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Highlights

Key Objective Is high body mass index (BMI) associated with survival outcomes in relation to systemic therapy in patients with metastatic melanoma?

Relevance In this multicenter, retrospective study of MelBase (French multicentric metastatic melanoma cohort) that included 1,214 patients, response to first-line of treatment with either chemotherapy, targeted or immunotherapy was not influenced by BMI

Knowledge Generated High BMI does not appear to be associated with improved progression-free survival and overall survival in metastatic melanoma patients treated with systemic therapy. Because it does not consider the whole-body composition, others approaches are needed.

ABSTRACT

Background

The "obesity paradox" suggests that higher body mass index (BMI) is associated with better survival values in metastatic melanoma patients, especially those receiving targeted and immune checkpoint inhibitor therapy. Higher BMI is also associated with higher incidences of treatment-related adverse events. This study assesses whether body mass index is associated with survival outcomes and adverse events in metastatic melanoma patients with systemic therapy.

Patients and methods: This multicentric retrospective study, conducted from March 1, 2013 to April 29, 2019, enrolled adults with unresectable stage III or IV melanoma from the French multicentric prospective cohort-MelBase (NCT02828202). Patients with first-line chemotherapy and targeted and immune therapy were included. Underweight people and those with metastatic mucosal or ocular melanoma were excluded. Body mass index was categorized using the World Health Organization criteria. Co-primary outcomes included the association between body mass index and progression-free survival and overall survival, stratified by treatment type, sex and age. Secondary endpoints were the association of body mass index with overall response and treatment-related adverse events. Multivariate analyses were performed.

Results: Totally, 1,214 patients were analyzed. Their median age was 66.0 years (range, 53-75). Male predominance was observed (n = 738 [61%]). Most patients received immune checkpoint inhibitor therapy (63%), followed by targeted therapy (32%), and had stage M1c disease (60.5%). Obese patients represented 22% of the cohort. The median follow-up duration was 13.5 months (range, 6.0-27.5). In the pooled analysis, no positive or negative association between body mass index and progression-free survival (p = 0.88)/overall survival (p = 0.25) was observed, regardless of treatment type, sex, and age. These results were

nonsignificant in the univariate and multivariate analyses. The objective response rate, according to body mass index category, did not differ significantly regardless of age. Treatment-related adverse events were not associated with body mass index.

Conclusion: The observed lack of an association between body mass index and survival demonstrates that body mass index is not a valuable marker of systemic treatment-related outcomes in metastatic melanoma. Future approaches might focus on the whole-body distribution.

Key words: melanoma, body mass index, clinical outcomes, systemic therapy, targeted therapy, immunotherapy

INTRODUCTION

In the last decade, the survival duration of patients with advanced melanoma has substantially increased with the use of targeted therapy (TT) as well as immune checkpoint inhibitors (ICIs), which are associated with response rates ranging from 40% to 60-70% in case of combination therapies.[1-4] However, a substantial proportion of patients does not respond to these therapies due to innate or acquired resistance.

The identification of populations that may not truly benefit from the aforementioned therapies is crucial. Several genomic, molecular, and cellular processes are involved in resistance development in such settings.[5-8] Unfortunately, there is a lack of robust and reliable biomarkers that can aid in the selection of appropriate candidates for ICI and TT. It is important, therefore, to identify clinical characteristics that are predictive of treatment-related outcomes.

Obesity, defined as a body mass index (BMI) > 30 kg/m^2, is a risk factor for several cancers and is associated with poorer prognosis.[9,10] It is also related to an increased melanoma risk among men[11] and shorter overall survival (OS) durations[12] and is a clinical independent risk factor for thick primary cutaneous melanoma.[13] However, contradictory findings have also been reported and the concept of the "obesity paradox" has recently emerged, wherein higher BMIs have been shown to be associated with longer survival in metastatic melanoma, especially among male patients receiving TT and ICIs.[14] However, smaller cohorts did not observe the same results, especially with immunotherapy, leaving this question open to further debate.[15] Accordingly, we aimed to investigate the association of BMI with survival in a large multicenter cohort of metastatic melanoma patients treated with ICIs, TT, and chemotherapy (CT) and explore the association of BMI with the incidence and severity of treatment-related adverse events (TRAEs), by BMI category.

PATIENTS AND METHODS

Study design and patient eligibility

In this retrospective study, we enrolled patients from MelBase, a French multicentric biobank and database dedicated to the prospective follow-up of adults with advanced melanoma at the time of metastasis declaration across 26 participating centers. The study protocol was approved by the French ethics committee (CPP Ile-de-france XI, n°12027, 2012), the local ethics committee, as well as the ethics committees of all the participating institutions. The study was registered in the NIH clinical trials database (NCT02828202). Written informed consent was obtained from all patients.

This study was conducted from March 1, 2013 to April 29, 2019. All patients with unresectable stage III and stage IV melanoma treated with first-line immunotherapy (anti-programmed cell death 1 [PD-1] and/or anti-CTLA-4), TT (BRAF and/or MEK inhibitors), and CT in real-life settings as well as clinical trial participants (open trials as well others after unblinding) with at least a 3-month follow-up period were included. Patients with unknown primary melanoma were also included. However, metastatic mucosal and ocular melanoma patients and those for whom the BMI could not be calculated were excluded. Underweight patients, comprising a small proportion (3%), were also excluded.

Four cohorts were defined: (1) whole treatment cohort, (2) TT cohort (including BRAF and/or MEK inhibitor therapy), (3) immunotherapy cohort (including anti-PD-1 and/or anti-CTLA-4 therapy), and (4) CT cohort.

Anthropometric measurements and procedures

All clinical and biological data were collected before treatment initiation from a standardized electronic case report form (eCRF). BMI was objectively measured by the investigator and

was collected at treatment initiation. BMI was calculated as the weight in kilograms divided by the square of the height in meters (kg/m^2) at treatment initiation and categorized using the World Health Organization criteria: underweight, BMI < 18.5 kg/m^2; normal weight, 18.5 kg/m^2 ≤ BMI ≤ 24.9 kg/m^2; overweight, 25 kg/m^2 ≤ BMI ≤ 29.9 kg/m^2; and obese, BMI ≥ 30 kg/m^2.[16]

Outcomes

The primary outcome was the association of each BMI category with progression-free survival (PFS) and (2) OS, stratified by treatment type (ICIs vs TT vs CT), age, and sex. PFS was defined as the time from the start of the first systemic therapy to the date of disease progression or death, whichever occurred first. Patients who were alive without disease progression were censored at the date of their last disease assessment. OS was defined as the time from the start of first systemic therapy to death. Patients who were still alive were censored at the date of the last contact. Disease progression and response were evaluated using the Response Evaluation Criteria in Solid Tumors (version 1.1) by radiologists at each participating institution.[17]

Secondary outcomes were the association of BMI with overall response (complete and partial response), TRAEs, and immune-related adverse events (irAEs). Data on TRAE and irAE incidence were collected and graded according to the US National Cancer Institute Common Toxicity Criteria for Adverse Events (version 4.0).

Data on relevant confounding factors were evaluated, including those on the patients' age (65 < vs ≥65 years, cutoff fixed at 65 years[18,19]), sex (female vs male), disease stage (M1c vs IIIc/M1a, M1b), Eastern Cooperative Oncology Group (ECOG) performance status (<2 vs ≥2), serum lactate dehydrogenase level (LDH, ≤ the upper limit of normal vs > normal), brain

metastases (absent or present), $BRAF^{V600}$ status (wild type vs mutated), and number of tumor sites (<3 vs ≥3).

Statistical Analyses

The baseline characteristics of the patients were compared across the BMI categories using chi-square tests for qualitative variables and linear regression test for age. The median PFS and OS values were evaluated using the Kaplan–Meier method and Cox proportional hazards regression models. The PFS and OS values across the subgroups were compared using the log-rank test. Using univariate and multivariable cox proportional hazard models, we analyzed the associations between BMI and PFS/OS, stratified by the type of treatment (ICI vs TT vs CT), age (<65 vs ≥65 years), and sex (male vs female). In the multivariate analysis, we adjusted for age (≥65 years vs not), sex, American Joint Committee on Cancer (AJCC) 7 disease stage (M1c vs others), ECOG performance status (<2 vs ≥2), LDH level (normal vs elevated), brain metastasis (yes vs no), $BRAF^{V600}$ status (wild type vs mutated), and number of disease sites (≥3 vs 0).

In terms of objective response, comparisons across the three BMI groups were performed using the chi-square test. The differences between the BMI groups in terms of the incidence of adverse events were evaluated using Fisher's exact test.

All statistical tests were two-sided, with $p<0.05$ indicating statistical significance.

All analyses were carried out using R statistical software version 3.5.2 (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Population

Totally, 1,597 patients with advanced melanoma were treated with first-line ICI, TT, or CT between March 1, 2013 and April 29, 2019; 331 (20.7%) were excluded because of missing height or weight data for BMI calculation. Of the 1,266 patients with available BMI data, 52 (4%) were excluded because they were underweight (n=38 [3%]) or their follow-up duration was too short (n=14 [1%]). Finally, 1,214 patients were included in the current analysis, and most of them were enrolled from real-life settings (n=945 vs n=269 enrolled from clinical trials). The median patient age was 66.0 years (interquartile range [IQR], 53-75), and a majority of the patients were male (n=738 [61%]). The median follow-up duration was 13.5 months (IQR, 6.0-27.5): 6.1 months (IQR, 3.4-20.1) in the CT cohort, 15.2 months (IQR, 6.8-30.9) in the TT cohort, and 13.9 months (IQR, 5.9-26.2) in the ICI cohort. Totally, 516 (43%) patients had a normal weight, 429 (35%) were overweight, and 269 (22%) were obese. The majority of patients received ICI (n=761 [63%]), followed by TT (n=389 [32%]), and most of them had stage M1c disease (60%). Approximately 19% of the patients had brain metastases and ~30% had elevated LDH levels. The baseline patient characteristics were distributed equally across the three BMI groups, except for sex (male predominance was observed in whole population and within each BMI category) and the AJCC stage (larger number of stage M1c disease cases in whole population and within each BMI category, Table 1).

Relationship between BMI and survival

The PFS durations of the overweight/obese melanoma patients did not differ from those of the patients with a normal BMI (Figure 1A, p=0.68). Stratification of this cohort by treatment type did not lead to data modification, with the following results observed: patients treated with ICIs (p=0.87, Figure 1B), those with TT (p=0.51, Figure 1C), and those with CT

(p=0.43, Figure 1D). These results remained nonsignificant after stratification by sex and age (supplementary Figures S1 and S2).

Compared with those in the normal-weight group, the OS values in the obese and overweight groups did not reach statistical significance. The OS values did not differ across the patients with a normal weight, overweight, and obesity (p=0.25, Figure 2A), regardless of treatment type (Figures 2B-D), sex, and age (supplementary Figures S3 and S4). The proportions of patients with PFS/OS at 6 months and 1, 2, and 3 years by BMI category are shown in supplementary Table S1).

In the pooled analysis of obese and overweight patients, we did not observe any differences in the parameters compared with those noted in the patients with a normal BMI, and no positive or negative association with PFS (p=0.85) and OS (p=0.37) was observed, regardless of treatment type and sex (supplementary Figures S5-S8).

In the univariate analysis, we did not observe a statistically significant PFS benefit in the overweight (HR=0.96 [0.82-1.11], p=0.57) and obese patients (HR=1.04 [0.87-1.23], p=0.69) compared with those with a normal BMI, regardless of treatment type (Table 2). The result trend showed the same direction for OS, with no statistically significant OS benefit observed in the overweight (HR=0.87 [0.72-1.05], p=0.15) and obese patients (HR=1.02 [0.83-1.24], p=0.87), regardless of treatment type, including combination-ICI (Table 2).

In the multivariate model, we did not observe a statistically significant PFS benefit in the overweight (HR=1.02 [0.87-1.18], p=0.84) and obese patients (HR=1.13 [.94-1.35], p=0.19), regardless of treatment type. The same result was observed for OS, with no statistically significant OS benefit noted in the overweight (HR=0.94 [0.78-1.14], p=0.55) and obese patients (HR=1.12 [0.9-1.39], p=0.33). These results remained nonsignificant after the exclusive consideration of the combination-ICI cohort (Table 3).

Relationship between BMI and objective response rate

The response to systemic therapy, according to BMI category, did not differ significantly, regardless of treatment type (supplementary Table S2). The same result was observed after stratification by age (supplementary Table S3 and Figure S9).

Toxicity analysis

Totally, 819 (67%) patients experienced adverse events (AEs) of any grade and 260 (21%) experienced grade 3-4 AEs. The incidence rates of AEs were not significantly different between the BMI categories (all grades: 65% [normal], 70% [overweight], and 68% [obese]; p=0.19, and grade 3-5: 19% [normal], 23% [overweight], and 24% [obese]; p=0.25, supplementary Table S4). The occurrence of the different types of AEs of any grade categorized according to the different organs/systems involved across the baseline BMI categories is described in supplementary Table S5. No statistically significant difference was observed by BMI, except in the ICI cohort in which overweight and obesity, respectively, were associated with significantly higher occurrence rates of cutaneous irAEs (p=0.05) and gastro-intestinal irAEs (p=0.02) than normal weight.

DISCUSSION

The present study, unlike that conducted by McQuade et al,[14] did not demonstrate the presence of any association between BMI and improved survival outcomes. No positive or negative association between BMI and PFS/OS as well as objective response was observed, regardless of treatment type, sex, and age both in the univariate and multivariable analyses. These data remained nonsignificant after adjustment for several clinically relevant

confounders, and pooled analyses of the overweight with obese patients did not lead to result modification.

The “obesity paradox” refers to the better outcomes observed in obese patients, in particular among melanoma patients with ICI/TT[14] and lung cancer patients with ICI,[20,21] despite obesity being a risk factor for the development of such cancers and its association with an aggressive tumor biology.[22] Obesity is also associated with an increased melanoma development risk in men[11], is an independent risk factor for thick melanoma and a positive association was observed between elevated BMIs and shorter survival durations[13] Interestingly, in the multivariable analysis conducted in the same cohort, C-reactive protein remained an independent marker of poorer survival but not BMI, suggesting that systemic inflammation may be implicated in BMI-associated melanoma progression.[12,13] These findings are reinforced by recent data, which reveal that obese-inflammatory patients have an immunosuppressed phenotype related to an increase in the rate of immune aging and PD-1-mediated T cell dysfunction, the effects of which are mediated by the leptin pathway.[22-25] However, a growing body of evidence suggests that obese patients have better outcomes .[14,20,26]

In our study, no relevant conclusion could be drawn with regards to the CT cohort which enrolled only 64 patients. However, our results pertaining to the ICI and TT cohorts merit further discussion, particularly as they are now the cornerstones of melanoma treatment. While caution must be exercised in the performance of head-to-head comparisons between studies, several factors may be involved in the heterogeneity of the published data. First, several studies investigated different tumors in the same analysis, [22,26] leading to the introduction of major selection bias. In fact, the clinical and demographic characteristics of populations may differ significantly by tumor histology. The tumor by itself may exhibit a different behavior depending on the treatment and metabolic context in which it evolves.

Second, while the performance of comparisons with studies with similar sample sizes is appropriate, McQuade et al[14] found a positive association between obesity and longer PFS/OS durations in the pooled analysis, contrary to our findings. This association was not statistically significant in the individual cohort analysis. The survival benefit particularly observed in men with ICI and TT did not extend to CT. Additionally, this benefit was not observed in women, regardless of treatment type, similar to our findings. It is important to consider that the vast majority of patients (87%) in the previous study were enrolled from clinical trials, whereas 78% of our population was enrolled from real-life settings. Knowing that patients from clinical trials are highly selected patients, with most of the time different outcomes compare to "real-life" patients, this must be considered in the interpretation of data related to the "obesity paradox." Moreover, it is noteworthy that in the anti-PD-1/PDL1 cohort, which is a real-life retrospective cohort, no statistically significant results were obtained.[14] Thus, our study leaves room for debate, particularly as the authors postulated initially that obesity would be associated with worse outcomes in patients with metastatic melanoma. In a correspondence published in *Lancet Oncology*, several limitations were emphasized, notably the imbalance in the prognostic factors across the BMI categories and the possibility of confounding and indication biases.[27] We believe that these points deserve strong consideration in the interpretation of results. Moreover, the high proportion of patients treated with CT (34%) and the absence of an anti-PD-1/anti-CTLA-4 cohort, which represents the most frequently used upfront treatment modality currently[2], are other limitations.

Similar to our study, Donnelly et al investigated 423 melanoma patients treated with ICI, most of whom (63%) received it as first-line therapy. A higher BMI was not associated with improved PFS/OS values. In considering only patients treated with first-line ICI, no significant positive association with both PFS/OS was observed in the overweight/obese patients. Interestingly, a negative association was observed among those treated with ICI non-

first-line therapy; we did not investigate this situation. Our results are consistent with those observed by Donnelly et al, except in terms of combination ICI, which, among overweight and obese patients was associated with a statistically significant survival benefit. Nevertheless, the small sample size of both studies requires caution in the interpretation of the results.[15] In a study conducted by Cortellini et al, 976 cancer patients were treated with ICIs, predominantly comprising lung cancer (65%), followed by melanoma (19%) and renal cell carcinoma (14%). Considering the whole population as well as the melanoma cohort in the pooled analysis of the overweight/obese patients, a significantly higher overall response rate and longer PFS/OS durations were observed compared with those noted in the normal-BMI participants both in the univariate and multivariate analyses. However, this PFS-related result was not confirmed among men. In our pooled ICI-overweight/obese cohort, we did not observe PFS/OS values that differed from those noted in the normal-BMI cohort, regardless of sex. Furthermore, their multivariate analysis on obese patients did not reveal better PFS values compared with those in the normal-BMI patients, similar to our findings.[26] Finally, Naik et al, in a cohort of 139 melanoma patients who received ICI and were further categorized into BMI groups (overweight and class I obesity, BMI 25- < 35 kg/m^2) vs class II/III, BMI ≥ 35 kg/m^2), revealed that the "obesity paradox" was restricted to those in the overweight/class I obesity group. Interestingly, a survival benefit was observed predominantly among men with a higher skeletal muscle mass.[28]

Except for overweighed and obese patients treated with ICI, for whom a significantly higher occurrence rates of cutaneous irAEs and gastro-intestinal irAEs were observed compare to normal BMI patients, we did not observe statistically significant differences in the incidence of any grade AEs as recently reported in a meta-analysis focusing on ICI.[21] Once again, results are heterogeneous, because some have found a relationship between higher BMI and increased risk of AEs, especially irAEs in patients on ICI.[29,30]

Overall, the observed heterogeneity in the results highlights the limitations associated with the use of BMI as a valuable marker of systemic therapy-related outcomes in metastatic melanoma patients, especially those with ICI and TT. The simplicity of its use in daily practice is attractive but does not guarantee reliable evaluation. The discrepancy between published studies may be explained by the use of BMI, which does not reflect a person's body composition owing to its inability to differentiate lean muscle and adipose tissue. Indeed, it is an imperfect surrogate of adiposity and its use can lead to the misclassification of body distribution, particularly in overweight people. The incorporation of a combination of clinical and biochemical markers and imaging would be more relevant. Therefore, we believe that the consideration of BMI as a stratification factor in future ICI /TT-focused trials would be unsuitable.

This study has several limitations. First, its results should be considered as exploratory and not preplanned and need to be confirmed prospectively. BMI was analyzed at a single timepoint, corresponding at first-line therapy initiation; future studies should include longitudinal BMI assessments. Our study did not account for the use of co-medications, which may have anticancer activity and/or effects on metabolism, such as metformin, statins, beta-blockers, aspirin, and oral steroids.

Despite these limitations, our data were obtained, to the best of our knowledge, from the second largest study on this topic, supporting their robustness. All our data were collected from a common and standardized eCRF used across all the participating centers. Furthermore, as the proportion of missing data was small, the accuracy of our analyses is high.

In conclusion, baseline BMI does not appear to be associated with systemic therapy-related outcomes in patients with metastatic melanoma. Future approaches considering the whole-body distribution are required.

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AUTHORS' CONTRIBUTIONS

Di Filippo and Dr Montaudié had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Di Filippo, Lebbé and Montaudié

Acquisition, analysis, or interpretation of data: Di Filippo, Dalle, Mortier, Dereure, Dalac, Dutriaux, Leccia, Legoupil, Saiag, Brunet-Possenti, Arnnault, Maubec, Granel-Brocard, De Quatrebarbes, Aubin, Lesimple, Beylot-Barry, Stoebner, Dupuy, Stephan, Grob, Lefevre, Oriano, Allayous, Lebbe, Montaudié,

Supervision: Montaudié

Statistical analysis, methodology and software: Lefevre, Oriano

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Figure legends

Figure 1. Progression-free survival by BMI category

Progression-free survival among patients in the (a) entire cohort, (b) immune checkpoint inhibitors cohort, (c) targeted therapy cohort, and (d) chemotherapy cohort. BMI: Body mass index (calculated as weight in kilograms divided by height in meters squared).

Figure 2. Overall survival by BMI category

Overall survival among patients in the (a) entire cohort, (b) immune checkpoint inhibitors cohort, (c) targeted therapy cohort, and (d) chemotherapy cohort. BMI: Body mass index (calculated as weight in kilograms divided by height in meters squared).

Table 1. Patient characteristics in each BMI group at treatment initiation

* Stage according to the American Joint Committee on Cancer 7th edition. ECOG PS: Eastern Cooperative Oncology Group Performance Status; LDH: Lactate dehydrogenase; ULN: Upper limit of normal; WT: Wild type; ICI: Immune checkpoint inhibitor; TT: Targeted therapy; CT: Chemotherapy; PD-1: Programmed cell death protein 1; BMI: Body mass index (calculated as weight in kilograms divided by height in meters squared). ** n=501 received anti-PD1 alone (nivolumab or pembrolizumab), n=164 received anti-CTLA-4 (ipilimumab) alone, and n=83 received anti-PD1 + anti-CTLA-4. *** n=129 received BRAF inhibitor (BRAFi) alone, n=9 received MEK inhibitor (MEKi) alone, n=241 received BRAFi +MEKi **** All patients received mono-chemotherapy ***** 59/99 received combined stereotactic ablative radiotherapy (delivered between 30 days prior and 30 days after the initiation of systemic therapy); 24/51 in the normal-weight cohort, 21/29 in the overweight cohort and 14/19 in the obese cohort.

Table 2. Univariate analysis of progression-free survival and overall survival versus BMI

CT: Chemotherapy; ICI: Immune checkpoint inhibitor (anti-PD-1 alone + anti-CTAL4 alone + anti-PD-1 combined with anti-CTLA-4); Combo-ICIs; anti-PD-1 + anti-CTLA-4; TT: Targeted therapy; BMI: Body mass index (calculated as weight in kilograms divided by height in meters squared); PD-1: Programmed cell death protein 1

Table 3. Multivariable cox proportional hazard models of progression-free survival and overall survival versus BMI

CT: Chemotherapy; ICI: Immune checkpoint inhibitor (anti-PD-1 alone + anti-CTAL4 alone + anti-PD-1 combined with anti-CTLA-4); Combo-ICI; anti-PD-1 + anti-CTLA-4; TT: Targeted therapy; BMI: Body mass index (calculated as weight in kilograms divided by height in meters squared); PD-1: Programmed cell death protein 1; ULN: Upper Limit of Normal

Supplementary

Supplementary Figure Legend

Supplementary Figure S1. Progression-free survival by BMI category and sex

Progression-free survival among patients in the (a) male total (ICI+TT+CT) cohort (b) male ICI cohort, (c) male TT cohort, (d) male CT cohort, (e) female total (ICI+TT+CT) cohort, (f) female ICI cohort, (g) female TT cohort, and (h) female CT cohort. BMI: Body mass index (calculated as weight in kilograms divided by height in meters squared); CT: Chemotherapy; ICI: Immune checkpoint inhibitor; TT: Targeted therapy.

Supplementary Figure S2. Progression-free survival by BMI category and age

Progression-free survival in patients in the (a) total cohort (ICI+TT+CT) age < 65 years (b) ICI age < 65 years cohort, (c) TT age < 65 years cohort, (d) CT age < 65 years cohort, (e) total cohort (ICI+TT+CT) age ≥ 65 years (f) ICI age ≥ 65 years cohort, (g) TT age ≥ 65 years cohort, and (h) CT age ≥ 65 years cohort. BMI: Body mass index (calculated as weight in kilograms divided by height in meters squared); CT: Chemotherapy; ICI: Immune checkpoint inhibitor; TT: Targeted therapy.

Supplementary Figure S3. Overall survival by BMI category and sex

Overall survival among patients in the (a) male total (ICI+TT+CT) cohort (b) male ICI cohort, (c) male TT cohort, (d) male CT cohort, (e) female total (ICI+TT+CT) cohort, (f) female ICI cohort, (g) female TT cohort, and (h) female CT cohort. BMI: Body mass index (calculated as weight in kilograms divided by height in meters squared); CT: Chemotherapy; ICI: Immune checkpoint inhibitor; TT: Targeted therapy.

Supplementary Figure S4. Overall survival by BMI category and age

Overall survival in patients in the (a) total cohort (ICI+TT+CT) age < 65 years (b) ICI age < 65 years cohort, (c) TT age < 65 years cohort, (d) CT age < 65 years cohort, (e) total cohort (ICI+TT+CT) age ≥ 65 years (f) ICI age ≥ 65 years cohort, (g) TT age ≥ 65 years cohort, and (h) CT age ≥ 65 years cohort. BMI: Body mass index (calculated as weight in kilograms divided by height in meters squared); CT: Chemotherapy; ICI: Immune checkpoint inhibitor; TT: Targeted therapy.

Supplementary Figure S5. Association between BMI and progression-free survival after pooled analyses of the overweight and obese cohorts

Progression-free survival among patients in the (a) total cohort (ICI+TT+CT), (b) ICI cohort, (c) TT cohort, and (d) CT cohort. BMI: Body mass index (calculated as weight in kilograms divided by height in meters squared); CT: Chemotherapy; ICI: Immune checkpoint inhibitor; TT: Targeted therapy.

Supplementary Figure S6. Association between BMI and progression-free survival, by sex, after pooled analyses of the overweight/obese cohorts. Progression-free survival among patients in the (a) male total (ICI+TT+CT) cohort, (b) male ICI cohort, (c) male TT cohort, (d) male CT cohort, (e) female total (ICI+TT+CT) cohort, (f) female ICI cohort, (g) female TT cohort, and (h) female CT cohort. BMI: Body mass index (calculated as weight in kilograms divided by height in meters squared); CT: Chemotherapy; ICI: Immune checkpoint inhibitor; TT: Targeted therapy.

Supplementary Figure S7. Association between BMI and overall survival after pooled analyses of the overweight and obese cohorts

Overall survival among patients in the (a) total cohort (ICI+TT+CT) , (b) ICI cohort, (c) TT cohort, and (d) CT cohort. BMI: Body mass index (calculated as weight in kilograms divided by height in meters squared); CT: Chemotherapy; ICI: Immune checkpoint inhibitor; TT: Targeted therapy.

Supplementary Figure S8. Association between BMI and overall survival, by sex, after pooled analyses of the overweight/obese cohorts

Overall survival among patients in the (a) male total (ICI+TT+CT) cohort, (b) male ICI cohort, (c) male TT cohort, (d) male CT cohort, (e) female total (ICI+TT+CT) cohort, (f) female ICI cohort, (g) female TT cohort, and (h) female CT cohort. BMI: Body mass index (calculated as weight in kilograms divided by height in meters squared); CT: Chemotherapy; ICI: Immune checkpoint inhibitor; TT: Targeted therapy.

Supplementary Figure S9. Response rates by BMI category and age

BMI: Body mass index

Supplementary Table 1. Additional outcomes

The proportions of patients with progression-free survival (PFS) and overall survival (OS) at 6 months and 1, 2, and 3 years by BMI category

Supplementary Table 2. Response to treatment according to BMI category at treatment initiation

*The best overall response was assessed by the investigator according to the Response Evaluation Criteria in Solid Tumors, version 1.1. ** Data included those on patients with complete response and partial response. *** Data included those on patients with complete response, partial response and stable disease. BMI: Body mass index

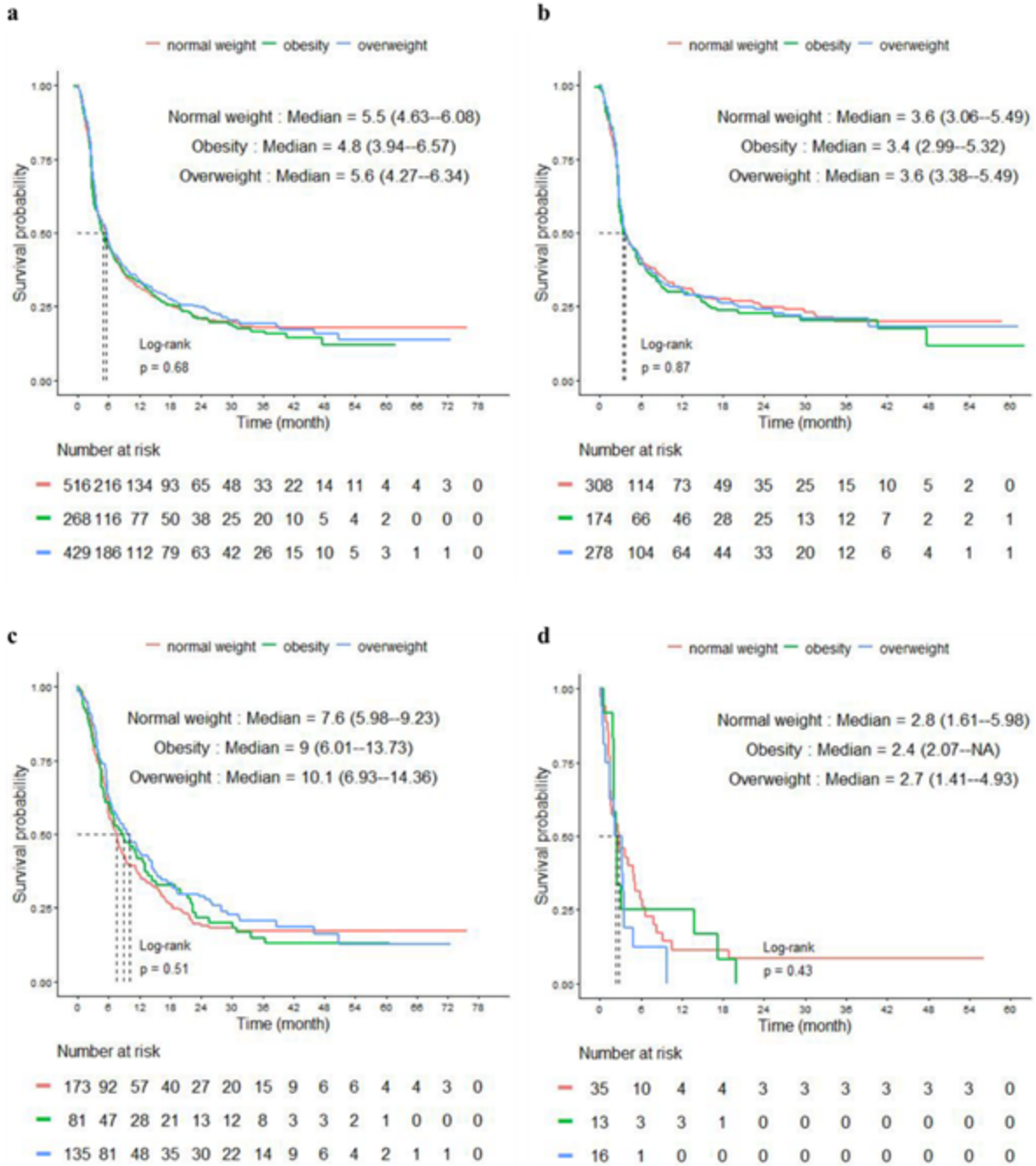
Supplementary Table 3. Response to treatment according to BMI category and stratified by age at treatment initiation

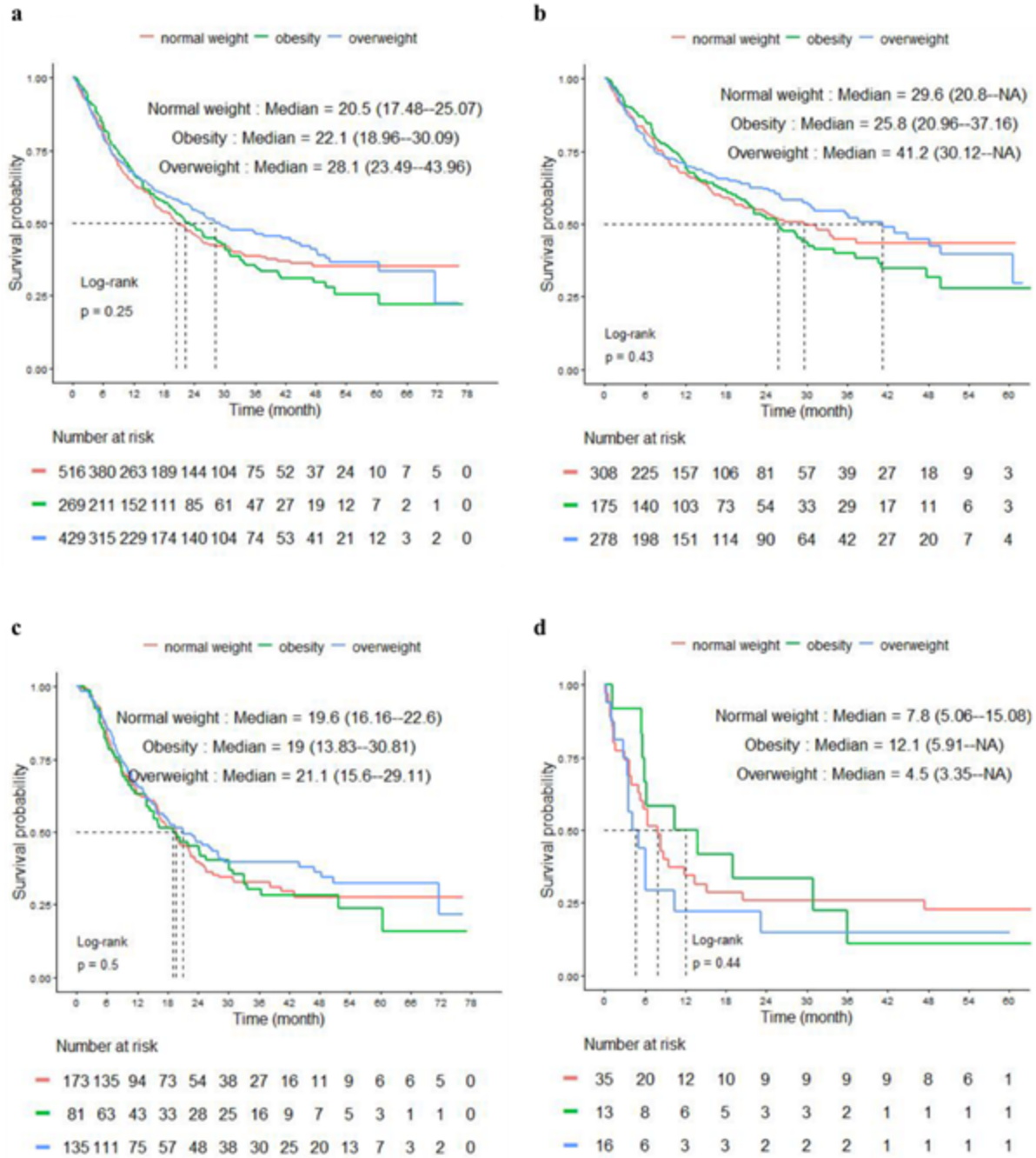
*The best overall response was assessed by the investigator according to the Response Evaluation Criteria in Solid Tumors, version 1.1. ** Data included those on patients with complete response and partial response. *** Data included those on patients with complete response, partial response and stable disease. BMI: Body mass index

Supplementary Table 4. Adverse events by BMI and sex. BMI: Body mass index, CT: Chemotherapy, ICIs: Immune Checkpoint Inhibitors; TT: Targeted Therapy

Supplementary Table 5. **Analysis of the occurrence of different type of AEs, of any grade, categorized according to the different organs/systems involved across different baseline BMI categories and treatment**

BMI: Body mass index; AE: Adverse event


a
normal weight
obesity
overweight
Normal weight : Median = 5.5 (4.63--6.08)
Obesity : Median = 4.8 (3.94--6.57)
Overweight : Median = 5.6 (4.27--6.34)
Survival probability
Log-rank
p = 0.68
Time (month)
Number at risk
516 216 134 93 65 48 33 22 14 11 4 4 3 0
268 116 77 50 38 25 20 10 5 4 2 0 0 0
429 186 112 79 63 42 26 15 10 5 3 1 1 0
b
normal weight
obesity
overweight
Normal weight : Median = 3.6 (3.06--5.49)
Obesity : Median = 3.4 (2.99--5.32)
Overweight : Median = 3.6 (3.38--5.49)
Survival probability
Log-rank
p = 0.87
Time (month)
Number at risk
308 114 73 49 35 25 15 10 5 2 0
174 66 46 28 25 13 12 7 2 2 1
278 104 64 44 33 20 12 6 4 1 1
c
normal weight
obesity
overweight
Normal weight : Median = 7.6 (5.98--9.23)
Obesity : Median = 9 (6.01--13.73)
Overweight : Median = 10.1 (6.93--14.36)
Survival probability
Log-rank
p = 0.51
Time (month)
Number at risk
173 92 57 40 27 20 15 9 6 6 4 4 3 0
81 47 28 21 13 12 8 3 3 2 1 0 0 0
135 81 48 35 30 22 14 9 6 4 2 1 1 0
d
normal weight
obesity
overweight
Normal weight : Median = 2.8 (1.61--5.98)
Obesity : Median = 2.4 (2.07--NA)
Overweight : Median = 2.7 (1.41--4.93)
Survival probability
Log-rank
p = 0.43
Time (month)
Number at risk
35 10 4 4 3 3 3 3 3 3 0
13 3 3 1 0 0 0 0 0 0 0
16 1 0 0 0 0 0 0 0 0 0


a
normal weight
obesity
overweight
Survival probability
Normal weight : Median = 20.5 (17.48--25.07)
Obesity : Median = 22.1 (18.96--30.09)
Overweight : Median = 28.1 (23.49--43.96)
Log-rank
p = 0.25
Time (month)
Number at risk
516 380 263 189 144 104 75 52 37 24 10 7 5 0
269 211 152 111 85 61 47 27 19 12 7 2 1 0
429 315 229 174 140 104 74 53 41 21 12 3 2 0
b
normal weight
obesity
overweight
Survival probability
Normal weight : Median = 29.6 (20.8--NA)
Obesity : Median = 25.8 (20.96--37.16)
Overweight : Median = 41.2 (30.12--NA)
Log-rank
p = 0.43
Time (month)
Number at risk
308 225 157 106 81 57 39 27 18 9 3
175 140 103 73 54 33 29 17 11 6 3
278 198 151 114 90 64 42 27 20 7 4
c
normal weight
obesity
overweight
Survival probability
Normal weight : Median = 19.6 (16.16--22.6)
Obesity : Median = 19 (13.83--30.81)
Overweight : Median = 21.1 (15.6--29.11)
Log-rank
p = 0.5
Time (month)
Number at risk
173 135 94 73 54 38 27 16 11 9 6 6 5 0
81 63 43 33 28 25 16 9 7 5 3 1 1 0
135 111 75 57 48 38 30 25 20 13 7 3 2 0
d
normal weight
obesity
overweight
Survival probability
Normal weight : Median = 7.8 (5.06--15.08)
Obesity : Median = 12.1 (5.91--NA)
Overweight : Median = 4.5 (3.35--NA)
Log-rank
p = 0.44
Time (month)
Number at risk
35 20 12 10 9 9 9 9 8 6 1
13 8 6 5 3 3 2 1 1 1 1
16 6 3 3 2 2 2 1 1 1 1

Characteristics	Whole population	18.5< BMI <24.9	25<BMI<29.9	30< BMI	*P* value
Number of patients (%)	1214	516 (43)	429 (35)	269 (22)	
Sex					
Male	738 (61)	281 (54)	299 (70)	158 (59)	**<0.01**
Female	476 (39)	235 (46)	130 (30)	111 (41)	
Age, median (range), years	66.0 (53.0-75.0)	64.0 (51.0-75.0)	67.0 (57.0-76.0)	66.0 (55.0-73.0)	0.20
BMI, median (range)	25.8 (23.0-29.3)	22.6 (21.0-23.8)	27.0 (26.0-28.1)	32.5 (30.9-35.1)	NA
Stage*					
III/M1a/M1b	479 (40)	182 (35)	169 (39)	128 (48)	**0.01**
M1c	735 (60)	334 (65)	260 (61))	141(52)	
Brain metastases					
Yes	228 (19)	112 (22)	75 (17)	41 (15)	
No symptomatic	131 (58)	61 (55)	43 (57)	27 (66)	0.06
Symptomatic	86 (37)	46 (41)	27 (36)	13 (32)	
Not available	11 (5)	5 (4)	5(7)	1 (2)	
No	986 (81)	404 (78)	354 (83)	228 (85)	
ECOG PS score, No. (%)					
0-1	1023 (84)	426 (82)	368 (86)	229 (85)	0.32
≥2	87 (7)	45 (9)	28 (6)	14 (5)	

Non applicable	104 (9)	45 (9)	33 (8)	26 (10)	
LDH levels					
Normal	603 (50)	249 (48)	214 (50)	140 (52)	0.96
ULN	351 (29)	145 (28)	122 (28)	84 (31)	
Non applicable	260 (21)	122 (24)	93 (22)	45 (17)	
Mutations Status					
BRAFV600	469 (39)	211 (41)	156 (36)	102 (38)	0.35
NRAS	219 (18)	86 (17)	86 (20)	47 (17)	0.39
First line treatment					
ICI	761 (63)	308 (60)	278 (65)	175 (65)	0.18
TT	389 (32)	173 (33)	135 (31)	81 (30)	
CT	64 (5)	35 (7)	16 (4)	13 (5)	
Concomitant radiotherapy*	99 (8)	51 (10)	29 (7)	19 (7)	0.27
Number of therapeutic lines					
1	480 (40)	202 (39)	178 (41)	100 (37)	0.54
2	342 (28)	144 (29)	125 (29)	73 (27)	
3	194 (16)	85 (16)	64 (15)	45 (17)	
≥4	198 (16)	85 (16)	62 (15)	51 (19)	

Table 1. Patient characteristics in each BMI group at treatment initiation

* Stage according to the American Joint Committee on Cancer 7th edition. ECOG PS: Eastern Cooperative Oncology Group Performance Status; LDH: Lactate dehydrogenase; ULN: Upper limit of normal; WT: Wild type; ICI: Immune checkpoint inhibitor; TT: Targeted therapy; CT: Chemotherapy; PD-1: Programmed cell death protein 1; BMI: Body mass index (calculated as weight in kilograms divided by height in meters squared). ** n=501 received anti-PD1 alone (nivolumab or pembrolizumab), n=164 received anti-CTLA-4 (ipilimumab) alone, and n=83 received anti-PD1 + anti-CTLA-4. *** n=129 received BRAF inhibitor (BRAFi) alone, n=9 received MEK inhibitor (MEKi) alone, n=241 received BRAFi +MEKi **** All patients received mono-chemotherapy ***** 59/99 received combined stereotactic ablative radiotherapy (delivered between 30 days prior and 30 days after the initiation of systemic therapy); 24/51 in the normal-weight cohort, 21/29 in the overweight cohort and 14/19 in the obese cohort.

	Total population HR (95% CI)	*P* value	CT HR (95% CI)	*P* value	ICI, HR (95% CI)	*P* value	ICI, anti-PD-1 HR (95% CI)	*P* value	Combo-ICI, HR (95% CI)	*P* value	TT HR (95% CI)	*P* value
	PROGRESSION-FREE SURVIVAL											
Overweight (vs Normal BMI)	0.96 (0.82-1.11)	0.57	1.51 (0.8-2.83)	0.2	1 (0.82-1.21)	1	1.04 (0.85-1.27)	0.72	0.63 (0.32-1.24)	0.18	0.86 (0.66-1.12)	0.26
Obese (vs Normal BMI)	1.04 (0.87-1.23)	0.69	1.07 (0.55-2.09)	0.85	1.05 (0.85-1.31)	0.63	1.16 (0.92-1.45)	0.21	0.55 (0.27-1.14)	0.11	0.98 (0.72-1.32)	0.88
	OVERALL SURVIVAL											
Overweight (vs Normal BMI)	0.87 (0.72-1.05)	0.15	1.46 (0.75-2.84)	0.27	0.89 (0.69-1.15)	0.35	0.89 (0.68-1.16)	0.37	0.78 (0.29-2.08)	0.62	0.87 (0.65-1.17)	0.35
Obese (vs Normal BMI)	1.02 (0.83-1.24)	0.87	0.9 (0.43-1.86)	0.77	1.07 (0.81-1.4)	0.77	1.09 (0.82-1.45)	0.57	0.88 (0.35-2.25)	0.79	1.05 (0.75-1.47)	0.77

Table 2. Univariate analysis of progression-free survival and overall survival versus BMI

CT: Chemotherapy; ICI: Immune checkpoint inhibitor (anti-PD-1 alone + anti-CTAL4 alone + anti-PD-1 combined with anti-CTLA-4); Combo-ICIs; anti-PD-1 + anti-CTLA-4; TT: Targeted therapy; BMI: Body mass index (calculated as weight in kilograms divided by height in meters squared); PD-1: Programmed cell death protein 1

	Total population HR (95% CI)	***P* value**	**CT HR (95% CI)**	***P* value**	**ICIs, HR (95% CI)**	***P* value**	**ICIs, anti-PD-1 HR (95% CI)**	***P* value**	**Combo-ICIs, HR (95% CI)**	***P* value**	**TT HR (95% CI)**	***P* value**
	PROGRESSION-FREE SURVIVAL											
Overweight (vs Normal BMI)	1.02 (0.87-1.18)	0.84	1.21 (0.59-2.46)	0.61	1.07 (0.89-1.36)	0.49	1.1 (0.38-1.84)	0.36	0.84 (0.66-1.13)	0.66	0.86 (0.66-1.13)	0.29
Obese (vs Normal BMI)	1.13 (0.94-1.35)	0.19	1.34 (0.58-3.12)	0.49	1.21 (0.96-1.52)	0.1	1.34 (1.06-1.7)	0.02	0.45 (0.19-1.06)	0.07	1.01 (0.74-1.39)	0.94
Age at Treatment Initiation 65 < vs ≥ 65 years	1.04 (0.9-1.19)	0.61	1.24 (0.65-2.38)	0.51	1.13 (0.94-1.35)	0.2	1.12 (0.92-1.37)	0.24	2.09 (1.07-4.09)	0.03	1.05 (0.82-1.34)	0.72
Sex Female vs male	1 (0.87-1.15)	0.96	0.91 (0.5-1.68)	0.77	0.99 (0.83-1.19)	0.92	1.08 (0.89-1.3)	0.45	0.55 (0.27-1.12)	0.1	1.02 (0.8-1.13)	0.85
Stage M1c (vs Stage III/M1a/Mb)	1.17 (0.99-1.37)	0.06	1.54 (0.69-3.46)	0.29	1.09 (0.88-1.34)	0.43	1.12 (0.9-1.42)	0.3	0.62 (0.27-1.42)	0.26	1.46 (1.07-2)	0.02
ECOG <2 vs ≥2	1.75 (1.36-2.23)	<0.001	2.07 (0.77-5.58)	0.16	1.87 (1.28-2.75)	<0.001	1.92 (1.28-2.89)	<0.001	1.31 (0.43-3.95)	0.63	1.53 (1.01-2.32)	0.05
LDH ULN vs > normal	1.42 (1.21-1.68)	<0.001	1.13 (0.46-2.78)	0.8	1.47 (1.2-1.82)	<0.001	1.42 (1.15-5.76)	<0.001	2.52 (1.13-5.62)	0.03	1.28 (1.28-1.71)	0.11

Brain metastases **Absent vs present**	1.26 (1.05-1.51)	0.01	2.98 (1.32-6.69)	0.01	1.14 (0.88-1.48)	0.32	1.13 (0.86-1.48)	0.4	1.4 (0.45-4.35)	0.56	1.36 (1.02-1.81)	0.04
BRAF status **Wild type vs mutated**	0.65 (0.56-0.75)	<0.001	0.45 (0.14-1.45)	0.18	0.76 (0.59-1.13)	0.04	0.85 (0.64-1.13)	0 0.27	0.81 (0.39-1.67)	0.56	1.19 (0.74-1.89)	0.47
Number of tumor sites **<3 vs ≥3**	1.34 (1.13-1.6)	<0.001	2.04 (0.83-5)	0.12	1.5 (1.18-1.9)	<0.001	1.48 (1.15-1.19)	<0.001	1.37 (0.6-3.12)	0.46	1.22 (0.91-1.62)	0.18
OVERALL SURVIVAL												
Overweight **(vs Normal BMI)**	0.94 (0.78-1.14)	0.55	1.22 (0.57-2.64)	0.61	0.98 (0.75-1.27)	0.85	1 (0.75-1.32)	0.99	2.38 (0.63-8.96)	0.2	0.91 (0.67-1.24)	0.55
Obese **(vs Normal BMI)**	1.12 (0.9-1.39)	0.33	1.44 (0.57-3.62)	0.44	1.19 (0.9-1.58)	0.24	1.21 (0.9-1.64)	0.2	0.88 (0.28-2.82)	0.83	1.13 (0.79-1.58)	0.51
Age at Treatment Initiation **65 < vs ≥ 65 years**	0.92 (0.77-1.09)	0.33	1.14 (0.55-2.34)	0.73	0.99 (0.78-1.26)	0.95	1.01 (0.78-1.31)	0.93	3 (1.07-8.44)	0.04	0.9 (0.68-1.19)	0.45
Sex **Female vs male**	0.92 (0.78-1.09)	0.35	1.12 (0.58-2.15)	0.74	0.86 (0.69-1.09)	0.22	0.89 (0.69-1.14)	0.35	0.18 (0.75-1.31)	<0.001	0.99 (0.68-1.09)	0.93
Stage M1c (vs Stage III/M1a/Mb)	1.48 (1.19-1.84)	<0.001	3.05 (1.22-7.64)	0.02	1.32 (0.99-1.76)	0.06	1.37 (1.02-1.86)	0.04	0.53 (0.17-2.09)	0.29	1.45 (1.01-2.09)	0.04
ECOG **<2 vs ≥2**	2.9 (2.16-3.91)	<0.001	3.46 (1.48-8.07)	<0.001	3.46 (2.3-5.2)	<0.001	4.3 (2.78-6.65)	<0.001	0.87 (0.16-4.77)	0.87	2.2 (1.4-3.47)	<0.001
LDH	1.64		1.13		1.83		1.89		3.17		1.55	

ULN vs > normal	(1.38-1.97)	<0.001	(0.45-2.85)	0.8	(1.43-2.5)	<0.001	(1.43-2.5)	<0.001	(0.89-11.29)	0.08	(1.15-2.1)	0.01
Brain metastases Absent vs present	1.39 (1.12-1.72)	<0.001	4.53 (1.84-11.15)	<0.001	1.24 (0.89-1.76)	0.2	1.25 (0.89-1.76)	0.2	0.5 (0.06-4.4)	0.53	1.32 (0.96-1.8)	0.09
BRAF status Wild type vs mutated	0.8 (0.66-0.95)	0.01	0.18 (0.04-0.81)	0.03	0.51 (0.35-0.75)	<0.001	0.55 (0.21-1.63)	0.01	0.59 (0.21-1.63)	0.3	1.16 (0.69-1.98)	0.57
Number of tumor sites <3 vs ≥3	1.72 (1.39-2.13)	<0.001	2.22 (0.8-6.14)	0.13	2.06 (1.54-2.76)	<0.001	2.26 (1.65-3.09)	<0.001	0.65 (0.16-2.56)	0.53	1.53 (1.12-2.09)	0.01

Table 3. Multivariable cox proportional hazard models of progression-free survival and overall survival versus BMI

CT: Chemotherapy; ICI: Immune checkpoint inhibitor (anti-PD-1 alone + anti-CTAL4 alone + anti-PD-1 combined with anti-CTLA-4); Combo-ICI; anti-PD-1 + anti-CTLA-4; TT: Targeted therapy; BMI: Body mass index (calculated as weight in kilograms divided by height in meters squared); PD-1: Programmed cell death protein 1; ULN: Upper Limit of Normal