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Influence of body mass index on outcome in advanced colorectal cancer patients receiving chemotherapy with or without targeted therapy

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ABSTRACT

Purpose: Obesity is associated with an increased risk of development and recurrence of colorectal cancer. However, the role of obesity in advanced colorectal cancer (ACC) patients is unknown. We investigated the effect of body mass index (BMI) on overall survival (OS) in ACC patients receiving systemic treatment in two large phase III studies (CAIRO and CAIRO2).

Patients and methods: Treatment data were obtained and analysed from 796 ACC patients who were treated with chemotherapy in the CAIRO study, and from 730 ACC patients who were treated with chemotherapy plus targeted therapy in the CAIRO2 study. Baseline height and weight were used to assign patients to one of the following BMI categories: A (<18.5 kg/m^2), B (18.5–24.9 kg/m^2), C (25.0–29.9 kg/m^2) and D (⩾30.0 kg/m^2).

Results: In 796 patients of the CAIRO study a high BMI was associated with better median OS (8.0, 14.9, 18.4 and 19.5 months for BMI categories A, B, C, and D, respectively; $P = 0.001$), and was an independent prognostic factor for OS in a multivariate analysis. BMI was not associated with OS in 730 patients who participated in the CAIRO2 study, although a trend was observed.

Conclusions: These results show that BMI is an independent prognostic factor for survival in patients receiving chemotherapy, but not in patients receiving chemotherapy and targeted therapy. The possible decreased efficacy of bevacizumab in obese patients may explain this discrepant result. The role of BMI in patients receiving targeted therapy should be further tested.

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1. Introduction

Obesity is associated with serious comorbidities, and its prevalence is increasing worldwide.[1] Increased body mass index (BMI) is a risk factor for the development of several types of cancer, including colorectal cancer.[2,3] Furthermore, several studies have shown an association between obesity and colon cancer recurrence and/or colon cancer specific mortality.[4–7] However, results are ambiguous and may differ per class of obesity and gender. For example, in a study among patients receiving adjuvant chemotherapy for colon cancer, very obese patients (BMI > 35 kg/m^2) had a statistically significant increase of 27% in cancer recurrence or death due to colon cancer compared to normal weight patients.[5] Also in patients with stage II or III rectal cancer, obese men were more likely to have local recurrence.[8] However, Meyerhart et al. found that in patients with stage III colon cancer, BMI was not associated with an increased risk of cancer recurrence and death.[9]

The mechanisms by which obesity induces or promotes tumourigenesis vary by cancer site and may include insulin resistance, bioavailability of endogenous sex steroids, and localised inflammation.[10] In obese patients receiving chemotherapy pathophysiological modifications may affect parameters, such as volume distribution and drug clearance.[11] Whether these mechanisms also influence survival in the advanced tumour stage is unknown. The role of obesity in patients with advanced colorectal cancer (ACC) has not been established. Therefore, we examined the influence of BMI on outcome in ACC patients participating in two large randomised phase III studies.

2. Patients and methods

2.1. Study population

For this analysis prospectively collected data were obtained from ACC patients participating in the CAIRO and CAIRO2 study. Both studies were performed by the Dutch Colorectal Cancer Group (DCCG). The CAIRO study is a randomised phase III study with 820 patients in which the sequential versus the combined use of capecitabine, irinotecan and oxaliplatin was investigated (ClinicalTrials.gov NCT00312000).[12,13] Patients were randomised to receive either first-line treatment with capecitabine, second-line irinotecan and third-line capecitabine plus oxaliplatin (sequential treatment) or first-line treatment capecitabine plus irinotecan and second-line capecitabine plus oxaliplatin (combination treatment). In the CAIRO2 study 755 patients were randomly assigned between first line treatment with capecitabine, oxaliplatin and bevacizumab with (arm B) or without (arm A) cetuximab (ClinicalTrials.gov NCT00208546).[14,15] In both studies, assessment of tumour response was scheduled every 3 cycles (9 weeks) according to Response Evaluation Criteria in Solid Tumours (RECIST).[16] Details of eligibility criteria and results have been reported elsewhere.[12,14]

2.2. BMI

Patient's length and body weight were measured by the local investigator at baseline. BMI was calculated as weight (in kilograms) divided by height squared (in meters). Patients were assigned to one of the following BMI categories: A (<18.5 kg/m^2, underweight), B (18.5–24.9 kg/m^2, normal weight), C (25–29.9 kg/m^2, overweight) and D ($\geqslant$30 kg/m^2, obese), according to international guidelines.[17] For each of the different BMI groups the incidence of grades 3–4 toxicities according to the National Cancer Institute Common Toxicity Criteria version 2.0 (CAIRO) and version 3.0 (CAIRO2) and progression-free survival (PFS) in first line treatment, and overall survival (OS) were analysed. PFS was defined as the interval from randomisation to first documented progression, death or last follow-up, whichever came first. Overall survival (OS) was defined as the interval from randomisation to death or last follow-up. To assess the influence of dose capping in obese patients, patients with a body surface area (BSA) of $\geqslant$2.10 m^2 who were dosed according to their actual body weight and height and patients who were given a maximum dose (a capping dose of chemotherapy based on a BSA of 2.00 m^2) were analysed separately for toxicity.

2.3. Statistical evaluation

Differences between patient characteristics among the four BMI categories were calculated using χ^2 test for categorical variables and the Kruskal–Wallis test for numerical variables. We also used χ^2 and Kruskal–Wallis test to analyse differences in toxicity and median number of cycles, respectively. OS and PFS curves were estimated using the Kaplan–Meier method and compared with the log-rank test. In order to determine whether BMI was an independent prognostic factor and to adjust for the impact of potential confounders, a Cox proportional hazard model was used including treatment arm, gender, WHO performance status, serum LDH level, leucocytes, and number of metastatic sites. Survivors were censored at the date of last follow up. SAS version 8.2 was used for statistical analysis. All tests were two-sided, and P values of less than 0.05 were considered as statistically significant.

3. Results

3.1. BMI baseline characteristics

The distribution over the four different BMI categories was comparable between the two study populations and was representative for the general Dutch population.[18] The study population of the CAIRO2 study was comparable to the CAIRO study population, except for age and performance status, since patients with a performance status of 2 were excluded in the CAIRO2 study.

Seven out of the 803 eligible patients in the CAIRO study were excluded because they never started with first line treatment. Of the 796 patients who were eligible for analysis, 14 (2%) patients were assigned to BMI category A, 380 (48%) to category B, 306 (38%) to category C and 96 (12%) to category D. Overweight patients were slightly older compared to the normal weight patients ($P = 0.006$). Baseline characteristics of the patients were comparable between the different BMI groups for gender, performance status (0–1 versus 2), LDH at randomisation (normal versus abnormal), leucocytes (<10 ver-

sus $\geqslant 10 \times 10^9$/l), prior adjuvant chemotherapy (yes versus no) and number of metastatic sites (Table 1).

In the CAIRO2 study, 730 out of the 736 eligible patients were included in this analysis; 6 patients were excluded because they never started with first line treatment and/or no data on baseline height and weight were available. Twelve (2%) patients were underweight, 359 (49%) had a normal weight, 274 (37%) were overweight and 85 (12%) patients were obese. Patient characteristics of the CAIRO2 study population are shown in Table 2. Although the numbers in category A and D are low, patients with low BMI were of younger age, more likely to be female, and more often had a worse performance status. Patients with high BMI more often had received adjuvant chemotherapy. Other baseline characteristics were well balanced between the different BMI categories.

3.2. BMI and outcome in CAIRO study

An increasing BMI was significantly associated with a better median OS (8.0, 14.9, 18.4 and 19.5 months for BMI category A, B, C and D, respectively; $P = 0.001$) (Table 3, Fig. 1). At the time of analysis, 719 of the 796 eligible patients had died, 367 in the sequential arm and 352 in the combination arm, the remainder was censored at the last date of follow-up. There was no difference in PFS between four BMI categories (4.4, 6.2, 7.2 and 7.0 months for category A, B, C, and D, respectively; $P = 0.153$). The median number of treatment cycles increased with increasing BMI, although this was not significantly different ($P = 0.392$). The percentage of patients that received all three cytotoxic drugs, second line treatment, and third line treatment was comparable between the four different groups. The incidence of first line grade 3–4 toxicity did not differ between the four BMI categories ($P = 0.363$). Furthermore, patients who received a capping dose experienced an equivalent amount of grades 3–4 toxicity compared to patients who did not receive a capping dose (sequential arm 25% versus 30%, $P = 0.708$; combination arm 60% versus 66%, $P = 0.793$).

A multivariate analysis including treatment arm, gender, serum LDH, leucocytes, number of metastatic sites, and performance status showed that BMI was an independent prognostic factor for OS with a hazard ratio (HR) for death of 1.644 (95% CI 0.893–3.025; $P = 0.110$), 0.807 (95% CI 0.675–0.963; $P = 0.018$) and 0.728 (95% CI 0.551–0.961; $P = 0.025$) for BMI category A, C and D, respectively, compared to category B (Table 5) HR for death was 0.42 (95% CI 0.24–0.75; $P = 0.002$) for obese patients compared to underweight patients in a test across categories.

3.3. BMI and outcome in CAIRO2 study

In the CAIRO2 study population, a total of 518 patients had died, 249 in arm A and 269 in arm B. The remainder was

Table 1 – Patient characteristics according to BMI in the CAIRO study cohort.

Characteristic	BMI category					
	A (<18.5) $n = 14$ (2%)	B (18.5–24.9) $n = 380$ (48%)	C (25.0–29.9) $n = 306$ (38%)	D ($\geqslant$30.0) $n = 96$ (12%)	Total $n = 796$	P value
Age						<0.006
Median (years)	61	62	65	63	63	
(Range)	(40–83)	(27–84)	(31–82)	(34–78)	(27–84)	
Sex						0.102
Male	6 (43%)	229 (60%)	206 (67%)	62 (65%)	503 (63%)	
Female	8 (57%)	151 (40%)	100 (33%)	34 (35%)	293 (37%)	
Treatment						0.517
Sequential	9 (64%)	195 (51%)	149 (49%)	44 (46%)	397 (50%)	
Combination	5 (36%)	185 (49%)	157 (51%)	52 (54%)	399 (50%)	
Performance status						0.337
0	6 (46%)	214 (56%)	205 (67%)	69 (73%)	494 (62%)	
1	6 (46%)	148 (39%)	90 (29%)	24 (26%)	268 (34%)	
2	1 (8%)	19 (5%)	12 (4%)	1 (1%)	33 (4%)	
LDH						0.415
Normal	7 (50%)	239 (63%)	198 (65%)	67 (70%)	511 (64%)	
Abnormal	7 (50%)	141 (37%)	108 (35%)	29 (30%)	285 (36%)	
Prior adjuvant chemotherapy						0.052
Yes	0	49 (13%)	41 (13%)	21 (22%)	111 (14%)	
No	14 (100%)	331 (87%)	265 (87%)	75 (78%)	685 (86%)	
Number of metastatic sites						0.833
1–2	6 (43%)	173 (46%)	129 (42%)	43 (45%)	351 (44%)	
>2	7 (50%)	204 (54%)	174 (57%)	50 (52%)	435 (55%)	
Unknown	1 (7%)	3 (<1%)	3 (<1%)	3 (3%)	9 (1%)	
Leucocytes						0.580
<10 (10^9/l)	10 (71%)	237 (62%)	184 (60%)	54 (56%)	485 (61%)	
$\geqslant$10 (10^9/l)	1 (7%)	85 (22%)	64 (21%)	16 (17%)	166 (21%)	
Unknown	3 (21%)	58 (15%)	58 (19%)	26 (27%)	45 (7%)	

Table 2 – Patient characteristics according to BMI in the CAIRO2 study cohort.

Characteristic	BMI category					
	A (<18.5) *n* = 12 (2%)	B (18.5–24.9)II *n* = 359 (49%)	C (25.0–29.9) *n* = 274 (37%)	D (⩾30.0) *n* = 85 (12%)	Total *n* = 730	*P* value
Age						0.016
Median (years)	57	61	63	66	62	
(Range)	(47–78)	(31–83)	(33–78)	(34–78)	(31–83)	
Sex						<0.001
Male	2 (17%)	198 (55%)	187 (68%)	48 (56%)	435 (60%)	
Female	10 (83%)	161 (45%)	87 (32%)	37 (44%)	295 (40%)	
Treatment						0.997
Arm A	6 (50%)	181 (50%)	136 (50%)	42 (49%)	365 (50%)	
Arm B	6 (50%)	178 (50%)	138 (50%)	43 (51%)	365 (50%)	
Performance status						0.003
0	4 (33%)	211 (59%)	192 (70%)	50 (59%)	457 (63%)	
1	8 (67%)	148 (41%)	82 (30%)	35(41%)	272 (37%)	
LDH						0.060
Normal	6 (50%)	184 (51%)	168 (62%)	46 (55%)	404 (56%)	
Abnormal	6 (50%)	175 (49%)	103 (38%)	38(45%)	322(44%)	
Prior adjuvant chemotherapy						0.010
Yes	2(17%)	37 (10%)	44 (16%)	20 (24%)	103 (14%)	
No	10 (83%)	322 (90%)	230 (84%)	65 (76%)	627 (80%)	
Number of metastatic sites						0.926
1	4 (33%)	127 (35%)	90 (33%)	30 (34%)	251 (34%)	
>1	8 (67%)	232 (65%)	184 (67%)	55 (65%)	477 (66%)	
Leucocytes						0.116
<10 (10^9/l)	6 (50%)	263 (73%)	212 (77%)	64 (75%)	545 (75%)	
⩾10 (10^9/l)	6 (50%)	95 (26%)	60 (22%)	19 (25%)	180 (25%)	
Unknown	0	1 (<1%)	2 (<1%)	0	5 (<1%)	

Table 3 – Efficacy and toxicity results according to BMI in the CAIRO study cohort.

Outcome	BMI category				
	A (<18.5) (*n* = 14)	B (18.5–24.9) (*n* = 380)	C (25.0–29.9) (*n* = 306)	D (⩾30.0) (*n* = 96)	*P* value
No. of treatment cycles					
Median	9	9	11	12	0.392
Range	0–27	0–55	0–48	1–66	
Patients that received all drugs					
No.	7	16,9	14,1	49	0.648
Percentage	50%	44%	46%	51%	
Patients that received subsequent treatment					
Second line	9 (64%)	210 (55%)	183 (60%)	61 (64%)	0.256
Third line	3 (21%)	66 (17%)	64 (21%)	17 (18%)	0.678
Overall survival (months)					
Median	8.0	14.9	18.4	19.5	0.001
95% CI	5.7–21.0	13.4–16.2	16.3–20.4	17.3–24.6	
Progression-free survival after first treatment line (months)					
Median	4.4	6.2	7.2	7.0	0.153
95% CI	2.5–8.7	5.9–6.5	6.7–8.2	5.5–8.3	
Any grade 3 or 4 toxicity					
Event	4	19,8	16,2	50	0.363
Percentage	29%	52%	53%	52%	

censored at the last date of follow-up. BMI was not associated with median OS, although a trend for better OS was observed in higher BMI categories (16.6, 17.8, 21.0, and 21.4 months for BMI category A, B, C, and D, respectively; $P = 0.807$) (Table 4,

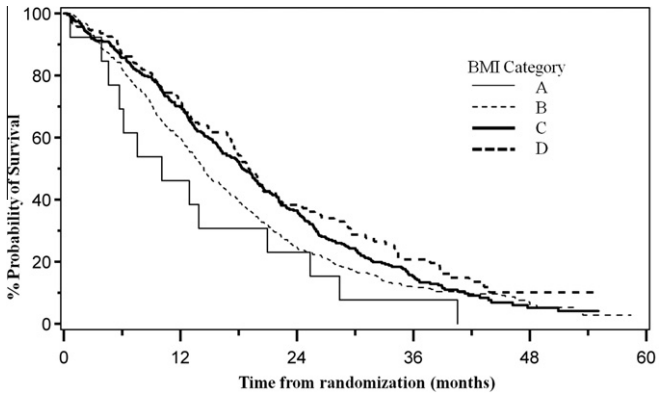

Fig. 1 – Kaplan–Meier estimates of overall survival rates by BMI category in the CAIRO study cohort. BMI category: A <18.5 kg/m^2, B 18.5–24.9 kg/m^2, C 25–29.9 kg/m^2, D ⩾30 kg/m^2.

Table 4 – Efficacy and toxicity results according to BMI in the CAIRO2 study cohort.

Outcome	BMI category				
	A (<18.5) (*n* = 12)	B (18.5–24.9) (*n* = 359)	C (25.0–29.9) (*n* = 274)	D (⩾30.0) (*n* = 85)	*P* value
No. of treatment cycles					
Median	9.5	9.0	9.5	10.0	0.417
Range	1–20	1–56	1–58	1–60	
Patients that received subsequent treatment					
Second line	8 (67%)	146 (41%)	137 (50%)	46 (54%)	0.017
Overall survival (months)					
Median	16.6	17.8	21.0	21.4	0.807
95% CI	(14.1–24.7)	(16.2–20.2)	(18.8–22.2)	(15.1–25.4)	
Progression-free survival (months)					
Median	10.1	9.7	9.7	9.5	0.528
95% CI	7.8–11.4	8.7–10.7	8.7–10.8	7.5–12.2	
Any grade 3 or 4 toxicity					
Event	10	28.8	21.6	66	0.924
Percentage	83%	80%	79%	78%	

Fig. 2). The median PFS, median number of cycles and incidence of grades 3–4 toxicity were comparable among the four BMI categories. Normal weight patients less often received second line treatment compared with the other BMI categories. In a multivariate analysis including treatment arm, gender, serum LDH, leucocytes, number of metastatic sites and performance status, BMI was not associated with OS. HR for death was 1.092 (95% CI 0.575–2.073; *P* = 0.788), 0.996 (95% CI 0.819–1.211; *P* = 0.965) and 0.992 (95% CI 0.740–1.331; *P* = 0.959) for BMI category A, C and D, respectively, compared to category B (Table 6).

4. Discussion

We observed that BMI was an independent prognostic factor for OS in the study cohort of ACC patients treated with chemotherapy. However, this finding was not confirmed in a second cohort of ACC patients treated with chemotherapy plus targeted therapy with comparable baseline characteristics who participated in a subsequent study.

In obese patients, hyperinsulinemia may increase the risk of colorectal cancer by increased levels of unbound insulin-like growth factor 1, which increases proliferation and metastasis of cancer cells.[19,20] Furthermore, adipose tissue-derived hormones may play a role in tumourgenesis.[10]

Though obesity has also shown to contribute to cancer-related mortality,[7] a high BMI has been associated with a favourable prognosis in various tumour types, including cervical cancer,[21] head and neck cancer, oesophageal cancer[22] and clear cell renal cell carcinoma.[23] However, these studies concerned all tumour stages, and BMI was associated with cofactors, such as age and tumour grading. It is assumed that underweight cancer patients have a worse survival because cachexia may be a reflection of advanced stage and an aggressive type of tumour. However, in the CAIRO study, not only a decreased OS was found in underweight patients compared to normal weight patients, but also a better OS was found in overweight and obese patients. Maybe obese patients have better nutritional resources to withstand the devastating effect of cancer itself. Of note, no difference in known

Table 5 – Multivariate analysis CAIRO study cohort.

	Hazard ratio (95% CI)	P value
Gender		
Male	R	
Female	0.795 (0.669–0.944)	0.009
Treatment		
Sequential	R	
Combination	0.867 (0.747–1.006)	0.061
Performance status		
0–1	R	
2	2.212 (1.530–3.197)	<0.001
LDH		
Normal	R	
Abnormal	1.905 (1.605–2.261)	<0.001
Leucocytes		
10 (10^9/l)	R	
⩾10 (10^9/l)	1.367 (1.127–1.657)	0.002
Number of metastatic sites		
1–2	R	
>2	1.470 (1.244–1.738)	<0.001
BMI		
A	1.644 (0.893–3.025)	0.110
B	R	
C	0.807 (0.675–0.963)	0.018
D	0.728 (0.551–0.961)	0.025

Table 6 – Multivariate analysis CAIRO2 study cohort.

	Hazard ratio (95% CI)	P value
Gender		
Male	R	
Female	1.067 (0.887–1.284)	0.489
Treatment		
Arm A	R	
Arm B	1.137 (0.951–1.358)	0.158
Performance status		
0	R	
1	1.220 (1.010–1.474)	0.039
LDH		
Normal	R	
Abnormal	1.448 (1.203–1.742)	<0.0001
Leucocytes		
10 (10^9/l)	R	
⩾10 (10^9/l)	1.318 (1.068–1.628)	0.010
Number of metastatic sites		
1–2	R	
>2	1.479 (1.201–1.820)	<0.001
BMI		
A	1.092 (0.575–2.073)	0.788
B	R	
C	0.996 (0.819–1.211)	0.965
D	0.992 (0.740–1.331)	0.959

prognostic factors was observed between the different BMI categories.

Several other hypotheses have been presented. In obese patients pathophysiological modifications may affect parameters, such as volume distribution and drug clearance. Therefore the efficacy and toxicity of chemotherapy may be altered in obese patients. For example, the more lipophilic an agent, the more likely the volume of distribution will be affected.[11] Miya et al. reported that BMI was an independent prognostic predictor of peak plasma concentrations of irinotecan.[24] However, in our study the incidence of toxicities was comparable between the obese and normal weight patients, and between the patients who had dose capping and those who were dosed according to their actual body weight. This does not support that a relative overdosing of obese patients of lipid insoluble drugs such as irinotecan might explain the difference in median OS.

BMI was not associated with OS in a multivariate analysis in the study cohort of patients treated with chemotherapy and targeted therapy, although a trend for better OS was observed in higher BMI categories. Patient characteristics were comparable in the two study cohorts. However, in the second cohort, age and performance status were significantly different among the four BMI categories, with patients in the higher BMI categories having a better performance status. The differences in age are of a magnitude that is unlikely to be clinically relevant. Possible potential confounders of both studies have to be taken into account. Data on smoking habits

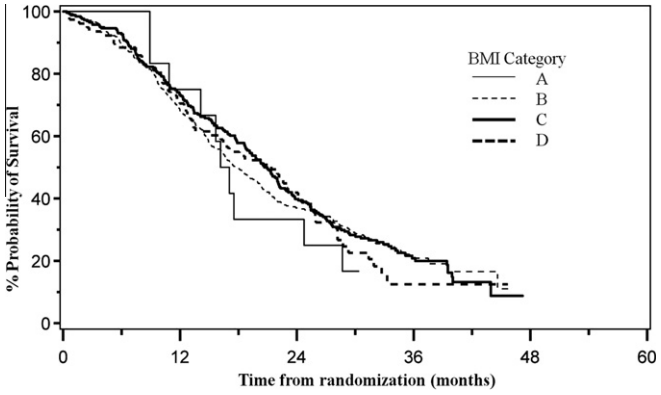

Fig. 2 – Kaplan–Meier estimates of overall survival rates by BMI category in the CAIRO2 study cohort. BMI category: A <18.5 kg/m^2, B 18.5–24.9 kg/m^2, C 25–29.9 kg/m^2, D ⩾30 kg/m^2.

were not collected. The influence of cardiovascular disease as potential confounder is probably limited, since patients with significant cardiovascular disease were excluded in both studies. We did analyse the use of statins in the CAIRO and CAIRO2 study, since statins may have a beneficial effect on colorectal cancer prognosis.[25] In both studies, no difference in statin use was observed among the four BMI categories and in univariate and multivariate analysis the use of statins was not correlated with OS (data not shown).

A major difference between the two study cohorts is that targeted therapy, including bevacizumab, was used in the CAIRO2 study but not in the CAIRO study, due to the fact that bevacizumab was not yet approved for use at that time. Guiu et al. showed that ACC patients with a high BMI who received first line bevacizumab-based therapy had a shorter time to progression compared to normal weight patients. Furthermore, a high visceral fat area was an independent negative predictor for survival. This association of body fatness with outcomes was not observed in patients treated with chemotherapy without bevacizumab. The authors explained these results by a larger volume of distribution of bevacizumab in obese patients or increased levels of vascular endothelial growth factor produced by visceral fat, which may be associated with resistance to bevacizumab.[26] This hypothesis is supported by our results which show a larger survival benefit for the addition of targeted therapy to chemotherapy in patients with BMI categories A and B versus patients with BMI categories C and D. However, this concerns a cross-study comparison (CAIRO versus CAIRO2), and, therefore, this should be interpreted with caution.

In conclusion, we found that BMI is an independent prognostic factor for OS in ACC patients receiving chemotherapy. However, this was not confirmed in a second cohort of ACC patients with comparable patient characteristics receiving chemotherapy plus targeted therapy, although a non-significant trend towards improved OS with higher BMI was observed. These results may be explained by a decreased efficacy of bevacizumab in obese patients. Further studies should confirm this finding.

Conflict of interest statement

None declared.

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