MELANOMA IN FOCUS

Current Developments in Melanoma

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Neoadjuvant Therapy in Melanoma: A New Standard of Care

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H&O How do you define neoadjuvant therapy in melanoma?

NK In true neoadjuvant therapy, a defined dose and schedule of preoperative therapy are given with the clear intent that surgery will follow. Sometimes, we administer preoperative therapy to a patient who has an unresectable or potentially borderline resectable tumor with the idea that the tumor might become resectable. That is not true neoadjuvant therapy; rather, it is management of an unresectable tumor. This is an important distinction because people often use the term *neoadjuvant* in different contexts. All the prospective studies of neoadjuvant therapy in resectable melanoma refer to patients who normally would have undergone surgery first, before further treatment.

H&O What key factors have driven the shift toward neoadjuvant therapy as a new standard of care in melanoma?

NK Resected *high-risk* melanoma is defined as either resectable node-positive (microscopic or macroscopic) melanoma or resectable stage IIB/C melanoma (node-negative) and even stage IV melanoma if resectable. The standard of care for these patients was consideration of adjuvant anti–programmed death 1 (anti–PD-1) monotherapy with either pembrolizumab (Keytruda, Merck) or nivolumab (Opdivo, Bristol Myers Squibb), or if the patient had stage III disease with the *BRAF* V600 mutation, in that case we could alternatively use a combination of dabrafenib (Tafinlar, Novartis) plus trametinib (Mekinist, Novartis) for 1 year. Despite this approach, many patients experienced relapse despite 1 year of adjuvant treatment.

That was why the CheckMate 238 study, which randomized patients to adjuvant therapy with nivolumab or ipilimumab (Yervoy, Bristol Myers Squibb), was so pivotal.[1] The recurrence-free survival rate, which was the primary endpoint in this study, was significantly higher at 5 years with nivolumab than with ipilimumab, at 50% vs 39%, respectively. Distant metastasis-free survival also was superior with nivolumab. Overall survivorship, however, was no different in the 2 groups, and 50% of patients still experienced relapse or mortality. So clearly, adjuvant immunotherapy was not curing everyone. Furthermore, we were relegating patients to 12 months of therapy without knowing the optimal duration of treatment.

Fortunately, 2 large clinical trials that were published in the *New England Journal of Medicine*, SWOG S1801 and NADINA,[2,3] clearly showed that neoadjuvant therapy with immune checkpoint inhibition was superior to adjuvant therapy for appropriately selected patients with high-risk resectable melanoma. As a result, neoadjuvant therapy is the current de facto standard of care for patients with melanoma who are appropriate candidates.

S1801 asked a very simple question: for patients who have stage III melanoma with evidence of macroscopic nodal metastases, can we move 3 of the 18 doses of pembrolizumab normally administered postoperatively to the preoperative setting? A total of 313 patients with clinically detectable stage IIIB to IVC melanoma that was considered amenable to surgical resection were randomly

assigned either to 3 doses of neoadjuvant pembrolizumab, surgery, and 15 doses of adjuvant pembrolizumab or to surgery followed by pembrolizumab for approximately 1 year. This trial clearly demonstrated superior 2-year landmark event-free survival with neoadjuvant/adjuvant therapy (72%) vs adjuvant therapy (49%).

In the NADINA study, 423 patients with resectable stage III melanoma were randomly assigned either to neoadjuvant ipilimumab plus nivolumab at fixed doses for two 3-week cycles or to adjuvant nivolumab. If a patient in the neoadjuvant therapy group had a pathologic complete response or a major pathologic response after surgery, no further therapy was given. If the patient had residual disease conforming to a pathologic partial response or nonresponse, nivolumab alone was given for the balance of 1 year of treatment if the patient's tumor was *BRAF* V600–wild type, and targeted therapy with dabrafenib and trametinib was given for 46 weeks if the patient's tumor harbored the *BRAF* V600E or V600K mutation. This trial clearly demonstrated superiority of the neoadjuvant approach for event-free survival, and we now are seeing longer-term results and follow-up from this trial.

H&O What other recent studies have affected our understanding of neoadjuvant therapy in melanoma?

NK A small study from MD Anderson and Memorial Sloan Kettering Cancer Center looked at the use of neoadjuvant nivolumab plus the anti-LAG3 agent relatlimab (Opdualag, Bristol Myers Squibb). This 30-patient trial demonstrated the safety and efficacy of 2 cycles of neoadjuvant nivolumab/relatlimab followed by surgery and additional postoperative therapy. In updated 4-year results, 95% of the patients who had a pathologic complete response or major pathologic response remained event-free.[4] In addition, an elegant biomarker analysis highlighted which patients were most likely to respond and which were most likely to become resistant to immunotherapy. These results clearly need validation in larger studies, but they help to shape how we evaluate neoadjuvant therapy as a standard of care.

We also saw results from several small phase 2 studies presented at the 2025 American Society of Clinical Oncology (ASCO) Annual Meeting that looked at various combination regimens of neoadjuvant therapy in melanoma, including CAP O3-NEO,[5] NeoACTIVATE,[6] NEO-MEL-T,[7] and EA6194.[8]

CAP O3-NEO is examining the use of a neoadjuvant triplet regimen for resectable stage II/III acral melanoma. Acral melanoma does not typically have a high tumor mutational burden or an activating mutation in *BRAF*, and it tends not to respond well to single-agent or dual immune checkpoint inhibition in the metastatic setting. The investigators chose a triplet regimen for this study that had already been shown to produce a high response rate in metastatic disease: the anti–PD-1 agent camrelizumab (Elevar Therapeutics), the oral anti–vascular endothelial growth factor drug apatinib, and the traditional alkylating chemotherapy agent temozolomide (Temodar, Merck). In the first part of their 2-part study, which reported on 30 patients, the major pathologic response rate was 43% and the 12-month median event-free survival rate was 77.6%, which are very impressive results in this population. Stage 2 of this trial is expanding the number of patients, and further data are awaited. Not all histologic subtypes require the same treatment, however. Importantly, the SWOG S1512 trial has shown that desmoplastic melanoma has an extraordinarily high rate of response to anti–PD-1 monotherapy with pembrolizumab, so that it behooves us to think about whether surgery is even needed in patients with this histology after an excellent clinical and radiographic response to systemic therapy.[9]

NeoACTIVATE is evaluating neoadjuvant therapy with atezolizumab (Tecentriq, Genentech) plus the anti–T-cell immunoglobulin and ITIM domain (anti-TIGIT) agent tiragolumab in 34 patients with resectable stage III melanoma. At a median follow-up of 19.9 months after registration, the rate of major pathologic response was 47.1%.

NEO-MEL-T is looking at the use of neoadjuvant dostarlimab (Jemperli, GSK) vs dostarlimab plus the anti-TIM3 agent cobolimab in 57 patients with stage III cutaneous melanoma. A primary analysis at a median follow-up of 22 months showed a numerically higher estimated 1-year relapse-free survival rate among those randomized to dostarlimab/cobolimab than among those randomized to dostarlimab alone, at 87% vs 82%. The rates of major pathologic response were 55.6% and 33.3%, respectively, with the latter in line with what we see with pembrolizumab monotherapy.

The ECOG-ACRIN EA6194 trial examined pembrolizumab alone vs pembrolizumab plus the intratumorally administered TLR9 agonist vidutolimod in patients with resectable stage III melanoma. At a median follow-up of 19 months after enrollment, a trend toward a higher estimated 1-year event-free survival rate was noted among those randomized to pembrolizumab/vidutolimod vs those randomized to pembrolizumab alone, at 89% vs 75%. The rates of major pathologic response were 79% and 59%, respectively.

As intriguing as these results are, validation in larger studies is required before they have the potential to change practice. The numbers of patients are not anywhere near what we see with SWOG S1801 and NADINA. I would

like to see studies comparing some of these newer combination regimens with ipilimumab/nivolumab, or with single-agent PD-1 inhibition.

H&O What makes neoadjuvant therapy more effective than adjuvant therapy?

NK We have very elegant preclinical data from murine models in breast cancer showing that the removal of cancerous tumors interferes with the body's production of T cells against those tumors, making the use of immune checkpoint inhibitors less effective in the adjuvant setting. Checkpoint inhibition can effectively counteract the immunosuppressive environment if the tumor is kept intact, leading to T-cell proliferation. This theory was initially tested in small clinical trials such as the OpACIN-neo study[10] of neoadjuvant ipilimumab plus nivolumab, before the larger SWOG S1801 and NADINA trials were conducted, which together clearly established that neoadjuvant therapy is superior to adjuvant therapy for appropriately selected patients with high-risk resectable melanoma.

Neoadjuvant therapy also has the benefit of helping us adapt our postoperative treatment. If a patient receives 6 to 9 weeks of neoadjuvant therapy and achieves a complete or major pathologic response at surgery, treatment can be halted. That means we have gone from 12 months of adjuvant treatment to potentially less than 3 months of neoadjuvant treatment, which is clearly better for the patient. It would be entirely appropriate to perform a pharmacoeconomic analysis of these approaches as the next step.

H&O How do physicians define an optimal pathologic response to neoadjuvant therapy, and why is this endpoint clinically meaningful?

NK Defining each endpoint is important, and the International Neoadjuvant Melanoma Consortium (INMC) made a concerted effort to describe the variations of pathologic response following neoadjuvant therapy.[11] Absolutely no viable tumor is present in the resection specimen in a pathologic complete response, no more than 10% of viable tumor is present in the resection specimen in a major pathologic response, and from more than 10% up to 50% of viable tumor is present in the resection specimen in a pathologic partial response.[12] If the resection specimen has more than 50% viable tumor, this is considered a pathologic nonresponse. These definitions need to be strongly highlighted across the pathology community. Communication between the surgeon and the pathologist is essential to ensure that the pathologist is aware when a specimen is from a patient treated with neoadjuvant therapy, so that appropriate guidelines for specimen processing can be followed.[11]

Pathologic complete response and major pathologic response clearly appear to correlate with longer-term outcome. An analysis of 818 patients with stage IIIB or higher melanoma from the INMC retrospective database,[12] which is collated from multiple centers around the world, found that the relapse-free survival rate at 3 years was 88% for patients who achieved a pathologic complete response and 89% for those who achieved a major pathologic response. The rates dropped to 68% for those who with a pathologic partial response and 40% for pathologic nonresponders. These numbers tell us that pathologic complete responses are useful in risk stratification, but they are not the be-all and end-all because a small number of patients who achieve a pathologic complete response do indeed still experience relapse. It is our job to understand better who those patients are and why that relapse is occurring.

H&O Which patients with melanoma are ideal candidates to undergo neoadjuvant therapy rather than proceed directly to surgery?

NK Ideal candidates for neoadjuvant therapy are those with resectable macroscopic nodal disease that is confirmed on biopsy to be metastatic melanoma, in addition to those who have resectable in-transit disease and no contraindication to immune checkpoint inhibitor therapy. This approach would also be appropriate for selected patients with resectable oligometastatic disease, but preferably with multidisciplinary input into management. Surgical oncologists and general surgeons, who often see these patients first in the community, should be educated to know that if they identify a patient with a history of melanoma who now has a palpable node in the regional nodal basin, they should *not* proceed directly to an excision or total lymph node dissection, as they did in the past. Instead, these patients should undergo image-guided bedside biopsy to confirm the diagnosis and molecular testing should be obtained if not done previously, plus cross-sectional imaging to ensure the absence of distant spread. If the disease is indeed regional and resectable, these are the patients who should be offered neoadjuvant therapy.

Contraindications to immunotherapy include solid organ transplant and active autoimmune disease requiring biologic therapy, so upfront surgery may be more appropriate for these patients. In addition, all these patients should have their tumors tested for an actionable *BRAF* mutation because neoadjuvant BRAF plus MEK inhibition can be used for patients with an actionable *BRAF* V600 mutation who are not candidates for immunotherapy. A large group of patients for whom we do

not yet know the optimal treatment are those who are receiving adjuvant anti–PD-1 monotherapy for previous microscopic nodal disease and experience regional nodal or in-transit relapse while undergoing adjuvant therapy or shortly thereafter. Should these patients be escalated to combination immunotherapy right away and then receive surgery? Or should they receive surgery first and additional adjuvant therapy then be considered? This is an important clinical question that requires prospective investigation.

H&O What safety considerations are critical when immunotherapy is administered before definitive surgery?

NK It is important to know about the adverse effects of immunotherapy. We know that combination immunotherapy is more toxic than single-agent immunotherapy, so that patients may not complete the entire course of therapy. Immune-related toxicity and the possible use of steroids and other immunosuppressive therapy may delay the planned surgical intervention. One adverse event of special importance in neoadjuvant therapy is adrenal insufficiency, which can be overlooked when it is subclinical. When these patients go on to surgery, the stress of surgery can unmask subclinical adrenal insufficiency and cause them to become symptomatic. In my practice, all patients who are undergoing neoadjuvant therapy receive a laboratory check of their adrenal axis (serum cortisol and serum adrenocorticotropic hormone [ACTH]) at baseline and again before surgery. If uncertainty remains regarding the diagnosis with these data, we pursue cosyntropin stimulation testing as well.

H&O What questions remain to be answered regarding neoadjuvant therapy and melanoma?

NK First, we want to learn the optimal regimen and duration of treatment. We have a couple of standard-of-care regimens right now, but can we improve on them? Second, we want to learn the optimal postoperative treatment if the patient has a poor response to neoadjuvant therapy. Is it worth continuing the same drug or drugs postoperatively for those who are nonresponders? How can we incorporate biomarkers to determine in advance whether a particular treatment will work (or not)? Third, we want to learn how to incorporate these biomarkers, including circulating tumor DNA, to predict which patients may experience relapses. Fourth, we want to understand the contribution of specific components to combination therapy. This means standardizing the designs of neoadjuvant trials, including the use of pathologic complete response as a surrogate endpoint for long-term outcome. Finally, we want to identify noninvasive ways to de-escalate therapy when possible. For example, some patients might be able to forego surgery if a biomarker were able to tell us whether they experienced an adequate response to neoadjuvant therapy.

Disclosures

Dr Khushalani has served as a consultant for or on the advisory board of Bristol Myers Squibb, Castle Biosciences, Delcath Systems, Immunocore, Instil Bio, IO Biotech, Iovance Biotherapeutics, Merck, Mural Oncology, MyCareGorithm, Nektar Therapeutics, Novartis, Regeneron Pharmaceuticals, Replimune Group, Sun Pharma, and T-knife Therapeutics; has received research funding (all to Institute) from Bristol Myers Squibb, Merck, Celgene, GSK, HUYABIO International, Replimune, Regeneron, Novartis, IDEAYA Biosciences, and Modulation Therapeutics; has common stock in Asensus Surgical and Bellicum Pharmaceuticals; has served on the data and safety monitoring board for AstraZeneca and Incyte; and has received travel support from Castle Biosciences and Regeneron.

References

1. Larkin J, Del Vecchio M, Mandalá M, et al. Adjuvant nivolumab versus ipilimumab in resected stage III/IV melanoma: 5-year efficacy and biomarker results from CheckMate 238. *Clin Cancer Res*. 2023;29(17):3352-3361.
2. Patel SP, Othus M, Chen Y, et al. Neoadjuvant-adjuvant or adjuvant-only pembrolizumab in advanced melanoma. *N Engl J Med*. 2023;388(9):813-823.
3. Blank CU, Lucas MW, Scolyer RA, et al. Neoadjuvant nivolumab and ipilimumab in resectable stage III melanoma. *N Engl J Med*. 2024;391(18):1696-1708.
4. Burton EM, Milton DR, Tetzlaff MT, et al. Long-term survival and biomarker analysis evaluating neoadjuvant plus adjuvant relatlimab (anti-LAG3) and nivolumab (anti-PD1) in patients with resectable melanoma [published online July 10, 2025]. *J Clin Oncol*. doi:10.1200/JCO-25-00494.
5. Mao L, Li C, Dai J, et al. Neoadjuvant camrelizumab plus apatinib and temozolomide for resectable stage II/III acral melanoma: the CAP 03-NEO trial [ASCO abstract 9512]. *J Clin Oncol*. 2025;43(16)(suppl).
6. Hieken TJ, Zahrieh D, Flotte TK, et al. NeoACTIVATE arm C: phase II trial of neoadjuvant atezolizumab and tiragolumab for high-risk operable stage III melanoma [ASCO abstract 9503]. *J Clin Oncol*. 2025;43(16)(suppl).
7. Mooradian M, Karunamurthy A, Wang H, et al. Randomized phase II study of neoadjuvant (neoadj) anti-PD-1 dostarlimab (D) vs. D + anti-TIM-3 cobolimab (C) in high-risk resectable melanoma (mel) (NEO-MEL-T): primary analysis [ASCO abstract LBA9504]. *J Clin Oncol*. 2025;43(17)(suppl).
8. Tarhini A, Lee S, Davar D, et al. A phase II randomized study of neoadjuvant pembrolizumab (P) alone or in combination with vidutolimod (V) in high-risk resectable melanoma: ECOG-ACRIN EA6194 [ASCO abstract LBA9505]. *J Clin Oncol*. 2025;43(suppl)(17).
9. Kendra KL, Moon J, Eroglu Z, et al. Neoadjuvant PD-1 blockade in patients with resectable desmoplastic melanoma (SWOG 1512) [ASCO abstract 9502]. *J Clin Oncol*. 2022;40(16)(suppl).
10. 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(4):420-430.
11. Tetzlaff MT, Messina JL, Stein JE, et al. Pathological assessment of resection specimens after neoadjuvant therapy for metastatic melanoma. *Ann Oncol*. 2018;29(8):1861-1868.
12. Long GV, Blank CU, Amaria RN, et al. Long-term survival with neoadjuvant therapy in melanoma: updated pooled analysis from the International Neoadjuvant Melanoma Consortium (INMC) [ESMO abstract LBA41]. *Ann Oncol*. 2024;35(2)(suppl).