The use of the PD-1 / PD-L1 pathway as an immunotherapy in oncological diseases, autoimmune diseases and infectious diseases

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Summary
Introduction:
PD-1 is programmed death receptor 1 belonging to the CD28 family of receptors. Immune cells have this receptor on their surface. PD-L1 allows cancer cells to avoid the host's response. Connection to the PD-1 receptor leads to the death of the immune cell.
Objective:
The use of PD-1 receptors in the treatment of oncological, autoimmune and infectious diseases.
Abbreviated description of the state of knowledge:
The development and progression of immunotherapy in recent years has resulted in the approval of five immunotherapy pathways targeting PD-1 (pembrolizumab and durvalumab) or PD-L1 (atezolizumab, nivolumab and avelumab) in patients with progression during or

after cisplatin based chemotherapy. The latest updates show that in some types of cancer, positive PD-L1 expression has an effect on treatment effect and qualification. These therapies are used, among others in melanoma, lymphomas, kidney cancer or breast cancer. PD-1 is also used to treat autoimmune and infectious diseases.

Conclusions:

Understanding the mechanism of the PD-1/PD-L1 pathway allows to design targeted therapy for individuals. It has been already used in NSCLC treatment program, whether bladder cancer or melanoma. Immunotherapy increases the survival time of patients with advanced stages of cancer. The therapies targeting the PD-1/PD-L1 pathway in autoimmune and infectious diseases are in clinical trials.

Key words: programmed death receptor-1 (PD-1); programmed death receptor ligand-1 (PD-L1); immunotherapy, oncology; autoimmunology; infectious diseases

1.Introduction

PD-1, or programmed death receptor-1 (CD279), belongs to the CD28 family of receptors. The PD-1 receptor is on the surface of immune cells. Tumor cells possessing PD-L1 have the ability to evade the host's response. They attach to the PD-1 receptor and lead to the death of host immune cells. Antibodies directed against PD-1 have been shown to be effective in increasing T cell anti-tumor activity in some types of cancer. However, the potential effect of PD-1 on cancer cells remains largely unknown [1]. In a laboratory test, the amount of PD-L1 present on cancer cells is determined, which allows you to determine how to treat specific cancers. In their work, Zak et al. explain that cancer cells can avoid and suppress the host's immune responses by activating immunological immune checkpoint proteins such as PD-1, PD-L1 and CTLA-4. Silencing PD-1 or its ligand, PD-1 ligand (PD-L1), promotes cell proliferation and colony formation *in vitro*, and tumor growth *in vivo*. And overexpression of PD-1 or PD-L1 inhibits tumor cell proliferation and colony formation. In addition, blocking antibodies directed against PD-1 or PD-L1 promote tumor growth in cell cultures and xenografts [2].

In treatment using the targeting of PD-1/PD-L1 pathway there are two types of actions. Anti-PD-1 monoclonal antibodies (nivolumab and pembrolizumab), blocking the PD-1 molecule present on the surface of T- lymphocytes. Anti-PD-L1 antibodies (atezolizumab and durvalumab), blocking the PD-L1 molecule located on the surface of cancer cells and on the surface of cells of the immune system infiltrating the tumor tissue [3].

State of knowledge:
2. SIDE EFFECTS OF IMMUNOTHERAPY

Immunotherapy is increasingly used to treat advanced malignancies. One of the therapeutic routes are inhibitors of the immunological checkpoint proteins PD-1 and PDL-1. Despite good results, there are reports of side effects of their use. Side effects are associated with over-activation of the immune system. They are known as immune-related adverse events (IRAEs) [4]. A retrospective study evaluated the safety of nivolumab in 576 patients with advanced melanoma. 71% of patients experienced adverse effects of varying degrees [5].

The spectrum described in the IRAE literature is broad. From rash and itching to encephalitis [6,7]. Common IRAEs are nonspecific symptoms such as fatigue or loss of appetite [5]. Commonly occurring IRAEs include myositis with and without myasthenia gravis. In turn, neurological side effects are rare but may be associated with poor prognosis [8]. One of the life-threatening IRAEs is Guillain-Barré Syndrome. From a clinical point of view, nonspecific symptomatology is initially important [9]. Gastroenterological IRAEs include: diarrhea, colitis, intestinal perforation, and hepatitis [10,11]. On the other hand, among the endocrine IRAEs there are thyroiditis, hypothyroidism, diabetes, and hypopituitarism [12,13]. Knowledge of IRAE is important in the prompt implementation of the appropriate procedure. For the treatment of IRAE, immunosuppression is recommended for a short period of time (from 2 weeks to 2 months). It is noted that immunosuppression longer than 28 days may be associated with opportunistic infections [14].

3.0 ONCOLOGICAL DISEASES
3.1. MELANOMA
The concept of immune surveillance of cancer is based on the fact that cancer cells can be recognized and eliminated by the immune system. The development of metastatic aggressive melanoma shows that selected variants can get out of immunological control. The most commonly studied negative control immunological molecules and widely accepted targets for immunotherapy are T-cell-associated cytotoxic protein 4 (CTLA-4) and programmed cell-1 (PD-1) death protein. The interaction of PD-1 with its ligands PD-L1 and PD-L2, in turn, inhibits the effector function of T cells in peripheral tissues. In addition, the combination of anti-CTLA-4 and anti-PD-1 antibodies has been shown to act synergistically by multiplying activated T-effector cells. Currently, anti-PD-1 antibodies are nivolumab, pembrolizumab, cemiplimab, and atezolizumab and avelumab for the target PD-L1. The expression of PD-L1 on tumor cells is also thought to be a clear predictor of response to treatment. Although PD-L1 overexpressing tumors have been shown to be associated with a higher response to immunotherapy, sustained responses could also be seen in PD-L1 negative tumors. Hence, further studies are needed to assess the actual prognostic value of tumor PD-L1, including dynamic monitoring of PD-L1 expression or PD-L RNA sequencing [15]. Therapies targeted at programmed death receptor-1 (PD-1) have been showing efficacy in treating patients with melanoma for years. Findings of the research group under the leadership of Tumeh PC. from 2014 indicate that tumor regression after therapeutic PD-1 blockade requires the prior existence of CD8 (+) T-cells negatively regulated by adaptive immune resistance mediated by PD-1/PD-L1. The correlation between T-cell activation and treatment outcome after the release of the PD-1 immune checkpoint can be driven by the production of interferons by tumor-infiltrating CD8 cells that induce PD-L1 expression on tumor-resident cells [16].

3.2 KIDNEY CANCER/ BLADDER CANCER/ UROTHELIAL CARCINOMA
The use of new checkpoint inhibitors has also been very promising in refractory muscular bladder cancer. Ongoing research into the role of checkpoint inhibitors in bladder cancer may change our approach to different stages of this cancer. For local bladder cancer, immunotherapy as neoadjuvant therapy may be associated with less toxicity and better

tolerability. Finally, in the setting of a BCG-refractory or BCG-naïve nonmuscle invasive disease checkpoint inhibitors may reduce/delay the risk of progression and subsequent cystectomy [17].

Kidney cancer (RCC) as well as urothelial cancer (UC) are highly immunogenic tumors. Advances in understanding cellular immunity have resulted in a new class of therapeutic agents. Anti-PD1 and anti-PD-L1 monoclonal antibodies are checkpoint inhibitors. They inhibit the immune response of PD1 on T cells (Treg) and PD-L1 on cancer cells. In metastatic or inoperable urothelial cancer, there is no effective second-line therapy, but checkpoint inhibitors have proved to be active and are increasingly being included in the guidelines for urothelial cancers. Numerous randomized phase II clinical trials are underway as well as adjuvant therapy for the efficacy of these substances [18]. Nivolumab was evaluated for safety and activity in a study by Sharma et al. Patients with progression or relapse over 18 were enrolled in the phase II study. They had previously received at least one platinum-based treatment regimen. Patients received the drug intravenously at a dose of 3 mg/kg every 2 weeks, until disease progression, clinical deterioration, drug toxicity or other causes. The study showed that ORR was higher in patients with high PD-L1 expression (28.4% for PD-L1 $\geq$ 5%, 23.8% for PD-L1 $\geq$ 1% and 16.1% for PD-L1 <1 %), while the OS index was also higher for tumors with PD-L1 expression $\geq$1% vs. PD-L1 <1%. Nivolumab monotherapy provided significant clinical benefit and demonstrated an acceptable level of safety.[19,20]. In 2017, nivolumab as a drug for locally advanced or metastatic urothelial cancer was included in therapy by the FDA [20]. The development of new targeted therapies and immunotherapy is a goal in the fight against kidney cancer. They are most often diagnosed accidentally, and 90% of kidney cancers are renal cell carcinoma, and as many as 17% of diagnosed patients have advanced stage of disease.

Programmed death 1 ligand (PD-L1) was analyzed in the Chandrasekaran et al study. It is the surface protein of transmembrane cells and is expressed on cancer cells. PD-L1 appears to play a major role in inhibiting the T-cell immune response. By targeting the host's immune system to the PD1/PD-L1 pathway, tumor progression can be inhibited. Protein expression in tumor and adjacent cells of renal cell carcinoma and the association of PD-L1 with tumor features were assessed. PD-L1 monoclonal antibodies were used. A high relationship between WHO high ISUP and PD-L1 positive expression was seen, 75% in RCC sarcomatic type and 46.8% in ccRCC, respectively. This shows that blocking the PD1/PD-L1 pathway can be an effective method of immunotherapeutic treatment (especially in RCC). The relationship between PD-L1 expression and high tumor malignancy was confirmed, which proves to be an important prognostic factor [21].

The study of Cimadamore A. et al. focused on studies that looked at using PD-1 alone and a PD-L1 inhibitor alone or in combination with another agent, and compared the different tests used in each study to assess the role of PD-L1 as a biomarker prognostic and predictive. It has been found that the current data on the use of PD-L1 expression alone are not sufficient to predict the response to treatment and have many limitations: lack of consensus between different biomarker assessment methods, PD-L1 heterogeneity between primary tumors and metastatic sites, different response criteria (RECIST vs. irRECIST), complex interaction with inflammatory components, prior treatment, administration of an antibiotic. Combinations of various biomarkers and biological traits such as angiogenesis associated gene expression,

immune response and osteomyelitis are promising biological variables that need to be reviewed in the context of future clinical trials [22].

The National Cancer Institute (NCI) defines targeted therapies as "drugs or substances that block the growth and spread of cancer, interfering with the action of specific molecules involved in the growth and progression of cancer." Nivolumab is a monoclonal antibody therapy designed to directly block the interaction between PD-1 and its ligands in the treatment of melanoma, lung cancer, kidney cancer and hematological cancers and has been used since 2014 [23]. The study of Nakamura et al. examined the efficacy and safety of anti-PD1 therapy (nivolumab) in advanced kidney cancer (RCC) in clinical settings. Previously, patients received other therapies. It was observed that the median progression-free survival was 10.3 months and the overall survival was 45.9 months. Nivolumab showed an objective response in 24% of cases. The results suggest that nivolumab may achieve comparable results under real-world clinical conditions to those in clinical trials [24].

Motzer et al. studied the efficacy and safety of an open-label, randomized phase III study of nivolumab in patients with RCC. Survival benefit in favor of nivolumab has been demonstrated over everolimus in patients who have received one or two previous anti-angiogenic therapies. The median OS was 25.0 months (95% CI: 21.8 - not estimable) with nivolumab and 19.6 months (95% CI: 17.6–23.1) with everolimus. ORR was greater for nivolumab than for everolimus (21.5% vs. 3.9%; P <0.001). Survival benefits were observed in each subgroup receiving nivolumab compared to everolimus, regardless of PD-L1 expression. Nivolumab was approved for the treatment of metastatic kidney cancer in November 2015 [20,25]. In the 2018, Motzer et al study, the effectiveness of nivolumab combined with ipilimumab was examined. Patients were randomly assigned to 3 groups: Group I received 4 doses of nivolumab 3 mg/kg plus ipilimumab 1 mg/kg every 3 weeks, Group II nivolumab 3 mg/kg every 2 weeks, Group III sunitinib 50 mg once a day for 4 weeks. The median was 25.2 months in patients with medium to low risk, 18 months overall survival was 75% (95% CI: 70-78) with nivolumab with ipilimumab and 60% (95% CI: 55-65) with sunitinib. The objective response rate was 42% compared with 27% (p <0.001), and the total response rate was 9% compared with 1%. The median progression and free survival was 11.6 months and 8.4 months, respectively. In summary, OS and ORR were significantly higher for nivolumab with ipilimumab than for sunitinib in patients at medium to low risk with previously untreated advanced renal cell carcinoma. In April 2018, combination therapy with nivolumab and ipilimumab was approved as first-line treatment for patients with advanced medium and low risk RCC based on study results [26,27].

In 2018, study of Koshkina et al tested the effectiveness of nivolumab in non-clear cell RCC subtypes, as this group of patients had previously been excluded from the original drug research. Monotherapy was well tolerated by patients. The study confirms the use of nivolumab in patients with metastatic, opaque renal cell carcinoma. However, more research is needed to demonstrate the effectiveness of the drug in this subtype of kidney cancer [28].

3.4 NON-SMALL-CELL LUNG CARCINOMA (NSCLC)

Lung cancer is the most common cancer in the world, and non-small cell lung cancer (NSCLC) is the most common subtype and accounts for 75% of all lung cancer cases. The course of the disease is often associated with high mortality.[29]. Reck et al. conducted a study in which they compared the immunological treatment with pemrolizumab for chemotherapy (platinum). Pembrolizumab is a humanized monoclonal antibody directed against the PD-1 receptor. The study included 305, previously untreated, patients whose PD-L1 expression was at least 50% of the cancer cells. It was shown that the median progression free survival was 10.3 months (95% [CI].) in the pembrolizumab group compared to 6.0 months (95% CI) in the chemotherapy group. After 6 months of therapy, the overall survival rate was 80.2% in the pembrolizumab group compared with 72.4% in the chemotherapy group [30]. A study by Forde et al. demonstrated the effectiveness of nivolumab in patients at an early stage of NSCLC (stage I, II or IIIA). The used treatment did not delay the planned surgery. Of the 21 tumors removed, 20 were completely resected. The main response to the treatment applied was in 9 out of 20 resected tumors (45%) [31]. Although PD-1/PD-L1 blockade has shown good results in clinical trials, NSCLC is not effective in many patients. Hu et al. assessed 1984 patients with NSCLS to determine genetic changes. It was shown that the mutations most often concerned: p53 protein (55.70%), epidermal growth factor receptor (52.47%), GTPase KRAS prototype (13.36%) [32].

3.5 BREAST CANCER

Unlike melanoma or lung cancer, breast cancer is not characterized by high immunogenicity. The use of PD-1 and PDL-1 checkpoint inhibitors in breast cancer is therefore limited. Still, there are promising results of immunotherapy in triple negative breast cancer (TNBC). This is the most aggressive and worst prognosis subtype of breast cancer. It is characterized by a high frequency of relapses.[33]. In one study, PDL-1 expression in TNBC cells was 8.5%. In contrast, PDL-1 expression in tumor infiltrating lymphocytes (TIL) accounted for 25.1%. Furthermore, PDL-1 expression in TIL and not in tumor cells was a bad prognostic factor [34]. In another study, PDL-1 expression co-occurring with low level of tumor infiltrating lymphocytes (TIL) was assessed as a negative prognostic factor in TNBC [35]. In 2019, the first checkpoint inhibitor approved - atezolizumab for the treatment of breast cancer. FDA approval of this drug was based on the results of an IMpassion130 phase III clinical trial. In this study, TNBC patients were divided into two groups of 451 patients each. In one of them, patients received atezolizumab and nab-paclitaxel. In contrast, the placebo group only nab-paclitaxel. Median progression-free survival was 7.2 months with atezolizumab and nab-paclitaxel, compared with 5.5 months with placebo and nab-paclitaxel (p = 0.002). In contrast, patients with PD-L1 positive tumors had a median progression free survival of 7.5 months and 5.0 months, respectively (p <0.001) [36,37]. FDA approval of atezolizumab is a promising point for personalized TNBC treatment. Tumors that do not express PDL-1 remain a challenge in the immunotherapy of this subtype of breast cancer.

3.6. LYMPHOMAS

Immunological agents that block control points, i.e. PD-1/PD-L1, allow the reconstruction of long-term anti-tumor immunity. For hematological cancers, this new therapeutic strategy is much less documented, although promising clinical responses have been seen in patients with refractory and recurrent Hodgkin's lymphoma. It has been accepted in the available literature that the expression of PD-1/PD-L1 on the cell surface is a key determinant for the identification of patients eligible for this immunotherapy [38].

Preclinical studies suggest that Reed-Sternberg cells use programmed death pathway 1 (PD-1) to avoid detection by the patient's immune system. In classic Hodgkin's lymphoma, changes in chromosome 9p24.1 increase the abundance of PD-1, PD-L1 and PD-L2 ligands. They also promote their induction through a Janus kinase signal transducer and transcription signaling activator (STAT). In Ansell SM research. et al. from 2015, it turned out that one of the anti-PD-1 drugs, nivolumab, showed significant therapeutic activity. Its safety profile in patients with previously intensively treated recurrent or refractory Hodgkin's lymphoma was acceptable.[39]. As a result of studies performed in relapsed/refractory classic Hodgkin's lymphoma, anti-PD-1 monotherapy showed satisfactory response rates - from 65% to 87%. The median duration of response was 16 months in the phase II study. PD-1 blockade was also promising in the phase I study of nivolumab in relapsed/refractory B-cell non-Hodgkin's lymphoma, including follicular lymphoma. In 2018, slightly different results were obtained when pembrolizumab was used in recurrent chronic lymphocytic leukemia (CLL) - the response to treatment was 0% and 44% in CLL with Richter transformation in the phase II study by XU-Monette ZY. et al. PD-1 expression was also found in marginal lymphoma, but not in mantle cell lymphoma [40]. Mechanisms and predictive biomarkers of PD-1 blocking immunotherapy, treatment-related adverse events, and combination therapies are the focus of current research.

4. AUTOIMMUNIZATION DISEASES

The PD-1 receptor is one of the most important human immunity checkpoints. PD-1 is mainly expressed on activated lymphocytes. PD-L ligands occur on many cells in the body, giving the possibility of treating autoimmune diseases [41]. The programmed death ligand pathway (PD)-1/PD-1 (PD-Ls) belongs to the B7/CD28 family. It consists of the PD-1 receptor and its ligands PD-L1 (B7-H1, CD274) and PD-L2 (B7-DC, CD273). Studies show that the PD-1/PD-Ls pathway affects induction and maintenance of immune tolerance. The PD-1/PD-Ls pathway protects tissues against the development of autoimmune reactions under physiological conditions.[42]. Autoimmune diseases include multiple sclerosis (MS). The pathomechanism of the disease is chronic inflammation. Kooij et al. noted that the different expression of mediators such as LXA4, LXB4, RvD1 and PD1 reduces monocyte activation and cytokine production under the influence of MS disease. In addition, those mediators are involved in the inhibition of inflammation-induced blood-brain barrier dysfunction and transepithelial migration of monocytes. Researchers have shown that the expression of PD-1 molecules can potentially be used as a biomarker in both diagnosis and treatment [43]. The PD-1/PD-L1 pathway is important in the pathogenesis of rheumatoid arthritis (RA). The *PDCD1, CD274* and *PDCD1LG2* genes have been shown to be upregulated in synovial

tissues at various stages of RA disease development. In addition, PD-1 expression was demonstrated on most of the CD4+ and CD8+ T-cells present in the synovium.[44].

5. INFECTIOUS DISEASES

Chronic infections involve persistent antigenic stimulation associated with antigen-specific T cell dysfunction and up regulation of inhibitory receptors, including PD-1. This receptor plays a role in many infectious diseases, including tuberculosis, hepatitis and cryptococcosis [45]. Expression of the PD-1 receptor increases, for example, in Mycobacterium avium complex (MAC) infections, which results from reduced secretion of interleukin IL-17 [46]. The 2018 Day CL research team concluded from their research that PD-1 was expressed at significantly higher levels on Mycobacterium-specific cytokine-producing CD4 T lymphocytes. Their research sheds new light on the role of the PD-1 pathway in regulating CD4 and CD8 T-cell responses in tuberculosis infection. Thus, they justify the need for future studies of the PD-1 pathway as a potential biomarker response to anti-tuberculosis therapy [47]. Exhaustion of antigen-specific T-cells is often seen in chronic liver infection due to hepatotropic viruses. Blocking overexpression of certain pathways, or modulation of immunological checkpoints, is a promising new therapy that can improve the treatment of liver disease with T-cell depletion features.[48]. In 2018, a team led by Mathur P. showed that after treatment with rituximab in patients with hepatitis C, a decrease in PD-1 expression was observed [49]. PD-1 associated pathways also seem to play a significant role in hepatocellular carcinoma (HCC) on the basis of chronic HCV infection. It turned out that CD8+ T-cells with PD-1 on their surface were clearly important in predicting the course of the disease and response to treatment. Modulation of this immune checkpoint can be a promising target in immunotherapy against HCC [50]. The 2018 study results also suggest that suppression of the PD-1/PD-L1 signaling pathway limits the development of cryptococcal meningitis by decreasing Th2-cell expression and inhibiting microglia and macrophage activation [51].

Conclusions:

Treatment using the achievements of immunology is increasingly important in the development of new therapies in many disease entities. Understanding the mechanism of action of the programmed PD-1/PD-L1 cell death pathway makes it possible to use this knowledge to design targeted therapy. By assessing the sensitivity of receptors to these antibodies, we can block the destructive effects of cancer cells on the lymphocytes involved in the fight against cancer. Individual adjustment of treatment to the needs of the patient can be embedded in already widely used treatment programs for small cell lung cancer, bladder cancer or melanoma. The effects of the treatment are satisfactory and they allow to extend the survival time of patients with advanced cancer. A number of factors directed at PD-1/PD-L1 pathway are currently in clinical trials in autoimmune and infectious diseases.

Bibliography:

[1] Wang X, Yang X, Zhang C Tumor cell-intrinsic PD-1 receptor is a tumor suppressor and mediates resistance to PD-1 blockade therapy. Proc Natl Acad Sci U S A. 2020 Mar 24;117(12):6640-6650.

[2] Zak KM, Grudnik P, Magiera K, Dömling A, Dubin G, Holak TA. Structural Biology of the Immune Checkpoint Receptor PD-1 and Its Ligands PD-L1/PD-L2. Structure. 2017 Aug 1;25(8):1163-1174

[3] Mengjia Song, Xinfeng Chen, Liping Wang, Yi Zhang.Future of anti-PD-1/PD-L1 applications: Combinations with other therapeutic regimens. Chin J Cancer Res. 2018 Apr; 30(2): 157–172.

[4] Spain L, Diem S, Larkin J. Management of toxicities of immune checkpoint inhibitors. Cancer Treat Rev. 2016 Mar;44:51-60.

[5] Weber JS, Hodi FS, Wolchok JD, Topalian SL, Schadendorf D, Larkin J. Safety Profile of Nivolumab Monotherapy: A Pooled Analysis of Patients With Advanced Melanoma. J Clin Oncol. 2017 Mar;35(7):785-792.

[6] Sibaud V, Meyer N, Lamant L, Vigarios E, Mazieres J, Delord JP. Dermatologic complications of anti-PD-1/PD-L1 immune checkpoint antibodies. Curr Opin Oncol. 2016 Jul;28(4):254-63.

[7] Johnson DB, McDonnell WJ, Gonzalez-Ericsson PI, Al-Rohil RN, Mobley BC, Salem JE et al. A case report of clonal EBV-like memory CD4+ T cell activation in fatal checkpoint inhibitor-induced encephalitis. Nat Med. 2019 Aug;25(8):1243-1250.

[8] Kolb NA, Trevino CR, Waheed W, Sobhani F, Landry KK, Thomas AA et al. Neuromuscular complications of immune checkpoint inhibitor therapy. Muscle Nerve. 2018 Jan 17.

[9] Pierrard J, Petit B, Lejeune S, Seront E. Isolated adrenocorticotropic hormone (ACTH) deficiency and Guillain-Barré syndrome occurring in a patient treated with nivolumab. BMJ Case Rep. 2019 Aug 21;12(8).

[10] Dougan M. Gastrointestinal and Hepatic Complications of Immunotherapy: Current Management and Future Perspectives. Curr Gastroenterol Rep. 2020 Mar 17;22(4):15.

[11] Celli R, Kluger HM, Zhang X. Anti-PD-1 Therapy-Associated Perforating Colitis. Case Rep Gastrointest Med. 2018 May 31;2018:3406437.

[12]Imblum BA, Baloch ZW, Fraker D, LiVolsi VA. Pembrolizumab-Induced Thyroiditis. Endocr Pathol. 2019 Jun;30(2):163-167.

[13] Sznol M, Postow MA, Davies MJ, Pavlick AC, Plimack ER, Shaheen M et al. Endocrine-related adverse events associated with immune checkpoint blockade and expert insights on their management. Cancer Treat Rev. 2017 Jul;58:70-76.

[14] Weber JS, Postow M, Lao CD, Schadendorf D. Management of Adverse Events Following Treatment With Anti-Programmed Death-1 Agents. Oncologist. 2016 Oct;21(10):1230-1240.

[15] Petrova V, Arkhypov I, Weber R, Groth C, Altevogt P, Utikal J et al. Modern Aspects of Immunotherapy with Checkpoint Inhibitors in Melanoma. Int J Mol Sci. 2020 Mar 30;21(7).

[16] Tumeh PC, Harview CL, Yearley JH, Shintaku IP, Taylor EJ, Robert L, et al. PD-1 blockade induces responses by inhibiting adaptive immune resistance. Nature. 2014 Nov 27;515(7528):568-71.

[17] Lenfant L, Aminsharifi A, Seisen T, Rouprêt M. Current status and future directions of the use of novel immunotherapeutic agents in bladder cancer. Curr Opin Urol. 2020 May;30(3):428-440.

[18] De Maeseneer DJ, Delafontaine B, Rottey S. Checkpoint inhibition: new treatment options in urologic cancer. Acta Clin Belg. 2017 Feb;72(1):24-28.

[19] Sharma P, Retz M, Siefker-Radtke A, Baron A, Necchi A, Bedke J, et al. Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): a multicentre, single-arm, phase 2 trial. Lancet Oncol. 2017 Mar;18(3):312-322.

[20] Xiaomo Wu, Zhongkai Gu, Yang Chen, Borui Chen, Wei Chen, Liqiang Weng, et al. Application of PD-1 Blockade in Cancer Immunotherapy Comput Struct Biotechnol J. 2019; 17: 661–674.

[21] Chandrasekaran D, Sundaram S, N K, R P. Programmed Death Ligand 1; An Immunotarget for Renal Cell Carcinoma. Asian Pac J Cancer Prev. 2019 Oct 1;20(10):2951-2957.

[22] Cimadamore A, Massari F, Santoni M, Lopez-Beltran A, Cheng L, Scarpelli M. PD1 and PD-L1 Inhibitors for the Treatment of Kidney Cancer: the Role of PD-L1 Assay. Curr Drug Targets. 2020 Mar 24.

[23] Jhaveri KD, Wanchoo R, Sakhiya V, Ross DW, Fishbane S. Adverse Renal Effects of Novel Molecular Oncologic Targeted Therapies: A Narrative Review. Kidney Int Rep. 2016 Sep 21;2(1):108-123.

[24] Numakura K, Horikawa Y, Kamada S, Koizumi A, Nara T, Chiba S, Kanda S, Saito M, Narita S, Inoue T, Shimoda N, Habuchi T. Efficacy of anti-PD-1 antibody nivolumab in Japanese patients with metastatic renal cell carcinoma: A retrospective multicenter analysis. Mol Clin Oncol. 2019 Sep;11(3):320-324.

[25] Motzer RJ, Escudier B, McDermott DF, George S, Hammers HJ, Srinivas S et al. Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. N Engl J Med. 2015 Nov 5;373(19):1803-13.

[26] Motzer RJ, Tannir NM, McDermott DF, Arén Frontera O, Melichar B, Choueiri TK et al. Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma. N Engl J Med. 2018 Apr 5;378(14):1277-1290.

[27] Xiaomo Wu, Zhongkai Gu, Yang Chen, Borui Chen, Wei Chen, Liqiang Weng et al. Application of PD-1 Blockade in Cancer Immunotherapy. Comput Struct Biotechnol J. 2019; 17: 661–674.

[28] Koshkin VS, Barata PC, Zhang T, George DJ, Atkins MB, Kelly WJ et al. Clinical activity of nivolumab in patients with non-clear cell renal cell carcinoma. J Immunother Cancer. 2018 Jan 29;6(1):9.

[29] Peters S, Kerr KM, Stahel R. PD-1 blockade in advanced NSCLC: A focus on pembrolizumab. Cancer Treat Rev. 2018 Jan;62:39-49.

[30] Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. N Engl J Med. 2016 Nov 10;375(19):1823-1833.

[31] Forde PM, Chaft JE, Smith KN, Anagnostou V, Cottrell TR, Hellmann MD et al. Neoadjuvant PD-1 Blockade in Resectable Lung Cancer. N Engl J Med. 2018 May 24;378(21):1976-1986.

[32] Hu J, Shang Y, Shi X, Zhang S, Shi J, Yao M et al. Characterization of genomic alterations and the significance of PI3K/mTOR pathway mutations and tumor mutational burden in non-small cell lung cancer. Oncol Rep. 2020 Mar 23.

[33] Praveen Vikas, Nicholas Borcherding, Weizhou Zhang. The clinical promise of immunotherapy in triple-negative breast cancer. Cancer Manag Res. 2018 Dec 10;10:6823-6833.

[34] Wang Xinran, Yueping Liu. PD-L1 expression in tumor infiltrated lymphocytes predicts survival in triple-negative breast cancer. Pathology - Research and Practice Volume 216, Issue 3, March 2020, 152802.

[35] Hitomi Mori, Makoto Kubo, Rin Yamaguchi, Reiki Nishimura, Tomofumi Osako, Nobuyuki Arima et al. The combination of PD-L1 expression and decreased tumor-infiltrating lymphocytes is associated with a poor prognosis in triple-negative breast cancer. Oncotarget. 2017; 8:15584-15592.

[36] Reddy SM, Carroll E, Nanda R. Atezolizumab for the treatment of breast cancer. Expert Rev Anticancer Ther. 2020 Mar;20(3):151-158.

[37] 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 Nov 29;379(22):2108-2121.

[38] Gravelle P, Burroni B, Péricart S, Rossi C, Bezombes C, Tosolini M2,3,4,5,6,7, Damotte D et al. Mechanisms of PD-1/PD-L1 expression and prognostic relevance in non-Hodgkin lymphoma: a summary of immunohistochemical studies. Oncotarget. 2017 Jul 4;8(27):44960-44975.

[39] Ansell SM, Lesokhin AM, Borrello I, Halwani A, Scott EC, Gutierrez M et al. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. N Engl J Med. 2015 Jan 22;372(4):311-9.

[40] Xu-Monette ZY, Zhou J, Young KH. PD-1 expression and clinical PD-1 blockade in B-cell lymphomas. Blood. 2018 Jan 4;131(1):68-83.

[41] Chamoto K, Al-Habsi M, Honjo T. Role of PD-1 in Immunity and Diseases. Curr Top Microbiol Immunol. 2017;410:75-97.

[42] Dai S, Jia R, Zhang X, Fang Q, Huang L. The PD-1/PD-Ls pathway and autoimmune diseases. Cell Immunol. 2014 Jul;290(1):72-9.

[43] Kooij G, Derada Troletti C, Leuti A, Norris PC, Riley I, Albanese M et al.Specialized pro-resolving lipid mediators are differentially altered in peripheral blood of patients with multiple sclerosis and attenuate monocyte and blood-brain barrier dysfunction. Haematologica. 2019 Nov 28. pii: haematol.2019.219519.

[44] Guo Y, Walsh AM, Canavan M, Wechalekar MD, Cole S, Yin X,et al. Immune checkpoint inhibitor PD-1 pathway is down-regulated in synovium at various stages of rheumatoid arthritis disease progression. PLoS One. 2018 Feb 28;13(2):e0192704.

[45] Day CL, Abrahams DA, Bunjun R, Stone L, de Kock M, Walzl G, et al. PD-1 Expression on *Mycobacterium tuberculosis*-Specific CD4 T Cells Is Associated With Bacterial Load in Human Tuberculosis.Front Immunol. 2018 Aug 31;9:1995.

[46] Shu CC, Wang JY, Wu MF, Lai HC, Chiang BL, Yu CJ. Interleukin 23/interleukin 17 axis activated by Mycobacterium avium complex (MAC) is attenuated in patients with MAC-lung disease. Tuberculosis (Edinb). 2018 May;110:7-14.

[47] Day CL, Abrahams DA, Bunjun R, Stone L, de Kock M, Walzl G, et al. PD-1 Expression on *Mycobacterium tuberculosis*-Specific CD4 T Cells Is Associated With Bacterial Load in Human Tuberculosis.Front Immunol. 2018 Aug 31;9:1995.

[48] Wuyts L, Janssens A, Vonghia L, Michielsen P, Raskin J, Driessen A, et al Nivolumab and anti-HCV activity, a case report. Acta Clin Belg. 2020 Mar 17:1-5.

[49] Mathur P, Emmanuel B, Sneller M, Zhang X, Poonia B, Kottilil S. Recovery of hepatitis C specific T-cell responses after rituximab therapy in hepatitis C mixed cryoglobulinemic vasculitis. J Med Virol. 2018 May;90(5):936-941.

[50] Zahran AM, Hetta HF, Rayan A, Eldin AS, Hassan EA, Fakhry H, et al. Differential expression of Tim-3, PD-1, and CCR5 on peripheral T and B lymphocytes in hepatitis C virus-related hepatocellular carcinoma and their impact on treatment outcomes. Cancer Immunol Immunother. 2020 Mar 13.

[51] Che YM, Zhang Y, Li M, Li XP, Zhang LL. In vitro and in vivo effect of PD-1/PD-L1 blockade on microglia/macrophage activation and T cell subset balance in cryptococcal meningitis. J Cell Biochem. 2018 Apr;119(4):3044-3057.