

## CUTANEOUS MELANOMA: A PROGNOSIS TRANSFORMED BY IMMUNOTHERAPY<sup>1</sup>

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The European Cancer Organization has ranked melanoma as the sixth most common cancer in 2023. In France, according to the *Institut National du Cancer*, the number of new cases (incidence) is increasing by 2% a year, despite prevention campaigns. Prevalence of cancer in France is currently 28/100,000 for men and 22/100,000 for women. At the same time, advances in treatment, in particular with the arrival of immunotherapy have improved survival rates for many cancers, including melanoma, with an evolution that can be described as dazzling for the latter between 2010 and 2015.

The story of immunotherapy and melanoma began in 2010 with the first study showing that a monoclonal antibody, anti-CTLA-4, could increase the chances of survival at the metastatic stage, what no treatment had previously allowed (1). In 2014, a second monoclonal antibody, anti PD-1, obtained response rates of 30-40% in metastatic forms, with complete and durable responses, making it possible to stop treatment (2).

However, hope offered by immunotherapy was counterbalanced by the discovery of autoimmune side effects. These side effects, linked to an activation of cytotoxic T lymphocytes, can affect all organs. They are severe in 15% of cases, and, above all, some, such as endocrine side effects, may persist after immunotherapy is stopped. In this therapeutic race, the idea of combining two monoclonal antibodies soon emerged. After a 7 years' hindsight, dual therapy combining "anti-PD-1" and "anti-CTLA4" in the metastatic stage has shown a greater efficacy than anti-PD-1 alone, but with a greater toxicity. The most remarkable fact about immunotherapy is the long duration of clinical responses, with "plateau" overall survival curves and the possibility of treatment discontinuation, opening the door to possible cures beyond prolonged remission. For example, the Checkmate 067 study (3) showed that 77% of living patients treated with both antibodies, and 69% of patients treated with anti-PD-1 alone, were treatment-free after a follow-up of more than 6.5 years. Today, other monoclonal antibodies, such as anti-LAG-3 combined from the outset with anti-PD-1, are being tested with evidence of a low toxicity (4). Margins for progress are also expected from triple therapy and the combination of immunotherapy and mRNA vaccine.

The therapeutic successes observed at the metastatic stage have led to changes in the management of melanoma at a less advanced stage:

- For the prevention of metastases: in 2019, the French National Authority for Health (HAS) authorized treatment with anti-PD-1 as adjuvant therapy after surgery for one year in patients with stage III lymph nodes, including the sentinel node, and stage IV lymph nodes following complete surgical removal of metastases;
- For facilitating surgical treatment: in a neoadjuvant strategy, these same immunotherapy

treatments were administered prior lymph nodes or metastases removal, in order to facilitate surgical treatment, or even to avoid some excisions. Initial studies have shown that there would indeed be a benefit in performing this medical treatment before surgery, with a superiority of the combination of anti-PD1 and anti-CTLA 4 over anti-PD1 monotherapy (5). The progressive substitution of lymph node surgery by medical treatments is therefore conceivable.

- For preventing recurrence in primary melanoma at high risk of relapse: the *Agence nationale de sécurité du médicament* (ANSM) recently authorized an early access to an anti-PD-1 agent, pembrolizumab, "as a single agent in the adjuvant treatment of patients (adults and) adolescents aged 12 years and over with stage IIB, IIC melanoma who have undergone a complete resection".

**Taking into account the very rapid development of immunotherapy in the treatment of melanoma, which has considerably improved the prognosis of this skin cancer, the French *Académie nationale de médecine* points out that:**

- the development and promotion of measures to prevent skin melanoma to the widest possible audience remains an extremely important public health initiative;
- the benefit/risk ratio should be assessed before any decision to use immunotherapy, particularly at an early stage of the disease, due to the possibly permanent nature of the autoimmune side-effects;
- two major challenges for the coming years are :
  - On one hand, the search for predictive markers of the risk of serious melanoma progression, to identify indications for an adjuvant treatment;
  - On the other hand, the identification of predictive markers of response or resistance to immunotherapy and of the profile of patients most at risk of severe side effects;
- some types of melanoma, such as ocular, mucosal or melanomas of the extremities, are not very sensitive to current immunotherapy;
- it is essential to set up cohorts for a long-term follow-up of patients undergoing adjuvant treatment, in particular to assess the benefit on overall survival;
- the considerable progress seen in recent years in the treatment of melanoma have been made possible by the access to introduction of very high-cost treatments (6)

## References

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- 3) Wolchok J.D. et al, J Clin Oncol 2022; 40 :127-137.
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- 5) Long G.V. et al, J Clin Oncol 2023 Jun 10; 41(17) :3236-3248.
- 6) Expensive anti-cancer drugs: availability and economic sustainability. Report by the Académie nationale de médecine working group on expensive cancer drugs (presented in plenary session on October 10, 2023).

[1] Communiqué from the Academy's Rapid Communication Platform.