

Aim of the study: The incidence of melanoma is increasing rapidly worldwide. Metastatic melanoma is still an incurable disease, although an era of new drugs is approaching. Current methods to predict outcomes in patients with advanced, metastatic melanoma are limited. A retrospective analysis of a contemporary large group of advanced melanomas was performed to determine clinical prognostic factors that accurately predict survival in patients with metastatic melanoma before the era of new targeted/immunological therapy.

Material and methods: The retrospective analysis of 427 patients with metastatic melanoma treated between 1995 and 2005 at two reference oncological centres.

Results: The median overall survival time (OS) was 7.1 months (95% CI: 6.7–7.9) and the 1-year, 2-year and 5-year survival rates were 32.3%; 12.5%; 3.9%, respectively. The median progression-free survival time (PFS) after the first line of treatment was 3.5 months (95% CI: 3.1–3.8). There were 19.1% objective responses (CR – 6.1%, PR – 13.0%) and SD – 45.5% after the first line of therapy. The most common adverse events were anaemia, neutropenia, thrombocytopenia, nausea and vomiting. In multivariate analyses: PS (performance status) 0–1, normal serum levels of lactate dehydrogenase (LDH) and aspartate transaminase (AspAT), older age in women, palliative surgical treatment and palliative radiotherapy, type of the first line of therapy (DTIC), and metastatic melanoma of unknown primary site were independent positive predictors for survival.

Conclusions: The survival rate of patients with metastatic melanoma has not changed significantly over the last years. We identified a set of independent positive predictors for OS treated with systemic therapy. DTIC still may be useful in treatment of patients in a good general condition and with normal serum levels of LDH. Because the results of treatment of metastatic melanoma are still not satisfactory, the majority of patients should be treated within prospective, randomized clinical trials.

Key words: melanoma, metastases, therapy, outcomes, prognostic factors.

Results of systemic treatment of cutaneous melanoma in inoperable stage III and IV

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Introduction

Skin melanomas are relatively rare neoplasms; the standardised incidence rate in Poland is about 4/100 000 [1]. However, in recent years there has been a sudden growth in the incidence. It is estimated that in the years 1982–2002 the morbidity increased three-fold [2].

Prognosis in cutaneous melanoma depends strongly on the primary stage according to TNM; thus 5- and 10-year survival rates in stage IA are 97% and 93% respectively, while in stage IIIC they are only 53% and 39%. Stage IV – metastasis to distant organs – is characterised by the worst prognosis, and 1-year survival is 62% for M1a, 53% for M1b and 33% for M1c [3].

Despite advances in diagnosis and treatment, the inoperable stage III and stage IV melanoma remains an incurable disease, and the median survival time in those stages is 6–11 months [4–7]. For this reason numerous patients with inoperable skin melanoma are still being included in clinical trials with various chemotherapy regimens, immunotherapy and targeted therapies, which give hope for changing the results of treatment in the near future. So far the greatest advance in the treatment of those patients has been connected with introduction of monoclonal anti-CTLA-4 antibodies, which have been registered in Europe for the treatment of advanced (unresectable or metastatic) melanoma in adults after previous therapy failure, but they lack predictive factors for response to treatment with simultaneous considerable side effects of this therapy. The second promising treatment is molecular-targeted therapy with tyrosine kinase inhibitors acting on BRAF or KIT protein mutations pathways. Currently there is no consensus regarding the role of systemic treatment in this group of patients, and in the era of novel treatment methods and still numerous group of patients treated only symptomatically, it is vital to define the results and potential role of chemotherapy in treatment of advanced, unresectable skin melanoma. Melanomas are cancers with low chemosensitivity, and the benefit from the chemotherapy is confined to selected subgroups of patients [8–10]. The most important drug used in monotherapy and as part of multidrug regimens is dacarbazine (DTIC), the only chemotherapeutic to have been approved by the FDA for the treatment of melanoma. The objective response rate to treatment with DTIC, after analysing 23 randomised, controlled clinical trials, was found to be 15.3% [11]. The impact of dacarbazine on overall survival was not evaluated, because no clinical trials comparing dacarbazine with placebo have been conducted [12]. The next group of chemotherapeu-

tics is vinca alkaloids: vindesine, vinblastine, used mostly with other chemotherapeutics, taxanes (mostly paclitaxel), and nitrosourea derivatives: carmustine (BCNU), lomustine (CCNU) and fotemustine. Their activity in monotherapy is similar to that of dacarbazine, but unfortunately they are characterised by greater toxicity, especially myelosuppression. Although fotemustine is not registered by the FDA, it is available in Europe and used for treating melanoma, especially in the case of brain metastases. Immunotherapy with interferon α -2b and interleukin 2 plays an important role in the treatment of melanoma. High dose interleukin 2 (HD IL-2) was approved by the FDA in 1998 for the treatment of patients with metastatic melanoma. The basis for registration was achieving durable complete responses correlating with prolonged overall survival in a small group of patients. Because of the high percentage of severe adverse events that can occur during HD IL-2 treatment, such immunotherapy is recommended for carefully selected younger patients, in good general condition [14, 15].

Because of an opinion that a combination of a few chemotherapeutics may increase the rate of objective responses to the treatment and lengthen overall survival, research on multidrug chemotherapy was carried out. However, no expected results were found, and the increase in objective responses to the treatment did not result in overall survival lengthening [16–19]. Similar results were acquired by adding interleukin 2 and/or interferon α -2b to the multidrug schemes (biochemotherapy). It increased the objective responses to the treatment with a simultaneous considerable increase in treatment toxicity, without a significant impact on overall survival [20–22].

Therefore, research regarding factors that predict the clinical course of advanced melanomas and their response to systemic treatment is being carried out in order to establish optimal criteria for selecting patients for the treatment. It is vital to fully determine the set of prognostic and predictive factors within the group of melanoma patients with unresectable metastases to regional lymph nodes/in-transit metastases or metastases to distant organs treated with classical therapeutic methods, taking into consideration the approaching introduction of drugs with new mechanisms of action which will change the landscape of advanced melanoma therapy.

Material and methods

We performed a retrospective analysis on 427 patients with inoperable stage III and IV melanoma, aged 51.4 on average (19–82 years), comprising 236 (55.27%) men and 191 (44.73%) women who started systemic treatment in the Department of Systemic and Generalized Malignancies of the Centre of Oncology (Cracow Branch) – 177 (41.45%) patients and in the Department of Soft Tissue/Bone Sarcoma and Melanoma of the Centre of Oncology (Warsaw) – 250 (58.55%) patients in the years 1995–2005. The analysed group included only patients with histologically confirmed diagnosis of skin melanoma. Patients with ocular and mucosal melanoma were not included in the analysis [8, 23–25]. Complete information on tested clinical factors, survival and treatment method was gathered. Evaluation of time-varying clin-

ical parameters such as stage of the disease (stage III or IV), affected sites, performance status, menopausal status in women and biochemical parameters was performed when diagnosing inoperable metastasis or disqualifying from surgical treatment. For each patient not only basic epidemiological information was recorded, such as age, sex, and the date of histological diagnosis, but also the date of dissemination of the disease (or qualifying changes as inoperable) and date of possible death.

The disease stage was assessed on the basis of the medical reports of clinical and imaging examinations (chest/bone X-ray, bone scan, ultrasonographic tests and CT/MR scans). No PET examinations were performed. In single cases additional data were provided by histological and cytological tests of the material obtained during diagnostic procedures (trepano-biopsy, cerebrospinal fluid collection, palliative resections). In the case of metastasis from an unknown primary melanoma, the date of diagnosis was treated as the date of metastasis.

Any form of systemic therapy used by an oncologist which is not standard symptomatic/supportive care was taken as systemic treatment (analgesics, treatment of non-oncological comorbidities, typical symptomatic treatments, e.g. administering dexamethasone in brain oedema, were excluded). Some forms of treatment with questionable efficacy, e.g. hormonal therapy with tamoxifen and medroxyprogesterone, were classified as systemic treatment. This is justified by the fact that, for the time being, there are no data from randomized clinical trials confirming the influence of any form of systemic treatments including dacarbazine (and excluding anti-CTLA4 and BRAF inhibitors) on overall survival in the entire group of patients with metastatic melanoma. The following active drugs were used in monotherapy or in multidrug regimens: dacarbazine (DTIC), carmustine (BCNU), vincristine, vinblastine, cisplatin, carboplatin, cyclophosphamide, dactinomycin, methotrexate, 5-fluorouracil, bleomycin, temozolomide, paclitaxel, tamoxifen, medroxyprogesterone, interleukin-2, interferon α -2b.

The kind of systemic treatment was classified in one of the following categories [15, 17, 18, 41]: DTIC monotherapy, multidrug chemotherapy with DTIC, multidrug chemotherapy without DTIC, immunotherapy, hormonal therapy, or other monotherapy (without DTIC). Single cases of chemoinmunotherapy (chemotherapy + interleukin-2) were classified as multidrug chemotherapy with respect to simultaneously used cytostatics (multidrug chemotherapy with or without DTIC), because it would be necessary to create an additional (small) category of treatment.

Response to treatment was evaluated according to RECIST – Response Evaluation Criteria in Solid Tumors v. 1.0. The assessment of toxicity in all cases was based on CTCAE – Common Terminology Criteria for Adverse Events v. 3.0. In all cases adverse symptoms from respective organs and systems are scored on a four-point scale (1–4). All forms of excision of metastatic lesions in patients with distant metastasis of melanoma were considered as palliative resection. Those were most commonly resections within soft tissues, brain, gastrointestinal tract, and in a few cases resections of metastatic changes from lungs or liver. Radiotherapy of dis-

tant metastases (mainly in central nervous system and skeletal system) were considered palliative radiotherapy.

Statistical analysis

Descriptive analysis was performed; averages and standard deviations, and medians and values for numerical variables as well as category rate distribution for categorical variables were given. For comparison of distribution of categorical variables between groups the chi-square test was used, and in smaller groups in four-field tables, Fisher's exact test. The overall survival (OS) was counted from the date of diagnosis of unresectable metastases in stage III/IV to the date of death, and in patients who lived after the end of the test (censored observations) to the date of the last follow-up. The date of starting the first cycle of the next treatment was taken as the starting date to calculate the time to progression after every line of therapy. The date of progression was adopted as the ending date (uncensored observations), or, if not exactly known, the date of introducing the next line of treatment or the date of the patient's death. In censored observations (patients who did not die and had no features of progression during the last visit) the date of the last follow-up is the end date.

The survival curves, the survival time median with confidence interval and 6-month, 1-, 2-, and 3-year survivals were estimated by Kaplan-Meier's method. Because of the low rate of patients who survived and were observed for a longer time, no rate of patients who survived over 3 years was assessed for overall survival estimations, as well as patients who survived over 2 years in case of progression after successive lines of treatment.

The univariate analysis of factors having an influence on overall survival was performed by comparing survival curves

with the log-rank test, and in the case of non-parallel curves the *p* values for Wilcoxon's test were also given (differences in the initial parts of a curve). Independent prognostic factors having an influence on the survival time were searched for with multivariate analysis using the Cox proportional hazards regression model including factors with a *p*-value ≤ 0.1 in univariate analysis. None of the tested factors diverged substantially from the assumption of parallel curves. Both statistically significant factors and those which changed the other parameters' values were included within the model using the backward selection method. Also statistically significant interactions between the variables were included in the model. Differences were considered statistically significant if *p*-values were < 0.05 . The statistical analysis was performed with SAS v. 9.1 software.

Results

In the entire analysed group the median overall survival (OS) was 7.1 months (95% CI: 6.7–7.9); 1-, 2-, and 5-year OS rates were 32.3%, 12.5%, and 3.9%, respectively (Fig. 1).

Univariate analysis for OS

The results of the univariate analysis for individual variables are shown in Table 1. The variables having a significant impact on OS were: sex, age at the time of diagnosis of unresectable metastases in women, initial activity of lactate dehydrogenase (LDH) (Fig. 2), ALAT and AspAT in serum, initial number of affected sites (organs), metastases in lungs and liver, performance status (Fig. 3), disease stage according to the AJCC/UICC (American Joint Committee on Cancer/International Union Against Cancer) staging system, type of first-line treatment, response to first-line treatment (Fig. 4), num-

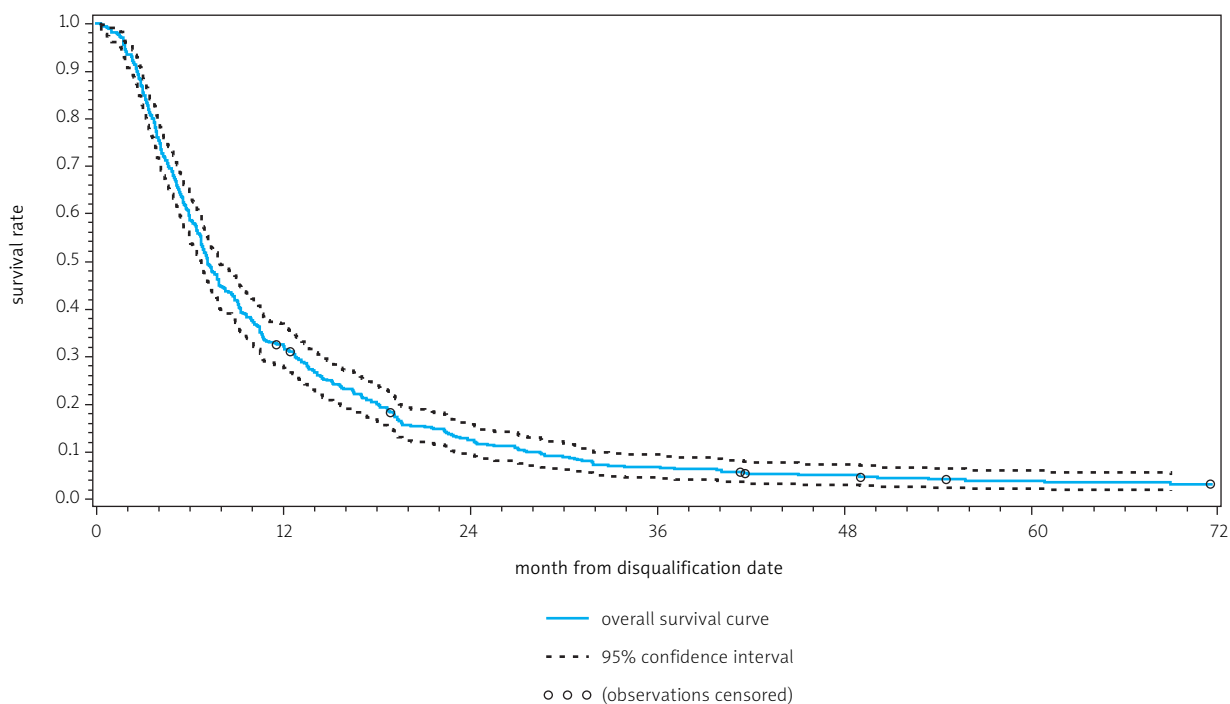


Fig. 1. OS curve for the whole group of patients diagnosed with advanced melanoma ($n = 427$)

Table 1. Results of single-factor analysis with estimated number of surviving patients depending on variable option

Tested variable	Variable option	N	Median in months	95% CI for median	1-year survival [%]	2-year survival [%]	5-year survivals [%]	P value (significance of difference for all survival curves)
whole group		427	7.1	6.7–7.9	32.3	12.5	3.9	
center	Cracow	177	7.1	6.7–9.0	30.5	10.7	3.2	0.9702
	Warsaw	250	7.1	6.3–8.2	33.6	13.8	4.4	
sex	female	191	10	7.8–12.7	44.5	20.0	6.6	< 0.0001
	male	236	6.5	5.8–7.0	22.5	6.5	1.7	
menopause	yes	85	12.7	8.8–15.1	51.8	24.7	8.6	0.0812
	no	105	7.8	6.4–10.2	38.1	15.4	4.9	
age at removing primary change (in years)	< 30	35	6.1	3.4–9.2	28.6	8.6	ne	0.357
	30+	392	7.1	6.7–8.0	32.7	12.9	4.0	
age at disqualification from radical treatment or distant metastasis (in years)	< 30	34	5.4	3.3–9.1	26.5	5.9	ne	0.2049 (log-rank) 0.0357 (Wilcoxon)
	30+	393	7.1	6.7–8.0	32.8	13.1	4.0	
age at disqualification from radical treatment or distant metastasis – among females (in years)	< 30	15	5.7	3.3–7.8	20	ne	ne	0.0029
	30+	176	10.6	8.2–12.9	46.6	21.7	7.1	
age at disqualification from radical treatment or distant metastasis (in years)	< 30	34	5.4	3.3–9.1	26.5	5.9	ne	0.0589
	30–< 50	159	6.4	5.6–7.2	27.7	10.7	1.3	
	50+	234	7.8	7.1–9.6	36.3	14.7	5.7	
age at disqualification from radical treatment or distant metastasis – among females (in years)	< 30	15	5.7	3.3–7.8	20.0	ne	ne	0.0008
	30–< 50	78	7.6	6.0–10.6	37.2	13.7	2.7	
	50+	98	12.8	10.4–15.6	54.1	28.1	10.6	
time from diagnosis to metastasis (in months)	< 36	339	6.8	6.3–7.8	30.4	10.9	3.9	0.1289 (log-rank) 0.0490 (Wilcoxon)
	≥ 36	88	8.4	7.2–11.3	39.8	18.8	3.9	
disease duration before diagnosis of melanoma metastasis	after primary source excision	124	6.8	5.7–9.3	31.5	15.3	3.0	0.114
	after regional lymph node metastasis	277	7.1	6.5–7.8	31.0	10.4	3.7	
	metastasis during diagnosis	26	12.4	7.5–19.1	50.0	21.6	ne	
metastasis during diagnosis	no	401	7	6.5–7.8	31.2	11.9	3.6	0.0599
	yes	26	12.4	7.5–19.1	50.0	21.6	ne	
metastasis from unknown primary source	no	398	7	6.4–7.8	31.4	12.0	3.6	0.0935
	yes	29	10.8	7.1–18.8	44.8	19.4	ne	
ECOG	0	194	9	7.8–10.0	38.1	17.2	4.9	< 0.0001
	1	177	6.7	5.6–7.8	31.1	8.6	2.7	
	2	49	4.6	2.9–6.9	16.3	9.7	ne	
	3	6	1.8	1.4–4.3	ne	ne	ne	
baseline LDH activity in serum	normal	191	9.6	7.6–11.5	42.9	17.9	6.4	< 0.0001
	elevated	145	5.2	4.2–6.4	19.3	5.7	1.4	
baseline AlAT activity in serum	normal	289	7.4	6.7–9.1	34.6	13.3	5.1	0.002
	elevated	64	5.6	4.3–7.2	21.9	7.8	ne	
baseline AspAT activity in serum	normal	301	7.5	6.8–9.1	35.5	13.8	4.9	< 0.0001
	elevated	53	5.1	3.7–7.0	13.2	3.8	ne	
baseline HbG level	normal	312	7.3	6.7–9.0	36.5	13.9	4.8	0.1557
	reduced	68	6.5	5.7–8.5	20.6	5.9	2.9	
number of involved loca- tions (organs) at the time of disqualification from radical treatment	1	172	7.9	7.0–9.6	34.9	15.7	6.1	0.0335
	2	213	6.7	5.5–7.3	30.0	9.5	ne	
	3 or > 3	38	8.6	5.6–11.3	34.2	15.8	2.6	

Table 1. cont.

Tested variable	Variable option	N	Median in months	95% CI for median	1-year survival [%]	2-year survival [%]	5-year survivals [%]	P value (significance of difference for all survival curves)	
location of metastasis at the moment of disqu- alification from radical treatment	soft tissues	no	232	6.9	6.3–7.8	28.0	9.6	3.2	0.0902
		yes	190	7.2	6.5–9.1	35.8	15.3	4.8	
	nodes	no	273	7.1	6.4–7.9	30.0	12.5	3.9	0.5814
		yes	149	7.1	6.4–9.1	34.2	11.6	4.1	
	lungs	no	249	7.8	7.0–9.5	36.5	15.4	5.1	0.0029
		yes	173	6.3	5.2–7.1	24.3	7.5	2.5	
	liver	no	339	7.1	6.7–8.3	33.6	12.8	4.7	0.0244
		yes	83	6.2	4.6–7.9	22.9	9.6	ne	
	bones	no	399	7	6.7–7.8	31.6	12.1	4.2	0.4725
		yes	23	7.2	2.9–9.8	30.4	ne	ne	
	CNS	no	400	7.1	6.6–7.8	31.5	12.2	4.2	0.8925
		yes	22	7.8	4.8–13.1	31.8	11.4	ne	
	other	no	341	7.1	6.7–7.9	31.4	12.1	3.8	0.9380
	yes	81	6.2	4.9–9.6	32.5	13.5	ne		
	liver/lungs	no	188	8.4	7.1–10.7	39.4	16.7	6.2	< 0.0001
	only in one location	212	6.7	5.7–7.8	26.9	9.0	2.3		
	in both locations	22	4.2	2.5–7.2	9.1	ne	ne		
stage according to AJCC/UICC	3	24	12.6	7.1–22.6	54.2	25	ne		
	4a	36	13.7	9.2–22.6	58.3	30.6	11.1	0.0029	
	4b	41	7.1	5.8–10.5	26.8	8.0	ne		
	4c	311	6.7	5.9–7.4	28.9	10.3	3.0		
stage according to AJCC/UICC	3	24	12.6	7.1–22.6	54.2	25.0	ne	0.0049	
	4	364	6.9	6.3–7.5	29.9	11.1	3.2		
first-line treatment (detailed division)	DTIC	80	9.8	7.4–13.0	43.8	22.5	11.6		
	multidrug with DTIC	302	6.7	5.9–7.4	29.1	9.9	2.4		
	multidrug without DTIC	9	6	3.9–9.0	11.1	ne	ne	0.0004	
	immunotherapy	4	19.6	10.7–22.5	75	ne	ne		
	hormonal therapy	25	9.3	6.2–15.6	40	20.0	ne		
	other monotherapy	7	4.1	1.4–7.1	ne	ne	ne		
first-line treatment (overall division)	chemotherapy	398	7.1	6.6–7.8	31.7	12.2	4.3		
	immunotherapy	4	19.6	10.7–22.5	75	ne	ne	0.3832	
	hormonal therapy	25	9.3	6.2–15.6	40	20.0	ne		
first-line treatment response	PD	150	4.1	3.7–4.6	9.3	2.7	0.6		
	SD	193	7.9	7.3–9.9	37.3	13.9	2.1	< 0.0001	
	CR + PR	82	17	12.9–18.7	62.2	27.7	14.2		
number of lines of treatment	1	251	5.7	5.1–6.4	22.7	11.5	4.80		
	2	126	8.2	7.1–10.5	38.1	8.3	ne	< 0.0001	
	3	36	13.9	10.5–18.0	61.1	25.0	ne		
	4+	14	17.2	12.9–31.9	85.7	ne	ne		
number of drugs used in the first-line treatment regimen	1	116	9.4	7.4–12.5	42.2	20.2	7.7		
	2–3	82	6.3	4.8–7.9	26.8	2.6	ne	0.0002	
	4+	229	6.7	5.8–7.8	29.3	12.1	ne		
palliative radiotherapy	no	282	6.7	5.9–7.1	26.6	9.2	ne		
	yes	139	9.8	7.5–12.0	42.4	18.3	4.0	0.0026	
palliative resections	no	342	6.7	6.0–7.1	27.8	9.7	2.9		
	yes	77	12.5	9.2–14.8	50.6	24.0	7.6	0.0004	
dacarbazine in monotherapy	1000 mg i.v. 1 day every 3 w	49	7.4	6.7–10.5	32.7	14.3	7.7		
	250 mg i.v. 1–5 days every 4 w	31	17.3	10.0–25.5	64.5	35.5	17.2	0.0309	

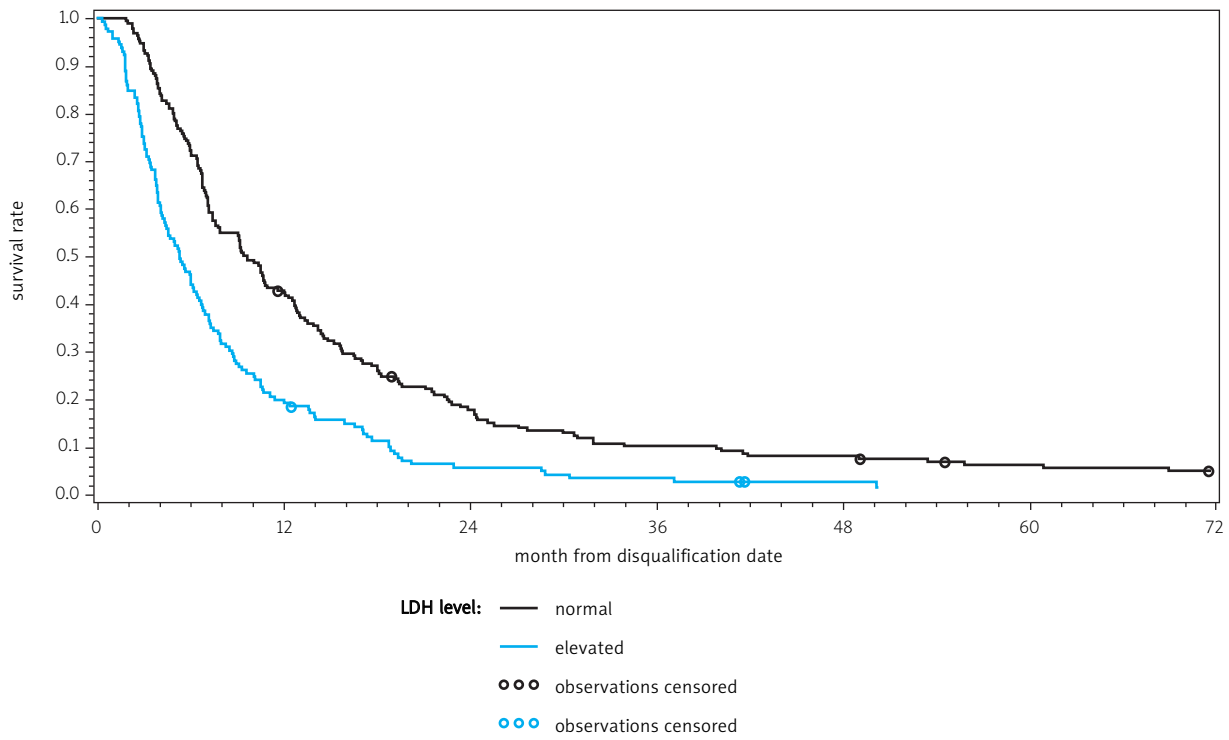


Fig. 2. OS curves in relation to baseline LDH activity in serum ($p < 0.0001$)

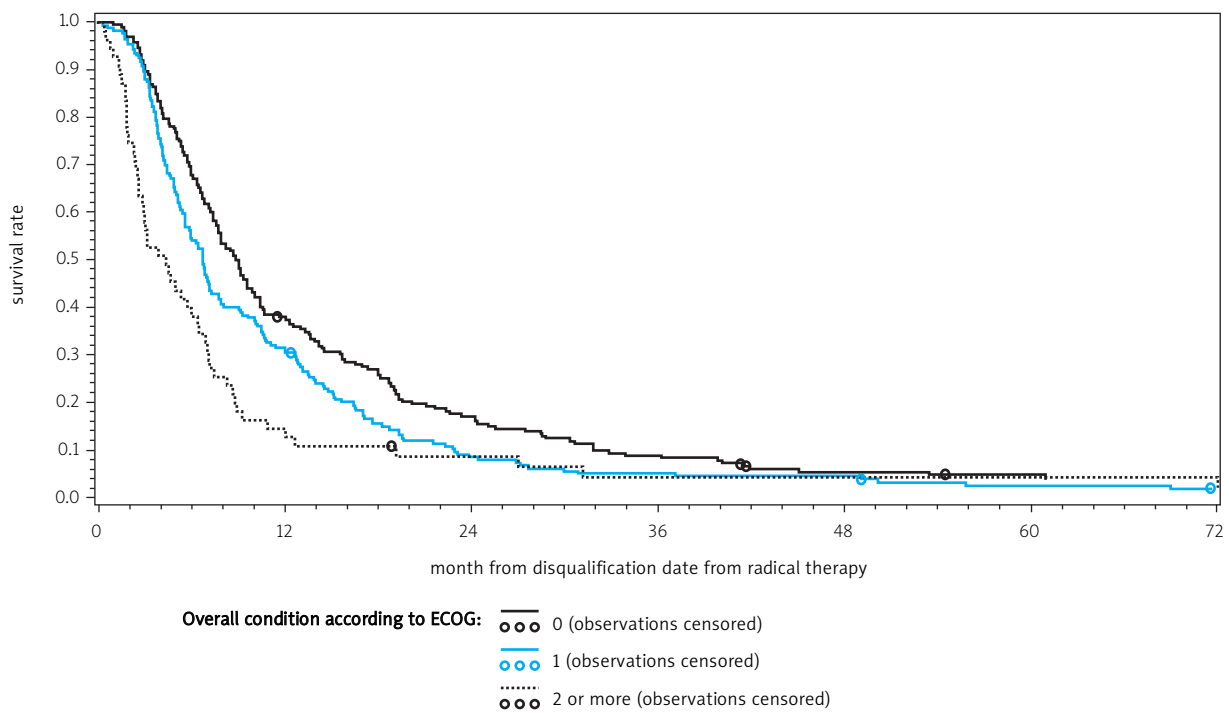


Fig. 3. OS curves depending on patient's general condition (ECOG) ($p < 0.0001$)

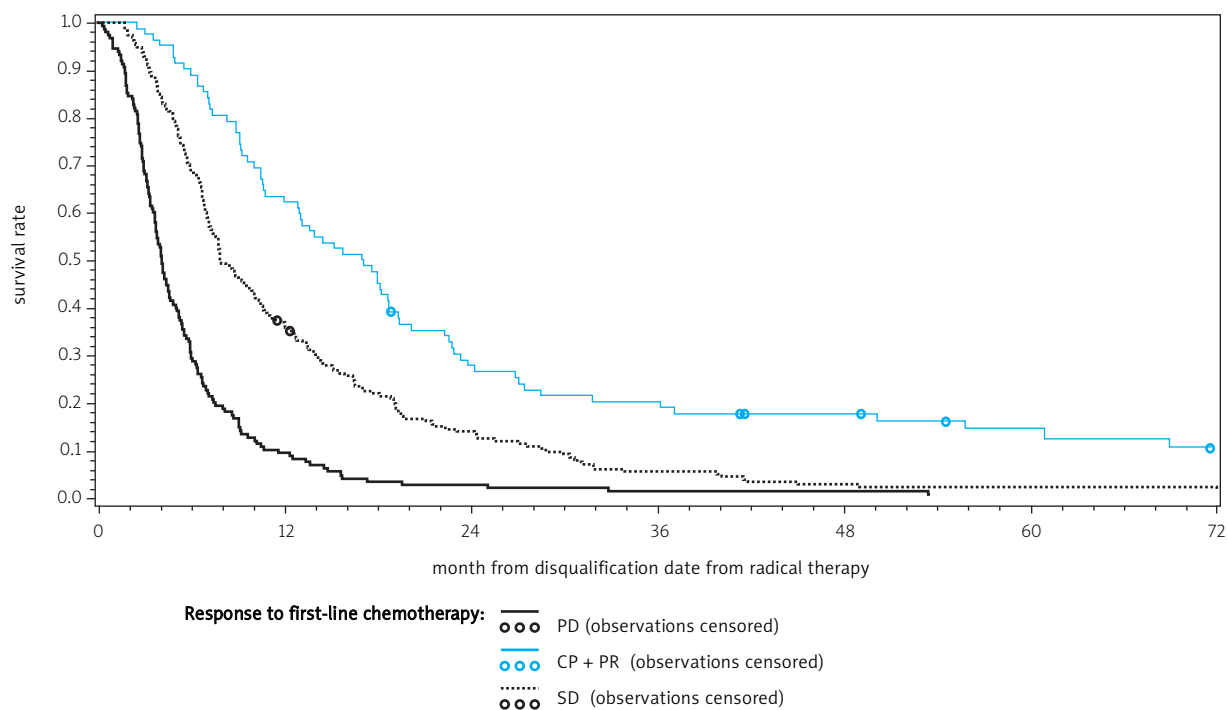


Fig. 4. OS curve in relation to first-line treatment response ($p < 0.0001$)

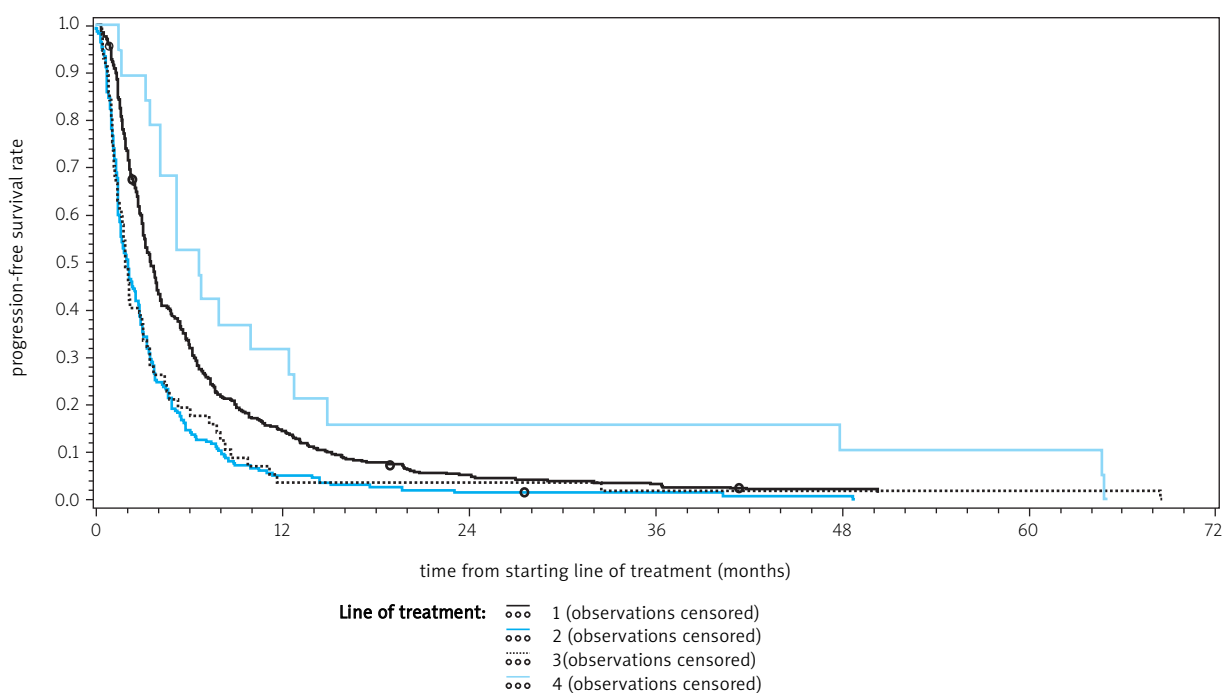


Fig. 5. Curves depicting PFS after successive lines of treatment

Table 2. Responses to treatment in successive lines

Type of treatment	CR N (%)	PR N (%)	SD* N (%)	PD N (%)	No data N	All N
Responses to first-line treatment depending on therapy type						
all	26 (6.1)	55 (13.0)	193 (45.5)	150 (35.4)	3	427
DTIC chemotherapy	8 (10.0)	8 (10.0)	34 (42.5)	30 (37.5)	0	80
multidrug chemotherapy with DTIC	18 (6.0)	41 (13.6)	143 (47.5)	99 (32.9)	1	302
multidrug chemotherapy without DTIC	0	1 (11.1)	1 (11.1)	7 (77.8)	0	9
immunotherapy	0	0	2 (66.7)	1 (33.3)	1	4
hormonal therapy	0	3 (12.0)	12 (48.0)	10 (40.0)	0	25
other monotherapy	0	2 (33.3)	1 (16.7)	3 (50.0)	1	7
Responses to second-line treatment depending on therapy type						
all	2 (1.0)	11 (5.6)	42 (21.2)	141 (72.1)	6	202
DTIC chemotherapy	0	1 (11.1)	1 (11.1)	7 (77.8)	0	9
multidrug chemotherapy with DTIC	0	6 (7.3)	16 (19.5)	60 (73.2)	0	82
multidrug chemotherapy without DTIC	1 (6.3)	0	8 (50.0)	6 (43.8)	1	16
immunotherapy	0	0	2 (50.0)	2 (50.0)	1	5
hormonal therapy	1 (1.5)	3 (4.5)	14 (21.2)	47 (72.7)	3	69
other monotherapy	0	1 (5.0)	1 (5.0)	18 (90.0)	1	21
Responses to third-line treatment depending on therapy type						
all	1 (1.85)	2 (3.7)	16 (29.64)	35 (64.81)	6	60
DTIC chemotherapy	0	0	1 (33.33)	2 (66.67)	0	3
multidrug chemotherapy with DTIC	1 (4.55)	1 (4.55)	8 (71.65)	12 (54.55)	2	24
multidrug chemotherapy without DTIC	0	0	6 (42.86)	8 (57.14)	1	15
immunotherapy	0	0	1 (33.33)	2 (66.67)	1	4
hormonal therapy	0	0	0	5 (100.0)	1	6
other monotherapy	0	1 (14.3)	0	6 (85.71)	1	8
Responses to fourth-line treatment depending on therapy type						
all	0	2 (11.0)	6 (33.3)	10 (55.6)	2	20
DTIC chemotherapy	0	0	0	0	0	0
multidrug chemotherapy with DTIC	0	1 (20.0)	2 (40.0)	2 (40.0)	0	5
multidrug chemotherapy without DTIC	0	0	1 (25.0)	3 (75.0)	0	4
immunotherapy	0	0	2 (100.0)	0	0	2
hormonal therapy	0	1 (50.0)	0	1 (50.0)	2	4
other monotherapy	0	0	1 (20.0)	4 (80.0)	0	5

ber of lines of treatment, number of used drugs in the first-line treatment regimen, use of palliative radiotherapy and palliative resections.

Analysis of the applied systemic treatment

Because of the widely discussed impact of systemic treatment on OS, and no definite answer on the effectiveness of the applied therapy in treating metastatic melanomas, a detailed analysis of the applied treatment (Table 2) and its influence on OS was performed. We assessed the possible impact of the number of treatment lines, the number of drugs in the first-line regimen and the kind of therapy used in first-line treatment. Longer survival of patients who received more lines of treatment may be related to survival bias, which means that the person had to live until the next lines, and so by assumption lived longer. However, it is worth noting

that in the majority of patients the treatment was changed after 2–3 cycles due to progression or complications, which also influenced the relationship between OS and number of treatment lines. The multidrug therapies containing dacarbazine were used the most often, both the first and the second line of treatment. The less numerous group of patients was treated with dacarbazine in monotherapy or with hormonal therapy. It can be concluded from the analysis that the best therapeutic choice in the first line of treatment within the tested group was dacarbazine in monotherapy.

Also the influence of the responses to the first-line treatment on OS was assessed. A statistically significant influence of the responses to the treatment on OS was demonstrated.

We also found that the rates of objective responses (CR + PR) drop, and they equal 19.1% in the first line, 6.6% in the second line, and 5.6% in the third line.

Table 3. Influence of clinical factors on progression-free survival after first line of treatment (in months)

Factor	Variable option	N	N progression	Average	Median	95% CI for median	p value
whole group		427	417	6.9	3.5	3.1–3.8	
type of first-line therapy	DTIC	80	75	10.1	5.5	3.8–6.4	0.0007
	multidrug with DTIC	302	297	6.2	3.2	3.0–3.7	
	multidrug without DTIC	9	9	3	1.7	1.5–2.0	
	immunotherapy	4	4	7.8	7.2	3.1–13.6	
	hormonal therapy	25	25	9.5	5.8	3.0–9.2	
other monotherapy	7	7	2.6	2.9	1.4–4.0		
center	Cracow	177	175	6.5	3.5	3.1–4.1	0.73
	Warsaw	250	242	7.1	3.5	3.0–3.9	
sex	female	191	183	8	3.8	3.5–5.6	0.0012
	male	236	234	5.7	3.2	3.0–3.8	
disqualification age (in years)	< 30	34	33	4.5	2.5	1.8–3.9	0.1392
	30+	393	384	7	3.7	3.2–4.0	
state at melanoma diagnosis	no metastasis	401	392	6.8	3.5	3.1–3.8	0.3279
	metastasis	26	25	7.1	5.3	3.9–7.4	
LDH level at disqualification	normal	191	184	8.2	3.9	3.4–5.2	0.0005
	elevated	145	144	5.1	3.1	2.5–3.8	
AspAT level at disqualification from radical therapy	normal	301	293	7.2	3.7	3.2–4.1	0.0116
	elevated	53	53	4.5	2.9	1.9–3.8	
AlAT level at disqualification from radical therapy	normal	289	281	7.3	3.7	3.2–4.1	0.0271
	elevated	64	64	4.7	3	2.1–3.9	
haemoglobin level from radical therapy initial	normal	312	303	7.2	3.7	3.2–4.0	0.2633
	reduced	68	67	5.9	3.1	2.7–4.2	
lung metastasis	no	249	242	6.9	3.8	3.4–4.8	0.0808
	yes	173	170	6.2	3	2.6–3.7	
liver metastasis	no	339	329	7.2	3.5	3.1–3.9	0.0296
	yes	83	83	4.8	3.2	2.6–4.0	
soft tissue metastasis	no	232	228	6.2	3.2	3.0–3.8	0.1129
	yes	190	184	7.2	3.8	3.2–4.6	
lymph nodes metastasis	no	273	265	6.9	3.5	3.0–3.8	0.9663
	yes	149	147	6.2	3.7	3.1–4.7	
CNS metastasis	no	400	391	6.6	3.5	3.0–3.8	0.1646
	yes	22	21	9.1	4.4	3.2–9.0	
bone metastasis	no	399	389	6.8	3.7	3.2–3.9	0.2506
	yes	23	23	5.6	2.3	1.8–3.0	
other metastasis	no	382	372	6.8	3.5	3.1–3.9	0.8115
	yes	40	40	6	3.6	2.2–5.5	
patient performance status according to ECOG scale	0	194	187	7.9	3.8	3.3–5.4	0.0006
	1	177	175	6.5	3.5	3.1–4.1	
	2	49	48	4.1	2.2	1.8–3.2	
	3	6	6	2.7	1.6	1.4–3.5	
stage according to AJCC/UICC staging	3	24	20	11.7	6.6	3.5–11.2	0.0076
	4a	12	12	9.1	6.6	2.1–13.0	
	4b	41	41	7.6	3.7	2.4–5.5	
	4c	311	307	5.7	3.3	3.0–3.7	

Univariate analysis for progression-free survival

The median progression-free survival (PFS) after the first line of treatment was 3.5 months (95% CI: 3.1–3.8) for the whole group of patients, and the 6-month PFS rate was 31.8%. We identified the following factors significantly influencing

PFS during the first-line treatment: type of therapy (Fig. 5), sex, initial level of LDH, AspAT, AlAT in serum, metastases to the liver, patient's performance status according to the ECOG scale and staging according to AJCC/UICC (Table 3). The PFS medians after the 1st, 2nd, and 3rd line of systemic treatment

Table 4. Multi-factor analysis of results for the whole group

Factor		Chi-Square	Pr > χ^2	Hazard ratio	95% Hazard ratio confidence limits	
age of disqualification from radical therapy among females	30–50 years vs. < 30 years	0.1916	0.6616	1.60	0.817	1.376
	≥ 50 years vs. < 30 years	17.8753	< 0.0001	0.576	0.446	0.744
age of disqualification from radical therapy among males	30–50 years vs. < 30 years	2.3173	0.1279	1.220	0.944	1.575
	≥ 50 years vs. < 30 years	1.352	0.1755	1.178	0.929	1.494
LDH level	elevated vs. N	16.8556	< 0.0001	1.697	1.318	2.184
AspAT level	elevated vs. N	9.737	0.0023	1.709	1.210	2.413
ECOG	≥ 2 vs. 0–1	15.6371	< 0.0001	2.034	1.431	2.893
first-line treatment	multidrug with DTIC vs. mono DTIC	8.7797	0.0030	1.349	1.107	1.644
	hormonal therapy vs. mono DTIC	1.200	0.1773	0.631	0.323	1.232
palliative resections	Y vs. N	3.9347	0.0473	0.733	0.539	0.996
palliative radiotherapy	Y vs. N	4.1804	0.0409	0.773	0.604	0.989
mestastasis during diagnosis	Y vs. N	5.1636	0.0231	0.569	0.350	0.925
metastasis from unknown primary source	Y vs. N	7.7595	0.0053	0.377	0.190	0.749

were 3.5, 2.0, 1.8, respectively. A trend for shortening of the PFS after successive lines of systemic treatment is visible.

The PFS after successive lines of treatment is shown graphically in Figure 2. The PFS length after the fourth line may be thought-provoking, but because of the small size of the group it does not seem meaningful, or it is a group of patients with natural long course of disease.

Multivariate analysis for OS

The variables showing an independent influence on OS in the constructed model are shown in Table 5. Due to the scarcity of groups receiving respective types of therapy in the first line of treatment, it was decided to include only the largest groups in the multivariate analysis – those treated with dacarbazine in monotherapy or multidrug schemes with dacarbazine and hormonal therapy.

The variables independently influencing overall survival were: initial serum LDH level, initial serum aspartate transaminase (AspAT) level, initial performance status (ECOG), the type of first-line treatment used, women's age, metastases at the time of diagnosis, metastases from an unknown primary site, using palliative radiotherapy and palliative resections.

Treatment toxicity

The most common grade 3 and 4 adverse events were haematological disturbances (anaemia, thrombocytopenia, neutropenia), nausea and vomiting. Both haematological and non-haematological complications were found more commonly in multidrug chemotherapy with DTIC. In 9.5% of patients the complications resulted in premature treatment termination.

Discussion

Melanomas at the inoperable/metastatic stage are still incurable, and lead to death within a few months. In routine

practice various kinds of therapy have been used, whose effectiveness is not always confirmed in clinical trials. The basic assessed parameter in the analysed large group of 437 patients was overall survival. The median OS in the whole analysed group was 7.1 months, with 1-, 2-, and 5-year survival rates of 32.3%, 12.5% and 3.9% respectively. Similar results were obtained by different authors who analysed overall survival of patients with inoperable, metastatic melanomas, with median OS ranging from 5.6 to 8.1 months [6, 7, 23, 26–29]. In a meta-analysis of 83 research projects of stage II performed in the years 1974–1999 (6322 patients) [29] the OS median was 8.1 months, and 2- and 5-year survival rates were 13.6% and 2.3% respectively. It is worth noting the significant differences between median OS before and after 1985: 5.8 and 8.9 months respectively. When taking confidence intervals for OS in the discussed analysis into consideration, the results of our group are fully within their range, which confirms the representativeness of the group.

A number of clinical factors which may affect OS in the patient group were analysed. In univariate analysis male sex proved to be a factor related to worse prognosis, which was not, however, confirmed in multivariate analysis. In some published studies male sex was a factor related to worse prognosis [6, 10, 26, 27, 32] (especially when assessing patients' survival in stages I-III), while in other works such a correlation was not confirmed [5, 13, 25, 28, 30, 31, 33–35]. We did not find an influence on OS by overall patient's age at the time of metastasis or by period of time between the melanoma diagnosis and metastases. However, we found a trend for worsening prognosis for younger patients and those whose metastasis has happened in a shorter time since the diagnosis. In the available literature, excluding a few works in which a positive influence of the time period before metastasis on OS was found [7, 35], this parameter was not statistically significant [5, 6, 10, 31–33]. Multivariate analysis also

showed that the patients already diagnosed with metastasis have better prognosis (analysing only stage IV) than those patients whose metastasis occurred after removing the primary source or metastasis to lymph nodes. A similar correlation occurred between patients with metastasis from an unknown primary site and patients with established diagnosis of cutaneous melanoma. The fact is confirmed by other studies regarding outcomes of melanomas from an unknown primary site [36–39]. Another important factor is patient general status according to ZUBROD/ECOG/WHO scales at the time of therapy initiation. It has to be underlined that worsening patient's condition is connected with occupying vital organs, which results in worse prognosis for the group. In the present study we found, both in uni- and multivariate analysis, a statistically significant correlation between shortening of OS and decreasing patient's performance status (PS 0-1 vs. ≥ 2) [5, 6, 10, 27, 28, 31–33]. In assessed biochemical tests a substantial influence on OS was shown in univariate analysis for LDH, AspAT and AlAT level in serum, and multi-factor analysis confirmed a relation between increased LDH and AspAT levels with shorten OS. Elevated lactate dehydrogenase (LDH) activity in serum is a negative prognostic factor, which was confirmed by several studies [5, 6, 23, 25, 26, 31]. In the TNM melanoma staging published by AJCC in 2001, elevated LDH level in serum was introduced to the stage IV melanoma classification, assigning patients to the category with the worst prognosis (IVc), which was the most important change in the metastatic melanoma categories in relation to the previous TNM staging [40]. However, the real biological meaning of elevated LDH activity in patients with advanced melanoma is still not fully understood. Another important factor affecting OS was the number of involved organs, which was not confirmed by multivariate analysis. The fact may be justified by the strong correlation between the number of occupied sites with bad prognosis and general condition, which often causes this variable to be excluded from multivariate analysis models. In uni- and multivariate analyses some authors have confirmed the influence of involved organs on the OS [6, 23, 27, 35]. The localization of metastases is also an important prognostic factor. Data from the literature suggest that the most common locations of the first melanoma metastases are skin, subcutaneous tissues and lymph nodes – 59%, lungs – 36%, liver – 20%, bones – 17%, and brain – 20% [24]. The frequency of a particular location as the place of first metastasis was similar in the discussed material. In a series of studies it was demonstrated that visceral metastases are an independent factor which worsens the prognosis [10, 28, 35]. Similarly, in meta-analyses [40] which were basis for TNM staging, a considerable difference in OS between the group with involved nodes and soft tissues, and the group with occupied visceral organs and lungs was found. Also in the present study a statistical significance between particular sub-groups in stage IV was demonstrated. It is to be noted, however, that the differences in OS between particular groups are small. In the tested group the metastasis sites having a negative influence on OS in univariate analysis were lung and liver. This relationship was not confirmed in the multivariate analysis. In the literature, the most common negative factors for OS were metastases to the liver and/or brain

[5, 6, 10, 26–28, 33, 41, 42]. Some authors have also reported a negative influence of metastases in lungs [6, 26, 41], bones [6], skin and soft tissues [6]. Table 5 summarizes the most important studies analysing the influence of various factors on OS.

We have demonstrated, both in uni- and multivariate analyses, a statistically significant lengthening of OS in patients undergoing palliative resections. Performing palliative resections of metastases in carefully selected patients has an influence on OS documented in some studies, with the resections of single brain metastases especially positively impacting OS [27, 43, 44]. Also performing palliative radiotherapy has lengthened the OS in the analysed group. This relationship may be connected with the type of radiotherapy or with its wider use in curing brain metastases. In our study the influence of performed systemic treatment on the OS was demonstrated both in single- and multi-factor analyses. The relationship is worth underlining, as in already performed randomised clinical trials comparing different types of systemic treatment, none of these types of therapy showed significant benefits in terms of OS as compared to dacarbazine (DTIC) [11, 18, 20, 21, 45–50]. We have compared OS curves for all types of first-line treatment. In univariate analysis patients treated in the first-line with dacarbazine in monotherapy demonstrated the longest OS and PFS. In multivariate analysis a statistically significant longer OS in patients treated with DTIC in monotherapy was confirmed. However, it is worth noting that these results may be biased by several factors as no random choice of patients was used in any of the analysed groups, and the choice of the therapy depended on the doctor assigning patients to the treatment and on the current trends. The heterogeneity of the used drug regimens also must be stressed – CVD (cisplatin, vinblastine, DTIC), Dartmouth scheme (cisplatin, carmustine, DTIC, tamoxifen), biochemotherapy with interleukin 2 and/or interferon, and in single cases other drug combinations. The important fact is that multidrug therapy is used mostly in younger patients, those with higher stages, or those with visceral organ metastases, which may explain the better results of DTIC monotherapy. In already published randomized clinical trials and meta-analyses, no influence on OS was proven in patients treated with tamoxifen in monotherapy or in combinations with other drugs [47, 49–53]. Only one test showed a positive influence on OS of tamoxifen with dacarbazine over DTIC monotherapy [54]. Currently, using tamoxifen is not recommended in treating advanced metastatic melanoma patients. Dacarbazine has been invariably used in treating advanced melanomas since the 1970s, despite lack of randomized trials confirming its influence on OS. Despite such long use, dacarbazine has no definitely recommended standard dosage. The drug is used in a 220–250 mg/m² dose for 4–5 days every 3–4 weeks, as well as in a 800–1000 mg/m² dose every 3 weeks [11]. There are no objective studies comparing both schemes. One of the basic factors analysed in most clinical trials is assessment of the response to applied systemic treatment. It was believed that increasing the rate of objective responses would directly influence OS. According to our data such a relationship was observed in the whole group of patients, but it was not

Table 5. Summary of research analysing prognostic factors in the group of patients with metastatic melanomas

Research	Time of treatment	Number of patients	OS – median (in months)	PFS – median (in months)	Factors influencing OS negatively in multi-factor analyses
Presant [33]	1974–1978	277	6.0	ne	– male sex – worse general condition – occupied liver – metastases in locations outside bone
Balch [35]	1955–1983	200	6.0	ne	– higher number of involved locations (organs) – metastases in parenchymal organs – shorter metastasis time
Ryan [41]	1975–1985	629	5.5	ne	– male sex – worse general condition – metastases in locations other than soft tissues and nodes – higher number of involved (without bone) locations (organs) – worse response to the treatment – clinical symptoms (appetite loss, nausea/vomiting, no fever)
Eton [23]	1979–1989	318	8.0	ne	– male sex – involvement of ≥ 2 parenchymal organs – elevated LDH level – hypoalbuminemia
Sirrot [26]	1984–1991	284	7.4	ne	– male sex – metastases in parenchymal organs – elevated LDH level – decreased albumin level – thrombocytopenia
Falkoson [42]	1972–1992	236	6.3	ne	– worse general condition – progression-free survival – type of therapy (DTIC + IFN vs. DTIC, fotemustine vs. other drug)
Barth [7]	1971–1993	1521	7.5	ne	– metastases in bones, liver, brain or lungs – shorter time to metastasis – primary illness stage
Keiholz [55]	before 1994	681	10.5	ne	– worse general condition – metastases location – elevated LDH level
Flaherty [28]	1982–1995	813	5.6	ne	– worse general condition – more than one involved location (organ) – higher number of involved locations (organs) – liver involvement – time of metastasis
Brand [44]	1976–1996	442	7.0	ne	– worse general condition – brain or skin metastases – more than one involved location (organ) – subsequent metastases – palliative resections
Manola [12]	1975–1998	1362	6.4	ne	– male sex – worse general condition – more than one involved location (organ) – metastases in parenchymal organs, lungs – worse response to treatment – precious immunotherapy (better prognosis) – elevated LDH level – elevated alkaline phosphatase level – thrombocytopenia
Korn [16]	1975–2005	2100	6.2	1.7	– male sex – worse general condition – metastases in parenchymal organs – metastases in brain
Minor [50] (only biochemical- therapy or im- munotherapy)	2002–2007	135	16.6	7.6	– metastases in organs other than skin or lymph nodes – elevated LDH level

confirmed in multivariate analysis. Similarly, it was not confirmed in several clinical studies, in which a statistically significant increase in objective responses did not influence OS [21, 22, 46]. Some authors have reported similar observations to us, that when a successive line of treatment is used, the objective response rate lowers. At present, the most important parameter influencing OS is progression-free survival (PFS) [10]. In the analysed group the median PFS during the first-line treatment was 3.5 months, which was similar to the data from the literature [5, 20]. In our study the type of therapy was statistically significantly related to PFS and OS. It was also demonstrated that similar factors shorten PFS and OS. Those are: male gender, raised LDH, ALAT and AspAT levels, worse performance status, presence of liver metastases and higher stage according to the AJCC/UICC staging system. The correlation between the number of treatment lines and OS was also analysed. Longer OS in patients who received more lines of treatment might stem from survival bias, which means that the patient had to live until the next lines, and so by assumption lived longer. It is worth noting that in several patients, the treatment was changed after 2–3 cycles due to progression or adverse events, which also affected the correlation between OS and number of treatment lines.

A trend for shorter PFS after successive lines of treatment was proven; median PFS for the first, second and third line of treatment was 3.5, 2.0, 1.8 months, respectively. The decreasing PFS times after successive lines of treatment make doubtful the utility of successive lines of cytotoxic chemotherapy in advanced melanoma.

To summarize, the analysed group comprises one of the largest ever analysed, contemporary groups of stage IV/unresectable stage III melanoma patients treated with systemic chemotherapy before the newer molecularly oriented treatments and anti-CTLA-4 immunotherapy. The results may provide a basis for proper selection of patients for clinical trials and treatment of some patients with classic chemotherapy in the era of modern drugs.

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