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ABSTRACT

Objective: To evaluate the prevalence and prognostic role of programmed death ligand (PD-L) expression and tumor mutational burden (TMB) in patients with non-immunotherapy-treated advanced cervical cancer.

Methods: Clinical data were retrospectively collected from medical records between January

, , and December , , at Asan Medical Center (Korea); archived tumor samples were assessed for PD-L expression (combined positive score [CPS]_) and TMB (_ 5 mutations/exome). Overall survival (OS) was defined as time from advanced diagnosis or initiation of first-line or second-line systemic therapy until death/last follow-up. The association of OS with PD-L expression and TMB were analyzed using the log-rank test and Cox proportional hazards model adjusted for covariates.

Results: Of patients, . % had squamous cell carcinoma (SCC), 4. % had adenocarcinoma (AC)/adenosquamous carcinoma (ASC), 4.4% had PD-L CPS_, and . % had TMB_ 5 mutations/exome. PD-L CPS_ and TMB_ 5 mutations/exome were more prevalent in SCC than in AC/ASC (.9% and . % vs. 4.4% and . %). There was no association between OS and PD-L expression (CPS_ vs. < : adjusted hazard ratio [HR]= . 4; 95% confidence interval [CI]= . 4– .5 from advanced diagnosis); OS trended shorter for the subgroup with TMB_ 5 versus < 5 mutations/exome (adjusted HR= . 9;

95% CI= .95– . 5).

Conclusion: Retrospective analysis of non-immunotherapy-treated patients with advanced cervical cancer demonstrated a higher prevalence of PD-L CPS_ and TMB_ 5 mutations/ exome in SCC versus AC/ASC. PD-L CPS_ was not associated with OS; TMB_ 5 mutations/exome showed a trend toward shorter OS. Additional studies are needed to confirm these findings.

Keywords: Cervical Cancer; PD-L Protein



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Presentation

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Conflict of Interest

J-YP and M-HB have nothing to disclose. LC, CS, and PJ are employees of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, and own stock in Merck & Co., Inc., Rahway, NJ, USA. CT and XYJ are employees of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA. RC is an employee of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, owns stock in Merck & Co., Inc., Rahway, NJ, USA, and has two pending patents (Angiogenesis and mMDSC gene expression-based biomarker of tumor response to PD-1 antagonists; patent WO 2020/167619). SI is an employee of MSD Korea (employment [JCAP asso RDMA]), registered pharmacist (Korea), and stockholder of Merck & Co., Inc., Rahway, NJ, USA.

Data Availability Statement

Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA (MSD), is committed to providing qualified scientific researchers access to anonymized data and clinical study reports from the company's clinical trials for the purpose of conducting legitimate scientific research. MSD is also

Synopsis

Programmed death ligand (PD-L) expression and tumor mutational burden (TMB) were evaluated in non-immunotherapy-treated patients with advanced cervical cancer. Overall, 4.4% were PD-L positive (combined positive score [CPS]_) and .% had TMB_ 5 mutations/exome. PD-L CPS_ was not associated with overall survival (OS). TMB_ 5 mutations/exome showed a trend toward shorter OS in patients with advanced cervical cancer.

INTRODUCTION

Cervical cancer is a leading cause of cancer-related mortality in women worldwide []. Chemotherapy with or without the anti-vascular endothelial growth factor monoclonal antibody bevacizumab has been the standard-of-care for patients with recurrent or metastatic cervical cancer for several years []. Recently, the programmed cell death protein (PD-) inhibitor pembrolizumab in combination with chemotherapy with or without bevacizumab showed efficacy benefit as first-line treatment in the all-comer population of the phase KEYNOTE- trial in patients with persistent, recurrent, or metastatic cervical cancer; the efficacy benefit was also observed in the programmed death ligand (PD-L)-positive population (combined positive score [CPS] (].

Human papillomavirus (HPV) infection, the cause of most cervical cancers [4], can activate the PD-L pathway, resulting in upregulated expression of PD-L in malignant squamous cells of the cervix [5]. PD-L expression is an adaptive mechanism of immune escape by cervical carcinomas and such tumors are associated with a poor prognosis [,]. At present, limited data have been reported on the prevalence and prognostic role of PD-L expression in patients with advanced cervical cancer. The prevalence of PD-L -positivity (CPS_) in patients with advanced cervical cancer was . % in the phase KEYNOTE- 5 trial [] and . % (including 5 .4% with PD-L CPS_) in the phase KEYNOTE- trial []. Among patients with locally advanced cervical cancer treated with radical chemoradiotherapy (95. % of patient samples expressed PD-L [tumor proportion score > %] and .9% had a PD-L tumor proportion score_ %), the expression of PD-L was not associated with progression-free survival (PFS) or overall survival (OS) [9].

HPV-induced master regulators may also play crucial roles in relation to mutation and neoantigen load as well as the immune microenvironment of cervical tumors []. Tumor mutations may generate a large proportion of immunogenic neoantigens that may be associated with response to immune checkpoint inhibitors []. Tumor mutational burden (TMB; the total number of somatic nonsynonymous mutations per coding area of a tumor genome), is an emerging prognostic biomarker in advanced tumors [-4]. A computational study showed that patients with TMB-high (_median) cervical squamous cell carcinoma (SCC) may have a favorable prognosis [5]. In the multi-cohort KEYNOTE- 5 study, which included patients with cervical cancer, patients with TMB_ 5 mutations/exome (concordant with_______ mut/Mb via FoundationOne[®] CDx []) were identified as a possible subgroup with a robust tumor response to pembrolizumab [].

Although immunotherapy-based combination therapy is an effective treatment option for advanced cervical cancer, especially when PD-L expression and TMB status are known, the independent prognostic value of PD-L expression and TMB status in patients with advanced cervical cancer not previously treated with immunotherapy is unclear. There is a

obligated to protect the rights and privacy of trial participants and, as such, has a procedure in place for evaluating and fulfilling requests for sharing company clinical trial data with qualified external scientific researchers. The MSD data sharing website (available at: http://engagezone.msd.com/ds_ documentation.php) outlines the process and requirements for submitting a data request. Applications will be promptly assessed for completeness and policy compliance. Feasible requests will be reviewed by a committee of MSD subject matter experts to assess the scientific validity of the request and



TMB was assessed by whole exome sequencing (WES) using SureSelect XT All Exon Target Enrichment System (Agilent Technologies, Inc.). The methods for TMB analysis via WES have been previously published [4]. TMB was defined as the number of somatic nonsynonymous single nucleotide variants and indels that met predetermined criteria as previously described [4,].

TMB was assessed using a cutoff of 5 mutations/exome (5 vs. < 5 mutations/exome; concordant with mut/Mb via FoundationOne[®] CDx []). The prognostic effects of PD-L and TMB were assessed separately as dichotomized variables without adjusting for the other.

3. Statistical analyses

Baseline demographic, clinical, and pathological characteristics were compared according to biomarker expression level (PD-L CPS_ vs. < and TMB_ 5 vs. < 5 mutations/exome) using a χ test. The association between PD-L and TMB was assessed using a χ test. The association between each clinical outcome and each biomarker was analyzed using Kaplan-Meier curves, log-rank test, and multivariate Cox proportional hazard models adjusted for covariates of interest.

RESULTS

1. Patients

Between January , , and December , , a total of , adult patients with advanced cervical cancer were retrospectively identified and screened for eligibility (Fig. S1). Samples from eligible patients were identified and collected. After the exclusion of duplications (n=) and non-evaluable samples (n=), samples from patients were included in this analysis. The median age at the time of advanced cervical cancer diagnosis was 4 years. Most patients had SCC (. %), early-stage (I/II) disease at initial diagnosis (.5%), and recurrent disease (.9%) (Table 1). There were 4 patients (.9%) who had received first-line therapy and 9 patients (5.4%) who had received second-line therapy. The most common first-line treatments were carboplatin/paclitaxel (. %), cisplatin/ paclitaxel/bevacizumab (. %), and cisplatin/paclitaxel (. %). Median follow-up from advanced cervical cancer diagnosis was months (range, -5).

2. Biomarker prevalence and correlation

The prevalence of biomarkers by disease characteristics and prior treatment is shown in **Table 1**. All patients had samples evaluable for PD-L expression; patients (4.4%) had PD-L CPS₁, the prevalence of which was higher in patients with SCC compared with AC/ASC (.9% vs. 4.4%). There were 5 patients who had samples evaluable for TMB status; 4 patients (.%) had TMB₂ 5 mutations/exome, the prevalence of which was higher in patients with metastatic disease compared with recurrent disease (5 .9% vs. .%) and in patients with SCC compared with AC/ASC (.% vs. .%). PD-L CPS₁ and TMB₂ 5 mutations/exome were not correlated (p= .5).

3. OS

For OS from advanced cervical cancer diagnosis, of patients (5. %) in the PD-L CPS_ subgroup and of 95 patients (4. %) in the PD-L CPS < subgroup had died; the median (95% confidence interval [CI]) OS was 9. months (.-5.) versus . months (.-5.) versus . months (.-5.) versus . months (.-5.) (Fig. 1A).

Results for OS from first-line therapy initiation (**Fig. S2A**) and from second-line therapy initiation (**Fig. S2B**) were similar.

For OS from advanced cervical cancer diagnosis, of 4 patients (9.%) in the TMB $_{\sim}$ 5 mutations/exome subgroup and of 4 patients (.%) in the TMB < 5 mutations/exome subgroup had died; the median (95% CI) OS was . months (4. – 4.) versus 4. months (..., .), respectively (adjusted HR= .9; 95% CI= .95– .5) (Fig. 1B). Results for OS from first-line therapy initiation (Fig. S3A) and from second-line therapy initiation (Fig. S3B) were similar.



4. rwPFS

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For PFS by first-line therapy initiation, of 55 patients (9. %) in the PD-L CPS_ subgroup and of 9 patients (9.9%) in the PD-L CPS < subgroup had experienced disease progression or died; the median (95% CI) rwPFS from first-line therapy initiation was 9. months (. - .) versus 9. months (. - .), respectively (adjusted HR= .; 95% CI= .9 - .) (**Table 2**). The median (95% CI) rwPFS from second-line therapy initiation was . months (. -5.) in the PD-L CPS_ subgroup versus 4. months (. - .) in the PD-L CPS < subgroup (adjusted HR= .; 95% CI= . -.55) (**Table 2**).

For PFS by first-line therapy initiation, of patients (9.4%) in the TMB \leq 5 mutations/ exome subgroup and 9 of 59 patients (.4%) in the TMB < 5 mutations/exome subgroup had experienced disease progression or died; the median (95% CI) rwPFS was . months (5. - .) versus 9. months (. - .), respectively (adjusted HR= .; 95% CI= . - . 5) (**Table 2**). The median (95% CI) rwPFS from second-line therapy initiation was . months (. -5.) in the TMB \leq 5 mutations/exome subgroup versus 4. months (. -5.) in the TMB < 5 mutations/exome subgroup (adjusted HR= .; 95% CI= .9 - .94) (**Table 2**). 5 5

9.



5. OS and biomarker association by clinical characteristics

Consistent with the overall population, PD-L status was not associated with OS when evaluated by subgroups based on clinical characteristics (**Fig. 2A**). Similarly, the trend for shorter median OS among patients with TMB 5 versus < 5 mutations/exome was observed across subgroups based on clinical characteristics, except for patients who received bevacizumab in the first-line treatment setting (**Fig. 2B**).

DISCUSSION

In this retrospective analysis of patients with non-immunotherapy standard-of-care-treated advanced cervical cancer, 4.4% of patients had tumors with PD-L CPS and .% of



B Tumor mutational burden ≥175 versus <175 mutations/exome			
Subgroup	Events (n/N)		Adjusted HR (95% CI)
Overall	194/258	⊫ 1	1.29 (0.95–1.75)*
No (neo)adjuvant treatment	118/166	┞═──┤	1.44 (0.97-2.14)†
First-line bevacizumab users	23/38		0.73 (0.30-1.77) [‡]
Squamous cell carcinoma	145/196	┟┓──┥	1.51 (1.06-2.15) [§]
Adenocarcinoma/ adenosquamous carcinoma	49/62		1.85 (0.85-4.02)
Recurrent cervical cancer	158/208		1.44 (1.01-2.05)
	0.1	1	10

Favors TMB ≥175 Favors TMB <175

Fig. 2. Overall survival from advanced cervical cancer diagnosis by (A) PD-L1 CPS and (B) TMB status in patient subgroups.

CPS, combined positive score; HR, hazard ratio; PD-L1, programmed death ligand 1; TMB, tumor mutational burden. *HR was adjusted for age at advanced cervical cancer diagnosis, prior (neo)adjuvant treatments (yes/no), history of chronic kidney disease, birth parity, and body mass index.

HR was adjusted for age at advanced cervical cancer diagnosis, history of chronic kidney disease, and tumor size for no (neo)adjuvant therapy.

HR was adjusted for age at advanced cervical diagnosis and body mass index.

HR was adjusted for age at advanced cervical diagnosis, birth parity, body mass index, history of chronic kidney disease, tumor size, and prior (neo)adjuvant therapy HR was adjusted for age at advanced cervical diagnosis, stage at tissue collection, smoking, and prior radiation.

HR was adjusted for age at advanced cervical cancer diagnosis, stage at tissue collection, and prior (neo)adjuvant therapy.



patients had tumors with TMB 5 mutations/exome. A higher prevalence of PD-L CPS and TMB 5 mutations/exome (concordant with mut/Mb) was observed in patients with SCC than in patients with AC/ASC. Additionally, PD-L CPS compared with PD-L CPS < was not associated with OS in the overall population or in subgroups based on clinical characteristics. Furthermore, TMB 5 mutations/exome showed a trend toward shorter OS compared with TMB < 5 mutations/exome in the overall population or in subgroups based on clinical characteristics, except for patients who received first-line bevacizumab. Similarly, starting from the point of first-line therapy initiation, PD-L expression was not associated with rwPFS or OS, and TMB 5 mutations/exome showed shorter OS compared to TMB < 5 mutations/exome. Because of the small sample size, trends were not clear for outcomes from second-line therapy initiation.

The prevalence of PD-L -positive cervical cancer has been reported to range from % to > % for SCC [9-] and from 4% to 9% for AC/ASC [9,]. The prevalence observed in this study is within the range reported, although different PD-L antibody clones and/ or cutoffs for PD-L positivity were used. Also consistent is our finding that more patients with cervical cancer have SCC versus AC/ASC histology and that SCC is more frequently PD-L -positive [9, , 4]. Previous reports have shown the prevalence of TMB-high advanced cervical cancer is 5%- % [, 5].

A recent pan-tumor investigation of the prognostic value of TMB using data from The Cancer Genome Atlas (TCGA) showed that TMB-high was a statistically significant prognostic indicator of decreased mortality compared with non-TMB-high in patients with cervical SCC and endocervical adenocarcinoma []. Contrary to our findings, a computational study using data of patients from TCGA showed TMB-high (median) cervical SCC may be associated with a higher OS [5]. However, observations from a recent single-institution study of patients with cervical cancer in Japan showed that those patients with TMB-H tumors (29.5 mut/Mb) had a worse 5-year OS rate than those with non–TMB-high tumors (<9.5 mut/Mb) after definitive radiotherapy (. % vs. . %) []. Various theories and interpretations may account for the conflicting findings between studies, including differences in treatment regimen/ modality, methods used for determining TMB, and thresholds for categorizing TMB as high or low. Additionally, a recent evaluation of TCGA datasets suggested that survival data from the database may not be adequately treated and processed, leading to misinterpretation and impacting survival analyses using this data source []. In addition, variations in treatment approaches, such as the use of different chemotherapy agents or targeted therapies, can impact treatment responses and, subsequently, survival outcomes. Studies conducted in neuroblastoma and lung cancer have further indicated that TMB-high tumors, characterized by elevated mutations and complex genetic profiles, may be more aggressive and resistant to current non-immunotherapies, leading to shorter OS [9,]. The findings in patients with cervical cancer from our study and Ota et al. [] further corroborate this theory and highlight a consistent trend of short OS in these patients with TMB-high tumors. The underlying biology of TMB-high tumors may contribute to their aggressiveness and resistance to conventional therapies []. TMB-high tumors are characterized by increased mutations and complex genetic profiles, which can lead to enhanced tumor heterogeneity and the emergence of treatment-resistant clones [,]. This heightened genomic instability may render TMB-high tumors less responsive to traditional non-immunotherapeutic approaches [4], potentially resulting in shorter OS. These mechanistic insights underscore the importance of considering both treatment-related factors and tumor biology when interpreting study findings and designing therapeutic strategies for patients with advanced cervical cancer.



This study was performed using extensive samples, and the results are based on a reliable analysis from a single institution that implements consistent standardized treatment. Detailed patient-level clinical data were collected, and the distribution of the baseline demographic and clinical characteristics were consistent with published country-specific characteristics of patients with cervical cancer; thus, eliminating potential selection bias. However, this retrospective study has several limitations. First, the sampling process did not generate a random sample of all patients with advanced cervical cancer treated at the Asan Medical Center, thereby limiting generalizability of findings. Second, because patients were from large tertiary teaching hospitals, it is conceivable that tumor samples may represent more severe cases of advanced cervical cancer compared with the broader patient population. Third, requiring slides may select for a population with only available and sufficient tissue samples, possibly characterizing an earlier stage of disease during which resection and transplantation were more likely. Furthermore, if the biomarker status changed over the course of disease due to internal and/or external factors, the biomarker data generated from this study may not be reflective of the later disease course; this limitation may reduce the generalizability of the data. Fourth, the variability in follow-up time relative to treatment may impact the evaluation of OS. Fifth, the heterogeneity of the study cohort, comprising .9% and 5.4% of patients who received prior first-line and second-line treatment, respectively, may impact the evaluation of the prognostic role of PD-L expression and TMB status. Lastly, the rwPFS outcome should be interpreted with caution given that the data were collected in routine clinical practice and analyzed retrospectively outside of a formal clinical trial.

The findings of this analysis suggest PD-L expression has no prognostic value for OS and TMB_ 5 mutations/exome showed a trend toward shorter OS in patients with advanced cervical cancer treated with non-immunotherapy standard of care therapy. Given the increasing use of immunotherapy, including PD- /PD-L inhibitors, for the treatment of patients with advanced cervical cancer, prevalence data can help better understand the patient population potentially benefiting from this type of treatment. The current study exploring the association between TMB and clinical outcomes with non-immunotherapy are necessary to demonstrate prognostic value of PD-L expression and TMB, to help identify potential unmet medical needs based on a patient's biomarker status, and to inform the management and treatment of patients with advanced cervical cancer.

In conclusion, this retrospective study observed a higher prevalence of PD-L expression (CPS_) and TMB_ 5 mutations/exome (concordant with_ mut/Mb) status in SCC versus AC/ASC advanced cervical cancer. PD-L CPS_ was not associated with OS, whereas TMB _ 5 mutations/exome trended toward a shorter OS compared with TMB < 5 mutations/ exome. Future prospective studies are warranted to confirm these findings and elucidate the predictive and prognostic value of potential immune biomarkers in cervical cancer.

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SUPPLEMENTARY MATERIALS

Fig. S1

Patient eligibility and data profile.

Fig. S2

OS from (A) first-line therapy initiation and (B) second-line therapy initiation by PD-L CPS.

Fig. S3

OS from (A) first-line therapy initiation and (B) second-line therapy initiation by TMB status.

REFERENCES

- . Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics : GLOBOCAN estimates of incidence and mortality worldwide for cancers in 5 countries. CA Cancer J Clin ; : 9-49. PUBMED | CROSSREF
- . Marth C, Landoni F, Mahner S, McCormack M, Gonzalez-Martin A, Colombo N, et al. Cervical cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol ; :iv - . PUBMED | CROSSREF
- . Colombo N, Dubot C, Lorusso D, Caceres MV, Hasegawa K, Shapira-Frommer R, et al. Pembrolizumab for persistent, recurrent, or metastatic cervical cancer. N Engl J Med ; 5: 5 . PUBMED | CROSSREF
- 4. Plummer M, de Martel C, Vignat J, Ferlay J, Bray F, Franceschi S. Global burden of cancers attributable to infections in : a synthetic analysis. Lancet Glob Health ;4:e 9- . PUBMED | CROSSREF
- Mezache L, Paniccia B, Nyinawabera A, Nuovo GJ. Enhanced expression of PD L in cervical intraepithelial neoplasia and cervical cancers. Mod Pathol 5; : 594-. PUBMED | CROSSREF
- . Yang W, Song Y, Lu YL, Sun JZ, Wang HW. Increased expression of programmed death (PD)- and its ligand PD-L correlates with impaired cell-mediated immunity in high-risk human papillomavirus-related cervical intraepithelial neoplasia. Immunology ; 9:5 . PUBMED | CROSSREF
- . Vinh-Hung V, Bourgain C, Vlastos G, Cserni G, De Ridder M, Storme G, et al. Prognostic value of histopathology and trends in cervical cancer: a SEER population study. BMC Cancer ; : 4. PUBMED | CROSSREF
- Chung HC, Ros W, Delord JP, Perets R, Italiano A, Shapira-Frommer R, et al. Efficacy and safety of pembrolizumab in previously treated advanced cervical cancer: Results from the phase II KEYNOTE- 5 study. J Clin Oncol 9; : 4 . PUBMED | CROSSREF
- 9. Enwere EK, Kornaga EN, Dean M, Koulis TA, Phan T, Kalantarian M, et al. Expression of PD-L and presence of CD -positive T cells in pre-treatment specimens of locally advanced cervical cancer. Mod Pathol ; :5 . PUBMED | CROSSREF
- Qin Y, Ekmekcioglu S, Forget MA, Szekvolgyi L, Hwu P, Grimm EA, et al. Cervical cancer neoantigen landscape and immune activity is associated with human papillomavirus master regulators. Front Immunol ; : 9. PUBMED | CROSSREF
- . Le DT, Durham JN, Smith KN, Wang H, Bartlett BR, Aulakh LK, et al. Mismatch repair deficiency predicts response of solid tumors to PD- blockade. Science ; 5 :4 9-. PUBMED | CROSSREF
- . Samstein RM, Lee CH, Shoushtari AN, Hellmann MD, Shen R, Janjigian YY, et al. Tumor mutational load predicts survival after immunotherapy across multiple cancer types. Nat Genet 9;5 : . PUBMED | CROSSREF
- Cao J, Yang X, Chen S, Wang J, Fan X, Fu S, et al. The predictive efficacy of tumor mutation burden in immunotherapy across multiple cancer types: a meta-analysis and bioinformatics analysis. Transl Oncol
 ; 5. PUBMED | CROSSREF
- Cristescu R, Aurora-Garg D, Albright A, Xu L, Liu XQ, Loboda A, et al. Tumor mutational burden predicts the efficacy of pembrolizumab monotherapy: a pan-tumor retrospective analysis of participants with advanced solid tumors. J Immunother Cancer ; e 9. PUBMED | CROSSREF
- Wen F, Ruan S, Huang W, Chen X, Wang Y, Gu S, et al. Prognostic value of tumor mutational burden related to immune infiltration in cervical squamous cell carcinoma. Front Med (Lausanne) ; : 55 5 .
 PUBMED | CROSSREF



- . Aurora-Garg D, Albright A, Qiu P, Li Y, Liu X, Fabrizio D, et al. Large-scale evaluation of concordance of genomic scores in whole exome sequencing and foundation medicine comprehensive genomic platform across cancer types. J Immunother Cancer 9; : .
- Marabelle A, Fakih M, Lopez J, Shah M, Shapira-Frommer R, Nakagawa K, et al. Association of tumour mutational burden with outcomes in patients with advanced solid tumours treated with pembrolizumab: prospective biomarker analysis of the multicohort, open-label, phase KEYNOTE- 5 study. Lancet Oncol
 ; 5 - 5. PUBMED | CROSSREF
- Cristescu R, Mogg R, Ayers M, Albright A, Murphy E, Yearley J, et al. Pan-tumor genomic biomarkers for PD- checkpoint blockade-based immunotherapy. Science ; :eaar 59 . PUBMED | CROSSREF
- 9. Heeren AM, Punt S, Bleeker MC, Gaarenstroom KN, van der Velden J, Kenter GG, et al. Prognostic effect of different PD-L expression patterns in squamous cell carcinoma and adenocarcinoma of the cervix. Mod Pathol ; 9: 5 - . PUBMED | CROSSREF
- . Koncar RF, Feldman R, Bahassi EM, Hashemi Sadraei N. Comparative molecular profiling of HPVinduced squamous cell carcinomas. Cancer Med ;: - 5. PUBMED | CROSSREF
- . Liang Y, Yu M, Zhou C, Zhu X. Variation of PD-L expression in locally advanced cervical cancer following neoadjuvant chemotherapy. Diagn Pathol ; 5: . PUBMED | CROSSREF
- . Saglam O, Conejo-Garcia J. PD- /PD-L immune checkpoint inhibitors in advanced cervical cancer. Integr Cancer Sci Ther ;5: . 5 /ICST. . PUBMED | CROSSREF
- . Omenai SA, Ajani MA, Okolo CA. Programme death ligand expressions as a surrogate for determining immunotherapy in cervical carcinoma patients. PLoS One ; :e 5. PUBMED | CROSSREF
- 4. Reddy OL, Shintaku PI, Moatamed NA. Programmed death-ligand (PD-L) is expressed in a significant number of the uterine cervical carcinomas. Diagn Pathol ; :45. PUBMED | CROSSREF
- 5. Shao C, Li G, Huang L, Pruitt S, Castellanos E, Frampton G, et al. Prevalence of high tumor mutational burden and association with survival in patients with less common solid tumors. JAMA Netw Open ; e 5 9. PUBMED | CROSSREF
- . Wu HX, Wang ZX, Zhao Q, Chen DL, He MM, Yang LP, et al. Tumor mutational and indel burden: a systematic pan-cancer evaluation as prognostic biomarkers. Ann Transl Med 9; : 4 . PUBMED | CROSSREF
- . Ota N, Yoshimoto Y, Darwis ND, Sato H, Ando K, Oike T, et al. High tumor mutational burden predicts worse prognosis for cervical cancer treated with radiotherapy. Jpn J Radiol ;4 :5 4-4 . PUBMED | CROSSREF
- . Idogawa M, Koizumi M, Hirano T, Tange S, Nakase H, Tokino T. Dead or alive? Pitfall of survival analysis with TCGA datasets. Cancer Biol Ther ; :5 . PUBMED | CROSSREF
- 9. Hwang WL, Wolfson RL, Niemierko A, Marcus KJ, DuBois SG, Haas-Kogan D. Clinical impact of tumor mutational burden in neuroblastoma. J Natl Cancer Inst 9; : 95-9. PUBMED | CROSSREF
- Offin M, Rizvi H, Tenet M, Ni A, Sanchez-Vega F, Li BT, et al. Tumor mutation burden and efficacy of EGFR-tyrosine kinase inhibitors in patients with EGFR-mutant lung cancers. Clin Cancer Res 9; 5: -9. PUBMED | CROSSREF
- . Fusco MJ, West HJ, Walko CM. Tumor mutation burden and cancer treatment. JAMA Oncol ; : . PUBMED | CROSSREF
- . Zhang A, Miao K, Sun H, Deng CX. Tumor heterogeneity reshapes the tumor microenvironment to influence drug resistance. Int J Biol Sci ; 9-. PUBMED | CROSSREF
- . Xie N, Shen G, Gao W, Huang Z, Huang C, Fu L. Neoantigens: promising targets for cancer therapy. Signal Transduct Target Ther ; :9. PUBMED | CROSSREF
- 4. Yang H, Yu M, Zhong S, You Y, Feng F. Neoantigens and the tumor microenvironment play important roles in the prognosis of high-grade serous ovarian cancer. J Ovarian Res ; 5: . PUBMED | CROSSREF