Neoadjuvant therapy for melanoma: rationale for neoadjuvant therapy and pivotal clinical trials

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Abstract: The treatment of malignant melanoma has drastically changed over the past decade with the advent of immune checkpoint blockade, targeted therapy with BRAF/MEK inhibition, and other novel therapies such as oncolytic virus intralesional therapy. Despite improvements in patient response rates and survival with these new treatments, there exists a large portion of patients with surgically resectable disease that are high risk for relapse. Patients with high-risk resectable melanoma account for up to 20% of newly diagnosed cases. For this high-risk group of patients, neoadjuvant therapy has many purposed advantages over adjuvant therapy, including a more robust immune response due to abundant tumor antigens at treatment initiation, the ability to assess pathologic response to therapy, tumor downstaging leading to increased disease resectability, and a potential decreased need for extensive lymphadenectomies. These findings have been backed by preclinical models and multiple neoadjuvant trials are underway. In this review, we will discuss the trials that have set the foundation for the current treatment standards and discuss the role and rationale for neoadjuvant therapy for high-risk malignant melanomas.

Keywords: BRAF/MEK inhibition, immune checkpoint blockade, malignant melanoma, neoadjuvant therapy

Introduction

Melanoma incidence has continued to steadily increase worldwide over the last five decades with over 100,000 estimated cases in the United States in 2021.[1] Overall survival (OS) rates for patients with stage I and II melanoma have remained favorable with 10-year survival rates ranging from 75% to 94%.[2] Ten to 20 percent of patients present with in-transit disease, satellite lesions, or clinically involved lymph nodes and their overall outcomes have been historically poor. Over the last 5 years, the treatment and management of melanoma has changed drastically with the advent of immune checkpoint inhibitors and targeted therapy with BRAF and MEK inhibitors. These new treatment options have now become the new standard of care for high-risk and metastatic melanoma. Prior to the introduction of these new treatments, the standard approach to patients with resectable regional disease was upfront

surgery including resection of in-transit disease and/or formal lymphadenectomy of the involved lymph node bed. Chemotherapy, high-dose interferon (IFN)-α2b, low dose IFN-α2b, and pegylated IFN-α2b were the mainstays of adjuvant therapy but were limited by toxicity and low efficacy.[3–6] Ipilimumab, a monoclonal antibody targeted against cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) was introduced in 2010 for treatment of patients with metastatic melanoma and significantly improved survival.[7–9] This was followed by the use of targeted therapy for patients with BRAF[V600E/K] mutations using dabrafenib and trametinib[10] which further expanded the oncologist's repertoire of melanoma treatments. Programmed death-1 (PD-1) inhibitors such as nivolumab and pembrolizumab[11–15] followed which showed similar efficacy to ipilimumab with less toxicity. During this time, the first trials using the oncolytic virus Talimogene laherparepvec

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(T-VEC) were being performed, introducing a new class of drug for the treatment of melanoma.[16–21]

Efficacy of these new agents was demonstrated in multiple adjuvant trials and consideration of neoadjuvant therapy was introduced as the next logical step to improve outcomes in high-risk patients. In this review, we will discuss the several compelling advantages of neoadjuvant therapy in detail and the adjuvant and neoadjuvant clinical trials that have shaped the current clinical approach to high-risk melanoma.

Rationale for neoadjuvant therapy in high-risk melanoma

While adjuvant therapy for high-risk resectable melanoma has improved outcomes, neoadjuvant therapy offers multiple potential advantages compared with adjuvant therapy. First, neoadjuvant therapy may decrease metastatic disease burden more so than adjuvant therapy. In two preclinical mouse models of breast cancer, Liu *et al.* demonstrated that neoadjuvant immunotherapy is more effective at eradicating distant metastases than adjuvant immunotherapy.[22] Of mice treated with adjuvant or neoadjuvant anti-PD-1 antibody, neoadjuvant-treated mice survived longer and had greater decreases in distant tumor burden compared with their adjuvant counterparts. Elevated tumor-specific CD8+ T cells were seen within the neoadjuvant groups likely accounting for the large differences seen in response. This was one of the first preclinical studies to demonstrate that the presence of a higher tumor burden prior to resection appears to elicit a greater immune response to immune checkpoint blockade. Multiple preclinical studies have shown that neoadjuvant immunotherapy increases levels of tumor-specific CD8+ T cells which correlates with overall survival.[22–24] Similar findings of increased circulating tumor specific CD8+ T cells with neoadjuvant treatment have been demonstrated in humans as well.[25,26] It is theorized that the larger tumor burden allows for increased antigen presentation from tumor cells leading to a more robust T cell response.[27,28] Removal of the tumor prior to initiation of immune checkpoint blockade results in fewer tumor-specific antigens available for eventual CD8+ T cell targeting. In patients with metastatic melanoma, after receiving PD-1 blockade, there is an increase seen in T cell receptor clonality which may be indicative of increased intratumoral T cell expansion seen with neoadjuvant therapy.[29] In the OpACIN trial (discussed later), patients treated with neoadjuvant checkpoint blockade demonstrated a larger number of intratumoral T cells compared with those treated with adjuvant therapy.[25] Those patients with greater T cell expansion had a greater likelihood of prolonged relapse-free survival. Spranger *et al.* demonstrated that specific tumor-residing Batf3+ dendritic cells were necessary for effector T cell trafficking.[30] Liu *et al.* further showed loss of Batf3+ dendritic cells abrogated tumor-specific CD8+ T cell response and reduced survival.[24] Analysis of patients who underwent adjuvant or neoadjuvant ipilimumab and nivolumab for high-risk melanoma showed that those who relapsed after treatment had low expression of Batf3+ dendritic cell-associated genes. This shows that the presence of tumor-residing Batf3+ dendritic cells is essential for adequate T cell responses following immunotherapy. In adjuvant therapy, surgical removal of the tumor prior to initiation of treatment would decrease tumor-residing Batf3+ dendritic cells and limit the potential immune response.

Neoadjuvant therapy allows for early assessment of pathologic response to treatment. The degree of intratumoral T cell expansion, presence of tertiary lymphoid structures, and percentage of viable tumor provide useful prognostic data[31–34] which provides more information when determining the need for additional adjuvant therapies. In a pooled analysis from data collected from six clinical trials with the use of anti-PD-1 or BRAF/MEK therapy performed by Menzies *et al.*, pathologic response rates strongly correlated with both recurrence-free survival (RFS) and OS.[33] Based on these findings, it was suggested that pathologic response should be used as a surrogate for endpoint for clinical trials which would increase the speed of drug development for melanoma. They also deduced that immunotherapy appeared to be more active when given in the neoadjuvant setting in agreement with preclinical models. Recognizing a poor response to therapy allows clinicians to alter therapy while complete responders can potentially receive de-escalated treatment.

For more locally advanced melanoma, neoadjuvant therapy has the potential to increase resectability and decrease the risk of incomplete resection. In the REDUCTOR trial, this was shown using neoadjuvant BRAF/MEKi targeted therapy. Among patients deemed unresectable prior to

neoadjuvant treatment, 18 of 21 (86%) were able to proceed to surgical resection after initiation of BRAF/MEKi treatment.[35] In those with locally advanced disease, resection prior to therapy can be significantly morbid. Excellent pathologic response after treatment may decrease the need for extensive surgeries such as regional lymphadenectomies for nodal disease. De-escalation of surgery in excellent responders is being studied in the PRADO trial where the presence of a major pathological response within the largest lymph node metastasis will determine whether a patient undergoes completion lymphadenectomy.[36]

An ancillary benefit of neoadjuvant therapy is that it gives researchers the opportunity to study the tumor microenvironment while on treatment. On treatment, samples can then be used for identification of novel biomarkers and targets for future drug development. There remains a substantial cohort of patients who will not maintain a durable response to immunotherapy or targeted therapy. Next-generation deep sequencing of on-treatment samples may provide further insights into the biological determinants of responders such as Brat3+ dendritic cell populations or interferon gamma (IFN-γ) signaling. Increased IFN-γ signaling was identified through transcriptomic analysis as a potential predictor of immunotherapy response as it correlated closely with pathologic response.[37] This finding of increased IFN-γ expression correlating with outcomes lead to the DONIMI trial which is a biomarker-driven phase Ib trial examining the combination of domatinostat, nivolumab, and ipilimumab in IFN-γ signature low and high stage III melanoma.[38]

Potential disadvantages of neoadjuvant therapy include delaying treatment and increasing the risk of disease progression in patients who do not respond to treatment. While this has been seen in neoadjuvant trials using monotherapy, it remains unclear whether upfront surgery would have been truly beneficial in patients who progressed or whether early recurrence would have taken place. The other factor that may delay surgery is treatment-related toxicity. A high rate of treatment-related toxicity has been seen in patients undergoing combination CTLA-4 and anti-PD-1 therapy and represents a valid concern. Immune-related adverse events have been shown to correlate with response to therapy, and dose reduction within this patient population may still provide the benefits neoadjuvant therapy provides.[39,40] In the next section, we will discuss the adjuvant studies that established our current treatment protocols and set the foundation for the neoadjuvant trials.

Adjuvant immune checkpoint blockade trials

EORTC 18071

In patients with stage III disease, recurrence is common with 5-year recurrence rates in stage IIIA being 37%; stage IIIB, 68%; and stage IIIC, 89%. The heterogeneity of the stage III recurrence and survival implied that adjuvant therapy may have the greatest benefit for stage III disease. EORTC 18071 was a phase III trial evaluating ipilimumab *versus* placebo in patients with stage III melanoma (excluding patients with in-transit metastasis or lymph node metastasis <1 mm) who had undergone adequate resection of their primary melanoma and involved lymph nodes.[9,41] Patients with metastatic disease greater than 1 mm were targeted in the study because of a significantly higher risk of recurrence and death compared with those with disease <1 mm in size.[42–44] In the study, 475 patients were assigned to the ipilimumab group and 476 to the placebo group. The median RFS within the ipilimumab group was 26.1 months [95% confidence interval (CI), 19.3–39.3] *versus* 17.1 months (95% CI, 13.4–21.6) in the placebo group [hazard ratio (HR) = 0.75; 95% CI, 0.63–0.88; $p < 0.001$]. At 5 years, the OS was 65.4% in the ipilimumab group compared with 54.4% in the placebo group (HR = 0.73; 95% CI, 0.60–0.89; $p = 0.002$). While these results were encouraging, the main problem with ipilimumab treatment was a high rate of toxicity with 54% of patients discontinuing due to toxicity at the dose of 10 mg/kg. This study first demonstrated the utility of checkpoint inhibition in increasing RFS and OS and further follow-up studies would utilize lower doses of ipilimumab in an effort to decrease treatment toxicity.

EORTC 1325/KEYNOTE-054

The use of PD-1 inhibition was investigated in EORTC/KEYNOTE-054 with a comparison between pembrolizumab and placebo used in the adjuvant setting.[45] In a similar comparison with the group used for EORTC 18071, patients with stage IIIA (>1-mm metastasis), IIIB, and IIIC melanoma after resection of their disease were randomized to 1 year of pembrolizumab (200 mg IV Q3W) *versus* placebo for 1 year. Patients with recurrence were eligible for crossover or repeat

treatment with pembrolizumab until progression or up to 2 years after the start of the trial. In total, 1019 patients were enrolled with 514 receiving pembrolizumab and 505 receiving placebos. RFS at a median follow-up of 3 years was 63.7% in the pembrolizumab group and 44.1% in the placebo group (HR = 0.56; 95% CI, 0.47–0.68). Among patients with PD-L1 positivity (n = 853), RFS was 65.3% among those receiving pembrolizumab *versus* 52.2% among those receiving placebo (HR = 0.57; CI, 0.43–0.74; $p < 0.001$). In those who were PD-L1 negative (n = 116), RFS was still significantly improved in the pembrolizumab group at 56.9% *versus* 33.3% in the placebo group (HR = 0.45; CI, 0.23–0.90; $p = 0.002$). Clinically meaningful improvement was consistent on subgroup analysis regardless of PD-L1 status or BRAF mutational status across all melanoma stages. The improvement seen in patients with BRAF mutations was similar to the benefit noted in the COMBI-AD trial (discussed later) using targeted therapy. In addition, pembrolizumab had fewer adverse events and a low discontinuation rate compared with ipilimumab. Patients who did experience an immune-related adverse event from their pembrolizumab treatment had a significantly longer RFS (HR = 0.61) which may indicate that the occurrence of an immune-related adverse reaction is evidence of clinical effectiveness.[39] This study did raise the question of whether adjuvant pembrolizumab treatment should be applied to all high-risk melanoma or if it should be saved to treat only those who recur.

CheckMate 238

The Checkmate 238 study was the first to compare a PD-1 inhibitor with a CTLA-4 inhibitor in the adjuvant setting for melanoma.[15] In the study, 906 patients with stage III or IV melanoma were randomized to either nivolumab or ipilimumab. At a median follow-up of 3 years, RFS was 58% in the nivolumab group *versus* 45% in the ipilimumab group (HR = 0.68; 95% CI, 0.56–0.82). Adverse reactions were significantly less in the nivolumab group compared with the ipilimumab group and similar to those seen to pembrolizumab in the EORTC 1325/KEYNOTE-054 trial. Grade 3–5 adverse reactions among the PD-1 inhibitors were 14.7% with pembrolizumab and 14.4% with nivolumab *versus* 54% with ipilimumab. While OS was not significantly different between the two treatment arms, the overall number of deaths was significantly lower than

anticipated with only 211 total deaths (100 in the nivolumab and 111 in the ipilimumab group) over the 4-year analysis period. This study again demonstrated the tolerability of PD-1 inhibition but also the effectiveness of both PD-1 inhibition and CTLA-4 inhibition.

IMMUNED trial

Evaluating combination therapy of a PD-1 inhibitor and CTLA-4 inhibitor or PD-1 inhibitor monotherapy compared with placebo was investigated in the IMMUNED trial but in patients with stage IV melanoma.[40] The IMMUNED trial was a randomized, phase 2 trial evaluating nivolumab plus ipilimumab *versus* nivolumab monotherapy *versus* placebo at 20 German academic centers excluding patients with uveal or mucosal melanoma, or history of previous checkpoint inhibitor therapy. At interim analysis with a median follow-up of 28.4 months, median RFS had not been reached in the combination therapy group while it was 12.4 months in the nivolumab monotherapy group and 6.4 in the placebo group. Hazard ratio for the combination group was 0.23 (97.5% CI, 0.12–0.45; $p < 0.0001$) *versus* placebo and was 0.566 (97.5% CI, 0.33–0.94; $p = 0.011$) for the nivolumab monotherapy group *versus* placebo. Treatment-related side effects of grades 3–4 were higher in the combination group (71%) and in the nivolumab monotherapy group (27%) compared with previously demonstrated studies. While the study was not powered to compare combination therapy to monotherapy, it did show the high rate of adverse events among the patients receiving combination therapy.

CheckMate 915

CheckMate 915 was the follow-up study to the IMMUNED trial to determine whether there is improvement with combination therapy compared with monotherapy with PD-1 inhibition. While final trial results have yet to be published, the combination of ipilimumab and nivolumab has failed to improve relapse-free survival in the intent-to-treat and PD-L1 negative groups compared with nivolumab alone. At 2 years, RFS was 64.6% *versus* 63.2% in the combination group and nivolumab monotherapy, respectively.[46] It was noted that the combination group of ipilimumab and nivolumab had an overall shorter median duration of therapy compared with the nivolumab alone (7.6 months *versus* 11.1 months) and received a lower median cumulative dose of nivolumab (3840 mg *versus*

6240 mg) which may account for the similar relapse-free survival. Grade 3/4 treatment-related adverse events were seen in 33% of the combination treatment patients and 13% of the nivolumab mono-therapy. Discontinuation of therapy occurred in 32% of the combination therapy group and 10% of the monotherapy group. This study reinforces anti-PD-1 therapy as the standard of care in the adjuvant setting and the additional benefit of CTLA-4 blockade must be balanced with treatment toxicity.

Neoadjuvant immune checkpoint blockade trials

Here we highlight and summarize landmark trials using neoadjuvant checkpoint blockade (Table 1). In a randomized phase II study at MD Anderson Cancer Center, 23 patients with high-risk resectable melanoma were treated with either neoadjuvant nivolumab monotherapy (3 mg/kg) for four doses or neoadjuvant nivolumab (1 mg/kg) plus ipilimumab (3 mg/kg) for three doses.[26] Patients receiving both CTLA-4 and PD-1 blockade had high response rates (pathologic complete response (pCR) in 45%) but high toxicity (73% with grade 3 adverse events) while monotherapy with nivolumab had less impressive responses (pCR in 25%) but much lower toxicity (8% grade 3 adverse events). The trial was closed early due to disease progression within the nivolumab monotherapy group. As anticipated, tissue samples from responders showed an increase in CD8+ T cell infiltrates relative to their non-responder counterparts.

Huang *et al.* evaluated single-dose neoadjuvant PD-1 blockade prior to high-risk melanoma resection.[47] Twenty-nine patients were enrolled and underwent a single dose of neoadjuvant pembrolizumab (200 mg) 3 weeks prior to surgery. Pathologic response was evaluated in 27 patients. In the cohort, 29.6% of patients had a major pathologic response or greater with 5 patients achieving a pCR and 3 patients with a less than 10% of viable tumor left. The 1-year disease-free survival rate was 63%. This study demonstrated that even very short course therapy provided prior to surgery can have significant benefit and help predict overall response.

OpACIN trial
The OpACIN trial was a phase Ib trial to evaluate neoadjuvant ipilimumab (3 mg/kg) plus nivolumab (1 mg/kg) for high-risk stage III melanoma

patients.[25] Twenty patients were randomized to either 4 weeks of adjuvant therapy *versus* 2 weeks of neoadjuvant followed by 2 weeks of adjuvant therapy. All patients were able to make it to surgery, but there was a 90% rate of either grade 3 or 4 adverse events in both groups. In the neoadjuvant arm, 3 patients had a pCR and 7/10 showed some pathologic response. At 3 years, all responders remain relapse free. In similar findings to the mouse studies, in patients who received neoadjuvant therapy, there was a significant increase in tumor infiltrating lymphocytes.

OpACIN-neo trial
The OpACIN-neo trial followed the OpACIN trial attempting to address the issue of toxicity.[37,48] In this phase II trial, there were three arms receiving neoadjuvant therapy: Arm A ($n = 30$) receiving ipilimumab + nivolumab at the same doses as the OpACIN trial (3 mg/kg and 1 mg/kg, respectively) for two cycles; Arm B ($n = 30$) received 1 mg/kg of ipilimumab plus 3 mg/kg of nivolumab for two cycles; or Arm C ($n = 26$) which received two cycles of ipilimumab at 3 mg/kg followed by two cycles of nivolumab at 3 mg/kg. Grade 3–4 toxicity was seen in 40% of patients in Arm A with a pathologic response seen in 80%, 20% in Arm B with a pathologic response seen in 77%, and 50% in Arm C with a pathologic response seen in 65% of patients. At a median follow-up of 24.6 months, 1 of the 64 patients who showed a pathologic response has relapsed.[49] The OpACIN-neo trial was vital in determining a tolerable dosing regimen that still provided high rates of pathologic responses.

PRADO trial
The Personalized Response-Driven Adjuvant Therapy After Combination of Ipilimumab and Nivolumab in Stage IIIB/C Melanoma (PRADO) trial looks to answer if therapeutic lymphadenectomy could be avoided in patients who achieved an excellent pathologic response to neoadjuvant therapy.[36] Patients with either de novo or recurrent Stage IIIB/C melanoma undergo two courses of 1 mg/kg of ipilimumab plus 3 mg/kg of nivolumab prior to resection of a marked lymph node.[36] If patients show a pCR or near pCR, they do not undergo lymphadenectomy. If they show a pPR, they undergo lymphadenectomy. If they do not show a pathologic response, then they undergo lymphadenectomy with adjuvant nivolumab treatment for 52 weeks (or BRAF+ MEK inhibition in

Table 1. Neoadjuvant trials with checkpoint inhibition.

Trial	Design	Intervention	Pathologic complete response	Grade 3–4 adverse events
Trials comparing adjuvant and neoadjuvant checkpoint inhibition				
NCT02437279 Blank et al.[25]	Phase Ib (n = 20)	Arm A: Adjuvant ipi + nivo for 4 cycles Arm B: Neoadjuvant ipi + nivo for 2 cycles before surgery, and 2 after surgery	Arm A: N/A Arm B: 30%	Arm A: 90% Arm B: 90%
Trials with only neoadjuvant arms				
NCT02519322 Amaria et al.[26]	Phase II (n = 23)	Arm A: Neoadjuvant nivo up to 4 cycles, adjuvant nivo up to 13 cycles Arm B: Neoadjuvant ipi + nivo up to 3 cycles, adjuvant nivo up to 13 cycles	Arm A: 25% Arm B: 45%	Arm A: 8% Arm B: 73%
NCT02434354 Huang et al.[47]	Phase I (n = 29)	200 mg of pembrolizumab, single cycle 3 weeks prior to surgery then pembrolizumab q3w for a year following surgery	18.5%	-
NCT02977052 Rozeman et al.[48,49]	Phase II (n = 86)	Arm A: Neoadjuvant ipi (3 mg/kg) + nivo (1 mg/kg) for 2 cycles Arm B: Neoadjuvant ipi (1 mg/kg) + nivo (3 mg/kg) for 2 cycles Arm C: Neoadjuvant ipi (3 mg/kg) for 2 cycles followed by neoadjuvant nivo (3 mg/kg) for 2 cycles	Arm A: 47% Arm B: 57% Arm C: 23%	Arm A: 40% Arm B: 20% Arm C: 50%
NCT02977052 Blank et al.[36]	Phase II (n = 99)	Neoadjuvant ipi + nivo for 6 weeks, target node resection, if pCR, no lymphadenectomy, if pPR, lymphadenectomy only, if no response, lymphadenectomy + adjuvant nivo for 52 weeks	61% MPR	24%

Ipi, ipilimumab; MPR, major pathologic response, defined as < 10% viable tumor cells; nivo, nivolumab; pCR, pathologic complete response.

BRAF$^{V600E/K}$ mutated patients) and adjuvant radiation therapy based on the physician's decision. Interim analysis confirmed high pathological response rates with combination therapy (71%) with modest toxicity (22% in first 12 weeks) using the dosing regimen learned from the OpACIN-neo trial. Thus far, lymphadenectomy was omitted in 59 (60%) of patients. This trial is the first to look at de-escalation of surgical care with the addition of neoadjuvant immunotherapy based on patient's personalized responses to therapy.

Targeted therapy

Targeted therapy in malignant melanoma has primarily consisted of combination BRAF/MEK inhibition which target the mitogen-activated protein kinase (MAPK) signaling pathway in patients with BRAF$^{V600E/K}$ mutations. In BRAF-mutated melanoma, BRAF kinase is constitutively active resulting in increased cell proliferation.[50] Multiple BRAF kinase inhibitors have been developed for the treatment of BRAF-mutant melanoma including dabrafenib, vemurafenib, and encorafenib.[51] Combination therapy with a MEK inhibitor, which targets another kinase within the MAPK signaling pathway has been shown to overcome resistance to BRAF monotherapy.[52] Current approved MEK inhibitors for melanoma include trametinib (paired with dabrafenib), cobimetinib (paired with vemurafenib), and binimetinib (paired with encorafenib). In the following section, we highlight a few major trials utilizing BRAF/MEK inhibition in melanoma in both the adjuvant and neoadjuvant setting (Table 2).

Adjuvant targeted therapy trials

COMBI-AD

In 2020, the 5-year analysis of the COMBI-AD trial was performed. The COMBI-AD trial was a phase 3 trial showing that 12 months of dabrafenib and trametinib had significantly longer RFS in patients with stage III resected melanoma with a BRAF V600E or V600K mutation.[55] Patients had

Table 2. Neoadjuvant targeted therapy trials.

Trial	Design	Intervention	Median recurrence-free survival (months)	Pathologic complete response	Grade 3–4 adverse events
Trials with neoadjuvant and adjuvant targeted therapy					
NCT02231775 Amaria *et al.*[53]	Phase II (*n* = 21)	Arm A: Upfront surgery with consideration of adjuvant therapy Arm B: Neoadjuvant dabrafenib and trametinib for 8 weeks followed by adjuvant dabrafenib and trametinib for 44 weeks	Arm A: 2.9 (*p* < 0.0001) Arm B: 19.7	Arm A: NA Arm B: 50%	Arm A: NA Arm B: 15%
NCT01972347 Long *et al.*[54]	Phase II (*n* = 35)	Neoadjuvant dabrafenib and trametinib for 12 weeks, adjuvant therapy for 40 weeks	23.3	49%	29%
Trials with only neoadjuvant arms					
NTR4654 Blankenstein *et al.*[35]	Phase II (*n* = 20)	Neoadjuvant dabrafenib and trametinib for 8 weeks in patients with unresectable disease followed by surgery if resectable	9.9	28.6%,	19%

to have completely resected stage III melanoma and no prior systemic therapy. In the study, 438 patients were randomized to the Dabrafenib and Trametinib group and 432 to the placebo group. They found that after 5 years, 52% of patients on dabrafenib and trametinib were alive without relapse (95% CI, 48–58) compared with 36% of patients on placebo (95% CI, 32–41; HR for relapse or death = 0.51; 95% CI, 0.44–0.70). There were no significant differences between incidence or severity of adverse events between the two groups. This study showed the value of adjuvant targeted therapy in patients with BRAF V600E or V600K mutation which now provided investigators both targeted therapy and immune checkpoint inhibition as potential treatment agents for patients with BRAF$^{V600E/K}$ mutations.

Neoadjuvant targeted therapy

Neoadjuvant targeted therapy using a BRAF and MEK inhibition was first evaluated in a phase II clinical trial by Amaria *et al.* where patients with resectable stage III melanoma or oligometastatic stage IV melanoma with a BRAF$^{V600E/K}$ mutation and no previous exposure to BRAF or MEK inhibitors were randomized to upfront surgery with consideration for adjuvant therapy *versus* neoadjuvant and adjuvant dabrafenib and trametinib (8 weeks of treatment followed by surgery followed by up to

44 weeks of adjuvant therapy).[53] Seven patients underwent upfront surgery and 14 underwent neoadjuvant treatment. Median follow-up was 18.6 months. The neoadjuvant treatment group had a significantly longer disease-free survival (19.7 months *versus* 2.9 months; HR = 0.016, 95% CI, 0.00012–0.14, *p* < 0.0001). Seven of the patients in the neoadjuvant treatment group had pCR. The trial was stopped after a quarter of the participants had been accrued because of the significantly longer event-free survival in the neoadjuvant group. Adverse events were very low with only 7% developing grade 3 adverse events. This was the first trial to demonstrate the utility of BRAF and MEK inhibition in the neoadjuvant setting for high-risk melanoma.

NeoCombi trial

The NeoCombi trial was a single-arm phase II study where neoadjuvant dabrafenib and trametinib was evaluated in resectable stage IIIB-C melanoma with a BRAF$^{V600E/K}$ mutation.[54] Thirty-five patients were enrolled with all of them showing some form of pathologic response; 17 (49%) had a pCR and the remainder a partial pathologic response. Twenty of the 35 patients recurred (57%), with 14 of them developing distant metastatic disease. Median disease-free survival was 38 months among the

patients with a pCR and 27.7 months in those with a pPR. Similar to the Amaria *et al.* trial, the treatment was well tolerated with few adverse events and significantly improved RFS, but overall relapse rates were higher than previously demonstrated.

REDUCTOR trial

The REDUCTOR trial was a single-arm, phase II trial that sought to determine whether short-term neoadjuvant treatment with dabrafenib and trametinib would allow for surgical resection in patients with stage III unresectable locally advanced melanoma or stage IV oligometastatic melanoma with BRAF^V600E/K mutations.[35] Twenty-one patients were enrolled, 20 of which were stage IIIC melanoma deemed locally advanced and unresectable. Of the group, 18/21 (86%) patients were able to proceed to surgical resection after neoadjuvant treatment; 17 underwent R0 resections. RFS was 9.9 months. This study showed that it was feasible to use neoadjuvant target therapy to turn borderline resectable patients to resectable patients.

BRAF/MEK inhibition plus checkpoint blockade

These trials have demonstrated the utility of BRAF and MEK inhibition as another tool for treatment of high-risk or recurrent melanoma for patients with BRAF ^V600E/K mutations. This raises the question of the timing of BRAF and MEK inhibition therapy relative to checkpoint inhibition. Preclinical models suggest that the addition of PD-1 blockade to BRAF and MEK inhibition results in improved responses with longer duration.[56–59] This has been investigated in the adjuvant setting for patients with metastatic melanoma. Ribas *et al.* enrolled 15 patients with BRAF^V600E/K mutations and treated them with dabrafenib, trametinib, and pembrolizumab.[60] Eleven patients (73%) experience grade 3–4 treatment-related adverse events. Eleven patients (73%) showed a response and six were continuing to respond at a median follow-up of 27 months. Median progression-free survival was 15 months and median OS had not been met at time of publication. Sullivan *et al.* performed a phase I trial enrolling 56 patients with metastatic melanoma and treated them with either vemurafenib with or without cobimetinib and atezolizumab (Anti-PD-L1) and found similarly high rates of toxicity requiring dose reduction of vemurafenib.[61] In the cohort,

67% developed grade 3–4 treatment-related toxicity. The objective response rate was 72% with a median progression-free survival of 13 months. The KEYNOTE 022 trial compared dabrafenib, trametinib, and pembrolizumab *versus* dabrafenib, trametinib, and placebo in patients with metastatic melanoma. They found similar response rates, 63% with triple therapy, and 72% with BRAF and MEK inhibition. While the first two studies suggest some benefit to combined therapy, it remains unclear whether combined therapy would be superior to staggered therapy or the utility of combination therapy in the neoadjuvant setting.

Oncolytic viral therapy

T-VEC is a genetically engineered virus created from an attenuated herpes simplex virus type 1 which has been modified to promote the selective lysis of cancer cells and promote local inflammation and antigen presentation to drive immune responses against cancer cells.[17] The virus has functional deletion of two genes, ICP34.5 and ICP47 with the insertion of granulocyte stimulating factor (GM-CSF) and the US11 gene.[20,62] The deletion of the ICP34.5 gene allows for viral replication within the cancer cells specifically, and deletion of ICP47 prevents downregulation of cancer cell antigens after infection.[63,64] This allows for the virus to replicate within tumor cells causing cell lysis and release of numerous tumor antigens. The addition of GM-CSF then promotes the patient's natural immune response to the recently released tumor cell antigens resulting in a robust immune response against the tumor.

T-VEC was approved in 2015 after the multicenter phase III trial OPTiM in which 436 patients with unresectable metastatic melanoma were randomized to intralesional T-VEC injections or subcutaneous GM-CSF injections[17,18] with 239 patients receiving T-VEC and 141 receiving GM-CSF. At final analysis, median follow-up was 49 months with a median OS of 23.3 months (95% CI, 19.05–29.6) in patients receiving T-VEC and 18.9 months (95% CI, 16.0–23.7) in patients receiving GM-CSF (T-VEC HR = 0.79, 95% CI, 0.62–1.0, $p = 0.049$). Complete responses were seen in 50 (16.9%) patients receiving T-VEC and 1 (0.7%) patient who received GM-CSF. This was the first trial demonstrating a durable response with oncolytic viral therapy for melanoma.

T-VEC was investigated in the neoadjuvant setting in a multicenter phase II trial in patients with stage IIIB-IVM1a resectable melanoma.[65,66] The study included 150 patients who were randomized to either T-VEC injection (6 doses/12 weeks) followed by surgery *versus* surgery alone. The primary endpoint of the study was recurrence-free survival at 2 years. There was no protocoled adjuvant therapy for either arm. At 2 years, 50.5% of patients in the neoadjuvant T-VEC arm were recurrence free as well as 30.2% of patients in the surgery alone arm. Patients receiving neoadjuvant T-VEC therapy showed a 3× increase in intratumoral CD8+ cells ($p < 0.001$) and an overall increase in PD-L1 expression ($p < 0.05$). Intratumoral CD8+ T cell density was correlated again with RFS.[65] Neoadjuvant T-VEC improved R0 resection rates (56% *versus* 41%) but 25% of patients progressed prior to surgical resection. The increase in PD-L1 expression seen in this study was encouraging, and there are numerous trials now evaluating combination therapy of T-VEC and PD-1 inhibition.

Conclusion

Neoadjuvant therapy for stage III and resectable stage IV melanoma is a rapidly evolving subject and is thus far supported by the evidence obtained from these landmark clinical trials and preclinical models. The number of novel therapeutics developed in the last decade has given clinicians many more options for patients with advanced disease. Further studies are currently being conducted to try to answer what is the most effective way to utilize immunotherapy, targeted therapy, and oncolytic viral intralesional therapy in relation to one another and to surgery.

Author contributions
Russell G. Witt: Conceptualization; data curation; formal analysis; investigation; methodology; writing – original draft; writing – review & editing.

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