Landscape of Immune Cell Infiltration in Cervical Cancer

Shasha Shi

Chengdu University of Traditional Chinese Medicine

Fu Peng

Sichuan University

Chenghao Yu (✉ yuchenghao@cdutcm.edu.cn)

Chengdu University of Traditional Chinese Medicine <https://orcid.org/0000-0001-6981-1045>

Primary research

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Abstract

Background

Cervical cancer is a life-threatening cancer among women. It is the second most prevalent malignant tumor in women. It ranks high in cancer deaths among women worldwide, including in the United States. Immune checkpoint inhibitors have emerged as an important therapeutic approach to treat several cancers, including cervical cancer. Notably, the development and progress of cervical cancer may be related to sustained immune response. This underlines the need to clarify immune cell infiltration (ICI) in cervical cancer tissues.

Methods

In this study, disease-related information of 964 cervical cancer patients was first retrieved from Gene Expression Omnibus (GEO) and The Cancer Genome Atlas (TCGA) database. We utilized bioinformatics data to analyze the expression profiles of immune genes in cervical cancer tissues.

Results

Patients were divided into high and low groups according to ICI score. High ICI scores corresponded with activation of immune signaling pathways and high tumor mutation burden (TMB), which was related to better prognosis of G1-2 cervical cancer. In addition, most immune checkpoints and immuno-related genes such as CD274, CD8A, CXCL10, etc. were over-expressed in the high ICI group.

Conclusions

This study demonstrated that ICI score can accurately predict the prognosis of cervical cancer. Understanding ICI patterns will deepen our understanding of tumor microenvironment (TME) of cervical cancer, which may create the foundation for the development of efficient immunotherapeutic strategies against the cancer.

Background

Cervical cancer is the second most prevalent tumor, only behind breast cancer^[1]. Globally, more than 500,000 women with cervical cancer have been reported yearly, resulting in more than 250,000 deaths within the same period. Over 80% of the cervical cancer cases occur in developing countries^[1]. The incidence of cervical cancer in China is high, accounting for 12% of the world's cases and about 10% of the total deaths^[1]. The current treatment methods for cervical cancer include surgery, chemotherapy and radiotherapy^[1]. However, only about 60% of the cervical cancer cases qualify for surgical resection^[1]. Overall, the prognosis of patients with local but advanced, metastatic and recurrent cervical cancers remains unsatisfactory^[1].

Immune escape is a significant aspect of all cancers^[1]. Treatments that stimulate the host immune response against tumors have been shown remarkable efficiency in several cancers^[1]. The first evidence on the potential of immunotherapy was reported in the 19th and 20th centuries, and involved injection of pro-inflammatory bacterial extracts into tumor tissues^[1]. Recent developments have further demonstrated the efficacy of immunotherapy against several canine cancers such as brain tumors, osteosarcoma, B-cell lymphoma, and malignant melanoma^[1]. IL2 immunotherapy has been approved in the treatment of renal metastatic carcinoma and metastatic melanoma, owing to their ability to activate the IL2- STAT5 signaling pathway^[1]. There is no doubt immunotherapy has revolutionized cancer treatment^[1].

Although human papilloma virus (HPV) infection is a risk factor for developing cervical cancer^[1], cellular immune responses participate in the development of the cancer^[1]. ADXS11-001 is currently the only approved immunotherapy against cervical cancer. It is an active, relatively non-low-toxic, bioengineered Lm-LLO immunotherapy effective against other cancers caused by HPV^[1]. Even so, the 5-year overall survival rate of patients with metastatic and recurrent cervical cancer is only around 17%^[1]. However, immune checkpoint inhibitors (ICPIs) are potential therapeutics against metastatic cervical cancer^[1].

The invention of next generation sequencing (NGS) has accelerated research in cancer genomics^[1]. Herein, we utilized bioinformatics data to analyze the expression profiles of immune genes in cervical cancer tissues. Cancer tissues were divided into three categories based on specific immune cells infiltrations scores. Finally, we constructed accurate diagnostic and prognosis prediction models for cervical cancer based on the ICI scores.

Materials And Methods

Transcriptome data for cervical cancer tissues

The transcriptome data for 964 cervical cancer tissues was downloaded from The Cancer Genome Atlas (TCGA) (<https://portal.gdc.cancer.gov/>) and Gene Expression Omnibus (GEO) (<https://www.ncbi.nlm.nih.gov/geo/>) databases. Tumor mutation burden (TMB) data is also derived from TCGA.

Clustering of infiltration of immune cells in cervical cancer tissues

The proportion of immune cells in tumor sites was quantized using “CIBERSORT” package in R software. The scores for infiltrated immune and stromal cells in the tissues were calculated using the ESTIMATE package. All analyses were performed using the R package.

Differently expressed genes (DEGs) between immune cell infiltration (ICI) subtypes

Differently expressed ICI related to cancer tissues were identified, and used for stratification of different ICI subtypes. Significance differential expression was based on an absolute fold-change > 1.4, at statistical significant of $p < 0.05$.

Calculation Of The Ici Score

ICI gene types adopt unsupervised clustering and are divided into two groups: positive correlation and negative correlation. The Boruta algorithm is used to reduce the dimension of data, and Boruta algorithm is used to identify the key characteristics of immune expression among ICI subtypes. The dimensionality of the data was performed using principle component analysis (PCA). PCA analysis was used to calculate the ICI score.

Data Source And Analysis Method Of Tmb

The mutation data of cervical cancer tissues was downloaded from TCGA database (<https://portal.gdc.cancer.gov/>). The TMB was based on the degree of somatic alterations in genes that drive cervical cancer. The respective genes were identified using the “maftool” R package.

Statistical Analyses

The Kruskal-Wallis test was employed to compare > 2 groups whereas Wilcoxon test was employed compared to two groups. Differences in survival between the two groups of patients were evaluated using log rank test. The correlation between somatic mutation frequency and ICI score was assessed with the Chi-square test, and the correlation was analyzed by Spearman. $P < 0.05$ was considered statistically significant.

Results

The Infiltration Landscape of Immune cells in tumor microenvironment (TME) of Cervical cancer tissues

Overall, transcriptome data for infiltration of immune cells in 964 cervical cancer tissues was downloaded from TCGA (cervixuteri) and GEO (GSE30760) databases. The Fragments Per Kilobase Million (FPKM) expression spectrum of the cervical cancer tissues in the TCGA was transformed into TPMs format. The abundance of immune cells in cervical cancer tissues was quantified using CIBERSORT and ESTIMATE algorithms (Table 1). Based on the infiltration profile of immune cells, the cervical cancer patients were classified into three groups.

Long rank test revealed significant difference in survival among patients in different ICI subtypes (Figs. 1C; $p = 0.028$). We compared the composition of immune cell subtypes in tumor tissues to further reveal intrinsic biological differences between different ICI clinical phenotypes (Figs. 1D). ICI cluster A patients had a good prognosis and a survival time of 7.56 years. Patients in this group exhibited high infiltration of naive memory resting CD4 + T cells, resting dendritic cells, macrophages M1, monocytes, activated natural killer (NK) cells, and resting mast cells in cancer tissues. The survival time of patients in ICI Cluster B was 12.21 years, and the survival time was the longest among the three groups. Cervical cancer tissues of patients in cluster B ICI exhibited higher infiltration of CD8 + T cells, activated memory CD4 + T cells, follicular helper T cells, and resting NK cells. The survival period of patients in cluster C ICI was significantly low (median survival time was 5.57 years). Patients in this group exhibited high infiltration of activated mast cells and M0 macrophages to TME. Heat map of the correlation between ICI group and TME immune cell infiltration and the interaction diagram of immune cells are shown in Fig. 1A and Fig. 1B. The darker the color, the stronger the relationship. Negative correlation is presented by blue line whereas the red line stands for positive correlation. Kruskal-Wallis analyses revealed that PD-L1 immune checkpoint was expressed highest in ICI cluster B tissues, whereas the lowest PD-L1 expression was observed in ICI cluster C tissues. The results can be seen in Fig. 1E.

Gene Expression Among Different Subgroups

We identified 111 DEGs among the ICI clusters (Table 2). The DEGs were divided into four clusters A-D (Figs. 2A and 2B). Genes (78) that positively correlated with better prognosis were classified in to ICI gene type A. The negative correlation was named ICI gene type B (Table 3). The dimensionality of the gene expression profile was appropriated using the Boruta algorithm. The heatmap for the DEGs in different genetic clusters is shown in Fig. 2A). Enrichment analysis of ICI gene type A and ICI gene type B by Gene Ontology (GO) (Fig. 2D, Table 4; Fig. 2E, Table 5). Figure 2B shows the downregulated expression of naive B cells in cluster B genes. Contrarily, there was up-regulated expression of CD8 + T cells, activated memory CD4 + T cells and M1 macrophage in gene cluster C tissues. Kaplan-Meier analysis results indicating gene expression in cluster A and D gene correlated with better prognosis, whereas expression of cluster B and C gene clusters was associated with poor prognosis (log rank test, $p = 0.031$; Fig. 2C).

Also, expression of clusters B and C genes corresponded with significantly higher immune scores. The expression levels of PD-L1 also varied significantly among the different genomic clusters (Fig. 2F; $p < 0.05$). Particularly, ICI gene clusters B and C express PD-L at high level, while ICI gene clusters A and D express PD - L 1 at low level. These findings highlight the dual nature of the immune system, which has both positive and inhibitory effects. Overall, gene clusters were linked to specific immune profile and prognostic profile, underlining the reliability of our classification model.

Analysis Of The Ici Score

The cervical Patients were stratified into high or low ICI score groups based on the median ICI score (Table 6). The distribution of patients with the four gene clusters in ICI score is shown in Fig. 3A. Genes strongly associated with immunoactivity included SOX2, CD274, CD8A, CXCL10, TBX2, TLR9, CTLA4, CD28, GZMB, IFNG, CXCL9, FOXP3 and TNF genes. Except SOX2, TBX2 and TLR9, the rest of immune checkpoint and immune activity related genes were overexpressed in individuals in the high ICI score group (Fig. 3B). Gene set enrichment analysis (GSEA) revealed that the B cell receptor, JAK-STAT and T cell receptor signaling pathways were most dysregulated in the high ICI score group (Figs. 3C; Table 7).

Further analyses revealed that high ICI score correlated with better prognosis, while the survival time of patients with low ICI score was only 8.48 years ($p = 0.041$, Fig. 3D).

Relationship Between Ici Score And Tmb

TMB is one of the greatest clinical factors that influences the prognosis of cancers. In this study, TMB data of cervical cancer was obtained from the TCGA database. We found TMB was directly proportional to the ICI score (Wilcoxon test $p = 0.046$, Fig. 4A). Based on TMB and immune score, patients were also divided into discrete subgroups. Overall, there was a strong positive correlation between ICI score and TMB (Fig. 4B; $R = 0.14$; $P = 0.017$), consistent with the above analysis.

High TMB was also associated with better prognosis of cervical cancer (Fig. 4C; $p = 0.042$). Analysis shows that ICI score is an independent predictor of cervical cancer prognosis. Under the classification of ICI score, there was a significant difference in survival rate between the low and high TMB subgroups. Here, four subgroups could be recognized; TMB high and ICI high (HH), TMB high and ICI low (HL), TMB low and ICI low (LH) and finally TMB low and ICI low (LL) (Fig. 4D, $p = 0.012$).

Significant genes in the low ICI group and high ICI group were also investigated (Figs. 4E and 4F). Analysis of TCGA data revealed significant differences in OBSCN, DNAH9, MXRA5 and CUBN gene mutations between low and high ICI score groups (Table 8). Overall, findings of this study lay the foundation for the development and assessment of response to cervical cancer immunotherapies.

Discussion

In recent years, significant progress has been made in the field of cancer immunotherapy^[1]. Given the critical roles of immune checkpoints in the immune system, ICPIs have been applied in immunotherapy cancer treatments^[2]. ICPIs acts by blocking the inhibitory checkpoint pathways and as well reactivates immune response in cancer tissues^[3]. TIGIT, LAG-3, TIM-3, CTLA-4, and PD-1/PD-L1, are among the anti-cancer immune checkpoint inhibitors currently being used^[4], with PD-1/PD-L1 being the most common^[5]. ICPIs is the choice checkpoint inhibitor for the treatment of metastatic cervical cancer^[6]. In this study, we quantified the tumor immune environment for cervical cancer. The expression profile of ICI can accurately predict the prognosis of cervical cancer. Accordingly, the establishment of ICI score may be used in developing immunotherapies against cervical cancer.

Accumulating evidences show that infiltration of immune cells in TME affects survival and proliferation of cervical cancer cells^[26]. Therefore, there is need to monitor the immune response of these groups of patients. Herein, we analyzed the expression profile of ICI in 964 cervical cancer tissues. On this basis, cervical cancer is divided into three different immune subtypes (A-C). Patients in ICI Cluster B exhibited the longest survival time. Notably, Cluster B was linked to high infiltration of CD8 + T cells, resting NK cells, follicular helper T cells, memory activated CD4 + T cells. Mice models revealed that under expression of Treg cells inhibit the proliferation and metastasis of cervical cancer cells^[7], the infiltration of activated CD8 + T cells promotes the participation of IL-10 in the immune response and has the characteristics of cervical cancer^[8]. TME of cervical cancer tissues comprises of numerous cytokines, chemokines and other host derived components, which reflects its immune ability.

Unraveling immune-related genes associated with expression of ICI can uncover strategies for developing personalized treatment for cervical cancer. The expression profile of immune-related genes in cervical cancer tissues was downloaded from the GEO and TCGA databases. Based on the gene expression, cervical cancer patients were divided into four ICI gene clusters. ICI gene cluster A and D displayed lower immune and stromal scores, but exhibited high expression of Macrophages M0, Neutrophils, activated Mast cells, activated dendritic cells, resting memory CD4 + T cells, and naive B cells. Conversely, the immune scores of the other two groups were significantly higher. High stromal score in both groups was associated with high infiltration of M1 macrophages, activated CD4 + memory T cells. In addition, expression of cluster B and C ICI genes was associated with shorter survival of cervical cancer patients. Contrarily, expression of cluster A and D ICI genes was associated with longer survival. Given that PD-L1 is highly expressed in ICI gene clusters B and C, we speculate that overactivated cells in these two groups may mediate immune escape. Indeed, previous studies show that immune escape promotes disease development, thus influencing the prognosis. Profiling of immune genes related to ICI can help in the development of more accurate immunotherapy.

Classification of cancer patients is motivated by cancer heterogeneity. In this study, according to ICI score, cervical cancer patients were divided into high rating group and low rating group, and a model of quantifying ICI with ICI score was established. JAK-STAT signal is involved in a variety of cellular regulatory processes and plays a key role in tumor genesis and immune response after activation^[9]. The B cell receptor (BCR) mediates B cell responses^[10]. Expression of BCR is also critical in the survival and development of B-cells^[11]. T cell receptor also mediates T cell specific effector functions^[12]. For instance, T cell receptor

(TCR) mediates functions of activated T Reg (AT Reg) cells, which also play a central role in immune tolerance of Foxp3 + regulatory T (T Reg) cells^[1]. GSEA analysis revealed the over-expression of genes associated with immunosuppressive pathways such as B cell receptor, JAK-STAT and T cell receptor signaling pathways in the high ICI score groups.

New studies have shown that genetic mutations occur in glycosylation sites of G protein in Respiratory syncytial virus (RSV), and maybe participate in immune escape^[2]. Herein, mutations in genes are to some extent related to the body's immunity. The results of this study show that ICI score was related to the degree of genetic mutations in multiple genes. Particularly, TMB positively correlated with ICI scores (0.017). Sub-group analysis further revealed that ICI score and TMB affected cervical cancer patients prognosis. Specifically, high TMB corresponded with longer overall survival. It is generally believed that before the occurrence of tumors, gene mutations first appear as preneoplastic lesions^[3]. However, recent gene sequencing efforts have uncovered millions of genetic mutations in numerous tumor tissues, suggesting that mutations are present in normal tissues and that does not necessarily lead to adverse outcomes^[4]. Surprisingly, high genetic mutations may benefit cervical cancer patients. Therefore, TMB can indirectly reflect the ICI score. Even so, in-depth researches are needed to fully unravel this relationship.

Conclusions

To sum up, we made a comprehensive and detailed analysis of ICI of cervical cancer, evaluated it from many aspects and levels, and painted a clear picture of immune response to cervical cancer. In addition, ICI patterns are closely related to the degree of tumor lesion. Findings of this study lay the foundation for identifying ideal biomarkers for developing cervical cancer immunotherapies. This study is of great significance to clinical work.

Abbreviations

- ICI Immune cell infiltration;
- GEO Gene Expression Omnibus
- TCGA The Cancer Genome Atlas
- TMB Tumor mutation burden
- TME Tumor microenvironment
- HPV Human papilloma virus
- ICPIs Immune checkpoint inhibitors
- NGS Next generation sequencing
- FPKM Fragments Per Kilobase Million
- NK Natural killer
- DEGs Differently expressed genes
- GSEA Gene set enrichment analysis
- TCR T cell receptor
- BCR B cell receptor
- RSV Respiratory syncytial virus
- GO Gene Ontology

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

All authors approved for publication.

Availability of data and materials

All data generated or analysed during this study are included in this published article [and its supplementary information files].

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

CHY conceived and designed the study. SSS did the data analysis and wrote the first draft. FP revised the manuscript. All authors read and approved the final manuscript.

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Not applicable.

References

1. Zhou J, Liang T, Wang D, et al. IFN α -Expressing Amniotic Fluid-Derived Mesenchymal Stem Cells Migrate to and Suppress HeLa Cell-Derived Tumors in a Mouse Model. *Stem Cells Int*. 2018;2018:1241323. Published 2018 Apr 2. doi:10.1155/2018/1241323
2. Kim YM, Muthuramalingam K, Cho M. Redox Regulation of NOX Isoforms on FAK(Y397)/SRC(Y416) Phosphorylation Driven Epithelial-to-Mesenchymal Transition in Malignant Cervical Epithelial Cells. *Cells*. 2020;9(6):1555. Published 2020 Jun 26. doi:10.3390/cells9061555
3. Xu J, Liu H, Yang Y, et al. Genome-Wide Profiling of Cervical RNA-Binding Proteins Identifies Human Papillomavirus Regulation of RNASEH2A Expression by Viral E7 and E2F1. *mBio*. 2019 Jan 29;10(1):e02687-18. doi: 10.1128/mBio.02687-18.
4. Hou H, Er P, Cheng J, et al. High expression of FUNDC1 predicts poor prognostic outcomes and is a promising target to improve chemoradiotherapy effects in patients with cervical cancer. *Cancer Med*. 2017;6(8):1871-1881. doi:10.1002/cam4.1112
5. Liu Y, Fan P, Yang Y, et al. Human papillomavirus and human telomerase RNA component gene in cervical cancer progression. *Sci Rep*. 2019;9(1):15926. Published 2019 Nov 4. doi:10.1038/s41598-019-52195-5
6. Wang Q, Schmoekel E, Kost BP, et al. Higher CCL22+ Cell Infiltration is Associated with Poor Prognosis in Cervical Cancer Patients. *Cancers (Basel)*. 2019;11(12):2004. Published 2019 Dec 12. doi:10.3390/cancers11122004
7. Ekdahl L, Wallin E, Alfonso E, et al. Increased Institutional Surgical Experience in Robot-Assisted Radical Hysterectomy for Early Stage Cervical Cancer Reduces Recurrence Rate: Results from a Nationwide Study. *J Clin Med*. 2020;9(11):3715. Published 2020 Nov 19. doi:10.3390/jcm9113715
8. Stevanović S, Draper LM, Langhan MM, et al. Complete regression of metastatic cervical cancer after treatment with human papillomavirus-targeted tumor-infiltrating T cells. *J Clin Oncol*. 2015;33(14):1543-1550. doi:10.1200/JCO.2014.58.9093
9. Rose PG, Java J, Whitney CW, et al, DiSilvestro PA. Nomograms Predicting Progression-Free Survival, Overall Survival, and Pelvic Recurrence in Locally Advanced Cervical Cancer Developed From an Analysis of Identifiable Prognostic Factors in Patients From NRG Oncology/Gynecologic Oncology Group Randomized Trials of Chemoradiotherapy. *J Clin Oncol*. 2015 Jul 1;33(19):2136-42. doi: 10.1200/JCO.2014.57.7122.
10. Jones TM, Carew JS, Nawrocki ST. Therapeutic Targeting of Autophagy for Renal Cell Carcinoma Therapy. *Cancers (Basel)*. 2020;12(5):1185. Published 2020 May 7. doi:10.3390/cancers12051185
11. Hiraoka N, Ino Y, Hori S, et al. Expression of classical human leukocyte antigen class I antigens, HLA-E and HLA-G, is adversely prognostic in pancreatic cancer patients. *Cancer Sci*. 2020;111(8):3057-3070. doi:10.1111/cas.14514
12. Coley WB. The treatment of malignant tumors by repeated inoculations of erysipelas. With a report of ten original cases. 1893. *Clin Orthop Relat Res*. 1991 Jan;(262):3-11.
13. Janosky M, Sabado RL, Cruz C, et al. MAGE-specific T cells detected directly ex-vivo correlate with complete remission in metastatic breast cancer patients after sequential immune-endocrine therapy. *J Immunother Cancer*. 2014;2(1):32. Published 2014 Sep 16. doi:10.1186/s40425-014-0032-2
14. Walker JM, Rolig AS, Charych DH, et al. NKTR-214 immunotherapy synergizes with radiotherapy to stimulate systemic CD8+ T cell responses capable of curing multi-focal cancer. *J Immunother Cancer*. 2020;8(1):e000464. doi:10.1136/jitc-2019-000464
15. Rosato PC, Wijeyesinghe S, Stolley JM, et al. Virus-specific memory T cells populate tumors and can be repurposed for tumor immunotherapy. *Nat Commun*. 2019;10(1):567. Published 2019 Feb 4. doi:10.1038/s41467-019-08534-1
16. Young AR, Duarte JDG, Coulson R, et al. Immunoprofiling of Breast Cancer Antigens Using Antibodies Derived from Local Lymph Nodes. *Cancers (Basel)*. 2019;11(5):682. Published 2019 May 16. doi:10.3390/cancers11050682
17. Naumann RW, Hollebecque A, Meyer T, et al. Safety and Efficacy of Nivolumab Monotherapy in Recurrent or Metastatic Cervical, Vaginal, or Vulvar Carcinoma: Results From the Phase I/II CheckMate 358 Trial. *J Clin Oncol*. 2019 Nov 1;37(31):2825-2834. doi: 10.1200/JCO.19.00739.
18. Wang Q, Schmoekel E, Kost BP, et al. Higher CCL22+ Cell Infiltration is Associated with Poor Prognosis in Cervical Cancer Patients. *Cancers (Basel)*. 2019;11(12):2004. Published 2019 Dec 12. doi:10.3390/cancers11122004

19. Ghamande S, Mauro D, Price C, et al. High-dose treatment with ADXS11-001, a listeria monocytogenes (Lm)-listeriolysin O (LLO) immunotherapy, in women with cervical cancer. *J Immunother Cancer*. 2015;3(Suppl 2):P151. Published 2015 Nov 4. doi:10.1186/2051-1426-3-S2-P151
20. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer*. 2015 Mar 1;136(5):E359-86. doi: 10.1002/ijc.29210.
21. Frenel JS, Le Tourneau C, O'Neil B, et al. Safety and efficacy of pembrolizumab in advanced, programmed death ligand 1-positive cervical cancer: results from the Phase Ib KEYNOTE-028 trial. *J Clin Oncol*. 2017;35(36):4035–4041. doi:10.1200/JCO.2017.74.5471.
22. Guo R, Zhao Y, Zou Q, Fang X, Peng S. Bioinformatics applications on Apache Spark. *Gigascience*. 2018;7(8):giy098. Published 2018 Aug 1. doi:10.1093/gigascience/giy098
23. Motz GT, Santoro SP, Wang LP, et al. Tumor endothelium FasL establishes a selective immune barrier promoting tolerance in tumors. *Nat Med*. 2014;20(6):607-615. doi:10.1038/nm.3541
24. Grosser R, Cherkassky L, Chintala N, Adusumilli PS. Combination Immunotherapy with CAR T Cells and Checkpoint Blockade for the Treatment of Solid Tumors. *Cancer Cell*. 2019;36(5):471-482. doi:10.1016/j.ccell.2019.09.006
25. Esfahani K, Al-Aubodah TA, Thebault P, et al. Targeting the mTOR pathway uncouples the efficacy and toxicity of PD-1 blockade in renal transplantation. *Nat Commun*. 2019;10(1):4712. Published 2019 Oct 17. doi:10.1038/s41467-019-12628-1
26. Song P, Zhang J, Shang C, et al. Real-world evidence and clinical observations of the treatment of advanced non-small cell lung cancer with PD-1/PD-L1 inhibitors [published correction appears in Sci Rep. 2020 Jan 27;10(1):1525]. *Sci Rep*. 2019;9(1):4278. Published 2019 Mar 12. doi:10.1038/s41598-019-40748-7
27. Anker JF, Naseem AF, Mok H, et al. Multi-faceted immunomodulatory and tissue-tropic clinical bacterial isolate potentiates prostate cancer immunotherapy. *Nat Commun*. 2018;9(1):1591. Published 2018 Apr 23. doi:10.1038/s41467-018-03900-x
28. Borcoman E, Le Tourneau C. Pembrolizumab in cervical cancer: latest evidence and clinical usefulness. *Ther Adv Med Oncol*. 2017;9(6):431-439. doi:10.1177/1758834017708742
29. Chen X, Zhu B, Luo Y, et al. Interleukin-28B Plays a Therapeutic Role on Mouse U14 Cervical Cancer Cells by Down-Regulating CD4+CD25+FoxP3+Regulatory T Cells In Vivo. *Int J Gynecol Cancer*. 2015 Oct;25(8):1369-76. doi: 10.1097/IGC.0000000000000528.
30. Li L, Ma Y, Liu S, et al. Interleukin 10 promotes immune response by increasing the survival of activated CD8+ T cells in human papillomavirus 16-infected cervical cancer. *Tumour Biol*. 2016 Oct 11. doi: 10.1007/s13277-016-5466-3.
31. Kucinski I, Dinan M, Kolahgar G, Piddini E. Chronic activation of JNK JAK/STAT and oxidative stress signalling causes the loser cell status. *Nat Commun*. 2017;8(1):136. Published 2017 Jul 26. doi:10.1038/s41467-017-00145-y
32. Berglund, Lucinda J et al. "IL-21 signalling via STAT3 primes human naive B cells to respond to IL-2 to enhance their differentiation into plasmablasts." *Blood* vol. 122,24 (2013): 3940-50. doi:10.1182/blood-2013-06-506865
33. Dobbs AK, Bosompem A, Coustan-Smith E, Tyerman G, Saulsbury FT, Conley ME. Agammaglobulinemia associated with BCR μ B cells and enhanced expression of CD19. *Blood*. 2011;118(7):1828-1837. doi:10.1182/blood-2011-01-330472
34. Dobenecker MW, Kim JK, Marcello J, et al. Coupling of T cell receptor specificity to natural killer T cell development by bivalent histone H3 methylation. *J Exp Med*. 2015;212(3):297-306. doi:10.1084/jem.20141499
35. Do MH, Wang X, Zhang X, et al. Nutrient mTORC1 signaling underpins regulatory T cell control of immune tolerance. *J Exp Med*. 2020;217(1):e20190848. doi:10.1084/jem.20190848
36. Chi H, Hsiao KL, Weng LC, Liu CP, Liu HF. Persistence and continuous evolution of the human respiratory syncytial virus in northern Taiwan for two decades. *Sci Rep*. 2019;9(1):4704. Published 2019 Mar 18. doi:10.1038/s41598-019-41332-9
37. Kannen V, de Oliveira EC, Motta BZ, Chaguri AJ, Brunaldi MO, Garcia SB. Trypanosomiasis-induced megacolon illustrates how myenteric neurons modulate the risk for colon cancer in rats and humans. *PLoS Negl Trop Dis*. 2015;9(4):e0003744. Published 2015 Apr 17. doi:10.1371/journal.pntd.0003744.
38. Zhang R, Dong L, Yu J. Concomitant Pathogenic Mutations and Fusions of Driver Oncogenes in Tumors. *Front Oncol*. 2021;10:544579. Published 2021 Jan 15. doi:10.3389/fonc.2020.544579
39. Zhao D, Zhang L, Zhang M, et al. Broad genic repression domains signify enhanced silencing of oncogenes. *Nat Commun*. 2020;11(1):5560. Published 2020 Nov 3. doi:10.1038/s41467-020-18913-8

Tables

Table1 Quantify the activity or enrichment levels of immune cells in cervical cancer tumor tissues.

ID	StromalScore	ImmuneScore	ESTIMATEScore
TCGA_TCGA-EK-A2R0	-3.517449176	359.8691358	356.3516866
TCGA_TCGA-VS-A8EB	-709.8741808	807.0570474	97.1828666
TCGA_TCGA-EA-A3Y4	-386.0278876	1881.382786	1495.354898
TCGA_TCGA-C5-A2LS	-1785.390236	-150.1739071	-1935.564143
TCGA_TCGA-C5-A1M8	-915.7614674	38.81439731	-876.9470701
TCGA_TCGA-HM-A6W2	-598.9564679	-164.6654706	-763.6219385
TCGA_TCGA-C5-A7CH	-694.3603208	233.9091487	-460.451172
TCGA_TCGA-C5-A3HE	-485.4265892	1503.586513	1018.159923
TCGA_TCGA-EK-A2RL	-1136.936501	-35.45517007	-1172.391671
TCGA_TCGA-EX-A1H6	-736.05654	163.5624482	-572.4940918
TCGA_TCGA-EK-A2R8	-723.2440422	445.1609468	-278.0830953
TCGA_TCGA-UC-A7PD	-989.4850413	358.0927629	-631.3922784
TCGA_TCGA-MA-AA3Z	-1206.62389	1186.075149	-20.54874097
TCGA_TCGA-VS-A9UD	-705.6616553	2129.940662	1424.279007
TCGA_TCGA-VS-A954	-473.1577822	460.847782	-12.31000024
TCGA_TCGA-ZJ-AB0H	-33.05644944	1625.549396	1592.492946
TCGA_TCGA-EK-A2PG	-1677.904481	85.39771252	-1592.506768
TCGA_TCGA-C5-A3HD	-1670.179662	-133.8448045	-1804.024467
TCGA_TCGA-JX-A3Q8	-1013.252346	904.6064875	-108.6458586
TCGA_TCGA-EA-A3HQ	-164.9285878	1265.187802	1100.259214
TCGA_TCGA-EX-A8YF	-745.637804	1331.735724	586.0979199
TCGA_TCGA-DS-A0VN	96.06312908	1938.482336	2034.545465
TCGA_TCGA-EK-A2H0	-1424.196051	516.4685973	-907.7274538
TCGA_TCGA-FU-A3HZ	-716.5630347	153.5333464	-563.0296883
TCGA_TCGA-C5-A1MH	161.6833058	1813.626223	1975.309529
TCGA_TCGA-IR-A3L7	-945.716623	-327.6656931	-1273.382316
TCGA_TCGA-MA-AA3W	-613.0827602	2075.151862	1462.069102
TCGA_TCGA-C5-A0TN	-820.495152	512.9653761	-307.5297759
TCGA_TCGA-IR-A3LB	214.1683343	468.9616823	683.1300166
TCGA_TCGA-VS-A952	-1419.601417	-6.124209929	-1425.725627
TCGA_TCGA-C5-A1MQ	213.6522559	1820.45415	2034.106406
TCGA_TCGA-C5-A3HF	-459.6248707	777.561337	317.9364663
TCGA_TCGA-EX-A69M	-860.9711719	1559.711461	698.740289
TCGA_TCGA-C5-A1MP	482.4491543	1773.714822	2256.163976
TCGA_TCGA-C5-A7CG	-219.5010539	2345.097808	2125.596754
TCGA_TCGA-C5-A1BN	-1341.462426	-217.5356484	-1558.998075
TCGA_TCGA-FU-A5XV	-918.0154845	394.4318583	-523.5836263
TCGA_TCGA-EA-A3QE	-320.1314106	1963.138981	1643.00757
TCGA_TCGA-C5-A2M2	-1541.419618	-43.4855884	-1584.905207
TCGA_TCGA-VS-A8Q8	-597.8779547	1371.075625	773.1976708
TCGA_TCGA-BI-A0VR	-284.5356228	1499.078289	1214.542666
TCGA_TCGA-EK-A2PL	-1183.836706	418.443716	-765.3929903
TCGA_TCGA-DR-A0ZL	-1422.258812	98.80157387	-1323.457239

TCGA_TCGA-LP-A5U3	-921.9545439	934.9840442	13.02950031
TCGA_TCGA-MY-A5BF	-798.3862125	1242.490612	444.1043999
TCGA_TCGA-Q1-A73S	-1029.23238	-444.2308477	-1473.463228
TCGA_TCGA-JW-A5VH	-523.5269879	-803.8486871	-1327.375675
TCGA_TCGA-VS-A9UP	-973.2298332	-954.7637513	-1927.993585
TCGA_TCGA-C5-A1BK	-326.9515519	2118.198037	1791.246485
TCGA_TCGA-VS-A8EC	-1684.840814	-967.4448746	-2652.285689
TCGA_TCGA-IR-A3LH	718.1406554	2346.511482	3064.652137
TCGA_TCGA-VS-A8QA	-1648.239453	419.2154507	-1229.024003
TCGA_TCGA-C5-A8XJ	-24.75696241	408.921766	384.1648035
TCGA_TCGA-EA-A5FO	-1914.620034	-375.2383147	-2289.858349
TCGA_TCGA-FU-A3HY	-1360.002029	-90.56546234	-1450.567491
TCGA_TCGA-FU-A3TQ	-510.7474105	928.2533221	417.5059117
TCGA_TCGA-FU-A57G	567.4999264	-70.75889343	496.741033
TCGA_TCGA-C5-A3HL	-964.788733	345.3041398	-619.4845932
TCGA_TCGA-DS-A0VM	-275.8149525	727.4419576	451.6270052
TCGA_TCGA-DS-A7WH	160.6913865	122.6190059	283.3103925
TCGA_TCGA-EK-A2RN	-718.7806814	1300.306434	581.5257528
TCGA_TCGA-ZJ-AAXB	-466.5292224	-233.941381	-700.4706033
TCGA_TCGA-C5-A2LX	-98.69039624	1990.166079	1891.475683
TCGA_TCGA-EA-A410	-26.14939323	222.8790757	196.7296824
TCGA_TCGA-JX-A3PZ	-121.1503796	1351.018929	1229.86855
TCGA_TCGA-EX-A69L	-113.7298328	1933.321369	1819.591537
TCGA_TCGA-Q1-A6DV	-1393.155808	251.2921932	-1141.863615
TCGA_TCGA-VS-A953	-1276.384822	506.9741839	-769.4106385
TCGA_TCGA-C5-A1M5	-589.8091487	1269.789491	679.9803427
TCGA_TCGA-C5-A902	-1124.330382	1351.535171	227.2047892
TCGA_TCGA-C5-A1M7	-594.8257437	1081.856128	487.0303838
TCGA_TCGA-VS-A9V1	-1319.023385	421.5251236	-897.498261
TCGA_TCGA-DG-A2KK	-913.3305072	681.488378	-231.8421293
TCGA_TCGA-EA-A3HU	-324.7868567	2025.649392	1700.862535
TCGA_TCGA-C5-A1BE	-697.1055116	543.3733898	-153.7321219
TCGA_TCGA-WL-A834	-726.3364379	-50.74384381	-777.0802817
TCGA_TCGA-FU-A3EO	-600.7886797	852.6806278	251.8919481
TCGA_TCGA-Q1-A730	-609.5107143	957.1637074	347.6529931
TCGA_TCGA-JW-AAVH	-1401.590513	114.5991125	-1286.9914
TCGA_TCGA-HM-A4S6	-51.37938551	1479.39012	1428.010734
TCGA_TCGA-VS-A9UV	-1196.084883	209.8263667	-986.2585165
TCGA_TCGA-EA-A5ZE	181.8827612	1466.478147	1648.360908
TCGA_TCGA-VS-A9V5	-1004.603226	-84.73569116	-1089.338917
TCGA_TCGA-C5-A1BJ	-236.9667608	1190.535512	953.5687513
TCGA_TCGA-Q1-A73R	-848.9287494	-201.4992809	-1050.42803
TCGA_TCGA-IR-A3LI	-2029.543167	-210.2596049	-2239.802772
TCGA_TCGA-C5-A1MN	-1085.220531	260.5920935	-824.628437

TCGA_TCGA-C5-A7XC	-213.7777491	1215.900332	1002.122583
TCGA_TCGA-ZJ-AAXJ	-1128.368998	594.7437696	-533.6252284
TCGA_TCGA-EA-A1QS	947.247913	687.2135582	1634.461471
TCGA_TCGA-C5-A7UE	-1228.10908	431.3165282	-796.7925517
TCGA_TCGA-EK-A3GM	-1516.595038	-196.5798703	-1713.174909
TCGA_TCGA-FU-A3WB	-903.1430352	-65.80861324	-968.9516484
TCGA_TCGA-JW-A5VJ	-992.9400605	285.6702048	-707.2698557
TCGA_TCGA-LP-A4AW	371.0461867	337.7423533	708.78854
TCGA_TCGA-VS-A9V4	-1363.771116	-101.7202335	-1465.491349
TCGA_TCGA-ZJ-AAXU	-660.539715	1394.391233	733.8515182
TCGA_TCGA-VS-A957	-1699.244839	25.55609825	-1673.68874
TCGA_TCGA-EX-A449	-1438.392458	-21.56747172	-1459.95993
TCGA_TCGA-HG-A2PA	-369.238852	856.6630634	487.4242114
TCGA_TCGA-MA-AA3Y	-244.0955242	1585.036527	1340.941002
TCGA_TCGA-VS-A9UI	-1000.148928	1143.034067	142.885139
TCGA_TCGA-JW-A5VL	-741.8043271	1380.285544	638.4812171
TCGA_TCGA-VS-A8EI	-466.7393567	1125.046965	658.3076082
TCGA_TCGA-EA-A97N	-37.71465464	288.7085343	250.9938797
TCGA_TCGA-EA-A78R	-73.74477264	1024.845054	951.1002812
TCGA_TCGA-C5-A7CK	-238.7828921	-431.7719983	-670.5548904
TCGA_TCGA-FU-A3NI	-371.6686291	585.1538048	213.4851757
TCGA_TCGA-EA-A556	81.71305586	-300.3816523	-218.6685965
TCGA_TCGA-C5-A8YQ	-863.879883	500.3247321	-363.5551509
TCGA_TCGA-IR-A3LF	-648.8358013	593.1839238	-55.65187752
TCGA_TCGA-C5-A7X8	333.6459707	726.3880539	1060.034025
TCGA_TCGA-VS-A9U6	-476.6330679	952.6290359	475.995968
TCGA_TCGA-VS-A94Z	-182.7203574	1991.456813	1808.736456
TCGA_TCGA-VS-A94Y	-428.3897417	574.0003368	145.6105951
TCGA_TCGA-C5-A2LV	-386.9532276	1272.911329	885.9581016
TCGA_TCGA-C5-A8YR	-488.0049364	1375.574494	887.5695572
TCGA_TCGA-JW-A852	-1134.055254	744.9438813	-389.1113727
TCGA_TCGA-VS-A9UJ	-1143.918846	-806.258864	-1950.17771
TCGA_TCGA-DS-A0VK	-515.7231744	114.8359859	-400.8871885
TCGA_TCGA-DG-A2KL	625.6458521	1028.661155	1654.307007
TCGA_TCGA-DG-A2KJ	-421.7395949	1594.224981	1172.485386
TCGA_TCGA-DS-A7WI	-1121.672277	816.0402482	-305.6320283
TCGA_TCGA-C5-A7CO	-1144.193903	600.1001728	-544.0937303
TCGA_TCGA-ZJ-AAX8	467.9466539	1320.022727	1787.969381
TCGA_TCGA-LP-A4AU	-661.4647825	758.5458042	97.08102165
TCGA_TCGA-EK-A3GK	-1581.999576	496.2670852	-1085.732491
TCGA_TCGA-JX-A5QV	-1044.836686	921.3671322	-123.4695542
TCGA_TCGA-C5-A907	-766.6361994	926.1615635	159.525364
TCGA_TCGA-MY-A5BD	-1372.469472	-33.4242051	-1405.893677
TCGA_TCGA-UC-A7PI	-1338.936186	34.47403452	-1304.462152

TCGA_TCGA-VS-A9UH	459.1957716	2097.076402	2556.272174
TCGA_TCGA-LP-A4AV	77.86580412	1585.554707	1663.420511
TCGA_TCGA-VS-A8QF	-436.5387686	1038.749223	602.2104542
TCGA_TCGA-UC-A7PG	-470.5358655	987.0114507	516.4755852
TCGA_TCGA-VS-A9UO	-2001.762547	1.280199848	-2000.482347
TCGA_TCGA-LP-A5U2	-1022.724769	369.4275906	-653.2971786
TCGA_TCGA-JX-A3Q0	-679.4389736	1324.13483	644.6958568
TCGA_TCGA-EX-A3L1	-302.2382658	1016.800406	714.5621406
TCGA_TCGA-EA-A3HS	-547.5266305	698.1771005	150.65047
TCGA_TCGA-C5-A2LT	-93.83312282	1111.99009	1018.156967
TCGA_TCGA-ZX-AA5X	764.3925104	1396.907233	2161.299743
TCGA_TCGA-EA-A439	270.7916549	206.753208	477.544863
TCGA_TCGA-C5-A7CL	-465.2903074	525.1645547	59.87424728
TCGA_TCGA-C5-A1MF	-384.4345727	1172.970732	788.5361597
TCGA_TCGA-VS-A8EL	-116.2846865	1853.050127	1736.76544
TCGA_TCGA-EK-A2GZ	-1102.891345	561.2555391	-541.6358056
TCGA_TCGA-VS-A8QM	228.9341028	1916.556875	2145.490977
TCGA_TCGA-EX-A1H5	-933.5408743	156.8791415	-776.6617328
TCGA_TCGA-Q1-A5R2	-204.2746895	1418.926543	1214.651854
TCGA_TCGA-HM-A3JK	807.2669787	1046.119735	1853.386714
TCGA_TCGA-C5-A7CJ	332.8680352	1432.481791	1765.349826
TCGA_TCGA-C5-A7UC	-1141.115109	-273.6018186	-1414.716928
TCGA_TCGA-C5-A1MJ	385.5113874	563.0109369	948.5223243
TCGA_TCGA-EA-A3QD	470.9935186	2350.17568	2821.169199
TCGA_TCGA-VS-A8QH	-1136.998123	34.97646496	-1102.021658
TCGA_TCGA-C5-A1ME	-829.5308508	935.8398811	106.3090303
TCGA_TCGA-C5-A901	-473.2097189	615.440169	142.2304501
TCGA_TCGA-C5-A8YT	251.234865	317.4189053	568.6537703
TCGA_TCGA-EK-A2PM	-1011.555055	-898.3083047	-1909.86336
TCGA_TCGA-FU-A770	-1161.09167	465.8278415	-695.263829
TCGA_TCGA-EK-A2RB	-1070.450209	501.3061983	-569.1440108
TCGA_TCGA-VS-A9UM	18.02377422	1236.059936	1254.08371
TCGA_TCGA-VS-A9V2	-538.5406233	1373.015137	834.4745136
TCGA_TCGA-FU-A3TX	-864.0318635	794.8723117	-69.15955181
TCGA_TCGA-C5-A2LZ	-1109.48228	939.9382015	-169.5440784
TCGA_TCGA-ZJ-A8QR	-1156.346218	516.3784466	-639.9677715
TCGA_TCGA-JW-A5VG	-951.9486988	1124.558863	172.6101644
TCGA_TCGA-MU-A5YI	536.7674403	992.3456936	1529.113134
TCGA_TCGA-Q1-A73P	-815.7320584	782.8764865	-32.85557187
TCGA_TCGA-JW-A5VK	-1319.567437	-13.40886695	-1332.976304
TCGA_TCGA-DS-A109	176.1914174	1549.299326	1725.490743
TCGA_TCGA-PN-A8MA	-312.6925898	608.952697	296.2601072
TCGA_TCGA-EA-A5ZF	-120.54748	-213.7386066	-334.2860866
TCGA_TCGA-VS-A9UQ	-480.2287179	124.8066813	-355.4220365

TCGA_TCGA-MA-AA42	-229.8031979	2505.710772	2275.907575
TCGA_TCGA-VS-A9U7	-592.0857561	1442.109912	850.0241561
TCGA_TCGA-DS-A10D	-46.81963607	2143.075936	2096.2563
TCGA_TCGA-ZJ-AAX4	-201.7105367	1572.711653	1371.001116
TCGA_TCGA-MY-A913	-636.7911152	1045.403194	408.6120789
TCGA_TCGA-UC-A7PF	-95.903713	1761.334085	1665.430372
TCGA_TCGA-C5-A2LY	-386.574892	1974.099208	1587.524316
TCGA_TCGA-VS-A9UU	-1301.377824	189.5481604	-1111.829663
TCGA_TCGA-C5-A8ZZ	460.0736037	-124.2734617	335.800142
TCGA_TCGA-EK-A3GJ	-792.3857356	1466.146123	673.7603876
TCGA_TCGA-C5-A2M1	-996.8974482	1280.598448	283.7010002
TCGA_TCGA-C5-A1MI	-560.5822769	672.1618437	111.5795669
TCGA_TCGA-EA-A6QX	-558.7044988	1053.504418	494.7999189
TCGA_TCGA-C5-A7X3	-84.09926964	1205.085782	1120.986512
TCGA_TCGA-EA-A3HT	335.596958	858.6483742	1194.245332
TCGA_TCGA-VS-A9UB	-619.9881179	1998.353273	1378.365155
TCGA_TCGA-VS-A8EK	-1256.929719	417.7072123	-839.2225071
TCGA_TCGA-VS-A9UC	-230.1593299	1038.296579	808.1372487
TCGA_TCGA-VS-A958	-531.2261653	2054.67681	1523.450645
TCGA_TCGA-EK-A2R7	-672.2173219	1000.238199	328.0208775
TCGA_TCGA-C5-A1M6	-1134.716655	-403.7313387	-1538.447994
TCGA_TCGA-EK-A2RA	-1063.157116	1578.328013	515.1708965
TCGA_TCGA-VS-A8EG	-1379.377795	253.9300987	-1125.447696
TCGA_TCGA-LP-A7HU	-422.4645492	1178.910301	756.4457519
TCGA_TCGA-VS-A9V3	-734.2446711	1041.021053	306.7763817
TCGA_TCGA-DS-A10C	-829.5993743	1034.004927	204.4055529
TCGA_TCGA-VS-A8Q9	-1330.95395	264.8772767	-1066.076674
TCGA_TCGA-EK-A2H1	23.35905784	1399.450279	1422.809336
TCGA_TCGA-ZJ-AAXT	-955.6035651	563.4141274	-392.1894377
TCGA_TCGA-EK-A2PI	-505.0369934	-251.0706943	-756.1076876
TCGA_TCGA-VS-A94X	-1209.460526	439.5217044	-769.9388212
TCGA_TCGA-VS-A9UT	313.3537646	2285.543244	2598.897008
TCGA_TCGA-EA-A509	-1101.932498	675.5935503	-426.3389481
TCGA_TCGA-VS-A9U5	-1009.13051	1108.636762	99.50625213
TCGA_TCGA-EK-A2IP	-1125.823602	456.9336372	-668.8899653
TCGA_TCGA-RA-A741	-393.8859229	1472.697472	1078.81155
TCGA_TCGA-IR-A3LC	-778.9225422	610.3006221	-168.6219201
TCGA_TCGA-DG-A2KM	629.5159409	3009.777513	3639.293454
TCGA_TCGA-FU-A3YQ	191.6052556	1687.745195	1879.350451
TCGA_TCGA-EK-A3GN	-1581.603156	-374.5774376	-1956.180594
TCGA_TCGA-C5-A8XH	-674.4599204	1063.067666	388.6077456
TCGA_TCGA-C5-A1BM	-192.7667125	1648.991992	1456.225279
TCGA_TCGA-DS-A10B	-519.4587668	735.8256001	216.3668332
TCGA_TCGA-EA-A43B	-356.2886286	1354.104212	997.815583

TCGA_TCGA-BI-A20A	-360.153404	1451.111472	1090.958068
TCGA_TCGA-VS-A9UZ	-945.6217839	524.0050507	-421.6167332
TCGA_TCGA-EA-A5ZD	-221.9022637	1333.924267	1112.022003
TCGA_TCGA-C5-A1BQ	-620.0845594	1318.472705	698.3881457
TCGA_TCGA-JW-A5VI	-144.6891627	933.2773853	788.5882225
TCGA_TCGA-ZJ-AAXF	9.595459022	1465.916044	1475.511503
TCGA_TCGA-IR-A3LA	-559.0027519	273.3464295	-285.6563223
TCGA_TCGA-EK-A2RK	-870.3433706	1145.043399	274.700028
TCGA_TCGA-C5-A7CM	-669.851336	-166.5530635	-836.4043995
TCGA_TCGA-LP-A4AX	-93.07808095	1785.985916	1692.907835
TCGA_TCGA-Q1-A5R3	-936.4204788	1113.328421	176.9079424
TCGA_TCGA-C5-A8XI	-750.0031169	1016.579925	266.576808
TCGA_TCGA-MA-AA3X	-115.8190089	1238.568435	1122.749426
TCGA_TCGA-VS-AA62	-254.4866139	1848.730288	1594.243674
TCGA_TCGA-C5-A1BF	-105.0486242	967.731125	862.6825008
TCGA_TCGA-C5-A1BI	-58.0100791	1540.509674	1482.499595
TCGA_TCGA-EK-A2IR	-1304.167649	-793.7949309	-2097.962579
TCGA_TCGA-VS-A9UL	-1498.176597	-1012.04193	-2510.218527
TCGA_TCGA-XS-A8TJ	-415.8137843	842.9995718	427.1857875
TCGA_TCGA-C5-A1M9	-1100.070736	241.6124479	-858.4582884
TCGA_TCGA-FU-A40J	-543.350472	924.8104378	381.4599658
TCGA_TCGA-HM-A3JJ	243.8157176	1059.668437	1303.484155
TCGA_TCGA-MA-AA41	-1034.881994	554.8744063	-480.0075874
TCGA_TCGA-EA-A411	389.1193117	629.6436112	1018.762923
TCGA_TCGA-DS-A3LQ	156.662756	547.7219289	704.3846849
TCGA_TCGA-EK-A2PK	-124.9477247	1787.060869	1662.113145
TCGA_TCGA-VS-A950	-647.9708375	338.7192408	-309.2515967
TCGA_TCGA-VS-A94W	-422.593049	1655.72381	1233.130761
TCGA_TCGA-VS-A959	-575.3865344	1063.399383	488.0128485
TCGA_TCGA-2W-A8YY	-768.7452746	317.7654295	-450.979845
TCGA_TCGA-DS-A5RQ	-636.5344114	1045.577299	409.0428876
TCGA_TCGA-Q1-A6DT	-940.3644863	133.1063149	-807.2581714
TCGA_TCGA-JW-A69B	-427.2618125	758.6454133	331.3836008
TCGA_TCGA-ZJ-AAXA	-612.1730053	38.7819838	-573.3910215
TCGA_TCGA-EA-A1QT	-771.7521508	418.7916854	-352.9604654
TCGA_TCGA-MY-A5BE	176.4889143	2750.907959	2927.396874
TCGA_TCGA-MU-A51Y	62.40181311	1776.664172	1839.065985
TCGA_TCGA-FU-A23K	-166.4086398	1337.448561	1171.039921
TCGA_TCGA-EA-A3HR	-743.389344	312.4310087	-430.9583354
TCGA_TCGA-VS-A8QC	-226.2125385	405.0229738	178.8104353
TCGA_TCGA-ZJ-ABOI	-812.9673635	627.3273764	-185.639987
TCGA_TCGA-GH-A9DA	-530.4467625	943.4849989	413.0382364
TCGA_TCGA-EK-A2RC	-101.1340749	1370.059306	1268.925231
TCGA_TCGA-DS-A7WF	-545.5414729	73.67548036	-471.8659925

TCGA_TCGA-EA-A44S	-485.0291818	1064.17311	579.1439281
TCGA_TCGA-Q1-A6DW	-713.5160555	531.907256	-181.6087996
TCGA_TCGA-FU-A2QG	-1425.847157	505.7380768	-920.1090798
TCGA_TCGA-C5-A1MK	297.5208271	691.9621969	989.4830239
TCGA_TCGA-ZJ-A8QO	58.06566867	1489.203447	1547.269115
TCGA_TCGA-MA-AA43	-125.4674714	173.4660605	47.99858919
TCGA_TCGA-C5-A1BL	-917.3475949	1204.534361	287.1867666
TCGA_TCGA-EA-A4BA	-333.275242	-686.5144923	-1019.789734
TCGA_TCGA-ZJ-A8QQ	-1185.616239	443.2437422	-742.3724969
TCGA_TCGA-VS-A8EJ	-940.3753982	336.2761249	-604.0992733
TCGA_TCGA-C5-A7UI	-447.3666879	1537.809048	1090.44236
TCGA_TCGA-Q1-A73Q	-1062.517489	77.79340569	-984.7240833
TCGA_TCGA-DS-A1OA	-191.8743139	1316.667973	1124.793659
TCGA_TCGA-C5-A8XK	-992.5315378	494.7106587	-497.8208791
TCGA_TCGA-C5-A905	-1490.330076	133.6652039	-1356.664872
TCGA_TCGA-C5-A7X5	-966.1945783	-311.7959346	-1277.990513
TCGA_TCGA-EK-A2RM	-113.9946959	110.8463844	-3.148311511
TCGA_TCGA-IR-A3LL	-365.6400699	2001.833667	1636.193598
TCGA_TCGA-DR-A0ZM	-125.7680585	1752.556985	1626.788926
TCGA_TCGA-R2-A69V	315.2989835	2657.804777	2973.10376
TCGA_TCGA-C5-A7UH	-555.9849629	595.0923908	39.10742784
TCGA_TCGA-IR-A3LK	-1065.601872	965.1497661	-100.4521057
TCGA_TCGA-EA-A50E	479.6667898	739.702461	1219.369251
TCGA_TCGA-EK-A2RE	-967.4665086	-213.0678691	-1180.534378
TCGA_TCGA-ZJ-AAXD	-268.0557241	239.3541971	-28.70152706
TCGA_TCGA-ZJ-AAXN	-550.262727	952.6847412	402.4220142
TCGA_TCGA-BI-A0VS	-257.4371793	811.1329752	553.6957959
TCGA_TCGA-C5-A1ML	-733.0641905	579.9900069	-153.0741835
TCGA_TCGA-MU-A8JM	-687.1408248	1029.290124	342.149299
TCGA_TCGA-EK-A2RJ	-507.1977501	1386.107158	878.9094077
TCGA_TCGA-VS-A9V0	-1203.936132	-478.2968754	-1682.233007
TCGA_TCGA-DS-A0VL	-853.6834801	918.8291416	65.14566157
TCGA_TCGA-VS-A9UR	-1347.213004	-58.00759679	-1405.220601
TCGA_TCGA-DG-A2KH	-2014.299315	-184.2341411	-2198.533456
TCGA_TCGA-4J-AA1J	-425.0915591	125.7447671	-299.346792
TCGA_TCGA-FU-A23L	-679.6378335	1442.509877	762.8720434
TCGA_TCGA-ZJ-AAXI	-1275.087202	444.9251641	-830.1620381
TCGA_TCGA-EK-A2R9	163.1585256	1290.084726	1453.243251
TCGA_TCGA-Q1-A5R1	-1163.11487	330.6470637	-832.4678061
TCGA_TCGA-VS-A9UY	-759.2167352	876.6643163	117.4475811
TCGA_TCGA-VS-A8EH	-1298.181447	86.91677473	-1211.264673
geoMatrix_GSM763220	-654.6590924	552.5747352	-102.0843572
geoMatrix_GSM763221	-329.3497723	962.3115346	632.9617622
geoMatrix_GSM763222	-478.6479886	716.789865	238.1418764

geoMatrix_GSM763223	-519.0665887	1008.697944	489.6313556
geoMatrix_GSM763224	-733.7975756	557.8742509	-175.9233247
geoMatrix_GSM763225	-699.8444846	950.5503157	250.7058311
geoMatrix_GSM763226	-474.2760364	858.7461463	384.47011
geoMatrix_GSM763227	-700.5041778	1132.889548	432.3853702
geoMatrix_GSM763228	-559.052671	1331.244576	772.1919053
geoMatrix_GSM763229	-690.1406598	914.3640605	224.2234007
geoMatrix_GSM763230	-726.9367019	476.7361043	-250.2005976
geoMatrix_GSM763231	-763.0001495	713.6874832	-49.31266632
geoMatrix_GSM763237	-593.134287	836.2078876	243.0736006
geoMatrix_GSM763238	-797.5289076	853.7989934	56.27008588
geoMatrix_GSM763239	-777.5015779	712.2706763	-65.23090161
geoMatrix_GSM763242	-745.046433	733.743796	-11.30263693
geoMatrix_GSM763243	-618.5795121	1022.397379	403.8178667
geoMatrix_GSM763244	-443.2070624	843.923292	400.7162296
geoMatrix_GSM763245	-818.513085	681.0526026	-137.4604824
geoMatrix_GSM763246	-874.8800976	919.8699159	44.9898183
geoMatrix_GSM763247	-581.2625053	1288.62569	707.3631847
geoMatrix_GSM763248	-375.4726787	1046.388	670.915321
geoMatrix_GSM763249	-661.319932	1163.091851	501.7719194
geoMatrix_GSM763250	-814.4967319	574.8527475	-239.6439845
geoMatrix_GSM763251	-850.5966847	780.4513574	-70.14532726
geoMatrix_GSM763257	-775.6140463	595.9868699	-179.6271764
geoMatrix_GSM763261	-490.1321126	1002.199725	512.0676128
geoMatrix_GSM763262	-912.8298201	816.2565947	-96.57322533
geoMatrix_GSM763263	-515.2547452	1219.404493	704.1497477
geoMatrix_GSM763264	-596.8242353	649.3632468	52.53901149
geoMatrix_GSM763265	-665.4111383	594.4840084	-70.92712993
geoMatrix_GSM763266	-783.4904633	881.9902504	98.4997871
geoMatrix_GSM763267	-672.6367895	683.7983735	11.16158393
geoMatrix_GSM763268	-756.32166	953.5677784	197.2461184
geoMatrix_GSM763269	-758.3283734	1134.109677	375.7813033
geoMatrix_GSM763270	-400.2306593	679.8181604	279.5875011
geoMatrix_GSM763271	-757.3202835	924.4170346	167.0967512
geoMatrix_GSM763272	-784.2815915	384.5697365	-399.711855
geoMatrix_GSM763273	-663.2651974	933.7910768	270.5258794
geoMatrix_GSM763274	-807.3929457	802.3143439	-5.078601808
geoMatrix_GSM763275	-813.2348183	813.9444015	0.709583281
geoMatrix_GSM763276	-522.9651263	1025.374188	502.4090612
geoMatrix_GSM763277	-885.1971675	455.635799	-429.5613685
geoMatrix_GSM763278	-797.3957918	791.6623296	-5.733462189
geoMatrix_GSM763279	-747.3085096	291.5437183	-455.7647914
geoMatrix_GSM763280	-675.1043158	894.3623368	219.258021
geoMatrix_GSM763281	-758.8591965	783.9186828	25.05948631

geoMatrix_GSM763282	-657.3158648	954.2923385	296.9764736
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Table2 List of differently expressed genes (DEGs).

Number	DEGs	Number	DEGs
1	CD8A	57	SIT1
2	GZMH	58	CST7
3	LAG3	59	GPR171
4	NKG7	60	IRF1
5	PDCD1	61	ITGAL
6	CD3D	62	SLAMF6
7	IFNG	63	APOL3
8	GZMM	64	SH2D1A
9	GZMB	65	GBP4
10	CCL4	66	CD74
11	CCL5	67	GZMA
12	PRF1	68	IL2RB
13	CXCL9	69	CTLA4
14	C1QA	70	HLA-DPB1
15	GBP5	71	HLA-DRA
16	APOE	72	ITM2A
17	APOC1	73	CD52
18	CXCL13	74	ETV7
19	C1QB	75	GZMK
20	UBD	76	IL2RG
21	AKR1C3	77	CIITA
22	CXCL11	78	HLA-DMA
23	CXCL10	79	HLA-DPA1
24	GLDC	80	HLA-DRB5
25	KRT23	81	CDH13
26	AKR1C2	82	HLA-DMB
27	LCN2	83	PLA2G2D
28	C10orf99	84	ACSL5
29	MMP9	85	HLA-DQB1
30	ITGA5	86	GBP1
31	FN1	87	HLA-DOA
32	FKBP10	88	BATF
33	G0S2	89	C1QC
34	CXCL5	90	C2
35	MMP1	91	AMIGO2
36	CDA	92	MFAP5
37	TMPRSS11A	93	IL1B
38	MMP3	94	INHBA
39	FST	95	COL5A1
40	DUOX2	96	THBS2
41	CEACAM7	97	COL12A1
42	MUC4	98	IL1A
43	CXCR6	99	AIM2

44	CD2	100	LAMC2
45	CD7	101	PPP1R14C
46	ZNF683	102	POSTN
47	CXCR3	103	HLA-DQA2
48	CD3E	104	LYZ
49	TBX21	105	MMP13
50	CD3G	106	KLHDC7B
51	SLA2	107	MMP10
52	FASLG	108	LCE3D
53	CRTAM	109	KLK5
54	CTSW	110	SBSN
55	CD96	111	PI3
56	TBC1D10C		

Table3 Grouping of ICI gene type A and B.

gene	positive correlation	gene	negative correlation
CD8A	A	AKR1C3	B
GZMH	A	KRT23	B
LAG3	A	AKR1C2	B
NKG7	A	LCN2	B
PDCD1	A	C10orf99	B
CD3D	A	MMP9	B
IFNG	A	ITGA5	B
GZMM	A	FN1	B
GZMB	A	MMP1	B
CCL4	A	CDA	B
CCL5	A	TMPRSS11A	B
PRF1	A	MMP3	B
CXCL9	A	FST	B
C1QA	A	DUOX2	B
GBP5	A	CDH13	B
APOE	A	AMIGO2	B
APOC1	A	MFAP5	B
CXCL13	A	IL1B	B
C1QB	A	INHBA	B
UBD	A	COL5A1	B
CXCL11	A	THBS2	B
CXCL10	A	COL12A1	B
GLDC	A	IL1A	B
FKBP10	A	AIM2	B
G0S2	A	LAMC2	B
CXCL5	A	PPP1R14C	B
CEACAM7	A	POSTN	B
MUC4	A	MMP13	B
CXCR6	A	MMP10	B
CD2	A	LCE3D	B
CD7	A	KLK5	B
ZNF683	A	SBSN	B
CXCR3	A	PI3	B
CD3E	A		
TBX21	A		
CD3G	A		
SLA2	A		
FASLG	A		
CRTAM	A		
CTSW	A		
CD96	A		
TBC1D10C	A		
SIT1	A		

CST7	A
GPR171	A
IRF1	A
ITGAL	A
SLAMF6	A
APOL3	A
SH2D1A	A
GBP4	A
CD74	A
GZMA	A
IL2RB	A
CTLA4	A
HLA-DPB1	A
HLA-DRA	A
ITM2A	A
CD52	A
ETV7	A
GZMK	A
IL2RG	A
CIITA	A
HLA-DMA	A
HLA-DPA1	A
HLA-DRB5	A
HLA-DMB	A
PLA2G2D	A
ACSL5	A
HLA-DQB1	A
GBP1	A
HLA-DOA	A
BATF	A
C1QC	A
C2	A
HLA-DQA2	A
LYZ	A
KLHDC7B	A

Table4 The significantly enriched biological processes of ICI gene type A (Each bar shows the top 30)

ONTOLOGY	ID	Description	BgRatio	pvalue	p.adjust	qvalue
BP	GO:0042110	T cell activation	464/18670	8.75E-17	1.24E-13	8.18E-14
BP	GO:0002449	lymphocyte mediated immunity	352/18670	3.20E-16	2.27E-13	1.50E-13
BP	GO:0030217	T cell differentiation	240/18670	3.57E-13	1.69E-10	1.11E-10
BP	GO:0030098	lymphocyte differentiation	353/18670	2.76E-12	9.78E-10	6.45E-10
BP	GO:0043368	positive T cell selection	34/18670	9.68E-12	2.74E-09	1.81E-09
BP	GO:0002460	adaptive immune response based on somatic recombination of immune receptors built from immunoglobulin superfamily domains	361/18670	6.13E-11	1.45E-08	9.55E-09
BP	GO:0045058	T cell selection	47/18670	1.10E-10	2.22E-08	1.46E-08
BP	GO:0070098	chemokine-mediated signaling pathway	88/18670	2.78E-10	4.93E-08	3.25E-08
BP	GO:0002683	negative regulation of immune system process	435/18670	6.07E-10	7.89E-08	5.21E-08
BP	GO:1990868	response to chemokine	97/18670	6.13E-10	7.89E-08	5.21E-08
BP	GO:1990869	cellular response to chemokine	97/18670	6.13E-10	7.89E-08	5.21E-08
BP	GO:0050863	regulation of T cell activation	314/18670	2.88E-09	3.40E-07	2.24E-07
BP	GO:0050866	negative regulation of cell activation	199/18670	1.00E-08	1.10E-06	7.23E-07
BP	GO:0010818	T cell chemotaxis	28/18670	2.26E-08	2.28E-06	1.51E-06
BP	GO:0051249	regulation of lymphocyte activation	485/18670	2.49E-08	2.35E-06	1.55E-06
BP	GO:0030593	neutrophil chemotaxis	104/18670	3.23E-08	2.86E-06	1.89E-06
BP	GO:0001909	leukocyte mediated cytotoxicity	107/18670	3.94E-08	3.28E-06	2.17E-06
BP	GO:0002228	natural killer cell mediated immunity	64/18670	4.49E-08	3.35E-06	2.21E-06
BP	GO:0048247	lymphocyte chemotaxis	64/18670	4.49E-08	3.35E-06	2.21E-06
BP	GO:0072676	lymphocyte migration	111/18670	5.08E-08	3.60E-06	2.37E-06
BP	GO:0045059	positive thymic T cell selection	13/18670	5.87E-08	3.96E-06	2.61E-06
BP	GO:0002695	negative regulation of leukocyte activation	175/18670	6.53E-08	4.20E-06	2.77E-06
BP	GO:1990266	neutrophil migration	118/18670	7.75E-08	4.59E-06	3.03E-06
BP	GO:0007159	leukocyte cell-cell adhesion	337/18670	7.78E-08	4.59E-06	3.03E-06
BP	GO:0071621	granulocyte chemotaxis	123/18670	1.03E-07	5.85E-06	3.86E-06
BP	GO:0006959	humoral immune response	356/18670	1.30E-07	7.06E-06	4.66E-06
BP	GO:0019835	cytolysis	40/18670	1.47E-07	7.64E-06	5.04E-06
BP	GO:0002697	regulation of immune effector process	462/18670	1.51E-07	7.64E-06	5.04E-06
BP	GO:0034341	response to interferon-gamma	199/18670	1.76E-07	8.59E-06	5.66E-06
CC	GO:0009897	external side of plasma membrane	393/19717	2.30E-14	2.51E-12	1.82E-12
CC	GO:0005623	cell	90/19717	7.30E-06	0.000397908	0.0002882
CC	GO:0001772	immunological synapse	36/19717	0.000169387	0.005381338	0.003897637
CC	GO:0030136	clathrin-coated vesicle	188/19717	0.000246494	0.005381338	0.003897637
CC	GO:0098802	plasma membrane signaling receptor complex	295/19717	0.00024685	0.005381338	0.003897637
CC	GO:0030665	clathrin-coated vesicle membrane	115/19717	0.000390298	0.007090412	0.005135499
CC	GO:0042101	T cell receptor complex	127/19717	0.000568109	0.008846273	0.006407247
CC	GO:0042627	chylomicron	13/19717	0.000672214	0.009158915	0.00663369
CC	GO:0045334	clathrin-coated endocytic vesicle	63/19717	0.000889621	0.0107743	0.007803694
CC	GO:0034361	very-low-density lipoprotein particle	20/19717	0.001615541	0.015570908	0.011277819
CC	GO:0034385	triglyceride-rich plasma lipoprotein particle	20/19717	0.001615541	0.015570908	0.011277819
CC	GO:0030135	coated vesicle	289/19717	0.001714228	0.015570908	0.011277819
CC	GO:0030662	coated vesicle membrane	182/19717	0.002152155	0.017571776	0.012727023

CC	GO:0005581	collagen trimer	87/19717	0.002256925	0.017571776	0.012727023
CC	GO:0034364	high-density lipoprotein particle	26/19717	0.002731754	0.019850743	0.014377651
CC	GO:0098636	protein complex involved in cell adhesion	34/19717	0.00464361	0.031634592	0.022912548
CC	GO:0034358	plasma lipoprotein particle	37/19717	0.005481135	0.033191315	0.024040064
CC	GO:1990777	lipoprotein particle	37/19717	0.005481135	0.033191315	0.024040064
CC	GO:0032994	protein-lipid complex	39/19717	0.006075065	0.034851687	0.025242651
CC	GO:0030669	clathrin-coated endocytic vesicle membrane	44/19717	0.007681889	0.041866296	0.030323246
CC	GO:0072562	blood microparticle	147/19717	0.009732433	0.050515963	0.036588095
CC	GO:0005771	multivesicular body	51/19717	0.010215893	0.050615105	0.036659902
CC	GO:0033655	host cell cytoplasm part	10/19717	0.02953033	0.139177035	0.100804226
CC	GO:0030430	host cell cytoplasm	11/19717	0.03243578	0.139177035	0.100804226
CC	GO:0043202	lysosomal lumen	95/19717	0.032904989	0.139177035	0.100804226
CC	GO:0062023	collagen-containing extracellular matrix	406/19717	0.033198192	0.139177035	0.100804226
CC	GO:0031089	platelet dense granule lumen	14/19717	0.041100921	0.148538855	0.107584878
CC	GO:0034362	low-density lipoprotein particle	14/19717	0.041100921	0.148538855	0.107584878
CC	GO:0043083	synaptic cleft	14/19717	0.041100921	0.148538855	0.107584878
CC	GO:0005770	late endosome	256/19717	0.041310995	0.148538855	0.107584878
MF	GO:0008009	chemokine activity	49/17696	1.07E-08	1.67E-06	1.13E-06
MF	GO:0045236	CXCR chemokine receptor binding	11/17696	3.14E-08	2.45E-06	1.65E-06
MF	GO:0042379	chemokine receptor binding	66/17696	6.67E-08	3.47E-06	2.34E-06
MF	GO:0019955	cytokine binding	128/17696	3.42E-06	0.0001332	8.99E-05
MF	GO:0005125	cytokine activity	220/17696	6.51E-06	0.000203036	0.000137001
MF	GO:0004252	serine-type endopeptidase activity	160/17696	1.23E-05	0.000315778	0.000213076
MF	GO:0004896	cytokine receptor activity	96/17696	1.42E-05	0.000315778	0.000213076
MF	GO:0008236	serine-type peptidase activity	182/17696	2.56E-05	0.0004512	0.000304453
MF	GO:0016825	hydrolase activity, acting on acid phosphorus-nitrogen bonds	186/17696	2.89E-05	0.0004512	0.000304453
MF	GO:0017171	serine hydrolase activity	186/17696	2.89E-05	0.0004512	0.000304453
MF	GO:0005126	cytokine receptor binding	286/17696	3.55E-05	0.000502771	0.000339252
MF	GO:0140375	immune receptor activity	128/17696	5.67E-05	0.00073727	0.000497483
MF	GO:0001540	amyloid-beta binding	78/17696	0.000115546	0.001386558	0.000935599
MF	GO:0008201	heparin binding	169/17696	0.000209875	0.002338608	0.001578008
MF	GO:0001664	G protein-coupled receptor binding	280/17696	0.000274286	0.00280468	0.001892496
MF	GO:0042287	MHC protein binding	40/17696	0.000287659	0.00280468	0.001892496
MF	GO:0048020	CCR chemokine receptor binding	43/17696	0.000356861	0.003274722	0.002209664
MF	GO:0004175	endopeptidase activity	427/17696	0.000423398	0.00366945	0.002476012
MF	GO:0005539	glycosaminoglycan binding	229/17696	0.000841331	0.006766255	0.004565624
MF	GO:0048018	receptor ligand activity	482/17696	0.000867469	0.006766255	0.004565624
MF	GO:0030546	signaling receptor activator activity	487/17696	0.000921369	0.006844454	0.00461839
MF	GO:0043395	heparan sulfate proteoglycan binding	16/17696	0.001188293	0.008426079	0.005685614
MF	GO:1901681	sulfur compound binding	250/17696	0.001244172	0.008438729	0.005694149
MF	GO:0016493	C-C chemokine receptor activity	23/17696	0.002469335	0.016050677	0.010830416
MF	GO:0019957	C-C chemokine binding	24/17696	0.002688263	0.016774763	0.011319003
MF	GO:0023023	MHC protein complex binding	25/17696	0.002915999	0.017495995	0.011805665

MF	GO:0001637	G protein-coupled chemoattractant receptor activity	26/17696	0.003152486	0.01756385	0.011851451
MF	GO:0004950	chemokine receptor activity	26/17696	0.003152486	0.01756385	0.011851451
MF	GO:0019956	chemokine binding	32/17696	0.004752011	0.025562543	0.017248679
MF	GO:0030159	signaling receptor complex adaptor activity	36/17696	0.005986289	0.030124549	0.020326956

Table5 The significantly enriched biological processes of ICI gene type B (Each bar shows the top 30).

Table6 List of the ICI score.

ONTOLOGY	ID	Description	BgRatio	pvalue	p.adjust	qvalue
BP	GO:0030198	extracellular matrix organization	368/18670	1.40E-09	5.28E-07	3.24E-07
BP	GO:0043062	extracellular structure organization	369/18670	1.43E-09	5.28E-07	3.24E-07
BP	GO:0022617	extracellular matrix disassembly	81/18670	1.52E-09	5.28E-07	3.24E-07
BP	GO:0030574	collagen catabolic process	47/18670	6.29E-09	1.64E-06	1.01E-06
BP	GO:0032963	collagen metabolic process	115/18670	5.89E-07	0.000122534	7.53E-05
BP	GO:0008544	epidermis development	464/18670	3.23E-06	0.00043412	0.000266894
BP	GO:0038034	signal transduction in absence of ligand	72/18670	3.34E-06	0.00043412	0.000266894
BP	GO:0097192	extrinsic apoptotic signaling pathway in absence of ligand	72/18670	3.34E-06	0.00043412	0.000266894
BP	GO:0032461	positive regulation of protein oligomerization	25/18670	6.07E-06	0.000702481	0.000431881
BP	GO:0043588	skin development	419/18670	2.45E-05	0.002222654	0.001366473
BP	GO:0016999	antibiotic metabolic process	122/18670	2.71E-05	0.002222654	0.001366473
BP	GO:0150077	regulation of neuroinflammatory response	41/18670	2.77E-05	0.002222654	0.001366473
BP	GO:0006692	prostanoid metabolic process	43/18670	3.20E-05	0.002222654	0.001366473
BP	GO:0006693	prostaglandin metabolic process	43/18670	3.20E-05	0.002222654	0.001366473
BP	GO:0032459	regulation of protein oligomerization	43/18670	3.20E-05	0.002222654	0.001366473
BP	GO:0035987	endodermal cell differentiation	45/18670	3.68E-05	0.002391321	0.001470169
BP	GO:2001239	regulation of extrinsic apoptotic signaling pathway in absence of ligand	47/18670	4.19E-05	0.002566884	0.001578104
BP	GO:0001706	endoderm formation	50/18670	5.05E-05	0.002921905	0.001796368
BP	GO:1904645	response to amyloid-beta	54/18670	6.37E-05	0.003489608	0.002145388
BP	GO:0001660	fever generation	10/18670	9.00E-05	0.004460805	0.002742474
BP	GO:0030647	aminoglycoside antibiotic metabolic process	10/18670	9.00E-05	0.004460805	0.002742474
BP	GO:0034614	cellular response to reactive oxygen species	168/18670	9.44E-05	0.004469157	0.002747608
BP	GO:0010623	programmed cell death involved in cell development	12/18670	0.000131746	0.005962944	0.003665979
BP	GO:0030656	regulation of vitamin metabolic process	13/18670	0.000155561	0.006477562	0.003982363
BP	GO:0045086	positive regulation of interleukin-2 biosynthetic process	13/18670	0.000155561	0.006477562	0.003982363
BP	GO:0150076	neuroinflammatory response	75/18670	0.000169917	0.006803198	0.004182562
BP	GO:0007492	endoderm development	76/18670	0.000176729	0.00681389	0.004189135
BP	GO:0042448	progesterone metabolic process	16/18670	0.000238685	0.008873961	0.005455653
BP	GO:0042446	hormone biosynthetic process	86/18670	0.00025481	0.009146785	0.005623384
BP	GO:0031649	heat generation	17/18670	0.000270268	0.009272206	0.005700491
CC	GO:0062023	collagen-containing extracellular matrix	406/19717	0.002136129	0.051050178	0.036241253
CC	GO:1904724	tertiary granule lumen	55/19717	0.002564317	0.051050178	0.036241253
CC	GO:0001533	cornified envelope	65/19717	0.00356164	0.051050178	0.036241253
CC	GO:0101002	ficolin-1-rich granule	124/19717	0.012426568	0.083621354	0.059363997
CC	GO:1904813	ficolin-1-rich granule lumen	124/19717	0.012426568	0.083621354	0.059363997
CC	GO:0001527	microfibril	10/19717	0.013612779	0.083621354	0.059363997
CC	GO:0043256	laminin complex	10/19717	0.013612779	0.083621354	0.059363997
CC	GO:0061702	inflammasome complex	14/19717	0.019007774	0.09004732	0.063925882
CC	GO:0043020	NADPH oxidase complex	15/19717	0.020352076	0.09004732	0.063925882
CC	GO:0070820	tertiary granule	164/19717	0.021062493	0.09004732	0.063925882
CC	GO:0042599	lamellar body	17/19717	0.023035361	0.09004732	0.063925882
CC	GO:0016342	catenin complex	29/19717	0.038987057	0.137670027	0.097733924

CC	GO:0008305	integrin complex	31/19717	0.041621171	0.137670027	0.097733924
CC	GO:0098636	protein complex involved in cell adhesion	34/19717	0.04555931	0.139932165	0.099339848
MF	GO:0004222	metalloendopeptidase activity	103/17696	4.42E-07	4.15E-05	2.00E-05
MF	GO:0004175	endopeptidase activity	427/17696	2.65E-06	0.000109225	5.26E-05
MF	GO:0004252	serine-type endopeptidase activity	160/17696	3.90E-06	0.000109225	5.26E-05
MF	GO:0008237	metallopeptidase activity	181/17696	7.12E-06	0.000109225	5.26E-05
MF	GO:0008236	serine-type peptidase activity	182/17696	7.32E-06	0.000109225	5.26E-05
MF	GO:0016825	hydrolase activity, acting on acid phosphorus-nitrogen bonds	186/17696	8.13E-06	0.000109225	5.26E-05
MF	GO:0017171	serine hydrolase activity	186/17696	8.13E-06	0.000109225	5.26E-05
MF	GO:0005126	cytokine receptor binding	286/17696	6.42E-05	0.000754495	0.000363307
MF	GO:0004032	alditol:NADP+ 1-oxidoreductase activity	13/17696	0.000173064	0.001807553	0.000870378
MF	GO:0005149	interleukin-1 receptor binding	16/17696	0.000265501	0.002495707	0.00120174
MF	GO:0005125	cytokine activity	220/17696	0.000325887	0.002784856	0.001340972
MF	GO:0008106	alcohol dehydrogenase (NADP+) activity	21/17696	0.000462445	0.003622484	0.001744309
MF	GO:0016651	oxidoreductase activity, acting on NAD(P)H	107/17696	0.000565634	0.004089967	0.001969413
MF	GO:0004033	aldo-keto reductase (NADP) activity	26/17696	0.000712329	0.004463931	0.002149485
MF	GO:0016628	oxidoreductase activity, acting on the CH-CH group of donors, NAD or NADP as acceptor	26/17696	0.000712329	0.004463931	0.002149485
MF	GO:0070851	growth factor receptor binding	134/17696	0.001087139	0.006386942	0.003075459
MF	GO:0016229	steroid dehydrogenase activity	35/17696	0.00129312	0.007150193	0.003442982
MF	GO:0016709	oxidoreductase activity, acting on paired donors, with incorporation or reduction of molecular oxygen, NAD(P)H as one donor, and incorporation of one atom of oxygen	39/17696	0.00160438	0.00837843	0.004034407
MF	GO:0016627	oxidoreductase activity, acting on the CH-CH group of donors	58/17696	0.003515711	0.017393517	0.008375378
MF	GO:0016655	oxidoreductase activity, acting on NAD(P)H, quinone or similar compound as acceptor	60/17696	0.003757496	0.017660233	0.008503808
MF	GO:0005518	collagen binding	67/17696	0.004662969	0.020872339	0.010050511
MF	GO:0048018	receptor ligand activity	482/17696	0.005802615	0.024589406	0.011840364
MF	GO:0030546	signaling receptor activator activity	487/17696	0.006016557	0.024589406	0.011840364
MF	GO:0004497	monooxygenase activity	99/17696	0.009928641	0.038887179	0.018725069
MF	GO:0042562	hormone binding	102/17696	0.01051312	0.039529331	0.01903428
MF	GO:0016616	oxidoreductase activity, acting on the CH-OH group of donors, NAD or NADP as acceptor	119/17696	0.014103922	0.050991101	0.024553386
MF	GO:0016614	oxidoreductase activity, acting on CH-OH group of donors	128/17696	0.016191085	0.053350738	0.025689605
MF	GO:0004865	protein serine/threonine phosphatase inhibitor activity	11/17696	0.016660672	0.053350738	0.025689605
MF	GO:0052650	NADP-retinol dehydrogenase activity	11/17696	0.016660672	0.053350738	0.025689605
MF	GO:0005178	integrin binding	132/17696	0.017158793	0.053350738	0.025689605

id	score	id	score	id	score
TCGA_TCGA-EK-A2RO	-2.54071166	TCGA_TCGA-JW-A852	-5.977347197	TCGA_TCGA-C5-A1BI	5.479592347
TCGA_TCGA-VS-A8EB	3.336169104	TCGA_TCGA-VS-A9UJ	-12.34112698	TCGA_TCGA-EK-A2IR	-17.46983067
TCGA_TCGA-EA-A3Y4	13.75275983	TCGA_TCGA-DS-A0VK	-4.330705974	TCGA_TCGA-VS-A9UL	-13.37486429
TCGA_TCGA-C5-A2LS	-13.67318601	TCGA_TCGA-DG-A2KL	4.450227671	TCGA_TCGA-XS-A8TJ	-1.764696857
TCGA_TCGA-C5-A1M8	-10.07226848	TCGA_TCGA-DG-A2KJ	-0.925294138	TCGA_TCGA-C5-A1M9	-3.047159887
TCGA_TCGA-HM-A6W2	-9.839891111	TCGA_TCGA-DS-A7WI	-2.966288156	TCGA_TCGA-FU-A40J	-1.258720378
TCGA_TCGA-C5-A7CH	-0.247655999	TCGA_TCGA-C5-A7CO	-6.049212096	TCGA_TCGA-HM-A3JJ	7.221917036
TCGA_TCGA-C5-A3HE	4.203872091	TCGA_TCGA-ZJ-AAx8	8.151965971	TCGA_TCGA-MA-AA41	-0.462999721
TCGA_TCGA-EK-A2RL	-9.826181848	TCGA_TCGA-LP-A4AU	2.772996448	TCGA_TCGA-EA-A411	-1.691132132
TCGA_TCGA-EX-A1H6	-9.456785867	TCGA_TCGA-EK-A3GK	-0.508824133	TCGA_TCGA-DS-A3LQ	-1.19124187
TCGA_TCGA-EK-A2R8	0.407229542	TCGA_TCGA-JX-A5QV	2.459990644	TCGA_TCGA-EK-A2PK	7.062794936
TCGA_TCGA-UC-A7PD	1.021870228	TCGA_TCGA-C5-A907	3.287397331	TCGA_TCGA-VS-A950	-2.299310726
TCGA_TCGA-MA-AA3Z	6.256155828	TCGA_TCGA-MY-A5BD	-5.943789649	TCGA_TCGA-VS-A94W	8.20276175
TCGA_TCGA-VS-A9UD	10.772257	TCGA_TCGA-UC-A7PI	-7.850537555	TCGA_TCGA-VS-A959	2.599503734
TCGA_TCGA-VS-A954	-3.694032999	TCGA_TCGA-VS-A9UH	15.50600314	TCGA_TCGA-2W-A8YY	-3.545554879
TCGA_TCGA-ZJ-AB0H	6.734512887	TCGA_TCGA-LP-A4AV	4.604864351	TCGA_TCGA-DS-A5RQ	0.699270192
TCGA_TCGA-EK-A2PG	-11.3460856	TCGA_TCGA-VS-A8QF	0.310340053	TCGA_TCGA-Q1-A6DT	-5.329180202
TCGA_TCGA-C5-A3HD	-5.492319552	TCGA_TCGA-UC-A7PG	2.015395148	TCGA_TCGA-JW-A69B	-6.4040671
TCGA_TCGA-JX-A3Q8	-2.184849993	TCGA_TCGA-VS-A9UO	-8.359823886	TCGA_TCGA-ZJ-AAXA	-12.09705813
TCGA_TCGA-EA-A3HQ	3.120047508	TCGA_TCGA-LP-A5U2	-3.702845995	TCGA_TCGA-EA-A1QT	-1.255998463
TCGA_TCGA-EX-A8YF	2.556743972	TCGA_TCGA-JX-A3Q0	3.853294857	TCGA_TCGA-MY-A5BE	15.97362264
TCGA_TCGA-DS-A0VN	14.79454955	TCGA_TCGA-EX-A3L1	2.666525333	TCGA_TCGA-MU-A51Y	6.676892352
TCGA_TCGA-EK-A2H0	-2.478829964	TCGA_TCGA-EA-A3HS	1.270682161	TCGA_TCGA-FU-A23K	0.0278827
TCGA_TCGA-FU-A3HZ	-3.559979005	TCGA_TCGA-C5-A2LT	8.516404738	TCGA_TCGA-EA-A3HR	-3.614981721
TCGA_TCGA-C5-A1MH	10.03351708	TCGA_TCGA-ZX-AA5X	4.196596819	TCGA_TCGA-VS-A8QC	-2.151013205
TCGA_TCGA-IR-A3L7	-11.38445801	TCGA_TCGA-EA-A439	-0.408580553	TCGA_TCGA-ZJ-AB0I	3.661913987
TCGA_TCGA-MA-AA3W	11.9846307	TCGA_TCGA-C5-A7CL	-2.752315584	TCGA_TCGA-GH-A9DA	3.851832465
TCGA_TCGA-C5-A0TN	4.007816964	TCGA_TCGA-C5-A1MF	-3.22001893	TCGA_TCGA-EK-A2RC	2.294605865
TCGA_TCGA-IR-A3LB	-1.514535151	TCGA_TCGA-VS-A8EL	11.43633034	TCGA_TCGA-DS-A7WF	-2.698408345
TCGA_TCGA-VS-A952	-9.104555124	TCGA_TCGA-EK-A2GZ	-2.239344531	TCGA_TCGA-EA-A44S	0.136309375
TCGA_TCGA-C5-A1MQ	4.796898364	TCGA_TCGA-VS-A8QM	10.80663267	TCGA_TCGA-Q1-A6DW	-2.422145784
TCGA_TCGA-C5-A3HF	1.975186932	TCGA_TCGA-EX-A1H5	-4.663195188	TCGA_TCGA-FU-A2QG	3.364783391
TCGA_TCGA-EX-A69M	1.95595032	TCGA_TCGA-Q1-A5R2	3.258456048	TCGA_TCGA-C5-A1MK	0.768420205
TCGA_TCGA-C5-A1MP	3.844860032	TCGA_TCGA-HM-A3JK	2.257805393	TCGA_TCGA-ZJ-A8QO	7.420103012
TCGA_TCGA-C5-A7CG	14.48842238	TCGA_TCGA-C5-A7CJ	6.174312999	TCGA_TCGA-MA-AA43	-0.294309802
TCGA_TCGA-C5-A1BN	-5.822965536	TCGA_TCGA-C5-A7UC	-3.48177418	TCGA_TCGA-C5-A1BL	4.238341386
TCGA_TCGA-FU-A5XV	-0.232331408	TCGA_TCGA-C5-A1MJ	-2.521305909	TCGA_TCGA-EA-A4BA	-12.03834527
TCGA_TCGA-EA-A3QE	12.25142295	TCGA_TCGA-EA-A3QD	11.67878971	TCGA_TCGA-ZJ-A8QQ	-2.35737794
TCGA_TCGA-C5-A2M2	-7.933218232	TCGA_TCGA-VS-A8QH	-11.26976998	TCGA_TCGA-VS-A8EJ	-5.487063239
TCGA_TCGA-VS-A8Q8	4.523098063	TCGA_TCGA-C5-A1ME	-2.873237436	TCGA_TCGA-C5-A7UI	3.172291539
TCGA_TCGA-BI-A0VR	8.907300753	TCGA_TCGA-C5-A901	-2.445905716	TCGA_TCGA-Q1-A73Q	-4.994995016
TCGA_TCGA-EK-A2PL	-4.133738725	TCGA_TCGA-C5-A8YT	-3.989617643	TCGA_TCGA-DS-A1OA	6.131239697
TCGA_TCGA-DR-A0ZL	-10.41700982	TCGA_TCGA-EK-A2PM	-16.61682714	TCGA_TCGA-C5-A8XK	-1.466029694

TCGA_TCGA-LP-A5U3	1.571253311	TCGA_TCGA-FU-A770	-7.746395707	TCGA_TCGA-C5-A905	-9.181771315
TCGA_TCGA-MY-A5BF	6.518956004	TCGA_TCGA-EK-A2RB	-7.204736463	TCGA_TCGA-C5-A7X5	-8.290850239
TCGA_TCGA-Q1-A73S	-14.31452683	TCGA_TCGA-VS-A9UM	3.670669876	TCGA_TCGA-EK-A2RM	-4.555972261
TCGA_TCGA-JW-A5VH	-13.42486764	TCGA_TCGA-VS-A9V2	4.006790609	TCGA_TCGA-IR-A3LL	8.908954053
TCGA_TCGA-VS-A9UP	-11.64565095	TCGA_TCGA-FU-A3TX	0.830403974	TCGA_TCGA-DR-A0ZM	2.035901154
TCGA_TCGA-C5-A1BK	9.541659251	TCGA_TCGA-C5-A2LZ	2.833759656	TCGA_TCGA-R2-A69V	15.49146066
TCGA_TCGA-VS-A8EC	-13.92338081	TCGA_TCGA-ZJ-A8QR	-1.220331245	TCGA_TCGA-C5-A7UH	1.698338394
TCGA_TCGA-IR-A3LH	17.31871961	TCGA_TCGA-JW-A5VG	8.843728013	TCGA_TCGA-IR-A3LK	1.88160382
TCGA_TCGA-VS-A8QA	-4.235006984	TCGA_TCGA-MU-A5YI	2.17694122	TCGA_TCGA-EA-A50E	-2.376950588
TCGA_TCGA-C5-A8XJ	2.123605089	TCGA_TCGA-Q1-A73P	0.803995635	TCGA_TCGA-EK-A2RE	-6.630039027
TCGA_TCGA-EA-A5FO	-13.23955222	TCGA_TCGA-JW-A5VK	-12.5387323	TCGA_TCGA-ZJ-AAXD	-3.016660888
TCGA_TCGA-FU-A3HY	-4.618332847	TCGA_TCGA-DS-A109	6.124086106	TCGA_TCGA-ZJ-AAXN	6.947893991
TCGA_TCGA-FU-A3TQ	1.043612445	TCGA_TCGA-PN-A8MA	-1.905474375	TCGA_TCGA-BI-A0VS	6.32003934
TCGA_TCGA-FU-A57G	-7.250447408	TCGA_TCGA-EA-A5ZF	-9.167086662	TCGA_TCGA-C5-A1ML	0.262952281
TCGA_TCGA-C5-A3HL	-2.509128331	TCGA_TCGA-VS-A9UQ	-4.849885944	TCGA_TCGA-MU-A8JM	4.113896899
TCGA_TCGA-DS-A0VM	0.560082269	TCGA_TCGA-MA-AA42	13.80602711	TCGA_TCGA-EK-A2RJ	6.115139042
TCGA_TCGA-DS-A7WH	-5.963197591	TCGA_TCGA-VS-A9U7	6.941557915	TCGA_TCGA-VS-A9V0	-11.58927694
TCGA_TCGA-EK-A2RN	-12.17305522	TCGA_TCGA-DS-A10D	12.71406892	TCGA_TCGA-DS-A0VL	4.01303131
TCGA_TCGA-ZJ-AAXB	-10.11404153	TCGA_TCGA-ZJ-AAX4	3.913928181	TCGA_TCGA-VS-A9UR	-4.737216631
TCGA_TCGA-C5-A2LX	9.154958136	TCGA_TCGA-MY-A913	10.81167396	TCGA_TCGA-DG-A2KH	-11.48823653
TCGA_TCGA-EA-A410	-3.359232797	TCGA_TCGA-UC-A7PF	7.920872376	TCGA_TCGA-4J-AA1J	-2.504913624
TCGA_TCGA-JX-A3PZ	4.591725831	TCGA_TCGA-C5-A2LY	9.747967365	TCGA_TCGA-FU-A23L	6.201905903
TCGA_TCGA-EX-A69L	10.03899066	TCGA_TCGA-VS-A9UU	-4.722837588	TCGA_TCGA-ZJ-AAXI	-11.19690183
TCGA_TCGA-Q1-A6DV	-6.992734238	TCGA_TCGA-C5-A8ZZ	-4.771806352	TCGA_TCGA-EK-A2R9	5.312495577
TCGA_TCGA-VS-A953	0.159293164	TCGA_TCGA-EK-A3GJ	8.306149082	TCGA_TCGA-Q1-A5R1	-5.814571053
TCGA_TCGA-C5-A1M5	6.620967293	TCGA_TCGA-C5-A2M1	2.75033415	TCGA_TCGA-VS-A9UY	5.051534751
TCGA_TCGA-C5-A902	5.797710832	TCGA_TCGA-C5-A1MI	1.856633263	TCGA_TCGA-VS-A8EH	-9.917200641
TCGA_TCGA-C5-A1M7	0.719718372	TCGA_TCGA-EA-A6QX	2.182392248	geoMatrix_GSM763220	-0.299285945
TCGA_TCGA-VS-A9V1	-9.480970164	TCGA_TCGA-C5-A7X3	4.419255599	geoMatrix_GSM763221	1.336117045
TCGA_TCGA-DG-A2KK	-0.848484847	TCGA_TCGA-EA-A3HT	2.574492088	geoMatrix_GSM763222	-2.561153878
TCGA_TCGA-EA-A3HU	11.69307759	TCGA_TCGA-VS-A9UB	11.53976097	geoMatrix_GSM763223	1.167623491
TCGA_TCGA-C5-A1BE	0.617949543	TCGA_TCGA-VS-A8EK	-5.617315359	geoMatrix_GSM763224	-0.390313016
TCGA_TCGA-WL-A834	-7.119756107	TCGA_TCGA-VS-A9UC	2.938996818	geoMatrix_GSM763225	1.512155504
TCGA_TCGA-FU-A3EO	-9.135934969	TCGA_TCGA-VS-A958	10.49839676	geoMatrix_GSM763226	-1.851877273
TCGA_TCGA-Q1-A730	7.72577025	TCGA_TCGA-EK-A2R7	0.664123017	geoMatrix_GSM763227	2.15499695
TCGA_TCGA-JW-AAVH	-6.268640232	TCGA_TCGA-C5-A1M6	-11.02821923	geoMatrix_GSM763228	3.090792152
TCGA_TCGA-HM-A4S6	5.205362436	TCGA_TCGA-EK-A2RA	6.522203791	geoMatrix_GSM763229	0.376988351
TCGA_TCGA-VS-A9UV	-8.678420186	TCGA_TCGA-VS-A8EG	-6.091344998	geoMatrix_GSM763230	-3.654720156
TCGA_TCGA-EA-A5ZE	2.458633697	TCGA_TCGA-LP-A7HU	2.614097337	geoMatrix_GSM763231	-1.487348435
TCGA_TCGA-VS-A9V5	-10.72653451	TCGA_TCGA-VS-A9V3	3.212604139	geoMatrix_GSM763237	1.089478693
TCGA_TCGA-C5-A1BJ	5.968054998	TCGA_TCGA-DS-A10C	4.308256583	geoMatrix_GSM763238	-0.039797269
TCGA_TCGA-Q1-A73R	-6.813621727	TCGA_TCGA-VS-A8Q9	-6.76015208	geoMatrix_GSM763239	-1.002883797
TCGA_TCGA-IR-A3LI	-19.94811989	TCGA_TCGA-EK-A2H1	10.19008147	geoMatrix_GSM763242	-0.48207114
TCGA_TCGA-C5-A1MN	2.055870244	TCGA_TCGA-ZJ-AAXT	3.6369477	geoMatrix_GSM763243	-0.695169273

TCGA_TCGA-C5-A7XC	5.836837664	TCGA_TCGA-EK-A2PI	-9.43216793	geoMatrix_GSM763244	-0.8016993
TCGA_TCGA-ZJ-AAXJ	-9.129633207	TCGA_TCGA-VS-A94X	1.39530028	geoMatrix_GSM763245	-0.900410406
TCGA_TCGA-EA-A1QS	1.817706798	TCGA_TCGA-VS-A9UT	8.300046584	geoMatrix_GSM763246	1.847129726
TCGA_TCGA-C5-A7UE	-7.193368059	TCGA_TCGA-EA-A509	-0.313222503	geoMatrix_GSM763247	4.290935334
TCGA_TCGA-EK-A3GM	-9.821719385	TCGA_TCGA-VS-A9U5	2.534109314	geoMatrix_GSM763248	1.366293508
TCGA_TCGA-FU-A3WB	-5.056935984	TCGA_TCGA-EK-A2IP	-2.259950443	geoMatrix_GSM763249	2.13622654
TCGA_TCGA-JW-A5VJ	-7.141558265	TCGA_TCGA-RA-A741	4.288804658	geoMatrix_GSM763250	-2.944344322
TCGA_TCGA-LP-A4AW	-0.066948636	TCGA_TCGA-IR-A3LC	-5.452055988	geoMatrix_GSM763251	1.289864092
TCGA_TCGA-VS-A9V4	-8.454138644	TCGA_TCGA-DG-A2KM	19.02893422	geoMatrix_GSM763257	-0.657853802
TCGA_TCGA-ZJ-AAXU	4.391367752	TCGA_TCGA-FU-A3YQ	5.970279744	geoMatrix_GSM763261	-1.071536318
TCGA_TCGA-VS-A957	-7.487805415	TCGA_TCGA-EK-A3GN	-12.52344152	geoMatrix_GSM763262	2.072759272
TCGA_TCGA-EX-A449	-10.46609677	TCGA_TCGA-C5-A8XH	4.871663868	geoMatrix_GSM763263	2.861720776
TCGA_TCGA-HG-A2PA	3.903954125	TCGA_TCGA-C5-A1BM	2.218477756	geoMatrix_GSM763264	-3.462975354
TCGA_TCGA-MA-AA3Y	14.17535305	TCGA_TCGA-DS-A1OB	-4.780962215	geoMatrix_GSM763265	-1.634466422
TCGA_TCGA-VS-A9UI	0.680499879	TCGA_TCGA-EA-A43B	6.959610722	geoMatrix_GSM763266	2.209722769
TCGA_TCGA-JW-A5VL	8.094338801	TCGA_TCGA-BI-A20A	2.881010572	geoMatrix_GSM763267	-1.851560731
TCGA_TCGA-VS-A8EI	8.408155188	TCGA_TCGA-VS-A9UZ	-2.042152658	geoMatrix_GSM763268	0.883399283
TCGA_TCGA-EA-A97N	0.095404551	TCGA_TCGA-EA-A5ZD	4.501349179	geoMatrix_GSM763269	1.306754875
TCGA_TCGA-EA-A78R	2.157242965	TCGA_TCGA-C5-A1BQ	5.684848588	geoMatrix_GSM763270	-2.001201845
TCGA_TCGA-C5-A7CK	-6.859436268	TCGA_TCGA-JW-A5VI	5.426028551	geoMatrix_GSM763271	1.133492765
TCGA_TCGA-FU-A3NI	-2.386545672	TCGA_TCGA-ZJ-AAXF	5.708218932	geoMatrix_GSM763272	0.374323391
TCGA_TCGA-EA-A556	-5.821674876	TCGA_TCGA-IR-A3LA	-8.848880643	geoMatrix_GSM763273	-1.918129576
TCGA_TCGA-C5-A8YQ	-7.884042725	TCGA_TCGA-EK-A2RK	-2.161029033	geoMatrix_GSM763274	0.199578218
TCGA_TCGA-IR-A3LF	0.390548601	TCGA_TCGA-C5-A7CM	-12.18124384	geoMatrix_GSM763275	0.389640459
TCGA_TCGA-C5-A7X8	-5.541056011	TCGA_TCGA-LP-A4AX	13.96307109	geoMatrix_GSM763276	-0.005450613
TCGA_TCGA-VS-A9U6	3.601390344	TCGA_TCGA-Q1-A5R3	-0.478173866	geoMatrix_GSM763277	0.574868038
TCGA_TCGA-VS-A94Z	13.70570675	TCGA_TCGA-C5-A8XI	6.618067774	geoMatrix_GSM763278	-0.344169864
TCGA_TCGA-VS-A94Y	1.792877641	TCGA_TCGA-MA-AA3X	-4.521882188	geoMatrix_GSM763279	-3.075864787
TCGA_TCGA-C5-A2LV	2.785636149	TCGA_TCGA-VS-AA62	12.66830065	geoMatrix_GSM763280	1.092066301
TCGA_TCGA-C5-A8YR	6.373521213	TCGA_TCGA-C5-A1BF	-0.540147549	geoMatrix_GSM763281	-0.496841402
				geoMatrix_GSM763282	-0.27659105

Table7

The gene set enrichment analysis (GSEA) data of the first ten gene sets in the high ICI score group

NAME	GS follow link to MSigDB	SIZE	ES	NES
KEGG_NATURAL_KILLER_CELL_MEDIATED_CYTOTOXICITY	KEGG_NATURAL_KILLER_CELL_MEDIATED_CYTOTOXICITY	117	0.74643344	2.5061
KEGG_T_CELL_RECEPTOR_SIGNALING_PATHWAY	KEGG_T_CELL_RECEPTOR_SIGNALING_PATHWAY	100	0.7515527	2.4381
KEGG_ANTIGEN_PROCESSING_AND_PRESENTATION	KEGG_ANTIGEN_PROCESSING_AND_PRESENTATION	73	0.8031184	2.4170
KEGG_TOLL_LIKE_RECEPTOR_SIGNALING_PATHWAY	KEGG_TOLL_LIKE_RECEPTOR_SIGNALING_PATHWAY	95	0.6967538	2.3883
KEGG_CHEMOKINE_SIGNALING_PATHWAY	KEGG_CHEMOKINE_SIGNALING_PATHWAY	168	0.68054503	2.3804
KEGG_FC_GAMMA_R_MEDIATED_PHAGOCYTOSIS	KEGG_FC_GAMMA_R_MEDIATED_PHAGOCYTOSIS	78	0.64212435	2.3112
KEGG_CYTOKINE_CYTOKINE_RECEPTOR_INTERACTION	KEGG_CYTOKINE_CYTOKINE_RECEPTOR_INTERACTION	232	0.6965659	2.2755
KEGG_B_CELL_RECEPTOR_SIGNALING_PATHWAY	KEGG_B_CELL_RECEPTOR_SIGNALING_PATHWAY	70	0.69253844	2.2720
KEGG_LEISHMANIA_INFECTION	KEGG_LEISHMANIA_INFECTION	63	0.8012066	2.2680
KEGG_JAK_STAT_SIGNALING_PATHWAY	KEGG_JAK_STAT_SIGNALING_PATHWAY	136	0.6426389	2.2679

Table8 List of significant differences in mutated genes between the low and high ICI score groups.

gene	H-wild	H-mutation	L-wild	L-mutation	pvalue
OBSCN	28(75.68%)	9(24.32%)	235(94.38%)	14(5.62%)	0.000344519
DNAH9	31(83.78%)	6(16.22%)	238(95.58%)	11(4.42%)	0.013911523
MXRA5	32(86.49%)	5(13.51%)	239(95.98%)	10(4.02%)	0.043088804
CUBN	31(83.78%)	6(16.22%)	235(94.38%)	14(5.62%)	0.044198604

Figures

Figure 1

The expression profile of immune cells in TME of Cervical cancer tissues (A) Aggregate analysis of tumor-infiltrating immune cells in cervical cancer. Rows show different immune cells and columns show specific details of samples. (B) Correlation between tumor infiltrating immune cells in cervical cancer. (C) Kaplan-Meier curve showing differences in survival rates among patients with cervical cancer based on ICI clusters. (D) The difference in infiltration of immune cells in TME of tissues in the three ICI clusters. The analysis was performed using Kruskal-Wallis test. (* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$). (E) The expression of PD-L1 among the ICI clusters.

Figure 2

Sub-typing of immune response related genes in cervical cancer tissues (A) The four gene clusters of patients with cervical cancer (A–D). (B) Differences of expression of tumor infiltrating immune cells among different gene clusters (* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$). (C) Survival curve of patients with cervical cancer in different gene clusters. GO enrichment analysis of ICI genes type A (D) and (E) B. (F) Expression of PD-L1 among different ICI gene clusters ($p < 0.05$).

Figure 3

The graph for ICI Scores (A) The relationship among different gene clusters, ICI scores and Fustat. (B) Analysis of immune related genes (SOX2, CD274, CD8A, CXCL10, TBX2, TLR9, CTLA4, CD28, GZMB, IFNG, CXCL9, FOXP3 and TNF). (C) The state of T cell receptor, JAK-STAT and B cell receptor pathways in the high ICI score subgroup. (D) The relationship between ICI score and prognosis of cervical cancer. (p = 0.041).

Figure 4

Relationship between ICI score and TMB (A) The difference in TMB between the high and low ICI score subgroups ($p = 0.046$). (B) Scatter plots for the correlation between ICI score and TMB ($p = 0.017$). (C) Kaplan-Meier Survival curves for patients in different TMB sub-groups ($p = 0.042$). (D) Kaplan-Meier curves for patients stratified based on both TMB and ICI scores ($p = 0.012$). (E) The TMB in high ICI score group. (F) The TMB of patients in low ICI score group.