PD-L1-Mediated Immunosuppression in Oral Squamous Cell Carcinoma: Relationship With Macrophage Infiltration and Epithelial to Mesenchymal Transition Markers

Tiantian Wu\textsuperscript{1,2,3,4†}, Caijin Tang\textsuperscript{1,2,3,4†}, Renchuan Tao\textsuperscript{1,2,3,4*}, Xiangzhi Yong\textsuperscript{1,2,3}, Qiaozhi Jiang\textsuperscript{1,2,3,4} and Cong Feng\textsuperscript{1,2,3,4}

\textsuperscript{1} Department of Periodontics and Oral Medicine, College of Stomatology, Guangxi Medical University, Nanning, China, \textsuperscript{2} Guangxi Health Commission Key Laboratory of Prevention and Treatment for Oral Infectious Diseases, Nanning, China, \textsuperscript{3} Guangxi Key Laboratory of Oral and Maxillofacial Rehabilitation and Reconstruction, Guangxi Universities and Colleges Key Laboratory of Oral and Maxillofacial Surgery Disease Treatment, Guangxi Clinical Research Center for Craniofacial Deformity, Nanning, China, \textsuperscript{4} Guangxi Key Laboratory of AIDS Prevention and Treatment, Guangxi Medical University, Nanning, China

To date, immune check-point inhibitors (ICIs), particularly inhibitors of programmed cell death-1 (PD-1) and PD ligand-1 (PD-L1) have become prominent in cancer treatment and also improved life expectancy of cancer patients. As key regulators of PD-1/PD-L1 axis, the recruitment of tumor-associated macrophages (TAMs) enhances aggressive and invasive properties of tumors in immunosuppressive tumor microenvironment (TME) and promotes epithelial-mesenchymal transition (EMT). The aims of the study were first to characterize the critical links among PD-L1, TME and EMT process and, further, to explore the sensitivity of different chemical agents to different PD-L1 expression groups. Bioinformatical analysis revealed that PD-L1 was highly expressed in OSCC and higher PD-L1 expression correlated with worse survival in patients. Notably, PD-L1 was positively correlated with macrophages infiltration and EMT markers gene expression. Moreover, patients in the PD-L1\textsuperscript{high} group were at a significant chance of benefiting from ICI treatment and they also showed higher sensitivity to the chemical drugs (olaparib, paclitaxel, docetaxel, and pazopanib). These findings implicate PD-L1 could serve as a novel target for prognostic and therapeutic approaches in OSCC patients; PD-L1-mediated immune evasion might be attributable to the infiltration of macrophages, resulting EMT progress; Chemical agents in combination with PD-L1 inhibitor could be served as personalized treatment plan for OSCC patients so as to maximize patient benefit.

Keywords: PD-L1, immunosuppressive tumor microenvironment, macrophages, epithelial-mesenchymal transition, chemical drugs
INTRODUCTION

Oral squamous cell carcinoma (OSCC), as one of the 10 most frequent cancers with approximately 300,000 new cases diagnosed annually, is perceived as an immunosuppressive cancer (1). Despite advances in therapeutic approaches, including surgical methods and radiotherapy, patients with locally advanced or metastatic OSCC still face the risk of a poor prognosis (2). Therefore, further efforts are still demanded to identify clinically relevant biomarkers, establish effective mechanism-based combinations, and develop effective targeted therapies for OSCC.

Cancer immunotherapy, including immune check-point inhibitors (ICIs), Oncolytic virotherapy (OVT), and chimeric antigen receptor (CAR) T cells has led to major improvements in tumor treatment over the past two decades (3). ICIs expressed on the cell surface, including programmed cell death-1 (PD-1) and PD ligand-1 (PD-L1), play crucial roles in activating negative regulatory pathways and evading immune surveillance (4). Upon activation, ICIs can dampen antitumor immune responses, leading to cancer cells escaping from host immune system (5). The interaction between these ligands can be blocked by ICIs, thereby reactivating the cytotoxic immune response. Unprecedented advances in tumor control have been made using therapeutic monoclonal antibodies (mAbs) to block ICIs. Particularly, mAbs targeting PD-1/PD-L1 have brought great clinical benefits in multiple indications, either as monotherapy or in combination regimens (6–8). Pembrolizumab and nivolumab as anti-PD-1 mAbs have shown remarkable antitumor activity in the treatment of head and neck squamous cell carcinoma (HNSCC), leading to their regulatory approval (9–11). The PD-1/PD-L1 interaction inhibits antitumor activity of cytotoxic lymphocytes (CTLs) (12), which contributes to multiple Suppressive effects, such as immune escape, tumor proliferation, invasion, angiogenesis, and epithelial-mesenchymal transition (EMT) (13). At present, the links among PD-L1, TME, and EMT process in OSCC are not well understood, and the expectation that immunotherapy in combination with standard-therapy can maximize patient benefit necessitates further research on PD-L1-mediated immunosuppression. The present study was aimed at characterizing the critical links among PD-L1, TME and EMT process in OSCC, and further exploring the sensitivity of ICI treatment and different chemical agents to different PD-L1 expression groups.

METHODS AND MATERIALS

Data Acquisition

All Clinical and sequencing data were obtained from the Cancer Genome Atlas (TCGA) and the Gene Expression omnibus (GEO) research network. Transcriptome data of 150 OSCC tissue samples and 30 normal oral tissue samples were extracted from TCGA. Patients’ information on age, tumor-node-metastasis (TNM), stage, survival time and status were organized (Supplementary Table 1). The GEO database was used to obtain the OSCC microarray data set GSE30784, and 167 OSCC cancer patient samples were selected as the validation set based on the sample information (14). The EMT related genes were extracted from the Molecular Signature Database (MSigDB) (15).

Bioinformatic Analysis

Differentially expressed genes (DEGs) in different groups were identified using EdgeR package and filtered by \[ \log_{2}(\text{Fold Change}) > 1 \] and adjusted \( P \) value < 0.05 which was adjusted using the Benjamini-Hochberg (BH) approach (16). Furthermore, the enrichment analysis including Gene ontology (GO) function and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway annotation was conducted by clusterProfiler package. The PD-L1 expression level in diverse cancer types and correlation between PD-L1 and immune infiltrates were conducted using Tumor Immune Estimation Resource (TIMER) database (17). Gene marker sets of immune cell types were obtained from Bindea et al. (18) and Newman et al. (19). Single-sample Gene Set Enrichment Analysis (ssGSEA) and relative abundance of immune cells were calculated by Gene Set Variation Analysis (GSVA) (20). The classical chemokines and markers of macrophages and EMT signaling pathway were also included (21–24). Tumor Immune Dysfunction and Exclusion (TIDE) algorithm was applied to get individual immunotherapy response (25, 26), and individual chemotherapeutic response was predicted based on Genomics of Drug Sensitivity in Cancer (GDSC) database (27, 28). Drug sensitivity prediction was perform using R package ‘pRRophetic’ (29).

Statistical Analysis

R statistical language and SPSS 22.0 software were used for statistical analyses. Expression differences among different tumor grade groups were compared using one-way analysis of variance (ANOVA) test. Overall survival (OS) distribution and survival curves were performed by R package survival. The optimal cutoff point for PD-L1 expression level was determined by the ‘surv_cutpoint’ function of ‘survminer’ R package and calculated utilizing the maximally selected rank statistics that calculated the most optimal cut-off for continuous variables using log-rank statistics. Independent prognostic factors were evaluated using univariate and multivariate Cox proportional hazards regression analyses, and relationships between variables were calculated using Pearson correlation coefficients. Differences of TIDE scores and chemotherapy responses between groups were analyzed using Wilcoxon rank sum test.

RESULTS

PD-L1 Was Highly Expressed in OSCC and Predicted Poor OS

PD-L1 was differentially expressed in different tumor types and was highly expressed in HNSCC (Supplementary Figure 1A). TIMER analysis revealed that PD-L1 had positive correlations with various types of immune cells in HNSCC (Supplementary Figure 1B). Similarly, in OSCC, PD-L1 was also highly expressed compared with control group, but it gradually decreased with the progress of
Prognostic value of PD-L1 in OSCC patients was further analyzed; Kaplan–Meier analysis of OS revealed that patients with high PD-L1 expression exhibited a shorter survival time (P < 0.05, Figures 1A, B). The cutoff point for PD-L1 was 3.66. Cox regression analyses revealed that PD-L1 upregulation was significantly associated with a poor OS (Table 1).

Functional Enrichment Analysis of DEGs
Differential expression analysis was performed to identify the DEGs between two groups, so as to further study the function of these genes (Figure 2A). Among these DEGs, 384 genes were up-regulated in PD-L1 high group, and 1090 genes up-regulated in PD-L1low group (Figure 2A).

Additionally, tumor-associated macrophages (TAMs) characteristic cytokines such as CXCL10 and CXCL11 were significantly differentially expressed (Figures 2A, B). Notably, the GO enrichment analysis indicated 745 immune-related GO terms including lymphocyte activation, activated leukocyte adhesion, and effector cytokine production were significantly enriched in PD-L1 high group, while 414 GO terms including digestion, regulation of postsynaptic membrane potential, drug transport, glutamate receptor signaling pathway, regulation of membrane potential were significantly enriched in PD-L1low group (Figures 2C, D). KEGG pathway analysis showed that 47 KEGG pathways were characteristic enriched in PD-L1 high group, and 23 KEGG pathways were characteristic enriched in PD-L1low group (Figures 2E, F).

PD-L1 Was Correlated With Macrophage Infiltration and Macrophage-Derived Chemokines
The results of GSVA revealed that PD-L1 was positively associated with cell proliferation of 12 immune cell types in...
OSCC (Supplementary Figure 2 and Figures 3A, B), especially with M0 macrophages (cor = 0.42, \( P < 0.001 \)), M1 macrophages (cor = 0.68, \( P < 0.001 \)), and M2 macrophages (cor = 0.53, \( P < 0.001 \)) (Figures 3C–E). In addition, the results of ssGSEA in the GEO OSCC validation set showed PD-L1 was strongly positively associated with cell proliferation in several types of immune cell infiltration (Supplementary Figures 3A–H), especially with M1 macrophages (cor = 0.63, \( P < 0.001 \), Supplementary Figure 3D) and M2 macrophages (cor = 0.54, \( P < 0.001 \), Supplementary Figure 3E).

To validate the above results, we further analyzed correlations between PD-L1 expression and macrophage markers, which revealed that M1-related chemokines (IL12A, IL-12B, IL-23A, TNF, and IFNG) and M2-related chemokines (TGFBs, IL-10, and IL-13) showed the strongest positive correlations with PD-L1 expression (\( P < 0.05 \), Figures 4A–D). We also observed statistically significant correlations between M1-related chemokines and M2-related chemokines (Figures 4B, D).

**Associations Between PD-L1 Expression, Macrophage Infiltration and EMT Biomarkers**

Since the EMT process has been considered to be particularly relevant to TME, we analyzed the potential association of EMT with immune infiltration, and found significant correlations between EMT biomarkers and various immune cells infiltration (Figure 5A), especially with M0 macrophages (cor = 0.568, \( P < 0.001 \)) and M2 macrophages (cor = 0.425, \( P < 0.001 \)). We also evaluated the association between PD-L1 and EMT biomarkers, which showed significant correlations between PD-L1 and vimentin (VIM) (cor = 0.322, \( P < 0.001 \)) (Figures 5B, C).

**Sensitivity Differences to Immunotherapy/Chemotherapy Between Groups**

TIDE algorithm was employed to assess individual immunotherapy response in different PD-L1 expression groups, and higher TIDE prediction score represented a higher
immune evasion potential (Figure 6A). The results revealed patients with higher PD-L1 expression had a higher microsatellite instability (MSI) score and T cell dysfunction score (Figures 6B, C), but a lower T cell exclusion score (Figure 6D), indicating that these patients were less likely to benefit from ICI treatment.

We also took into account the differences in the response of chemotherapy in OSCC patients, and evaluated sensitivity of two patient groups to four chemical drugs (olaparib, docetaxel, paclitaxel, and pazopanib). The IC50 value of each sample in OSCC was estimated, and significant differences were observed between groups, which revealed that PD-L1high group showed higher sensitivity to all drugs (Figures 6E–H, P < 0.001).

DISCUSSION

PD-L1 overexpression has been demonstrated in many common cancers, inducing T-cell tolerance and promoting immune escape. Blockades targeted on PD-1/PD-L1 have already shown striking effectiveness in clinical applications (6–8). Immune characteristics relevant to PD-L1 in TME and EMT process during cancer progression were depicted in our study. Firstly, PD-L1 expression was highly expressed in OSCC, but it gradually decreased with the progress of tumor stages. As an immunosuppressive cell surface molecule that promotes T cell depletion, PD-L1 upregulation may link with increased cancer aggression and poorer prognosis, as proposed in several previous studies (29, 30). In contrast to this expectation, we observed a decrease in PD-L1 expression as disease progressed; Some previous studies on the association between PD-L1 expression and improved prognosis also supported our findings (31–34). The most likely explanation for this paradox is that PD-L1 expression can be induced by cytokines, primarily the production of interferon-γ within TME, and therefore, its expression actually reflects the contribution of endogenous anti-tumor immune response, which typically occurred in the early stages of tumor development and progression (35, 36). Moreover, our results also showed that PD-L1 was positively associated with cell proliferation in activated TAMs and EMT process. The DEGs in PD-L1 high group were significantly enriched in canonical signaling pathways that related to regulation of lymphocyte activation, suggesting the critical involvement of PD-L1 in regulating TAMs function. Additionally, our results suggested that patients in the PD-L1 high
group were at a significant chance of benefiting from ICI treatment and they also showed higher sensitivity to the chemical drugs (olaparib, paclitaxel, docetaxel, and pazopanib). This study provided preliminary evidence regarding the tight correlations among PD-L1, TAMs and EMT process, further supporting the notion that clinical efficacy of both chemotherapy and immunotherapy could be greatly improved by utilizing PD-L1 inhibitors in OSCC.

A previous research on PD-L1 regulating the proliferation of macrophages revealed that the phenotype and function of macrophages could be altered by anti-PD-L1 treatment, suggesting a crucial role of PD-L1 in regulating macrophages activation and function (37). Circulating monocytes can be recruited into TME and further polarize into TAMs. Classically, in response to microenvironmental stimuli, TAMs polarize to M1-like phenotype exhibiting proinflammatory and tumor-inhibiting phenotypic effects, while certain cytokines convert TAMs into an M2-like phenotype with anti-inflammatory but tumor-promoting functions (38, 39). Previous studies have shown that M2 macrophages elevated PD-L1 expression in cancer cells and at the same time facilitating immune escape (40, 41). As for M1 macrophages, the PD-L1 expressed on the surface was also reported to result in immune escape of cancer cells, resulting in bidirectional effects of both anti-tumoral and pro-tumoral activities (42): On one hand, M1-like phenotype had the unique ability to promote the activation and recruitment of various immune effectors, performing surveillance tasks (43), and their infiltration indicated good prognosis in some cancers (44). On the other hand, M1 macrophages involved in cancer phenotype maintenance and tumorigenicity regulation in vivo. For example, previous studies confirmed the important protumorigenic factor role of M1 macrophages in urethane-induced lung tumorigenesis (45); Higher aggregation level of human leukocyte antigen-DR+ (HLA-DR+) M1-like TAMs was related to poor response to

![FIGURE 4 | Relationship between PD-L1 and macrophage-derived chemokines in OSCC samples.](image.png)

(A) Scatter plot showing correlation between PD-L1 and M1-derived chemokines. (B) Correlation between PD-L1 and M1-derived chemokines. (C) Scatter plot showing correlation between PD-L1 and M2-derived chemokines. (D) Correlation between PD-L1 and M2-derived chemokines. *P < 0.05; **P < 0.01; ***P < 0.001.
ionizing radiotherapy in rectal cancers patients (46). In the present study, positive association between PD-L1 expression and TAMs infiltration (both M0, M1 and M2) was observed in OSCC, which was in consistent with previous findings. These findings suggested that TAMs may contribute to pro-tumorigenic effects by promoting PD-L1 expression in OSCC.

EMT is a novel mechanism involved in cancer metastasis, by which epithelial cells acquire both mesenchymal and epithelial phenotypes for cell migration and proliferation. The type III intermediate filament protein VIM that constitutes a key cytoskeletal element of mesenchymal cells, is a canonical marker of EMT process, and EMT process is characterized by marked VIM upregulation (47, 48). It is generally accepted that epithelial cells undergoing EMT are able to survive better under adverse environmental conditions, which enables tumor cells to evade immune destruction (49, 50). In addition, accumulating evidences have suggested strong correlations between EMT and immune evasion by activating multiple ICIs (51, 52); Cancer cells with PD-L1 upregulation displays an EMT phenotype that aids in immune escape. Macrophages and cancer cells were reported to establish a two-way cross-talk: Macrophages facilitated EMT changes in the latter while the latter skewed TAMs polarization into an M2 phenotype (53). Interestingly, recent evidences have indicated that in addition to M2 phenotype, M1-like macrophages also promoted EMT and chemoresistance (54); TAMs generally share both M1- and M2-like phenotypes instead of being strictly classified into above two phenotypes (55), which does not rule out the possibility that these two phenotypes are exchangeable (56, 57).

Immuono-oncology revolutionized cancer treatment. Pembrolizumab and nivolumab as anti-PD-1 mAbs have shown remarkable anti-tumor activity in the treatment of patients with recurrent/metastatic HNSCC. Ferris et al. (10) experienced nivolumab in a population of 347 HNSCC patients to evaluate the efficacy of nivolumab comparable to that of single-agent chemotherapy (CheckMate 141): Both ORR (13.3% vs 5.8%) and median OS (7.5 vs 5.1 months) were significantly improved in the nivolumab group. The estimated 12-month OS in nivolumab group was 36% versus 16.6% in standard-therapy group, while there was little difference in median progression-free survival.
(PFS) of these two groups. Similarly, the KEYNOTE-040 phase III study also compared the clinical efficacy of pembrolizumab versus current standard-therapy with a total of 495 patients enrolled: Both ORR (14.6% vs 10.1%) and median OS (8.4 vs 6.9 months) were significantly improved in the pembrolizumab group (11). These randomized phase III trials indicated that survival benefit could be well conferred by immunotherapy. Thus, it is of great importance to perform immune monitoring on patients, thereby identifying potential biomarkers, accurately stratifying patients and delineating responders and non-responders. Olaparib (AZD. 2281), a competitive inhibitor of poly (ADP-ribose) polymerase-1 (PARP-1), has been used in the clinical treatment of ovarian cancer with BRCA1/2 gene mutations (58, 59). An ongoing phase 1/2 study of olaparib and the PD-L1 inhibitor durvalumab in breast cancer patients with BRCA1/2 mutations demonstrated that 24 of 30 patients who were eligible for trial entry by study design achieved durable and adaptable cancer control at 12 weeks of combination therapy (60). Olaparib in combination with durvalumab exhibited promising anti-tumor efficacy and safety, which was confirmed in numerous clinical studies (61–63). In addition, paclitaxel, including nanoparticle albumin-bound paclitaxel (nab-paclitaxel), is a widely used chemotherapy drug for various cancers; Combination therapy of anti-PD-L1 mAb atezolizumab and nab-paclitaxel as first-line treatment exhibited significantly improved PFS in patients with PD-L1-positive tumors (64, 65). In this study, we analyzed the sensitivity differences of immunotherapy and chemotherapy between different PD-L1 expression groups with the expectation of screening potential beneficiaries, immunotherapy and chemotherapy can harnessed to maximize the immunostimulatory effects of therapeutic agents.

**DATA AVAILABILITY STATEMENT**

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

**AUTHOR CONTRIBUTIONS**

Conceived and designed the study: TW, CT, and RT. Data collection and analysis: TW and RT. Writing and revising the manuscript: TW, CT, XY, QJ, CF, and RT. All authors contributed to the article and approved the submitted version.

**FUNDING**

This study was funded by Guangxi Medical High-level Talents Training Program, National Natural Science Foundation of
**SUPPLEMENTARY MATERIAL**

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fimmu.2021.693881/full#supplementary-material

**REFERENCES**

1. Seiwert TY, Zuo Z, Keck MK, Khattri A, Pedamallu CS, Stricker T, et al. Integrative and Comparative Genomic Analysis of HPV-Positive and HPV-Negative Head and Neck Squamous Cell Carcinomas. *Clin Cancer Res* (2015) 21(3):632–41. doi: 10.1158/1078-0432.CCR-13-3310

2. Cohen EE, Davis DW, Karrison TG, Seiwert TY, Wong SJ, Nattam S, et al. Erlotinib and Bevacizumab in Patients With Recurrent or Metastatic Squamous-Cell Carcinoma of the Head and Neck: A Phase II/III Study. *Lancet Oncol* (2009) 10(3):247–57. doi: 10.1016/S1470-2045(09)70002-6

3. Dougan M, Dranoff G. Immune Therapy for Cancer. *Annu Rev Immunol* (2009) 27:83–117. doi: 10.1146/annurev.immunol.021908.132544

4. Pardoll DM. The Blockade of Immune Checkpoints in Cancer Immunotherapy. *Nat Rev Cancer* (2012) 12(4):252–64. doi: 10.1038/nrc3239

5. Dong H, Strome SE, Salomao DR, Tamura H, Hirano F, Flies DB, et al. Tumor-Associated B7-H1 Promotes T-Cell Apoptosis: A Potential Mechanism of Immune Evasion. *Nat Med* (2002) 8(8):793–800. doi: 10.1038/nm730

6. Okazaki T, Chikuma S, Iwai Y, Fagarasan S, Honjo T. A Rheostat for Immune Responses: The Unique Properties of PD-1 and Their Advantages for Clinical Application. *Nat Immunol* (2013) 14(12):1212–8. doi: 10.1038/ni.2762

7. Sharma P, Allison JP. Immune Checkpoint Targeting in Cancer Therapy: Toward Combination Strategies With Curative Potential. *Cell* (2015) 161(2):205–14. doi: 10.1016/j.cell.2015.03.030

8. Sharma P, Allison JP. The Future of Immune Checkpoint Therapy. *Science* (2015) 348(6290):56–61. doi: 10.1126/science.aaa8172

9. Seiwert TY, Burtness B, Mehran R, Weiss J, Berger R, Eder JP, et al. Safety and Clinical Activity of Pembrolizumab for Treatment of Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck (KEYNOTE-012): An Open-Label, Multicentre, Phase 1b Trial. *Lancet Oncol* (2016) 17(7):956–65. doi: 10.1016/s1470-2045(16)30066-3

10. Ferris RL, Blumenschein Jr., Fayette J, Guigay J, Colevas AD, Licitra L, et al. Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck. *N Engl J Med* (2016) 375(19):1856–67. doi: 10.1056/NEJMoa1602252

11. Cohen EEW, Soulières D, Le Tourneau C, Dinis J, Licitra L, Ahn MJ, et al. Heat map of OSCC samples by using the ssGSEA scores from 26 immune cell types. (A) PD-L1 significantly associated with immune cells. Scatter plot showing correlation between PD-L1 and various immune cells, including aDC (C), M1 macrophages (D), M2 macrophages (E), Cytotoxic cells (F), T cells (G) and Th1 cells (H).

12. Hanahan D, Weinberg RA. Hallmarks of Cancer: The Next Generation. *Cell* (2011) 144(5):646–74. doi: 10.1016/j.cell.2011.02.013

13. Cohen EEW, Soulières D, Le Tourneau C, Dinis J, Licitra L, Ahn MJ, et al. Heat map of OSCC samples by using the ssGSEA scores from 26 immune cell types. (B) Scatter plot showing correlation between PD-L1 and various immune cells, including aDC (C), M1 macrophages (D), M2 macrophages (E), Cytotoxic cells (F), T cells (G) and Th1 cells (H).

14. Duggal P, Gillanders EM, Holmes TN, Bailey-Wilson JE. Establishing an Adjusted P-Value Threshold to Control the Family-Wide Type 1 Error in Genome Wide Association Studies. *BMC Genomics* (2008) 9:516. doi: 10.1186/1471-2164-9-516

15. Shen J, Houck J, Fan W, Lohavanichbutr P, Doody D, et al. Reuse to Model Immunotherapy Response and Resistance. *Genome Med* (2014) 6:109. doi: 10.1186/s13073-014-0136-1

16. Jiang P, Gu S, Pan D, Fu J, Sahu A, Hu X, et al. Signatures of T Cell Infiltration in OSCC. *BMC Genomics* (2016) 17(7):956–65. doi: 10.1038/s41467-019-13441-6

17. Fu J, Li K, Zhang W, Nan C, Zhang J, Jiang P, et al. Large-Scale Public Data Reuse to Model Immunotherapy Response and Resistance. *Genome Med* (2020) 12(1):21. doi: 10.1186/s13073-020-02712-z

18. Nduom EK, Wei J, Yaghi NK, Huang N, Kong LY, Gabrusiewicz K, et al. PD-L1 Expression and Prognostic Impact in Glioblastoma. *Neuro Oncol* (2012) 14(8):958–78. doi: 10.1093/neuonc/nos116

19. Bara C, Mirzadeh A, Seow Y, Toyoda S, et al. Spatiotemporal Dynamics of Intratumoral Immune Cells Reveal the Immune Landscape in Human Cancer. *Immunity* (2013) 39(4):782–95. doi: 10.1016/j.immuni.2013.10.003

20. Newman AM, Liu CL, Green MR, Gentles AJ, Feng W, Xu Y, et al. Robust Enumeration of Cell Subsets From Tissue Expression Profiles. *Nat Methods* (2015) 12(3):453–7. doi: 10.1038/nmeth.3337

21. Hanahan D, Weinberg RA. Hallmarks of Cancer: The Next Generation. *Cell* (2011) 144(5):646–74. doi: 10.1016/j.cell.2011.02.013

22. Newman AM, Liu CL, Green MR, Gentles AJ, Feng W, Xu Y, et al. Robust Enumeration of Cell Subsets From Tissue Expression Profiles. *Nat Methods* (2015) 12(3):453–7. doi: 10.1038/nmeth.3337

23. Li W, Graeber MB. The Molecular Pro...
Patients Affected by Metastatic Gastrointestinal Stromal Tumors: Can Immune Checkpoints Act as a Sentinel for Short-Term Survival? *Cancers* (2018) 10(3);2118. doi: 10.3390/cancers10032118

31. Buig Yf, Ruiz EY, Van Cutsem E, Lee KW, Wyrwicz L, Schenker M, et al. Phase III, Randomised Trial of Avelumab Versus Physician’s Choice of Chemotherapy as Third-Line Treatment of Patients With Advanced Gastric or Gastro-Oesophageal Junction Cancer: Primary Analysis of JAVELIN Gastric 300. *Ann Oncol* (2018) 29(10):2052–60. doi: 10.1093/annonc/mdy264

32. Taube JM, Anders RA, Young GD, Xu H, Sharma R, McMuller TL, et al. Colocalization of Inflammatory Response With B7-H1 Expression in Human Melanocytic Lesions Supports an Adaptive Resistance Mechanism of Immune Escape. *Sci Transl Med* (2012) 4(172):172ra37. doi: 10.1126/scitranslmed.3003689

33. Badoual C, Hans S, Merillon N, Van Rysswick C, Ravel P, Benhamouza N, et al. PD-1-Expressing Tumor-Infiltrating T Cells are a Favorable Prognostic Biomarker in HPV-Associated Head and Neck Cancer. *Cancer Res* (2013) 73(1):128–38. doi: 10.1158/0008-5472.Can-12-2066

34. Roper E, Lum T, Palme CE, Ashford B, Ch’ng S, Ransom M, et al. PD-L1 Expression Predicts Longer Disease Free Survival in High Risk Head and Neck Cutaneous Squamous Cell Carcinoma. *Pathology* (2017) 49(5):499–505. doi: 10.1016/j.pathol.2017.04.004

35. Davar D, Wang H, Chauvin JM, Pagliano O, Fourcade JJ, Ka M, et al. Phase II/II Study of Pembrolizumab and Pegylated-Interferon Alfa-2b in Advanced Melanoma. *J Clin Oncol* (2018) 36(35);JCO1800632. doi: 10.1002/jco.201800632

36. Carey CD, Gussenleitner D, Lipschitz M, Roemer MGM, Lipschitz M, et al. Topological Analysis Reveals a PD-L1-Associated Microenvironmental Niche for Reed-Sternberg Cells in Hodgkin Lymphoma. *Blood* (2017) 130(22):2420–30. doi: 10.1182/blood-2017-03-770719

37. Cheng H, Wang Z, Fu L, Xu T. Macrophage Polarization in the Development of Epithelial-to-Mesenchymal Transition Induced by Tumor-Associated Macrophages Confers Chemoresistance in Peritoneally Disseminated Pancreatic Cancer. *J Exp Clin Cancer Res* (2018) 37(1):307. doi: 10.1186/s13046-018-0981-2

38. Mooney K, Colombo N, Scambia G, Kim BG, Oaknin A, Friedlander M, et al. Clinical Activity of Durvalumab Plus Olaparib in Metastatic Castration-Resistant Prostate Cancer in Recurrent Ovarian Cancer: A Proof-Of-Concept Phase II Trial. *J Immunother Cancer* (2020) 8(11):351. doi: 10.2147/jicr.v8i11.2020075

39. Moore SM, Pastel-Vinay S, Im SA, Delord JP, Italiano A, et al. Phase II, Basket Study. *Lancet Oncol* (2020) 21(9):1155–64. doi: 10.1016/s1470-224x(20)30324-7

40. Fumet JD, Limagne E, Thibaudin M, Trunzer C, Bertaut A, Redorffeur E, et al. Precision Medicine Phase II Study Evaluating the Efficacy of a Double Immunotherapy by Durvalumab and Tremelimumab Combined With Olaparib in Patients With Solid Cancers and Carriers of Homologous Recombination Repair Genes Mutation in Response or Stable After Olaparib Treatment. *BMC Cancer* (2020) 20(1):748. doi: 10.1186/s12885-020-07253-x

41. Karzai F, Vander-Weele D, Madan RA, Owens H, Cordes LM, Hankin A, et al. Activity of Durvalumab Plus Olaparib in Metastatic Castration-Resistant Prostate Cancer in Men With and Without DNA Damage Repair Mutations. *J Immunother Cancer* (2018) 6(1):141. doi: 10.1186/s41445-018-0452-3

42. Lampret E, Zimmer A, Padget M, Cimino-Mathews A, Nair JR, Liu Y, et al. Oligonucleotide Treatment for Solid Tumors: A Randomised, Double-Blind, Placebo-Controlled, Phase 3 Trial. *Lancet Oncol* (2020) 21(9):1155–64. doi: 10.1016/s1470-224x(20)30324-7

43. O’Sullivan T, Saddawi-Konefka R, Vermi W, Koebel CM, Arthur C, White JM, et al. Cancer Immunoeediting: Integrating Adaptive Immunity's Roles in Cancer Suppression and Promotion. *Science* (2011) 331(6024):1565–70. doi: 10.1126/science.2034866

44. Yao JX, Chen X, Zhu YJ, Wang H, Hu XY, Guo JM. Prognostic Value of PD-L1 is Associated With Immunosuppression in Metastatic Renal Cell Carcinoma. *Front Oncol* (2020) 10:1181. doi: 10.3389/fonc.2020.01181

45. Schmit P, Rugo HS, Adams S, Schneeweiss A, Barrios CH, Iwata H, et al. Atezolizumab Plus Nab-Paclitaxel as First-Line Treatment for Unresectable, Locally Advanced or Metastatic Triple-Negative Breast Cancer (IMpassion130): Updated Efficacy Results From a Randomised, Double-Blind, Placebo-Controlled, Phase 3 Trial. *Lancet Oncol* (2020) 21(1):44–59. doi: 10.1016/s1470-224x(19)30689-8
65. Schmid P, Adams S, Rugo HS, Schneeweiss A, Barrios CH, Iwata H, et al. Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer. *N Engl J Med* (2018) 379(22):2108–21. doi: 10.1056/NEJMoai1809615

**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

**Publisher’s Note:** All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.