Review article
UDC: 616-006:615.37



Nevenka STANOJEVIĆ-BAKIĆ
Ljiljana VUČKOVIĆ-DEKIĆ

# Interferons in the therapy of solid tumors. Part III. Interferon and various solid malignancies

## ABSTRACT

*Interferons exert a consistent therapeutic effect in a proportion of patients with renal cell carcinoma and melanoma. In other solid malignancies, this therapeutic approach is investigated at more limited extent; therefore, it is still in experimental area. In this review, we analyzed the clinical trials that used the IFN as monotherapy or, more frequently, as combined biochemotherapeutic regimen. This therapeutic strategy was not justified in colon cancer. Similarly, IFNs did not make a major progress in the treatment of lung cancer regardless the tumor type. Very limited activity was seen also in advanced breast cancer. In most other solid tumors, clinical experience is insufficient and only anecdotal benefits were reported. This is equally true for premalignant lesions, the possibilities of IFN-therapy of which are largely overlooked. In the future, some approaches such as combination of IFN and hormonotherapy in breast cancer, and with retinoic acid in squamous cell carcinomas, deserve further investigation. The optimization of IFN regimens in solid malignancies is the aim of current efforts. Better understanding of biological mechanisms of specific tumor sensitivity, and also the mechanisms of resistance of sensitive tumor types to IFN, will probably lead to the defining features of tumor responsiveness.*

***Key words:*** *Colon cancer; Lung cancer; Breast cancer; Immunotherapy*

INSTITUTE FOR ONCOLOGY AND RADIOLOGY OF SERBIA, BELGRADE, YUGOSLAVIA

*Archive of Oncology 2000,8(2):65-72©2000, Institute of oncology Sremska Kamenica, Novi Sad, Yugoslavia*

## INTRODUCTION

Although at the first glance the results of interferon (IFN) therapy of solid tumors might seem discouraging, some metastatic tumors such as renal cell carcinoma (RCC) (1) and malignant melanoma (MM) (2) undergo regression in a fraction of treated patients. Apart from these tumors, IFNs were tried in a wide range of other solid malignancies. In the therapy of common solid tumors such as colon and lung cancers, the use of IFN is still experimental. In this review we summarize the results of clinical studies that used IFN, alone or in combination with other oncological treatment modalities, in the therapy of various cancers.

*Abbreviations used in text: IFN - interferon; RCC - renal cell carcinoma; MM - malignant melanoma; CC - colorectal cancer; 5-FU - 5-fluorouracil; LV - leucovorin; CR - complete response; PR - partial response; OR - overall response; NSCLC - non-small cell lung cancer; SCLC - small cell lung cancer; SCC - squamous cell carcinoma; IL-2 - interleukin 2; sIL-2R - soluble IL-2 receptors; ChT - chemotherapy; RT - radiotherapy; RA - retinoic acid; BRMs - biological response modifiers*

*Address correspondence to:*
*Dr. Nevenka Stanojević-Bakić, Institute for oncology and radiology of Serbia, Pasterova 14, POB 228, 11000 Belgrade, Yugoslavia*

*The manuscript was received: 22. 02. 2000.*

*Provisionally accepted: 28. 02. 2000.*

*Accepted for publication: 10. 03. 2000.*



### Colorectal cancer

There is, presently, no satisfactory standard treatment for advanced colorectal carcinoma (CC). Most commonly used chemotherapeutic agent, 5-fluorouracil (5-FU), definitely has some, but only modest activity, giving the response rates of 10-15% and no consistent effect on survival. Because of that, the developments of new therapeutic strategies are ongoing, with the aim to improve the response rate, time to progression and survival. Many of them include IFN, which was stimulated by preclinical data and encouraging results obtained in RCC and MM patients.

#### *IFN as a single agent therapy*

Several clinical trials used IFNα monotherapy in advanced colorectal cancer; a response rate of only 2% was obtained, regardless dose or schedule (3). Therefore, such a therapy seems to have no activity and virtually no clinical effects.

Few studies with IFNβ (4) or IFNγ (5) also showed very limited activity. These disappointing results were the reason for abandonment of the IFN single-agent therapy of advanced CC.

The very poor responsiveness of this gastrointestinal malignancy to IFN treatment may be ascribed, at least in part, to the presence of both specific and non-specific IFN inactivators/inhibitors in sera of the patients (6,7); the nature of these factors is still unclear.

#### *IFN and chemotherapy drug combinations*

*IFN and 5-FU combination.* Preclinical data suggesting that IFNα and 5-FU have a synergistic cytostatic effect upon cultured colon carcinoma cells (8), stimulated an increasing number of clinical investigations to evaluate the therapeutic potential of this combination. This was also supported by the observation that IFN-chemotherapy combination may reduce the IFN-inhibitors/inactivators in cancer patients (9). The results of 25 selected trials are presented in Table 1 (10-32). In various treatment schedules, 5-FU was used at doses ranging from 225-750mg/m$^2$ (usually 750mg/m$^2$), and IFNα at doses of 0,5 - 20MU/day. The overall response (OR) rates varied very much (3-70%), giving an average OR of 27%. These divergent therapeutic results may be accounted, at least in part, to the small number of patients in some trials, and inclusion of patients refractory to 5-FU monotherapy. It is evident that the initial impressive response rate (63%) obtained in the Wadler's report (11) has failed to be reproduced; the only exception is the recent study of Kimm et al. (28), the relevance of which is hampered by the small number of patients. However, the overall response rate of about 30%, although modest, is still higher than that of the each agent

monotherapy. In terms of survival, the results of several randomized trials gave no indication that the IFNα-5-FU combination had any advantage over the 5-FU monotherapy.

It should be noted that the constant evidence from most clinical trials was the increased systemic toxicity of 5-FU by IFNα, requiring the reduction of IFN dose in some patients (33).

Therefore, although these two drugs' synergism was reported in several preclinical studies, the results of trials analyzed in this review did not justify this therapeutical strategy. The enhanced toxicity, no survival benefit, along with cost consideration, compromise the beneficial effect on the OR rate.

Similarly to IFNα, IFNβ also potentiates the antitumor activity of 5-FU against human colon cancer cells *in vitro* and *in vivo* (34). Based on these findings, three recent clinical studies used IFNβ for the 5-FU biomodulation (Table 1).

The mean OR rate of 27% is similar to that of IFNα+5-FU combination. It seems that IFNβ does not increase the toxicity of 5-FU (30,32), and that this combination is less toxic than that of IFNα+5-FU. A significant increase of survival was reported in one study (32), suggesting that this combination might deserve further investigation.

### *IFN+5-FU+LV combination*

Another strategy aiming to enhance cytotoxicity of 5-FU is focused on the use of triple drug combination - 5-FU, leucovorin (LV) and IFNα. The potential advantage might be double modulation of 5-FU by LV and IFN, the drugs with different mechanisms of action. The results of 15 clinical trials with 908 patients are presented in Table 2 (35-43). The average OR of 29% was obtained with different doses and schedules of these drugs' administration (range 10-54%). The response rate and survival duration were not significantly better than that obtained with 5-FU alone or combined with either LV or IFN. In addition, virtually all trials have demonstrated a significantly higher rate of adverse events, and decreased quality of life. This is because such regimens cannot presently be recommended for routine use outside clinical investigation (43).

**Table 1.** Response of advanced colorectal cancer patients to the IFN+5-FU combinations.

| Study | Evaluable patients | CR | PR | OR (%) | Mean survival (months) |
|---|---|---|---|---|---|
| **IFN α+5-FU** | | | | | |
| Wrighley 1984* | 14 | 0 | 2 | 14 | |
| Clark 1987[10] | 29 | 0 | 1 | 3 | |
| Wadler 1990[11] | 32 | 0 | 20 | 63 | |
| Pazdur 1990[12] | 45 | 1 | 15 | 36 | |
| Kemeny 1990[13] | 35 | 0 | 9 | 26 | |
| Fornasiero 1990[14] | 21 | 4 | 5 | 43 | |
| Huberman 1991* | 33 | 0 | 13 | 39 | |
| Wadler ECOG 1991[15] | 36 | 1 | 14 | 42 | |
| Meadows 1991[16] | 17 | 2 | 2 | 23 | |
| Weh 1992[17] | 55 | 0 | 17 | 31 | |
| Rubio 1992[18] | 33 | 3 | 5 | 24 | |
| Pazdur 1993[19] | 39 | 1 | 11 | 31 | |
| John 1993[20] | 18 | 1 | 5 | 33 | |
| York 1993* | 121 | | | 31 | |
| Findlay 1994[21] | 118 | 0 | 5 | 8 | |
| Hill 1994* | 63 | | | 31 | 11 |
| CORFU-A 1995[22] | 243 | | | 21 | 11 |
| DiConstanzo 1995* | 92 | | | 9 | |
| Hill 1995[23] | 52 | | | 19 | 8 |
| Kohne 1995* | 68 | | | 19 | |
| Piga 1996[24] | 64 | 2 | 4 | 9 | 12 |
| Dufour 1996[25] | 56 | 3 | 8 | 20 | 12,3 |
| Patt 1997[26] | 45 | 3 | 12 | 33 | |
| Perez 1998[27] | 33 | 0 | 2 | 6 | 5 |
| Kim 1998[28] | 10 | 1 | 6 | 70 | |
| Kohne 1998[29] | 90 | | | 18 | 12,7 |
| Total: 26 | 1462 | | | 27 | (mean) |
| **IFN β+5-FU** | | | | | |
| Joffe 1997[30] | 21 | 1 | 3 | 19 | 8,4 |
| Wadler 1998[31] | 59 | | | 28 | |
| Villar-Grimalt 1999[32] | 25 | | | 33 | 15,9 |
| Total: 3 | 105 | | | 27 | |

* References cited in Kjaer[3]

**Table 2.** Response of advanced colorectal cancer patients to the IFN+5-FU+LV combinations.

| Study | Evaluable patients | CR | PR | OR (%) | Mean survival (months) |
|---|---|---|---|---|---|
| Recchia 1992* | 32 | 2 | 5 | 22 | |
| Schmoll 1992* | 43 | | | 10 | |
| Cascinu 1992* | 45 | | | 51 | |
| Sobrero 1992[35] | 15 | | | 20 | |
| Pensel 1993* | 24 | 4 | 6 | 41 | |
| Kocha 1993* | 240 | 7 | 43 | 21 | |
| Grem 1993[36] | 44 | 3 | 21 | 54 | |
| Punt 1993[37] | 45 | | | 25 | 11 |
| Seymour 1994* | 83 | | | 30 | |
| Pazdur 1994[38] | 47 | 3 | 11 | 30 | |
| Kosmidis 1996[39] | 51 | | | 10 | 7,2 |
| Tournigand 1997[40] | 50 | 1 | 21 | 44 | 25 |
| Kohne 1997[41] | 33 | | | 15 | 9,9 |
| Kohne 1998[42] | 49 | | | 27 | 19,6 |
| Hausmaninger 1999[43] | 107 | 5 | 33 | 36 | |
| **Total: 15** | **908** | | | **29** | (mean) |

* References cited in Raderer[33] and Kjaer[3]

There exist little data for IFN and antineoplastic drugs other than 5-FU and LV for patients with advanced colorectal cancer (44,45); they provided no evidence of any therapeutic advantage over the 5-FU regimens.

### *IFNα-5-FU combination and other biotherapeutics*

Further attempts to improve response rate and survival of advanced CC patients introduced IFNγ or interleukin-2 (IL-2) to the combination of 5-FU and IFNα (with or without LV). The rationale for such combinations was the preclinical data suggesting synergy between these biological agents, which was confirmed in clinical studies in RCC and MM patients (1,2). Few trials (46-49) using different scheduling and doses of these biochemotherapeutics, showed that these multiagent combinations failed to improve clinical benefit of 5-FU monotherapy, and were accompanied by severe toxicity that required the treatment interruptions or dose reductions.

As in RCC and MM (1,2), it is not possible to define the responders to IFN combination therapies. The predictors of response are still lacking. It is unlikely that ras mutations (such as c-Ki-*ras*2, which occurs early in the pathogenesis of CC and is found in about 40% of patients) will have significant prognostic value for either response to therapy or survival (50). Similarly, the immunostimulation obtained by IFN treatment did not predict improved clinical outcome (51).

In conclusion, after the initial hopes, the combination of IFN-α with 5-FU and other biochemotherapeutics does not seem to fulfill the original expectations. It is not sufficiently effective, it is toxic, and it is costly. Further research efforts are required and new treatment strategies are needed if progress is to be

obtained. Some attempts in this direction are already ongoing; for instance, an important approach to enhance the efficacy of monoclonal antibodies-based protocols in the therapy of this malignancy (52) utilizes the ability of IFNs to up-regulate carcinoembrionic and other tumor-associated antigens (53).

### Lung cancer

Although chemo- and radiotherapy do have activity in lung cancer, the results of these therapeutic options are unsatisfactory. Therapeutic regimens that are currently used in advanced non-small cell lung cancer (NSCLC) yield the average OR rates of 20-30%, while median survival may be as low as 6-8 months. Small-cell lung cancer (SCLC), which distinguishes itself from NSCLC by more aggressive clinical course and median survival less than 3 months in the absence of treatment, has greater responsiveness to chemotherapy, but median survival remains 12-14 months.

In the search of new systemic strategies against lung cancer, biologic agents such as IFNs have been reconsidered for the treatment programs. Clinical studies that include IFNs are heterogeneous in regard to the IFN type and other biochemotherapeutics used in combination therapy; they frequently dealt with small sample series, and patients groups are often unmatched by stage of disease and category of responses.

*IFNs in advanced non-small cell lung cancer (NSCLC)*

The IFN monotherapy is inactive in this disease; the responses were rare and no impact on survival was seen (54).

Clinical experiences with IFNs as adjunctive treatment of NSCLC are limited. The summarized data of trials that used IFN in combination with other agents are presented in Table 3 (55-72). It is evident that addition of IFNs to conventional chemotherapy confers little or no benefit; these combinations are usually accompanied by increased toxicity. When IFNs were combined with radiotherapy (RT), different results have been reported. The IFNβ-therapy preceding RT gave encouraging response rate in the McDonald's study (65); concurrent treatment with IFNα and RT did not provide any advantage over RT alone (64), while the concomitant treatment of NSCLC patients with IFNγ and fractionated thoracic radiation was associated with severe, life-threatening toxicity without effect on survival (66).

In the studies using IFN in combination with retinoic acid (RA) or IL-2, no antitumor response was seen (Table 3.). Multiagent regimens including chemotherapy, IFN and the thymic preparation thymosin-a1, gave an improved response rate (71,72), which was associated with reduced toxicity. These promising results need to be confirmed in larger randomized trials.

**Table 3.** Response of advanced non-small lung cancer patients to IFN in combination with standard oncologic therapy and various biotherapeutics.

| Study | Therapy | Evaluable patients | CR | PR | OR (%) | Median survival (months) |
|---|---|---|---|---|---|---|
| Schiller 1989[55] | IFNγ+IFNβ+ ChT | 18 | 0 | 2 | 11 | 8 |
| Bowman 1990[56] | IFNα+ChT | 60 | 0 | 18 | 30 | |
| Rosell 1991[57] | IFNα+ChT | 30 | | | 13 | |
| Lind 1991[58] | IFNα+ChT | 45 | 2 | 7 | 20 | |
| Ardizzoni 1993[59] | IFNα+ChT | 90 | | | 19 | 5,5 |
| Halme 1994[60] | IFNγ+ChT | 27 | 0 | 8 | 29 | 6-7 |
| | IFNγ+IFNα+ChT | 27 | 0 | 9 | 35 | 6-7 |
| Quan 1994[61] | IFNα+ChT | 6 | 0 | 2 | 33 | |
| Quan 1996[62] | IFNα+ChT | 18 | 0 | 7 | 39 | |
| Prior 1999[63] | IFNγ+ChT | 32 | 0 | 5 | 15 | 11 |
| Maasilta 1992[64] | IFNα+RT | 10 | 0 | 6 | 69 | |
| McDonald 1993[65] | IFNβ+RT | 32 | 14 | 12 | 81 | |
| Show 1995[66] | IFNγ+RT | 18 | | | | 7-8 |
| Krigel 1991[67] | IFNβ+IL-2 | 73 | 1 | 2 | 4 | 9 |
| Rinaldi 1993[68] | IFNα+RA | 37 | 0 | 1 | 4 | |
| Arnold 1994[69] | IFNα+RA | 34 | 0 | 1 | 3 | |
| Athanasiadis 1995[70] | IFNα+RA | 25 | 2 | 2 | 16 | 14 |
| Garaci 1995[71] | IFNα+ChT+Tα$_1$ | 56 | 2 | 22 | 43 | 12,6 |
| Salvati 1996[77] | IFNα+ChT+Tα$_1$ | 11 | | | 33 | |

**ChT**-chemotherapy; **RA**-retinoic acid; **Tα1**-thymosin α1; **RT**-radiotherapy

*IFNs in small-cell lung cancer (SCLC)*

Similarly to NSCLC, the IFN trials in SCLC are heterogeneous, which makes the interpretation of the results difficult. The available data on this matter are presented in Table 4 (73-83). In most studies, IFNα was used as maintenance therapy for patients in whom complete (CR) or partial responses (PR) were achieved by induction chemo- and radiotherapy. In contrast to Mattson et al. (74,75), whose results were significantly in favor of IFNα therapy (in patients for whom other prognostic factors were favorable), other reports were negative or inconclusive (76,81,82). In the trials that used IFNγ, no beneficial effect on survival was observed (78-80). It is noteworthy that IFN-therapy was usually associated with toxic effects, which frequently required the discontinuation of treatment.

Presently, it seems that IFNs do not make a major progress in the treatment of lung cancer. Further investigations to define the active biochemotherapeutic combination and optimal dosing schedules are necessary.

### Breast cancer

Numerous attempts to improve the efficacy of chemotherapy of metastatic breast cancer by the additions to, and substitutions of one or other chemotherapeutic agent/s in conventional regimens, have failed to produce further substantial improvement of response rate or response duration. Because of that, the biotherapy, including IFNs, in a combination strategy against breast cancer has been tried. However, limited number of clinical trials are available thus far and this approach is still in experimental area.

Encouraging data of initial reports concerning therapeutic potential of IFNα, have not been confirmed in subsequent clinical trials (84-88): in most patients, IFN therapy had negligible activity.

In few clinical studies, IFNα was used in combination with IL-2; minor objective response associated with considerable toxicity was reported (89-91).

In patients with subcutaneous metastases, the intralesional therapy with IFNα+IFNγ has been tested in two small trials. Promising locoregional antitumor activity associated with extensive immunomodulation was found (92,93), but further follow-up studies are needed to confirm these results.

Another combination of biotherapeutics - IFNα and thymostimulin, was evaluated in

**Table 4.** Interferons in small-cell lung cancer patients responsive to induction chemotherapy.

| Study | IFN type | Number of patients | Median time to progression (months) | Median survival (months) | 2-year survival (%) |
|---|---|---|---|---|---|
| Kohne 1992[73] | IFN-α | 25 | 13.5 | 16.5 | |
| | control | | | | |
| Mattson 1992[74] | IFN-α | 91 | | 11 | 18* |
| | ChT | 59 | | 11 | 7 |
| | control | 87 | | 10 | 6 |
| Mattson 1997[75] | IFNα | 91 | | | 10« |
| | ChT | 59 | | | 2« |
| | control | 87 | | | 2« |
| Kelly 1993[76] | IFN-α | 64 | 9 | 13 | 35 |
| | control | 68 | 10 | 16 | 35 |
| Glisson 1993[77] | IFN-α | 14 | | 10 | |
| Jett 1994[78] | IFN-γ | 51 | 6,9 | 13,3 | 27[ns] |
| | control | 49 | 8,1 | 18,8 | 33 |
| Bitran 1995[79] | IFN-γ | 41 | 3,6 | | |
| van Zandwijk 1997[80] | IFN-γ | 59 | | 8,9 | 17 |
| Tummarello 1997[81] | IFN-α | 14 | 12 | 15 | 28[ns] |
| | control | 12 | 7 | 9 | 25 |
| #Zarogoulidis 1996[82] | IFN-α+ChT | 42 | | 11,3 | |
| | ChT | 39 | | 10 | |
| #Prior 1997[83] | IFNα+ChT | 43 | 7,6 | | 14 |
| | ChT | 34 | 5,4 | ** | 0 |

*** p<0,01** in comparison to control
**** p<0,02** in comparison to control
**ns -** not significant in comparison to control
**# IFN** concomitant with chemotherapy
**ChT -** chemotherapy
« 5 year survival

advanced breast cancer by Munno et al. (94). In clinical terms, patients administering this combination could complete chemotherapeutic cycles without interruptions; they had fewer infections in comparison to patients receiving different therapeutic regimen.

Generally, all these data show that IFNs, used either as single agent or in combination with other biotherapeutics, have no or very limited clinical activity in advanced breast cancer.

During the last few years, there is an increasing number of trials using IFNs in combination with hormonotherapy in the treatment of this malignancy. Such an approach is based on *in vitro* and *in vivo* evidence that IFNs can induce estrogen receptors and reconstitute the sensitivity of mammary carcinoma to tamoxifen (95-97). In the first clinical trial that included 43 tamoxifen-resistant patients, 26% tamoxifen-responders were seen after IFNβ pretreatment (98). Similarly, in a small pilot study of Seymour (99), four out of seven patients responded to treatment with IFNα and tamoxifen. However, subsequent clinical studies reported either no substantial improvement of the efficacy of tamoxifen after IFN treatment, or the higher response in selected patients (predominant soft tissue disease) only (100-102). In a recent randomized study of Barak et al. (103), IFNβ and IFNγ combined with hormonotherapy were used. Clinical response was correlated with various cytokine levels. A favorable response to the therapy was associated with significant increase of the IFNγ levels. Baseline levels of IFNγ and sIL-2R were found to be prognostic for clinical response, and to be the most sensitive cytokine parameter for defining the clinical utility of the combination of IFNs and hormonotherapy in this malignancy.

Based on the synergistic antiproliferative effect of IFN, retinoids and tamoxifen on the breast cancer cell lines (96,104,105), this combination was tested in the studies of Recchia et al. (106-108); such regimen was effective, with acceptable toxicity, as salvage therapy in pretreated advanced breast cancer patients.

Taking altogether, the true value of these combination regimens cannot be recognized until additional information, obtained in larger number of patients, became available. At present, the use of IFNs-tamoxifen combinations in the treatment of advanced breast cancer remains investigational, and the optimal scheduling is still undetermined.

Either alone or combined with different biotherapeutics, IFN has also been tried, although less frequently, in tumors other than the abovementioned ones. In several clinical trials IFNα, usually combined with RA, was given to patients with squamous cell carcinoma (SCC) of uterine cervix; such an approach is of special interest, since both agents have been shown to suppress the growth of human papilloma virus type 16 (HPV-16)(109), which is related to cervical carcinoma. Moreover, IFN might correct the RT-due, long-lasting depression of lymphocytes (110,111). However, the results obtained in these trials are very heterogeneous. The high OR rates of 50% and 42% reported by Lippman et al. (112,113) were not confirmed in later studies (114,115).

The Lippman's group also reported very high (68%) objective response of patients with inoperable SCC of the skin; again, IFNα was combined with retinoic acid (116). The high response rates seen in these initial trials were not obtained in other squamous tumors (head and neck, oesophagus), in which this regimen (117-119), or the combination of IFN with IL-2 (120,121), was used. Further studies integrating such therapy with other treatment modalities are warranted in cervix and skin cancers.

Interferons were also tried as local-intravesical therapy in superficial bladder cancer. The average OR rate was 40% (122,123). Intravesical instillation of IFN lowers the relapse rate from 70-80%, seen after surgery alone, to 30-50%. It is noteworthy that this treatment has few and usually mild side effects, which is in contrast to the routine local BCG therapy; however, the latter has significantly higher response rates (60-70%). Because of that, an ongoing multi-center trial (123) uses low doses of both agents in the therapy of superficial bladder cancer.

The local (intra- and perilesional) or systemic IFN therapy was tried, with some success, in patients with various other solid tumors: hondrosarcoma (124), malignant pleural mesothelioma (125,126), glioma (127), prostatic cancer (128) and AIDS-related Kaposi's sarkoma (129,130). This latter entity is of special interest, since it is the most common complication of HIV infection and AIDS; therefore, all biological activities of IFN (antiviral, antitumor and immunological), may be of relevance. It is agreed that IFN monotherapy may be effective in a proportion of patients (those with CD4 cell number > 150 cells/mm$^3$)(131). However, the doses necessary to achieve a significant antitumor effect are often poorly tolerated. The therapy with IFN and zidovudine (132-135) resulted in tumor regression in a substantial percentage

of patients, but was usually associated with dose-limited toxicity. Generally, this disease remains a challenging problem; larger studies using IFN combined with antiretroviral treatment and chemotherapy are warranted.

## CONCLUSIONS AND FUTURE DIRECTIONS

Athough IFNs have been tried in the therapy of solid malignancies other than RCC and MM for several years, it can be stated presently that this approach is still in experimental area. Despite the wide variety of clinical trials using IFNs either as monotherapy or in combination with other BRMs, no clear-cut enhancement of therapeutic efficacy of standard treatment has been substantiated. However, it seems that some combinations, such as IFN and hormonotherapy for breast cancer, and IFN+retinoic acid in squamous cell carcinomas, deserve further investigation. The disappointing results of IFN therapy may be primarily due to its use mainly in advanced cancer. As it has been known for several years, the biotherapy might be more effective in the early stages of tumor development. Therefore, the optimal effects of IFN therapy may be expected during the early evolution of cancer (136), and in premalignant lesions as well (137,138). The kinetics of tumor cell populations influence the expression of specific receptors, which is a common denominator of the action of BRMs. Thus, the response of human tumors to IFN strongly depends on the tumor cell growth kinetics (136,137): the stationary cell populations are killed, whereas the fast growing ones are only reversibly inhibited. This may be the reason for different sensitivity of primary tumors and metastases (139).

In future investigations of therapeutic potential of IFNs in solid malignancies, the key question to be addressed is the better understanding of biological mechanisms of specific tumor sensitivity, i.e., why some tumors of the same histologic type are responsive and some are not. Furthermore, the mechanisms of resistance of sensitive tumor types also have to be resolved. Such research may lead to better defining the biological features related to tumor responsiveness (140, 141).

In addition, several other points remain to be elucidated: the relative contribution of antiviral, antitumor and immunologic effects of IFNs in exerting the beneficial effect in some malignant lesions, the defining predictive factors for clinical response and the optimal therapeutic schedule, the reduction of toxicity, the treatment duration, new indications and new drug combinations - all are expected to be resolved in near future.

***Acknowledgements***

We thank Mr Novak Vuletić for his help in preparing the manuscript.

## REFERENCES

**1.** Stanojević-Bakić N, Vučković-Dekić Lj. Interferons in therapy of solid tumors. Part I. Interferons and renal cell carcinoma. Arch Oncol 1999;7:75-80.

**2.** Vučković-Dekić Lj, Stanojević-Bakić N. Interferons in the therapy of solid tumors. Part II. Interferons and malignant melanoma. Arch Oncol 1999;7:176.

**3.** Kjaer M. Combining 5-fluorouracil with interferon-α in the treatment of advanced colorectal cancer: optimism followed by disappointment. Anti-Cancer Drugs 1996;7:35-42.

**4.** Lillis PK, Brown TD, Beougher K, Koeller J, Marcus SG, Von Hoff DD. Phase II trial of recombinant beta interferon in advanced colorectal cancer. Cancer Treat Rep 1987;71:965-7.

**5.** O'Connell MJ, Ritts RA, Moertel CG. Recombinant interferon-g lacks activity against metastatic colorectal cancer but increases serum levels of CA-19-9. Cancer 1989;63:1998-2004.

**6.** Bendtzek K, Hansen MB, Diamant M, Ross C, Svenson M. Naturally occurring autoantibodies to interleukin 1a, interleukin 6, interleukin 10 and interferon α. J Interferon Res 1994;14:157-8.

**7.** Karmaniolas KD, Papalampros TS, Papavassiliou D, Liatis STH, Kalantzis N. Detection of interferon inhibitors or antagonists in gastrointestinal malignancies. Hepato-Gastroenterology 1998;45:2244-7.

**8.** Schwartz EL, Hoffman M, O'Connor CJ. Stimulation of 5-fluorouracil metabolic activation by interferon-α in human colon carcinoma cells. Biochem Biophys Res Commun 1992;182:1232-9.

**9.** Huschart T, Medenica R, Hankenson R, Corbitt W. Response to interferon therapy is dependent on interferon inhibitor factor levels. J Interferon Res 1994;14:116-20.

**10.** Clark RI, Slevin ML, Reznek RH. Two randomised phase II trials of intermittent intravenous versus subcutaneous alpha-2-interferon alone (trial 1) and in combination with 5-fluorouracil (trial 2) in advanced cancer. Int J Colon Dis 1987;2:262-9.

**11**. Wadler S, Wiernik PH. Clinical up-date on the role of fluorouracil and recombinant interferon alpha-2a in the treatment of colorectal carcinoma. Semin Oncol 1990;17 (suppl 1):16-21.

**12.** Pazdur R, Ajani JA, Patt YZ. Phase II study of fluorouracil and recombinant interferon alpha-2a in previously untreated advanced colorectal carcinoma. J Clin Oncol 1990;8:2027-31.

**13.** Kemeny N, Younes A, Seiter K, Kelsen D, Sammarco P, Adams L et al. Interferon alpha-2a and 5-fluorouracil for advanced colorectal carcinoma: assessment of activity and toxicity. Cancer 1990; 66:2470-5.

**14.** Fornasiero A, Daniele O, Ghiotto C. Alpha-2a interferon and 5-fluorouracil in advanced colorectal cancer. Tumori 1990;76:385-8.

**15.** Wadler S, Lembersky B, Atkins M, Kirkwood J, Petrelli N. Phase II trial of 5-fluorouracil and recombinant interferon alpha-2a in patients with advanced colorectal carcinoma: an Eastern Cooperative Oncology Group study. J Clin Oncol 1991;9:1806-10.

**16.** Meadows LM, Walther P, Ozer H. a-Interferon and 5-fluorouracil: possible mechanisms of antitumor action. Semin Oncol 1991;18(Suppl 7):71-6.

**17.** Weh HJ, Platz D, Braumann D. Phase II trial of 5-fluorouracil and recombinant interferon alpha-2B in metastatic colorectal carcinoma. Eur J Cancer 1992;28A:1820-3.

**18.** Rubio D, Jimeno J, Camps C. Treatment of advanced colorectal cancer with recombinant interferon alpha and fluorouracil: activity in liver metastases. Cancer Invest 1992;10:259-64.

**19.** Pazdur R, Ajani JA, Patt YZ, Gomez J, Bready B, Levin B. Phase II evaluation of recombinant alpha-2a-interferon and continuous infusion fluorouracil in previously untreated metastatic colorectal adenocarcinoma. Cancer 1993;71:1214-8.

**20.** John WJ, Neefe JR, MacDonald JS, Cantrell J, Smith M. 5-fluorouracil and interferon-alpha-2a in advanced colorectal cancer. Results of two treatment schedules. Cancer 1993;72:3191-5.

**21.** Findlay M, Hill A, Cunningham D. Protracted venous infusion 5-fluorouracil and interferon-α in advanced and refractory colorectal cancer. Ann Oncol 1994;5:239-43.

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

**23.** Hill MH, Norman A, Cunningham D, Findlay M, Watson M, Nicolson V et al. Royal Marsden phase II trial of fluorouracil with or without interferon alfa-2b in advanced colorectal cancer. J Clin Oncol 1995;13:1297-1302.

**24.** Piga A, Cascinnu S, Latini L, Marcellini M, Bavosi M, Acito L et al. A phase II randomised trial of 5-fluorouracil with or without interferon alpha-2a in advanced colorectal cancer. Br J Cancer 1996;74:971-4.

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

**26.** Patt YZ, Hoque A, Lozano R, Pazdur R, Chase J, Carrasco H et al. Phase II trial of hepatic arterial infusion of fluorouracil and recombinant human interferon alfa-2b for liver metastases of colorectal cancer refractory to systemic fluorouracil and leucovorin. J Clin Oncol 1997;15:1432-8.

**27.** Perez JE, Lacava JA, Dominguez ME, Rodriguez R, Barbieri MR, Romero-Acuna LA et al. Biomodulation with sequential intravenous IFN-alpha2b and 5-fluorouracil as second-line treatment in patients with advanced colorectal cancer. J Interferon Cytokine Res 1998; 18:565-9.

**28.** Kim J, Zhi J, Satoh H, Koss-Twardy SG, Passe SM, Patewl IH et al. Pharmacokinetics of recombinant human interferon-alpha 2a combined with 5-fluorouracil in patients with advanced colorectal carcinoma. Anti-Cancer Drugs 1998;9:689-96.

**29.** Kohne CH, Schoffski P, Wilke H, Kaufer C, Andreesen R, Ohl U et al. Effective biomodulation by leucovorin of high-dose infusion fluorouracil given as a weekly 24-hour infusion: results of a randomized trial in patients with advanced colorectal cancer. J Clin Oncol 1998;16:418-26.

**30.** Joffe JK, Perren TJ, Bradley C, Primrose J, Hallam S, Ward U et al. A phase II study of recombinant interferon-beta (r-hIFN-β 1a) in combination with 5-fluorouracil (5-FU) in the treatment of patients with advanced colorectal carcinoma. Br J Cancer 1997;75:423-6.

**31.** Wadler S, Haynes H, Rosenblit A, Hu X, Kaleya R, Wiernik PH. Sequential phase II trials of fluorouracil and interferon beta ser with or without sargramostim in patients with advanced colorectal carcinoma. Cancer J Sci Am 1998;4:331-7.

**32.** Villar-Grimalt A, Candel MT, Massuti B, Lizon J, Sanchez B, Frau A et al. A randomized phase II trial of 5-fluorouracil with or without human interferon-beta for advanced colorectal cancer. Br J Cancer 1999;80:786-91.

**33.** Raderer M, Scheithauer W. Treatment of advanced colorectal cancer with fluorouracil and interferon-α: an overview of clinical trials. Eur J Cancer 1995;31A:1002-8.

**34.** Kase S, Kubota T, Watanabe M, Furukawa T, Tanino H, Ishibiki K et al. Interferon beta increases antitumour activity of 5-fluorouracil against human colon carcinoma cell lines in vitro and in vivo. Anticancer Res 1993;13:69-74.

**35.** Sobrero A, Nobile MT, Guglielmi A, Mori A, Aschele C, Bolli E et al. Phase II study of 5-fluorouracil plus leucovorin and interferon alpha-2b in advanced colorectal cancer. Eur J Cancer 1992;28A:850-2.

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

**37.** Punt CJ, Burhouts JT, Croles JJ, van Liessum PA, de Mulder PH, Kamm Y. Continuous infusion of high-dose 5-fluorouracil in combination with leucovorin and recombinant interferon-alpha-2b in patients with advanced colorectal cancer. A multicenter phase II study. Cancer 1993;72:2107-11.

**38.** Pazdur R, Roach R, Braud E. Phase II study of folinic acid, 5-fluorouracil, and interferon alfa-2a for patients with advanced colorectal carcinoma. Proc Am Soc Clin Oncol 1994;13:224-7.

**39.** Kosmidis PA, Tsavaris N, Skarlos D, Theocharis D, Samantas E, Pavlidis N et al. Fluorouracil and leucovorin with or without interferon alfa-2b in advanced colorectal cancer: Analysis of a prospective randomized phase III trial. Hellenic Cooperative Oncology Group. J Clin Oncol 1996;14:2682-7.

**40.** Tournigand C, Louvet C, de Gramont A, Lucchi E, Seitz JF, Mal F et al. Bimonthly high dose leucovorin and 5-fluorouracil 48-hour infusion with interferon-alpha-2a in patients with advanced colorectal carcinoma. Groupe d'Etude et de Recherche sur les Cancers de l'Ovaire et Digestifs (GERCOD). Cancer 1997;79:1094-9.

**41.** Kohne CH, Wilke H, Hiddemann W, Bokemeyer C, Lohrmann HP, Bodenstein H et al. Phase II evaluation of 5-fluorouracil+folinic acid and alpha 2b-interferon in metastatic colorectal cancer. Oncology 1997;54:96-101.

**42.** Kohne CH, Schoffski P, Wilke H, Kaufer C, Andreesen R, Ohl U et al. Effective biomodulation by leucovorin of high-dose infusion fluorouracil given as a weekly 24-hour infusion. Results of randomized trial in patients with advanced colorectal cancer. J Clin Oncol 1998;16:418-26.

**43.** Hausmaninger H, Moser R, Samonigg H, Mlineritsch B, Schmidt H, Pecherstorfer M et al. Biochemical modulation of 5-fluorouracil by leucovorin with or without interferon-α-2c in patients with advanced colorectal cancer: final results of a randomised phase III study. Eur J Cancer 19999;35:380-5.

**44.** Ajani JA, Abbruzzese JL, Markowitz AB, Patt YZ, Daughtery K. Phase II sudy of etoposide and alpha-interfeon in patients with advanced measurable colorectal cancer. Invest New Drugs 1993;11:67-9.

**45.** Royce ME, McGarry W, Bready B, Dakhil SR, Bett RJ, Goodwin JW et al. Sequential biochemical modulation of fluorouracil with folinic acid, N-phosphonacetyl-L-aspartic acid and interferon alfa-2a in advanced colorectal cancer. J Clin Oncol 1999;17:3276-82.

**46.** Ridolfi R, Maltoni R, Riccoban A, Flamini E, Fedriga R, Milandri C et al. A phase II study of advanced colorectal cancer patients treated with combination 5-fluorouracil plus leucovorin and subcutaneous interleukin-2 plus alpha interferon. J Chemother 1994;6:265-71.

**47.** Atzpodien J, Kirchner H, Hanninen EL, Menzel T, Deckert M, Franzke A et al. Treatment of metastatic colorectal cancer patients with 5-fluorouracil in combination with recombinant subcutaneous human interleukin-2 and alpha-interferon. Oncology 1994;51:273-5.

**48.** Goey SH, Gratamo JW, Primarose JH, Ward U, Mertelsmann RH, Osterwalder B. Interleukin 2 and interferon alpha-2a do not improve anti-tumour activity of 5-fluorouracil in advanced colorectal cancer. Br J Cancer 1996;74:2018-23.

**49.** Grem JL, McAtee N, Murphy RF, Balis FM, Cullen E, Chen AP et al. A pilot study of gamma-1b-interferon in combination with fluorouracil, leucovorin, and alpha-2a-interferon. Clin Cancer Res 1997;3:1125-34.

**50.** Wadler S, Bajaj R, Neuberg D, Agarwal V, Haynes H, Benson AB. Prognostic implications of c-Ki-ras2 mutations in patients with advanced colorectal cancer treated with 5-fluorouracil and interferon: a study of the Eastern Cooperative Oncology Group (EST 2292). Cancer J Sci Amer 1997;3:284-8.

**51.** Tsavaris N, Baxevanis C, Kosmidis P, Papamichael M. The prognostic significance of immune changes in patients with renal cancer, melanoma and colorectal cancer, treated with interferon alpha 2b. Cancer Immunol Immunother 1996;43:94-102.

**52.** Meredith RF, Khazaeli MB, Plott WE, Guizzh WE, Lui T, Schlom J et al. Phase II study of dual 131I-labeled monoclonal antibody therapy with interferon in patients with metastatic colorectal cancer. Clin Cancer Res 1996;2:1811-8.

**53.** Roselli M, Guadagni F, Buonomo O, Belardi A, Vittomini V, Mariani-Constantini R et al. Systemic administration of recombinant interferon alfa in carcinoma patients upregulates the expression of the carcinoma-associated antigens tumor-associated glycoprotein-72 and carcinoembrionic antigen. J Clin Oncol 1996;14:2031-42.

**54.** John WL, Foon KA. Clinical applications of interferon in other tumors. In: DeVita, Hellman S, Rosenberg SA, eds. Biologic therapy of cancer: principles and practice. Philadelphia: Lippincott-Raven, 1995:427-33.

**55.** Schiller JH, Storer B, Dreicer R, Rosenquist D, Frontiera M, Carbone PP. Randomized phase II-III trial of combination beta and gamma interferons and etoposide and cisplatin in inoperable non-small cell cancer of the lung. J Natl Cancer Inst 1989;81:1739-43.

**56.** Bowman A, Fergusson RJ, Allan SG. Potentiation of cisplatin by alpha-interferon in advanced non-small cell lung cancer (NSCLC): a phase II study. Ann Oncol 1990;1:351-3.

**57.** Rosell R, Carles J, Ariza A, Moreno I, Ribelles N, Solano V et al. A phase II study of days 1 and 8 cisplatin and recombinant alpha-2B interferon in advanced non-small cell lung cancer. Cancer 1991;15:2448-53.

58. Lind MJ, Gomm S, Simmonds AP, Ashcroft L, Kamthan A, Gurney H et al. A phase II study of ifosphamide and alpha-2b interferon in advanced non-small-cell lung cancer. Cancer Chemother Pharmacol 1991;28:142-4.

**59.** Ardizzoni A, Salvati F, Rosso R. Combination of chemotherapy and recombinant alpha-interferon in advanced non-small cell lung cancer: multicenter randomized FONICAP trial report. Cancer 1993;72:2929-35.

**60.** Halme M, Maasilta PK, Pyrhonen SO, Mattson KV. Interferons combined with chemotherapy in the treatment of stage III-IV non-small cell lung cancer - a randomised study. Eur J Cancer 1994;30A:11-5.

**61.** Quan DYW, Madajewicz S, Smith MR. Alpha interferon, leucovorin, and 5-fluorouracil (ALF) in advanced cancer: results of a dose-finding study and evidence of activity in non-small cell lung cancer. Cancer Invest 1994;12:367-74.

**62.** Quan DYW, Casal R, Rosenfeld M, Walker RP. Alpha interferon-2b, leucovorin, and 5-fluorouracil (ALF) in non-small cell lung cancer. Cancer Biother Radiopharm 1996;11:229-34.

**63.** Prior C, Oroszy S, Oberaigner W, Ambrosch G, Mohn-Staudner A, Pfeifer W et al. Advanced non-small cell lung cancer: adjunctive interferon γ in induction and maintenance therapy. J Cancer Res Clin Oncol 1999;125:42-6.

**64.** Maasilta P, Holsti LR, Halme M, Kivisaari L, Cantell K, Maltson K. Natural alpha-interferon in combination with hyperfractionated radiotherapy in the treatment of non-small cell lung cancer. Int J Radiat Oncol Biol Phys 1992;23:863-8.

**65.** Mc Donald S, Chang AY, Rubin P, Wallenberg J, Kim IS, Sobel S et al. Combined betaseron R (recombinant human interferon beta) and radiation for inoperable non-small cell lung cancer. Int J Radiat Oncol Biol Phys 1993;20:753-6.

**66.** Shaw EG, Deming DL, Creagan ET, Nair S, Su JQ, Levitt R et al. Pilot study of human recombinant interferon gamma and accelerated hyperfractionated thoracic radiation therapy in patients with unresectable stage IIIA/B non-small cell lung cancer. Int J Radiat Oncol Biol Phys 1995;31:827-31.

**67.** Krigel R, Padovic K, Weiner L. Phase I study of sequential recombinant tumor necrosis factor (rTNF) and recombinant interleukin-2 (rIL-2). Proc Am Assoc Cancer Res 1991;32:268-71.

**68.** Rinaldi DA, Lippman SM, Burris HA, Chon C, Von Hoff D, Hong WK. Phase II study of 13-cis-retinoic acid and interferon-alpha-2a in patients with advanced squamous cell lung cancer. Anti-Cancer Drugs 1993;4:33-6.

**69**. Arnold A, Ayong J, Douglas L, Hoogendoozu P, Skingley L, Gelmon K et al. Phase II trial of 13-cis-retinoic acid plus interferon α in non-small cell lung cancer. J Natl Cancer Inst 1994;86:306-9.

**70.** Athanasiadis I, Kies MS, Miller M, Ganzenko N, Joob A, Marymont M et al. Phase II study of all-trans-retinoic acid and α-interferon in patients with advanced non-small cell lung cancer. Clin Cancer Res 1995;1:973-9.

**71.** Garaci E, Lopez M, Bonsignore G. Sequential chemoimmunotherapy for advanced non-small cell lung cancer using cisplatin, etoposide, thymosin-$\alpha_1$ and interferon-α2a. Eur J Cancer 1995;31A:2403-5.

**72.** Salvati F, Rasi G, Portalone L, Antili A, Garaci E. Combined treatment with thymosin-alpha1 and low-dose interferon-alpha after ifosfamide in non-small cell lung cancer: a phase II controlled trial. Anticancer Res 1996;16:1001-4.

**73.** Kohne-Wompner CH, Koschel G, Pawel JV, Wilke H, Vallee D, Bremer K et al. Small-cell lung cancer (SCLC) limited disease (LD): carboplatin (C), etoposide (E), vincristine (V) chemotherapy (CT) and radiotherapy (RT) followed by α 2b interferon (IFN) maintenance vs observation for patients (pts) with response after CT/RT. Ann Oncol 1992;(S3):40.

**74.** Mattson K, Niiranen A, Pyrhonen S. Natural interferon alfa as maintenance therapy for small cell lung cancer. Eur J Cancer 1992;28:1387-91.

**75.** Mattson K, Niiranen A, Ruotsalainen T, Maasilta P, Halme M, Pyrhonen S et al. Interferon maintenance therapy for small-cell lung cancer: improvement in long term survival. J Interferon Cytokine Res 1997;17:103-5.

**76.** Kelly K, Punn P, Hazuka M. The role of alpha interferon maintenance in patients with limited stage SCLC responding to concurrent chemoradiation. A SWOG study. Proc Am Soc Clin Oncol 1993;12:330 (Abstr. 1099).

**77.** Glisson BS, Palmer JL, Shin DM, Wester M, Markowitz AB. Phase II trial of interferon alpha (IFN) plus etoposide/cisplatin (EP) induction and IFN/Megau (M) maintenance in extensive small cell lung cancer (ESCLC). Proc Am Soc Clin Oncol 1993;12:354.

**78.** Jett RJ, Maksymiuk WA, Su QJ, Mailliard JA, Krook EJ, Tschetter KL et al. Phase III trial of recombinant interferon gamma complete responders with small-cell lung cancer. J Clin Oncol 1994;12:2321-6.

**79.** Bitran DJ, Green M, Perry M, Hollis RD, Herndon EJ. A phase II study of recombinant interferon-gamma following combination chemotherapy for patients with extensive small cell lung cancer. Am J Clin Oncol 1995;18:67-70.

**80.** vanZandwijk N, Groen HJM, Postmus PE, Burghouts JTW, Velde GPM, Ardizzoni A et al. Role of recombinant interferon-gamma maintenance in responding patients with

small cell lung cancer. A randomised phase III study of the EORTC Lung Cancer Cooperative Group. Eur J Cancer 1997;33:1759-66.

**81.** Tummarello D, Mari D, Graciano F, Isidori P, Cetto G, Pasini F et al. A randomized controlled phase III study of cyclophosphamide, doxorubicin, and vincristine with etoposide (CAV-E) or teniposide (CAV-T), followed by recombinant interferon-a maintenance therapy or observation, in small cell lung carcinoma patients with complete responses. Cancer 1997;80:2222-9.

**82.** Zarogoulidis K, Ziogas E, Papagiannis A, Charitopoulos K, Dimitriadis K, Economides D et al. Interferon alpha-2a and combined chemotherapy as first line treatment in SCLC patients: a randomised trial. Lung Cancer 1996;15:197-205.

**83.** Prior C, Oroszy S, Oberaigner W, Schenk E, Kummer F, Aigner K et al. Adjunctive interferon-alpha-2c in stage IIIB/IV small-cell lung cancer: a phase III trial. Eur Respir J 1997;10:392-6.

**84.** Hadden JW. The immunology and immunotherapy of breast cancer: an update. Int J Immunopharmacol 1999;21:79-101.

**85.** Laszlo J, Hood L, Cox E, Goodwin B. A randomized trial of low doses of alpha interferon in patients with breast cancer. J Biol Resp Modif 1986;5:206-10.

**86.** Fentiman SI, Balkwill RF, Cuzick J, Hayward LJ, Rubens DR. A trial of human alpha interferon as an adjuvant agent in breast cancer after loco-regional recurrence. Eur J Surg Oncol 1987;13:425-8.

**87.** Stanojević-Bakić N, Vučković-Dekić Lj, Inić M, Tomin R. Effect of interferon treatment on general immune competence in breast cancer patients. Glas de l'Academie Serbe des Sciences et des Arts 1994;44:71-82.

**88.** Walters RS, Theriault RL, Booser DJ, Espazza L, Hortobagyi GN. Phase II study of recombinant alpha-interferon (rIFN alpha) and continuous-infusion 5-fluorouracil in metastatic breast cancer. J Immunother Emphasis Tumor Immunol 1995;18:185-7.

**89.** Oldham RK, Blumenschein G, Schwartzberg L. Continuous biotherapy utilizing interleukin-2 and alpha interferon in patients with advanced cancer: a National Biotherapy Study Group trial. Mol Biother 1992;4:March.

**90.** Walters RS, Theriault RL, Holmes FA, Espazza L, Hortobagyi GN. Phase II study of recombinant alpha-interferon and recombinant interleukin-2 in metastatic breast cancer. J Immunother Emphasis Tumor Immunol 1994;16:303-5.

**91.** Tonini G, Nunziata G, Prete SP, Pepponi R, Turriziani M, Masci G et al. Adjuvant treatment of breast cancer: a pilot immunochemotherapy study with CMF, interleukin-2 and interferon alpha. Cancer Immunol Immunother 1998;47:157-66.

**92.** Ozzello L, Habif DV, DeRosa CM, Cantell K. Cellular events accompanying regression of skin recurrences of breast carcinomas treated with intralesional injections of natural interferons α and γ. Cancer Res 1992;52:4571-81.

**93.** Habif DV, Ozzello L, DeRosa CM, Cantell K, Lattes R. Regression of skin recurrences of breast carcinomas treated with intralesional injections of natural interferons alpha and gamma. Cancer Invest 1995;13:165-72.

**94.** Munno I, Marinaro M, Gesario A, Cannuscio B, Michel Y, Paulling E. Immunomodulatory effects of alpha interferon and thymostimulin in patients with neoplasias. Clin Diagn Lab Immunol 1995;July:503-5.

**95.** Bezwoda WR, Meyer K. Effect of alpha-interferon, 17b-oestradiol and tamoxifen on oestrogen receptor concentration and cell cycle kinetics of MFC7 cells. Cancer Res 1990;50:5387-91.

**96.** Coradini D, Biffi A, Pirronello E, DiFronzo G. Tamoxifen and beta-interferon: effect of simultaneous or sequential treatment on breast cancer cell lines. Anticancer Res 1995;15:315-9.

**97.** DiMartino L, Demontis B, Saccani Iotti G, Murenu G. *In vivo* effect induced by interferon beta on steroid receptor status, cell kinetics and DNA ploidy in operable breast cancer patients. Anticancer Res 1995;15:537-41.

**98.** Buzzi F, Burgia M, Rossi G, Giustini L, Scoponi G, Sica G. Combinaton of beta-interferon and tamoxifen as a new way to overcome clinical resistance to tamoxifen in advanced breast cancer. Anticancer Res 1992;12:869-71.

**99.** Seymour L, Bezwoda WR. Interferon plus tamoxifen treatment for advanced breast cancer: in vivo biologic effects of two growth modulators. Br J Cancer 1993;68:352-6.

**100.** Buzzi E, Burgia M, Trippa F, Rossi G, Trivisonne R, Guistini L et al. Natural interferon-beta and tamoxifen in hormone-resistant patients with advanced cancer. Anticancer Res 1995;15:2187-90.

**101.** Repetto L, Giannessi PG, Campora E, Pronzato P, Vigani A, Naso C et al. Tamoxifen and interferon-beta for the treatment of metastatic breast cancer. Breast Cancer Res Treat 1996;39:235-8.

**102.** Kornek G, Reiner A, Sagaster P, Stierer M, Mayer A, Ludwig H. Effect of interferon alpha-2a on hormone receptor status in patients with advanced breast cancer. Cancer Invest 1999;117:189-94.

**103.** Barak V, Kalickman I, Nisman B, Farbstein H, Fridlender ZG, Baicler L et al. Changes in cytokine production of breast cancer patients treated with interferons. Cytokine 1998;10:977-83.

**104.** Lindner DJ, Borden EC, Kalvakolanu DV. Synergistic antitumor effects of a combination of interferons and retinoic acid on human tumor cells *in vitro* and *in vivo*. Clin Cancer Res 1997;3:931-7.

**105.** Lama G, Angeluca C, Recchia F, Sica G. Combined effect of 13-cis-retinoic acid, tamoxifen and interferon on the growth of human breast cancer. Cancer Lett 1996;149:203-8.

**106.** Recchia F, Sica G, DeFilipps S, Discepoli S, Rea S, Torchio P et al. Interferon-beta, retinoids and tamoxifen in the treatment of metastatic breast cancer: a phase II study. J Interferon Cytokine Res 1995;15:605-10.

**107.** Recchia F, Rea S, DeFilipps S, Rosselli M, Corrao G, Gulino A, Sica G. Beta-interferon and tamoxifen combination in advanced breast cancer. Clin Ther 1998;149:203-8.

**108.** Recchia F, Frati L, Rea S, Torchio P, Sica G. Minimal residual disease in metastatic breast cancer: treatment with IFN-beta, retinoids and tamoxifen. J Interferon Cytokine Res 1998,18:41-7.

**109.** Agarwal C, Hembree JR, Rorke EA. Interferon and retinoic acid suppress the growth of human papilloma virus type 16 immortalized cervical epithelial cells, only interferon suppresses the level of human papilloma virus transforming oncogenes. Cancer Res 1994;54:2108-12.

**110.** Angioli R, Sevin BU, Perras JP, Untch M, Hightower R,Nguyen HN et al. Rationale of combining radiation and interferon for the treatment of cervical cancer. Oncology 1992;49:445-9.

**111.** Vučković-Dekić Lj, Spremo B, Stanojević-Bakić N, Garzičić B, Durbaba M. Immunosuppressive and cytogenetic effects of pelvic irradiation on the peripheral lymphocytes of patients with cervical cancer. Arch Immunol Ther Exp 1994;42:63-6.

**112.** Lippman SM, Kavanagh JJ, Paredes-Espinoza M. 13-cis-retinoic acid+interferon α-2a in locally advanced squamous cell carcinoma of the cervix. J Natl Cancer Inst 1993;85:499-500.

**113.** Lippman SM, Kavanagh JJ, Paredes M. 13-cis-retinoic acid (13 cRA), interferon α-2a (IFN-αa) and radiotherapy for locally advanced cancer of the cervix. Proc Am Soc Clin Oncol 1993; 12:257 (abstr.).

**114.** Murad AM, Oliveira M, Saldanha TM. Phase II trial of isotretinoin and interferon α-2a in the treatment of advanced recurrent cervical carcinoma. Int J Gynecol Cancer 1994;4:414-8.

**115.** Hallum AV, Alberts DS, Lippman SM. Phase II study of 13-cis retinoic acid + interferon-alpha 2a in heavily pretreated squamous carcinoma of the cervix. Gynecol Oncol 1995;56:382-6.

**116.** Lippman SM, Parkinson DR, Itri LM, Weber RS. 13-cis retinoic acid and interferon α-2a: effective combination therapy for advanced squamous cell carcinoma of the skin. J Natl Cancer Inst 1992;84:235-41.

**117.** Temeck KB, Liebmann EJ, Theodossiou C, Steinberg MS, Cook AJ, Metz CD et al. Phase II trial of 5-fluorouracil, leucovorin, interferon-α-2a, and cisplatin as neoadjuvant chemotherapy for locally advanced oesofageal carcinoma. Cancer 1996;77:2432-9.

**118.** Kok TC, van der Gaast, Splinter TAW. 12-cis-retinoic acid and alpha-interferon in advanced squamous cell cancer of the oesofagus. Eur J Cancer 1997;33:165-6.

**119.** Vlock DR, Andersen J, Kalish LA, Johnson JT, Kirkwood JM, Whiteside T et al. Phase II trial of interferon-α in locally recurrent or metastatic squamous cell carcinoma of the head and neck: immunological and clinical correlates. J Immunother 1997;19:433-42.

**120.** Schantz SP, Dimetry I, Lippman SM. A phase II study of interleukin-2 and interferon-alpha in head and neck cancer. Invest New Drugs 1992;10:217-33.

**121.** Urba SG, Forastiere AA, Wolf GT. Intensive recombinant interleukin-2 and alpha-interferon therapy in patients with advanced head and neck squamous carcinoma. Cancer 1993;71:2326-31.

**122.** Tanneberger S, Hrelia P. Interferons in precancer and cancer prevention: where are we? J Interferon Cytokine Res 1996;16:339-46.

**123.** Gan YH, Mahendran R, James K, Lawrencia C, Esuvaranathan K. Evaluation of lymphocytic responses after treatment with Bacillus Calmette-Guerin and interferon-a 2b for superficial bladder cancer. Clin Immunol 1999;90:230-7.

**124.** Baltić VV. Intratumor immunotherapy chondrosarcoma pelvis with recombinant interferon alpha 2a. Arch Oncol 1993;1:47-9.

**125.** Purohit A, Moreau L, Dietemann A, Seibert R, Pauli G, Wihlm JM et al. Weekly systemic combination of cisplatin and interferon α2a in diffuse malignant pleural mesothelioma. Lung Cancer 1998;22:119-25.

**126.** Trandafir L, Ruffie P, Borel C, Monnet I, Soulie P, Adams D et al. Higher doses of a-interferon do not increase the activity of the weekly cisplatin-interferon combination in advanced malignant mesothelioma. Eur J Cancer 1997;11:1900-2.

**127.** Buckner JC, Brown LD, Kugler JW, Cascino TL, Krook JE, Mailliard JA et al. Phase II evaluation of recombinant interferon alpha and BCNU in recurrent glioma. J Neurosurg 1995;82:430-5.

**128.** Morales A, Johnson B, Emerson L, Heaton JWP. Intralesional administration of biological response modifiers in the treatment of localized cancer of the prostate: a feasibility study. Urology 1997;50:495-502.

**129.** Krown S. Approaches to interferon combination therapy in the treatment of AIDS. Sem Oncol 1990;17(Suppl 1):11-5.

**130.** Salma S, Baltic V, Todorovic V. Clinical effects of interferon-α-2a treatment of Kaposi's sarcoma. Arch Oncol 1994;2:223.

**131.** Sneller MC. Consensus symposium on combined antiviral therapy: overview of interferon and IL-2 combinations for the treatment of HIV infection. Antiviral Res 1996;29:15-9.

**132.** Fischl MA, Finkelstein DM, He W, Powderly WG, Triozzi PL, Steigbigel RT. A phase II study of recombinant human interferon-alpha 2a and zidovudine in patients with AIDS-related Kaposi's sarcoma. AIDS Clinical Trial Group. J Acquir Immune Defic Syndr Hum Retrovirol 1996;11:379-84.

**133.** Shepherd FA, Beaulieu R, Gelmon K, Thuot CA, Sawka C, Read S et al. Prospective randomized trial of two dose levels of interferon alfa with zidovudine for the treatment of Kaposi's sarcoma associated with human immunodeficiency virus infection: a Canadian HIV Clinical Trials Network study. J Clin Oncol 1998;16:1736-42.

**134.** Miles S, Levine A, Feldstein M, Carden J, Cabriallas S, Marcus S et al. Open-label phase I study of combination therapy with zidovudine and interferon-beta in patients with AIDS-related Kaposi's sarcoma: AIDS Clinical Trials Group Protocol 057. Cytokines Cell Mol Ther 1998;4:17'23.

**135.** Aversa SM, Cattelan AM, Salvagno L, Meneghetti F, Francavilla E, Sattin L et al. Chemo-immunotherapy of advanced AIDS-related Kaposi's sarcoma. Tumori 1999;85:54-9.

**136.** Gutterman JU. Cytokine therapeutics: lessons from interferon-α. Proc Natl Acad Sci USA 1994;91:1198-205.

**137.** Tanneberger S, Hrelia P. Interferons in precancer and cancer prevention: where are we? J Interferon Cytokine Res 1996;16:339-46.

**138.** Kuwana K, Ichida T, Kamimura T, Ohkoshi S, Ogata N, Harada T et al. Risk factors and the effect of interferon therapy in the development of hepatocellular carcinoma: A multivariate analysis in 343 patients. J Gastroenterol Hepatol 1997;12:149-55.

**139.** Tanneberger S, Pannuti F. Disillusionments and hopes in the field of biological response modifiers. Anticancer Res 1993;13:185-92.

**140.** Eisenhauer EA, Lippman SN, Kavanagh JJ, Parades-Espinoza M, Arnold A, Hong WK et al. Combination 13-cis-retinoic acid and interferon alpha-2a in the therapy of solid tumors. Leukemia 1994;8(Suppl.3):S38-41.

**141.** Witt PL, Lindner DJ, D'Cunha , Borden CE. Pharmacology of interferons: induced proteins, cell activation, and antitumor activity. In: Chabner BA, Longo DL, eds. Cancer Chemotherapy and Biotherapy, second edition. Philadelphia: Lippincott-Raven Publishers, 1996:585-607.


The next ESMO congress will be held in Hamburg from 13-14 October, 2000. It will be the 25th congress of our Society and it will mark a substantial period of time during which ESMO has grown steadily as regards number of members, quality of its official journal, *Annals of Oncology*, and relevance of its role in the political issues of oncology in Europe.