Real-world clinical outcomes of anticancer treatments and prognostic factors in patients with advanced melanoma in China

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\textbf{Purpose:} China has much lower 5-year survival rates among melanoma patients than Western countries. This retrospective study describes real-world clinical outcomes and prognostic factors in locally advanced/metastatic melanoma in China.

\textbf{Materials and methods:} Adults with unresectable stage III or IV melanoma treated between January 1, 2014 and December 31, 2015, at the Beijing Cancer Hospital were eligible (data cutoff: December 31, 2017). The Kaplan-Meier method and Log-Rank test were used to estimate the median value of time-to-event outcomes. A Cox proportional hazards model was simulated to evaluate associations of patients’ characteristics with survival.

\textbf{Results:} Overall, there were 221 and 116 Chinese locally advanced and/or metastatic melanoma patients were enrolled in the first line (1L) and the second line (2L) treatments, respectively. The real-world objective response rate was <10% (1L: 6.3%; 2L: 3.4%); median progression-free survival was under 4 months (1L: 3.5; 2L: 2.3); median overall survival (OS) was <1 year (1L: 10.5; 2L: 7.5) with a low 12-month OS rate (43.5% for 1L, 30.5% for 2L). Based on univariate analyses, those with Eastern Cooperative Oncology Group (ECOG) Performance Status ≥2 (vs. ECOG = 0) in 1L, and 2L treatment (vs. 1L treatment) or ECOG ≥2 (vs. ECOG = 1) among 1L/2L were associated with statistically significantly worse outcomes.

\textbf{Conclusion:} The current clinical outcomes in advanced melanoma patients in China are poor. High ECOG performance score independently increase risk of death both from 1L and 2L treatments, suggesting a high unmet medical need for immunotherapy in advanced melanoma.

\textbf{Keywords:} Melanoma, Prognosis, China, Observational study, Treatment

Malignant melanoma is one of the most aggressive types of skin cancer with the highest rates of metastasis and mortality, accounting for >75% of skin cancer deaths\cite{1}. In 2018, it was estimated by GLOBOCAN that worldwide 287,723 new cases and 60,712 deaths were caused by melanoma, with age standardized rates of 3.1/100,000 for incidence and 0.63/100,000 for mortality, respectively\cite{3}. Although China has relatively lower annual melanoma incidence (7379 cases) and mortality (3766 deaths) than western countries, the 5-year survival rates among Chinese melanoma patients (45.1%, 2012–2015)\cite{4} were much lower than those from the United States (91.8%, 2008–2014)\cite{5} and Europe (91%, 2011–2015)\cite{5}.

The relatively poor prognosis of Chinese melanoma patients might be attributed to late stage at diagnosis, histopathologic characteristics, and treatment patterns. In China, about 40% of Chinese melanoma patients have advanced-stage disease at the time of diagnosis (stage III, 25.1% and stage IV, 12.8%)\cite{6}, while a population-based retrospective study conducted in Sweden indicated 92.0% of melanoma patients were diagnosed with localized diseases (stage I and II)\cite{7}. A significant difference in histopathologic patterns of Chinese melanoma cases from those from Western countries may also explain outcomes. In the United States <5% of melanoma cases are classified as mucosal and acral\cite{8}, whereas 22.6% and 41.8% of Chinese melanoma cases are mucosal and acral melanomas, respectively\cite{6}.

Despite the steady progress that has been made in the development of targeted therapies and immunotherapies for locally advanced and metastatic melanoma in Western countries\cite{9,10,11,12}, our previous investigations (unpublished data with cut-off date as December 31st of 2017) found that the treatment options for Chinese unresectable locally advanced or metastatic melanoma are still limited to chemotherapeutic agents. Only 1.4% of first line (1L) and 3.5% of second line (2L) from Chinese advanced melanoma patients had previously received targeted and/or immunotherapy.
In our previous study among 248 Chinese locally advanced/metastatic melanoma patients (95% stage IV; 40.7% acral and 30.6% mucosal histology), we reported that dacarbazine plus cisplatin plus rh-endostatin and paclitaxel plus carboplatin plus bevacizumab were the most used therapeutic regimens in the 1L setting, accounting for 36.7% and 22.2%, respectively. With those chemotherapeutic agents, the objective response rate (ORR) was 6.3% [95% confidence interval (CI), 3.5%–10.4%]; the median progression-free survival (PFS) and overall survival (OS) being 3.5 and 10.5 months, respectively. The paclitaxel albumin plus carboplatin plus bevacizumab; paclitaxel plus carboplatin plus Endostar and paclitaxel albumin plus cisplatin plus Endostar accounted for 36.7% and 22.2%, respectively. With those chemotherapeutic agents, the objective response rate (ORR) was 3.4% (95% CI, 0.9%–8.6%) and median of PFS and OS as 2.3 and 7.5 months, respectively.

Given the varied tumor stages at diagnosis, histopathologic and treatment patterns observed among Chinese melanoma patients, it would be valuable to identify the most important prognostic factors for their poor outcomes. To our knowledge, there are few real-world evidence studies that have addressed these issues both for 1L and 2L therapies in patients with melanoma in China. Therefore, a retrospective analysis was conducted to estimate the prognostic impact of age, sex, stage at diagnosis, histopathologic characteristics, metastatic stage, serine/threonine-protein kinase B-Raf (BRAF) gene mutation, Eastern Cooperative Oncology Group (ECOG) Performance Status, and serum lactate dehydrogenase (LDH) on survival among patients with advanced and metastatic melanoma in China.

### Materials and methods

#### Study setting and data sources
This was a retrospective, observational cohort study using electronic medical records (EMRs) from the Beijing Cancer Hospital (BCH) in China, 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 treatments between January 1, 2014 and December 31, 2015 (index date) were enrolled according to study inclusion/exclusion criteria.

#### Table 1

| Objective response rates by treatment line and patients’ characteristics (all-patients-as-treated population). |
|---|---|---|
| **1L Treatment** | **2L Treatment** |
| N | Number of Responders | ORR (95% CI) | N | Number of Responders | ORR (95% CI) |
| Overall | 221 | 14 | 6.3 (3.5–10.4) | 116 | 4 | 3.5 (1.0–8.6) |
| Age (y) | | | | | | |
| < 65 | 182 | 9 | 5.0 (2.3–9.2) | 103 | 3 | 2.9 (0.6–8.3) |
| ≥ 65 | 39 | 5 | 12.8 (4.3–27.4) | 13 | 1 | 7.7 (0.2–36.0) |
| Sex | | | | | | |
| Male | 111 | 9 | 8.1 (3.8–14.8) | 66 | 3 | 4.6 (1.0–12.7) |
| Female | 110 | 5 | 4.6 (1.5–10.3) | 50 | 1 | 2.0 (0.1–10.7) |
| TNM stage | | | | | | |
| Unresectable III | 13 | 0 | 0.0 (0–24.7) | 3 | 0 | 0.0 (0–70.8) |
| N | 208 | 14 | 6.7 (3.7–11.0) | 112 | 4 | 3.6 (1.0–8.9) |
| Metastases | | | | | | |
| M0 | 13 | 0 | 0.0 (0–24.7) | 3 | 0 | 0.0 (0–70.8) |
| M1A | 41 | 2 | 4.9 (0.6–16.5) | 23 | 1 | 4.4 (0.1–22.0) |
| M1B | 48 | 5 | 10.4 (3.5–22.7) | 21 | 2 | 9.5 (1.2–30.4) |
| M1C | 118 | 7 | 5.9 (2.4–11.8) | 67 | 1 | 1.5 (0.0–8.0) |
| BRAF | | | | | | |
| Wild type | 122 | 9 | 7.4 (3.4–13.5) | 72 | 2 | 2.8 (0.3–9.7) |
| Mutant | 26 | 2 | 7.7 (1.0–25.1) | 15 | 1 | 6.7 (0.2–32.0) |
| Unknown | 73 | 3 | 4.1 (0.9–11.5) | 27 | 1 | 3.7 (0.1–19.0) |
| ECOG | | | | | | |
| 0 | 66 | 5 | 7.6 (2.5–16.8) | 37 | 1 | 2.7 (0.1–14.2) |
| 1 | 113 | 8 | 7.1 (3.1–13.5) | 45 | 1 | 2.2 (0.1–11.8) |
| ≥ 2 | 11 | 0 | 0.0 (0–28.3) | 6 | 0 | 0.0 (0–45.9) |
| Unknown | 31 | 1 | 3.2 (0.1–16.7) | 27 | 2 | 7.4 (0.9–24.3) |
| LDH | | | | | | |
| Normal (< 1.1 x ULN) | 29 | 1 | 3.5 (0.1–17.8) | 28 | 2 | 7.1 (0.9–23.5) |
| Elevated (≥ 1.1 x ULN) | 192 | 13 | 6.8 (3.7–11.3) | 87 | 2 | 2.3 (0.3–8.1) |
| Histology | | | | | | |
| Acral | 67 | 4 | 6.0 (1.6–14.6) | 41 | 1 | 2.4 (0.1–12.9) |
| Mucosal | 95 | 6 | 6.3 (2.3–13.2) | 29 | 1 | 3.5 (0.1–17.8) |
| NCSD | 36 | 2 | 5.6 (0.7–18.7) | 24 | 1 | 4.2 (0.1–21.1) |
| CSD | 13 | 2 | 15.4 (1.9–45.4) | 14 | 1 | 7.1 (0.2–33.9) |
| Unknown | 10 | 0 | 0.0 (0–30.8) | 7 | 0 | 0.0 (0–41.0) |

Data cutoff date: December 31, 2017.

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

1L indicates first line; 2L, second line; CI, confidence interval; CSD, chronically sun damaged; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase level; NCSD, nonchronically sun damaged; ORR, objective response rate; ULN, upper limit of normal.
criteria. The cohort end date was December 31, 2017 and served as the cut-off value for censoring survival follow-up.

Medical charts in BCH contain detailed information about patient disease characteristics, therapies, laboratory data, computable tomography (CT), magnetic resonance imaging (MRI), and clinical outcomes. This hospital performs regular imaging in patients with melanoma as a 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 v 1.1)[14] and patients are followed up after discharge to Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST v 1.1)[14] and patients are followed up after discharge to

| Study population |

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

| Inclusion criteria |

(1) Eighteen years or older at the time of initiation of 1L or 2L therapy.

| Table 2 |

Overall survival by treatment line and patients’ characteristics (all-patients-as-treated population).

| N | Events | Person-month | Median OS (mo, 95% CI) | OS | OS | OS |
|---|---|---|---|---|---|---|
| Overall | 221 | 171 | 2988.1 | 5.7 | 10.5 (9.2-12.1) | 74.5 | 43.5 | 21.1 |
| Age (y) | | | | | | | | |
| < 65 | 182 | 145 | 2379.0 | 6.1 | 10.3 (8.4-11.6) | 72.4 | 42.0 | 19.2 |
| ≥ 65 | 39 | 26 | 609.1 | 4.3 | 13.4 (8.4-20.6) | 83.9 | 50.3 | 30.3 |
| Sex | | | | | | | | |
| Male | 111 | 85 | 1469.6 | 5.8 | 10.6 (8.0-13.1) | 75.7 | 43.5 | 19.7 |
| Female | 110 | 86 | 1518.5 | 5.7 | 10.5 (8.2-13.3) | 73.2 | 43.5 | 22.6 |
| TNM stage | | | | | | | | |
| Unresectable III | 13 | 8 | 181.9 | 4.4 | 8.9 (5.8-0.0) | 67.7 | 42.3 | 31.7 |
| IV | 208 | 163 | 2806.2 | 5.8 | 10.6 (9.3-12.1) | 74.9 | 43.6 | 20.6 |
| Metastases | | | | | | | | |
| M0 | 13 | 8 | 181.9 | 4.4 | 8.9 (5.8-0.0) | 67.7 | 42.3 | 31.7 |
| M1A | 41 | 28 | 673.3 | 4.2 | 14.5 (10.8-22.1) | 92.2 | 66.9 | 29.1 |
| M1B | 48 | 33 | 755.7 | 4.4 | 13.9 (9.9-18.8) | 84.2 | 53.6 | 28.9 |
| M1C | 118 | 101 | 1375.1 | 7.4 | 8.4 (6.7-10.5) | 66.3 | 32.8 | 15.1 |
| BRAF | | | | | | | | |
| Wild type | 122 | 92 | 1682.1 | 5.5 | 10.3 (8.0-13.2) | 73.8 | 43.8 | 22.4 |
| Mutant | 26 | 22 | 270.8 | 8.1 | 10.3 (6.5-12.8) | 71.3 | 31.8 | 9.1 |
| Unknown | 73 | 57 | 1035.2 | 5.5 | 10.8 (8.7-14.6) | 76.4 | 46.6 | 23.0 |
| ECOG | | | | | | | | |
| 0 | 66 | 48 | 965.6 | 5.0 | 13.6 (10.3-17.3) | 81.8 | 56.1 | 23.5 |
| 1 | 113 | 86 | 1547.1 | 5.6 | 9.8 (7.7-12.1) | 74.4 | 41.6 | 22.5 |
| ≥ 2 | 11 | 10 | 61.0 | 16.4 | 4.1 (2.2-7.1) | 30.7 | 10.2 | 8.8 |
| Unknown | 31 | 27 | 144.4 | 6.5 | 10.7 (8.1-13.3) | 74.1 | 35.9 | 18.0 |
| LDH | | | | | | | | |
| Normal (<1×ULN) | 29 | 21 | 423.4 | 5.0 | 12.2 (8.4-18.6) | 81.4 | 57.9 | 24.8 |
| Elevated (≥1×ULN) | 192 | 150 | 2564.7 | 5.9 | 10.3 (8.7-11.5) | 73.4 | 41.4 | 20.6 |

Data cutoff date: December 31, 2017.

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

1L indicates first line; 2L, second line; CI, confidence interval; CSD, chronically sun damaged; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase level; NA, not available; NCSD, nonchronically sun damaged; OS, overall survival; ULN, upper limit of normal.
(2) Histologically confirmed diagnosis of stage IIIB, IIIC, or IV melanoma.
(3) At least 1 measurable lesion as defined by RECIST v1.1 on imagine studies (CT or MRI).
(4) Initiated either systemic 1L or 2L anticancer therapy in the BCH between January 1, 2014 and December 31, 2015 (adjuvant therapy was not considered 1L treatments).
(5) Documented response status data (ie, complete response, partial response, progressive disease, and stable) available in the EMRs according 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 was allowed).
(3) Enrolled as a clinical trial participant for any melanoma therapies between January 1, 2014 and December 31, 2015.
(4) Known to be HIV positive or have active hepatitis B or C infection at the time of treatments under evaluation.

Measurements

Patients received 1L or 2L anticancer therapy during routine care. This information was extracted from EMRs. Outcomes of interest included real-world ORR, disease control rate, duration of response, time to response, PFS, time to progression, and OS. Outcomes were stratified according to 1L and 2L regimens.

### Table 3

| Event Rate/100 Person-months | Median PFS (months, 95% CI) | PFS ≥ 3 mo | PFS ≥ 6 mo | PFS ≥ 12 mo |
|----------------------------|-----------------------------|-----------|-----------|-------------|
| 1L Treatment*              |                             |           |           |             |
| N  | Events | Person-month | Median PFS | PFS ≥ 3 mo | PFS ≥ 6 mo | PFS ≥ 12 mo |
| Overall  | 221 | 203 | 1119.3 | 18.1 | 3.6 (2.9–4.2) | 55.1 | 28.2 | 10.6 |
| Age (y) < 65  | 182 | 170 | 795.1 | 21.4 | 3.2 (2.7–4.1) | 52.1 | 24.8 | 8.1 |
| ≥ 65  | 39 | 33 | 324.2 | 10.2 | 5.5 (3.0–7.2) | 69.2 | 43.6 | 21.8 |
| Sex Male  | 111 | 101 | 518.2 | 19.5 | 3.6 (2.8–4.2) | 56.8 | 26.3 | 10.0 |
| Female  | 110 | 102 | 601.1 | 17.0 | 3.3 (2.7–4.5) | 53.5 | 30.0 | 11.0 |
| Tumor stage Unresectable III  | 13 | 11 | 64.9 | 16.9 | 4.2 (1.6–10.6) | 69.2 | 34.6 | 11.5 |
| IV  | 208 | 192 | 1054.4 | 18.2 | 3.3 (2.9–4.2) | 54.2 | 27.9 | 10.5 |
| Metastases MD  | 13 | 11 | 64.9 | 16.9 | 4.2 (1.6–10.6) | 69.2 | 34.6 | 11.5 |
| M1A  | 41 | 40 | 184.8 | 21.6 | 3.6 (2.0–5.6) | 58.0 | 30.3 | 5.1 |
| M1B  | 48 | 41 | 352.3 | 11.6 | 5.8 (4.2–7.1) | 77.0 | 47.9 | 21.6 |
| M1C  | 118 | 110 | 516.3 | 21.3 | 2.7 (1.6–3.6) | 44.1 | 19.3 | 8.3 |
| BRAF Wild type  | 122 | 111 | 630.2 | 17.6 | 3.3 (2.8–4.2) | 53.9 | 24.5 | 11.6 |
| Mutant  | 26 | 25 | 116.7 | 21.4 | 3.6 (1.6–4.7) | 61.5 | 21.6 | 4.3 |
| Known  | 73 | 67 | 372.4 | 18.0 | 4.1 (2.0–5.7) | 54.8 | 36.6 | 11.5 |
| EGOG 0  | 66 | 57 | 392.4 | 14.5 | 4.1 (3.0–5.0) | 61.8 | 29.1 | 18.8 |
| 1  | 113 | 104 | 584.6 | 17.8 | 4.2 (2.9–5.2) | 58.4 | 31.9 | 7.9 |
| ≥ 2  | 11 | 11 | 25.9 | 42.5 | 1.6 (1.0–3.6) | 36.4 | 9.1 | NA |
| Unknown  | 31 | 31 | 116.4 | 26.6 | 1.6 (1.3–3.6) | 35.5 | 19.4 | 6.5 |
| LDH Normal (<1.1 x ULN)  | 29 | 28 | 103.5 | 27.1 | 2.7 (1.4–4.6) | 44.8 | 19.0 | 3.8 |
| Elevated (≥1.1 x ULN)  | 192 | 175 | 1015.8 | 17.2 | 3.6 (3.0–4.2) | 56.7 | 29.6 | 11.6 |
| Histology Acral  | 67 | 63 | 342.8 | 18.4 | 3.3 (1.7–4.2) | 53.7 | 25.4 | 12.5 |
| Mucosal  | 95 | 87 | 509.2 | 17.1 | 4.1 (2.9–4.7) | 56.6 | 31.1 | 11.4 |
| NCS  | 36 | 34 | 136.7 | 24.9 | 1.8 (1.0–4.2) | 41.7 | 14.9 | 3.0 |
| CS  | 13 | 9 | 76.9 | 11.7 | 5.8 (2.4–7.0) | 76.9 | 43.1 | 21.5 |
| Unknown  | 10 | 10 | 53.7 | 18.6 | 5.4 (0.8–7.1) | 70.0 | 50.0 | 10.0 |

Data cutoff date: December 31, 2017.
*Analysis population includes patients with valid treatment lines and histologic types.
1L indicates first line; 2L, second line; CI, confidence interval; CSD, chronically sun damaged; EGOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase level; NCS, nonchronically sun damaged; PFS, progress-free survival; ULN, upper limit of normal.
**Statistical analysis**

ORR point estimates and 95% CIs were calculated using the binomial exact method. The Kaplan-Meier method and Log-Rank test were used to estimate the median value of time to event outcomes and statistical difference among patients with varied characteristics. A Cox proportional hazards model was simulated to evaluate the impact of age (below 65 as reference), gender (female as reference), TNM stage at diagnosis (unresectable stage III as reference), histopathologic characteristics (histopathology types other than mucosal and acral melanomas as reference), metastases (M0 as reference), ECOG status (0 as reference), and LDH (normal as reference) on survival among patients with advanced and metastatic melanoma in China. R software was used for data analysis (Version 1.1.453-2009-2018 RStudio, Inc.).

**Results**

**Baseline characteristics**

Overall, there were 221 and 116 Chinese locally advanced and/or metastatic melanoma patients enrolled in 1L and 2L treatments, respectively. In the 1L setting, 17.6% of enrolled patients were 65 years and above; 50.2% were male; ~95% were stage IV with distant metastasis; 26 out of 148 patients with definite BRAF genotyping were mutant; 124 of 190 with ECOG results had score $\geq 1$; and 86.9% had elevated LDH. Among 116 patients receiving 2L treatments, 11.2% were 65 years and above; 56.9% were male; 97.4% were stage IV with distant metastasis; 15 of 87 and 54 of 90 were BRAF mutant and ECOG $\geq 1$, respectively; and 75.7% patients had elevated LDH.

|                | N   | Number of Events | Median OS |
|----------------|-----|-----------------|-----------|
| **Age (year)** |     |                 |           |
| <65            | 162 | 145             | 10.3      |
| $\geq 65$      | 39  | 26              | 13.4      |
| **Gender**     |     |                 |           |
| Male           | 111 | 85              | 10.6      |
| Female         | 110 | 86              | 10.5      |
| **TNM stage**  |     |                 |           |
| Unresectable III | 13 | 8              | 8.9       |
| IV             | 208 | 163             | 10.6      |
| **Metastases** |     |                 |           |
| M0             | 13  | 8               | 8.9       |
| M1A            | 41  | 28              | 14.5      |
| M1B            | 48  | 33              | 13.9      |
| M1C            | 118 | 101             | 8.4       |
| **BRAF**       |     |                 |           |
| Wild type      | 122 | 92              | 10.3      |
| Mutant         | 26  | 22              | 10.3      |
| Unknown        | 73  | 57              | 10.8      |
| **ECOG**       |     |                 |           |
| 0              | 66  | 48              | 13.6      |
| 1              | 113 | 86              | 9.8       |
| $\geq 2$       | 11  | 10              | 4.1       |
| Unknown        | 31  | 27              | 10.7      |
| **LDH**        |     |                 |           |
| Normal ($<1.1 \times $ULN) | 29 | 21             | 12.2      |
| Elevated ($\geq 1.1 \times $ULN) | 192 | 150           | 10.3      |
| **Histology**  |     |                 |           |
| Acral          | 67  | 55              | 10.6      |
| Mucosal        | 95  | 73              | 10.3      |
| NCSD           | 36  | 27              | 10.8      |
| CSD            | 13  | 6               | 13.1      |
| Unknown        | 10  | 10              | 10.0      |

*Figure 1.* Overall survival of advanced melanoma patients after receiving 1L treatments and potential prognostic factors. 1L, indicates first line; CSD, chronically sun damaged; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase level; NCSD, nonchronically sun damaged; OS, overall survival; ULN, upper limit of normal.
Descriptive characteristics of ORR, OS, and PFS measurements

Tables 1–3 and Figs. 1–4 show the ORR, OS, and PFS estimates for Chinese locally advanced and/or metastatic melanoma patients. Data indicate that clinical outcomes in advanced melanoma patients in this study were poor: real-world ORR was <10% (1L: 6.3% [95% CI: 3.5%–10.4%]; 2L: 3.4% [95% CI: 0.9%–8.6%]); median PFS was under 4 months (1L: 3.5 mo [95% CI: 2.9–4.2]; 2L: 2.3 mo [95% CI: 2.0–3.0]); median OS was <1 year (1L: 10.5 mo [95% CI: 9.2–12.1]; 2L: 7.5 mo [95% CI: 6.5–8.7]) with a low 12-month OS rate (43.5% for 1L, 30.5% for 2L).

Among patients receiving 1L treatments, the median OS (months) among those patients with ECOG ≥2 and ECOG = 1 were 4.1 (95% CI: 2.2–7.1) and 9.8 (95% CI: 7.7–12.1) respectively, which was significantly shorter than those with ECOG = 0 (OS = 13.6 mo; 95% CI: 10.3–17.3). Similar statistically significant trends were found among patients receiving 2L treatments in Table 2. The median PFS (months) for patients with ECOG = 0, 1 and ≥2 were 4.1 (95% CI: 3.0–5.0), 4.2 (95% CI: 2.9–5.2) and 1.6 (95% CI: 1.0–3.6) for those receiving 1L treatments; findings were statistically significant. Similar statistically significant trends were found among patients receiving 2L treatments in Table 3. Those patients with ECOG ≥2 had significantly lower ORRs, compared with those with ECOG = 0 and 1 regardless of line of therapy.

No statistically significant difference was observed neither in the 1L nor 2L treatments for ORR, OS and PFS between age, sex, stage at diagnosis, histopathologic characteristics, metastatic stage, BRAF gene mutation, and LDH status among locally advanced and/or metastatic melanoma patients.

![Figure 2. Overall survival of advanced melanoma patients after receiving 2L treatments and potential prognostic factors. 2L indicates second line; CSD, chronically sun damaged; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase level; NCSD, nonchronically sun damaged; OS, overall survival; ULN, upper limit of normal.](image-url)
Multivariate analysis for the decreased prognosis

Cox regression analyses were performed to evaluate the association between multiple potential factors (including age, sex, TNM stage, metastases, ECOG score, and LDH status) with poor outcomes of melanoma patients enrolled from 1L (n = 181 patients), 2L treatments (n = 81 patients), and both (n = 262 patients), respectively (Table 4). BRAF gene mutation status was not included in multivariate analyses because a high proportion of missing data was observed in the present study.

Data indicated that among those melanoma patients with ECOG Performance Status ≥ 2 (vs. ECOG = 0, P < 0.001) in 1L, and 2L treatment (vs. 1L treatment, P = 0.006) or ECOG ≥ 2 (vs. ECOG = 1, P < 0.001) among 1L/2L were associated with statistically significantly worse outcomes, while no significant risk increases from those ECOG = 1, compared with those ECOG = 0 (P = 0.503), nor from those ECOG ≥ 2 (P = 0.359) to those ECOG = 0 in the 2L due to limited patients (n = 6). The present study did not observe statistical significance independently (P > 0.05) among melanoma patients within age group, sex, TNM stages, metastatic and LDH status, as well as histologic types, regardless of whether they had received 1L, 2L treatments, or both.

Discussion

The retrospective longitudinal, population-based China study aimed to demonstrate the importance and utility of potential covariates as prognostic factors for survival among patients with unresectable, locally advanced (stage IIIb or IIIc) or metastatic (stage IV) melanoma during a chemotherapy-dominated era in China. We showed that those patients with ECOG ≥ 2 had only one-third to one-half median OS (months) and PFS (months)
compared with those with ECOG = 0. When considering late stage at diagnosis, histopathologic characteristics and treatment patterns, poor performance status (ECOG ≥ 1) was associated with poor prognosis. Among Chinese melanoma patients with ECOG ≥ 2, prior chemotherapy would significantly associate with poor outcomes, especially for those receiving 1L treatments. A pooled analysis conducted by Manola and colleagues using 1362 eligible patients with metastatic melanoma treated in 8 ECOG trials conducted in the past 25 years found factors conferring the highest increased risk of death to be ECOG performance status of 1 or more, with relative risk of 1.5 (95% CI: 1.3–1.7)\(^{[15]}\). These authors also suggest that “chemoresistance needs to be considered in planning long term therapy and that immunotherapy may be a better option in early treatments of melanoma.”

The present study also demonstrated a statistically significant increase in odds of death for patients enrolled from 2L treatments, compared with those from 1L treatments. The median OS (months) of patients enrolled from 1L treatments was 10.5 (95% CI: 9.2–12.1), which was statistically significantly higher than those enrolled from 2L treatments (7.5 mo, 95% CI: 9.2–12.1), as was median PFS (months) inpatients from 1L treatments (3.6, 95% CI: 2.9–4.2) and from 2L treatments (2.3, 95% CI: 2.0–3.0). A Cox regression model considering age, sex, TNM stage, metastases, ECOG score, and LDH status, estimated 50% increased odds of death from those patients enrolled from 2L treatments, compared those from 1L treatments. These findings are different from what has been reported previously. Pflugfelder et al (2011) reported that response, PFS and OS were equivalent in 61 German patients with metastatic melanoma using carboplatin and paclitaxel as 1L and 2L treatments\(^{[16]}\). A retrospective observational study conducted in 1170 Polish advanced metastatic melanoma patients treated with vemurafenib, dabrafenib and ipilimumab, indicated no significant

| N | Number of Events | Median PFS |
|---|-----------------|------------|
| Overall | 116 | 115 | 2.3 |
| Age (year) | | | |
| <65 | 103 | 102 | 2.2 |
| ≥65 | 13 | 13 | 2.7 |
| Gender | | | |
| Male | 66 | 66 | 2.1 |
| Female | 50 | 49 | 2.6 |
| TNM stage | Unresectable II | 3 | 3 | 2.4 |
| | IV | 112 | 111 | 2.3 |
| Metastases | MO | 3 | 3 | 2.4 |
| | M1A | 23 | 23 | 2.5 |
| | M1B | 21 | 21 | 3.5 |
| | M1C | 67 | 66 | 2.0 |
| BRAF | Wild type | 72 | 72 | 2.7 |
| | Mutant | 15 | 15 | 2.1 |
| | Unknown | 27 | 26 | 2.0 |
| ECOG | 0 | 37 | 37 | 3.7 |
| | 1 | 45 | 45 | 2.0 |
| | ≥2 | 6 | 6 | 1.9 |
| | Unknown | 27 | 26 | 2.8 |
| LDH | Normal (<1.1×ULN) | 28 | 28 | 2.4 |
| | Elevated(>1.1×ULN) | 87 | 86 | 2.2 |
| Histology | Acral | 41 | 41 | 3.3 |
| | Mucosal | 29 | 26 | 2.1 |
| | NCSD | 24 | 24 | 2.0 |
| | CSD | 14 | 14 | 2.1 |
| | Unknown | 7 | 7 | 1.0 |

Figure 4. PFS of advanced melanoma patients after receiving 2L treatments and potential prognostic factors. 2L indicates second line; CSD, chronically sun damaged; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase level; NCSD, nonchronically sun damaged; PFS, progress-free survival; ULN, upper limit of normal.
difference in response rates regardless of line of vemurafenib (first, second, or next)\[^{15}\]. However, those published studies did not consider the overall impact from metastases, ECOG score, and LDH status, and they included immunotherapeutic agents or had limited sample size.

Acral lentiginous melanoma and mucosal melanoma are the most common subtypes of melanoma in the Asian population, accounting for >60% of all melanomas in China\[^{6}\], while only 5% among all types of melanoma from Caucasians in Europe and United States\[^{18}\]. The present study did not observe significant difference in ORR, OS, and PFS measurements among those with different histologic types, nor an increased odds of death from those with chronic sun-induced (CS) or non–chronic sun-induced damage to those with acral lentiginous melanoma or mucosal melanoma (P > 0.05). These results were not consistent with previous publications in China\[^{19}\], Korea\[^{20,21}\], and Japan\[^{22}\], however, those studies did not include covariate factors potentially related to therapeutic outcomes, like ECOG status.

There are some limitations in the present study that should be acknowledged. Because few patients enrolled were unresectable stage III/prior metastases (n = 13), the present study did not observe significantly increased odds of death from patients at TNM stage IV compared with those at unresectable stage III, nor from those with metastases to those without. BRAF mutation status was not included into the Cox regression analysis, because 33.0% and 24.7% of mutation data were missing from patients receiving 1L and 2L treatments, respectively. In addition, 14.1% and 23.5% of ECOG scores were missing from patients enrolled from 1L and 2L treatments which reduced the statistical power for ECOG = 1 for 1L treatment and ECOG ≥ 2 for 2L treatment.

This study used EMR from BCH, which is the largest melanoma hospital in China and treats patients from all over the country. Our findings indicate a poor clinical outcome from those advanced melanoma patients using current chemotherapies, especially for those with the poor level of functioning in terms of their ability to care for themselves, daily activity, and physical ability (walking, working, etc.), suggesting immunotherapy as a better option in early treatments of melanoma. Although there is a proportion of missing data for key variables (eg, ECOG score, BRAF mutation, histologic types), our findings suggest a high unmet medical need for advanced melanoma patients in China.

### Ethical approval

A waiver of patient consent was applied for and approved by the medical ethics committee of Beijing Cancer Hospital (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., and J.G.: 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.L., and J.G.: acquired the data. C.C., X.Y., B.L., and J.G.: analyzed the data. C.C., X.Y., and J.G.: interpreted the results. C.C., X.Y., and J.G.: drafted the manuscript with contributions from all authors. C.C., X.Y., L.S., Z.C., X.S., B.L., X.W., L.M., B.T., L.Z., X.B., S.L., B.L., J.G.: critically reviewed or revised the manuscript for important intellectual content. B.L.: provided statistical expertise.

### Conflict of interest disclosure

B.L. report employment at MSD Beijing, China. The remaining authors declare that they have no financial conflict of interest with regard to the content of this report.

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### Table 4

| 1L Treatment* | Coefficients | Odds Ratio (95% CI) | P   |
|---------------|--------------|---------------------|-----|
| Age\[^{1}\]  | -0.33        | 0.72 (0.44–1.15)    | 0.169|
| Sex\[^{2}\]   | 0.13         | 1.14 (0.80–1.62)    | 0.461|
| TNM stage\[^{3}\] | 0.32       | 1.38 (0.60–3.17)    | 0.454|
| M stage = 1\[^{4}\] | 0.27    | 1.31 (0.75–2.27)    | 0.343|
| ECOG = 1\[^{5}\] | 0.13       | 1.14 (0.78–1.67)    | 0.502|
| ECOG ≥ 2\[^{6}\] | 1.36      | 3.87 (1.90–7.89)    | <0.001|
| LDH = evaluated\[^{7}\] | 0.11     | 1.12 (0.58–2.17)    | 0.734|
| Histology\[^{8}\] | -0.13      | 0.88 (0.56–1.39)    | 0.583|
| Second line\[^{9}\] | —         | —                   | —   |

| 2L Treatment | Coefficients | Odds Ratio (95% CI) | P   |
|---------------|--------------|---------------------|-----|
| Age\[^{1}\]  | 0.49         | 1.63 (0.75–3.54)    | 0.215|
| Sex\[^{2}\]   | -0.03        | 0.97 (0.58–1.61)    | 0.897|
| TNM stage\[^{3}\] | -1.09     | 0.34 (0.04–2.81)    | 0.315|
| M stage = 1\[^{4}\] | -0.36     | 0.70 (0.32–1.51)    | 0.362|
| ECOG = 1\[^{5}\] | 0.53       | 1.69 (1.00–2.85)    | 0.048|
| ECOG ≥ 2\[^{6}\] | 0.49      | 1.63 (0.57–4.66)    | 0.359|
| LDH = evaluated\[^{7}\] | 0.07      | 1.07 (0.53–2.15)    | 0.855|
| Histology\[^{8}\] | -0.19      | 0.83 (0.49–1.40)    | 0.478|
| Second line\[^{9}\] | —         | —                   | —   |

| 1L/2L Treatment | Coefficients | Odds Ratio (95% CI) | P   |
|-----------------|--------------|---------------------|-----|
| Age\[^{1}\]  | -0.17        | 0.85 (0.57–1.26)    | 0.412|
| Sex\[^{2}\]   | 0.01         | 1.01 (0.76–1.34)    | 0.923|
| TNM stage\[^{3}\] | 0.23       | 1.26 (0.58–2.72)    | 0.559|
| M stage = 1\[^{4}\] | 0.14     | 1.15 (0.74–1.79)    | 0.536|
| ECOG = 1\[^{5}\] | 0.23       | 1.26 (0.93–1.71)    | 0.136|
| ECOG ≥ 2\[^{6}\] | 0.94      | 2.56 (1.44–4.55)    | 0.001|
| LDH = evaluated\[^{7}\] | 0.01      | 1.01 (0.64–1.60)    | 0.906|
| Histology\[^{8}\] | 0.12       | 0.88 (0.63–1.24)    | 0.472|
| Second line\[^{9}\] | 0.42       | 1.52 (1.12–2.05)    | 0.006|

Data cutoff date: December 31, 2017.

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

†Those age <65 as reference.

‡Those female as reference.

§Those unresectable stage III as reference.

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

\[^{1}\] Those age <65 as reference.

\[^{2}\] Those female as reference.

\[^{3}\] Those unresectable stage III as reference.

\[^{4}\] Those M0 as reference.

\[^{5}\] Those ECOG with 0 as reference.

\[^{6}\] Those age <65 as reference.

\[^{7}\] Those with normal LDH as reference.

\[^{8}\] Those enrolled in the first line treatment as reference.

\[^{9}\] 1L indicates first line; 2L, second line; CI, confidence interval; CSD, chronically sun damaged; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase level; NCSD, nonchronically sun damaged; PFS, progression-free survival; ULN, upper limit of normal.
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Guarantor

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