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REVIEW

# How we treat locoregional melanoma

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Cutaneous melanoma is the most lethal form of skin cancer and its incidence has been increasing in the past 30 years. Although this is completely resectable in most cases, thicker melanoma and those with regional lymph-node involvement are at a high risk of relapse. In recent years, the management of locoregional disease has drastically changed. In particular, in the 8th Edition of the American Joint Committee on Cancer (AJCC), subgroup classification of TNM (tumor—node—metastasis) has been modified, with the addition of the IIID stage. Furthermore, in recent randomized trials, completion lymph node dissection in case of sentinel lymph node biopsy positivity has not been shown to offer any improvement in overall survival versus observation. Consequently, radical dissection has been recommended as the standard treatment, but only in patients with palpable nodal metastases. However, the major novelty in the treatment of locally advanced melanoma has been the introduction of drugs, already used for metastatic disease, that have also shown clinical efficacy in the adjuvant setting. In fact, immunotherapies and, in the case of BRAF V600E/K-mutated melanoma, combination treatment of BRAF and MEK inhibitors have improved recurrence-free survival in these patients. In this paper, we will describe the current management of a patient with radically resectable melanoma and discuss the key points in light of the latest scientific evidence.

**Key words:** melanoma, How I treat melanoma, locoregional melanoma, adjuvant treatment

## INTRODUCTION

Melanoma of the skin is a rare cancer with ∼290 000 new cases reported in 2018; however, its incidence has been on the rise in the past 50 years, faster than for any other type of cancer. It primarily occurs in aged patients, but also remains one of the most common cancers diagnosed in younger adults and accounts for the majority of skin cancer-related deaths.[1] Even though most are diagnosed at early stages (I and II), a large proportion of melanomas will locally relapse. Until a few years ago, the pharmacological weapons available for the treatment of melanoma were limited and surgery was almost the only strategy with a clear benefit. The advent of immunotherapy and targeted therapy (in BRAF-mutated melanoma), however, has drastically changed the scenario in both adjuvant and metastatic settings.[2] In this brief review, we will summarize the main strategies applied today in the management of locoregional melanoma from diagnosis to treatment.

## DIAGNOSIS AND STAGING

Excisional biopsy is the standard of care for the diagnosis of melanoma and the histology report should include the following criteria: melanoma subtype, Breslow thickness, presence of ulceration, and clearance of the margins. Furthermore, mitotic rate, regression assessment, tumor-infiltrating lymphocytes, lymphovascular invasion, and microsatellitosis are important factors to better define the prognostic category of the melanoma. Wide local excision of the primary lesion and an accurate physical examination to evaluate the presence of other suspicious lesions are the only necessary procedures for the *in situ* (Tis) and pT1a melanoma (Breslow thickness <0.8 mm without ulceration). In particular, in case of pT1a melanoma the probability of sentinel lymph node (SLN) metastasis is <5%; therefore the SLN biopsy (SLNB) is not routinely recommended. Instead, for pT1b and higher stages, further investigation with locoregional ultrasound and computed tomography scan (for stages ≥pT3) is mandatory.[3] Positron emission tomography scans and brain magnetic resonance imaging represent an option in doubtful cases. In pT1b melanoma, SLN metastasis are reported in 5%-12%[4] of cases

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and consequently SLNB should be discussed with patients. SLNB in case of clinically occult disease is mandatory for stages ≥pT2a. For all pT1 melanomas, a recently obtained predictive nomogram could be used to identify patients that are likely candidates for SLNB.[5] However, wide local excision is always recommended while carrying out the SLNB procedure to avoid lymph drainage modifications with safe margins (1 cm for Breslow thickness ≤2 mm and 2 cm for >2 mm).

## CLND VERSUS NON-CLND

Completion lymph node dissection (CLND) has been the standard for years for patients with SLN metastasis and for those with clinically locoregional detectable disease. Results of the Multicenter Selective Lymphadenectomy Trial II[6] and the German Dermatologic Cooperative Oncology Group-selective lymphadenectomy trial[7] have clearly demonstrated that there is no advantage in melanoma-specific survival with CLND, compared with periodic ultrasonographic surveillance in patients with positive SLN. The decrease in nodal relapse at 3 years observed in the dissection group of the aforesaid trial does not justify the risks of the procedure and the sequalae (24% of patients experiencing lymphedema). Nowadays, therapeutic lymph node dissection is indicated only in case of isolated locoregional clinically detectable (macroscopic, nonsentinel node) LN metastases. Anyway, if the CLND is not carried out, periodic US follow-up is mandatory. In case of lymph node with uncertain characteristics, a cytologic examination without altering the anatomical site is preferred before the surgery.

## IN-TRANSIT OR SATELLITE METASTASES

In-transit metastases are skin or subcutaneous metastases that are >2 cm from the primary lesion but not beyond the regional nodal basin. By contrast, lesions occurring within 2 cm of the primary tumor are classified as satellite metastases. Both represent a manifestation of intralymphatic disease and are included in stage III in the American Joint Committee on Cancer (AJCC) classification. Few trials specifically addressed the treatment of these lesions, but radical surgery can be considered in cases of few, small, and nonrapidly recurrent lesions.[8] By contrast, bulky lesions belonging to this category must be treated with systemic therapy (stage III inoperable). An additional type of therapy such as talimogene laherparepvec (T-VEC), PV-10, and regional chemotherapy has shown moderate efficacy in several trials but must to be practiced only in experienced centers. T-VEC is a herpes simplex virus—based oncolytic immunotherapy, which demonstrated a durable response rate and a survival benefit ($P = 0.051$) in the OPTIM trial[9] and, recently, also as a neoadjuvant treatment[10] in resectable-stage IIIB-IVM1a melanoma. PV-10 is another type of injection therapy that induces a phototoxic reaction and subsequently triggers an immune response, resulting in a complete response (CR) rate of 42.2% for in-transit melanoma metastases.[11] Both T-VEC and PV-10 showed an abscopal effect. Regional chemotherapy is another option for in-transit melanoma of the limbs, which involves isolation of the affected area, after which chemotherapy, usually melphalan, is delivered at very high doses with or without hyperthermia (hyperthermic isolated limb perfusion and isolated limb infusion). Isolated limb infusion is less invasive than hyperthermic isolated limb perfusion and, although has a lower CR rate, it has a similar survival rate in comparative retrospective trials.[12] Finally, electrochemotherapy is a technique based on electric pulses directed toward in-transit lesions used to determine permeabilization of cell membranes to facilitate chemotherapy delivery (usually bleomycin). In the trials evaluating this option, electrochemotherapy reached a CR in 53%-89% of treated lesions with a good duration of response.[13]

## ADJUVANT AND NEOADJUVANT THERAPY

Until 2010, management of radically resected melanoma included only observation and clinical-instrumental follow-up. Previously, only interferon-α (IFN-α) demonstrated a modest benefit in overall survival (OS) of 3.0% and 2.8% at 5 and 10 years, respectively. These results were obtained by a metanalysis including trials with very different study population and with different doses of IFN-α, but only patients with ulcerated tumors appeared to obtain benefit from treatment.[14] However, to date, there is no role for IFN-α in treating stage III melanoma, although, for now, it can be considered in ulcerated stage IIB-C melanoma until the results of an immunotherapy trial are evaluated (KEYNOTE-716).

Discovery of immune checkpoint inhibitors revolutionized the treatment of both metastatic and locoregional melanomas. Ipilimumab, a monoclonal antibody blocking cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) in the EORTC 18071 study, was compared with placebo in stage III melanoma (Table 1). It was the first drug to demonstrate a significant benefit at 3 years in recurrence-free survival (RFS), distant metastasis-free survival, and OS [65.4 versus 54.4%; hazard ratio (HR) for death 0.72; 95.1% confidence interval (CI) 0.58-0.88; $P = 0.001$]. However, this treatment was burdened by grade 3 or 4 adverse events (54.1%) as well as five treatment-related deaths, which precluded the use of this drug in this clinical setting.[15]

Instead, practice-changing results were reported in recent phase III trials evaluating the impact of 1-year anti-programmed cell death protein 1 (anti-PD-1) therapies and target therapy (Table 1). Nivolumab, in the CheckMate-238 trial,[16] demonstrated a significant RFS benefit compared with ipilimumab in stage IIIB-C and IV radically resected melanoma (HR 0.71; 95% CI 0.60-0.86, $P = 0.0003$).[17] The benefit concerns all stage subgroups regardless of BRAF mutational status. Another anti-PD-1, pembrolizumab, demonstrated its superiority versus placebo in the KEYNOTE-054 trial.[18] Different from the previous one, this study did not include resected stage IV (and In-transit metastases), but did include stage IIIA (with a disease of SLN > 1 mm); after 3.5 years of follow-up, RFS

**Table 1. Main clinical trial in adjuvant setting for radically resected melanoma**

| Clinical trial | Population[a] | Treatment arms | RFS rate | | OS rate | | TRAE of grade 3-4 | Type of TRAE in the experimental group |
|---|---|---|---|---|---|---|---|---|
| EORTC 18071 | Stage IIIA (SN > 1 mm) and IIIB-C melanoma (without ITM) | *Ipilimumab* 10 mg/kg every 3 weeks for 4 doses and then every 12 weeks for up to 3 years versus placebo | *7-years RFS*: 39.2%(46.5% at 3 years) vs 30.9% (34.8% at 3 years) | HR 0.75 $P = 0.0004$ | *7-years OS*: 60.0%(65.4% at 3 years) vs 51.3% (54.4% at 3 years) | HR 0.73 $P = 0.0021$ | −99% versus 91% of any grade.<br>−54% versus 25% of grade 3-4-5 [5 ipilimumab-related death due to colitis ($n = 3$) myocarditis and MOF ($n = 2$)].<br>−53.3% had adverse events leading to permanent discontinuation of ipilimumab | Fatigue 40%; pruritus 43%; rash 39%; diarrhea 49%; headache 32%; weight loss 32%; nausea 25%; immune related: 92% (hypothyroidism 10%; hypophysitis 19%; colitis 16%; liver function test increased 19%) |
| CheckMate-238 trial | Stage IIIB-C (81.3%) and IV (18.7%) radically resected melanoma | *Nivolumab* 3 mg/kg every two weeks versus *Ipilimumab* 10 mg/kg every 3 weeks for 4 doses and every 12 weeks thereafter for 1 year | *4-years RFS*: 52.4% vs 24.1% | HR 0.71 $P = 0.0003$ (0.69 in BRAF wild-type pts) | *4-years OS*: 78% vs 77% | HR 0.87 $P = 0.315$ | −85.2% versus 95.8% of any grade.<br>−14.4% versus 45.9% of grade 3-4-5(1 ipilimumab related death due to marrow aplasia and colitis)<br>−9.7% had adverse events leading to permanent discontinuation of nivolumab | Fatigue 34.5%; diarrhea 24.3%; pruritus 23.2%; rash 19.9%; nausea 15.0%; arthralgia 12.6%; hypothyroidism 10.8% |
| KEYNOTE-054 | Stage IIIA (SN > 1 mm) and IIIB-C melanoma (without ITM) | *Pembrolizumab* 200 mg versus placebo for 1 year | *3.5-years RFS*: 59.8% vs 41.4% | HR 0.59 $P < 0.001$ | — | — | −77.8% versus 66.1% of any grade.<br>−14.7% versus 3.4% of grade 3-4-5 (1 pembrolizumab-related death due to myositis).<br>−13.8% had adverse events leading to permanent discontinuation of a trial drug | Fatigue 37.1%; skin reaction 28.3%; diarrhea 19.1%; arthralgia 12.0%; nausea 11.4%; immune-related: 37.3% (hypothyroidism 14.3%; hyperthyroidism 10.2%; vitiligo 4.7%; colitis 3.7%; pneumonitis or interstitial lung disease 3.3%) |
| COMBI-AD | Stage IIIA(SN > 1 mm) and IIIB-C BRAF V600E/K mutant melanoma | *Dabrafenib* 150 mg twice daily plus *trametinib* 2 mg once daily versus placebo for 1 year | *3-years RFS*: 58% vs 39% | HR 0.47 $P < 0.001$ | *3-yearsOS* : 86% vs 77% | HR 0.57 $P = 0.0006$ (not reached the prespecified $P = 0.000019$) | −97% versus 88% of any grade.<br>−41% versus 14% of grade 3-4-5 (1 death in the combination group due to pneumonia)<br>−26% had adverse events leading to permanent discontinuation of a trial drug | Pyrexia 63%; fatigue 47%; nausea 40%; headache 39%; chills 37%; diarrhea 33%; vomiting 28%; arthralgia 28%; rash 24%; cough 17%; myalgia 16%; liver function test increased 15% |

—, not reported; BRAF, V-Raf murine sarcoma viral oncogene homolog B1; HR, hazard ratio; ITM, in transit metastases; MOF, multiorgan failure; OS, overall survival; PD-L1, programmed death-ligand 1; RFS, recurrence-free survival; SN, sentinel node; TRAE, treatment-related adverse event.

[a] In all the four trials patients were staged according to the 7th edition of AJCC classification instead of the actual 8th edition and always underwent lymphadenectomy if sentinel lymph node was positive.


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was consistently prolonged across all subgroups (HR 0.59; 95% CI 0.49-0.70), and distant metastasis-free survival results improved, in particular in patients with BRAF-V600 E/K mutation (HR 0.51) and negative programmed death-ligand 1 expression (HR 0.45).[19] Finally, the COMBI-AD trial[20] evaluated dabrafenib and trametinib versus placebo in patients with BRAF V600 E/K mutant stage IIIA (SLN $>$ 1 mm) and IIIB-C melanoma. The 3-year RFS and OS rates were 58% and 86% with the regimen and 39% and 77% with placebo, respectively. In the 5-year update RFS benefit was confirmed across all substages [HR (95% CI): IIIA, 0.61 (0.35-1.07); IIIB, 0.50 (0.37-0.67); IIIC, 0.48 (0.36-0.64)].[21]

Efficacy of these therapies is undoubted, but several questions remain open. First, OS data in the COMBI-AD trial showed an improvement but it did not cross the prespecified interim analysis boundary of $P = 0.000019$. Unexpectedly, OS rates between nivolumab and ipilimumab were similar in both groups after 48 months of follow-up, but events were fewer than expected (73% of power).[17] This raises the question of whether introducing the treatment only at the time of relapse leads to similar long-term results. Importantly, the cross-over permitted in KEYNOTE-054 could give us an indication about this issue.

In addition, most melanoma recurrences after radical surgery occurred locoregionally and only few data are available for the efficacy of adjuvant treatment on this subgroup. By contrast, benefit of pembrolizumab was higher in preventing distant metastasis (HR 0.57) than locoregional recurrence (HR 0.73).[19]

Furthermore, benefit for stage IIIA remains to be demonstrated considering that (i) inclusion criteria of EORTC 1325 and COMBI-AD trials do not include patients with SLN metastases $<$1 mm (CheckMate 238 does not include stage IIIA at all) because of its very favorable prognosis[22]; (ii) all patients of these trials were staged with the 7th edition of AJCC classification instead of the actual 8th edition and so the stage IIIA melanoma evaluated had worst prognosis than those seen in clinical practice today; (iii) all study patients underwent CLND if SLN was positive; however, because this is no longer the standard treatment, we could downgrade some melanoma from IIIB-C to IIIA and avoid unintentional adjuvant therapies to these high-risk patients.

Finally, there are no predictive factors that help to choose which is the best adjuvant treatment for every patient. Patient's performance status, comorbidities, and age according to different toxicity profiles of the agents could help in decision making. In particular, on the one hand, dabrafenib and trametinib resulted in a higher percentage of grade 3-4 adverse events (41%) compared with nivolumab (14.4%) and pembrolizumab (14.7%), and on the other hand, immunotherapy has longer lasting endocrinological side-effects.[23]

The therapeutic strategies for patients that relapse on or after adjuvant treatment remain another challenging aspect. Relapses on treatment are more frequent during treatment with immunotherapy, whereas more relapses are seen at the end of 1 year with targeted treatment. In easily resectable tumors and those with limited progression, radical surgery and continuing adjuvant therapy remain a reasonable choice. However, tumors with bulky progression require a change in treatment strategy. If the progression occurs after at least 6 months from adjuvant therapy, a treatment rechallenge is feasible. A recent retrospective work in BRAF-mutant melanoma recurring after adjuvant targeted therapy revealed a response rate of 69.7% to anti-PD-1 and 46% to rechallenge targeted therapy.[24]

Recently, new strategies in the management of clinical stage III melanoma are derived from neoadjuvant trials. This approach offers some additional benefit allowing for a less demolitive surgery with inferior morbidity and higher chance to be radical. Moreover, neoadjuvant therapy offers the possibility to better define the tumor response to the drugs and personalize the postoperative treatments. OpACIN and OpACIN-neo trials evaluated the combination of ipilimumab and nivolumab in this setting and obtained durable responses, especially in patients with CR.[25] In particular, in the phase Ib OpACIN trial, neoadjuvant ipilimumab plus nivolumab was compared with adjuvant ipilimumab plus nivolumab, whereas the subsequent OpACIN-neo trial evaluated three different dosing schedules of neoadjuvant ipilimumab plus nivolumab. OpACIN showed for the first time a potential benefit of neoadjuvant versus adjuvant immunotherapy, whereas OpACIN-neo confirmed the high pathologic response rates which can be achieved by neoadjuvant ipilimumab plus nivolumab. Translational data revealed a broader activation of immune response with this strategy and a predictive role for baseline IFN-$\gamma$ gene expression score and tumor mutational burden.[25] Neoadjuvant targeted therapy with dabrafenib plus trametinib achieved slightly higher CR rates, but higher rates of relapse have been reported in the Neo Combi trial.[26] A pooled analysis by Menzies et al.,[27] including 189 patients with macroscopic stage III resectable melanoma enrolled in six neoadjuvant clinical trials, confirmed that the degree of pathological response could be considered a surrogate of both RFS and OS. In particular, the achievement of pathologic CR (pCR) or near pCR or even pathologic partial response correlates with excellent survival reported using immunotherapy combination, whereas only pCR is a surrogate marker of long-term outcomes with targeted therapy. However, even with a pCR the 2-year RFS with targeted therapy is lower (79%) than that with immunotherapy (96%), underlining the long-term efficacy of these treatments. By contrast, single-agent immunotherapy does not seem to be an adequate neoadjuvant treatment.

In conclusion, immunotherapy and targeted treatments bring meaningful benefit in melanoma patients, so the question is not if to use them but 'when' and 'how': definitive OS data from the trials being carried out and results from promising neoadjuvant studies will address these issues in the next years. Discovery of predictive biomarkers, in addition, will be extremely useful to identify the right treatment for the right patient.

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## DISCLOSURE

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