Overweight and Checkpoint Inhibitor for Gynecologic Cancer

Subjects: Oncology

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Checkpoint inhibitors (CPIs) marked a paradigm shift in the therapy of a variety of advanced solid tumors, CPIs were successfully implemented as first-line options for many non-gynecologic malignancies, such as malignant melanoma, non-small cell lung cancer (NSCLC), or renal cell cancer.

immunotherapy immune checkpoint inhibitor biomarker overweight RECIST

1. Introduction

Recent studies previously approached the predictive and prognostic value of pretherapeutic body mass index (BMI) in both metastatic melanoma patients and advanced NSCLC [1][2]. An Italian multicenter trial recently reported a pretherapeutic BMI ≥ 25 kg/m^2 to be independently predictive for CPI therapy response in a cohort of 976 non-gynecologic cancer patients [3].

As CPIs have demonstrated promising results in late line treatment for some gynecologic malignancies, defining cost-effective and readily available biomarkers of therapy response is of utmost clinical interest. As no respective data is available for gynecologic cancer patients to date, the present study aimed to assess the association of a pretherapeutically elevated BMI on both therapy response and survival in a cohort of patients with recurrent gynecologic cancers who received the PD-1 inhibitor pembrolizumab.

2. Predictive Value of a Pretherapeutic BMI for CPI Therapy

Receiver operating characteristics (ROC) demonstrated a classifying ability of pretherapeutic BMI to predict therapy response and disease control with an area under the curve (AUC) of 0.862 and 0.659, respectively (Supplementary Figures S1 and S2).

The BMI per 5 kg/m^2 increase was predictive for overall response in both the univariate (OR 10.93 [CI 2.39–49.82], p = 0.002) and multivariate analyses (OR 64.09 [CI 1.90–2160.48], p = 0.020) (**Table 1**a). Regarding disease control, BMI was also predictive in univariate analysis (OR 2.19 [CI 0.99–4.83], p = 0.048) and multivariate analysis (OR 10.07 [CI 1.33–76.51], p = 0.026) as depicted in **Table 1**b.

Table 1. Univariate and multivariate analysis to assess parameters predictive for overall response (**a**) and disease control (**b**) at the timepoint of pembrolizumab therapy initiation.

a. Parameters	Overall Response after CPI Therapy			
	Univariate Analysis		Multivariable Analysis	
	p-Value	OR (95% CI)	*p*-Value	OR (95% CI)
combined positive score	0.608	0.99 (0.97–1.02)	-	-
body mass index (5 kg/m^2 increment)	0.002	10.93 (2.39–49.82)	0.020	64.09 (1.90–2160.48)
neutrophile-to-lymphocyte ratio	0.572	0.95 (0.81–1.13)	0.681	0.94 (0.68–1.28)
age-adjusted charlson comorbidity index	0.373	1.19 (0.81–1.74)	0.418	0.71 (0.31–1.62)
subcutaneous fat volume (100 mL increment)	0.023	1.20 (1.03–1.41)	0.186	0.712 (0.44–1.17)
visceral fat volume (100 mL increment)	0.108	1.26 (0.95–1.66)	-	-
b. Parameters	**Disease Control after CPI Therapy**			
	Univariate Analysis		Multivariable Analysis	
	p-Value	OR (95% CI)	*p*-Value	OR (95% CI)
combined positive score	0.163	0.98 (0.96–1.01)		
body mass index (5 kg/m^2 increment)	0.048	2.19 (0.99–4.83)	0.026	10.07 (1.33–76.51)
neutrophile-to-lymphocyte ratio	0.144	0.89 (0.76–1.04)	0.199	0.87 (0.51–1.40)
age-adjusted charlson comorbidity index	0.968	0.972 (0.241–3.93)	0.506	0.84 (0.51–1.40)
subcutaneous fat volume (100 mL increment)	0.745	1.02 (0.89–1.17)	0.063	0.720 (0.51–1.02)
visceral fat volume (100 mL increment)	0.474	1.10 (0.84–1.44)	-	-

Therapy response according to iRECIST criteria and broken down by BMI was further depicted by a waterfall plot in **Figure 2**. Patients with a pretherapeutic BMI < 25 kg/m^2 demonstrated a median increase of the target lesion size of 33.8% (1.33 [14.5–62.9]) after four cycles of pembrolizumab as compared to a median decrease of 30.5% (0.70 [0.44–1.21]) in patients with a BMI ≥ 25 kg/m^2.

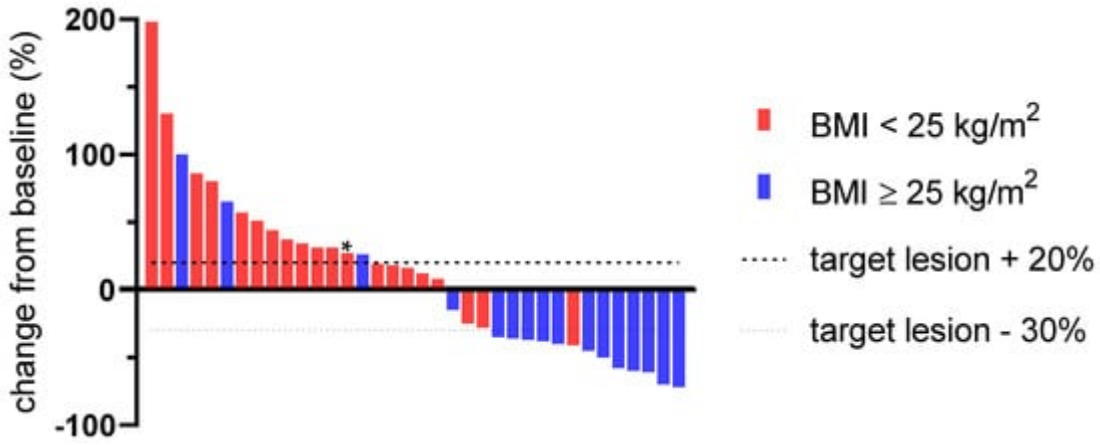

Figure 2. Waterfall plot depicting therapy response assessment after four courses of pembrolizumab according to iRECIST criteria, broken down by pretreatment body mass index. Dashed and dotted lines mark the respective progressive disease and partial response thresholds. The bar marked by an asterisk (*) represents a case which was defined as unconfirmed PD after initial restaging. Progression was not confirmed after eight weeks and was therefore labeled as “stable disease” for further analyses.

3. Prognostic Value of a Pretherapeutic BMI on Patient Survival during CPI Therapy

A pretherapeutic elevated BMI per 5 kg/m^2 increase was prognostic for both PFS (HR 1.54 [CI 1.03–2.34], p = 0.038) and OS (HR 1.87 [CI 1.07–3.29], p = 0.028) in the univariate analyses. Results could be confirmed in the multivariate analyses for PFS (HR 3.73 [CI 1.63–8.50], p = 0.002) (**Table 2**a) and OS (HR 7.44 [1.62–34.16], p = 0.010) (**Table 2**b).

Table 2. Univariate and multivariate Cox-regression analysis of parameters prognostic for PFS (**a**) and OS (**b**) at the timepoint of pembrolizumab therapy initiation.

a. Parameters	PFS after CPI Therapy			
	Univariate Analysis		Multivariable Analysis	
	p-Value	OR (95% CI)	*p*-Value	OR (95% CI)
combined positive score	0.746	1.00 (0.99–1.01)	-	-
body mass index (5 kg/m^2 increment)	0.038	1.54 (1.03–2.34)	0.002	3.73 (1.63–8.50)
neutrophile-to-lymphocyte ratio	0.767	1.01 (0.95–1.08)	0.789	0.99 (0.93–1.06)
age-adjusted charlson comorbidity index	0.675	1.04 (0.85–1.28)	0.419	1.11 (0.87–1.41)
subcutaneous fat volume (100 mL increment)	0.992	1.00 (0.92–1.08)	0.007	1.23 (1.06–1.43)

visceral fat volume (100 mL increment)	0.487	0.95 (0.82–1.10)	-	-

b. Parameters	OS after CPI Therapy			
	Univariate Analysis		Multivariable Analysis	
	p-Value	OR (95% CI)	*p*-Value	OR (95% CI)
combined positive score	0.220	1.01 (0.991.–1.03)	-	-
body mass index (5 kg/m^2 increment)	0.028	1.87 (1.07–3.29)	0.010	7.44 (1.62–34.16)
neutrophile-to-lymphocyte ratio	0.397	1.04 (0.95–1.15)	0.478	1.04 (0.94–1.14)
age-adjusted charlson comorbidity index	0.959	0.99 (0.73–1.36)	0.694	1.07 (0.75–1.53)
subcutaneous fat volume (100 mL increment)	0.620	0.973 (0.873–1.08)	0.035	1.36 (1.02–1.81)
visceral fat volume (100 mL increment)	0.201	0.868 (0.70–1.08)	-	-

Kaplan-Meier curves including confidence intervals graphically depicting the association between a BMI ≥2 5 kg/m^2 and both PFS and OS are given in **Figure 2** and **Figure 3**, respectively. At a six-months follow-up, 68.8% (n = 11/16) of patients with a pretherapeutic BMI ≥ 25 kg/m^2 were still receiving ongoing CPI-treatment as compared to 45.0% (n = 9/20) of patients with a pretherapeutic BMI < 25 kg/m^2. OS remained comparable at a six-months FU with 75.0% (n = 12/16) in the BMI ≥ 25 kg/m^2-cohort as compared to 70.0% (n = 14/20) in the BMI < 25 kg/m^2-cohort but diverge at a 12-months FU with 62.5% (n = 10/16) in the BMI ≥ 25 kg/m^2-cohort as compared to 35.0% (n = 7/20) in the BMI < 25 kg/m^2-cohort.

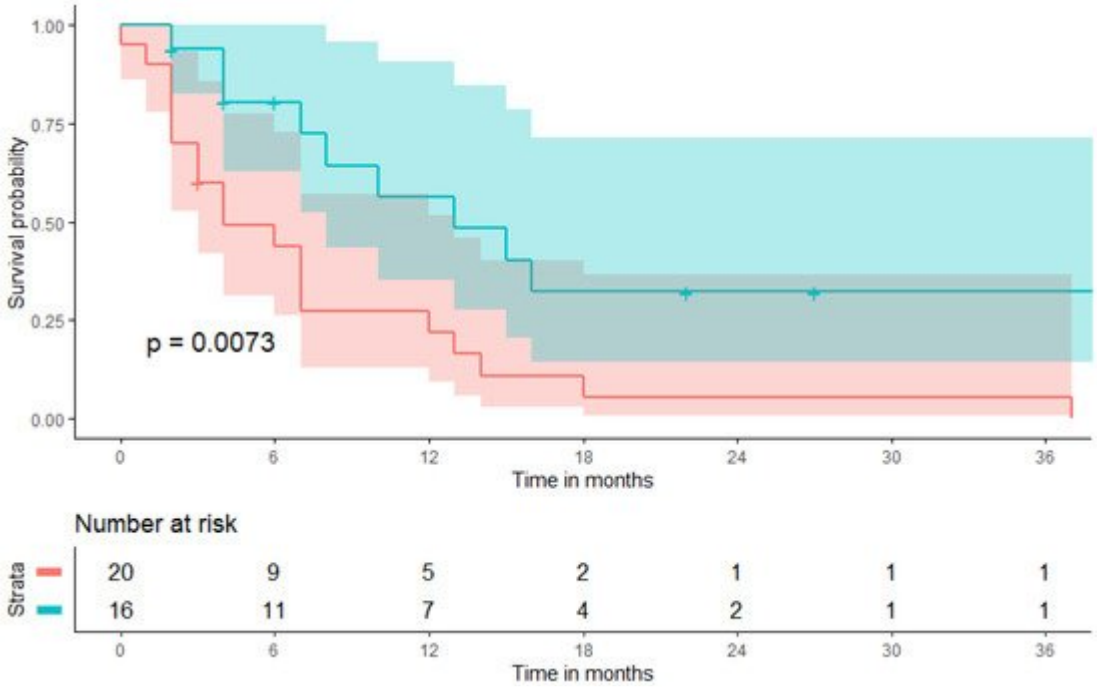

Figure 2. Kaplan-Meier curve depicting progression-free survival (PFS) with confidence interval estimates at the timepoint of pembrolizumab therapy initiation broken down by pretherapeutic body mass index. The blue line

depicts the cohort with a pretherapeutic BMI ≥ 25 kg/m^2, the red line depicts the cohort with a pretherapeutic BMI < 25 kg/m^2.

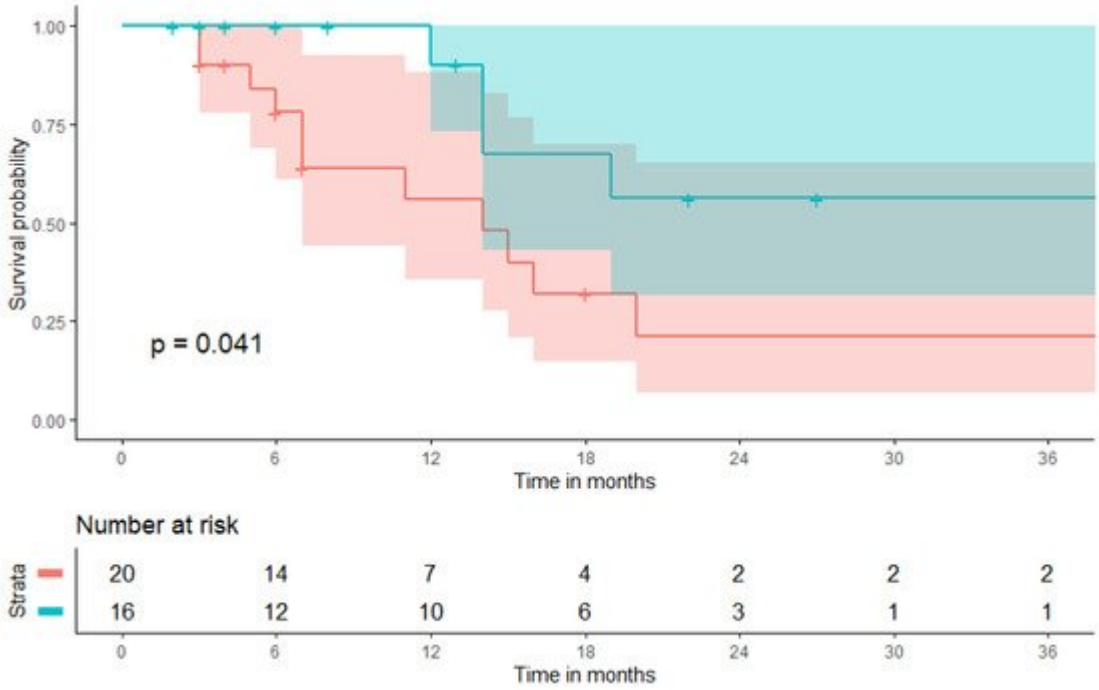

Figure 3. Kaplan-Meier curve depicting overall survival (OS) with confidence interval estimates at the timepoint of pembrolizumab therapy initiation broken down by pretherapeutic body mass index. The blue line depicts the cohort with a pretherapeutic BMI ≥ 25 kg/m^2, the red line depicts the cohort with a pretherapeutic BMI < 25 kg/m^2.

4. Subgroup Analysis Excluding Vaginal Cancer Patients

To account for the slight disbalance in between cohorts regarding vaginal cancer, a subgroup analysis was performed to rule out gross confounding. In the subgroup of all cervical, endometrial, and vulvar cancer patients, excluding vaginal cancer patients (n = 34), associations between a pretherapeutic BMI at a 5 kg/m^2 increment, ORR (OR 10.66 [CI 2.30–49.38] p = 0.002), DCR (OR 2.35 [CI 0.99–5.57], p = 0.048), PFS (HR 1.47 [CI 0.98–2.27], p = 0.036) and OS (HR 1.89 [CI 1.02–3.52], p = 0.044) remained stable in univariate analyses. Results could be reproduced in multivariate analyses for ORR (OR 63.44 [CI 1.86–2167.10], p = 0.021), DCR (OR 12.36 [CI 1.26–121.01], p = 0.031), PFS (HR 4.27 [CI 1.61–11.13], p = 0.004) and OS (HR 4.93 [1.06–1.57], p = 0.042) (Supplementary Tables S2 and S3).

5. Immune-Related Adverse Events (irAEs)

Overall, six cases (16.7%) of irAEs were observed during pembrolizumab therapy. One case of a grade 3 irAE (hepatitis, 2.8%), one case of a grade 2 irAEs (colitis, 2.8%), and four cases of a grade 1 irAEs (thyroiditis, 11.1%) were recorded (Supplementary Table S4). Of note, the grade 1 and 2 irAEs could be managed symptomatically or

respective of temporary discontinuation of therapy, but the grade 3 irAE led to permanent discontinuation of CPI therapy after five cycles despite partial response [4].

6. Discussion

An elevated pretherapeutic BMI appears to be a positive predictive factor for therapy response to pembrolizumab in patients with recurrent, PD-L1-positive gynecologic cancers. In line, an elevated BMI was associated with improved prognosis in the present cohort. Patients who experienced at least disease control demonstrated a particularly prolonged PFS and OS.

Response rates observed appear comparable as previously reported for pembrolizumab monotherapies. The KEYNOTE-158 reported an ORR of 57% (CI 42–71) for recurrent MSI-high endometrial cancer patients (n = 49) as compared to 62.5% [5]. The KEYNOTE-158 also provides the largest sample of PD-L1-positive cervical cancer patients treated with pembrolizumab (n = 82) available to date, describing an ORR of only 14.6% (CI 7.8–24.2) [6]. A retrospective Irish multicenter study, however, demonstrates a remarkably higher ORR of 25%, which appears more in line with present results [7]. More modest response rates of the KEYNOTE-158 may be attributed to a different patient selection, as a disproportionally high number of patients was reported with a FIGO IV stage (93.9% in the KEYNOTE-158 as compared to 19.0% here).

Evidence on vulvar and vaginal cancer remains particularly scarce. The KEYNOTE-028 reports an ORR of only 5.6% for PD-L1-positive vulvar cancer patients, whereas for vaginal cancer only a case series of two patients has been published to date, of which one responded and one progressed during pembrolizumab treatment [8][9].

The entry is the first to evaluate the predictive and prognostic value of pretreatment BMI in a cohort of gynecologic cancer patients. In contrast to the so-called ‘obesity paradox’ in cancer, a controversially discussed observation of seemingly improved survival of obese cancer patients, the observed phenomenon of both higher response rates and improved survival appears to be specific to CPI treatment [10]. Whereas exact molecular pathological mechanisms are yet to be elucidated, preclinical studies led to the explanatory model that adipogenesis and the overexpression of adipocytokine leptin may modulate the antitumor effects of CPIs [11]. Obesity may also foster a pro-inflammatory state within adipose tissues, resulting in both an increase in total lymphocyte count and an evolution of immune-competent cells to a pro-inflammatory phenotype, which may render them more receptive for immunotherapeutic approaches [12].

The association between an elevated BMI and increased response rates to CPI therapy has been broadly validated in the limited spectrum of cancer types, which already experienced broad introduction of CPIs into their treatment algorithms: A recent meta review, which included 13 studies and 5279 cancer patients who have NSCLC, melanoma, or renal cell carcinoma, supports the hypothesis, reporting an elevated BMI to be associated with improved OS and PFS with no significant association to the incidence of irAEs. [13] In a similar vein, a retrospective multicenter study of 976 patients (NSCLC n = 635; melanoma n = 183; renal cell carcinoma n = 135; other n = 23)

reported both improved response rates and survival for patients with a pretreatment BMI ≥ 25 kg/m^2. Patient sex did not significantly influence response rates or survival [3].

As observed, a remarkably strong effect of the pretherapeutic BMI in a small sample of gynecologic cancer patients is in line with recently published sizeable cohorts of other solid tumors. In an era of emerging personalized precision medicine, novel approaches to define reliable biomarkers for therapy response to CPI therapy are urgently needed. The pretherapeutic BMI may thereby represent a promising cost-effective and readily available predictor of respective therapy response and survival, which may find quick adaption in clinical routine after prospective validation.

The first to consider CT-derived quantifications of visceral and subcutaneous abdominal fat volume in comparison to the predictive and prognostic value to a pretherapeutic BMI in gynecologic patients. As the BMI cannot differentiate between different patterns of body fat distribution and thereby identify potential specific fat distribution patterns predictive of CPI therapy response, it was previously hypothesized that CT-derived body fat quantifications might outperform the predictive value of the BMI in this particular question. One study by Young et al. investigating a cohort of 287 metastatic melanoma patients could not observe any predictive value of the BMI and reported only a modest association between very high subcutaneous abdominal fat values and poor survival in female patients. Whereas differing results might be attributed different preconditions in metastatic disease and the different primary, it is to be noted that Young et al. also contradicted a previously published meta-analysis, reporting an improved OS at a BMI ≥ 25 kg/m^2 for almost 1000 melanoma patients included [14]. No respective evidence is available for NSCLC to date [15].

In the present cohort, subcutaneous body fat demonstrated a significant association with the ORR in univariate analysis; multivariable analysis, however, failed to confirm this observation. Moreover, BMI outperformed its predictive value in direct comparison. As the BMI would also be easier to apply in clinical routine as compared to CT-derived variables, it failed to demonstrate any additional diagnostic value of CT-derived quantifications of visceral or subcutaneous abdominal fat. Of note, the present cohort is too small to allow for generalizable assumptions, and further assessments of CT-derived quantifications as a potential biomarker in larger cohorts appear worthwhile.

In summary, BMI appears to be a promising clinical biomarker to predict CPI therapy response and prognosis in patients with PD-L1-positive recurrent gynecologic malignancies. After validation in larger patient cohorts, the BMI may complement established immunohistochemical biomarkers as a readily available and cost-effective stratification factor to improve personalized treatment strategies in the future

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