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Association of body-mass index and outcomes in patients with metastatic melanoma treated with targeted therapy, immunotherapy, or chemotherapy: a retrospective, multicohort analysis

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Summary

Background Obesity has been linked to increased mortality in several cancer types; however, the relation between obesity and survival outcomes in metastatic melanoma is unknown. The aim of this study was to examine the association between body-mass index (BMI) and progression-free survival or overall survival in patients with metastatic melanoma who received targeted therapy, immunotherapy, or chemotherapy.

Methods This retrospective study analysed independent cohorts of patients with metastatic melanoma assigned to treatment with targeted therapy, immunotherapy, or chemotherapy in randomised clinical trials and one retrospective study of patients treated with immunotherapy. Patients were classified according to BMI, following the WHO definitions, as underweight, normal, overweight, or obese. Patients without BMI and underweight patients were excluded. The primary outcomes were the associations between BMI and progression-free survival or overall survival, stratified by treatment type and sex. We did multivariable analyses in the independent cohorts, and combined adjusted hazard ratios in a mixed-effects meta-analysis to provide a precise estimate of the association between BMI and survival outcomes; heterogeneity was assessed with meta-regression analyses. Analyses were done on the predefined intention-to-treat population in the randomised controlled trials and on all patients included in the retrospective study.

Findings The six cohorts consisted of a total of 2046 patients with metastatic melanoma treated with targeted therapy, immunotherapy, or chemotherapy between Aug 8, 2006, and Jan 15, 2016. 1918 patients were included in the analysis. Two cohorts containing patients from randomised controlled trials treated with targeted therapy (dabrafenib plus trametinib [n=599] and vemurafenib plus cobimetinib [n=240]), two cohorts containing patients treated with immunotherapy (one randomised controlled trial of ipilimumab plus dacarbazine [n=207] and a retrospective cohort treated with pembrolizumab, nivolumab, or atezolizumab [n=331]), and two cohorts containing patients treated with chemotherapy (two randomised controlled trials of dacarbazine [n=320 and n=221]) were classified according to BMI as normal (694 [36%] patients), overweight (711 [37%]), or obese (513 [27%]). In the pooled analysis, obesity, compared with normal BMI, was associated with improved survival in patients with metastatic melanoma (average adjusted hazard ratio [HR] 0·77 [95% CI 0·66–0·90] for progression-free survival and 0·74 [0·58–0·95] for overall survival). The survival benefit associated with obesity was restricted to patients treated with targeted therapy (HR 0·72 [0·57–0·91] for progression-free survival and 0·60 [0·45–0·79] for overall survival) and immunotherapy (HR 0·75 [0·56–1·00] and 0·64 [0·47–0·86]). No associations were observed with chemotherapy (HR 0·87 [0·65–1·17, $p_{interaction}$=0·61] for progression-free survival and 1·03 [0·80–1·34, $p_{interaction}$=0·01] for overall survival). The association of BMI with overall survival for patients treated with targeted and immune therapies differed by sex, with inverse associations in men (HR 0·53 [0·40–0·70]), but no associations observed in women (HR 0·85 [0·61–1·18, $p_{interaction}$=0·03]).

Interpretation Our results suggest that in patients with metastatic melanoma, obesity is associated with improved progression-free survival and overall survival compared with those outcomes in patients with normal BMI, and that this association is mainly seen in male patients treated with targeted or immune therapy. These results have implications for the design of future clinical trials for patients with metastatic melanoma and the magnitude of the benefit found supports further investigation of the underlying mechanism of these associations.

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Research in context

Evidence before this study

We searched PubMed up to Aug 15, 2017, with the terms "melanoma" and "body mass index" and identified 149 articles. Of these, 14 analyses examined the association between body-mass index (BMI) and risk of melanoma, including 12 primary studies and two meta-analyses. Overall, findings from the studies support that high BMI is associated with increased risk of melanoma in men, but not in women. Two studies found that increased BMI is associated with increased primary melanoma thickness, which is associated with an increased risk of recurrence. Only two studies have reported on the association between BMI and outcomes in melanoma. We recently reported that increased BMI was associated with worse survival in patients with surgically resected melanoma. A report of a clinical trial of dacarbazine with or without tamoxifen in patients with metastatic melanoma contained an exploratory analysis suggesting that increased BMI in men and postmenopausal women was associated with benefit from the addition of tamoxifen to dacarbazine. We did not identify any studies that examined the association of BMI with outcomes in patients with metastatic melanoma or in patients with melanoma treated with targeted and immune therapies.

Added value of this study

Our study examined the association of BMI with outcomes in six independent cohorts, which together included more than 1900 patients with metastatic melanoma. The cohorts included patients from several randomised clinical trials that led to US Food and Drug Administration approval of immune and targeted therapies, as well as their chemotherapy control groups, and one retrospective cohort of patients treated with immunotherapy. Our analysis showed that obesity was associated with improved survival in metastatic melanoma, an association that, to our knowledge, has not been identified previously. This association was independent of traditional prognostic factors. Furthermore, the survival benefit of obesity was restricted to patients treated with targeted and immune therapies and was not detected in chemotherapy cohorts. Finally, we identified that BMI was associated with marked improvements in survival in obese men compared with men with normal BMI, but found no such association in women.

Implications of all the available evidence

Our results have implications for the design of future clinical trials for patients with metastatic melanoma. The magnitude of the effects, as well as the novel interaction observed between BMI, sex, and treatment type suggest possible underlying mechanisms that should be examined further.

Introduction

Metastatic melanoma is an aggressive disease with poor outcomes historically. However, the outcomes of patients with this disease have improved substantially after the US Food and Drug Administration (FDA) approval of targeted therapies directed at the MAPK pathway and checkpoint inhibitor immunotherapies.[1–4] Despite these multiple new treatment options, overall survival in patients with metastatic melanoma remains heterogeneous. An improved understanding of factors associated with clinical benefit could improve personalised treatment and provide new insights into resistance mechanisms.

Obesity is an established risk factor for many malignancies, and is associated with worse outcomes in several cancers.[5,6] However, higher body-mass index (BMI) has also been associated with improved outcomes in some cancers,[7–9] a phenomenon dubbed the obesity paradox.[10] The role of obesity in melanoma has not been well studied to date.[5] Existing data suggest that obesity is associated with an increased risk of melanoma in men[11] and increased primary tumour Breslow staging scale thickness.[12] We recently reported that higher BMI was associated with worse survival in a large cohort of patients with surgically resected melanoma.[13] However, the association of BMI with survival outcomes in patients with metastatic melanoma, particularly in those treated with contemporary targeted and immune therapies, is unknown. Notably, several associations have been described that could link obesity with worse survival outcomes in patients with melanoma, including germline genetic variants in obesity-related genes associated with melanoma risk,[14] inflammation,[14] obesity-related cytokines,[15] and pro-tumorigenic adipocyte cross-talk.[16] Of particular interest, the IGF-1/PI3K/AKT pathway has been shown to have a key role in the pathogenesis of obesity in cancer,[17] and has also been implicated in resistance to both targeted and immune therapies in melanoma.[18,19]

On the basis of these data, we postulated that obesity would be associated with worse outcomes in patients with metastatic melanoma. To test this hypothesis, we assessed the association of BMI with progression-free survival and overall survival in independent cohorts of patients with metastatic melanoma treated with targeted therapy, immunotherapy, or chemotherapy. Because of the well documented sex disparity in melanoma outcomes,[20] as well as sex differences in body composition, we examined associations in male and female patients separately.

Methods

Study design and cohort populations

We collated data from six clinical cohorts of patients with metastatic melanoma treated with the three categories of FDA-approved therapies in this disease: targeted therapy, immunotherapy, or chemotherapy (two cohorts each). We included contemporaneous cohorts of patients with metastatic melanoma treated with dacarbazine chemotherapy, a control group in several trials with low

activity in this disease, to assess whether BMI was associated with outcome only in patients treated with highly active contemporary therapies or was generally prognostic in metastatic melanoma. All cohorts consisted of patients treated in randomised controlled trials, apart from a retrospective cohort including patients treated with immunotherapy.

The targeted therapy cohorts included a cohort of a cohort of previously untreated patients with *BRAF*^{V600}-mutant metastatic melanoma (with V600E as well as other activating V600 mutations) treated with the BRAF inhibitor dabrafenib plus the MEK inhibitor trametinib in the BRF113220 (part C), COMBI-d, and COMBI-v trials (n=617, 599 patients analysed),[4] and a cohort treated with the BRAF inhibitor vemurafenib plus the MEK inhibitor cobimetinib in the phase 3 coBRIM trial (n=247, 240 patients analysed).[1] The immunotherapy cohorts were a cohort of patients treated with ipilimumab (anti-CTLA-4 antibody) plus dacarbazine in the phase 3 CA184-024 trial (n=250, 207 patients analysed)[2] and a retrospective cohort of patients treated with the anti-programmed-cell-death protein 1 (anti-PD-1) or anti-PD ligand 1 (anti-PDL1) antibodies (n=342, 331 patients analysed) at four centres in the USA and Australia (pembrolizumab [n=250] or nivolumab [n=73; both anti-PD1] or atezolizumab [n=8; anti-PDL1]). The chemotherapy cohorts consisted of patients treated with dacarbazine in the control group of either the CA184-024 trial (n=252, 221 patients analysed)[2] or the phase 3 BRIM3 trial (n=338, 320 patients analysed).[21] The full list of eligibility criteria for the patients included in these cohorts is in the appendix (p 1).

Procedures

BMI at treatment initiation was calculated as weight (kg) divided by the square of height (m) and categorised according to standard WHO definitions of underweight (BMI <18·5 kg/m²), normal weight (18·5–24·9 kg/m²), overweight (25–29·9 kg/m²), and obese (≥30 kg/m²). Underweight patients were excluded from analyses because of low prevalence (<2%) across the cohorts. Patients without height or weight data available for BMI calculation were excluded from all analyses.

Disease progression and response were assessed by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria. Outcome data were provided by the sponsors of each of the trials and based on intention-to-treat analyses, other than the retrospective cohort, for which outcomes were provided by medical oncologists of the collaborating institutions.

Outcomes

Primary outcomes were the association of BMI category with progression-free survival (defined as time from date of treatment initiation or baseline randomisation until disease progression or death) and overall survival (defined as time from date of treatment initiation or baseline randomisation until death) stratified by cohort and sex. Secondary outcomes were the association of BMI with overall response (complete or partial response), adverse events, and pharmacokinetics.

Statistical analysis

For each clinical cohort, we assessed the association of baseline BMI category with progression-free survival and overall survival outcomes. Survival curves for progression-free survival and overall survival across BMI category and by sex were generated with the Kaplan-Meier method. Confidence intervals for the Kaplan-Meier probability estimates were computed on the log scale by use of the Greenwood formula.

We assessed the association of BMI with prospective survival outcomes in Cox proportional hazards regression models adjusted for the following prognostic factors: age, AJCC 7 disease stage, lactate dehydrogenase (LDH) status, *BRAF*^{V600} mutation type, Eastern Cooperative Oncology Group (ECOG) performance status, sum of target lesion diameters, number of disease sites, and previous adjuvant therapies received in the dabrafenib plus trametinib cohort; age, AJCC 7 disease stage, LDH status, *BRAF*^{V600} mutation, and ECOG performance status in the vemurafenib plus cobimetinib, and dacarbazine (BRIM3) cohorts; and age, AJCC 7 disease stage, LDH status, and ECOG performance status in the ipilimumab plus dacarbazine, pembrolizumab, nivolumab, or atezolizumab, and dacarbazine (CA 184-024) cohorts. Additional prognostic factors considered included concomitant medications (dabrafenib and trametinib cohort) and serum albumin in the pembrolizumab, nivolumab, or atezolizumab cohort. Because female sex was previously shown to be independently associated with improved survival,[4] and because there were sex differences in BMI distribution in our cohorts, we assessed associations in men and women separately. Interaction for sex by BMI was tested using BMI as a categorical variable (obese *vs* normal BMI) using multivariable hazard ratios. We used logistic regression to assess associations of BMI with treatment response and pharmacokinetics. In all analyses, normal BMI was used as the reference category. Missing data were left out and not imputed.

See Online for appendix

In addition to the analysis of each individual cohort, we combined adjusted hazard ratios (HRs) using mixed-effects meta-analysis methods to assess the prognostic effect of BMI on patient survival in all patients, by treatment type, and by sex. We explored possible sources of heterogeneity by use of meta-regression analyses. We calculated separate average HRs for each treatment class, for each sex, and for each treatment class within each sex. Heterogeneity was evaluated using the Q and I^2 statistic: I^2 values of 25%, 50%, and 75% correspond to low, moderate, and high degrees of heterogeneity. Statistical tests for interaction assessed the significance of categorical cross-product terms in multivariable-adjusted models.

Statistical analyses were done with SAS 9.4, JMP (SAS) 12, R 3.1.1, and S+ 8.0. All statistical tests were two-sided and considered significant at $p<0·05$.

	Dabrafenib plus trametinib cohort (n=599)			Vemurafenib plus cobimetinib cohort (n=240)			Ipilimumab plus dacarbazine cohort (n=207)			Pembrolizumab, nivolumab, or atezolizumab cohort (n=331)			Dacarbazine cohort (BRIM3; n=320)			Dacarbazine cohort (CA 184-024; n=221)		
	BMI 18·5–24·9	BMI 25·0–29·9	BMI ≥30	BMI 18·5–24·9	BMI 25·0–29·9	BMI ≥30	BMI 18·5–24·9	BMI 25·0–29·9	BMI ≥30	BMI 18·5–24·9	BMI 25·0–29·9	BMI ≥30	BMI 18·5–24·9	BMI 25·0–29·9	BMI ≥30	BMI 18·5–24·9	BMI 25·0–29·9	BMI ≥30
Number of patients	222 (37%)	231 (39%)	146 (24%)	85 (35%)	88 (37%)	67 (28%)	68 (33%)	88 (43%)	51 (25%)	102 (31%)	109 (33%)	120 (36%)	143 (45%)	107 (33%)	70 (22%)	74 (33%)	88 (40%)	59 (27%)
Age, years	52 (18–91)	56 (22–82)	56 (30–82)	51 (23–85)	59 (29–88)	55 (25–78)	53 (24–83)	60 (31–87)	60 (34–80)	57 (18–86)	63 (34–86)	63 (22–86)	49 (17–86)	56 (22–84)	53 (31–78)	55 (23–83)	60 (24–88)	56 (32–88)
Sex																		
Men	109 (49%)	156 (68%)	82 (56%)	40 (47%)	58 (66%)	44 (66%)	41 (60%)	64 (73%)	33 (65%)	75 (56%)	78 (72%)	79 (66%)	70 (49%)	73 (68%)	31 (44%)	38 (51%)	66 (75%)	36 (61%)
Women	113 (51%)	75 (32%)	64 (44%)	45 (53%)	30 (34%)	23 (34%)	27 (40%)	24 (27%)	18 (35%)	45 (44%)	31 (28%)	41 (34%)	73 (51%)	34 (32%)	39 (56%)	36 (49%)	22 (25%)	23 (39%)
Stage*																		
III/M1a/M1b	71 (32%)	81 (35%)	59 (40%)	34 (40%)	34 (39%)	32 (48%)	17 (25%)	38 (43%)	26 (51%)	19 (19%)	32 (29%)	40 (33%)	42 (29%)	29 (27%)	31 (44%)	24 (32%)	37 (42%)	33 (56%)
M1c	151 (68%)	150 (65%)	87 (60%)	50 (60%)	54 (61%)	35 (52%)	51 (75%)	50 (57%)	25 (49%)	81 (79%)	76 (70%)	80 (67%)	101 (71%)	78 (73%)	39 (56%)	50 (68%)	51 (58%)	26 (44%)
LDH >ULN†	78 (36%)	79 (34%)	48 (33%)	39 (46%)	41 (47%)	26 (40%)	26 (38%)	31 (35%)	18 (25%)	40 (39%)	38 (35%)	39 (32%)	68 (48%)	44 (41%)	23 (33%)	37 (50%)	36 (41%)	23 (39%)
ECOG performance status																		
0	159 (72%)	168 (73%)	103 (70%)	65 (77%)	72 (82%)	43 (64%)	46 (68%)	65 (74%)	35 (69%)	60 (59%)	64 (59%)	72 (60%)	95 (66%)	77 (72%)	46 (66%)	55 (74%)	63 (72%)	38 (64%)
≥1	61 (28%)	62 (27%)	43 (30%)	19 (22%)	15 (17%)	24 (36%)	22 (32%)	23 (26%)	16 (31%)	41 (40%)	45 (41%)	48 (40%)	48 (34%)	30 (28%)	24 (34%)	19 (26%)	25 (28%)	21 (36%)
Mutation status‡																		
BRAF mutant	222 (100%)	231 (100%)	146 (100%)	85 (100%)	88 (100%)	67 (100%)	..	..	..	34 (33%)	32 (29%)	34 (28%)	143 (100%)	107 (100%)	70 (100%)	..	..	..
V600E	201 (91%)	192 (83%)	129 (88%)	61 (72%)	62 (70%)	44 (66%)	..	..	..	..	..	..	132 (92%)	94 (88%)	62 (89%)	..	..	..
Other V600	21 (9%)	39 (17%)	17 (12%)	6 (7%)	10 (11%)	8 (12%)	..	..	..	..	..	..	8 (5%)	10 (9%)	5 (7%)	..	..	..
NRAS mutant	..	..	..	..	..	..	..	..	..	24 (24%)	21 (19%)	18 (15%)	..	..	..	..	..	..
WT	..	..	..	..	..	..	..	..	..	37 (36%)	50 (46%)	67 (57%)	..	..	..	..	..	..

Data are n (%) or mean (range). ..=not available. BMI=body-mass index (kg/m^2). LDH=lactate dehydrogenase. ULN=upper limit of normal. ECOG=Eastern Cooperative Oncology Group. WT=wild type. *Data missing for three patients in the pembrolizumab, nivolumab, or atezolizumab cohort. †Data missing for two patients in the dabrafenib plus trametinib cohort, three patients in the vemurafenib plus cobimetinib cohort, two patients in the pembrolizumab, nivolumab, or atezolizumab cohort, and one patient in the dacarbazine CA 184-024 cohort. ‡Data missing for three patients in the dabrafenib plus trametinib cohort, two patients in the vemurafenib plus cobimetinib cohort, and one patient in the pembrolizumab, nivolumab, or atezolizumab cohort.

Table 1: **Patient characteristics in each cohort**

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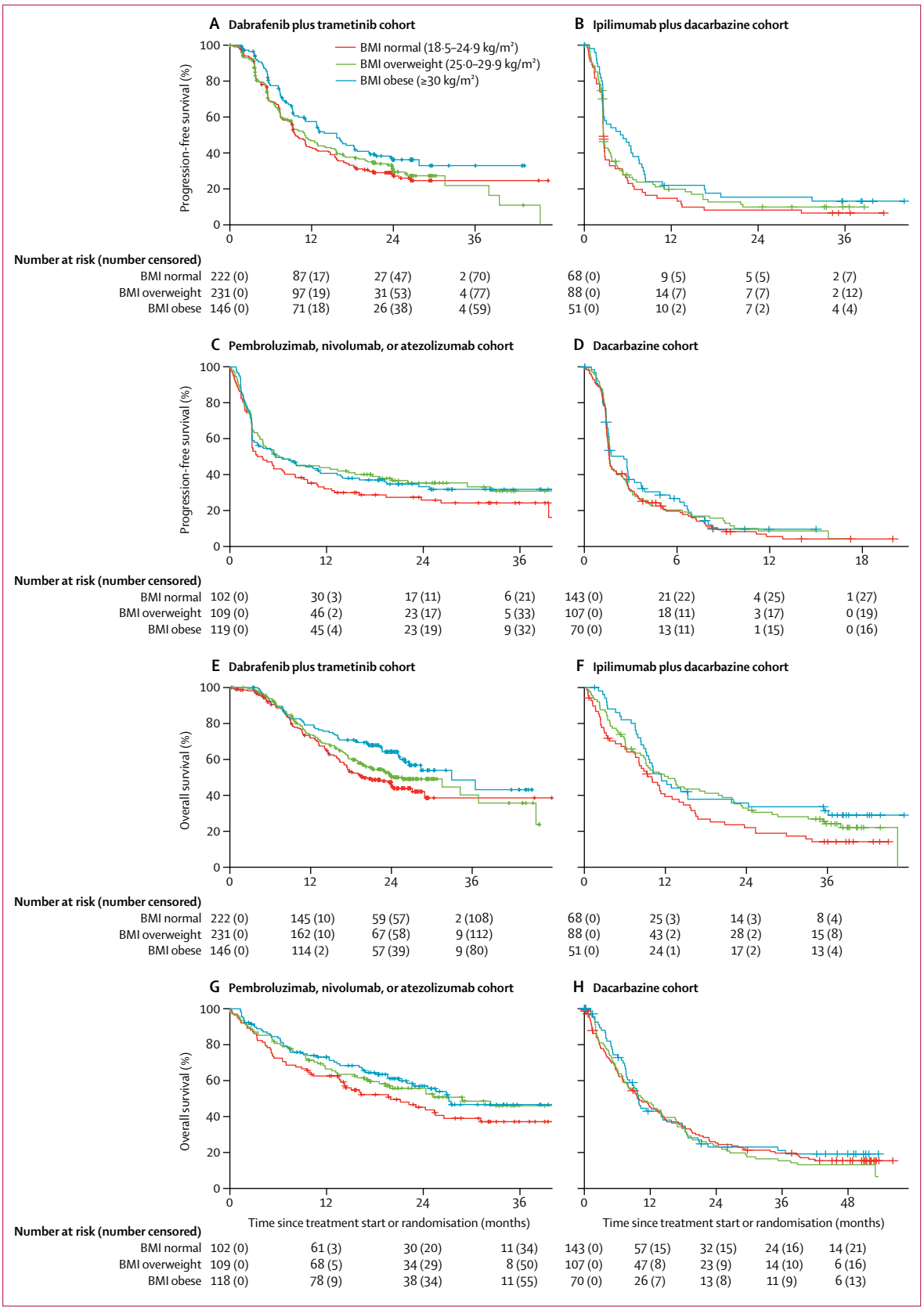

Figure 1: **Progression-free survival and overall survival by BMI category**
Progression-free survival in patients in the (A) dabrafenib plus trametinib cohort, (B) ipilimumab plus dacarbazine cohort, (C) pembrolizumab, nivolumab, or atezolizumab cohort, and (D) dacarbazine (BRIM3) cohort. Overall survival in patients in the (E) dabrafenib plus trametinib cohort, (F) ipilimumab plus dacarbazine cohort, (G) pembrolizumab, nivolumab, or atezolizumab cohort, and (H) dacarbazine chemotherapy (BRIM3) cohort. BMI=body-mass index.

	Events/ patients	Median, months (95% CI)	Univariable HR (95% CI)	Multivariable adjusted HR (95% CI)	p value for interaction*
Dabrafenib plus trametinib cohort†					
All patients (n=599)	..	..	..	..	0·56
BMI 18·5–24·9	150/222	9·6 (9·0–12·1)	1 (ref)	1 (ref)	..
BMI 25·0–29·9	153/231	11·0 (9·2–14·9)	0·90 (0·76–1·19)	0·95 (0·75–1·21)	..
BMI ≥30	83/146	15·7 (11·0–20·4)	0·73 (0·56–0·95)	0·75 (0·57–0·99)	..
Men (n=347)	..	..	..	..	..
BMI 18·5–24·9	79/109	7·4 (7·2–10·0)	1 (ref)	1 (ref)	..
BMI 25·0–29·9	110/156	10·1 (8·1–12·1)	0·85 (0·63–1·13)	0·93 (0·69–1·25)	..
BMI ≥30	51/82	12·8 (9·1–20·4)	0·69 (0·49–0·99)	0·75 (0·52–1·08)	..
Women (n=252)	..	..	..	..	..
BMI 18·5–24·9	71/113	14·5 (9·7–18·2)	1 (ref)	1 (ref)	..
BMI 25·0–29·9	43/75	15·5 (9·3–21·4)	0·95 (0·65–1·39)	1·05 (0·69–1·59	..
BMI ≥30	32/64	17·1 (13·0-NR)	0·74 (0·48–1·12)	0·83 (0·54–1·29)	..
Vemurafenib plus cobimetinib cohort‡					
All patients (n=240)	..	..	..	..	0·06
BMI 18·5–24·9	68/85	9·0 (7·3–12·9)	1 (ref)	1 (ref)	..
BMI 25·0–29·9	59/88	13·3 (9·0–20·0)	0·73 (0·51–1·04)	0·65 (0·43–1·00)	..
BMI ≥30	43/67	15·2 (11·1–22·1)	0·62 (0·42–0·91)	0·66 (0·42–1·02)	..
Men (n=142)	..	..	..	..	..
BMI 18·5–24·9	38/40	8·8 (5·8–12·9)	1 (ref)	1 (ref)	..
BMI 25·0–29·9	42/58	12·6 (7·3–14·7)	0·69 (0·44–1·07)	0·62 (0·38–1·03)	..
BMI ≥30	25/44	16·6 (9·3-NR)	0·44 (0·26–0·73)	0·59 (0·31–1·08)	..
Women (n=98)	..	..	..	..	..
BMI 18·5–24·9	30/45	9·3 (7·3–16·7)	1 (ref)	1 (ref)	..
BMI 25·0–29·9	17/30	33·6 (7·6–34·1)	0·64 (0·35–1·16)	0·66 (0·27–1·58)	..
BMI ≥30	18/23	14·8 (10·6–24·8)	0·92 (0·50–1·64)	0·75 (0·37–1·51)	..
Ipilimumab plus dacarbazine cohort§					
All patients (n=207)	..	..	..	..	0·28
BMI 18·5–24·9	59/68	2·6 (2·6–3·5)	1 (ref)	1 (ref)	..
BMI 25·0–29·9	74/88	2·6 (2·5–3·7)	0·87 (0·62–1·22)	0·88 (0·61–1·26)	..
BMI ≥30	43/51	5·2 (2·7–8·0)	0·67 (0·45–0·99)	0·63 (0·41–0·95)	..
Men (n=138)	..	..	..	..	..
BMI 18·5–24·9	37/41	2·6 (2·5–2·8)	1 (ref)	1 (ref)	..
BMI 25·0–29·9	54/64	2·6 (2·6–3·6)	0·76 (0·50–1·16)	0·77 (0·49–1·22)	..
BMI ≥30	25/33	3·9 (2·6–16·6)	0·53 (0·32–0·88)	0·55 (0·32–0·93)	..
Women (n=69)	..	..	..	..	..
BMI 18·5–24·9	22/27	2·9 (2·6–8·0)	1 (ref)	1 (ref)	..
BMI 25·0–29·9	20/24	2·8 (2·6–9·5)	1·02 (0·56–1·88)	1·29 (0·66–2·51)	..
BMI ≥30	18/18	5·6 (3·1–8·4)	1·02 (0·55–1·92)	0·92 (0·45–1·86)	..

(Table 2 continues on next page)

Role of the funding source

The funder of the study had no role in study design, data collection, analysis, or interpretation, or writing of the report. The corresponding authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

The six cohorts consisted of a total of 2046 patients with metastatic melanoma treated with targeted therapy, immunotherapy, or chemotherapy between Aug 8, 2006, and Jan 15, 2016. 101 (5%) patients were excluded because of missing data on height or weight to calculate BMI. Of the 1945 patients with available BMI, 27 (1%) were underweight and were excluded because of low prevalence, leaving 1918 patients in this analysis. Of these, 694 (36%) were normal weight, 711 (37%) were overweight, and 513 (27%) were obese (table 1). More than half the patients (1155 [60%]) were male.

BMI distribution for the cohort treated with dabrafenib plus trametinib was similar to all the other cohorst analysed (table 1, appendix p 2). Clinical and tumour characteristics were similar across normal, overweight, and obese BMI groups (table 1; appendix p 2). A greater proportion of obese patients than those with normal or overweight BMI were prescribed metabolic syndrome-associated medications (metformin, statins, beta-blockers, and aspirin; appendix p 2).

In the dabrafenib plus trametinib cohort, at a median follow-up of 9·3 months (IQR 5·1–21·2) for progression-free survival, 386 events had occurred. An association was seen between obesity and improved progression-free survival in both univariable and multivariable-adjusted analyses (figure 1; table 2). Analysis of BMI as a continuous variable demonstrated a dose-dependent inverse relation between BMI and progression-free survival that extended through morbid obesity (appendix p 3).

With a median follow-up of 20·9 months (IQR 10·5–24·8) for overall survival, 282 patients in the dabrafenib plus trametinib cohort had died. In both univariable analysis and multivariable-adjusted analyses incorporating clinicopathological factors previously associated with outcomes with dabrafenib plus trametinib treatment,[4] obese patients had improved overall survival compared with patients with normal BMI (figure 1; table 3). After adjustment for concomitant medication use, obesity remained associated with improved overall survival, whereas there was no longer an association with progression-free survival (appendix p 3). The proportion of patients with an overall response by BMI category is shown in the appendix (pp 4–5).

With a median follow-up of 21·2 months (IQR 10·5–32·7) in the cohort treated with vemurafenib and cobimetinib, there were 132 deaths and 170 progression-free survival events. Progression-free survival and overall survival results were similar to those seen in the dabrafenib plus trametinib cohort (tables 2, 3; appendix p 6). However, after adjustment for clinical prognostic factors in this cohort, there was no longer an association of BMI with progression-free survival or overall survival (tables 2, 3). Cobimetinib pharmacokinetic data available for this cohort showed no significant differences in serum drug concentrations between BMI groups (appendix p 7).

In male patients in the dabrafenib plus trametinib cohort, obesity was associated with improved

progression-free survival and overall survival compared with those for patients with normal BMI (figure 2; tables 2, 3; appendix p 8). Differences in progression-free survival and overall survival between BMI categories in men remained after adjustment for other prognostic features (tables 2, 3). 2-year progression-free survival and overall survival, and overall response, for men in this cohort are shown in the appendix (p 4). By contrast, progression-free survival, overall survival, and overall response did not differ significantly between BMI categories in female patients in the dabrafenib plus trametinib cohort (figure 2; tables 2, 3; appendix pp 4, 5, and 8). Differences in progression-free survival, overall survival, and overall response by sex were also seen in patients in the vemurafenib and cobimetinib cohort (tables 2, 3; appendix p 6).

BMI distributions of patients in both immunotherapy cohorts were similar to those in the targeted therapy cohorts (table 1; appendix p 9). With a median follow-up of 28·7 months (IQR 2·5–36·6) for progression-free survival in patients in the ipilimumab plus dacarbazine cohort, 176 events had occurred. With a median follow-up of 38·4 months (IQR 35·6–40·4) for overall survival, 158 patients had died. Obesity was associated with improved progression-free survival and overall survival compared with those for patients with normal BMI (figure 1, tables 2, 3). These associations remained after adjustment for confounders in multivariable analysis (tables 2, 3). In men in the ipilimumab plus dacarbazine cohort, obesity was associated with improved overall survival and progression-free survival compared with that for patients with normal BMI (tables 2, 3; appendix p 4). By contrast, BMI was not associated with progression-free survival or overall survival in women in this cohort (tables 2, 3; figure 2).

In the 330 patients who were evaluable in the cohort treated with pembrolizumab, nivolumab, or atezolizumab, with a median follow-up of 25·4 months (IQR 18·4–34·2) for progression-free survival, 221 events had occurred. With a median follow-up of 24·1 (IQR 17·4–33·9) months for overall survival, 162 patients had died. Obesity was not associated with progression-free survival or overall survival in this cohort overall (figure 1; tables 2, 3; appendix p 8). Obesity was associated with improved outcomes in men in univariable analysis, but not multivariable analysis (figure 2; tables 2, 3; appendix p 8). By contrast, in women, no associations were seen between BMI and progression-free survival or overall survival (tables 2, 3; figure 2, appendix p 8). Overall, associations were consistent with those seen in patients in the ipilimumab plus dacarbazine cohort.

Serum albumin levels available for this cohort were similar across BMI categories (appendix p 9). In the 331 patients in the BRIM3 dacarbazine cohort, with a median follow-up of (IQR 3·0–21·0) months, 257 progression-free survival events occurred and 245 patients died. In the 221 patients in the CA 184-024 dacarbazine cohort, with a median follow-up of 28·5 months (IQR 0·4–36·2), 211 progression-free survival events occurred, and with a median follow-up of 38·2 months (35·9–41·3), 196 patients died. BMI was not associated with progression-free survival or overall

	Events/ patients	Median, months (95% CI)	Univariable HR (95% CI)	Multivariable adjusted HR (95% CI)	p value for interaction*
(Continued from previous page)					
Pembrolizumab, nivolumab, or atezolizumab cohort§					
All patients (n=330)	..	..	..	..	0·07
BMI 18·5–24·9	76/102	3·8 (2·8–8·1)	1 (ref)	1 (ref)	..
BMI 25·0–29·9	71/109	6·2 (4·7–17·7)	0·78 (0·56–1·07)	0·82 (0·58–1·16)	..
BMI ≥30	78/119	5·7 (3·0–13·3)	0·80 (0·58–1·10)	0·85 (0·61–1·19)	..
Men (n=213)	..	..	..	..	..
BMI 18·5–24·9	46/57	2·7 (2·7–6·8)	1 (ref)	1 (ref)	..
BMI 25·0–29·9	50/78	7·5 (3·8–22·1)	0·62 (0·42–0·93)	0·69 (0·45–1·07)	..
BMI ≥30	49/78	7·6 (4·1–23·5)	0·62 (0·41–0·92)	0·69 (0·45–1·06)	..
Women (n=117)	..	..	..	..	..
BMI 18·5–24·9	30/45	5·4 (2·9–26·2)	1 (ref)	1 (ref)	..
BMI 25·0–29·9	21/31	5·8 (2·7-NR)	1·08 (0·62–1·88)	1·10 (0·60–2·03)	..
BMI ≥30	29/41	3·0 (2·7–19·2)	1·18 (0·70–1·96)	1·25 (0·72–2·16)	..
Dacarbazine (BRIM3) cohort‡					
All patients (n=320)	..	..	..	..	0·51
BMI 18·5–24·9	115/143	1·6 (1·5–2·1)	1 (ref)	1 (ref)	..
BMI 25·0–29·9	88/107	1·6 (1·5–2·1)	0·93 (0·70–1·23)	0·94 (0·70–1·25)	..
BMI ≥30	54/70	2·6 (1·5–2·9)	0·86 (0·62–1·25)	0·91 (0·64–1·26)	..
Men (n=174)	..	..	..	..	..
BMI 18·5–24·9	60/70	1·6 (1·5–2·7)	1 (ref)	1 (ref)	..
BMI 25·0–29·9	62/73	1·6 (1·5–2·7)	0·87 (0·61–1·25)	0·91 (0·63–1·32)	..
BMI ≥30	23/31	2·8 (1·5–3·3)	0·75 (0·46–1·20)	0·73 (0·43–1·17)	..
Women (n=146)	..	..	..	..	..
BMI 18·5–24·9	55/73	1·6 (1·5–3·2)	1 (ref)	1 (ref)	..
BMI 25·0–29·9	26/34	1·6 (1·4–2·4)	0·97 (0·60–1·53)	0·84 (0·49–1·40)	..
BMI ≥30	31/39	1·6 (1·3–3·9)	0·97 (0·60–1·53)	1·02 (0·63–1·65)	..
Dacarbazine cohort (CA 184-024)§					
All patients (n=221)	..	..	..	..	0·79
BMI 18·5–24·9	71/74	2·6 (2·6–2·7)	1 (ref)	1 (ref)	..
BMI 25·0–29·9	81/88	2·6 (2·6–3·0)	0·73 (0·52–1·01)	0·81 (0·58–1·14)	..
BMI ≥30	59/59	2·6 (2·4–4·5)	0·83 (0·59–1·18)	0·96 (0·67–1·39)	..
Men (n=140)	..	..	..	..	..
BMI 18·5–24·9	37/38	2·6 (2·5–2·8)	1 (ref)	1 (ref)	..
BMI 25·0–29·9	62/66	2·8 (2·6–3·9)	0·62 (0·41–0·94)	0·77 (0·50–1·18)	..
BMI ≥30	36/36	2·7 (2·1–5·4)	0·70 (0·44–1·12)	1·06 (0·63–1·78)	..
Women (n=81)	..	..	..	..	..
BMI 18·5–24·9	34/36	2·6 (2·5–2·9)	1 (ref)	1 (ref)	..
BMI 25·0–29·9	19/22	2·6 (2·5–2·8)	1·08 (0·62–1·90)	1·13 (0·63–2·01)	..
BMI ≥30	23/23	2·5 (2·4–5·4)	1·04 (0·61–1·77)	1·02 (0·58–1·77)	..

BMI=body-mass index (kg/m²). ECOG=Eastern Cooperative Oncology Group. HR=hazard ratio. LDH=lactate dehydrogenase. ..=not analysed. *Interaction for sex by BMI was tested using BMI as a categorical variable (obese *vs* normal patients) on multivariable HRs. †Adjusted for sex, age, disease AJCC 7 stage, LDH status, *BRAF*^{V600} mutation type, ECOG performance status, sum of target lesion diameters, number of disease sites, and previous adjuvant therapies in the overall cohort. ‡Adjusted for sex, age, stage, LDH status, *BRAF* mutation status, and ECOG performance status in overall cohort. §Adjusted for sex, age, stage, LDH status, and ECOG performance status in overall cohort.

Table 2: **Association between BMI and progression-free survival**

survival in either cohort (tables 2, 3; figure 1). Furthermore, BMI was not associated with outcome in either men or women (tables 2, 3; figures 2, 3; appendix pp 8 and 10).

We assessed frequencies of adverse events by BMI, sex, and grade in each cohort (appendix pp 11–12). There was no evidence that adverse events were more frequent in patients with normal BMI than in patients who were overweight and obese.

Pooling and analysing the results from all cohorts using meta-analysis, obesity, compared with normal BMI, was associated with improved outcomes (average adjusted HR 0·77 [95% CI 0·66–0·90] for progression-free survival and 0·74 [0·58–0·95] for overall survival; figure 3). We found heterogeneity in the prognostic effect of BMI by treatment type across the six cohorts for overall survival but not progression-free survival (figure 3). Associations between BMI and outcome were observed with targeted therapy and immunotherapy but not chemotherapy (figure 3). BMI associations with overall survival in combined targeted and immune therapy cohorts significantly differed from pooled associations observed for chemotherapy ($p_{interaction}$=0·002; figure 3). Although the association of obesity with progression-free survival for the combined targeted and immune therapy cohorts was consistent with that for overall survival, no significant interaction by treatment type was observed ($p_{interaction}$=0·34; figure 3). Consistent with findings from individual targeted therapy and immunotherapy cohorts, we observed differences in the association of BMI with outcome by sex in the combined cohort analysis ($p_{interaction}$=0·08 for progression-free survival and $p_{interaction}$=0·03 for overall survival; figure 3). Within the combined targeted and immune therapy cohorts, the survival benefit of obesity was restricted to men (figure 3). BMI was not associated with outcomes in the pooled chemotherapy cohorts overall or when stratified by sex (figure 3).

	Events/ patients	Median, months (95% CI)	Univariable HR (95% CI)	Multivariable adjusted HR (95% CI)	p value for interaction*
Dabrafenib plus trametinib cohort†					
All patients (n=599)	..	..	..	..	0·02
BMI 18·5–24·9	112/222	19·8 (17·3–29·0)	1 (ref)	1 (ref)	..
BMI 25·0–29·9	112/231	25·6 (20·2–NR)	0·84 (0·65–1·10)	0·78 (0·59–1·02)	..
BMI ≥30	58/146	33·0 (26·7–NR)	0·63 (0·46–0·86)	0·59 (0·43–0·83)	..
Men (n=347)	..	..	..	..	..
BMI 18·5–24·9	68/109	16·0 (14·1–19·2)	1 (ref)	1 (ref)	..
BMI 25·0–29·9	84/156	21·3 (18·1–27·0)	0·73 (0·53–1·00)	0·80 (0·57–1·11)	..
BMI ≥30	32/82	36·5 (28·4–NR)	0·46 (0·30–0·70)	0·44 (0·29–0·69)	..
Women (n=252)	..	..	..	..	..
BMI 18·5–24·9	44/113	NR (24·1-NR)	1 (ref)	1 (ref)	..
BMI 25·0–29·9	28/75	NR (25·6-NR)	0·84 (0·52–1·35)	0·65 (0·37–1·13)	..
BMI ≥30	26/64	33·0 (25·3-NR)	0·89 (0·55–1·45)	0·93 (0·56–1·55)	..
Vemurafenib plus cobimetinib cohort‡					
All patients (n=240)	..	..	..	..	0·44
BMI 18·5–24·9	53/85	21·5 (16·3–28·4)	1 (ref)	1 (ref)	..
BMI 25·0–29·9	48/88	22·3 (16·7–34·1)	0·86 (0·58–1·28)	0·67 (0·43–1·06)	..
BMI ≥30	31/67	NR (21·3-NR)	0·64 (0·41–0·98)	0·62 (0·37–1·02)	..
Men (n=142)	..	..	..	..	..
BMI 18·5–24·9	29/40	18·9 (10·0–22·0)	1 (ref)	1 (ref)	..
BMI 25·0–29·9	36/58	19·0 (13·5–26·0)	0·82 (0·51–1·35)	0·67 (0·39–1·15)	..
BMI ≥30	20/44	26·5 (19·2-NR)	0·53 (0·29–0·93)	0·68 (0·35–1·29)	..
Women (n=98)	..	..	..	..	..
BMI 18·5–24·9	24/45	26·9 (13·6-NR)	1 (ref)	1 (ref)	..
BMI 25·0–29·9	12/30	NR (18·1-NR)	0·71 (0·34–1·39)	0·72 (0·27–1·83)	..
BMI ≥30	11/23	NR (19·1-NR)	0·75 (0·35–1·50)	0·59 (0·25–1·29)	..
Ipilimumab plus dacarbazine cohort§					
All patients (n=207)	..	..	..	..	0·15
BMI 18·5–24·9	56/68	10·0 (8·1–14·0)	1 (ref)	1 (ref)	..
BMI 25·0–29·9	67/88	12·4 (9·1–21·9)	0·76 (0·53–1·08)	0·70 (0·48–1·03)	..
BMI ≥30	35/51	11·4 (9·2–24·3)	0·64 (0·42–0·97)	0·54 (0·34–0·86)	..
Men (n=138)	..	..	..	..	..
BMI 18·5–24·9	35/41	8·2 (3·4–15·7)	1 (ref)	1 (ref)	..
BMI 25·0–29·9	50/64	11·9 (7·3–22·1)	0·69 (0·45–1·07)	0·63 (0·39–1·01)	..
BMI ≥30	20/33	13·6 (9·5-NR)	0·46 (0·27–0·80)	0·40 (0·22–0·72)	..
Women (n=69)	..	..	..	..	..
BMI 18·5–24·9	21/27	11·3 (8·4–25·4)	1 (ref)	1 (ref)	..
BMI 25·0–29·9	17/24	13·5 (9·1-NR)	0·79 (0·42–1·50)	0·84 (0·43–1·64)	..
BMI ≥30	15/18	9·9 (7·9–35·4)	1·13 (0·58–2·18)	1·16 (0·55–2·46)	..

(Table 3 continues on next page)

Discussion

Our analyses of multiple, large, independent cohorts of patients with metastatic melanoma treated with contemporary targeted and immune therapies showed that obesity was associated with improved outcomes compared with those in patients with a normal BMI. These associations seemed to be independent of traditional prognostic factors and concomitant medications, and were not explained by differences in treatment tolerance or pharmacokinetics. Our findings further suggest that the relation between BMI and outcomes in patients with metastatic melanoma might vary by sex and treatment, with a survival advantage seen in obese men treated with targeted and immune therapies, but not in women or in patients of either sex treated with chemotherapy, within either individual cohorts or in the pooled analysis.

Our findings in patients with metastatic melanoma contrast with previous data linking obesity with a slightly increased risk of developing melanoma,[11,12] as well as a recent analysis of melanoma patients with clinically localised disease in which higher BMI was associated with worse survival.[13] In aggregate, the findings support the presence of an obesity paradox across the spectrum of melanoma development, progression, and treatment response. This phenomenon, wherein higher BMI is associated with increased disease risk but confers a survival advantage in patients with established or advanced disease, has been described in other malignancies.[7–9] Whether this inverse relationship is

causal remains poorly understood.[10] However, several features of our study suggest a potential biological role of adiposity in survival of patients with metastatic melanoma. In other malignancies in which the obesity paradox has been reported, the survival advantage is often limited to overweight or only mildly obese patients.[8] Although BMI is widely used, it is an imperfect surrogate of adiposity and can misclassify body composition (fat *vs* muscle), particularly in the overweight range. By contrast, our data suggest a dose effect of BMI with modestly improved outcomes in overweight patients and a strong, consistent survival advantage seen in obese patients. We also observed a nearly linear association between increasing BMI and progression-free survival that extended to morbid obesity (where body composition is unlikely to be misclassified) in the dabrafenib plus trametinib cohort.

In several malignancies in which obesity has been associated with a survival advantage, either the cancer or its treatment (ie, chemotherapy) often cause weight loss, raising the possibility of reverse causality.[10] Because BMI was analysed at a single timepoint (therapy initiation) for the cohorts assessed in our study, we cannot rule out potential antecedent weight loss, and future studies should include longitudinal BMI assessment. However, underweight BMI was rare (<2%) in these cohorts and such patients were excluded from our analyses. Moreover, the BMI distribution of each cohort mirrored that of the general population, with more than 60% of patients classified as overweight or obese.[22] ECOG performance status and albumin concentrations (immunotherapy cohort) did not differ by BMI category, supporting the notion that patients in the normal BMI group were not cachectic at baseline. Perhaps most importantly, the obesity survival advantage was specifically observed in patients treated with targeted and immune therapy, regimens that are not usually associated with the substantial weight loss typical of chemotherapy-treated cohorts.

Our analyses also accounted for the potential contribution of traditional prognostic factors and the use of concomitant medications, which might have anticancer activity, including metformin, statins, beta-blockers, and aspirin. To interrogate other potential causes of the observed differences, we also examined frequencies of adverse events and available pharmacokinetic data (cobimetinib). These analyses again showed no differences by BMI category, supporting the notion that treatment tolerance and drug exposure are unlikely to explain the observed associations. Differences in drug absorption are also an unlikely cause given that associations were seen in cohorts of patients treated with agents given orally at a fixed dose (targeted therapies) and with agents with weight-based intravenous dosing (immunotherapies). The association of BMI with outcomes in patients treated with immunotherapy should be investigated again in future cohorts of patients treated with flat-dose regimens of these agents, which are now generally used.

The strength and consistency of these associations support the need for focused investigations into their biological basis. The interactions between BMI, sex, and therapy in the pooled analyses are provocative and

	Events/ patients	Median, months (95% CI)	Univariable HR (95% CI)	Multivariable adjusted HR (95% CI)	p value for interaction*
(Continued from previous page)					
Pembrolizumab, nivolumab, or atezolizumab cohort§					
All patients (n=329)	..	..	..	..	0·84
BMI 18·5–24·9	59/102	19·9 (14·2–31·1)	1 (ref)	1 (ref)	..
BMI 25·0–29·9	51/109	28·8 (18·6–NR)	0·75 (0·52–1·10)	0·78 (0·52–1·17	..
BMI ≥30	52/118	27·2 (22·0–NR)	0·70 (0·48–1·01)	0·72 (0·48–1·06)	..
Men (n=213)	..	..	..	..	..
BMI 18·5–24·9	37/57	14·3 (6·5–25·5)	1 (ref)	1 (ref)	..
BMI 25·0–29·9	36/78	28·8 (18·6-NR)	0·59 (0·37–0·93)	0·71 (0·44–1·17)	..
BMI ≥30	37/78	26·9 (19·6-NR)	0·62 (0·39–0·98)	0·69 (0·42–1·12)	..
Women (n=116)	..	..	..	..	..
BMI 18·5–24·9	22/45	26·6 (19·7-NR)	1 (ref)	1 (ref)	..
BMI 25·0–29·9	15/31	24·3 (10·9-NR)	1·08 (0·56–2·08)	1·00 (0·47–2·10)	..
BMI ≥30	15/40	NR (25·6-NR)	0·77 (0·40–1·49)	0·72 (0·36–1·45)	..
Dacarbazine (BRIM3) cohort‡					
All patients (n=320)	..	..	..	..	0·49
BMI 18·5–24·9	108/143	9·7 (7·8–14·2)	1 (ref)	1 (ref)	..
BMI 25·0–29·9	86/107	10·6 (7·2–14·1)	1·05 (0·79–1·39)	0·98 (0·73–1·31)	..
BMI ≥30	51/70	9·9 (7·7–14·3)	0·92 (0·66–1·28)	0·94 (0·66–1·32)	..
Men (n=174)	..	..	..	..	..
BMI 18·5–24·9	56/70	9·7 (6·3–14·9)	1 (ref)	1 (ref)	..
BMI 25·0–29·9	61/73	10·6 (7·0–14·0)	1·09 (0·76–1·57)	0·97 (0·66–1·41)	..
BMI ≥30	24/31	9·9 (7·6–15·9)	1·05 (0·64–1·68)	0·92 (0·56–1·51)	..
Women (n=146)	..	..	..	..	..
BMI 18·5–24·9	52/73	9·6 (5·9–14·2)	1	1	..
BMI 25·0–29·9	25/34	14·0 (3·5–18·4)	1·00 (0·61–1·60)	0·85 (0·50–1·40)	..
BMI ≥30	27/39	9·9 (7·1–18·9)	0·82 (0·51–1·29)	0·94 (0·57–1·52)	..
Dacarbazine cohort (CA 184-024)§					
All patients (n=221)	..	..	..	..	0·39
BMI 18·5–24·9	68/74	8·3 (6·8–11·4)	1 (ref)	1 (ref)	..
BMI 25·0–29·9	75/88	9·0 (7·1–10·6)	0·85 (0·61–1·19)	0·91 (0·64–1·28)	..
BMI ≥30	53/59	7·9 (5·3–13·9)	0·95 (0·66–1·37)	1·16 (0·79–1·70)	..
Men (n=140)	..	..	..	..	..
BMI 18·5–24·9	37/38	7·5 (5·4–11·0)	1 (ref)	1 (ref)	..
BMI 25·0–29·9	56/66	8·6 (5·4–11·8)	0·72 (0·48–1·10)	0·89 (0·58–1·36)	..
BMI ≥30	33/36	6·1 (2·2–10·5)	0·97 (0·60–1·56)	1·55 (0·91–2·66)	..
Women (n=81)	..	..	..	..	..
BMI 18·5–24·9	31/36	10·8 (7·4–11·7)	1 (ref)	1 (ref)	..
BMI 25·0–29·9	19/22	10·2 (7·1–14·2)	1·06 (0·60–1·88)	1·29 (0·70–2·36)	..
BMI ≥30	20/23	14·3 (10·2–28·3)	0·88 (0·50–1·55)	0·91 (0·51–1·64)	..

BMI=body-mass index (kg/m²). ECOG=Eastern Cooperative Oncology Group. HR=hazard ratio. LDH=lactate dehydrogenase. NR=not reached. ..=not analysed. *Interaction for sex by BMI was tested using BMI as a categorical variable (obese *vs* normal patients) on multivariable HRs. †Adjusted for sex, age, disease AJCC 7stage, LDH status, *BRAF*^{V600} mutation type, ECOG performance status, sum of target lesion diameters, number of disease sites, and previous adjuvant therapies in the overall cohort. ‡Adjusted for sex, age, stage, LDH status, *BRAF* mutation status, and ECOG performance status in overall cohort. §Adjusted for sex, age, stage, LDH status, and ECOG performance status in overall cohort.

Table 3: **Association between BMI and overall survival**

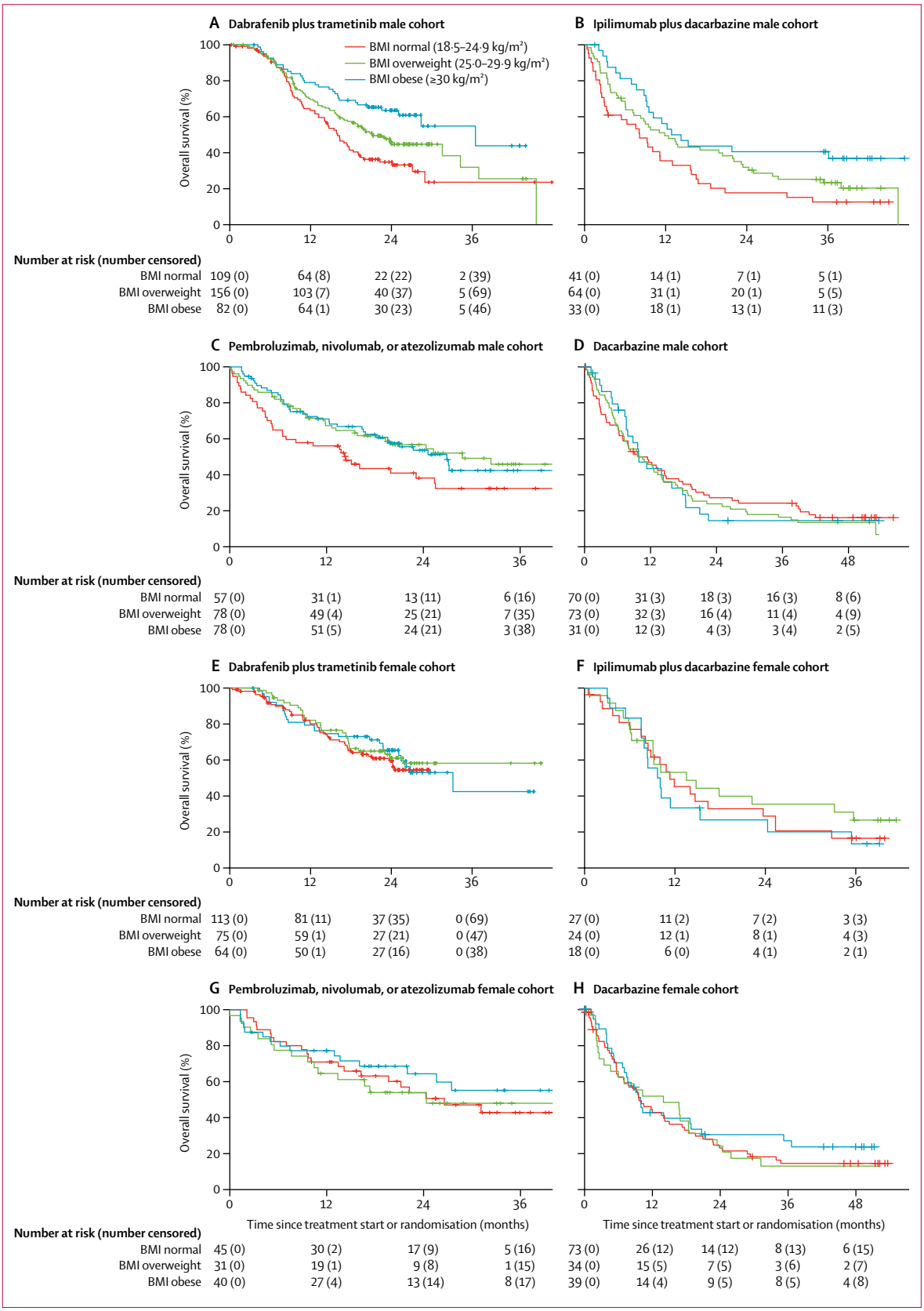

Figure 2: **Overall survival by BMI category and sex**
Overall survival in male patients in the (A) dabrafenib plus trametinib cohort, (B) ipilimumab plus dacarbazine cohort, (C) pembrolizumab, nivolumab, or atezolizumab cohort, and (D) dacarbazine BRIM3 cohort. Overall survival in female patients in the (E) dabrafenib plus trametinib cohort, (F) ipilimumab plus dacarbazine cohort, (G) pembrolizumab, nivolumab, or atezolizumab cohort, and (H) dacarbazine BRIM3 cohort. BMI=body-mass index.

hypothesis-generating regarding potential mechanisms. Although targeted therapy and immunotherapy are fundamentally different treatment modalities, cross-talk between oncogenic signalling pathways and the antitumour immune response has been implicated in response and resistance to both treatments in melanoma.[19,23,24] Although the impact of obesity-associated inflammation on carcinogenesis has been well studied, the effect of energy balance on the antitumour immune response has not been examined to date and should be investigated as a potential explanation underlying the observed interaction between BMI and both targeted and immune therapy. A study in renal cell carcinoma in which high BMI was associated with improved outcomes with targeted therapy found that alterations in fatty acid metabolism were associated with both obesity and outcomes.[9] In view of emerging evidence implicating tumour and immune cell metabolism in melanoma therapeutic response,[25] the relation between tumour metabolism and clinical metabolic phenotype should also be explored in this disease. Analyses examining the molecular, immunological, and metabolic correlates of obesity in melanoma are currently ongoing (or underway). However, the striking differences in BMI and outcome associations by sex reported here also suggest a potential hormonal mediator of the BMI effects.

In male patients, obesity was associated with a near doubling in survival whereas no associations were seen in female patients. Female sex has long been recognised as a predictor of improved outcomes in melanoma.[20] Intriguingly, our data suggest that obesity could confer a similar survival advantage in male patients with metastatic melanoma treated with targeted therapy and immunotherapy. Obesity in men results in higher concentrations of circulating oestradiol as adipose tissue aromatase activity converts androgens to oestrogen compounds.[26] Interestingly, a previous randomised, controlled trial[27] of dacarbazine with or without tamoxifen, a selective oestrogen receptor modulator, showed no benefit in patients with metastatic melanoma overall. However, high BMI in men and postmenopausal women were predictive of benefit from the addition of tamoxifen to chemotherapy, but not with chemotherapy alone, in this trial. Although menopausal status was not available for the cohorts in our analysis, this interaction should be investigated in future studies and would further strengthen the hypothesis of a hormonal mediator driving the observed associations. Melanoma lacks substantial oestrogen receptor α expression, the receptor responsible for the proliferative effects of oestrogen on breast cancer. However, previous reports have suggested high oestrogen receptor β expression in primary melanoma, which might have antiproliferative activity.[28,29] More recently, non-classical oestrogen receptor signalling through a G protein-coupled oestrogen receptor (GPER) has been found to regulate melanoma differentiation status, which has been implicated in resistance to both targeted and

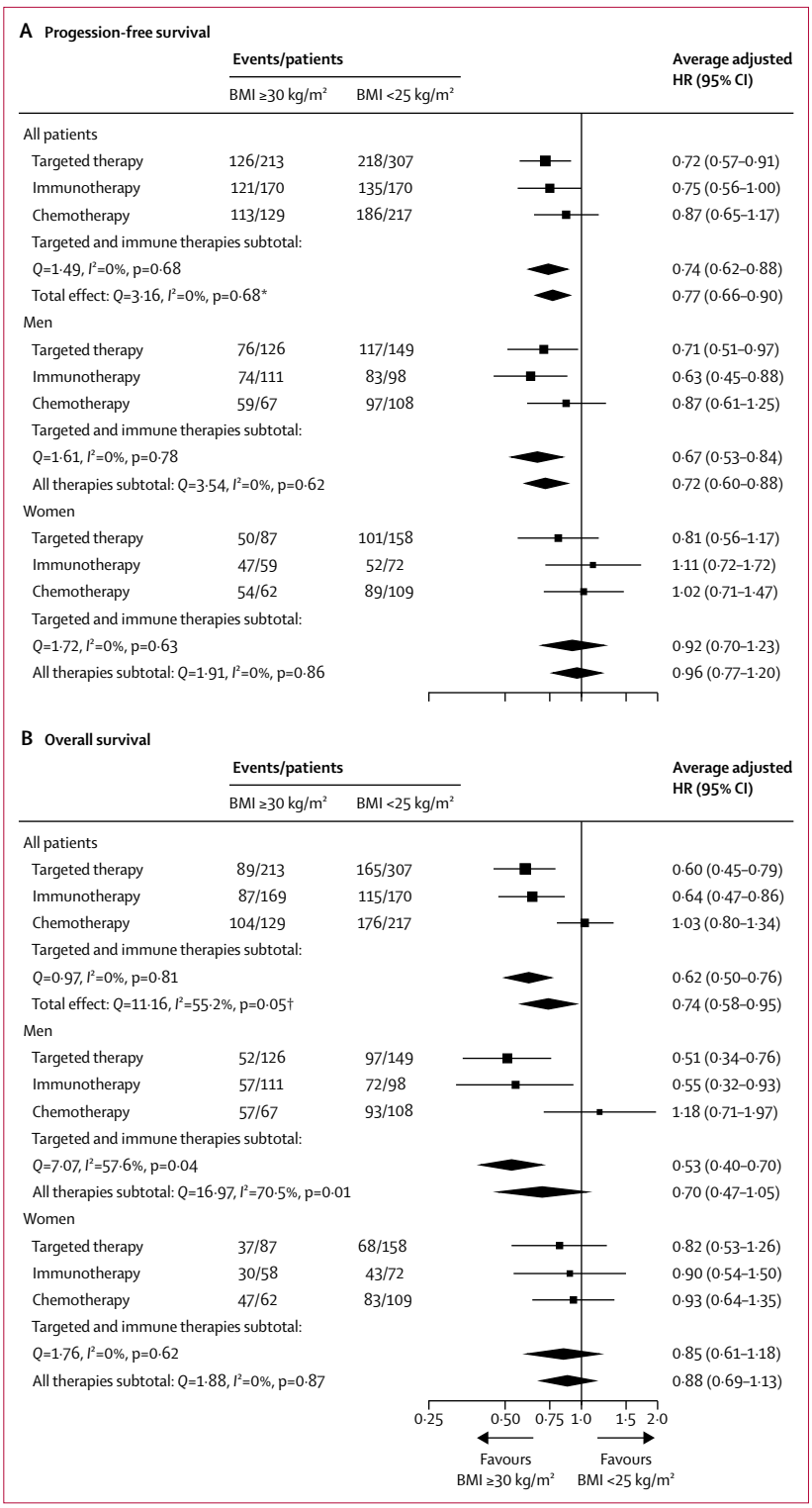

Figure 3: **Pooled analysis**
Forest plots of average adjusted hazard ratios (HRs) for patients with obese BMI (≥30 kg/m²) compared with normal BMI (<25 kg/m²) by treatment type and sex for (A) progression-free survival and (B) overall survival. The dashed line shows the effect size for all cohorts. BMI=body-mass index. *p for interaction for treatment p=0·61.†p for interaction for treatment p=0·01.

immune therapy in this disease. Importantly, a GPER agonist has further been shown to synergize with anti-PD1 immunotherapy by increasing immunogenicity.[30] Moreover, the effect of oestrogen on immune function has been well studied in the context of sex disparities in the frequency of autoimmune disease, and immune response to vaccines and pathogens, and is another potential mechanism by which hormones could mediate the observed BMI effect.

The pooled analysis has several limitations and should be viewed as exploratory given that there were only six cohorts, because meta-analysis methods are problematic with small numbers of studies. As further data on the associations between BMI and outcomes in melanoma become available, full meta-analyses should be done. Within the pooled analysis, we observed significant interactions between BMI, therapy, and sex, which support the associations seen within the individual cohorts. However, even with the pooled analysis, a smaller number of women (particularly obese women) included in the cohorts could have limited the statistical power to detect associations in this group. Moreover, our analysis could be underpowered to detect the association between BMI and outcomes in a treatment that has a low frequency of response (ie, chemotherapy). However, the striking survival advantage seen in obese men in the ipilimumab plus dacarbazine cohort would argue against this possibility because the proportion of patients with response to ipilimumab (10–15%) is only marginally higher than that observed with chemotherapy.

In conclusion, obesity is associated with improved outcomes in male patients with metastatic melanoma treated with targeted and immune therapies. The use of pooled data from the dabrafenib plus trametinib treatment groups from multiple clinical trials, which had previously been analysed for clinical prognostic factors, allowed for robust covariate adjustment and examination of RECIST response in addition to survival.[4] As survival data matures from the anti-PD-1 immunotherapy trials, we will validate the findings of the multi-institutional retrospective anti-PD-1 cohort presented here with clinical trial level data. The association of BMI and outcomes in other malignancies in which targeted or immune therapies are approved should also be examined. The observed differences in overall survival in male patients were similar to or larger than differences seen in several previous registration trials in metastatic melanoma.[1,31] These findings support the need to consider sex and BMI as stratification factors in trials, and to investigate the biological mechanisms underlying these unexpected results.

Contributors

JLM and MAD designed the study. All authors contributed to data acquisition, analysis, and interpretation. JLM CRD, and MAD wrote the report. All authors critically reviewed and revised the report. JLM and MAD 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.

Declaration of interests

KRH reports non-financial support from AngioChem. CM has received consultant fees from Novartis. CS has a patent on microbiome and immunotherapy response pending. MW is an employee of Roche/Genentech and is a stockholder in Roche and ARIAD Pharmaceuticals. SLa is a former employee of Novartis and a current employee of Bristol-Myers Squibb. D-YL and MK are employees of Novartis. IR, LM, NB, and JH are employees of Genentech and LM and NB are also shareholders of Genentech. AA is an employee of Bristol-Myers Squibb. TH is an employee and shareholder of Novartis. JAW has received compensation for speaker's bureau and honoraria from Dava Oncology, Bristol-Myers Squibb, and Illumina, and has served on advisory committees for GlaxoSmithKline, Roche/Genentech, Novartis, and AstraZeneca. JEG is on advisory boards for Merck and Castle Biosciences. PH has received fees from Dragonfly, Immatics, Iovance, Sanofi, and GlaxoSmithKline, and non-financial support from MedImmune. PBC is a consultant for Daiichi, Hoffman-LaRoche, Genentech, and Merck, has received research support from Pfizer and Bristol-Myers Squibb, and is a stockholder in Rgenix. JAS has received fees from Bristol-Myers Squibb, Incyte, Merck, Genentech, and Array. DS is a consultant for Amgen, Boehringer Ingelheim, Leo Pharma, Roche, Merck/MSD, Novartis, Sysmex, GlaxoSmithKline, and Bristol-Myers Squibb. JJG is on the advisory board for Bristol-Myers Squibb, MSD, Novartis, Roche, Amgen, Merck/Pfizer, and Pierre Fabre. KTF is a consultant to Novartis. DW is an employee of Bristol-Myers Squibb. YY is an employee and shareholder of Roche/Genentech. EM is an employee and shareholder of Roche/Genentech. JJL is an employee and shareholder of Novartis. MSC is a consultant for Bristol-Myers Squibb, Merck, Novartis, and Amgen. AR is on the advisory board of Roche/Genentech, Novartis, Merck, Takeda, and Pierre Fabre. JMK has received personal fees from Bristol-Myers Squibb, Roche/Genentech, Novartis, EMD Serono, Merck, Array Biopharma, Amgen, SolaranRX, and Checkmate Pharmaceuticals, and research funding from Merck and Prometheus. GVL is a consultant for Amgen, Array, Bristol-Myers Squibb, Merck/MSD, Novartis, Pierre Fabre, and Roche/Genentech. DBJ is on advisory boards for Bristol-Myers Squibb and Genoptix and receives research funding from Incyte. AMM is on the advisory board for Novartis, MSD, Chugai, and Pierre Fabre, and has received honoraria from Bristol-Myers Squibb and Roche. MAD has served on advisory boards for Novartis, Roche/Genentech, GlaxoSmithKline, Bristol-Myers Squibb, Sanofi-Aventis, and Vaccinex, and is the principal investigator on research funding to MD Anderson Cancer Center (MDACC) from Roche/Genentech, GlaxoSmithKline, Sanofi-Aventis, Merck, and AstraZeneca. All other authors declare no competing interests.

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