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Full length article

# Prognostic significance of programmed death-1 (PD-1) and programmed death-ligand 1 (PD-L1) expression in uterine carcinosarcoma

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ABSTRACT

*Objective:* The aim of this study was to evaluate the clinical and prognostic importance of programmed death-1 (PD-1) and/ or programmed death-ligand 1 (PD-L1) in uterine carcinosarcoma (UCS).
*Study Design:* Formalin-fixed, paraffin-embedded tissue samples from 59 cases with UCS were analyzed. PD-1 and PD-L1 expressions in tumor tissue and microenvironment were detected by immunohistochemistry. Clinical and pathological characteristics including age, stage, initial symptom, surgical approach, myometrial invasion, lymphovascular space invasion (LVSI), lymph node invasion, adjuvant therapy, and survival were evaluated. The Kaplan-Meier and Cox proportional hazards models were used to compare the outcomes and prognostic factors.
*Results:* PD-1 expression in tumor tissue and microenvironment was detected in 15 (25 %) and 18 (30 %) cases, respectively. PD-L1 expression in tumor tissue and microenvironment was detected in 15 (25 %) and 12 cases (20 %), respectively. PD-L1 expression in tumor was associated with longer survival and median survival was 38 and 15 months in cases with and without PD-L1 expressions, respectively ($p = 0.019$). Lymphovascular space invasion (LVSI) ($p = 0.014$), myometrial invasion ($p = 0.008$) and PD-L1 expression were found to be prognostic for UCS's. PD-L1 expression was found to be an independent good prognostic factor with Cox regression analysis (OR 3.9; 95 % CI: 1.4–11.0) for overall survival.
*Conclusion:* PD-1 and/or PD-L1 expression are important due to their expressions in one fourth of the cases with UCS and PD-1/PD-L1 blockade may be a new avenue in UCS.
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## Introduction

Carcinosarcoma also known as malignant mixed Mullerian tumors are uncommon and highly aggressive malignancies including both malignant sarcomatous and carcinomatous components. Uterine carcinosarcoma (UCS) are challenging in terms of clinical management. Its prognosis is poor even in the early stage of the disease [1]. UCS coexists with an extrauterine disease in 60 % of cases and its recurrence rate is more than 50 % despite definitive surgery and adjuvant therapy [2–4].

Immune checkpoints play an essential role in providing self-tolerance and regulating the T cell responses. Programmed death-1 (PD-1) acts as an immunosuppressive co-inhibitory molecule. It is an immune checkpoint that is expressed in several malignant tumors and has two cognate ligands as programmed death-ligand 1 (PD-L1) and PD-L2. PD-L1 is excreted in tissues such as tonsils, trophoblasts, lung; PD-L2 expresses predominantly in dendritic cells and they suppress autoimmunity and inflammatory response [5]. PD-1 and PD-L1 are new targets for immunotherapy. The therapeutic effects of PD-1 blocking antibodies have been investigated in some solid tumors and have been approved for malignant melanoma and non-small cell lung cancer by Food and Drug Administration (FDA) in USA [6]. By that time it is highly important to determine the patients whom may get benefit from this treatment modality.

To our knowledge, the present study will be the first one that investigated the PD-1 and PD-L1 expression in UCS. In this study we explored the expression of the PD-1 and PD-L1 in tumor and microenvironment and prognostic importance of these expressions.

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## Material and methods

Formalin-fixed, paraffin-embedded tissue samples from 59 cases with UCS, who were operated and followed in our university clinic between January 1996 and December 2016 were analyzed. The pathologic diagnoses were established based on hysterectomy material evaluated by two gynecological pathologists (E.K.B, D.G.) and the evaluation of the PD-1, PD-L1 staining was performed one pathologist (E.K.B). The study was approved by the local ethic committee of our medical faculty (2015.037.IRB.044). Patients who were operated and followed-up in our clinic were included in this study. Patients who were not histopathologically diagnosed as uterine carcinosarcom, who were not operated in our clinic, and those who received neo-adjuvant therapy prior to primary surgical treatment were not included in the study.

Demographic variables including age (years), parity, menopausal status, main presenting symptoms, and medical history (comorbidity was defined as presence of a second disease or condition such as hypertension, diabetes, bronchial asthma influencing the care or treatment of a patient) as well clinic and pathologic variables including stage, the degree of myometrial invasion, lymph node involvement, lymphovascular space invasion (LVSI), choices of adjuvant therapy, and survival outcomes were evaluated. The staging was performed according to the International Federation of Gynecology and Obstetrics (FIGO) 2009 guidelines [7]. Laparotomic or laparoscopic total hysterectomy and bilateral salpingo-oophorectomy (TH + BSO for all patients) and pelvic/para-aortic lymphadenectomy with or without omentectomy were the main surgical procedures.

Chemotherapy was administered for a systemic control and radiotherapy was used for a locoregional control in high-risk patients. Patients were followed up every 3 months in the first year and then every 6 months up to 5 years. During follow-up, patients underwent gynecological examination, transvaginal sonography, and thoracic and abdominopelvic computed tomography (every 6 months in the first two years and then yearly). Overall survival (OS) was defined as the time (months) between the date of surgery/diagnosis and the date of death or last follow-up.

## Immunohistochemical staining

Immunohistochemical staining was performed on 5-mm sections of formalin-fixed, paraffin-embedded tissue using Monoclonal antibody MRQ-22 (Ventana; Kaysersberg, France) was used to detect PD-1 and CD274/PDL1 AM26531AF-N (Acris; Herford, Germany) was used to detect PD-L1. The visualization system used was the BenchMark XT with enzymatic digestion ISH protease 2 (Ventana; Arizona, USA) and the iView Blue Detection Kit (Ventana; Arizona, USA). Tonsil tissue was used as a positive and negative control. Cytoplasmic and membranous staining for PD-1, and membranous staining for PD-L1 were considered positive. Tumor cells and microenvironments were evaluated separately. Staining in tumor cells and microenvironment were considered as positive when more than 5 % staining. Cases stained with anti-PD-1 and PD-L1 were scored according to intensity as follows: 0 (no staining), 1+ (weak or equivocal staining), 2+ (moderate staining) or 3+ (strong staining). The cut-off value of 5 % was performed based on previous studies [8,9]. Since 2+ and 3+ staining were not observed in our cases, the assessment were performed as positive or negative for the staining.

## Statistical analysis

Data were analyzed using the SPSS software version 20.0 (IBM, Armonk, NY, USA). The variables were tested to determine whether or not they were normally distributed by using visual (histograms, probability plots) and analytical methods (Shapiro-Wilk's test). Continuous variables for the groups were compared using the Student's *t*-test and the Mann-Whitney *U* test according to their distribution and they were expressed as mean ± SD. Chi-square and Ficher's exact tests were used for cross-tables. Expression of PD-1 and PD-L1 and survival times were computed using the Kaplan–Meier method. The Cox proportional hazard model was used to assess the significance of multiple variables. The p value < 0.05 was considered statistically significant. The p-value was presented as a two-tailed test.

## Results

Fifty-nine cases with UCS were evaluated for expression of PD-1 and PDL-1 in tumor and microenvironment. Mean age was 62 ± 10.3. The main presenting symptom was abnormal uterine bleeding (85 %). Demographics and main clinical characteristics were shown in Table 1. Four patients had additional cancer: three of them had breast cancer and they used tamoxifen. Fourth case had colorectal cancer and she has been received radiotherapy. Fifty-nine percent of the patients (n = 35) had an early-stage disease (stage 1–2). The myometrial invasion was higher than 50 % for 20.3 percent of the patients (n = 12). Forty patients had lymphovascular invasion (67.8 %) and 62.8 % of patients had a lymph node involvement. Chemotherapy and radiotherapy as adjuvant treatment were given in 69.0 % and 50.8 % of the cases; respectively while twenty of the cases received both of the adjuvant therapies (Table 2).

PD-1 and PD-L1 were positive in the tumor for a quarter of the patients (Fig. 1). Expression of the PD-1 and PD-L1 in the microenvironment and PD-1 in the tumor were not found to be associated with survival times (p = 0.170, p = 0.488, p = 0.641, respectively). However, PD-L1 expression was found to be associated with better survival (36 months vs 18 months; p = 0.019) (Fig. 2). The results of PD-1 and PD-L1 expression and association with OS have been demonstrated in Table 2.

Age (p = 0.826), menopausal status (p = 0.887), stage (p = 0.304), and lymph node involvement (p = 0.773) were not found as prognostic factors; however, LVSI (p = 0.017), myometrial invasion (p = 0.008) and the expression of the PD-L1 in tumor (p = 0.019) were found to be associated with survival (Table 2). In multivariate analysis, PD-L1 expression in the tumor was found as an independent prognostic factor (Table 3).

## Discussion

PD-L1 is one of the most studied immuno-oncological biomarker to date [2]. Immunotherapy is an important modality in cases with cancer in addition to well-known and conventional treatments including surgery, chemotherapy, and radiotherapy. Although the promising effects of immunotherapy in cases with non-small cell

**Table 1**
Demographics and main clinical characteristics of the studied population.

| | | n | % |
|---|---|---|---|
| Age (years) | <55 | 17 | (28.8) |
| | 55–64 | 18 | (30.5) |
| | >64 | 24 | (40.7) |
| Parity (n = 53) | none | 7 | (13.2) |
| | positive | 46 | (86.8) |
| Menopause | none | 8 | (13.6) |
| | positive | 51 | (86.4) |
| Medical history | Cance | 4 | (6.8) |
| | Comorbidity | 21 | (35.6) |
| Main presenting symptom | Abnormally uterine bleeding | 45 | (76.3) |
| | Bloating | 4 | (6.8) |
| | Pain | 10 | (16.9) |

**Table 2**
Clinicopathologic characteristics, the PD-1 and PD-L1 expressions in the tumor and microenvironment and the association with prognosis.

| | | n (%) | Mean survival time (month ± SD) | p |
|---|---|---|---|---|
| Surgery | Laparotomy | 56 (94.9) | | |
| | Laparoscopy | 3 (5.1) | | |
| LND | Unable to | 16 (27.1) | | |
| | PPALND | 41 (69.5) | | |
| | PLND | 2 (3.4) | | |
| Omentectomy | Performed | 34 (57.6) | | |
| Optimal cytoreduction | No | 5 (8.5) | 12.8 ± 3.4 | 0.839 |
| | Yes | 54 (91.5) | 24.3 ± 2.8 | |
| Secondary cytoreductive surgery | No | 53 (89.8) | 23.6 ± 2.8 | 0.564 |
| | Yes | 6 (10.2) | 28.1 ± 9.0 | |
| Stage | 1 + 2 | 35 (59.3) | 26.1 ± 3.4 | 0.304 |
| | 3 + 4 | 24 (40.7) | 18.1 ± 3.1 | |
| Nodal involvement | Negative | 16 (37.2) | 22.5 ± 3.3 | 0.773 |
| | Positive | 27 (62.8) | 22.8 ± 5.3 | |
| Myometrial invasion | <50% | 47 (79.7) | 31.4 ± 4.3 | 0.008 |
| | ≥50% | 12 (20.3) | 16.1 ± 2.1 | |
| LVSI | Negative | 19 (32.2) | 34.5 ± 4.9 | 0.017 |
| | Positive | 40 (67.8) | 18.9 ± 3.0 | |
| PD-L1 TM expression | Negative | 44 (74.6) | 18.4 ± 2.1 | 0.019 |
| | Positive | 15 (25.4) | 36.1 ± 5.9 | |
| PD-L1 MC expression | Negative | 47 (79.7) | 24.2 ± 3.6 | 0.488 |
| | Positive | 12 (20.3) | 28.9 ± 5.0 | |
| PD-1 TM expression | Negative | 44 (74.6) | 23.7 ± 3.3 | 0.641 |
| | Positive | 15 (25.4) | 26.0 ± 5.4 | |
| PD-1 MC expression | Negative | 41 (69.5) | 27.5 ± 3.6 | 0.170 |
| | Positive | 18 (30.5) | 17.8 ± 3.7 | |
| Radiotherapy | None | 29 (49.2) | | |
| | Received | 30 (50.8) | | |
| Chemotherapy (n = 58) | None | 18 (31.0) | | |
| | Received | 40 (69.0) | | |
| Combination adjuvant therapy | None | 39 (66.1) | | |
| | Received | 20 (33.9) | | |
| Status | Alive | 20 (33.9) | | |
| | Exitus | 39 (66.1) | | |

Programmed Death-1 (PD-1); Programmed Death-Ligand 1 (PD-L1); LND (Lymph node dissection); TM (Tumor); MC(Microenvironment); LVSI (lymphovascular space invasion); PPALND (Pelvic-paraaortic lymph node dissection); PLND (Pelvic lymph node dissection). SD (Standart Deviation); p (p-value by log-rank test).

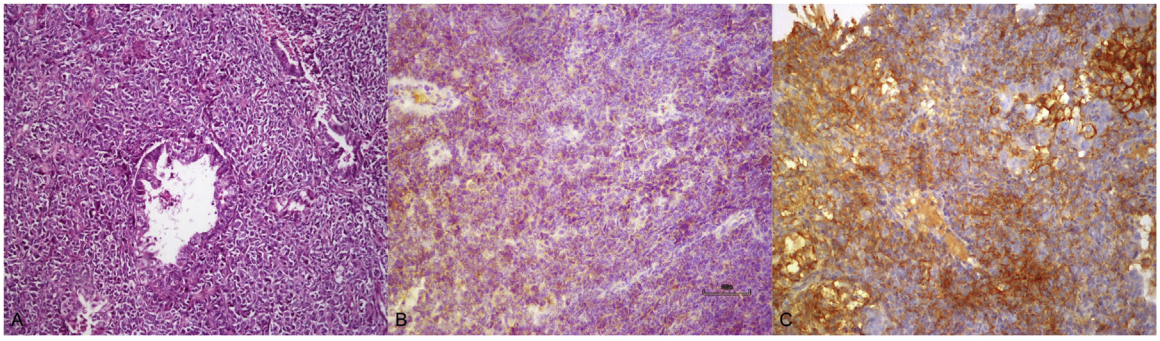



**Fig. 1.** Malignant tumor containing epithelial and stromal components (figure A), immunohistochemically PD-1 (figure B) and PD-L1 (figure C).

lung cancer, malignant melanoma, Hodgkin lymphoma, there is no clear data about immunotherapy in gynecologic tumors including UCS [5,6]. We aimed to evaluate the relationship between the expression of PD-1 and PD-L1 in tumors as well in microenvironment and the prognosis in UCS. In this aspect our study will be the first study in the literature that were searching the PD-1 and PD-L1 expressions in UCS. In the present study PD-L1 expression was found an independent prognostic factor. Although it was shown that PD-L1 expression was related with worse prognosis in tumors such as melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), prostate cancer, and colorectal cancer, we found that PD-L1 expression was associated with better prognosis in UCS [5,6]. Similar to our study PDL-1 positivity has been found to be associated with good prognosis in ovarian carcinosarcoma [10]. By this time the prognostic effect of PD-L1 expression in ovarian cancer is controversial. While its positivity was showed to be related with good prognosis in some studies [11,12], another study found it to be associated with worse prognosis [13]. Interpretation of the PD-L1 expression in UCS is difficult due to biphasic nature of this tumor. Zu at al. revealed the negative impact of the mesenchymal PD-1 expression on survival [10]. Paydas at al. demonstrated 30 % PD-L1 expression cases with sarcoma [14]. While PD-1 and PDL-1 expression analysis were performed, sarcomatous and epithelial component were not evaluated separately, as the number and percentage of positive cases were not enough.

Increasing frequency for UCS has been reported based on SEER data [2]. UCS is recurs in more than 50 % of patients despite definitive surgery and adjuvant therapy [3,4]. Stage, poor

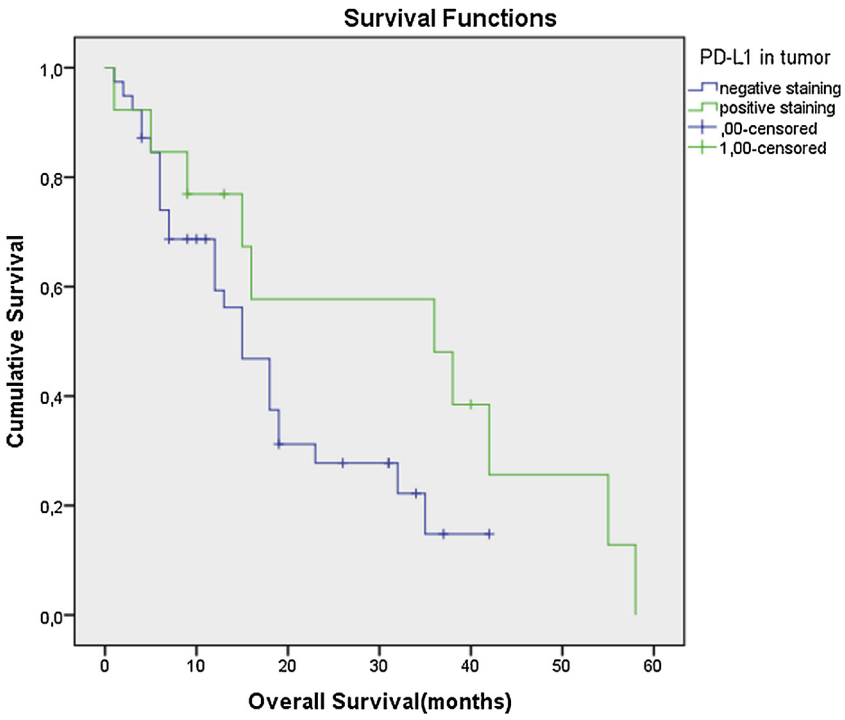



**Fig. 2.** Survival times according to the PD-L1 staining in tumor cells.

**Table 3**
Multivariate analysis of the studied parameters and survival.

| | p | HR | 95.0% CI | |
|---|---|---|---|---|
| | | | Lower | Upper |
| Stage | 0.822 | 1.092 | 0.509 | 2.341 |
| LVSI | 0.100 | 2.096 | 0.868 | 5.061 |
| Myometrial invasion | 0.240 | 1.749 | 0.688 | 4.443 |
| PD-L1 tumor | 0.029 | 3.067 | 1.123 | 8.379 |
| PD-1 tumor | 0.538 | 1.294 | 0.570 | 2.939 |
| Age | 0.567 | 1.012 | 0.973 | 1.052 |

Programmed Death-1 (PD-1); Programmed Death-Ligand 1 (PD-L1); LVSI (lymphovascular space invasion); HR: (Hazard Ratio); CI (Confidence interval).

performance status, deep myometrial invasion, and > 1 cm residual tumor were determined as prognostic factors for OS in a large, multicenter, retrospective Japanese study [1]. In our study, stage was not found as a prognostic factor and the prognosis was poor even in stage 1 and 2 patients with UCS. In compatible with the literature, 40.7 % of our cases had advanced stage disease at the time of diagnosis. Although lymphadenectomy is recommended for staging and planning treatment in cases with UCS we did not found the nodal involvement as poor prognostic; this may be due to the small sample size. Five-year survival in patients with UCS is ranging from 33 to 39% [3]. Large national data (n = 4272) in USA demonstrated that 40 % of the women with UCS did not receive adjuvant chemo or radiotherapy [15]. Imaging is not currently part of the staging process for UCS, however, CT, MRI and PET-CT can be used to detect metastatic disease and provide useful information on surgical planning [16]. UCS typically appears as an intracavitary mass that is hyperechoic to the myometrium by ultrasonography [16]. Although lymphadenectomy, adjuvant chemotherapy, and brachytherapy were found to be associated with longer survival, Seagle et al. demonstrated that 42 % of the patients with stage 1 disease did not receive adjuvant therapy after surgery [17]. In our study 69 % of the patients received chemotherapy as well as a half of all patients received the radiotherapy. There are some studies showing positive effect of adjuvant radiotherapy on the prognosis for all stages of the UCS [18,19]. It is not possible to discuss the contribution of radiotherapy or chemotherapy in our cases due to low number of patients. The most commonly used adjuvant chemotherapy is platinum-paclitaxel combination and it has survival advantage in recurrent UCS cases [20]. Its incidence is increasing and treatment options are controversial and it has a high recurrence rate therefore patient with UCS may be a good candidate for immunotherapy [21]. In support of this Zhang et al. reported a significant response with nivolumab treatment in 64 years old Chinese man with a carcinosarcoma of lung showing positive expression for PD-L1 [22].

The most important point is to find out to predictive factors in immunotherapeutic agents response due to the tumor and host characteristics and so display the potential candidate which sort of diseases and patients will get benefit from immunotherapy. Mismatch repair (MMR) deficient status has been found to be predictive for response to checkpoint blocker treatments [23,24]. MMR status and PD-L1 relationship were also studied in endometrial cancer and suggested that MMR deficiency may be predictor of response to PD-1 blokage [25]. Higher PD-L1 expression has been found to be associated with high-grade endometrial tumors (56 %) than low-grade ones (35 %) and PD-L1 expression found to be correlated with MMR status [26]. This point may suggest the beneficial effect of PD-L1 blockade in cases with UCS. Recently the first case was reported as anti PDL-1 (pembrolizumab) response in DNA polymerase epsilon (POLE)-mutant UCS [27]. Due to the atypical pathogenesis and poor prognosis despite conventional adjuvant chemotherapies, it is imperative to try to better understand the molecular pathogenesis of UCS and to find targeted therapies. A systematic review on this topic emphasizes HER 2 in these tumors [21].

Because of its biphasic nature, it may be more effective to evaluate the expression separately in the carcinoma and sarcoma areas of the tumor and to give a rate in these tumors. Sarcomatous component as well as carcinomatous component is accepted as important on prognosis and management [28]. As mentioned above, this is the most serious limitation of our study. In a

multicentre study with a higher number of cases because it is relatively rare tumors, the evaluation of staining separately in both compartments should be performed. It is also necessary to answer the question whether the sarcomatous component is homologous or heterologous. Another limitation of this study is not studied of the molecular characteristics such as the MMR status of the tumor and inflammation markers such as tumor infiltrating T lymphocyts (TILs). Adding these will make the results much more effective.

In conclusion, we detected PD-1 or PD-L1 expressions in 25 % of the cases with UCS and PD-L1 expression was found to be associated with better clinical outcome. PD-L1 may be an important target for UCS therapy but we need additional data about this matter.

## Author contributions

Conceptualization: UKG, EKB, SP; Methodology: UKG, EKB, SP; Formal analysis and investigation: UKG, EKB; Writing - original draft; UKG, EKB; preparation, Writing - review and editing; UKG, EKB, SP, MAV, ABG, DG; Funding acquisition: BAP; Resources, and Supervision: UKG, MAV, ABG, E.K.B, DG, SP.

## Statement of prior presentation

This study was presented as poster and e-poster at 20th International Meeting of The European Society of Gynecological Oncology (ESGO 2017), November 04-07, Vienna.

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## Declaration of Competing Interest

None.

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