DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE

FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

Division of Biostatistics and Epidemiology (HFM-215)

Memorandum

DATE: November 4, 1997

FROM: *Teresa Neeman, Ph.D.*

THROUGH: *Peter A. Lachenbruch, Ph.D., Chief, Biostatistics Branch*

SUBJECT: *BLA Supplement 97-0501, Proleukin (IL-2) in Metastatic Melanoma, Chiron Corporation*

TO: *Dr. Rebecca Dachman, Clinical Reviewer*
Division of Clinical Trial Design and Analysis (DCTDA) HFM-573

BACKGROUND

Data for this submission was summarized from eight trials. Some of these eight trials were single-arm studies. Others were open-label randomized studies with Il-2 treatment serving as a control arm. In every case, only the data from the patients with metastatic melanoma receiving IL-2 were reported. Below are summaries of the eight trials.

T84-0524 was a Phase 1 trial at the National Cancer Institute of purified recombinant IL-2 in patients with metastatic cancer who have failed conventional therapy. Although patients with different cancers were treated on this protocol, the only patients with melanoma treated via short IV infusion were included in the final study report. There were twenty-eight such patients, 19 males and 9 females, who enrolled between September 1985 and February 1993. Due to a pharmacy error, patients received 720,000 IU/kg per dose rather than the 600,000 IU/kg planned in the protocol. Although the protocol called for doses up to 6,000,000 IU/kg, the MTD was established at 720,000 IU/kg.

There were 4 objective responses: 2 CRs and 2 PRs. The durations of the PR were 6.6 months and 8.2 months. The CRs remain in complete remission without further treatment at 72 months and 103 months.

There were no deaths on study.

T86-0097 was a randomized trial on high-dose IL-2 alone or with lymphokine-activated killer cells to study the objective response rate in patients with established tumors who have failed standard therapy. Of the 342 patients entered into the study, only the 84 patients, 53 males and 31 females, who had metastatic melanoma and were in the IL-2 alone arm were included in this report. Administration of IL-2 was the same as in the previous study; as before, due to a pharmacy error, patients actually received 720,000 IU/kg per dose rather than the 600,000 IU/kg planned in the protocol. Grade 3 adverse events were reported in 81 of the 84 patients. Grade 4 AEs were reported in 20 of the 84 patients.

There were 6 complete responses, two of which were of 6 and 13 months in duration, and 4 of which are still ongoing at 24, 40, 41 and 59 months, respectively. In addition, there were 8 partial responders, with response durations 3.5, 3.8, 3.9, 4.2, 7.4, 9.5, 16.8, and 29.5 months.

One death occurred within 28 days of the last dose of IL-2.

T90-0053 was a randomized trial designed to study the efficacy of a standard, high-dose bolus regimen of recombinant human IL-2 versus a single-cycle of high-dose rIL-2 followed by a low-dose maintenance regimen of PEG-IL-2 in patients with metastatic renal cell carcinoma or metastatic melanoma. It was anticipated that 200 patients would enroll in the study over 3 years. The study opened accrual in March 1990, and completed accrual of 124 patients as of February 1991. The study was closed in July 1993. Of the 124 patients entered, 32 patients, 22 males and 10 females, with metastatic melanoma had been randomized to IL-2 arm and were included in this report. All received 720,000 IU/kg per dose. Grade 3 adverse events were reported in 29 of the 32 patients. Grade 4 AEs were reported in 2 of the 32 patients.

There were 2 complete responses, both of which are ongoing at 62 and 65 months, respectively. In addition, there were 3 partial responders, with response durations 2, 2, and 18 months.

There were no deaths within 28 days of last dose nor any treatment related deaths on study.

92C-0094 was a continuing treatment protocol for patients with cancer/AIDS/skin disease. Patients were eligible for this protocol if they had a diagnosis of cancer/AIDS/skin disease and had been previously followed or treated on an approved NCI research protocol. The first patient entered in March 1993; the last patient entered April 1993. Three of the patients had melanoma; 2 males and 1 female. All received 720,000 IU/kg per dose. Grade 3 adverse events were reported in 2 of the 3 patients. Grade 4 AEs were reported in 1 of the 3 patients.

There were no objective responses, nor were there any deaths within 28 days of last dose nor any treatment related deaths on study.

T86-0063 was a study designed to assess a tumor response rate with IL-2 in patients with metastatic or recurrent inoperable malignant melanoma. It was planned that 35 patients would be enrolled. However, if no response was seen in the first 9 patients, the study would be terminated

early. Nine patients entered the study, and one partial response was seen. All received 600,000 IU/kg per dose. Grade 3 adverse events were reported in all 9 patients. Grade 4 AEs were reported in 4 of the 9 patients.

There were no deaths reported in this study.

C87-0002 was an randomized open-label trial to compare tumor response rates between patients with malignant melanoma receiving IL-2 alone or IL-2 plus autologous lymphokine activated killer cells (LAK). The study opened accrual in January 1988, and completed accrual in September 1990. Forty-five patients, 28 males and 17 females, with metastatic melanoma were entered on the IL-2 alone treatment arm. All received 600,000 IU/kg per dose. Grade 3 adverse events were reported in all 45 patients. Grade 4 AEs were reported in 14 of the 45 patients.

There was one complete response, although this patient had progressive disease 6 months after being declared a responder. In addition, there were 5 partial responders, with response durations 1, 2, 6, 6, and 14 months.

There were 3 deaths within 28 days of last dose. All of these patients had sepsis related to treatment.

CS-L291-06 was a Phase 1 study of IL-2 administered by rapid IV bolus injection in patients with solid tumors. Study enrollment was between July 1991 and August 1992. Five melanoma patients were admitted into the study, 3 males and 2 females. Two of the five patients received 360,000 IU/kg and three received 540,000 IU/kg. Grade 3 adverse events were reported in all 5 patients. Grade 4 adverse events were reported in 2 of the 5 patients.

Two of the three patients treated at the higher dose level achieved objective responses. The patient who achieved a PR was an ongoing responder after 55 months. The patient with a complete remission had progressive disease after 2 months. Following a number of other therapies, the tumor was ultimately excised, and the patient has been in remission since that time.

There were no deaths within 28 days for any of the 5 melanoma patients.

DATA SUMMARY

The data from the eight submitted trials is summarized in the table below:

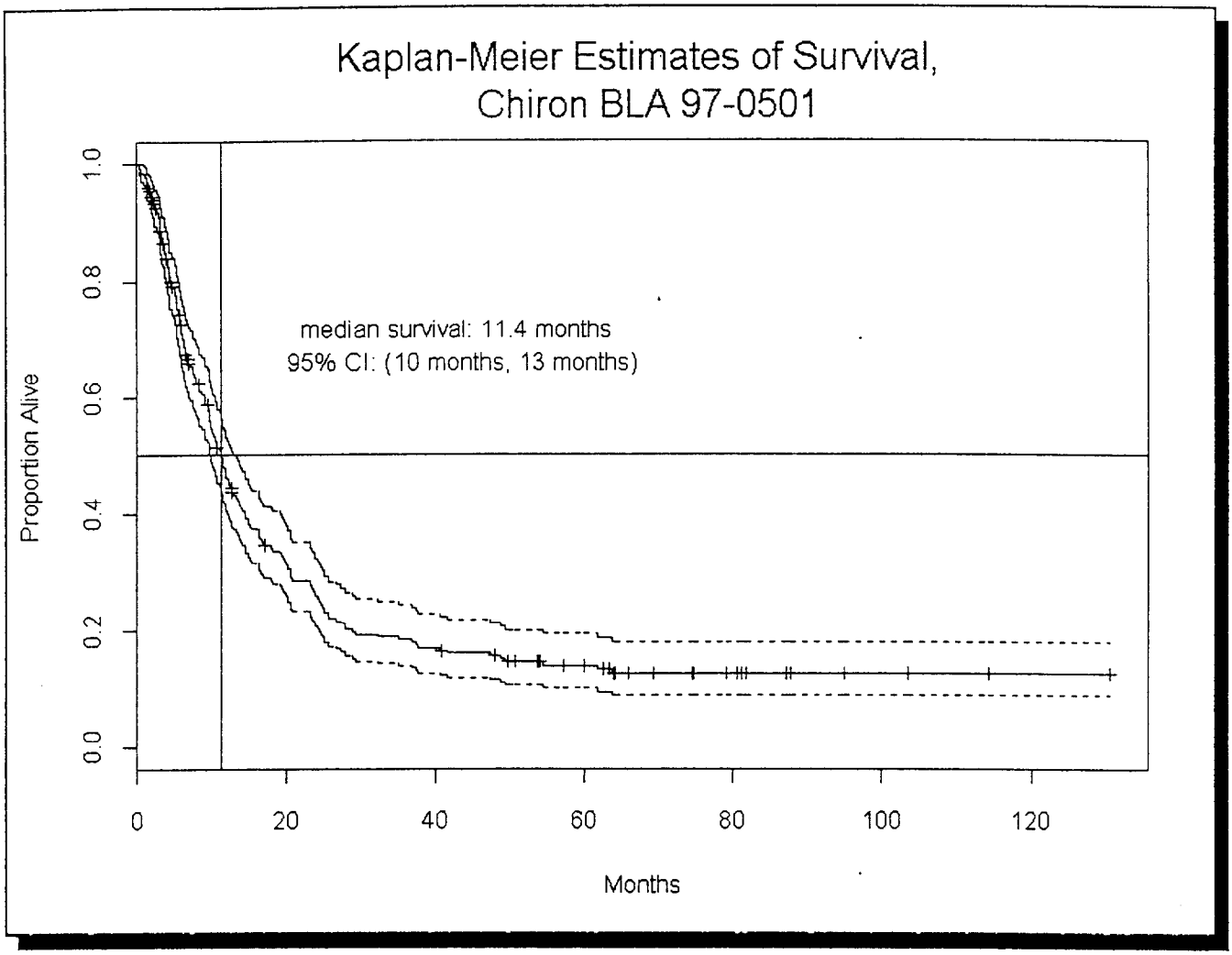
Table 1: Summary of Eight Submitted Trials, BLA Supplement 97-0501

	T84-0524	T86-0097	T90-0053	92C-0094	T86-0063	T86-0170	C87-0002	L29106
time of entry on study	9/85-2/93	4/86-8/92	3/90-2/91	3/93-4/93	4/86-12/87	9/86-10/89	1/88-9/90	7/91-8/92
first dose (IU/kg)	720,000	720,000	720,000	720,000	600,000	600,000	600,000	360,000 540,000
no. of patients	28	84	32	3	9	64	45	5
# PR	2 (7%)	8 (10%)	3 (9%)	0	1 (11%)	6 (9%)	5 (11%)	1 (20%)
# CR	2 (7%)	6 (7%)	2 (6%)	0	0	5 (8%)	1 (2%)	1 (20%)
# on-study deaths	0	1 (1%)	0	0	0	4 (6%)	2 (4%)	0
# Grade 3 AE	24 (86%)	81 (96%)	29 (91%)	2 (67%)	9 (100%)	61 (95%)	45 (100%)	5 (100%)
# Grade 4 AE	5 (18%)	20 (24%)	2 (6%)	1 (33%)	4 (44%)	36 (56%)	14 (31%)	2 (40%)
duration of responses (months) (PR)	7, 8	4, 4, 4, 4, 7, 9, 17, 30	2, 2, 18	-	3	2, 3, 3, 6+, 12, 91+	1, 2, 6, 6, 14	55+
duration of responses (months) (CR)	72+, 103+	6, 13, 24+, 40+, 41+, 49+	62+, 65+	-	-	8, 9, 18, 86+, 106+	6	2

EXPLORATORY DATA ANALYSIS

Overall Survival: Kaplan-Meier estimates of survival were computed and plotted using S-PLUS software. The median survival time was 11.4 months, with a 95% confidence interval of (10, 13.5) months. Although no direct comparisons can be made, in a recent controlled study submitted to the FDA in patients with metastatic melanoma treated with either tumor vaccine or chemotherapy(control), the median survival times were 9.2 months and 12 months, respectively [redacted]. A graph of the Kaplan-Meier estimates is shown below:

(b)(4)



Overall Response: It was noted that, among the partial responders, the duration of response was short-lived in many cases. The median duration of response among partial responders was 6 months. At 12 months, only 7/26 (27%) partial responders had not progressed. Among the complete responders, the median duration of response was not reached. Seven (7) of the 17 complete responders had progressive disease within 18 months. The remaining 10 complete responders had continued responses for at least 24 months after being declared a complete responder. Among all 43 responders (26 PR+ 17 CR), the median duration of response was 9 months.

Covariates Related to Response: Because there was homogeneity of response across the studies, both with respect to adverse events and response rates, the studies were pooled for the purposes of exploratory analyses. The purpose of these analyses was to possibly identify a subgroup of patients which may be likely to benefit from this therapy.

Baseline characteristics included ECOG status, number of tumor sites, age, gender and evidence of

visceral disease (Y/N). Each of these covariates was tested in a logistic regression model for their prognostic value in predicting a complete response or an objective response (PR or CR). The analyses suggested that patients with ECOG status 1 may be less likely to obtain an objective response than patients with ECOG status 0. Although the proportion of complete responders with ECOG status 0 was higher then the proportion of enrolled patients with ECOG status 0, this difference was not found to be statistically significant. There was insufficient evidence to demonstrate that any of the other covariates were prognostic for response.

Baseline Tumor Measurements: Of the 43 responders, 40 had baseline tumor measurements, given as two diameters. No baseline tumor measurements for nonresponders were submitted. Areas were computed for each tumor site by multiplying the two diameters. Although patients may have had numerous sites of tumor, the FDA clinicians were interested to know if there were cases of significant tumor shrinkage in patients with bulky disease. The site of the largest lesions varied among the 40 responders. In 11/40 cases, the lymph nodes harbored the largest lesion; in 7 cases, it was the liver; in 9 cases, the lung; 9 were subcutaneous. The distribution of the area of the largest lesion for the 40 responders with baseline tumor measurements was plotted using a stem and leaf plot. Among all responders, the median largest tumor area was 8.85 square centimeters. Two patients had a baseline lesion which measured 10 x 10 centimeters; in one case, in the liver, and in the other case, in the adrenal gland. The patient with the liver lesion (N1339382) was considered to be a complete responder, although no measurement was ever below 14 square centimeters. The output listed below is from S-PLUS:

N = 40 Median = 8.85
Quartiles = 4.5, 31

Decimal point is 1 place to the right of the colon

0 : 011222444455566678899
1 : 003578
2 : 07
3 : 0249
4 : 12
5 : 00
6 : 0

High: 100 100

A stem and leaf plot was also generated for the 15/17 complete responders with baseline tumor measurements. The median largest tumor was 8.12 square centimeters. Although in most cases, the largest lesion was less than 10 square centimeters, there were 4 patients who experienced a significant shrinkage in tumors which were greater than 30 square centimeters. The S-PLUS output for the complete responders appears on the following page:

N = 15 Median = 8.12
Quartiles = 3.75, 39.05

Decimal point is 1 place to the right of the colon

0 : 112445688
1 : 08
2 :
3 : 9
4 : 2
5 : 0
6 :
7 :
8 :
9 :
10 : 0

LIMITATIONS OF THE STUDIES

In any single-arm study, a true statistical evaluation of efficacy is not possible. However, when meaningful response rates are unusually high with respect to what has been seen in the past and toxicities are low, a clinical consensus may be reached that the responses seen can be attributed to the drug and that the toxicity is acceptable given the seriousness of the disease. The more life-threatening the disease, the more toxicity may be acceptable. This decision is not based upon a strict quantitative assessment of the data, but rather upon clinical judgment relying upon prior experience and expectations. If the apparent benefits do not clearly outweigh the observed risks, then the new drug or therapy should be studied in a controlled setting to better measure the treatment effect upon relevant clinical endpoints.

The studies presented in this application leave many questions unanswered. Does this therapy prolong survival in a substantial proportion of patients, or does it shorten survival in most patients at the expense of saving a small fraction of the patients? Or, is there evidence that the therapy prolongs survival in any patient?

Does the therapy have long-lasting adverse effects which could result in decreasing the effectiveness of subsequent therapies? Could the immune system become substantially impaired from this therapy. Can organs such as the heart or kidney or liver suffer permanent damage?

Could this therapy accelerate the time to progression of the cancer?

CONCLUSIONS

From a statistical point of view, the data are inadequate to demonstrate that IL-2 provides a net benefit to patients with metastatic melanoma which outweighs the considerable risk. It is not enough to consider only the small number of patients who achieved a complete response while under this therapy, without considering also the number of patients whose lives were adversely affected by this therapy. Such a measure of risk/benefit is difficult at best in a controlled setting, when one can observe a potential detrimental effect (e.g. on survival), but it is impossible in a study such as this one. If it is possible to study IL-2 in a controlled setting, then the company should be encouraged to do so.

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