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**REVIEW ARTICLE**

# Where do we stand on adjuvant melanoma therapy?

## *Qual é a nossa posição sobre a terapia do melanoma adjuvante?*

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## Abstract

Melanoma remains the deadliest form of skin cancer, and its incidence is increasing. In recent years, melanoma adjuvant therapy has been regarded as a revolution when it comes to prognostic of high-risk melanoma adjuvant therapy has been regarded as a revolution in the prognostic of high-risk melanoma, but questions concerning its indications still challenge the clinical approach. A better understanding of what patients to treat and how to treat them is imperative. Adjuvant therapy is now considered standard of care in many clinical contexts, and currently approved therapies have shown benefit in patients staged III or higher on the American Joint Committee on Cancer (AJCC) 7th edition, which raised issues of adequacy in present clinical settings (AJCC 8th edition). Nevertheless, clinical practice guidelines are unavailable. Furthermore, clinical settings have evolved since the trials that led to the approval of current adjuvant treatments. Completion lymph node dissection is no longer considered standard of care for all sentinel lymph node (SLN)—positive patients, and staging was reconfigured. In light of AJCC's new staging data, early adjuvant therapy –for stage II melanoma– is now under scrutiny. Several breakthroughs are expected in the upcoming years. This review summarizes where we came from, where we are and where we are heading on adjuvant melanoma therapy.

***Keywords:*** Adjuvant. High-risk. Melanoma.

## Resumo

O melanoma mantém-se como o mais letal dos cancros de pele e a sua incidência continua a aumentar. Nos últimos anos, o tratamento adjuvante desta patologia contribuiu para uma revolução terapêutica com impacto importante no prognóstico do melanoma de alto risco. Apesar disto, afigura-se como imperativo, ainda, compreender mais detalhadamente quem tratar e quando atuar. A terapêutica adjuvante é atualmente indicada em vários contextos clínicos. As terapêuticas inicialmente aprovadas demonstraram benefício em doentes em estádio III ou superior conforme a 7.ª edição do American Joint Committee on Cancer (AJCC), o que suscitou dúvidas acerca da sua adequação ao atual contexto clínico (8.ª edição do AJCC). Destaca-se, ainda, a reforma à abordagem clínica do melanoma, que evoluiu desde os ensaios que conduziram à aprovação de muitos dos regimes de adjuvância atualmente preconizados. A linfadenectomia total já não é recomendada em todos os doentes com biópsia de gânglio sentinela positiva e o estadiamento foi reconfigurado. Atualmente, à luz da 8.ª edição da AJCC, a terapêutica adjuvante precoce, para os doentes com melanoma em estádio II, é uma realidade sob escrutínio. Esperam-se vários avanços terapêuticos nos próximos anos. Esta revisão pretende explorar de onde viemos, onde nos encontramos e para onde nos dirigimos no que respeita à terapêutica adjuvante no melanoma.

***Palavras-chave:*** Adjuvância. Alto risco. Melanoma.

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## Introduction

Melanoma remains one of the most aggressive skin cancers worldwide, and its incidence continues to increase, but a therapeutic revolution has been taking place in the past years[1]. The prognosis is encouraging for early stages, and recent therapeutic options have changed the disease course for more advanced stages with unfavorable prognosis. In fact, low-risk melanomas can be effectively treated with surgery only, but high-risk melanomas with no evidence of disease after excision are associated with worse survival rates[2].

Aiming to offer better therapeutic approaches in the high-risk disease, advances in systemic treatment in the metastatic setting have translated additionally into effective adjuvant therapy for patients with resected but regionally advanced disease[3]. Recently, concerns regarding the choice of optimal adjuvant therapy, evaluation of possible biomarkers, the benefit of adjuvant therapies in stage II patients versus its associated toxicity, as well as the possibility of subsequential treatments over time have been debated.

## Where did we come from?

For many years, interferon-α was the only approved option for adjuvant therapy of high-risk melanoma[4]. Since the 1990s, different schedules and protocols were investigated, with a notable effect on relapse-free survival (RFS) but none (or limited effect in specific subgroups) on overall survival (OS)[5]. In fact, despite the apparent benefit from interferon-α in patients with ulcerated primary melanomas[1], the inconsistent improvements shown in OS, along with substantial toxic effects, led to the definite abandonment of this adjuvant therapy, which had never been considered as standard of care in Portugal and worldwide.

Checkpoint inhibitor immunotherapies, including those that target programmed cell death 1 (PD-1) or cytotoxic T-lymphocyte antigen 4 (CTLA-4) and drugs that target the mitogen-activated protein kinase pathway [v-raf murine sarcoma viral oncogene homolog B1 (BRAF) and mitogen-activated protein kinase kinase (MEK) inhibitors and their combination] have recently gained a determinant role in the adjuvant setting[6].

In 2015, ipilimumab, a human antibody against CTLA-4, showed improvement in recurrence-free survival in patients with resected melanoma with involvement of lymph nodes > 1 mm versus placebo. Subsequently, it was shown to improve OS versus placebo (OS at 5 years was 65.4% in the ipilimumab group, as compared with 54.4% in the placebo group) but was associated with serious adverse events leading to early discontinuation in a substantial proportion of patients and death in 1.1%[7]. Nonetheless, this merited approval by the United States Food and Drug Administration, but not the European Medicines Agency (EMA), in the adjuvant setting for melanomas stage III in 2016.

Around 2 years later, nivolumab, a PD-1 checkpoint inhibitor, was approved as adjuvant therapy for melanoma. The CheckMate-238 study compared nivolumab with ipilimumab as adjuvant treatment for patients with high-risk resected stage IIIB-IIIC or resected stage IV melanoma (classified by the AJCC, 7th edition) and has shown the superiority of nivolumab coupled with less toxicity (4-year RFS was 51.7% in the nivolumab group and 41.2% in the ipilimumab group; 4-year OS was 77.9% with nivolumab and 76.6% with ipilimumab; late-emergent grade 3–4 treatment-related adverse events were reported in 1% of patients in the nivolumab group and 2% of patients in the ipilimumab group)[8].

In 2019, another PD-1 inhibitor, pembrolizumab, was approved for melanoma adjuvant treatment as it showed improved RFS versus placebo with no new toxic effects identified (1-year rate of RFS of 75.4% in the pembrolizumab group and 61% in the placebo group)[9].

Regarding targeted therapy, the COMBI-AD study in 2018 established an improvement in RFS when comparing the BRAF inhibitor dabrafenib and MEK inhibitor trametinib to placebo (estimated 3-year rate of RFS was 58% in the combination-therapy group and 39% in the placebo group; 3-year OS rate was 86% in the combination-therapy group and 77% in the placebo group; serious adverse events occurred in 36% of patients in the combination therapy group and in 10% patients in the placebo group)[6]. This data led to the approval of dabrafenib and trametinib as adjuvant treatments for melanoma stage IIIB and higher in 2018.

## Where are we?

Adjuvant therapy is changing the way melanoma patients are treated today and is now considered standard of care in most stage III and resected stage IV patients. Both targeted therapy and immune checkpoint inhibitors reduce the risk of recurrent melanoma in high-risk disease[10], as previously discussed. Still, clinical practice guidelines are unavailable, and the decision to prescribe a specific adjuvant therapy requires a detailed selection of patients, evaluating the likelihood of therapeutic efficacy and its associated risks.

**Table 1.** Comparison between AJCC 7th and 8th edition for stage III subgroups[12]

| Stage | AJCC 8th editions | | | AJCC 7th editions | | |
|---|---|---|---|---|---|---|
| | T | N | M | T | N | M |
| IIIA | T1a/b-T2a | N1a or N2a | M0 | T1–4a | N1a or N2a | M0 |
| IIIB | T0 | N1b, N1c | M0 | | | |
| IIIB | T1a/b-T2a | N1b/c or N2b | M0 | T1–4b | N1a or N2a | M0 |
| IIIB | T2b/T3a | N1a-N2b | M0 | T1–4a | N1b, N2b or N2c | M0 |
| IIIC | T0 | N2b, N2c, N3b or N3c | M0 | | | |
| IIIC | T1a-T3a | N2c or N3a/b/c | M0 | T1–4b | N1b, N2b or N2c | M0 |
| IIIC | T3b/T4a | Any N ≥N1 | M0 | Any T | N3 | M0 |
| IIIC | T4b | N1a-N2c | M0 | | | |
| IIID | T4b | N3a/b/c | M0 | | | |

The difficulty of the clinician's approach is highlighted by the absence of measurable disease, making it impossible, contrarily to the metastatic setting, to readily assess a clinical response[11]. As such, a better selection of high-risk of relapse patients could help reduce the costs of toxicity by applying it to the patients that would benefit the most from it. Further research into biomarkers is imperative in this setting.

The 8th edition AJCC melanoma staging system intends to provide a standardized and contemporary cancer staging system that facilitates accurate risk stratification, aiming to guide patient treatment. Well-known clinical-pathological features allowed for this classification: ulceration and Breslow thickness were the most important predictors of survival with respect to the primary tumor (also the extent of vascular invasion in thin melanomas) and, in the N category, the number of the metastatic nodes and whether they present on a clinically occult or clinically apparent fashion and also the presence of in-transit, satellite or locally recurring lesions are of significant prognostic value[12]. Stage III is defined as the presence of nodal, satellite or in-transit metastasis. Most stage III patients are disease-free after surgery, with significantly different relapse risks between subgroups. In AJCC 8th edition, stage III has been further divided into four subgroups allowing for better risk stratification, but there is still room for improvement. Current approval for adjuvant melanoma therapy relied on the 7th AJCC staging system, which raised issues of adequacy in present clinical settings (Table 1). For example, stage III disease in the 7th edition included T1-4a and N1a-2a disease, and the current edition included T1a, T1b and T2a, and N1a-2a status. This is particularly relevant when discussing IIIA or IIIB stages according to the 8th edition because some of these patients would have been classified differently at the time of enrolment in most adjuvant trials[10].

Additionally, other concerns regarding adjuvant trial results validity in today's patient approach have been raised. Since 2015, several adjuvant therapies have been approved based on randomized trials with adjuvant therapy after resection of high-risk disease, and inclusion criteria required performance of a completion lymph node dissection (CLND) after positive sentinel lymph node (SLN) disease. In fact, CLND is no longer considered standard of care for all SLN-positive patients. After the results of the German Dermatologic Cooperative Oncology Group (DeCOG-SLT)[17] and the Multicenter Selective Lymphadenectomy Trial II(MSLT-II)[18], that showed no melanoma-specific survival benefit even if achieving a reduced rate of regional recurrence, some patients are being managed with active nodal surveillance and considered for adjuvant therapy. Some studies have been addressing this issue. Farrow et al. found that adjuvant therapy in patients with a positive SLN who did not undergo CLND has a similar RFS as patients included in adjuvant therapy trials that required CLND[19]. Some authors even believe it is time to reconsider the role of SLN biopsy in melanoma[20]. There is evidently a high need for sensitive and reproducible biomarkers to guide the clinical decision-making process. Efforts have been made to address the issue of better prognostication in melanoma, and additional clinical and histologic features, as well as new biomarkers, have been proposed[11]. Single molecules or specific signatures have been investigated in the monitoring and prognostication of patients: circulating tumor cells are cancer cells circulating in the peripheral blood shed from the primary

tumor or its metastasis, and its utility may land on the real-time detection of subclinical tumor spreading, although lack of standardization remains an issue. Their value relies on the possibility of acting earlier in the case of recurrence[1]. It is also known that melanoma-specific PD-1 overexpression enhances tumor antigenicity. In stage III patients, Madore et al. showed that a PD-L1 negative status related to a worse melanoma-specific survival[13]. Trials with immunotherapy in the adjuvant and advanced setting showed that patients with low immune gene expression had relatively poor clinical outcomes on immunotherapy compared with all other biomarkers subgroups of interest, suggesting a relevant role for immune gene expression status in identifying patients that may derive a clinical benefit from immunotherapy. Dummer et al. recognized the need for the identification of highly predictive clinical and biological characteristics in the attempt to isolate patients with BRAFV600-mutant melanoma who would benefit the most from targeted therapy or checkpoint inhibitor therapy in adjuvant and metastatic settings. Their results showed that a high interferon-γ gene expression signature was prognostic for prolonged RFS in both dabrafenib plus trametinib and placebo groups. Tumor mutational burden (TMB) provided prognostic value in the placebo group but not the dabrafenib plus trametinib group, with a low TMB associating with a greater benefit from treatment with dabrafenib plus trametinib and a high TMB correlating with less benefit from dabrafenib plus trametinib treatment, particularly if there was a low interferon-γ signature[14]. On the other hand, high TMB was associated with improved RFS with adjuvant nivolumab therapy. However, the efficacy of PD-1 blockade in this setting with concomitant low interferon-γ gene expression signature or other negative immune biomarkers is unclear[15]. This discussion seems particularly important when realizing that, ultimately, in the treatment groups of several published trials on adjuvant therapy, many patients still relapsed (42% for dabrafenib plus trametinib[6], nearly 30% for nivolumab[16] and approximately 25% for pembrolizumab[9]). A better understanding of what patients to treat and how to treat them is imperative.

## Where are we heading?

Early adjuvant therapy is under scrutiny. The discussion centers itself around the potential positive impact on overall deaths from melanoma as we begin to treat more patients with early-stage disease, given the large number of patients diagnosed in this stage and its unnecessary prospective toxicity costs.

It is known that patients with stage IIC disease have a worse prognosis than those with stage IIIA disease. Also, patients with stage IIA or IIIA disease have a similar melanoma-specific survival - of 94% or 93%, respectively at 5 years[10]. Estimates of the number of patients with stages IIB and IIC melanomas that remain at high-risk of relapse and may benefit from adjuvant therapy are significant. Approximately one-half of patients with stage II melanoma will have stage IIB or IIC disease and are at the highest risk of recurrence, which roughly parallels the number of stage III melanoma patients, for which adjuvant therapy is standard of care[21]. In stage II patients, rates of distant recurrence after resection can reach 44%[22].

On the other hand, consideration of the potential permanent adjuvant treatment toxicity may imbalance the risk/benefit appreciation as we consider the treatment of patients with earlier-stage disease, many of whom may already have been cured by surgery[21].

Unlike interferon-alfa, associated with substantial adverse events and fatalities, modern adjuvant therapies are expected to have a more favorable safety profile. To date, monotherapy with pembrolizumab or nivolumab has been shown to have a considerably better tolerability profile than ipilimumab, and the dabrafenib plus trametinib combination demonstrated similar grades of adverse events rates as pembrolizumab and nivolumab. Combination immunotherapy with ipilimumab/nivolumab and ipilimumab monotherapy was associated with the highest toxicity.

Considering the curative setting where adjuvant treatment plays a role, potentially permanent toxicities involved with immune checkpoint inhibitors became particularly relevant, especially hypophysitis, hypothyroidism, primary adrenal insufficiency, and insulin-dependent diabetes[2]. In fact, chronic adverse events associated with anti-PD-1 therapy appear to be more common than previously recognized and frequently persist even with prolonged follow-up. Although most are low-grade, the risk of triggering chronic adverse events should be integrated into treatment decision-making[23].

Another limitation of a protocoled approach to these patients is the lack of comparative analysis between different treatment options. Although there is a phase III trial comparing ipilimumab and nivolumab versus dabrafenib plus trametinib in stage III-IV unresectable BRAFV600 positive melanoma, there are no results from a head-to-head comparison of immune checkpoint

inhibition versus targeted therapy, leaving the decision-making to be guided by individual patient and tumor characteristics in BRAFV600 positive patients[10]. Review using Bayesian network meta-analysis investigated RFS, distant metastasis-free survival and OS in adjuvant trials that tested dabrafenib plus trametinib, nivolumab, pembrolizumab, ipilimumab, vemurafenib, chemotherapy, and interferon-α. The study concluded that efficacy was comparable between targeted therapy (dabrafenib plus trametinib) and anti-PD-1 inhibitors[24]. However, the optimal sequencing of therapy options in BRAF-mutated patients remains to be determined[25].

Although interferon-α remains an adjuvant alternative for patients with stages IIB and IIC, it is rarely used due to its toxicity[4,26]. Given the clinical benefit observed with adjuvant pembrolizumab in patients with stage III melanoma, a strong rationale exists to determine if a similar benefit could be attained in adult and pediatric patients with high-risk resected stage II disease. KEYNOTE-716 is a randomized, double-blind, phase 3 trial that compared pembrolizumab to placebo as adjuvant therapy in completely resected stage IIB or IIC melanoma. Its results have been recently published (March 2022) and demonstrate that pembrolizumab, as adjuvant therapy for up to approximately 1 year for stage IIB or IIC melanoma, resulted in a significant reduction in the risk of disease recurrence or death versus placebo, with a manageable safety profile[22]. These initial conclusions will change the way we treat high-risk melanoma patients. As previously discussed, stage IIB and IIC RFS parallels with the RFS for stages IIIA and IIIB. Following this rationale, it is expected that adjuvant therapy could be used, with favorable results, in these, not previously considered, high-risk patients. In December 2021, the Food and Drug Administration approved pembrolizumab for adjuvant treatment of stage IIB or IIC melanoma patients based on KEYNOTE-716 results. Recently, the EMA also approved pembrolizumab for adjuvant treatment of completely resected stage IIB and IIC melanoma patients. Naturally, more mature data regarding follow-up and survival will only be available in the upcoming years.

Another phase II trial is currently studying how well nivolumab works in treating patients with stage IIB-IIC melanoma that can be removed by surgery and is expected to be completed in 2023 (ClinicalTrials.gov Identifier: NCT03405155).

Melanoma adjuvant therapy will most certainly not be limited to the previously discussed treatments. Desmoplastic neurotropic melanomas show higher rates of local recurrence after wide local excision, and data suggests that adjuvant radiation in this setting can be helpful. ANZMTG 01.02/TROG 02.01 trial looked at the utility of adjuvant nodal radiotherapy after lymphadenectomy. After a median follow-up of 73 months, nodal relapse occurred in 21% of the adjuvant radiotherapy group compared with 36% in the observation group, but there was no difference in OS or RFS[27]. Agrawal et al. stated that radiotherapy was significantly associated with a lower risk of regional recurrence[28]. Although these data suggest a potential benefit to adjuvant radiotherapy in well-selected patients, most data are from before the era of immunotherapy[29].

Vaccines have also been trying to take their place in adjuvant therapy, such as whole cells (cell lysates), peptide vaccines, and ganglioside antigen vaccines, but have generally failed to demonstrate significant benefits[24].

Neoadjuvancy, beyond the scope of this review, has also been recently discussed, with promising results. The OpACIN-neo phase II trial was designed to identify an effective and safe dosing schedule for the combination of neoadjuvant ipilimumab and nivolumab in stage III melanoma. PRADO, an extension cohort of this trial, aims to confirm the pathologic response rate and safety of neoadjuvant ipilimumab 1 mg/kg and nivolumab 3 mg/kg to assess response-driven subsequent therapy in stage III melanoma. Its recent results seem to show that patients with resectable stage III melanoma who have a major pathologic response to neoadjuvant therapy can skip therapeutic lymph node dissection and adjuvant therapy, which is associated with morbidity and still achieve high 2-year rates of RFS[30].

Adjuvant treatment in melanoma has come a long way since its early years. New treatments have changed the management of the disease, and more breakthroughs are to be expected in the next few years. Not only the discovery of novel or reinvented drugs is anticipated but also a better understanding of what patients to treat, how to do it and when to act, all to the benefit of melanoma patients.

## Ethical disclosures

**Protection of human and animal subjects.** The authors declare that no experiments were performed on humans or animals for this study.

**Confidentiality of data.** The authors declare that no patient data appear in this article.

**Right to privacy and informed consent.** The authors declare that no patient data appear in this article.

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