Choosing the appropriate adjuvant therapy in patients with melanoma undergoing neoadjuvant treatment

Gabriela Franco Katz,[1] Beatriz Mendes Awni Cidale,[2] Ana Zélia Leal Pereira,[2] Alline Guimarães de Castro,[3] Giulia Kodja Zanetta,[2] Gustavo Benfatti Olivato[2] and Rodrigo Ramella Munhoz[2]

1. Chesterfield Royal Hospital, Chesterfield, UK; 2. Oncology Center, Sírio-Libanês Hospital, São Paulo, Brazil; 3. Oncology Center, Sírio-Libanês Hospital, Brasília, Brazil

https://doi.org/10.17925/OHR.2026.22.2.3

Cutaneous melanoma is an aggressive malignancy, and patients with resectable stage III disease remain at high risk of recurrence despite advances in systemic therapy following surgical resection. Adjuvant immune checkpoint inhibitors and BRAF (B-Raf proto-oncogene, serine/threonine kinase)/MEK (mitogen-activated protein kinase) inhibitors have been incorporated into clinical practice based on improvements in recurrence-free survival. However, relapse rates remain substantial, and consistent overall survival benefits have yet to be confirmed, highlighting the limitations of adjuvant-only treatment approaches. Neoadjuvant immunotherapy has demonstrated improved event-free survival in randomized studies, enabling *in vivo* assessment of tumor response; pathologic response is strongly associated with favorable outcomes and has emerged as a key stratification tool and surrogate endpoint, allowing for adaptive adjuvant strategies. This article discusses pivotal neoadjuvant trials, evaluates limitations in cross-trial comparisons due to heterogeneity in post-neoadjuvant treatment strategies and examines emerging biomarkers such as circulating tumor DNA and immune profiling. Finally, it addresses unresolved challenges in selecting optimal post-neoadjuvant therapy, particularly in patients with residual disease.

Keywords

Biomarkers, disease-free survival, melanoma, neoadjuvant therapy, skin neoplasms, tumor

Disclosures: Beatriz Mendes Awni Cidale has received payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from Adium Pharma, AstraZeneca, Astellas, BMS and worked as a sub-investigator in the following clinical studies funded by pharmaceutical industries: HARMONY R3767-ONC-2055 (NCT05608291), HARMONY R3767-ONC-2011 (NCT05352672), INSIGHT (NCT05734105), STARBOARD C4221016 (NCT04657991), AGENUS C-800-23 (NCT05529316) and BP43963 (NCT05419388). Giulia Kodja Zanetta has participated as a sub-investigator in the following clinical studies funded by the pharmaceutical industries: HARMONY R3767-ONC-2055 (NCT05608291), HARMONY R3767-ONC-2011 (NCT05352672), INSIGHT (NCT05734105), STARBOARD C4221016 (NCT04657991), AGENUS C-800-23 (NCT05529316) and BP43963 (NCT05419388). Gustavo Benfatti Olivato has received fees as a speaker for the following companies: MSD, AstraZeneca, Adium, Daiichi Sankyo, Amgen and Pfizer and has participated as a sub-investigator in the following clinical studies funded by the pharmaceutical industries: HARMONY R3767-ONC-2055 (NCT05608291), HARMONY R3767-ONC-2011 (NCT05352672), INSIGHT (NCT05734105), STARBOARD C4221016 (NCT04657991), AGENUS C-800-23 (NCT05529316) and BP43963 (NCT05419388). Rodrigo Ramella Munhoz has received payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from Adium Pharma, BMS, Medison, Merck Serono, MSD, Novartis, Pfizer; participation on a data safety monitoring board or advisory board from BMS, Dechipera, Merck KGaA and research funding from Bayer, Roche, Agenus, Regeneron, Feciphera. Gabriela Franco Katz, Ana Zélia Leal Pereira and Alline Guimarães de Castro have no financial or non-financial relationships or activities to declare in relation to this article.

Acknowledgements: During the preparation of this manuscript, the authors used artificial intelligence (AI)-assisted software (ChatGPT, OpenAI, GPT-5) to enhance the clarity, readability, and language of the text. All AI-generated suggestions were carefully reviewed, edited, and verified by the authors, who accept full responsibility for the accuracy and integrity of the final manuscript. AI tools were not used to perform the literature search, select studies, extract or analyse data, or interpret the study findings.

Review process: Double-blind peer review.

Compliance with ethics: This article is an opinion piece and does not report on new clinical data or any studies with human or animal subjects performed by any of the authors.

Data availability: Data sharing is not applicable to this article as no datasets were generated or analyzed during the writing of this article.

Authorship: All named authors meet the criteria of the International Committee of Medical Journal Editors for authorship for this manuscript, take responsibility for the integrity of the work as a whole and have given final approval for the version to be published.

Access: This article is freely accessible at touchONCOLOGY.com. ©Touch Medical Media 2026.

Received: 13 May 2026

Accepted: 13 July 2026

Published online: 6 October 2026

Citation: *touchREVIEWS in Oncology & Haematology.* 2026;22(2):6–10

Corresponding author: Beatriz Mendes Awni Cidale, 115 Dona Adma Jafet Street, Bela Vista, São Paulo, SP 01308-050, Brazil.
E: beatrizawni@gmail.com, biaawni@hotmail.com

Support: No funding was received in the publication of this article.

This article examines current evidence supporting the use of neoadjuvant immunotherapy in patients with resectable macroscopic stage III melanoma and critically discusses the selection of appropriate adjuvant therapy following surgery. It is written in the context of emerging evidence from recent neoadjuvant trials, both in melanoma and across multiple tumor types, suggesting that pathologic response may serve as a surrogate marker for long-term outcomes. The article also highlights current uncertainties surrounding response-adapted treatment strategies and future directions for prospective validation.

Cutaneous melanoma is an aggressive malignancy arising from melanocytes within the skin. In patients with non-metastatic disease, the risk of recurrence is primarily assessed using the tumor-node-metastasis staging system of the American Joint Committee on Cancer, which incorporates tumor thickness, ulceration, nodal and non-nodal regional involvement and distant metastases.[1] Among these factors, lymph node status and non-nodal regional disease (satellitosis/microsatellitosis/in-transit metastases) are key determinants of prognosis. Macroscopic regional involvement, defined as clinically detectable disease with pathologic confirmation, is associated with a substantially higher risk of recurrence compared with microscopic involvement identified only through sentinel lymph node biopsy.[2] Stage III melanoma is defined by regional lymph nodal or non-nodal (satellitosis/microsatellitosis/in-transit metastases) involvement in the absence of distant metastasis and encompasses a heterogeneous group of patients. Stage IIIA disease is associated with a relatively lower risk of recurrence, whereas stages IIIB–D carry a significantly higher risk, with reported recurrence rates of approximately 33%, 58% and 71%, respectively.[3] This heterogeneity underscores the importance of accurate risk stratification in guiding treatment decisions.

Adjuvant systemic therapy with immune checkpoint inhibitors or targeted therapy aiming at the mitogen-activated protein kinase (MAPK) pathway is established as the standard of care for patients with resected high-risk melanoma, based on pivotal randomized trials including CheckMate 238 (A Phase 3, Randomized, Double-blind Study of Adjuvant Immunotherapy With Nivolumab Versus Ipilimumab After Complete Resection of Stage IIIb/c or Stage IV Melanoma in Subjects Who Are at High Risk for Recurrence; ClinicalTrials.gov identifier: NCT02388906), KEYNOTE-054 (Adjuvant Immunotherapy With Anti-PD-1 Monoclonal Antibody Pembrolizumab [MK-3475] Versus Placebo After Complete Resection of High-risk Stage III Melanoma: A Randomized, Double-blind Phase 3 Trial of the EORTC Melanoma Group; ClinicalTrials.gov identifier: NCT02362594) and COMBI-AD (A Phase III Randomized Double Blind Study of Dabrafenib (GSK2118436) in Combination With Trametinib [GSK1120212] Versus Two Placebos in the Adjuvant Treatment of High-risk BRAF V600 Mutation-positive Melanoma After Surgical Resection; ClinicalTrials.gov identifier: NCT01682083) trials.[4–6] These trials demonstrated significant improvements in recurrence-free survival (RFS) and distant metastasis-free survival (DMFS) compared with placebo or active control groups.[4] Among these trials, COMBI-AD was the first to demonstrate the benefit of adjuvant targeted therapy in patients with *BRAF* (B-Raf proto-oncogene, serine/threonine kinase) V600-mutant melanoma, showing sustained long-term efficacy with recently reported 10-year follow-up data. In the COMBI-AD trial, relapse-free survival was 48% with dabrafenib plus trametinib versus 32% with placebo at 10 years, while DMFS was 63% versus 48%, respectively, confirming the durability of benefit.[5]

However, neither trial showed a consistent overall survival (OS) benefit, highlighting the limitations of adjuvant-only strategies. Despite adjuvant therapy, recurrence remains high, at approximately 30–40%.[7] Furthermore, adjuvant therapy is associated with potential overtreatment of patients who are cured by surgery alone, as well as cumulative toxicity, prolonged treatment duration and substantial financial burden. Importantly, treatment decisions in the adjuvant setting are made without direct assessment of tumor sensitivity, thereby limiting opportunities for treatment individualization.[8]

In this context, neoadjuvant immunotherapy has emerged as a paradigm shift in the management of patients with resectable, clinically detectable stage III melanoma, with the aim of reducing recurrence risk.[9,10] This approach is supported by a broader oncological rationale that has been explored across multiple tumor types, including triple-negative breast cancer and non-small cell lung cancer (NSCLC). From a biological perspective, neoadjuvant programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) blockade promotes expansion of tumor-specific T-cell clones within the intact, antigen-enriched tumor microenvironment, thereby enhancing antitumor immune priming.[10] These activated T cells may persist following surgical resection, contributing to sustained immune surveillance and the potential eradication of residual microscopic disease. In parallel, neoadjuvant therapy enables an *in vivo* assessment of tumor response, providing an opportunity to inform subsequent postoperative treatment decisions.[9–11]

Currently, decisions regarding adjuvant treatment after neoadjuvant immunotherapy are guided by the design of the mentioned randomized clinical trials; however, they are made without appropriate prospective validation.[10] Pathologic assessment of residual viable tumor following neoadjuvant therapy has emerged as a key indicator of treatment efficacy and a surrogate for long-term benefit. Standardized response categories include pathologic complete response (pCR), defined as no residual viable tumor cells; major pathologic response (MPR), defined as ≤10% viable tumor; partial pathologic response (pPR), defined as 10–50% viable tumor; and pathologic non-response (pNR), defined as >50% viable tumor cells.[10] These classifications provide a consistent framework for response assessment and have been widely used across clinical trials in solid tumors.[11]

Despite these advances, important uncertainties remain regarding the optimal use of pathologic response to guide post-neoadjuvant management. While pCR and MPR are consistently associated with favorable outcomes, the appropriate treatment strategy for patients with residual disease remains unclear, and the extent to which pathologic response can reliably inform escalation or de-escalation of adjuvant therapy is not yet fully defined.[11] This article synthesizes current evidence supporting neoadjuvant immunotherapy in stage III melanoma, with a focus on the prognostic and potential predictive value of pathologic response and the unresolved challenges in post-neoadjuvant treatment decision-making.

Evidence from key neoadjuvant trials

While early-phase trials established proof of concept, larger randomized studies have since defined the current clinical landscape of neoadjuvant therapy in stage III melanoma. Among the earliest clinical evidence was the pilot study by Huang et al., which investigated a single dose of neoadjuvant pembrolizumab administered 3 weeks before surgery in patients with high-risk resectable melanoma.[12] This short-duration neoadjuvant treatment was shown to be feasible and potentially effective, with 8 of 27 patients (30%) achieving either pCR or MPR; of note, correlative studies were able to demonstrate a marked variation in the tumor microenvironment and T-cell infiltration in responders.[13] More

Table 1: Key neoadjuvant trials in resectable stage III melanoma[8,10,11,14]

Trial	Phase	n	Treatment strategy	Primary endpoint	pCR (%)	MPR (%)	Key efficacy outcomes
OpACIN (NCT02437227)[10]	II	20	Ipi + nivo (neo versus adj)	Safety	33	67	Higher 5y RFS/OS in neo arm
OpACIN-neo (NCT02977052)[10]	II	86	Ipi 1 + nivo 3	Path response	43	60	Response correlates with RFS
PRADO (NCT02977052)[11]	II	99	Ipi + nivo, response-adapted	Path response	49	61	24-mo RFS ~93% (MPR)
SWOG S1801 (NCT03698019)[14]	II, randomized	345	Periop versus adj pembro	EFS	38	53	EFS benefit (HR 0.58)
NADINA (NCT04949113)[8]	III, randomized	423	Neo ipi + nivo versus adj nivo	EFS	59	59*	EFS benefit (HR 0.32)

**MPR includes ≤10% viable tumor.*
adj = adjuvant; EFS = event-free survival; HR = hazard ratio; ipi = ipilimumab; mo = month; MPR = major pathologic response; NADINA = Neoadjuvant Ipilimumab and Nivolumab versus Standard Adjuvant Nivolumab in Macroscopic Stage III Melanoma; neo = neoadjuvant; nivo = nivolumab; OpACIN = Opdivo and Yervoy in Advanced Melanoma; OpACIN-neo = Neoadjuvant ipilimumab plus nivolumab in melanoma; OS = overall survival; path = pathologic; pCR = pathologic complete response; pembro = pembrolizumab; periop = perioperative; PRADO = Personalized Response-Driven Adjuvant Therapy in Stage III Melanoma; RFS = recurrence-free survival; SWOG S1801 = Southwest Oncology Group S1801; y = year.

robust evidence supporting neoadjuvant immunotherapy in melanoma was subsequently endorsed by the phase II OpACIN (Opdivo and Yervoy in Advanced Melanoma; ClinicalTrials.gov identifier: NCT02437227) and OpACIN-neo (Neoadjuvant ipilimumab plus nivolumab in melanoma; ClinicalTrials.gov identifier: NCT02977052) trials. OpACIN demonstrated high rates of MPR with short-course neoadjuvant ipilimumab–nivolumab. In the neoadjuvant cohort, 7 of 10 patients achieved a pathologic response after two cycles of ipilimumab 3 mg/kg plus nivolumab 1 mg/kg. At a median follow-up of 69 months, only one recurrence was observed among pathologic responders. Five-year RFS and OS were higher in the neoadjuvant than adjuvant arm (70% versus 60% for RFS and 90% versus 70% for OS). The subsequent OpACIN-neo study optimized dosing strategies to improve tolerability while maintaining efficacy. It investigated three different doses and timings of ipilimumab for resectable stage III melanoma, ultimately demonstrating that two cycles of ipilimumab 1 mg/kg plus nivolumab 3 mg/kg preserved pathologic response rates with improved safety. Radiological responses were observed in 52% of patients, while 74% achieved pPR. Notably, no recurrences occurred among responders, and this outcome persisted over a 69-month follow-up period. Furthermore, pathologic response was the strongest predictor of recurrence, with ≤50% residual tumor associated with higher 3-year RFS (95% versus 37%), supporting response-adapted strategies.[14] Key neoadjuvant trials are summarized in *Table 1*.[8,10,11,14]

Building upon these findings, an extension cohort of the OpACIN-neo study, the PRADO (Personalized Response-Driven Adjuvant Therapy in Stage III Melanoma; ClinicalTrials.gov identifier: NCT02977052) trial (n=99), demonstrated that pathologic response assessed in the index lymph node may be used to guide subsequent surgical and adjuvant management. Patients with an MPR in the index lymph node were able to avoid completion lymph node dissection and adjuvant therapy, which reduced treatment-related morbidity and improved quality of life. Those with a pPR proceeded to therapeutic lymph node dissection alone, while patients without a pathologic response received both surgery and adjuvant systemic therapy with immune checkpoint inhibitors or BRAF/MEK (mitogen-activated protein kinase) targeted treatment. This supported the initial steps toward response-adapted strategies, as patients achieving MPR showed a 24-month relapse-free survival and DMFS rates of 93% and 98%, respectively.[15] These findings have informed the design of the on-going phase III MSLT-3 (Multicenter Selective Lymphadenectomy Trial 3; ClinicalTrials.gov identifier: NCT00003254) trial, which will prospectively evaluate response-adapted surgical de-escalation from total lymph node dissection to index lymph node resection following neoadjuvant immunotherapy.[15]

More recently, randomized trials have confirmed the clinical benefit of neoadjuvant approaches. The randomized phase II SWOG S1801 (Southwest Oncology Group S1801; ClinicalTrials.gov identifier: NCT03698019) trial (n=345) evaluated two treatment strategies for resectable stage III–IV melanoma, comparing standard adjuvant pembrolizumab alone with a perioperative approach incorporating both neoadjuvant and adjuvant pembrolizumab with the same total treatment duration. The perioperative arm demonstrated significantly improved event-free survival (EFS), supporting the clinical activity of neoadjuvant immune checkpoint inhibition and providing a strong rationale for further investigation in melanoma. Exploratory analyses further demonstrated a strong association between pathologic response and outcomes, with 2-year relapse-free survival rates of 97% in patients achieving a complete pathologic response, 80% in those with near-complete response, 73% in patients with a pPR and 48% in non-responders, indicating a strong correlation between depth of pathologic response and survival in patients treated with neoadjuvant pembrolizumab; however, this finding raises the question of whether the prognosis of those achieving a pCR is indeed the same as those with an MPR.[10,16]

The phase III NADINA (Neoadjuvant Ipilimumab and Nivolumab versus Standard Adjuvant Nivolumab in Macroscopic Stage III Melanoma; ClinicalTrials.gov identifier: NCT04949113) trial provided definitive evidence of the superiority of neoadjuvant immunotherapy, demonstrating that two cycles of neoadjuvant ipilimumab (80 mg) plus nivolumab (240 mg) followed by response-adapted adjuvant therapy significantly improved 12-month EFS compared with upfront surgery and standard adjuvant nivolumab (84% versus 57%; hazard ratio (HR) 0.32, 99% confidence interval 0.15–0.66).[15] Although complete lymph node dissection remained the standard surgical procedure in both arms, adjuvant therapy was omitted in patients achieving pCR or MPR (59%), whereas those with residual disease received *BRAF*-guided adjuvant treatment; dabrafenib–trametinib for *BRAF* V600E-mutant melanoma and up to 1 year of nivolumab for *BRAF* wild-type disease. Notably, in the neoadjuvant group, 12-month relapse-free survival was closely associated with the degree of pathologic response, with rates of 95.1% in patients achieving an MPR, 76.1% in those with a pPR and 57.0% among non-responders.[10,16]

Collectively, these trials have established neoadjuvant immunotherapy as a standard-of-care approach for resectable macroscopic stage III melanoma and support pathologic response as a clinically meaningful prognostic marker strongly associated with long-term outcomes in this setting.[10,16]

Pathologic response as a surrogate endpoint and driver of response-adapted therapy

As previously highlighted, pathologic response is now accepted as a clinically meaningful surrogate endpoint in neoadjuvant melanoma treatment. Pooled analyses from the International Neoadjuvant Melanoma Consortium (INMC) demonstrated a strong association between residual viable tumor and RFS for patients treated with immunotherapy, with increasingly favorable outcomes observed across response categories.[10] Updated INMC data confirmed durable survival benefits across neoadjuvant regimens.[17] These findings have informed the use of the previously discussed standardized response categories; the ≤10% threshold was derived from early pooled data sets showing a survival inflection below this level and has since been adopted as a pragmatic consensus definition across neoadjuvant studies. However, in melanoma, where neoadjuvant systemic therapy is a relatively recent development, these criteria remain largely based on retrospective correlations and are still undergoing prospective validation. Early consensus recommendations published in 2018 provided the first framework for standardizing neoadjuvant response assessment, but on-going refinement is expected as longer-term data mature.[10,11]

Beyond melanoma, pathologic response, particularly pCR, has been established as a robust intermediate endpoint associated with long-term outcomes across multiple tumor types, with the strongest evidence derived from breast, lung and gastrointestinal malignancies.[11] In NSCLC, neoadjuvant and perioperative immuno-chemotherapy have demonstrated a clear association between pathologic response and survival outcomes. Early neoadjuvant studies reported MPR rates of approximately 45% and pCR rates of approximately 10%, findings that were subsequently confirmed in phase III trials. In CheckMate 816 (A Neoadjuvant Study of Nivolumab Plus Ipilimumab or Nivolumab Plus Chemotherapy Versus Chemotherapy Alone in Early Stage Non-Small Cell Lung Cancer [NSCLC]; ClinicalTrials.gov identifier: NCT02998528), neoadjuvant nivolumab plus chemotherapy improved EFS compared with chemotherapy alone and increased pCR rates (24% versus 2%), with the greatest survival benefit observed in patients achieving pCR.[18] Similarly, KEYNOTE-671 (Efficacy and Safety of Pembrolizumab [MK-3475] With Platinum Doublet Chemotherapy as Neoadjuvant/Adjuvant Therapy for Participants With Resectable Stage II, IIIA, and Resectable IIIB [T3-4N2] Non-small Cell Lung Cancer [MK-3475-671/KEYNOTE-671]; ClinicalTrials.gov identifier: NCT03425643) showed improved EFS with perioperative pembrolizumab plus chemotherapy (HR 0.58) alongside higher pCR rates (18.1% versus 4.0%).[11,19] Collectively, these data support a consistent relationship between deeper pathologic responses and improved survival outcomes in NSCLC.[11]

A similar pattern is observed in triple-negative breast cancer, where neoadjuvant chemo-immunotherapy has reinforced the prognostic value of pathologic response. In KEYNOTE-522 (Study of Pembrolizumab [MK-3475] Plus Chemotherapy vs Placebo Plus Chemotherapy as Neoadjuvant Therapy and Pembrolizumab vs Placebo as Adjuvant Therapy in Participants With Triple Negative Breast Cancer [TNBC] [MK-3475-522/KEYNOTE-522]; ClinicalTrials.gov identifier: NCT03036488), the addition of pembrolizumab to neoadjuvant and adjuvant chemotherapy increased pCR rates and improved EFS (HR 0.63), with subsequent data also demonstrating an OS benefit.[11] Outcomes are strongly stratified by residual disease burden, with patients achieving pCR experiencing the most favorable survival, while increasing residual cancer burden is associated with progressively worse outcomes. Similar associations have also been reported in HER2-positive breast cancer and locally advanced rectal cancer, where pCR has been incorporated into treatment decision-making and clinical trial design.[11]

Table 2: A 24-month recurrence-free survival by pathologic response: SWOG S1801 versus NADINA[8,14]

Pathologic response	SWOG S1801[14] (24-month RFS, %)	NADINA[8] (24-month RFS, %)
pCR	97	95.1
Near pCR	80	81.2
pPR	73	69.4
pNR	48	48.4

NADINA = Neoadjuvant Ipilimumab and Nivolumab versus Standard Adjuvant Nivolumab in Macroscopic Stage III Melanoma; pCR = pathological complete response; pNR = pathological no response; pPR = pathological partial response; RFS = relapse-free survival; SWOG S1801 = Southwest Oncology Group S1801.

Beyond prognostication, pathologic response has emerged as a clinically actionable endpoint, informing postoperative management. Trials such as PRADO and NADINA have incorporated response-adapted strategies to reduce treatment-related morbidity while identifying patients at higher risk who may benefit from therapeutic escalation. Favorable pathologic responses have been associated with omission of radical lymph node dissection and de-intensification of adjuvant therapy.[10] However, these approaches are supported by limited prospective data and should be regarded as hypothesis-generating rather than established standards. In addition, recent updates from SWOG S1801 and NADINA question whether outcomes are indeed the same for patients with no viable tumor cells (pCR) compared with those with >0–10% viable cells, populations originally grouped together as major responders and subject to group data interpretations and adaptive strategies. *Table 2* displays pathologic response rate for SWOG S1801 and NADINA trials.[8,14]

In parallel, emerging biomarkers may further refine postoperative decision-making. Correlative analyses from pivotal neoadjuvant trials have provided important biological insights, with Huang et al. demonstrating expansion of tumor-resident T-cell clones following PD-1 blockade, and OpACIN/OpACIN-neo identifying interferon (IFN)-γ-associated gene expression signatures and tumor mutational burden (TMB) as correlates of pathologic response and relapse-free survival, with the combination of high IFN-γ signature and high TMB associated with a 100% pathologic response rate.[20,21] Biomarker data from more recent trials remain comparatively limited: correlative studies in SWOG S1801 were announced alongside the primary results but have not yet been reported in mature form, while NADINA's first biomarker analysis presented alongside its 2-year update similarly identified TMB, PD-L1 expression and IFN-γ signature as associated with improved EFS, with combined high-biomarker subgroups reaching close to 100% EFS at 24 months. These findings are broadly consistent with the OpACIN/OpACIN-neo data but still require longer follow-up and prospective validation before they can inform clinical decision-making. Taken together, increasing evidence supports IFN-γ-associated immune activity as a broader predictor of response and outcome in melanoma immunotherapy.[22,23]

Therefore, the consistent association between pathologic response and outcomes, long-term validation of this surrogate endpoint and

the prospective identification of optimal response cutoffs to guide treatment decisions remain an unmet need. Although response-adapted strategies are supported by emerging prospective and randomized data, caution should be exercised before their routine incorporation into standard clinical practice across different scenarios and they should still be considered, at least in part, hypothesis-generating.[15,17,24]

The unresolved challenge of adjuvant therapy selection after neoadjuvant treatment

Despite growing adoption of neoadjuvant strategies, optimal post-neoadjuvant management remains uncertain. While pCR is consistently associated with excellent outcomes and may support complete treatment de-escalation following surgery, translating intermediate pathologic responses into adjuvant treatment decisions remains challenging.

Patients achieving pCR demonstrate 2-year EFS exceeding 90% even in the absence of additional therapy. In the NADINA trial, patients with MPR who omitted adjuvant therapy had outcomes comparable to those with pCR, with estimated 24-month RFS rates exceeding 90% in both groups. Reported MPR rates of approximately 53% in SWOG S1801 and 59% in NADINA have been interpreted as suggesting greater neoadjuvant efficacy with combination immunotherapy.[11,16] However, direct comparisons between these trials are limited by fundamental differences in study design and post-neoadjuvant management. While SWOG S1801 administered adjuvant pembrolizumab irrespective of pathologic response, NADINA employed a response-adapted strategy incorporating *BRAF*-directed therapy in selected patients.[10,17] These differences in post-neoadjuvant treatment strategies may influence long-term outcomes, although they do not affect the initial assessment of pathologic response. These findings support the strong prognostic value of pathologic response, although uncertainty remains regarding the optimal management of patients with residual disease beyond the 0% threshold. Indirect, cross-trial comparisons with SWOG S1801, in which all patients received adjuvant immunotherapy, raise the hypothesis that continuation of systemic therapy may improve outcomes in selected subgroups. However, such comparisons are inherently unadjusted and should be interpreted with caution.[16,17]

Uncertainty is greatest among patients with residual disease within the non-MPR spectrum, a biologically heterogeneous group often under-represented in binary pCR versus non-pCR frameworks. In the PRADO trial, patients with pNR who did not receive adjuvant therapy experienced markedly inferior outcomes, with 24-month RFS around 33%, compared with approximately 71% for nivolumab and up to 90% for dabrafenib plus trametinib, suggesting that omission of adjuvant treatment in this subgroup may be inadequate. Moreover, exploratory analyses demonstrated heterogeneous outcomes between adjuvant strategies, without consistent evidence favoring immunotherapy over targeted therapy. Similarly, in the NADINA trial, non-MPR patients showed numerically improved RFS with dabrafenib plus trametinib compared with nivolumab (approximately 67% versus 38% at 24 months). However, treatment allocation was determined by *BRAF* mutation status rather than randomization, and the trial was not designed to compare the efficacy of adjuvant nivolumab with dabrafenib plus trametinib. Consequently, these findings should be interpreted as exploratory and hypothesis-generating. Across studies, outcomes in these subgroups remain inferior to those observed in patients achieving pCR, underscoring an on-going unmet need and suggesting that protocol-driven approaches may fail to capture underlying biological heterogeneity, with a potential risk of undertreatment.[10,15,17]

Overall, although pathologic response provides valuable prognostic information, its direct translation into fixed adjuvant treatment algorithms remains premature. Prospective validation is required to define both optimal response thresholds and tailored post-neoadjuvant treatment strategies. Until such data are available, response-adapted approaches should be interpreted cautiously and considered, at least in part, hypothesis-generating. On-going prospective studies, including MSLT-3, are expected to provide further evidence to validate response-adapted postoperative strategies and refine patient selection for treatment de-escalation.[25]

Conclusion

Neoadjuvant therapy is increasingly incorporated into the management of high-risk, resectable stage III melanoma with clinically detectable nodal disease. The integration of pathologic response into postoperative decision-making represents a meaningful step toward personalized treatment strategies. However, important uncertainties remain regarding optimal adjuvant therapy selection, the management of residual disease and the choice between immunotherapy and targeted therapy. Addressing these challenges will require prospective, response-stratified trials to optimize long-term outcomes. Overall, pathologic response is best established as a patient-level prognostic marker, whereas its role as a validated trial-level surrogate for OS in melanoma remains unproven. ❑

1. Keung EZ, Gershenwald JE. The eighth edition American Joint Committee on Cancer (AJCC) melanoma staging system: Implications for melanoma treatment and care. *Expert Rev Anticancer Ther*. 2018;18:775–84. DOI: 10.1080/14737140.2018.1489246.
2. Eggermont AMM, Chiarion-Sileni V, Grob J-J, et al. Prolonged survival in stage III melanoma with ipilimumab adjuvant therapy. *N Engl J Med*. 2016;375:1845–55. DOI: 10.1056/NEJMoa1611299.
3. Helvind NM, Brinch-Møller Weitemeyer M, Chakera AH, et al. Stage-specific risk of recurrence and death from melanoma in Denmark, 2008-2021: A national observational cohort study of 25 720 patients with stage IA to IV melanoma. *JAMA Dermatol*. 2023;159:1213–22. DOI: 10.1001/jamadermatol.2023.3256.
4. Weber J, Mandala M, Del Vecchio M, et al. Adjuvant nivolumab versus ipilimumab in resected stage III or IV melanoma. *N Engl J Med*. 2017;377:1824–35. DOI: 10.1056/NEJMoa1709030.
5. Long GV, Hauschild A, Santinami M, et al. Final results for adjuvant dabrafenib plus trametinib in stage III melanoma. *N Engl J Med*. 2024;391:1709–20. DOI: 10.1056/NEJMoa2404139.
6. Eggermont AMM, Blank CU, Mandala M, et al. Adjuvant pembrolizumab versus placebo in resected stage III melanoma. *N Engl J Med*. 2018;378:1789–801. DOI: 10.1056/NEJMoa1802357.
7. Lo V, Francescutti V, McWhirter E, et al. Recurrent disease in patients with stage III melanoma in the era of adjuvant immune and targeted therapy. *J Clin Oncol*. 2021;39 (Suppl_15):e21570. DOI: 10.1200/JCO.2021.39.15_suppl.e21570.
8. Lucas MW, Menzies AM, Dimitriadis P, et al. Two-year clinical update and first biomarker analyses of the phase III NADINA trial comparing neoadjuvant nivolumab plus ipilimumab versus adjuvant nivolumab in resectable stage III melanoma. 2025 ESMO Congress; 2025. Berlin, GermanyOctober 17–25, 2025Abstr LBA57.
9. Amaria RN, Reddy SM, Tawbi HA, et al. Neoadjuvant immune checkpoint blockade in high-risk resectable melanoma. *Nat Med*. 2018;24:1649–54. DOI: 10.1038/s41591-018-0197-1.
10. Blank CU, Lucas MW, Scolyer RA, et al. Neoadjuvant nivolumab and ipilimumab in resectable stage III melanoma. *N Engl J Med*. 2024;391:1696–708. DOI: 10.1056/NEJMoa2402604.
11. Sugiyama K, Gordon A, Popat S, et al. Is pathological response an adequate surrogate marker for survival in neoadjuvant therapy with immune checkpoint inhibitors? *ESMO Open*. 2025;10:104122. DOI: 10.1016/j.esmoop.2024.104122.
12. Huang Y-C, Hsu SPC, Chiang K-W, Wang M-C. Cochlear obliteration after translabyrinthine resection for large cerebellopontine angle tumor. *Audiol Neurootol*. 2023;28:63–74. DOI: 10.1159/000524820.
13. Lee JH, Long GV, Boyd S, et al. Circulating tumour DNA predicts response to anti-PD1 antibodies in metastatic melanoma. *Ann Oncol*. 2017;28:1130–6. DOI: 10.1093/annonc/mdx026.
14. Versluis JM, Menzies AM, Sikorska K, et al. Survival update of neoadjuvant ipilimumab plus nivolumab in macroscopic stage III melanoma in the OpACIN and OpACIN-neo trials. *Ann Oncol*. 2023;34:420–30. DOI: 10.1016/j.annonc.2023.01.004.
15. Reijers ILM, Menzies AM, van Akkooi ACJ, et al. Personalized response-directed surgery and adjuvant therapy after neoadjuvant ipilimumab and nivolumab in high-risk stage III melanoma: The PRADO trial. *Nat Med*. 2022;28:1178–88. DOI: 10.1038/s41591-022-01851-x.
16. Patel SP, Othus M, Chen Y, et al. Neoadjuvant-adjuvant or adjuvant-only pembrolizumab in advanced melanoma. *N Engl J Med*. 2023;388:813–23. DOI: 10.1056/NEJMoa2211437.
17. Long GV, Blank CU, Amaria RN, et al. LBA41 long-term survival with neoadjuvant therapy in melanoma: Updated pooled analysis from the International Neoadjuvant Melanoma Consortium (INMC). *Ann Oncol*. 2024;35:S1232. DOI: 10.1016/j.annonc.2024.08.2282.
18. Forde PM, Spicer J, Lu S, et al. Neoadjuvant nivolumab plus chemotherapy in resectable lung cancer. *N Engl J Med*. 2022;386:1973–85. DOI: 10.1056/NEJMoa2202170.

19. Wakelee H, Liberman M, Kato T, et al. Perioperative pembrolizumab for early-stage non-small-cell lung cancer. *N Engl J Med*. 2023;389:491–503. DOI: 10.1056/NEJMoa2302983.
20. Huang AC, Orlowski RJ, Xu X, et al. A single dose of neoadjuvant PD-1 blockade predicts clinical outcomes in resectable melanoma. *Nat Med*. 2019;25:454–61. DOI: 10.1038/s41591-019-0357-y.
21. Blank CU, Rozeman EA, Fanchi LF, et al. Interferon-gamma signature as prognostic and predictive marker in macroscopic stage III melanoma. *Nat Med*. 2018;24:965–72. DOI: 10.1038/s41591-018-0198-0.
22. Lucas MW, Menzies AM, Dimitriadis P, et al. LBA57 Two-year clinical update and first biomarker analyses of the phase III NADINA trial comparing neoadjuvant nivolumab plus ipilimumab versus adjuvant nivolumab in resectable stage III melanoma. Ann Oncol. 2025;36:S1600–1. DOI: 10.1016/j.annonc.2025.09.069.
23. Hoeijmakers LL, Dimitriadis P, Wijnen S, et al. Neoadjuvant ipilimumab plus nivolumab in melanoma: 5-year survival and biomarker analysis from the phase 2 PRADO-trial. *Nat Med*. 2026;32:952–63. DOI: 10.1038/s41591-025-04158-9.
24. Menzies AM, Amaria RN, Rozeman EA, et al. Pathological response and survival with neoadjuvant therapy in melanoma: A pooled analysis from the international Neoadjuvant Melanoma Consortium (INMC). *Nat Med*. 2021;27:301–9. DOI: 10.1038/s41591-020-01188-3.
25. ClinicalTrials.gov. The Multicentre Selective Lymphadenectomy Trial - 3 (MSLT-3). ClinicalTrials.gov identifier: NCT07049276. Available at: https://clinicaltrials.gov/study/NCT07049276 (accessed: 12 August 2026).