Double immune checkpoint inhibition as first-line treatment for BRAF-mutant advanced melanoma: a cost-effectiveness analysis from the Brazilian private healthcare system perspective

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Introduction

- Melanoma accounts for only 4% of all skin cancer cases, however it is responsible for 75% of skin cancer-related deaths.[1]
- BRAF mutations are frequently found in melanoma occurring in about 50% of melanoma-affected patients.[2]
- The main systemic therapy for BRAF-mutated advanced melanoma patients includes targeted therapy and immunotherapy.[3-5]
- The approval of BRAF and MEK inhibitors improved the median overall survival (mOS) of melanoma BRAF-mutated patients from approximately 9 months to at least 2 years, producing a high number of objective responses whereas double immunotherapy with nivolumab + ipilimumab has shown durable survival rates for all melanoma patients, with a mOS of 71.9 months. This includes patients with BRAF mutations, whose mOS was not reached (NR) according to the final 10-year results of the CheckMate 067 study.[6,7,8]
- Until recently, there was limited prospective data to guide the selection of initial therapy or treatment sequencing for this patient population. This gap has been addressed by evidence such as the DREAMseq trial (ECOG-ACRIN EA6134), which provided valuable insights into optimal treatment strategies.[9]
- The latest findings show that initiating treatment with dual immunotherapy significantly enhances overall survival (OS) and progression-free survival (PFS) in patients with BRAFV600-mutant advanced melanoma.[10-12] These compelling results have prompted revisions to the current melanoma treatment guidelines.[3,4,13]
- However, in resource-limited settings, assessing the economic impact of clinical practices is crucial. To date, there has been no economic evaluation of treatment sequencing for advanced BRAF-mutated patients from the perspective of the Brazilian Private Healthcare System.

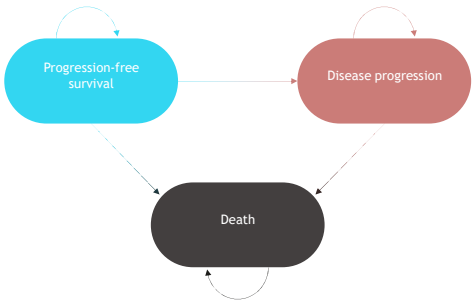
Objective

- To evaluate the cost-effectiveness of starting with nivolumab + ipilimumab followed by dabrafenib/trametinib versus the reverse sequence for advanced melanoma with BRAF mutation from the Brazilian Private Healthcare System perspective.

Methods

- A partitioned survival model with three health states was developed. Model structure is shown in Figure 1.

Figure 1. Model structure



- Table 1 summarizes main characteristics of the economic model.
  - The target population comprised adult patients with advanced melanoma with BRAF mutation.
  - The model projected OS and PFS to estimate drug and follow-up costs over a lifetime horizon of up to 39 years (average age at diagnosis: 61 years).
  - Clinical data were sourced from the Phase 3 DREAMseq Trial (ECOG-ACRIN EA6134).[9] Extrapolations methods were applied for OS and PFS curves to determine the curve that would best represent the expected cohort behavior, a visual inspection of the parameterizations was conducted, followed by a statistical analysis considering the lowest AIC (Akaike Information Criterion) and BIC (Bayesian Information Criterion) values. Finally, expert opinion was used to select the best parameterization.
  - The primary outcome was the incremental cost-utility ratio (ICUR), expressed as cost per quality-adjusted life year (QALY) and life-year (LY) gained.
  - Utility data were obtained through a systematic search focused on EQ-5D values, as described by Pike et al. (2017).[14] For the treatments with dabrafenib and trametinib, the values from Grob et al. (2015) were utilized for both PFS and progressive disease health states[15]. In the case of immunotherapies, the values were adapted from a comparison of pembrolizumab versus ipilimumab.[14]
  - Costs, reported in Brazilian real (BRL), included drug acquisition, follow up and adverse event management, calculated using a microcosting approach and discounted at an annual rate of 5% from the Brazilian Private Market Perspective.
  - A factory price (PF0%) was considered for the acquisition costs of the four medications, in accordance with the ICMS (Imposto sobre Circulação de Mercadorias e Serviços - Tax on the Circulation of Goods and Services) 162/94 agreement. Treatment costs were calculated based on the dosing regimens from the DREAMseq study and the proportion of patients receiving treatment over time.[9]Additionally, a microcosting analysis, developed with expert opinion, included costs associated with adverse events with an incidence ≥5%, as reported in DREAMseq[9]
  - Deterministic and probabilistic sensitivity analyses were performed.

Table 1. Summary of the main characteristics of the economic model

Characteristics	Definitions
Intervention and comparator	Intervention: Nivolumab + Ipilimumab (arm A) followed by Dabrafenib + Trametinib (arm C) Comparators: Dabrafenib + Trametinib (arm B) followed by Nivolumab + Ipilimumab (arm D).
Outcomes	Quality-adjusted life years (QALYs) and life years gained
Time horizon	Lifetime
Discount rate	5% discount rate for costs and outcomes
Clinical parameters	Clinical parameters were estimated based on the Phase 3 DREAMseq Trial (ECOG-ACRIN EA6134).[8]
Cost estimation	Medications: Estimated based on the June 2024 CMED price list. PF0% was used as reference considering ICMS tax exemption for all drugs. Other costs: Resource use patterns estimated from expert opinion, with costs based on the 2023 CBHPM.

CMED: Chamber of Regulation of the Market for Medicines; CBHPM: Brazilian Hierarchical Classification of Medical Procedures.

Results

Base case

- Table 2 summarizes the results (mean costs, LYG and QALY) for each treatment regimen. Incremental cost-effectiveness ratios (ICER) and incremental cost-utility rations (ICUR) were calculated.
  - Cost savings of 165,400 BRL with the treatment sequence initiating with nivolumab + ipilimumab followed by dabrafenib/trametinib were observed.
  - An incremental gain of 2.69 LY and 2.26 QALY were estimated by using this proposed strategy versus initial treatment with drabrafenib + trametinib.
  - Initial dual immunotherapy was considered dominant (superior outcome at a lower cost).

Table 2. Results for the base case analysis

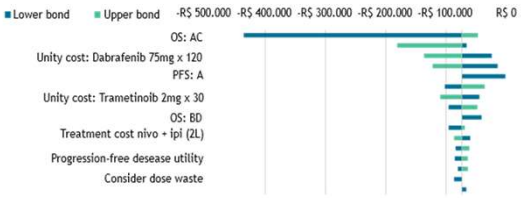
Parameters	Arm A/C	Arm B/D	Incremental
Total cost (BRL)	1,097.309	1,262.709	-165,400
First-line treatment (BRL)	827,588	997,639	-170,051
Progression-free survival (BRL)	78,982	22,076	56,906
Second-line treatment (BRL)	128,096	154,438	-26,343
Disease progression (BRL)	54,594	80,529	-25,935
Adverse events (BRL)	2,439	1,225	1,214
Death (BRL)	5,610	6,801	-1,191
LYs	7.49	4.81	2.69
Progression-free survival	5.22	1.46	3.76
Disease progression	2.27	3.35	-1.08
QALYs	5.77	3.51	2.26
Progression-free survival	4.18	1.17	3.01
Disease progression	1.59	2.34	-0.75
ICER (BRL/LYs)			Cost-saving
ICUR (BRL/QALYs)			Cost-saving

BRL: Brazilian real; QALY: Quality-Adjusted Life Years; LY: Life Years; ICUR: Incremental Cost-Utility Ratio; ICER: Incremental Cost-Effectiveness Ratio.

Sensitivity analysis

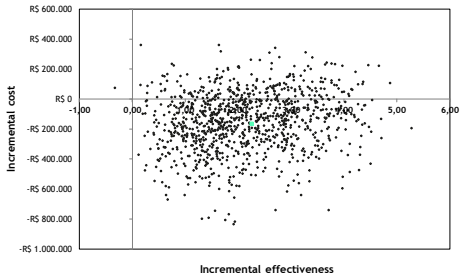
- Figure 2 shows results from deterministic sensitivity analysis.
  - The results indicate that the global survival curve of the intervention arms has the greatest impact on the analysis.
  - This suggests that it is the parameter with the highest uncertainty.

Figure 2. Deterministic sensitivity Analysis



- Figure 3 shows results from probabilistic sensitivity analysis.
  - The probabilistic analysis shows that the majority of results fall in the 4th quadrant (78.4%), indicating that in most scenarios, the initial treatment with nivolumab + ipilimumab demonstrates lower incremental costs and higher incremental effectiveness.

Figure 3. Cost-effectiveness plan



Discussion

- In this analysis, the treatment sequence involving double-immunotherapy PD-1 inhibitor and the CTLA-4 inhibitor nivolumab + ipilimumab, followed by the BRAF and MEK inhibitors dabrafenib + trametinib, resulted in cost savings of 165,400.00 BRL, along with an incremental gain of 2.69 LY and 2.26 QALYS.
- Probabilistic sensitivity analysis confirmed that, with a high degree of certainty, initiating treatment with this dual immunotherapy was cost-saving in the Brazilian private healthcare system in most scenarios (78.4%).
- From our knowledge, this is the first economic evaluation of treatment sequencing for advanced BRAF-mutated patients from the perspective of the Brazilian Private Healthcare System.
- Blommestein et al.[16] conducted a cost-effectiveness analysis of 21 treatment sequences for advanced melanoma patients with BRAF mutations in the Netherlands.
  - Despite the inability to perform direct comparisons due to differing perspectives and datasets, findings from both Blommestein's study and ours consistently indicated that a first-line regimen of nivolumab + ipilimumab, followed by a second-line treatment with a BRAF inhibitor and a MEK inhibitor, achieved the highest QALYs and the most favorable ICER.
- This study has limitations, particularly regarding the reliance on data for efficacy, safety, and medication usage obtained from the DREAMseq trial.[9] As a result, the findings may not fully align with real-world clinical practice, where variations in treatment implementation and patient management may occur.

Conclusions

- First line nivolumab + ipilimumab followed by dabrafenib/trametinib proved to be a cost-effective strategy for managing BRAF-mutant advance melanoma, dominating the reverse sequence from the Brazilian private healthcare perspective. This economic evaluation reinforces the clinical benefit and efficient use of resources of initiating treatment with this dual immunotherapy.

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- All authors contributed to and approved the presentation.

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