Proceedings of the 2nd International Conference on Biological Engineering and Medical Science (ICBioMed 2022), Part I
DOI: 10.54254/2753-8818/3/20220435

The Role Ipilimumab Plays in the Treatment of Melanoma

Yumeng Yan[1,2]

[1]Shenzhen College of International Education, Shenzhen, China

[2]21849.yan@stu.scie.com.cn

Abstract. While melanoma is not as common as other types of skin cancer among the whole dermatologic cancer category, it appears to be extremely aggressive for its high death rates. Conventional treatments like radiation therapy (RT), chemotherapy, and surgery have showed either significant side effects or limited improvement to the disease. Ipilimumab, anti-CTLA-4 antibodies, is immune checkpoint Inhibitor (ICI) approved by the FDA for being one source of treatment in the advanced melanoma in 2011 as an immunotherapeutic approach. Anti-CTLA-4 is authorized for usage as monotherapy treatment for advanced metastatic melanoma. it licensed as combination treatment for melanoma. The new study shown that the ipilimumab combined with pembrolizumab may be feasible in treating more cancerous diseases. For individuals that suffer from advanced malignant melanoma, ipilimumab decrease the overall death rates in randomized trials. The combined approach of anti-PD-1 and anti-CTLA-4 antibodies has shown feasibility.

Keywords: Melanoma, CTLA-4, Ipilimumab, Nivolumab.

1. Introduction

Treatment of melanoma is always in progress [1,2]. However, the most hazardous kind of dermatologic cancer, known as malignant melanoma, arises from melanocytes, the cells that produce the pigment melanin [3], attributing to around 80 percent of death from skin cancer while occupying merely 4 percent among all skin cancers [4]. Even though the cumulative and excessive exposure to the ultraviolet (UV) radiation-caused DNA damage could be an explanation to the continuous increases in the risk of the development of melanoma, the location of melanoma is, however, not restricted. It is not only often found developing in the areas with slightly higher sunlight exposure, but is also sometimes on unveil regions with only limited UV radiation received.

Melanoma Five-Year Survival Rate Stage: 98.4% of localized melanoma cases were in stages 0 through 2. Stage III melanoma in the region: 63.6% Stage IV metastatic melanoma: 22.5% (Among cases diagnosed from 2011 to 2017, followed through 2018) [5].

Surveillance, Epidemiology and CDC's National Center for Health Statistics published a series of data and graphs on documented and projected incidence rates and mortality rates of malignant melanoma from 1980 to 2030 in the United States, in 2015. The rate of incidents has gone through general increases from 1982 to 2011 in the absence of new interventions. The incidence rates from the latest data in 2011 is twice the amount of incidence rates in 1982 with 0.25% and 0.1%, respectively. The incidence rates of both females and males from 2011 to 2030 was predicted to remain at a general constant with slight fluctuation with the help of the intervention of a now comprehensive skin cancer prevention programme.

© 2026 The Authors. This is an open access article distributed under the terms of the Creative Commons Attribution License 4.0 (https://creativecommons.org/licenses/by/4.0/).

DOI: 10.54254/2753-8818/3/20220435

As for the mortality rates, the situation turned out different. Not only the recorded period 1982-2011 had not shown significant alterations in the mortality rates among Americans, the future 20 years are also forecasted to possess around 5 deaths per 100,000 citizens.

The immunological checkpoint and immune response suppressor cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) is a glycoprotein receptor. CTLA-4 is from CD28-family and functions similarly with CD28. It is a protein receptor on CD4+ cells and binds to CD80 and CD86 on dendritic cells and B-lymphocytes with a considerable measure more avidity and affinity than CD28. The biggest difference between a CTLA-4 protein and CD28 protein is that the former one binds with the ligands and acr as an inhibitor to the T-lymphocyte to prevent its continual functioning, while the latter one boosts the further functioning of the T lymphocyte. The genetic ablation of CTLA-4 may lead to a fulminating and even lethal lymphocyte-proliferative disorder [6].

The immunoglobulin, commonly referred to as "antibody," is used to disrupt CTLA-4's interaction with the universal ligands CD80 and CD86 in order to avoid CTLA-4 from being distracted and to boost immunological feedback, anti-tumor immunity included. There are currently two CTLA-4 blocking antibodies that have been going through extensive tests and have gone through clinical trials [7,8].

This review article provides an overview of the role ipilimumab plays in malignant melanoma, including (i) timeline of the history of the development of anti-CTLA-4 immunotherapeutic drugs, (ii) CTLA-4 pathway in malignant melanoma, (iii) comparison of monotherapy and combination therapy in treatment of melanoma, (iv) irAEs of both monotherapy and combination therapy treatments.

2. Timeline of the development of anti-ctla-4 immunotheraputic drugs

The history of the discovery of immune checkpoint inhibitors could be traced back to 1966. That year, the Swedish couple Karl and Ingegerd Hellstrom recognized from their experiment that the reaction of lymphocytes could be minimized or even suppressed after meeting the exposure to the blood serum extracted from mice with chemically induced tumors. As a result, blocking antibodies "bind to the target tumor cells and so disguise their antigens from recognition by immune lymphocytes," the researchers found. At the time, the current technology and understanding in the field was not able to allow anybody to unveil the exact blocking mechanism [9].

However, years later in 1982, scientist James Allison and his colleagues became the first to have discovered the T-cell receptor and to have utilized antibodies with monoclonal structures to first attain the identification and description of tumor-specific antigens in mouse models of T-cell lymphoma [10]. Brunet and his team discovered the very first immune checkpoint molecule while searching for cytotoxic cell surface molecules when they isolated a newly emerged protein from the surface of activated CD8+ T cells in just five years later in 1987 [11]. They named this protein CTLA-4. However, scientists were not able to figure out the function of CTLA-4.

A group of scientists was studying the interactions between B7-CD28 and CD28 but in a soluble version in 1991. The results given out by Allison had definitely caught their attention which directly resulted in them constructing a soluble CTLA-4 protein and putting it in to their experiments to test if CTLA-4 can also bind to B7 like CD28 did. Surprisingly, the tests gave out the critical information that the soluble CTLA-4 bind with B7 with 20-fold higher avidity than its homolog----CD28 [12].

The role the molecule plays remained mysterious until 1995, when a team demonstrated that CTLA-4 could bind to T cells and restrain its normal function [13]. they revealed that CTLA-4 can regulate T cells. This checkpoint protein CTLA-4 possesses the ability to leash the activated T cells and affect its indiscriminate antigen elimination, therefore avoid accidental healthy-cell-damage. Meanwhile, it also stops the immune system’s ability in continuously fighting against cancer. The group of scientists realized that and soon pinpointed the great possibility its mechanism has in future anti-cancer therapy and researches. Allison was the first to discover in 1995 that blocking CTLA-4 with an antibody might improve tumor immunity and tumor rejection.

Just one year later when the same team was injecting antibodies which can block CTLA activity to the tumor-transplanted mice, they found out that the mice under tests conditions rejected different types of tumors and turned out this made the mice had long-lasting anti-tumor immunity [14]. This proved

DOI: 10.54254/2753-8818/3/20220435

that the enhancement of T lymphocyte feedback through blocking CTLA-4 strengthens the anti-tumor immunity. Another point worth highlighting is the fact that Allison JP, a scientist, was the first to come up with the idea of employing anti-CTLA-4 antibodies to treat cancer when he published his ideas on the immunological therapeutic use of CTLA-4 blocking antibodies in 1996.

Ipilimumab (sold under YERVOY®) was the earliest antibody that is monoclonal to be authorized by FDA, that target CTLA-4, in March of this year for treating malignant melanoma. For its "targeting CTLA-4 to activate the immune system" nature and for the great therapeutic effects it has shown, it is now under many clinical trials testing whether it can be utilized to cope with other types of cancers.

Tremelimumab is also a monoclonal antibody which targets CTLA-4 but unlike Ipilimumab, Tremelimumab is an lgG2 isotype and it has not obtained approval for any. It has gone through clinical trials aiming to treat melanoma and mesothelioma.

3. Ctla-4 pathway in malignant melanoma

3.1. Mechanism of CTLA-4

The modes of action that how the CTLA-4 binds to T lymphocytes to prohibit it from continuing its normal function has by far been the best studied among all the identified immune checkpoint proteins for the fact that it is the first immune checkpoint protein discovered. The immunological co-stimulatory protein CD28's homolog, CTLA-4, is a glycoprotein with approximately 20 times higher binding affinity and avidity for B7 protein, including B7-1 (CD80) and B7-2 (CD86) [14]. However, not like CD28, stimulatory signals will not be generated when CTLA-4 binds with B7. Moreover, scientists Fallarino F et el. found that CTLA-4 suppresses T cell activation in the absence of CD28 [15]. As shown in figure 1.

CTLA-4's own localisation inside the cell controls it. The intracellular compartment of naive T lymphocytes is where CTLA-4 is mostly found while they are at rest [16]. Exocytosis of vesicles containing CTLA-4 results in that the positive regulation of CTLA-4 to its extrinsic surface in response to a stimulation induced by TCR and CD28:B7 binding [16]. This procedure is presented in a graded response and adjustment loop making more powerful TCR signaling evokes more CTLA-4 to translocate to the surface of the cell. Inhibiting the generation of IL-2 and cell cycle progression stops T lymphocytes from fully activating when CTLA-4:B7 binding generates a consistent series of negative signals [17].

CTLA-4 also plays a vital role in distinct manners of immune regulation. The regulatory T lymphocytes (T-regs) have the ability to retain the peripheral tolerance of the species for that it is capable of controlling the effector T lymphocytes' function [18]. The Tregs produce it and is to some extend responsible for the suppressive nature for the CTLA-4, as a consequence of CTLA-4's suppression of the Tregs. B7 molecules on the antigen-presenting cells may be internalized or isolated as a result of the Tregs' constitutive production of CTLA-4. Furthermore, the proliferation of T lymphocytes will be restricted and the functionality of the effectors will be reduced.

DOI: 10.54254/2753-8818/3/20220435

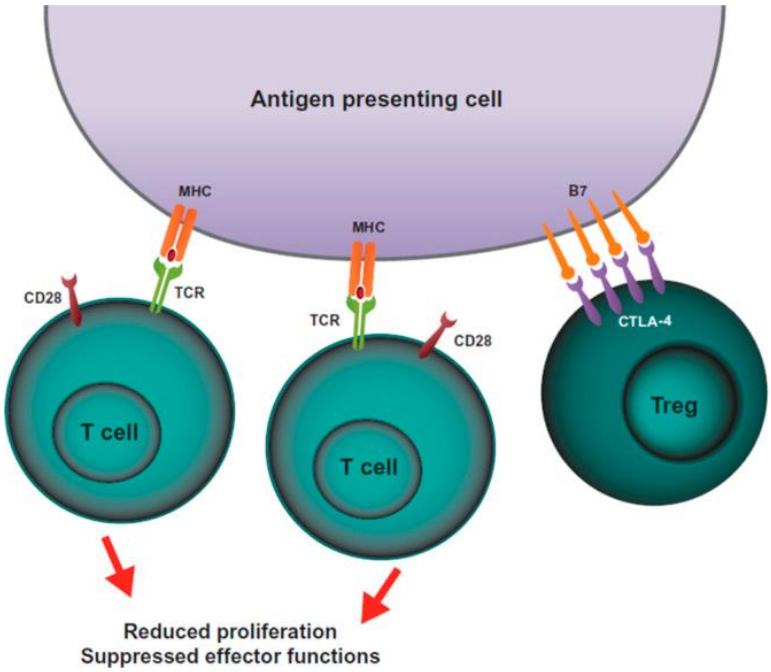


Figure 1. CTLA-4-mediated inhibition of T cells.

3.2. Mechanism of anti-CTLA-4

2011, Ipilimumab granted by FDA for advanced malignant melanoma. Ipilimumab block CTLA-4 in order to remove the inhibitory signal, sent by CTLA-4, from downsizing the T lymphocyte activity [19]. This CPI can induce long-lasting favorable effects in advanced malignant melanoma. Although the modes of action of anti-CTLA-4 induced tumor rejection is, however, only partially figured out but it has presently reached a consensus that ipilimumab works by direct blockage to the place where the bindings between CTLA-4 and ligands, and therefore contribute to the costimulation of CD28 and the following activation of T lymphocyte, as shown in figure 2. It is hypothesized that ipilimumab can stop the stimulation put on T cell. In addition, Liakou's research suggests that the usage of ipilimumab in the treating the cancerous melanoma disease may be linked with an increase in ICOS+ CD4+ T cells. [20,21].

The recruitment of regulatory T cells, often referred to as Tregs, mediates the immunosuppressive impact of tumor cells in malignant melanoma. Those CTLA-4 checkpoints have a high level by Tregs. Researchers, including Romano, used antibody-dependent cell-mediated cytotoxicity to evaluate the PBMCs and matching melanoma metastases of 29 individuals diagnosed with malignant melanoma, 15 of whom responded to ipilimumab and 14 of whom did not (ADCC). They became the first group of scientists to find out that the lysis of ADCC-mediated Tregs would be achieved. In addition, they had also proved the decrease in Treg infiltration after ipilimumab treatment [22]. The presence of Fc receptor-expressing macrophages is necessary for the depletion of Treg cells in trans, which is context-dependent. [23]. The function of Fc effector promotes the activity of human anti-CTLA-4 antibodies. They came up with a result that antibodies with isotypes that work the same way like ipilimumab and tremelimumab does is able to mediate intra-tumoral Treg cell elimination in vivo, and therefore rise the CD8+ to Treg cell ratio and promot the tumor rejection [24]. However, a study published one years later set disapprovals on this statement by proving that anti-CTLA-4 immunotherapy does not do the elimination job on Tregs in human cancer responses [25]. The deciphering of how anti-CTLA-4 antibodies actually work became even more challenging after Quezada's team identified how different and how many times more complicated it is, in the context of real-life clinical studies when comparing with the murine models [26]. Overall, the deciphering of how anti-CTLA-4 antibodies process is until now, still vague and have a long way to go.

DOI: 10.54254/2753-8818/3/20220435

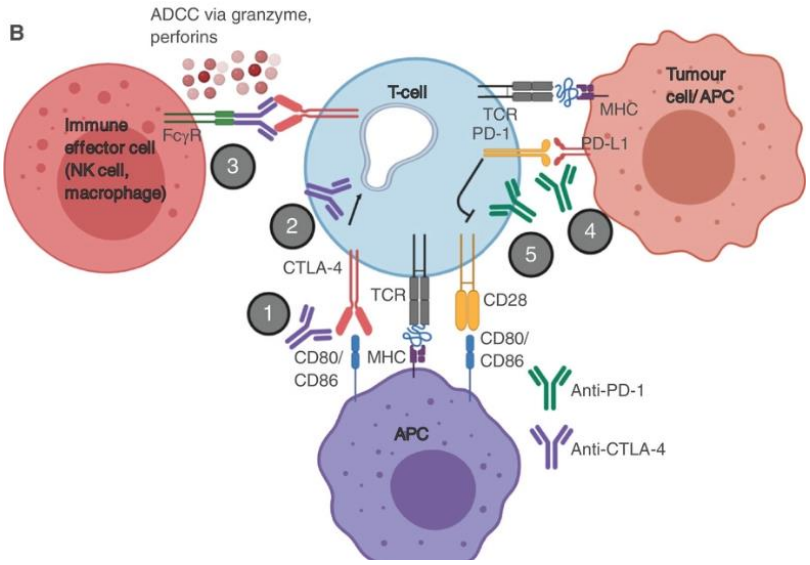


Figure 2. Anti-CTLA-4 and anti-PD-1 antibodies' suggested modes of action).

4. Anti-ctla-4 monoclonal antibodies for malignant melanoma

4.1. Comparison of immunotherapeutic approaches (Phase 1 dose-escalation study)

Scientists have set up and reported several randomized, double blind trial comparing the combination therapy of prescribing nivolumab and ipilimumab at the same time and with ipilimumab in the past few years. In this section of the report, their methods and results of the researches will be summarized and displayed.

The FDA has authorized ipilimumab, a kind of anti-CTLA-4 antibody, based on an increase in overall survival of advanced metastatic melanoma. In the patients with metastatic melanoma comparison study, scientists randomly assigned them combination group or monotherpy group in a 2:1 ratio. Intravenously administered placebo will be given to patients once every three weeks at a dose of 1 milligram per kilogram of body weight every 60 minutes. There will be a total of four treatments. Patients will have 3 milligrams of ipilimumab per kilogram over the course of 90 minutes, 30 minutes following the end of each placebo infusion. Ipilimumab was stopped after the fourth administration of both medications, and from that point on. Patients receiving ipilimumab alone as monotherapy experienced a verified objective feedback rate of 11%. None of the patients was observed to achieve a complete response. A 5.5% increase of median alteration in the tumor-volume was observed.

Checkpoint CTLA-4 and PD-1, together, prohibit anti-tumor immunity from normal functioning through complementary and non-redundant modes of action. Nivolumab is a type of monoclonal anti-PD-1 antibody. It has already shown its ability in improving the overall survival among individuals with advanced BRAF wild-type melanoma. Previous clinical studies have already showed that the combination can increase infiltrating T cells, decrease regulatory T lymphocytes and blood cells that originate from bone marrow, and increase anti-tumor activity in B16 melanoma tumors [27,28].

In patients with metastatic melanoma comparison study, scientists randomly assigned them combination group or monotherpy group in a 2:1 ratio. Nivolumab will be injected intravenously into patients once every three weeks at a dose of 1 milligram per of body weight every 60 minutes. There will be a total of four injections. Patients will have 3 milligrams of ipilimumab per kilogram over the course of 90 minutes, 30 minutes after the end of each nivolumab infusion. Ipilimumab was stopped after the fourth dosage of both medications, and from that point on, nivolumab will be given as the only source of medication at a dose of 3 milligrams per kilogram over the course of 60 minutes, once in every other two weeks. Patients of combination group had a verified objective response rate of 61%. A total

DOI: 10.54254/2753-8818/3/20220435

of 16 patients, occupying 22% of the total sample, was observed to receive a complete response. A 68.1% decrease of intermediate data change in the tumor-volume was observed. For individuals with advanced melanoma who had not formerly been medication, the progression-free survival was shown to be enormously greater with nivolumab and ipilimumab as combination therapy than with ipilimumab as monotherapy in the randomized, double-blind trial. The safety profile of combination treatment was satisfactory.

4.2. Immune-related adverse events of ipilimumab as monotherapy and combination therapy with nivolumab

The use of ipilimumab as monotherapy and combined with nivolumab as combination therapy has shown significant transformation in the management of malignant melanoma. However, there are also presence of some new irAEs. In this section of the report, the latent incidence of irAEs in monotherapeutic and combined therapeutic approach will be profiled. Only less than 1% of individuals experienced hypopituitarism after receiving the dosage of ipilimumab, while the prevalence of all-grade hypophysitis was 2.6% and that of grade≥3 hypophysitis was 1.2%. Ipilimumab users had a risk of meningitis with 1.7%. After the combination of ICIs, reports of raised or aberrant levels of the majority of enzymes and hormones (all grade) increased. ALT, AST and other markers levels were frequently elevated after the combination treatment. However, as for using only ipilimumab itself as monotherapy,it would be 3.9%. Arthroralgia and myalgia were the two most prevalent musculoskeletal and connective diseases, or probable irAEs. They were often reported following combination therapies. In patients receiving ipilimumab monotherapy, arthralgia and myalgia were the most prevalent probable irAEs.

The incidence of ventricular arrhythmias in the combination therapy group was approximately 1.1%. Prospective endocrine irAEs are common. The most common endocrine irAEs are alterations in the thyroid gland, such as hyperfunction or depression, and less commonly, inflammatory responses can also occur. There was also a significant increase in the incidence of uveitis, to 2.0%, after receiving this combination therapy. Hepatitis is the most common irAE whether treated with monotherapy or in combination. For example, with the combined use of nivolumab and ipilimumab, the incidence of hepatitis was 3-5%, respectively. The incidence of hypersensitivity reactions was approximately 2.9% in combination therapy with nivolumab and ipilimumab [29]. And, in a recent study, it was found that some enzymes and hormones were abnormal in the body of immunotherapy patients. Frequently elevated indicators include liver function indicators, renal function indicators and blood lipids. However, some studies have also found that when combined with nivolumab, the incidence of abnormal TSH is significantly reduced, which can be reduced to 6.7%. There were also some other common side effects, such as the incidence of GGT after ipilimumab and nivolumab treatment was 3.3% and 1.0%, respectively. Of all the FDA-approved doses, the combination of nivolumab and ipilimumab showed the highest incidence of grade 3 and all grade elevations or abnormal hormones or enzymes. Combination of treatment resulted in a 1.0% incidence of type 1 diabetes mellitus. The incidence of hyperglycemia was about 1.6 -2.6%.

5. Conclusion

The immune response to cancer requires antigen-presenting cells to detect the tumor, move to lymph node, present tumor antigen to the CTLA-4 on T regulatory cells to stop activation. Before immune checkpoint inhibitors became a possible treatment plan, most solid tumor immuno-therapies were based on interleukin-2 or alpha interferon immune cytokines that are poorly effective or have higher toxicity to the patients. Therefore, the T cell targeted immune checkpoint blockage is a paramount achievement in cancer research and molecular biology. The primary purpose of the checkpoint inhibitors is to block the surface proteins taken advantage of by the cancer cells for immune system evasion, proliferation, and migration; and to inform the immune system when cancer cells have undergone mutation. The FDA-approved immune checkpoint inhibitors like ipilimumab, have demonstrated promising results in treating advanced malignant melanoma as monotherapy. It is also the most frequently used CTLA-4

DOI: 10.54254/2753-8818/3/20220435

inhibitor that targets cytotoxic T-lymphocytes associated with antigen four on antigen-presenting cells. The blockade function of CTLA-4 enhances T-cell activation and proliferation. Moreover, ipilimumab is still the subject of important study, which includes examining how well it works when combined with other treatments (such anti-PD-1) to potentially enhance the proportion of patients who have a therapeutic benefit. Even though the CPI is by far the most well-studied among all the anti-CTLA-4 checkpoint inhibitors, its modes of action is still not fully deciphered in both clinical and preclinical level of trials. For a treatment that has shown such significant benefit if put in real-life usage, more money and time must be sponsored by the government and cancer-care related organization to put into further study. There are also many immune-related adverse events with ipilimumab, either being used as monotherapy or combination therapy as mentioned in this report and many unmentioned side effects that are common to most monotherapies and combined therapies. However, no matter if it is using ipilimumab as monotherapeutic treatment or combining it with nivolumab, it has aided filling a sizable gap in the treating the disease malignant melanoma and strengthened the case for immunotherapy's value in fighting against cancer.

References

[1] M. Bozic et al. Evolutionary dynamics of cancer in response to targeted combination therapy, 25 June, 2013.
[2] K. Long et al. Standard-dose pembrolizumab in combination with reduced-dose ipilimumab for patients with advanced melanoma (KEYNOTE-029): an open-label, phase 1b trial. Lancet. Oncol. 2017.
[3] Melanoma Treatment-for health professionals, National Cancer Institute, 26 June, 2015. Archived from the original on 4 July 2015. Retrieved 30 June 2015.
[4] Cancer facts & figures, 2003. Atlanta: American Cancer Society, 2003.
[5] Surveillance, Epidemiology, and End Results (SEER) 18 registries, National Cancer Institute, 2021.
[6] S.Karl, Peggs et al. 'Blockade of CTLA-4 on both effector and regulatory T cell compartments contributes to the antitumor activity of anti–CTLA-4 antibodies', 06 July 2009.
[7] A. Ribas Overcoming immunologic tolerance to melanoma: targeting CTLA-4 with tremelimumab (CP-675,206) Oncologist. 2008.
[8] J. Weber Overcoming immunologic tolerance to melanoma: targeting CTLA-4 with ipilimumab (MDX-010) Oncologist. 2008.
[9] I. HELLSTRÖM, K. HELLSTRÖM et al. Cellular and Humoral immunity to Different Types of Human Neoplasms. Nature 220, 1352–1354 ,1968.
[10] J P Allison et al. The Journal of Immunology, 1 November, 1982.
[11] JF. Brunet, et al. A new member of the immunoglobulin superfamily—CTLA-4. Nature 328, 267–270, 1987.
[12] P. Linsley et al. CTLA-4 is a second receptor for the B cell activation antigen B7. J Exp Med. 01 September 1991.
[13] J. P. Allison et al. "CD28 and CTLA-4 have opposing effects on the response of T cells to stimulation", J Exp Med, 01 August 1995.
[14] E.S. Kim et al. Immune checkpoint modulators: An emerging antiglioma armamentarium. J Immunol, 2015.
[15] F. Fallarino et al. B7–1 engagement of cytotoxic T lymphocyte antigen 4 inhibits T cell activation in the absence of CD28. J Exp Med. 1998.
[16] P.S. Linsley et al. Intracellular trafficking of CTLA-4 and focal localization towards sites of TCR engagement. Immunity. 1996.
[17] M.F. Krummel et al. CTLA-4 engagement inhibits IL-2 accumulation and cell cycle progression upon activation of resting T cells. J Exp Med. 1996.
[18] C.A. Piccirillo et al. Naturally-occurring CD4+CD25+ immunoregulatory T cells: central players in the arena of peripheral tolerance. Semin Immunol. 2004.

DOI: 10.54254/2753-8818/3/20220435

[19] D.B. Johnson et al.Clinical Activity of Ipilimumab in Acral Melanoma: A Retrospective Review. Oncologist. June 2015.
[20] L. iakou et al. CTLA-4 blockade increases IFNγ-producing CD4+ICOShi cells to shift the ratio of effector to regulatory T cells in cancer patients. Proc. Natl. Acad. Sci. 2008.
[21] Chen et al. Anti-CTLA-4 therapy results in higher CD4+ ICOShi T cell frequency and IFN-γ levels in both nonmalignant and malignant prostate tissues. Proc. Natl. Acad. Sci. 2009.
[22] Romano et al. Ipilimumab-dependent cell-mediated cytotoxicity of regulatory T cells ex vivo by nonclassical monocytes in melanoma patients. Proc. Natl. Acad. Sci. U.S.A. 2015.
[23] Simpson et al. Fc-dependent depletion of tumor-infiltrating regulatory T cells co-defines the efficacy of anti-CTLA-4 therapy against melanoma. J. Exp. Med. 2013.
[24] Vargas et al. Fc effector function contributes to the activity of human anti-CTLA-4 antibodies. Cancer Cell. 2018.
[25] Sharma et al. Anti–CTLA-4 immunotherapy does not deplete Foxp3þ regulatory T cells (Tregs) in human cancers—Response. Clin. Cancer Res. 2019.
[26] Quezada et al. Lost in translation: Deciphering the mechanism of action of anti-human CTLA-4. Clin. Cancer Res. 2019.
[27] M.A. Curran et al. PD-1 and CTLA-4 combination blockade expands infiltrating T cells and reduces regulatory T and myeloid cells within B16 melanoma tumors. Proc Natl Acad Sci U S A 2010.
[28] M. Selby et al. Antitumor activity of concurrent blockade of immune checkpoint molecules CTLA-4 and PD-1 in preclinical models. J Clin Oncol 2013.
[29] A. Robert et al. A decade of immune-checkpoint inhibitors in cancer therapy. Nat Commun 11, 3801, 2020.