Atezolizumab plus Bevacizumab in Patients with Unresectable or Metastatic Mucosal Melanoma: A Multicenter, Open-Label, Single-Arm Phase II Study

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ABSTRACT

Purpose: Anti–programmed cell death-1 monotherapy is part of standard therapy for cutaneous melanoma but has low efficacy in mucosal melanoma. We evaluated the efficacy and safety of atezolizumab plus bevacizumab as first-line therapy for advanced mucosal melanoma.

Patients and Methods: This multicenter, open-label, single-arm, phase II study used a Simon's two-stage design. Atezolizumab (fixed-dose, 1,200 mg) and bevacizumab (7.5 mg/kg) were administered by intravenous infusion every 3 weeks. The primary endpoint was objective response rate (ORR), determined per RECIST v1.1. Secondary endpoints included progression-free survival (PFS), overall survival (OS), duration of response (DOR), and safety, with adverse events (AE) summarized using NCI-CTCAE v5.0.

Results: Overall, 43 patients were enrolled, including 20 (46.5%) with unresectable and 23 (53.5%) with metastatic mucosal melanoma. Median follow-up was 13.4 months at data cutoff (July 30, 2021). Forty patients were evaluable for response: ORR was 45.0% [95% confidence interval (CI), 29.3%–61.5%; one complete response, 17 partial responses]. Median PFS was 8.2 months (95% CI, 2.7–9.6); 6- and 12-month PFS rates were 53.4% (95% CI, 36.6%–67.6%) and 28.1% (95% CI, 14.2%–43.9%), respectively. Median OS was not reached (NR; 95% CI, 14.4–NR). Six- and 12-month OS rates were 92.5% (95% CI, 78.5%–97.5%) and 76.0% (95% CI, 57.1%–87.5%), respectively. Median DOR was 12.5 months (95% CI, 5.5–NR). Overall, 90.7% (39/43) of patients experienced treatment-related AEs; 25.6% (11/43) experienced grade ≥3 events.

Conclusions: Atezolizumab in combination with bevacizumab showed promising efficacy and manageable safety in patients with advanced mucosal melanoma.

Introduction

Mucosal melanoma is a rare subtype of melanoma that arises from melanocytes in mucosal surfaces of the body (including the nasal cavity, sinuses, mouth, anus, and vagina; refs. 1, 2). In Caucasians, mucosal melanoma has a relatively low incidence compared with the overall incidence of all melanomas diagnosed (1.3%; ref. 3), while among Asians it is the second most common subtype after acral melanoma, accounting for 22.6% to 30.6% of melanomas (4–7).

Previous studies have shown that immune checkpoint inhibitors (ICI) have modest efficacy in patients with mucosal melanoma. Response rates to anti–programmed death-1/programmed death ligand-1 (PD-1/PD-L1) antibody monotherapy in patients with advanced mucosal melanoma ranged from 0% to 23.3%, while the median progression-free survival (PFS) was 1.9–5.9 months (8–12).

Combined therapy with cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) and PD-1 inhibitors showed a relatively higher objective response rate (ORR) of 37.1%, but the addition of CTLA-4 inhibitors led to an increased risk of grade 3/4 treatment-related adverse events (TRAE; 54% vs. 26%; ref. 10). A similar finding was observed in a Japanese study (13). There remains an unmet need for new, more effective, and tolerable strategies in patients with mucosal melanoma.

VEGF is highly expressed in patients with melanoma and contributes to disease progression (14, 15). In addition to its role in vascular growth, VEGF has also emerged as an important immunosuppressive agent in the tumor microenvironment. Therefore, combining VEGF inhibitors with ICIs has been investigated as a treatment strategy across multiple cancer types with positive outcomes (16–18). In patients with advanced mucosal melanoma, axitinib, a VEGF receptor inhibitor, in combination with toripalimab, a humanized IgG4 monoclonal antibody that targets PD-1, has been reported to exert strong antitumor activity (ORR; 48.3%; ref. 19). These results suggest that combination therapy with a VEGF receptor inhibitor and PD-1/PD-L1 inhibitor may be a promising strategy in treating mucosal melanoma.

Combined therapy with atezolizumab, a humanized IgG1 monoclonal antibody that targets PD-L1, and bevacizumab, a recombinant humanized monoclonal IgG1 antibody that inhibits VEGF, has shown strong antitumor activity in advanced liver and lung cancer (17, 20). Furthermore, both of these agents have shown some efficacy in melanoma as monotherapy. For example, in a phase I study of atezolizumab, a response was noted in 1 patient with mucosal melanoma (1/5; 20%; ref. 21). Bevacizumab monotherapy showed an ORR of 17% in 35 patients with metastatic melanoma in an open-label,

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Translational Relevance

Immune checkpoint inhibitors (ICI) have modest efficacy in patients with mucosal melanoma. Anti–programmed death-1/programmed death ligand-1 (PD-1/PD-L1) antibody monotherapy has limited benefit, and while combined therapy with cytotoxic T lymphocyte–associated protein 4 and PD-1 inhibitors improves response rates, toxicity is increased. VEGF is highly expressed in melanoma and contributes to progression, and combined treatment with ICIs and VEGF inhibitors has shown positive outcomes across various cancer types. This phase II study evaluated the PD-L1 inhibitor atezolizumab and the VEGF inhibitor bevacizumab as first-line therapy in Chinese patients with advanced mucosal melanoma. Over a median follow-up of 13.4 months, the objective response rate was 45.0% in 40 evaluable patients. Atezolizumab in combination with bevacizumab showed promising efficacy and manageable safety. This study sheds light on the dual strategy of VEGF and PD-L1 inhibition in patients with this rare melanoma subtype, for whom prognosis is otherwise generally poor.

single-arm, phase II study (22). In addition, in a randomized phase II study of bevacizumab in combination with carboplatin plus paclitaxel in patients with previously untreated advanced mucosal melanoma, the ORRs for bevacizumab plus chemotherapy compared with chemotherapy alone were 19.7% and 13.2%, respectively (23).

Considering that bevacizumab increases the expression of favorable chemokines in the tumor microenvironment and improves the efficacy of immunotherapy (24, 25), along with the positive results seen with axitinib plus toripalimab, the combination of atezolizumab and bevacizumab may be a promising treatment regimen for patients with advanced mucosal melanoma. Here, we report the results from a multicenter, open-label, single-arm, phase II study, which evaluated the efficacy and safety of atezolizumab plus bevacizumab in patients with unresectable or metastatic mucosal melanoma.

Patients and Methods

Study design

This was an open-label, single-arm, phase II study conducted at three independent melanoma centers in China, including Peking University Cancer Hospital and Institute, Fujian Cancer Hospital, and the Cancer Hospital of the University of Chinese Academy of Sciences, from November 20, 2019 to December 3, 2020. We adopted a Simon's two-stage design (26).

The study protocol was reviewed and approved by the institutional review boards at each participating institution and the study was conducted in accordance with the principles of the Declaration of Helsinki. All patients provided written informed consent prior to screening. The study was registered at ClinicalTrials.gov (NCT04091217).

Patients

This study included adult (≥18 and ≤75 years) patients with histologically and radiologically confirmed unresectable (Stage III) or metastatic (Stage IV) mucosal melanoma, measurable disease per RECIST v1.1 at baseline, an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1, life expectancy ≥12 weeks, and adequate organ and bone marrow function. Exclusion criteria included a history of autoimmune diseases; ongoing infections; prior anti–PD-1, anti–PD-L1, or anti–PD-L2 immunotherapy; and unstable brain metastasis.

The anatomic locations of mucosal melanoma were divided into the "upper" and "lower" regions; upper sites included the head and neck and upper gastrointestinal tract, while lower sites included the lower gastrointestinal tract, anorectal, and genital regions (27).

Treatment

Atezolizumab was administered at a fixed dose of 1,200 mg by intravenous infusion every 3 weeks (1,200 mg on day 1 of each 21-day cycle). Bevacizumab was administered at a dose of 7.5 mg/kg by intravenous infusion every 3 weeks (7.5 mg/kg on day 1 of each 21-day cycle). If a body-weight change of > 10% from baseline was observed, the treatment dosage was modified accordingly. No other dose modification was allowed for atezolizumab or bevacizumab. Atezolizumab was administered first, followed by bevacizumab, with a minimum of 5 minutes between dosing. Atezolizumab and/or bevacizumab were administered until disease progression or unacceptable toxicity. A list of prohibited therapies is included in the Supplementary Methods.

Endpoints and measurements

Efficacy

The primary efficacy endpoint was ORR, defined as the proportion of patients with a complete response (CR) or partial response (PR) on two consecutive occasions ≥4 weeks apart, as determined by the investigator according to RECIST v1.1. The secondary efficacy endpoints were also determined by the investigator. These included PFS (the time from the date of first treatment to the first occurrence of disease progression or death from any cause); overall survival (OS; the time from the date of first treatment to death from any cause); duration of objective response (DOR; the time from the first occurrence of a documented confirmed objective response to disease progression or death from any cause).

Patients underwent tumor assessments at baseline, every 6 weeks (±1 week) for the first 54 weeks following treatment initiation, and every 12 weeks thereafter, regardless of dose delays, until radiographic confirmed disease progression per RECIST v1.1, discontinuation criteria were met, or trial completion or termination occurred.

Safety

Safety was evaluated by recording the incidence and severity of adverse events (AE), with severity determined according to the NCI Common Terminology Criteria for Adverse Events, Version 5.0 (CTCAE v5.0). Dose delays or discontinuations were used to manage toxicity, but dose reduction was not allowed.

Mutation analysis

Detection of mutations in the *BRAF*, *NRAS*, and *KIT* genes were performed on the primary or metastatic tumor tissue from patients enrolled in this study during routine testing, and these results were collected at screening.

Statistical methods

The sample size calculation was based on a Simon's two-stage design. For the sample size calculation, the primary outcome of ORR was estimated as 40%, the two-sided alpha level was set to be 0.05 and statistical power 80%. This provided a required sample size of 22 fully evaluable patients for Stage I. If more than 3 patients of 22 achieved a CR or PR at the end of Stage I, then an additional 16 fully evaluable patients were enrolled into Stage II. Accounting for a dropout rate of

10%, the total enrollment target was 25 patients for Stage I and 18 patients for Stage II, giving a total of 43 patients [intention-to-treat (ITT) population]. If more than 12/38 patients had achieved a CR or PR at the end of Stage II, then a statistically significant improvement in ORR could be concluded.

Baseline demographic and clinical characteristics were evaluated in all enrolled patients, regardless of whether they received any assigned study drug (ITT population). The efficacy analysis was performed in a full analysis set (FAS) population, defined as all enrolled patients who received any amount of study treatment and were evaluable for efficacy endpoints. PFS and OS data were also analyzed in the ITT population. Patients who completed at least one imaging evaluation after treatment were considered evaluable and formed the FAS population. The safety analysis included all enrolled patients who received at least one dose of any study treatment.

For baseline characteristics, frequencies were calculated for categorical variables and summary statistics [median (range), mean (SD), or 95% confidence interval (CI)] were calculated for continuous data. For the primary efficacy endpoint (ORR), the number and percentage of confirmed responders (CR/PR) with corresponding Clopper–Pearson 95% CIs were presented. Time-to-event variables, such as PFS, OS, and DOR, were estimated using the Kaplan–Meier method with associated 95% CIs and compared using a log-rank test. All statistical analyses were conducted using SAS version 9.4 (SAS Institute, Inc.).

Data availability

The datasets used in the current analysis are available from the corresponding author upon reasonable request.

For up-to-date details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here: https://go.roche.com/data_sharing.

Anonymized records for individual patients across more than one data source external to Roche cannot, and should not, be linked due to a potential increase in risk of patient reidentification.

Results

Patient demographics

A total of 53 patients were screened; 43 were enrolled, received atezolizumab and bevacizumab, and were therefore included in the ITT and safety populations. Of these patients, 40 were included in the FAS population. Three patients were unevaluable for response: one was lost from follow-up after two cycles; one died after one course due to an immune-related AE of pneumonitis; and one developed new lesions and withdrew from the study. A patient flow diagram is shown in Supplementary Fig. S1.

Patient demographics and baseline clinical characteristics are summarized in **Table 1**. The median age (range) was 61 (33–73) years, most patients had an ECOG PS of 0 [32/43 (74.4%)], and 23 (53.5%) patients had metastatic disease. The median baseline sum of diameters of target lesion was 36.3 mm (range 10.0–217.0). Twenty-two (51.2%) patients had mucosal melanomas arising in the upper region and 21 (48.8%) in the lower region. The most common metastatic sites included the lung [13/23 (56.5%)], lymph node [10/23 (43.5%)], and liver [5/23 (21.7%)]. *BRAF*, *NRAS*, and *KIT* mutations were detected in 1 (2.3%), 6 (14%), and 6 (14%) patients, respectively.

Table 1. Patient demographics and baseline clinical characteristics (ITT population).

		Atezolizumab + bevacizumab *N* = 43
Age (years)	Median (range)	61.0 (33–73)
Sex, *n* (%)	Female	22 (51.2)
	Male	21 (48.8)
Ethnicity, *n* (%)	Asian	43 (100)
ECOG PS at baseline, *n* (%)	0	32 (74.4)
	1	11 (25.6)
LDH at baseline, *n* (%)	≤ULN	33 (76.7)
	>ULN	10 (23.3)
BSLD (mm)	Median (range)	36.3 (10.0–217.0)
Advanced stage classification, *n* (%)	Unresectable disease	20 (46.5)
	Metastatic disease	23 (53.5)
Number of metastatic organ sites, *n* (%)	*n*[a]	23
	<3	20 (87.0)
	≥3	3 (13.0)
Metastatic site	*n*[a]	23
	Lung	13 (56.5)
	Lymph node	10 (43.5)
	Liver	5 (21.7)
	Bone	2 (8.7)
	Other	2 (8.7)
	Adrenal gland	1 (4.3)
BRAF	Wild-type	42 (97.7)
	Mutant	1 (2.3)
NRAS	Wild-type	37 (86.0)
	Mutant	6 (14.0)
KIT	Wild-type	36 (83.7)
	Mutant	6 (14.0)
	NA	1 (2.3)
Primary disease site	Urogenital	11 (25.6)
	Head-neck	15 (34.9)
	Gastrointestinal	17 (39.5)
Disease stage	Stage III	19 (44.2)
	Stage IV	24 (55.8)

Abbreviations: BSLD, baseline sum of longest diameter; ULN, upper limit of normal.
[a]Percentages are based on the population with metastatic mucosal melanoma.

Efficacy

In Stage I analysis set ($n = 22$), the best confirmed ORR according to RECIST v1.1 was 40.9% (9/22; 95% CI, 20.7%–63.6%), including one CR and eight PRs. As the Stage I results did not cross the futility boundary, the study then ran into Stage II. As of July 30, 2021, the median follow-up duration was 13.4 months (range: 10.9–15.2). The best confirmed ORR in the FAS population was 45.0% (18/40; 95% CI, 29.3%–61.5%), including one CR and 17 PRs (**Table 2**). The best confirmed ORR for unresectable and metastatic mucosal melanoma patients was 50.0% (95% CI, 26%–74%) and 40.9% (95% CI, 21%–64%), respectively (Supplementary Table S1). The sum of diameters of target lesions decreased (any size) from baseline in 65% ($n = 26$) of patients (**Fig. 1A**). The median time-to-objective response was 2.7 months (95% CI, 1.31–2.99; **Fig. 1B**). Changes from baseline in individual tumor burden over time are shown in **Fig. 1C**.

Regarding the secondary efficacy endpoints, the median PFS was 8.2 months (95% CI, 2.7–9.6; **Fig. 2**), the 6-month PFS rate was 53.4% (95% CI, 36.6%–67.6%), and the 12-month PFS rate was 28.1% (95% CI, 14.2%–43.9%). Among all 18 responders, the median DOR was 12.5 months (95% CI, 5.5–NR), with ongoing responses in 8 patients at data cutoff. The median OS was not reached (NR; 95% CI, 14.4–NR;

Table 2. Confirmed best overall response rates according to RECIST v1.1 (FAS).

	Atezolizumab + bevacizumab *N* = 40
Best overall response, *n* (%)	
CR	1 (2.5)
PR	17 (42.5)
SD	8 (20.0)
PD	13 (32.5)
Not evaluable	1 (2.5)
ORR (CR+PR), *n* (%)	18 (45.0)
(95% CI)	(29.3–61.5)
Disease control rate (CR+PR+SD), *n* (%)	26 (65.0)
(95% CI)	(48.3–79.4)
DOR, months (95% CI)	12.5 (5.5–NR)

Abbreviations: PD, progressive disease; SD, stable disease.

Supplementary Fig. S2), the 6-month OS rate was 92.5% (95% CI, 78.5%–97.5%), and the 12-month OS rate was 76.0% (95% CI, 57.1%–87.5%).

In the ITT population ($N = 43$), the median PFS was 6.9 months (95% CI, 2.7–9.5), the 6-month PFS rate was 52.1% (95% CI, 35.6%–66.3%), and the 12-month PFS rate was 27.5% (95% CI, 13.9%–42.9%).

In the ITT population, the median OS was NR (95% CI, 13.1–NR), the 6-month OS rate was 90.7% (95% CI, 77.1%–96.4%), and the 12-month OS rate was 72.9% (95% CI, 54.9%–84.7%).

Descriptive analysis demonstrated that median PFS was significantly improved in patients with primary lesions that originated from the upper region (15.2 months) compared with those with tumors in the lower region (5.3 months; HR, 0.31; 95% CI, 0.13–0.72). For patients with an *NRAS* mutation (five were evaluable), a favorable trend of PFS was observed; the median PFS was 9.6 months for *NRAS*-mutant patients versus 6.9 months for *NRAS*-wild-type patients (HR, 0.41; $P = 0.21$). Moreover, patients with *NRAS* mutations exhibited a higher ORR than *NRAS*-wild-type patients (100% vs. 37.1%, $P = 0.01$; Supplementary Table S2 and S3).

Safety

All 43 patients were evaluable for safety. The overall incidence of AEs of any grade was 95.3% (41/43 patients), and the incidence of grade ≥3 AEs was 25.6% (11/43 patients; **Table 3**).

The most frequent AEs of any grade were blood lactate dehydrogenase (LDH) increased (37.2%), blood cholesterol increased (25.6%), aspartate aminotransferase (AST) increased (23.3%), alanine aminotransferase (ALT) increased (20.9%), and hypothyroidism (20.9%; **Table 4**). The incidence of TRAEs was 90.7% (39/43 patients); 39 patients (90.7%) developed TRAEs attributed to atezolizumab and 38 patients (88.4%) had a bevacizumab-related TRAE (**Table 3**). One death occurred on day 17, which was considered to be treatment-related and

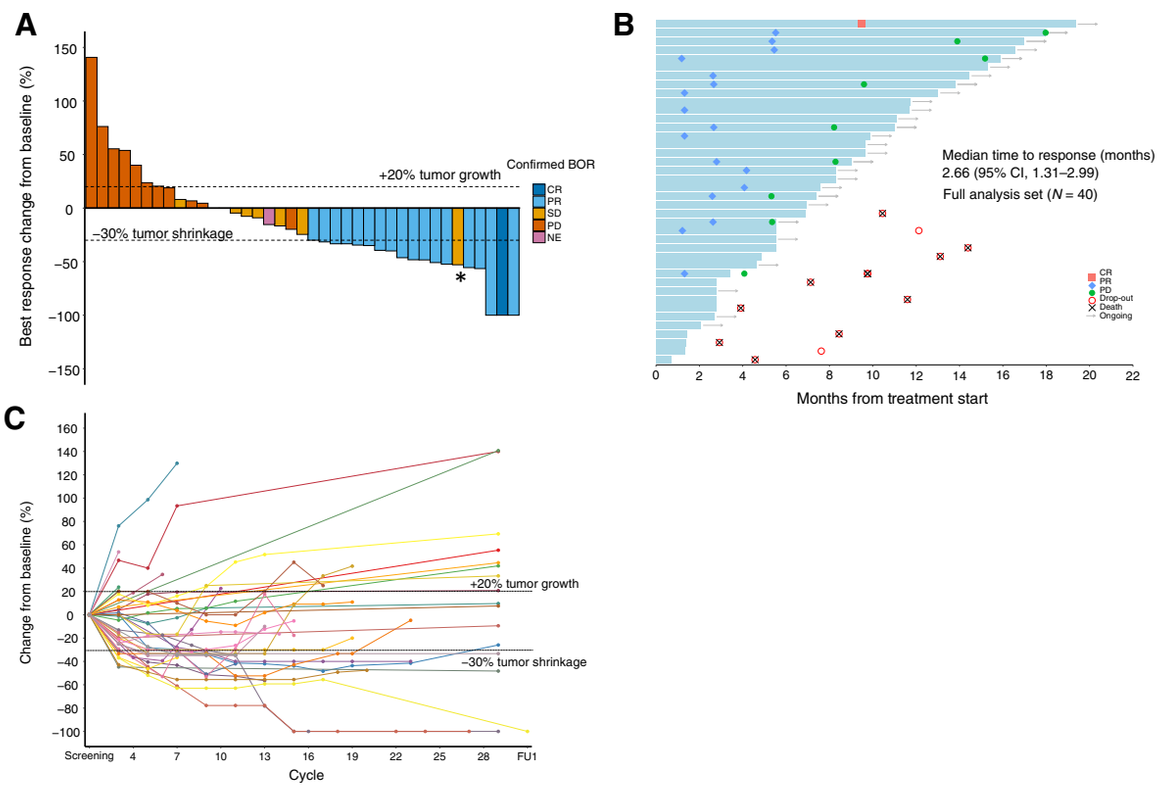

Figure 1.
Waterfall (**A**)[a], swimmer (**B**), and spider (**C**) plots for confirmed best overall response. [a]Data for 39/40 evaluable patients are presented because 1 patient had baseline data but subsequently had new lesions and withdrew from the study. No data regarding changes in tumor size were available for this patient. *The patient with tumor shrinkage of 50% was considered to have SD owing to an initial response followed by an assessment of SD. Each color line in **C** corresponds to an individual patient. BOR, best overall response; FU, follow-up; SD, stable disease; PD, progressive disease; NE, not evaluable.

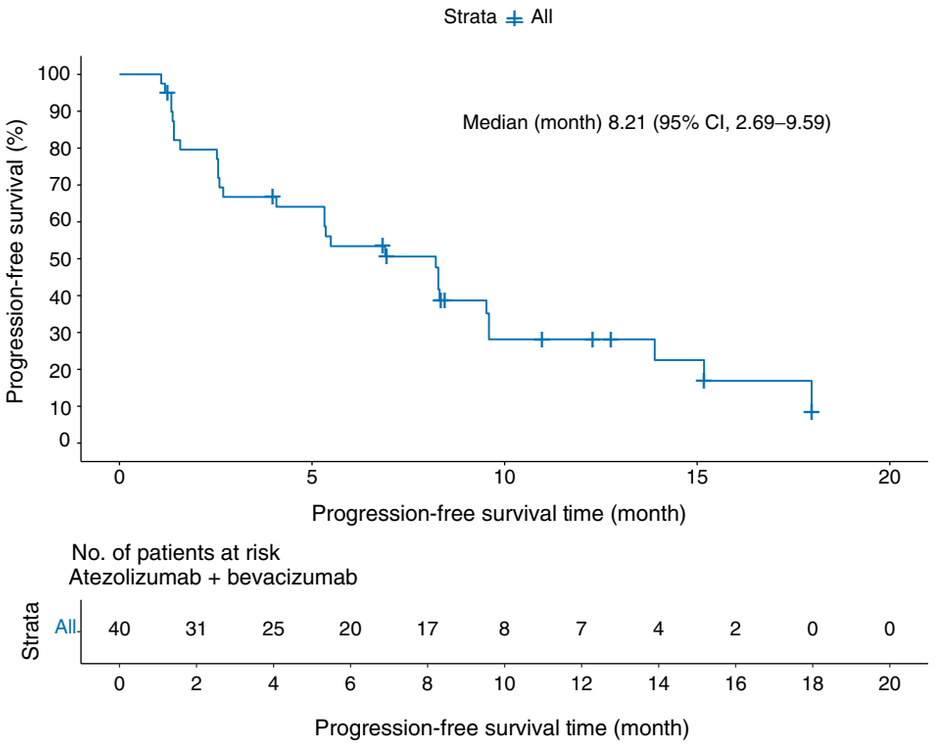

Figure 2.
Kaplan–Meier curve for PFS.

attributed to immune-related pneumonitis/acute respiratory distress syndrome. No patients required dose reductions. One patient discontinued treatment due to grade 5 pneumonitis (Supplementary Table S4).

Of note, 11 of 43 patients included in the ITT population had temporary treatment disruptions due to the COVID-19 pandemic. Among them, 2 patients had detailed information missing, and treatment was delayed in the remaining 9 patients. Three of these 9 patients discontinued due to disease progression before treatment could be resumed. For the other 6 patients, the median days of delayed treatment was 50.5 (range: 21–223 days).

Discussion

This open-label, single-arm, phase II trial demonstrated that atezolizumab plus bevacizumab has antitumor activity in patients with advanced mucosal melanoma. We observed a median PFS of 8.2 months and an ORR of 45.0%. Our results are consistent with a prior study of axitinib in combination with toripalimab in patients with advanced mucosal melanoma that reported an ORR and median PFS of 48.3% and 7.5 months, respectively (19). Taken together, these findings highlight the value of combination therapy with a VEGF inhibitor and anti–PD-1 antibodies in the treatment of advanced mucosal melanoma.

Previous studies have shown that ICI monotherapy has lower efficacy in patients with mucosal melanoma compared with those with cutaneous melanomas. In contrast, the ORR and median PFS observed with atezolizumab plus bevacizumab in the current study were higher than these previous reports of PD-1/PD-L1 inhibitor monotherapy in mucosal melanoma (7–11).

Furthermore, in our study, atezolizumab plus bevacizumab demonstrated better efficacy than reported in a prior study of bevacizumab plus chemotherapy in the first-line treatment of advanced mucosal melanoma (22). It is possible that the high antitumor efficacy associated with the combination of PD-1/PD-L1 blockade and VEGF-targeted therapy is not only due to a combined suppressive effect on tumor growth, but may also be exerted through a transient additive effect of the drugs, resulting in remodeling of the immunosuppressive tumor microenvironment by anti-VEGF therapy into an immunostimulatory state, thereby increasing the effectiveness of ICI therapy (28).

NRAS mutations were observed in 6 patients in this study. Of these patients, five were evaluable for response and achieved a PR. These findings were supported by a multi-institutional retrospective analysis which reported an ORR of 64% in 11 patients with *NRAS* mutations who received anti–PD-1/PD-L1 treatment (29). A potential explanation for this finding is that PD-L1 expression appeared to be modestly higher in *NRAS*-mutation–positive resected tumor samples compared with those with *BRAF* mutations or wild-type melanoma (29). Another possible explanation is that *NRAS* mutations may occur in melanomas with a higher tumor mutational burden (30). As the PD-L1 status and

Table 3. Summary of AEs (safety analysis set).

	Atezolizumab + bevacizumab *N* = 43
Any AE	41 (95.3)
Grade ≥3 AE	11 (25.6)
AE leading to treatment interruption	7 (16.3)
AE leading to treatment discontinuation	2 (4.7)
AE leading to death	1 (2.3)
Atezolizumab-related AE	39 (90.7)
Atezolizumab-related serious AE	7 (16.3)
Bevacizumab-related AE	38 (88.4)
Bevacizumab-related serious AE	7 (16.3)

Note: Data are *n* (%).

Table 4. Summary of AEs with an incidence ≥ 10% (safety analysis set).

	Any grade $N = 43$	Grade ≥3
Blood LDH increased	16 (37.2)	0
Blood cholesterol increased	11 (25.6)	0
AST increased	10 (23.3)	0
ALT increased	9 (20.9)	1 (2.3)
Hypothyroidism	9 (20.9)	0
Blood bilirubin increased	8 (18.6)	0
Blood triglycerides increased	8 (18.6)	0
Pyrexia	8 (18.6)	0
Blood uric acid increased	7 (16.3)	0
Blood creatine phosphokinase increased	6 (14.0)	1 (2.3)
Gamma-glutamyltransferase increased	6 (14.0)	1 (2.3)
Rash	6 (14.0)	1 (2.3)
Bilirubin conjugated increased	5 (11.6)	0
Blood glucose increased	5 (11.6)	0
White blood cell count decreased	5 (11.6)	0
Constipation	5 (11.6)	0
Hypertension	5 (11.6)	0

Note: Data are n (%).

tumor mutational burden are not yet available in our study, as the tissue samples are still being processed, this requires additional testing and further exploration. It should be noted that the better outcomes seen in patients with *NRAS* mutations in the current study were only observational, and the relationship between *NRAS* mutations and response to immunotherapy is currently unclear. In a previous study, *NRAS* mutations were found to be associated with better outcomes in patients with metastatic melanoma (31), while another study showed that *NRAS* mutations had no impact on the outcomes of immunotherapy (32). However, in a pooled analysis of four clinical trials conducted in Asia, *NRAS* mutations were associated with worse outcomes of immunotherapy (33). Therefore, the effect of *NRAS* on the efficacy of immunotherapy is unknown and needs to be verified in large-scale prospective studies.

We also observed a higher ORR and a significantly longer PFS among patients with upper-region mucosal melanoma. A meta-analysis of mucosal melanoma suggested that mutational profiles are different between patients with mucosal melanoma in the upper and lower regions, with splicing factor 3b subunit 1 (*SF3B1*) mutations being more common in mucosal melanomas of the lower region (3). However, the correlation between clinical efficacy and mutational profiles remains to be defined. Further investigation is required to confirm these observations and to explore the underlying pathophysiologic reasons for these findings and their possible prognostic implications.

TRAEs observed with atezolizumab plus bevacizumab in this study were consistent with the reported safety profiles of this regimen in other malignancies with no new safety signals observed (17, 34, 35). The most frequent any-grade TRAEs were elevated LDH, hypercholesterolemia, abnormal AST/ALT, and hypothyroidism, suggesting this combination was well tolerated. However, one death occurred on day 17, which was considered to be treatment-related and attributed to immune-related pneumonitis/acute respiratory distress syndrome. No other TRAE leading to treatment discontinuation was observed. Overall, the toxicity profile of this combination was manageable with appropriate monitoring.

The current study has several limitations. First, this is a single-arm, open-label study with a relatively small sample size. Because this is a pilot exploratory trial to investigate the efficacy and safety of atezolizumab plus bevacizumab in advanced mucosal melanoma, data from future larger studies will be important to confirm these preliminary findings. Second, the follow-up period in this study is short. It remains to be seen whether or not the ORR benefit demonstrated in this study can translate into long-term survival advantages. Finally, 11 of 43 patients had temporary treatment disruptions due to the COVID-19 pandemic, which may have negatively influenced the efficacy data of this study.

In conclusion, treatment with atezolizumab plus bevacizumab showed promising efficacy and acceptable tolerability in patients with advanced mucosal melanoma. These early data support the rationale for further evaluation of anti-VEGF and PD-1/PD-L1 inhibitor combinations in patients with advanced mucosal melanoma. Double-blind, randomized controlled studies with larger sample sizes, together with evaluations of biomarkers, are required to provide more data to support and inform the use of atezolizumab plus bevacizumab in patients with advanced mucosal melanoma.

Authors' Disclosures

L. Mao reports nonfinancial support from Shanghai Roche Pharmaceuticals Ltd. during the conduct of the study. M. Fang reports nonfinancial support from Shanghai Roche Pharmaceuticals Ltd. during the conduct of the study. J. Cao reports nonfinancial support from Shanghai Roche Pharmace during the conduct of the study. J. Lin reports nonfinancial support from Shanghai Roche Pharmaceuticals Ltd. during the conduct of the study. P. Zhang reports nonfinancial support from Shanghai Roche Pharmaceuticals Ltd. during the conduct of the study. L. Chen reports nonfinancial support from Shanghai Roche Pharmaceuticals Ltd. during the conduct of the study. Yujun Chen is an employee of Roche company. J. Guo reports nonfinancial support from Shanghai Roche Pharmaceuticals Ltd. during the conduct of the study; and personal fees from MSD, Roche, Novartis, Shanghai Junshi Biosciences, Pfizer, Bayer, Simcere, and Oriengene outside the submitted work. L. Si reports nonfinancial support from Shanghai Roche Pharmaceuticals Ltd. during the conduct of the study; and personal fees from MSD, Roche, Novartis, Shanghai Junshi Biosciences, and Oriengene outside the submitted work. No disclosures were reported by the other authors.

Authors' Contributions

L. Mao: Conceptualization, resources, investigation, writing–original draft, project administration, writing–review and editing. **M. Fang:** Conceptualization, resources, writing–review and editing. **Y. Chen:** Conceptualization, resources, writing–review and editing. **X. Wei:** Resources, writing–review and editing. **J. Cao:** Resources, writing–review and editing. **J. Lin:** Resources, writing–review and editing. **P. Zhang:** Resources, writing–review and editing. **L. Chen:** Resources, writing–review and editing. **X. Cao:** Data curation, supervision, funding acquisition, project administration. **Y. Chen:** Data curation, software, formal analysis, writing–review and editing. **J. Guo:** Conceptualization, resources, project administration, writing–review and editing. **L. Si:** Conceptualization, resources, data curation, formal analysis, writing–original draft, writing–review and editing.

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Note

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