Conitec

Recomendation report

DRUGS

Nº 541
June/2020

Targeted therapies (vemurafenib, dabrafenib, cobimetinib, trametinib) and immunotherapies (ipilimumab, nivolumab, pembrolizumab) for the first-line treatment of advanced (unresectable and metastatic) melanoma

Brasília – DF
2020

Technologies: Targeted therapies (vemurafenib, dabrafenib, cobimetinib, trametinib) and immunotherapies (ipilimumab, nivolumab, pembrolizumab).

Indication: First-line treatment of advanced (unresectable or metastatic) melanoma.

Applicants: Secretariat of Science, Technology and Strategic Inputs (SCTIE)/Ministry of Health of Brazil, and Bristol-Myers Squibb Pharmaceutical Ltd. (Brazil) (nivolumab).

Background: Although melanoma is not among the malignant tumours with the highest incidence, it is considered the most aggressive form of skin cancer with a high propensity to spread to distant sites and consequently with high lethality. In 2018, it was estimated that 6,260 new cases of malignant melanoma were diagnosed in Brazil, with around 26% at metastatic stage. 1,794 deaths were reported in 2015. This Report considered the systemic therapeutic options registered with the Brazilian National Health Surveillance Agency (Anvisa) for the first-line treatment of advanced (unresectable and metastatic) melanoma.

Question: Is the use of targeted therapies or immunotherapies more effective, safe and cost-effective compared with dacarbazine chemotherapy for the first-line treatment of advanced (unresectable and metastatic) melanoma?

Scientific evidence: Based on the studies analysed, all these therapies showed a statistically significant superiority compared with standard treatment with dacarbazine, for both Progression-Free Survival (PFS) and Overall Survival (OS) outcomes, except dabrafenib alone. Regarding OS, immuno-combination therapy with nivolumab plus ipilimumab reduced the risk of death by 67% (23% in a worst-case scenario); immuno-monotherapy with nivolumab or pembrolizumab by 54% (41% in a worst-case scenario); targeted combination therapies by 44-46% (23-27% in a worst-case scenario); immuno-monotherapy with ipilimumab by 32% (7% in a worst-case scenario); and targeted monotherapy with vemurafenib by 20% (3% in a worst-case scenario). Grade 3-4 adverse events were assessed for the following therapeutic classes: targeted therapy, immunotherapy, and chemotherapy. A lower risk of adverse events was reported for immuno-monotherapy with anti-PD-1 agents (nivolumab and pembrolizumab) compared with dacarbazine, and the therapeutic classes that showed the highest risk of adverse events were: targeted monotherapy, targeted combination therapy, anti-CTLA-4 immunotherapy, and immuno-combination therapy, with a relative risk above 1.40.

Economic evaluation: The cost-effectiveness analysis demonstrated that ipilimumab was the option with the lowest Incremental Cost-Effectiveness Ratio (ICER) compared with dacarbazine. Nivolumab and its combination with ipilimumab had better results in effectiveness, but at a higher cost. An 8-fold reduction in the price of nivolumab would result in a ICER below 1 GDP per capita compared with dacarbazine. The probabilistic sensitivity analysis showed that there was uncertainty over the analysis, and nivolumab plus ipilimumab had a higher probability of being cost-effective than dacarbazine at thresholds around BRL 322,000/QALY.

Budget impact analysis: The incremental budget impact over 5 years ranged from BRL 617,226,282.43 to BRL 2,880,924,401.13 for ipilimumab and its combination with nivolumab, respectively. Targeted combination therapies resulted in a lower budget impact compared with nivolumab, as in these strategies only half of patients with BRAF mutation would be treated. Medication costs as well as direct costs associated with treatment were considered.

Initial Recommendation: The members of Conitec's plenary session present at the 84th Ordinary Meeting, on December 5th, 2019, decided that the subject matter should be made available in a public consultation with an unfavourable preliminary recommendation for the incorporation of targeted therapies and immunotherapies for the first-line treatment of advanced (unresectable and metastatic) melanoma, in the scope of the Brazilian Public Health System (SUS). Although these therapies have been shown to have higher efficiency compared with

dacarbazine, the high cost of treatment resulted in an incremental cost-effectiveness ratio and budget impact, which made their incorporation impracticable.

Public consultation: The Public Consultation No. 85/2019 was held from January 2nd to 21st, 2020. A total of 2,300 contributions were received, of which 305 were technical-scientific, and 1,995 were experience or opinion contributions. Almost all of them (92% of experience and opinion and 95% of technical-scientific contributions) disagreed with the preliminary recommendation, pointing out the efficacy of targeted therapies and immunotherapies compared with dacarbazine; the obsolescence of dacarbazine, a medication widely used in SUS; and the right to access high-cost treatment. Four manufacturers of the technologies took part in the public consultation. Some contributions led to the updating of the economic model, but they also showed that nivolumab and its combination with ipilimumab remained the non-dominant strategies. Other therapies were expected to be extendedly dominated, but they did not become dominant. After analysing the contributions, the members of Conitec's plenary session considered that the "cure of patients with metastatic melanoma" outcome indicated by a manufacturer was not appropriate, because it was an indirect evaluation using data from the literature on sustained complete responses for a defined period of time. Overall, the evaluated therapies, mainly immunotherapies with anti-PD1 agents, represent a progress of the treatment of metastatic melanoma, however, their cost is still very high. The manufacturers of the anti-PD1 agents (nivolumab and pembrolizumab), which demonstrated satisfactory efficacy and safety profiles, submitted new price proposals. Therefore, the economic evaluation was updated with the new prices, as well as with additional information on new treatment duration of pembrolizumab. For nivolumab, the proposal was to reduce the price from BRL 27,882.36 to BRL 20,939.69, with the treatment duration established until disease progression or death. For pembrolizumab, the proposal was to reduce the price from BRL 28,954.80 to BRL 23,724 (ICMS 17% [a tax on the circulation of goods and services]) or BRL 19,690.02 (ICMS 0%) until disease progression or death, or up to 24 months in patients without progression.

Final Recommendation: The Conitec's members present at the 88th Ordinary Meeting, on July 8th, 2020, unanimously decided to recommend the incorporation of the anti-PD1 agents (nivolumab or pembrolizumab), in the scope of SUS, for the first-line treatment of advanced (unresectable and metastatic) melanoma, in accordance with the SUS model of cancer care. The new price proposals submitted by the manufacturers of the anti-PD1 agents (nivolumab and pembrolizumab), as well as their satisfactory efficacy and safety profiles, were considered. The monthly cost of treatment should be reduced according to a reference value of 3 GDP per capita for a favourable incremental cost-effectiveness ratio. Finally, the possibility of establishing a maximum value for the procedure in the SIGTAP (which stands for Management System of the Table of Procedures, Medicines, Orthotics, Prosthetics and Special Materials), with recommendation of the therapeutic class, was also considered. The Deliberation Record No. 533/2020 was signed.

Decision: To incorporate the anti-PD1 agents (nivolumab and pembrolizumab) for the first-line treatment of advanced (unresectable and metastatic) melanoma, in accordance with the model of cancer care, in the scope of SUS, according to Ordinance No. 23, published in the Official Gazette of the Federal Executive No. 149, Section 1, page 91, on August 5th, 2020.