td>
</tr>
<tr>
<td>Female</td>
<td>16</td>
<td>49</td>
</tr>
<tr>
<td>ECOG PS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>16</td>
<td>49</td>
</tr>
<tr>
<td>1</td>
<td>9</td>
<td>27</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
<td>24</td>
</tr>
<tr>
<td>Site of primary tumor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colon</td>
<td>24</td>
<td>73</td>
</tr>
<tr>
<td>Rectum</td>
<td>9</td>
<td>27</td>
</tr>
<tr>
<td>Prior adjuvant chemotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>29</td>
<td>88</td>
</tr>
<tr>
<td>Yes</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td>Site of disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver only</td>
<td>17</td>
<td>52</td>
</tr>
<tr>
<td>Lung only</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Liver and lung</td>
<td>5</td>
<td>15</td>
</tr>
<tr>
<td>Pelvis and other sites</td>
<td>6</td>
<td>18</td>
</tr>
<tr>
<td>Other sites</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>Median no. of lesions:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evaluated/patient</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>1–11</td>
<td></td>
</tr>
<tr>
<td>Median baseline tumor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Area (cm²)</td>
<td>28.2</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>4.8–224</td>
<td></td>
</tr>
</tbody>
</table>
A substantial percentage of patients had a minor response or stable disease (42%), with a median duration of 7.5 (range, 2–19) months (Fig. 2). Only three patients progressed after the first cycle (2 months).

All patients are now off treatment. The patient with minimal residual disease in the liver, who was rendered disease free at surgery, was considered to have failed at the time of surgery; all the rest have progressed. With a median follow-up time of 26 (range, 12–34) months, 23 deaths have occurred. The median actual PFS for all 33 patients is 9.5 (range, 2–21) months (Fig. 3), and it is 10 (range, 5.6–16.6) months for patients achieving CR or PR. The median survival time for all patients is 20.2 months (Fig. 4).

Progression occurred in 14 patients because of enlargement of the same lesions, appearance of new lesions in 8 patients, and because of both patterns in 7 patients. The site of progression was the initial site of metastatic disease in 24 patients, while 5 patients had the appearance of new lesions at a different organ site.

**Toxicity.** The total number of cycles (2 months each) administered to the 33 patients was 130. The slightly higher than expected number of bolus MTX → FUra administrations (300) is due to two factors: (a) treatment discontinuation most often occurred just prior to the beginning of the CI part of the cycle, and (b) in occasional patients local skin irritation secondary to catheter placement prevented the timely beginning of the CI. In these patients (n = 4), a third MTX → FUra cycle was given, and the cycle thus consisted of three bolus administrations and 3 weeks of CI.

The slightly lower than expected number of weeks of CI FUra (359 weeks) is due to the fact that a few patients did not complete the 3 weeks of CI because of toxicity. In these patients a new cycle was started and the previous cycle was considered to be made up by two bolus administrations and less than 3 weeks of CI FUra. Thirty-six (12%) of 300 bolus FUra administrations and 37 (10.3%) of 359 weeks of CI FUra were administered at reduced doses. The median FUra dose intensity actually delivered to our patients was 280 mg/m²/week for the bolus part (range, 172–366) and 840 mg/m²/week for the CI part (range, 588–1428). These values represent 93.3% and 60% of planned dose intensity values, respectively.

Table 3 gives the worst toxicity (each type) suffered by each patient across all cycles. The two parts of the regimen are considered separately. No toxic deaths or grade IV toxicities were observed, and in general the treatment was well tolerated with no need for hospitalizations. No prophylactic antiemetics were used during CI FUra, while either metoclopramide plus steroids or ondansetron were used during the first 3 days of the bolus schedule of FUra following MTX therapy. Mucositis and hand-foot syndrome were much more prominent during CI FUra. Conjunctivitis was observed only after several weeks of treatment and could not be attributed to either of the two schedules.

**Discussion**

This trial was based on laboratory research that produced evidence that the mechanism of cell kill by FUra differs, de-
Fig. 3 Kaplan-Meier PFS for all 33 patients.

Table 3 Toxicity: worst WHO grade per patient across all cycles

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>MTX → FUra toxicity grade (%)</th>
<th>CI FUra + (6S)LV toxicity grade (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I</td>
<td>II</td>
</tr>
<tr>
<td>Mucositis</td>
<td>18</td>
<td>15</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td>Conjunctivitis*</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>Hand-foot syndrome</td>
<td>6</td>
<td>0</td>
</tr>
</tbody>
</table>

*Scored as grade 1 if present.

Fig. 4 Kaplan-Meier survival curve for all 33 patients. Twenty-three patients have died.

pending on its mode of administration, and that FUra modulation should therefore be selective for the FUra schedule used (13). Sequential MTX → FUra and CI FUra + LV were chosen as the two components of the regimen mainly because they satisfied our concept of schedule-oriented biochemical modulation. Maximum enhancement of bolus FUra is more likely obtained with drugs that enhance the RNA effect of this fluoropyrimidine such as MTX, N-phosphonacetyl-l-aspartic acid, pyrazofurine, 6-methylthioinosine, acivicin etc. On the other hand, LV represents a selective method of enhancement of the TS inhibitory effect of FUra that in our in vitro experimental tumor system appeared to be the major mechanism of action of CI FUra. Indeed, other investigators also found that maximum FUra antitumor poteniation by LV was obtained in conditions of prolonged exposure (14). The sequence bolus-CI-bolus-CI and not the reverse was chosen because we demonstrated in vitro that cells resistant to bolus FUra were still sensitive to CI FUra but not the reverse, and we and others have suggested that this phenomenon may occur in the clinic as well (20, 21).

It may be argued that equivalent or better results may have been obtained by using these two regimens sequentially, as first- and second-line treatments, and not in an alternate fashion from the beginning. This approach is also worth testing provided that CI FUra + LV is initiated as soon as no additional tumor shrinkage is obtained with MTX → FUra.

Patients with advanced colorectal carcinoma, treated systemically with FUra + LV or MTX, have a median survival of 10–12 months, a median PFS of 3–6 months, and an overall response rate of 20–30% (3, 4). Occasional studies report better results, but these are obtained either at the cost of prohibitive toxicity (22) or in a highly selected patient population (23).

Among five clinical trials conducted in this disease at our institute utilizing FUra, in the last 10 years, the best response rate was 22%, with a maximum PFS of 5 months (24) and a maximum overall survival of 13 months (25). Some of the regimens used in these trials have been very toxic (26). The 20.2 months in median survival time and 9.5 months in median PFS, along with almost a 50% overall response rate represent an improvement in outcome, compared to our previous regimens.

These results are particularly encouraging if we consider the following points: (a) all patients were consecutive; (b) the responses were independently evaluated and the maximum percentage of reduction in tumor mass plotted at each time; also, there were four patients with mass reductions ranging between 45 and 49%; (c) the toxicity was "adequate" for the CI part, but it was very low for the bolus part, leaving room for improvement; and (d) our protocol allowed treatment discontinuation a few months after achieving the best clinical response. Duration of response, PFS, and, possibly, survival may be further improved with more prolonged treatment. Although 50% of the responses were attained within the first cycle of treatment, the median time to the best clinical response was 5 months, suggesting the value of continued treatment for maximum benefit.

There are several possibilities that may further improve these results. First, as previously mentioned, continuing treatment in responsive patients may prolong the duration of response and survival. Treatment to maximum response with MTX → FUra followed by treatment with CI FUra is also worth testing. It might also be possible, with appropriate dose-finding studies, to administer the two different schedules concomitantly in order to take advantage of the synergy between bolus and CI FUra that we have recently described in vitro (13). Partially
similar programs have already been used in the clinic (27, 28), but their outcome has not been particularly satisfactory; possible explanations include the lack of biochemical modulation and the use of schedules of FUra that were not optimal.

Because this is a Phase II study, this approach deserves additional testing in a randomized Phase III trial, comparing this regimen with one or both of the LV- or MTX-modulated FUra schedules. This type of trial is now ongoing at our institute.

References
Schedule-selective biochemical modulation of 5-fluorouracil: a phase II study in advanced colorectal cancer.

A F Sobrero, C Aschele, A P Guglielmi, et al.


Updated version
Access the most recent version of this article at:
http://clincancerres.aacrjournals.org/content/1/9/955

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, contact the AACR Publications Department at permissions@aacr.org.