is unfortunately associated with poor to mediocre performance on unseen data. Tschandl and colleagues[5] also tested the machine-learning algorithms on images from sources different from those of the training set to properly quantify the overfitting issue.

Creating a gold standard of medical diagnosis is not a straightforward process. In a previous study by Tschandl and colleagues,[7] more than 50% of lesions, including all malignant tumours, were analysed histopathologically. Identification of benign unexcised lesions included more than 1·5 years of follow-up of sequential dermatoscopic imaging without changes, and judgment on the basis of expert consensus in cases of benign, banal, non-melanocytic lesions. For conclusive classification, seven simplified classes of diseases were generated, with specific attention paid to avoiding ambiguous classifications, and cases with uncertain histopathological diagnoses were excluded.

Where and when to appropriately use artificial intelligence is a matter of initial, but already intense, debate. Although appreciated as a powerful tool, artificial intelligence does not seem ready to replace the refined cognitive process of integrating morphological observations within a clinical context. In a real-world situation, in addition to dermatoscopic images clinicians consider several other features, including anatomical site, age, sex, and clinical history and evolution. Machine learning and humans should also be compared in terms of turnaround time and cost-effectiveness before becoming a standard of care.

In certain high-need settings, such as low-income and middle-income countries or health-care systems with few human resources, artificial intelligence might bring additional value, particularly as a screening tool. Furthermore, artificial intelligence could also be useful for the development of clinical support tools for inexperienced physicians and general practitioners, in view of an increasing demand for points of care for dermatology screening.[8] However, in future, automated classifiers and artificial intelligence algorithms could be integrated into clinical dermatology practice for a more accurate and effective triage of lesions in the context of human–machine collaboration. Although there is little doubt that artificial intelligence and machine-learning algorithms for skin cancer diagnosis are already gaining a central role in dermatology research, it is possible to anticipate that their application to clinical practice will require serious and robust validation in large, prospective studies.

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Neoadjuvant therapy for melanoma: is it ready for prime time?

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See Articles pages 948 and 961

In the past, advanced melanoma with nodal or distant metastases was almost universally fatal, with a median overall survival of less than 1 year with few effective therapies.[1] However, with the advent of treatment with immune checkpoint blockade and *BRAF*-targeted therapy, among other strategies, a dramatic improvement has been seen in the survival of patients with stage IV disease, substantiating approval of such

regimens for patients with metastatic melanoma.[2] *BRAF*-targeted therapy and immune checkpoint inhibitors have also shown efficacy in the adjuvant setting,[3] with approval of these drugs for adjuvant use after surgical resection in the setting of high-risk disease.

Additionally, scientific rationale for such a strategy is compelling because preclinical studies have shown that treatment with neoadjuvant immunotherapy is associated with improved outcomes and enhanced antitumor T-cell responses compared with adjuvant treatment.[4]

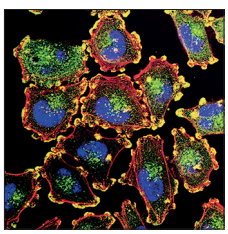
This treatment approach has numerous other advantages, including the potential use of pathological response as a surrogate endpoint for long-term benefit, as in the case of other diseases, and the potential to increase the ease of resection. The neoadjuvant setting also allows testing of novel combination strategies and investigational drugs with access to surgical samples for correlative analyses, and studies in this patient population might provide advantages over studies in patients with widespread metastatic disease (since these patients are less likely to have been heavily pretreated and might be less immunosuppressed than patients with more advanced disease). Potential disadvantages also exist, with a risk of disease progression during neoadjuvant treatment and the potential for increased perioperative complications. So far, the advantages of such an approach seem to outweigh the disadvantages; however, additional studies and further iterative advances are needed to optimise these strategies.

Two Articles in *The Lancet Oncology* galvanise a neoadjuvant treatment strategy in melanoma, reporting results of clinical trials testing the use of neoadjuvant *BRAF*-targeted therapy with dabrafenib and trametinib (NeoCombi)[5] and neoadjuvant combined immune checkpoint blockade with ipilimumab and nivolumab (OpACIN-neo)[6] in patients with high-risk resectable disease—both trials showing acceptable safety and encouraging antitumour activity with such an approach. In these studies, high proportions of patients achieved complete pathological responses (pCR), with nearly half of patients achieving a pCR on *BRAF*-targeted therapy in NeoCombi[5] and with combined immune checkpoint blockade (targeting the CTLA-4 and PD-1 immune checkpoints) in OpACIN-neo.[6] These data are in line with previously published work showing efficacy and toxicity with such approaches[7,8] and with monotherapy immune checkpoint regimens targeting PD-1.[7,9]

Importantly, these Articles further address crucial questions in the field, including efforts to explore optimal dosing and schedules of combined immune checkpoint blockade to balance efficacy and toxicity with this regimen,[6] and a critical assessment of patterns of relapse in these patients, particularly in relation to pCR.[5,6] No relapse was noted in patients achieving a pCR on neoadjuvant immune checkpoint blockade in OpACIN-neo,[6] albeit with somewhat short follow-up, whereas a fairly high risk of relapse was noted in the setting of treatment with neoadjuvant *BRAF*-targeted therapy in NeoCombi,[5] even in the setting of pCR (with eight [47%] of 17 patients relapsing in the setting of a pCR, and 12 [67%] of 18 in the setting of an incomplete pathological response).[5] Assessment of ease of surgical resection was included in NeoCombi,[5] reporting increased ease of resection in nearly half of patients. Importantly, both trials included biospecimen collection at baseline and during therapy (including during surgical resection), with insights gained from initial analyses reported within each Article and opportunities to learn more through deeper analysis of these samples.

Of particular interest, these manuscripts also highlight a valuable team approach in such efforts. Several of the authors on these important bodies of work (and others) have founded an organisation, the International Neoadjuvant Melanoma Consortium (INMC), to harmonise such efforts to gain maximum insight. This group works with key stakeholders worldwide to coordinate neoadjuvant efforts in melanoma and has helped to set a standardised approach to such efforts, with guidelines for pathological assessment and guidelines for duration of therapy and biospecimen collection, among other variables.[10]

However, important questions remain as we work together to use these strategies to improve clinical outcomes for our patients. In the case of targeted therapy, high response rates and increased ease of resectability are observed in patients treated using a neoadjuvant approach; however, risk of relapse is high. This provides an opportunity to use *BRAF–MAPK* pathway blockade as a backbone on which to add additional drugs, such as checkpoint inhibitors—eg, anti-PD-1-based regimens in the neoadjuvant setting (NCT03554083). In the case of



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immune checkpoint blockade, provocative findings regarding long-term benefit in the setting of a pCR need to be validated. The hypothesis that treatment with neoadjuvant therapy in patients provides an advantage over adjuvant therapy alone also needs to be tested. Translational data in patients from earlier clinical trials suggests enhanced antitumour immune responses in patients given neoadjuvant compared with adjuvant checkpoint blockade,[8] although this outcome needs to be evaluated carefully in larger clinical trials. Additionally, a subset of patients clearly benefit from anti-PD-1 monotherapy in the neoadjuvant setting[7,9] and could be spared the potential toxicity of combined immune checkpoint blockade. However, a subset of patients will not benefit from monotherapy;[7] thus better pretreatment biomarkers are needed to identify these cohorts. Similarly, better understanding of toxicity of these regimens and identification of biomarkers and strategies to mitigate treatment-related adverse events is needed because toxicity is higher in these patients with earlier stage disease and might affect perioperative management. Furthermore, analysis of on-treatment or surgical samples might help to guide the choice of adjuvant therapy long-term. Finally, additional combination strategies should be taken into consideration; however, these combinations need to have a sound scientific basis and potential added toxicity must be taken into account.

Is neoadjuvant therapy for melanoma ready for prime time? It is certainly time to embrace this concept in melanoma (and for other cancers) in light of the tremendous advances in management of systemic disease; although the adoption of neoadjuvant therapy needs to be done in the context of carefully planned clinical trials (ideally in collaboration with cooperative groups and the INMC). Through such studies and through engagement with regulatory bodies and other key stakeholders, the full potential of this approach will be realised and we will continue to transform cancer care for patients.

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Quantifying survival disparities among children diagnosed with cancer on a global scale

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The remarkable increase in 5-year net survival for children diagnosed with cancer from nearly 0% to 80% over the past six decades highlights notable success in cancer treatment and research.[1] These improvements have been the most striking in high-income countries such as the UK. Although it is largely accepted that