Interferon Alfa-2a and Interleukin-2 With or Without Cisplatin in Metastatic Melanoma: A Randomized Trial of the European Organization for Research and Treatment of Cancer Melanoma Cooperative Group

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Purpose: **The combination of interferon alfa-2a (IFNα) and high-dose interleukin-2 (IL-2) is active in metastatic melanoma. The addition of cisplatin (CDDP) has resulted in response rates greater than 50%. This study was performed to determine whether the addition of CDDP to a cytokine treatment regimen with IFNα and high-dose IL-2 influences survival of patients with metastatic melanoma.**

Patients and Methods: **Patients with advanced metastatic melanoma were randomly assigned to receive treatment with IFNα 10×10^6 U/m² subcutaneously on days 1 through 5 and a high-dose intravenous decrescendo regimen of IL-2 on days 3 through 8 (18 mIU/m²/6 hours, 18 mIU/m²/12 hours, 18 mIU/m²/24 hours, and 4.5 mIU/m²/24 hours × 3) without (arm A) or with (arm B) CDDP 100 mg/m² on day 1. Treatment cycles were repeated every 28 days to a maximum of four cycles.**

Results: **One hundred thirty-eight patients with advanced metastatic melanoma, of whom 87% had visceral metastases, were accrued for the trial. Both regimens were feasible in a multicenter setting. The objective response rate was 18% without and 33% with CDDP ($P = .04$). The progression-free survival was 53 days without and 92 days with CDDP ($P = .02$, Wilcoxon; $P = .09$, log-rank). There was no statistically significant difference in survival between treatment arms, with a median overall survival duration for all patients of 9 months.**

Conclusion: **The addition of CDDP to cytokine treatment with IFNα and IL-2 does not influence survival of patients with advanced metastatic melanoma, despite a significant increase in response rate and progression-free survival.**

THERE IS NO STANDARD treatment for advanced metastatic melanoma. With dacarbazine as a single agent, an approximately 15% objective remission rate can be achieved with a duration of 4 to 6 months.[1,2] Combination chemotherapy may increase response rates up to 40%, but without an impact on survival.[1,3] The activity of interleukin-2 (IL-2) has been extensively tested during the past decade.[4-7] Up to 20% of patients have experienced tumor responses with IL-2 administered in high-dose regimens, and some long-term survivors have been reported in most trials. Interferon alfa (IFNα) is also an active agent in melanoma.[8] Twenty percent to 40% of patients achieve objective remissions with the combination of IL-2 and IFNα.[9-12]

The addition of dacarbazine to IL-2 in phase II trials resulted in response rates similar to those achieved with IL-2 treatment alone.[13-15] More recently, several single-institution trials have investigated the combination of various cytotoxic agents with IFNα and high-dose IL-2[16-18] and a multicenter phase II trial that combined cisplatin (CDDP), dacarbazine, and tamoxifen with high-dose IL-2 has been performed by the Cytokine Working Group.[19] Sixteen percent to 56% objective response rates were achieved with these combinations that involved two to six agents. When the three agents CDDP, IFNα, and high-dose IL-2 were part of the treatment regimen, the response rates were greater than 50% in all phase II trials reported. Concurrent administration of cytokines and cytotoxic agents was suggested to be more efficacious than alternating administration, unless chemotherapy immediately preceded cytokine treatment.[18] However, it remains uncertain whether these increased response rates, which

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were sometimes achieved with considerable toxicity, translate into a survival benefit.

The toxicity of high-dose intravenous administration of IL-2 plus IFNα is of major concern and has for a long time prohibited larger multicenter trials.[20,21] However, when IL-2 is not administered at a continuous dose rate, but according to a decrescendo regimen, adverse effects may be significantly reduced without apparently compromising efficacy.[11]

The addition of CDDP to IFNα and high-dose IL-2 was found feasible for a multicenter setting in a phase II trial.[22] Furthermore, CDDP did not impair the induction of secondary cytokines and serum CD25 by IL-2, which suggests that this cytotoxic drug does not impair the immunologic effects mediated by IL-2. Previously, it has been shown that CDDP does not abolish the IL-2–mediated cellular responses (eg, lymphocytosis and lymphokine-activated killer [LAK] activity) in the peripheral blood.[23] There is even evidence that CDDP may to some extent enhance endogenous LAK activity.[24]

We report here on a randomized multicenter trial performed within the European Organization for Research and Treatment of Cancer (EORTC) Melanoma Cooperative Group that investigated whether the addition of CDDP to a combination of IFNα and IL-2 significantly influences survival of patients with advanced metastatic melanoma. The trial was designed to detect a significant doubling of the median survival time by adding CDDP. Secondary objectives of the trial included response rate and time to treatment failure.

PATIENTS AND METHODS

The inclusion criteria for this trial were metastatic melanoma with measurable disease parameters, which could not be controlled by surgery, and a Karnofsky performance status of at least 60%. Exclusion criteria were the presence of brain metastases on brain computed tomographic (CT) scan or magnetic resonance imaging (MRI); prior therapy with CDDP; chemotherapy within 3 months of protocol treatment; symptomatic cardiac, pulmonary, renal, liver, or thyroid disease; autoimmune diseases; corticosteroid treatment; and significant bone marrow dysfunction. The protocol was approved by the institutional review committees of all participating hospitals and informed consent was obtained from all patients before randomization. Only centers with experience in the administration of high-dose IL-2 ($\approx$ 20% of hospitals that participate in clinical trials of the EORTC Melanoma Cooperative Group) participated in this trial.

Treatment Plan

Patients randomized to arm A received IFNα-2a (Roferon; Roche, Basel, Switzerland) 10×10^6 U/m^2/d subcutaneously on days 1 through 5. IL-2 (Proleukin; Chiron, Amsterdam, the Netherlands) was given as continuous intravenous infusion in a decrescendo schedule starting on day 3 with 18 mIU/m^2 every 6 hours followed by 18 mIU/m^2 every 12 hours, 18 mIU/m^2 every 24 hours, and a maintenance dose of 4.5 mIU/m^2 every 24 hours for 72 hours. Arm B consisted of the same regimen of IFNα and IL-2 with the addition of CDDP 100 mg/m^2 intravenously as a single dose on day 1. Cycles were repeated every 4 weeks for a maximum of four cycles in the absence of disease progression.

In patients who had completed at least one treatment cycle, tumor assessment was performed after the second and the fourth treatment cycle according to standard World Health Organization (WHO) criteria.[25] In addition to the WHO criteria, a minor response category was defined as a 25% to 50% reduction in the sum of the product of the two largest perpendicular diameters of all measurable lesions for the purpose of decisions on further treatment after the second cycle. For analysis of objective responses, minor response (MR) has been classified as stable disease (SD) in agreement with WHO criteria. Patients who responded to two cycles of treatment with a MR or better received two additional treatment cycles. Patients with SD or progressive disease after two treatment cycles were monitored without further protocol treatment.

In case of any grade 4 toxicity, protocol treatment was discontinued, except in case of grade 4 hematologic toxicities if they had resolved at the time of re-treatment. In case of grade 3 ototoxicity or renal toxicity in patients randomized to the CDDP arm, CDDP was omitted in subsequent treatment cycles. For all other grade III toxicities (except fever, nausea/vomiting, and diarrhea, which were treated symptomatically), treatment was withheld until the toxicity improved to grade 1. In case of the following grade 3 toxicities during the IL-2 infusion, the infusion was interrupted and the toxicity reassessed every 2 hours, until resolution to at least grade 1: hypotension not responding to concomitant therapy, cardiac arrhythmia, suspicion of myocardial ischemia, agitation or persistent confusion, elevation of bilirubin level to greater than 60 μmol/L, bacterial sepsis, or dyspnea at rest. In case of the following toxicities, subsequent IL-2 was administered at 50% dose: increase in serum creatinine concentration to greater than 265 μmol/L or grade IV neurotoxicity in the previous cycle.

After completion of study treatment, patients were monitored every 2 months during the first 6 months and every 3 months thereafter. Surgical removal of residual lesions aiming at resection of all remaining metastases was considered in all patients who achieved at least an MR with protocol treatment.

Statistical Evaluation

The median survival duration in the arm without CDDP was expected to be 9 to 12 months. Assuming an underlying exponential distribution of survival, a median survival time of 12 months corresponds with a 2-year survival rate of approximately 25%. Doubling the median survival duration from 12 months in the arm without CDDP to 24 months in the arm with CDDP would correspond with a doubling of the 2-year survival rate from 25% to 50%. Using the log-rank test with a one-sided α error of 5% and β error of 10%, 2×62 patients would allow the detection of a significant doubling of the median survival time. The number of patients randomized was 138 to safeguard for up to 10% of possible noneligible patients and patients not available for follow-up evaluation.

Before randomization, patients were stratified according to treatment center and extent of disease to assure equal assignment of risk groups to the two treatment arms. Patients with a serum lactate dehydrogenase (LDH) level within the institutional normal limits and a cross-sectional surface area of all measurable metastases of

Table 1. Patient Characteristics

Characteristic	% of Patients		
	All Patients (N = 137)	Arm A: Without CDDP (n = 71)	Arm B: With CDDP (n = 66)
Karnofsky performance status (%)			
≥ 90	82	82	82
< 90	18	18	18
Site of disease			
Cutaneous, subcutaneous only	2	2	2
Lymph nodes with or without cutaneous, subcutaneous	11	12	9
Visceral	87	86	88
Extent of disease			
1 organ site	37	41	33
2 organ sites	38	39	37
> 2 organ sites	25	20	30
< 30 cm^2	75	77	72
> 30 cm^2	25	23	28
Normal LDH	56	58	53
Elevated LDH	44	42	47
Pretreatment			
No systemic pretreatment	78	77	80
Cytotoxic agents	11	10	11
Adjuvant IFNα	15	12	18
Adjuvant IL-2	7	5	9

NOTE. None of the differences was statistically significant.

Table 2. Toxicity of Treatment (worst toxicity of any cycle)

Toxicity	% of Patients in Arm A: Without CDDP (grade)		% of Patients in Arm B: With CDDP (grade)		P
	3	4	3	4	
Fever	15		4		.07
Hematologic					
Anemia	4		13		.02
Leukopenia	2		25	2	< .01
Thrombocytopenia	8		23	15	< .01
Renal	0		13	2	< .01
Liver	0		4		NS
Nausea	6		35		< .01
Vomiting	4		32		< .01
Diarrhea	12		14		NS
Anorexia	25		40		.02
Skin	4		9		NS
Alopecia	100		91	9	< .01
Pain	8		6		NS
Fatigue	12		15		NS
Cardiac	0		1		NS
Mental change	0		4		NS
Neurologic	0		1		NS

NOTE. Subjective hearing loss was reported by patients who received CDDP. However, the frequency of ototoxicity cannot be accurately assessed, since no hearing tests were performed.

Abbreviation: NS, not significant ($P > .05$).

less than 30 cm^2 were entered into stratum I, and patients with a serum LDH level above the institutional normal limits and/or a cross-sectional surface of all measurable metastases greater than 30 cm^2 were entered in stratum II.

Fisher's exact test was used to compare response rates and toxicities between treatment arms. Survival curves were computed according to the Kaplan-Meier method and compared using the Wilcoxon and the log-rank tests.

RESULTS

A total of 138 patients was accrued for the trial and randomized between April 1993 and May 1995. One hundred thirty-seven patients met the inclusion criteria. Four patients from one institution could not be analyzed. The treatment had reportedly been administered to all four patients according to protocol without major toxicity, but unfortunately no follow-up data are available, which reduces the total number of assessable patients to 133. Patient characteristics are listed in Table 1. Most patients had a Karnofsky performance status of at least 90%. In both patient strata, more than 85% of patients had metastases that involved visceral organs. Nine patients had received prior chemotherapy for metastatic disease (always dacarbazine), while the remaining 93% of patients had not received any prior systemic treatment for metastatic melanoma.

Toxicity

A total of 301 treatment cycles were administered (147 without and 154 with CDDP) and all 133 patients were assessable for toxicity of treatment. The administration of cytokines (arm A) was associated with known side effects as a flu-like syndrome, capillary leak syndrome, fluid retention, hypotension, gastrointestinal symptoms (nausea and diarrhea), CNS symptoms (lethargy, depression, and agitation), and abnormal kidney and liver function tests (Table 2). Grade III toxicities, mostly fever, occurred in 58% of patients; grade IV toxicities were not observed. The addition of CDDP (arm B) resulted in an increase of variety of toxicities, and 65% of patients in arm B experienced grade III toxicities and 20% grade IV toxicities, mainly thrombocytopenia and nausea. CDDP was associated with significantly increased renal toxicity. Three patients (two with and one without CDDP) with large liver metastases that replaced more than one third of the liver tissue developed significant hepatic toxicity with hyperbilirubinemia and abnormal coagulation tests for several days. All side effects could be managed by standard care and disappeared within a few days of treatment completion, except for peripheral neurotoxicity and

elevated serum creatinine concentration due to CDDP in some patients.

In 91% of treatment cycles, the planned dose of all study drugs was administered; treatment had to be modified in only 9% of cycles. Treatment modifications consisted mostly (7% of cycles) of transient interruption of the IL-2 infusion because of fatigue, vomiting, diarrhea, bowel obstruction (in a patient with a large bowel metastasis), cardiac arrhythmia, or hypotension. CDDP was omitted after the first cycle in a total of seven patients. In three patients, CDDP was omitted after the first cycle, in one patient after the second cycle, and in three patients after the third cycle for reasons of neurotoxicity (three patients), nausea (two patients), and nephrotoxicity (two patients). The dose of CDDP was reduced in one additional patient because of liver toxicity. Hearing loss was also noted in conjunction with CDDP; however, the frequency cannot be accurately assessed, since no routine hearing tests were performed prospectively. In conclusion, acute toxicity was considerable, as expected, but manageable, and no major long-term toxicities occurred.

One patient who did not fulfill the inclusion criteria because of symptomatic chronic obstructive lung disease and stable angina pectoris was randomized and received one cycle of protocol treatment that included CDDP. On day 6 of treatment, he developed pulmonary infiltrates with subsequent septicemia and he died of disseminated intravascular coagulopathy 3 days after discontinuation of IL-2.

Autoimmune phenomena were noted in six patients. One patient developed hyperthyroidism after the third treatment cycle and five patients developed arthritic changes (n = 2) or arthralgias (n = 3) of large joints following the second or third treatment cycle. No overt vitiligo was observed. Less pronounced vitiligo may have been overlooked, because no systematic screening for vitiligo was implemented in the study.

Response to Treatment

A total of 126 patients received at least one complete cycle of treatment and were assessable for response. Eight patients were not assessable for response because of the following reasons: four patients (two from arm A and two from arm B) refused further treatment and follow-up examinations after one treatment cycle in the absence of persisting toxicity or overt disease progression; thus intention-to-treat analysis is not affected or different from analysis by protocol. One patient died suddenly of unknown reason at home 2 weeks after completion of two treatment cycles in absence of overt disease progression.

Table 3. Response to Treatment

Response	IFNα/IL-2	IFNα/IL-2/CDDP	
No. of patients	66	60	
CR	4	3	
PR	8	17	$P = .04$
SD	12	13	(CR/PR v SD/PD)
PD	42	27	
% OR	18	33	
95% CI	9.8-29.6	21.7-46.7	
Stratum I			
No. of patients	35	26	
CR	2	1	
PR	6	9	$P = .14$
SD	7	8	(CR/PR v SD/PD)
PD	20	8	
% OR	23	38	
95% CI	10.4-40.1	20.2-59.4	
Stratum II			
No. of patients	31	34	
CR	2	2	
PR	2	8	$P = .09$
SD	5	5	(CR/PR v SD/PD)
PD	22	19	
% OR	13	29	
95% CI	3.6-29.8	15.1-47.5	

Abbreviations: OR, objective remissions; CI, Pearson-Clopper confidence interval; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

A relationship of the sudden death to the protocol treatment could not be established. One patient with a history of peptic ulcers developed bleeding from a peptic ulcer on day 1 of the first cycle of treatment that coincided with (but was not related to) the first administration of IFNα; protocol treatment was not resumed. Two patients received less than 24 hours of IL-2 infusion because of transient grade III toxicities (bowel obstruction and cardiac arrhythmia, respectively), which led to treatment discontinuation.

Eighteen percent of patients (23% in stratum I and 13% in stratum II) achieved objective remissions with cytokine treatment alone, 18% had SD, and 64% had disease progression (Table 3). The addition of CDDP significantly ($P = .04$) increased the objective response rate to 33% (38% in stratum I and 29% in stratum II); 22% of patients had SD and 45% progressed. Responses in both treatment arms occurred at all organ sites, as summarized in Table 4.

Sixteen patients (nine without CDDP and seven with CDDP) underwent surgical resection of residual lesions, which resulted in a clinical complete remission (CR) in

Table 4. Characteristics of Responders

Characteristic	IFNα/IL-2 (n = 12)	IFNα/IL-2/CDDP (n = 20)
Karnofsky performance score		
Range	80-100	60-100
Median	100	95
Sites of response (n)		
Lung	4	10
Lymph nodes	3	6
Liver	4	4
Soft tissue	2	3
Skin/subcutaneous	2	2
Adrenal	2	
Spleen	3	
Bone	1*	

*PR of extraosseous mass with evidence of bone recalcification.

seven patients (two without CDDP and five with CDDP). Residual lesions visible on CT scan were resected in two additional patients, but no remaining tumor cells were found on histology; therefore, these two patients were reclassified as having achieved CR by protocol treatment. Thus, 14 patients (11%) were free of macroscopic disease after treatment without (n = 7) or with (n = 7) second-line surgery (Table 5).

The median duration of objective responses without further medical treatment was 17 months without CDDP and 6 months with CDDP (P = .057, log-rank test; Fig 1A). Immediate treatment failures with overt disease progression after one treatment cycle occurred in 23% of patients without CDDP (14% in stratum I and 32% in stratum II) and in 17% patients with CDDP (8% in stratum I and 24% in stratum II). The median time to treatment failure of all patients was 53 days without CDDP and 92 days with CDDP (P = .02, Wilcoxon test; Fig 1B). However, the curves merge at 9 months and there is no significant difference in time to progression between the two treatment arms using the log-rank test (P = .09). If the progression-free survival is calculated according to stratum, there is also a doubling in median time to progression in both strata and the curves merge at 10 and 8 months, respectively (Fig 1C and D).

Survival

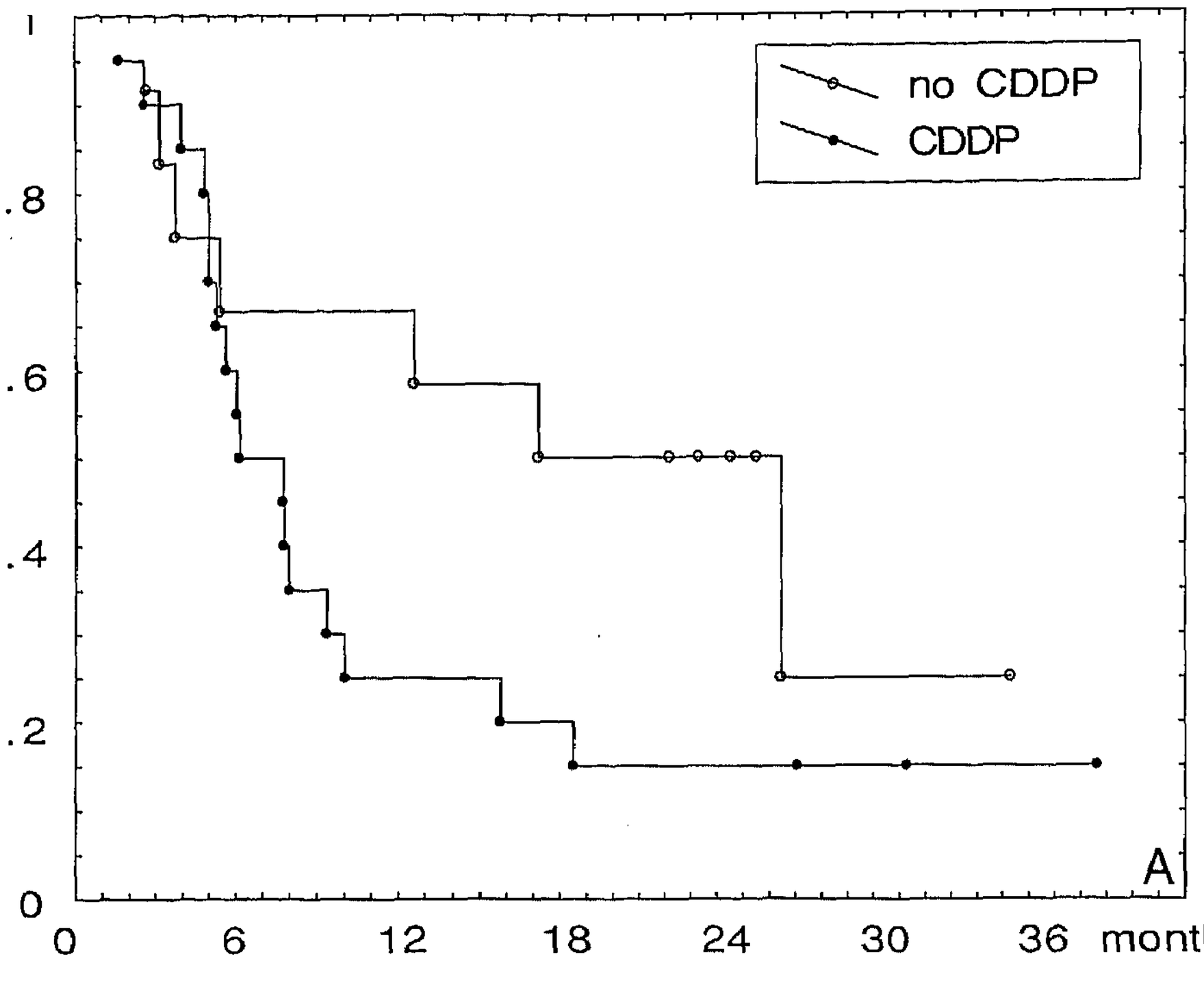
One patient was lost to follow-up evaluation, which left 132 patients assessable for survival analysis (Fig 2). The median survival duration is 9 months and there is no difference in survival between both treatment arms. The median survival duration of stratum I is 11 months (Fig 3) and the median survival duration of stratum II is 7 months (P = .004, log-rank test). Comparative analyses within both patient strata are descriptive, because the patient number per stratum is limited. There is no apparent difference in survival between both treatments arms within either stratum. Only in stratum II is there a hint toward a longer survival rate after 12 months with CDDP, but this is not statistically significant.

Sixteen patients are still alive with a median follow-up time greater than 2 years, nine treated with cytokines

Table 5. Characteristics of 14 Patients Rendered Free of Visible Disease by Protocol Treatment With or Without Second-Line Surgery

Patient No.	Sites of Metastases	Pretreatment Serum LDH	+/− CDDP	Response to Treatment	Second-Line Surgery	Time to Relapse (months)	Sites of Relapse	Overall Survival (months)
13	Mediastinal Pancreas, liver	elev	+	CR	NA	NA	CCR	38+
44	Liver	elev	−	SD	Liver	4	Liver	10
48	Lung	n	−	CR	NA	NA	CCR	35+
58	Lung, ln	n	+	PR	Hilar ln	4	ln, subcut.	11
60	Uterus, ascites	n	+	PR	Uterus	3	Skin, bone	11
66	Skin, ln, spleen Liver, pancreas	n	+	PR	Liver	10	Skin, ln Adrenal	15
75	Spleen, ln	n	+	PR	Spleen	NA	CCR	31+
77	Skin, subcutaneous	n	+	CR	NA	5	Brain	7
81	Liver, ln	n	−	PR	Liver, ln	NA	CCR	25+
83	ln, spleen	n	+	PR	ln	4	Brain	12
88	Liver	n	−	CR	NA	NA	CCR	24+
89	Liver, lung, ln	elev	+	CR*	NA	NA	CCR	27+
127	Lung	n	−	CR*	NA	NA	CCR	23+
135	Lung	n	−	CR	NA	NA	CCR	22+

Abbreviations: ln, lymph nodes; elev, elevated; n, within normal limits; NA, not applicable; CCR, continuous CR; NED, no evidence of disease.
*Residual lesions were suspected after 4 treatment cycles on CT scan, which on histology proved to be scar tissue in patients no. 89 and 127.



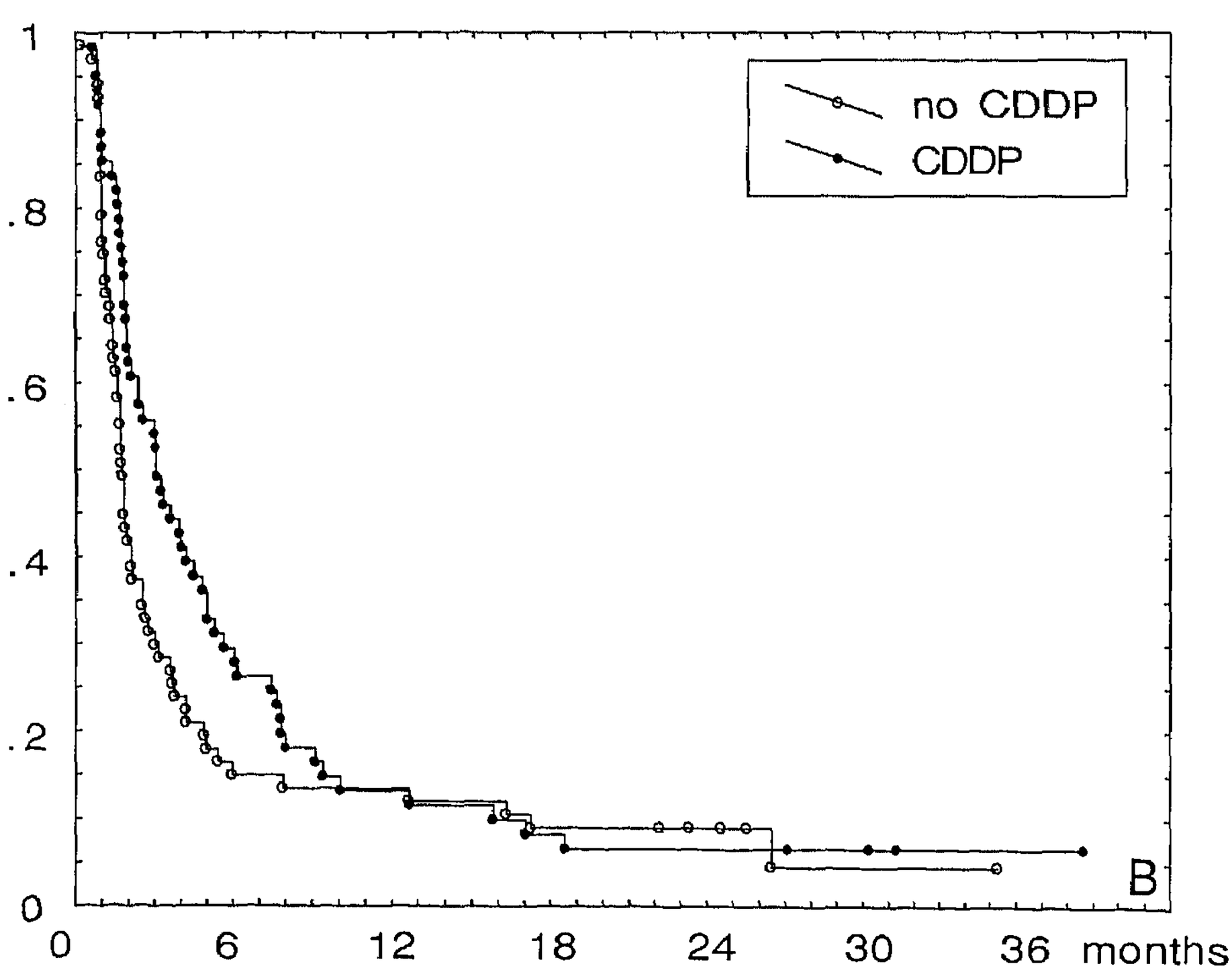
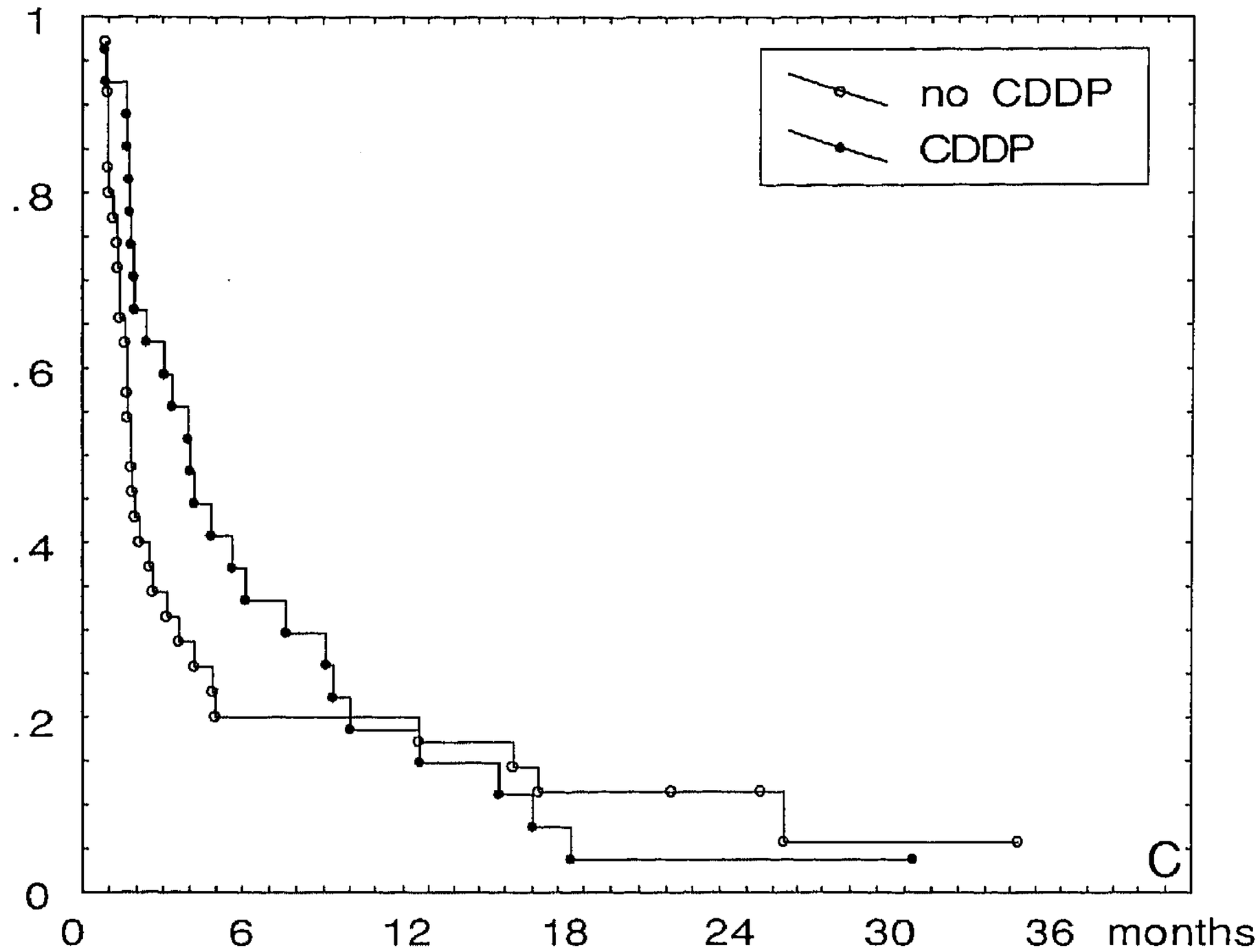


Fig 1. (A) Duration of overall response according to treatment arm. Time to treatment failure according to (B) treatment arm and (C) stratum 1 or (D) stratum 2.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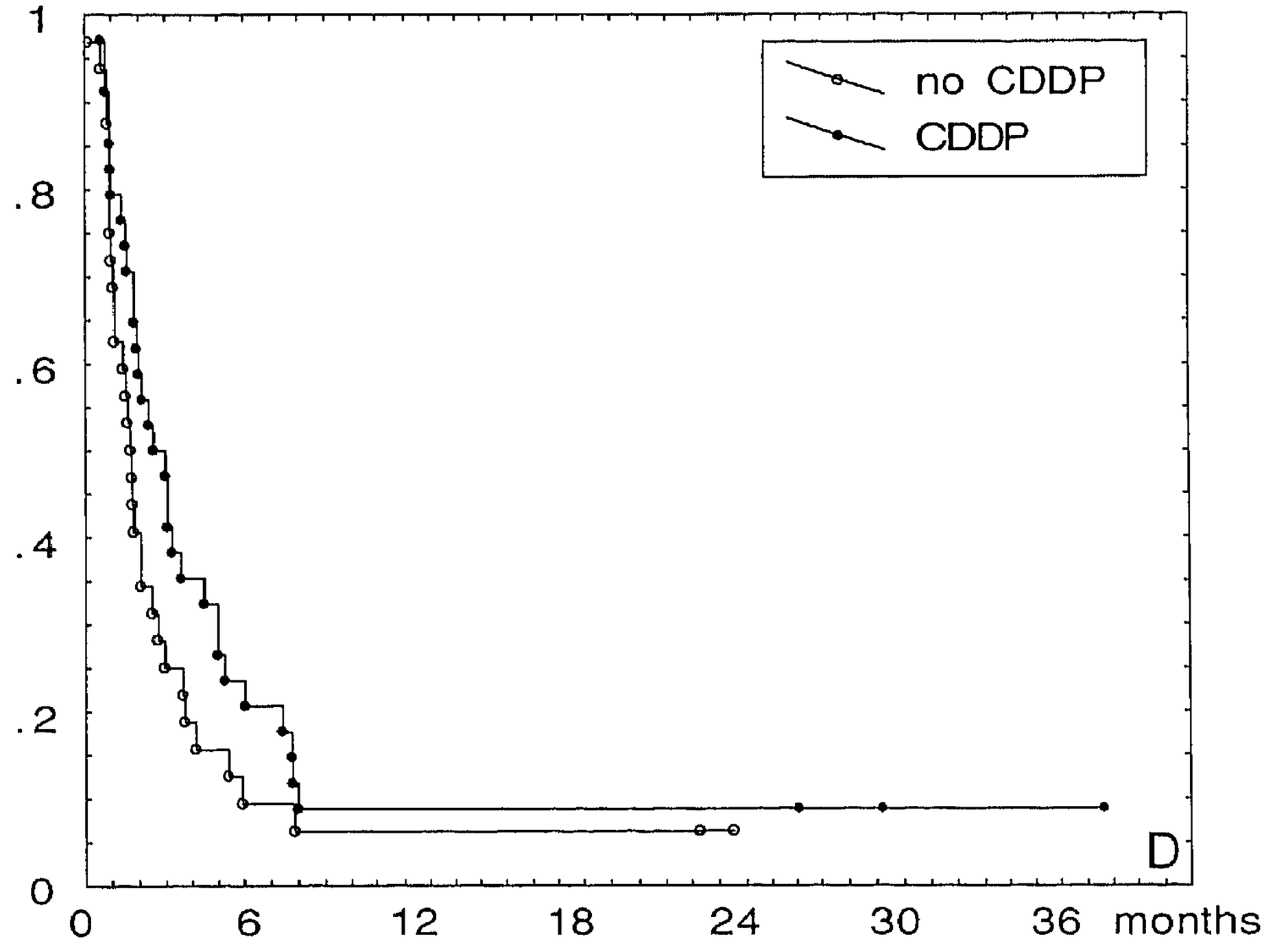
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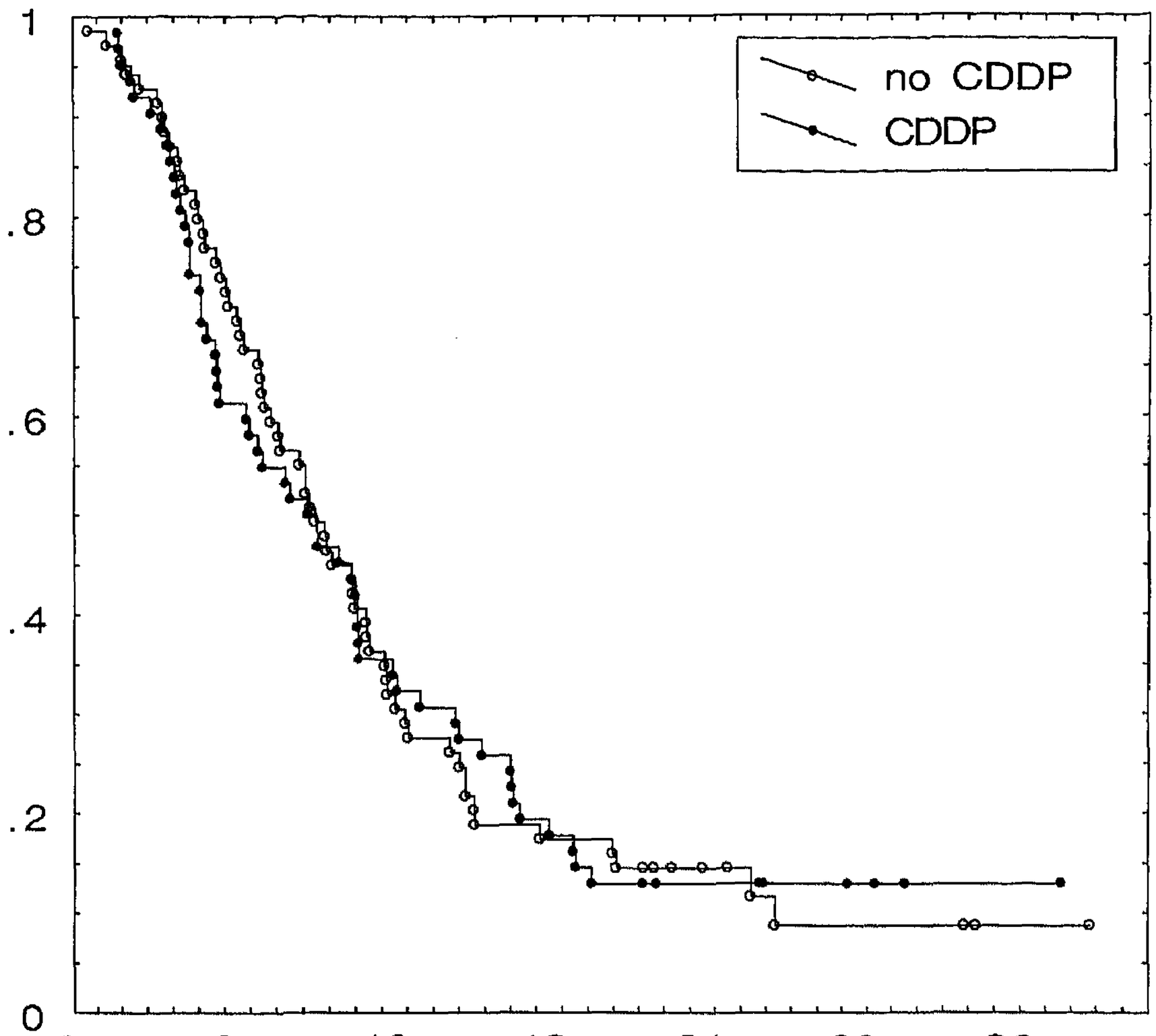

Fig 2. Survival of all patients according to treatment arm. Minimum follow-up time of surviving patients, 22 months.

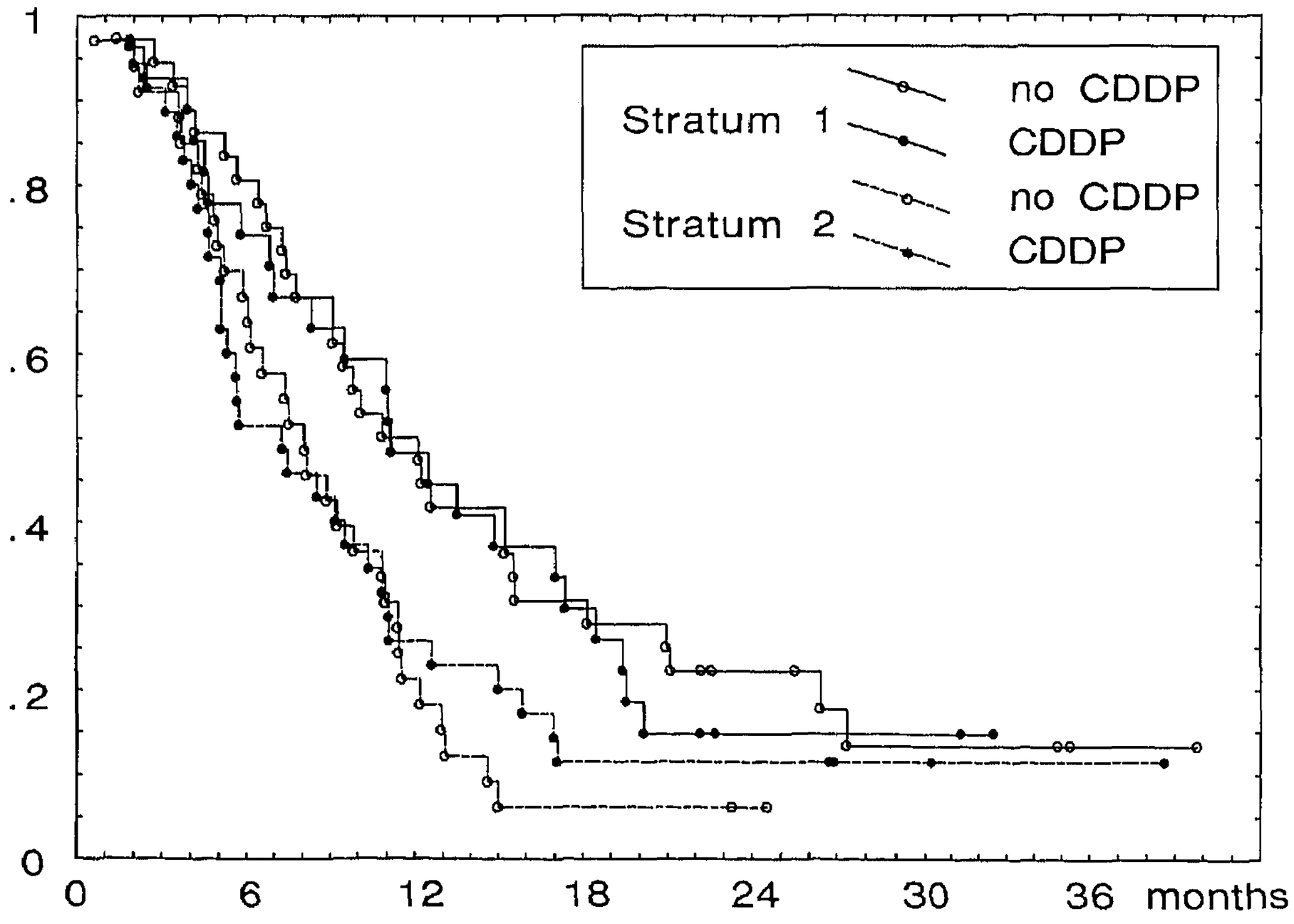

Fig 3. Survival according to stratum and treatment arm. Stratum I, n = 69 (—, normal pretreatment LDH and a cross-sectional surface of all measurable metastases < 30 cm^2); stratum II, n = 64 (---, elevated pretreatment serum-LDH and/or a cross-sectional surface of all measurable metastases > 30 cm^2).

alone and seven with CDDP. Nine patients were in the favorable stratum I (six treated without CDDP and three with CDDP) and seven patients in stratum II (three without CDDP and four with CDDP). Of the surviving patients, eight (five without and three with CDDP) are still without evidence of disease recurrence between 22 and 38 months postrandomization (Table 5), including six of seven compete responders by protocol treatment and two of seven surgical complete responders. The patient with relapse after CR by protocol treatment and one patient with a surgical CR developed brain metastases as the only site of relapse.

DISCUSSION

The results of phase II trials have suggested that a high response rate can be achieved in patients with advanced melanoma with chemoimmunotherapy that includes IL-2, IFNα, and CDDP.[16-19,26] This trial confirms that the addition of CDDP significantly increases the response rate over cytokine treatment alone. However, the response rates in both treatment arms were lower as compared with phase II trials. This may be explained by differences in patient cohorts, since in contrast to most of the phase II trials with metastases confined to extravisceral sites in half of the patients, 87% of patients in this trial had visceral metastases, which was associated with lower response rate to IFNα/IL-2 treatment in phase II trials.[27]

The addition of CDDP also decreased the rate of early treatment failures and increased the median progression-free survival in both patient strata. However, the duration of responses in arm B, with a median of 6 months, was much shorter than the median of 17 months with cytokine treatment alone, and the percentage of patients without progression beyond 1 year after randomization was not influenced by CDDP. Furthermore, the CR rate of was not improved by CDDP. Therefore, the improvement in response rate by the addition of CDDP did not translate into prolonged survival, except for a small hint in the more advanced disease stratum (stratum 2). This is in accordance with the observation that most partial responses after chemotherapy alone last for only a few months.[1-3] Efforts to maintain partial responses by additional treatment do not seem feasible given the toxicity of the current regimen. It is conceivable that the addition of CDDP to immunotherapy only induced an additional number of short-lived responses, without influence on survival. An alternative explanation is that CDDP may compromise the biologic agents efficacy and thereby reduce the quality of some responses. Furthermore, resection of residual lesions may have had a small impact on long-term analysis.

CRs achieved by protocol treatment proved to be rather durable. Strategies to improve the number of CRs may therefore improve survival. The addition of CDDP alone did not result in an increase of the number of CRs. One could conceive that the CDDP dose-intensity of 100 mg/m^2/4 weeks has not been sufficient, arguing for intensifying the chemotherapy regimen, but intensification of CDDP is prohibited by toxicity and may compromise cytokine-mediated effects.

The surgical resection of residual tumor lesions is another approach to achieve CRs. In most instances, the initial site of recurrence after cytokine-induced regression of melanoma is from remaining metastases or from lymph nodes draining previous metastases.[28] The duration of partial remissions converted into CRs by surgery was similar to the duration of cytokine-induced CRs in a series of selected patients.[28] For this trial, we prospectively adopted a policy of resecting residual lesions in an attempt to achieve better local control. An attempt to resect residual lesions was made in 15 patients and a total of seven could be rendered free of disease by removal of residual lesions after protocol treatment. However, only two of these surgical CRs have been durable. Four of the patients with surgical CR, including three patients who received CDDP and one patient with SD after cytokine treatment, relapsed after a few months, and one patient developed brain metastases as the only site of relapse. Based on the observations described previously, as well as in this trial, second-line surgery could perhaps be beneficial in selected cases, but cannot be generally recommended.

Twenty percent of patients from the more favorable stratum I are still alive with a median follow-up duration of 2 years, and there is a suggestion of a plateau in the Kaplan-Meier plot. This corresponds to the results of phase II trials of IL-2–based treatment in metastatic melanoma, in which always a proportion of long-term survivors have been observed. This is in contrast to trials of chemotherapy or IFNs, in which the 2-year survival rate is less than 10% and the 5-year survival rate is approximately 2%.[29,30] Current randomized trials within the EORTC Melanoma Cooperative Group and at the National Cancer Institute are investigating prospectively whether the addition of high-dose IL-2 to treatment regimens with IFNα and chemotherapy influences survival in patients with advanced melanoma.

The stratification procedure of this trial was based on limited single-institution experience, where serum LDH and tumor load were found to be the most significant

independent prognostic factors for survival in a cohort of patients treated with IFNα and IL-2[27] and on retrospective analyses of chemotherapy and IFN trials.[31] With this trial, we prospectively confirm the importance of these prognostic factors for response and survival, which could be useful for stratification in future randomized trials, which are needed to establish whether chemoimmunotherapy combinations provide a meaningful benefit to patients with advanced melanoma as compared with single-agent chemotherapy.

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