Human Cancer Immunotherapy with PD-1/PD-L1 Blockade

Libertas Academica
FREEDOM TO RESEARCH

Supplementary Issue: Signaling Pathways as Biomarkers

Peilin Zheng and Zhiguang Zhou

Institute of Metabolism and Endocrinology, The Second Xiangya Hospital, Key Laboratory of Diabetes Immunology, Ministry of Education, Central South University, National Clinical Research Center for Metabolic Diseases, Changsha, Hunan, China.

ABSTRACT: The ligation of programmed cell death-1 (PD-1) to its ligands PD-L1 and PD-L2 counteracts T-cell activation, which is critical in immune tolerance. The persistent high expression of PD-1 and PD-L1 are also observed on tumor-infiltrating lymphocytes and various tumor cells, maintaining the highly suppressive microenvironment in tumor sites and promoting tumor malignancies. The blockade of PD-1 axis with PD-L2 fusion protein or monoclonal antibodies against either PD-1 or PD-L1 has been clinically evaluated in various tumor types. This short review summarizes the progress of PD-1 axis blockade in clinical trials to evaluate its effectiveness in the antitumor immunotherapy.

KEYWORDS: PD-1, PD-L1, PD-L2, blockade, antitumor immunotherapy, clinical trials

SUPPLEMENT: Signaling Pathways as Biomarkers

CITATION: Zheng and Zhou. Human Cancer Immunotherapy with PD-1/PD-L1 Blockade. *Biomarkers in Cancer* 2015:7(S2) 15–18 doi:10.4137/BIC.S29325.

TYPE: Short Review

RECEIVED: May 26, 2015. **RESUBMITTED:** July 19, 2015. **ACCEPTED FOR PUBLICATION:** July 22, 2015.

ACADEMIC EDITOR: Barbara Guinn, Editor in Chief

PEER REVIEW: Four peer reviewers contributed to the peer review report. Reviewers' reports totaled 531 words, excluding any confidential comments to the academic editor.

FUNDING: Dr. Peilin Zheng was supported by the National Natural Science Foundation of China (Grant No. 81500600). The authors confirm that the funder had no influence over the study design, content of the article, or selection of this journal.

COMPETING INTERESTS: Authors disclose no potential conflicts of interest.

CORRESPONDENCE: zhouzg@hotmail.com

Paper subject to independent expert blind peer review. All editorial decisions made by independent academic editor. Upon submission manuscript was subject to anti-plagiarism scanning. Prior to publication all authors have given signed confirmation of agreement to article publication and compliance with all applicable ethical and legal requirements, including the accuracy of author and contributor information, disclosure of competing interests and funding sources, compliance with ethical requirements relating to human and animal study participants, and compliance with any copyright requirements of third parties. This journal is a member of the Committee on Publication Ethics (COPE).

Published by Libertas Academica. Learn more about this journal.

Programmed cell death-1 (PD-1) is encoded by *PDCD1* gene, which was first identified by exploring genes involved in stimulation-induced programmed cell death in murine T- and B-cell lines in 1992.[1] The human homolog *PDCD1* was isolated using murine PD-1 probe to screen a human T-cell cDNA library in 1994.[2] PD-1 possesses three domains: an N-terminal extracellular binding domain, a transmembrane domain, and a C-terminal cytoplasmic domain bearing an immunoreceptor tyrosine-based switch motif (ITSM) and an immunoreceptor tyrosine-based inhibitory motif (ITIM).[3]

PD-1 can bind two ligands, PD-L1 (B7-H1)[4,5] and PD-L2 (B7-DC),[6,7] to attenuate phosphorylation signaling and to further suppress immune cell activation.[8] The expression of PD-L1 and PD-L2 are unregulated upon stimulation. PD-L1 is broadly expressed on both hematopoietic and non-hematopoietic cells. In contrast, PD-L2 expression is restricted to antigen-presenting cells and T_H2 cells.[8,9] Although PD-L1 is the dominant ligand for PD-1, PD-L2 can compete with PD-L1 as the affinity of PD-L2 to PD-1 is two- to six-fold higher than that of PD-L1.[10] In addition to PD-1, PD-L1 and PD-L2 serve as binding partners for B7-1[11] and repulsive guidance molecule B,[12] respectively, indicating the complexity associated with the regulation of costimulatory signals for T-cells.

Despite the name of "programmed cell death-1," the main function of PD-1 is not involved in the cell death, instead, to counteract T- and B-cell activation at different levels. First, PD-1 can directly affect immunological synapse (IS) formation of T-cells, which is the very early event in T-cell activation.[13,14] Second, the ligation of PD-1 and PD-L1/2 attenuates TCR and essential costimulatory signaling in activated T-cells. The cytoplasmic tail of PD-1 will be phosphorylated. Subsequently, the phosphatase SHP-2 can be recruited to the phosphorylated ITSM, dephosphorylating CD3zeta, ZAP-70, PI3K, and PKCθ that are essential for T-cell activation.[15,16] Although ITIM domain of PD-1 is shared by most of the inhibitory receptors, the exact contribution of ITIM to PD-1-mediated immune suppression is still not clear. Third, in addition to PD-1, PD-L1 could dampen T-cell activation by interacting with B7.1, blocking CD28-B7.1 costimulatory signaling.[11] Forth, PD-1 is highly expressed on regulatory T-cells, a cell subset essential in immune suppression. In the presence of TCR stimuli and transforming growth factor beta (TGF-β), PD-1 ligation induces the conversion of naïve T-cells into functional induced regulatory T-cells.[17] Therefore, PD-1 axis functions as an immune checkpoint, playing an important role in the immune tolerance and suppression.

The microenvironment in tumors are highly immune suppressive. It is evident that the PD-1/PD-L1 pathway contributes to immune suppression.[18] It has been noted that

PD-1 expression is highly upregulated on tumor-infiltrating lymphocytes (TILs) in breast cancer, prostate cancer, ovarian cancer, melanoma, non-small cell lung cancer (NSCLC), and hepatocellular carcinoma (HCC). The upregulation of PD-1 expression on TILs has been functionally evaluated. Compared to PD-1 negative TILs, PD-1 positive TILs possess an exhausted phenotype, illustrated by blunt TCR signaling, defective calcium flux, and reduced cytokine (IL-2 and INF-γ) production.[19–26] It is evidenced that a higher expression level of SHP-2 could be found in PD-1$^+$ TILs, resulting in the impaired T-cell activation and Tc1/Th1 skewing through PD-1/SHP-2/STAT-1/T-bet signaling axis.[20] More importantly, growing evidences confirm that PD-1 expression on TILs correlates positively with tumor grade, size, lymph node status, and metastasis in breast cancer and melanoma, signifying the role of PD-1 in tumor malignancies.[19,23] A large proportion of TILs express high levels of PD-1. Correspondingly, PD-L1 is highly expressed on many tumor cells. As mentioned above, PD-1 ligation may induce de novo Treg cell formation in the presence of TGF-β. All these factors contribute to the highly immune-suppressive tumor microenvironment, resulting in an exhausted phenotype of lymphocytes in the tumor sites. Similar to PD-1, the ligands PD-L1 and PD-L2 are also clinically relevant to tumor prognosis, recurrence, and patient survival in pancreatic cancer, breast cancer, ovarian, HCC, NSCLC, and melanoma.[27–33]

Considering the importance and relevance of PD-1 and PD-L1/2 in tumor malignancies and patient survival, it has been hypothesized that PD-1 or PD-L1/2 blockade may provide a promising immunotherapy for patients with cancer. This is supported by the positive preclinical data. PD-1 knockout leads to delayed onset and organ-specific autoimmunity in mice from different genetic backgrounds, providing strong evidence for the negative regulation of immune responses by PD-1.[34,35] Likewise, the deficiency of PD-L1 results in an autoimmune phenotype.[36] In the cancer scenario, PD-1/PD-L1 deficiency or blockade augments effector T-cell function and accumulation at tumor sites.[37,38] The promising preclinical data have paved the way for the application of PD-1/PD-L1 blockade in clinical trials.

The principle of PD-1/PD-L1 blockade in clinical trials is developing humanized antibodies or human IgG to bind either PD-1 or PD-L1, thereby blocking the ligation of PD-1 and PD-L1 and the downstream inhibitory signaling events. So far, several anti-PD-1 or PD-L1 monoclonal antibodies have been developed by various pharmaceutical companies.[39] Some of the blockade agents, which are summarized in Table 1, have been in different stages of clinical trials against various types of tumor. The clinical outcomes differ between antibodies, which could be because of the discrepancies in antibody sources, antibody isotypes (IgG, IgG1, or IgG4), and antibody affinities. CT-011 (pidilizumab), a humanized IgG1, is the first biological inhibitor of PD-1 in clinical trials.[40] The objective response rates (ORR) of CT-011 to follicular lymphoma and advanced melanoma are 66% and 5.9%, respectively, indicating that different mechanisms might be involved in hematologic malignancies and solid tumors. The treatment-associated severe adverse event (SAE) in melanoma is 4%, showing a good tolerance.[41,42] MK-3475 (pembrolizumab), a humanized IgG4, is the first FDA approved anti-PD-1 mAb to treat metastatic melanoma.[43] The ORR of MK-3475 to advanced melanoma and NSCLC are 38% and 21%, respectively. The drug-related SAEs are acceptable (13% in melanoma).[43,44] BMS-936558

Table 1. Summary of current PD-1 and PD-L1 blockade agents in clinical trials.

TARGET	BLOCKADE AGENT	MOLECULAR PROPERTY	PHASE	EVALUATED CANCER	COMPANY	REF
PD-1	CT-011 (pidilizumab)	Humanized IgG1	II	Hematologic cancer, melanoma	CureTech	40–42
	MK-3475 (pembrolizumab)	Humanized IgG4	III	Advanced solid tumors, Melanoma, NSCLC	Merck & Co	43, 44
	BMS-936558 (nivolumab)	Fully human IgG4	III	Melanoma, RCC, NSCLC, HNSCC, Advanced solid tumors	Bristol-Myers Squibb	45, 46
	AMP-224	PD-L2 fusion protein	I	Advanced solid tumors	Amplimmune/ GlaxoSmithKline	47
PD-L1	BMS-936559	Fully human IgG4	I	Advanced solid tumors	Bristol-Myers Squibb	48
	MEDI4736	Humanized IgG	I/III	Advanced solid tumors NSCLC	MedImmune	49, 50
	MPDL3280A	Fully human IgG4	I/II	Melanoma, RCC, NSCLC, Bladder cancer, Advanced solid tumors	Roche	51, 52
	MSB0010718C	Fully human IgG4	I/II	Advanced solid tumors, Merkel cell carcinoma	Merck & Co	53

Abbreviations: NSCLC, non-small cell lung cancer; RCC, renal cell carcinoma; HNSCC, head and neck squamous-cell carcinoma.

(nivolumab) is a human IgG4 mAb against PD-1 developed by Bristol-Myers Squibb and currently in phase III clinical trials in various tumors. The use of nivolumab has achieved an improved outcome in metastatic melanoma and NSCLS. A study reported that compared to dacarbazine (a drug used in chemotherapy), the ORR could be increased from 13.9% to 40% in the nivolumab arm. Similarly, the overall survival (OS) was increased from 42.1% to 72.9%. Moreover, the drug-related SAEs were decreased in the nivolumab arm (11.7% vs 17.6%).[45] In NSCLC, the OS was significantly better in the nivolumab arm when compared to docetaxel (9.2 vs 6 months).[46] The efficacy of AMP-224, a PD-L2 IgG2a fusion protein, has also been evaluated in clinical trials. As opposed to the direct blocking PD-1/PD-L1 interaction, PD-L2 promotes the apoptosis of lymphocytes with high PD-1 expression.[47] To block PD-1/PD-L1 axis, an alternative approach is to block the predominant ligand, PD-L1. Blockade of PD-L1 may cause less side effects and toxicity as PD-L2 can serve as an alternate ligand for PD-1. However, it may also compromise the antitumor effects, as PD-L2 on tumor cells might be sufficient to induce and maintain the exhausted phenotype of PD-1$^+$ TILs. So far, four different anti-PD-L1 mAbs (BMS-936559, MEDI4736, MPDL3280A, MSB0010718C) are in clinical trials with the rationale being the high PD-L1 expression on various tumor cells.[48–53] The efficacy of BMS-936559 has been evaluated in melanoma, renal cell cancer, NSCLC, and ovarian cancer. The ORR and progression-free survival (PFS) are 6%–17% and 12%–41%, respectively. The SAEs are acceptable.[48] MEDI4736, an humanized IgG antibody, was tested in NSCLC patients, showing 38.5% ORR and very low SAEs.[49,50] MPDL3280A, a fully human IgG4 antibody, showed 21% ORR and 44% PFS at 24 weeks in advanced solid tumors.[51,52] MSB0010718C, a fully human IgG4 antibody developed by Merck & Co., is recruiting participants with Merkel cell carcinoma or advanced solid tumors.[53]

It has to be noted that PD-1 and PD-L1 blockade are effective only in patients with high PD-1 or PD-L1 expression. Topalian and colleagues conducted a phase I clinical trial to evaluate the efficacy of BMS-936558 (nivolumab) in tumor malignancies. Nine out of the 25 patients with PD-L1$^+$ tumors exhibited a strong response to BMS-936558.[54] In contrast, no response to PD-1 blockade was observed in the 17 patients with PD-L1$^-$ tumors.[53] This observation suggests that PD-L1 expression on tumor cells can be used as a potential biomarker to further stratify patients with cancer and to predict the efficacy of immunotherapy using PD-1 axis blockade. Further efforts are required to standardize the measurement of PD-L1 on tumor cells, which is critical for the prediction and evaluation of treatment efficacy.

To break the highly immune-suppressive microenvironment in tumors and potentiate antitumor immune responses mediated by T-cells, the concurrent therapy combining PD-1/PD-L1 blockade with antiangiogenic therapy, radiation therapy, chemotherapy, or chimeric antigen receptor T-cell therapy or other immune checkpoint inhibitors may enhance the immune priming, effector/memory phase, and improve the clinical outcome. CTLA-4, similar to PD-1, is another important immune checkpoint.[55] Ipilimumab, a blocking antibody for CTLA-4, is currently in phase II/III clinical trials.[56] A recent study reported that the efficacy of the concurrent therapy using ipilimumab and nivolumab is significantly greater than ipilimumab alone in patients with melanoma.[57] However, we do not know if this concurrent therapy is superior to nivolumab alone yet. We also do not know if PD-L1 blockade is superior to PD-1 blockade in practice. Future efforts should be made to compare the efficacies of different regimens (concurrent therapy vs PD-1 axis blockade alone; PD-1 blockade vs PD-L1 blockade) to advance the improvement of treatment using PD-1 axis blockade.

Acknowledgments

We thank Dr. Julie Joseph for critical reading and comments.

Author Contributions

Wrote the first draft of the manuscript: PZ. Contributed to the writing of the manuscript: ZZ. Agreed with manuscript results and conclusions: PZ and ZZ. Jointly developed the structure and arguments for the paper: PZ and ZZ. Made critical revisions and approved the final version: PZ and ZZ. All the authors reviewed and approved the final manuscript.

REFERENCES

1. Ishida Y, Agata Y, Shibahara K, Honjo T. Induced expression of PD-1, a novel member of the immunoglobulin gene superfamily, upon programmed cell death. *EMBO J*. 1992;11(11):3887–3895.
2. Shinohara T, Taniwaki M, Ishida Y, Kawaichi M, Honjo T. Structure and chromosomal localization of the human PD-1 gene (PDCD1). *Genomics*. 1994;23(3):704–706.
3. Sharpe AH, Wherry EJ, Ahmed R, Freeman GJ. The function of programmed cell death 1 and its ligands in regulating autoimmunity and infection. *Nat Immunol*. 2007;8(3):239–245.
4. Dong H, Zhu G, Tamada K, Chen L. B7-H1, a third member of the B7 family, co-stimulates T-cell proliferation and interleukin-10 secretion. *Nat Med*. 1999;5(12):1365–1369.
5. Freeman GJ, Long AJ, Iwai Y, et al. Engagement of the PD-1 immunoinhibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation. *J Exp Med*. 2000;192(7):1027–1034.
6. Latchman Y, Wood CR, Chernova T, et al. PD-L2 is a second ligand for PD-1 and inhibits T cell activation. *Nat Immunol*. 2001;2(3):261–268.
7. Tseng SY, Otsuji M, Gorski K, et al. B7-DC, a new dendritic cell molecule with potent costimulatory properties for T cells. *J Exp Med*. 2001;193(7):839–846.
8. Keir ME, Butte MJ, Freeman GJ, Sharpe AH. PD-1 and its ligands in tolerance and immunity. *Annu Rev Immunol*. 2008;26:677–704.
9. Lesterhuis WJ, Steer H, Lake RA. PD-L2 is predominantly expressed by Th2 cells. *Mol Immunol*. 2011;49(1–2):1–3.
10. Youngnak P, Kozono Y, Kozono H, et al. Differential binding properties of B7-H1 and B7-DC to programmed death-1. *Biochem Biophys Res Commun*. 2003;307(3):672–677.
11. Butte MJ, Keir ME, Phamduy TB, Sharpe AH, Freeman GJ. Programmed death-1 ligand 1 interacts specifically with the B7-1 costimulatory molecule to inhibit T cell responses. *Immunity*. 2007;27(1):111–122.
12. Xiao Y, Yu S, Zhu B, et al. RGMb is a novel binding partner for PD-L2 and its engagement with PD-L2 promotes respiratory tolerance. *J Exp Med*. 2014;211(5):943–959.
13. Fife BT, Pauken KE, Eagar TN, et al. Interactions between PD-1 and PD-L1 promote tolerance by blocking the TCR-induced stop signal. *Nat Immunol*. 2009;10(11):1185–1192.

14. Yokosuka T, Takamatsu M, Kobayashi-Imanishi W, Hashimoto-Tane A, Azuma M, Saito T. Programmed cell death 1 forms negative costimulatory microclusters that directly inhibit T cell receptor signaling by recruiting phosphatase SHP2. *J Exp Med*. 2012;209(6):1201–1217.
15. Sheppard KA, Fitz LJ, Lee JM, et al. PD-1 inhibits T-cell receptor induced phosphorylation of the ZAP70/CD3zeta signalosome and downstream signaling to PKCtheta. *FEBS Lett*. 2004;574(1–3):37–41.
16. Chemnitz JM, Parry RV, Nichols KE, June CH, Riley JL. SHP-1 and SHP-2 associate with immunoreceptor tyrosine-based switch motif of programmed death 1 upon primary human T cell stimulation, but only receptor ligation prevents T cell activation. *J Immunol*. 2004;173(2):945–954.
17. Francisco LM, Salinas VH, Brown KE, et al. PD-L1 regulates the development, maintenance, and function of induced regulatory T cells. *J Exp Med*. 2009; 206(13):3015–3029.
18. Hirano F, Kaneko K, Tamura H, et al. Blockade of B7-H1 and PD-1 by monoclonal antibodies potentiates cancer therapeutic immunity. *Cancer Res*. 2005;65(3): 1089–1096.
19. Muenst S, Soysal SD, Gao F, Obermann EC, Oertli D, Gillanders WE. The presence of programmed death 1 (PD-1)-positive tumor-infiltrating lymphocytes is associated with poor prognosis in human breast cancer. *Breast Cancer Res Treat*. 2013;139(3):667–676.
20. Li J, Jie HB, Lei Y, et al. PD-1/SHP-2 inhibits Tc1/Th1 phenotypic responses and the activation of T cells in the tumor microenvironment. *Cancer Res*. 2015; 75(3):508–518.
21. Sun S, Fei X, Mao Y, et al. PD-1(+) immune cell infiltration inversely correlates with survival of operable breast cancer patients. *Cancer Immunol Immunother*. 2014; 63(4):395–406.
22. Ahmadzadeh M, Johnson LA, Heemskerk B, et al. Tumor antigen-specific CD8 T cells infiltrating the tumor express high levels of PD-1 and are functionally impaired. *Blood*. 2009;114(8):1537–1544.
23. Chapon M, Randriamampita C, Maubec E, et al. Progressive upregulation of PD-1 in primary and metastatic melanomas associated with blunted TCR signaling in infiltrating T lymphocytes. *J Invest Dermatol*. 2011;131(6):1300–1307.
24. Matsuzaki J, Gnjatic S, Mhawech-Fauceglia P, et al. Tumor-infiltrating NY-ESO-1-specific CD8+ T cells are negatively regulated by LAG-3 and PD-1 in human ovarian cancer. *Proc Natl Acad Sci U S A*. 2010;107(17):7875–7880.
25. Zhang Y, Huang S, Gong D, Qin Y, Shen Q. Programmed death-1 upregulation is correlated with dysfunction of tumor-infiltrating CD8+ T lymphocytes in human non-small cell lung cancer. *Cell Mol Immunol*. 2010;7(5):389–395.
26. Shi F, Shi M, Zeng Z, et al. PD-1 and PD-L1 upregulation promotes CD8(+) T-cell apoptosis and postoperative recurrence in hepatocellular carcinoma patients. *Int J Cancer*. 2011;128(4):887–896.
27. Nomi T, Sho M, Akahori T, et al. Clinical significance and therapeutic potential of the programmed death-1 ligand/programmed death-1 pathway in human pancreatic cancer. *Clin Cancer Res*. 2007;13(7):2151–2157.
28. Muenst S, Schaerli AR, Gao F, et al. Expression of programmed death ligand 1 (PD-L1) is associated with poor prognosis in human breast cancer. *Breast Cancer Res Treat*. 2014;146(1):15–24.
29. Maine CJ, Aziz NH, Chatterjee J, et al. Programmed death ligand-1 overexpression correlates with malignancy and contributes to immune regulation in ovarian cancer. *Cancer Immunol Immunother*. 2014;63(3):215–224.
30. Hamanishi J, Mandai M, Iwasaki M, et al. Programmed cell death 1 ligand 1 and tumor-infiltrating CD8+ T lymphocytes are prognostic factors of human ovarian cancer. *Proc Natl Acad Sci U S A*. 2007;104(9):3360–3365.
31. Gao Q, Wang XY, Qiu SJ, et al. Overexpression of PD-L1 significantly associates with tumor aggressiveness and postoperative recurrence in human hepatocellular carcinoma. *Clin Cancer Res*. 2009;15(3):971–979.
32. Azuma K, Ota K, Kawahara A, et al. Association of PD-L1 overexpression with activating EGFR mutations in surgically resected nonsmall-cell lung cancer. *Ann Oncol*. 2014;25(10):1935–1940.
33. Hino R, Kabashima K, Kato Y, et al. Tumor cell expression of programmed cell death-1 ligand 1 is a prognostic factor for malignant melanoma. *Cancer*. 2010;116(7):1757–1766.
34. Nishimura H, Nose M, Hiai H, Minato N, Honjo T. Development of lupus-like autoimmune diseases by disruption of the PD-1 gene encoding an ITIM motif-carrying immunoreceptor. *Immunity*. 1999;11(2):141–151.
35. Nishimura H, Okazaki T, Tanaka Y, et al. Autoimmune dilated cardiomyopathy in PD-1 receptor-deficient mice. *Science*. 2001;291(5502):319–322.
36. Latchman YE, Liang SC, Wu Y, et al. PD-L1-deficient mice show that PD-L1 on T cells, antigen-presenting cells, and host tissues negatively regulates T cells. *Proc Natl Acad Sci U S A*. 2004;101(29):10691–10696.
37. Wong RM, Scotland RR, Lau RL, et al. Programmed death-1 blockade enhances expansion and functional capacity of human melanoma antigen-specific CTLs. *Int Immunol*. 2007;19(10):1223–1234.
38. Iwai Y, Terawaki S, Honjo T. PD-1 blockade inhibits hematogenous spread of poorly immunogenic tumor cells by enhanced recruitment of effector T cells. *Int Immunol*. 2005;17(2):133–144.
39. Ohaegbulam KC, Assal A, Lazar-Molnar E, Yao Y, Zang X. Human cancer immunotherapy with antibodies to the PD-1 and PD-L1 pathway. *Trends Mol Med*. 2015;21(1):24–33.
40. Berger R, Rotem-Yehudar R, Slama G, et al. Phase I safety and pharmacokinetic study of CT-011, a humanized antibody interacting with PD-1, in patients with advanced hematologic malignancies. *Clin Cancer Res*. 2008;14(10):3044–3051.
41. Westin JR, Chu F, Zhang M, et al. Safety and activity of PD1 blockade by pidilizumab in combination with rituximab in patients with relapsed follicular lymphoma: a single group, open-label, phase 2 trial. *Lancet Oncol*. 2014;15(1):69–77.
42. Atkins MB, Kudchadkar RR, Sznol M, et al. Phase 2, multicenter, safety and efficacy study of pidilizumab in patients with metastatic melanoma. *J Clin Oncol*. 2014;32(suppl; abstr 9001):5s.
43. Hamid O, Robert C, Daud A, et al. Safety and tumor responses with lambrolizumab (anti-PD-1) in melanoma. *N Engl J Med*. 2013;369(2):134–144.
44. Garon EB, Gandhi L, Rizvi N, et al. Antitumor activity of pembrolizumab (PEMBRO; MK-3475) and correlation with programmed death ligand (PD-L1) expression in a pooled analysis of patients (pts) with advanced non small cell lung carcinoma (NSCLC). *Ann Oncol*. 2014;25(suppl):4s.
45. Robert C, Long GV, Brady B, et al. Nivolumab in previously untreated melanoma without BRAF mutation. *N Engl J Med*. 2015;372(4):320–330.
46. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. *N Engl J Med*. 2015;373:123–135.
47. Mkrtichyan M, Najjar YG, Raulfs EC, et al. B7-DC-Ig enhances vaccine effect by a novel mechanism dependent on PD-1 expression level on T cell subsets. *J Immunol*. 2012;189(5):2338–2347.
48. Brahmer JR, Tykodi SS, Chow LQ, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. *N Engl J Med*. 2012;366(26):2455–2465.
49. Beck A, Wurch T, Reichert JM. 6th Annual European Antibody Congress 2010: November 29-December 1, 2010, Geneva, Switzerland. *MAbs*. 2011;3(2): 111–132.
50. Brahmer JR, Rizvi NA, Lutzky J, et al. Clinical activity and biomarkers of MEDI4736, an anti-PD-L1 antibody, in patients with NSCLC. *ASCO Meet Abstr*. 2014;32:8021.
51. Powles T, Vogelzang JN, Fine G, et al. Inhibition of PD-L1 by MPDL3280A and clinical activity in pts with metastatic urothelial baldder cancer (UBC). *ASCO Meet Abstr*. 2014;32:5011.
52. Herbst RS, Gordon MS, Fine GD, et al. A study of MPDL3280A, an engineered PD-L1 antibody in patients with locally advanced or metastatic tumors. *ASCO Meet Abstr*. 2013;31:3000.
53. Heery CR, O'Sullivan Coyne GH, Madan RA, et al. Phase I open-label, multiple ascending dose trial of MSB0010718C, an anti-PD-L1 monoclonal antibody, in advanced solid malignancies. *ASCO Meet Abstr*. 2014;32:3064.
54. Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med*. 2012;366(26):2443–2454.
55. Weber J. Immune checkpoint proteins: a new therapeutic paradigm for cancer—preclinical background: CTLA-4 and PD-1 blockade. *Semin Oncol*. 2010;37(5): 430–439.
56. Tarhini A. Immune-mediated adverse events associated with ipilimumab ctla-4 blockade therapy: the underlying mechanisms and clinical management. *Scientifica (Cairo)*. 2013;2013:857519.
57. Postow MA, Chesney J, Pavlick AC, et al. Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. *N Engl J Med*. 2015;372(21):2006–2017.