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Immunotherapy or targeted therapy as first-line treatment of patients with advanced/metastatic melanoma with the *BRAF* mutation — a single-center analysis

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ABSTRACT

Introduction. One of the most important achievements of contemporary oncology is the discovery of new therapeutic possibilities: targeted therapy and immunotherapy associated with checkpoint inhibitors. It has not been unequivocally determined so far which therapy should be used as first-line treatment in patients with advanced/metastatic melanoma with the *BRAF* mutation.

Material and methods. 137 patients with advanced/metastatic melanoma with the *BRAF* mutation were analyzed. They received anti-PD1-1 therapy (IT) or molecularly targeted therapy iBRAF ± iMEK (TT) as first-line treatment in the scope of the national drug program. IT and TT therapies used as first-line treatment were compared.

Results. Median OS and PFS in the group were 14.0 and 7.3 months. Unfavorable prognostic factors for OS and PFS were metastases to the central nervous system, increased LDH levels and performance status > 1. Metastatic sites in > 2 locations were only unfavorable prognostic factors for OS. A statistically significant difference was found between TT and IT for OS ($p = 0.0011$; median for TT was 12.6 months and was not reached for IT). It should be noted that the group treated with TT was characterized by a worse prognostic factors. No differences in PFS were observed ($p = 0.292$, medians 7.2 and 9.0 months, respectively).

Conclusion. In patients with advanced/metastatic melanoma with a *BRAF* mutation without rapid progression, IT should be considered as first-line therapy.

Key words: melanoma, immunotherapy, targeted therapy, sequential therapy, *BRAF* mutation

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Introduction

In recent years treatment of patients with a melanoma diagnosis has changed greatly. The presence of specific mutations in melanoma cells, including the *BRAF* [1] mutation, was discovered. The *BRAF V600* mutation is present in approximately 50% of patients with metastatic melanoma and is a predictive factor for response to targeted therapies [2]. The use of targeted therapies with inhibitors of BRAF ± MEK (iBRAF ± iMEK) has contributed to a considerable improvement of the treatment results in respect to overall survival (OS) and progression-free survival (PFS) which has been confirmed in randomized trials [3–8]. Moreover, the development of immunotherapy associated with immune checkpoint inhibitors (ICIs) has improved the results of treatment of melanoma patients [9–18]. ICI action is independent of the presence of the *BRAF* mutation

[16–19]. Administration of ICIs may lead to long-term remission [8–16]. The dominant problem, however, is the low percentage of responses to immune checkpoint inhibitors as well as the length of time from the moment of initiating the therapy to the response to treatment [9–16]. The response to targeted therapies is different, as the percentage of responses to treatment is high and the time to response is very short [3–8].

Systemic treatment of patients with the *BRAF* mutation poses a significant therapeutic challenge. So far the therapy which should be applied as first-line treatment has not been determined unequivocally in patients with advanced/metastatic melanoma. There is little data on this subject and the results of randomized trials, which would directly compare the effectiveness of anti-PD-1 immunotherapy (IT) and targeted therapy iBRAF ± iMEK (TT) as first-line treatment in this group of patients are missing [20–26]. Currently, two clinical studies are ongoing DREMseg (NCT02224781) and SECOMBIT (NCT02631447) and EORTC EBIN which should answer to this question but the results are still awaited [27].

Therefore we decided to undertake a retrospective analysis comparing first-line TT or IT treatment in patients with advanced/metastatic melanoma with a *BRAF* mutation. The paper presents the analysis of 137 patients with advanced/metastatic melanoma with a *BRAF* mutation who received immunotherapy or targeted therapy as first-line treatment.

Material and methods

All patients with advanced/metastatic melanoma treated in the frame of national drug programs from January 2013 to June 2019 in the Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Cracow branch were analyzed. 137 patients from the group with the *BRAF* mutation who had received IT or TT as first-line treatment were selected from this group. First-line IT treatment in patients with the *BRAF* mutation in the scope of national drug programs was initiated in 2017 as then new indications were included. In all analyzed patients data were collected concerning age, sex, location of the primary tumor, stage of the disease and type of therapy used as first, second and subsequent line. Information concerning the stage of the disease, metastasis location, lactate dehydrogenase (LDH) levels (LDH) and ECOG (Eastern Cooperative Oncology Group) performance status [17] were collected at the start of systemic first-line treatment.

Statistical analysis

To determine the p value of defined factors between the group treated with IT and the larger group treated with TT Fisher's exact test was used. The final points encompassed evaluation of progression-free survival (PFS), overall survival (OS) and evaluation of the overall response rate (ORR) and disease control rate (DCR) defined by the criteria of response evaluation RECIST 1.1. PFS or OS were calculated from the beginning of IT or TT to disease progression according to RECIST, death or the last documented contact. The Kaplan-Meier method was used to evaluate PFS and OS with a 95% confidence interval (CI) and survival curves were analyzed by log-rank analysis. The Cox proportional hazard model was used to evaluate, in a multidimensional model, the significance of the effect of prognostic variables on PFS and OS at the moment of initiation IT or TT therapy. Differences are considered significant if $p < 0.05$. All statistical analyses were performed using the STATISTICA 12 program.

Results

General characteristics of the analyzed group

In the group of 137 patients with advanced/metastatic melanoma with the *BRAF* mutation 110 (80%) patients received first-line TT therapy and 27 (20%) IT. TT in 45 (41%) patients was iBRAF (vemurafenib or dabrafenib) and in 65 (55%) iBRAF + iMEK (vemurafenib + cobimetinib or dabrafenib + trametinib). Before 2017, 64 patients received TT treatment. As IT anti-PD-1 (nivolumab or pembrolizumab) was used. 57 (42%) patients received second line treatment, among them 39 patients received the IT-TT sequence and 4 patients the TT-IT sequence. In the group receiving the TT-IT sequence, the second line treatment was nivolumab or pembrolizumab (19 patients) and ipilimumab (20 patients). In the IT-TT group, the second line treatment in all patients was iBRAF + iMEK. Third line and fourth line treatment were administered to 15 (11%) patients and 3 (2%) patients, respectively. In the group receiving TT, there were statistically significantly more patients with metastases to the CNS, elevated LDH levels and a higher grade of the tumor. Precise characteristics of the analyzed group are presented in Table 1.

Results of treatment in the whole *BRAF*+ group

Median overall survival (OS) and progression-free survival (PFS) in the whole analyzed group were 14.8 and 7.4 months, respectively. In monofactorial analysis unfavorable effects on OS and PFS were observed for metastases to the brain ($p < 0.0003$ and $p = 0.0071$, respectively), increased LDH levels ($p < 0.0001$ and $p = 0.0028$, respectively) and ECOG performance status > 1 ($p = 0.0002$ and $p = 0.0033$, respectively).

Table 1. Characteristics of patients in respect to first-line therapy used

Factors		IT n = 27 (20%)	TT n = 110 (80%)	p	Whole group n = 137
Age	Median (years)	59	58	0.5997	59
	≤ 65	20 (74%)	78 (71%)	0.9294	98 (72%)
	> 65	7 (26%)	32 (29%)		39 (28%)
Sex	Male	18 (67%)	60 (45%)	0.2497	78 (57%)
	Female	9 (33%)	50 (55%)		59 (43%)
Tumor stage	M1a	8 (26%)	15 (14%)	0.0096	23 (17%)
	M1b	7 (25%)	17 (15%)		24 (18%)
	M1c	10 (37%)	60 (55%)		70 (51%)
	M1d	2 (7%)	18 (16%)		20 (14%)
Presence of metastases to CNS	No	25 (96%)	92 (84%)	0.0071	127 (93%)
	Yes	2 (8%)	18 (16%)		20 (7%)
Number of metastatic sites	≤ 2	16 (59%)	50 (45%)	0.2840	66 (48%)
	> 2	11 (40%)	60 (55%)		71 (52%)
LDH	Normal	22(81%)	44 (40%)	0.0002	66 (48%)
	Above normal	5 (19%)	62 (56%)		67 (49%)
	No data	0 (0%)	4 (4%)		4 (3%)
LDH (×2)	≤ 2 × normal	26 (96%)	82 (78%)	0.0039	106 (81%)
	> 2 × normal	1 (4%)	24 (22%)		25 (19%)
ECOG/PS	0	4(15%)	11 (10%)	0,4326	15 (11%)
	1	22 (81%)	84 (76%)		106 (77%)
	2	1 (4%)	14 (13%)		15 (11%)
	3–4	0 (0%)	1 (1%)		1 (1%)
Localization of primary tumor	Skin	24 (89%)	91 (83%)	0,1337	115 (84%)
	Mucous membrane	1(4%)	0		1(1%)
	From unknown primary tumor location	2 (7%)	19 (17%)		21 (15%)

T — anti-PD-1 immunotherapy; TT — targeted therapy with BRAF ± MEK inhibitors; LDH — lactate dehydrogenase; CNS — central nervous system; ECOG/PS — performance status

The presence of metastases in > 2 sites had a statistically significant unfavorable effect only on OS (p = 0.0113). Sex, age > 65 years, location of the primary site did not have a statistically significant effect on OS and PFS.

Treatment results depending on the type of first line therapy TT *vs*. IT in *BRAF*+ patients

Median overall survival (OS) in the group receiving TT was 13.3 months whereas median OS was not attained in the IT group (median observation in the TT and IT groups was TT and IT 22 and 18 months, respectively). A statistically significant difference in OS was observed between groups treated with TT and IT (p = 0.0011) (Figure 1A) as well as between groups treated with iBRAF + iMEK, only iBRAF and IT (p = 0.0084) and iBRAF + iMEK *vs.* IT (p = 0.0074) (Figure 1B and 1C). A statistically significant difference was also observed in OS between the group receiving TT before 2017 (p = 0.0071) and the group treated with IT (Figure 1 D). There was no difference in OS between groups receiving TT before 2017 and from the beginning of 2017 (p = 0.2634) (Figure 1E). Median progression-free survival (PFS) in the groups receiving TT and IT were 7.2 and 9.0 months, respectively, and no statistically significant difference between them was observed (p = 0.292). Similarly, there was no statistically significant difference in PFS between the group receiving IT and the group treated with TT iBRAF + iMEK (p = 0.1001), as well as between the group receiving IT and the group treated only with TT before 2017 (p = 0.3498). A precise analysis of the

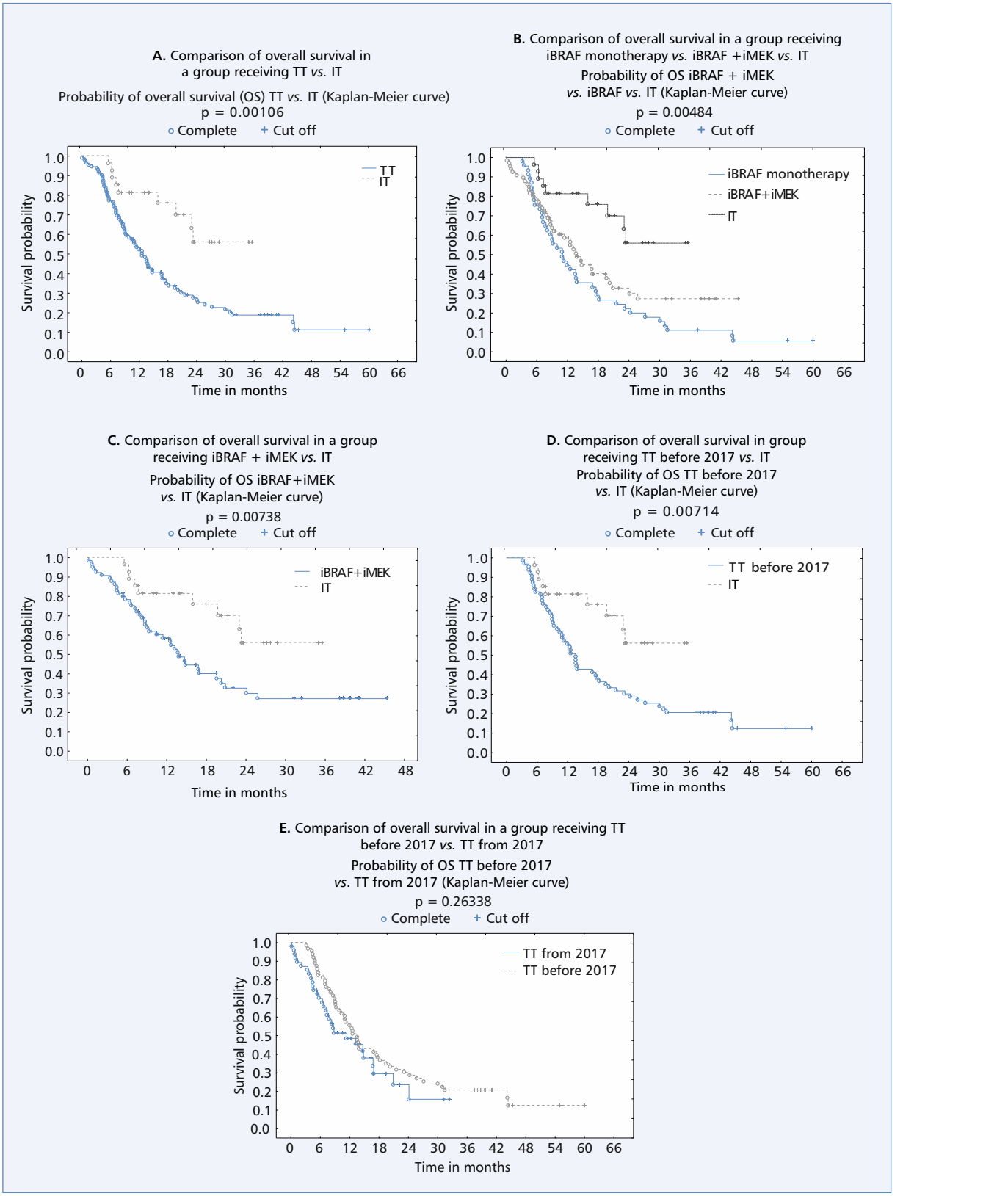

Figure 1. Kaplan-Meier survival curves. IT — anti-PD-1 immunotherapy; TT — targeted therapy with BRAF ± MEK inhibitors (iBRAF ± iMEK)

Table 2. Results of treatment depending on the first-line therapy used

Type of therapy	IT n = 27 (20%)	TT n = 110 (80%)	Total n = 137 (100%)
OS (median in months) p = 0.0011	Not reached	12.6 (6.7–24.6)	14.0 (7.2–31.2)
6-month OS	94%	76%	80%
1-year OS	81%	52%	57%
2-year OS	56%	26%	29%
PFS (median in months) p = 0.292	9.0 (3.7–26.6)	7.2 (4.2–12.7)	7,3 (4.1–14.4)
Response to treatment			
CR	4%	5%	4%
PR	41%	58%	55%
ORR (CR + PR)	45%	63%	59%
SD	44%	24%	29%
DCR (CR + PR + SD)	89%	77%	88%
PD	11%	13%	12%

IT — anti-PD-1 immunotherapy; TT — targeted therapy with BRAF ± MEK inhibitors; OS — overall; PFS — progression-free survival; CR — complete response; PR — partial response; SD — stable disease; PD — progression of disease; ORR — overall response rate; DCR — disease control rate

Table 3. Cox multifactorial analysis

Analyzed factors	PFS			OS		
	p	HR	CI	p	HR	CI
TT *vs.* IT	0.9768	1.0	0.6–1.7	0.0753	1.92	0.9–3.9
> 65 *vs.* ≤ 65	0.5618	0.88	0.6–1.4	0.5968	0.88	0.6–1.4
Female *vs.* male sex	0.7086	0.92	0.6–1.4	0.6881	0.91	0.6–1.4
Lack of metastases to CNS *vs.* metastases to CNS	0.0129	0.55	0.3–0.9	0.0021	0.46	0.3–0.8
Number of locations ≤ 2 *vs.* > 2	0.5334	1.15	0.7–1.8	0.7619	0.93	0.6–1.5
LDH normal *vs.* elevated	0.0150	0.58	0.4–0.9	0.0019	0.47	0.3–0.8
ECOG ≤ 1 *vs.* > 1	0.0013	0.38	0.2–0.7	< 0.001	0.28	0.2–0.5

T — anti-PD-1 immunotherapy; TT — targeted therapy with BRAF ± MEK inhibitors; LDH — lactate dehydrogenase; CNS — central nervous system; ECOG/PS — performance status

treatment results for group TT and IT is presented in Table 2. In multifactorial analysis a statistically significant unfavorable effect on OS and PFS was found for increased LDH levels, the presence of metastases to the CNS and ECOG > 1. The other factors were not statistically significant (Table 3).

Discussion

In the presented analysis a comparison was made between first-line IT or TT treatments in patients with advanced/metastatic melanoma with the *BRAF* mutation. This is one of the very few analyses which encompass very homogeneous patient groups. All patients were treated in the frame of national drug programs and thus had to fulfil the same criteria for inclusion.

Among the first trials which determined the effectiveness of using immunotherapy before or after iBRAF were those performed by Ascierto et al. and Ackerman et al. [24, 25]. In these trials. ipilimumab was mainly used for immunotherapy and it was shown that immunotherapy administered before iBRAF does not decrease their effectiveness [24, 25]. Subsequent trials and (indirect) analyses confirmed that the use of immunotherapy in first-line treatment in patients with

a *BRAF* mutation could be a better option than targeted therapy [22, 23, 26].

Our analysis indicated higher effectiveness in first-line IT as compared to TT treatment in respect to OS ($p = 0.0011$) and lack of differences in respect to PFS ($p = 0.292$). This was, however, not confirmed in multifactorial analysis, which could be due to the small group receiving IT. Moser et al. and Schilling et al. who analyzed larger patient groups showed greater effectiveness in respect to OS for immunotherapy in first-line treatment in patients with advanced/metastatic melanoma with the *BRAF* mutation [20, 23]. In both these analyses, the OS for TT were similar (13.2 and 12.4 months) to our results (13.3 months) which indicates that the groups were similar and thus can confirm the similarity of the remaining results. It is worth mentioning that when immunotherapy was used in the BRAF+ group of the CheckMate067 trial, better results were obtained for combined anti-PD1 and anti-CTLA-4 immunotherapy than for anti-PD-1 monotherapy.

As recruitment of patients for IT treatment started in 2017, analysis of groups treated before 2017 and from 2017 was performed. The aim was to check if differences in OS between groups treated with TT and IT could be due to the fact that from 2017 patients with a worse prognosis qualified for TT treatment. No statistically significant difference was found for OS for patients receiving TT before and after 2017. A statistically significant difference was observed for patients treated with TT before 2017 and IT. The effectiveness of therapy with iBRAF, iBRAF + iMEK and IT was also compared. In all cases, IT was shown to prolong OS. It is worth noting that the results of treatment are worse in the analyzed group than in clinical trials, but better than in historical groups before new therapies were introduced.

Of course, our analysis has some limitations. First, it is retrospective, second, we compare small groups and moreover, they are unequal in size. Also, the fact that in the group receiving TT there were more patients with metastases to the CNS and elevated LDH levels (thus unfavorable prognostic factors) can affect the results of our analysis. Therefore, in order to unequivocally compare the effectiveness of TT and IT prospective, randomized trials should be conducted.

It can be stated with considerable certainty that in patients with advanced/metastatic melanoma with the *BRAF* mutation without rapid progression IT should be considered as first-line therapy.

Conflict of interest

Grants and consultancies:

Bożena Cybulska-Stopa — BMS, Novartis, Roche, Pierre Fabre, MSD; Karolina Piejko — MSD; Agata Sałek-Zań — BMS

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