Review Article

Combination of CTLA-4 and PD-1/PD-L1 Immune Checkpoints Inhibitors for Treatment of Cancer

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ABSTRACT

Blockade checkpoints of immune cell activation has been illustrated to be the most powerful approach for activation of anticancer immune responses. PD-1 and CTLA-4 checkpoints have mainly on activated T-cells to be the most solid targets for the cancer treatment. The drugs when administered as monotherapy had substantial increase in durable response rates and had possible safety profile, but 50 % or more of patients failed to respond to treatment. Combination of CTLA-4 and PD-1 blockers was estimated to increase the response rates, and ipilimumab (anti-CTLA-4) plus nivolumab (anti-PD-1) combination was seen to importantly boost efficiency in metastatic melanoma patients. The success of combination immune checkpoints therapy motivated several clinical examinations in other cancer types.

Keywords: Immunotherapy, Cancer, Checkpoints Blockers, Combined therapy.

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INTRODUCTION

For some decades treatment of advanced cancer has been faced by unreliable therapeutic strategies. Patients with metastatic cancers that were not surgically removable had to depend on chemotherapy, commonly associated with severe adverse occasions as well as high rates of degeneration.[1] Acknowledging of the immune system and surveillance grew the idea of using immune cells to eliminate cancer, obtained significance and different strategies to activate the immune response. Administration of interleukin-2 (IL-2) for stimulating T-cell proliferation, is one of the earliest tested as well as oldest immune based drug approved for the treatment of cancer.[2]

While the first generation of immunotherapies were low response rate, high incidence of serious adverse effects. The hunt for reliable targets for immune responses modulation lead the way of checkpoints of T-cell activation and development of targeting monoclonal antibodies. Cytotoxic T-lymphocyte associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1) have been found to be the most reliable drugs targets and changed the results of treatment for advanced cancers.[3] Drugs targeting CTLA-4 or PD-1/PD-L1 are approved for treatment of various types of cancers involving melanoma, lung cancer, breast cancer, head and neck cancer, bladder cancer, cervical cancer, hepatocellular cancer, gastric cancer, cutaneous squamous cell cancer, classic Hodgkin's lymphoma and B-cell lymphoma (**Table 1**).

Table 1. List of approved drugs targeting CTLA-4 and PD-1

Drug	Brand Name	Indication
CTLA-4 blockers ipilimumab	Yervoy	Metastatic melanoma
PD-1 blockers nivolumab	Opdivo	Metastatic melanoma, head and neck cancer, hepatocellular carcinoma, colorectal cancer, classical Hodgkin's lymphoma
pembrolizumab	Keytruda	Melanoma, B-cell lymphoma, classical Hodgkin's lymphoma, gastric cancer, cervical cancer, hepatocellular cancer
Cemiplimab	Libtayo	Cutaneous squamous cell cancer
PD-L1 blockers Atezolizumab	Tecentriq	Head and neck cancer, lung cancer, breast cancer
Avelumab	Bevencio	Merkel cell carcinoma
Durvalumab	Imfinzi	Lung cancer
Combined (CTLA-4 and PD-1) Ipilimumab plus Nivolumab	Yervoy plus opdivo	Metastatic melanoma, renal cell cancer, colorectal cancer

The influence of CTLA-4 and PD-1 inhibitors on oncological research and their success in cancer treatment is appreciated by scientist. The 2018 Nobel Laureate in Medicine, James P. Allison, USA and Tasuku Honjo, Japan was discovered negative immune regulation independently (CTLA-4 and PD-1 respectively).[4] Main benefits of CTLA-4 and PD-1 inhibitors are magnificent substantial response rates and possible adverse effects. Combined CTLA-4 and PD-1 inhibitors was recommended to have symbiotic effect on activation and increase rates of anti-cancer immune response in patients. Various medical studies were exploited to test both the safety and efficiency of the combination in different cancer subtypes.[5]

The proceeding in approval of the ipilimumab and nivolumab combination for their treatment demonstrated remarkable increase in response rates and median survival times in melanoma and renal cell carcinoma. In addition, studies in hard to diagnose cancers like non-small cell lung cancer, mesothelioma, and sarcoma have shown enhanced response rates in patients treated with combined therapy.[6]

2. CTLA-4 immune checkpoint

CTLA-4 is a receptor found on surface of activated T-cells. The location of human CTLA-4 gene and the details of the protein encoded discovered through screening of mouse cytolytic T-cell derived cDNA libraries (**Table 2**). While CTLA-4 expression is commonly seen upon activation of T-cells, however regulatory T-cells (Tregs) express CTLA-4 constitutively because of their high levels of transcription factor FoxP3.[7] CTLA-4 basically acts by competing with CD28 receptors for binding to B7 ligands present on antigen presenting cells (APCs). During T-cell activation, CD28 receptors bind to B7 ligands on APCs and give the necessary second activation signal.[8]

Table 2. Summary of CTLA-4 and PD-1

Receptor	CTLA-4	PD-1
Synonyms	CD152	PD CD1, CD279
Gene location	Chromosome 2q33	Chromosome 2q373
Protein details	AA # 223	AA # 288
Cells expressing receptor	Effector T-cells, Treg	Effector T-cells, Treg, NK cells, macrophages
Ligands	CD80 (B7-1), CD86 (B7-2)	PD-L1 (B7-H1), PD-L2 (B7-DC)
Cells expressing ligands	APCs	APCs, Cancer cell, hematopoietic cells

Although, CTLA-4 receptors bind to B7 ligands with higher affinity and lower surface density and outcompete CD28 receptors for binding. Lack of second activation signal in presence of CTLA-4 receptors lead to anergy in T-cell.[9] Additionally, CTLA-4 receptors are shown to sequester B7-ligands from the surface of the APCs and effect in exceptional depletion of the ligands on their surface. Interesting, because of its structural similarity with CD28 and its expression on activated T-cells, CTLA-4 was belief to be a positive regulator of T-cells.[10]

James P. Allison is credited for illustrating the negative role of CTLA-4 and showing the opposing effects of CTLA-4 and CD28 in response to T-cell stimulation. CTLA-4 engagement with B7-ligands repealed IL-2 secretion through T-cells and its proliferation that followed TCR activation.[11] Blockade of CTLA-4 using anti-CTLA-4 antibodies resulted in rejection of initiated cancers and that the mice lacking gene result severe lymphoproliferative and lethal autoimmune phenotype. CTLA-4 activation was recorded to inhibit IL-2 production and T-cell proliferation and induce cell cycle disruption by cross-talks with pathways regulating cell survival and proliferation.[12]

3. PD-1/PD-L1 immune checkpoint

PD-1 is a cell surface receptor commonly seen on T-cells, B-cells and NK cells. Honjo and coworkers are credited for the discovery of PD-1 gene location and encoded protein through their studies on pathways of programmed cell death (**Table 2**).[13] Similarity between extracellular domain of PD-1 and CTLA-4, however unlike CTLA-4, a dimeric protein, PD-1 lacks the extracellular cysteine residue required for covalent dimerization and presents as a monomer on cell surface. Basic level of PD-1 is noticed on B-cells and not on immature T-cell, whereas its expression is induced upon activation of TCR/BCR.[14]

Besides T-cells, NK cells and B-cells, PD-1 is further expressed on Tregs, NKT cells, activated monocytes and myeloid DCs. The ligands for PD-1, PD-L1 and PD-L2 are generally showed on macrophages and DCs.[15] PD-L1 is also revealed on T-cells, B-cells, vascular endothelial cells, fibroblastic reticular cells, epithelial cells, pancreatic cells, astrocytes, neurons as well as placental trophoblasts and retinal epithelial cells. On binding with their ligands, PD-1 receptors restrict cell proliferation, cytokine secretion and cytotoxic ability of immune cells and so hijack the immune response.[16]

PD-1/PD-L1 pathway is found to play a major role in escape of cancer cells from immunosurveillance, with PD-1 expression seen on effector T-cells. Also depleted T-cells in tumor microenvironment (TME) and PD-L1 expression shown different types of cancers cell surface involving bladder, lung, colon, breast, kidney, cervix, melanoma, glioblastoma, myeloma and T-cell lymphoma.[17] Blockade of PD-1/PD-L1 pathway to stimulate anti-tumor immune responses has been the most successful current strategy. Monoclonal antibodies such as pembrolizumab, nivolumab,

cemiplimab, atezolizumab, avelumab and durvalumab are approved by US FDA for the treatment of different types of cancer.[18]

4. Rational for combined immunotherapy

Delivered monotherapy in clinical studies, CTLA-4 and PD-1 blockers illustrated impressive strong response rates, increased the survival time of patients and possible safety profile.[19] Benefits of monotherapy were limited by low response rates, moreover, only a fraction of patients found to respond to the therapy. For instance, 50 % or most of metastatic melanoma patients failed to respond against monotherapy as shown by objective response rates (ORR) for ipilimumab (10-16 %) as well as nivolumab and pembrolizumab (30-40 %).[20]

Combined blockade was thus presented to increase the response and survival rates. It was thought that blockade of CTLA-4, which is primarily involved in regulation of T-cell activation in lymph nodes and in DC suppression activity through Treg cells, would act collaboratively with PD-1 blockade that is commonly included in inhibition of T-cell and NK cell activation in peripheral tissues and also in introduction of Treg cell differentiation (**Fig. 1**). Outcomes from clinical data estimated the efficiency of CTLA-4 plus PD-1 checkpoint inhibitors and illustrated the benefits of therapy.[21]

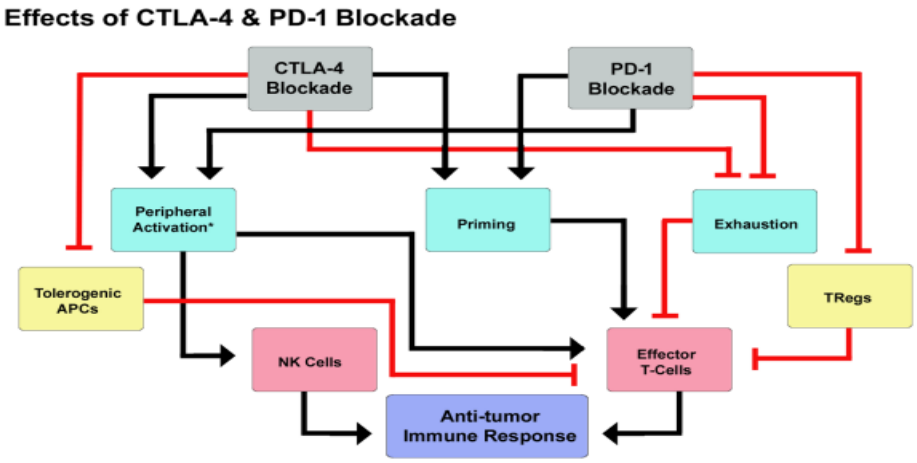

Fig. 1. Effects of combined blockade of CTLA-4 and PD-1.

5. Clinical evidences for various cancers

5.1 Melanoma

Combination of ipilimumab with nivolumab and pembrolizumab was examined extensively in metastatic melanoma patients. Moreover, the efficiency of the combination was illustrated in several clinical trials. Phase I considered, ipilimumab plus nivolumab combination was disclosed to increase the ORR (61 %), with complete responses seen in 22 % patients.[22] Patients allocated to combined therapy in the investigation reportedly had lower incidence of disease progression or death. Hazard ratio (HR) for disease progression in combined therapy vs. ipilimumab monotherapy was 0.40 ($p< 0.001$ for both) compared to ipilimumab and nivolumab monotherapy.[23]

Outcomes from analysis of results after 3-4 years follow-up of the patients in the investigation further demonstrated the excellent benefits of combined therapy over monotherapy. Combined therapy illustrated assisted OS rate of over 50 % at both 3-4 years evaluation.[24] Data showed from patients treated with nivolumab alone or combined with ipilimumab in clinical investigations involving phase III trials, further demonstrated that patients receiving combined therapy had higher median PFS, for cutaneous melanoma (11.7 months) and mucosal melanoma (5.9 months) patients compared to nivolumab monotherapy group (6.2 and 3.0 months).[25]

The improved incidence of adverse circumstances shown with combined therapy, variations in the sequence of distribution of nivolumab and ipilimumab was tested in a phase II. Patients received nivolumab for 6 doses attended by outlined switch to ipilimumab for 4 doses or vice versa.[26] Fascinating, disease continuation was lower and overall survival was better when nivolumab was distributed first followed by ipilimumab, but there was not particular difference in frequencies of treatment related grade 3-5 adverse incidents between the 2 groups.[27]

Pembrolizumab plus ipilimumab combination

In Phase-I b, efficiency of combine regular dose pembrolizumab with low dose ipilimumab was evaluated in metastatic melanoma patients. Fascinating, pembrolizumab and low dose ipilimumab combination also demonstrated comparable efficiency with ORR (61 %), 1-year PFS rate (69 %) and 1 year OS rate (89 %) but had lower events of grade 3-4 adverse events (46 %).[28] Outcomes from investigation of 'true-world' results illustrated that metastatic cutaneous melanoma patients treated with pembrolizumab combination and low-dose ipilimumab had an overall response rate (38 %) and lower event of grade 3-4 adverse incidence (18 %).[29]

5.2 Renal cell carcinoma

Combination of CTLA-4 (ipilimumab) and PD-1 (nivolumab) antibodies for the treatment of metastatic renal cell

carcinoma was first explored from phase I to phase III.[30] Phase I was planned to test multiple dose processes of the combination. Outcomes illustrated that while the ORR is 40.4 % for both arms and 2-year OS rate (67.3 % and 69.6 %) was similar between patients who received nivolumab 3 mg/kg plus ipilimumab 1 mg/kg (N3/I1) and nivolumab 1 mg/kg plus ipilimumab 3 mg/kg (N1/I3), treatment-related grade 3-4 adverse effects were comparatively higher in N1/I3 group (38.3 % and 61.7 %).[31]

In the randomized phase III trial nivolumab (3 mg/kg) plus ipilimumab (1 mg/kg) was selected for the treatment. The investigate presented 18-month OS rate (75 %), ORR (42 %) and median PFS (11.6 months) in the combined group.[32] The events of death and/or disease progression in the combined group was lower compared to control group. Interestingly, patient studied results from the phase III trial were investigated, which demonstrated that patients in nivolumab plus ipilimumab group had fewer symptoms as well as better health related quality of life compared to the control.[33]

5.3 Colorectal cancer

Colorectal cancer with DNA mismatch repair-deficient or microsatellite instability high positive tumors was awaited to immunotherapy response because of high levels of tumor neoantigens, tumor-infiltrating lymphocytes and checkpoints expression.[34] In an open-label phase II investigation, PD-1 receptors inhibitor with nivolumab noted an ORR (31 %), disease control rate (69 %) and 12 months OS rate (73 %). From the investigation illustrated that nivolumab and ipilimumab combined had an investigator-assessed ORR (55 %) and disease control rate (80 %). PFS rates at 9 and 12-month were 76 % and 71 % and OS rates were 87 % and 85 %. Authors concluded that nivolumab and ipilimumab combination had comparatively better efficiency and was a promising alternative treatment strategy for metastatic colorectal cancer patients.[35]

5.4 Lung cancer

Durvalumab plus tremelimumab for NSCLC (non-small cell lung cancer)

Multiple investigation marked the efficiency of anti-CTLA-4 with anti-PD-1/PD-L1 antibodies in lung cancer. Phase-I (b) estimated the safety and efficiency of durvalumab (anti-PD-L1) and tremelimumab (anti-CTLA-4) combination in patients with advanced squamous or non-squamous NSCLC across 5 cancer centers in USA. The investigation recorded clinical activity in patients with PD-L1 positive cancers and PD-L1 negative cancers with researcher evaluated ORR in 23 % patients.[36]

Nivolumab plus ipilimumab for NSCLC

Safety and activity of combined nivolumab and ipilimumab as first-line therapy for NSCLC was evaluated in a phase I. Two different dosage administrations of the combination involving, nivolumab every 2 weeks plus ipilimumab every 12 weeks with nivolumab every 2 weeks plus ipilimumab every 6 weeks were estimated in the investigation. At the time of recording, ORR emerged to be slowly higher (47 % vs. 38 % each) in patients receiving ipilimumab every 12 weeks compared to 6 weeks.[37]

In phase II investigation, the efficiency and safety of nivolumab with 'low-dose' ipilimumab as first-line treatment for metastatic NSCLC was examined and the cooperation of efficiency with PD-L1 expression and cancer mutational load was evaluated.[38] Investigation illustrated that ORR was higher in patients with cancer mutational load of at least 10 mutations per MB and was independent on PD-L1 expression (48 % in PD-L1≥1 % and 47 % in PD-L1≤1 % group), and proposed ≥10 mutations per MB as the cutoff for cancer mutational load.[39]

Nivolumab plus ipilimumab for SCLC (small cell lung cancer)

Additionally, to NSCLC, nivolumab and ipilimumab combination was examined in patients with advanced SCLC. In a multicenter phase I/II, patients who degenerated after at least one previous platinum-including administration were treated with nivolumab plus ipilimumab or nivolumab alone.[40] At the time of estimation, patients receiving nivolumab and ipilimumab combination had higher ORR (23 % vs. 10 %) and longer survival (median OS, 7.7 vs. 4.4 months and 1-year OS rate, 43 % vs. 33 %) compared to nivolumab monotherapy, further confirming the combining PD-1 and CTLA-4 blockers advantages.[41]

5.5 Mesothelioma

Combined anti-CTLA-4 and anti-PD-1 antibodies was examined in phase II with malignant pleural mesothelioma. In the first investigation, a perspective single center, single arm trial, malignant pleural mesothelioma patients who proceeded after at least one line of platinum-including chemotherapy, were managed with combination of nivolumab plus ipilimumab. The investigation recorded that in the suitable patients with interpretable response, stable disease was reached (38 %), partial response (29 %) and disease control (68 %) patients.[42]

Second investigation, a prospective, randomized, non-comparative, open-label, multicenter trial, patients progressing after first or second-line platinum-based treatments were served with combination of nivolumab plus ipilimumab or nivolumab alone. The investigation recorded that in the intention-to-treat population, disease control was reached in combination patients (52 %) and monotherapy group (40 %).[43] From both examinations concluded that nivolumab and ipilimumab combination demonstrated promising activity in malignant pleural mesothelioma patients who proceeded after chemotherapy and suggested confirming the larger trails efficiency.

5.6 Esophagogastric cancer

Advantages of combined PD-1 and CTLA-4 blockade was estimated in patients with normally advanced or metastatic esophagogastric cancers. Patients who worsen after primary chemotherapy received either nivolumab

monotherapy or nivolumab plus ipilimumab combined therapy in the investigation.[44] Study of the results disclosed that investigator-assessed ORR were shown in patients receiving the nivolumab and ipilimumab combination (24 %) and nivolumab alone (12 %). 12 months PFS rates 17 % and 8 %, whereas 12 months OS rates were 35 % and 39 % each.[45]

Fascinating, out of the 2 different dose groups involved to estimate the combination, patients receiving nivolumab (1 mg/kg) and ipilimumab (3 mg/kg) had comparatively superior ORR (24 % vs. 8 %), 12 months PFS rate (17 % vs. 10 %) and 12 months OS rate (35 % vs. 24 %). Concluded that phase III investigations testing the combination efficiency in earlier lines of therapy for esophagogastric cancer were in progress.[46]

5.7 Prostate Cancer

Efficiency of anti-CTLA-4 and anti-PD-1 antibodies in metastatic prostate cancer patients was examined in a single center perspective trail phase II. Patients with androgen receptor variant 7 (AR-V7) positive cancers were administered with combi nation of nivolumab plus ipilimumab. During testing, ORR in patients with measurable disease (25 %), median PFS (3.7 months) and OS (8.2 months) was recorded. Results occurred to be superior in cancers with DNA repair deficiency (DRD) positive cancers compared to DRD negative (ORR, 40 % vs 0 %; HR for disease progression, 0.31 and HR for death, 0.41) and indicated that further investigations in larger group were needed to favorable combined efficiency.[47]

5.8 Sarcoma

Safety measures and activity of PD-1 alone or in combine with CTLA-4 blockade was investigated in an open-label, non-comparative, randomized phase II examination in sarcoma patients who received at least one primary line of systemic therapy.[48] Patients registered in the evaluation received either nivolumab alone or nivolumab and ipilimumab combination. Nivolumab and ipilimumab combined group had comparably more confirmed responses (16 % vs 5 %), longer median PFS (4.1 months vs 1.7 months) and longer median OS (14.3 months vs 10.7 months). Therefore, concluded that nivolumab monotherapy illustrated limited efficiency in sarcoma patients, whilst nivolumab and ipilimumab combined therapy demonstrated promising efficiency.[49]

SUMMARY

Based on mechanism of action, combined PD-1 and CTLA-4 blockers has been successful in rising the response rates and median survival time in cancer patients. Combination of nivolumab plus ipilimumab has been authorized for metastatic melanoma, advanced renal cell carcinoma and colorectal cancer.[50] More investigations illustrated increased response and survival rates in lung cancer patients administered with nivolumab and ipilimumab combination, and this shown to be efficacious in difficult to treat cancers like mesothelioma and sarcoma. Moreover, most of the investigations evaluated the nivolumab and ipilimumab combination and also other PD-1/PD-L1 and CTLA-4 blockers.[51]

Furthermore, nivolumab and ipilimumab combination was informed to rise in the adverse events frequency and precipitate autoimmunity.[52] Also, the severity was seen to be diminished partly through dose variance, regimen and sequence of the drugs administrations.[53] Fascinatedly, the dose of nivolumab and ipilimumab that illustrated promising efficiency and limited toxicity occurred to vary with cancer type. The differences in successive doses of CTLA-4 and PD-1 blockers in the combination point to the complex variances in cancer microenvironment in various cancer sub-types.[54] Further investigations are in-progress to titrate the dose, regimen and the administration sequence of the combined therapy. The outcomes from the investigations could involve additional insights into immunosuppressive mechanisms in TME. The advantages of PD-1 plus CTLA-4 blockade therapy in specific cancer types help in identifying the combine dose with desired efficiency.[55]

CONCLUSIONS

To conclude, CTLA-4 and PD-1 combined blockers was effective and approachable in increasing the response and survival rates in several types of cancer, also increased the occurrence of adverse events.[56] Furthermore, investigations may be needed to lower down the occurrence and adverse events potency while preserving the efficiency of the combination. Additional investigations are also needed to confirm the combination efficiency of other PD-1/PD-L1 and CTLA-4 immune checkpoints blockers.[57]

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The author has alone responsible for writing this article.

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