

# Neoadjuvant systemic therapy in stage III and IV resectable melanoma: an update to management and future directions

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## ABSTRACT

**AIM:** This article aims to review the role of neoadjuvant systemic therapy (NAST) in the management of clinical stage III or IV resectable melanoma. The review focusses on the evidence behind neoadjuvant systemic therapies and on developing a protocol for widespread implementation within the New Zealand health system. We outline suggested future directions for this evolving treatment.

**METHODS:** A detailed literature review was conducted, examining the rationale, mechanisms of action and recent clinical trial data supporting the use of NAST in melanoma management.

**RESULTS:** NAST provides notable immunological advantages by harnessing tumour antigen presence *in situ*, enhancing immune response and improving event-free survival (EFS) rates. Recent randomised phase II and III controlled trials have demonstrated significant improvements in EFS rates with NAST compared to standard adjuvant therapy alone. The SWOG-S1801 trial reported a 2-year EFS rate of 72% with neoadjuvant–adjuvant pembrolizumab compared to 49% for adjuvant-only therapy. The NADINA trial found a remarkable increase in 1-year EFS with neoadjuvant ipilimumab and nivolumab (83.7%) compared to adjuvant nivolumab alone (57.2%).

**CONCLUSION:** Current evidence strongly supports incorporating NAST into standard clinical practice for resectable clinical stage III and IV melanoma, promising substantial improvements in patient outcomes with acceptable safety profiles.

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Melanoma is a major public health concern in New Zealand, with incidence rates among the highest in the world. Furthermore, *in situ* melanoma rates have more than doubled in the last 20 years,<sup>1</sup> highlighting significant health system burden and risk of conferred mortality without timely and effective management.

Melanoma is currently staged using the *TNM Classification of Malignant Tumours, 8th Edition*, issued by the Union for International Cancer Control (UICC).<sup>2</sup> Stage III melanoma, which is characterised by clinically and/or pathologically detectable regional lymph node involvement without distant metastasis, has traditionally been managed by surgical resection followed by adjuvant therapy.<sup>3</sup> However, given high rates of both locoregional recurrence and progression to distant metastatic disease, improvement in this historic standard-of-care has been warranted.

In recent years, the emergent strategy of neoadjuvant systemic therapy (NAST) has demonstrated improved comparative efficacy in multiple recent clinical trials. Use of neoadjuvant therapies

in the management of stage III and resectable stage IV melanoma has been increasingly adopted overseas and holds great promise with growing implementation within New Zealand.

## Mechanism of action of systemic therapies

### Immunotherapy

Melanoma-targeted immunotherapy utilises immune checkpoint blockade, centred on the use of programmed cell death protein 1 (PD-1) inhibitors and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) inhibitors, either alone or in combination with one another.<sup>4</sup> These pathways are negative regulators of T-cell immune function, with their inhibition enhancing T-cell-mediated anti-tumour immune response.

PD-1 is a receptor protein found predominantly on the surface of T-cells, as well as other immune system constituents (B-cells, natural killer cells and monocytes). It serves to dampen the immune response when bound to programmed cell death ligand 1 (PD-L1), a transmembrane protein

expressed in disproportionately high levels on tumour cells.<sup>5</sup> Monoclonal antibodies have been developed as inhibitors of this pathway (pembrolizumab, nivolumab).

Similarly, CTLA-4 is another transmembrane receptor expressed on the surface of T-cells. It competes with CD28 (a co-stimulatory pathway for the T-cell receptor) for binding to B7 ligands on antigen-presenting cells, thereby downregulating T-cell activation. Inhibition with monoclonal antibodies (ipilimumab) is particularly effective in melanoma given a high mutational burden and immunogenicity.<sup>6</sup>

### Targeted therapy

Targeted therapies have also been utilised in the management of metastatic melanoma, most successfully in the form of *BRAF/MEK* inhibitors. The *MAPK* (mitogen-activated protein kinase) signalling pathway plays a central role in regulating cellular proliferation and survival. The *BRAF* protein is frequently mutated in melanoma, resulting in unregulated pathway activation and tumour proliferation. Currently approved *BRAF* inhibitors, such as dabrafenib, vemurafenib and encorafenib, and *MEK* inhibitors (a downstream protein within the *MAPK* pathway), trametinib, vemurafenib and cobimetinib, act synergistically to suppress this aberrant signalling cascade. Combined *BRAF/MEK* inhibition has been shown to enhance anti-tumour efficacy, delay resistance and reduce adverse events compared to *BRAF* inhibition alone.<sup>7</sup> Targeted therapy is efficacious only in patients with activating *BRAF*-mutation positive tumours in which the mutation substitutes the valine at position 600 for either glutamate (V600E) or lysine (V600K).

### Rationale for neoadjuvant therapy in melanoma

Neoadjuvant therapy in resectable stage III/IV melanoma is guided by several key principles: it enables early treatment of micrometastatic disease, it may reduce tumour volume to facilitate surgical resection and it provides an opportunity to assess pathological and radiological response to therapy. Both *BRAF*-targeted therapy and immune checkpoint inhibitors have been investigated in this setting, with immunotherapy showing distinct promise—potentially due to enhanced antigen presentation and immune activation in the presence of *in situ* tumour antigen.<sup>8</sup>

Administering systemic immunotherapy before surgical resection (neoadjuvant therapy) lever-

ages the presence of *in situ* tumour antigens to potentiate an immune response. Administering PD-1 inhibitors in this setting facilitates the *in situ* expansion of tumour-specific T-cell clones within the tumour microenvironment, a process supported by antigen presentation from PD-L1-expressing dendritic cells. Similarly, CTLA-4 inhibition enhances T-cell priming in tumour-draining lymph nodes by amplifying costimulatory signals during early T-cell activation. When used in combination in the neoadjuvant setting, PD-1 and CTLA-4 inhibitors provide synergistic benefits by augmenting both the priming and effector phases of the anti-tumour immune response. Evidence from the OpACIN-NEO trial demonstrated this phenomenon with significantly increased expansion of existing T-cell clones and more numerous novel T-cell clones in patients treated with neoadjuvant compared to standard adjuvant immunotherapy.<sup>9</sup> Furthermore, in patients with *BRAF*-mutant melanoma, *BRAF/MEK* inhibitors have been shown to increase tumour immunogenicity and T-cell infiltration, providing a potential rationale for sequencing or combining targeted therapy and immunotherapy with tumour antigen *in situ*.<sup>10</sup>

### Evidence for neoadjuvant treatment in melanoma

A growing wealth of evidence supports the routine utilisation of NASTs in the management of resectable clinical stage III and IV melanoma across both foundational phase II and larger phase III trials. Measures utilised to examine efficacy are typically pathologic response rate, disease-free survival (DFS) rate and response evaluation criteria in solid tumours objective response rate (RECIST ORR). Pathological response is assessed in degrees: complete pathological response (pCR, 0% viable tumour), near-complete response (near-pCR, ≤10% viable tumour), partial response (pPR, 10–50% viable tumour) and no response (pNR, >50% viable tumour). Major pathological response (MPR) is a combined category encompassing both pCR and near-pCR, defined as ≤10% viable tumour remaining. RECIST ORR is a standardised set of guidelines used to measure tumour response to treatment based on changes in the size of target lesions on imaging.<sup>11</sup>

### Foundational studies (phase Ib and II trials)<sup>9,12–16</sup>

The OpACIN trial (2015–2016) was a phase Ib study comparing neoadjuvant versus adjuvant

ipilimumab plus nivolumab in patients with resectable stage III melanoma. Neoadjuvant therapy induced a pathological response in 78% of patients and led to a greater expansion of tumour-specific T-cells into the circulation compared to adjuvant therapy. However, both treatment arms were associated with high toxicity rates, with grade 3–4 adverse events occurring in 90% of patients, raising concerns around tolerability. This prompted the OpACIN-neo trial (2016–2019), a phase II multicentre study that tested three different neoadjuvant dosing regimens. Pathologic response rates ranged from 65 to 80%, with pCR rates of up to 60%. The arm using low-dose ipilimumab (1mg/kg) and high-dose nivolumab (3mg/kg) demonstrated the most favourable balance of efficacy and safety, with a 77% response rate and only 20% incidence of grade 3–4 toxicities. This established a more tolerable regimen for neoadjuvant therapy moving forward.

A third study, Neoadjuvant Immune Checkpoint Blockade in High-Risk Resectable Melanoma (2015–2018), directly compared neoadjuvant nivolumab monotherapy with combination ipilimumab (3mg/kg)/nivolumab (1mg/kg) in patients with resectable stage III and oligometastatic stage IV melanoma. Combination therapy achieved higher pCR (45% vs 25%) and ORR (73% vs 25%) but came at the cost of significantly greater toxicity—grade 3 adverse events occurred in 73% of combination therapy recipients compared to just 8% with monotherapy. Moreover, two patients on monotherapy progressed to unresectable disease during the neoadjuvant period, highlighting a potential risk associated with delayed surgery.

A Single Dose of Neoadjuvant PD-1 Blockade Predicts Clinical Outcomes in Resectable Melanoma (2016–2019) investigated the feasibility of a single dose of neoadjuvant PD-1 blockade. In this phase II single-arm trial, patients with resectable stage IIIB–IV melanoma received one 200mg dose of pembrolizumab followed by surgery 3 weeks later. A pCR or near-pCR was achieved in 30% of patients, all of whom remained recurrence-free at 25 months. The 1-year DFS was 63%, and no unexpected toxicities were observed, supporting the potential predictive value of early response to treatment.

Two additional trials evaluated neoadjuvant targeted therapy in *BRAF*-mutant melanoma. The Neoadjuvant Plus Adjuvant Dabrafenib and Trametinib Trial (2014–2017) was a randomised phase II study in which patients treated with neoadjuvant plus adjuvant dabrafenib/trametinib

had markedly improved outcomes compared to standard-of-care, with 71% remaining disease-free at 18.6 months versus 0% in the comparator group. Likewise, the NeoCombi trial (2014–2018) explored a 12-week neoadjuvant course of dabrafenib/trametinib followed by 40 weeks of adjuvant therapy. All patients achieved a pathological response, with 49% achieving pCR. Despite this, relapse occurred in nearly half of those with pCR, underscoring that pathologic response alone may not guarantee durable remission in those treated with *BRAF/MEK* inhibitors. Importantly, no patients progressed during the neoadjuvant period, and the regimen was generally well tolerated.

A pooled analysis of these early neoadjuvant trials showed the significance of pathological response, with 96% of those achieving a pCR with immunotherapy remaining disease-free at 2 years compared with 79% of those treated with targeted therapy. In this cohort, 52% in the immunotherapy group achieved an MPR and 47% with targeted therapy, showing that durability of immunotherapy-induced pCR was likely due to the means of achieving pCR rather than a difference in the rates achieved.<sup>17</sup>

Together, these foundational studies highlighted both the therapeutic promise and challenges of neoadjuvant strategies, laying the groundwork for subsequent large-scale trials and response-adapted treatment models. In addition, the durable responses demonstrated with neoadjuvant checkpoint inhibitors, as opposed to *BRAF*-targeted treatment, suggested immunotherapy may be more promising in the neoadjuvant setting.

## Further studies (larger phase II and III trials)<sup>18,19</sup>

### 1. SWOG S1801 trial (2018–2022)

The SWOG S1801 trial was a phase II randomised trial, comparing neoadjuvant plus adjuvant pembrolizumab versus adjuvant-only pembrolizumab in patients with resectable stage III/IV melanoma (n=313). Patients received 18 doses of pembrolizumab either in a neoadjuvant plus adjuvant manner (three doses prior to surgery and 15 post-surgery) or purely adjuvant manner (18 doses post-surgery), with the primary end point being event-free survival (EFS).

With a median follow-up of 14.7 months, EFS was significantly longer in the neoadjuvant–adjuvant group than in the adjuvant-only group (n=0.004), with a predicted EFS at 2 years being 23% greater in the neoadjuvant group (72%

vs 49%). Significant treatment-related adverse events were close to equivocal (12% vs 14%) between the two groups. The study showed that administering pembrolizumab before and after surgery significantly enhances EFS in high-risk resectable melanoma, without significant adverse effects. MPR in this study was 51% on *post hoc* analysis (pCR 40%, near-pCR 11%), with patients experiencing complete response also sustaining a 97% 2-year EFS.

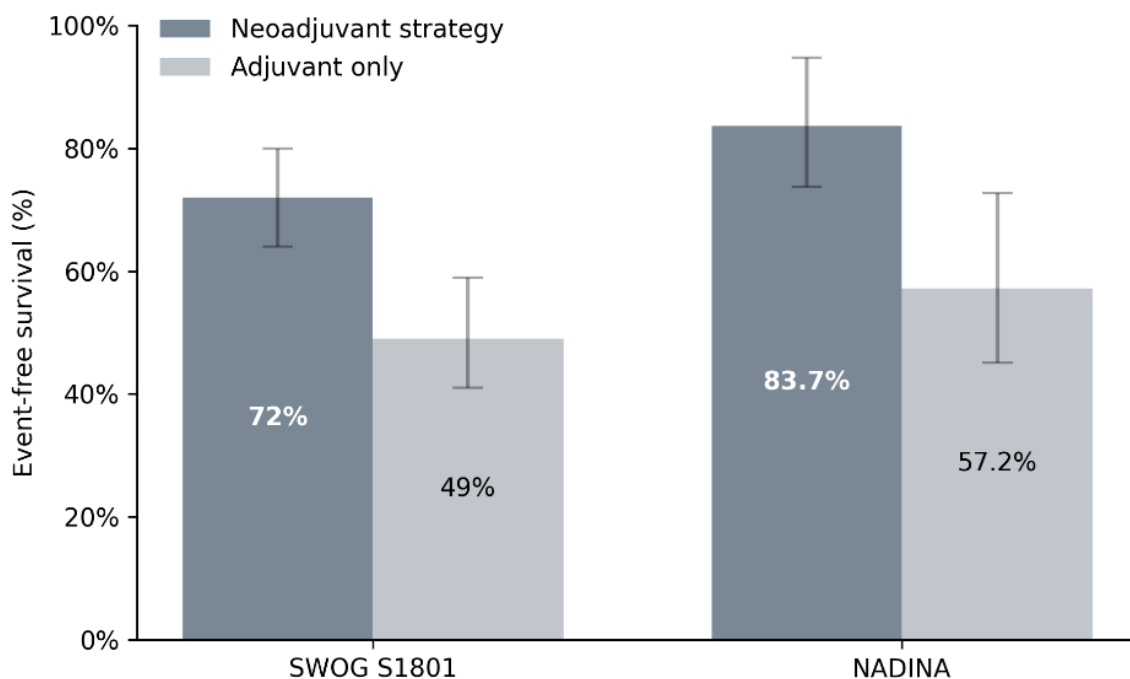
**2. NADINA trial (2021–2023)**

This landmark trial extended the neoadjuvant paradigm with a randomised design, the use of combination anti-PD-1 and anti-CTLA-4 therapy and response-driven adjuvant therapy. This was a phase III randomised trial comparing neoadjuvant ipilimumab plus nivolumab followed by surgery and response-driven adjuvant therapy versus surgery followed by adjuvant nivolumab, in patients with resectable stage III melanoma (n=423). Patients in the neoadjuvant group were given two cycles of neoadjuvant ipilimumab (80mg) plus nivolumab (240mg) every 3 weeks, prior to surgery. They only received further adjuvant therapy if they displayed a partial response or non-response to the neoadjuvant therapy. In these patients, further systemic therapy was dictated by tumour *BRAF*-mutation presence. If present, they received dabrafenib (150mg twice daily) plus trametinib

(2mg once daily) for 46 weeks. If not present (*BRAF* wild-type), they received an additional 11 cycles of adjuvant nivolumab (480mg every 4 weeks). Patients in the adjuvant group received 12 cycles of adjuvant nivolumab every 4 weeks starting between week 6 and 12. The primary outcome of the study was EFS, defined as the time from randomisation to the occurrence of progression to unresectable melanoma before surgery, disease recurrence, or death due to melanoma or due to treatment.

The neoadjuvant group demonstrated a paradigm-shifting 68% reduction in risk of recurrence or progression (hazard ratio 0.32,  $P < 0.0001$ ) resulting in an estimated 12-month EFS of 83.7%, which was significantly greater than in the adjuvant-only group (57.2%). The estimated 12-month recurrence-free survival was 95.1% in neoadjuvant patients with major pathological response, compared to 76.1% in those with partial response and 57.0% in non-responders. There was a greater incidence of grade 3–4 adverse events in the neoadjuvant group compared to the adjuvant group (29.7% vs 14.7%). The study showed that neoadjuvant combination immunotherapy followed by surgery and tailored adjuvant systemic therapy significantly improves outcomes in resectable stage III melanoma, implicating a potential new standard-of-care. The study also re-affirmed the prognostic value in index-response to neoadjuvant systemic

**Figure 1:** Event-free survival in landmark trials.



therapy upon survival.

## Future directions

As discussed, the role of systemic therapies in the management of stage III melanoma is a rapidly evolving one. There is growing evidence towards increasingly personalised approaches in the treatment of high-risk stage III melanoma, based on tumour response to neoadjuvant therapies. The recent PRADO trial<sup>20</sup> supported de-escalation of surgery. This was an extension of the OpACIN-neo trial. Patients in this trial underwent neoadjuvant immunotherapy followed by excision of the index node, defined as the largest lymph node metastasis prior to neoadjuvant therapy. In those patients who achieved an MPR ( $\leq 10\%$  viable tumour) after neoadjuvant immunotherapy, it was safe to omit a full therapeutic lymph node dissection and instead perform only an index lymph node excision (93% recurrence-free survival at 2 years). This would potentially save the patient from the morbidity of a therapeutic lymph node dissection. Evidence from this trial has provided further basis for larger scale randomised controlled trials currently underway, which have the potential to be practice-changing. This movement toward personalised therapy based on pathologic response is similarly supported by the earlier-mentioned NADINA trial. In this case, patients who had a MPR

to neoadjuvant therapy were able to avoid the subsequent adjuvant portion, while maintaining the highest estimated 12-month recurrence-free survival (95.1%) of those in the study. Overall, the field holds great future potential, with future study and practice exploring de-escalation of therapy (both surgically and immunologically) in suitable patients to avoid unnecessary adverse effects, morbidity and complications. A further area of interest is in the group of patients who do not achieve an MPR and investigating interventions which will improve outcomes in this challenging group of patients.

## Conclusion

Effective systemic therapies have resulted in a quantum leap in the improvement of outcomes for patients with melanoma. Neoadjuvant therapy reflects a further paradigm shift, resulting in additional improvement in outcomes. We have reached a level of evidence where it can be considered standard-of-care for patients with resectable stage III and stage IV disease. With the recent funding of these therapies in New Zealand we look forward to offering these therapies as a routine, and we await the results of further studies to continue to improve outcomes and potentially reduce the morbidity of surgical interventions.

**COMPETING INTERESTS**

Nil.

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