Chapter 5

Equal benefit from ipilimumab for elderly melanoma patients

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Abstract

Approximately 45% of patients with metastatic melanoma are above 65 years, which is seldom mirrored in trial populations. Ipilimumab can induce long-term benefit in metastatic melanoma. Since autoimmunity is associated with older age and female gender, we aimed to investigate whether efficacy and toxicity of ipilimumab are different in the elderly melanoma patient population or between genders.

Patients participating in the Dutch Named Patient Program in 2010 and 2011 in 7 centers were included. Response assessment was performed and side-effects were recorded. In addition, to evaluate reported real world side-effects the public pharmacovigilance FDA database was analyzed.

Of the 172 patients with a median age of 55 years (range 22–88), 51 (30%) were ≥ 65 years and 74 (43%) were women. Median overall survival was 6.7 months (95% CI 4.7–8.7) in patients < 65 years and 10.4 months (95% CI 6.3–14.6) in patients ≥ 65 years. Grade 3–4 bowel toxicity was observed in 8.3% of patients < 65 years and 9.8% of patients ≥ 65 years. Discontinuation because side-effects occurred in 7.6% of the younger versus 8.3% of the older patients. No difference in efficacy and toxicity profile was observed between genders. 3,771 serious side-effects were reported as of November 2015 to the FDA database without major differences in toxicity profile between ages.

In conclusion, treatment with ipilimumab for metastatic melanoma is equally effective in elderly and younger patients, is safe in patients ≥ 65 years and has similar efficacy and toxicity for both genders.

Introduction

The incidence of melanoma is rising and as a consequence metastatic melanoma is an increasing problem worldwide [1]. Particularly in people above 65 years of age, an increase in melanoma-related deaths is observed [2]. A major breakthrough in the treatment of metastatic disease is the availability of the immune checkpoint inhibitors including ipilimumab, a monoclonal antibody against cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) on the cell surface of T-lymphocytes. Ipilimumab was the first drug to demonstrate an overall survival benefit in these patients [3]. The drug, approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in 2011, has become part of the standard treatments for metastatic melanoma patients. Increasingly more mature data show that this treatment results in a long-lasting survival plateau stabilizing at 3 years at about 20% [4]. Higher response rates in metastatic melanoma are observed with programmed cell death 1 (PD-1), but the combination of ipilimumab with PD-1 inhibition has the most potent antitumor efficacy [5].

CTLA-4 is an immune checkpoint protein preventing autoimmunity in physiological circumstances [6]. Blocking CTLA-4 with ipilimumab therefore can induce immune-related adverse events including colitis, dermatitis, hepatitis and hypophysitis [7], showing similarities with autoimmune diseases. Autoimmune diseases are commonly more frequent diagnosed in elderly patients [8], and more often in women compared to men [9]. At the same time, elderly are still underrepresented in clinical cancer trials [10]. Due to the lack of data, some oncologists might be more reluctant to treat older patients with ipilimumab given the potential higher burden of side effects for elderly. However, it is yet unknown whether it is justified to offer ipilimumab cautiously in elderly and/or women.

The FDA has implemented an initiative named Drug Trials Snapshots in which data from clinical trials is made transparent concerning age, gender and ethnicity of the participants [11]. Also a description of any difference in efficacy and toxicity for the same demographic subgroups is provided. Unfortunately, ipilimumab is not included in the limited number of drugs currently available. In 2015, the American Society of Clinical Oncology released a series of recommendations to improve the generation of evidence in elderly cancer patients [12]. Both initiatives underscore the importance of availability of clinical treatment data for elderly cancer patients and other important subgroups.

Information on ipilimumab treatment effects obtained from the phase I–III trials may not necessarily reflect results in daily practice. Therefore, we aimed to investigate whether gender or age below of 65 years or above affect efficacy or toxicity of ipilimumab treatment. To do so, we analyzed information of patients participating in the Dutch Named Patient Program (DNPP) with relative liberal inclusion criteria. Moreover we studied reported 'real world' information retrieved from the public pharmacovigilance FDA database.

Materials and methods

Patients

We included all metastatic melanoma patients who received ipilimumab in 7 centers in the Netherlands, as part of the DNPP (NCT00495066). Patients signed written informed consent prior to participation in this program. Data were collected retrospectively.

Eligible patients who progressed on at least one prior systemic therapy for melanoma were required to have a modified World Health Organization (mWHO) performance status of 0–2 and an expected life expectancy of ≥ 16 weeks. Asymptomatic brain metastases were allowed. Required laboratory values were: white blood cells ≥ $2 \cdot 10^9$/L, antigen neutrophil count ≥ $1 \cdot 10^9$/L, platelets ≥ $75 \cdot 10^9$/L, hemoglobin ≥ 9 g/dL, creatinine ≤ 2.0 times the upper limit of normal (ULN), aspartate transaminase and alanine transaminase ≤ 5

times the ULN and ≤ 2.5 times for subjects with and without liver metastases, respectively, and a bilirubin ≤ 2 times the ULN.

Treatment consisted of 4 doses of ipilimumab (3 mg/kg) intravenously every 3 weeks, unless this was prematurely terminated because of toxicity, severe deterioration or unequivocal progression. Re-induction therapy was permitted for patients with progressive disease when the induction treatment initially led to stable disease ≥ 3 months or to partial or complete response.

Efficacy measurement

Tumor response was assessed by CT scanning, with or without ^{18}F-FDG PET. Baseline imaging was compared with imaging results after completion of the four ipilimumab cycles (week 12) or earlier on clinical indication. The Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 were used [13], as well as immune-related response criteria [14]. A confirmation CT scan was performed at least 4 weeks later. Follow-up consisted of a CT scan every 3 months thereafter or at clinically suspected progressive disease.

Serum lactate dehydrogenase (LDH) was measured at baseline and before every ipilimumab infusion. S100 calcium-binding protein B (S-100B) was measured in serum in a limited number of centers at the physicians' discretion, normally also before every ipilimumab infusion.

Toxicity measurement

The National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 was used to track and score immune-related adverse events from the case records. Clinical evaluation was done prior to each infusion and included biochemistry parameters. Toxicity was treated according to standard of care.

Pharmacovigilance database

We also analyzed the public pharmacovigilance database of the FDA for ipilimumab [15]. Post-licensing reports of adverse events (AEs) send directly to the FDA from healthcare professionals and consumers, as well as reports received by the FDA from manufacturers are entered in this database. We looked at the top 12 most reported serious AEs resulting in death, a life threatening condition, hospitalization, disability or other serious condition in patients ≥ 65 years of age. We displayed patients < 65 years as a reference. The AE-entities 'death' and 'malignant neoplasm progression' were left out from analysis since we did not consider them single side effects.

Statistical analysis

For data analyses of the DNPP, we used SPSS statistical software version 20.0.0.1. Univariate analyses were performed using the ANOVA test. Differences between groups were depicted using Kaplan-Meier survival curves and tested using the log-rank test. The Cox regression analyze method was used to calculate hazard ratios (HR). Progression free survival (PFS) was defined as time from start of ipilimumab to the onset of progression or death. Overall survival (OS) was defined as time from start of ipilimumab to death of any

cause. Patients without progression and still alive at time of analysis were censored. *P* values < 0.05 tested 2-sided were considered significant for all analyses. Results from the FDA database are of descriptive nature – differences in adverse event outcomes were calculated with Pearson's χ^2 test.

Results

Between April 2010 and November 2011, 172 patients were included in the DNPP. Their mean age was 55.5 years, ranging from 22–88 years of age. Other patient characteristics are summarized in Table 1. Baseline parameters for both age groups (≥ 65 years of age and < 65 years of age) as well as for men and women are presented in Table 2. The elderly patients (≥ 65 years of age) had a higher number of lymphocytes at baseline, namely $1.45 \cdot 10^9$/L versus $1.24 \cdot 10^9$/L for younger patients. The median OS for the total population was 7.5 months (95% CI 5.6–9.3) and the overall response rate was 11%.

Baseline parameters are for the 73 patients that survived at least 1 year are given in the Supplemental Table. The percentage of males in this group was 60% and a similar percentage, namely 55% males, was found in the 99 patients with a survival < 1 year. The mean age of patients that survived beyond 1 year was 56.7 years and 54.8 years for patients that lived shorter. Patients that lived over 1 year had a lower serum LDH and serum S-100B levels at baseline as well as a better mWHO performance status.

Median OS was 6.7 months in the younger, compared to 10.4 months in older patients (Figure 1) with a HR of 0.86 (95% confidence interval (CI) 0.56–1.25) for elderly. OS determined per age group in quartiles of the whole population showed that OS improved with age, with for the youngest 25% a median OS of 4.6 months and in the oldest 25% a median OS of 11.1 months (Table 3 and Figure 2).

Of the patients ≥ 65 years of age, 8.3% discontinued ipilimumab because of adverse events. This was 7.6% in the younger patients. Old and young patients completed the whole treatment of four courses in 67 and 66%, respectively. Immune-related toxicity grade ≥ 3 was similar in both age groups (see Table 2).

An mWHO performance status of 0 was present in 53% of the elderly and 63% of the young patients. Patients with an mWHO score of 0 had a longer median OS (11.0 months, 95% CI 7.5–14.6) compared to patients with a score of 1 (4.1 months, 95% CI 2.8–5.3, $p = 0.002$).

The median OS was 7.9 months for men and 6.7 months for women with an HR for death of 0.77 for men (95% CI 0.56–1.10). The Kaplan-Meier curve tends towards a higher survival plateau in men (see Figure 3).

For ipilimumab, 6,013 AEs were reported to the FDA at time of analysis (November 2015) of which 3,771 were serious. The vast majority of ipilimumab was administered for melanoma and small proportions for lung cancer, prostate cancer, sarcoma or other malignancies. In Table 4 the 12 most common reported serious AEs are mentioned in patients ≥ 65 years of age. No notable differences were found, except that the serious AEs colitis,

diarrhea and dehydration resulted in death in 22% of elderly patients and in 16% of patients < 65 years of age ($p < 0.01$).

	Number of patients* (%)
Age	
mean in years (range)	55.5 (22–88)
Sex	
Male	98 (57)
Female	74 (43)
Performance status	
mWHO 0	103 (60)
mWHO 1	61 (35)
mWHO 2	8 (5)
M-stage	
M1a	9 (5)
M1b	22 (13)
M1c	141 (82)
Sites of metastases	
Single	35 (20)
Multiple	137 (80)
Cycles ipilimumab	
1	17 (10)
2	19 (11)
3	22 (13)
4	114 (66)
Responders	19 (11)

Table 1: Baseline characteristics of the patients in the Dutch Named Patient Program, (*n* = 172).
mWHO = modified World Health Organization performance criteria. * Except otherwise indicated.

	Age < 65, *n* = 121	**Age ≥ 65, *n* = 51**	**Men, *n* = 98**	**Women, *n* = 74**
Reason for < 4 courses administered				
AE (%)	7.6	8.3	6.2	10.1
PD/death (%)	25.4	22.9	24.7	24.6
other (%)	0.8	2.0	2.1	2.9
NA (%)	66.1	66.7	67.0	62.3
Number of courses				
1 (%)	8.3	13.7	9.2	10.8
2 (%)	14.0	3.9	10.2	12.2
3 (%)	11.6	15.7	13.3	12.2
4 (%)	66.1	66.7	67.3	64.9
Biochemical profile				
median serum LDH (U/L)	223 (*n* = 116)	252 (*n* = 50)	241 (*n* = 96)	221 (*n* = 70)
median serum S-100B (µg/L)	0.27 (*n* = 84)	0.25 (*n* = 34)	0.29 (*n* = 76)	0.19 (*n* = 42)
median lymphocyte count (· 10^9/L)	1.24* (*n* = 96)	1.45* (*n* = 40)	1.20* (*n* = 80)	1.45* (*n* = 56)
Performance status				
mWHO 0 (%)	62.8	52.9	64.3	54.1
mWHO 1 (%)	33.9	39.2	31.6	40.5
mWHO 2 (%)	3.3	7.8	4.1	5.4
M-stage				
M1a (%)	6.6	2.0	5.1	5.4
M1b (%)	12.4	13.7	14.3	10.8
M1c (%)	81.0	84.3	80.6	83.8
Sex				
male (%)	51.2	70.6		
female (%)	48.8	29.4		
Age				
< 65 (%)		63.3	79.7	
≥ 65 (%)		36.7	20.3	

Table 2: Characteristics for young and elderly patients and for men and women treated with ipilimumab in the Dutch Named Patient Program.

	Age < 65, *n* = 121	Age ≥ 65, *n* = 51	Men, *n* = 98	Women, *n* = 74
Colitis				
none (%)	81.8	80.4	83.7	78.4
grade 1 (%)	6.6	3.9	6.1	5.4
grade 2 (%)	3.3	5.9	3.1	5.4
grade 3 (%)	5.0	7.8	5.1	6.8
grade 4 (%)	2.5	2.0	2.0	2.7
grade 5 (%)	0.8	0.0	0.0	1.4
Dermatitis				
none (%)	82.6	76.5	79.7	81.6
grade 1 (%)	12.4	13.7	13.5	12.2
grade 2 (%)	3.3	5.9	2.7	5.1
grade 3 (%)	1.7	3.9	4.1	1.0
grade 4 (%)	0.0	0.0	0.0	0.0
grade 5 (%)	0.0	0.0	0.0	0.0
Hepatitis				
any grade (%)	5.0	3.9	2.0	8.1
Hypophysitis				
any grade (%)	2.5	3.9	5.1	0.0

Table 2: continued.

AE = adverse event; PD = progressive disease; LDH = lactate dehydrogenase; S-100B = S100 calcium binding protein B; mWHO = modified World Health Organization performance criteria; NA = not applicable, * indicates a significant difference.

Age	Median OS (months)	95% CI
youngest quartile	4.6	0.3–8.9
second youngest quartile	7.5	4.4–10.5
second oldest quartile	6.7	1.8–11.6
oldest quartile	11.1	5.7–16.4

Table 3: Overall survival time for all patients per age-quartile.

OS = overall survival; CI = confidence interval. Quartiles are respectively 0–25%, 25–50%, 50–75% and 75–100%.

Serious AE	**< 65 years**	**≥ 65 years**
Diarrhea	302	311
Colitis	255	207
Dehydration	115	110
Pyrexia	161	100
Fatigue	87	85
Nausea	127	72
Vomiting	155	62
Decreased appetite	43	62
Hypophysitis	81	60
Pneumonia	38	59
Dyspnea	66	59
Rash	50	56
Total number reported	2,160	1,611
Total number resulted in death	512	410
Total number life-threatening	98	88
Total number resulted in hospitalization	1,478	1,149

Table 4: Top 12 most common reported serious AEs to the public pharmacovigilance FDA database in patients ≥ 65 years.

AE = adverse event.

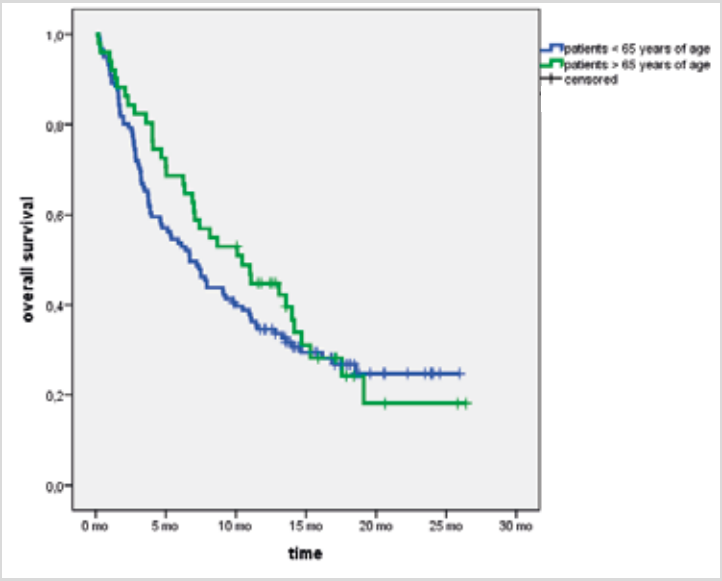

Figure 1: Kaplan-Meier curve for overall survival in months for elderly patients treated with ipilimumab compared to patients < 65 years of age.
mo = months.

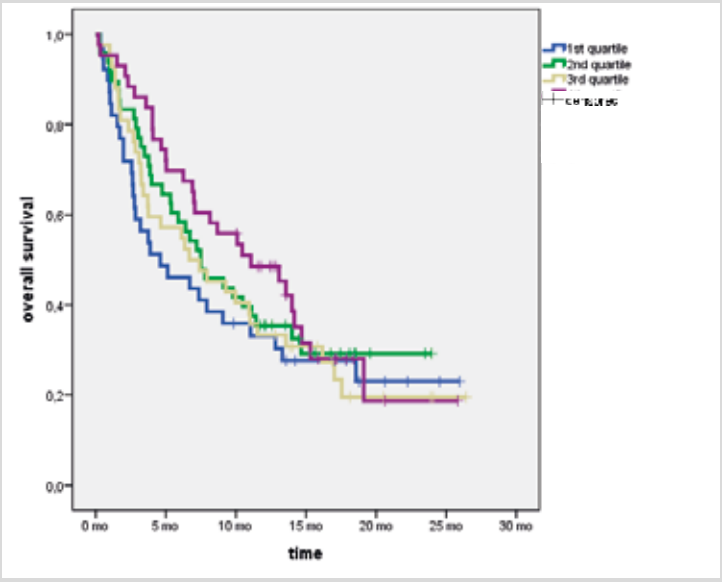

Figure 2: Kaplan-Meier curve for overall survival in months for patients treated with ipilimumab when divided in quartiles.
mo = months.

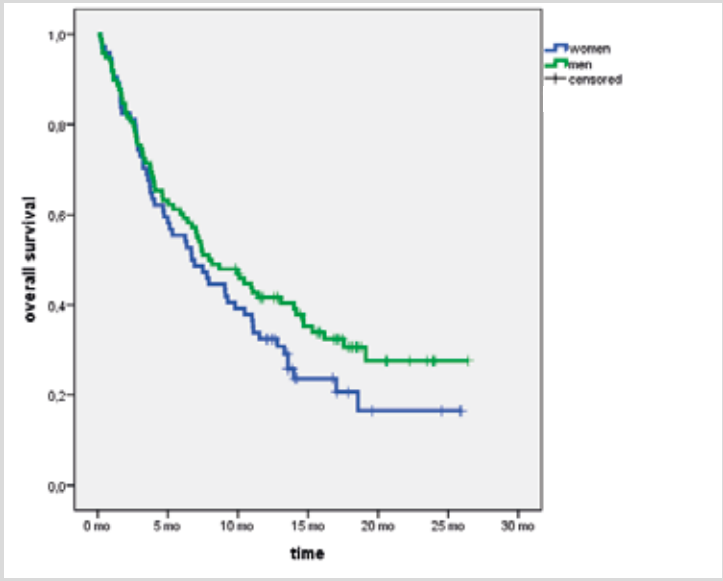

Figure 3: Kaplan-Meier curve for overall survival in months for men and women treated with ipilimumab. mo = months.

Discussion

The analysis of the results of the DNPP, which can be regarded a pattern of care study, shows that elderly treated with ipilimumab have similar OS compared to younger patients, and women have similar survival compared to men. Moreover, no important difference in toxicity profile was found regarding age and gender in the DNPP cohort. Toxicity data from the public domain, as provided by information from the FDA database, also did not reveal notable differences between patients < 65 and ≥ 65 years of age.

It is encouraging to observe that the large group of elderly patients with metastatic melanoma does not encounter more serious side effects of ipilimumab. Despite the concern among physicians about AEs in the elderly cancer patients, the rate of low-grade and high-grade side effects in our cohort was similar for the age groups. Also, no difference was found for the reasons to discontinue treatment. The discontinuation rate in the DNPP cohort was even slightly lower than in the phase III melanoma trial by Hodi et al [3] that led to the registration of ipilimumab.

Surprisingly, despite the relative liberal inclusion criteria in the DNPP, patient characteristics regarding age and gender in our study were comparable to the patient characteristics in the ipilimumab-arm of the phase III trial [3]. While the median age of death from metastatic melanoma in general is 69 years and 60% of deaths are ≥ 65 years of age [16], the proportion of patients ≥ 65 years was ~30% in the DNPP and in the phase III trial. This suggests an underrepresentation of elderly in the phase III trial as well as in our cohort. In the phase III trial, the mean age was 56.8 years and the mean age in the DNPP was 55.5 years. Unfortunately, no age-range was provided in the phase III trial.

The OS in the DNPP cohort was however inferior with 7.5 months compared to 10.1 months in the ipilimumab arm in the phase III trial [3]. This is also likely due to the more liberal inclusion criteria used in the DNPP. The DNPP allowed patients with a performance status of 2 and asymptomatic brain metastases while a performance status of 0–1 and absence of brain metastases was necessary for inclusion in the phase III trial. Moreover, in the phase III trial 71% had M1c disease compared to 82% in the DNPP. An elevated serum LDH was more common in the DNPP as well, suggesting a population with a more advanced disease process. On the other hand, the proportion of patients with an mWHO performance status of 2 was just 4.7% in our study, which is quite low for second line treatment in metastatic melanoma [17]. We found that a high mWHO performance status was associated with a worse outcome after ipilimumab. The relatively high number of elderly patients with an mWHO performance status of 1–2 makes their longer median survival compared to younger patients even more remarkable.

Both our own data set as well as information from the FDA database provides interesting information on side effects. Most frequently reported serious AEs for ipilimumab to the public pharmacovigilance FDA database in elderly were diarrhea, colitis and dehydration with combined a relatively high death rate of 22%. Although there is likely a bias towards the reporting of more severe toxicity, this indicates a serious problem in daily practice. In our study, one patient aged 59 died due to complications of ipilimumab-induced colitis.

To our knowledge, no age-related mortality data is published for ipilimumab-induced colitis. For inflammatory bowel disease (IBD), we know that no increased mortality risk exists for elderly-onset IBD [18]. However, for more acute and severe elapsing colitis like *Clostridium difficile* infection a higher mortality rate is reported in elderly [19]. Unfortunately, we are still unable to elucidate whether elderly treated with ipilimumab die more frequent from colitis-related toxicity. However, since ipilimumab-induced colitis appears semi-acute, we can imagine that elderly are more prone to develop life-threatening complications.

We observed a relatively low incidence of serious autoimmune hepatitis (n = 11) and hypophysitis (n = 60) among elderly in the FDA database.

With regard to gender, no difference was found concerning the rate of adverse events in the DNPP. One prospective phase III trial suggested that women ≥ 50 years of age do not benefit from the addition of 10 mg/kg ipilimumab to dacarbazine compared to dacarbazine only [20]. In our study, no survival difference was found for women ≥ 50 years of age compared to younger women.

Interestingly, a lower absolute lymphocyte count at baseline was found in young patients compared to elderly patients and also in men compared to women. A high absolute lymphocyte count at baseline and an increasing lymphocyte number during ipilimumab therapy are associated with superior survival [21]. Although we found no significant differences in survival between the age groups, the impact of a high absolute lymphocyte count on ipilimumab efficacy might explain the relative favorable outcome for elderly in our study.

The EMA and the FDA have approved ipilimumab also for treatment-naïve metastatic melanoma patients [22]. First-line treatment with ipilimumab has superior efficacy compared to the administration after one or more prior therapies [4]. In elderly patients this is even more important since their tumors are less often BRAF-V600E mutated (only 25% in patients ≥ 70 years of age), which means that they lack this highly effective alternative first line therapy [23].

Our report illustrates that ipilimumab is effective and does not lead to more side effects in the elderly. This is also of interest for treatment combinations with ipilimumab [24]. A phase III trial in melanoma patients compared the addition of the anti-PD-1 antibody nivolumab to ipilimumab with ipilimumab monotherapy and showed a superior median PFS of 11.5 months for the combination compared to 2.9 months for single agent ipilimumab therapy (p < 0.001) [5]. However, treatment-related grade 3–4 adverse events were found to be higher in the combination arm, with 55% versus 27% for ipilimumab only. Although it is uncertain whether this combination represents an additive or a synergistic effect between both drugs on efficacy and toxicity, the toxicity of this regimen mirrors mostly the ipilimumab pattern.

Our results do not legitimize a reluctant prescription policy of ipilimumab as single agent in elderly patients when they meet the inclusion criteria of our DNPP. We further emphasize that safety and efficacy data focused on elderly are a desirable element of the implementation of the ipilimumab plus nivolumab or another immune checkpoint inhibitor in clinical practice.

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	Patients that lived < 1 year (*n* = 99)	Patients that lived ≥ 1 year (*n* = 73)
Biochemical profile		
median serum LDH (U/L)*	329 (*n* = 95)	202 (*n* = 71)
median serum S-100B (µg/L)*	0.46 (*n* = 65)	0.14 (*n* = 53)
median lymphocyte count (• 10^9/L)	1.20 (*n* = 78)	1.35 (*n* = 58)
Performance status*		
mWHO 0 (%)	49.5	73.4
mWHO 1 (%)	45.5	21.9
mWHO 2 (%)	5.1	4.1
M-stage		
M1a (%)	4.0	6.8
M1b (%)	9.1	17.8
M1c (%)	86.9	75.3
Sex		
male (%)	54.5	60.3
female (%)	45.5	39.7
Age		
< 65 (%)	74.7	64.4
≥ 65 (%)	25.3	35.6

Supplemental Table: Characteristics of patients treated with ipilimumab that lived shorter or beyond 1 year since start of treatment in the Dutch Named Patient Program.

AE = adverse event; PD = progressive disease; LDH = lactate dehydrogenase; S-100B = S100 calcium binding protein B; mWHO = modified World Health Organization performance criteria, * indicates a significant difference.