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REVIEW

Combination Atezolizumab, Cobimetinib, and Vemurafenib as a Treatment Option in BRAF V600 Mutation–Positive Melanoma: Patient Selection and Perspectives

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Abstract: The treatment landscape for advanced and metastatic melanoma has drastically changed in recent years, with the advent of novel therapeutic options such as immune checkpoint inhibitors and targeted therapies offering remarkable efficacy and significantly improved patient outcomes compared to traditional approaches. Approximately 50% of melanomas harbor activating BRAF mutations, with over 90% resulting in BRAF V600E. Tumors treated with BRAF inhibitor monotherapy have a high rate of developing resistance within six months. Combination therapy with MEK inhibitors helped to mitigate this treatment resistance and led to improved outcomes. Due to the up-regulation of PD-1/PD-L1 receptors in tumors treated with BRAF/MEK inhibitor therapy, further studies included a third combination agent, anti-PD-1/PD-L1 inhibitors. This triple combination therapy may have superior efficacy and a manageable safety profile when compared with single or double agent therapy regimens.

Plain Language Summary: Effective treatment of advanced and metastatic melanoma can be challenging. Newer treatment methods for patients with BRAF-mutated tumors include a combination of drugs with different complementary mechanisms. These drugs include BRAF-inhibitors, MEK-inhibitors, and PD-1/PD-L1 inhibitors. When these three medications are used in combination, patients may have better response rates and survival outcomes, when compared to using just one or two of these medications together. Toxicity rates are higher with a triple-medication regimen, so careful patient selection is important to consider.

Keywords: BRAF inhibitor, MEK inhibitor, metastatic melanoma, BRAF-mutant melanoma, combination BRAF therapy, triple therapy

Introduction

The treatment landscape for advanced and metastatic melanoma has drastically changed in recent years, with the advent of novel therapeutic options such as immune checkpoint inhibitors (ICI) and targeted therapies (TT) offering remarkable efficacy and significantly improved patient outcomes compared to traditional approaches.[1–3] Immune checkpoint inhibitors include anti-programmed death-1 (PD-1) agents such as pembrolizumab and nivolumab; anti-programmed death-ligand 1 (PD-L1) agents such as atezolizumab; and anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA4) inhibitors such as ipilimumab. Targeted therapies include BRAF inhibitors such as vemurafenib, encorafenib, and dabrafenib; MEK inhibitors such as cobimetinib, binimetinib, and trametinib; and dual MEK and VEGF inhibitors such as sorafenib.

Approximately 50% of melanomas harbor activating BRAF mutations, with over 90% resulting in BRAF V600E.[4] BRAF is a serine/threonine protein kinase which activates the mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK)-signaling pathway, easily activated by Ras; the V600E mutation is a single nucleotide mutation at codon 600, resulting in a substitution of glutamic acid for valine.[4] This mutation causes tumors to become resistant to down-regulation of signaling feedback pathways, which leads to constitutive activation of the kinase and proliferation of tumor cells.[4,5]

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The most common cause of treatment failure with BRAF inhibitor monotherapy is acquired resistance; which has been found to occur within 5–6 months.[6,7] Investigators have found that the mechanism of resistance involves reactivation of the MAPK pathway, upstream of MEK.[7,8] This MAPK reactivation predicts MEK inhibitor sensitivity, which has led to the use of combination BRAF and MEK inhibitor therapy.[8] In patients with BRAF V600 metastatic melanoma, combined BRAF and MEK inhibition is the current standard of care.[6,9–11]

Further studies discovered that treatment with BRAF and MEK inhibitors leads to the up-regulation of melanoma-specific T cells and PD-L1. Therefore, it is understood that these actions may sensitize tumors to PD-1 and PD-L1 targeted immunotherapy.[11] Subsequent studies focused on triple combination therapy with a BRAF inhibitor, a MEK inhibitor, and a PD-1 or PD-L1 inhibitor, have shown promising results.[2,12]

Double Combination Therapy with BRAF and MEK Inhibitors

A multicenter, double-blind, Phase 3 randomized controlled trial by Long et al in 2015 helped to establish combination therapy with BRAF and MEK inhibition as standard of care.[9] This study evaluated 423 patients from 113 sites and 14 countries with BRAF V600-mutant stage IIIC or stage IV melanoma. Patients were randomly assigned to receive dabrafenib and trametinib (n = 211) or dabrafenib only (n = 212). Median overall survival (OS) was 25.1 months in the combination therapy group compared to 18.7 months in the dabrafenib group (HR 0.71, 95% CI 0.55–0.92; P=0.01). OS at 1and 2 years in the combination group was 74% and 51%, respectively, compared to 68% and 42%, respectively in the dabrafenib only group. Median progression-free survival (PFS) was 11 months in the combination group and 8.8 months in the dabrafenib only group (HR: 0.67, 95% CI: 0.53–0.84; P=0.0004). Adverse event rates were similar between the groups.[9]

The coBRIM trial, a double-blind, phase 3 randomized controlled trial in 2015 also supported combination therapy with BRAF and MEK inhibition.[13] This study evaluated 495 patients with unresectable stage IIIC-IV BRAF-mutant melanoma, who received either vemurafenib and cobimetinib (n = 247) or vemurafenib and placebo (n = 248). Median PFS was 9.9 months in the combination therapy group, compared to 6.2 months in the vemurafenib and placebo group (HR: 0.51, 95% CI: 0.39–0.68; P<0.001). Overall response rate (ORR) was 68% in the in the combination therapy group, compared to 45% in the vemurafenib and placebo group (P<0.001). OS at 9 months was 81% in the combination therapy group, compared to 73% in the vemurafenib and placebo group (HR: 0.65, 95% CI: 0.42–1; P=0.046).[13] A follow up study of the coBRIM trial was conducted at a median follow up of 14.2 months, and found a median PFS of 12.3 months in the combination therapy group, compared to 7.2 months in the vemurafenib and placebo group (HR: 0.58, 95% CI: 0.46–0.72; P<0.0001). Median OS was 22.3 months in in the combination therapy group, compared to 17.4 months in the vemurafenib and placebo group (HR: 0.7, 95% CI: 0.55–0.9; P=0.005).[6]

A five-year outcome study in 2019 pooled the survival data from the COMBI-d and COMBI-v trials, both of which studied combination therapy with dabrafenib plus trametinib versus dabrafenib plus placebo, for previously untreated BRAF V600-mutant unresectable or metastatic stage IIIC or IV melanoma. A total of 563 patients received combination therapy with dabrafenib and trametinib, with a PFS of 21% at four years and 19% at five years. OS was 37% at four years and 34% at five years. A complete response was observed in 19% of patients, and was associated with an improved long-term survival, with OS of 71% at five years.[14,15]

Triple Combination Therapy with BRAF, MEK, and Immune Checkpoint Inhibitors

A review by Schmitt, Dumas, and Larkin in 2022 suggested that combination therapy with BRAF/MEK inhibitors and immune checkpoint inhibitors might achieve improved outcomes compared to single-mechanism therapy, due to high rates of progression or primary resistance to single-therapy type treatment regimens. They also suggested that triple therapy with atezolizumab, cobimetinib, and vemurafenib showed superior PFS in metastatic melanoma compared to double therapy with cobimetinib and vemurafenib.[16]

The Keynote-022 trial in 2020 randomly assigned 120 patients from 22 sites in 7 countries with previously untreated BRAF V600-mutated advanced melanoma to receive pembrolizumab plus dabrafenib plus trametinib (n = 60), or placebo plus dabrafenib plus trametinib (n = 60).[17] After 36.6 months of follow-up, this study found a median PFS of 16.9 months in the triple therapy group, compared to 10.7 months in the double therapy group (HR: 0.53, 95% CI: 0.34–0.83). At 2 years, PFS was 41% in the triple therapy group compared to 16.3% in the double therapy group. Median duration of response (DOR) was 25.1 months in the triple therapy group and 12.1 months in the double therapy group. Median OS was not reached in the triple therapy group and was 26.3 months in the double therapy group (HR: 0.64, 95% CI: 0.38–1.06). At 2 years, OS was 63% in the triple therapy group and 51.7% in the double therapy group.[17] (Table 1)

Table 1 Triple Combination Therapy Trials with BRAF, MEK, and Immune Checkpoint Inhibitors for BRAF V600-Mutated Melanoma

Trial	Year	Sample Size	Therapeutic Agents	Follow-up (Months)	Median PFS (Months)	2-Year PFS	OS (Months)	2-Year OS	ORR	DOR (Months)	2-year DOR
Keynote 022[17]	2020	120	P/D/T (n = 60) vs Placebo/D/T (n = 60)	36.6	16.9 vs 10.7	41% vs 16.3%	Not reached vs 26.3	63% vs 51.7%	63% vs 72%	25.1 vs 12.1	N/A
COMBI-i[18]	2022	532	S/D/T (n = 267) vs Placebo/D/T (n = 265)	27.2	16.2 vs 12	44% vs 36%	Not reached vs Not reached	68% vs 62%	69% (20% CR) vs 64% (18% CR)	Not reached vs 20.7	55% vs 48%
Phase I trial by Shaikh et al[19]	2022	9	P/C/V (n = 5) vs P/V (n = 4)	N/A	Not reached vs 20.7	N/A	Not reached vs 23.8	N/A	N/A	N/A	N/A
IMspire 150[12]	2020	514	A/C/V (n = 256) vs Placebo/C/V (n = 258)	18.9	15.1 vs 10.6	N/A	N/A	N/A	N/A	N/A	N/A
IMspire 150 follow-up by Ascierto et al[20]	2023	514	A/C/V (n = 256) vs Placebo/C/V (n = 258)	29.1 (A/C/V) and 22.8 (Placebo/C/V)	N/A	N/A	39 vs 25.8	N/A	N/A	N/A	N/A

Abbreviations: PFS, Progression-free survival; OS, Overall survival; ORR, Overall response rate; DOR, Durable response rate; P, Pembrolizumab; D, Dabrafenib; T, Trametinib; S, Spartalizumab; C, Cobimetinib; V, Vemurafenib; A, Atezolizumab.

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The COMBI-i trial in 2022, a randomized, double-blind, placebo-controlled phase 3 trial, conducted at 173 centers in 29 countries, evaluated triple combination therapy with spartalizumab, dabrafenib, and trametinib in patients with BRAF V600-mutant unresectable or metastatic melanoma.[18] A total of 532 patients received either triple therapy with spartalizumab, dabrafenib, and trametinib (n = 267), or double therapy with a placebo, dabrafenib, and trametinib (n = 265). Median follow up was 27.2 months. The median PFS was 16.2 months in the triple therapy group compared to 12 months in the double therapy group. Estimated 2-year PFS rates were 44% in the triple therapy group compared to 36% in the double therapy group. Patients with PD-L1-positive tumors had a longer median PFS in both treatment arms. Median OS was not reached in either treatment arm. Estimated 2-year OS rates were 68% in the triple therapy group and 62% in the double therapy group. The ORR for triple therapy was 69%, with 20% of patients achieving a complete response (CR). The ORR for double therapy was 64%, with 18% of patients achieving CR. The median DOR was not reached in the triple therapy group and was 20.7 months in the double therapy group. Estimated 2-year DOR rates were 55% in the triple therapy group and 48% in the double therapy group.[18]

Similar findings were supported by a smaller phase I trial which compared triple therapy with vemurafenib, cobimetinib, and pembrolizumab (n = 5) versus double therapy with vemurafenib and pembrolizumab (n = 4) for untreated BRAF V600E/K-mutant advanced melanoma. Median PFS was not reached for patients receiving triple therapy, compared to 20.7 months with double therapy. Median OS was not reached for patients receiving triple therapy, compared to 23.8 months with double therapy.[19]

Therapy Specifically with Atezolizumab, Cobimetinib, and Vemurafenib

The United States Food and Drug Administration (FDA) approved the use of atezolizumab in combination with cobimetinib and vemurafenib for patients with BRAF V600-mutant unresectable or metastatic melanoma in July 2020. Critical study results leading to FDA approval were from the IMspire150 trial.

The IMspire150 trial in 2020, a randomized, double-blind, placebo-controlled, phase 3 trial, evaluated triple combination therapy with atezolizumab, cobimetinib, and vemurafenib as first-line treatment for unresectable advanced BRAF V600 mutation-positive melanoma, including 112 institutions in 20 countries between 2017 and 2018. After a median follow-up of 18.9 months, the triple therapy group (n = 256) was found to have significantly longer PFS than the control group, who received cobimetinib, vemurafenib, and placebo (n = 258) (15.1 vs 10.6 months; HR 0.78; 95% CI 0.63–0.97; P=0.025).[12] A subsequent biomarker analysis of these patients was undertaken by Robert et al, which found that the PFS benefits in the atezolizumab, cobimetinib, and vemurafenib group were most evident in patients with elevated LDH and PD-L1-negative tumors.[10] A follow-up study by Ascierto et al with a median follow-up of 29.1 months for the atezolizumab, cobimetinib, and vemurafenib group and 22.8 months for the control group, found a median OS of 39 months for the triple therapy group and 25.8 months for the control group, although the difference was not statistically significant.[20]

The TRICOTEL trial in 2023, a multicenter, open-label, single-arm Phase 2 study evaluated the triple therapy regimen atezolizumab, cobimetinib, and vemurafenib in patients with previously untreated BRAF V600-mutant melanoma with brain metastases at least 5 mm (n = 65). Median follow up time was 9.7 months. Intracranial ORR was 42%.[21]

A phase Ib study in 2019 by Sullivan et al treated patients with BRAF V600-mutant metastatic melanoma with either atezolizumab and vemurafenib or cobimetinib and vemurafenib for 28 days, and then triple therapy with atezolizumab, cobimetinib, and vemurafenib (n = 48). The ORR was 71.8% and median DOR was 17.4 months, with ongoing response in 39.3% of patients after 29.9 months of follow-up.[11]

A systematic review in 2022 by Corrie et al, which analyzed multiple treatment regimens for BRAF-mutant melanoma, found that combination therapy was superior to monotherapy with respect to OS, PFS, and ORR. Furthermore, this study found that combination therapy with atezolizumab, cobimetinib, and vemurafenib had similar results to combination therapy with encorafenib and binimetinib, with respect to OS and PFS. The ORR for atezolizumab, cobimetinib, and vemurafenib was superior to double-regimen therapies, with the exception of encorafenib and binimetinib.[22] The encorafenib and binimetinib regimen was also found to have fewer treatment-related adverse events (TRAEs) compared to triple therapy with atezolizumab, cobimetinib, and vemurafenib.[22]

Toxicity

Triple-therapy combination regimens tend to have a substantial but manageable toxicity.[11,12,20] The Keynote-022 trial found a higher rate of grade 3–5 TRAEs in patients who received triple therapy (58% with pembrolizumab, dabrafenib, and trametinib) compared to those who received double therapy (25% with dabrafenib and trametinib).[17] The COMBI-i trial had similar findings, with 70% of the triple therapy group and 57% of the double therapy group experiencing at least one grade 3 or higher TRAE; discontinuation of treatment due to TRAEs was 19% in the triple therapy group and 9% in the double therapy group.[18] A small phase I trial which treated five patients with triple therapy (vemurafenib, cobimetinib, and pembrolizumab) was closed early due to significant adverse events.[19] The TRICOTEL trial found that 68% of patients who received atezolizumab, cobimetinib, and vemurafenib experienced grade 3 or higher TRAEs.[21] Adverse effects of the atezolizumab, cobimetinib, and vemurafenib combination regimen include increased lipase, increased blood creatine phosphokinase, hepatotoxicity, nausea, fatigue, musculoskeletal pain, diarrhea, pyrexia, and rash.[12,20,21] Overall, the increased risk of toxicity with a triple therapy regimen must be weighed against the superior progression and survival outcomes of triple therapy compared to single or double agent therapy.

Discussion

Based on current literature, triple combination therapy with BRAF, MEK, and anti-PD-1/PD-L1 inhibition is an effective treatment regimen for patients with advanced or unresectable metastatic BRAF V600-mutant melanoma. Nearly all studies have shown superior short and long-term outcomes with this triple therapy regimen compared to monotherapy or double therapy regimens with BRAF and MEK inhibitors alone. Each of the three therapy modalities complement each other with respect to mechanism of action and sensitization. Resistance to BRAF inhibitor monotherapy predicts sensitization to MEK inhibition, and combination therapy with BRAF and MEK inhibition leads to up-regulation of PD-1/PD-L1 and sensitization to PD-1 and PD-L1 inhibition.[8,10] The specific regimen with atezolizumab, cobimetinib, and vemurafenib has a high efficacy rate and a reasonable safety profile when used as first-line therapy.

One systematic review found a similar OS and PFS, and a higher ORR in patients treated with encorafenib and binimetinib, compared to those treated with atezolizumab, cobimetinib, and vemurafenib.[22] These regimens should be compared with head-to-head randomized controlled trials to validate these results.

Various immunotherapy regimens may be considered in combination with targeted BRAF and MEK inhibition. For example, a phase 2/3 global double-blind randomized trial found that combining relatlimab, a LAG-3 blocking antibody, with nivolumab for untreated metastatic or unresectable melanoma had superior PFS (10.1 vs 4.6 months; HR 0.75; 95% CI 0.62–0.92; P=0.006) when compared to therapy with single-agent nivolumab.[23]

Patient Selection

Data from randomized controlled trials support the use of upfront triple therapy with BRAF, MEK, and PD-1/PD-L1 inhibition for patients at high risk for rapid progression or death, such as those with high tumor burden at multiple distant metastatic sites.[2] The increased risk of toxicity with triple therapy compared to double agent therapy must be considered to maximize disease control while maintaining treatment tolerability. Ideal patient selection for triple therapy would include an acceptable baseline activity status, relatively low-risk medical comorbidities, and high disease burden. However, even in the setting of a patient with high-risk comorbidities, if the disease burden is high with multiple distant metastatic sites, triple therapy should still be considered to attempt to achieve rapid disease control. In these patients, dose modifications can be especially useful to improve tolerability.

Conclusion

Patients with advanced unresectable or metastatic BRAF V600-mutant melanoma at high risk of rapid disease progression, such as those with a high tumor burden, may benefit from upfront triple combination therapy with BRAF, MEK, and PD-1/PD-L1 inhibition. Triple therapy regimens are associated with higher toxicity, but offer superior short and long-term outcomes including OS, PFS, ORR, and DOR, when compared to single or double agent therapy. The specific regimen with atezolizumab, cobimetinib, and vemurafenib has a high efficacy rate and a reasonable safety profile.

Abbreviations

ICI, immune checkpoint inhibitors; TT, targeted therapies; PD-1, programmed death-1; PD-L1, programmed death-ligand 1; CTLA4, cytotoxic T-lymphocyte-associated protein 4; MAPK, mitogen-activated protein kinase; ERK, extracellular signal-regulated kinase; OS, overall survival; PFS, progression-free survival; ORR, overall response rate; DOR, duration of response; TRAEs, treatment-related adverse events.

Data Sharing Statement

All data supporting the statements in this manuscript have been referenced and can be found by utilizing any search engine to obtain published articles in peer-reviewed medical journals.

Ethics Approval and Informed Consent

This study, being a review article, is exempt from IRB approval and informed consent.

Consent for Publication

No previously published images or other media are being presented in this manuscript.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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