

Ketty Peris

Chair; Full Professor of Dermatology, Department of Dermatology, Catholic University of the Sacred Heart, Rome, Italy

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The diagnosis of melanoma has evolved considerably in recent years, shifting from an approach based on clinical examination to an integrated diagnostic strategy combining clinical and dermoscopic evaluation

Q1 How has the approach to melanoma diagnosis evolved in recent years?

The diagnosis of melanoma has evolved considerably in recent years, shifting from an approach based on clinical examination to an integrated diagnostic strategy combining clinical and dermoscopic evaluation. Dermoscopy significantly improves the diagnostic accuracy allowing the detection of melanoma in a very early stage.

Sequential digital dermoscopy and total-body photography are particularly useful for the surveillance of high-risk individuals, including patients with a high total nevus count, and those with a family and/or personal history of melanoma.

By enabling the identification of newly developed atypical lesions and the detection of subtle changes in pre-existing lesions over time, these techniques improve the early detection of melanoma while reducing unnecessary excisions.

Current guidelines from the European Association of Dermato-Oncology (EADO) strongly recommend the use of dermoscopy for the assessment of pigmented and non-pigmented skin lesions. Beyond dermoscopy, emerging non-invasive techniques, such as reflectance confocal microscopy and line-field optical coherence tomography, provide additional diagnostic information in selected challenging lesions due to high resolution, near-histological imaging. Finally, the development of advanced imaging platforms integrating automated total body mapping and digital dermoscopy is likely to further transform melanoma detection and patient monitoring.

Q2 What role do dermoscopy and digital technologies play in improving early detection? Could AI meaningfully change melanoma detection in clinical practice?

Dermoscopy and digital technologies have long been shown to improve the early diagnosis of melanoma and are an integral part of clinical practice worldwide.

AI represents another important step forward. AI-based algorithms, some of which are already integrated into the imaging systems we use, may support clinicians in identifying suspicious lesions, assessing diagnostically challenging lesions, and improving the consistency of diagnostic evaluation. However, AI should be better regarded as a rapidly developing complementary technology to assist rather than replace the dermatologist.

Q3 How can clinicians improve recognition of melanomas that do not present with typical clinical features?

My first advice is to maintain a high index of suspicion whenever a new lesion appears or a pre-existing lesion changes, and also when a lesion simply looks different from the patient's other lesions (the so-called 'ugly duckling'), even if it does not show the conventional features of melanoma. For diagnostically

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equivocal lesions, especially located on the face or genitalia, the use of additional non-invasive imaging, such as reflectance confocal microscopy or line-field optical coherence tomography, can sometimes be decisive.

> **When uncertainty persists, surgical excision and histopathological examination remain essential**

Short-term digital monitoring may be another option in selected lesions, but it should be used with caution, since patients might not always return for follow-up and, in my experience, some melanomas can show very rapid changes within a few days or weeks. Therefore, when uncertainty persists, surgical excision and histopathological examination remain essential.

Q4 Once melanoma has been diagnosed, what are the most important factors in determining a patient's prognosis and treatment pathway?

Since about 90% of melanomas are diagnosed as primary tumours without evidence of metastatic disease, surgery remains the first-line treatment. The key prognostic parameters are tumour thickness in mm (Breslow depth) and presence or absence of ulceration, in accordance with the American Joint Committee on Cancer (AJCC) 8th edition staging system. Microsatellites (defined as discontinuous nest of metastatic cells separated from the invasive component of the tumour) are less frequently identified but represent an additional important prognostic parameter. An appropriate staging work-up is then performed according to the Breslow thickness and other clinicopathologic risk factors to assess potential regional lymph node involvement and distant metastases. From that point onwards, the treatment pathway varies considerably depending on the stage of disease.

Q5 What role do biomarkers currently play in guiding treatment decisions?

At present, *BRAF* mutation status remains the biomarker with the clearest impact on routine treatment decisions in melanoma. Identifying a *BRAF* V600 mutation is clinically important, because it determines whether a patient is eligible for targeted therapy with the combination of B-raf proto-oncogene, serine/threonine kinase (BRAF) and mitogen-activated protein kinase kinase (MEK) inhibitors. Beyond *BRAF*, however, we still lack a single biomarker capable of reliably predicting which patient will benefit from immunotherapy. Programmed death-ligand 1 (PD-L1) expression has a limited role in the treatment selection with one exception: in patients with unresectable Stage III



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and IV melanoma, tumour cell PD-L1 expression <1% may be relevant to consider the combination of nivolumab and relatlimab.

Other potential biomarkers such as tumour mutational burden and features of the tumour microenvironment are biologically relevant, but they do not provide sufficiently robust discrimination to guide treatment decisions in melanoma. Circulating tumour DNA (ctDNA) is particularly interesting, but its role in routine clinical decision-making is still evolving. Current European Society for Medical Oncology (ESMO) recommendations recognise ctDNA as a potential alternative for mutation assessment when tumour tissue is unavailable, although with a relatively modest level of evidence.

Q6 The treatment landscape for advanced melanoma has changed dramatically. Which developments have had the greatest impact on patient outcomes?

The introduction of immune checkpoint inhibitors (anti-cytotoxic T-lymphocyte-associated protein 4 [CTLA4], anti-programmed cell death protein 1 [PD-1], and anti-lymphocyte-activation gene 3 [LAG3]), together with BRAF/MEK-targeted therapy, has profoundly changed the clinical course of advanced melanoma. Before these treatments became available, metastatic melanoma was associated with limited therapeutic options, short-lived clinical responses, and poor survival. Immune checkpoint inhibitors have had the greatest impact on long-term outcome, because they can induce durable responses that may persist even after treatment has been discontinued. Anti-PD-1 therapy, either alone or in combination with other immune checkpoint inhibitors, has therefore become a cornerstone of the management of advanced melanoma.

More recently, combined PD-1 and LAG-3 inhibition has provided another immunotherapeutic option. For patients with *BRAF*-mutant melanoma, combined BRAF and MEK inhibition represent another highly effective treatment strategy, particularly in patients with a high tumour burden. Perhaps the most important change is that we are no longer treating advanced melanoma with the expectation of transient disease control, but, particularly with immunotherapy, we now see long-term survival as a realistic goal. Finally, the therapeutic paradigm is progressively moving into earlier stages of the disease, first with adjuvant therapy and, more recently, with neoadjuvant treatment as a new treatment strategy.

Q7 How have immune checkpoint inhibitors transformed the management of advanced melanoma?

The most important change has been the possibility of achieving durable disease control and long-term survival in a disease where such outcomes were previously exceptional. Anti-PD-1 antibodies, such as nivolumab and pembrolizumab, established a new standard of care, while combination immunotherapy (nivolumab plus ipilimumab) can achieve higher response rates and more durable disease control, although at the cost of substantially higher toxicity. More recently, dual checkpoint inhibition targeting PD-1 and LAG-3 has further expanded the therapeutic options.

One of the most interesting developments is that immunotherapy has moved from the metastatic setting into early stages of melanoma. Adjuvant anti-PD-1 therapy is now established in patients at high risk of recurrence, including those with Stage IIb–IIc. In addition, neoadjuvant immunotherapy is now providing particularly exciting results in resectable macroscopic Stage III disease. Accordingly, current ESMO recommendations incorporate neoadjuvant nivolumab plus ipilimumab as an important option for clinically detectable resectable Stage III melanoma.

> **Targeted therapy remains an important component of melanoma treatment for patients with *BRAF* V600-mutant melanoma**

Q8 What is the current role of targeted therapies, particularly for patients with actionable mutations such as *BRAF*?

Targeted therapy remains an important component of melanoma treatment for patients with *BRAF* V600-mutant melanoma. The combination of a BRAF inhibitor with a MEK inhibitor allows the achievement of high response rates and often very rapid tumour regression. However, acquired resistance frequently develops over time, and responses may be less durable than those achieved with immunotherapy. In patients who are eligible for both approaches, the optimal sequencing of targeted therapy and immunotherapy should always be carefully considered

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and individualised in the context of a multidisciplinary team. The key point is that targeted therapy and immunotherapy should not be viewed as competing strategies, since they offer different advantages and have distinct toxicity profiles. Therefore, treatment selection should consider previous therapy, *BRAF* mutation status, disease burden, comorbidities, the individual clinical situation, and patient preference.

Q9 What are the key challenges in managing patients who develop resistance to immunotherapy or targeted treatment?

Resistance is one of the major challenges in the treatment of melanoma. It is important to distinguish primary resistance from acquired resistance, as they may reflect biologically different mechanisms and may require different therapeutic strategies. According to the current European Association of Dermato-Oncology (EADO) recommendations, for patients with *BRAF* V600-mutant melanoma who develop resistance to immunotherapy, BRAF/MEK inhibitors should be offered if no clinical trial is available. For patients with resistance to PD-1 monotherapy, several strategies may be considered, including combined immunotherapy with anti-PD-1 and anti-CTLA-4, CTLA-4 monotherapy, PD-1 plus LAG-3, or tumour-infiltrating lymphocyte therapy. For patients with *BRAF* V600-mutant tumour, targeted therapy remains an additional option.

Clinical trials are particularly important in this setting, because therapeutic options become more limited and offer very scarce clinical benefit.

Q10 How might emerging molecular and genomic approaches influence melanoma treatment in the coming years?

Comprehensive genomic profiling may help us better understand the mechanisms underlying treatment resistance and, in selected patients, identify actionable molecular alterations that could potentially be targeted with specific therapies.

In parallel, liquid biopsy approaches, particularly ctDNA, are emerging as a promising tool for providing a dynamic picture of tumour burden and molecular evolution during treatment. Unlike a single tissue biopsy, ctDNA has the potential to capture changes in the disease over time and, therefore, may help us monitor treatment response and the emergence of resistance.

Looking ahead, one of the most exciting perspectives is the integration of genomic data with transcriptomic, immunological, pathological, and clinical information. This multidimensional approach may ultimately allow us to move towards truly personalised treatment strategies and selecting the optimal treatment sequence.

Q11 Are there particular patient populations in which we still have significant gaps in treatment or outcomes?

Some patient populations remain particularly challenging and continue to have important unmet clinical needs. These include patients with autoimmune diseases, immunosuppressed patients (e.g., recipients of organ transplants), patients who develop resistance to currently available therapies, and those with active brain metastases.

Rare melanoma subtypes, particularly acral and mucosal melanomas, represent another major challenge. Because of their distinct biological and molecular characteristics, they tend to be less responsive to currently available systemic therapies and have historically been underrepresented in clinical trials. There is therefore a clear need for more effective, specifically tailored therapeutic strategies for these patients.

Finally, as outcomes continue to improve, we also need to consider the long-term consequences of treatment. Long-term survivors, as well as patients with earlier-stage disease receiving adjuvant immunotherapy, may experience persistent or even permanent immune-related adverse events and other treatment-related sequelae. Careful monitoring and early recognition and management of toxicity are therefore essential

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to minimise these risks and preserve quality of life.

At the same time, as we become better at identifying patients who are likely to have an excellent outcome, developing strategies to avoid unnecessary treatment and reduce treatment-related toxicity is becoming an increasingly important goal.

Q12 What areas of melanoma research are you most excited about at the moment?

Neoadjuvant immunotherapy is a very important example of how the treatment paradigm is evolving. The NADINA trial has shown that administering nivolumab plus ipilimumab before surgery in patients with resectable macroscopic Stage III melanoma can substantially improve event-free survival compared with surgery followed by adjuvant nivolumab. Also important is that pathological response to neoadjuvant treatment can provide valuable information to guide subsequent therapeutic decisions, opening the way to a more response-adapted approach.

Another particularly exciting development is personalised mRNA-based neoantigen therapy. The recent results with intismeran in combination with pembrolizumab in patients with resected high-risk melanoma are highly encouraging and further support the potential of individualised immunotherapeutic strategies. However, it will be important to define which patients are most likely to benefit and where this approach will ultimately fit into clinical practice.

Ultimately, I believe that the future of melanoma care will come from bringing all these advances together: earlier and more accurate diagnosis, non-invasive diagnostic technologies, AI-assisted imaging, biomarkers capable of detecting minimal residual disease, and increasingly precise biological and molecular stratification. Integrating these tools should allow us to move towards a truly personalised approach and, equally importantly, to understand when treatment can safely be reduced or avoided.



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