

COMBINATION CHEMOTHERAPY FOR MULTIPLE MYELOMA

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Response rate, remission duration, and survival time were compared in 236 patients with multiple myeloma receiving a melphalan-prednisone-procarbazine combination and in 156 patients receiving only melphalan-prednisone. Response was confirmed when myeloma protein production had been reduced to less than 25% of the pretreatment value. Of the evaluable trials, 59% of patients responded to the procarbazine combination, and 48% to melphalan and prednisone. In both treatment groups, the survival time of all patients (22 months) and the remission duration of responding patients (21 months) were similar. Maximum degrees of myeloma protein reduction were associated with longer remissions and survival. Previously reported resistance to treatment of patients with only lambda Bence Jones protein was not apparent with these superior treatment regimens. Results support the value of combination chemotherapy with melphalan-prednisone-procarbazine for remission induction in patients with multiple myeloma.

MELPHALAN (ALKERAN, BURROUGHS WELLCOME) is an alkylating agent which has induced tumor response in about one third of patients with multiple myeloma.^{2,4,6} As in certain other malignant conditions in animals⁸ and man,¹ the schedule of drug administration has an important influence on the therapeutic response. Thus, using older

criteria for defining response, an intermittent schedule of melphalan treatment induced clinical remissions in about 40% of patients with myeloma, in contrast to about 20% of patients receiving a daily regimen.³ When large doses of melphalan and prednisone (Deltasone, Upjohn) were given concurrently in short courses, about 70% of myeloma patients improved.³ In a separate study, clinical activity had been found from procarbazine (Matulane, Roche) alone in two of four previously untreated patients with myeloma.¹³ This observation has been confirmed by others⁹ and formed the rationale for the evaluation of this drug in combination with melphalan and prednisone. This report compares the incidence, degree, and duration of objective response using a melphalan-prednisone-procarbazine combination with response to a similar combination of melphalan and prednisone in a randomized treatment trial.

METHODS

Included in this report are results on 315 patients with multiple myeloma treated at 10 Southwest Cancer Chemotherapy Study Group (SWCCSG) institutions between February 1968 and June 1971. Patients not treated previously with an alkylating agent or with pro-

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carbazine were considered eligible when objective manifestations of multiple myeloma, such as protein abnormalities, were available for measurement.

Laboratory studies: Diagnosis was established by confirming in symptomatic patients that plasma cells constituted more than 10% of the cells in aspirated bone marrow in association with a myeloma globulin peak on serum or urine electrophoresis. After the institution of chemotherapy, myeloma globulin levels were measured serially as previously described.³ In 259 patients whose cases could be evaluated in this study and in 163 patients from previous studies, the antigenic type of heavy and/or light chains of the myeloma protein was confirmed by immunoelectrophoresis. The antigenic subclass was also determined in 97 of 186 evaluable patients with an IgG peak who received combination therapies (courtesy of Dr. Peter Schur). Measurements of hemoglobin, white blood cell count, platelet count, and levels of blood urea nitrogen and serum calcium were performed in all subjects, and repeated at appropriate intervals.

Treatment regimens: From February 1968 to January 1970, 162 patients were assigned at

random to one of two melphalan treatment regimens (Table 1). Treatment "M + P + P" consisted of intermittent *melphalan* in concurrent combination with large doses of *prednisone* and *procarbazine* every 6 weeks. Prednisone was given for 4 days, the dose then tapered and discontinued within 4 subsequent days. Procarbazine courses were given for 9 days beginning on the day after initiation of melphalan and prednisone. Schedule "M + P" consisted of an identical schedule of *melphalan* and *prednisone* therapy without procarbazine. The melphalan dose in Treatment M + P + P was 20% less than in Treatment M + P. From February 1970 to June 1971, 153 consecutive patients were also treated with the triple-drug combination, but procarbazine was given concurrently for 6 days in similar total dose (Table 1). Results from both combination regimens (M + P and M + P + P) were compared with a previous SWCCSG study conducted between 1965 and 1968, in which patients were allocated at random to either intermittent melphalan alone (M) or intermittent melphalan with prednisone (M + P) in similar dose regimens (Table 1). In the latter analysis, all patients were included from

TABLE 1. Incidence of Response Following Treatment with Different Melphalan Regimens

	No. treated	Not evaluable		No. evaluable	No. responding	Response rate per cent evaluable	Per cent all (excludes inadequate reports)
		Early death	Inade- quate report				
<i>M + P + P</i> (1968-1971)							
Melphalan 0.20 mg/kg/day × 4, q. 6 weeks							
Prednisone 2.0 mg/kg/day × 4, q. 6 weeks							
+ Procarbazine 3.0 mg/kg/day × 9	83*	8	1	74	43	58	52
or Procarbazine 4.0 mg/kg/day × 6, q. 6 weeks	153†	17	5	131	77	59	52
Combined results from <i>M + P + P</i>	236	25	6	205	120	59	52
<i>M + P</i> (1968-1970)							
Melphalan 0.25 mg/kg/day × 4, q. 6 weeks	79*	6	0	73	32	44	41
Prednisone 2.0 mg/kg/day × 4, q. 6 weeks							
<i>M + P</i> (1965-1968)	77‡	9	2	66	35	53	47
Combined results from <i>M + P</i>	156	15	2	139	67	48	44
<i>M</i> (1965-1968)							
Melphalan 0.25 mg/kg/day × 4, q. 6 weeks	65‡	9	2	54	13	24	21

* Randomized comparison 1968-1970.

† Consecutive series 2/70-6/71.

‡ Randomized comparison 1965-1968.

the same institutions that had contributed to the 1968 to 1970 study.* Identical criteria for eligibility in the study were required. Detailed analyses of the frequency of anemia, azotemia, and hypercalcemia indicated that the pretreatment severity of disease was similar in all patient groups.

In all patients, melphalan and/or procarbazine dosage was adjusted in serial increments or decrements to a level that produced either mild leukopenia (white blood cell count $< 3,500/\text{mm}^3$) or mild thrombocytopenia (platelets $< 150,000/\text{mm}^3$) about 4 weeks after each course. Response was evaluated not sooner than 3 months after institution of therapy. If an objective response occurred (vide infra), treatment was continued indefinitely through the remission period. Localized radiotherapy for symptomatic bone lesions was given when indicated.

Evaluation of response: Clinical response was evaluated in accordance with modifica-

tions of criteria previously presented in detail.³ Objective response was defined as one or both of the following sustained for at least 2 months: 1. decrease in calculated production rate of serum myeloma globulins to less than 25% of the pretreatment value with serum concentrations falling to less than 2.5 g/100 ml, or 2. decrease in Bence-Jones protein excretion to less than 10% of the pretreatment value and to less than 200 mg/day. In addition, patients were considered responsive only when there were improvement or maintenance of hemoglobin above 9 g/100 ml, serum albumin above 3.0 g/100 ml, and serum calcium below 12 mg/100 ml. Bone pain and impaired physical performance improved in all patients responding to treatment in accordance with these criteria. In patients with IgA and IgG₃ peaks, the degree of remission was measured from the ratio between the lowest myeloma protein level and the pretreatment value expressed as a per cent of control. (Of the 97 patients with an evaluable clinical trial and an IgG subtype, four had an IgG₃ and three had an IgG₄ subclass.) The "fractional catabolic rate" for IgG myeloma protein of the 1, 2, and 4 subclasses declines markedly with progressive decline in concentration below 3.2 g/100 ml^{10,14} (Fig. 1). Thus, changes in tumor mass will be underestimated when calculations are based only on the measured decline in the serum concentration of IgG peaks.¹² For patients with IgG myeloma protein, changes in plasma cell tumor mass were estimated from changes in calculated "synthetic index" (product of serum concentration and fractional catabolic rate).^{12,14}

Survival analyses: All patients were included in the survival analysis except those who had received less than 4 days of melphalan treatment. Survival was calculated by the life-table method of Kaplan and Meier⁷ from the institution of chemotherapy to death for all patients, including those who died of diseases considered unrelated to myeloma. The remission duration of each responding patient was calculated from a decline to less than 25% of control in myeloma protein level (IgA or Bence Jones proteins) or synthetic index (IgG proteins) to the earliest occurrence of either return to more than 25% of control, or doubling in level. This change almost always preceded or developed concurrently with other evidence of disease relapse, such as increasing anemia, hypercalcemia, or progression of lytic bone lesions.

* The total number of patients with evaluable records by institution from 1968-1971 was: Baylor College of Medicine, 20; Cleveland Clinic, 25; Henry Ford Hospital, 32; Ohio State University, 20; Scott & White Clinic, 20; Tulane University School of Medicine, 12; University of Arkansas Medical Center, 29; University of New Mexico School of Medicine, 6; University of Texas M. D. Anderson Hospital, 112; University of Utah School of Medicine, 2.

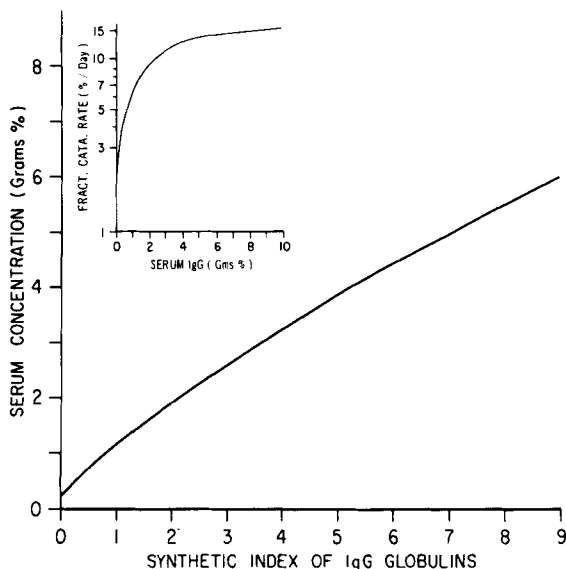


FIG. 1. Relationship between serum concentration of IgG globulin and synthetic index (product of serum level and fractional catabolic rate). This curve was calculated from data provided by Waldmann (insert) defining the relationship between fractional catabolic rate and serum level for the 1, 2, and 4 subclasses.^{10,14}

RESULTS

Frequency and degree of response: Of 315 patients who received melphalan combinations between 1968–1971, the records of 278 could be evaluated. Response could not be determined in 37 patients, in six because of incomplete data and in 31 because death occurred within 3 months of the start of therapy. Objective improvement was found in 44% of those with evaluable records receiving melphalan and prednisone, a result similar to that (53%) in patients receiving an identical dose regimen between 1965 and 1968 (Table 1). When all patients treated in both studies with melphalan and prednisone were analyzed as a single group (M + P for 1965–1970), a response rate of 48% resulted. Since the response rates from both procarbazine regimens were also similar (58% and 59%), all patients receiving procarbazine combinations were analyzed as a single group (Table 1). The response rate for the procarbazine combination (59%) was superior to that for the combined melphalan-prednisone group (48%), $p < 0.1$. More than 50% of responding patients achieved remission within 3 months, and more than 75% had responded by 6 months. Serum peaks disappeared from the electrophoresis strip in 15% of evaluable patients receiving both treatment programs.

Seventy-seven patients considered “unresponsive” to treatment showed significant clinical improvement. Such “improvement” was recognized separately from “response” when the concentration of IgA myeloma proteins or the synthetic index of IgG myeloma proteins declined to less than 50%, but not to less than

25%, of the pretreatment value. In all of these patients, most major complications due to myeloma were alleviated. As indicated in Table 2, 22% of evaluable patients receiving both combination regimens showed such “improvement.”

Survival and remission duration: Patients treated with the triple-drug combination had a median survival time (23 months) similar to that for patients receiving only melphalan-prednisone (21 months), but longer than that for the 65 patients receiving intermittent melphalan alone between 1965 and 1968 (18 months), $p < 0.1$. Figure 2 portrays the survival curves for all patients in each treatment group. Responsive patients lived about 18 months longer than unresponsive patients, and Fig. 3 presents the survival curves for the responsive and unresponsive patients in each treatment group. For all treatments, the median survival time of responsive patients was similar at about 36 months; the median survival of unresponsive patients was also similar at about 18 months (Table 3). The median survival time for those unresponsive patients who “improved” (decline in myeloma protein production to 25–49% of control) was only 19 months. This duration was 6 months longer ($p < .05$) than that found in unresponsive patients without improvement (13 months), but 12 months shorter ($p < .01$) than measured in responsive patients with reduction of myeloma proteins to less than 25% of control (Table 2).

The median remission duration was 21 months for responding patients receiving both combination treatments. The median duration of “improvement” in patients with mye-

TABLE 2. Degree and Duration of Remission from Combination Chemotherapy for Myeloma

Degree of remission (Per cent control)	Per cent evaluable		Remission duration*	Survival from treatment*
	M + P	M + P + P		
<i>Unresponsive</i>				
Only Bence Jones protein	7	4	—	14
50-100 } with serum peak	22	16	—	13
25-49 }	22	22	9†	19
<i>Responsive</i>				
10-24 } with serum peak	15	20	17	31
<10‡ }	20	25	25	37
Only Bence Jones protein	14	13	23	33
TOTAL	100	100		

* Median months for all 344 evaluable patients receiving both combination regimens.

† Duration of myeloma protein reduction below 50% of control.

‡ Serum peaks disappeared from the electrophoresis strip in 65% of these patients.

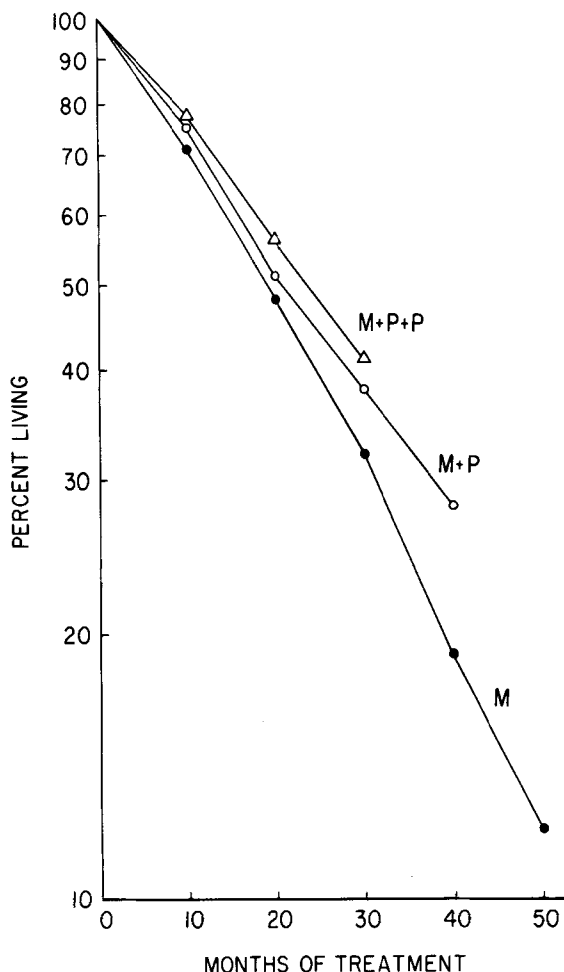


FIG. 2. Survival from initiation of chemotherapy for all patients treated with melphalan alone (solid circles), melphalan + prednisone (open circles), and melphalan + prednisone + procarbazine (triangles).

loma proteins reduced to only 25–49% of control was only 9 months, a figure shorter ($p < .01$) than measured in patients with greater tumor reduction (Table 2). Responding patients with marked degrees of reduction of serum myeloma proteins ($< 10\%$ of pretreatment value) had disease control for 8 months longer ($p < .01$) than patients with lesser degrees of protein reduction (10–24% of control). Responsive patients with only Bence Jones protein had a remission duration and survival time that was similar to that for other responsive patients with serum peaks (Table 2).

Toxicity: With both treatment programs, serious toxicity occurred infrequently, side effects were mild, and the maximum degrees of leukopenia and thrombocytopenia were com-

parable. Moderate nausea occurred in most patients treated with procarbazine, but in only 10 of 236 patients did protracted vomiting preclude further treatment with this drug. Skin eruptions were reported in 14 patients receiving procarbazine and consisted of a transient pruritic, maculopapular eruption over most of the body. In only five patients was this rash so severe that all subsequent courses were given without procarbazine. No serious toxicity was associated with the short duration of prednisone therapy used in these patients. During the initial treatment period, 15% of patients treated with either M + P or M + P + P showed a decline in white blood count to less than 1,500 or a fall in platelet count to less than 50,000. Severe bone marrow suppres-

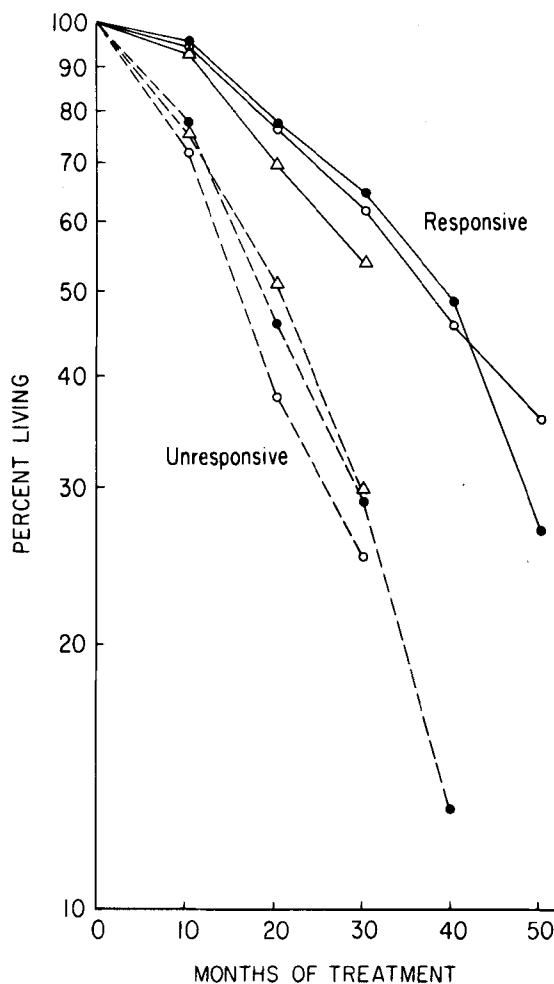


FIG. 3. Survival from initiation of chemotherapy for responsive (solid line) and unresponsive (dashed line) patients treated with melphalan alone (closed circles), melphalan + prednisone (open circles), and melphalan + prednisone + procarbazine (triangles).

TABLE 3. Median Survival in Months from Chemotherapy

	All patients	Unresponsive (excludes early deaths)	Responsive
<i>M</i> + <i>P</i> + <i>P</i> (1968–1971)	23* (109/236)	20 (43/85)	32* (40/120)
<i>M</i> + <i>P</i> (1965–1970)	21 (111/156)	15 (55/72)	36 (39/67)
<i>M</i> (1965–1968)	18 (59/65)	18 (38/41)	39 (10/13)

* Extrapolated estimate since less than 50% were dead.
Figures in parentheses indicate number dead/total.

sion causing or contributing significantly to death occurred in 2% of all patients receiving the doses of melphalan and procarbazine used in this study.

Myeloma protein type: The antigenic type of heavy and light chains of the myeloma protein was identified in 363 of the 398 patients treated since 1965, whose cases could be evaluated, and in 59 additional evaluable patients treated with melphalan alone in the SWCCSG between 1960 and 1965 (Table 4). The response rate of myeloma patients with different protein types was compared after three different melphalan treatment programs. Table 4 indicates that the previously reported low response rate for patients producing only lambda light chains was not confirmed in patients receiving combination therapies. In addition, there was no apparent difference in response rate between patients with IgG myeloma proteins of the 1 or 2 subclass.

DISCUSSION

The clinical evaluation of a new treatment program in a chronic disease with a variety of manifestations, such as multiple myeloma, requires standardized criteria for eligibility in the study, for comparing patient groups, and for evaluating response to treatment. In this study, all patients were symptomatic, had significant marrow plasmacytosis, and showed a monoclonal peak on serum or urine electrophoresis. A large number of eligible patients were assigned at random to one of two treatment groups; results were compared with those found from similar study of a large number of patients treated previously at the same institutions, and all treatment groups were comparable in terms of the frequency and severity of specific disease complications. The rationale for evaluating response to therapy from significant changes in myeloma proteins and control of most major disease complications has been presented previously.^{2,3} Further precision was added by evaluating

changes in tumor mass in patients with IgG myeloma peaks from changes in myeloma protein production rate.¹² This was based on recent observations that the intravascular catabolic rate for IgG proteins of the 1, 2, and 4 subclasses varies greatly with the serum concentration.^{10,14}

Response to treatment was not confirmed unless calculated myeloma protein production had been reduced to less than 25% of the pretreatment value. These criteria were more stringent than those used previously, and accounted for the lower response rates in this report in comparison with previous SWCCSG studies.²⁻⁴ Greater reductions in myeloma protein production were required for response because less marked changes to only 25–49% of the pretreatment value were associated with short remissions and slight survival prolongation. These findings emphasize the value of calculating the degree and duration of remission from changes in myeloma protein production rate, the need for accurate typing to distinguish IgG from IgA myeloma proteins, and the importance of inducing maximal tumor reduction in patients with multiple myeloma.

An objective response to treatment occurred more frequently with a melphalan-prednisone-procarbazine combination than with therapy using only melphalan-prednisone. Procarbazine was used in a combination regi-

TABLE 4. Antigenic Type of Myeloma Globulin and Response to Melphalan

	No. responsive/evaluable (response rate in parenthesis)	
	Melphalan alone (1960–1968)	Melphalan + prednisone ± procarbazine (1965–1971)
IgG	24/57 (42)	98/186 (53)
IgA	13/29 (45)	34/76 (45)
Kappa only	7/11 (64)	23/30 (77)
Lambda only	1/11 (9)	16/22 (73)

IgG₁ 46/73 (63)
IgG₂ 9/17 (53)

men only after clinical responses were found in two of four previously untreated patients.¹³ Such activity in myeloma from procarbazine has also been reported by others.⁹ Vomiting and skin eruptions from procarbazine contraindicated its further use in less than 10% of treated patients. Because the superiority for the triple-drug combination was slight in terms of response rate, it was not surprising that only one clinical response was seen in 20 patients with established prior resistance to the two-drug treatment.

The low response rate from melphalan therapy in myeloma patients producing only lambda Bence Jones proteins, reported in previous SWCCSG communications,⁵ was not confirmed for treatment regimens associated with high response rates. While only one of 11 patients with this type of myeloma responded to intermittent melphalan alone, 16 of 22 responded to treatment regimens including combinations with prednisone and procarbazine. These observations emphasize the superiority of recent treatment combinations, and eliminate the concept that any disease manifestation is likely to predict a response to melphalan in patients with multiple myeloma. It is conceivable that the small number of patients in the earlier series contained an unrepresentative sample of patients resistant to chemotherapy. Thus, these results in a larger number of patients conform with those reported by Osserman who failed to detect any correlation between protein type and resistance to melphalan treatment.¹¹

The response rate and survival from intermittent melphalan and prednisone in this series confirm previous results in the SWCCSG with an identical treatment regimen used from 1965 to 1968. Results from this combination were significantly superior to results from intermittent melphalan alone.³ Whether the survival prolongation documented previously for patients treated with melphalan-prednisone resulted mainly from the higher response rate or from a longer remission duration in responding patients could not be determined in the earlier study because the evaluation pe-

riod was too short. Since median survival and remission duration for responsive patients were now confirmed to be similar for all treatments, the higher response rate must have been the major factor accounting for the improved survival in the groups of patients receiving combination therapies. With the addition of procarbazine, a further increase in response rate occurred without evident prolongation in either median survival or remission duration. However, more than 50% of treated patients died without long-term disease control, particularly those who died after less than 3 months of therapy (10%), who were unresponsive (40%), or who responded and had either short remissions (10%) or died from diseases unrelated to their myeloma (10%). Thus, one would not have expected a significant extension of median survival, although a group of patients with longer lifespan may be identified from future analyses of survival (i.e., flattening of survival curve after several more years of evaluation). In any case, combination therapy with melphalan-prednisone-procarbazine provided a response rate superior to that from any other treatment evaluated by the SWCCSG in patients with multiple myeloma.

These studies provide a perspective for designing future treatments for patients with myeloma. If all patients had responded to treatment, their median survival time would probably not exceed the 36 months found for responsive patients. This figure is only about one year longer than the 22 months found for all patients treated with melphalan combinations. Although about 50% of all patients responded to treatment, about 75% showed some evidence of clinical improvement. Thus, a further increase in the frequency of slight improvement is not likely to improve long-term control of this disease. Rather, treatments should be developed that induce more marked degrees of disease remission, prolong the duration of remission by different remission maintenance programs that may reduce tumor mass further, and reinstate remissions in patients relapsing on their initial therapy.

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