Combination of pembrolizumab plus temozolomide therapy in unresectable and advanced melanoma: a multicenter retrospective analysis in China

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Background: This study aimed to evaluate the effect of anti-PD-1 combined with temozolomide as front-line therapy in patients with unresectable advanced melanoma.

Methods: The records of patients with unresectable advanced melanoma first treated with pembrolizumab plus temozolomide, pembrolizumab alone, or temozolomide-based chemotherapy at three cancer centers from May 2018 to February 2020 were reviewed. Patients were followed up until death or October 30, 2020. Data were retrospectively reviewed and statistically analyzed for the best objective response rate (ORR) and progression-free survival (PFS), as well as toxicities.

Results: Sixty-nine individuals were identified, including 28 (40.6%) with acral melanoma, 18 (26.1%) with cutaneous melanoma, 21 (30.4%) with mucosal melanoma, and two (2.9%) with unknown primary melanoma. The ORR of pembrolizumab plus temozolomide (8/20, 40.0%) in advanced melanoma was higher than pembrolizumab (3/24, 12.5%) and chemotherapy (1/25, 4.0%) alone as front-line therapies. The median PFS of pembrolizumab plus temozolomide as front-line therapy for advanced melanoma was 9.8 months [95% confidence interval (CI): 1.7–17.9 months], which was a significant improvement on the chemotherapy PFS of 4.2 months (95% CI: 2.6–5.8 months) [hazard ratio (HR) 0.415, 95% CI: 0.185–0.931, P=0.033]. The median PFS of pembrolizumab was 6.2 months (95% CI: 2.5–9.9), with no significant difference compared with chemotherapy (HR 0.647, 95% CI: 0.334–1.252, P=0.196).

Conclusions: Combining anti-PD-1 with temozolomide has better efficacy than temozolomide-based chemotherapy or anti-PD-1 alone for advanced melanoma treatment without increasing toxicity. Therefore, anti-PD-1 combined with temozolomide may be preferentially used as a front-line regimen for unresectable advanced melanoma.

Keywords: Anti-PD-1; temozolomide; combination therapy; advanced melanoma

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Introduction

Metastatic melanoma has always presented arduous clinical problems and is generally associated with poor prognosis and a limited response to chemotherapy (1). The introduction of targeted therapy towards the B-Raf proto-oncogene (BRAF) mutation and constitutive activation of the mitogen activated protein kinase (MAPK) pathway with BRAF and mitogen/extracellular signal-regulated kinase (MEK) inhibitors and checkpoint inhibitors are two major therapeutic advances in advanced metastatic melanoma (2,3). Indeed, the median overall survival has increased from 9 months in the chemotherapy era to almost 24 months with the combined use of BRAF and MEK inhibitors, dabrafenib, and trametinib (4,5), and 37.5 months with the anti-programmed death 1 (PD-1) nivolumab (6). As a PD-1 blocking antibody, pembrolizumab was approved for patients with unresectable or metastatic melanoma as front-line therapy since 2014 and showed significant advantages than chemotherapy. Even more important is the large fraction of long-term survivors, with early reports of a 41% 5-year survival rate with first-line treatment with pembrolizumab (7) and a 52% 5-year survival rate with combined checkpoint inhibition (8). However, in Chinese patients, checkpoint inhibitors have not obtained the satisfying results seen in Caucasians. In an analysis of 52 Chinese patients with metastatic melanoma, the objective response rates (ORRs) were 0%, 20%, and 25% for patients treated with ipilimumab, pembrolizumab plus ipilimumab, and pembrolizumab monotherapy, respectively (9). Furthermore, one multicenter phase Ib trial with many enrolled patients demonstrated that the ORR was 16.7% in Chinese patients with advanced melanoma treated with pembrolizumab as second-line therapy (10). To improve the low clinical response rate of checkpoint inhibitors, the effects of combining them with other agents, including cytotoxic chemotherapy, immuno-stimulatory molecules, cancer vaccines, high-dose interleukin-2 (IL-2), and other checkpoint inhibitors, has been studied (1,2,6). A recent study found that, although it did not directly affect immune cells, the first-line chemotherapy drug dacarbazine (DTIC) activated NK cells and their interferon (IFN)γ secretion by upregulating NKG2D ligands on melanoma cells. The secreted IFNγ subsequently favored the upregulation of major histocompatibility complex class I molecules on tumor cells, rendering them sensitive to cytotoxic $CD8^+$ T cells. These results disclosed the immunogenic properties of DTIC and provided the rationale to combine DTIC with immunotherapeutic agents (11).

Temozolomide is an oral multifunctional DNA alkylating agent. It is a prodrug which delivers a methyl group to purine bases of DNA (O6-guanine, N7-guanine, and N3-adenine) (12). Temozolomide is a congener of dacarbazine, the only chemotherapeutic agent approved by the FDA for metastatic melanoma, and has 100% oral bioavailability and similar clinical activity for patients with metastatic melanoma (13). A randomized phase III trial of temozolomide versus dacarbazine in patients with metastatic melanoma demonstrated similar response rates between the two cohorts (13.5% for temozolomide-treated patients and 12.1% for dacarbazine-treated patients) (14). In contrast to dacarbazine, temozolomide crosses the blood–brain barrier, and reportedly induced the depletion of Tregs and suppression of Treg function in preclinical and clinical studies (15,16). Similar results were verified in one report including 3 cases of patients with advanced melanoma who showed radiological response with metronomic temozolomide treatment after failure on pembrolizumab (17). Therefore, temozolomide may enhance the antitumor immune-stimulation activity of pembrolizumab through depleting or inhibiting Tregs in the tumor microenvironment, which needs further research to elucidate the underlying mechanism. To better verify the synergetic effect of chemotherapy and immunotherapy, this current study was performed to retrospectively investigate the efficacy and safety of pembrolizumab at 2 mg/kg in combination with the oral alkylating agent temozolomide as first-line therapy for unresectable advanced melanoma. We present the following article in accordance with the STROBE reporting checklist (available at https://dx.doi.org/10.21037/atm-21-5738).

Methods

This was a multicenter retrospective study carried out at the Fudan University Shanghai Cancer Center (FUSCC, Shanghai, China), Fudan University Shanghai Cancer Center Minhang Branch (FUSCCMB, Shanghai, China), and Shanghai Electric Power Hospital (SEPH, Shanghai, China). Patients were included if they had a histologically confirmed diagnosis of untreated stage III (unresectable) or stage IV melanoma with measurable lesions and had received immunotherapy with the PD-1 inhibitor pembrolizumab, chemotherapy based on temozolomide, or immunochemotherapy with temozolomide plus pembrolizumab as a first-line therapy between May 2018

and February 2020. Patients were excluded if they received any other first-line therapies such as the involvement of targeted therapy, other chemo-immunotherapy combinations, or combination immunotherapy. Patients were followed up until death or October 30, 2020. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of FUSCC, FUSCCMB, and SEPH (No. 2109243-22), and each participant signed an informed consent document.

Response to treatment was assessed based on a direct review of scan images and radiology reports according to response evaluation criteria in solid tumors (RECIST) 1.1 and immune-related RECIST (irRECIST) criteria. Complete response (CR) was defined as the resolution of all imaging evidence of disease, and partial response (PR) was defined as a decrease in the size of a tumor in response to treatment; stable disease (SD) was the absence of a change in size over two sequential imaging tests; and progressive disease (PD) was an increase in the size of at least one of the lesions. The primary endpoint was the ORR which was assessed by measuring the rate of a PR and CR. Treatment-related adverse events (AEs) were collected from a review of the electronic medical records retrospectively graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.

Statistical analysis

Progression-free survival (PFS) was measured from the initiation of therapy to the date of death or disease progression and was summarized descriptively using Kaplan-Meier survival analysis. We used the Cox model for hazard ratio (HR), confidence intervals of 95%, and a P level of 0.05. All statistical analyses were performed using SPSS software version 21.0. Pearson's chi-squared test or Fisher's exact test was used for univariable analysis of the different category groups. A two-sided P value of <0.05 was considered statistically significant.

Results

Patient characteristics

A total of 69 patients who presented between May 2018 and February 2020 were enrolled and their baseline characteristics are listed in *Table 1*. The median follow-up time was 11.4 months with range from 5.9 to 46.8 months. Their median age was 56.8 years, ranging from 14 to 86 years, and 30 patients (43.5%) were male. All enrolled patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and of the entire cohort, 18 (26.1%) had cutaneous melanoma, 28 (40.6%) had acral melanoma, 21 (30.4%) had mucosal melanoma, and two (2.9%) had unknown primary melanoma. Eight (11.6%) patients were found to have BRAF mutations, most of whom (six patients) had cutaneous melanoma, while other common mutations were NRAS proto-oncogene (NRAS) (5.8%) and KIT proto-oncogene (KIT) (7.2%). As all patients received first-line therapy targeting the BRAF mutation, the percentage of patients with it was low, and these patients were excluded from further analysis. Of included patients, there were 20 (29.0%) diagnosed with stage III, 49 (71.0%) with stage IV, and two (2.9%) who had elevated lactate dehydrogenase. One patient (1.4%) had brain metastases before starting first-line treatment. Before progressing to unresectable stage III or IV melanoma, 41 (59.4%) patients received adjuvant therapy which was mostly interferon-α (IFN-α) plus IL-2 (18, 26.0%). Furthermore, no significant differences were found in the Breslow index, ulceration, N stage, American Joint Committee on Cancer 8th edition (AJCC) disease stage, gender, Clark level, or adjuvant therapy among the three treatment groups. However, most patients (13, 52.0%) in the chemotherapy group had mucosal melanoma and were clinically different from patients in the other groups.

Treatment

Of the 69 patients, 24 (34.8%) (six with cutaneous melanoma, 11 with acral melanoma, and seven with mucosal melanoma) received pembrolizumab alone with standard dosing of 2 mg/kg every 3 weeks. Twenty-five (36.2%) patients (four with cutaneous melanoma, seven with acral melanoma, 13 with mucosal melanoma, and one with primary melanoma of unknown site) received temozolomide-based chemotherapy at a standard recommended dosing schedule (2), in which temozolomide was given 200 mg/m^2 on days 1–5, cisplatin 85 mg/m^2 within 3 days, and endostatin 210 mg civ 168 h, repeated every 4 weeks. Pembrolizumab plus temozolomide was given to 20 (29.0%) patients (eight with cutaneous melanoma, 10 with acral melanoma, one with mucosal melanoma, and one with primary melanoma of unknown site) with the same dosage used for each treatment alone.

Table 1 Baseline characteristics of the patients

Characteristic	Total (n=69)	Pembrolizumab	Chemotherapy	Pembrolizumab plus temozolomide	χ^2	P value
Sex, n (%)					0.155	0.925
Male	30 (43.5)	11 (36.7)	11 (36.7)	8 (26.7)		
Female	39 (56.5)	13 (33.3)	14 (35.9)	12 (30.8)		
Age, years					1.688	0.430
<65	55 (79.7)	17 (31.5)	20 (37.0)	17 (31.5)		
≥65	14 (20.3)	7 (50.0)	4 (28.6)	3 (21.4)		
Mean	56.8	57.9	56.3	56.0		
Range	14–86	14–86	39–71	23–74		
ECOG performance status, n (%)					1.746	0.418
0	1 (1.4)	1 (100.0)	0 (0.0)	0 (0.0)		
1	68 (98.6)	24 (35.8)	20 (29.9)	23 (34.3)		
Histology, n (%)					14.008	0.015*
Cutaneous	18 (26.1)	6 (33.3)	4 (22.2)	8 (44.4)		
Acral	28 (40.6)	11 (39.3)	7 (25.0)	10 (35.7)		
Mucosal	21 (30.4)	7 (33.3)	13 (61.9)	1 (4.8)		
Primary site unknown	2 (2.9)	0 (0.0)	1 (50.0)	1 (50.0)		
Breslow thickness, n (%)					3.794	0.435
0–1 mm	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)		
>1–2 mm	0 (0.0)	1 (50.0)	1 (50.0)	0 (0.0)		
>2–4 mm	2 (2.9)	4 (36.4)	1 (9.1)	6 (54.5)		
>4.0 mm	11 (15.8)	13 (36.1)	11 (30.6)	12 (33.3)		
Metastatic stage, n (%)					6.489	0.593
M0	19 (27.5)	10 (52.6)	6 (31.6)	3 (15.8)		
M1a	3 (4.3)	1 (33.3)	1 (33.3)	1 (33.3)		
M1b	23 (33.3)	6 (26.1)	9 (39.1)	8 (34.8)		
MIc	24 (34.7)	8 (33.3)	7 (29.2)	9 (37.5)		
Overall stage, n (%)					2.961	0.227
III	20 (29.0)	10 (50.0)	6 (30.0)	4 (20.0)		
IV	49 (71.0)	14 (34.8)	25 (36.2)	20 (29.0)		
Gene mutation status, n (%)					10.834	0.043*
BRAF	8 (11.6)	6 (75.0)	1 (12.5)	1 (12.5)		
NRAS	4 (5.8)	0 (0.0)	1 (25.0)	3 (75.0)		
KIT	5 (7.2)	3 (60.0)	1 (20.0)	1 (20.0)		
No	52 (75.4)	15 (28.8)	22 (42.3)	15 (28.8)		

Table 1 (*continued*)

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Characteristic	Total (n=69)	Pembrolizumab	Chemotherapy	Pembrolizumab plus temozolomide	χ^2	P value
Baseline lactate dehydrogenase level, n (%)					1.358	0.750
Normal (<1.1 ULN)	65 (94.2)	23 (35.4)	23 (35.4)	19 (29.2)		
Elevated (≥1.1 ULN)	2 (2.9)	0 (0.0)	1 (50.0)	1 (50.0)		
Brain metastases, n (%)					1.788	0.290
Yes	1 (01.4)	0 (0.0)	0 (0.0)	1 (100.0)		
No	28 (40.6)	24 (35.3)	25 (36.8)	19 (27.9)		
Prior adjuvant therapy, n (%)					1.511	0.470
Yes	41 (59.4)	14 (34.1)	13 (31.7)	14 (34.1)		
No	28 (40.6)	10 (35.7)	12 (42.9)	6 (21.4)		
Type of prior adjuvant therapy, n (%)					7.719	0.461
Chemotherapy	8 (11.6)	4 (50.0)	3 (37.5)	1 (12.5)		
Immunotherapy	30 (43.5)	9 (30.0)	10 (33.3)	11 (36.7)		
Pembrolizumab	12 (17.4)	4 (33.3)	2 (16.7)	6 (50.0)		
IFN-α plus IL-2	18 (26.1)	5 (27.8)	8 (44.4)	5 (27.8)		
Others	3 (4.3)	1 (33.3)	0	2 (66.7)		

*, these P values indicate statistically significant differences. ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; ULN, upper limits of normal; BRAF, B-Raf proto-oncogene; NRAS, NRAS proto-oncogene; KIT, KIT proto-oncogene; IFN-α, interferon-α; IL-2, interleukin-2.

Efficacy

At data cutoff, most patients (66.7%) experienced disease progression. However, 11 patients (55.0%) remained on PD-1 blockade combined with temozolomide without progression compared with 25.0% in the pembrolizumab cohort and 24.0% in the chemotherapy cohort. Among the patients treated with pembrolizumab plus temozolomide, three had a CR (one with primary melanoma of unknown site, two with acral melanoma) and five had a PR (two with cutaneous melanoma and three with acral melanoma), for an ORR of 40% (8/20). For those treated with pembrolizumab alone, the ORR was 12.5% (one had CR with acral melanoma, one PR with acral melanoma, and one PR with cutaneous melanoma). Only one patient (mucosal melanoma) reached PR in the chemotherapy cohort, and the ORR was 4.0% (1/25). The data of best percentage change in tumor size from baseline of patients in different groups was measured based on RECIST v1.1 and is shown in *Figure 1*. Treatment with pembrolizumab plus temozolomide showed significantly higher ORR than pembrolizumab alone (P=0.036) or chemotherapy alone (P=0.003), and no difference was found in ORR between pembrolizumab and chemotherapy therapy (P=0.277). The DCRs of pembrolizumab plus temozolomide, pembrolizumab alone, and chemotherapy alone were 80%, 75%, and 68%, respectively, with no significant difference (P=0.658) (*Table 2*).

As shown in *Figure 2*, the median PFS (mPFS) of pembrolizumab plus temozolomide as front-line therapy for advanced melanoma was 9.8 months (95% CI: 1.7–17.9 months), a significant improvement on the PFS of chemotherapy at 4.2 months (95% CI: 2.6–5.8 months) (HR 0.415, 95% CI: 0.185–0.931, P=0.033). The mPFS of pembrolizumab was 6.2 months (95% CI: 2.5–9.9 months) with no significant difference compared with chemotherapy (HR 0.647, 95% CI: 0.334–1.252, P=0.196), while no significant difference in mPFS was found between the combination therapy cohort and pembrolizumab cohort (P=0.278). Similar results were seen in patients diagnosed with stage IV melanoma, whereas there was no difference

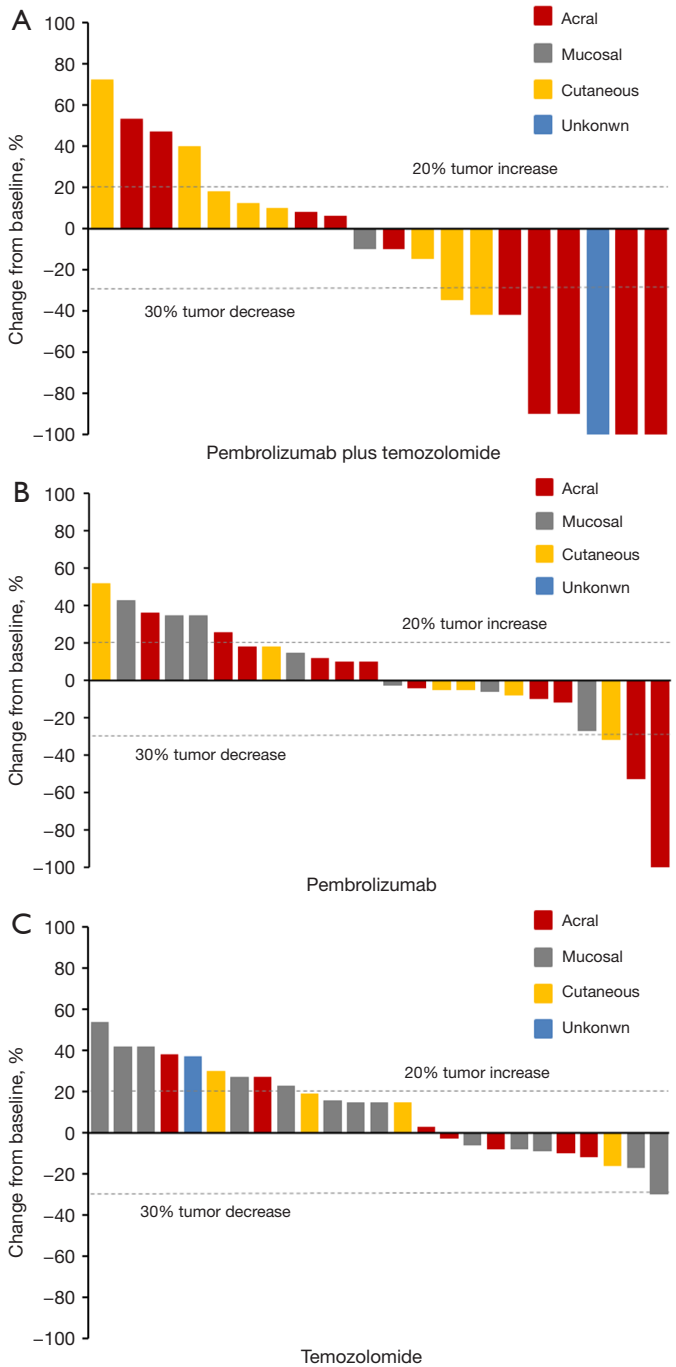

Figure 1 The depth of response of patients in different subgroups. Best percentage change in tumor size from baseline was based on RECIST v1.1 in patients receiving treatment of pembrolizumab plus temozolomide, pembrolizumab alone, or temozolomide-based chemotherapy alone: acral (red), mucosal (gray), cutaneous (orange), and primary site unknown (blue). Values ≥100% were set to 100%. RECIST, Response Evaluation Criteria in Solid Tumors.

Table 2 Efficacy results

Best overall response	Pembrolizumab (n=24), n (%)	Chemotherapy (n=25), n (%)	Pembrolizumab plus temozolomide (n=20), n (%)
CR	1 (4.2)	0 (0.0)	3 (15.0)
PR	2 (8.3)	1 (4.0)	5 (25.0)
ORR (CR + PR)	3 (12.5)	1 (4.0)	8 (40.0)
SD	15 (62.5)	16 (64.0)	8 (40.0)
DCR (CR + PR + SD)	18 (75.0)	17 (68.0)	16 (80.0)
PD	6 (25.0)	8 (32.0)	4 (20.0)

Response was assessed according to Response Evaluation Criteria in Solid Tumors (RECIST version 1.1). CR, complete response; PR, partial response; ORR, objective response rate; SD, stable disease; DCR, disease control rate; PD, progressive disease.

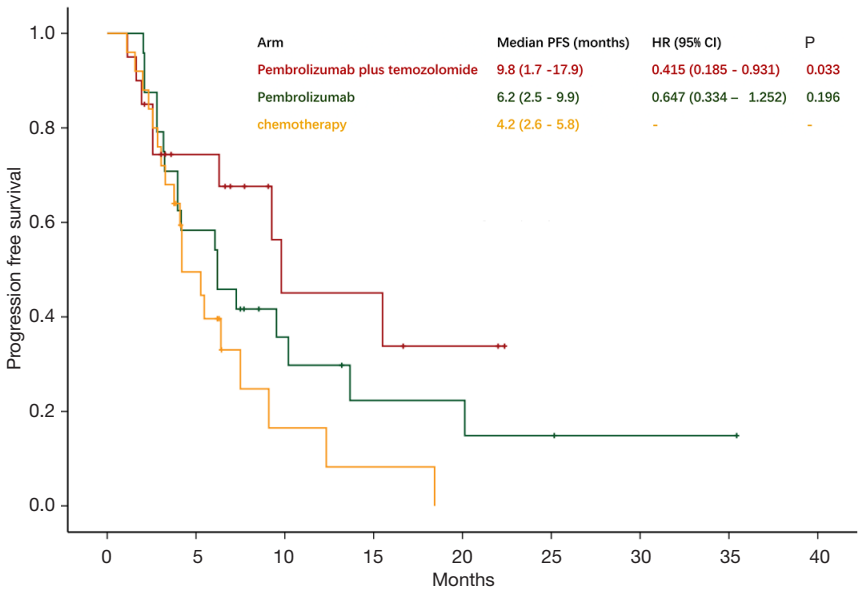

Figure 2 Kaplan-Meier plot curves for the PFS of patients in different subgroups. Compared with chemotherapy alone, pembrolizumab plus temozolomide showed higher mPFS (P=0.030) while no significant improvement in mPFS was seen in pembrolizumab (P=0.196). PFS, progression-free survival.

among the three cohorts of patients with unresectable stage III melanoma subject to limited cases.

In acral and mucosal melanoma, most seen in Chinese patients, the ORR of pembrolizumab plus temozolomide (5/11, 45.5%) was significantly higher than pembrolizumab alone (2/18, 11.1%; P=0.036) or chemotherapy (1/20, 5.0%; P=0.006). However, the difference of ORR between pembrolizumab alone and chemotherapy was not statistically significant (P=0.485) in these two types (all P>0.05). In acral melanoma, the mPFS of patients assigned pembrolizumab plus temozolomide was 9.8 months (95% CI: 3.0–16.6 months), significantly higher than that of the chemotherapy cohort (mPFS was not reached, P=0.030) and with no significant difference versus pembrolizumab (6.2 months, 95% CI: 3.0–16.6, P=0.516). In addition, no difference was found between pembrolizumab and chemotherapy (P=0.775). The three treatments showed no obvious difference in mPFS for cutaneous melanoma (pembrolizumab plus temozolomide: 9.3 months, pembrolizumab: 6.2 months, and chemotherapy: 3.0 months) or mucosal melanoma (9.1, 6.1, and 4.2 months, respectively).

Two cases were described as having significant responses to the combination of temozolomide and pembrolizumab as first-line therapy in supplementary data, as shown in Figure S1.

Table 3 Treatment-related adverse events

Adverse events	Pembrolizumab (n=20)		Chemotherapy (n=24)		Pembrolizumab plus temozolomide (n=25)	
	Grade I–II	Grade III–IV	Grade I–II	Grade III–IV	Grade I–II	Grade III–IV
Summary, n (%)						
Any	10 (41.7)	1 (4.2)	6 (24.0)	2 (8.0)	5 (25.0)	2 (10.0)
Led to discontinuation	0	0	0	0	0	1 (5.0)
Specific categories, n (%)						
Fatigue	2 (8.3)	0	2 (8.0)	0	2 (10.0)	0
Nausea	2 (8.3)	0	3 (12.0)	0	3 (15.0)	0
Anemia	0	0	0	1 (4.0)	0	0
Diarrhoea	1 (4.2)	0	0	0	0	0
Rash	2 (8.3)	0	1 (4.0)	0	0	1 (5.0)
Vomiting	2 (8.3)	0	3 (12.0)	0	3 (15.0)	0
Hypothyroidism	1 (4.2)	0	0	0	0	0
Dry mouth	1 (4.2)	0	0	0	0	0
Thrombocytopenia	0	0	0	1 (4.0)	2 (10.0)	1 (5.0)
Leukocytopenia	0	0	1 (4.0)	0	2 (10.0)	0
Neutropenia	0	0	1 (4.0)	0	2 (10.0)	0
Constipation	1 (4.2)	0	0	0	0	0
Elevated transaminase	1 (4.2)	0	0	0	2 (10.0)	0
Autoimmune hepatitis	0	1 (4.2)	0	0	0	0
Glucose intolerance	1 (4.2)	0	0	0	0	0
Fever	1 (4.2)	0	0	0	0	0
Arthralgia	1 (4.2)	0	0	0	0	0
Blurred vision	1 (4.2)	0	0	0	0	0

Toxicity and immune-related adverse events

Table 3 summarizes the toxicities attributable to the three therapies, and shows no grade 4 AEs. Two treatment-related grade 3 AEs were seen in those given pembrolizumab combined with temozolomide (one case of rash and one of thrombocytopenia) compared with two treatment-related grade 3 AEs in those given chemotherapy (one case of thrombocytopenia and one of anemia), and one case of autoimmune hepatitis of grade 3 was seen in the pembrolizumab group. Other common AEs of grade 1 or 2 included nausea and vomiting (10.0%, 8.3%, 8.0% in pembrolizumab plus temozolomide, pembrolizumab, and chemotherapy, respectively), fatigue (15.0%, 8.3%, 12.0%, respectively), elevated transaminase (10.0%, 4.2%, 0.0%, respectively), and leukocytopenia (10.0%, 0.0%, 4.0%, respectively). One case of hypothyroidism in the pembrolizumab cohort was subclinical in nature as diagnosed with thyroid function tests. In addition, the rate of treatment-related AEs was not significantly higher in the chemo-immunotherapy cohort compared with patients who received anti-PD-1 or chemotherapy alone.

Discussion

Prior to the recent therapeutic advances, the mainstay of treatment option for Chinese patients with advanced or metastatic melanoma has been dacarbazine-based

chemotherapy, but its use has been associated with poor outcomes. In a phase II study of first-line dacarbazine or placebo treatment of Chinese patients with advanced melanoma, the median PFS was 1.5 months, the median OS was 8.0 months, and the ORR was 3.7% (18). However, patients in that trial who received the recombinant human endostatin (endostar plus dacarbazine) experienced a median PFS of 4.5 months and a median OS of 120 months (18). Our data was consistent with the above-mentioned results for the cohort provided temozolomide-based chemotherapy, as the median PFS of first-line treatment was 4.2 months in all subtypes and the response rate to chemotherapy was 4.0% in all subtypes. The poor outcomes of chemotherapy in treating advanced or metastatic melanoma have prompted research into other therapy choices.

The introduction of checkpoint inhibitors for the treatment of metastatic melanoma marked a turning point in clinical responses to a disease that was essentially incurable, as clinical trials with both pembrolizumab and nivolumab reported clinical response rates of approximately 40% in patients with treatment-naïve stage IV melanoma and low rates of high-grade toxicities (7,8,19). However, unlike the impressive results obtained in white populations, Chinese patients with locally advanced or metastatic melanoma treated with pembrolizumab had an ORR of 16.7%. In this series, our results showed a similar trend, in which patients treated with pembrolizumab had an ORR of 12.5% (3/24) in all subtypes. This phenomenon may be attributable to the different distributions of melanoma subtypes in different populations, as unlike white patients, the subtypes of melanoma most common in Asian patients are acral and mucosal, which account for up to 58% of all melanoma tumors in that patient population (20). In addition, acral and mucosal melanomas are more frequently characterized by DNA structural changes and mutation signatures of unknown etiology and are generally regarded as more aggressive subtypes. In the pembrolizumab cohort of this study, the ORR was 16.7% (1/6) for cutaneous melanoma, 18.2% (2/11) for acral melanoma, and 0.0% (0/6) for mucosal melanoma, respectively, indicating that immunotherapy might have limited effects on mucosal melanoma.

The disappointing results of chemotherapy regimens for melanoma and unsatisfactory effects of checkpoint inhibitors in the treatment of metastatic melanoma have urged researchers to investigate new therapies or therapy combinations. Studies have recently shown that the PD-1/PDL1 pathway can impact the chemoresistance of melanoma tumor cells through the p38MAPK pathway (21). Recent studies also showed that chemotherapy might have an immunological effect on metastatic melanoma following immune checkpoint inhibition. The median PFS in a chemotherapy post-immunotherapy group was 5.2 months, which was significantly higher than that of a chemotherapy without prior immunotherapy group (2.5 months). Another study went a step further and found that, for malignant melanoma patients in whom PD-1 blockade had failed, the addition of chemotherapy increased the CX3CR1+ therapy-responsive CD8+ T-cell population with enhanced anti-tumor activity, resulting in improved clinical responses. However, little data was gathered for the combination of chemotherapy and immunotherapy as first-line therapy in treating advanced malignant melanoma. In this retrospective study, we explored the clinical outcomes of pembrolizumab combined with temozolomide as first-line therapy for patients with advanced malignant melanoma and found improved response rates compared with immunotherapy or chemotherapy alone, with no additional toxicities. An ORR of 40% was reached in the combination treatment cohort, which was significantly higher than that of the anti-PD-1 immunotherapy and chemotherapy groups, and 55% of patients achieved a durable response and showed no progression until the follow-up deadline. Although not statistically significant compared with the immunotherapy group, a trend towards improvement in PFS among patients who received immunotherapy plus chemotherapy could be clinically meaningful, and by involving more cases in future studies, we believe a clear answer will become apparent. Our current findings are in line with previous data supporting the belief that temozolomide-based chemotherapy has not only cytotoxic effects but also immunostimulatory effects, although the intrinsic interplay between chemotherapy and immunotherapy requires additional investigation. Interestingly, one patient showed a good response to the combined therapy, but the disease progressed when she quit chemotherapy after six courses because she could not tolerate the side effects. However, after reverting to a regime of pembrolizumab combined with temozolomide, she regained a CR, and after retreatment with temozolomide for another four courses, reached a durable response with no relapse until the cutoff date. As illustrated by this case, when to stop chemotherapy and how long the effects of combined therapies last are crucial issues. Other reports suggest six to eight courses are appropriate for treatment with dacarbazine and temozolomide (2). Despite this, we suggest that following chemotherapy for 1 year

(12 courses) might be a better choice for obtaining a durable response. The second case described above demonstrated the immunological effect of chemotherapy in metastatic melanoma, as the effects of immune checkpoint inhibition were exerted after PD-1 blockade failure.

In this report, pembrolizumab combined with temozolomide showed an acceptable safety profile for the treatment of Chinese patients with unresectable and metastatic melanoma. The safety of this combination, according to the current study, is consistent with other reports relating to combined immunotherapy and chemotherapy (18-20). Most treatment-related AEs were low grade, and grade 3 or 4 treatment-related AEs were experienced in just 10.0% (n=2) of cases, 5% (n=1) of which resulted in patient discontinuation, and none resulted in death. Most AEs were subclinical, based on the results of laboratory inspection, and did not require medication or were manageable with supportive care. Given the limitations of retrospective studies, our results need to be further validated in a prospective study with a larger patient size to minimize the heterogeneity in the patient population. Further research is warranted for validation, with special consideration of the molecular and genetic features of the disease.

In conclusion, the treatment of Chinese patients with advanced melanoma, particularly those with acral or mucosal subtypes, represents a serious unmet medical need. In this retrospective study, we found pembrolizumab combined with temozolomide was a good choice as first-line therapy in patients with advanced melanoma, as it provided durable improved response rates and no additional toxicities compared with monotherapy of chemotherapy or anti-PD1-based immunotherapy. Thus, if patients with advanced melanoma were found with BRAF wild-type, pembrolizumab combined with temozolomide might be first choice, especially for acral and mucosal melanoma. For patients with BRAF V600E-mutated advanced melanoma, combination of pembrolizumab plus temozolomide therapy could be a useful alternative after disease progression on dabrafenib (BRAF inhibitor) and trametinib (MEK inhibitor).

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of FUSCC, FUSCCMB, and SEPH (No. 2109243-22), and each participant signed an informed consent document.

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