Phase I Trial of BAY 50-4798, an Interleukin-2–Specific Agonist in Advanced Melanoma and Renal Cancer

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Abstract

Purpose: BAY 50-4798 is an analogue of interleukin-2 that selectively activates T cells over natural killer cells. This phase I study was designed to determine the maximum tolerated dose (MTD) and safety of BAY 50-4798, screen for tumor response, and assess pharmacokinetics.

Experimental Design: Forty-five patients with metastatic melanoma or renal cancer were enrolled, 31 on escalating doses to determine the MTD, with 20 renal cell carcinoma patients treated at MTD to detect antitumor activity. BAY 50-4798 was delivered i.v. every 8 h, days 1 to 5 and 15 to 19, and could be repeated after 9 weeks if tumor was stable or responding.

Results: The MTD was defined by and reported in terms of doses received. The doses tested ranged from 1.3 to 26.1 μg/kg, and the MTD was defined as 10.4 μg/kg based on toxicities similar to those of aldesleukin. Two patients achieved partial responses, one with melanoma and one with renal cell carcinoma. Among all 45 patients, 53% and 9% experienced a grade 3 and 4 toxicity, respectively. Among the patients treated at the MTD of 10.4 μg/kg, 71% and 10% experienced a grade 3 and 4 toxicity, respectively. Pharmacokinetics showed dose-dependent peak concentrations (C_{max}) and area under the curve with a half-life of ~2 h and no evidence of accumulation. Lymphocyte subset analysis confirmed the preferential expansion of T-cell subsets over natural killer cells.

Conclusions: The antitumor activity of BAY 50-4798 in malignancies that respond to high-dose interleukin-2 was low. BAY 50-4798 might provide advantages over aldesleukin in antigen-specific immunotherapies.

High-dose bolus interleukin-2 (IL-2; aldesleukin) is approved by the U.S. Food and Drug Administration as a single agent treatment for metastatic melanoma and renal cell carcinoma (RCC). Different exposure levels and dosing schedules with human IL-2 promote different effects on tumor cells depending on the cell type, its IL-2 receptors, and the cellular microenvironment (1). For advanced RCC and melanoma, i.v. treatment with high doses of aldesleukin has provided reproducible antitumor activity (2–4). This therapy induced partial plus complete tumor responses in 15% to 20% of patients and durable complete responses in 5% to 7% of patients with either melanoma or RCC (2–5). However, the relatively low objective response rates and high incidence of end-organ toxicities associated with high-dose aldesleukin have made it difficult to administer to many patients with these advanced cancers (6, 7). These same drawbacks have provided the impetus for developing related molecules with more favorable therapeutic indices. However, success in these endeavors relies on a better understanding of the precise mechanisms of antitumor activity and toxicity as well as effective and safe strategies for their modulation.

It is believed that, even in the absence of an active vaccination strategy, most of the antitumor activity of human IL-2 derives from its stimulation of T cells, whereas most of its toxicities are mediated largely by the release of inflammatory molecules by natural killer (NK) cells (8). BAY 50-4798 is an IL-2 analogue featuring a single amino acid substitution (arginine for asparagine at position 88) that alters its binding to the high-affinity IL-2 receptor on T cells and the lower-affinity receptor on NK cells. This results in a preferential activation of T cells over NK cells that is 3,000-fold higher than observed with aldesleukin (9–11). Data from primate models show a superior safety profile for BAY 50-4798 over aldesleukin at doses and schedules that provide equivalent activation of T lymphocytes (12, 13). In rodent models, the antitumor activity was similar at equivalent doses for aldesleukin and BAY 50-4798, whereas toxicity was less for BAY 50-4798 (13–15).

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Table 1. Patient baseline characteristics

Characteristic	*n* (%)
Total patients	45
Sex	
Male	27 (60)
Female	18 (40)
Age	
Median	60
Range	35-81
ECOG performance status	
0	32 (71)
1	13 (29)
Tumor histology	
Renal clear cell	33
Melanoma	12
Prior therapies*	
1 regimen	6
2 regimens	2
3 regimens	1

Abbreviation: ECOG, Eastern Cooperative Oncology Group.
*A regimen was defined as all drugs taken on the same day.

This suggests that therapeutic efficacy can be separated from treatment toxicity using a molecule with preferential binding characteristics to the IL-2 receptor of T cells over that of NK cells (8, 16).

The standard approach to high-dose aldesleukin therapy for solid tumors involves the administration of aldesleukin at fixed doses and intervals until the development of individual patient-specific dose-limiting toxicity (DLT), which is subsequently managed by aggressive supportive measures and withholding of full doses without dose compensation or dose adjustment during the treatment cycle. This study presents results from the first-in-human trial of BAY 50-4798 and is composed of a phase I investigation to determine the maximum tolerated dose (MTD) and pharmacologic and safety profile followed by an extension phase with the goal of evaluating anticancer activity in patients with advanced RCC. The doses chosen for evaluation were based in part on data showing the equivalence of BAY 50-4798 and aldesleukin for the high-affinity IL-2 receptor on T lymphocytes. The standard dose of aldesleukin used in "high-dose IL-2" regimens is 6×10^5 IU/kg or 33 μg/kg. Toxicity data from the monkey model showed a MTD of 8 μg/kg (data on file, Bayer). To provide a 6-fold safety advantage, we therefore selected a starting dose of 1.3 μg/kg/dose. The goal of this study was to take advantage of the extreme selectivity of this molecule for the high-affinity T-cell IL-2 receptor over the lower-affinity NK cell IL-2 receptor and thus to escalate the dose to the range used for aldesleukin or even higher, with less toxicity and potentially greater efficacy.

Materials and Methods

Patient selection

Patient eligibility criteria included histologically confirmed malignancy for which curative or palliative measures had failed or were considered ineffective, Eastern Cooperative Oncology Group performance status of 0 or 1, life expectancy of at least 12 weeks, age ≥18 years, good organ function (WBC count ≥3,500/μL, platelets ≥100,000/μL, hemoglobin ≥9 g/dL, serum transaminases ≤2 × the institutional upper limit of normal, serum bilirubin <1.5 × the upper limit of normal, serum creatinine ≤1.5 × the upper limit of normal, or calculated clearance 60 mL/min), and adequate pulmonary function (forced expired volume in 1 s ≥2.0 L or 75% of that predicted for height and weight). Exclusion criteria included more than two prior chemotherapy or biological therapy regimens or any prior IL-2; any systemic anticancer therapy within 3 weeks of study entry; adrenal insufficiency requiring replacement steroid therapy; history of significant cardiac disease; history of central nervous system metastases or seizure disorder, autoimmune disease, or any other significant medical or psychiatric illness; or anticipated need for steroid therapy. All patients over the age of 50 years or with any cardiac risk factors were required to undergo cardiac stress testing. Patient characteristics at baseline are presented in Table 1.

Study design

The primary objective of this phase I study was to determine the MTD and define the safety profile of BAY 50-4798 when given as a single agent to patients with advanced, refractory solid tumors. Secondary objectives included evaluation of pharmacokinetics and tumor response in patients treated with BAY 50-4798.

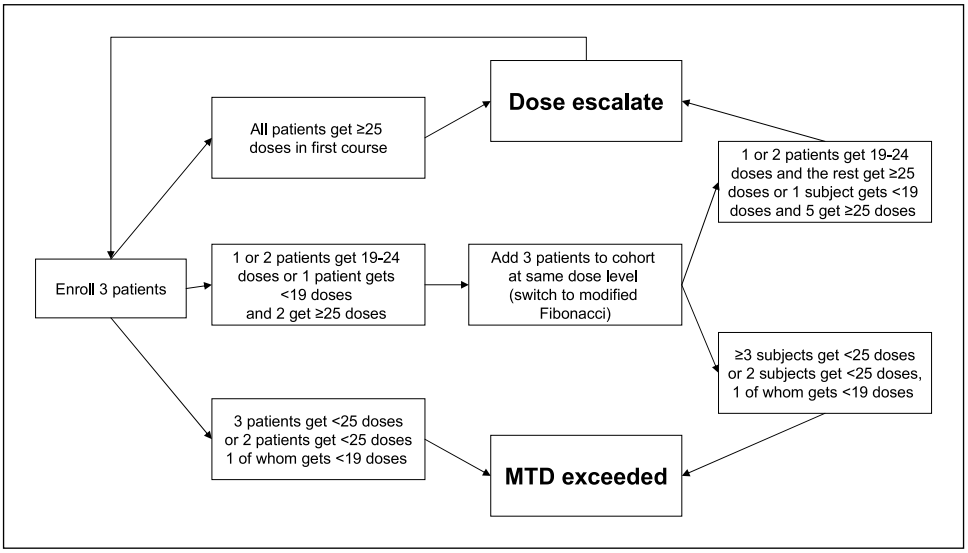


Fig. 1. Dose-escalation schema.

Table 2. Number of patients and courses administered

Dose, μg/kg (no. patients)	<1 course	1 course	1 1/2 courses	2 courses	3 courses
1.3 (3)		3			
2.6 (4)		3		1	
5.2 (4)		4			
10.4 (21)	2	12		5	2
17.4 (7)	1	4		2	
26.1 (6)	1	2	1	2	
Total (45)	4	28	1	10	2

NOTE: One course is defined as two 5-d cycles (2 × 14 planned doses) of BAY 50-4798.

Doses of BAY 50-4798 were administered to eligible patients by i.v. infusion over 15 min, every 8 h on days 1 to 5 and 15 to 19, to a maximum of 14 doses per 5-day cycle. One course of BAY 50-4798 consisted of two cycles separated by 9 days of rest (19 days in total). A maximum of two additional courses could be administered to patients with evidence of antitumor activity and adequate tolerance of therapy. Toxicities were assessed according to the National Cancer Institute Common Toxicity Criteria version 2.0. Before escalation to the next dose level, all patients from the previous dose level were required to have completed the first course and recovered from any treatment-related toxicities. Intrapatient dose escalation was not permitted. For patients with evidence of antitumor activity who tolerated therapy well, a maximum of two additional courses could be administered.

Because this trial was based on principles used to guide high-dose IL-2 therapy, the method for identifying DLT was based on the total number of doses tolerated without surpassing the toxicity threshold. This toxicity threshold for withholding one or more doses of BAY 50-4798 was lower than that used for withholding doses of high-dose aldesleukin. One or more doses of BAY 50-4798 were withheld if patients experienced grade 3 toxicity on the National Cancer Institute Common Toxicity Criteria version 2, and the number of doses tolerated by patients in each dose level cohort was used to decide about escalation of the dose for the subsequent cohort as illustrated in Fig. 1.

Dose-escalation phase. BAY 50-4798 was administered to successive patient cohorts in a dose-escalating fashion to identify the MTD using a traditional three or six patient-per-cohort design. The starting dose

Table 3. Drug administration and toxicities

A. Phase I dose-escalation cohorts

Dose level (μg/kg)	No. patients	No. doses (course 1)				DLTs (no. doses)*,†,‡	Other events, dose limiting but not related to BAY 50-4798
		28	25-27	19-24	<19		
1.3	3	3					
2.6	4	3		1 (24)			Progressive malignant pleural effusion
5.2	4	4					
10.4	6	2	2	1	1	See Table 3B	
17.4	7	4	2 (25, 25)		1 (2)	Atrial fibrillation (2); creatinine (28); hypotension (25)	
26.1	6	4			2 (20, 14)	Hypotension; creatinine (20); ulcer/gastrointestinal bleed (14)	

B. Extension at the MTD level of 10.4 μg/kg, all 21 RCC patients

No. doses (course 1)	No. patients	DLTs (no. doses)	Other events, dose limiting but not related to BAY 50-4798
28	10	Atrial fibrillation, 1 patient	
25-27	5		1-3 doses withheld for multiple grade 2 toxicities
19-24	3	Rash (23) Fatigue (21)	
<19	3	Urticaria (10) Hypotension (17)	Cerebrovascular ischemia (12)

NOTE: Numbers in parentheses denote the number of doses of Bay 50-4798 administered.
*Defined as grade 3 treatment-related toxicities that led to withholding one or more doses of BAY 50-4798 or that occurred after all 28 doses in course.
† No grade 4 toxicities occurred.
‡ Dose withholding for multiple grade 2 toxicities was not reportable.

(1.3 μg/kg) was calculated based on preclinical toxicology studies as one sixth of the highest nonlethal dose in monkeys, the most sensitive species that had undergone testing.

Three patients were initially treated at each dose level. Dose levels were doubled in successive cohorts until at least one patient had received fewer than 25 doses in the first course because of toxicity related to BAY 50-4798. After an initial DLT was documented, dose escalation proceeded according to a modified Fibonacci series, in which the dose was increased by a factor of 167%, 150%, 140%, and then 133% of the prior dose for all subsequent levels. Among the six-patient cohorts, the MTD was exceeded if at least three patients received only 19 to 24 doses or one received 19 to 24 doses and one received fewer than 19 doses. If the MTD was not exceeded in a 3-patient cohort, up to three additional patients were enrolled. The MTD was then defined as the highest dose level in a six-patient cohort that did not meet these DLT criteria.

RCC extension phase. The study then evaluated BAY 50-4798 therapy in an extension phase at the identified MTD in RCC patients to obtain a detailed safety profile and a preliminary estimate of antitumor activity. A total of 20 RCC patients was treated at MTD, 6 from the initial dose-escalation phase and 14 subsequent patients during the extension phase.

Clinical assessment

Cardiac and pulmonary eligibility tests and tumor measurements were required within 28 days before initiation of therapy. Laboratory measurements were taken within 14 days before initiation of therapy. During treatment, all patients were required to have complete blood counts and 18-parameter serum chemistry panels daily. Prothrombin time, prothrombin time-international normalized ratio, partial thromboplastin time, and urinalysis were done on days 1, 4, 15, and 18 before the first dose of the day during the first course of therapy and on days 1 and 15 for subsequent courses.

Safety. All adverse events pertinent to the safety profile of BAY 50-4798 were recorded, and an assessment was made of the severity, intensity, and possible relationship to the study drug. Physical examinations, vital sign data, and laboratory tests were also closely monitored exactly as for high-dose aldesleukin.

Tumor response. Tumor assessments were done at weeks 7 and 11 (approximately 4 and 8 weeks after completion of the first course), and response was assessed according to the Response Evaluation Criteria in Solid Tumors criteria. A maximum of two additional courses, at the same dose level, could be administered to patients with any evidence of antitumor activity, including stable disease. The same method of assessment and the same technique were used to characterize each lesion at baseline and at follow-up.

Pharmacokinetics and pharmacodynamics. To evaluate the pharmacokinetics of BAY 50-4798, blood samples were collected before therapy on days 1 and 15 and on days 2 and 19 (or the last day of treatment) at 15 min, 30 min, and 1, 2, 4, and 8 h following the dose. Plasma assays of the level of BAY 50-4798 at these time points were determined by ELISA assay (Bayer 50-4798 investigator brochure; at ALTA Analytical Laboratory, San Diego, CA) to define the area under the curve for the 8-h dosing interval ($AUC_{0\text{-}8}$), maximum concentration (C_{max}), time of maximum concentration (T_{max}), and elimination half-life. Four-color flow cytometry for determination of lymphocyte subsets was done at National Jewish Medical and Research Center (Denver, CO) to quantitate the maximum change by treatment dose level of all lymphocytes, CD4 and CD8 T cells and NK cells, using samples from day 1 (before therapy) and days 8, 15, 23, and 45. The maximum percentage of $CD3^+CD4^+$, $CD3^+CD8^+$, and $CD16^+CD56^+$ expressing IL-2 receptor (CD25 on $CD4^+$ or $CD8^+$ cells and CD122 on $CD16^+CD56^+$ cells) and of the mean fluorescence intensity of these cells, reflecting their activation by BAY 50-4798, was also determined. To assess serum IgG antibody (the assay did not test IL-2 neutralization by antibody) to BAY 50-4798, serum was drawn before therapy (day 1) and at day 23 and day 45 in the first course of therapy and at day 100 (day 23 in the second course of therapy). All serum samples were analyzed using ELISA assays at ALTA Analytical Laboratory.

Table 4. Summary statistics of BAY 50-4798 pharmacokinetic variables

Dose (μg/kg)	Statistics	T_{max} (h)		C_{max} (μg/L)		C_{max} ratio*	$AUC_{(0\text{-}8)}$ (μg·h/L)		$AUC_{(0\text{-}8)}$ (ratio)*
		Day 1	Day 19	Day 1	Day 19	Day 19/day 1	Day 1	Day 19	Day 19/day 1
1.3	*n*	3	3	3	3	3	3	3	3
	Geometric mean	0.315	0.315	20.184	6.775	0.617	28.476	12.893	0.671
	SD	1.49	1.49	1.54	4.13	0.50	1.72	2.36	0.49
	%CV	40.02	40.02	43.07	141.93	ND	54.35	85.98	ND
2.6	*n*	4	4	4	4	4	4	4	4
	Geometric mean	0.297	0.297	31.964	45.829	1.493	32.801	42,232	1.342
	SD	1.41	1.41	1.94	1.41	0.48	1.86	1.40	0.43
	%CV	34.66	34.66	66.42	34.68	ND	62.21	33.51	ND
5.2	*n*	4	4	4	4	4	4	4	4
	Geometric mean	0.297	0.354	55.746	72.695	1.320	76.319	97.084	1.557
	SD	1.41	1.49	1.27	1.21	0.24	1.16	1.97	1.26
	%CV	34.66	40.02	23.90	19.10	ND	15.23	67.97	ND
10.4	*n*	20	12	20	12	12	20	12	12
	Geometric mean	0.268	0.315	117.33	109.43	1.064	173.02	181.94	1.342
	SD	1.24	1.41	1.55	1.71	0.30	1.45	1.97	0.56 ND
	%CV	21.33	34.13	44.01	53.84	ND	37.03	67.76	5
17.4	*n*	6	5	6	5	5	6	5	1.384
	Geometric mean	0.281	0.250	161.05	140.94	1.005	183.79	201.21	0.51
	SD	1.33	1.00	1.60	1.32	0.30	2.00	1.68	ND
	%CV	28.30	0.00	46.86	28.04	ND	69.27	52.16	3
26.1	*n*	6	3	6	3	3	6	3	1.305
	Geometric mean	0.250	0.250	264.95	266.56	1.355	328.21	317.36	0.57
	SD	1.00	1.00	1.79	1.53	0.72	1.78	1.52	ND
	%CV	0.00	0.00	57.98	42.74	ND	57.77	42.15	

Abbreviations: ND, not determined; %CV, percentage coefficient of variation.
*Day 19/day 1 ratio was determined based on arithmetic means.

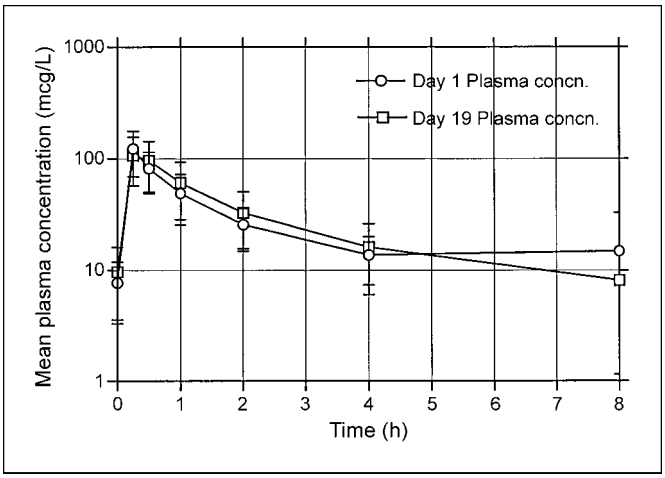


Fig. 2. Day 1 and day 19 plasma concentration versus time plot at the MTD dose of 10.4 μg/kg. Points, arithmetic mean of BAY 50-4798; bars, SD.

Statistical analysis

This was a phase I safety and tolerability trial conducted to determine the MTD of BAY 50-4798. In addition, tumor response and pharmacokinetics were also evaluated as secondary objectives. For the safety analysis, incidence rates of adverse events, drug-related adverse events, and hematologic/biochemical toxicities were summarized based on National Cancer Institute Common Toxicity Criteria version 2 worst grade by dose level. In addition, time to progression and overall survival were summarized using a Kaplan-Meier method.

For the pharmacokinetic analysis, descriptive statistics of plasma concentrations at each sampling time were presented by dose level as were descriptive statistics for derived pharmacokinetic variables. In addition, the ratio of plasma concentration at day 19 to day 1 was evaluated for AUC and C_{max} to determine the extent of accumulation. A descriptive summary of biomarker and antibody data was presented by dose level.

The sample size was based on the standard phase I design of toxicity assessment. The enrollment of 20 patients with RCC at the expanded MTD level of BAY 50-4798 provided additional data for clinical evaluation of the safety profile and to screen for anticancer activity in this patient population.

Results

Patient characteristics. Between November 2000 and June 2002, 45 patients (33 renal clear cell and 12 melanoma) were treated with at least one dose of BAY 50-4798, and all patients were included in the safety, pharmacokinetic/pharmacodynamic, and tumor evaluations. Patient characteristics at baseline are summarized in Table 1. Only nine patients had received prior therapy for metastatic disease, six of whom received only one prior treatment. The only cytokine therapy received by these patients was IFN-α.

MTD and safety. In the first phase of the study, the dose of BAY 50-4798 was escalated from 1.3 to 26.1 μg/kg across six dose levels according to the schema shown in Fig. 1. Although the protocol required withholding doses of BAY 50-4798 on the occurrence of any grade >3 toxicity, some of these toxicities did not occur until patients had already received all or nearly all of the 28 planned doses in the first course. Therefore, although the schema shown in Fig. 1 for escalating the dose level and expanding cohorts from three to six patients was followed closely, the final designation of the MTD was based on a composite of the toxicities reported and the number of doses received at the three highest doses studied. The number of patients and the number of courses for each dose level are shown in Table 2. The MTD was defined as 10.4 μg/kg during the dose-escalation phase based on dose withholding for grade 3 hyponatremia (one patient), creatinine elevation (one patient), and atrial fibrillation (one patient; Table 3A). Toxicity data from the 14 additional RCC patients treated in the extension phase at that dose, shown in Table 3B, confirmed the selection of 10.4 μg/kg as the MTD and that which would be recommended for further study. Overall, the toxicities of BAY 50-4798 were considered dose related, and the pattern of these multisystem effects was qualitatively similar to those of aldesleukin.

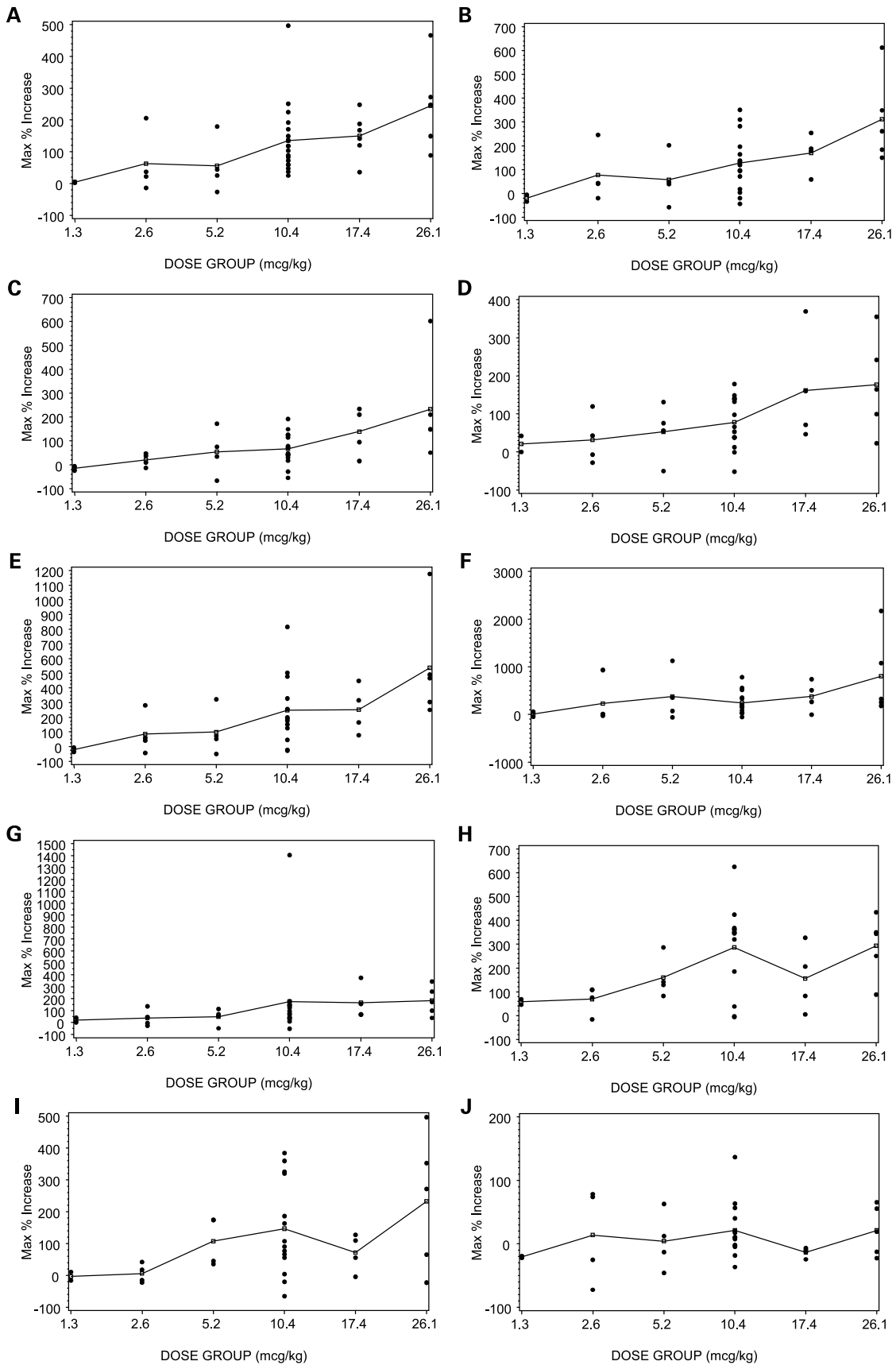
After the first course, 12 patients developed significant increases in BAY 50-4798 antibodies, with peak antibody titers of 5-fold (eight patients), 125-fold (three patients), and 625-fold (one patient) elevation over baseline at various time points. There was no clinical toxicity consistently associated with antibody development. None of the seven patients treated at the two lowest dose levels developed antibodies, and there was no trend toward a dose-dependent increase in antibody titer.

Tumor response. Of the 20 patients in the RCC extension phase, 1 had confirmed partial response lasting ~4 months, 13 had stable disease for at least 2 months as their best response (1 of these patients remains progression-free at 5+ years following protocol therapy), and 6 had progressive disease. The median (25th, 75th percentiles) time to progression was ~2.5 (range, 2-6) months. Among all 45 patients receiving BAY 50-4798, 2 (4%) had confirmed partial response (including the RCC patient described above and an additional patient with melanoma treated at the highest dose who experienced a transient 2.5-month partial response). Among all 45 study patients, 51% had stable disease for at least 2 months, whereas 20 (44%) patients had progressive disease after one course of treatment. The median (25th, 75th percentiles) time to progression was ~2.5 (range, 1.5-4.5) months.

Pharmacokinetics. Pharmacokinetic results of BAY 50-4798, shown in Table 4, were assessed in all patients in the dose-escalation phase. In these patients, BAY 50-4798 C_{max} and $AUC_{(0-8)}$ values generally seemed to show a proportional increase with increasing dose on both day 1 and day 19 after multiple dosing. At treatment doses ranging from 1.3 to 26.1 μg/kg, day 1 C_{max} ranged from 20.18 to 265.0 μg/L; day 19 C_{max} ranged from 6.78 to 266.56 μg/L. Day 1 $AUC_{(0-8)}$ ranged from 28.48 to 328.21 μg·h/L, whereas day 19 ranged from 12.89 to 317.36 μg·h/L.

BAY 50-4798 did not seem to accumulate in the plasma after multiple dosing with increased dosage based on the day 19 to day 1 ratio for both C_{max} and $AUC_{(0-8)}$. BAY 50-4798 was rapidly cleared from human plasma with a short half-life in this study. This ranged from 1.45 to 2.70 h.. The treatment also

Fig. 3. *A* to *J*, maximum percentage from baseline of each phenotype marker by dose level. *A*, absolute lymphocyte count. *B*, $CD4^+/CD3^+$ T cells. *C*, $CD8^+/CD3^+$ T cells. *D*, $CD56^+$ NK cells. *E*, $CD4^+/CD25^+$ IL-2 receptor$^+$ T cells. *F*, $CD8^+/CD25^+$/IL-2 receptor$^+$ T cells. *G*, $CD56^+/CD122^+$ IL-2 receptor$^+$ NK cells. *H* to *J*, mean fluorescence intensity of cells from (*E*), (*F*), and (*G*) respectively. □, mean; ●, patients.



seemed to show moderate to high interpatient pharmacokinetic variability. Figure 2 displays plasma concentrations over time for patients at the MTD of 10.4 μg/kg.

Pharmacodynamics (lymphocyte subset analysis by dose level). Results from the pharmacodynamic analysis revealed a dose-dependent increase in all lymphocyte subsets. Fig. 3 shows maximum percentage charge for values that peaked on days 8 and 23, consistent with the expected time course of IL-2 effects. Interestingly, whereas the mean fluorescence intensity of CD4/CD25 and CD8/CD25 cells increased modestly with increasing dose of BAY 50-4798, the mean fluorescence intensity for NK/CD122 cells (NK cells expressing the intermediate-affinity IL-2β receptor) did not seem to increase. We believe that this was consistent with the intended pharmacologic activity of BAY 50-4798 to selectively activate T lymphocytes over NK lymphocytes through differences in binding to their IL-2 receptors.

Discussion

The use of high-dose aldesleukin therapy in patients with advanced cancer has been limited to those who have essentially normal organ function and a good performance status, enabling them to tolerate the temporary but severe multiorgan toxicities (9, 17–19). Furthermore, only 15% to 25% of patients with "sensitive" tumors achieve an objective response to this therapy, and fewer than half of these responders enjoy durable complete responses (6, 20).

It is probable that high-dose aldesleukin treatment acts, in part, by an antigen-independent stimulation of NK cells to develop cytotoxicity against tumor cells. These tumor cells may or may not possess the elements required to target them for antigen-specific T-cell–mediated cytotoxicity, such as expression of class I major histocompatibility determinants, immunodominant peptide epitopes, and various accessory and signaling molecules (8, 17, 19). However, the important interactions between the cells and cytokines of the "innate" immune system, and those acquired by optimal immunization, raise the possibility that the long-term control of tumors requires a highly antigen-specific memory T-cell response. Despite the rapidly expanding understanding of the cellular and molecular components of these complex systems, the success of antigen-specific immunotherapy strategies has been limited. The endogenous or acquired mechanisms of escape, resistance, and other variables diminishing an effective antitumor immune response have outpaced therapeutic advances (20, 21).

Alterations of the IL-2 molecule that result in preferential activation of T cells, using their high-affinity IL-2 receptor, over NK cells, through their intermediate-affinity IL-2 receptor, could lead to enhanced antigen-specific T-cell responses over NK responses. NK cells are believed to be the predominant source of large quantities of the "secondary" cytokines and inflammatory mediators that cause most of the toxicities of high-dose human IL-2 and aldesleukin (1). Therefore, if T-cell responses were sufficient for the antitumor activity of BAY 50-4798, this would result in an improvement in the therapeutic ratio of IL-2. In the absence of active vaccination, these responses would have to develop from preexisting immune responses that are stimulated effectively by the exposure to large doses of exogenous IL-2. Paradoxically, it is possible that, as suggested by substantial published data, NK cells are the essential antitumor effectors and that the toxicities of high-dose aldesleukin cannot be separated from the therapeutic benefit of activating and expanding these cells (23).

Although proof of this mechanism of activity has been difficult to demonstrate, even in the setting of active, antigen-specific immunization studies in patients with cancer, the successful achievement of durable complete responses in some patients suggests that human IL-2 and high-dose aldesleukin therapy are capable of promoting an effective memory response against tumor antigens (2–5). Further evidence of antigen-specific immune reactions induced by nonspecific immunotherapeutic interventions in cancer patients is seen in conditions such as autoimmune thyroiditis and colitis, provoked by IL-2 and anti-CTLA4 antibody therapy for melanoma (23, 24).

In this study, pharmacodynamic results have confirmed the anticipated differential activation of T cells over NK cells with BAY 50-4798. Overall, the specific findings in this trial also confirmed that doses of BAY 50-4798 could be escalated to the equivalent of one half to one third that of high-dose aldesleukin, which normally involves dose administration to maximum tolerable grade 3 to 4 toxicities, sometimes in multiple organ systems. In this patient population, treatment with the higher doses of BAY 50-4798 was stopped on development of grade 3 toxicity. However, the effects on lymphocytes, as measured in this study, were not sufficiently potent to confirm the hypothesis that this approach has promise in the current design of clinical treatment strategies. This study has shown a qualitative similarity between the toxicities emerging at the highest BAY 50-4798 dose levels and those of high-dose aldesleukin (17, 19), suggesting that T cells are partially responsible for the toxic secondary inflammatory mediators resulting from aldesleukin therapy or that the selectivity for the higher-affinity IL-2 receptor on T cells over the lower-affinity IL-2 receptor on NK cells is not absolute or is diminished at the doses used in this study. Despite the fact that patients in this trial were relatively untreated, compared with those who participate in traditional phase I trials of cytotoxic agents, and despite the similarities of this investigational molecule to aldesleukin, we found that, in the cohort of 20 patients with advanced RCC who were treated at the MTD, there was insufficient antitumor activity to support further evaluation of BAY 50-4798.[11] Although we observed low antitumor activity of this agent as a substitute for high-dose IL-2 in RCC, the possibility that BAY 50-4798 could provide advantages over aldesleukin in antigen-specific immunotherapeutic strategies was not tested. We recommend that any further investigation of this agent be focused on T-cell–based, antigenically defined systems.

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[11] Steppan et al. have recently reported the differences in gene expression induced in the peripheral blood mononuclear cells of normal human subjects on exposure to either aldesleukin or BAY 50-4798. Of interest was their observation of differential expression of genes known to be induced by IL-2 as well as the induction by the mutein of higher levels of >100 genes in categories predominantly associated with cell metabolism and transcription (Steppan S, Kupfer K, Mayer A, et al. Genome wide expression profiling of human peripheral blood mononuclear cells stimulated wih BAY 50-4798, a novel T cell selective interleukin-2 analog. J Immunother 2007; 30: 150-68.

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