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Grade 3/4 Adverse Event Costs of Nivolumab Versus Dabrafenib Plus Trametinib as Adjuvant Treatment in Patients With Stage III *BRAF*-Mutant Cutaneous Melanoma in Portugal

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Background

- According to the World Health Organization, an estimated 132,000 new cases of melanoma are diagnosed globally each year[1]
- Patients with stage III or IV melanoma are at increased risk for recurrence or death compared with those who have less-advanced disease. The 5-year risk of recurrence was 48% for stage IIIA, 71% for stage IIIB, and 85% for stage IIIC[2]
- In July 2018, the European Medicines Agency approved nivolumab (NIVO), an immuno-oncology agent that mediates checkpoint inhibition, for treatment of patients with melanoma with lymph node involvement or metastatic disease who had undergone complete resection in the adjuvant setting[3,4]
  - In the CheckMate 238 trial, patients with resected stage IIIB, IIIC, or IV melanoma receiving NIVO 3 mg/kg experienced significantly longer recurrence-free survival (RFS) than those receiving ipilimumab (IPI) as adjuvant therapy[5]
  - The all-cause grade 3/4 adverse events (AEs) reported for NIVO versus IPI were 25% versus 55%, respectively[5]
- Combination therapy with dabrafenib plus trametinib (DAB+TRAM), targeted inhibitors of *BRAF/MEK*, was approved in 2018 for the adjuvant treatment of resected *BRAF*-mutant stage III melanoma[6,7]
  - In the COMBI-AD trial, DAB+TRAM adjuvant therapy showed significant improvements in the 3-year RFS rate compared with placebo[8]
  - All-cause grade 3/4 AEs reported by the groups receiving combination therapy versus placebo were 41% and 14%, respectively[8]
- With the availability of 2 new adjuvant treatments for melanoma, there is a need to assess the associated benefits and risks for treatment decision-making

Objective

- To assess the per-patient costs of all-cause grade 3/4 AEs associated with NIVO versus DAB+TRAM when used as adjuvant therapies in resected stage IIIB/C *BRAF*-mutant cutaneous melanoma in Portugal

Methods

Data sources

- All-cause grade 3/4 AE rates associated with NIVO were estimated using individual patient-level data (IPD) from the CheckMate 238 trial[5]
- All-cause grade 3/4 AE rates associated with DAB+TRAM were obtained from published results of the COMBI-AD trial[8]
- Unit costs of all-cause grade 3/4 AEs (in 2019 EUR) were obtained from the Portaria n.º 254/2018 ordinance and other official sources[9]

AE cost calculations

- Per-patient costs of all-cause grade 3/4 AEs were calculated by multiplying the AE rates by the unit AE costs
- AE rates
  - The assessment periods for AE rates were similar for the CheckMate 238[5] and COMBI-AD trials[8]
    - Patients were required to receive study treatment for up to 1 year
    - AEs were assessed from the first dose of the study treatment until 30 days after discontinuation of the study treatment
  - AE rates in stage IIIA/B/C patients receiving DAB+TRAM in COMBI-AD[8] were assumed to be similar
  - **Main analysis:** All-cause grade 3/4 AEs from the list of any-grade AEs reported in > 10% of patients
    - For each type of AE, it was assumed that an individual patient could have a specific type of grade 3/4 AE only once during the assessment period for both NIVO and DAB+TRAM. This is because COMBI-AD[8] reported only the prevalence of AEs
  - **Sensitivity analysis:** All-cause grade 3/4 AEs, including less common any-grade AEs (other all-cause grade 3/4 AEs), reported in ≤ 10% of patients
    - Calculation of the percentage of patients with other all-cause grade 3/4 AEs: It was assumed that an individual patient could not have multiple types of grade 3/4 AEs during the assessment period. This is due to the lack of patient-level data on other all-cause grade 3/4 AEs in the COMBI-AD trial[8]
- Unit AE costs
  - It was assumed that grade 3/4 AEs would require hospitalization based on the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03[10]
  - In the sensitivity analysis, the unit cost associated with other all-cause grade 3/4 AEs was the weighted average unit cost based on the CheckMate 238 clinical trial data[5]
- All costs are presented in 2019 EUR

Results

Main analysis

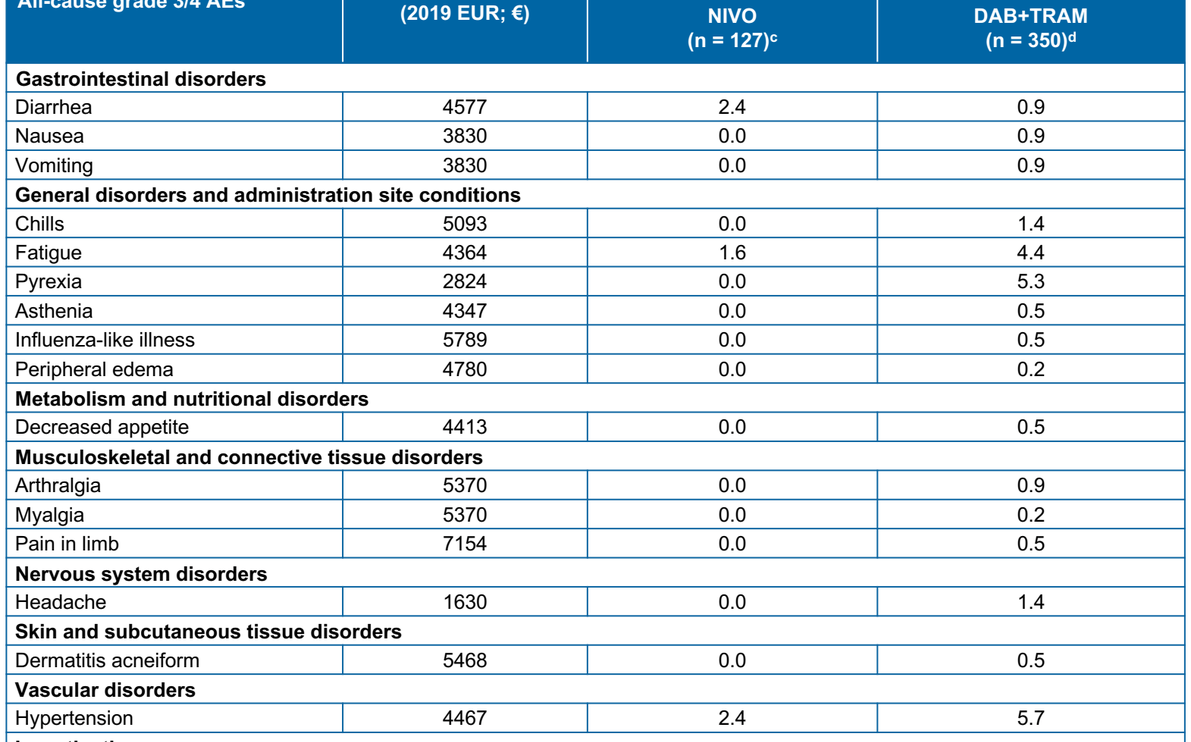
- The rates and corresponding unit costs of all-cause grade 3/4 AEs are reported in **Table 1.** Per-patient all-cause grade 3/4 AE costs of NIVO versus DAB+TRAM are provided in **Figure 1**
  - The per-patient costs of all-cause grade 3/4 AEs were €314 for NIVO versus €1291 for DAB+TRAM (a cost difference of €977)
  - The 3 most common AEs were diarrhea (€108), hypertension (€106), and fatigue (€69) for NIVO, and hypertension (€257), pyrexia (€149), and fatigue (€191) for DAB+TRAM

Table 1. All-cause grade 3/4 AE rates and unit costs in patients with resected stage IIIB/C *BRAF*-mutant melanoma (main analysis)[a]

All-cause grade 3/4 AEs	AE unit cost[b] (2019 EUR; €)	AE rate (%)	
		NIVO (n = 127)[c]	DAB+TRAM (n = 350)[d]
Gastrointestinal disorders			
Diarrhea	4577	2.4	0.9
Nausea	3830	0.0	0.9
Vomiting	3830	0.0	0.9
General disorders and administration site conditions			
Chills	5093	0.0	1.4
Fatigue	4364	1.6	4.4
Pyrexia	2824	0.0	5.3
Asthenia	4347	0.0	0.5
Influenza-like illness	5789	0.0	0.5
Peripheral edema	4780	0.0	0.2
Metabolism and nutritional disorders			
Decreased appetite	4413	0.0	0.5
Musculoskeletal and connective tissue disorders			
Arthralgia	5370	0.0	0.9
Myalgia	5370	0.0	0.2
Pain in limb	7154	0.0	0.5
Nervous system disorders			
Headache	1630	0.0	1.4
Skin and subcutaneous tissue disorders			
Dermatitis acneiform	5468	0.0	0.5
Vascular disorders			
Hypertension	4467	2.4	5.7
Investigations			
Elevated ALT	3956	0.8	3.7
Elevated AST	3956	0.0	3.7

[a]Only grade 3/4 AEs with corresponding any-grade AEs reported in > 10% of patients were considered.
[b]AE unit costs were based on the Portaria n.º 254/2018.[9]
[c]AE rates were calculated based on the IPD from the CheckMate 238 trial.[5]
[d]AE rates were obtained from published data from the COMBI-AD trial.[8]
ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Figure 1. Per-patient all-cause grade 3/4 AE costs in patients with resected stage IIIB/C *BRAF*-mutant melanoma (main analysis)[a,b]



[a]Only all-cause grade 3/4 AEs with corresponding any-grade AEs reported in > 10% of patients were considered.
[b]The per-patient costs used in the calculation were rounded to the last significant digit to ensure precision.

Sensitivity analysis

- The per-patient all-cause grade 3/4 AE costs of NIVO versus the DAB+TRAM combination are provided in **Table 2** and **Figure 2**
  - The per-patient costs of all-cause grade 3/4 AEs were €1347 for NIVO compared with €1853 for DAB+TRAM (a cost difference of €506)
  - The costs associated with any other all-cause grade 3/4 AEs accounted for 76.7% and 30.3% of all the AE costs for NIVO versus DAB+TRAM, respectively

Table 2. All-cause grade 3/4 AE rates and unit costs in patients with resected stage IIIB/C *BRAF*-mutant melanoma (sensitivity analysis)[a]

All-cause grade 3/4 AEs	AE unit cost[b] (2019 EUR; €)	AE rate (%)	
		NIVO (n = 127)[c]	DAB+TRAM (n = 350)[d]
Percentage of patients with all-cause grade 3/4 AEs	NA	24.4	41.4
Gastrointestinal disorders			
Diarrhea	4577	2.4	0.9
Nausea	3830	0.0	0.9
Vomiting	3830	0.0	0.9
General disorders and administration site conditions			
Chills	5093	0.0	1.4
Fatigue	4364	1.6	4.4
Pyrexia	2824	0.0	5.3
Asthenia	4347	0.0	0.5
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Metabolism and nutritional disorders			
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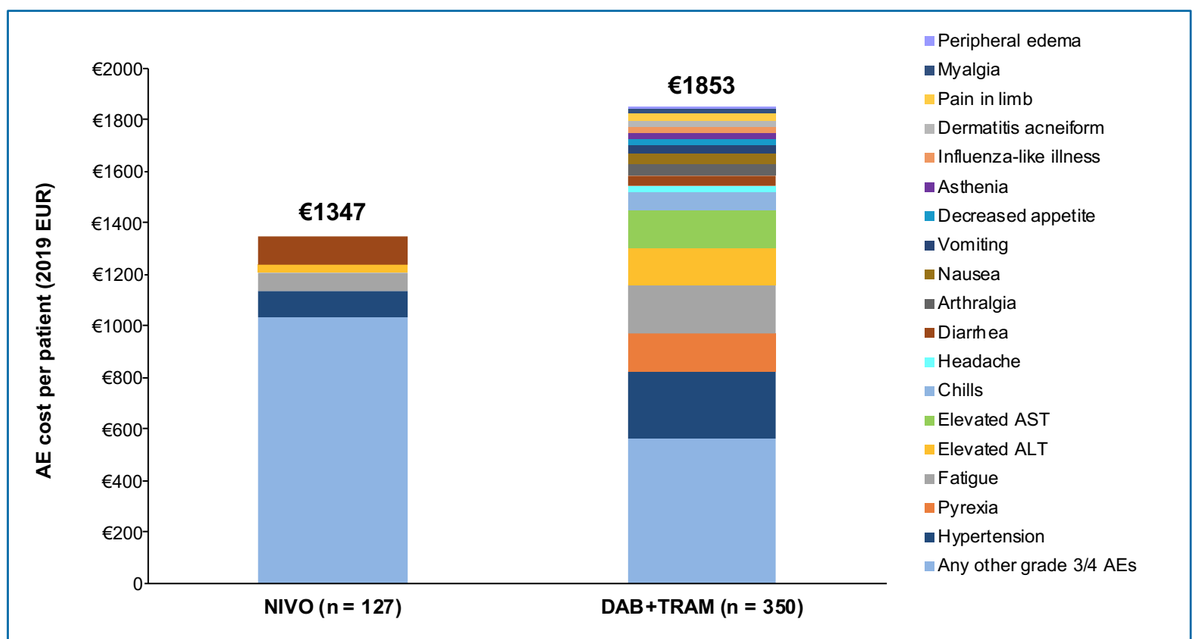
Vascular disorders			
Hypertension	4467	2.4	5.7
Investigations			
Elevated ALT	3956	0.8	3.7
Elevated AST	3956	0.0	3.7
Patients with other all-cause grade 3/4 AEs[e,f]	5964	17.3	9.4

[a]All-cause grade 3/4 AEs were considered. Values represent grade 3/4 AEs with corresponding any-grade AEs reported in > 10% of patients.
[b]AE unit costs were based on the Portaria n.º 254/2018.[9]
[c]AE rates were calculated based on the IPD from the CheckMate 238 trial.[5]
[d]AE rates were obtained from published data from the COMBI-AD trial.[8]
[e]Other all-cause grade 3/4 AEs included the all-cause grade 3/4 AEs not included in the list of AEs reported above. The proportion of patients with any other all-cause grade 3/4 AE was calculated as the difference between the proportion of patients with any grade 3/4 AE and the sum of all-cause grade 3/4 AE rates in the core analysis.
[f]The unit costs associated with other all-cause grade 3/4 AEs were the weighted average unit cost based on the CheckMate 238 clinical trial data.[5]
NA, not applicable.

Figure 2. Per-patient all-cause grade 3/4 AE costs in patients with resected stage IIIB/C *BRAF*-mutant melanoma (sensitivity analysis)[a,b]



[a]All all-cause grade 3/4 AEs were considered.
[b]The per-patient costs used in the calculation were rounded to the last significant digit to ensure precision.

Discussion

- Using individual patient data from the CheckMate 238 trial[5] and published data from the COMBI-AD trial,[8] this study assessed the AE costs associated with NIVO and DAB+TRAM as adjuvant therapies for patients with resected stage IIIB/C *BRAF*-mutant melanoma
  - The findings contribute to the current understanding of the comparative AE costs of new adjuvant therapies for patients with melanoma
  - Compared with DAB+TRAM, NIVO was associated with lower all-cause grade 3/4 AE costs per patient during the trial period
- Costs associated with other all-cause grade 3/4 AEs with corresponding any-grade AEs in ≤ 10% of patients were sizable; further real-world studies are warranted to comprehensively assess the AE costs

Limitations

- The current analysis focused on costs associated with all-cause grade 3/4 AEs
  - Costs associated with grade 1/2 AEs were not included in this analysis because these events are considered to be of low cost impact
  - As a result, this study may underestimate the total AE costs associated with both treatments
- Due to the lack of data from the COMBI-AD trial,[8] assumptions were made in both the main and sensitivity analyses that may underestimate the AE costs for both treatments. Further real-world studies to comprehensively assess the AE costs are warranted
- Because unit costs for AEs were mostly obtained from the Portaria n.º 254/2018,[9] they may not reflect the true costs incurred during the trial and were subject to measurement errors. This may have resulted in either underestimation or overestimation of costs

Conclusions

- Based on the clinical trial data from CheckMate 238[5] and published AE data from the COMBI-AD trial,[8] patients with resected stage IIIB/C *BRAF*-mutant melanoma who were treated with NIVO incurred lower costs related to all-cause grade 3/4 AEs compared with those treated with DAB+TRAM as adjuvant therapy
- Future studies are needed to assess the cost of a broader range of AEs and associated costs beyond the trial period

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