*Radiol Oncol* 1998; 32(4): 407-15.

# Phase II study of fluorouracil, leucovorin and interferon alpha-2a in patients with advanced colon cancer

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*Based on in vitro studies that have demonstrated synergy between fluorouracil (5-FU) and leucovorin (LV) as well as between 5-FU and recombinant alpha-2a interferon (IFN) against colon cancer cell lines a phase II study was carried out to evaluate the toxicity and clinical activity of 5-FU modulated with LV and IFN in patients with metastatic colon cancer. Twenty-two chemotherapy naive patients with measurable metastases of colon cancer have been treated with daily doses of 5-FU 600 mg/m$^2$ in 6-hr intravenous infusion, and of LV 20 mg/m$^2$ intravenously and IFN 6 MU subcutaneously, for 5 days every 4 weeks. Median age was 60 years, median PS (ECOG) was 1 (range 0-2). Liver, soft tissue and lung metastases were found in 12, 5 and 8 patients, respectively. Nineteen patients had a single metastatic site, two double, whereas one had more than two metastatic sites. Patients had 2-9 (mean 5) cycles of treatment. Objective response was observed in 7 patients (32%), and stable disease in 7 patients (32 %). Overall median survival was 12.5 months, and for responders 14.4 months. Responses were generally short and median time for progression was 5.5 months. The most frequent adverse reactions were flu-like syndrome (50%), nausea/vomiting (36%), diarrhoea (13%), stomatitis (27%) and leucopenia (13%).*

*This regimen of 5-FU with LV and IFN administration does not appear to be superior to previously published schedules of 5-FU with IFN or 5-FU with LV.*

*Key words: colonic neoplasms-drug therapy; clinical trials phase II; fluorouracil; leucovorin; interferon-alpha; neoplasms metastasis*

## Introduction

Colon cancer is one of the most common malignancies in Slovenia, with more than 400 new cases diagnosed each year. In 1995, the incidence of colon cancer per 100,000 population in Slovenia was 22.2 for male and 21.7 for female.[1]

Despite better surgical treatment and adjuvant chemotherapy, approximately 50% patients develop metastases. Patients with metastatic colon cancer have uniformly poor prognosis, because there is no effective therapy.

For more than 40 years fluorouracil (5-FU) has been the mainstay in the treatment of

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colorectal cancer. As a single agent or in combinations with other chemotherapeutic agents, the overall response in advanced colorectal cancer is in the range of 17% to 24%, with median survival time of approximately 11 months.[2] In an attempt to improve these results several approaches have been adopted. The most promising is the adjunction of a modulatory agent, leucovorin (LV), which interferes with the mechanisms of 5-FU cytotoxicity. Experimental studies have demonstrated that LV is metabolised to a compound that stabilised the ternary complex formed between the 5-FU metabolite fluorodeoxyuridilate and enzyme thymidylate synthase, a key enzyme in DNA synthesis thereby inhibiting enzymatic function and increasing cytotoxicity of 5-FU.[3-5] In several randomised trials in metastatic colorectal cancer, 5-FU/LV combination produced statistically significant improvements in response rate compared with 5-FU alone, and a modest improvement in survival.[6-8]

In preclinical models, combining the recombinant interferon alpha-2a (IFN) and 5-FU resulted in the augmentation of the cytotoxic effects of 5-FU. The principal mechanism of IFN modulation of 5-FU is currently uncertain. However, evidence exists that this agent alters the 5-FU plasma pharmacokinetics by increasing the area under the concentration (AUC)[9] and the formation of fluorodeoxiuridine-monophosphate,[10] inhibiting the 5-FU induced upregulation of thymidilate synthase, as well as thymidine kinase,[11] and enhancing incorporation of fluorodeoyiuridine triphosphate into DNA.[12]

In 1989, Wadler published promising results of the treatment of metastatic colorectal carcinoma with a combination of 5-FU and IFN. The reported response rate was 76% in a subgroup of non-pre-treated patients.[13] In 1991, inspired by these results, we started a clinical trial in patients with metastatic colon cancer using double modulation of 5-FU with LV and IFN. The aim of this study was to evaluate the toxicity, response rate and overall survival in the treatment with this drug combination. However, as the recent reports of studies on 5-FU double modulation by LV and IFN are conflicting,[14] we reviewed and discussed available clinical studies using double modulation of 5-FU with LV and IFN.

## Patients and methods

Between December 1991 and January 1994, 22 patients with measurable metastatic colon cancer and Eastern Co-operative Oncology Group (ECOG) performances status of 0 to 2 were entered into the study protocol approved by Medical Ethics Committee at the Ministry of Health of the Republic of Slovenia. The patients who had received no prior chemotherapy for metastatic disease had to meet the following additional criteria: metastatic disease not amenable to surgery, prior adjuvant therapy with 5-FU alone or with levamisol had to be completed >8 months before study entry, no evidence of cardiovascular disease, adequate organ function including normal bone marrow function (leukocyte count >3,500/μL, platelet count >100,000/μL), renal function (creatinin <1.5 mg/dL or creatinin clearance >60 ml/min), and normal hepatic function (bilirubin < 38 mmol/L, liver transaminase level < 3 times the normal values, an albumen value>36 g/L, negative hepatitis B surface antigen).

Patients with active cardiac disease, infection, clinically significant pulmonary and neurologic dysfunction, cerebral metastases, any significant intercurrent illness, requirement of systemic steroids, psychiatric history, or those who had undergone surgery, chemo-immuno- or radiation therapy were not eligible.

In the 4 weeks before entering the trials, the size of the metastatic lesions was determined by computed tomography and/or

ultrasound and /or X-ray examinations and the serum levels of the carcinoembryonic antigen (CEA) was measured. The size of the lesions was determined after every second treatment cycle. The patients with disease progression had the best supportive care with no additional second line chemotherapy.

*Treatment plan*

Patients received LV (Leucovorin Ben Venue Laboratories Bedford) 20 mg/m$^2$/day intravenously (i.v.) and half-an hour later 5-FU which was administered in 6-hr continuos intravenous infusion at a dose of 600 mg/m$^2$/day diluted in 1,000 ml of normal saline. 5-FU was obtained commercially. Recombinant human IFN α-2a (Roferon; Hoffman La-Roche) was administered subcoutaneusly (s.c.) in a dose of 6 MIU consecutively after each 5-FU administrations. Patients received all three drugs for 5 consecutive days. Cycles were repeated at 28-day intervals. The dose of 5-FU was modified for myelosupression, diarrhoea and stomatitis. In grade 3 or 4 toxicity the dose of 5-FU was reduced for 20%. Subsequent courses were delayed until haematological recovery to the following values: granulocytes, 1,500 /μL or higher and platelets 100,000 or higher, and resolution of all nonhematologic toxicity to Grade I or baseline. There was no reduction of the doses of LV and IFN.

*Response criteria*

Treatment response was evaluated after each 2$^{nd}$ cycle. The responders and those with stable disease were subjected to regular clinical and radiological follow up every two months until progression, and then after 3 months until deaths. Tumor response was defined according to World Health Organisation (WHO) criteria.[15] A complete response (CR) was defined as the disappearance of all known disease symptoms on two separate measurements performed in at least 4 week interval; partial response (PR) was defined as a ≥ 50% decrease in the sum of products of the largest perpendicular diameters of all measurable lesions for a minimum of 4 weeks, without the appearance of new lesions; stable disease (SD) was defined as a decrease by <50% or increase by <25%, with no new lesions; progressing disease (PD) was defined as a 25% or greater increase in measurable disease or appearance of new lesions. The duration of response was measured for patients with objective response from the onset of objective response to the time of progression. The duration of survival was measured from the first day of treatment until the date of death.

*Statistical Analysis*

The survival, duration of response and the time to progression were calculated using log-rank test,[16,17] while the calculations of the 95% confidence interval for response rate were made by Brookmeyer and Crowley's method.[18]

## Results

The characteristics of the 22 patients entered into this study are listed in Table 1. Seven patients received prior adjuvant therapy consisting of 5-FU and levamisol. The majority of patients had minimal cancer related symptoms. Their ECOG PS was 0-1 except in 1 patient. Patients received 2 to 9 cycles of chemoimmunotherapy (mean 5 cycles). All patients were eligible and evaluable.

*Tumour response*

The overall response rate was 32% (95% confidence interval (CI) 14% to 52%) (Table 2). All

**Table 1.** Patients' characteristic

| Characteristic | No. of patients |
|---|---|
| Age, years | |
| Median | 60 |
| Range | 31-78 |
| Male/Female | 11/11 |
| ECOG performace status | |
| 0/1/2 | 13/8/1 |
| Prior adjuvant therapy | 7 |
| Sites of disease: | |
| - Liver | 12 |
| - Lung | 8 |
| - Peritoneum | 2 |
| - Lymph nodes | 3 |
| No. of metastatic sites | |
| 1 | 19 |
| 2 | 2 |
| 3 | 1 |

responses were partial. There was no complete response. The median time to achieve initial response was 2.5 months (range 1.5 to 4.0). Most responding patients showed continued improvement in their disease status, and the median time to achieve best clinical response was 4.0 months (range 1.5 to 5.0). In addition, 32% of patients had stable disease (range 3 to 14 months). Two of twelve patients with metastases involving liver only, two of eight patients involving lung only and two patients with the involvement of both, lung and an extrahepatic site responded. In two patients with lung and soft tissue metastases, CR was observed in one metastatic site, in the lung of one patient and in the soft tissue of the other. In one patient who had liver, lung and soft tissue metastases CR was observed in the lung and soft tissue whereas in the liver only PR was noticed. The patient who had experienced daily hectic fever to 38.5°C caused by liver metastases, completely resolved the fever within 2 weeks of the initiation of therapy. In the group of seven patients, treated with adjuvant chemotherapy, we did not see any response to chemoimmunotherapy.

*Survival*

Overall median survival time was 12.5 months and of responders 14.4 months (Figure 1). Median follow up was 12 months. Among 22 patients, 20 patients died. Their survival ranged from 4 to 30 months. Two patients are still alive 26 and 36 months after beginning the study. The median time to progression was 5.5 months in 20 patients. In the patients with objective response the median time to progression was 8.7 months. The two survivors have been without any

**Table 2.** Tumor response

| Response | No. of patients | Response rate (%) |
|---|---|---|
| Objective response | 7 | 32 (95% C.I. 14-52%) |
| CR | 0 | 0 |
| PR | 7 | 32 |
| Stable disease | 7 | 32 |
| Progressive disease | 8 | 36 |

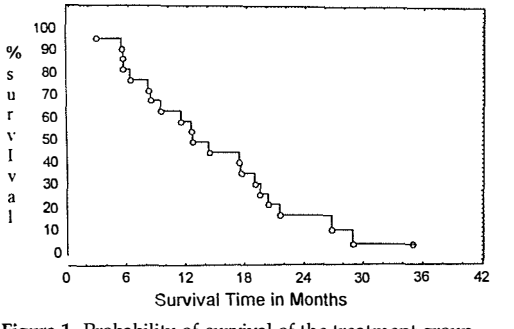


**Figure 1.** Probability of survival of the treatment group.

sign of progression in the last 22 and 30 months, respectively.

*Toxicity*

As shown in Table 3, the side effects of chemotherapy were generally mild and not exceeding the toxicity grade of 3 to 4, neither causing toxicity related deaths nor requiring discontinuation of chemotherapy due to toxicity. In one patient chemotherapy was postponed for 14 days due to grade 2 leucopenia. One patient requested a dose reduction of 5-FU due to anorexia and plantar-palmar erytroderma. The most common toxicity was flu-like syndrome which occurred in 11 patients. After the 3rd cycle, the majority of the patients did not complain anymore of any of these types of toxicity. Nausea and vomiting grade 1 and 2, mild diarrhoea, leucopenia and plantar-palmar erythroderma occured in 8,3,3, and 6 patients, respectively.

**Table 3.** Toxicity: The worst grade per patient across all cycles

| | Toxcity grade per patient | | | |
|---|---|---|---|---|
| | 1 | 2 | 3 | 4 |
| Flu-like | 7 | 4 | | |
| Nausea/vomiting | 6 | 2 | | |
| Stomatitis | 3 | 2 | | |
| Diarrhoea | 3 | 2 | | |
| Anorexia | 3 | 3 | | |
| Leukopenia | 2 | 3 | | |
| Plantar-palmar Erythrodema | 5 | 1 | | |

## Discussion

In an effort to improve its antitumor activity, a number of strategies to modulate the cytotoxicity of 5-FU have been investigated. One approach has focused on the use of the LV in combination with 5-FU to stabilise the binding of the active metabolite fluorodeoxyuridine monophosphate to its target enzyme, thymidylate sinthase. The 5-FU/LV combination produced statistically significant improvements in response rates compared with 5-FU alone in several randomised trials in metastatic colorectal cancer,[19-21] although improved survival was noted in two trials only.[7,8] Inhibition of thymidine incorporation into DNA is likely to be enhanced by IFN as a result of its inhibitory effect on thymidine kinase.[11] Based on this biochemical rationale of inhibiting two key enzymes of 5-FU metabolism, a number of trials have been performed in order to investigate the possibility of biochemical double modulation and to assess the feasibility of this combination (Table 4).

We have demonstrated the feasibility of administering 6 MIU IFN with 5-FU and low dose LV. Our combination of 5-FU/LV/IFN has activity in previously untreated patients with colon cancer. We have observed a 32% overall response rate. The reason for such a response rate and low toxicity may lie in a relatively high dose of 5-FU and the administration of 5-FU in prolonged infusion. A dose - response relationship has been suggested for 5-FU in colon cancer. 5-FU is a drug with very short plasma half-life of approximately 12-18 minutes. The drug has cytotoxic activity against cells in S phase. With bolus administration, a small proportion of cancer cells would be susceptible.[22,23] Thus, there exists a sound rationale for the preference of continu-

**Table 4.** Results of trials of 5-fluorouracil (5-FU), leucovorin (LV) and interferon alpha (IFN) for treatment of meatastatic colorectal cancer

| Reference | 5 - FU/LV/ IFN regimen | No. of patients | Objective response (%) |
|---|---|---|---|
| Yalavarthi[27] | 5-FU 370 mg/m2 i.v. d 2 - 6q 21 d<br>LV 500 mg/m2 i.v. d 2 - 6 q 21<br>5 MIU INF s.c. d 1 -7 q 21 d | 31 | 23 |
| Seymour[28] | 5FU 400 mg/m2 bolus, then 5FU 400 mg/m2 by i.v. infusion over 22 hours d 1.2 q 14 d<br>LV 200 mg/m2 i.v.<br>6 MIU IFN s.c. every 48 hours troughout | 128 | 31 |
| Recchia[29] | 5-FU370mg/m2 i.v. d 2 -6 q 21 d<br>LV 500 mg/m2 i.v. d 2 - 6 q 21 d<br>3 MIU IFN x 3 s.c. d q 28 d | 32 | 22 |
| Grem[30] | 5-FU 370 mg/m2 i.v. d 2- 6q 21 d<br>LV 500 mg/m2 i.v. d 2 - 6 q 21 d<br>5 MIU IFN s.c. d 1 - 7 q 21 d | 54 | 44 |
| Labianca[31] | 5-FU 400 mg/m2 i.v. x 5 d q 28 d<br>LV 200 mg/m2 i.v. x 5 d q 28 d<br>3 MIU IFN - α2b s.c. x 5 d q 21 d | 36 | 22 |
| Kreuser[32] | 5-FU 500 mg/m2 i.v. x 7 d q 21 d<br>LV 200 mg/m2 i.v. x 7 d q 21 d<br>5 MIU IFN - α2b s.c. x 7 d q 21 d | 62 | 29 |
| Cascinu[33] | 5-FU 370 mg/m2 i.v. d 2 - 6 q 21 d<br>LV 200 mg/m2 i.v. d 2 - 6 q 21 d<br>3 MIU IFN s.c. d1 -7 q 21 d | 45 | 51 |

ous infusion 5-FU to bolus injections. In many trials, objective response rate was higher and toxicity much lower in the patients who received continuous infusion of 5-FU than in the patients treated by bolus injections.[24,25]

Numerous trials have been performed with different doses of LV (15 to 500 mg/m$^2$). In general, in clinical trials no difference was indicated in the activity between low (20 mg/m$^2$) and higher doses of LV (250 mg/m$^2$).[19,26]

The first clinical results of the 5-FU/LV/IFN combination were published in 1990.[27] The treatment schedule consisted of 1-20 MIU IFN/day for 5 days and 370-425 mg/m$^2$/day 5-FU, and 500 mg/m$^2$/day LV, given in 5 consecutive days. Only 7 of 31 patients (23%) demonstrated PR, which was disappointing. In the next three years various modes of drug administration were studied in order to define an optimal therapeutic approach (Table 4). Although the majority of phase II studies with 5-FU, LV and IFN have

demonstrated objective response in approximately 30% of patients with advanced colorectal cancer, their relevance seems hampered by small numbers of patients.

Despite some clinical trials which showed that 5-FU plus IFN is more effective than 5-FU alone in terms of response rate and event free survival, but not of overall survival,[34] in three recent randomised clinical trials using double modulation of 5-FU, the investigators found that no benefit could be achieved with the addition of IFN. An Italian trial was aimed to clarify whether IFN could further enhance the therapeutic potential of 5-FU in combination with LV. Eighty-three patients were entered into this trial. The therapy in the first treatment arm consisted of 200 mg/m$^2$/day LV, followed by 370 mg/m$^2$/day 5-FU on days 1-5. In the second treatment arm, 3MIU IFN was administered three times a week subcoutaneusly. The response rates in the 5-FU/LV and IFN arms was 45% and 22%, respectively.[29] Pensel randomised 55 patients between treatment with 5-FU/LV with or without IFN administered at a daily dose of 5MIU. Preliminary results did not suggest any statistically significant difference in terms of treatment outcome between the two arms.[35] Disappointing results were also reported by the Hellenic Co-operative Oncology Group. Among 95 patients enrolled in trial the response rates in the arm without IFN and in the arm with IFN were 19% and 6%.[36]

According to phase II studies and preliminary results of three randomised trials, the concept of 5-FU double modulation using IFN and LV does not seem to fulfil its promise either. Therefore, for cost considerations and because combined treatment with 5-FU, LV and IFN seems to result in enhanced toxicity, currently used dose regimens of this approach cannot be recommended for routine use. As the modulatory effects of IFN on chemotherapy in experimental models are highly dependent on the timing and the dose of IFN, alternative schedules of 5-FU and IFN combination are worth exploring in clinical trials.

## References


1. *Incidenca raka v Sloveniji 1995.* Ljubljana: Onkološki inštitut-Register raka za Slovenijo, 1998.
2. Mayer JR. Systemic therapy for colorectal cancer: an overview. *Semin Oncol* 1991; **18** Suppl 2: 62-75.
3. Schmoll HJ, Harstrick A, Kohne-Wompner CH, Schober C, Wilke H, Poliwoda H. Modulation of cytotoxic drug activity by dipyridamole. *Cancer Treat Rev* 1990;**17:** Suppl A: 57-66.
4. Allegra CJ. Thymidylate synthase as a rational clinical target for the treatment of epithelial malignancies. *Hematol Oncol Ann* 1994; **2:** 203-12.
5. Johnston PG, Fisher ER, Rockette HE, Fisher B, Wolmark N, Drake JC, et al. The role of the thymidylate synthase expression in prognosis and outcome of adjuvant chemotherapy in patients with rectal cancer. *J Clin Oncol* 1994; **12:** 2649-7.
6. Nobile MT, Vidili GM, Sobrero A, Sertoli MR, Cannobio L, Fassio T, et al. 5- fluorouracil alone or combined with high dose folinic acid in advanced colorectal cancer patients: a randomized trial [abstract]. *Proc Am Soc Clin Oncol* 1988; **7:** 97.
7. Erlichman C, Fine S, Wong A, Elhakim T. A randomized trial of fluorouracil and folinic acid in patients with metastatic colorectal carcinoma. *J Clin Oncol* 1988; **6:** 469-75.
8. Tempero M, Berg A, Block M, Hutchins M, Moravec D, Langdon R. A phase ll trial of protracted therapy with 5-fluorouracil and leucovorin in metastatic colorectal cancer [abstract]. Proc Am Soc Clin Oncol 1993; **12:** 594.
9. Meadows LM, Walther P, Ozer H. Interferon and 5-fluorouracil: possible mechanisms of antitumor action. *Semin Oncol* 1991; **18** Suppl 7: 1-6.
10. Elias L, Sandoval JM. Interferon effects upon fluorouracil metabolism by HL- 60 cells. *Biochem biophys Res Commun* 1989; **163:** 867-74.
11. Pfeffer LM, Tamm I. Interferon inhibition of thymidine incorporation into DNA through efects on thymidine transport and uptake. *J Cell Physiol* 1984; **121:** 431-6.
12. Houghton JA, Morton CL, Adkins DA. Locus of the interaction among 5 - fluorouracil, leucovorin

and interferon-α2a in colon carcinomas cell. *Cancer Res* 1993; **53:** 4243-50.

13. Wadler S, Schwartz EL, Goldman M, Lyver A, Rader M, Zimmerman M, Itri L, et al. Fluorouracil and recombinant alpha 2a interferon: An active regimen against advanced colorectal carcinoma. *J Clin Oncol* 1989; **7:** 1769-75.

14. Kohne C H, Wilke H, Hecker H. Interferon alpha does not improve the antineoplastic efficacy of high-dose infusional 5-fluorouracil plus folinic acid in advanced colorectal cancer. *Ann Oncol* 1995; **6:** 461-6.

15. World Health Organization. *Handbook for reporting results of cancer treatment.* Geneva: WHO (WHO offset publication No. 48);1979.

16. Peto R, Pike MC, Armitage P. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. Part I. *Br J Cancer* 1976; **34:** 585-612.

17. Peto R, Pike MC, Armitage P. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. Part II. *Br J Cancer* 1977; **35:** 1-39.

18. Brookmeyer R, Crowley C. A confidence interval for the median survival time. *Biometrics* 1982; **38:** 29-41.

19. Poon MA, O¨ Connel MJ, Moertel CG, Wieand HS, Cullinan SA, Everson LK, et al. Biochemical modulation of fluorouracil: Evidence of significant improvement of survival and quality of life in patients with advanced colorectal carcinoma. J *Clin Oncol* 1991; **9:** 967-72.

20. Petrelli B, Douglass HO, Herrera L, Russell D, Stablein DM, Bruckner HW, et al. The modulation of fluorouracil with leucovorin in metastatic colorectal carcinoma: A prospective randomized phase lll trial. *J Clin Oncol* 1989; **10:**1 419-26.

21. Labianca R, Pancera G, Beretta G. Aitini E, Barni S, Beretta GD, et al. A randomized study of intravenous fluorouracil +/- folinic acid in advanced metastatic colorectal carcinoma. *Ann Oncol* 1991; **2:** 673-9.

22. Hryniuk WM, Figueredo A, Goodyear M. Applications of dose intensity to problems in chemotherapy of breast and colorectal cancer. *Sem Oncol* 1987; 14 Suppl **4:** 3-11.

23. Lokich JJ. Optimal schedule for 5-fluorouracil chemotherapy. Intermittent bolus or continuous infusion? Am J Clin Oncol 1985; **8:** 445-8.

24. Lokich JJ, Ahlgren JD, Gullo JJ, Philips JA, Fryer JG. A prospective randomized comparison of continuous infusion with a conventional bolus schedule in metastatic colorectal carcinoma: A Mid - Atlantic Oncology Program Study. *J Clin Oncol* 1989; **7:** 425-32.

25. Weinerman B, Shah A, Fields A, Kerr I, Cripps C, Shepherd F, et al. A randomized trial of continuous systemic infusion (SI) vs bolus therapy (B) with 5-fluorouracil (5-FU) in metastatic measurable colorectal cancer (MCC). *Am J Clin Oncol* 1992; **15:** 518-23.

26. O'Connel MJ. A phase lll trial of 5-fluorouracil and leucovorin in the treatment of advanced colorectal cancer. *Cancer* 1989; **63:** 1026-30.

27. Yalavarthi P, Murthy S, Budd GT, Andresen S, Koletsky A, Avashia J. Phase l / ll trial of 5 - FU,leucovorin (LV) and rhuIFN(2a in metastatic colorectal cancer: possible decrease in myelosuppression [abstract]. *Proc Am Soc Clin Oncol* 1990; **9:** 125.

28. Seymour M, Slevin M, Cunningham D, Johnson P, Davis C, Hall M, et al. A randomized trial to assess the addition of interferon-α2a (IFNα) to 5 - fluorouracil (5 - FU) and leucovorin (LV) in advanced colorectal cancer[abstract]. *Proc Am Soc Clin Oncol* 1994; **13:** 621.

29. Recchia F, Nuzzo A, Lombardo M, Lalli A, Fabiani F, Fanini R, et al. 5- fluorouracil (5FU) and high dose folinic acid (HDFA) chemotherapy (CT) with or without alfa 2B interferon (IFN) in advanced colorectal cancer (ACC). Preliminary report of a randomized trial [abstract]. *Proc Am Soc Clin Oncol* 1992; **11:** 162.

30. Grem JL, Jordan E, Robson ME, Binder RA, Hamilton JM, Steinberg SM, et al. Phase ll study of fluorouracil, leucovorin, and interferon alfa - 2a in metastatic colorectal carcinoma. *J Clin Oncol* 1993; **11:** 1737-45.

31. Labianca R, Giaccon G, Barni S, Pancera G, Ambrosini G, Amichetti G, et al. Double modulation of 5 - fluorouracil in advanced colorectal cancer with low-dose interferon alpha 2b and folinic acid. The GISCAD experience. *Eur J Cancer* 1994; **30:** 1611-6.

32. Kreuser ED, Hilgenfeld RU, Matthias M, Hoksch B, Boewer C, Oldenkott B, et al. Final update on a phase ll trial of interferon alfa- 2b with folinic acid and a 4 - hour infusion of 5 - fluorouracil in advanced colorectal carcinoma. *Semin Oncol* 1992; **2** Suppl 4: 57-62.

33. Cascinu S, Fedeli A, Fedeli SL, Catalano G. Double biochemical modulation of 5 - fluorouracil by

leucovorin and cyclic low dose interferon alpha 2b in advanced colorectal cancer patients. *Ann Oncol* 1991; **3:** 489-91.

34. Dufour P, Husseini F, Dreyfus B, Cure H, Martin C, Prevost G, et al. 5 - fluorouracil versus 5 - fluorouracil plus a - interferon as treatment of metastatic colorectal carcinoma. A randomized study. *Ann Oncol* 1996; **7:** 575-9.

35. Pensel R. Advanced colon cancer: a randomised trial of fluorouracil (5-FU) + folinic acid (FA) and 5-FU + FA + interferon alpha 2b [abstract]. *Proc Am Soc Clin* Oncol 1992; **11:** 162.

36. Corfu A Study Group. Phase lll randomized study of two fluorouracil combinations with either interferon alfa-2a or leucovorin for advanced colorectal cancer. *J Clin Oncol* 1995; **13:** 921-8.