Cross Sectional Study

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# Real-world clinical outcomes of anticancer treatments in patients with advanced melanoma in China: retrospective, observational study

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**Introduction:** Treatment options for advanced melanoma in China are lacking, particularly second-line therapies. The aim of this retrospective observational study was to describe the real-world effectiveness of available anticancer therapies in patients with locally advanced/metastatic melanoma in China.

**Methods:** Adult patients with unresectable stage III or IV melanoma treated between January 1, 2014, and December 31, 2015, at the Beijing Cancer Hospital (BCH) were eligible (data cutoff: December 31, 2017). Data were obtained from patient electronic medical records. Responders were adjudicated per Response Evaluation Criteria in Solid Tumors, version 1.1. Progression-free survival (PFS) and overall survival (OS) were estimated using the Kaplan-Meier method.

**Results:** Of 248 eligible patients, 221 and 116 were treated with anticancer therapies in first-line and second-line settings, respectively (89 received both at BCH). Approximately 95% of patients had stage IV melanoma; 40.7% had acral melanoma, and 30.6% had mucosal histology. By data cutoff, 195 of 248 (78.6%) patients had died. Median OS for all patients was 10.5 months; 12-month OS rate was 43.9%. In the first-line setting, the objective response rate was 6.3% (95% confidence interval, 3.5%–10.4%) and the median duration of response was 9.1 months. Median PFS was 3.5 months and 12-month PFS rate was 10.6%; median OS was 10.5 months and 12-month OS rate was 43.5%. In the second-line setting, objective response rate was 3.4% (95% confidence interval, 0.9%–8.6%) and median duration of response was 7.5 months. Median PFS was 2.3 months and 12-month PFS rate was 5.2%; median OS was 7.5 months and 12-month OS rate was 30.5%.

**Conclusion:** In China, first-line and second-line anticancer therapy seems to be associated with suboptimal clinical outcomes in advanced melanoma, indicating a need for effective therapies.

**Keywords:** Melanoma, Metastatic, China, Observational study, Treatment

Melanoma is a malignant tumor of melanocytes, which are neural-crest–derived cells responsible for the production of melanin. Melanoma is the most lethal form of skin cancer, accounting for > 75% of skin cancer–related deaths[1]. Approximately 232,000 new cases of melanoma are diagnosed globally per year, with > 70% of these cases diagnosed in Australia, Europe, and North America[2]. In Asian countries, the incidence of melanoma is relatively low. In 2015, estimates of new cases of melanoma and melanoma-related deaths in China were ~8000 and 3200, respectively[3].

In China, nearly 40% of patients with melanoma have advanced disease at the time of diagnosis (stage III, 25.1%; stage IV, 12.8%)[4]. Five-year survival rates for stages I, II, III, and IV melanoma are 94%, 44%, 38%, and 4.6%, respectively; median survival is 5.00, 4.25, 2.83, and 1.42 years, respectively[4]. The proportions of patients with mucosal (22.6%) and acral melanoma (41.8%) are higher in China than in Western countries[5]. For example, mucosal and acral melanomas account for <5% of melanoma cases in the United States[6]. Prognosis is poor for patients with mucosal melanoma; reported median overall survival (OS) in patients with advanced mucosal melanoma hospitalized in Beijing is 11 months[7].

Outside China, steady progress has been made in the development of targeted therapies and immunotherapies for locally advanced and metastatic melanoma. Anticytotoxic T-lymphocyte–associated antigen-4 (CTLA-4) monoclonal antibodies (eg, ipilimumab), the combination of BRAF plus mitogen-activated protein kinase (MEK) inhibitors (eg, dabrafenib and trametinib), and programmed death ligand 1 (PD-L1) inhibitors (eg, nivolumab and pembrolizumab) have been approved for the treatment of locally advanced or metastatic melanoma in > 50 countries, including the United States and across

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Europe. In China, treatment options for unresectable locally advanced or metastatic melanoma have been limited to chemotherapeutic agents, such as dacarbazine.

Available treatment options for Chinese patients, such as cytotoxic chemotherapies, have limited activity even in the first-line setting. According to the Chinese Guidelines on the Diagnosis and Treatment of Melanoma (2015 edition)[4], the efficacy of dacarbazine-based regimens is marginal, with an objective response rate (ORR) of 7%, progression-free survival (PFS) of 1.6 months, and OS of 0–6 months. In a multicenter, randomized, double-blind phase 2 trial, the ORR of Chinese patients with advanced mucosal melanoma who were receiving first-line therapy was 3.7% in the dacarbazine arm[8].

There is no standard treatment regimen for second-line therapy in China. In a phase 2 trial conducted to evaluate recombinant human endostatin (rhES; Endostar; Shandong Simcere Medgenn Bio-Pharmaceutical Co. Ltd, Nanjing, China) plus dacarbazine in patients with metastatic melanoma, this combination was associated with significant improvement in median PFS (4.5 vs. 1.5 mo; $P = 0.013$) and OS (12.0 vs. 8.0 mo; $P = 0.005$) compared with dacarbazine plus placebo[8]. The most commonly used second-line regimen in patients with advanced mucosal melanoma who were hospitalized in Beijing was paclitaxel plus carboplatin plus bevacizumab, which was associated with a median PFS of only 2.5 months[7]. Data reflecting the real-world effectiveness of first-line and second-line therapies in patients with melanoma in China are limited. To address this issue, we conducted a study to describe real-world clinical outcomes in patients with advanced and metastatic melanoma in China.

## Methods

### *Study setting and data sources*

This was a retrospective, observational cohort study using patient electronic medical records (EMRs) obtained in an academic setting of the Beijing Cancer Hospital (BCH), which treats the highest volume of patients with melanoma locally and nationwide. A melanoma patient pool was identified from EMRs, and eligible patients who initiated treatment between January 1, 2014, and December 31, 2015 (index date) were enrolled according to study inclusion/exclusion criteria. The cohort end date of December 31, 2017, was used to censor survival follow-up.

Medical charts in BCH contain detailed information about patient disease characteristics, therapies, laboratory data, computed tomography, magnetic resonance imaging, and clinical outcomes. This hospital performs regular imaging in patients with melanoma as part of routine care, which was a valuable resource for confirmation of clinical responses in the current study. Generally, clinical responses are assessed according to Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST v1.1), and patients are followed up after discharge from the hospital. Trained researchers retrospectively reviewed all available EMRs (eg, medical charts, clinical notes, imaging scans, and follow-up records) to extract relevant information into a structured case report form for each patient who met study inclusion and exclusion criteria. The study protocol (EP05026.036.01) and a waiver of patient consent were approved by the medical ethics committee of BCH (No. 52 Fu-cheng Road, Haidian District, Beijing 1000142, P.R. China) on November 20, 2017. Reporting of data for this study adheres to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) and STROCSS (Strengthening the Reporting of Cohort studies in Surgery) guidelines[9,10].

### *Study population*

Adult patients with unresectable, locally advanced (stage IIIB or IIIC) or metastatic (stage IV) melanoma were enrolled in this retrospective study based on the following selection criteria.

### *Inclusion criteria*

(1) Eighteen years or older at the time of initiation of first-line or second-line therapy.
(2) Histologically confirmed diagnosis of stage IIIB, IIIC, or IV melanoma.
(3) At least one measurable lesion as defined by RECIST v1.1 on imaging studies (computed tomography or magnetic resonance imaging).
(4) Initiated either systemic first-line or second-line anticancer therapy in the selected hospital between January 1, 2014, and December 31, 2015 (adjuvant therapy was not considered first-line).
(5) Documented response status data [ie, complete response (CR), partial response (PR), progressive disease (PD), and stable disease (SD)] available in the EMRs according to RECIST v1.1.

### *Exclusion criteria*

(1) Diagnosis of uveal or ocular melanoma.
(2) Immunotherapy between January 1, 2014, and December 31, 2015 (adjuvant treatments such as interferon were allowed).
(3) Enrollment as a clinical trial participant for any melanoma therapies between January 1, 2014, and December 31, 2015.
(4) Diagnosis of human immunodeficiency virus or active hepatitis B or C infection at the time of treatment under evaluation.

### *Objectives*

Primary objectives were to describe the demographic and disease characteristics of patients with unresectable locally advanced and metastatic melanoma at the time of initiation of first-line or second-line anticancer therapies and to describe the systematic treatment pattern and estimate the real-world ORR per RECIST v1.1 by first-line or second-line therapy in these patients. Exploratory objectives included duration of response (DOR), disease control rate (DCR), time to progression (TTP), PFS per RECIST v1.1, and OS by first-line or second-line therapy.

### *Assessments*

Patients received first-line or second-line anticancer therapy during routine care. This information was extracted from EMRs. Outcomes of interest included real-world ORR, DCR, DOR, time to response, PFS, TTP, and OS. Real-world ORR was defined as the proportion of patients in the analysis population who had CR (disappearance of all target lesions and any pathologic lymph nodes) or PR (a reduction in the sum of diameters of the target lesions of $\geq 30\%$ from baseline).

Assessment of preliminary response was conducted by the investigator handling the chart review and based on radiography at baseline (within 4 wk before treatment) and radiography during treatment and was confirmed by subsequent radiographic assessment at least 4 weeks from the first date of documentation of response. The principal investigator then reviewed this decision; in the case of a disagreement, the principal investigator rereviewed the original records/images before making a final judgement. DCR was defined as

the proportion of patients in the analysis population who had CR, PR (decrease in the sum of diameters of target lesions of ≥30% from the baseline sum of diameters), SD (neither PR nor PD). Patients with missing data were considered to have PD. DOR was defined as the time from first documented evidence of CR or PR until PD (increase in the sum of diameters of target lesions of ≥20% from the smallest sum on study, including baseline) or death for patients who demonstrated CR or PR. Patients who died without documented PD were counted as event (PD) at the death date. Response duration for patients whose disease had not progressed or who had not died by the time of analysis was censored. PFS was defined as the time from the first day of treatment to the first documented PD or death from any cause, whichever occurred first. Those who did not have an event during follow-up were censored. TTP was defined as the time from the first day of treatment to the first documented PD (death not included per RECIST v1.1). Those who did not have an event during follow-up were censored. OS was defined as the time from the first day of treatment to death from any cause. Patients whose death was not document by the time of the final analysis were censored.

Outcomes were stratified according to first-line and second-line regimens. Evaluations of CR, PR, PD, and SD were consistent with RECIST v1.1[11]. Best overall response was assigned.

### *Statistical analysis*

ORR point estimates and 95% confidence intervals (CIs) were provided using the binomial exact method. For the TTP, DOR, PFS, and OS end points, Kaplan-Meier curves and median estimates of time from the Kaplan-Meier curves were provided as appropriate. SAS 9.4 software (SAS Institute, Cary, NC) was used for data. Descriptive analysis was applied to demographic and disease characteristics and to treatment pattern, yielding summary statistics. The estimated sample sizes to allow estimation of ORR with acceptable precision are presented in **Table 1**.

## Results

### *Baseline characteristics*

In total, 248 eligible adult patients with unresectable locally advanced (stage IIIB or IIIC) or metastatic (stage IV) melanoma were identified in the EMRs of BCH from January 2014 to December 2015. Twenty-eight provinces in China were represented in the study population. Approximately 70% of patients were diagnosed with acral or mucosal histology; the remaining patients were categorized as nonchronically sun-damaged or chronically sun-damaged subtypes. Approximately 95% of patients had stage IV melanoma; the proportions of patients with stage M1a, M1b, and M1c were 18.9%, 20.4%, and 54.9%, respectively. Approximately 5% of patients had brain metastases and ~40% had liver metastases. Approximately 80% of patients had elevated lactate dehydrogenase levels before receiving anticancer treatment (86.9% for first-line; 75.0% for second-line).

Baseline patient characteristics are summarized in **Table 2**. Of the 248 patients included in the study, 221 received first-line therapy, 116 received second-line therapy (they received first-line therapy in other hospitals), and 89 received both first- and second-line therapy

**Table 1**

**Determination of sample size.**

| | Width of 95% Confidence Interval | | |
|---|---|---|---|
| **ORR Assumptions (%)** | **5%** | **6%** | **7%** |
| 3 | 233 | 167 | 133 |
| 5 | 334 | 238 | 179 |
| 7 | 443 | 314 | 228 |

ORR indicates objective response rate.

**Table 2**

**Baseline characteristics of patients with advanced melanoma (all-patients-as-treated population).**

| | n (%) | |
|---|---|---|
| **Characteristics** | **First Line (N = 221)** | **Second Line (N = 116)** |
| Sex | | |
| Male | 111 (50.2) | 66 (56.9) |
| Female | 110 (49.8) | 50 (43.1) |
| Age (y) | | |
| < 65 | 182 (82.4) | 103 (88.8) |
| ≥ 65 | 39 (17.6) | 13 (11.2) |
| Mean | 54.4 | 52.4 |
| SD | 11.5 | 11.0 |
| Median | 55.0 | 52.6 |
| Range | 22–78 | 23–81 |
| ECOG performance status | | |
| 0 | 66 (29.9) | 37 (31.9) |
| 1 | 113 (51.1) | 45 (38.8) |
| > 1 | 11 (5.0) | 6 (5.2) |
| Unknown | 31 (14.0) | 28 (24.1) |
| Histology | | |
| Acral | 67 (30.3) | 41 (35.3) |
| Mucosal | 95 (43.0) | 29 (25.0) |
| Nonchronically sun-damaged | 36 (16.3) | 24 (20.7) |
| Chronically sun-damaged | 13 (5.9) | 14 (12.1) |
| Unknown primary site or missing | 10 (4.5) | 8 (6.9) |
| Stage | | |
| III | 13 (5.9) | 3 (2.6) |
| IV | 208 (94.1) | 112 (96.6) |
| Unknown | 0 (0.0) | 1 (0.9) |
| Metastatic staging | | |
| M0 | 13 (5.9) | 3 (2.6) |
| M1 | 1 (0.5) | 0 (0.0) |
| M1a | 41 (18.6) | 23 (19.8) |
| M1b | 48 (21.7) | 21 (18.1) |
| M1c | 118 (53.4) | 67 (57.8) |
| Unknown | 0 (0.0) | 2 (1.7) |
| *BRAF* mutation | | |
| Wild type | 122 (55.2) | 72 (62.1) |
| Mutant | 26 (11.8) | 15 (12.9) |
| Unknown | 73 (33.0) | 29 (25.0) |
| Lactate dehydrogenase level | | |
| Normal (< 1.1 × ULN) | 29 (13.1) | 28 (24.1) |
| Elevated (≥ 1.1 × ULN) | 192 (86.9) | 87 (75.0) |
| Unknown | 0 (0.0) | 1 (0.9) |
| Brain metastasis | | |
| No | 210 (95.0) | 108 (93.1) |
| Yes | 11 (5.0) | 7 (6.0) |
| Unknown | 0 (0.0) | 1 (0.9) |
| Liver metastasis | | |
| No | 133 (60.2) | 69 (59.5) |
| Yes | 88 (39.8) | 46 (39.7) |
| Unknown | 0 (0.0) | 1 (0.9) |
| Baseline tumor size (mm) | | |
| No. patients with data | 17 | 4 |
| Mean | 47.8 | 69.5 |
| SD | 30.2 | 52.9 |
| Median | 42.0 | 49.5 |
| Range | 12–130 | 32–147 |
| Prior systemic therapy | | |
| Chemotherapy | 43 (19.5) | 106 (91.4) |
| Targeted therapy | 2 (0.9) | 1 (0.9) |
| Radiation therapy | 8 (3.6) | 3 (2.6) |
| Immunotherapy | 1 (0.5) | 3 (2.6) |
| Surgery | 131 (59.3) | 69 (59.5) |

Data cutoff date: December 31, 2017.

ECOG indicates Eastern Cooperative Oncology Group; ULN, upper limit of normal.

at BCH. In patients receiving first-line therapy, Eastern Cooperative Oncology Group (ECOG) performance status was 0, 1, or >1, in 29.9%, 51.1%, and 5.0%, respectively. The median tumor size at baseline in first-line patients was 42.0 mm. Before enrollment at BCH, 19.5% of first-line patients received chemotherapy and 59.3% underwent surgery. In patients who received second-line therapy, ECOG performance status was 0, 1, or >1, in 31.9%, 38.8%, and 5.2%, respectively. Median tumor size at baseline in second-line patients was 49.5 mm. Before enrollment at BCH, 91.4% of second-line patients had received chemotherapy and 59.5% of patients had undergone surgery.

### *Treatment regimens*

The most commonly used first-line regimens were combination therapies: dacarbazine plus cisplatin plus rhES (36.7%) and paclitaxel plus carboplatin plus bevacizumab (22.2%). The most commonly used second-line regimens were paclitaxel albumin plus carboplatin plus bevacizumab (22.4%), paclitaxel plus carboplatin plus rhES (15.5%), and paclitaxel albumin plus cisplatin plus rhES (12.1%). Other regimens are shown in **Table 3**.

Treatment duration for first-line therapies ranged from 0.1 to 25.4 months; treatment duration was 3 months or more in ~40% of patients and was 6 months or more in 9.5% of patients. Treatment duration for second-line therapies ranged from 0.5 to 15.3 months; fewer patients undergoing second-line therapies had a treatment duration of 3 months or more (27.6%) than in those receiving first-line therapy (40.7%), although the proportions of patients with a treatment duration of 6 months or more was the same for first-line and second-line therapy, at 9.5%.

### *Clinical outcomes*

As of December 31, 2017, median follow-up was 14.7 months. All patients were followed-up until end of study. Of the 248 patients included in the study, 195 (78.6%) had died. In the overall study population, median OS was 10.5 months (95% CI, 9.4–12.1 mo), and the 12-month OS rate was 43.9%. Clinical outcomes in patients receiving first-line therapies are summarized in **Table 4**. Among the 221 patients who received first-line therapy, 2 confirmed CRs and 12 confirmed PRs were reported, confirmed by follow-up imaging, resulting in an ORR of 6.3% (95% CI, 3.5%–10.4%). The median DOR of the 14 confirmed cases of CR or PR was 9.1 months (range, 1.7–28.4 mo), and DCR was 68.3% (95% CI, 61.8%–74.4%). Median PFS was 3.5 months (95% CI, 2.9–4.2 mo) and the 12-month PFS rate was 10.6%. Median TTP was 3.5 months (95% CI, 2.9–4.2 mo). As of December 31, 2017, a total of 171 (77.4%) deaths had occurred; median OS was 10.5 months (95% CI, 9.2–12.1 mo) and the 12-month OS rate was 43.5%.

Clinical outcomes in patients receiving second-line therapies are summarized in **Table 4**. There were 4 confirmed cases of PR, substantiated by follow-up imaging, among the 116 patients who received second-line therapy, resulting in an ORR of 3.4% (95% CI, 0.9%–8.6%). The median DOR of the 4 confirmed cases of

**Table 3**

**First-line and second-line treatment regimens for advanced melanoma (all-patients-as-treated population).**

| | n (%) | |
|---|---|---|
| **Regimen** | **First Line (N = 221)** | **Second Line (N = 116)** |
| Dacarbazine + cisplatin + rhES | 81 (36.7) | 4 (3.4) |
| Paclitaxel + carboplatin + bevacizumab | 49 (22.2) | 7 (6.0) |
| Temozolomide + cisplatin + rhES | 18 (8.1) | 12 (10.3) |
| Temozolomide + sorafenib + bevacizumab | 18 (8.1) | 12 (10.3) |
| Paclitaxel + carboplatin | 16 (7.2) | 3 (2.6) |
| Paclitaxel albumin + cisplatin + rhES | 11 (5.0) | 14 (12.1) |
| Imatinib | 7 (3.2) | 2 (1.7) |
| Paclitaxel + carboplatin + rhES | 5 (2.3) | 18 (15.5) |
| Vemurafenib | 4 (1.8) | 8 (6.9) |
| Temozolomide + sunitinib | 3 (1.4) | 5 (4.3) |
| Paclitaxel albumin + carboplatin + bevacizumab | 2 (0.9) | 26 (22.4) |
| Others | 7 (3.2) | 3 (2.6) |
| Unknown | 0 (0) | 2 (1.7) |

rhES indicates recombinant human endostatin (Endostar; Shandong Simcere-Medgenn Bio-Pharmaceutical Co. Ltd, Nanjing, China).

**Table 4**

**Real-world clinical outcomes in advanced melanoma by treatment line based on RECIST v1.1 (all-patients-as-treated population).**

| **End Points** | **First Line (N = 221)** | **Second Line (N = 116)** |
|---|---|---|
| ORR | | |
| Patients with CR (n) | 2 | 0 |
| Patients with PR (n) | 12 | 4 |
| ORR (95% CI)* (%) | 6.3 (3.5–10.4) | 3.4 (0.9–8.6) |
| DOR†‡§ | | |
| Median (range) (mo) | 9.1 (1.7–28.4‖) | 7.5 (4.6–24.2‖) |
| Patients with ≥3-mo DOR, n (%) | 11 (78.6) | 4 (100) |
| Patients with ≥6-mo DOR, n (%) | 7 (50.0) | 2 (50.0) |
| TTR | | |
| Median (range) (mo) | 1.7 (0.3–4.8) | 2.1 (1.9–3.1) |
| DCR | | |
| Patients with CR + PR + SD (n) | 151 | 67 |
| Median (95% CI) (%) | 68.3 (61.8–74.4) | 57.8 (48.2–66.9) |
| TTP | | |
| Median (95% CI‡) (mo) | 3.5 (2.9–4.2) | 2.3 (2.0–3.0) |
| PFS | | |
| PFS events, n (%) | 203 (91.9) | 115 (99.1) |
| Person-months | 1119 | 482 |
| Event rate (1/100 person-months) | 18.1 | 23.9 |
| Median PFS§ (mo) | 3.5 | 2.3 |
| 95% CI for median PFS‡ | 2.9–4.2 | 2.0–3.0 |
| PFS rate at 3 mo (%) | 55.1 | 40.5 |
| PFS rate at 6 mo (%) | 28.2 | 20.7 |
| PFS rate at 12 mo (%) | 10.6 | 5.2 |
| OS | | |
| OS events, n (%)§ | 171 (77.4) | 101 (87.1) |
| Person-months | 2988 | 1177 |
| Event rate (1/100 person months) | 5.7 | 8.6 |
| Median OS‡ (mo) | 10.5 | 7.5 |
| 95% CI for median OS‡ | 9.2–12.1 | 6.5–8.7 |
| OS rate at 6 mo (%) | 74.4 | 63.6 |
| OS rate at 12 mo (%) | 43.5 | 30.5 |
| OS rate at 24 mo (%) | 21.1 | 11.7 |

*On the basis of binomial exact confidence interval method.
†Includes cases with confirmed CR or PR.
‡Product-limit (Kaplan-Meier) method for censored data.
§As of December 31, 2017.
‖There was no progressive disease/death by the time of last disease assessment.
CI indicates confidence interval; CR, complete response; DCR, disease control rate; DOR, duration of response; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease; TTP, time to progression; TTR, time to response.

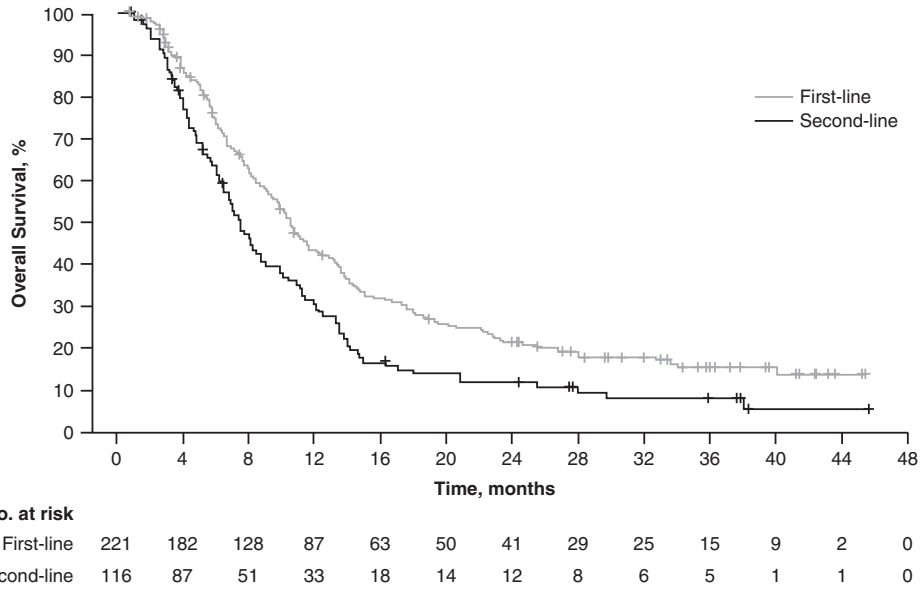


**Figure 1.** Real-world overall survival in advanced melanoma. All-patients-as-treated population.

PR was 7.5 months (range, 4.6–24.2 mo), and the DCR was 57.8% (95% CI, 48.2%–66.9%). Median PFS was 2.3 months (95% CI, 2.0–3.0 mo), and the 12-month PFS rate was 5.2%. Median TTP was 2.3 months (95% CI, 2.0–3.0 mo). As of December 31, 2017, a total of 101 (87.1%) deaths had occurred; median OS was 7.5 months (95% CI, 6.5–8.7 mo) and the 12-month OS rate was 30.5%. Compared with patients receiving first-line therapy, those receiving second-line therapy had shorter median OS (7.5 vs. 10.5 mo) and median PFS (2.3 vs. 3.5 mo) (**Table 4**), as was apparent from the Kaplan-Meier estimates of OS (**Fig. 1**) and PFS (**Fig. 2**) for first-line and second-line therapy.

Subgroup analyses of clinical outcomes (ORR, PFS, and OS) by treatment line and by different histologic groups (acral, mucosal, nonchronically sun-damaged, and chronically sun-damaged) are summarized in **Table 5**. For first-line patients, ORR in the acral and mucosal subgroups was 6.0% and 6.3%, respectively, and was 15.4% in the chronically sun-damaged subgroup. Median PFS in the acral and mucosal subgroups was 3.3 months and 4.1 months, respectively, and was 5.7 months in the chronically sun-damaged subgroup. Median OS in the acral and mucosal subgroups was 10.5 months and 10.3 months, respectively, and 13.1 months in the chronically sun-damaged

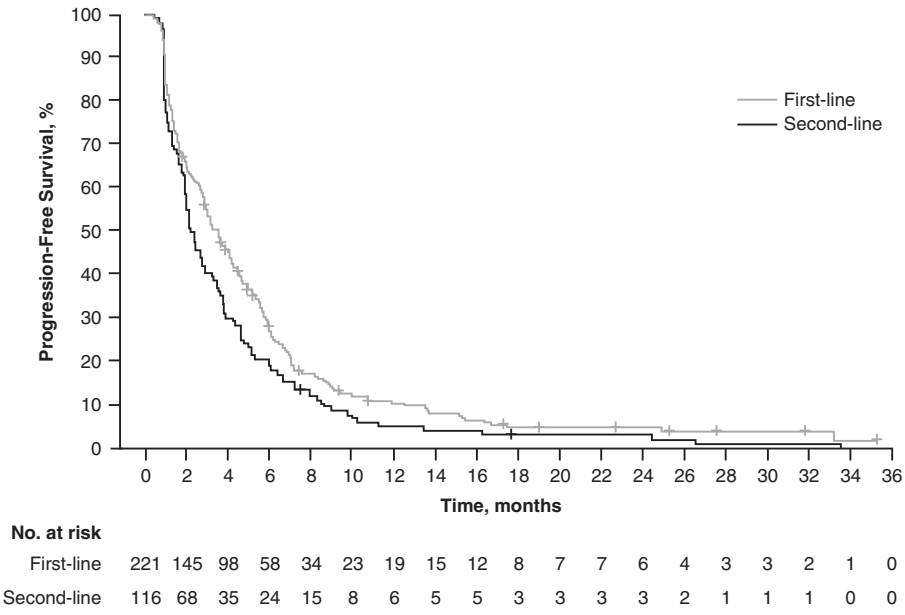


**Figure 2.** Real-world progression-free survival in advanced melanoma. All-patients-as-treated population.

**Table 5**

**Summary of clinical outcomes by treatment line and by histology (all-patients-as-treated population).**

| | First Line (N = 211)* | | | | Second Line (N = 108)* | | | |
|---|---|---|---|---|---|---|---|---|
| **End Points** | **Acral (n = 67)** | **Mucosal (n = 95)** | **NCSD (n = 36)** | **CSD (n = 13)** | **Acral (n = 41)** | **Mucosal (n = 29)** | **NCSD (n = 24)** | **CSD (n = 14)** |
| ORR | | | | | | | | |
| Patients with PR or CR (n) | 4 | 6 | 2 | 2 | 1 | 1 | 1 | 1 |
| ORR (95% CI, %) | 6.0 (1.7–14.6) | 6.3 (2.4–13.2) | 5.6 (0.7–18.7) | 15.4 (1.9–45.4) | 2.4 (0.1–12.9) | 3.4 (0.1–17.8) | 4.2 (0.1–21.1) | 7.1 (0.2–33.9) |
| PFS | | | | | | | | |
| PFS events, n (%) | 63 (94.0) | 87 (91.6) | 34 (94.4) | 9 (69.2) | 41 (100.0) | 28 (96.6) | 24 (100.0) | 14 (100.0) |
| Person-months | 343 | 509 | 137 | 77 | 216 | 102 | 94 | 56 |
| Event rate (1/100 person-months) | 18.4 | 17.1 | 24.9 | 11.7 | 19.0 | 27.4 | 25.6 | 24.8 |
| Median PFS (mo) | 3.3 | 4.1 | 1.8 | 5.7 | 3.3 | 2.1 | 2.0 | 2.1 |
| 95% CI for median PFS | 1.7–4.2 | 2.9–4.7 | 1.0–4.2 | 2.4–7.0 | 2.1–5.0 | 1.1–3.5 | 1.3–4.4 | 1.0–3.6 |
| PFS rate at 3 mo (%) | 53.7 | 56.6 | 41.7 | 76.9 | 51.2 | 34.5 | 37.5 | 42.9 |
| PFS rate at 6 mo (%) | 25.4 | 31.1 | 14.9 | 43.1 | 29.3 | 20.7 | 20.8 | 7.1 |
| PFS rate at 12 mo (%) | 12.5 | 11.4 | 3.0 | 21.5 | 4.9 | 3.4 | 8.3 | N/A |
| OS | | | | | | | | |
| OS events, n (%) | 55 (82.1) | 73 (76.8) | 27 (75.0) | 6 (46.2) | 38 (92.7) | 27 (93.1) | 18 (75.0) | 10 (71.4) |
| Person-months | 875 | 1305 | 493 | 182 | 445 | 273 | 266 | 145 |
| Event rate (1/100 person-months) | 6.3 | 5.6 | 5.5 | 3.3 | 8.5 | 9.9 | 6.8 | 6.9 |
| Median OS (mo) | 10.5 | 10.3 | 10.8 | 13.1 | 10.4 | 7.4 | 7.5 | 8.4 |
| 95% CI for median OS | 7.5–12.8 | 9.2–13.9 | 6.6–14.1 | — | 6.5–12.5 | 4.0–9.6 | 5.3–14.0 | 3.7–11.4 |
| OS rate at 6 mo (%) | 75.3 | 71.4 | 71.3 | 90.0 | 68.3 | 62.1 | 68.8 | 59.8 |
| OS rate at 12 mo (%) | 40.8 | 46.5 | 37.8 | 58.3 | 37.9 | 25.6 | 36.7 | 17.1 |
| OS rate at 24 mo (%) | 17.3 | 23.6 | 22.0 | 35.0 | 10.1 | 11.0 | 17.2 | NA |

*Analysis population includes patients with valid treatment lines and histologic types.

— indicates data not available; CI, confidence interval; CR, complete response; CSD, chronically sun-damaged; NCSD, nonchronically sun-damaged; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response.

subgroup. No statistical testing was conducted to analyze these differences. Similar trends were observed in second-line patients (**Table 5**); estimates of clinical outcomes between the various subgroups were similar, although the ORR in the chronically sun-damaged histologic subgroup seemed to be higher than those reported for other subgroups (7.1% vs. 2.4%–4.2%).

## Discussion

To our knowledge, this is one of the few real-world studies to report the most commonly used anticancer regimens and associated clinical outcomes in patients with advanced melanoma in China. As previously noted, BCH treats patients with melanoma from all over China, including rural and urban areas. Most patients received combination regimens for first-line and second-line therapies; the most common regimens were dacarbazine plus cisplatin plus rhES for first-line therapy and paclitaxel albumin plus carboplatin plus bevacizumab for second-line therapy. These therapies seem to be associated with suboptimal clinical outcomes in advanced melanoma, with low rates of tumor response (6.3% and 3.4%) and limited survival rates (12-mo PFS, 10.6% and 5.2%; 12-mo OS 43.5% and 30.5%) in the real-world setting.

Although commonly considered therapies for advanced melanoma, dacarbazine-based regimens were reported to have limited clinical efficacy. In a randomized, double-blind clinical trial of first-line dacarbazine therapy in Chinese patients, the ORR was 3.7%, median PFS was 1.5 months, and median OS was 8 months[8]. Better outcomes were observed for first-line therapy in the current study, which may be at least in part attributable to the use of combination therapies by most patients; however, these clinical outcomes in a real-world setting still seem suboptimal, with an ORR of 6.3%, a median PFS of 3.5 months, and a median OS of 10.5 months for first-line therapy. Second-line versus first-line patients treated with combination chemotherapy tended to have lower ORR and shorter OS, PFS, and TTP; DOR was short for first-line and second-line therapies. The high proportion of patients with acral or mucosal subtypes in China may be an important reason for the poor outcomes because these patients tended to have relatively late-stage disease at diagnosis and a more aggressive natural history of disease, were more often at M1c stage, and had elevated lactate dehydrogenase levels.

Subgroup analysis of clinical outcomes by histologic subtypes noted differences between chronically sun-damaged and other subtypes in the first-line setting. However, caution should be used when interpreting these findings given the wide CIs and small sample sizes for the different subtypes.

Data generated from this study provide evidence of the real-world effectiveness of anticancer treatments in the first-line and second-line settings for advanced melanoma in China; however, the study has several limitations. A high proportion of data were missing for some variables of interest, such as ECOG performance status (14.0% of first-line patients and 24.1% of second-line patients). Approximately 6% of second-line patients could not be assessed for ORR because of insufficient information in the EMRs. Variability in follow-up schedules among patients may have had an impact on the precision, interpretation, and

generalizability of some of the clinical data. However, to increase the reliability of clinical end-point assessments, each CR/PR case was adjudicated by additional reviewers and escalated for further confirmation by the principal investigator, when needed.

The findings of this study provide insight into the treatment patterns and associated clinical outcomes in patients with advanced melanoma in China. Both first-line and second-line anticancer therapies seem to be associated with suboptimal clinical outcomes in patients with advanced melanoma. These findings demonstrate a high unmet medical need in patients with advanced melanoma patients in China.

## Ethical approval

A waiver of patient consent was applied for and approved by the medical ethics committee of BCH (Address: No.52 Fu-cheng Road, Haidian District, Beijing 1000142, P.R. China) on November 20, 2017.

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## Author contribution

C.C., X.Y., S. Liu, A.C.D., J.L., J. Ge, H.W., and J. Guo: conceived, designed, or planned the study. C.C., X.Y., L.S., Z.C., X.S., B.L., X.W., L.M., B.T., L.Z., X.B., S. Li, and J. Guo: acquired the data. C.C., X.Y., B.L., and J. Guo: analyzed the data. C.C., X.Y., J.L., H.W., and J. Guo: interpreted the results. C.C., X.Y., S. Liu, and J. Guo: drafted the manuscript with contributions from all authors. C.C., X.Y., A.C.D., L.S., Z.C., X.S., B.L., J.L., J. Ge, X.W., L.M., B.T., L.Z., X.B., S. Li, B.L., H.W., and J. Guo: critically reviewed or revised the manuscript for important intellectual content. B.L., and H.W.: provided statistical expertise.

## Conflict of interest disclosure

A.C.D. reports employment at Merck Sharp & Dohme Corp., a subsidiary of Merck & Co. Inc., Kenilworth, NJ. J.L., J.Ge., B.L., and H.W. report employment at MSD Beijing, China. S. Liu reports employment at MSD Beijing, China, and holds stock in the company. The remaining authors declare that they have no financial conflict of interest with regard to the content of this report.

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