Adjuvant anti-PD-1 antibody treatment in stage III/IV melanoma: real-world experience and health economic considerations

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Summary

Background: Anti-programmed death 1 (PD-1) antibodies have evolved as a new standard of care in the adjuvant treatment of completely resected melanoma. Real-world data on treatment efficacy and safety as well as cost-effectiveness are still limited.

Patients and Methods: Treatment outcomes were retrospectively analyzed in a continuous patient cohort receiving adjuvant nivolumab (91 patients) or pembrolizumab (9 patients). Based on the obtained clinical data, a semi-Markov model was developed to evaluate cost-effectiveness.

Results: After a median follow-up of 11.5 months, disease recurrence was observed in 39 patients (39 %). The site of first recurrence was locoregional in 17, distant in 19, and combined locoregional and distant in three patients. Twelve-month estimates for recurrence- and distant-metastasis-free survival were 64.8 % and 77.4 %, respectively. Sixteen patients experienced grade 3 or 4 treatment-related adverse events, while 22 patients discontinued treatment due to adverse events. The base-case Markov model yielded an incremental cost-effectiveness ratio of 13,330 € per quality-adjusted life year for adjuvant anti-PD-1 antibody treatment compared to a simulated observation cohort.

Conclusions: Real-world outcomes of adjuvant anti-PD-1 antibody therapy in completely resected melanoma appear comparable to clinical trial data. Moreover, our data suggests this treatment strategy to be cost-effective according to Austrian health economic standards.

Introduction

Based on conclusive efficacy data regarding recurrence-free survival in pivotal phase III trials, anti-programmed-death-1 (PD-1) antibody-based immunotherapy and combined targeted therapy with BRAF and MEK-inhibitors have recently become the new standard of care in adjuvant treatment of completely resected stage III or IV melanoma [1–6]. Despite the widespread routine use of these modern therapeutics in the adjuvant setting, real-world data on post-approval experience in terms of efficacy and safety are limited and inconsistent, owing to inclusion and combined analysis of both immune and targeted therapy patient cohorts [7, 8]. Yet, real-life data are essential to explore pending clinical issues.

For instance, it is largely unknown how recent evidence-based changes in treatment algorithms such as the omission of completion lymph node dissection (CLND) in patients with sentinel lymph node (SLN) melanoma micrometastases may affect adjuvant treatment outcomes [4–6, 9–11].

Moreover, analysis of clinical application data should adequately reflect the actual distribution of disease stages in patients receiving adjuvant treatment according to the 8th edition American Joint Committee on Cancer (AJCC) staging criteria [12]. In this regard, adjuvant treatment of patients with stage IIIA disease, who are subject to a relatively low risk of melanoma recurrence, is controversial from a medical perspective [13]. In terms of health economics, the proportion of low-risk patients in an adjuvant treatment population additionally
has a substantial impact on key parameters of cost-effectiveness. While adjuvant pembrolizumab and nivolumab have been deemed cost-effective based on the KEYNOTE-054 and CheckMate 238 patient populations [14–16], a comparable real-world analysis which takes into account health economic prerequisites of largely publicly funded health care systems as encountered in Austria has not been performed to date.

Thus, the objectives of the present study were first to summarize the real-world experience gathered with adjuvant PD-1 antibody treatment since its availability in late 2017 and second, to perform a cost-effectiveness analysis of this therapeutic strategy based upon the obtained clinical data.

Patients and Methods

Study design and Data Collection

Patients with completely resected AJCC stage III or IV melanoma in whom adjuvant anti-PD-1 antibody treatment was initiated between December 1, 2017 and March 31, 2020 were retrospectively identified at three dermat-oncological centers in Austria (Paracelsus Medical University Salzburg, Medical University Graz, and Medical University Innsbruck). The inclusion period was chosen to begin shortly after the pivotal trial on adjuvant nivolumab treatment had been published in November 2017 [1], whereas its end allowed for a minimum individual follow-up period of three months after initiation of treatment. Local ethics committee approval was obtained before commencement of data collection at the respective locations. Data regarding patient and tumor characteristics, sentinel lymph node (SLN) biopsy and other surgical procedures, radiotherapy, systemic treatment, adverse events (AEs) as well as recurrence-free survival (RFS), distant-metastasis-free survival (DMFS) and overall survival were independently collected through review of electronic medical records at each participating institution. After anonymization and transfer of data, all subsequent analyses were performed at the coordinating center (Salzburg).

Assessments

Melanoma staging was conducted according to the AJCC Cancer Staging Manual, 8th edition [12]. Adverse events during treatment were graded according to the Common Terminology Criteria (CTC) for Adverse Events, version 5.0 [17]. Assessments for disease recurrence were routinely performed at all participating sites as recommended in the current German melanoma guideline: physical examination, S100 blood test and lymph node sonography every three months; PET- or iv-contrast CT and brain MRI every six months in both stage III and IV patients [4]. As clinically indicated, frequency of CT and MRI scans was higher (three months interval) in certain patients with stage IV disease. Recurrence-free survival was calculated from the time of first anti-PD-1 treatment until the date of documented disease recurrence (assessed radiologically, clinically or pathologically during follow-up) or the date of death. Distant-metastasis-free survival was calculated from the time of first anti-PD-1 treatment until the date of documented distant metastases or death.

Statistical analysis

For statistical analysis, Microsoft Excel 2016 (Microsoft Inc., Redmond, WA, USA) and SPSS Statistics, Version 24 (SPSS Inc., Chicago, IL, USA) were used. Owing to the study design and sample size, most analyses were descriptive. Patients were stratified by disease recurrence status and AJCC stage for comparative analyses. Kaplan-Meier estimation and log-rank test were conducted for survival analyses. Statistical significance was defined by a P-value of < 0.05.

Cost-effectiveness analysis

A deterministic modified Markov state transition model with non-constant transition probabilities was constructed in Microsoft Excel to evaluate cost-effectiveness of adjuvant anti-PD-1 antibody treatment based on the obtained patient data from a national (Austrian) healthcare payer perspective. Therefore, only direct, healthcare-related costs were considered. Costs for systemic adjuvant and (subsequent) palliative treatment and disease management (surgical treatments, follow-up) were included. Costs for terminal care and AE management were not considered, as we were unable to identify reliable unit cost sources for these costs in Austria. Adjuvant anti-PD-1 treatment was compared to a hypothetical identical (regarding age, gender, and tumor stage) patient cohort undergoing observation only. Four mutually exclusive health states were defined: recurrence-free (RF), local recurrence (LR), distant recurrence (DR) and death (Figure 1). A cycle-length of three months was selected, as this time period corresponds to the routine clinical and radiological follow-up intervals. Since most recurrences are detected by these follow-up examinations, no half-cycle corrections were conducted except for the calculation of state-specific utilities. Consistent with the analyzed anti-PD-1 treatment cohort, patients entered the model in the RF state, were 61 years old, male in 55 and female in 45% of cases, respectively. Based on the mean patient age, a lifetime horizon of 39 years (156 cycles) was selected. Weibull, Gompertz and log-logistic distributions were used for parametric survival modelling of transition probabilities between states. Further information regarding details of the constructed Markov model available as online supplement (Online Supplementary File 1). Patients in all states were subject to age and gender-specific background mortality rates.
as published by the Austrian statistical institute [18]. Melanoma-related death could only occur in patients in the DR state. In case of development of disease recurrence in patients receiving adjuvant anti-PD-1 treatment, subsequent efficacy of immunotherapy for the treatment of locally advanced or metastatic disease was assumed to be impaired, particularly in patients experiencing “on-treatment recurrence” (occurring during or within three months after cessation of therapy). This assumption is supported by recent data on anti-PD-1 treatment failure [19, 20]. Consequently, estimated melanoma-specific survival of patients in the DR state was superior in the observation compared to the adjuvant anti-PD-1 cohort of the model (median: 3.3 versus 2.3 years).

All costs in the model are in Euros valorized to the year 2020, unless otherwise stated. An annual discount rate of 3\% for costs and treatment effects was applied as recommended for health technology assessments by national authorities in Austria [21]. Drug prices were obtained from local hospital pharmacies for immunotherapies and the national health plan reimbursement catalogue (Erstattungscodex, Dachverband der österreichischen Sozialversicherung) for targeted therapies. The base case analysis was based on official (ex-factory) drug prices. Potential price discounts were considered in one-way sensitivity analyses. Unit costs of treatment administration (day-care), surgical procedures (day-care or inpatient) and follow-up examinations were calculated utilizing local hospital-level information, health care insurance reimbursement tariffs, publicly available governmental inpatient health care cost information [22] or an Austrian online database of unit-costs, developed subsequent to a recent review article by Mayer et al. [23, 24].

Utility values for each health state were adapted from a recent cost-effectiveness analysis of adjuvant pembrolizumab [14]. A one-time discount (0.074 points) for AEs was employed in the first RFS period in the treatment cohort based on the observed AE frequency. An identical discount of 0.074 points was deducted in patients with progressive disease in the DR state as proposed by Paly et al. [25].

Outcomes of the cost-effectiveness analysis are summarized as life years, quality-adjusted life years and incremental cost-effectiveness ratios (ICERs) representing costs per additional (gained) life years (LYs) or quality adjusted life years (QALYs) comparing the adjuvant PD-1 antibody to the observation cohort.

To ensure completeness and robustness of the model, one-way deterministic sensitivity analyses were conducted through variation of one model input at a time. The analyzed input parameters concerned utilities, disease management costs, costs of adjuvant and subsequent treatment, discount rates as well as the effect of adjuvant treatment (variation of the weighted RFS and DMFS hazard ratios of adjuvant anti-PD-1-antibody treatment compared to observation). Input values were individually altered by 25\% above and below their base-case values. Regarding discount rates, a range of 0 to 6\% was evaluated.

Results

Patients and treatment

A total of 100 patients who first received adjuvant anti-PD-1 antibody treatment during the selected inclusion period were identified. Median follow up was 11.5 months (range: 3.0–28.4 months). At treatment initiation, median age of patients was 61 years (range: 22–87 years). ECOG performance status was 0 in 82 (82\%), 1 in 14 (14\%), 2 in one (1\%) and 3 in two (2\%) patients. Fifteen patients (15\%) had previously received systemic adjuvant melanoma treatment: eleven with interferon alfa (of which one additionally received adjuvant ipilimumab), three with dabrafenib and trametinib, and one with ipilimumab plus nivolumab. The majority of patients had completely resected stage IIIB (31\%) or IIIC (52\%) disease, while only 5\% had stage IIIA and 8\% stage IV disease at start of therapy (Table 1). Eighteen patients (18\%)
Table 1  Baseline patient and tumor characteristics.

|                        | All patients (n = 100) | Stage IIIA/B (n = 36) | Stage III C/D (n = 56) | Stage IV (n = 8) |
|------------------------|------------------------|------------------------|------------------------|------------------|
| **Median age, years (range)** | 61 (22–87)            | 54 (22–81)            | 64 (31–87)            | 61.5 (37–73)     |
| **Sex, no. (%)**       |                        |                        |                        |                  |
| – female               | 45 (45)                | 17 (47.2)             | 25 (44.6)             | 3 (37.5)         |
| – male                 | 55 (55)                | 1 (2.8)               | 31 (55.4)             | 5 (62.5)         |
| **Median Breslow of primary tumor (range)** | 2.65 mm (0.15–17) | 1.85 mm (0.15–13) | 3.52 mm (0.5–17) | 2.50 mm (0.4–5.5) |
| **Ulceration of primary tumor, no. (%)** |                        |                        |                        |                  |
| – present              | 38 (38)                | 3 (8.3)               | 34 (60.7)             | 1 (12.5)         |
| – absent               | 45 (45)                | 22 (61.1)             | 17 (30.4)             | 6 (75)           |
| – N/A                  | 17 (17)                | 11 (30.6)             | 5 (8.9)               | 1 (12.5)         |
| **AJCC Stage, no. (%)**|                        |                        |                        |                  |
| – IIIA                 | 5 (5)                  | 5 (13.9)              | N/A                   | N/A              |
| – IIIB                 | 31 (31)                | 31 (86.1)             | N/A                   | N/A              |
| – IIIC                 | 52 (52)                | N/A                   | 52 (92.9)             | N/A              |
| – IIID                 | 4 (4)                  | N/A                   | 4 (7.1)               | N/A              |
| – IV                   | 8 (8)                  | N/A                   | N/A                   | 8 (100)          |
| **LN-status at treatment initiation, no. (%)** |                        |                        |                        |                  |
| – micrometastases      | 26 (26)                | 10 (27.8)             | 14 (25.0)             | 2 (25)           |
| – macrometastases      | 52 (52)                | 17 (47.2)             | 33 (58.9)             | 2 (25)           |
| – no LN involvement    | 21 (21)                | 9 (25.0)              | 9 (16.1)              | 3 (37.5)         |
| – unknown              | 1 (1)                  | 0 (0)                 | 0 (0)                 | 1 (12.5)         |
| **Satellite/in-transit metastases, no. (%)** |                        |                        |                        |                  |
| – yes                  | 38 (38)                | 9 (25)                | 27 (48.2)             | 2 (25)           |
| – isolated             | 19 (19)                | 9 (25)                | 9 (16.1)              | 1 (12.5)         |
| – with LN metastases   | 19 (19)                | 0 (0)                 | 18 (32.1)             | 1 (12.5)         |
| – no                   | 62 (62)                | 27 (75)               | 29 (51.8)             | 6 (75)           |
| **SLN-biopsy**         |                        |                        |                        |                  |
| – positive             | 42 (42)                | 13 (36.1)             | 27 (48.2)             | 2 (25)           |
| – negative             | 18 (18)                | 3 (8.3)               | 12 (21.4)             | 3 (37.5)         |
| – not performed**      | 40 (40)                | 20 (55.6)             | 17 (30.4)             | 3 (37.5)         |
| **SLN tumor deposit (mm)** |                        |                        |                        |                  |
| – < 1 mm               | 6 (6)                  | 2 (5.6)               | 3 (5.4)               | 1 (12.5)         |
| – 1–4.99 mm            | 17 (17)                | 6 (16.7)              | 10 (17.9)             | 1 (12.5)         |
| – 5–10 mm              | 8 (8)                  | 1 (2.8)               | 7 (12.5)              | 0 (0)            |
| – > 10 mm              | 5 (5)                  | 3 (8.3)               | 2 (3.6)               | 0 (0)            |
received adjuvant treatment after resection of isolated satellite/in-transit metastases without lymph node involvement (N-stage: N1c).

After initial melanoma diagnosis, sentinel lymph node biopsy (SLNB) was successfully conducted in 60 patients, yielding a positive histopathologic result in 42 patients. The median size of the tumor deposit in all positive SLNs was 2.6 mm (range: < 0.1–15 mm) (Table 1). In 31 patients, SLNB was conducted shortly before and was a decisive factor for initiation of adjuvant treatment. In this subgroup of patients, additional completion lymph node dissection (CLND) was performed in nine patients (29 %), revealing affected non-sentinel lymph nodes in two patients. The remaining 22 patients (71 % of this subgroup) received adjuvant treatment directly subsequent to positive SLNB. Overall, CLND was performed in 47 patients (47 %) while 53 patients (53 %) did not undergo CLND. The latter subgroup included the 22 patients with SLN micrometastases mentioned above (of which five patients had additional in-transit disease), 18 patients with isolated satellite or in-transit metastases (N1c), two stage IV patients (one with N0 and one with N1c status) as well as eleven patients with macrometastatic lymph node involvement with or without satellite/in-transit disease, in which only the affected lymph nodes and, if applicable, the locoregional metastases were surgically removed.

Ninety-one patients (91 %) received adjuvant treatment with nivolumab and nine patients (9 %) with pembrolizumab. Additional adjuvant radiotherapy was conducted in 20 patients (20 %). The median time between the last surgical procedure and initiation of anti-PD-1 antibody treatment was 51 days or 1.7 months (range: 7–360 days). Median duration of treatment was 7.9 months (range: 0–25 months). Treatment was ongoing at the time of data analysis in 23 patients (23 %), while 77 patients (77 %) had stopped treatment: 30 patients as scheduled after a duration of twelve months, 22 patients owing to occurrence of AEs, 23 patients because of disease progression and two due to other reasons (one loss to follow-up, one second malignancy [colorectal cancer]).

### Disease recurrence, survival and subsequent treatment

Within the described follow-up period, disease recurrence was observed in 39 patients (39 %). Median RFS has not been reached and was estimated at 16.7 months (95 % confidence interval [CI]: 14.0 to 19.4 months) by Kaplan-Meier analysis (Figure 2). The 12-months estimate for RFS was 64.8 %. As expected, there was a (borderline) significant RFS difference between AJCC subgroups III A/B and III C/D ($P = 0.052$) (Figure 2). The site of first recurrence was locoregional (satellite/in-transit metastases, lymph nodes) in 17 of 39 patients (43.6 %), distant in 19 patients (48.7 %), and combined locoregional and distant in three patients (7.7 %).

The rate of disease recurrence was similar in patients who had undergone prior CLND and those who had not (19/47 patients [40.4 %] and 20/53 patients [37.7 %], respectively). Of note, CLND patients tended to have higher disease stages according to the AJCC classification (CLND compared

### Table 1

Continued.

|                      | All patients (n = 100) | Stage IIIA/B (n = 36) | Stage III C/D (n = 56) | Stage IV (n = 8) |
|----------------------|------------------------|-----------------------|------------------------|-----------------|
| LN dissection performed |                        |                       |                        |                 |
| yes                  | 47 (47)                | 13 (36.1)             | 28 (50.0)              | 6 (75)          |
| no                   | 53 (53)                | 23 (63.9)             | 28 (50.0)              | 2 (25)          |
| BRAF status          |                        |                       |                        |                 |
| mutated              | 43 (43)                | 19 (52.8)             | 22 (39.3)              | 2 (25)          |
| wildtype             | 56 (56)                | 16 (44.4)             | 34 (60.7)              | 6 (75)          |
| not reported         | 1 (1)                  | 1 (2.8)               | 0 (0)                  | 0 (0)           |

*Information regarding Breslow thickness was available for 84 primary tumors (83.2 %). Sixteen patients (15.8 %) were diagnosed with melanoma of unknown primary. Information regarding Breslow thickness was not available in one patient.

**In 14 of these patients no SLN biopsy was performed due to melanoma of unknown primary, the remaining patients either primarily presented with macrometastatic disease or did not undergo (successful) primary SLN biopsy and developed macrometastatic disease later during the course of the disease.

***Information regarding SLN tumor deposit was available in 36 of 42 patients (85.7 %) with pos. SLN biopsy. In four patients, tumor deposits in more than one SLN were detected. In these patients, the sum of the largest diameter of all tumor deposits was considered for the overall tumor deposit size.

Abbr.: N/A, unknown primary/not documented.
to no-CLND patients: 13/47 [27.7 %] versus 23/53 [43.4 %] with stage IIIA/B, 28/47 [59.6 %] vs. 28/53 [52.8 %] with stage IIIC/D, and 6/47 [12.8 %] vs. 2/53 [3.8 %] with stage IV disease, respectively). Of 20 total progression events in the no-CLND subgroup, 13 (65 %) were locoregional and 7 (35 %) distant; eleven events occurred in patients with lymph node micrometastases, five in patients with macrometastatic lymph node disease and four in patients with isolated satellite/in-transit metastases.

Development of distant metastases occurred in 26 patients. In addition to the 22 patients who were diagnosed with distant metastases at the time of first recurrence, four patients developed distant disease subsequent to initial locoregional progression. Distant-metastasis-free survival estimates in patients with stage III disease are depicted in Figure 3. The estimated 12-months DMFS rate was 77.4 % while actual median DMFS was not reached, with a respective Kaplan Meier estimate of 21.0 months (95 % CI: 18.4 to 23.6 months).
Detailed analysis of overall survival was not conducted as only four deaths were reported during the observation period.

Information regarding subsequent treatment after development of disease recurrence was available in 32 of 39 patients (82.1 %) who developed disease recurrence. A total of 44 subsequent therapies were conducted. Treatment was frequently surgical (10 patients) or consisted of either adjuvant or palliative BRAF-/MEK-inhibitor (12 patients) or anti-CTLA-4/anti-PD-1 antibody (8 patients) combination therapies (Table S1, online Supplement Information).

Safety

Overall, 111 treatment-related adverse events of any grade were documented in 61 patients (61 %) (Table 2). Thirty of these patients (49.2 %) experienced one AE, 21 patients two AEs (34.4 %), and ten patients (16.4 %) three or more AEs. Eighteen CTC grade 3 or 4 AEs were documented in 16 patients (16 %). There was no treatment-related death. Anti-PD-1 antibody treatment was paused due to AEs in 28 patients (28 %), eventually leading to treatment discontinuation in 22 patients (22 %). Thyroid function disorders, elevation of pancreatic enzymes and dermatitis were the AEs most frequently documented, occurring in 16 %, 13 % and 9 % of patients, respectively (Table 2).

Cost-effectiveness analysis

Cost and utility outcomes of the base-case Markov model and the conducted sensitivity analyses are summarized in Table 3 and 4. Table 5 depicts an overview of imputed costs and utilities in the base-case model.

The weighted cost of adjuvant anti-PD-1 antibody therapy with nivolumab/pembrolizumab including treatment administration during the active treatment period (first year) was valued at 67,913 €. Based on the obtained real-life data, patients receiving adjuvant anti-PD-1 antibody treatment were estimated to gain an additional 0.98 life years and 1.11 QALYs, respectively, compared to the simulated observation cohort. Taking into account total direct costs, the ICER for adjuvant anti-PD-1 treatment compared to observation was 13,330 € per QALY. Deterministic one-way sensitivity analyses showed that the ICER was most sensitive to changes in the effect (hazard ratio) of adjuvant treatment and changes in subsequent treatment prices (Table 4).

As depicted in Table 3, the QALY gain in the treatment versus the observation cohort mainly resulted from an increase of QALYs in the RF state (7.51 versus 4.12) and was attenuated by a decreased number of experienced QALYs in the DR state (2.28 versus 4.28). The latter difference is attributable to the assumed superior efficacy of systemic treatments for advanced or metastatic disease in the observation cohort.

Discussion

This study represents both a clinical analysis of real-world data regarding adjuvant anti-PD-1 antibody treatment in completely resected melanoma and a cost-effectiveness analysis of this treatment strategy compared to observation.
Table 3 Cost and survival outcomes of the base-case Markov model by type of cost and health state.

| Costs/Life years | Adjuvant anti-PD-1 treatment | Observation | Incremental |
|------------------|-----------------------------|-------------|-------------|
| Total costs (€)  | 142,413                     | 127,676     | 14,737      |
|                  | - adjuvant treatment costs' | 67,913      | 0           | 67,913      |
|                  | - subsequent treatment costs' | 50,091      | 98,097      | -48,006     |
|                  | - disease management costs** | 24,409      | 29,579      | -5,171      |
| Costs per health state (€) | | | |
| RF state         | 79,793                      | 8,440       | 71,353      |
| LR state         | 2,412                       | 3,503       | -1,091      |
| DR state         | 60,207                      | 115,732     | -55,525     |
| QALYs            | 10.42                       | 9.31        | 1.11        |
| Life years       | 11.77                       | 10.79       | 0.98        |
| RF state         | 8.24                        | 4.52        | 3.73        |
| LR state         | 0.72                        | 1.06        | -0.33       |
| DR state         | 2.80                        | 5.21        | -2.41       |

Abbr.: RF, recurrence-free; LR, locoregional recurrence; DR, distant recurrence
*Including drug and administration costs (see Table 5).
**Including costs for clinical and radiological follow-up examinations and surgical interventions.

Distribution of baseline patient and tumor characteristics in the examined patient population was comparable with pivotal studies leading to regulatory approval of adjuvant anti-PD-1 treatment [1, 2], except for median patient age which was markedly higher in our real-life cohort (61 years versus 56 and 54 years in the Checkmate-238 and Keynote-054 trial, respectively). As opposed to clinical trial populations, a considerable number of patients with isolated satellite or in-transit metastases without lymph node involvement were included in the present study. Moreover, as a result of MS-LT-II and Decog-SLT trial data [9–11, 26], approximately 70 % of patients with micro-metastatic SLN involvement did not undergo CLND, which, however, had been a prerequisite for inclusion into the pivotal adjuvant anti-PD-1 trials [1, 2]. The overall frequency of disease recurrence in the investigated patient population appears to be increased compared to these trials, which is largely attributable to the higher rate of locoregional recurrences in patients who were spared CLND. Accordingly, in contrast to the one-year RFS rate (64.8 % vs. 70 %), the one-year DMFS rate is rather similar in the present cohort and the Checkmate-238 trial (77.4 % vs. 80 %, respectively) [27, 28].

The frequency of treatment-related AEs during pembrolizumab or nivolumab therapy in the real-life setting was also comparable to clinical trial data [1, 2]. However, the observed 22 % rate of AE-related treatment discontinuations appears considerably higher than previously reported. Of note, certain AEs such as elevated pancreatic enzymes or increased CPK with or without clinical signs of myalgia/myositis were observed at an increased frequency in the present study. Although these AEs are often asymptomatic, reports of fatal outcomes or long-term sequelae have been published [29, 30]. This warrants further research regarding the nature and optimal management strategies of such AEs [31]. Particularly in patients with BRAF-mutated melanomas, potentially fatal AEs of PD-1-inhibition must be critically considered in the adjuvant setting, as these patients are eligible for an alternative adjuvant treatment option.

The present study also evaluated cost-effectiveness comparing the investigated adjuvant anti-PD-1 cohort with a simulated observation cohort featuring identical baseline characteristics. Considering a willingness-to-pay threshold of 40,000 € per QALY, which represents a realistic guidance level for public health care payers in Austria according to
Table 4 Cost-effectiveness outcomes comparing adjuvant anti-PD-1 antibody treatment and observation. Results of the base-case Markov model and conducted one-way deterministic sensitivity analyses.

| Base-case model | Costs (€) | LYS | QALYs | Incremental Costs (€) | LYS | (€/LY) | ICER (€/LY) | ICER (€/QALY) |
|----------------|----------|-----|-------|-----------------------|-----|-------|-----------|-------------|
| Adjuvant anti-PD-1-antibody treatment | 142,413 | 11.77 | 10.42 | 14,737 | 0.98 | 1.11 | 14,999 | 13,330 |
| No adjuvant treatment (observation) | 127,676 | 10.79 | 9.31 | | | | | |
| Equal distribution of nivo and pembro pts | Costs (€) | LYS | QALYs | Costs (€) | LYS | (€/LY) | ICER (€/LY) | ICER (€/QALY) |
| Adjuvant anti-PD-1-antibody treatment | 151,262 | 11.77 | 10.42 | 20,883 | 0.98 | 1.11 | 21,254 | 18,890 |
| No adjuvant treatment (observation) | 130,379 | 10.79 | 9.31 | | | | | |
| 15%/30% discount on drug prices | Costs (€) | LYS | QALYs | Costs (€) | LYS | (€/LY) | ICER (€/LY) | ICER (€/QALY) |
| Adjuvant anti-PD-1-antibody treatment | 151,262 | 11.77 | 10.42 | 20,883 | 0.98 | 1.11 | 21,254 | 18,890 |
| No adjuvant treatment (observation) | 130,379 | 10.79 | 9.31 | | | | | |
| Subsequent treatment costs +25%/-25% | Costs (€) | LYS | QALYs | Costs (€) | LYS | QALYs | ICER (€/LY) | ICER (€/QALY) |
| Adjuvant anti-PD-1-antibody treatment | 154,936 | 11.77 | 10.42 | 2,735 | 0.98 | 1.11 | 2,784 | 2,474 |
| No adjuvant treatment (observation) | 152,200 | 10.79 | 9.31 | | | | | |
| Disease management costs +25%/-25% | Costs (€) | LYS | QALYs | Costs (€) | LYS | QALYs | ICER (€/LY) | ICER (€/QALY) |
| Adjuvant anti-PD-1-antibody treatment | 148,515 | 11.77 | 10.42 | 13,444 | 0.98 | 1.11 | 13,683 | 12,161 |
| No adjuvant treatment (observation) | 135,071 | 10.79 | 9.31 | | | | | |
| 0%/6% discounting of costs and treatment effects (QALYs) | Costs (€) | LYS | QALYs | Costs (€) | LYS | QALYs | ICER (€/LY) | ICER (€/QALY) |
| Adjuvant anti-PD-1-antibody treatment | 148,996 | 16.51 | 14.62 | 12,600 | 1.47 | 1.65 | 8,567 | 7,644 |
| No adjuvant treatment (observation) | 136,396 | 15.04 | 12.97 | 8,730 | 1.47 | 1.65 | 7,644 | 7,644 |
| RFS/DMFS hazard ratio of 0.426/0.666* | Costs (€) | LYS | QALYs | Costs (€) | LYS | QALYs | ICER (€/LY) | ICER (€/QALY) |
| Adjuvant anti-PD-1-antibody treatment | 142,413 | 11.77 | 10.42 | 4,106 | 0.98 | 0.97 | 4,230 | 5,508 |
| No adjuvant treatment (observation) | 127,676 | 10.79 | 9.31 | | | | | |
| QoL parameters (utilities) +25%/-25% | Costs (€) | LYS | QALYs | Costs (€) | LYS | QALYs | ICER (€/LY) | ICER (€/QALY) |
| Adjuvant anti-PD-1-antibody treatment | 142,413 | 11.77 | 11.75 | 14,737 | 0.98 | 0.97 | 14,999 | 15,253 |
| No adjuvant treatment (observation) | 127,676 | 10.79 | 10.79 | | | | | |

Abbr.: LYS, live years; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; nivo, nivolumab; pembro, pembrolizumab; pts, patients; QoL, quality of life.

*The weighted hazard ratio for both RFS and DMFS in the base-case model was 0.533.

**The maximum input value for utility parameters was 1.
Table 5  Cost and utility inputs in the base-case Markov model.

| Item/Parameter                          | Cost/Point Value | Comment/Sources                                                                 |
|----------------------------------------|------------------|---------------------------------------------------------------------------------|
| **RF state**                           |                  |                                                                                  |
| **Drug costs**                         |                  |                                                                                  |
| – nivolumab 12 months (13 cycles)      | 92,400 €         | Official drug price (ex-factory) plus administration cost, 480 mg flat-dose Q4W|
| – pembrolizumab 12 months (17 cycles)  | 120,696 €        | Official drug price (ex-factory) plus administration cost, 200 mg flat-dose Q3W|
| – anti-PD-1 treatment weighted 12 months | 94,947 €   | Based on the observed 91 : 9 distribution of nivolumab and pembrolizumab patients |
| – anti-PD-1 treatment weighted 12 months (AE deducted) | 79,518 €   | Cost reduction based on observed AE-related treatment discontinuations in the cohort |
| – administration costs per cycle       | 244 €            | Day-care administration; sources: [23], local hospital-level information     |
| **Disease management/Follow-up**       |                  |                                                                                  |
| – follow-up year 1–2 (per year)        | 5,534 €          | Clinical and radiological FU; sources: [23], reimbursement tariffs, local information |
| – follow-up year 3 (per year)          | 4,996 €          | See year 1–2                                                                   |
| – follow-up year 4–5 (per year)        | 876 €            | See year 1–2                                                                   |
| – follow-up year 5–10 (per year)       | 82 €             | Clinical FU only                                                                |
| **Utilities**                          |                  |                                                                                  |
| – treatment cohort: Period 1 (one-time AE deduction) | 0.899 Source: [14] |                                                                                     |
| – treatment cohort: Period 2–156       | 0.912 Source: [14] |                                                                                     |
| – observation cohort: Period 1–156     | 0.912 Source: [14] |                                                                                     |
| **LR state**                           |                  |                                                                                  |
| **Disease management / Follow-up**     |                  |                                                                                  |
| – one-time surgery cost upon state entry | 2,842 €     | Assumed distribution: 60 % inpatient surgeries, 20 % daycare, 20 % unresectable; [22] |
| – follow-up year 1–10                  | See RF state     | Procedures and costs equal to RF state                                          |
| **Utilities**                          |                  |                                                                                  |
| – treatment and observation cohort:    | 0.858 Source: [14] |                                                                                     |
|  Period 1–156                          |                  |                                                                                  |
| **DR state**                           |                  |                                                                                  |
| **Drug costs**                         |                  |                                                                                  |
| – treatment cohort weighted cost upon state entry | 104,322 € | Weighted distribution of 5 treatment scenarios (see Online Supplementary File 1) |
| – observation cohort weighted cost upon state entry | 142,232 € | Weighted distribution of 3 first-line treatment scenarios (see Online Supplementary File 1) |
expert opinion (author H.O.), adjuvant treatment with nivolumab or pembrolizumab (in a 91 : 9 distribution) was highly cost-effective with an ICER of 13,330 € per QALY in the base-case Markov model. The low proportion (5 %) of patients with AJCC stage IIIA disease in the present real-world sample may be considered beneficial in terms of cost-effectiveness. However, recent updates of adjuvant melanoma trials show that even in this often-termed “low risk” subgroup approximately 30 % of patients develop disease recurrence [32, 33]. Hence, adjuvant treatment appears vindicated also in patients with stage IIIA disease, provided that the prognostically critical extent of SLN involvement (> 1 mm deposit size) complies with the inclusion criteria of the above quoted clinical trials [32, 33].

Deterministic sensitivity analyses showed that cost-effectiveness outcomes (ICERs) were most sensitive to changes in the assumed effect of adjuvant treatment. Still limited data on DMFS and overall survival in the pivotal adjuvant anti-PD-1 trials currently represent a source of uncertainty in this context. Sensitivity analyses also showed that discounts on drug prices, as typically negotiated by hospital pharmacies or public insurances in Austria, would improve cost-effectiveness as expected, whereas a higher proportion of pembrolizumab-treated patients (assumed 50 : 50 distribution) might increase the estimated cost per QALY. The latter finding results from a considerably higher official drug price of fixed-dose pembrolizumab compared to nivolumab.

Other cost-effectiveness analyses of adjuvant pembrolizumab and nivolumab treatment published to date have been based on clinical trial data of the Keynote-054 and Checkmate-238 trial, respectively [14–16]. The ICER compared to observation for adjuvant pembrolizumab reported in the literature by Bensimon et al. was 15,009 US $ per QALY, whereas for nivolumab the French analysis by Bregman et al. yielded an ICER of 36,553 € per QALY [14, 16]. The absolute QALY gains in these studies differed remarkably (3.29 versus 1.5 QALYs for pembrolizumab and nivolumab, respectively), as did the estimated costs for subsequent treatments, both in absolute numbers and in relation to total costs (305,438 of 489,820 US $ [62.3 %] and 35,996 of 139,841 € [25.7 %], respectively) [14, 16]. In both analyses, costs for subsequent treatment were approximately 25 % higher in the observation cohort, reflecting the increased proportion of patients developing disease recurrence in this subgroup. In our base-case model, subsequent treatment costs in the observation cohort were even almost doubled compared to the anti-PD-1 cohort, as we additionally took into account recent findings suggesting decreased efficacy and hence a shortened median treatment duration of subsequent immunotherapies in patients progressing during or shortly after adjuvant PD-1-antibody treatment [19]. Taken together, the listed differences reveal main issues and sources of uncertainty regarding current cost-effectiveness models of adjuvant melanoma treatments, which are mainly related to the efficacy and costs of subsequent treatments in conjunction with immature
survival data. Yet, adjuvant anti-PD-1 treatment has been suggested to be cost-effective with a high probability in numerous simulated scenarios so far, including the one at hand [14–16, 34].

Our study harbors certain limitations including its retrospective character, limited sample size and relatively short follow-up period. However, the obtained results indicate that real-world outcomes of adjuvant anti-PD-1 antibody treatment are largely comparable to pivotal clinical trial data. Owing to changes in clinical practice (increasing omission of CLND), efficacy appears to be slightly impaired in the real-life setting in terms of an increased rate of locoregional recurrences.

The conducted cost-utility analysis suggests that adjuvant anti-PD-1 therapy is a cost-effective strategy according to health economic standards of central European countries such as Austria. Of note, the efficacy of subsequent immunotherapy in patients developing disease recurrence during or after cessation of adjuvant treatment remains to be determined, which currently implies a relevant degree of contextual uncertainty.

Conflict of Interest

P. Koelblinger has received honoraria for travel/congress support and consulting/advisory roles for Roche, Bristol Myers Squibb (BMS), Merck Sharp & Dome (MSD), Novartis, Amgen, Pierre Fabre and Sanofi Aventis unrelated to the submitted work.

E. Richtig: Honoraria: Amgen, Bayer, Bristol-Myers Squibb, MSD, Merck, Novartis, Pierre Fabre, Roche, Sanofi. Consulting or advisory role: Amgen, Bayer, Bristol-Myers Squibb, MSD, Merck, Novartis, Pierre Fabre, Roche, Sanofi. Speakers’ Bureau: Amgen, Bristol-Myers Squibb, MSD, Merck, Novartis, Pierre Fabre, Roche, Sanofi. Research Funding at the institution (Medical University of Graz) site PI: Amgen, Bristol-Myers Squibb, MSD, Novartis, Pierre Fabre, Roche. Research Funding steering committee: Novartis. Travel, accommodations, expenses: Amgen, Bristol-Myers Squibb, MSD, Merck, Novartis, Pierre Fabre, Roche, Sanofi.

V.A. Nguyen has received speaker’s honoraria and consultancy fees from Amgen, Bristol-Myers Squibb, GlaxoSmithKline, Merck Sharp & Dohme, Novartis, Pierre Fabre, Roche, Sanofi and Takeda outside the submitted work.

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M. Hoellwerth, M.T. Dernoscheg, L. Koch, M. Wanner, H. Ostermann: No conflicts of interest to declare.

References

1 Weber J, Mandala M, Del Vecchio M et al. Adjuvant nivolumab versus ipilimumab in resected stage III or IV melanoma. N Engl J Med 2017; 377(19): 1824–35.

2 Eggermont AMM, Blank CU, Mandala M et al. Adjuvant pembrolizumab versus placebo in resected stage III melanoma. N Engl J Med 2018; 378(19): 1789–801.

3 Long GV, Hauschild A, Santinami M et al. Adjuvant dabrafenib plus trametinib in stage III BRAF-mutated melanoma. N Engl J Med 2017; 377(19): 1813–23.

4 Leitlinienprogramm Onkologie. Diagnostik, Therapie und Nachsorge des Melanoms, Langversion 3.3, 2020, AWMF Registernummer: 032/024OL 2020. Available from: http://www.leitlinienprogramm-onkologie.de/leitlinien/melanom/ [Last accessed October 1, 2020].

5 Michielin O, van Akkooi ACJ, Ascierto PA et al. Cutaneous melanoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2019; 30(12): 1884–901.

6 National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology. Cutaneous Melanoma (Version 4.2020). Available from: https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf [Last accessed October 1, 2020].

7 Rauwerdink DJW, Molina G, Frederick DT et al. Adjuvant therapy failure patterns in the modern era of melanoma management. Ann Surg Oncol 2020; 27(13): 5128–36.

8 Farrow NE, Raman V, Williams TP et al. Adjuvant therapy is effective for melanoma patients with a positive sentinel lymph node biopsy who forego completion lymphadenectomy. Ann Surg Oncol 2020; 27(13): 5121–5.

9 Fairies MB, Thompson JF, Cochran AJ et al. Completion dissection or observation for sentinel-node metastasis in melanoma. N Engl J Med 2017; 376(23): 2211–22.

10 Leiter U, Stadler R, Mauch C et al. Complete lymph node dissection versus no dissection in patients with sentinel lymph node biopsy positive melanoma (DeCOG-SLT): a multicentre, randomised, phase 3 trial. Lancet Oncol 2016; 17(6): 757–67.

11 Leiter U, Stadler R, Mauch C et al. Final analysis of DeCOG-SLT trial: no survival benefit for complete lymph node dissection in patients with melanoma with positive sentinel node. J Clin Oncol 2019; 37(32): 3000–8.
12 Gershenwald JE, Scolyer RA, Hess KR et al. Melanoma staging: Evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer J Clin 2017; 67(6): 472–92.
13 Hindie E. What is the role of dabrafenib plus trametinib adjuvant therapy in stage IIIA melanoma? J Clin Oncol 2019; 37(15): 1355–6.
14 Bensimon AG, Zhou ZY, Jenkins M et al. Cost-effectiveness of pembrolizumab versus other adjuvant treatment strategies for resected high-risk stage III melanoma in the United States. J Med Econ 2019; 22(10): 981–91.
15 Bensimon AG, Zhou ZY, Jenkins M et al. An economic evaluation of pembrolizumab versus other adjuvant treatment strategies for resected high-risk stage III melanoma in the USA. Clin Drug Invest 2020; 40(7): 629–43.
16 Bregman B, Teitsson S, Orsini I et al. Cost-utility analysis of nivolumab in adjuvant treatment of melanoma in France. Dermatol Ther (Heidelb) 2020; 10(6): 1331–43.
17 National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) v5.0. 2017. Available from: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf [Last accessed October 1, 2020].
18 Statistik Austria. Jaehrliche Sterbetafeln 1947 bis 2019 für Oesterreich. Available from: https://www.statistik.at/wcm/idc/idcplg?IdcService=GET_PDF_FILE&RevisionSelectionMethod=LatestReleased&dDocName=022707 [Last accessed October 1, 2020].
19 Owen CN, Shoushtari AN, Chauhan D et al. Management of early melanoma recurrence despite adjuvant anti-PD-1 antibody therapy. Ann Oncol 2020; 31(8): 1075–82.
20 Pires Da Silva J, Ahmed T, Lo S et al. Ipilimumab (IPI) alone or in combination with anti-PD-1 (IPI+PD1) in patients (pts) with metastatic melanoma (MM) resistant to PD1 monotherapy. J Clin Oncol 2020; 38(7_suppl): 10005–10005.
21 Attema AE, Brouwer WBF, Claxton K. Discounting in economic evaluations. Pharmacoeconomics 2018; 36(7): 745–58.
22 Bundesministerium fuer Soziales/Gesundheit/Pflege und Konsumentenschutz. Krankenanstalten in Zahlen. Available from: http://www.kaz.bmg.gv.at/fileadmin/user_upload/Kosten/re_Kosten_Kostenarten.pdf [Last accessed October 1, 2020].
23 Department of Health Economics (Medical University of Vienna). DHE Unit Cost online Database: Cost Collection from Existing Studies. Version 3.1/2019. 2019. Available from: https://healtheconomics.meduniwien.ac.at/downloads/dhec-unit-cost-online-database/ [Last accessed October 1, 2020].
24 Mayer S, Kiss N, Laszewska A, Simo J. Costing evidence for health care decision-making in Austria: a systematic review. PLoS One 2017; 12(8): e0183116.
25 Paly V, Colby C, Gilloteau I et al. Predictors of utility over time among patients with treatment-naive advanced melanoma from the phase 3 Checkmate 066 trial. Value in Health 2015; 18: A335–A766.
26 Stadler R, Leiter U, Garbe C. Lack of survival benefit in sentinel lymph node-positive melanoma with immediate complete lymphadenectomy – a review. J Dtsch Dermatol Ges 2019; 17(1): 7–13.
27 Weber J, Del Vecchio M, Mandala M et al. Adjuvant nivolumab (NIVO) versus ipilimumab (IPI) in resected stage III/IV melanoma: 3-year efficacy and biomarker results from the phase III Checkmate 238 trial. conference abstract: Oxford University Press; 2019: v533–4.
28 Ascierto PA, Del Vecchio M, Mandala M et al. Adjuvant nivolumab versus ipilimumab in resected stage IIIB-C and stage IV melanoma (CheckMate 238): 4-year results from a multicentre, double-blind, randomised, controlled, phase 3 trial. Lancet Oncol 2020; 21(11): 1465–77.
29 Abu-Sbeih H, Tang T, Lu Y et al. Clinical characteristics and outcomes of immune checkpoint inhibitor-induced pancreatic injury. J Immunother Cancer 2019; 7(1): 31.
30 Moreira A, Loquai C, Pfihler C et al. Myositis and neuromuscular side-effects induced by immune checkpoint inhibitors. Eur J Cancer 2019; 106: 12–21.
31 Kahler KC, Hassel JC, Heinzerling L et al. Side effect management during immune checkpoint blockade using CTLA-4 and PD-1 antibodies for metastatic melanoma – an update. J Dtsch Dermatol Ges 2020; 18(6): 628–609.
32 Eggermont AMM, Blank CU, Mandala M et al. Longer follow-up confirms recurrence-free survival benefit of adjuvant pembrolizumab in high-risk stage III melanoma: updated results from the EORTC 1325-MG/KEYNOTE-054 Trial. J Clin Oncol 2020; 38(33): 3925–36.
33 Dummer R, Hauschild A, Santinami M et al. Five-year analysis of adjuvant dabrafenib plus trametinib in stage III melanoma. N Engl J Med 2020; 383(12): 1139–48.
34 Freeman M, Betts KA, Jiang S et al. Indirect treatment comparison of nivolumab versus observation or ipilimumab as adjuvant therapy in resected melanoma using pooled clinical trial data. Adv Ther 2019; 36(10): 2783–96.