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A REVIEW: CHECKPOINT INHIBITORS IN CANCER IMMUNOTHERAPY

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ABSTRACT

Immunotherapy is a promising cancer treatment that focuses on boosting one's immunity to fight cancer instead of directly attacking the cancer cells like is done in the case of chemotherapy, radiotherapy, and other conventional therapies. Immunotherapy along with other kinds of therapies has shown favorable results during clinical trials. Immune Responses are supervised by a very intricate system of checks and balances which enables protective immunity and toleration. The immune check points prevent the immune response being so strong that may destroy healthy cells in the body. Immune checkpoint inhibitors (ICIs) are molecules that stop these checkpoints from aiding the cancer cells to grow further. They do so by binding to the T-cell receptors before the receptors on the tumor cell can bind to them, hence retaining the activity of the T-lymphocytes. In this review article, we highlight the various checkpoint inhibitors involved in immunotherapy. We address important issues related to pharmacodynamics (PD), pharmacokinetics (PK) and the safety and efficacy of ICIs.

KEYWORDS: Cancer, check point inhibitors, immune response, immunotherapy, pharmacodynamics, pharmacokinetics.

INTRODUCTION

Cancer is the uncontrolled growth of abnormal cells in the body. These abnormal cells are malignant or tumor cells. Often cancer cells, undergo metastasis whereby they travel through the blood and lymph system and lodge in other organs where they can again repeat the unchecked growth cycle. These cells fail to undergo programmed cell death or apoptosis as normal body cells do. Our immune system is most successful in eliminating damaged and abnormal cells from the body. However, these cancer cells manage to trick the system. They have ways to avoid destruction by the

immune system and have their unique mechanisms to evade the immune system. These cells make genetic changes that make them less visible to the immune system, they may express proteins on their surface that turn off the immune cells, and they can change the normal cells around the tumor and thus interfere with the response of the immune systems to cancer cells.

Treatment of cancer is done by the traditional cancer treatment designed to act directly on tumors by inhibiting their growth and ultimately leading to resistance mechanisms. As a class of anticancer agents, immunotherapies are designed to harness the patient's immune system to fight cancer. Several types of immunotherapies are used to treat cancer. These include Immune checkpoint inhibitors, Therapeutic proteins – Cytokines and monoclonal antibodies (MAbs), Cancer vaccines, Adoptive cell transfer.[1]

Immune Checkpoint

The immune-surveillance system of our body keeps a check of the foreign antigens that are presented either by MHC I or MHC II. It keeps the inflammatory response of the immune system constantly activated. The Cytotoxic T lymphocyte (CTL) is activated by the antigen-presenting cells (APCs) that present the tumor antigen with their MHC molecules as cancer-specific neo-antigens. The process of full activation takes place with an additional interaction of the co-stimulatory TCR CD28 and B7 ligand. This interaction is crucial for the destruction of cancer cells because it fabricates an antigen-specific immune response in which numerous CTLs are activated and flood the tumor cell to destroy it. Thus, activation of the immune system through the CTLs helps to achieve the desired outcome of tumor control, but on the other hand, can be responsible for autoimmunity. The Immune Check point inhibitors (ICIs) tightly regulate or suppress the receptor-ligand binding to avoid collateral damage from autoimmunity.[2,3] The cytotoxic T lymphocyte associated protein 4 (CTLA-4) was demonstrated to have a potent inhibitory role in regulating T cell responses. In resting T cells, CTLA-4 is an intracellular protein; however, after T cell receptor (TCR) engagement and a co-stimulatory signal through CD28, CTLA-4 translocate to the cell surface, where it outcompetes CD28 for binding to critical co-stimulatory molecules (CD80, CD86) and mediates inhibitory signaling into the T cell, resulting in the arrest of both proliferation and activation.[4,5] Immunological checkpoints consist of inhibitory immune response proteins (PD1, CTLA-4, and VISTA) and stimulatory immune response proteins (CD28, ICOS, CD137) that help to maintain the immune response.[6]

Cancer cells cleverly escape from immune attacks by dysregulating immune checkpoint-related proteins. They do so by developing a similar set of defense mechanisms to evade the immune system in the form of Programmed cell death receptor-1 (PD-1) and Programmed Cell Death Ligand-1 (PD-L1). PD-L1 and PD-L2 are expressed on the surface of cancer cells and APCs and exert an inhibitory effect on interaction with PD-1 receptors that are present on CD-8 cells. The complex formed between PD-1 and PD-L1 or PD-L2 acts as a negative regulator by blocking CTL functions through an inhibitory signal downstream to the T-cell Receptor (TCR).[7,8,9] This way cancer cells achieve immune tolerance. Immune checkpoint therapy relies on a functioning immune system with agonists of stimulatory signals or antagonists of inhibitory signals. Cytotoxic T lymphocyte-associated molecule-4 (CTLA-4), Programmed cell death receptor-1 (PD-1) and Programmed Cell Death Ligand-1 (PD-L1) is the most studied and acknowledged inhibitory checkpoint pathways. At present, six ICIs have been approved by the US Food and Drug Administration (FDA), of which five ICIs also received market authorization by the European Medicines Agency (EMA).[10,11]

Immune Checkpoint Inhibitors (ICIs)

PD-1 and PD-L1 or PD-L2 Blockers: Nivolumab and Pembrolizumab

Nivolumab

Nivolumab is the first anti-PD-1 genetically engineered fully human immunoglobulin G4 (Ig G4) monoclonal antibody and is specific for the human PD-1. Antibody-dependent cellular cytotoxicity (ADCC), if intact, has the potential to attenuate activated T-cells and tumor-infiltrating lymphocytes and dampen activity as PD-1 is expressed on T-cells. Hence, the IgG4 iso-type of Nivolumab was engineered in a way that precludes ADCC.[12] Unlike most monoclonal antibodies used in immunotherapeutic oncology, like IgG1, IgG4 possesses minimal ADCC activity. Nivolumab disrupts the interaction between PD-L1 or PD-L2 with PD-1 and thus inhibiting cellular immune response, acting as an anti-PD-1 drug.[13,14]

Pharmacokinetics: Once injected, nivolumab is likely to degrade through catabolic pathways into small peptides and amino acids like endogenous immunoglobulins. In addition to this, nivolumab is expected to be cleared by proteolytic degradation.

Safety and Efficacy: Nivolumab was found to be superior to the chemotherapy treatments and has the potential as identifying predictive biomarkers for therapeutic oncology and drug development.[15,16] A series of phase I, II, and III clinical trials done by using nivolumab in the treatment of renal cell carcinoma (RCC)[17-19], Non-small cell lung cancer (NSCLC)[20-24] and melanoma[25-26] revealed that the Progression-Free Survival (PFS) rate was greater. There was an increased response rate and it proved to be an effective and safe alternative for patients.

Pembrolizumab

Pembrolizumab is a humanized, potent, IgG4 kappa monoclonal anti-PD1 antibody that binds to the PD-1 receptor. By binding to the receptor, it ceases the formation of any complex between PD-1 and its ligands PD-L1 and PD-L2. Thus, leading to the activation of T-cell mediated immune response, putting an end to the co-inhibitory pathway mediated by the interaction between PD-1 and PD-L1 or PD-L2.[27] It was observed that the tumor growth visibly decreased in genetically identical mouse tumor models.[28]

Pharmacokinetics: No specific process has been noted for the metabolism of pembrolizumab in the body but it has been suggested that the cells in the reticuloendothelial system metabolize these IgG monoclonal antibodies by the process of phagocytosis. It was also suggested that it must be the phagocytes that break down the monoclonal antibodies into fragments of peptides with a lower molecular weight, which are eventually eliminated by the renal glands from the body. However, the metabolism of the drug is dependent on patient-specific factors. These factors include antigen concentrations, antigen properties, and protective Fcγ and FcRn receptor expression. The clearance rate of pembrolizumab remains unaffected by age or gender, which is 0.22L/day and has a long half-life of 26 days.[29]

Safety and Efficacy: Pembrolizumab has therapeutically gained accelerated approval for the treatment of PD-L1 positive cervical cancer by the US Food and Drug Association.[30,31] Pembrolizumab showed a discrete mechanism of action, response rate, and toxicity level distinct from other chemotherapies for gastric cancer.[32] It is a humanized monoclonal antibody against PD-1 and has shown anti-tumor activity with an acceptable safety profile in phase II and III studies in patients with PD- L1 positive advanced gastric and gastroesophageal junction cancers.[33] There is still

intensive research going to assess the efficacy of Pembrolizumab in combination with other therapies for gastric cancer.[34]

Anti- CTLA-4 antibodies **- Ipilimumab and Tremelimumab**

Ipilimumab

Ipilimumab is a fully-humanized IgG1 type monoclonal antibody that acts on CTLA-4. They antagonize and bind to CTLA-4 and stop cause cessation of ligand binding. Anti-CTLA-4 antibodies like Ipilimumab inhibit CD80 and CD86, present on the antigen-presenting cells (APCs), from binding to CTLA-4 on the T-lymphocytes. This blockade leads to extended T-cell activation, which in turn paves a way for the restoration of T-cell proliferation and amplification of T-cell mediated immune response.[35] Ipilimumab causes a more robust response in cancer patients with reduced CTLA-4 expression and decreases the likelihood of subsequent relapse.[36] Its significant impact on melanoma ushered it into the world of medical immune-oncology and it gained acceptance for the treatment of other types of cancers.[37]

Pharmacokinetics: The pharmacokinetic studies indicated the half-life of Ipilimumab to be 12 to 14 days and permitted to have 3 to 4 weeks dosing design. The metabolism does not involve the cytochrome P450 enzyme system. Ipilimumab is a monoclonal antibody, proteinic in nature, so it is degraded into small peptides and amino acids by the proteolytic enzymes.

Safety and Efficacy: Ipilimumab has been approved by FDA in March 2011 as monotherapy (3mg/kg every 3 weeks for 4 doses) for the treatment of advanced (unresectable or metastatic) melanoma both in pre-treated or chemotherapy-naive patients.[38,39] However, mono-therapy leads to immune-related gastrointestinal adverse reactions like colitis and gastrointestinal perforation. However, the adverse events reported with Ipilimumab are manageable with supportive measures and the occasional use of systemic corticosteroids.[40,41] It is generally recommended for combined treatment with Nivolumab or any two chemotherapy regimens.[42,43]

Tremelimumab

Tremelimumab (formerly ticilimumab) is a fully-humanized monoclonal antibody; which is the antibody for CTLA-4. It is also an interleukin-2 (IL-2) stimulant. Hanson and his co-workers described the structure as an antagonist immunoglobulin IgG2 whose complement activation and FcγR binding is reduced, compared to IgG1 antibodies. Tremelimumab has a higher affinity for CTLA-4 than towards CD-28, hence effectively binding to it and avoiding immune suppression. It has been successfully used to treat patients with metastatic melanoma and other types of cancers.[44] The combination therapy approach leads to the improved response, in which tremelimumab is used in combination with durvalumab (another anti-CTLA-4 antibody). This plays a role in activation and increase in the frequency of memory cells, along with an effect on T-regulatory cells and monocytes.[45]

Pharmacokinetics: The half-life of tremelimumab is 25.6 days. It has produced promising anticancer responses in early clinical trials. The Phase I clinical trials indicated it increased plasma concentrations of > 10µg/ml for > 4 weeks after a dose of > 6mg/kg. The phase II trial showed promising efficacy for its combination at a concentration of 15mg/kg with high dose interferon -α2b of 20MU/m2 for 5days/ week in patients with stage IV melanoma. However, a phase III trial of tremelimumab mono-therapy versus chemotherapy in advanced melanoma was stopped due to a lack of statistically significant difference in overall survival and Standard of care chemotherapy. Although the durable

responses observed suggest that a subset of patients with metastatic melanoma may benefit from treatment with tremelimumab.[46]

Safety and Efficacy: Tremelimumab monotherapy demonstrated durable antitumor response and an acceptable safety profile.[47,48]

Durvalumab

It is a human IgG1 kappa monoclonal antibody focusing on programmed cell death ligand-1 (PD-L1) that was created by AstraZeneca and has been affirmed by Food and Drug Administration (FDA).[49] Both PD-L1 and PD-1 are co-inhibitory molecules that block T cell-mediated immune response. Durvalumab blocks PD-L1 restricting to both PD-1 and CD80 but does not cohere to PD-2 thus, bringing an end of tumor cells by T-cells by re-establishing T cell activity, thereby enhancing detection and ablation of tumor cells. It is hastily designed to incapacitate cytotoxic effector capacities, for instance, antibody-reliant intervened cytotoxicity and not antibody-dependent cell mediated cytotoxicity (ADCC) against cells communicating PD-L1 in a concentration-dependent way in an anti-CD-3-based T-cell activation and a mixed lymphocyte reaction assay.[50] The pharmacodynamic study indicates that the binding of durvalumab to PD-L1 involves both its variable heavy chain (VH) and light chain (VL).[51] All of the three complementarity-determining regions (CDRs) of VH and CDR1 and CDR3 of VL contribute to interactions with PD-L1, leaving LCDR2 without any contacts. A detailed analysis of the interactions between durvalumab and PD-L1 shows an unbiased contribution from VH and VL of durvalumab in binding to PD-L1.[52] As we know, blocking the binding of PD-L1 to PD-1 with an immune checkpoint inhibitor (anti-PD-L1 or anti-PD-1) allows the T cells to kill tumor cells, Thus, the molecular basis of durvalumab-based PD-1/PD-L1 blockade is that the unbiased binding of durvalumab VH and VL to PD-L1 provides steric clash to abrogate the binding of PD-1/PD-^{L1}.[53] Durvalumab has been affirmed for the therapy of patients with metastatic urothelial carcinoma, non-small cell lung cancer (NSCLC), and is now being assessed in many different solid tumors and hematological malignancies, including non-Hodgkin lymphoma (NHL), numerous myeloma (MM), myelodysplastic conditions (MDS), and intense myeloid leukemia (AML).[54,55]

Pharmacokinetics: Durvalumab exhibits a dose-proportional pharmacokinetic profile. It is subjected to protein catabolism via the reticuloendothelial system. The mean terminal half-life is 18 days with a clearance of 8.2ml/h.[56] durvalumab clearance is dependent on the concentration of albumin protein and the concentration of immunoglobulin G (multiple myeloma patients). As per the studies conducted by Ogasawara and his co-workers on patients with multiple myeloma, if the concentration of Ig G>20g/L showed a 30% decrease in the durvalumab clearance unlike when the IgG <20g/L.[57]

Safety and Efficacy: Durvalumab showed clinical efficacy and a manageable safety profile in advanced non-small-cell lung cancer, particularly the ≥25% PD-L1+ population. Similar findings were reported by Baverel and his team stating a slight decrease in durvalumab clearance with time and suggested that it may be associated with a decrease in nonspecific protein catabolic rate amongst the cancer patients.[58] The anti–PD-L1 antibody durvalumab has demonstrated durable clinical activity and a manageable safety profile in multiple tumor types, including metastatic gastric or gastro-esophageal junction cancer.[59]

Atezolizumab

Atezolizumab is a high-affinity human IgG1 monoclonal antibody, developed by Genentech as a treatment for a variety of hematological malignancies and solid tumors.[60] It binds selectively to PD-L1 and prevents the binding of PD-L1 to PD-1 and B7-1, which complements the magnitude and quality of the tumor-specific T-cell responses, resulting in better anti-tumor activity.[61] It is sold under the trade name Tecentriq, a genetically engineered IgG1 monoclonal antibody across the Fc area, to decrease the Fc effector function and minimize antibody-dependent cell mediated cytotoxicity (ADCC) thus leading to hypothetical loss of PD-L1 expressing T effector cells and consequently conferring anti-tumor activity.[62,63] It interrupts PD-L1 and PD-1, consequently preventing T cell exhaustion, downstream inhibition of cytokines, and late immune response and thereby leading to increased anti-tumor activity. It has been approved as a first-line treatment for metastatic non-small cell lung cancer and as a second–line therapy for urothelial carcinoma.[64] Additionally, atezolizuamb is approved in combination with carboplatin and etoposide for the first-line treatment of adults with extensive-stage SCLC.[65]

Pharmacokinetics: The half-life of atezolizumab is 27 days with a clearance of 0.200L/day.[66,67]

Safety and Efficacy: Safety for atezolizumab appeared to be consistent with its known safety profile, and no new safety signals were reported.[68] Moreover, grade 3 to 4 treatment-related adverse events were reported in 12.9% of patients receiving atezolizumab, compared with 44.1% of those receiving chemotherapy.[69]

DISCUSSION

Several studies on the reciprocity between immune activation and suppression have demonstrated the important role that checkpoint inhibitors play in the pathogenesis of malignant tumors. Based on the literature review, checkpoint inhibitors have a promising future in serving as a targeted immunotherapy for a diverse range of cancers. The checkpoint inhibitor drugs mentioned have shown different levels of safety and efficacy in clinical trials. The pharmacokinetics of these checkpoint inhibitors depends on factors like clearance and position of target-mediated drug which involves pharmacodynamics. Both the anti-PD-1 antibodies, Nivolumab and Pembrolizumab, have a linear clearance which gradually decreases with time and depends on factors like gender, age, body weight, and sex.[80,81]

Nivolumab has shown an appreciable efficacy in the treatment of various cancers like – RCC, NSCLC and melanoma; and Pembrolizumab gained accelerated approval for cervical cancer treatment and has shown acceptable safety in clinical trials. The anti-PD-L1 antibodies, Durvalumab and Atezolizumab, again show a linear clearance over a broad range of doses. For Atezolizumab, the clearance is stable and the rate fluctuates due to factors like body weight and serum albumin concentration. The clearance of Durvalumab, on the other hand, is dependent on factors like albumin, body weight, cancer type and gender. Durvalumab and Atezolizumab have shown moderate safety and efficacy in cancer immunotherapy. Although a few ADRs as mentioned in Table 1 like grade 3 and 4 adverse events were observed with their treatment, the incidence was lesser than in the case of chemotherapy.[83] Lastly, anti-CTLA 4 antibodies, Ipilimumab and Tremelimumab, have also shown great potential in immunotherapy. No time-varying clearance was observed for Tremelimumab.[84] The FDA has approved Tremelimumab only for the treatment of Mesothelioma and has been given orphan drug designation. However, it is still surrounded by some controversy over its efficacy. On the other hand, Ipilimumab has shown remarkable efficacy in treating melanoma. Being proteinic it is easily degraded by proteolytic enzymes present in the body and has a half-life of 12-14 days. While Ipilimumab was

approved for monotherapy of advanced melanoma, studies have shown that Ipilimumab works best when administered with Nivolumab as a combination therapy.[85]

The combination therapy of Ipilimumab and Nivolumab has shown promising safety and efficacy in recent clinical trials. The overall survival rate had also improved with the combination therapy. The optimum clinical benefit to patients can only be achieved by studying in-depth the mechanisms responsible for a robust anti-tumor response. Hence, more clinical trials and research in administering these drugs would pave way for checkpoint inhibitors to dominate the immunotherapeutic sector.

Figure & Table Legends

Figure 1: Targets of ICIs at the molecular level. It is known that not only do tumor cells quash the host's immune system but also dampen the anti-tumor response of the host entirely. There are several mechanisms harnessed by the tumor to evade the host's immune system, one of them being – thwarting the T-cell response. This is brought about by two main phases. In the *primary phase*, the naïve T-cells in the lymphoid organs mature and differentiate into effector T-cells after being introduced to cancer neo-antigens. This is meant to act as an adaptive reaction against cancer cells accompanied by the co-stimulatory effect of CD28 receptors with CD80/86. However, CTLA-4 receptors have a higher affinity for CD80/86 ligands and hence, impede the anti-tumor response of effector T-cells. In the *effector phase*, the T-cells remove tumor cells by cell-to-cell communication. But this is dampened by PD-1 receptors on T-cells that interact with PD-L1 or PD-L2. ICIs have been designed to antagonize these reactions by competitively binding to the inhibitory proteins that play a role in hindering the anti-tumor response of the host.[72]

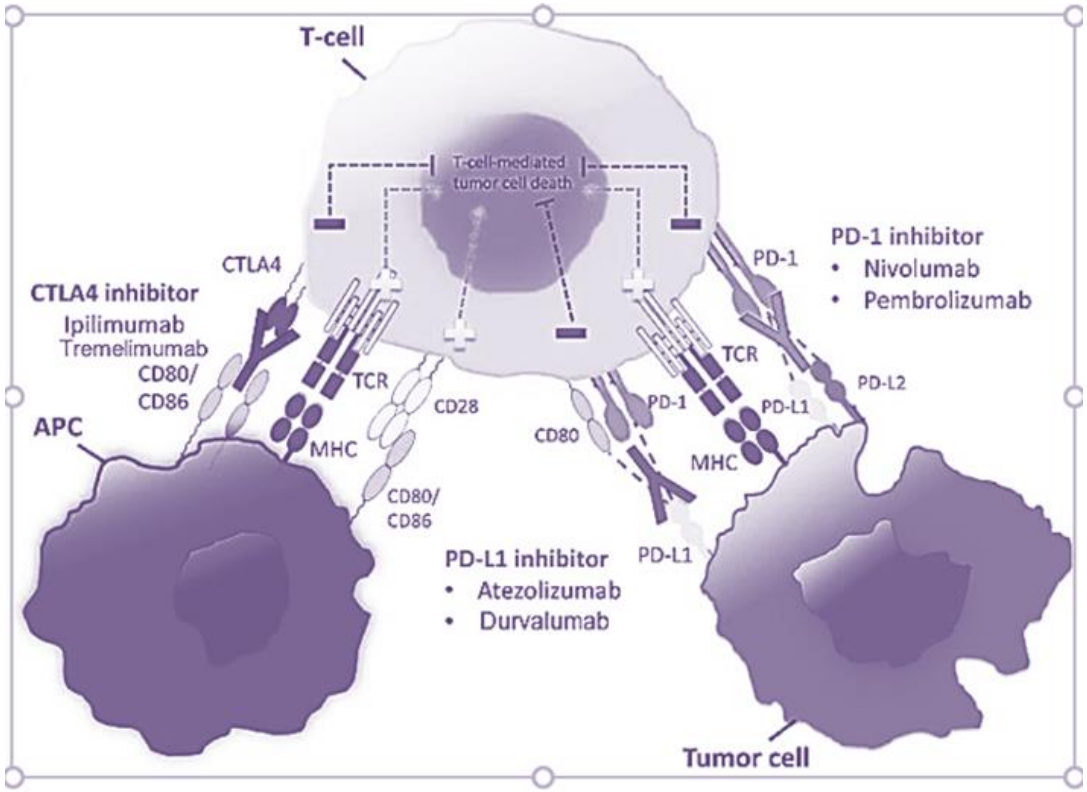

Figure 1.

Table 1: Immune checkpoint inhibitors their therapeutic indication with adverse effects and pharmacokinetic parameters.

Generic Name	Marketing Holder	Therapeutic Indication	Recommended Dose (FDA)	AEs/OS	Clearance, Vd, Half-life	Reference No
Nivolumab (PD-1)	Bristol-Myers Squibb	Melanoma Non-small Lung Cancer Renal cell carcinoma Classic Hodgkin Lymphoma Squamous cell cancer of the head and neck Urothelial carcinoma Microsatellite instability-high mismatch repair-deficient cancer Colorectal cancer Hepatocellular Carcinoma	240 mg; 2-weekly OR 480 mg; 4-weekly	Withhold for any of the following: Grade 2- Pneumonitis, Diarrhea or Colitis, Adrenal Insufficiency Grade 3- Hyperglycemia, Encephalitis or Rash Permanently discontinue for any of the following: Grade 3 or 4 Pneumonitis, Adrenal Insufficiency Grade 4- diarrhea or Colitis, Hypo- physitis, Hyperglycemia	Clearance: 9.4 mL/h. (Volume of distribution) Vd: The volume of distribution at steady state when a dose of 10 mg/kg of nivolumab is administered is reported to be 91.1 mL/kg. At doses ranging from 0.1 to 20 mg/kg the volume of distribution is reported to be 8L. Half-life: The serum half-life of nivolumab is ≈ 20 days with an elimination half-life of 26.7 days.	24, 74, 78, 77, 79
Pembrolizumab (PD-1)	Merck	Melanoma Non-small lung cancer Squamous cell cancer of the head and neck Classical Hodgkin Lymphoma Urothelial Carcinoma Microsatellite Instability-high cancer Gastric cancer	200 mg; 3-weekly	Withhold for any of the following: Grade 2- Pneumonitis, Nephritis, Grade 2 or 3- Endocrinopathies Permanently discontinue for any of the following: Grade 3 or 4- Pneumonitis, Nephritis Grade 3 or 4 infusion related reactions	Clearance: It is increased proportionally with the body weight and the mean clearance is registered to be 0.22 L/day. Vd: The volume of distribution at steady state of pembrolizumab is 7.5 L Half-life: The terminal half-life of pembrolizumab is 26 days	29, 33, 80, 81
Ipilimumab (CTLA-4)	Bristol-Myers Squibb	Melanoma Renal cell carcinoma	Metastatic: 3 mg/ kg; 3-weekly (four doses) Adjuvant: 10 mg/ kg; 3-weekly (four doses); followed by 12-weekly (for advanced stage) Nivolumab 3 mg/kg administered intravenously over 30 minutes followed by YERVOY 1 mg/kg administered intravenously over 30 minutes on the same	Withhold for any of the following: Grade 3 or 4 Rash Permanently discontinue for any of the following: Grade 4 Very Severe Rash Grade Pruritus	Clearance: Ipilimumab has a clearance of 15.3 mL/hr. Vd: The volume of distribution at steady-state of ipilimumab is 7.21L. Half-life: Ipilimumab has a half-life of 14.7 days.	37, 39, 75, 82

		Microsatellite Instability-high or mismatch repair-deficient cancer Colorectal cancer	day, every 3 weeks for a maximum of 4 doses, then nivolumab 240 mg every 2 weeks or 480 mg every 4 weeks, administered intravenously over 30 minutes.			
Tremelimumab (CTLA-4)	Astra Zeneca[*1]	Mesothelioma (Orphan Drug Designation)	Investigational[*3]	Skin reaction, skin rash, itching sensation, diarrhea, nausea, fatigue and immune-mediated disorders[*2]	Investigational	48, 49, 84
Durvalumab (PD-L1)	Astra Zeneca	Urothelial Carcinoma Non-small cell lung cancer	10 mg/kg; 2-weekly	Withhold for any of the following: Grade 2 Pneumonitis Grade 2 Hepatitis Permanently discontinue for any of the following: Grade 3 or 4 Pneumonitis Grade 3 or 4 Hepatitis (ALT or AST greater than 8)	Clearance: Clearance is 8.2 mL/h following 365 days of initial drug administration Vd: In patients receiving the dose range of ≥ 10 mg/kg every 2 weeks, the mean steady state volume of distribution (Vd) was 5.64 L. Half-life: The geometric mean terminal half-life is 18 days.	50, 73, 78
Atezolizumab (PD-L1)	Genentech/ Roche	Urothelial Carcinoma Non-small cell lung cancer	1200 mg; 3-weekly	Withhold for any of the following: Grade 2- Pneumonitis, Colitis, Hepatitis Grade 2 or 3- Nephritis Permanently discontinue for any of the following: Grade 3 or 4- Pneumonitis Grade 4- Colitis Grade 3 or 4 Hepatitis (ALT or AST greater than 8), Neurological Toxicities Grade 4 Nephritis with Renal dysfunction Grade 2,3 or 4 Myocarditis	Clearance: The clearance is 0.200L/day. Vd: The volume of distribution is 6.91L. Half-life: The half-life is 27 days.	66, 67, 68, 83

[*1] Manufacturer

[*2] FDA Warning's

[*3] Still ongoing clinical trials- Tremelimumab has been designated as an Orphan drug for treating Mesothelioma by FDA in April, 2015.

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Conflict of interest

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