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Review article

Long-term responses to molecularly targeted treatment and immunotherapy – groups of patients, management

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The use of immune checkpoint inhibitors and BRAF and MEK protein inhibitors in patients with advanced melanoma resulted in the overall survival median exceeding 2 years. For ipilimumab and anti-PD-1 antibodies, the percentage of 5-year survival is about 20% and 35%, respectively. Better results are obtained by patients treated in the first-line treatment. The most effective option seems to be the combined use of anti-CTLA-4 antibody with anti-PD antibody – in this case the percentage of 4-year overall survival was 53%. The 5-year overall survival rate of patients treated with BRAF/MEK inhibitors is 34%. Patients with a early stage of disease and normal lactate dehydrogenase concentration before systemic treatment are more likely to benefit from treatment.

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Key words: ipilimumab, pembrolizumab, nivolumab, dabrafenib, trametinib, long-term survival, melanoma

Introduction

In 2011, two new drugs were approved, which changed the prognosis of patients with advanced melanoma – ipilimumab [1] and vemurafenib [2]. Both drugs became representatives of new groups of drugs – immune checkpoints inhibitors and BRAF protein inhibitors. Less than a decade ago, the median overall survival rate for patients with advanced melanoma was 6–8 months, and the chance of 5- year survival ranged from 5% to 10% [3]. Molecularly targeted drugs and immunotherapy currently allow to reach the median total survival of more than 2 years.

Immunotherapy

Ipilimumab

In 2015, data on 3-year survival in patients treated with ipilimumab in phase II and phase III studies were published. 1861 patients were included in the analysis; 1257 patients received ipilimumab in the second or subsequent lines. The majority of patients [n = 965] received 3 mg/kg of body weight; 706 patients received 10 mg/kg of body weight; the remaining 190 patients received ipilimumab in a different dose. All patients received at least 4 doses of the drug at three-week intervals. In some studies, patients may have received maintenance treatment or may have been re-treated inductively after the progression of the disease. Overall survival (OS) was 11.4 months (95% confidence interval – CI): 10.7–12.1 months) with a 3-year OS percentage estimated at 22% (95% CI: 20%–24%). The median of the follow-up period was 11 months. Ten percent of patients were followed-up for at least 50 months. The maximum follow-up time was impressive and it was 119 months. The overall survival curve flattened at about 3 years after the start of treatment (fig. 1).

Longer overall survival was observed in patients receiving ipilimumab in the first line of treatment (median 13.5 months) compared to patients previously receiving systemic treatment (median 10.7 months). The 3-year survival rate for these groups was 26% and 20% respectively.

No significant differences in overall survival were observed in patients depending on ipilimumab doses.

To this group 2985 patients from the program of extended access to ipilimumab (EAP) (4846 patients in total) were

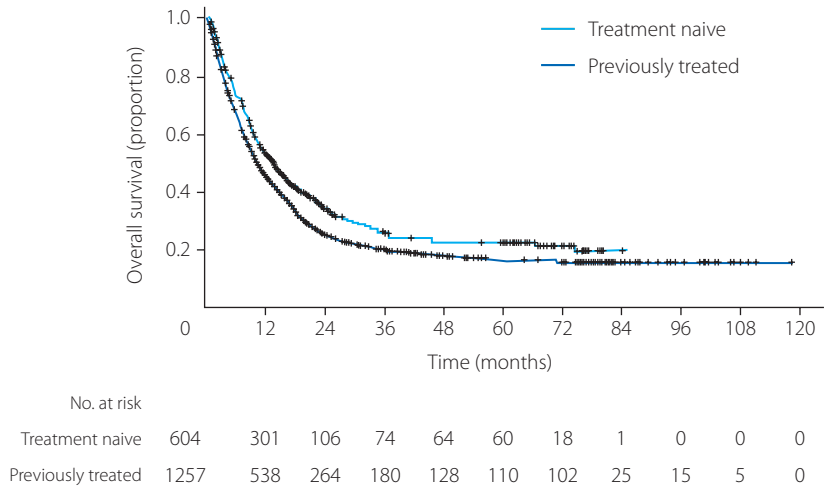

Figure 1. Long-term survival in patients treated with ipilimumab depending on the treatment line [4]

added. In this program, ipilimumab was also used to treat patients who would not meet the criteria for inclusion in the majority of clinical trials: patients with efficiency level 2 on the ECOG scale, patients with metastases in the brain, patients with melanoma of mucous membranes and eyeballs. The OS median for the entire group was 9.5 months with a 3-year total survival rate of 21%.

Among 88 patients who survived at least 4 years and were treated in studies CA 184-007, CA 184-008 and CA 184-022, 35 (40%) obtained an objective response, 29 (33%) disease stabilization and in 22 (25%) there was a progress in the disease. Therefore, the lack of an objective answer did not prejudge the short-term survival.

This data confirms observations from other studies included in this analysis, as well as coincides with observations from clinical practice [4].

In 2015, an analysis of the long-term survival o patients who were treated in the third phase of the study CA 184-024 (dacarbazine + ipilimumab 10 mg/kg of body weight) *vs.* dacarbazine + placebo) was published. The study showed significantly longer OS in the group treated with ipilimumab and dacarbazine than in the group treated with dacarbazine in monotherapy: 11.2 months *vs.* 9.1 months (hazard ratio [HR] 0.72, $p < 0.001$).

502 patients were treated with 250 ipilimumab with dacarbazine and 252 with dacarbazine. After 5 years, 40 patients receiving ipilimumab and 20 patients receiving monotherapy still lived (fig. 2).

The percentage of 5-year overall survival for combined therapy was 18.2%, and for dacarbazine 8.8%. Responses to treatment were assessed using modified WHO criteria. In the group of patients receiving ipilimumab with dacarbazine, complete response (CR) was observed in 7.5%, while partial response (PR) was observed in 42.5% of patients. In the group of patients receiving dacarbazine in monotherapy, no complete responses were observed, and partial responses were observed in 35% of treated patients.

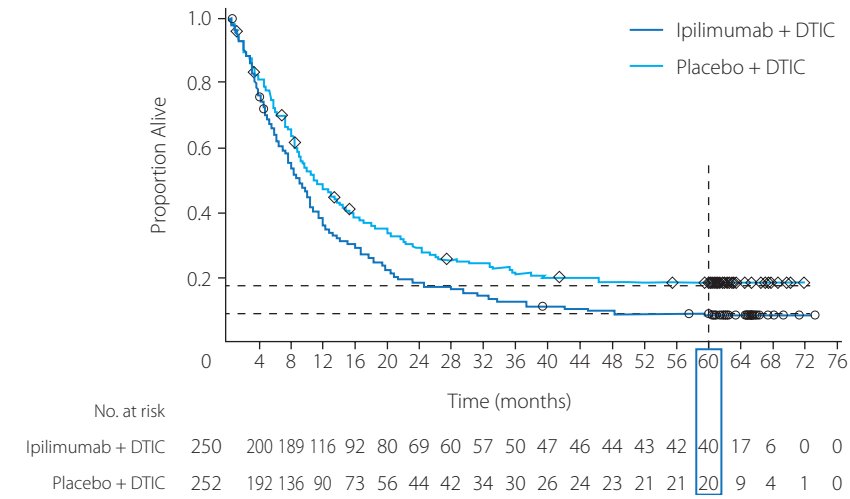

Figure 2. Long-term survival in patients treated with ipilimumab compared with dacarbazine [5]

Longer overall survival was observed in patients with objective response to treatment. In the group treated with ipilimumab with dacarbazine, median OS was not achieved in patients with objective response to treatment. In the group of patients where no response was achieved, the median OS was 14.3 months (HR 0.28; 95% CI: 0.16–0.47). Similarly, better survival rates were observed in patients with objective response to dacarbazine in monotherapy compared to patients with no response to treatment. The median OS was 20.2 and 12.3 months respectively (HR 0.51; 95% CI: 0.32–0.84) [5].

Two studies on patients treated with ipilimumab in phase I and II studies are interesting in terms of long-term survival. The first one describes 177 patients [6], who were treated in 3 studies, for which recruitment was conducted in the years 2003–2005. Ipilimumab was administered in combination with gp100 peptide, high-dose interleukin 2 or alone. The drug was administered in different patterns. The analysis presents data of 15 patients with complete response (CR). At the time of publication, 14 patients were alive. The time to obtain CR was very different – from 3 to even 70 months. The longest duration of CR was 99 months. In 1 patient the disease progressed after 42 months of complete response.

The data of 18 patients who were alive at the time of the analysis and who did not obtain CR were also presented. For 3 of them, a partial response has been maintained for 56, 66 and 71 months. In 6 patients metastasectomy or other local treatment, including radiation therapy or percutaneous radio--frequency ablation (RFA) was chosen. The remaining patients underwent other systemic treatment – chemotherapy, targeted therapy, biological treatment, immunotherapy.

The percentage of 5-year overall survival; for the three analysed studies was 13%, 25% and 23% respectively.

The second analysis concerns 733 patients treated with ipilimumab in 6 phase II studies. They received ipilimumab at a dose of 0.3, 3 or 10 mg/kg of body weight. In the group of patients who were previously treated, the percentage of 5-year overall survival was 12.3%, 12.3–16.5% and 15.5–28.4%, respectively. The percentage of 5-year overall survival in the group of patients untreated earlier was 26.8% for those receiving 3 mg/kg of body weight and 21.4–49.5% for those receiving 10 mg/kg of body weight [7].

In 2017, a retrospective analysis of 1034 patients treated under the European extended access programme (EURO--VOYAGE) was published.

The OS median was 6.8 months, with 3- and 4-year survival rates of 10.9% and 8%, respectively. The patient survival in this group was much shorter than in other studies. The reason for such results was the wider criteria for inclusion in the extended access program than in clinical trials [8].

According to the available data, patients in the first-line treatment received a greater benefit from ipilimumab treatment. Since 2014, when the results of anti-PD-1 antibodies tests were published, it has been known that they are a better choice for patients than ipilimumab. Data on the efficacy of ipilimumab after progression during anti-PD-1 treatment are limited, however, this drug remains an option in the second line in patients without *BRAF* mutations.

Anti-PD-1 antibodies

In the first line of treatment of patients with advanced melanoma, anti-PD-1 antibodies, i.e. pembrolizumab [9] and nivolumab [10], are currently the preferred choice.

Pembrolizumab

In 2019, the analysis of long-term survival of patients treated in the phase Ib of the open-label study KEYNOTE -001 was published. The study included 655 patients with advanced melanoma, including 8 patients with diagnosis of advanced untreated melanoma of the eyeball. Most patients (n = 496) had previously received systemic treatment (205 received one line of treatment, 178 received two lines of treatment, 113 received 3 or more lines of treatment). The percentage of 5-year PFS was 21% for the whole population; and 29% for patients treated in line 1. The median of the follow-up period was 55 months. The longest response lasts for 66 months. The percentage of 5-year survival in the whole group was 34%, and 41% in the subgroup treated in the first line. The OS median for the whole population was 23.8 months (95% CI: 20.2–30.4), whereas for patients treated in the first line it was 38.6 months (95% CI: 27.2 – not reached) (fig. 3).

Complete response to treatment was obtained in 16% of patients, partial response in 25% of patients, and stabilization of the disease in 24% of patients. At the time of analysis of the response data, 93 patients (89%) still had a complete response and 102 (63%) had a partial response. The protocol assumed that pembrolizumab could be discontinued in patients after a good response to treatment. Among the patients who ended CR treatment in this way, 67 patients were observed, and 5 patients were treated with PR. Only 7 of these patients developed progression after discontinuation of pembrolizumab (6 CR, 1 PR); 90% of the responses were still present. Of these 7 patients, 4 received pembrolizumab again. One patient obtained CR again, one SD; 2 patients experienced further progression of the disease [11] (fig. 4).

KEYNOTE-006 was the second study to analyse the long--term survival in patients with advanced melanoma. In this phase III study patients were randomized to 3 arms:

- pembrolizumab 10 mg/kg of body weight every 2 weeks,
- pembrolizumab 10 mg/kg of body weight every 3 weeks,
- ipilimumab 3 mg/kg of body weight (4 applications).

Patients could receive only one line of treatment beforehand. Pembrolizumab was administered for a maximum of 2 years.

The OS median for both arms of pembrolizumab was 32.7 months (95% CI: 24.5–41.6), for ipilimumab was 15.9 months (95% CI: 13.3–22.0), (HR 0.73, 95% CI: 0.61–0.88, p = 0.00049].

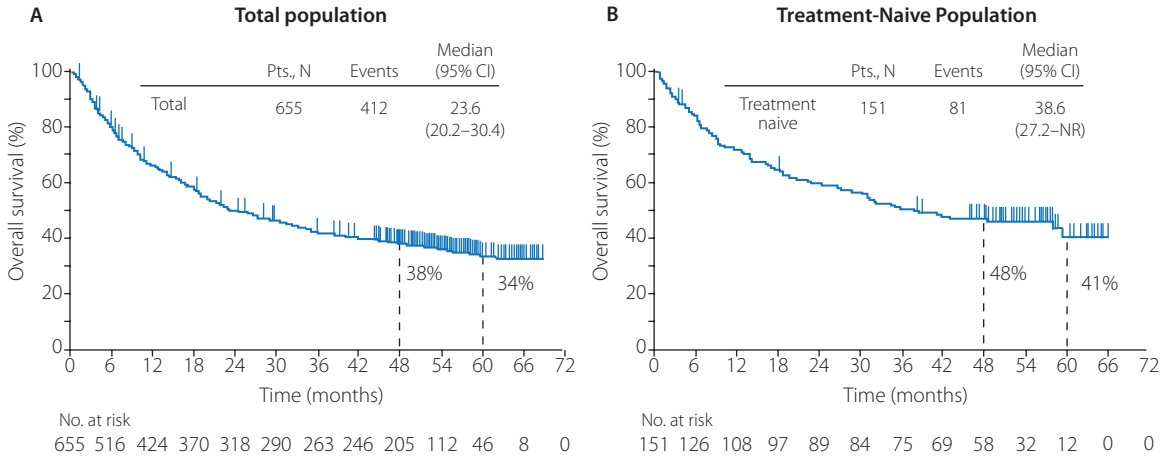

Figure 3. Long-term survival in the whole population (A) and in the previously untreated group (B) [11]

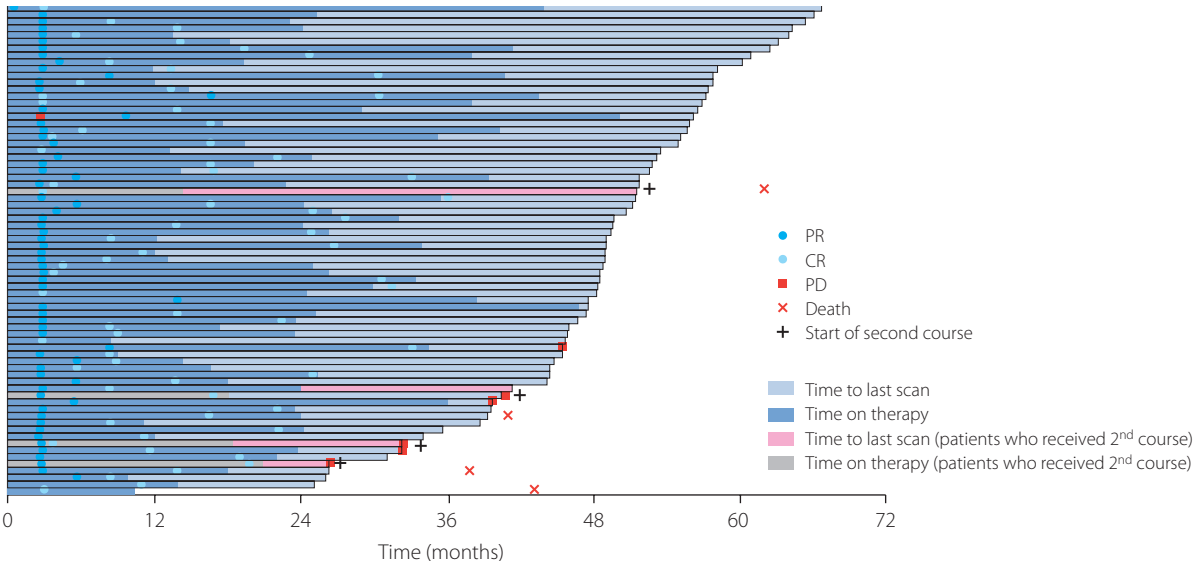

Figure 4. Analysis of the response in 72 patients who discontinued treatment with pembrolizumab in a clinical trial [11]

The percentage of 5-year overall survival was 38.7% for both groups of pembrolizumab and 31% for ipilimumab group. Patients who received pembrolizumab or ipilimumab in the first line had better results – median OS in these groups was 38.7 months (95% CI: 27.3–50.7) and 17.1 months (95% CI: 13.8–26.2).

Pembrolizumab used in the second line of treatment allowed to reach the median OS at the level of 23.5 months (95% CI: 16.8–34.2). The OS median for ipilimumab used in the 2nd line was 13.6 months (95% CI: 10.7–22.0).

For 2 years 103 patients (19%) received pembrolizumab; 21 of them obtained CR, 69 – PR and 13 – SD as the best response. After the median observation period at the end of pembrolizumab 34.2 months, the studied percentage of 2-year PFS was 78.4% (95% CI: 68.3–85.6). The percentage of 2-year and 3-year OS was 95.9% (95% CI: 89.4–98.4) and 93.8% (95% CI: 86.7–97.2).

In the group of patients who ended treatment with pembrolizumab after 2 years, the median time to progression of the disease was 33.3 months after the end of pembrolizumab administration. Thirteen patients in whom the disease progressed after the end of treatment received pembrolizumab again. In this group the percentage of CR was 23%, PR – 31% and SD – 15%. In one patient the disease progressed further and in 2 patients the response to treatment was not assessed yet [12, 13].

Nivolumab

One of the first studies of long-term survival was the analysis of patients participating in the first phase of the study CA209–003. The percentage of 5-year survival in the group of patients treated for advanced melanoma was 34% – a similar result was obtained in patients treated with pembrolizumab [14].

Recently, the long-term results of Checkmate-067 have been published. It was a phase III study in which patients were randomly assigned to one of the three arms:

- nivolumab,
- ipilimumab or
- nivolumab and ipilimumab.

Nivolumab in monotherapy or in combination with ipilimumab significantly improved PFS and OS compared to ipilimumab in monotherapy. After at least 48 months of observation the median OS was not achieved for the group treated with ipilimumab and nivolumab (95% CI: 38.2 – not reached) In the remaining arms, the median OS for nivolumab and ipilimumab was 36.9 (95% CI: 28.3 – not achieved) months and 19.9 (95% CI: 16.9–24.6) months.

The percentage of 4-year overall survival was 53% for combined therapy, 46% for nivolumab and 30% for ipilimumab. Both groups treated with nivolumab achieved significantly longer overall survival compared to those treated with ipilimumab. No statistically significant differences in overall survival between nivolumab and ipilimumab and nivolumab were found (HR 0.84, 95% CI: 0.67–1.05). An interesting observation from this analysis was the comparison of total survival depending on the initial concentration of lactate dehydrogenase (LDH). In the group of patients in whom LDH concentration exceeded the upper limit of norm by more than 2 times, the percentage of 4-year overall survival was as high as in the group of patients in whom LDH concentration exceeded the upper limit of norm: 28% in patients receiving nivolumab with ipilimumab, 14% in patients receiving nivolumab and only 7% in patients receiving ipilimumab [15].

Anti-PD-1 antibodies

For anti-PD-1 antibodies the overall survival curves after 3 years reach a plateau at about 40%. The problem with treating patients with immunotherapy with anti-PD-1 antibodies in monotherapy or in combination with anti-CTLA-4 antibodies is to determine the optimal duration of treatment. PET-TK examination, in some cases in combination with biopsy, may be a helpful tool in deciding to discontinue immunotherapy [16, 17].

Another problem is the relapse of the disease after an earlier discontinuation of immunological treatment after a long-term response. Available data confirm the need for this type of treatment again due to the possibility of a further response [18]. In Poland, however, current records of drug programs with anti-PD-1 antibodies do not allow for the possibility of re-treatment with anti-PD-1 in patients with advanced melanoma.

Achieving a long-term response to treatment is desirable for any patient who is struggling with a deadly disease. One may feel that the patients who get these results are constantly satisfied, but they have to struggle with a constant fear of relapse. There are currently no data on potential long-term adverse effects on cognitive capacity or emotional sphere in this group of patients [19].

Treatment with BRAF or MEK inhibitors

One of the analyses concerning the long-term survival of patients with advanced melanoma with *BRAF* V600 mutation treated with BRAF inhibitors is a study concerning the second phase (randomized) of BRF113220 study [20]. Part C of the study included 162 patients who were assigned to one of three groups (54 patients in each group) treated with:

- dabrafenib as monotherapy (D),
- dabrafenib 150 mg/day + trametinib 1 mg/day (D + T 150/1) or
- dabrafenib 150 mg/day + trametinib 2 mg/day (D + T 150/2).

The percentage of 4-year and 5-year PFS was 13% (95% CI: 5–25) in the arm D + T 150/2, 9% and 3% (95% CI: 0–11%) in the arm with monotherapy. The percentage of 4-year and 5-year OS was 30% (95% CI: 18–43%) and 28% (95% CI: 17–41%) respectively for D + T 150/2 and 23% (95% CI: 13-35%) and 21% (95% CI: 11–33%) for D with monotherapy. The percentage of 5-year overall survival was similar in patients treated with D + T 150/1 and D + T 150/2 (33% *vs.* 28%).

Further anticancer treatment resulted in a higher number of patients on the D arm in monotherapy than in the D + T 150/2 arm. The most frequent subsequent treatment regimens were immunotherapy (37% *vs.* 43% for D + T 150/2 and D respectively as monotherapy) and targeted treatment (24% *vs.* 87%).

A complete response to treatment according to Response Evaluation Criteria in Solid Tumors (RECIST) was reported in 9 (17%) patients in the D + T 150/2 arm and 2 (4%) patients in the monotherapy arm. In the subgroup of patients with CR in the D + T 150/2 arm, the percentage of 4- and 5-year OS was 56% and 44%, respectively, at the median OS 53.4 months.

In the subgroup of patients with normal LDH levels, the percentage of 4-year and 5-year survival in the D + T 150/2 arm was 48% (95% CI: 30–64%) and 45% (95% CI: 27–61%). In the monotherapy arm, the values were 31% (95% CI: 15–50%) and 26% (95% CI: 11–45%). Patients with normal LDH levels, in whom the cancer developed in three (or less) locations, benefited most from treatment [21, 22]. The percentage of 4-year and 5-year OS was 57% (95% CI: 32–76%) and 51% (95% CI: 27–71%) respectively for D + T 150/2 and 42% (95% CI: 15–67%) and 31% (95% CI: 8–58%) for the arm treated with dabrafenib.

Five-year survivals were analysed in a group of 563 patients who received dabrafenib and trametinib in two phase III studies: COMBI-d (211 patients) and COMBI-v (352 patients) [23]. The percentage of 4- and 5-year progression-free survival was 21% and 19%, respectively. In patients with normal LDH levels at initiation of treatment, the 5-year PFS percentage was 25%, compared to 8% in patients with LDH levels above the upper limit of normal.

Previous analysis, including the data of patients treated in the above two studies and one phase II study (617 patients in total), allowed us to identify a subgroup reaching a significan-

tly longer time to progression of the disease. There were 216 patients (38%) who had normal LDH levels at the beginning of treatment and at locations of the disease [21]. This group reached a 5-year PFS of 31%. The OS median for the whole population was 25.9 months (95% CI: 22.6–31.5). The percentage of 4- and 5-year overall survival was 37% and 34%, respectively. Patients with normal LDH concentration had better prognosis than patients with elevated LDH concentration. The percentage of 5-year OS was 43% and 16% respectively. In the subgroup of patients with normal LDH concentration and limited to

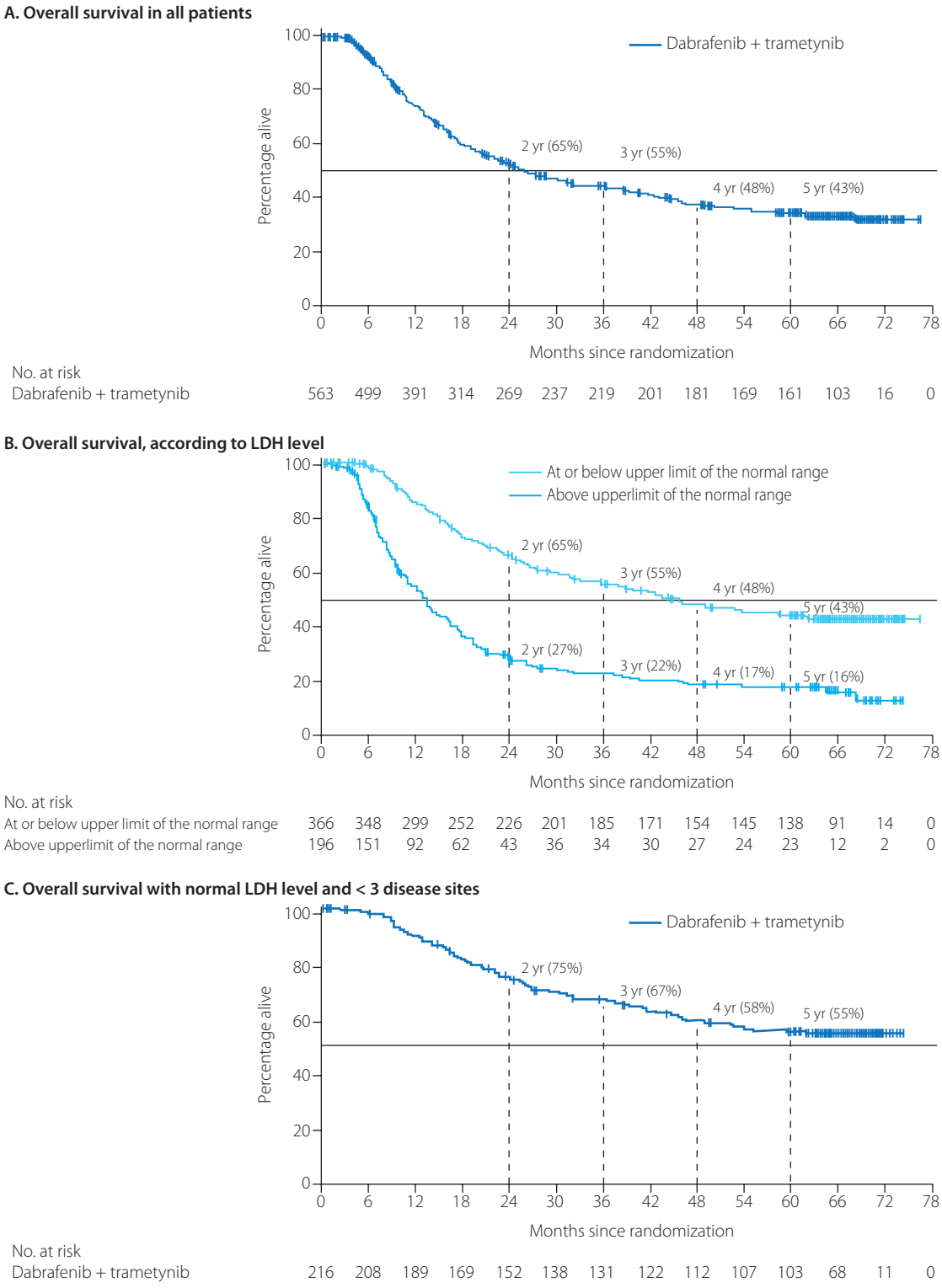

Figure 5. OS in the general population (A), depending on LDH (B) concentration, and in the group of patients with normal LDH concentration and with fewer than 3 locations of disease (C) [23]

3 occupied areas, the percentage of 5-year OS was estimated at 55 % (95% CI: 48–61) (fig. 5).

Of the 161 patients who lived at the time of analysis, 69 (43%) received dabrafenib, trametinib or both. Further anticancer therapy was administered to 72 patients (45%). Most often it was immunotherapy – 56 patients (78%), 42 (67%) received anti-PD-1 and 30 (42%) anti-CTLA-4 antibodies. In the remaining 89 patients (55%) no anticancer treatment of the next line was administered.

In the whole analysed population, further treatment lines were administered in 299 out of 563 patients (53%). Immunotherapy was the most frequent choice – 196 of 299 patients (66%) received it, including 151 (51%) treated with anti-PD-1 and 102 (34%) with anti-CTLA-4 antibodies.

Objective responses were recorded in 68% of patients, including total responses at 19% (109 patients). The percentage of 5-year OS in the group of patients with CR was 71%; in patients with PR this percentage was 32%, and in patients with disease stabilization – 16% (fig. 1). 6). The median of the CR period was 36.7 months. Table I shows the factors influencing survival free from disease progression and overall survival.

Summary

The use of anti-PD-1 antibodies and BRAF/MEK inhibitors in the group of patients with positive *BRAF* mutation allows to achieve long-term overall survival in about 1/3 of patients with advanced melanoma. Long-term responses to treatment are most often observed in patients with low disease severity and normal lactate dehydrogenase concentration before systemic treatment. In patients with melanoma with more aggressive course, a combination of anti-CTLA-4 and anti-PD-1 antibodies seems to be more effective in immunotherapy. However,

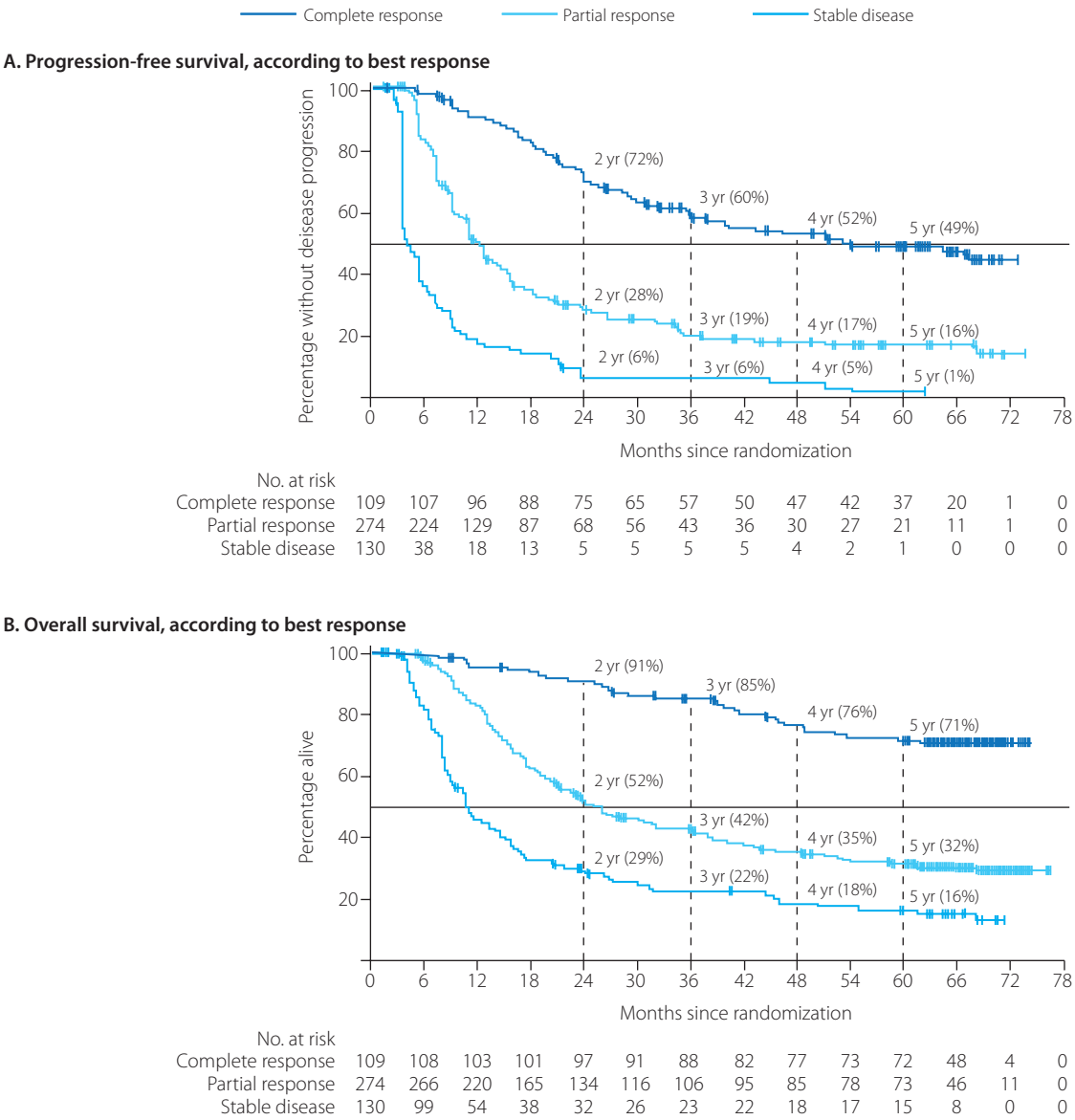

Figure 6. PFS depending on the response to treatment (A), OS depending on the response to treatment (B) [23]

Table I. Analysis of factors influencing survival free from disease progression and overall survival

Variable	Result tested (n)	PFS		OS	
		HR (CI 95%)	p	HR	p
Sex	Women (238) *vs.* men (313)	0.74 (0.61–0.90)	0.003	0.68 (0.55–0.84)	<0.001
BRAF mutation	V600E (482) *vs.* V600E or V600K plus V600K (69)	0.65 (0.49–0.87)	0.004	0.77 (0.55–1.06)	0.11
General condition	ECOG 0 (398) *vs.* ECOG ≥1 (153)	0.68 (0.55–0.85)	<0.001	0.49 (0.39-0.62)	<0.001
LDH concentration	Normal (359) *vs.* elevated (192)	0.50 (0.40–0.64)	<0.001	0.47 (0.37–0.61)	<0.001
Number of locations with disease	<3 locations (282) *vs.* ≥3 locations (269)	0.72 (0.58–0.91)	0.005	0.58 (0.46–0.74)	<0.001

this group of patients still requires new therapeutic options. Several ongoing clinical trials are aimed at answering the question about the correct sequence of treatment and the appropriateness of using immunotherapy in combination with targeted treatment.

Conflict of interest: none declared

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