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Prognostic factors for survival and factors associated with long-term remission in patients with advanced melanoma receiving cytokine-based treatments: second analysis of a randomised EORTC Melanoma Group trial comparing interferon-α2a (IFNα) and interleukin 2 (IL-2) with or without cisplatin

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Abstract

The aim of this study was to define prognostic factors for survival, and especially for long-term survival in a mature data-set of patients with stage IV melanoma treated within a randomised trial of cytokine-based protocols. Long-term follow-up data on patients enrolled into a European Organization for Research and Treatment of Cancer (EORTC) trial comparing interferon-α (IFNα) plus interleukin-2 (IL-2) with or without cisplatin were collected. Univariate and multivariate Cox regression analyses wereperformed to define prognostic factors for survival. The characteristics of patients alive at 2 and 5 years after randomisation were compared with the entire cohort using the χ^2 test. The minimum potential follow-up of the 131 evaluable patients was 5 years. 18 patients (14%) were alive 2 years after randomisation, and 11 (8%) 5 years after randomisation. Pretreatment performance status (PS), serum lactate dehydrogenase (LDH) and tumour mass were significant predictors for survival, whereas site of metastases and number of sites were non-significant. PS and LDH were the only independent prognostic factors. All except 1 patient alive at 2 and 5 years had a pretreatment PS of 100%, and only three long-term survivors had elevated pretreatment LDH. There was no association between the site of metastases and long-term survival. Response to treatment was a major predictor for long-term survival, whereas addition of cisplatin did not impact upon overall survival probability or on long-term survival. The probability of long-term survival in stage IV melanoma patients after IL-2-based treatments is governed by pretreatment PS, serum LDH and response to treatment. Site of metastases, the basis for the M-subcategories of the new AJCC staging system, was not informative in this study.

Keywords: Melanoma; IL2; Cytokines; Prognostic factors

1. Introduction

A variety of approaches to improve the outcome for patients with stage IV melanoma have been investigated during the past decade in multi-institutional randomised phase III trials. The investigational chemotherapeutic approaches have included combination chemotherapy regimens [1–6] and combinations of chemotherapy with tamoxifen [7–10] or interferon-α (IFNα) [9,11–13], all of which have proved to be unsuccessful in large randomised trials with regard to impacting on median survival or the 2-year survival rate compared with single

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agent dacarbacine (DTIC). The DTIC analogue, temozolamide, also offers no survival advantage [14]. All of these randomised trials have been reported with a median follow-up time of approximately 2 years after randomisation; therefore, there is currently no information on patients with prolonged survival after chemotherapy within phase III trials for stage IV melanoma.

Previous analyses of compiled data, mostly from phase II chemotherapy trials or from extended single institution experiences, have suggested that there is no clear link between the response to chemotherapy and long-term survival, and in these reports the proportion of patients surviving at 5 years varied between 2 and 6% [15–19].

Another group of randomised trials has investigated the role of the two cytokines, IFNα and interleukin-2 (IL-2), for treatment of stage IV melanoma patients. The response rate achieved in larger phase II and in phase III trials with IL-2 as a single agent is small, in the order of 5–20% [20–22]. The combination of IL-2 and IFNα has resulted in response rates between 10 and 40% [21,23–25]. Only the combination of cytotoxic agents and cytokines, termed chemo-immunotherapy or bio-chemotherapy, has resulted in higher response rates in phase II trials, and this only in cases where the three drugs IL-2, IFNα and cisplatin were included in the regimen [26–33]. Therefore, chemo-immunotherapy is currently the preferred treatment for patients with stage IV melanoma in many institutions. However, this preference is not based on results from randomised studies. However, in early phase II trials, a proportion of patients with prolonged complete responses to IL-2-based treatments have been observed and summarised in several reports [22,34]. Based on the observation of these long-term responses, IL-2 has been registered for the treatment of stage IV melanoma in a number of countries.

Between 1993 and 1995, the European Organization for Research and Treatment of Cancer (EORTC) Melanoma Group accrued stage IV melanoma patients into a randomised trial comparing immunotherapy with IFNα and IL-2 to chemo-immunotherapy with cisplatin, IFNα and IL-2. The first analysis has been published in 1997 [29] showing that the addition of cisplatin doubled the response rate and nearly doubled the time to progression, but did not impact upon the median survival, which was 9 months in both treatment arms. Because at the time of the first analysis, the median follow-up was only 30 months, no information on long-term remissions with these two IL-2-based treatment regimens were available.

Now, 6 years after the randomisation of the last patient, we update and re-analyse the data to address two major questions: First, we investigated the relationship of known pretreatment prognostic factors with survival. Since this is the first such analysis of a mature phase III trial in stage IV melanoma patients, the results advance previous analyses on compiled data from phase II trials or single institution experiences. Furthermore, this analysis was performed to investigate the validity of the new American Joint Committee (AJCC) staging system, especially the M subcatogeries in this study. Second, we analysed whether any of the pretreatment prognostic factors would specifically predict long-term survival and therefore be potentially useful to select patients for cytokine-based treatments in the future.

2. Patients and methods

2.1. Patient selection

The major inclusion criteria for the trial were metastatic melanoma with measurable disease parameters that could not be controlled by surgery, a Karnofsky performance status (PS) of at least 60%, and absence of brain metastases. Basic information including Karnofsky PS, serum lactate dehydrogenase (LDH), and number, site and dimensions of tumour lesions were collected at the time of randomisation. A Karnofsky score of 100% was accepted in patients without any impairment by the tumour manifestations.

2.2. Treatment

The treatment schedules have been described in detail in the first report in Ref. [29]. Briefly, patients with stage IV melanoma were randomised to receive either IFNα and IL-2 (arm A) or IFNα, IL-2 and cisplatin (arm B). IFNα (Roferon, Roche) was administered at a dose of 10 MU/m^2 on days 1–5. IL-2 (Proleukin, Chiron) was given by intravenous (i.v.) infusion beginning on day 3 according to the decrescendo regimen (18 MIU/m^2 over 6 h, immediately followed by 18 MIU/m^2 over 12 h, 18 MIU/m^2 over 24 h and a maintenance dose of 4.5 MIU/m^2 per 24 h for 3×24 h). Thus, the IL-2 infusion was administered on days 3–8. Cisplatin was given at a dose of 100 mg/m^2 i.v. on day 1. Two cycles of the allocated treatment were administered and, in cases where at least a minor tumour regression was observed after these first two cycles, two further identical treatment cycles were given. Response to treatment was again assessed 4 weeks after the fourth treatment cycle, and patients were then followed-up without further protocol treatment. Upon disease progression, further treatment was at the discretion of the responsible physician, although the use of cisplatin was discouraged.

As specified by the protocol, surgical removal of the residual lesions aiming at resection of all remaining metastases was considered in all patients achieving at least a minor response with the protocol treatment.

After completion of the protocol treatment, patients were routinely followed-up every 2 months for the first 6 months, every 3 months for the first 2 years, and every 6–12 months thereafter to assess time to progression and survival. In March 2001, all investigators were contacted to report on the current status of their patients to facilitate this second analysis.

2.3. Statistical methods

Univariate and multivariate analyses were performed to investigate the prognostic impact of pretreatment factors and of response to protocol treatment. For the latter, the landmark method [35] was applied, i.e. patients who were censored (not applicable) or who had died within the first 4 months were excluded from the analysis of the relationship between response and survival. However, all patients were included in the analysis of the relationship between pretreatment prognostic factors and survival. Most established pretreatment prognostic factors for survival in other previous analyses had been obtained for all of the patients at the time of randomisation and are considered in this analysis, including serum LDH, Karnofsky PS, location of metastases, tumour mass and number of metastatic sites.

One combination factor, the M category according to the new AJCC staging system [36] was derived from the above information: M1a defined as metastases confined to cutaneous, subcutaneous and nodal sites with normal serum LDH, M1b with the inclusion of lung metastases, and M1c including any other visceral site or elevated serum LDH.

Our own analysis led to a novel combination factor of LDH and PS with a score of 1 for normal LDH and Karnofsky PS of 100%, a score of 2 for elevated LDH *or* impaired PS, and a score of 3 for elevated LDH *and* impaired PS.

All variables were categorised based on previous analyses [15–17,20,35] prior to constructing survival curves. Thereafter, in univariate analysis survival curves were estimated using the Kaplan–Meier method and compared using the log-rank test.

All prognostic factors were subsequently considered in Cox models using forward as well as backward variable selection criterion. For the final prognostic model, assumptions were examined using time-dependent covariates [37].

Long-term survival (2 years, 5 years) was analysed using χ^2 tests. No patient had been censored before 2 years, and only 1 patient had been censored before 5 years.

All analyses were performed using Statistical Package for the Social Sciences (SPSS) for Windows (release 9.0). The level of significance was 0.05 in all statistical tests. The graphs were prepared using Statistica software (release 4.1).

3. Results

3.1. Survival according to treatment arm (Fig. 1)

In agreement with the initial analysis, both treatment arms displayed virtually identical survival curves. 18 patients (14% of all 131 patients evaluable for follow-up) were alive 2 years after randomisation and 11 patients (8% of all evaluable patients) were alive at 5 years.

3.2. Univariate analysis of pretreatment factors and survival (Table 1 and Fig. 2)

Three pretreatment variables describing tumour lesions (location of metastases, number of involved organs and tumour mass), as well as serum LDH and PS were considered. LDH ($P=0.0003$), PS ($P=0.0005$), and tumour mass ($P=0.040$) were found to be significantly associated with survival, whereas location of metastases and number of involved organs were non-significant ($P=0.073$ and 0.33, respectively).

To better describe the impact of these factors on survival, univariate Cox regression analysis was performed to estimate the respective hazard ratios. In cases of the variables PS and number of metastatic sites, the assumptions for linearity were fulfilled, and only one hazard ratio is provided, which is applicable to estimate the risk between the first and the second level, as well as between the second and the third level. For tumour mass, the hazard ratio of 1.58 between the first and the second level (<10 cm^2 versus 10–30 cm^2) is similar to the hazard ratio of 1.52 between the second and the third level (>30 cm^2), but the linearity assumptions were not fulfilled; therefore, both ratios are given. For the discrete variables, location of metastases and the

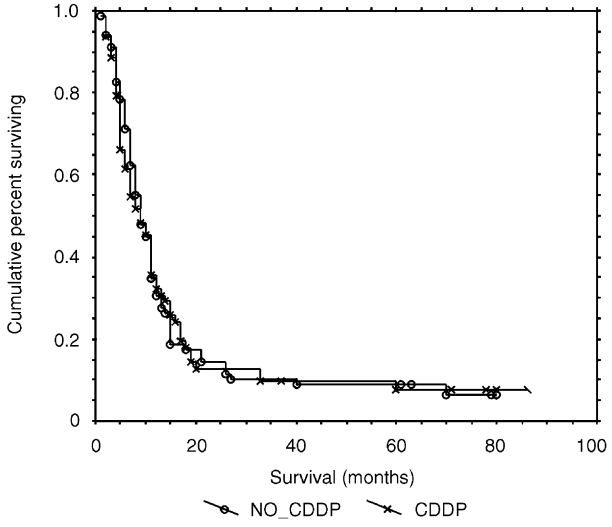

Fig. 1. Kaplan–Meier survival estimates for all patients according to treatment.

Table 1
Risk factor distribution and univariate analysis (log-rank test and univariate Cox analysis) for survival

	n	%	Median survival		*P* value	Univariate Cox analysis	
			months	95% C.I.	(log-rank)	Hazard ratio	*P* value
All patients	131	100	9.0				
Single criteria							
PS (Karnofsky)							
100%	77	58.8	10	8.5–11.5	0.0005	1.54	0.0004
90%	32	24.4	7	3.7–10.3			
<90%	22	16.8	4	1.7–6.3			
LDH							
Normal	74	56.5	11	8.9–13.1	0.0003	1.89	0.0006
Elevated	57	43.5	7	5.3–8.7			
Location of metastases							
s.c., nodes	23	17.6	9	5.9–12.1	0.073	1.0	
+ lung	44	33.6	12	9.6–14.4		0.82	0.53
+ other visceral	64	48.9	7	5.3–8.7		1.20	0.49
Number of metastatic sites							
1	47	35.9	11	9.4–12.7	0.33	1.18	0.15
2	52	39.7	9	6.7–11.4			
>2	32	24.4	7	4.6–9.4			
Tumour mass							
<10 cm^2	61	46.6	11	8.2–13.8	0.040	1.0	
10–30 cm^2	39	29.8	9	6.7–11.3		1.58	0.031
>30 cm^2	31	23.7	7	5.2–8.8		1.52	0.072
Combined criteria							
M stage (AJCC)							
M1a	13	9.9	11	8.4–13.6	0.0057	1.0	
M1b	36	27.5	13	8.3–17.7		0.97	0.93
M1c	82	62.6	7	5.4–8.6		1.74	0.088
PS/LDH							
PS 100, normal LDH	45	34.4	11	8.4–13.6	<0.0001	1.0	
PS < 100 or elevated LDH	60	45.8	10	8.3–11.7		1.51	0.051
PS < 100 and elevated LDH	26	19.8	5	4.2–5.8		4.03	<0.0001

95% CI, 95% confidence interval; LDH, lactate dehydrogenase; PS, performance status; s.c., subcutaneous; AJCC, American Joint Committee on Cancer.

two combination factors hazard ratios between all levels were estimated separately.

3.3. Combination factors (Table 1)

The proposal for the AJCC staging system is to use a combination factor of site of metastases and LDH. Because site of metastases was not significantly associated with survival, the M subcategories were no more informative than serum LDH alone, as shown in Fig. 3a. The M1a and M1b subcategories, in particular, did not lead to distinct survival curves.

A combination factor of PS and LDH, however, clearly discriminated the three patient categories with distinct survival probabilities early on, and this distinction remained throughout the entire follow-up period (Fig. 3b).

3.4. Multivariate analysis of pretreatment factors and survival (Table 2)

The multivariate evaluation of the impact of pretreatment parameters on survival was performed by Cox's regression. The final Cox model of individual factors only included PS and serum LDH as independent prognostic variables, substituting for all the variables describing tumour lesions. The treatment arm did not show any relationship with survival, if forced into the model.

3.5. Patients alive 2 and 5 years after randomisation (Table 3)

18 patients were alive 2 years after randomisation (10 from the arm without and 8 from the arm with cisplatin), and 11 patients were alive 5 years after randomisation (6 from the arm without and 5 from the arm with

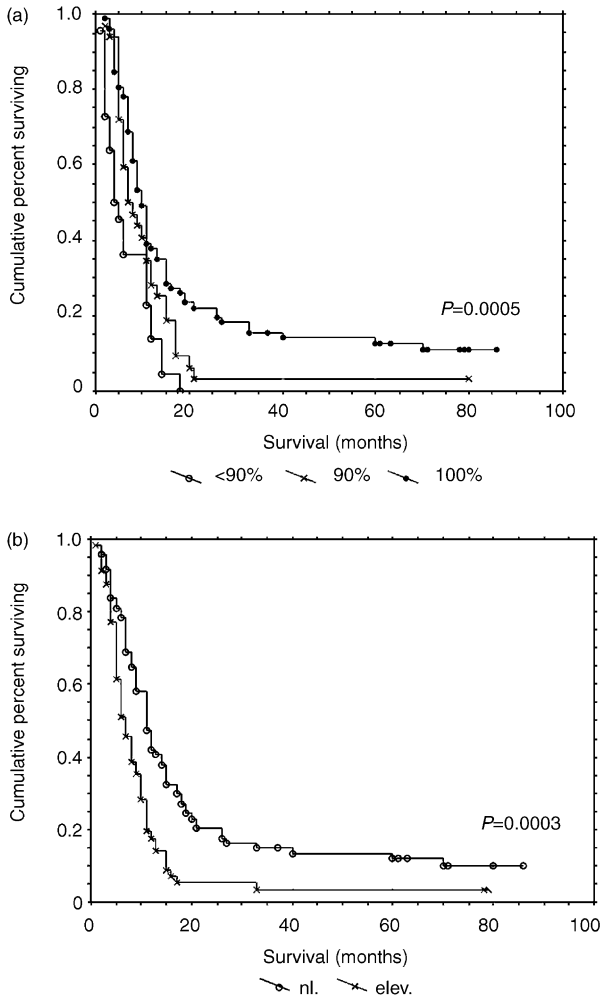

Fig. 2. Kaplan–Meier survival estimates according to independent prognostic factors: (a) performance status (PS) catagorised as Karnofsky 100, 90 and <90%; (b) pretreatment serum lactate dehydrogenase (LDH), categorised within the normal range (1), and above the institution's upper normal limit (2). nl, normal; elev, elevated.

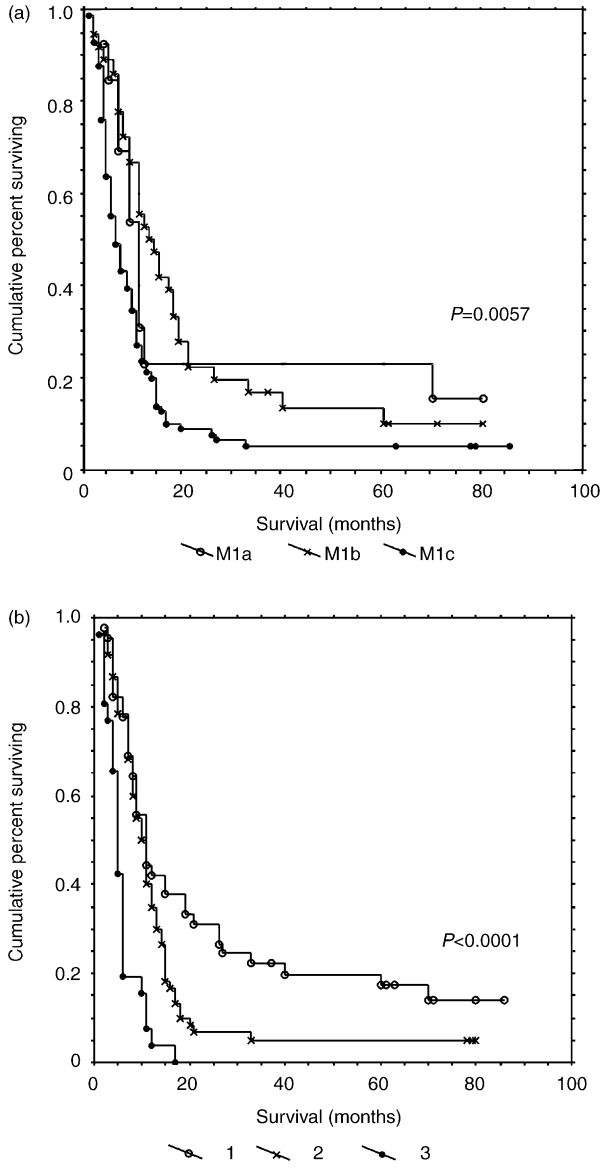

Fig. 3. Kaplan–Meier survival estimates according to combination factors: (a) AJCC criteria: AJCC M1a: normal serum lactate dehydrogenase (LDH) and metastases confined to cutaneous/subcutaneous (s.c.) sites and lymph nodes, M1b including lung metastases, M1c including other visceral organs or elevated serum LDH; (b) performance status (PS)/LDH combination factor: 1 for normal LDH and Karnofsky PS of 100%, 2 for elevated LDH *or* impaired PS, and 3 for elevated LDH *and* impaired PS.

cisplatin), of whom 4 have died since then, leaving 7 patients alive at the time of this analysis. There were no deaths reported to be caused for reasons other than melanoma. 3 patients have been lost to follow-up between 2 and 6 years after randomisation because they had moved to a different city (patient 61) or country (patients 88 and 106). Patients 61 and 106 have most likely died shortly after the last contact with the investigator, because they were experiencing significant progressive disease at that time; therefore they are listed among the patients alive at 2, but not at 5 years. Patient 88, however, had an ongoing CR at the time of the last contact 63 months after randomisation.

3.6. Distribution of pretreatment prognostic factors in long-term survivors

Tables 4–7 summarise the pretreatment prognostic factors in patients alive 2 and 5 years after randomisation. Pretreatment PS was decisive for prolonged survival: All patients except 1 had a pretreatment Karnofsky index of 100%, resulting in 2- and 5-year survival rates of 22 and 13%, respectively, in patients entering the study with a Karnofsky PS of 100%. The other patient still alive had a PS of 90%. Normal LDH was also common in the patients with prolonged survival, with 20% of this group surviving 2 years and 12% surviving 5 years. However, 3 patients (5%) of the 57 with elevated pretreatment LDH were alive at 2 years, and 2 of them (4%) still at 5 years.

Table 2
Independant prognostic factors for survival (Cox model)

Factor		Multivariate Cox analysis	
		Hazard ratio	*P* value
PS (Karnofsky)	100/90/<90	1.55	0.0003
LDH	Normal/elevated	1.93	0.0004

All other variables (location of metastases, number of metastatic sites, and tumour mass) were not significant and therefore excluded from the model. PS, performance status; LDH, lactate dehydrogenase.

Pretreatment factors describing the tumour lesions, including disease sites categorised as in the proposal for the new AJCC-M stage subcutaneous (s.c.) and nodal involvement versus addition of lung versus addition of other sites), the number of involved organs, and the tumour mass were all not decisive for long-term survival. Accordingly, low AJCC M stage was more frequent in patients with long-term survival, since it included LDH, but M stage was not decisive: 13 patients entered the study with M1a, of whom 4 (27%) were alive at 2 years and 2 (15%) at 5 years, 36 patients entered with M1b, of whom 6 (17%) were alive at 2 years and 4 (11%) at 5 years, and 82 patients entered with M1c, of whom 7 (9%) were alive at 2 years and 5 (6%) at 5 years, respectively.

3.7. Relationship of response to treatment and long-term survival (Tables 5–7)

At the time of the response analysis after completion of the protocol treatment (4 months after randomisation), 105 patients were alive. Of these, 7 patients had a complete response (CR), 24 a partial response (PR), 25 stable disease (SD) and 49 progressive disease (PD) (Table 5). This time point was used for the landmark analysis to investigate the relationship between response to treatment and survival. It is apparent from Fig. 4 and Table 5 that there is a clear link between response to treatment and survival. The survival curves were distinct for patients with CR, with SD or PR, and with PD ($P<0.0001$). Interestingly, patients with PR and with SD after treatment had almost identical survival probabilities, with the curves overlapping.

Table 3
Characteristics of patients alive 2 years and 5 years after randomisation

ID[a]	KI	LDH	Disease sites	No. of organs	Tumour mass[b]	AJCC stage	Cisplatin	No. of cycles	Response to treatment	Status at		Survival (months)
										2 years (TTP, months)	5 years	
Alive at 2 years, but not at 5 years												
50	100	nl	Nodes	1	1	M1a	No	4	PR	CR(26)	DOD	40
61	100	nl	Nodes	1	3	M1a	Yes	2	SD	PD (30) lost to f/u 37+		
63	100	nl	s.c., adrenal, soft t.	3	1	M1c	No	4	PR	PD(17)	DOD	27
67	100	nl	Lung	1	1	M1b	Yes	4	SD	PD(4)	DOD	33
101	100	nl	Intestinum	1	1	M1c	No	2	PD	PD(2)	DOD	26
106	100	elev.	Nodes	1	2	M1c	Yes	4	PR/sCR[c]	PD(8)	DOD	33
130	100	nl	Lung, nodes	2	1	M1b	No	2	SD	PD(4)	DOD	26
Alive at 5 years												
11	100	nl	s.c.	1	2	M1a	No	2	SD	PD(5)	PD	70
13	100	nl	Lung, nodes, liver	2	3	M1c	Yes	4	CR	CR	CR	86+
48	100	nl	Lung	1	1	M1b	No	4	CR	CR	CR	80+
75	90	nl	Nodes, spleen	2	1	M1c	No	4	PR/sCR[c]	CR	CR	80+
81	100	elev.	Liver, nodes	2	1	M1c	Yes	4	PR/sCR[c]	PD(37)	PD	79
88	100	nl	s.c., liver	2	1	M1c	No	4	CR	CR	CR[d]	63+
89	100	elev.	Nodes, liver, lung	3	1	M1c	Yes	4	CR	CR	CR	78+
117	100	nl	s.c., lung	2	1	M1b	Yes	2	SD	PD(9)	PD	71
127	100	nl	Nodes[e]	1	3	M1a	No	4	CR	CR	CR	70+
133	100	nl	Lung, nodes	2	1	M1b	Yes	4	SD	PD(4)	PD	68
135	100	nl	Lung	1	1	M1b	No	2	CR	CR	CR	61+

DOD, died of disease, s.c., subcutaneous; CR, complete responder; PD, progressive disease; SD, stable disease; PR, partial responder; TTP, time to progression; f/u, follow-up; soft t, soft tissue; nl, normal; elev., elevated; ID, identification no.; KI, Karnofsky index; AJCC, American Joint Committee on Cancer; LDH, lactate dehydrogenase.

[a] ID numbers correspond to the ID numbers in the initial report [29].

[b] 1, <10 cm^2, 2, 10–30 cm^2, 3, >30 cm^2.

[c] sCR, PR converted into CR by surgery after protocol treatment.

[d] Patient was in CR at last contact, but emigrated to a different country outside of the EU.

[e] Uncertain histology.

Table 4
Comparison of pretreatment characteristics and treatment results of all patients and of patients alive at 2 and 5 years after randomisation

	All patients $n=131$ (%)	Patients surviving at			
		2 years $n=18$ (%)	5 years P value (χ^2)	$n=11$ (%)	P value (χ^2)
Individual factors					
PS					
100	77 (58.8)	17 (94)		10 (91)	
90	32 (24.4)	1 (6)		1 (9)	
<90	22 (16.8)	0	0.002	0	0.025
LDH					
Normal	74 (56.5)	15 (83)		9 (82)	
Elevated	57 (43.5)	3 (17)	0.013	2 (18)	0.073
Number of metastatic sites					
1	47 (35.9)	8 (44)		5 (45)	
2	52 (39.7)	7 (39)		4 (36)	
>2	32 (24.4)	3 (17)	0.33	2 (18)	0.77
Tumour mass (cm^2)					
<10	61 (46.6)	13 (72)		8 (73)	
10–30	39 (29.8)	2 (11)		1 (9)	
>30	31 (23.7)	3 (17)	0.054	2 (18)	0.19
Metastatic sites					
sc, nodes	23 (17.6)	4 (22)		3 (27)	
+ lung	44 (33.6)	6 (33)		4 (36)	
+ other	64 (48.9)	8 (44)	0.36	4 (36)	0.59
Combination factors					
AJCC stage					
M1a	13 (9.9)	4 (17)		3 (27)	
M1b	36 (27.5)	8 (44)		4 (36)	
M1c	82 (62.6)	7 (39)	0.081	4 (36)	0.069
PS/LDH					
PS 100, normal LDH	45 (34.4)	14 (78)		8 (73)	
PS<100 or elevated LDH	60 (45.8)	4 (22)		3 (27)	
PS<100 and elevated LDH	26 (19.8)	0	<0.0001	0	0.013

PS, performance status; LDH, lactate dehydrogenase; s.c., subcutaneous; AJCC, American Joint Committee on Cancer.

Table 5
Relationship between response to treatment and survival after completion of protocol treatment according to the landmark method (univariate analysis)

	n	%		Median survival[a] months 95% C.I.	P value (log-rank)	Univariate Cox analysis	
						Hazard ratio	P value
Patients alive at 4 months[b]	105	100					
Response to treatment							
CR	7	6.7	>80	Not reached	<0.0001	1.0	
PR	24	22.9	12	9.6–14.4		16.3	0.0065
SD	25	23.8	15	10.1–19.9		15.5	0.0077
PD	49	46.7	9	6.7–11.2		38.6	0.0004

95% C.I., 95% confidence interval; CR, complete responder; PR, partial responder; SD, stable disease; PD, partial disease.
[a] Calculated from the time of response assessment, four months after randomisation.
[b] Time of response assessment after completion of protocol treatment.

Table 6
Treatment efficacy and long-term survival

	All evaluable patients[a] $n=105$ (%)	Patients surviving at			
		2 years		5 years	
		$n=18$ (%)	P value (χ^2)	$n=11$ (%)	P value (χ^2)
Response to treatment					
CR	7 (6.7)	6 (33)		6 (55)	
PR	24 (6 sCR) (22.9)	5 (3 sCR) (28)		2 (2 sCR) (18)	
SD	25 (1 sCR) (23.8)	6 (33)		3 (27)	
PD	49 (46.7)	1 (6)	0.001	0	0.02

CR, complete responder; PR, partial responder; SD, stable disease; PD, progressive disease.
[a] Only patients alive at time of response evaluation (fourth month after randomisation) are considered for the analysis of treatment efficacy and survival (Landmark method).

Regarding patients with long-term survival, several interesting observations can be made (Table 6):

1. 6 of the 7 patients with a CR to treatment were alive at 2 and 5 years after randomisation, and all are still alive.
2. Of the 24 patients who had achieved a PR to treatment, 3 were alive at 2 years and 2 of these patients at 5 years. The latter 2 have still not relapsed. It is of interest that all 3 patients were among the 6 patients in whom the PR could be converted into a surgical CR (sCR) after completion of the protocol treatment.
3. 6 of the 25 patients with SD after protocol treatment were alive at 2 years and 3 of these patients were alive at 5 years; 2 patients have subsequently died with disease progression. In 1 patient with SD, surgical removal of metastases was also performed. However, this patient relapsed at 4 months and died at 10 months.
4. No patient with PD or NE after protocol treatment was alive 5 years later; in fact, the last patient with PD died 26 months after randomisation.
5. A total of 14 patients had no evidence of disease (NED) after treatment with or without subsequent surgery. 8 of these 14 patients (57%) were alive and without relapse 5 years later.

3.8. Pretreatment factors, treatment efficacy, and survival (Table 7)

In order to evaluate whether the pretreatment factors are still related to survival after completion of treatment and response assessment, multivariate Cox models were used to evaluate the relationship between the two combination factors AJCC M stage and PS/LDH score and survival using the landmark method. Two separate models had to be considered, because LDH is part of both combination factors. Interestingly, both combination factors remained significant in the two multivariate models, suggesting that the pretreatment factors remained informative for the survival probability, even when the response to treatment is known. As in the pretreatment evaluation, the impact of PS/LDH was more pronounced compared with the impact of the AJCC M stage.

Table 7
Combination factors, response to treatment, and survival (Cox models)

Factor	Multivariate Cox analysis	
	Hazard ratio	P value
Cox Model 1: Response and AJCC M stage		
Response		
CR	1.0	
PR	16.3	0.0066
SD	18.1	0.0050
PD	41.2	0.0003
AJCC		
M1a/M1b/M1c	1.48	0.022
Cox Model 2: Response and PS/LDH		
Response		
CR	1.0	
PR	11.3	0.019
SD	14.0	0.010
PD	30.5	0.0009
PS/LDH		
score 1/2/3	1.98	0.0004

CR, complete responder; PR, partial responder; SD, stable disease; PD, progressive disease; AJCC, American Joint Committee on Cancer.

4. Discussion

The two main questions addressed in this study were (a) whether pretreatment prognostic factors for survival of stage IV melanoma patients previously defined in retrospective analyses would be confirmed from mature

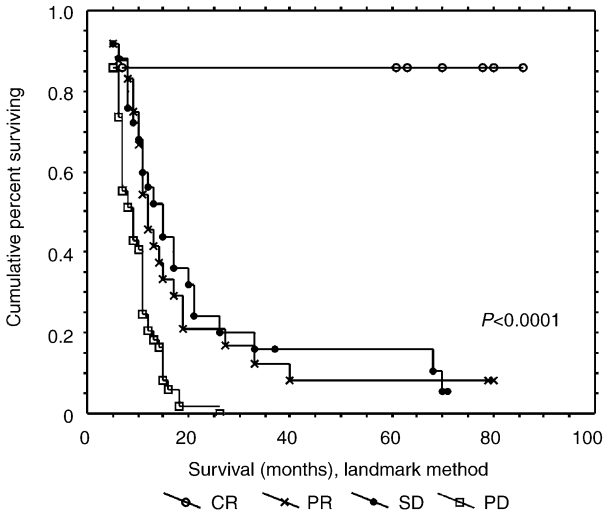

Fig. 4. Survival estimates from time of completion of protocol treatment according to response to treatment. According to the Landmark method, this graph includes only patients alive 4 months after randomisation. The numbers per category are given in Table 5.

data of a randomised trial, and (b) whether it is possible to characterise specifically the long-term survivors with pretreatment prognostic factors or response to treatment.

A number of independent pretreatment prognostic factors for survival of patients with stage IV melanoma have been defined in several analyses, including site of metastases [17–19,22], number of metastatic sites [19,22], pretreatment performance status [19,22] and serum LDH [17,19,22]. An important limitation of these analyses is that patients were treated according to various protocols, mostly within phase I or II trials [17,19,22], or patients were not necessarily entered on an intent-to-treat basis [18].

The study presented here is the first long-term follow-up analysis of a patient cohort treated within a single randomised study. In this analysis, pretreatment performance status and LDH could be confirmed as robust prognostic factors for survival, separating the survival curves early on and maintaining an informative value throughout the entire follow-up period. Of the factors describing the extent of tumour manifestations, only tumour load was significantly associated with survival, although this factor did not maintain the importance for the entire follow-up period and was non-significant in the multivariate analysis. The other parameters, site of metastases and number of sites, did not show a significant relationship to survival.

Three explanations can be offered for the lack of a relationship between factors describing the extent of tumour manifestations and survival in this study: One possibility is the relative small number of patients in our analysis, especially in the category of patients with metastases confined to subcutaneous sites and lymph nodes. A second possibility is that these variables lose their predictive value with prolonged follow-up. A third alternative is that these factors may not be applicable for patients treated with biochemotherapy. It is impossible to rank these three possibilities, the hypotheses can only be tested by analysing in a similar manner data from other randomised trials which have been performed once the data from those trials are mature. This would be of particular importance, since the factor, site of metastases is the basis for the M subcategories of the new AJCC staging system. If the lack of a relationship between site of metasteses and survival is confirmed in further analyses from mature randomised trials, the AJCC M subcategories may have to be adjusted.

A potential robust combination factor to group patients according to survival probability and potentially use for stratification is offered by a combination score of PS and LDH. A combination of both variables suggest high-risk long-term survival is unlikely. Interestingly, there was no difference in median survivals in the stratification of this group, but the patient group with no unfavourable factors had a much higher probability for long-term survival compared with the group of patients with one unfavourable factor.

All these considerations are important to categorise and stratify patient groups for randomised studies, but to date no treatment modality has changed the median survival for patients with stage IV melanoma. However, a proportion of long-term responders has been described in numerous studies employing high-dose IL-2, and this observation formed the basis for the registration of this drug in melanoma. Therefore, it would be of great interest in future studies to define a patient subgroup with an increased likelihood for long-term survival. According to our analysis, this task appears to be surprisingly simple, since pretreatment PS is decisive for long-term survival. The distinction is already apparent comparing the patient groups with a Karnofsky score of 100% versus 90%. Also LDH is an another important factor for long-term survival, and the combination score, which resembles the combination of LDH and B-symptoms generally used to classify patients with non-Hodgkin's lymphoma [38], clearly defines a subset of patients with a good chance for prolonged survival, in our analysis 31% survival at 2 years and 18% at 5 years. If confirmed in mature data from other randomised studies, PS and LDH could potentially also be employed as factors for stratifying standard or experimental treatment options in the future.

In contrast to PS and LDH, the variables describing the extent of tumour manifestations were evenly distributed in patients surviving at 2 and 5 years. A most striking finding is that even the presence of liver metastases did not interfere with prolonged survival, as 4 of the 11 patients alive at 5 years after randomisation had liver metastases at the time of randomisation. Previous analyses have failed to establish a relationship between response to chemotherapy and prolonged survival in

melanoma patients [39]. However, for IL-2-based treatment protocols, there was the suggestion of a link between response and survival in many studies. In our analysis, this link is obvious, since 6 out of 7 patients achieving a CR were alive at 5 years follow-up without relapse. However, the survival curves of patients with PR and SD after treatment were superimposable, suggesting that a PR to cytokine-based treatment is not sufficient for long-term survival, and not that different from SD. Thus, attempts need to be made in future trials not to increase the overall response rate, but specifically the CR rate.

In the clinical trial, based on previous anecdotal experience [39], we had prospectively adopted the policy of resection of residual melanoma lesions after incomplete response to protocol treatment, but it was uncertain whether this may result in long-term relapse-free survival in a fraction of patients. Interestingly, the only 2 patients with a PR after protocol treatment alive without relapse were among the 6 patients in whom a PR by protocol treatment could be converted into a CR by subsequent surgery. These results are still anecdotal, and it remains speculative whether the surgical removal of residual lesions was necessary to achieve a durable relapse-free interval, but the presence of vital tumour cells in all resection specimens argue in favour of this approach. In both patients, surgery had been (rightfully) declined prior to systemic treatment because of multiple sites involving lymph nodes and liver in 1 patient and lymph nodes and spleen in the other.

Our observations argue in favour of a concept of reaching a CR, not only by cytokine-based treatments, but also in selected patients by subsequent surgery thereby offering a patient with stage IV melanoma a reasonable probability for long-term relapse-free survival. However, this argument is not proposed to encourage aggressive or mutilating surgery in less well-selected patients. Further studies may evaluate whether long-term responses can also be achieved by combining remission-inducing chemotherapy followed by various immunotherapies, potentially ranging from modern vaccine approaches to allogeneic minitransplants.

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