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A phase II trial of murine monoclonal antibody 17-1A and interferon-γ: clinical and immunological data*

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Summary. A group of 15 patients with metastatic colorectal adenocarcinoma received a combination of interferon γ (0.1 mg/m^2, days 1–15) and the murine monoclonal antibody 17-1A (400 mg, days 5, 7, 9 and 12). The treatment was tolerated with minimal toxicity. Of the 14 evaluable patients, 13 developed human antibody to murine 17-1A, with 11 patients demonstrating antibody to the variable region of 17-1A (anti-idiotype). Antibody to the variable region was inhibited by 17-1A but not by mouse immunoglobulin. Sera from patients with substantial anti-idiotype reactivity were capable of inhibiting the binding of murine 17-1A to antigen expressing LS174-T cells thus indicating the presence of antibody directed against the 17-1A combining site (mirror-image anti-idiotype). The median survival of the whole group was 56 weeks and there was no correlation between clinical response/survival and the development of anti-idiotype antibody.

Introduction

Over the past decade, a variety of murine monoclonal antibodies have entered phase I and II clinical trials. Several studies have reported clinical antitumor effects [19, 17, 30] but other studies have had little, if any, clinical responses [3, 14, 24]. Tumor heterogeneity [8], inadequate delivery of antibody to tumor target [7], suboptimal effector cell function in vivo [1] and the development of human antibodies against mouse mAbs [9, 23] have been cited as some of the possible causes for the poor clinical responses, despite well documented anti-tumor activity of the mAb in vitro [6, 27]. The effect of unconjugated murine mAb is primarily mediated via the stimulation of the immune effector arm following binding to the tumor target. Biological agents that can enhance the expression of tumor surface antigens and/or enhance human effector cell function offer the opportunity to improve the therapeutic effectiveness of unconjugated monoclonal antibodies. When administered in combination, these reagents may potentially be synergistic in vivo. A number of in vitro studies [4, 25, 31] as well as some recent in vivo data [22] have documented the ability of interferon γ (IFNγ) to increase the expression of tumor-associated antigens. IFNγ has also been shown to potentiate the cytolytic function of peripheral blood effector cells in vitro [20, 29] and in vivo [32].

We have previously reported on a phase I trial of murine 17-1A monoclonal antibody, which documented that 2-h infusions of 400 mg administered four times over an 8-day period resulted in continuous serum levels of 17-1A varying between 120–140 μg/ml (peak) and 10–24 μg/ml (nadir) during a 10-day period [9]. The treatment was well tolerated and no anti-(mouse mAb) response was noted during the 10 days of therapy. A phase I trial of recombinant IFNγ (Genentec, Inc.) documented that a dose of 0.1 mg/m^2 was well tolerated and enhanced mononuclear cell function [21]. We have carried out a trial using the above IFNγ regimen and this dose and schedule of 17-1A in a phase II trial in metastatic colon cancer.

Materials and methods

Patient selection. The protocol was designed to treat patients with objectively measurable, metastatic gastrointestinal adenocarcinoma, who have high performance status (≥60, Karnofsky). All patients in this study had pathologically proven colon or rectal adenocarcinoma with small to moderate tumor burden as defined previously [4] and progressive disease; they had received no more than one previous trial of chemotherapy. Patients with prior chemotherapy were registered no sooner than 4 weeks from the last chemotherapy administration. Laboratory selection criteria included normal creatinine and bilirubin levels and alkaline phosphatase, serum glutamic-oxaloacetic transaminase, and glutamate-pyruvate transaminase not exceeding three times the normal levels. All patients signed

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Table 1. Colon cancer patient characteristics

Patient	Metastatic sites	Tumor burden	KPS(%)[a]	Prior therapy
1	Lung	Moderate	90	RT/chemo
2	Lung/liver	Small	100	RT
3	Lung	Small	100	Chemo
4	Prostate	Small	80	Chemo
5	Lung/liver	Moderate	100	Chemo
6	Lung/liver	Small	100	None
7	Lung/liver	Moderate	60	Chemo
8	Liver	Small	60	Chemo
9	Liver	Small	60	Chemo
10	Lung/liver	Moderate	80	None
11	Pancreas/abdomen	Small	100	None
12	Abdomen	Small	100	Chemo
13	Liver	Small	100	Chemo
14	Liver	Small	100	None
15	Pancreas/liver	Moderate	90	Chemo

[a] Karnofsky performance status

an informed consent form approved by the Institutional Review Board. The protocol was conducted in accordance with an Investigational New Drug application submitted to the Food and Drug Administration.

Treatment plan. All patients received IFNγ at a dose of 0.1 mg/m^2 (2×10^6 U/m^2) daily for 15 days (days 1–15). Patients also received 400 mg mAb 17-1A mid-cycle on days 5, 7, 9 and 12.

All patients had follow-up for 8 weeks, at which time they they were re-evaluated for evidence of objective response or disease progression. The criteria for response were as follows: *complete remission*, complete disappearance of all measurable lesions; *partial response*, >50% reduction in the sum of the products of the diameters of all measurable lesions; *progressive disease*, >50% increase in the products of the diameters of all measurable lesions or clinical evidence of disease progression, i.e., decrease in performance status or increase in symptoms; and *stable disease*, failure to meet criteria for partial response or disease progression. All patients with stable disease or objective response were continued on the protocol without alternative therapy until they fulfilled the criteria for progressive disease. Survival was measured from the date of registration in the study. Patient accrual took place from June 1986 to June 1988 and follow-up was completed through March 1989.

17-1A infusions. The 17-1A was provided by Centocor, Inc. (Malvern, Pa), in a solution of 10 mg/ml in 5-ml vials and stored at 4° C prior to use. The antibody was diluted in 200 ml saline for administration. All infusions were performed in the General Clinical Research Unit. All patients had a main i. v. access established in one arm and a heparin-lock vascular access in the other arm for blood sampling. The antibody preparation was piggybacked through a freely running i. v. access to allow independent control of the antibody infusion. All patients received an i. v. test dose of 0.7 mg with 30 min of careful monitoring for evidence of allergic reaction. If no adverse effect resulted from the test dose, the 400-mg treatment dose was infused over 120 min, and vital signs were determined four times at 15-min intervals, four times at 30-min intervals, or more frequently if problems arose.

IFNγ therapy. Recombinant IFNγ (Genentec Inc.) was provided as a sterile lyophilized powder with >98% purity and a specific activity of approximately 2×10^7 units/mg protein on the basis of anti-viral activity using NIH reference standard for IFNγ. The drug was reconstituted in physiological saline at a concentration of 0.1 mg/ml and administered as an intramuscular injection. Vital signs and systemic symptoms were monitored daily prior to each injection. On a day of 17-1A infusion, the IFNγ was administered 4 h following the antibody infusion.

Patient monitoring. Patients had a complete blood count, chemistry profile and clinical evaluation on day 1 (prior to IFNγ therapy), day 5 (prior to initiating 17-1A therapy), day 12 (last day of 17-1A therapy), day 15 (last day of IFNγ therapy) and at 2-week intervals for a total of 8 weeks at which time a complete follow-up evaluation was performed.

Human immune response. Human antibodies to murine 17-1A and to the variable region of 17-1A (anti-idiotype) were assayed using the "double-antigen" system previously described [16]. Polystyrene beads (Precision Plastic Ball, Chicago, Ill.) were coated with murine 17-1A and stored in phosphate-buffered saline/bovine serum albumin (PBS/BSA). Murine 17-1A or chimeric mouse/human 17-1A were radiolabeled with ^{125}I by the chloramine-T bead technique. The assay was performed in triplicate and consisted of incubation of a single 17-1A-coated bead with 100 µl test serum on a shaker for 60 min at room temperature. This was followed by a single 5-ml wash using PBS/BSA and an incubation with 100 µl ^{125}I-labeled 17-1A or ^{125}I-labeled chimeric 17-1A (2 µg/ml; ≈200 000 cpm). Unbound radiolabeled antibody was washed off and the radioactivity bound to the bead was counted in a micromedic automatic gamma counter. Results obtained as mean cpm/bead were converted to ng antibody using the specific activity of ^{125}I-labeled 17-1A or chimeric 17-1A and expressed as ng antibody bound/ml patient serum. Each serum sample was assayed for binding of murine and chimeric 17-1A in the same assay to compare reactivity with the whole antibody or the variable region (anti-idiotype).

Sera from 38 patients with colorectal cancer never exposed to 17-1A were used to define the normal range of this assay system. The values for binding of murine 17-1A were 4.8 ± 2.4 ng/ml and for chimeric 17-1A were 2.8 ± 1.0 ng/ml. Thus, a positive assay result was defined as >10 ng/ml for murine 17-1A and >5 ng/ml for chimeric 17-1A.

To confirm the anti-variable-region specificity of selected sera, competitive inhibition studies were carried out using normal mouse immunoglobulin (Ig). For these studies, a 200-fold excess (40 µg) unlabeled 17-1A or normal mouse Ig was added to the incubation of patient sera with the 17-1A-coated bead in step 1 of the above assay and then the assay completed as described above with ^{125}I-labeled murine 17-1A. The difference between inhibition by 17-1A and mouse Ig reflects antibody binding due to antibody to the variable region of 17-1A (anti-idiotypic antibody). For these studies, a rabbit antiserum to 17-1A F(ab)$_2$ served as a positive control while human serum containing antibody to a melanoma-reactive murine monoclonal antibody served as a negative control [14].

We also examined selected sera for the presence of "mirror-image" anti-idiotype reactivity by determining the ability of patient sera to inhibit the binding of 17-1A to a colon cancer cell line that expresses the 17-1A antigen. A sample of 100 ng ^{125}I-labeled 17-1A (100 µl) was incubated with 1×10^6 LS-174T colon cancer cells in the presence of 10 µl pre-therapy or post-therapy patient sera at 37° C for 60 min (total volume 175 µl). Duplicate 70-µl samples of the mixture were layered on top of 15% isotonic Percoll in a microfuge tube and centrifuged at 10 000 *g* for 5 min. The cell button with bound ^{125}I-labeled 17-1A was counted and the number of molecules of 17-1A bound per cell calculated from the number of cells per tube and the specific activity of the ^{125}I-labeled 17-1A [16]. The tumor cells incubated with ^{125}I-labeled 17-1A in the presence of pre-therapy sera bound 16 000–20 000 molecules of 17-1A per tumor cell. The percentage inhibition of the ^{125}I-labeled 17-1A binding to tumor cells by post-therapy serum as compared to pre-therapy serum was calculated as a measure of human antibody binding to the 17-1A antigen-binding site (mirror-image anti-idiotype antibody). Sera not containing anti-(variable region) antibody activity (n = 15) were tested and produced <30% inhibition (mean ±2 SD). A positive assay was therefore defined as inhibition of >30%.

Results

Patient characteristics

The clinical characteristics of the patients are summarized in Table 1; 15 patients with metastatic colon cancer underwent treatment, 10 patients had a small tumor burden

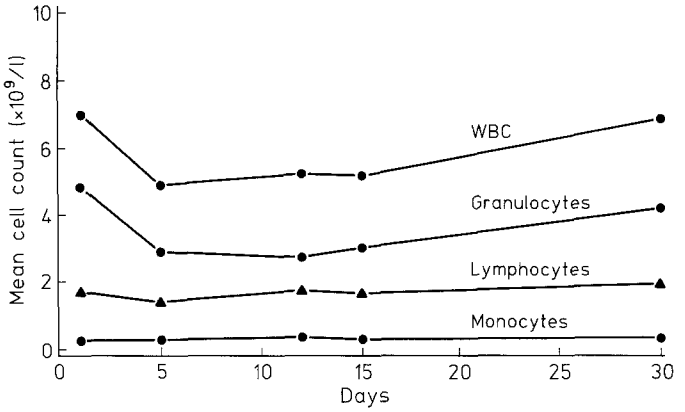

Fig. 1. Mean white blood cell profile of patients receiving 17-1A + interferon γ for the treatment of metastatic colorectal cancer

Table 2. Human immune response to murine and chimeric 17-1A

Patient	Response (ng/ml)[a]				
	Pre-treatment	Week 2	Week 3	Week 6	Week 8
1	5/3	9/4	8/4	9/ 4	9/ 4
2	8/5	7/5	8/5	13/ 5	16/ 5
3	6/4	33/6	25/6	31/ 7	0/ 0
4	7/4	11/5	15/6	9/ 5	0/ 0
5	5/3	7/4	18/3	43/16	92/ 40
6	5/5	10/5	38/7	452/90	651/221
7	6/4	74/4	86/9	24/ 5	43/ 7
8	6/4	7/4	68/9	16/ 5	17/ 6
9	7/4	43/8	17/5	12/ 5	11/ 5
10	6/4	23/4	61/7	172/22	526/146
11	0/0	16/4	13/5	19/ 4	23/ 4
12	14/3	24/7	11/5	12/ 6	23/ 14
13	5/4	8/4	0/0	10/ 5	13/ 7
14	6/5	6/5	6/6	0/ 0	16/ 10

[a] Results are expressed as ng murine 17-1A/chimera 17-1A bound per ml sera (see Materials and methods)

(measurable lesions <5 cm in diameter) while 5 patients had moderate disease (measurable lesions 5–10 cm in diameter). Two-thirds of patients had a Karnofsky performance status of 90%–100% and all but 4 patients had received prior therapy. All 15 patients are evaluable for toxicity. One patient refused follow-up evaluation at 8 weeks and is excluded from response analysis.

Toxicity

The most common side-effect was flu-like symptoms consisting of mild fever, malaise and arthralgias noted in 14/15 patients following IFNγ therapy. Symptoms were tolerable (grades I–II) and subsided within 24 h following completion of IFNγ therapy. One patient developed temporary blurred vision during therapy. The symptoms lasted for 48 h and resolved spontaneously without any modification in treatment. No other neurological symptoms were observed. Out of 15 patients, 5 noted gastrointestinal symptoms associated with 17-1A therapy. Symptoms consisted of mild (grades I–II) nausea/vomiting and/or diarrhea. In all cases, symptoms subsided within 24–48 h of onset.

Table 3. Competitive inhibition of serum antibody reactivity to murine 17-1A

Serum source	Sample time (week)	Inhibitor[a]		
		None	17-1A	MIg
Patient 5	Pre	4	3	3
	3	14	6	8
	4	14	4	7
	6	23	4	18
	8	57	4	48
Patient 6	Pre	7	4	3
	3	30	3	12
	4	81	5	33
	6	407	7	153
	8	546	8	368
Patient 10	Pre	6	4	3
	3	46	7	16
	4	30	5	8
	6	116	6	26
	8	425	7	161
3196[b]		312	6	180
DR[b]		186	6	7

[a] Results expressed as ng murine 17-1A bound/ml serum (see Materials and methods). Patient sera were incubated with no competing substance (None), 40 μg murine 17-1A (17-1A) or 40 μg normal mouse immunoglobulin (MIg)

[b] 3196 is a rabbit anti-17-1A $F(ab)_2$ and DR is a human anti-melanoma monoclonal antibody serum

Laboratory studies

All patients developed a reduction in white blood cells by day 5 with spontaneous resolution following completion of IFNγ therapy. The mean white blood cell count fell by 30%. This appeared to be selectively due to a reduction in neutrophils. The proportion of lymphocytes and monocytes remained unchanged throughout this period (Fig. 1). None of the patients developed absolute neutropenia (granulocytes <500/mm^3). A similar though less pronounced reduction in platelet count was also noted. No other abnormalities in laboratory studies were noted.

Immune response

Serial serum samples were available from 14 of the 15 patients. Table 2 provides the sera reactivities with murine 17-1A. One patient (no. 12) had a pretherapy value exceeding 10 ng/ml. Out of 14 patients, 13 developed a positive assay following 17-1A therapy. Antibody levels were low (10–25 ng/ml) in 6 patients (nos. 2, 4, 11, 12, 13, 14), moderately elevated (26–100 ng/ml) in 5 patients (nos. 3, 5, 7, 8, 9) and high (>100 ng/ml) in 2 patients (nos. 6, 10). Two patterns of peak antibody response were seen: 5 patients (nos. 3, 4, 7, 8, 9) achieved their peak

Table 4. Inhibition of ^{125}I-labeled 17-1A binding to tumor cells by patient sera

Sample time (week)	Inhibition (%)[a] by sera from patient				
	1	5	6	10	11
2	13	13	0	0	18
3	0	7	33	9	2
6	0	33	97	23	2
8	0	69	100	50	6

[a] Results expressed as percentage inhibition of ^{125}I-labeled 17-1A binding to LS-174T colon cancer cells by post-therapy serum compared to pre-therapy serum (Patient nos. 1, 5, 6, 10, 11). Significant inhibition is >30% (see Materials and methods)

Table 5. Response characteristics

Patient	Toxicity[a]	Response	Survival (weeks)	Immune response	anti-idiotype response
1	Flu/GI	P	56	None	None
2	Flu/GI	P	80	Low	None
3	GI	P	56	Moderate	Low
4	Flu	NA	60	Low	Low
5	Flu	S	40	Moderate	Moderate
6	Flu	P	56	High	High
7	Flu	S	60	Moderate	Low
8	Flu	P	24	Moderate	Low
9	Flu/GI	P	40	Moderate	Low
10	Flu	P	80	High	High
11	Flu	P	12	Low	None
12	Flu	S	72	Low	Low
13	Flu/GI	P	68	Low	Low
14	Flu	P	44	Low	Low
15	Flu	P	24	NA	NA

[a] Flu, influenza-like symptoms; GI, gastrointestinal symptoms; P, disease progression; S, stable diseae; NA, data not available

response early (2–3 weeks) while 7 patients (nos. 2, 5, 6, 10, 11, 13, 14) had their peak response late (6–8 weeks). Indeed, patients 2, 13 and 14 would have been categorized as not having achieved an antibody response if only examined 2 and 3 weeks following therapy.

Table 2 also provides the serum antibody reactivity to chimeric 17-1A in these same samples. All patients had values ≤ 5 ng/ml prior to therapy. Eleven patients developed a positive assay following therapy with 17-1A and these positive assays coincided with the peak reactivity to murine 17-1A. The 3 patients (nos. 5, 6, and 10) with the largest anti-idiotype response were also those patients with the highest reactivity to murine 17-1A. All 3 of these patients were in the category of late antibody responders achieving their peak response at week 8.

Sera of these 3 patients were also studied by assaying for competitive inhibition by mouse Ig to define anti-idiotype reactivity. As illustrated in Table 3, there was excellent correlation between high serum binding of murine 17-1A in the presence of competing mouse Ig and the serum binding of chimeric 17-1A in Table 2 confirming the anti-(variable region) specificity of the antibody response.

Mirror-image anti-idiotype reactivity (Table 4) was examined in 2 patients with no anti-idiotype reactivity (nos. 1 and 11) and 3 patients with the highest anti-idiotype reactivity (nos. 5, 6 and 10). All 3 patients with high anti-idiotype reactivity produced inhibition of 17-1A binding to colon cancer cells. Serial dilution of week-8 serum samples from patients 5, 6 and 10 had significant inhibition of binding at dilutions out to 1:32, 1:64 and 1:64, respectively (data not shown).

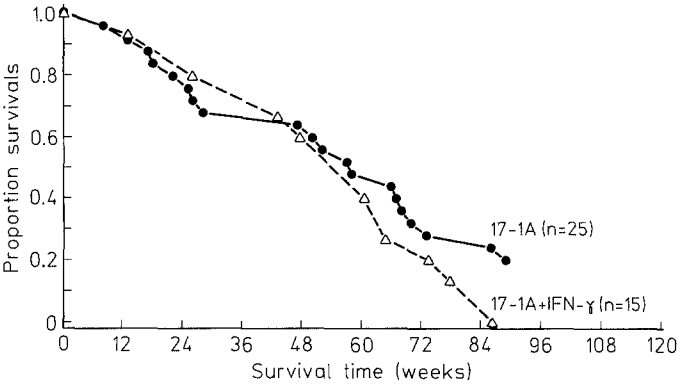

Fig. 2. Overall survival of patients with metastatic colorectal cancer treated with murine monoclonal antibody 17-1A or 17-1A plus interferon γ

Clinical response

Of the 14 evaluable patients, 3 had disease stabilization at 8 weeks (nos. 5, 7 and 12) and survived 40, 60 and 72 weeks, respectively. Eleven patients progressed on therapy. Their survival ranged from 12 to 80 weeks (Table 5). Figure 2 shows the overall survival of the study population, which was not significantly different from our previous experience in 25 patients treated with varying doses of 17-1A alone. The median survival for this study group was 56 weeks as compared to 57 weeks in the prior study [4].

Discussion

Our study demonstrates that the combination of IFNγ and mAb 17-1A is well tolerated and associated with minimal toxicity. The toxicity of the combined modality followed the predictable side-effects noted with either of the agents administered individually [12, 11]. The infusion of 17-1A over a 2 h period significantly reduced the acute gastrointestinal toxicity previously noted when the antibody was delivered more rapidly [15]. The reduction of peripheral blood granulocytes and platelets with sparing of the monocytes and lymphocytes has been previously noted with IFNα as well as INFγ. The etiology of this early onset granulocytopenia/thrombocytopenia does not appear to be due to bone marrow suppression [2] but may be related to events outside the marrow cavity. This is supported by the rapid reversibility following cessation of IFNγ therapy noted in this as well as other studies [11, 2].

In our previously reported phase I study using 17-1A alone, 21 of 25 patients developed an anti-(mouse mAb) response including all five patients who received the identical dose and schedule of 17-1A used in this trial. A

similar frequency of anti-(mouse mAb) response occurred in this combination regimen of IFNγ and 17-1A with 13 of 14 patients developing a response. We would conclude that this large dose (1.6 g) of antibody and high circulating blood levels of 17-1A for 10 days provided no evidence for induction of tolerance. The addition of IFNγ to the regimen did not dramatically change the anti-(mouse mAb) response, although direct comparison of the two trials is limited by differences in dose and schedule of 17-1A.

A second aspect of the immune response relates to the human antibody response to the variable region of the 17-1A monoclonal antibody, i.e. anti-idiotype response. We have recently described the use of chimeric mouse/human monoclonal antibody molecules, which have the variable region of the murine monoclonal reagent in the absence of murine constant region, as a convenient reagent for detection of anti-idiotype (i.e. anti-variable-region) reactivity. As depicted in Table 2, the simultaneous measurement of murine and chimeric 17-1A reactivity allows one to quantify the proportion of antibody response directed to the variable region or constant regions of the molecule. Some degree of variable-region response were seen in 11 of 14 patients although many were of modest extent. Three patients developed relatively large amounts of anti-idiotype antibodies. This occurred in the 3 patients who had the largest amount of anti-(mouse mAb) in this series and were characterized by having a late surge of antibody response (6–8 weeks) containing both constant- and variable-region specificity. Prior studies have also suggested that anti-idiotype responses may occur in the later phases of the human immune response to monoclonal antibodies [10]. The clinical response and survival of patients did not correlate with the presence of absence of anti-idiotype responses in general and the 3 patients with the highest levels of anti-idiotype response had a clinical course similar to that of the remaining patients (Table 5). The inability of polyclonal mouse Ig to block serum antibody binding to murine 17-1A confirms that these sera had antibody reactivity specific to the variable region of 17-1A and the results in this independent assay system correlated well with the reactivity with chimeric 17-1A.

In addition, we have been able to demonstrate that in patients who develop antibodies to the variable region of 17-1A, a component of this immune response was able to inhibit the binding of 17-1A to tumor cell targets. This component of the anti-idiotype response is presumably directed against the 17-1A combining site and may consequently mimic the 17-1A antigen (mirror-image anti-idiotype antibody).

Our results indicate that the enhancement of effector function and tumor antigen expression that has been associated with IFNγ in vitro [4, 20, 25, 29, 31] and in vivo [22, 32] did not translate into therapeutic effectiveness in this combined therapy strategy. The median survival observed in our current study is identical to that obtained with 17-1A alone, the survival curves being nearly superimposable (Fig. 2). The dose and schedule of 17-1A maintained a serum concentration of more than 10 μg/ml for a duration of 10 days. The dose and type of IFNγ were selected upon the basis of previous studies showing in vivo monocyte activation in man [21]. To ensure optimal synergy based upon in vitro findings, IFNγ was administered 5 days prior to and was continued 2 days beyond the duration of 17-1A therapy.

A previous study using the combination of 17-1A and IFNγ also reported no clinical responses [32]. This study used a lower dose of 17-1A and a different IFNγ preparation, dose and schedule. This led some investigators to imply that improvement in antibody delivery by escalating the therapeutic doses of 17-1A might improve antitumor effects. Our present study indicates that despite the administration of large doses of 17-1A (1.6 g total dose), no clinical responses were achieved. It may be that antibodies with a higher binding affinity or ability to activate other arms of the human immune system (e.g., complement activation) need to be developed in order to enhance the in vivo effect. The use of genetically engineered monoclonal reagents with a greater ability to circulate [16], reduced immunogenicity [15] and enhanced biological activity [13] may improve in vivo efficacy. Dramatic responses in patients with non-Hodgkin's lymphoma have been achieved using such reagents [5]. Finally, several additional reagents to improve antibody-dependent cellular cytotoxicity, including interleukin-2 [26] and growth factors like granulocyte/macrophage and macrophage colony-stimulating factors [18, 28], are appropriate for studying in combination with monoclonal antibodies.

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