

Prognostic effect of body mass index in patients with advanced NSCLC treated with chemoimmunotherapy combinations

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ABSTRACT

Introduction It has been recognized that increasing body mass index (BMI) is associated with improved outcome from immune checkpoint inhibitors (ICIs) in patients with various malignancies including non-small cell lung cancer (NSCLC). However, it is unclear whether baseline BMI may influence outcomes from first-line chemoimmunotherapy combinations.

Methods In this international multicenter study, we evaluated the association between baseline BMI, progression-free survival (PFS) and overall survival (OS) in a cohort of patients with stage IV NSCLC consecutively treated with first-line chemoimmunotherapy combinations. BMI was categorized according to WHO criteria.

Results Among the 853 included patients, 5.3% were underweight; 46.4% were of normal weight; 33.8% were overweight; and 14.5% were obese. Overweight and obese patients were more likely aged ≥ 70 years ($p=0.00085$), never smokers ($p<0.0001$), with better baseline Eastern Cooperative Oncology Group—Performance Status ($p=0.0127$), and had lower prevalence of central nervous system ($p=0.0002$) and liver metastases ($p=0.0395$). Univariable analyses showed a significant difference in the median OS across underweight (15.5 months), normal weight (14.6 months), overweight (20.9 months), and obese (16.8 months) patients (log-rank: $p=0.045$, log rank test for trend: $p=0.131$), while no difference was found with respect to the median PFS (log-rank for trend: $p=0.510$). Neither OS nor PFS was significantly associated with baseline BMI on multivariable analysis.

Conclusions In contrast to what was observed in the context of chemotherapy-free ICI-based regimens, baseline BMI does not affect clinical outcomes from chemoimmunotherapy combinations in patients with advanced NSCLC.

INTRODUCTION

Increasing evidence suggests the presence of an obesity-driven proinflammatory state in

patients with cancer, with positive implications with regard to clinical benefit from immune checkpoint inhibitors (ICIs).^{1–3} In patients with non-small cell lung cancer (NSCLC), baseline obesity is associated with an incremental survival benefit with programmed death-1 (PD-1)/programmed death-ligand 1 (PD-L1) inhibitors compared with normal-weight patients, a finding confirmed across different treatment lines and levels of PD-L1 tumor expression.^{4,5} In a prior study evaluating patients with advanced NSCLC treated with either first-line pembrolizumab monotherapy or standard chemotherapy, we showed that the positive effect of body mass index (BMI) on oncological outcomes was restricted to immunotherapy recipients, lending further credence to the view that obesity may exert an immune modulatory rather than a simply prognostic role.⁶

Considerable research efforts are under way to identify tumorous and host determinants of response and survival in the context of chemoimmunotherapy combinations, which have significantly improved the first-line treatment landscape of NSCLC^{7,8}; however, to date, there is no clear evidence about the role of baseline BMI in this setting.

METHODS

In this international multicenter study, we evaluated the association between baseline BMI and clinical outcomes in a cohort

Table 1 Patients' characteristics at baseline for the overall cohort and according to body mass index WHO categories

	Overall (%) N=853	Underweight (%) N=45	Normal weight (%) N=396	Overweight (%) N=288	Obese (%) N=124	P value
Age (years), n (%)						
Median	65	59	63	67	66	0.0085
Range	19–88	40–79	19–88	35–87	36–80	
<70	593 (69.5)	38 (84.4)	288 (72.7)	183 (63.5)	84 (67.7)	
≥70	260 (30.5)	7 (15.6)	108 (27.3)	105 (36.5)	40 (32.3)	
Gender, n (%)						
Female	338 (39.6)	18 (40.0)	141 (35.6)	119 (41.3)	60 (48.4)	0.0719
Male	515 (60.4)	27 (60.0)	255 (64.4)	169 (58.7)	64 (51.6)	
ECOG-PS, n (%)						
0–1	633 (75.0)	28 (62.2)	282 (71.8)	227 (80.2)	96 (78.0)	0.0127
≥2	211 (25.0)	17 (37.8)	111 (28.2)	56 (19.8)	27 (22.0)	
Missing	9	–	3	5	1	
Histology, n (%)						
Adenocarcinoma	679 (79.6)	36 (80.0)	312 (78.8)	231 (80.2)	100 (80.6)	0.7143
Squamous	115 (13.5)	5 (11.1)	52 (13.1)	43 (14.9)	15 (12.1)	
Carcinoma NOS/others	59 (6.9)	4 (8.9)	32 (8.1)	14 (4.9)	9 (7.3)	
Smoking status, n (%)						
Never smokers	82 (9.6)	2 (4.4)	35 (8.8)	27 (9.4)	18 (14.5)	<0.0001
Former smokers	598 (70.3)	26 (57.8)	263 (66.4)	213 (74.5)	96 (77.4)	
Current smokers	171 (20.1)	17 (37.8)	98 (24.7)	46 (16.1)	10 (8.1)	
Missing	2	–	–	2	–	
CNS metastases, n (%)						
No	657 (77.4)	24 (53.3)	298 (75.8)	236 (82.2)	99 (79.8)	0.0002
Yes	192 (22.6)	21 (46.7)	95 (24.2)	51 (17.8)	25 (20.2)	
Missing	4	–	3	1	–	
Bone metastases, n (%)						
No	520 (61.2)	23 (51.1)	236 (60.1)	181 (63.1)	80 (64.5)	0.3701
Yes	329 (38.8)	22 (48.9)	157 (39.9)	106 (36.9)	44 (35.5)	
Missing	4	–	3	1	1	
Liver metastases, n (%)						
No	731 (86.1)	33 (73.3)	336 (85.5)	250 (87.1)	112 (90.3)	0.0395
Yes	118 (13.9)	12 (26.7)	57 (14.5)	37 (12.9)	12 (9.7)	
Missing	4	0	3	1	–	
PD-L1 TPS, n (%)						
<1%	383 (44.9)	19 (42.2)	178 (44.9)	136 (47.2)	50 (40.3)	0.4704
1%–49%	281 (32.9)	13 (28.9)	134 (33.8)	95 (33.0)	39 (31.5)	
≥50%	140 (16.4)	11 (24.4)	66 (16.7)	39 (13.5)	24 (19.4)	
Not available	49 (5.7)	2 (4.4)	18 (4.5)	18 (6.2)	11 (8.9)	
EGFR mutational status, n (%)						
Wild type	761 (89.2)	40 (88.9)	353 (89.1)	255 (88.5)	113 (91.1)	0.8042
Mutant	18 (2.1)	–	9 (2.3)	8 (2.8)	1 (0.8)	
Unknown	74 (8.7)	5 (11.1)	34 (8.6)	25 (8.7)	10 (8.1)	
ALK molecular status, n (%)						
Wild type	777 (91.1)	40 (88.9)	362 (91.4)	261 (90.6)	114 (91.9)	0.9176
Unknown	76 (8.9)	5 (11.1)	34 (8.6)	27 (9.4)	10 (8.1)	
ROS-1 molecular status, n (%)						
Wild type	687 (80.5)	36 (80.0)	319 (80.6)	228 (79.2)	104 (83.9)	0.7999
Unknown	166 (19.4)	9 (20.0)	77 (9.4)	60 (20.8)	20 (16.1)	

Continued

Table 1 Continued

KRAS molecular status, n (%)						
Wild type	338 (39.6)	14 (31.1)	173 (43.7)	114 (39.6)	37 (29.8)	0.0011
Mutant	226 (26.5)	14 (31.1)	85 (21.5)	75 (26.0)	52 (41.9)	
Unknown	289 (33.9)	17 (37.8)	138 (34.8)	99 (34.4)	35 (28.2)	
STK11 molecular status, n (%)						
Wild type	247 (29.0)	9 (20.0)	115 (29.0)	86 (29.9)	37 (29.8)	0.7273
Mutant	91 (10.7)	5 (11.1)	39 (9.8)	30 (10.4)	17 (13.7)	
Unknown	515 (60.4)	31 (68.9)	242 (61.1)	172 (59.7)	70 (56.5)	
KEAP-1 molecular status, n (%)						
Wild type	244 (28.6)	12 (26.7)	105 (26.5)	84 (29.2)	43 (34.7)	0.4988
Mutant	67 (7.9)	2 (4.4)	36 (9.1)	19 (6.6)	10 (8.1)	
Unknown	542 (63.5)	31 (68.9)	255 (64.4)	185 (64.2)	71 (57.3)	
TP53 molecular status, n (%)						
Wild type	233 (27.3)	17 (37.8)	102 (25.8)	72 (25.0)	42 (33.9)	0.2687
Mutant	211 (24.7)	9 (20.0)	105 (26.5)	73 (25.3)	24 (19.4)	
Unknown	409 (47.9)	19 (42.2)	189 (47.7)	143 (49.7)	58 (46.8)	
Median TMB (mut/megabase)						
Median (range)	9.1 (1.0–67.6)	12.2 (5.3–36.5)	9.1 (1.2–67.6)	8.4 (1.0–25.1)	8.4 (1.3–25.1)	0.1590
<10	148 (59.7)	3 (27.3)	68 (60.2)	49 (61.2)	28 (63.6)	
≥10	100 (40.3)	8 (72.7)	45 (39.8)	31 (38.7)	16 (36.4)	
Available patients	248	11	113	80	44	
Other potentially targetable oncogenes*						
Mutant	61 (7.1)	1 (2.2)	31 (7.8)	23 (7.9)	6 (4.8)	–
Regimen						
Pembrolizumab/histology-based chemotherapy	825 (96.7)	44 (97.8)	387 (97.7)	276 (95.8)	118 (95.2)	–
Atezolizumab–bevacizumab/platinum doublet	10 (1.2)	–	2 (0.5)	6 (2.1)	2 (1.6)	
Atezolizumab/histology-based chemotherapy	18 (2.1)	1 (2.2)	7 (1.8)	6 (2.1)	4 (3.2)	

*Includes HER2 (available for 466 patients), MET (available for 477 patients), BRAF (available for 526 patients) and RET (available for 448 patients). ALK, anaplastic lymphoma kinase; CNS, central nervous system; ECOG-PS, Eastern Cooperative Oncology Group—Performance Status; EGFR, epidermal growth factor receptor; PD-L1, programmed death-ligand 1; TMB, tumor mutational burden; TPS, Tumor Proportion Score.

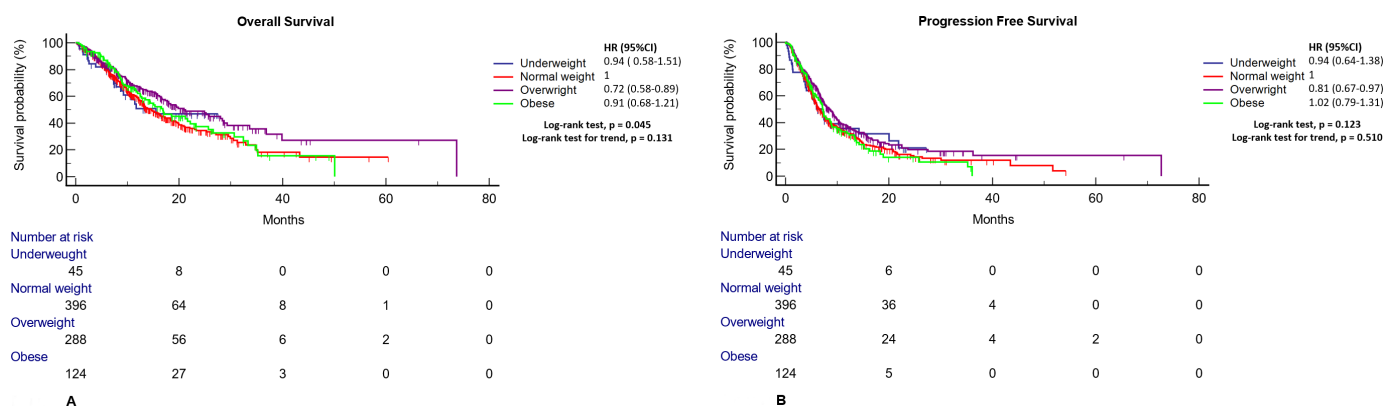


Figure 1 Kaplan-Meier survival estimates. (A) Overall survival: underweight: 15.5 months (95% CI 8.8 to 15.5, 20 events), normal weight: 14.6 months (95% CI 13.1 to 17.2, 207 events), overweight: 20.9 months (95% CI 17.3 to 28.7, 116 events), obese: 16.8 months (95% CI 12.5 to 23.2, 64 events). (B) Progression-free survival: underweight: 6.9 months (95% CI 4.0 to 14.2, 30 events), normal weight: 6.6 months (95% CI 5.8 to 7.3, 283 events), overweight: 8.4 months (95% CI 7.2 to 9.7, 182 events), obese: 7.2 months (95% CI 6.0 to 8.6, 87 events).

**Table 2** Fixed multivariable analysis for risk of disease progression (PFS) and death (OS)

Variable (comparator)	PFS	OS
	aHR (95% CI), P value	aHR (95% CI), P value
Body mass index WHO categories		
Underweight	0.90 (0.61 to 1.33), 0.6261	0.87 (0.54 to 1.40), 0.5844
(Normal weight)	1	1
Overweight	0.83 (0.68 to 1.01), 0.0676	0.79 (0.62 to 1.01), 0.0587
Obese	1.04 (0.81 to 1.33), 0.7214	0.99 (0.74 to 1.32), 0.9601
PD-L1 TPS		
(<1%)	1	1
1%–49%	0.92 (0.77 to 1.12), 0.4424	1.04 (0.83 to 1.30), 0.7288
≥50%	0.63 (0.48 to 0.82), 0.0008	0.73 (0.53 to 1.01), 0.0547
Not available	0.65 (0.43 to 0.96), 0.0317	0.81 (0.52 to 1.29), 0.3658
Histology		
(Adenocarcinoma)	1	1
Squamous cell carcinoma	1.32 (1.03 to 1.70), 0.0246	1.39 (1.05 to 1.86), 0.0231
Carcinoma NOS/others	1.44 (1.05 to 1.97), 0.0207	1.43 (0.99 to 2.07), 0.0566
ECOG-PS		
≥2 vs 0–1	1.36 (1.12 to 1.64), 0.0013	1.93 (1.55 to 2.41), <0.0001
Sex		
Male versus female	1.12 (0.95 to 1.34), 0.1656	1.10 (0.89 to 1.36), 0.3462
Age		
≥70 vs <70 years old	1.20 (1.01 to 1.45), 0.0484	1.27 (1.01 to 1.58), 0.0337
Smoking status		
(Never smoker)	1	1
Former smoker	0.89 (0.68 to 1.17), 0.4363	1.18 (0.84 to 1.65), 0.3386
Current smoker	0.82 (0.59 to 1.14), 0.2508	1.26 (0.84 to 1.89), 0.2565
CNS metastases		
Yes versus no	1.31 (1.07 to 1.60), 0.0082	1.25 (0.98 to 1.59), 0.0612
Bone metastases		
Yes versus no	1.23 (1.03 to 1.46), 0.0198	1.26 (1.02 to 1.54), 0.0272
Liver metastases		
Yes versus no	1.49 (1.18 to 1.88), 0.0006	1.59 (1.21 to 2.09), 0.0008

838 patients included due to missing values.

aHR, adjusted HR; CNS, central nervous system; ECOG-PS, Eastern Cooperative Oncology Group—Performance Status; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival.

of patients with stage IV NSCLC treated with first-line chemoimmunotherapy combinations.

In total, 15 institutions across seven countries participated in the study (online supplemental table 1) and retrospectively included patients treated from December 2014 to August 2021, with data cut-off in November 2021.

Patients with oncogene-addicted disease previously treated with targeted agents only were considered eligible. Clinical endpoints included overall survival (OS) and progression-free survival (PFS). Tumor imaging was assessed at baseline and during treatment at participating institutions, with a frequency of 8–12 weeks according to local practice. Investigators from participating centers independently reviewed disease response following Response Evaluation Criteria in Solid Tumors (RECIST)

criteria V.1.1. PFS and OS were measured from treatment initiation to disease progression and/or death. Patients without documented disease progression were censored on the date of last imaging follow-up.

Evaluation of baseline BMI

Patients' BMI was calculated using the formula of weight/height² (kilogram/square meter) and categorized according to the WHO categories: underweight (BMI <18.5), normal weight (18.5 ≤ BMI ≤ 24.9), overweight (25 ≤ BMI ≤ 29.9), and obese (BMI ≥ 30). Weight and height were retrieved from patient medical records at baseline and derived within 30 days of treatment initiation.

First, we evaluated the distribution of patients' characteristics across BMI subgroups, in order to explore

possible associations between baseline BMI and clinicopathological features. Subsequently, we assessed the impact of baseline BMI on outcome using univariable analysis. Considering the results of the univariable analysis, we then used fixed multivariable regression models to further validate our findings. Covariates were chosen on a clinical prioritization basis, in view of their known prognostic role, including PD-L1 tumor expression ($\geq 50\%$ vs 1%–49% vs negative vs not available), primary tumor histology (adenocarcinoma vs squamous cell carcinoma vs carcinoma not otherwise specified-/others), Eastern Cooperative Oncology Group—Performance Status (ECOG-PS, 0–1 vs ≥ 2), sex (male vs female), age (< 70 vs ≥ 70 years old), smoking status (current smokers vs former smokers vs never smokers), presence of central nervous system (CNS) metastases (yes vs no), bone metastases (yes vs no), and liver metastases (yes vs no).

Considering the incremental benefit reported with ICIs for obese patients over normal-weight patients in PD-L1 selected populations,^{5,6} we added two exploratory analyses including patients with PD-L1 negative and positive tumors, and with PD-L1 high ($\geq 50\%$) and low (1%–49%) tumor expression, respectively. An additional ancillary analysis including only patients with an ECOG-PS of 0–1 was also performed. In all the regression analyses, normal-weight patients were considered as the comparator group.

Statistical analysis

Baseline patients' characteristics were reported with descriptive statistics as appropriate. The χ^2 test was used to compare categorical variables. PFS/OS were evaluated and compared using the Kaplan-Meier method, the log-rank test, and the log-rank test for trend. Duration of follow-up was calculated according to the reverse Kaplan-Meier method. Cox proportional hazards regression was used for the multivariable analysis of PFS and OS and to compute the HRs with 95% CIs. Missing values for clinicopathological characteristics included in the regression analyses were excluded from the descriptive analysis and the multivariable models. All p values were two-sided and CIs set at the 95% level, with significance predefined to be at < 0.05 . All statistical analyses were performed using the MedCalc Statistical Software V.20 (MedCalc Software, Ostend, Belgium; <https://www.medcalc.org>; 2021).

RESULTS

After the exclusion of 26 patients due to missing BMI data, 853 patients were included in the present analysis. Characteristics of the study population stratified by WHO BMI subgrouping are summarized in [table 1](#).

In total, 45 patients (5.3%) were underweight; 396 (46.4%) were normal weight; 288 (33.8%) were overweight; and 124 (14.5%) were obese. A total of 211 patients had a baseline ECOG-PS of ≥ 2 (25.0%). PD-L1 tumor expression was evaluable in 804 patients (94.2%), showing a Tumor Proportion Score of $\geq 50\%$ in 140 (16.4%), 1%–49% in

281 (32.9%), and $< 1\%$ in 383 (44.9%) patients, respectively. Most of the patients were epidermal growth factor receptor (762, 89.2%), anaplastic lymphoma kinase (777, 91.1%), and ROS proto-oncogene 1 (687, 80.5%) wild type. Other molecular findings relevant for ICI outcomes were also reported (when available).

Several baseline clinicopathological features were significantly different across BMI categories. Overweight and obese patients were more likely aged ≥ 70 years ($p=0.00085$) and never smokers ($p<0.0001$), with better baseline ECOG-PS ($p=0.0127$) and lower prevalence of liver metastases ($p=0.0395$). Prevalence of baseline CNS metastases was also different across BMI categories ($p=0.0002$), with the lowest prevalence reported for the overweight subgroup (17.8%), as well as the distribution of the Kirsten rat sarcoma virus (KRAS) mutational status ($p=0.0011$), with the highest prevalence of mutant patients within the obese subgroup (41.9%).

With a median follow-up of 17.5 months (95% CI 15.9 to 18.7), the median PFS and OS of the entire cohort were 7.2 months (95% CI 6.7 to 7.8, 582 events) and 16.8 months (95% CI 15.2 to 19.3, 407 events), respectively.

The median OS across underweight, normal weight, overweight, and obese patients were 15.5 months (95% CI 8.8 to 15.5, 20 events), 14.6 months (95% CI 13.1 to 17.2, 207 events), 20.9 months (95% CI 17.3 to 28.7, 116 events), and 16.8 months (95% CI 12.5 to 23.2, 64 events), respectively (log rank: $p=0.045$, log-rank test for trend: $p=0.131$; [figure 1A](#)), while the median PFS across underweight, normal weight, overweight and obese patients were 6.9 months (95% CI 4.0 to 14.2, 30 events), 6.6 months (95% CI 5.8 to 7.3, 283 events), 8.4 months (95% CI 7.2 to 9.7, 182 events), and 7.2 months (95% CI 6.0 to 8.6, 87 events), respectively (log rank: $p=0.123$, log rank test for trend: $p=0.510$; [figure 1B](#)).

[Table 2](#) reports the multivariable analyses for PFS and OS. No association was confirmed between baseline BMI and clinical outcomes. PD-L1 tumor expression, ECOG-PS, primary tumor histology, age, CNS, and bone and liver metastases were confirmed significant determinants of PFS, while ECOG-PS, primary tumor histology, age, bone and liver metastases were confirmed significant determinants for OS.

Online supplemental figure 1 and online supplemental figure 2 summarize the exploratory analyses including patients with PD-L1 negative and positive tumors, and with PD-L1 of $\geq 50\%$ and 1%–49% tumor expression, according to which baseline BMI was not associated with clinical outcomes in any of the PD-L1 expression subgroups.

The ancillary analysis including only patients with a good PS (ECOG-PS 0–1) is summarized in online supplemental figure 3; no association between baseline BMI and OS/PFS was confirmed.

DISCUSSION

In this study, we did not find any significant association between baseline BMI and clinical outcomes in patients

with NSCLC treated with first-line chemoimmunotherapy combinations, regardless of PD-L1 tumor expression.

The addition of chemotherapy to ICI is known to enhance tumor antigenicity and can improve treatment efficacy. This changing algorithm has led to the shifting of some of the associative paradigms we observed with chemotherapy-free, ICI-based regimens. For instance, our group recently showed that a previous antibiotic therapy does not impair treatment outcomes in patients with NSCLC treated with chemoimmunotherapy combinations, as reported with single-agent ICI instead.^{9,10} The absence of a BMI-dependent effect on clinical outcome mirrors these findings and highlights how the host determinants of benefit from ICI might have different roles depending on the specific treatment modality. In the context of single-agent ICI regimens, obesity has been interpreted as a driver of reduced responsiveness of peripheral T cells, due to the a dysfunctional PD-1/PD-L1-driven immune exhaustion, which could explain the magnified effect of PD-1/PD-L1 inhibitors in restoring T-cell activity in obese individuals.³ The addition of the chemotherapy backbone could potentially mitigate this mechanism through the enhanced immunogenicity, which minimizes in turn the role of BMI and obesity.

Improved outcome has been documented for ever-smokers in the context of single-agent ICI.¹¹ Interestingly, in our population, overweight and obese patients were more likely never smokers. This could be partially linked to the alleged historical association between the smoking behavior and body weight/fat distribution.^{12,13} However, in our population and in chemoimmunotherapy trials as well, the role of the smoking status as a strong driver of improved outcomes with chemotherapy-free ICI regimens has also been dimensioned.¹⁴

Evidence for a positive prognostic role for a high baseline BMI was already described in patients with NSCLC treated with first-line chemotherapy during the 'pre-ICI era'.¹⁵ Several evidence highlights that a systemic inflammatory overactivation plays a central role as cancer cachexia mechanism,¹⁶ and in an aggressive disease such as metastatic lung cancer, baseline nutrition, weight loss, and performance status were historically considered closely intertwined.¹⁷ From this perspective, the 30-day time window for baseline BMI data collection could even be considered as a partial limitation to our study.

In previous reports including single-agent ICI recipients, a linear trend between increasing BMI and incremental benefit was reported, with obese patients experiencing the best outcome^{5,6}; in this cohort, overweight patients are those who achieved the longest survival in absolute terms. Importantly, we also found an association between increasing BMI and better ECOG-PS/lower burden of disease, which are major drivers of better outcome with ICIs,¹⁸ with the lowest prevalence of patients with poor performance status for the overweight group.

Despite acknowledging several limitations, mainly coming from the retrospective design, the lack of matched control cohorts receiving first-line single-agent

immunotherapy and chemotherapy, the lack of centralized data/imaging review, and incomplete molecular profile for all the patients, our study provides a powered analysis and reliable evidence about the absence of a significant role for the baseline BMI in this setting. As additional limitation, the lack of comorbidity data, especially those closely linked to dysmetabolism, such as cardiopulmonary diseases, hypertension, diabetes mellitus, and dyslipidemia, also needs to be mentioned.

Our findings suggest that, in contrast to what has been reported in the context of single-agent ICI, baseline BMI should not be taken into consideration when counseling patients with NSCLC for a first-line chemoimmunotherapy.

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