The Role of Recombinant Interferon Alfa-2a in the Therapy of Cutaneous T-Cell Lymphomas

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Maximally tolerated doses of interferon alfa-2a, 50×10^6 U/m^2 administered intramuscularly (IM) 3 times weekly, were given to 20 patients with advanced stages of cutaneous T-cell lymphoma (CTCL) to determine the efficacy and toxicity of this therapy. All patients were heavily pretreated and had failed standard therapies. Objective remissions were noted in 45% of the patients, including two patients who achieved complete remissions and seven patients who had partial remissions. The median duration of response was 5.5 months, with responses lasting a minimum of 3 months and a maximum of more than 3 years. Responses in excess of 2 years occurred in three of the nine responding patients. These results were achieved with moderate toxicities. The dose-limiting toxicity was a flu-like syndrome consisting of malaise, anorexia, weight loss, and falling performance status. Toxicity was observed in all patients but was always alleviated by dose reduction. Patients with indolent B-cell non-Hodgkin's lymphoma who received the same therapy had a similar objective response rate (54%) and showed the same toxicities. These trials were followed by an ongoing trial using the same dose of interferon in a different schedule given for 12 weeks followed by a dose escalation to 100×10^6 U/m^2. Three partial responses were observed in the first 13 patients on this trial treatment. Other studies examining lower dose interferon compared to the 50×10^6 U/m^2 are in progress. This study establishes interferon alfa-2a as a treatment of choice for patients with advanced cutaneous T-cell lymphomas refractory to chemotherapy and other standard therapies. Trials combining interferon with other standard treatments and the use of interferon in earlier stages of disease are needed.

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INTERFERONS ARE GLYCOPROTEINS that make up a complex family of several species and subspecies of hormone-like molecules.[1,2] Naturally produced interferons are induced by viruses, antigens, and other nonviral stimuli. Interferons are potent inhibitors of viral replication in cultured cells and inhibit growth of certain human tumor cells *in vitro*.[1] Recent clinical trials have suggested that interferons may be active as antiviral and anticancer agents in humans.[2] The interferons were initially categorized according to their cell of origin, the inductive stimuli used to obtain them, or their physicochemical properties. The major classifications of interferon are summarized in Table 1 and designated as alpha, beta, and gamma according to their antigenic type. Leukocytes from peripheral blood and lymphoblastoid cell lines produce mainly interferon alpha; fibroblasts produce primarily interferon beta; and T-lymphocytes produce primarily immune or gamma interferon.

The recent advent of recombinant DNA technology has allowed for the cloning of various interferon genes. Currently more than 16 genes code for interferon alpha, and these have all been assigned to chromosome number 9.[2] Naturally occurring interferon alpha used in clinical trials includes the lymphoblastoid interferon alpha (interferon alfa-N1) produced by the Burroughs Wellcome Company (Research Triangle Park, NC) from a Burkitt lymphoblastoid line (Namalva) with purification by immunoaffinity chromatography. The Cantell-type leukocyte interferon has also received considerable clinical testing in the United States and Europe. The recombinant

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TABLE 1. Types of Interferon and Abbreviations

Leukocyte interferon	IFN-α (Le)
Lymphoblastoid interferon	IFN-α (Ly); IFN alfa-N1
Fibroblast interferon	IFN-β (natural)
Immune interferon	IFN-γ (natural)
Recombinant interferons	
Alpha-2	rIFN-α 2; IFN alfa-2b
Alpha-A	rIFN-α A; IFN alfa-2a
Alpha-1	rIFN-α 1
Alpha-D	rIFN-α D
Beta	rIFN-β
Gamma	rIFN-γ

interferon alpha studied to date has included the clone alpha-2 interferon (interferon alfa-2b) of Schering Corporation (Kenilworth, NJ) and the alpha-A (interferon alfa-2a) of Hoffmann-La Roche Inc. (Nutley, NJ). Clinical trials with the recombinant beta and gamma interferons are in early Phase I development.

Early studies performed with natural interferons at Stanford University and at the M. D. Anderson Hospital suggested that these preparations had some activity in the indolent non-Hodgkin's lymphomas.[3,4] A Phase I trial conducted by the National Cancer Institute (NCI) also suggested that interferon alfa-2a had some activity in the lymphoproliferative malignancies.[5] These Phase I trials demonstrated that 118×10^6 U was the maximally tolerated dose when given intramuscularly (IM) 3 times weekly (tiw). This dose of interferon was seen to cause hepatic enzyme elevations, fevers, and flu-like syndromes in these patients. The trial reported here used a maximally tolerated dose of interferon (50×10^6 U/m^2, given IM tiw) to determine its efficacy and toxicity.[6]

Interferon Treatment in Cutaneous T-Cell Lymphomas

Study 1

The cutaneous T-cell lymphomas (CTCL), comprising primarily mycosis fungoides and the Sézary syndrome, are indolent T-cell non-Hodgkin's lymphomas.[7] Phenotypic and functional studies have shown that the malignant cells in these disorders are the helper T-cells.[8,9] These lymphomas are characterized by initial symptoms in the skin and subsequent spread to peripheral blood, lymph nodes, and other organs. The prognosis is highly dependent on the stage, as determined by the type of skin lesions and the presence or absence of peripheral blood, lymph node, and visceral involvement. Overall, the cutaneous T-cell lymphomas are indolent in nature with median survivals of approximately 8 to 10 years, similar to the B-cell indolent non-Hodgkin's lymphomas. Systemic spread is nearly universal and can be documented by light microscopic examination in up to one half of the patients at the time of diagnosis.[10] Initial therapies developed for these disorders were directed at the skin. These included the use of topical nitrogen mustard applied daily to the skin,[11] the 3-times-weekly use of psoralen plus ultraviolet A light irradiation (PUVA),[12] and the total body application of electron beam irradiation.[13] These treatment approaches effectively alleviate skin lesions and produce skin clearing in the majority of patients. For all three treatments, the complete response rate is directly related to the disease stage and occurs in the majority of patients with plaque lesions but in a minority of those with tumors or erythroderma. The median duration of response for these therapies is 1 to 2 years, and 10% to 20% of patients remain disease-free at 3 years. This long disease-free interval occurs exclusively in patients with early plaque lesions. Relapses after 3 years were reported with topical nitrogen mustard but were not observed with total skin electron irradiation. This observation suggests that some of these patients may in fact be cured of this malignant neoplasm. Long-term data are not available for PUVA therapy but late relapses appear to be common.

Patients with more advanced disease stages have been treated with chemotherapy, either with single drugs or in multiagent combinations.[14,15] These treatments produced objective remissions in the majority of patients, but complete remissions in only 20% to 25% of the patients. Furthermore, relapse is universal; there has been no suggestion of cures reported to date. Because of the propensity for early systemic spread and the lack of cure with known treatments, new systemic approaches are clearly needed. For these reasons, the maximally tolerated doses of interferon alfa-2a were studied in these neoplasms.

Materials and Methods

Patient Population

All patients in our initial Phase II trial had histologically confirmed cutaneous T-cell lymphoma (mycosis fungoides or the Sézary syndrome). No patients had human adult T-cell leukemia or peripheral T-cell lymphoma. All patients were ambulatory with an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2. Routine laboratory tests showed acceptable hematologic, hepatic, and renal function in all patients. All patients had clearly identifiable measurable lesions that could be used to monitor response to the interferon. The median patient age was 57 (range, 41–72 years), and included 13 men and 7 women. Sixteen of the patients were white and 4 were black. All patients had advanced stages. There were five patients with generalized plaque lesions, ten with cutaneous tumors, and five with generalized erythroderma

(Sézary syndrome). Fifteen patients had peripheral blood or lymph node involvement and two had visceral involvement. Using the recommended staging classification for mycosis fungoides, 5 patients were Stage II, 2 were Stage III, and 13 were Stage IV.

All patients had failed prior multiple therapies. Topical mechlorethamine had been given to 18 patients, PUVA to 12 patients, total skin electron beam irradiation to 14 patients, systemic chemotherapy to 16 patients, and other systemic therapies to 6 patients. These other therapies included T101 serotherapy in two patients, total body photon irradiation in one, retinoic acid in one, and hyperthermia in one. All patients had also received topical and oral steroids. A minimum of 4 weeks had elapsed between the time of the last treatment with any of these agents and entry into the trial. Patients included in this trial underwent complete history and physical examinations as well as routine laboratory tests, along with radiologic and nuclear medicine studies as needed to determine response. All patients gave informed consent before starting the therapy.

Methods

The study plan for this trial is shown in Table 2. The recombinant interferon (Roferon®-A, interferon alfa-2a) was provided to the National Cancer Institute by Hoffmann-La Roche Inc. (Nutley, NJ). A dose of 50×10^6 U/m^2 IM was given 3 times weekly; the initial dose was reduced by 50% for severe toxicity, and was further reduced to 10% of the starting dose if toxicity persisted. Patients who responded were continued on therapy indefinitely; patients with mixed or minor response and stable disease received therapy for 3 months; and patients who progressed had therapy discontinued at the time of disease progression. All patients received 600 mg of acetaminophen orally prior to interferon doses and every 4 hours thereafter as needed for fever.

Patients were monitored for tumor response by measurement of indicator lesions, repeated radiologic and nuclear medicine studies, and biopsies when appropriate. Complete responses included complete resolution of all clinically evaluable disease for at least 4 weeks, including a negative skin biopsy result. A partial response consisted of more than a 50% decrease in measurable lesions for at least 4 weeks. A minor response was defined as more than a 25% but less than a 50% decrease in measurable lesions lasting for at least 4 weeks. Mixed responses included objective remissions in some lesions, but stable or progressive lesions in other areas. Stable disease included no objective response or progression for at least 3 months, and disease progression consisted of a 25% or greater increase in measurable lesions or the appearance of new lesions.

TABLE 2. Study Design

	Treatment
Interferon alfa-2a	50×10^6 U/m^2 IM three times weekly
Dose modification	50% reduction for severe toxicity 90% reduction for persistent toxicity
Treatment	
Responders	Indefinite
Mixed/minor response	3 mo
Stable disease	3 mo
Disease progression	Discontinue at progression

Results

Response to Treatment

Objective antitumor responses were noted in 9 of the 20 patients in this study, representing a response rate of 45% with a 95% confidence interval of 25% to 69%. The objective responses were all noted within 1 month, and lasted a minimum of 3 months to a maximum of more than 36 months. At 3 months, none of the remissions were complete; however, two patients later developed normal skin biopsy results and have been scored as complete responders. Thus, the complete response rate is 10% and the partial response rate is 35%. Responses were seen in extracutaneous and cutaneous sites and did not correlate with prior therapy. Eight of the nine responders had previously received systemic chemotherapy. An example of the cutaneous responses is shown in Figure 1 for a patient who had a partial response lasting 9.5 months. Extracutaneous responses were documented by a decrease in the size of palpable lymph nodes in 8 of 16 patients with adenopathy, and by a greater than 50% decrease in the number of circulating malignant cells in 2 patients, documented by cytologic study and DNA content analysis.

The duration of response is illustrated in Figure 2. The median duration of response was 5.5 months. Notably, three patients representing one-third of the responders and 15% of all patients have responded for more than 2 years.

Mixed or minor responses were noted in five patients, and three others remained stable for 3 months; therapy was discontinued in these eight patients at 3 months. Another three patients progressed during the initial 3 months of therapy: one patient received only the initial dose of therapy and two others progressed after 1 and 2 months, respectively.

In this Phase II trial, it is difficult to assess survival. The three patients with progressive disease died 1.5, 6,

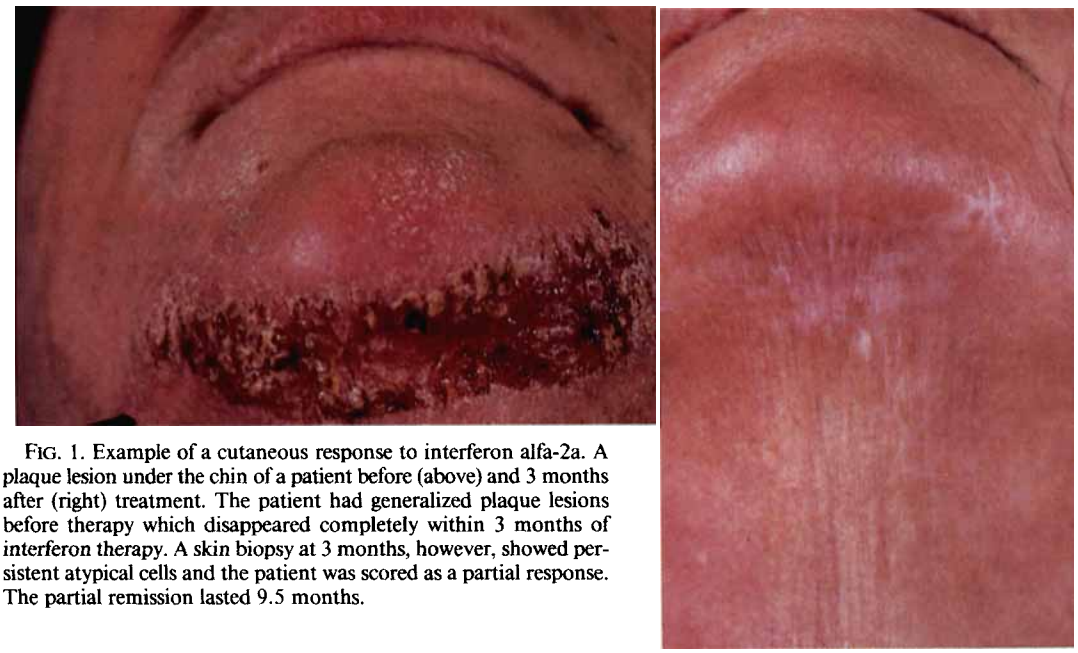

FIG. 1. Example of a cutaneous response to interferon alfa-2a. A plaque lesion under the chin of a patient before (above) and 3 months after (right) treatment. The patient had generalized plaque lesions before therapy which disappeared completely within 3 months of interferon therapy. A skin biopsy at 3 months, however, showed persistent atypical cells and the patient was scored as a partial response. The partial remission lasted 9.5 months.

and 11 months, respectively, after initiation of interferon therapy. The remaining 17 patients lived from 3 to >36 months after the initiation of interferon therapy.

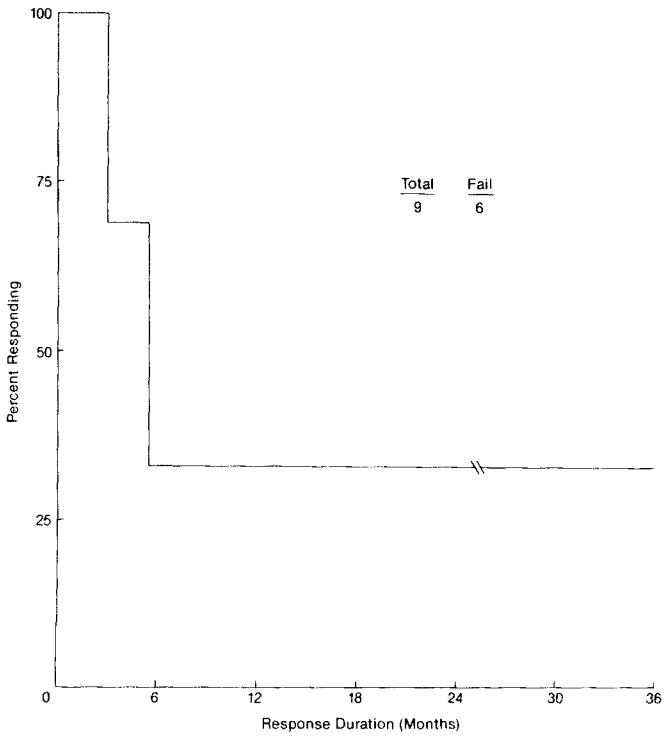

FIG. 2. Response duration. Actuarial duration of complete and partial responses. The median duration of response was 5.5 months. Responses in excess of 2 years have been noted in three of the responders.

Toxicity

All 20 patients received at least an initial dose of interferon and all had marked febrile responses. The median fever was 39.9°C (range, 38.4–40.2°C). This febrile reaction was most prominent after the first dose and gradually abated over time. One patient developed a cutaneous palpable purpura, possibly allergic in nature, after the initial dose. No further doses of interferon were given to this patient. The other 19 patients developed a flu-like syndrome consisting of malaise, anorexia and weight loss, fatigue, a decreased performance status, depression, and, in severe cases, mental confusion. To alleviate this syndrome, the initial doses were reduced by 50% in all 19 patients receiving more than one dose. In addition, nine patients required a further dose reduction to 10%. The syndrome produced a median decline in Karnofsky performance status of 30% (range, 10%–80%). There was a mean fall in weight of 5.4 kg (range, 0–17.7 kg). Dose reduction alleviated these symptoms in all patients, and two patients have remained on a reduced level of therapy for more than 2 years.

There appeared to be a tachyphylaxis to both the febrile response and the flu-like syndrome. While on the reduced dose, ten patients had some worsening of their skin lesions and their dose was re-escalated. The flu-like syndromes did not recur following this escalation. In addition, clinical benefits from the dose escalation were noted in four of these ten patients, suggesting there may be a dose–response effect for interferon.

Hematologic toxicity was mild and not dose-limiting. Two patients had a fall in leukocyte count to less than 2000/μl, but both were heavily pretreated with systemic therapy and one also with total body irradiation. Reversible elevations (>25%) in hepatic enzyme levels occurred in six patients. The dose was reduced in all of these patients due to the flu-like syndrome, and the hepatic enzyme levels returned to normal. None of the patients developed jaundice. One patient developed a reversible nephrotic syndrome and renal failure with minimal-change glomerulonephritis.[16] This syndrome disappeared after discontinuation of the interferon. One patient developed an acute monocytic leukemia after 11 months on interferon therapy; therapy was discontinued at this time. The patient had been heavily pretreated with alkylating agents and electron irradiation. This patient was then treated with high-dose cytosine arabinoside which produced a complete remission of his leukemia; he has been in remission from the leukemia and the Sézary syndrome for more than 16 months since completion of therapy.

Study 2

After the completion of Study 1, a second study was instituted for patients with the same entry criteria. The treatment plan was considerably different in this study in an attempt to increase the complete response rate. The study design and results are summarized in Table 3. Patients in this study received an initial dose of 10×10^6 U/m^2 on day 1 after pretreatment with acetaminophen. The patients then received 50×10^6 U/m^2 for 4 days. Therapy was given intermittently at 3-week intervals for a total of 12 weeks. Then, if patients were stable or responding, the dose was escalated two-fold: on the first day, 20×10^6 U/m^2 was given intramuscularly, followed by 4 days at 100×10^6 U/m^2. These cycles of therapy were given intermittently every 3 weeks. To date, 13 patients have been entered in this trial and there are 3 partial responses. Only three of the patients received the high-dose treatment at 12 weeks and they all tolerated it. One partial responder was included in this group.

TABLE 3. Preliminary Results of Interferon Alfa-2a in Study 2

Dose	Response
50×10^6 U/m^2 IM d 2–5 q 3 w × 12 w* followed by: 100×10^6 U/m^2 IM d 2–5 q 3 w†	3 partial responses in 13 patients

* 10×10^6 U/m^2 given on the first day of each cycle.
† 20×10^6 U/m^2 given on the first day of each cycle.
d: day; q: every; w: weeks.

Use of Interferon Alfa-2a in Indolent B-Cell Lymphomas

During this period, the NCI conducted trials, using the same interferon alfa-2a dose as in study 1 (50×10^6 U/m^2 tiw) in patients with advanced indolent B-cell non-Hodgkin's lymphomas.[17] These results are summarized in Table 4. There were 24 evaluable patients with indolent low-grade non-Hodgkin's lymphomas. Of these, complete responses were noted in four patients (17%) and partial responses were seen in nine patients (38%).[17] Thus, 54% of the patients had an objective response to therapy with a median duration of 8 months. The toxicities were similar to those seen in patients with cutaneous T-cell lymphoma. These results are similar to other trials in the literature with various doses and schedules of interferon in patients with indolent B-cell lymphomas, which are summarized in Table 4.[3,4,17–22] Of the 138 patients entered in these trials, complete remissions were noted in 7% and partial remissions in 28%, for a total objective response rate of 35%.

Discussion

The interferons have shown great promise as anticancer agents since the studies of Strander and colleagues demonstrated interferon activity in the management of osteosarcoma.[23] Unfortunately, much of the initial enthusiasm for interferon as an anticancer agent has been dampened by subsequent disappointing results. Recent clinical studies have shown, however, that interferons do have considerable activity in a limited spectrum of disease. The study reported here establishes the activity of interferon alfa-2a in the cutaneous T-cell lymphomas. In this study of patients with advanced disease refractory to one or more standard treatments, including systemic chemotherapy, interferon was more active than other, recently evaluated experimental therapies. The observed high response rate and long duration of response in this study suggest that interferon should be evaluated in earlier disease stages and added to standard treatments so the efficacy of this combined approach can be compared with that of standard agents used alone.

The optimal dose of interferon for any malignancy is unknown. The responses observed in this study were to

TABLE 4. Results of Interferon in Indolent B-Cell Lymphomas

	Patients (n)	% CR	% PR	% CR + PR
NCI Study[17]	24	17	38	54
Published literature[3,4,18–22]	138	7	28	35

CR: complete response; PR: partial response; NCI: National Cancer Institute.

a high dose of interferon which was associated with considerable toxicity and required dose reduction in all patients. Lower doses of interferon, such as 3×10^6 U/m^2, have reduced significant response rates in patients with hairy cell leukemia.[24] Whether lower doses of interferon would be effective in the cutaneous T-cell lymphomas is unknown. Fortunately, a randomized trial with low- and high-dose interferon is currently in progress in CTCL patients. The tachyphylaxis to the side effects of interferon, noted in this study, suggests that perhaps higher doses of interferon could be evaluated after a period of treatment with lower doses, although a preliminary study with very high-dose interferon conducted at the NCI with 13 patients did not demonstrate a higher response rate with this approach.

The toxicities noted in this study suggest that acetaminophen should be given routinely to all patients, especially at the institution of interferon therapy, to alleviate the fever. Patients with severe cardiac disease or those in whom high temperature is life-threatening should not be placed on interferon. The flu-like syndrome can perhaps be alleviated by initiating therapy with low-dose interferon and then escalating the dose. Whether this provides equivalent therapeutic results is being evaluated in a randomized trial, as previously noted. Renal and hepatic function should be monitored routinely since occasionally patients will have a dose-limiting toxicity to one of these organs. The lowering of blood counts does not appear to be direct bone marrow suppression but is important when considering combined chemotherapy and interferon trials because the chemotherapy doses are modified according to the peripheral blood counts.

Several Phase II trials have been designed to evaluate the efficacy and toxicities of interferon in combination with chemotherapy. In some trials, interferon will be given for 1 month to establish baseline leukocyte and platelet levels; chemotherapy doses will be subsequently modified based on these baseline counts. The optimal schedule for combinations of chemotherapy and interferon is not yet known. Since chemotherapy is immunosuppressive and interferons may be immunostimulatory, chemotherapy should be given intermittently and interferon continuously. Phase II trials of these combinations are in development.

The mechanism of the antitumor response noted in these patients is uncertain. In our study there was no correlation between the development of antibodies to interferon, response rate, or response duration.[6] No obvious correlation existed between response and *in vitro* laboratory tests of T-cell subsets or response to phytohemagglutinin. The responses were not likely to be due to the fever, since there was no correlation with the degree of febrile response, and responses continued long after the patients ceased having fevers. Whether there is a direct cytotoxic effect is unknown. *In vitro* laboratory studies have failed to show antiproliferative effects of recombinant interferon alpha in three malignant T-cell lines and direct specimens from two patients with the Sézary syndrome; however, these cell lines and tumor specimens were not from the patients studied in this report. Interferons may also increase the expression of tumor-associated antigens and histocompatibility antigens on malignant cells,[25] suggesting the possibility of combining interferon with monoclonal antibodies or other biological therapies. Phase II studies of such combinations will also need to be performed in the future.

The results of the studies reported here show considerable activity for interferon in the indolent B-cell non-Hodgkin's lymphomas. Phase II studies will also need to be conducted, combining interferon with standard chemotherapeutic approaches in these disorders. In addition, for patients with complete response to chemotherapy, use of interferon as an agent to prolong remission could be considered.

In summary, high-dose interferon alfa-2a has been shown to be an active agent in advanced cutaneous T-cell lymphomas refractory to standard agents, including chemotherapy. Interferon was also shown to be active in indolent and low-grade B-cell non-Hodgkin's lymphomas. Future trials to evaluate these interferons in earlier stages of disease in patients in remission, and in combinations with chemotherapy or monoclonal antibodies, are in progress or in the planning stages.

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