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Neoadjuvant Therapy for Melanoma – New and Evolving Concepts

Derek J. Erstad[1], **Russell G. Witt**[1], **Jennifer A. Wargo**[1,2]

[1]Department of Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA

[2]Department of Genomic Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA

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 upfront 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.

Keywords

Neoadjuvant therapy; malignant melanoma; BRAF/MEK inhibition; immune checkpoint blockade

Introduction

Effective targeted BRAF/MEK inhibitors and immune checkpoint blockade 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

Corresponding Author: Jennifer A. Wargo, MD, MMSc, The University of Texas MD Anderson Cancer Center, Surgical Oncology, 1515 Holcombe Blvd. / Unit 1484, Houston, TX 77030-4009, Phone: 713-745-1553, jwargo@mdanderson.org.

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J.A.W. is an inventor on a US patent application (PCT/US17/53.717) relevant to the current work; reports compensation for speaker's bureau and honoraria from Imedex, Dava Oncology, Omniprex, Illumina, Gilead, PeerView, MedImmune, and Bristol-Myers Squibb (BMS); serves as a consultant/advisory board member for Roche/Genentech, Novartis, AstraZeneca, GlaxoSmithKline (GSK), BMS, Merck, Biothera Pharmaceuticals, and Micronoma.

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and as adjuvant therapy, both with promising results, and their usage in the neoadjuvant context is now an expanding field of investigation.[3] This review will focus on neoadjuvant therapy for melanoma and will include 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

There are multiple theoretical advantages associated with a neoadjuvant approach to systemic therapy, particularly for immune modulating treatments.[4] From a surgical perspective, neoadjuvant therapies have the potential to downstage unresectable disease and allow for curative-intent operative resection. Furthermore, the rate of R0 resection might be improved with preoperative therapy, as has been shown with certain gastrointestinal epithelial malignancies.[5] Neoadjuvant administration of systemic immunotherapy and targeted BRAF/MEK inhibition might also have greater efficacy compared to their respective usage in the adjuvant setting. For both, 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] Post-treatment tissue evaluation provides a plethora of valuable information that can inform prognosis, decision making for additional therapy, and scientific discovery by providing information about the cellular and molecular effects of therapy on the tumor microenvironment.[8] Thus, the neoadjuvant treatment approach is useful for evaluating treatment efficacy, for ascertaining mechanisms of disease resistance, and for biomarker development.

Despite these numerous potential advantages, there remain theoretical downsides to neoadjuvant therapy. First, this approach inevitably delays time to surgical resection, which is the current standard of care and the primary curative modality, carrying the risk that some patients will progress and become unresectable.[9] Both targeted therapy and checkpoint blockade are associated with distinct and sometimes severe toxicities that could theoretically delay timing to surgery, preclude surgery altogether, or potentially complicate the surgical course due complications from drug toxicities. A summary of the theoretical advantages and disadvantages of neoadjuvant therapy are displayed 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] BRAF encodes the gene for 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, 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 and Dabrafenib in patients with BRAF-mutated metastatic melanoma was shown to improve 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]

Based on promising findings in metastatic disease, Amaria et al. 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 standard of care upfront surgery with consideration of adjuvant therapy vs. perioperative dabrafenib and trametinib.[16] Seven patients were assigned to standard of care and 14 patients to neoadjuvant therapy. The trial was stopped early due to significantly longer event-free survival (EFS) in the neoadjuvant therapy group (median EFS 19.7 vs 2.9 months; HR 0.016, $p < 0.0001$).

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-C BRAF-mutated melanoma were treated with perioperative dabrafenib plus trametinib with surgical resection. Thirty-five patients enrolled, and a pathologic response was observed in 100% of cases, of which 17 (49%) had a complete pathologic response (pCR). There was no progression during the 12 weeks of neoadjuvant therapy. The 2-year RFS for the entire cohort was 43% and was 63% for patients who experienced a pCR. Taken together, the trials conducted by Amaria et al. 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 there exists a dynamic interaction between the immune system and malignant melanoma. Standard of care systemic therapies historically included cytokine infusions with Interferon-alpha (IFNa) and Interleukin-2 (IL-2), both of which were designed to stimulate anti-tumor immune activation, though often with prohibitive inflammatory side-effects. Immune checkpoint blockade had a revolutionary impact in melanoma because these medications were highly effective, easy to administer, and exhibited side effect profiles that were generally less severe than for cytokine infusions and adoptive cell therapies.

Checkpoint inhibition was initially studied in advanced melanoma, where it was demonstrated that PD-1 checkpoint blockade provided superior survival outcomes compared to CTLA-4 inhibition.[2,18] Subsequent adjuvant trials for high-risk, resectable melanoma were a natural next step as there was a historic precedent for adjuvant therapy with cytokine infusions, and this approach still allowed for standard of care upfront surgery. There have been several notable checkpoint blockade trials in the adjuvant space. The European Organization for Research and Treatment of Cancer (EORTC) 1325/KEYNOTE-054 trial was a phase 3 double-blind trial evaluating adjuvant pembrolizumab vs. placebo in patients with stage III melanoma.[19] 1,019 patients were treated with complete lymph node dissection followed by randomization to receive pembrolizumab vs. placebo for one year. The 3-year RFS for immunotherapy treatment was 63.7% vs. 44.1% for placebo, while the 3.5-year distant metastasis-free survival (DMFS) was 65% and 49%, respectively.[20] KEYNOTE-054 thus provided evidence for a survival benefit with checkpoint blockade compared to close

observation. CheckMate 238 was another adjuvant phase 3 double-blind trial for resected stage IIIB-IV melanoma that directly compared nivolumab versus ipilimumab.[21] Recent long-term follow up was reported, and 4-year RFS for nivolumab was 51.7% vs. 41.2% for ipilimumab, while there was no difference in OS (77.9% vs. 76.6%, respectively).[22] This trial corroborated the finding in advanced disease that PD-1 inhibition provided a more significant treatment effect than CTLA4 blockade in melanoma.[18,21,23] More recently, preliminary results for 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 randomized over 1,800 patients with stage III-IV melanoma to adjuvant combination ipilimumab plus nivolumab vs. nivolumab alone. Unexpectedly, there was no difference in 2-year RFS between the treatment arms (64.6% for combination therapy and 63.2% for monotherapy).

Given this background, multiple neoadjuvant trials have been implemented and reported over the last 5 years. The Optimal Adjuvant Combination Scheme of Ipilimumab and Nivolumab in Melanoma Patients (OpACIN) study was a seminal clinical trial that investigated combination checkpoint blockade with ipilimumab and nivolumab in both adjuvant and perioperative contexts.[6] This was a phase 1B trial in which patients were randomized to either 12 weeks of adjuvant therapy or 6 weeks of neoadjuvant plus six weeks of adjuvant therapy. Nine of 10 patients in both arms experienced grade 3/4 toxicities when dosed at ipilimumab 3 mg/kg and nivolumab 1 mg/kg.[6] The 4-year EFS was 80% for perioperative therapy and 60% for adjuvant therapy, while the 4-year overall survival (OS) was 90% and 70%, respectively.[25]

Another groundbreaking neoadjuvant trial in melanoma was conducted by Amaria et al., which was published concomitantly with the OpaCIN study findings. In this trial, the authors investigated neoadjuvant PD-1 monotherapy with nivolumab (3mg/kg) for four doses versus combination nivolumab (1mg/kg) plus ipilimumab (3mg/kg) for three doses in patients with high-risk, resectable melanoma.[9] Twenty-three patients were enrolled (n = 12 monotherapy, n = 11 combination therapy), and the trial was stopped early due to disease progression that prohibited subsequent surgery in two patients receiving nivolumab monotherapy. Combination therapy was associated with high objective response rate (ORR) (73%) and pCR rate (45%), though there was high associated toxicity (73% grade 3 adverse events). In contrast, nivolumab monotherapy was associated with only a modest ORR (25%) and pCR rate (25%), though only 8% of patients experienced a grade 3 toxicity. There were no significant differences in survival outcome measures (RFS, DMFS, and OS), though 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 higher CD8+ tumor infiltrate, increased tumor cell PD-L1 expression, and greater presence of lymphoid markers in responders vs. non-responders. They also identified a higher rate of T-cell clonality in responders, as previously described.[26]

Shortly thereafter, Huang et al. investigated the impact of a single dose of pembrolizumab 3 weeks prior to surgical resection.[8] In this study, 27 patients with stage IIIB-IV melanoma treated with surgical resection were enrolled, and 8/27 (29.6%) exhibited a major or complete pathologic response after a single dose. One-year DFS was 63%, though no

patients with complete/major responses had recurred by the study endpoint. Similar to the study by Amaria et al., a higher quantity of CD8+ tumor infiltrate was associated with better response to checkpoint blockade.

Finally, findings from the OpaCIN trial inspired the subsequent OpaCIN-neo trial, which was a phase 2b study investigating optimal dosing for combination ipilimumab plus nivolumab neoadjuvant therapy for stage III melanoma.[27] In this trial, 86 patients were randomized to three different treatment arms with different dosing regimens, and the investigators observed that the optimal combination, as evidenced by minimal toxicity and maximal effect, was two cycles of ipilimumab 1 mg/kg plus nivolumab 3 mg/kg once every three weeks intravenously. Rozeman et al. recently published long-term survival data, and the overall 2-year RFS for all three treatment arms was 84% but was 97% for patients with an observed pathologic response vs. only 36% for non-responders.[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 Southwest Oncology Group (SWOG) S1801 is an ongoing phase 2 clinical trial investigating survival outcome measures for patients with stage III-IV resectable melanoma treated with neoadjuvant vs. adjuvant pembrolizumab (PD-1 inhibitor).[28] Results for this head-to-head comparison have not yet been published. Cross-trial comparisons are inherently limited, though cautious interpretation of completed studies does suggest a trend in favor of neoadjuvant therapy. Considering the aforementioned clinical trials, on aggregate adjuvant therapy was associated with an RFS of approximately 50-65% at 2-4 years of follow up. In contrast, neoadjuvant studies provided evidence of more durable responses, with recurrence-free intervals ranging from 80-84% at 1-4 years of follow up.

It is also interesting to note that combination CTLA4 plus PD-1 inhibition was shown to provide an additive effect in advanced disease (CheckMate067) and as neoadjuvant therapy (Amaria et al.), 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 might have greater impact 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 neoadjuvant therapy was associated with greater expansion of tumor-resident T cell clones compared to adjuvant therapy.[27]

Treatment Response Biomarkers Drive the Next Generation of Neoadjuvant Trials

Despite the excitement and promise of checkpoint blockade for the treatment of metastatic melanoma, only about half of patients will have an objective response to combination therapy, while even lower response rates are observed with single agents.[2] There are

multiple ongoing efforts to better understand the biologic determinants of treatment response, and this work could have two pragmatic implications for clinical care. First, improved pre-treatment response prediction would allow for more accurate prognostication and could inform management decisions, e.g. surveillance frequency. Second, this work could lead to the development of personalized therapeutic regimens that are designed to optimize treatment effect.

One important avenue of investigation involves 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 based on treatment type.[29] Among patients treated with neoadjvuant BRAF/MEK inhibition, evidence of pCR was associated with superior survival outcomes, while those who had a near-complete response or partial response behaved more similar to non-responders over time. Conversely, for patients treated with immunotherapy, partial and near complete responses behaved similar to complete responders with very few recurrences during the observation period. While no patients with a pCR to immunotherapy have recurred to date, recurrence has been observed for patients with targeted therapy who similarly had a complete response. These findings indicate that that pathologic response, of any degree, is a more sensitive marker of durable response for immunotherapy than for targeted BRAF/MEK inhibition.

Several studies have also investigated the relationship between pathologic response and preoperative clinicopathologic traits in the hope of identifying pre-treatment prognostic markers. Menzies et al. recently evaluated pathologic response and survival of 192 stage III melanoma patients treated with neoadjuvant therapy.[29] In this study, there were no significant associations observed in BRAF/MEK inhibitor-treated patients, and 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, as there was no association 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 based on pretreatment clinical factors.

Technological advances, particularly next generation sequencing, have allowed for deeper investigations into the biologic determinants of response to neoadjuvant therapy for melanoma. By transcriptomic analysis, Interferon-gamma (IFN-y) expression has been shown to associate with pathologic response to checkpoint blockade. IFN-y is a cytokine produced by activated T cells, NK cells, and NK T cells, which has multiple effects on immune signaling resulting in an inflammatory state that is critical to the innate immune response.[30] With respect to the tumor microenvironment, INF-y has been shown to stimulate expression of HLA proteins, theoretically supporting neoantigen presentation and immune cell recruitment. However, IFN-y also co-stimulates inhibitory signals including PD-L1 and PD-L2, and this combination of immunologic stimulation and dampening represents a complex interplay that is not fully understood. Nonetheless, the presence of INF-y signaling has been associated with a reduced risk of 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 high IFN-y gene expression was significantly associated with the degree of pathologic response and the risk of relapse.[25] In this study, the authors observed an association between EFS and tumor mutational burden (TMB). However, no correlation between TMB and IFN-y expression was observed, though patients who exhibited both high TMB and IFN-y signaling had a 100% rate of partial pathologic response and zero recurrences at 2 years. Conversely, presence of both low TMB and low IFN-y signaling was associated with a 2-year EFS rate of only 49% in comparison to 83% or greater for all other combinations in which at least one biomarker (TMB or IFN-y expression) was elevated.[25]

Translational discovery of IFN-y expression in the TME inspired the DONIMI trial, a biomarker driven, multicenter phase 1b trial evaluating Domatinostat, Nivolumab, and Ipilimumab in IFN-y signature-low and IFN-y signature-high stage III melanoma.[31] Domatinostat is a selective class I histone deacetylase inhibitor (HDACi) that is thought to potentially stimulate IFN-y gene expression. The intention of this trial is to convert pre-treatment IFN-y low tumors to an IFN-y high phenotype in order 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 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 (VEGFR-2), CX3CL1, and PD-L2 after neoadjuvant therapy were associated with non-responders. 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 II study of neoadjuvant pembrolizumab and lenvatinib for stage III melanoma. Lenvatinib is a multiple RTK inhibitor that selectively inhibits VEGF receptors, including VEGFR-2.[36] Similar to the DONIMI trial, the goal of this study is to increase immunotherapy susceptibility among non-responders.

The Impact 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 with 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 melanoma patients treated with

immunotherapy.[39-42] In each case, it was found that patterns in the microbiome could be linked to “responder” and “non-responder” states, though the patterns were variable between studies. It is not fully understood why there has been limited overlap in microbiome signatures between studies, though it 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, both as a means for disease prevention and for effect modification of immunotherapy. Thus, work is ongoing to identify consortia of bacteria that enhance immune response in the setting of checkpoint blockade. In addition, there are active clinical trials investigating interventions and behaviors that influence microbial diversity, including diet, exercise, and the use of antibiotics.[44,45] Delivery of therapeutic microbiota is an area of active investigation, including fecal microbial transplant (FMT) and biotherapeutics comprised of one or multiple strains of bacteria. Although obstacles remain, it might be possible in the future to sample the stool of melanoma patients to contextualize their baseline microbial signature as immunotherapy responder vs. non-responder status. Then by means such as dietary changes, an “off the shelf” biotherapeutic, or fecal transplant, it may be possible to convert patients to responder states prior to 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, there might be an additive effect with combined checkpoint blockade.

There is precedent for combination BRAF/MEK plus checkpoint blockade in studies of advanced melanoma. The Keynote-022 trial was a phase II multicenter, double-blinded clinical trial for patients with metastatic or unresectable BRAF-mutated melanoma who were randomized to treatment with dabrafenib and trametinib plus pembrolizumab or placebo.[49,50] PFS 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 progression-free survival.

More recently, the COMBI-i trial was a placebo-controlled, phase 3 clinical trial investigating spartalizumab, an anti-PD-1 antibody, vs. placebo in combination with dabrafenib and trametinib for patients with BRAF-mutated advanced melanoma.[51] There was no difference in the primary endpoint of PFS between treatment arms, though some

beneficial trends were observed with the addition of anti-PD-1 therapy. Objective response rates were 68.5% for the spartalizumab arm vs. 64.2% for the placebo arm.

Finally, a third study, the IMspire150 trial, was a phase III multicenter, double-blinded, randomized controlled trial investigating atezolizumab, an anti-PD-L1 antibody, vs. placebo plus cobimetinib and vemurafenib 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, $p = 0.025$). There was no difference on overall survival with limited duration of 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 German Dermatologic Cooperative Oncology Group-Selective Lymphadenectomy Trial (DeCOG-SLT) and Multicenter Selective Lymphadenectomy Trial II (MSLT-II) provided supporting evidence for observation rather than therapeutic lymph node dissection for clinical node negative, sentinel node positive melanoma.[53,54] For patients with clinical node positive disease, the standard of care remains therapeutic lymph node dissection. However, for patients with clinically positive nodes who experience an objective response to neoadjuvant checkpoint blockade, there is often no evidence of residual malignancy 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 for resectable stage III melanoma.[55] In this study, which is an extension cohort of the OpaCIN-neo trial, patients with clinical node positive melanoma were treated with 2 cycles of ipilumumab and nivolumab after fiducial marker placement in the index lymph node (ILN), which was defined as the largest node with pathologically confirmed metastatic disease. Resection of the ILN was performed at 6 weeks after initiation of neoadjuvant therapy, and patients with a major pathologic response in the ILN underwent no further intervention, patients with a partial response were treated with completion lymph node dissection, and patients 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 new precedent to further limit the indications for therapeutic lymphadenectomy.

While neoadjuvant therapy may lead to narrowed surgical indications for resectable, regional disease, it might also expand indications for unresectable locally advanced and metastatic melanoma. Blankenstein et al. recently published their findings from the REDUCTOR

trial, which was a prospective, single arm, phase II 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 which 18 (86%) were treated with surgical resection, and 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 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. While preliminary trial data is very supportive for the use of neoadjuvant therapy for stage III/IV melanoma, there are multiple active lines of investigation designed to further optimize its application, which we have described in this review and summarized in Table 2. Going forward, it is likely that neoadjuvant therapy will increasingly be utilized with expanded indications, and hopefully more durable responses.

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Table 1.

Neoadjuvant Therapy in Context

Advantages		Disadvantages	
1	Tumor downstaging: increase resectability, negative margins	**1**	Potential delay in standard of care surgery
2	Immunologic Priming: more tumor biomass may increase likelihood of neoantigen detection and response to IO	**2**	Risk of disease progression to unresectable state
3	Biologic assessment: pathologic response to therapy; surrogate endpoint	**3**	Treatment toxicity could impact surgical resection and outcomes
4	Inform prognosis, guide adjuvant therapy		
5	Mitigate surgical intervention		
6	Study novel drugs, mechanisms of resistance, development of biomarkers		

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-y high) with HDACi and IFN therapy[31,57] • Stimulating Responder Gut Microbiome Signature with diet, FMT, biotherapeutics[44,45] • Abrogating Non-Responder Signature (Circulating VEGF2) with Anti-VEGF therapy[36]
Novel Treatment Combinations	• Combination BRAF/MEK plus immune checkpoint blockade[58] • Combination immune checkpoint blockade plus viral oncolysis[59] • Trialing novel checkpoint and targeted inhibitors

FMT, fecal microbiota transplantation; HDACi, histone deacetylase inhibitor; IFN, interferon; VEGF, vascular endothelial growth factor.