Long-term Survival with Ipilimumab: Experience from a National Expanded Access Program for Patients with Melanoma

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Abstract. *Aim: Evaluation of efficacy and safety of ipilimumab in patients with advanced, refractory melanoma enrolled into a national ipilimumab Expanded Access Program. Patients and Methods: Adult patients with advanced/metastatic refractory melanoma were eligible for study inclusion. Ipilimumab was administered up to a total of four doses. Results: One hundred and ninety-six patients were analyzed. Full ipilimumab induction was administered to 66.8% of patients. Median overall survival (OS) in the entire cohort was 7.5 months. Median OS for patients after four doses of ipilimumab was significantly longer than for patients with fewer doses (12.3 months vs. 2.0 months respectively; p<0.001). Median OS for patients with objective tumor response was 42.3 months. Normal baseline serum lactate dehydrogenase (LDH) and C-reactive protein (CRP) levels, and the number of affected organs correlated with improved OS. Conclusion: The number of affected organs and combination of baseline LDH and CRP levels could potentially serve as predictors for both treatment response and OS.*

Metastatic melanoma represents a highly aggressive malignancy with median survival of 6-8 months (1). Until 2010, dacarbazine was considered to represent the standard of care, however, cases of patients with durable response and long-term survival have only rarely been observed (2, 3).

Increased understanding of the immune system and its regulatory mechanisms led to identification of several primary immune check points that play a major role in tumor evasion of immune surveillance, and tumor progression, and, consequently, could serve as targets for effective antitumor therapy. Cytotoxic T-lymphocyte-associated protein 4 (CTL4) was the first identified as a potential target for development of novel forms of anticancer immunotherapy. Results of pre-clinical studies suggested that the blockade of CTLA4 receptor activity induced a strong antitumor immune response, especially in immunogenic tumors (4). Ipilimumab, a fully human monoclonal antibody blocking CTLA4, has been developed for clinical use. Melanoma is regarded as an immunogenic tumor. Moreover, melanoma is resistant to most cytotoxic drugs. Thus, not surprisingly, melanoma was the first tumor type in which clinical efficacy of ipilimumab was tested. In clinical trials, the administration of ipilimumab resulted in significantly improved overall survival (OS) of patients with metastatic melanoma (5, 6).

Herein we report data on the efficacy and safety of ipilimumab treatment of 196 patients with advanced/metastatic melanoma, treated with ipilimumab within a national expanded access program (EAP) that was carried-out in six large Teaching Hospitals across the Czech Republic for 19 months (November 2010 – May 2012). With the current median follow-up of over 3 years, this cohort of patients represents one with the longest follow-up intervals among EAPs already reported worldwide (7-10). Besides the evaluation of ipilimumab therapeutic efficacy and safety,

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exploratory analyses of potential predictive factors, including lactate dehydrogenase (LDH) and C-reactive protein (CRP), were performed along survival analysis of different patient sub-populations.

Patients and Methods

Patients. Patients 18 years of age or older, with histologically confirmed, unresectable stage III or stage IV melanoma, including those with asymptomatic brain metastases, and Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-2 were eligible for enrolment in this EAP. Patients were required to have failed (or be intolerant to) at least one prior systemic treatment, with no other therapeutic option available. An interval of at least 28 days since the previous treatment with chemotherapy, surgery, radiation, or immunotherapy was required.

The EAP protocol was approved by Ministry of Health of the Czech Republic and all participating patients signed written informed consent, before the enrolment.

Design of the EAP and data collection. Patients were scheduled for ipilimumab 3 mg/kg intravenously, administered as a 90-min infusion, every 3 weeks (*q3w*). Patients with no PS deterioration and no dose-limiting toxicities proceeded to receive four doses (full induction). Patients were scheduled to receive the entire induction regimen, regardless of the appearance of new lesions or progression of existing tumor lesions.

Decrease or escalation of the ipilimumab dose was not allowed, but it was possible to skip the ipilimumab dose based on pre-specified safety criteria. However, re-induction with the same dosing schedule was allowed in patients whose disease progressed following initial objective response or durable stable disease of 3 or more months.

Laboratory examinations were performed and evaluated before administration of each ipilimumab dose. Toxicity and safety were monitored during every single visit of the patient to the center, along with the general assessment of the patient condition and disease status. Tumor assessment was performed at week 12 (after expected completion of the full induction). All patient data were registered electronically into a central EAP database. All laboratory assessments, including serum LDH and CRP were performed locally.

The study was carried out in accordance with local regulatory requirements and the Declaration of Helsinki.

Toxicity and treatment response assessments. Adverse events (AEs) were monitored in all patients administered at least one dose of ipilimumab and were classified using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 3 (11). All AEs, regardless of the grade and drug causality were reported, starting with the first dose of ipilimumab until 70 days after ipilimumab discontinuation. More than one AE could be reported for a single patient.

Treatment responses were classified according to the modified World Health Organization (mWHO) criteria using bi-dimensional measurement (12). The overall response rate (ORR) included patients with complete response (CR) and partial response (PR). The disease control rate (DCR) was defined as the proportion of patients with ORR plus stable disease (SD) lasting at least 24 weeks. Treatment response according to Immune-related Response Criteria (irRC) (13) was evaluated in parallel. Treatment responses were assessed locally. There was no central independent review of the response.

Progression-free survival (PFS) was defined as the time from the date of the ipilimumab therapy initiation until the date of progression or death from any cause and OS as the time from ipilimumab therapy initiation until death from any cause. Patients without an event were censored at the last visit.

Statistical analysis. Standard descriptive statistics were used in the analysis, including the absolute and relative frequencies for categorical variables, and the mean, median, minimum and maximum for continuous variables. Statistical significance of differences between groups of patients was analyzed using Fisher's exact test for categorical variables and Mann–Whitney or Kruskal–Wallis test for quantitative variables. Survival rates were based on Kaplan–Meier estimates and differences in survival among patient groups were assessed by the log-rank test. The Cox proportional hazards model was used for the multivariate analyses of prognostic factors and the results were expressed as hazard ratios (HR).

Logistic regression was used for the multivariate analysis of parameters predicting long-term survival (>24 months) and the results were expressed as odds ratios (OR). All reported *p*-values are two-sided with α=0.05 as the level of statistical significance; confidence intervals are given at the 95% level. Statistical analyses were computed using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp. Armonk, NY, USA).

Results

Patients and therapy. The ipilimumab EAP was conducted between November 2010 and May 2012 in six specialized cancer centers, affiliated with University Hospitals in the Czech Republic.

One-hundred and ninety-six patients (112 males and 84 females) received at least one dose of ipilimumab and were included in the present analysis. The baseline characteristics of the entire study cohort are shown in Table I. The full induction therapy that included four subsequent doses of ipilimumab *q3w* was administered to 131 (66.8%) patients. In total, 24 patients (12.2%) received only one dose of ipilimumab, 23 patients (11.7%) received two doses and 18 patients (9.2%) received three doses. The most frequent reasons for not being able to receive entire induction regimen were disease progression (n=43; 66.2%) and adverse events (n=14; 21.5%). Six patients refused to continue therapy (9.2%), one patient was intolerant and one patient died. Re-induction was administered to 12 patients (6.1%).

Safety and tolerability. AEs of any grade were reported in 41 patients (20.9%). The most frequent AEs were gastrointestinal (9.7%) followed by dermatological (8.2%) and endocrine (2.6%) toxicities. Thirteen patients (6.6%) were reported to experience grade 3/4 toxicity. Among gastrointestinal AEs there were two cases of grade 4 diarrhea, both of which were ultimately managed by corticosteroid administration. There was no death directly related to ipilimumab administration.

Table I. *Baseline demographic and clinical characteristics. Characteristics of patients in the Early Access Program (EAP) in the Czech Republic compared to characteristics of patients in the ipilimumab arm of the phase III registration trial (5).*

Parameter	Ipilimumab EAP in the Czech Republic	Ipilimumab arm of phase III registration trial (5)
Number of subjects	N=196	N=137
Gender, n (%)		
Male	112 (57.1)	81 (59.1)
Female	84 (42.9)	56 (40.9)
Age, years		
Mean	59	56.8
Median	61	-
Min-Max	22-86	-
ECOG performance status, n (%)		
0	120 (61.0)	72 (52.6)
1/2	76 (39.0)	65 (47.4)
Primary melanoma origin, n (%)		
Cutaneous	159 (81.1)	137 (100%)
Ocular	15 (7.7)	0
Unknown	22 (11.2)	0
Metastatic stage classification, n (%)		
M0	5 (2.6)	1 (0.7)
M1a	55 (28.1)	14 (10.2)
M1b	27 (13.8)	22 (16.1)
M1c	109 (55.6)	100 (73.0)
Number of affected organs, n (%)		
1	72 (36.7)	-
2	47 (24.0)	-
≥3	77 (39.3)	-
Location of metastasis, n (%)		
Lymph nodes	106 (54.1)	-
Lung	99 (50.5)	-
Liver	84 (42.9)	-
Skin	61 (31.1)	-
CNS	13 (6.6)	15 (10.9)
Others	95 (49.7)	-
None	5 (2.6)	-
Target tumour lesion, n (%)		
Measurable	171 (87.2)	-
Non-measurable	25 (12.8)	-
Size of measurable lesions (mm^2)		
Mean	3122	-
Median	1500	-
Baseline serum LDH, n (%)		
≤ULN	64 (32.7)	84 (61.3)
>ULN	122 (62.2)	53 (38.7)
Unknown	10 (5.1)	0
Baseline serum CRP, n (%)		
<10 mg/l	108 (55.1)	-
≥10 mg/l	79 (40.3)	-
Unknown	9 (4.6)	-

CNS: Central nervous system; CRP: C-reactive protein; EAP: early access program; ECOG: Eastern Cooperative Oncology Group; LDH: lactate dehydrogenase; ULN: upper limit of normal.

Tumor response. In the entire cohort of 196 evaluated patients, the ORR and DCR, according to modified WHO criteria, were 8.2% and 23.5%, respectively. Using the irRC criteria, the corresponding ORR and DCR values were 8.2% and 25.0%, respectively.

DCR in patients who received the full induction of four ipilimumab doses (n=131) was 33.6%, compared to 3.1% in 65 patients with fewer than four doses of ipilimumab ($p<0.001$).

An exploratory analysis of relationship between baseline characteristic and the best treatment response identified six parameters significantly related to the individual treatment response. With use of a multivariate logistic model, the number of affected organs (<3 *vs*. ≥3; $p<0.001$), baseline serum LDH levels (normal range *vs*. ≥1 ULN; $p=0.028$) and baseline serum CRP levels (<10 mg/l *vs*. ≥10 mg/l; $p=0.028$) were identified as independent predictors of treatment response.

An analysis of CRP concentrations before and after ipilimumab therapy revealed a significant increase during the course of the treatment (from a mean of 20 mg/l to 39 mg/l; $p<0.001$). While the median increase of CRP was 0 and 1 mg/l in patients with CR/PR and SD, respectively, it was 4 mg/l in patients with PD ($p=0.02$).

Survival. As of November 2014, the median follow-up was 39.6 months (range=27.1-47.1 months). The median PFS was 2.07 months (95% CI=2.06-2.08 months). In total, 173 patients (88.3%) had died by the time of this analysis. In 146 (84.4%) patients, the death was due to their tumor progression. The median OS of the entire patients cohort (N=196) was 7.5 months (95% CI=5.9-9.0 months).

The median OS of 12.3 months (95% CI=9.3-15.3 months) in patients who received all four doses of ipilimumab (n=131) was significantly superior ($p<0.001$) when compared to the 2.0 months (95% CI=1.8-2.2 months) for patients who received fewer than four doses (n=65) (Figure 1). The median OS of patients achieving an objective tumor response (CR/PR) was 42.3 months compared to 20.0 month for patients with SD, and 5.1 months for patients with PD (Figure 2).

An exploratory analysis of the relationship between baseline characteristics and the OS identified six parameters significantly related to the individual treatment response. OS appeared to be significantly better for females, for patients with ECOG PS 0, for patients with tumors classified as M0/M1a/M1b (*vs*. M1c), with fewer than three affected organs, with baseline serum LDH <ULN and baseline serum CRP <10 mg/l (Table II). In multivariate survival analysis, using a Cox regression model, baseline characteristics predicting superior survival of treated patients included gender (female *vs*. male), number of affected organs (<3 *vs*. ≥3), baseline ECOG PS (0 *vs*. 1/2), baseline serum LDH

(≤ULN *vs*. >ULN) and baseline serum CRP (<10 mg/l *vs*. ≥10 mg/l). Probability of survival for 24 months or longer was significantly higher for patients with one affected organ only and baseline serum LDH <ULN compared to patients with both two or more affected organ and serum LDH level ≥ULN at baseline (Figure 3).

Long-term survival. As of November 14, 2014, 23 patients out of 196 evaluated (11.7%) were alive. The median follow-up for surviving patients was 36.6 months (range=27.1-47.1 months). All patients survived more than 24 months. Ten of the long-term survivors (43.5%) achieved CR or PR and nine of them (39.1%) SD, while only four patients with PD or unknown disease status survived for more than 24 months. Differences in proportions of long-term survivors between DCR *vs*. PD/unknown sub-groups was statistically significant ($p<0.001$).

Among treatment characteristics, in addition to best treatment response the number of ipilimumab doses was identified as a parameter significantly related to survival exceeding 24 months; 91.3% (21/110) of patients who had had four doses were alive after more than 24 months compared to 8.7% (2/63) of patients who had had fewer doses ($p=0.008$).

In an exploratory analysis, we tried to identify baseline and treatment characteristics associated with long-term survival. Based on an arbitrary cut-off (median tumor size in the evaluated cohort was 1500 mm^2), the proportion of patients with tumor size <1500 mm^2 surviving more than 24 months was 73.9% (17/23), compared to 13.0% (3/23) of patients with tumor size >1500 mm^2 ($p=0.002$).

In a univariate logistic model classification of metastatic stage (pM0/1a/1b *vs*. pM1c; $p=0.037$), number of affected organs (1 *vs*. ≥2; $p=0.041$), baseline serum LDH levels (<ULN *vs*. >ULN; $p=0.039$) were associated with long-term survival (>24 months). However, only the baseline number of affected organs and baseline serum LDH seemed to be significantly related to long-term survival in the multivariate logistic model.

Table II. *Patients' baseline characteristics and overall survival (OS).*

Parameter	n (%) (95% CI), months	Median OS (log-rank test)	*p*-Value
Gender			
Female	84 (42.9)	11.0 (7.6-14.4)	0.035
Male	112 (57.1)	6.6. (4.4-8.8)	
ECOG performance status			
0	120 (61.2)	9.6 (6.2-13.0)	0.012
1/2	76 (38.8)	6.0 (3.7-8.4)	
Metastatic classification			
M0, M1a, M1b	87 (44.4)	12.3 (10.5-14.1)	<0.001
M1c	109 (55.6)	4.9 (3.3-6.5)	
Number of affected organs			
1	72 (36.7)	11.9 (7.2-16.5)	<0.001
2	47 (24.0)	8.2 (6.6-9.8)	
≥3	77 (39.3)	4.8 (3.2-6.4)	
Baseline LDH			
≤ ULN	64 (32.7)	14.6 (9.9-19.3)	*
>1x ULN <2x ULN	59 (30.1)	7.0 (5.3-8.8)	
≥2x ULN	63 (32.1)	3.9 (1.7-6.0)	
Baseline CRP, n (%)			
<10 mg/l	108 (57.8)	11.7 (8.2-15.3)	<0.001
≥10 mg/l	79 (42.2)	3.9 (2.3-5.5)	
Combined baseline LDH and baseline CRP			
LDH <ULN and CRP <10 mg/l	52 (28.3)	15.8 (11.8-19.9)	**
LDH ≥ULN and CRP <10 mg/l or LD <ULN and CRP ≥10 mg/l	65 (35.3)	7.9 (5.8-9.9)	
LDH ≥ULN and CRP ≥10 mg/l	67 (36.4)	3.3 (1.6-4.9)	

CI: Confidence interval; CRP: C-reactive protein; ECOG: Eastern Cooperative Oncology Group; LDH: lactate dehydrogenase; OS: overall survival; ULN: upper limit of normal. Log-rank test results: *≤ULN *vs*. >1x ULN <2x ULN, *p*-value=0.017; ≤ULN *vs*. ≥2x ULN $p<0.001$; >1x ULN <2x ULN *vs*. ≥2x ULN, $p=0.061$; **LDH <ULN and CRP < 10 mg/l *vs*. LDH ≥ULN and CRP <10 mg/l or LD <ULN and CRP ≥ 10 mg/l, $p=0.053$; LDH <ULN and CRP <10 mg/l *vs*. LDH ≥ULN and CRP ≥10 mg/l, $p<0.001$; LDH ≥ULN and CRP <10 mg/l or LD <ULN and CRP ≥10 mg/l *vs*. LDH ≥ULN and CRP ≥10 mg/l, $p=0.004$.

Discussion

The results of the present analysis not only confirm the activity of ipilimumab in a real-world population of patients with advanced/metastatic melanoma, but also identify potential biomarkers that could help to select patients likely to benefit from this therapy. Patients with life-threatening conditions and without other therapeutic options are eligible to enter the EAP. There are obviously inherent scientific limitations for any EAP, which is commonly designed as a non-interventional study, with the diagnostic and therapeutic decisions being at the discretion of the attending physician. Furthermore, data collection is often retrospective and can, therefore, be affected by selection and analysis biases.

Ipilimumab EAPs were opened in a number of countries before ipilimumab was approved for the treatment of melanoma (7-10, 14-16). The majority of these EAPs used the same ipilimumab treatment schedule (*i.e*. 3 mg/kg of ipilimumab q3w, up to four doses) for patients with advanced/metastatic refractory melanoma, reflecting the regimen used in the registration phase III trial (5).

Baseline characteristics, including sex and age distribution, of patients enrolled in this EAP were, in general, similar to those of the phase III registration trial (5), although in the present EAP there were 15 patients (7.7%) with ocular melanoma enrolled compared to none in the registration trial (Table I). The proportion of patients who received the full induction regimen (four doses of ipilimumab) was similar 66.8% and 64.2%, and the re-

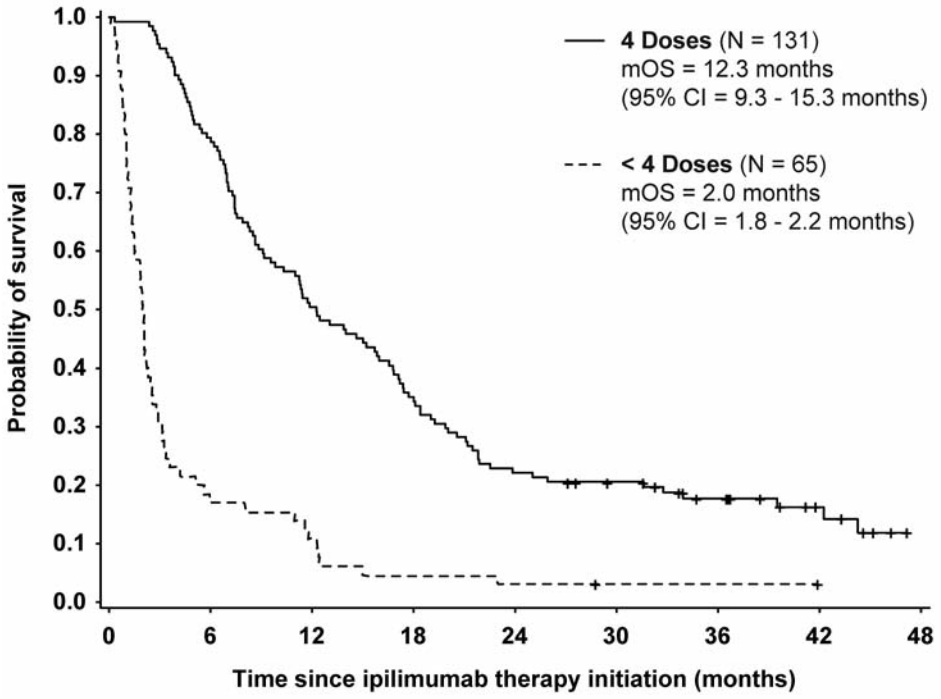

Figure 1. *Relationship between number of ipilimumab doses and overall survival. mOS median overall survival; CI confidence interval. Log-rank test result: p-value <0.001.*

induction was administered to 6.1% and 6.6% of patients, respectively. The best objective response rates of 8.2% in the present EAP and 11% in the registration trial, as well as DCR of 23.5% and 28.5% are comparable.

The median follow-up was 39.6 months in this EAP compared to 27.8 months in the registration trial and 88.2% and 73.0% of deaths were recorded, respectively.

The median OS of 7.5 months in the EAP was inferior to that of 10.0 months in the registration trial (5). Because patients with baseline serum LDH >ULN had worse prognosis both in the registration trial and the EAP, we may speculate that the difference in the survival outcome might be related to the higher proportion of patients with baseline serum LDH ≥ULN in the present EAP (62.2% in EAP *vs.* 38.7% in the trial).

The present results are in agreement with the results of other EAPs reported to date. Analyses of several ipilimumab EAPs have been published (7-10, 14-16). Treatment response rate (according to modified WHO criteria) ranged from 8% to 13%, the DCR from 22% to 34%, median PFS from 2.0 to 3.7 months and median OS from 6.5 months to 10.0 months in unselected study cohorts. Two-year survival was reported at between 22% and 29%, however, survival exceeding 2 years declined further to 14-18%. The full ipilimumab induction was delivered to 60-64% of patients. Rapid tumor progression, rather than ipilimumab toxicity, was the most common reason for the failure to administer all four doses of the induction regimen. In Spain, 153 patients were treated with ipilimumab within the EAP, with 144 patients being evaluable. The ORR was 11.2%, DCR 25.7%, and median OS 6.5 months. Plasma LDH levels >1.5×ULN were predictive for shorter OS (15). Chasset et al. published the single-center results of the ipilimumab EAP in France, reporting on 45 patients with melanoma (16). A baseline plasma level of LDH >500 UI/ml (1.8×ULN) predicted poorer OS.

In the present EAP, 44.2% of patients had baseline serum CRP value ≥10 mg/l. In patients surviving at least 24 months, 72.7% of patients had baseline serum CRP <10 mg/l, while only 27.3% patients were with baseline serum CRP ≥10 mg/l. During the treatment with ipilimumab, CRP increase was significantly higher in the non-responder cohort. In the multivariate analysis, baseline serum CRP <10 mg/l, combined with baseline plasma LDH <ULN was a significant independent predictor of improved survival in the present study. These results suggest that the baseline serum CRP might be a potential predictive factor. In the registration trial, impact of serum CRP on treatment outcomes was not evaluated. In a smaller EAP, reporting on 50 patients with melanoma, the baseline CRP correlated with survival (7).

Obviously, like other EAPs, the present report has some limitations associated with the retrospective nature of the

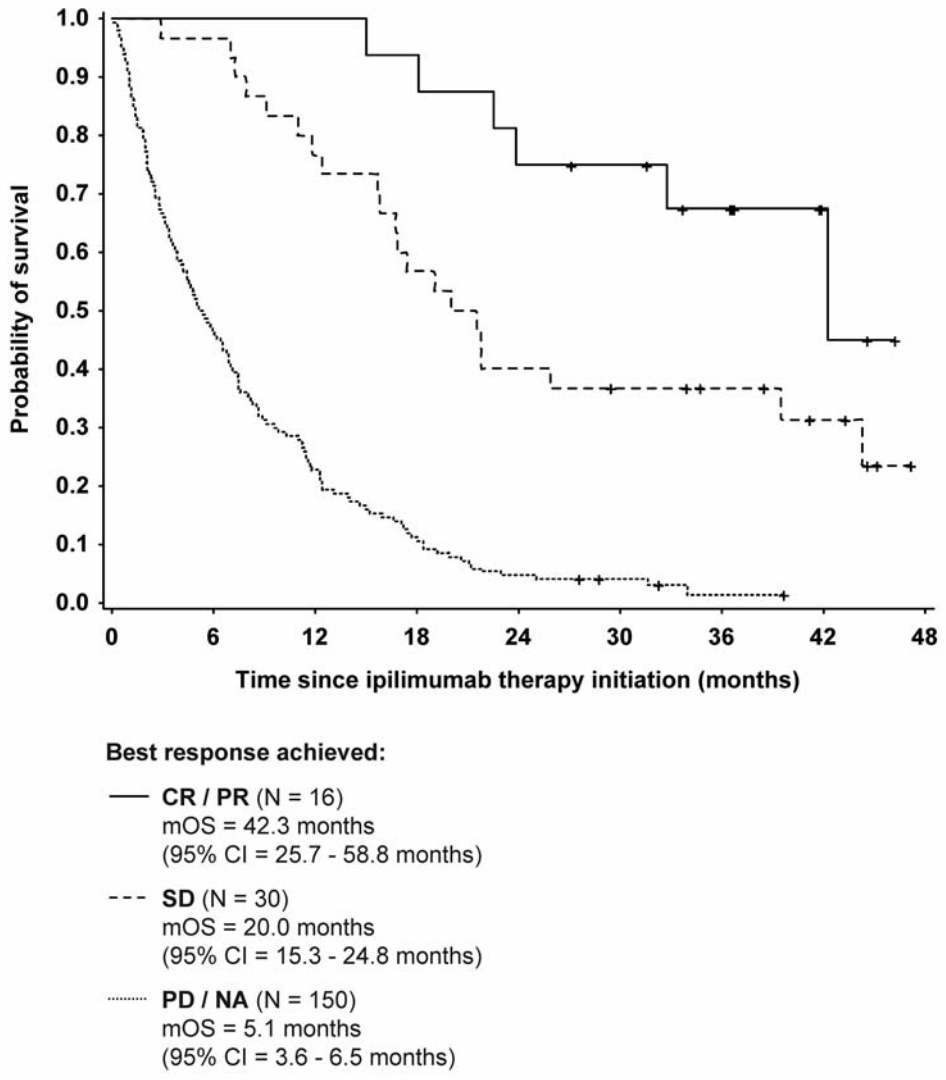

Figure 2. *The best treatment response and overall survival. CR complete response; PR partial response; SD stable disease; PD progressive disease; NA not available/unknown; mOS median overall survival; CI confidence interval. Log-rank test results: CR/PR vs. SD p-value=0.027; CR/PR vs. PD/NA p-value <0.001; SD vs. PD/NA p-value <0.001.*

analysis. There was no central confirmation of response, and AEs, especially mild to moderate, may be under reported. Moreover, data on biomarkers such as CRP and LDH, or the size of the lesions was missing for some patients. The association between the number of cycles of ipilimumab administered and OS is affected by a selection bias. A significant proportion of patients died before the four cycles of induction therapy could be completed, and in these patients, the poor prognosis is the cause rather than the consequence of the failure to complete the treatment. On the other hand, it is important to have real-life data from routine clinical practice to confirm the efficacy of new agents that have so far been used only in strictly selected patient populations in clinical trials. Because of the existence of a national death registry, it is possible that all patients could be followed-up for death.

Despite the fact that ipilimumab has been approved for the treatment of advanced unresectable or metastatic melanoma, with no further specification of the melanoma primary or metastatic sites, the final confirmation of consistent ipilimumab treatment efficacy in different clinical scenarios in patients with advanced melanoma is still lacking. Several retrospective studies indicated that ipilimumab efficacy in mucosal and ocular melanoma could be similar to that in cutaneous melanoma (17, 18). Comparable efficacy has also been reported in patients with brain metastases (16, 19). However, confirmation of these retrospective results in a prospective controlled clinical trial is

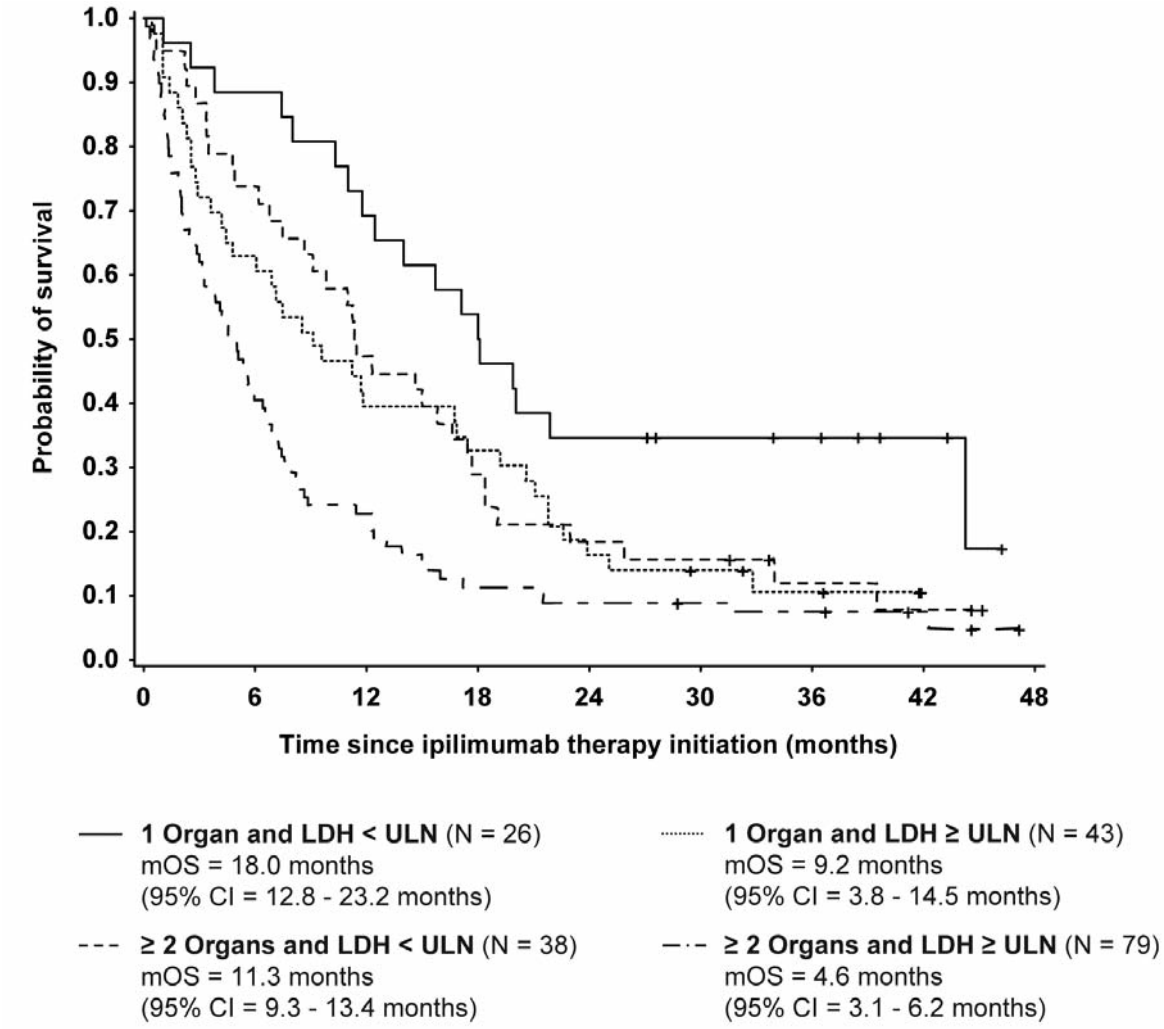

Figure 3. *Survival according to baseline number of affected organs and baseline serum LDH levels. LDH lactate dehydrogenase; ULN upper limit of normal; mOS median overall survival; CI confidence interval. Log-rank test results: 1 organ and LDH < ULN vs. ≥2 organs and LDH < ULN p-value=0.037; 1 organ and LDH < ULN vs. 1 organ and LDH ≥ ULN p-value=0.019; 1 organ and LDH < ULN vs. ≥2 organs and LDH ≥ ULN p-value < 0.001; ≥2 organs and LDH < ULN vs. 1 organ and LDH ≥ ULN p-value=0.761; ≥2 organs and LDH < ULN vs. ≥2 organs and LDH ≥ ULN p-value=0.005; 1 organ and LDH ≥ ULN vs. ≥2 organs and LDH ≥ ULN p-value=0.022.*

not yet available. The lack of reliable predictive biomarkers, as well as an uncertainty about ipilimumab efficacy in rare presentations, such as an extracutaneous primary, could limit future willingness to pay for this therapy.

In conclusion, the results of the present EAP, as well as of a number of other ipilimumab EAPs already published, demonstrate that despite differences in baseline clinical characteristics of the enrolled patients , the treatment outcomes in patients with metastatic melanoma are more or less similar and consistent with results from the registration study. Baseline LDH and CRP levels, as well as the number of affected organs appear to predict long-term outcome in advanced melanoma patients treated with ipilimumab.

Conflicts of Interest

IK, PA, RL, EK, BM, and IB, served in a consultancy/advisory role for Bristol-Myers Squibb, Merck Sharp & Dohme, Roche. MŠ is an employee of Bristol-Myers Squibb Czech Republic Ltd.; JM has no conflicts of interest to declare.

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