Neoadjuvant Therapy for Melanoma: New and Evolving Concepts

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Abstract: Effective systemic therapies, including targeted BRAF/MEK inhibition and immune checkpoint blockade, have significantly changed the treatment landscape for malignant melanoma. Specifically, there have been promising clinical trial findings associated with the use of neoadjuvant therapy for clinically node-positive and oligometastatic disease, conditions that have historically been managed with up-front surgical resection when possible. This review focuses on the burgeoning field of neoadjuvant therapy for melanoma. We review the rationale for this treatment approach, summarize completed and ongoing neoadjuvant clinical trials, and contextualize these findings within the growing body of knowledge about targeted and immune checkpoint therapy. Finally, we discuss future directions for neoadjuvant trials in melanoma, with particular focus on biomarker development, treatment effect modification, novel therapeutic regimens, and evolving surgical indications for regional and oligometastatic disease.

Introduction

Effective targeted BRAF/MEK inhibitors and immune checkpoint blockers have led to improved survival outcomes in malignant melanoma that are unprecedented in the history of modern cancer therapy.[1,2] These medications were initially studied in metastatic disease and as adjuvant therapy, in both cases with promising results, and their use in the neoadjuvant context is now an expanding field of investigation.[3] This review focuses on neoadjuvant therapy for melanoma and includes the rationale for this treatment approach, a summary of translational and clinical trial findings, and a discussion of future directions for treatment strategies.

Rationale for Neoadjuvant Therapy

A neoadjuvant approach to systemic therapy has multiple theoretical advantages, particularly in the case of immune-modulating treatments.[4] From a surgical perspective, neoadjuvant therapies have

Table 1. Neoadjuvant Therapy in Context

Advantages	Disadvantages
• Tumor downstaging: increase resectability, negative margins • Immunologic priming: presence of tumor biomass may increase the likelihood of neoantigen detection and a response to immuno-oncology • Biological assessment: pathologic response to therapy, surrogate endpoint • Inform prognosis, guide adjuvant therapy • Mitigate surgical intervention • Study novel drugs, mechanisms of resistance, development of biomarkers	• Potential delay in standard-of-care surgery • Risk for disease progression to unresectable state • Possibility that treatment toxicity will affect surgical resection and outcomes

the potential to downstage unresectable disease and allow operative resection to be undertaken with a curative intent. Furthermore, preoperative therapy may improve the rate of microscopically margin-negative (R0) resection, as has been shown in certain gastrointestinal epithelial malignancies.[5] Systemic immunotherapy and targeted BRAF/MEK inhibition may be more effective in the neoadjuvant than in the adjuvant setting. For both types of treatment, it is thought that the presence of tumor biomass may increase the probability of immunologic activation against tumor neoantigens.[6] Finally, a neoadjuvant approach has the unique advantage of allowing for biologic response assessment to treatment.[7] The evaluation of tissue after treatment provides a plethora of valuable information that can inform prognosis, decision making regarding additional therapy, and scientific discovery by providing information about the cellular and molecular effects of therapy on the tumor microenvironment (TME).[8] Thus, the neoadjuvant treatment approach is useful for evaluating the efficacy of treatment, ascertaining mechanisms of disease resistance, and developing biomarkers.

Despite these numerous potential advantages, theoretical downsides to neoadjuvant therapy remain. First, this approach inevitably delays the time to surgical resection, which is the current standard of care and the primary curative modality, and it carries the risk that the disease of some patients will progress and become unresectable.[9] Both targeted therapy and checkpoint blockade are associated with distinct and sometimes severe toxicities that theoretically could delay surgery, preclude surgery altogether, or complicate the surgical course owing to complications from drug toxicities. The theoretical advantages and disadvantages of neoadjuvant therapy are summarized in Table 1.

Neoadjuvant Clinical Trials Investigating BRAF/MEK Combined Inhibition

The discovery of recurrent somatic driver mutations in cancer has led to the development of highly effective targeted therapies. In melanoma, activating mutations in *BRAF* V600 are present in approximately 50% of patients.[10] The *BRAF* gene encodes human B-Raf, a serine/threonine kinase that functions downstream of the Ras proto-oncogene. Mutated B-Raf inappropriately phosphorylates, and thereby activates, downstream kinases—including MAPK/ERK—thereby leading to inappropriate signaling through proliferative and anti-apoptotic gene expression programs.[11] Initial forays into single-agent, targeted inhibition of B-Raf with vemurafenib (Zelboraf, Genentech/Daiichi Sankyo) and dabrafenib (Tafinlar, Novartis) in patients with *BRAF*-mutated metastatic melanoma demonstrated improved survival, but progression frequently occurred after several months through MAPK reactivation.[12,13] It was subsequently observed that combination inhibition of BRAF and MEK partially addressed issues of MAPK reactivation, resulting in more durable responses.[14,15]

On the basis of promising findings in metastatic disease, Amaria and colleagues performed a single-center, open-label, randomized phase 2 trial in which patients with surgically resectable clinical stage III or oligometastatic stage IV *BRAF*-mutated melanoma were randomly assigned to up-front surgery (the standard of care) with consideration of adjuvant therapy or to perioperative dabrafenib and trametinib (Mekinist, Novartis).[16] In this trial, 7 patients were assigned to standard of care and 14 patients to neoadjuvant therapy. The trial was stopped early owing to significantly longer event-free survival (EFS) in the neoadjuvant therapy group (median EFS, 19.7 vs 2.9 months; hazard ratio [HR], 0.016; *P*<.0001).

Shortly thereafter, the findings from the NeoCombi study were published.[17] This was a single-arm, open-label, phase 2 study in which patients with stage IIIB or IIIC *BRAF*-mutated melanoma were treated with perioperative dabrafenib plus trametinib and surgical resection. Of the 35 patients enrolled, a pathologic response was observed in 100%, and 17 (49%) had a pathologic complete

response (pCR). No progression occurred during the 12 weeks of neoadjuvant therapy. The 2-year relapse-free survival (RFS) rate was 43% for the entire cohort and 63% for the patients who had a pCR. Taken together, the trials conducted by Amaria and colleagues and the NeoCombi study provided evidence for high rates of durable response with neoadjuvant targeted therapy.

Neoadjuvant Clinical Trials Investigating Checkpoint Inhibitor Therapy

It has long been known that a dynamic interaction exists between the immune system and malignant melanoma. Standard-of-care systemic therapies historically included cytokine infusions with interferon alfa (IFN-α) and interleukin 2 (IL-2), both of which were designed to stimulate antitumor immune activation, although often with prohibitive inflammatory side effects. Immune checkpoint blockers had a revolutionary effect in the treatment of melanoma because these medications were highly effective and easy to administer, with side effect profiles that were generally less severe than those for cytokine infusions and adoptive cell therapies.

Checkpoint inhibition was initially studied in advanced melanoma, in which it was demonstrated that survival outcomes with programmed death 1 (PD-1) checkpoint blockade were superior to survival outcomes with cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) inhibition.[2,18] Subsequent adjuvant trials for resectable high-risk melanoma were a natural next step because of a historical precedent for adjuvant therapy with cytokine infusions, and this approach still allowed standard-of-care up-front surgery. Several notable checkpoint blockade trials have been conducted in the adjuvant space. The double-blind phase 3 European Organization for Research and Treatment of Cancer (EORTC) 1325-MG/KEYNOTE-054 trial evaluated adjuvant treatment with the PD-1 inhibitor pembrolizumab (Keytruda, Merck) vs placebo in patients who had stage III melanoma.[19] A total of 1019 patients were treated with complete lymph node dissection followed by randomization to receive pembrolizumab vs placebo for 1 year. The 3-year RFS rate was 63.7% for immunotherapy treatment vs 44.1% for placebo, and the 3.5-year distant metastasis-free survival (DMFS) rate was 65% vs 49%, respectively.[20] KEYNOTE-054 thus provided evidence for a survival benefit with checkpoint blockade vs close observation. CheckMate 238 was another double-blind adjuvant phase 3 trial of resected stages IIIB through IV melanoma that directly compared nivolumab (Opdivo, Bristol Myers Squibb) vs ipilimumab (Yervoy, Bristol Myers Squibb).[21] Recent long-term follow-up has been reported; the 4-year RFS rate was 51.7% for nivolumab vs 41.2% for ipilim-

umab, with no difference in the overall survival (OS) rate (77.9% vs 76.6%, respectively).[22] This trial corroborated the finding that PD-1 inhibition provides a more significant treatment effect than CTLA-4 blockade in advanced melanoma.[18,21,23] More recently, preliminary results from the CheckMate 915 trial were presented at the American Association for Cancer Research (AACR) Annual Meeting 2021.[24] This was an Australian trial with an intent-to-treat design that randomly assigned more than 1800 patients with stage III or IV melanoma to adjuvant ipilimumab plus nivolumab vs nivolumab alone. Unexpectedly, no difference in the 2-year RFS rate was found between the treatment arms (64.6% for combination therapy vs 63.2% for monotherapy).

Given this background, multiple neoadjuvant trials have been implemented and reported during the last 5 years. The phase 1b OpACIN study was a seminal clinical trial that investigated combination checkpoint blockade with ipilimumab and nivolumab in both adjuvant and perioperative contexts.[6] Patients were randomly assigned to either 12 weeks of adjuvant therapy or 6 weeks of neoadjuvant therapy plus 6 weeks of adjuvant therapy. In each arm, 9 of 10 patients experienced grade 3 or 4 toxicities when dosed with ipilimumab at 3 mg/kg and nivolumab at 1 mg/kg.[6] The 4-year EFS rate was 80% for perioperative therapy vs 60% for adjuvant therapy, and the 4-year OS rate was 90% vs 70%, respectively.[25]

Another groundbreaking neoadjuvant trial in melanoma, which was conducted by Amaria and colleagues, was published concomitantly with the OpACIN study findings. In this trial, the authors investigated neoadjuvant PD-1 monotherapy with nivolumab (3 mg/kg) for 4 doses vs combination nivolumab (1 mg/kg) plus ipilimumab (3 mg/kg) for 3 doses in patients who had resectable high-risk melanoma.[9] The trial enrolled 23 patients, with 12 receiving monotherapy and 11 receiving combination therapy. It was stopped early owing to disease progression that precluded subsequent surgery in 2 of the patients receiving nivolumab monotherapy. Combination therapy was associated with a high objective response rate (ORR; 73%) and pCR rate (45%), although the rate of associated toxicity was also high (grade 3 adverse events in 73%). In contrast, nivolumab monotherapy was associated with only a modest ORR (25%) and pCR rate (25%); however, only 8% of patients experienced a grade 3 toxicity. No significant differences were found in survival outcome measures (RFS, DMFS, and OS), although this analysis was limited by small sample sizes. The authors performed extensive translational analyses of tumor samples to identify signatures of response, and they identified a greater quantity of CD8+ tumor infiltrate, increased tumor cell programmed death ligand 1 (PD-L1) expression, and higher levels of lymphoid markers in responders vs

nonresponders. They also identified a higher rate of T-cell clonality in responders, as previously described.[26]

Shortly thereafter, Huang and colleagues investigated the effect of a single dose of pembrolizumab given 3 weeks before surgical resection.[8] In this study, 27 patients with stages IIIB through IV melanoma treated with surgical resection were enrolled, and 8 of the 27 (29.6%) exhibited a major or complete pathologic response after a single dose. The 1-year disease-free survival (DFS) rate was 63%, although no patients with complete/major responses had a recurrence by the study endpoint. Much as in the study by Amaria and colleagues, a greater quantity of CD8+ tumor infiltrate was associated with a better response to checkpoint blockade.

Finally, findings from the OpACIN trial inspired the subsequent OpACIN-neo trial, which was a phase 2b study investigating the optimal dosing of combination ipilimumab plus nivolumab as neoadjuvant therapy for stage III melanoma.[27] In this trial, 86 patients were randomly assigned to 1 of 3 treatment arms with different dosing regimens. The investigators observed that the optimal combination, as evidenced by minimal toxicity and maximal effect, was 2 cycles of ipilimumab at 1 mg/kg plus nivolumab at 3 mg/kg given intravenously once every 3 weeks. Rozeman and colleagues recently published long-term survival data. The overall 2-year RFS rate was 84% for all 3 treatment arms, but it was 97% for patients with an observed pathologic response vs 36% for nonresponders.[25]

Neoadjuvant vs Adjuvant Immunotherapy for Melanoma

It remains unknown whether neoadjuvant therapy is superior to adjuvant therapy, or vice versa. To date, no phase 3 clinical trials comparing these approaches have been completed to provide more clarity on the topic. The ongoing phase 2 S1801 clinical trial from the Southwest Oncology Group (SWOG) is investigating survival outcome measures in patients with resectable stage III or IV melanoma treated with neoadjuvant vs adjuvant pembrolizumab.[28] Results of this head-to-head comparison have not yet been published. Cross-trial comparisons are inherently limited, although cautious interpretation of completed studies does suggest a trend in favor of neoadjuvant therapy. When the clinical trials mentioned earlier are considered together, adjuvant therapy was associated with an RFS rate of approximately 50% to 65% at 2 to 4 years of follow-up. In contrast, neoadjuvant studies provided evidence of more durable responses, with recurrence-free rates ranging from 80% to 84% at 1 to 4 years of follow-up.

It is also interesting to note that inhibition with the combination of CTLA-4 plus PD-1 was shown to provide an additive effect in advanced disease (CheckMate 067) and as neoadjuvant therapy (Amaria and colleagues), but not in the adjuvant context (CheckMate 915). The biologic underpinnings of these differences in treatment efficacy require further investigation, though one noticeable difference is that tumor biomass is present at the time of checkpoint inhibitor treatment for advanced disease and neoadjuvant therapy, unlike for adjuvant treatment. It is conceivable that dual checkpoint blockade may have a greater effect when immunologic exposure to neoantigens is theoretically more plentiful. In support of this argument, it was observed in the OpACIN and OpACIN-neo trials that a greater expansion of tumor-resident T-cell clones occurred with neoadjuvant therapy than with adjuvant therapy.[27]

Biomarkers of Treatment Response Drive the Next Generation of Neoadjuvant Trials

Despite the excitement and promise of checkpoint blockade for the treatment of metastatic melanoma, an objective response to combination therapy is noted in only about half of patients, and even lower response rates are observed with single agents.[2] Multiple efforts are ongoing to better understand the biological determinants of treatment response, and this work may have two pragmatic implications for clinical care. First, improved pretreatment prediction of response would allow more accurate prognostication and could inform management decisions, such as the frequency of surveillance. Second, this work could lead to the development of personalized therapeutic regimens designed to optimize treatment effects.

One important avenue of investigation involves the assessment of pathologic tumor response, which has been shown to correlate with RFS and OS for both targeted inhibition and immunotherapy. Interestingly, the degree of pathologic response, and its association with outcome measures, appears to differ according to treatment type.[29] Among patients treated with neoadjuvant BRAF/MEK inhibition, evidence of a pCR was associated with superior survival outcomes, whereas the outcomes of patients who had a near-complete response or partial response were more like those of nonresponders over time. Conversely, among patients treated with immunotherapy, the outcomes of partial and near-complete responders were similar to those of complete responders, with very few recurrences during the observation period. Although no patients with a pCR to immunotherapy have experienced a recurrence to date, recurrences have been observed among patients who received targeted therapy and similarly had a complete response. These findings indicate that a pathologic response, of any degree, is a more sensitive

marker of durable response for immunotherapy than it is for targeted BRAF/MEK inhibition.

Several studies have investigated the relationship between pathologic response and preoperative clinicopathologic traits in the hope of identifying pretreatment prognostic markers. Menzies and colleagues recently evaluated pathologic response and survival in 192 patients who had stage III melanoma treated with neoadjuvant therapy.[29] No significant associations were observed in the patients treated with BRAF/MEK inhibitors in this study. For immunotherapy, only the treatment regimen—combination vs monotherapy checkpoint blockade—was significant on multivariable analysis. Post hoc analysis of participants in the OpACIN-neo trial support these findings; no association was found between tumor ulceration, size, or PD-1 expression and pathologic response to therapy.[27] These studies capture the current state of knowledge, which is that it remains difficult to predict who will have a good response to neoadjuvant therapy on the basis of pretreatment clinical factors.

Technologic advances, particularly next-generation sequencing, have allowed deeper investigations into the biological determinants of response to neoadjuvant therapy in melanoma. By transcriptomic analysis, interferon gamma (IFN-γ) expression has been shown to correlate with pathologic response to checkpoint blockade. IFN-γ is a cytokine produced by activated T cells, natural killer (NK) cells, and NK T cells that has multiple effects on immune signaling, resulting in an inflammatory state that is critical to the innate immune response.[30] With respect to the TME, INF-γ has been shown to stimulate the expression of human leukocyte antigen proteins, theoretically supporting neoantigen presentation and immune cell recruitment. However, IFN-γ also co-stimulates inhibitory signals, including PD-L1 and PD-L2. This combination of immunologic stimulation and dampening represents a complex interplay that is not fully understood. Nonetheless, the presence of INF-γ signaling has been associated with a reduced risk for relapse, and thus it may have empiric value as a predictor of immunotherapy response.[6] A recent post-treatment analysis of 65 patients from the OpACIN-neo trial confirmed that a high level of IFN-γ gene expression was significantly correlated with a high degree of pathologic response and a low risk for relapse.[25] In this study, the authors observed an association between EFS and tumor mutational burden (TMB). However, no correlation between TMB and IFN-γ expression was observed, although patients who exhibited both high TMB and high IFN-γ signaling had a 100% partial pathologic response rate and zero recurrences at 2 years. Conversely, the presence of both low TMB and low IFN-γ signaling was associated with a 2-year EFS rate of 49%, in comparison with 83% or greater for all other combinations in which at least one biomarker (TMB or IFN-γ expression) was elevated.[25]

Translational discovery of IFN-γ expression in the TME inspired the DONIMI trial, a biomarker-driven, multicenter phase 1b trial evaluating domatinostat, nivolumab, and ipilimumab in IFN-γ signature–low and IFN-γ signature–high stage III melanoma.[31] Domatinostat is a selective class I histone deacetylase inhibitor (HDACi) that is thought to potentially stimulate IFN-γ gene expression. The intention of this trial is to convert pretreatment IFN-γ–low tumors to an IFN-γ–high phenotype to enhance tumor response.

Immune infiltrates are another potential marker of susceptibility to checkpoint blockade. Post-treatment analysis of tumor samples from the OpACIN-neo trial revealed that the quantity of immune cell infiltrate was associated with the degree of pathologic response.[25] In this study, the authors also reported that increased circulating levels of vascular endothelial growth factor receptor 2 (VEGFR2), CX3CL1, and PD-L2 after neoadjuvant therapy were associated with nonresponse. VEGF signaling is thought to have multiple pro-tumor functions, including inhibition of effector T-cell function, abrogation of immune cell trafficking to the TME, suppression of antigen presentation by dendritic cells, and stimulation of myeloid-derived suppressor cells and regulatory T cells.[32-35] Based on these findings, the Neo PeLe trial is a phase 2 study of neoadjuvant pembrolizumab and lenvatinib (Lenvima, Eisai) for stage III melanoma. Lenvatinib is a multiple receptor tyrosine kinase (RTK) inhibitor that selectively inhibits VEGF receptors, including VEGFR2.[36] Similar to the DONIMI trial, the goal of this study is to increase immunotherapy susceptibility among nonresponders.

Effect of the Gut Microbiome

Our understanding of the complex interplay between gut microbiota and the immune system is still in its infancy, but several seminal studies have implicated the microbiome in the response to immune-based therapies. The intestines contain the largest reservoir of lymphocytes in the human body, and continuous communication between bacteria and immune cells, primarily contained in Peyer's patches in the lamina propria of the intestinal wall, influences both local and systemic immune activation states. Alterations in the diversity and abundance of gut bacterial species have been associated with multiple diseases that have immunologic underpinnings, including inflammatory bowel disease, hepatic steatohepatitis, and various types of cancer. In 2015, it was shown in preclinical melanoma models that variation in the quality and quantity of gut bacterial species influences susceptibility

to checkpoint blockade.[37,38] These studies inspired a series of clinical investigations that corroborated such findings in patients who had melanoma treated with immunotherapy.[39-42] In each case, it was found that patterns in the microbiome could be linked to "responder" and "nonresponder" states, although the patterns were variable between studies. It is not fully understood why overlap in microbiome signatures between studies has been limited, although this finding may be partly related to technical considerations such as sequencing pipelines and differences in patient populations.[43]

Nonetheless, the gut microbiome has been identified as a novel target for cancer therapy, as a means both to prevent disease and to modify the effect of immunotherapy. Thus, work is ongoing to identify consortia of bacteria that enhance immune response in the setting of checkpoint blockade. In addition, active clinical trials are investigating interventions and behaviors that influence microbial diversity, including diet, exercise, and the use of antibiotics.[44,45] The delivery of therapeutic microbiota is an area of active investigation, by means such as fecal microbiota transplant and the administration of biotherapeutics comprising one or multiple strains of bacteria. Although obstacles remain, it may become possible in the future to sample the stool of patients with melanoma and contextualize their baseline microbial signature as one indicating immunotherapy responder or nonresponder status. Then, by such means as dietary changes, an "off-the-shelf" biotherapeutic, or fecal transplant, it may be possible to convert patients to responder states before the initiation of checkpoint blockade.

Combination Targeted BRAF/MEK Inhibition Plus Immunotherapy

Although targeted therapy is not mechanistically thought of as an immune-modulating therapy, it has been previously shown in both preclinical animal models and patient samples that targeted BRAF/MEK inhibition is associated with multiple immunologic changes in the TME, the majority of which are immune-activating. These changes include increased expression of antigen-presenting machinery (major histocompatibility complex proteins), increased presentation of immune-stimulating melanocyte differentiation antigens, and infiltration of cytotoxic (CD8+) T cells without a concomitant rise in immune-suppressive cells.[46-48] Given these immunologic changes incurred with targeted therapy, an additive effect might be possible with combined checkpoint blockade.

A precedent for combination BRAF/MEK plus checkpoint blockade can be found in studies of advanced melanoma. In the multicenter, double-blind, phase 2 KEYNOTE-022 clinical trial, patients with metastatic or unresectable BRAF-mutated melanoma were randomly assigned to treatment with dabrafenib and trametinib plus pembrolizumab or placebo.[49,50] The progression-free survival (PFS) rate at 24 months was 41% for combination therapy vs 16% for BRAF/MEK therapy. Median OS was not reached for combination therapy and was 26.3 months for BRAF/MEK therapy.[49] Triplet therapy consisting of pembrolizumab plus targeted BRAF/MEK inhibition was associated with a higher incidence of treatment-related adverse events. The study did not achieve statistical significance for the prespecified primary endpoint of PFS.

A more recent trial was COMBI-I, a placebo-controlled phase 3 clinical trial investigating the anti–PD-1 antibody spartalizumab vs placebo in combination with dabrafenib and trametinib for patients with BRAF-mutated advanced melanoma.[51] The primary endpoint of PFS did not differ between the treatment arms, although some beneficial trends were observed with the addition of anti–PD-1 therapy. The ORR was 68.5% for the spartalizumab arm vs 64.2% for the placebo arm.

Finally, a third study, IMspire150, was a multicenter, double-blind, randomized controlled phase 3 trial investigating the anti–PD-L1 antibody atezolizumab (Tecentriq, Genentech) vs placebo plus cobimetinib (Cotellic, Genentech) and vemurafenib (Zelboraf, Genentech) for advanced and locally unresectable melanoma.[52] The primary endpoint of this study was PFS, which was found to be significantly increased by investigator assessment with combination checkpoint and BRAF/MEK therapy (15.1 vs 10.6 months; P=.025). No difference in OS was observed with limited-duration follow-up.

In summary, it remains to be determined whether the combination of immune checkpoint blockade plus BRAF/MEK inhibition provides a survival advantage. As more checkpoint inhibitors and targeted therapies are developed, identifying the optimal combinations and dosing regimens remains an area of active investigation, particularly given the high toxicity profile of combination therapy. Further investigation of this therapeutic strategy in the neoadjuvant space is required to determine its potential benefit.

Evolving Indications for Surgical Intervention With Neoadjuvant Therapy

The advent of highly effective neoadjuvant therapies comes with new questions about the role of surgery for locally advanced and metastatic disease. With regard to regional nodal disease, the DeCOG-SLT trial from Germany and the MSLT-II trial provided supporting evidence for observation rather than therapeutic lymph node dissection in clinically node-negative, sentinel

Table 2. Future Directions of Neoadjuvant Trials

Redefining Surgical Indications	• Mitigating unnecessary lymphadenectomy in neoadjuvant responders (PRADO trial)[55] • Downstaging unresectable disease (REDUCTOR trial)[56]
Optimizing Treatment Response	• Stimulating responder transcriptomic signature (IFN-γ–high) with HDACi and IFN therapy[31,57] • Stimulating responder gut microbiome signature with diet, FMT, biotherapeutics[44,45] • Abrogating nonresponder signature (circulating VEGF2) with anti-VEGF therapy[36]
Assessing Novel Treatment Combinations	• Combination BRAF/MEK inhibition plus immune checkpoint blockade[58] • Combination immune checkpoint blockade plus viral oncolysis[59] • Trialing novel checkpoint and targeted inhibitors

FMT, fecal microbiota transplant; HDACi, histone deacetylase inhibitor; IFN-γ, interferon gamma; VEGF2, vascular endothelial growth factor 2.

node–positive melanoma.[53,54] For patients with clinically node-positive disease, the standard of care remains therapeutic lymph node dissection. However, for patients with clinically positive nodes who have an objective response to neoadjuvant checkpoint blockade, often no evidence of residual malignancy is found on pathologic analysis of the surgical specimen.[27] This observation provided the inspiration for the personalized response-driven surgery and adjuvant therapy after neoadjuvant ipilimumab and nivolumab (PRADO) trial in resectable stage III melanoma.[55] In this study, which is an extension cohort of the OpACIN-neo trial, patients with clinically node-positive melanoma were treated with 2 cycles of ipilimumab and nivolumab after fiducial marker placement in the index lymph node (ILN), which was defined as the largest node with pathologically confirmed metastatic disease. The ILN was resected at 6 weeks after the initiation of neoadjuvant therapy; patients with a major pathologic response in the ILN underwent no further intervention, those with a partial response were treated with completion lymph node dissection, and those with no response were treated with node dissection followed by adjuvant nivolumab. This trial is ongoing, with long-term survival outcomes pending. Findings from this study may set a new precedent for further limiting the indications for therapeutic lymphadenectomy.

Although neoadjuvant therapy may narrow the indications for surgery in resectable regional disease, it may also expand the indications for surgery in unresectable locally advanced and metastatic melanoma. Blankenstein and colleagues recently published their findings from the REDUCTOR trial, which was a prospective, single-arm, phase 2 trial investigating the downstaging potential of neoadjuvant BRAF/MEK inhibition for unresectable regionally advanced and oligometastatic melanoma.[56] This trial enrolled 21 patients with stage IIIC melanoma, of whom 18 (86%) were treated with surgical resection. An R0 resection was achieved in 17 of 18 patients, with a median RFS of 9.9 months. The findings from this trial reveal the potential of neoadjuvant BRAF/MEK inhibition to downstage unresectable disease. By inference, it is conceivable that the extent of downstaging and rate of durable response might be even better with checkpoint blockade or with combination targeted inhibition and checkpoint blockade.

Conclusion

The advent of effective systemic therapies with targeted BRAF/MEK inhibition and immune checkpoint blockade has drastically changed the treatment landscape for melanoma, particularly the prospect of neoadjuvant therapy for locally advanced and metastatic disease. Although preliminary trial data are very supportive of the use of neoadjuvant therapy for stages III and IV melanoma, multiple active lines of investigation have been designed to optimize its application further; we have described them in this review, and they are summarized in Table 2. Going forward, it is likely that neoadjuvant therapy will be utilized increasingly with expanded indications, and hopefully this trend will be associated with more durable responses.

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