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Economic evaluation of adverse events of dabrafenib plus trametinib versus nivolumab in patients with advanced BRAF-mutant cutaneous melanoma for adjuvant therapy in Germany

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ABSTRACT

Background: Adjuvant treatment options have become the standard therapy for stage III and IV resectable cutaneous melanoma. Two recent studies led to the registration of dabrafenib and trametinib as targeted therapies for BRAF-mutated melanoma, and of immunotherapy with nivolumab irrespective of BRAF-mutation status. Both therapies have different spectrums of adverse events.

Objective: To estimate the financial impact of side effects from the perspective of the German statutory sick funds to compare both therapeutic options and to relate the burden to the overall costs of the treatment.

Study design and setting: Thirty-six adverse event categories for the combination of dabrafenib and trametinib ('combi treatment') and for nivolumab were extracted from the original publications of the studies named COMBI-AD and CheckMate 238.

Patients and intervention: For all event categories a diagnosis and therapy recommendation were determined according to current national or international guidelines or from leading German textbooks.

Main outcome measure: The resulting diagnostic steps, treatments, and therapies were evaluated with unit costs based on the German fee schedule for ambulatory physicians, the German G-DRG scheme, and the German drug price list.

Results: The number of events with nivolumab per one hundred treatments amounted to 3.8 mandatory hospitalizations, 3.5 emergency care events and 0.8 life-threatening events. For the combi treatment, the respective number of events per one hundred treatments was 2.7, 1.8, and 0.5. The overall cost burden was calculated as €899 for nivolumab and €861 for combi-treatment.

Conclusion: The treatment of adverse events resulting from adjuvant melanoma therapy showed comparable costs for both therapies.

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Combi-treatment; cost burden; dabrafenib; nivolumab; therapeutic strategy; trametinib

Introduction

Melanoma is a cancer that develops from melanocytes and typically occurs in the skin [1]. Global incidence of melanoma was estimated to be 288,000 in 2018 [2]. In Germany, around 23,000 patients were newly diagnosed with cutaneous melanoma in 2016 [3].

Surgical resection is the preferred treatment for localized melanoma and frequently cures stage I and II diseases [4]. Adjuvant treatment was explored in patients with a high risk of recurrence following complete surgical resection in order to reduce the risk of relapse, and has recently become the standard of therapy [5,6].

For cutaneous melanoma, long-term data have shown that 37%, 68%, and 89% of the patients with stage IIIA, IIIB, and IIIC, respectively, relapse within five years after resection [7,8]. The estimated five-year survival rates for stages IIIA, IIIB, and IIIC from the time of first relapse were 20%, 20%, and 11%, respectively [9]. Thus, in staging databases, more than half of patients with stage III had died within ten years after diagnosis; the findings for stage IV were even worse [4,10].

Since 2011, several new therapeutic options have been approved that demonstrated efficacy for advanced stage melanoma. This improved the outcome for patients with melanoma [8,11]. The main new options at present are immunotherapy and targeted therapy.

Ipilimumab, an anti-CTLA-4 antibody, was the first new drug to show significant survival benefit in melanoma patients [12]. Other cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1) immune checkpoint inhibitors

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were subsequently shown to improve long-term survival when applied to defined patient cohorts [13,14].

The discovery of activating somatic BRAF V600 mutations in melanoma cells led to the success of kinase inhibitors as a targeted therapy [14]. The response rates were better than those of all previously used chemotherapies, and the outcome improved significantly with combined mitogen-activated protein kinase (MAPK) inhibition [15].

In approximately 45% of advanced melanomas, B-Raf proto-oncogene, serine/threonine kinase (BRAF) V600 mutations can be found, which result in consecutive activation of the MAPK pathway [15,16]. The targeted agents to block MAPK pathway activation are BRAF inhibitors and mitogen-activated protein kinase inhibitors. They have demonstrated significant clinical benefit in patients with BRAF V600-mutated melanomas [17–20].

Different therapies have been investigated in the adjuvant setting after potentially curative resection. However, to date, no studies have shown any improved overall survival [21–23]. The first trials with the new therapeutic options could only demonstrate improved relapse-free survival [24,25].

Almost simultaneously, two further new therapies underwent major clinical trials in comparable populations with advanced cutaneous melanoma for adjuvant therapy after resection: the combination of two targeted therapies, dabrafenib and trametinib, and the checkpoint inhibitor nivolumab. Both trials, COMBI-AD [26] for the targeted combination and CheckMate 238 [27] for the checkpoint inhibitor were published back to back in 2017 in the same journal. They laid the foundation for registration of both therapeutic options by the European Medicines Agency and the US Food and Drug Administration [28–30], because both demonstrated significantly improved outcomes thus far in both relapse-free survival and distant metastasis-free survival. COMBI-AD was limited to patients with a proven BRAF mutation. Both therapies were also reflected in current treatment guidelines [31,32].

The focus of the research was on the effects of both therapies on relapse-free and overall survival [33], but there is also clinical interest in the different side effect profiles of the two therapeutic options [34–38]. The economic analyses for both strategies also stressed mostly efficacy in a comparative setting, which was facilitated due to the very comparable study designs [39–43].

A rather neglected question in the published health economic literature is the role of the adverse event profiles of both therapies, their comparisons, and their economic consequences [44]. Here, we attempt to analyze the economic impact of the side effects in both therapies, based on the published results of both trials. Our first objective was to relate the findings to the overall costs of a therapy for advanced melanoma, and our second was to compare the side effect cost of both therapeutic options. The results should be useful for further cost-benefit assessments or health technology assessments. We chose the perspective of the German statutory sick funds (GKV) covering about 90% of the German population for the cost analysis of the reported adverse events. Thus far there is only limited knowledge, how the costs of side effects of melanoma treatment impact the German health-care system.

Materials and methods

The adverse events for the combination of dabrafenib and trametinib and for the checkpoint inhibitor nivolumab were extracted from the original publications of the studies COMBI-AD [26] and CheckMate 238 [27]. Both articles presented tables of adverse events in a remarkably similar structure. In addition, CheckMate 238 provided additional data in an appendix. Both tabulations relate to very similar settings (e.g., intention of one-year therapy) and were registered with the same documentation system for adverse events (Common Terminology Criteria for Adverse Events, CTCAE 4.0) [45].

In the study CheckMate 238, the number of patients at baseline was 453 in each group. In Combi-AD there were 438 patients in the combi-treatment group and 432 in the placebo group.

All cause and all grade adverse events associated with nivolumab were estimated from the published results of the CheckMate 238 trial. All cause and all grade adverse events associated with dabrafenib and trametinib were estimated from the published results from the COMBI-AD trial.

In both cases, patients were treated with the medication for up to a year. Both studies assessed adverse events from the first dose of the study medication until 30 days after discontinuation of the study medication.

The inclusion criteria in both studies were slightly different, but seemed comparable (melanoma grade IIIB, IIIC, and IV in CheckMate 238 and melanoma grade IIIA/B/C in COMBI-AD). The list of adverse events in the Combi AD publication was restricted to events that occurred in at least 10% of patients in the respective treatment group. In Checkmate-238, adverse events were reported if they had occurred in at least 5% of patients. In addition, the events had to be treatment related. For these reasons, the lists of adverse events

are incomplete in both publications. Both publications documented the number of patients experiencing an event in two categories, all grades and grade 3/4. Thus, grade 1 and 2 events could be determined by subtraction. But it had to be assumed that every patient experienced a specific event in the given category only once.

Thirty-six categories of adverse events were extracted from the combined publications, mostly differentiated according to the CTCAE 4.0 mapping (see Table 1). Adverse events were described as grade 1 or 2 events and as grade 3 or 4 events. This mapping has previously been applied in economic analyses [46,47]. All specifically published adverse events were considered. The adverse events that were undefined in the publications (all-other cause) were calculated with averaged costs. Grade 1 and 2 events were assumed to be evenly split, and the grade 3 and 4 events assumed to have proportions of 80% grade 3 and 20% grade 4. Little information could be found about the proportion of grade 3 and 4 in closely related studies. Only one study investigating the use of Nivolumab in metastatic non-small cell lung cancer [48] mentions the proportions of grade 3 and 4 events explicitly. Therefore, we performed a sensitivity analysis to estimate the impact of this assumption.

For each of the 36 adverse event categories, the exact description of the four defined grades of severity was extracted. Sixteen of the 36 categories had no grade 4 definition, and one had no grade 1 definition. For each grade of each category a recommendation for diagnosis and therapy according to current national or international guidelines was identified. If no applicable guideline could be identified, recommendations from leading German textbooks were considered. Thus, a practical diagnostic and treatment scheme was developed for each situation, basically a table of 36 times four boxes, minus 17 events without a defined grade.

Table 1. Reported adverse events per 100 treatments from the studies Combi AD for dabrafenib and trametinib and Checkmate 238 for nivolumab. Explanation of the necessary level of care for each adverse event.

CTCAE		Any grade		Grade 1/2		Grade 3/4		Demanding		
#	Category	nivolumab	mek/taf	nivolumab	mek/taf	nivolumab	mek/taf	No G 4	Hospit.	Urgent.
1	Decreased appetite	0.0	11.0	0.0	10.5	0.0	0.5			Urgent.
2	Fatigue	34.5	46.6	34.1	42.2	0.4	4.3	No G 4		
3	Asthenia	12.6	13.2	12.4	12.8	0.2	0.5	No G 4		
4	Nausea	15.0	39.3	14.8	38.4	0.2	0.9	No G 4	Hospit.	
5	Vomiting	0.0	27.9	0.0	26.9	0.0	0.9		Hospit.	Urgent.
6	Diarrhea	24.3	32.9	22.8	32.0	1.5	0.9		Hospit.	Urgent.
7	Constipation	0.0	11.6	0.0	11.6	0.0	0.0	No G 4		Urgent.
8	Abdominal pain	6.4	0.0	6.4	0.0	0.0	0.0	No G 4		
9	Colitis	2.0	0.0	1.3	0.0	0.7	0.0			Urgent.
10	Pruritus	23.2	0.0	23.2	0.0	0.0	0.0			
11	Dry skin	0.0	12.6	0.0	12.6	0.0	0.0	No G 4		
12	Rash	19.9	24.2	18.8	24.2	1.1	0.0	No G 4		
13	Maculopapular rash	5.3	0.0	5.3	0.0	0.0	0.0	No G 4		
14	Erythema	0.0	11.0	0.0	11.0	0.0	0.0			Urgent.
15	Dermatitis acneiformis	0.0	12.3	0.0	11.9	0.0	0.5			Urgent.
16	Headache	9.7	38.8	9.5	37.4	0.2	1.4	No G 4		
17	Pyrexia	1.5	62.3	1.5	57.1	0.0	5.3			
18	Chills	0.0	36.8	0.0	35.4	0.0	1.4	No G 4		
19	Influenza-like illness	0.0	15.3	0.0	14.8	0.0	0.5	No G 4		
20	Cough	0.0	16.7	0.0	16.7	0.0	0.0	No G 4		
21	Myalgia	0.0	16.0	0.0	15.8	0.0	0.2	No G 4		
22	Arthralgia	12.6	27.4	12.4	26.5	0.2	0.9	No G 4		
23	Pain in limb	0.0	13.7	0.0	13.2	0.0	0.5	No G 4		
24	Infusion reaction	2.4	0.0	2.0	0.0	0.4	0.0		Hospit.	Urgent.
25	Increase/Elevated ALT	6.2	15.3	5.1	11.6	1.1	3.7			
26	Increase/Elevated AST	5.5	14.4	5.1	10.7	0.4	3.7			
27	Increase/Elevated GGT	0.0	0.0	0.0	0.0	0.0	0.0			
28	Peripheral edema	0.0	13.2	0.0	13.0	0.0	0.2	No G 4		
29	Hypertension	0.0	11.2	0.0	5.5	0.0	5.7			Urgent.
30	Hypothyroidism	10.8	0.0	10.6	0.0	0.2	0.0		Hospit.	Urgent.
31	Hyperthyroidism	8.0	0.0	7.7	0.0	0.2	0.0		Hospit.	Urgent.
32	Hypophysitis	1.5	0.0	1.1	0.0	0.4	0.0		Hospit.	Urgent.
33	Adrenal disorder	1.3	0.0	0.9	0.0	0.4	0.0		Hospit.	Urgent.
34	Diabetes	0.4	1.6	0.2	1.6	0.2	0.0		Hospit.	Urgent.
35	Renal (not defined)	1.3	0.0	1.3	0.0	0.0	0.0			
36	Pulmonary (not defined)	1.3	0.0	1.3	0.0	0.0	0.0			
	Sum	206.2	525.1	198.0	493.4	8.2	31.7			

Calculated events per 100 treatments. CTCAE: Common Terminology Criteria for Adverse Events, Version 4.0.
CTCAE definitions: No G 4 = no grade 4 defined; Hosp.: Hospitalization demanded; Urgent.: Immediate intervention demanded.
AST = aspartate aminotransferase; ALT = alanine aminotransferase; GGT = gamma glutamyltransferase.
mek/taf: Combination Dabrafenib and Trametinib.

The definition of adverse event grades by CTCAE is heterogenous. Some definitions explicitly cite the level of care that is expected at the given grade, e.g., hospitalization or intensive care. Many describe the loss of daily living activity regarding self-care and supply. Others are only specified by a threshold of a laboratory test (e.g., alanine aminotransferase or aspartate aminotransferase levels) or a physiological parameter (e.g., blood pressure in mmHg).

The CTCAE provide some general description, which implies possible hospitalization with grade 3. In our model, hospitalization was assumed only if this was explicitly mentioned in the CTCAE scheme or if hospitalization was recommended by the guidelines. In general, hospitalization was assumed for all CTCAE of grade 4. Intensive care unit (ICU) care was only assumed if the CTCAE implied intensive care in grade 4 or this could be derived from the description or guidelines.

The treatment path is based on the dermatological oncologist's perspective, who, presumably, cares for the patient regularly in follow-up and therapy, in addition to conducting regular laboratory tests, ultrasonography, and radiologic investigations. The patient should first visit this physician based on symptoms and from there be sent to other specialists, such as diabetologists or radiologists for further investigations and treatment.

For each type of event, direct costs were derived for ambulatory physicians' services, laboratory services, and inpatient services. The cost perspective of the German statutory sick fund was chosen, which covers costs for hospitalization and medication directly. In Germany, physicians are reimbursed by a fee-for-service remuneration from their regional physician organizations. These organizations receive a lump sum from the statutory sickness funds, a sum negotiated every year. In this study, the costs for ambulatory care were estimated by employing the fee-schedules used for patients covered by statutory sickness funds.

In addition to the cost scheme of the German ambulatory physicians [49] the German G-DRG scheme [50], as of April 2020 was applied for hospitalizations. For the inpatient care by nursing staff, which is not part of the DRG, the cost assumptions of the DRG-Research Group Münster were employed [51] and the 2020 federal average base case value was used as a multiplier [52].

The cost calculation procedure for adverse events was straightforward. Costs of each sector for each event grade were added and then multiplied by the share of patients with this specific event, separated for the two studies. Results could be shown for each adverse event and further refined for single grades or disease groups (see Table 5).

To check the robustness of the results according to a variation of the cost variables, a sensitivity analysis was undertaken, simulating an isolated increase of treatment costs by 25% for each organ class. Calculations were performed using Microsoft Excel Version 2019.

Results

The calculated cost for the described adverse events was found to average €706.02 per treatment for the combi-treatment (dabrafenib and trametinib) and €700.52 per treatment for the checkpoint inhibitor (nivolumab). Adding the remaining events with no diagnoses reported in the publications resulted in a cost of €861.89 for the combi-treatment and €899.28 for nivolumab, assuming average costs for each unspecified event.

In total, 96.3% of patients experienced any adverse event with the combi-treatment and 96.6% with nivolumab. The analysis was based on events; patients could experience several adverse events. The number of reported events with the combi-treatment was 41.1 CTCAE grade 3 and 4 events, 31.7 with reported diagnosis, and 525.1 grade 1 and 2 events, all per hundred treatments. For nivolumab, the numbers were 25.4 events of CTCAE grade 3 and 4, 8.2 with reported diagnosis, and 206.1 grade 1 and 2 events, per hundred treatments (see Table 1).

The spectrum of adverse events for the two therapeutic strategies is different. With the combi-treatment, there are more frequent reports of general gastrointestinal issues, pain, and hypertension. With nivolumab, several endocrine dysfunctions, diarrhea, colitis, and infusion reaction were more common (see Table 1).

The cost calculation for grade 1 and 2 events led to comparable results for most types of events. Hospitalization was infrequent, the diagnostic tests were rather simple, and the medication consisted mainly of generic drugs, which are usually extremely low priced in Germany. The average cost of a grade 1 or 2 adverse event was calculated at €105. This low amount is explained mainly due to the lump sum payments to physicians in Germany, which do not cover additional visits and include basic investigations only. The average cost per therapy was calculated at €423 with the combi-treatment and €343 with nivolumab for grade 1 and 2 events (see Table 2).

For all CTCAE grade 3 and 4 events, 3.8 per hundred treatments involved mandatory hospitalization for nivolumab, and 2.7 per hundred for the combi-treatment. CTCAE grade 3 and 4 events requiring emergency care and hospitalization amounted to 3.5 events per

Table 2. Calculated costs per reported adverse event in Euro and per treatment derived from the studies Combi AD for dabrafenib and trametinib and Checkmate 238 for nivolumab. Calculated from the perspective of the German statutory health insurance.

		Cost per adverse event by grade			Per treatments gr. 1/2		Per treatments gr. 3/4		Per treatments all	
#	CTCAE category	Grade 1/2	Grade 3	Grade 4	Nivolumab	Mek/taf	Nivolumab	Mek/taf	Nivolumab	Mek/taf
1	Decreased appetite	€51.06	€356.46	€2,751.36	€0.00	€5.60	€0.00	€3.81	€0.00	€9.41
2	Fatigue	€101.44	€654.87	-	€35.01	€47.25	€2.90	€28.41	€37.91	€75.65
3	Asthenia	€101.44	€654.87	-	€12.79	€13.43	€1.45	€2.99	€14.24	€16.42
4	Nausea	€55.82	€714.14	-	€8.40	€21.92	€1.58	€6.52	€9.98	€28.44
5	Vomiting	€54.25	€1,127.02	€19,890.59	€0.00	€15.11	€0.00	€44.56	€0.00	€59.67
6	Diarrhea	€138.76	€3,208.91	€20,212.87	€33.77	€45.62	€102.36	€60.36	€136.13	€105.98
7	Constipation	€95.43	€914.41	€8,449.56	€0.00	€11.11	€0.00	€0.00	€0.00	€11.11
8	Abdominal pain	€323.09	€1,132.73	-	€20.73	€0.00	€0.00	€0.00	€20.73	€0.00
9	Colitis	€501.00	€11,015.53	€26,992.77	€9.98	€0.00	€94.32	€0.00	€104.30	€0.00
10	Pruritus	€142.44	€2,429.03	-	€33.09	€0.00	€0.00	€0.00	€33.09	€0.00
11	Dry skin	€65.15	€2,312.53	-	€0.00	€8.18	€0.00	€0.00	€0.00	€8.18
12	Rash	€69.21	€2,380.58	-	€13.78	€16.75	€26.33	€0.00	€40.11	€16.75
13	Maculopapular rash	€137.19	€2,416.07	-	€7.28	€0.00	€0.00	€0.00	€7.28	€0.00
14	Erythema	€142.44	€2,389.82	-	€0.00	€15.61	€0.00	€0.00	€0.00	€15.61
15	Dermatitis acneiformis	€136.26	€2,414.21	€2,879.63	€0.00	€16.80	€0.00	€11.45	€0.00	€28.25
16	Headache	€88.21	€591.14	-	€8.59	€34.24	€1.31	€8.10	€9.89	€42.33
17	Pyrexia	€53.05	€355.31	€2,338.50	€0.82	€33.07	€0.00	€39.49	€0.82	€72.55
18	Chills	€62.33	€295.68	-	€0.00	€22.91	€0.00	€4.05	€0.00	€26.96
19	Influenza-like illness	€84.80	€492.53	-	€0.00	€12.97	€0.00	€2.25	€0.00	€15.22
20	Cough	€85.71	€493.44	-	€0.00	€14.29	€0.00	€0.00	€0.00	€14.29
21	Myalgia	€60.95	€468.68	-	€0.00	€9.74	€0.00	€1.07	€0.00	€10.81
22	Arthralgia	€60.95	€488.73	-	€7.69	€16.70	€1.08	€4.46	€8.77	€21.16
23	Pain in limb	€60.95	€468.68	-	€0.00	€8.35	€0.00	€2.14	€0.00	€10.49
24	Infusion reaction	€230.50	€3,308.36	€14,693.51	€5.61	€0.00	€24.71	€0.00	€30.32	€0.00
25	Increase/Elevated ALT	€116.81	€150.06	€1,074.65	€7.24	€17.87	€3.71	€12.24	€10.94	€30.10
26	Increase/Elevated AST	€116.81	€150.06	€1,074.65	€6.46	€16.80	€1.48	€12.24	€7.94	€29.04
27	Increase/Elevated GGT	€116.81	€150.06	€1,074.65	€0.00	€0.00	€0.00	€0.00	€0.00	€0.00
28	Peripheral edema	€63.20	€466.40	-	€0.00	€8.37	€0.00	€1.06	€0.00	€9.43
29	Hypertension	€69.09	€300.46	€2,072.72	€0.00	€7.73	€0.00	€37.38	€0.00	€45.11
30	Hypothyroidism	€559.15	€3,088.24	€14,618.96	€60.62	€0.00	€11.93	€0.00	€72.55	€0.00
31	Hyperthyroidism	€436.17	€3,368.46	€14,899.18	€34.74	€0.00	€12.55	€0.00	€47.29	€0.00
32	Hypophysitis	€1,558.57	€4,490.86	€16,021.58	€24.14	€0.00	€30.08	€0.00	€54.21	€0.00
33	Adrenal disorder	€528.98	€3,058.07	€14,588.79	€7.02	€0.00	€23.74	€0.00	€30.76	€0.00
34	Diabetes	€189.79	€6,005.01	€17,429.04	€0.84	€3.03	€18.34	€0.00	€19.18	€3.03
35	Renal (not defined)	€116.32	€2,220.05	-	€1.51	€0.00	€0.00	€0.00	€1.51	€0.00
36	Pulmonary (not defined)	€196.16	€2,816.12	-	€2.55	€0.00	€0.00	€0.00	€2.55	€0.00
				Sum	€342.64	€423.44	€357.87	€282.58	€700.52	€706.02
				Cost per treatment for not listed events (averaged)					€198.76	€155.87
								Sum	€899.28	€861.89

CTCAE: Common Terminology Criteria for Adverse Events, Version 4.0.
Calculated from defined German payment schemes; Grade 4 only calculated where applicable.
mek/taf: combination dabrafenib and trametinib.
AST=aspartate aminotransferase; ALT = alanine aminotransferase; GGT = gamma glutamyltransferase.

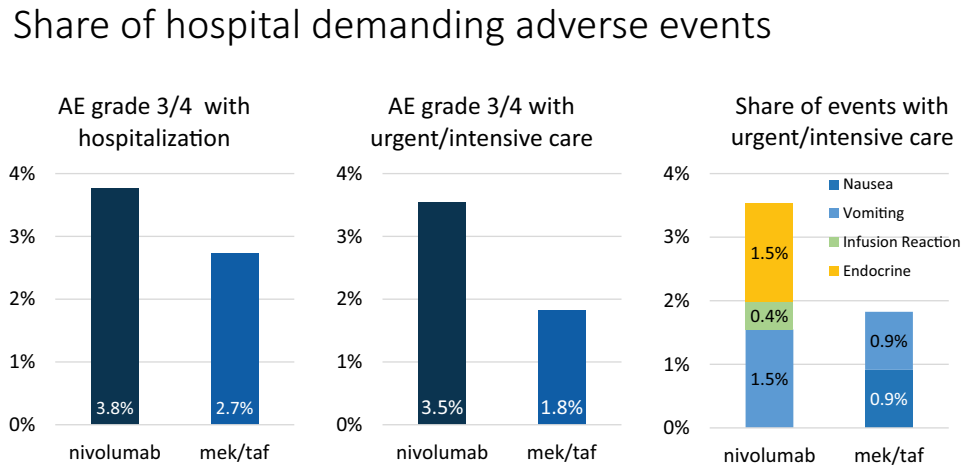
hundred treatments with nivolumab, compared to 1.8 events with the combi-treatment (see Figure 1). Events requiring hospitalization with the combi-treatment were mainly, and nearly evenly, split between nausea (0.9) and vomiting (0.9). With nivolumab, CTCAE grade those 3 and 4 events were vomiting (1.5), endocrine emergencies (1.5), and to a lesser extent, infusion reaction (0.4) (see Figure 1). The endocrine emergencies were named as severe events of hypo- and hyperthyroidism, hypophysitis, adrenal disorders, and diabetic emergencies.

Grade 4 events that were acutely life-threatening were found in 0.8 per hundred treatments with nivolumab and in 0.5 per hundred treatments with the combi-treatment.

The grade 3 events demanding hospitalization (e.g., colitis, as an autoimmune-related event) were found to have average costs of €3,131 per event, whereas events that did not require hospitalization (e.g., a systolic blood pressure of 160 mmHg), showed an average cost of €1,444. Table 1 shows the share of hospitalization for each CTCAE.

Costs were highest for diseases for which innovative high-priced drugs are recommended under the current guidance, such as for colitis (treated with infliximab) or for endocrinological diseases.

Most grade 4 events demanded hospitalization, some ICU admission, and 14 of them urgent medical action, such as immediate surgery (see Table 1). Thus, hospitalization was assumed in general. Some grade 4 events, such as a single episode of systolic blood pressure of 160 mmHg, may in real life result in the patient staying in ambulatory care. Average costs of CTCAE grade 4 events were estimated at €11,287. The



mek/taf: combination dabrafenib and trametinib; AE: adverse event

Figure 1. Shares adverse events (AE) demanding hospitalization or urgent/intensive care.

average cost per therapy was calculated as €438 with the combi-treatment and €567 with nivolumab for grade 3 and 4 events, including those with no diagnosis mentioned.

The single most cost-contributing adverse event in all grades was diarrhea for both therapies; €106 for the combi-treatment and €136 for nivolumab. For the combi-treatment, this was followed by fatigue (€76) and vomiting (€60), whereas for nivolumab, diarrhea was followed by colitis (€104) and thyroidal hypofunction (€73) (see Table 2).

Additionally, the cost of adverse events reported for the control groups of both trials was calculated. In COMBI-AD, the costs for events reported in the placebo control group averaged to €373.49. In Checkmate 238, average costs for adverse events in the ipilimumab arm amounted to €2,744.16.

Sensitivity analyses showed that the overall results were robust. The largest effects of price changes were seen in both treatment arms with changes in treatment costs for adverse events in the gastrointestinal system. The spread of treatment costs between the combi-treatment and nivolumab, which amounted to €37.39 in the base case, was only moderately affected by the simulated changes of unit prices. An isolated price increase of 25% for the treatment of adverse events in the endocrine system increased the cost benefit of combi-treatment to €91.70, while the same price increase for the treatment of hypersensitivity and infusion reactions resulted in a cost benefit of Nivolumab of €11.88. The effects of price changes to deal with adverse events in the other organ systems were in between (see Table 3).

Table 3. Sensitivity analysis: effect of price changes of 25% for AE treatments by organ system.

Scenario	Treatment costs		
	Nivolumab	Mek/taf	Spread
Base case	€899.28	€861.89	€37.39
Treatment cost changes (+25%) for AE related to:	**Overall cost delta** (% change to base case)		
Gastrointestinal system	+11.5%	+10.9%	€47.54
Skin	+2.9%	+2.4%	€42.23
Hypersensitivity and infusion reaction	+1.8%	+7.6%	€11.88
Hepatic system	+0.7%	+2.1%	€25.40
Endocrine system	+8.0%	+2.0%	€91.70
Renal and pulmonary systems	+0.1%	NR	NR
Other (uncategorized AE)	+5.5%	+4.5%	€48.11

AE: adverse event
mek/taf: combination dabrafenib and trametinib

AE: adverse event; mek/taf: combination dabrafenib and trametinib.

The proportion of Grade 4 AE has an impact on total AE treatment costs per patient. The cost difference increases moderately in absolute terms with the proportion of grade 4 AE in the category 'grade 3/4'. However, the total AE treatment costs per patient are still at the same level for both treatment arms (see Table 4).

Table 4. Sensitivity analysis: effect of the different splits of the AE grade 3/4 category into AE grade 3 vs. grade 4.

Scenario	Treatment costs		Spread *
	Overall cost delta (% change to base case)		
Grade 3: 95%; grade 4: 5%	−13.1%	−13.0%	31.63 €
Grade 3: 90%; grade 4: 10%	−8.7%	+8.7%	33.55 €
Grade 3: 80%; grade 4: 20% (base)	0.0%	0.0%	37.39 €
Grade 3: 70%; grade 4: 30%	+8.7%	+8.7%	41.23 €
Grade 3: 60%; grade 4: 40%	+17.5%	+17.4%	45.07 €

AE: Adverse events; *: cost advantage of combination mek/Tt over Nivolumab.

Table 5. Distribution of financial burden in for each adverse event and each grade, when applicable.

	Specialist/ outpatient	Medication	Laboratory	Hospital	Specialist outpatient	Medication	Laboratory	Homecare	Hospital	Specialist outpatient	Medication	Laboratory	Homecare	Hospital
Decreased appetite	79.8%		20.2%		41.8%	41.2%	17.0%			1.5%		0.4%	14.7%	83.5%
Fatigue	40.2%		59.8%		6.2%	22.9%	9.3%	61.6%						
Asthenia	40.2%		59.8%		6.2%	22.9%	9.3%	61.6%						
Nausea	81.5%		18.5%		21.5%	20.6%	1.4%	56.5%						
Vomiting	75.1%	5.9%	19.0%		8.4%	14.6%	0.9%	35.8%	40.3%	0.5%	0.8%	0.1%	2.0%	96.6%
Diarrhea	87.0%	2.4%	10.6%		3.8%	0.1%	0.5%	12.6%	83.1%	0.6%	0.0%	0.1%	2.0%	97.3%
Constipation	80.2%	13.6%	6.2%		53.8%	1.4%	0.6%	44.1%		5.8%	0.2%	0.1%	4.8%	89.2%
Abdominal pain	94.7%	0.7%	4.5%		62.9%	0.2%	1.3%	35.6%						
Colitis	96.4%	0.7%	2.9%		4.4%	70.7%	0.1%	0.0%	24.8%		72.1%			27.9%
Pruritus	28.6%	25.8%	45.6%		3.3%	1.5%	2.7%	16.6%	75.9%					
Dry skin	62.6%	23.0%	14.4%		1.8%	0.6%	0.4%	17.4%	79.7%					
Rash	58.9%	19.9%	21.2%		1.7%	3.3%	0.6%	16.9%	77.5%					
Maculopapular rash	29.7%	23.0%	47.3%		3.0%	1.3%	2.7%	16.7%	76.3%					
Erythema	28.6%	25.8%	45.6%		1.7%	1.5%	2.7%	16.9%	77.2%					
Dermatitis acneiformis	29.9%	22.4%	47.7%		3.0%	1.3%	2.7%	16.7%	76.4%	2.5%	1.1%	2.3%	14.0%	80.2%
Headache	86.1%	2.5%	11.4%		27.8%	2.3%	1.7%	68.2%						
Pyrexia	76.8%	4.2%	18.9%		38.5%	1.9%	2.8%	56.7%		5.9%	0.5%	0.4%	17.2%	76.0%
Chills	65.4%	18.5%	16.1%		24.5%	3.9%	3.4%	68.2%						
Influenza-like illness	85.5%	2.6%	11.9%		14.7%	1.4%	2.0%	81.9%						
Cough	84.6%	3.7%	11.7%		14.7%	1.6%	2.0%	81.7%						
Myalgia	66.9%	3.7%	29.5%		8.7%	1.4%	3.8%	86.0%						
Arthralgia	66.9%	3.7%	29.5%		8.3%	5.5%	3.7%	82.5%						
Pain in limb	66.9%	3.7%	29.5%		8.7%	1.4%	3.8%	86.0%						
Infusion reaction	92.8%	3.0%	4.2%		6.5%	0.2%	0.3%	12.2%	80.8%	1.5%		0.1%	2.7%	95.7%
Increase/Elevated ALT	49.7%		50.3%		50.2%	10.7%	39.2%			8.6%	1.5%	5.5%		84.4%
Increase/Elevated AST	49.7%		50.3%		50.2%	10.7%	39.2%			8.6%	1.5%	5.5%		84.4%
Elevated GGT	49.7%		50.3%		50.2%	10.7%	39.2%			8.6%	1.5%	5.5%		84.4%
Peripheral edema	64.5%	18.7%	16.9%		8.7%	2.5%	2.3%	86.4%						
Hypertension	59.0%	20.9%	20.1%		85.9%	9.5%	4.6%			12.5%	1.4%	0.7%		85.5%
Hypothyroidism	61.6%	10.4%	28.0%		11.2%	1.9%	5.1%		81.9%	2.4%	0.4%	1.1%		96.2%
Hyperthyroidism	41.6%	22.5%	35.9%		5.4%	2.9%	4.6%	12.0%	75.1%	1.2%	0.7%	1.0%	2.7%	94.4%
Hypophysitis	11.2%	4.1%	3.6%	81.1%	3.9%	1.4%	1.2%	9.0%	84.5%	1.1%	0.4%	0.3%	2.5%	95.6%
Adrenal disorder	80.0%	12.1%	7.9%		13.8%	2.1%	1.4%		82.7%	2.9%	0.4%	0.3%		96.4%
Diabetes	21.5%	67.3%	11.2%		36.6%	19.1%	0.4%		43.9%	12.6%	6.6%	0.1%		80.7%
Renal	84.9%		15.1%		4.4%		0.8%		94.8%					
Pulmonary	91.2%		8.8%		6.4%		0.6%		93.0%					

Discussion

The use of reported data from the COMBI-AD and CheckMate 238 trials allowed us to assess the costs associated with adverse events related to both examined treatments, the combination of dabrafenib with trametinib and the checkpoint inhibitor nivolumab, as adjuvant therapies for patients with resected advanced melanoma.

The benefit assessments from the German Institute for Quality and Efficiency in Health Care qualified the results of both studies as applicable for German population and practice, and estimate the overall costs for both therapies in the adjuvant treatment of resected advanced melanoma in the range of €100,000 per treatment before the negotiation of an unpublished rebate [53]. Thus, the cost burden for adverse events of the treatment, given the German setting, is relatively small. This is true for both examined treatments, the combi-treatment and nivolumab, with costs caused by adverse events below €900 per treatment in both cases.

This result may contribute to further economic or cost-effectiveness analyses. The side effects of the treatment will remain a factor in the economic analysis, but possibly not the decisive one. A similar study by Alves, et al. for Portugal [34] found higher average costs, in the range of €1,500 per treated patient, even without examining the grade 1 and 2 events. The analysis resulted in side effect costs of €1,346 for Nivolumab and €1,853 for the combi-therapy. Alves assumed all grade 3 events to require hospitalization and only hospitalization, which does not reflect clinical reality, at least in Germany. In addition, the remainder of non-reported events was calculated differently. Seventy-one percent of the Nivolumab events had been summarized as 'all other cause' and averaged. But in this group, we found nearly all extreme cost and burden outliers. Nevertheless, their result confirms the finding of a minor impact on the total costs of the complete therapy.

The different side-effect profiles of both therapies resulted in discriminative cost structures. The immune therapy was estimated to result in around 40% more mandatory hospitalizations and twice as many emergency situations as the combined targeted therapy. These findings may be relevant for the burden of side effects imposed on the patients' quality of life.

On the other hand, the way the costs were derived from the reporting of events in the publications may suffer from systematic underestimation. First, there is the assumption that any event happened only once to every patient. With severe grade 3 and 4 events, the adjuvant therapy may be stopped, which makes a repetition impossible. However, events with the lower grades may occur multiple times, and this could be a factor to be included in a more informed analysis. Secondly, not all events had been reported with a diagnosis. The possibility that some rare high-cost events were not listed in the publications cannot be excluded. In this case, the assumption of average cost as a proxy would not hold. Moreover, we assumed that the costs for those unreported events were equal for both therapies, which may not be the case.

Although there are other studies estimating the cost of adverse events, this is the first one using German claims data. Most of the other studies are based on US claims data and do not differentiate between CTCAE grades [54,55]. Wong, et al.`s, study [55] also calculated average costs for 36 adverse events, 11 of which are identical with those in research. The results of the mentioned studies are within a reasonable range of our findings, despite the different settings.

Claims data studies, like Wong et al., are usually derived from databases which represent treated patients. While in RCT patients always undergo a defined selection. Thus, later studies, based on adverse events found in databases may vary.

Our second finding is that both treatments ended up close in terms of the overall costs. Given all uncertainties of the analysis, there is no unambiguous result. There is a higher count of adverse events with the combination, but this is offset by substantially higher costs of some events reported for the checkpoint inhibitor.

The result for nivolumab suffers from the fact that only 13.0 of 25.4 grade 3 and 4 events per hundred treatments had been reported with a diagnosis, which adds uncertainty.

We considered calculating the loss of quality-adjusted life-years (QALYs) in addition to the costs. However, for many of the adverse events, there are no available data for the QALY-losses. Thus, modeling would be based on many assumptions, and we decided not to perform this calculation. We speculate that the result would correlate with the costs of grade 3 and 4 events with hospitalizations, and the QALY losses due to adverse events would be overall small in comparison to the currently measured effects of both therapies.

Finally, the overall clinical outcome and costs of therapy may drive economic considerations, rather than the other way round. After three years, the relapse-free survival rate in COMBI-AD for the combi-treatment was 59% versus 40% in the control arm (hazard ratio [HR] 0.49; 95% confidence interval [CI], 0.40 to 0.59) [56,57]. CheckMate 238 has reported three-year data with 58% relapse-free survival rate for

nivolumab versus 45% in the control arm (HR 0.79; 95% CI 0.59 to 1.06 for BRAF mutation) [58]. Further long-term data are expected.

Limitations

However, our study had several limitations. In the setting of the two clinical studies, adverse events were probably rigorously reported. The study outcome was uncertain, and there was special and regular care and control of the patients. In the COMBI-AD double-blinded placebo arm, 88% of patients had at least one documented adverse event. In the current treatment, now outside the study setting and with knowledge about the long-term benefit of both therapies, the rate of reported minor events may change. Follow-up investigations by future observational trials may contribute important information.

Conclusions

The data derived for adverse events from the published trials in adjuvant therapies for patients with resected advanced melanoma showed comparable costs for both examined therapeutic strategies. Overall, the costs for the combination of dabrafenib and trametinib were slightly lower because of fewer mandatory hospitalizations and many fewer emergency situations. Nivolumab had a lower number of overall events.

The average cost burden of adverse events is low in relation to the overall costs of the therapy. Thus, other aspects may determine treatment decisions, such as overall survival, relapse-free survival, or the disease burden of the adverse events.

The study has limitations. Further research may build on a complete set of events and a rigorous collection of claims.

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