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*Review Article*

# Effects of hepatic or renal impairment on the pharmacokinetics of immune checkpoint inhibitors

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**Abstract:** Immune checkpoint inhibitors (ICIs) have become the cornerstone in treating many solid and hematological cancers. The ICIs, including anti-cytotoxic T lymphocyte-associated protein 4 (CTLA-4), anti-programed cell death 1 (PD-1), and anti-programed death-ligand 1 (PD-L1) monoclonal antibodies, have significantly improved the prognosis of cancer patients. Meanwhile, the incidence of hepatic or renal impairment in cancer patients is increasing. However, data about the efficacy and safety of ICIs in patients with hepatic or renal impairment are limited. In this review, we characterize and summarize the pharmacokinetics (PK) of ICIs as well as the effects of hepatic or renal function on the PK of ICIs, and provide specific recommendations for clinicians when prescribing ICIs in patients with hepatic or renal impairment.

**Keywords:** Immune checkpoint inhibitor, cancer, hepatic impairment, renal impairment, pharmacokinetics

## Introduction

Immunotherapy has become one of the most important breakthroughs in treating cancer patients over the last decade. Immune checkpoint inhibitors (ICIs) are widely used in treating multiple cancers including, but not limited to melanoma, lung cancer, colorectal cancer, renal cell carcinoma, head and neck squamous cell cancer, urothelial carcinoma, gastric cancer, esophageal cancer, cervical cancer, endometrial carcinoma, hepatocellular carcinoma, triple-negative breast cancer, and lymphoma [1-3]. Seven ICIs have been approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA). Among them, pembrolizumab, nivolumab, and cemiplimab are anti-programed cell death 1 (PD-1) monoclonal antibodies; atezolizumab, durvalumab, and avelumab are anti-programed death-ligand 1 (PD-L1) monoclonal antibodies; ipilimumab is an anti-cytotoxic T lymphocyte-associated protein 4 (CTLA-4) monoclonal antibody [4]. These ICIs inhibit co-inhibitory checkpoint signaling pathways to promote T cell activation, thereby unleashing anti-tumor immune responses [5].

The ICIs have a large molecular weight, which leads to a poor ability to cross the cell membrane. Thus, ICIs are distributed mainly in the central compartment with a small volume of distribution after parenteral administration [6, 7]. The ICIs are metabolized to peptides and amino acids by circulating phagocytic cells or by their target cells rather than via the liver and kidneys under normal circumstances [6, 7]. Theoretically, the hepatic or renal function may have little influence on the clearance of ICIs. However, the elimination of ICIs is complicated, hepatic or renal function may have a clinically significant effect on the pharmacokinetics (PK) of ICIs via an unknown pathway. In addition, several ICIs have been shown to induce hepatotoxicity or nephrotoxicity [8-10]. Therefore, patients with hepatic or renal impairment represent a population that may be more susceptible to adverse events. In a retrospective observational study, patients with baseline hepatic or renal impairment displayed shorter real-world time to treatment discontinuation and overall survival compare with patients with normal baseline organ function [11]. Therefore, dose adjustment of ICIs may be needed to avoid exposure alteration and drug toxicity for pa-

tients with hepatic or renal impairment. In this review, we summarized the potential hepatotoxicity and nephrotoxicity of the seven ICIs and their PK in patients with hepatic or renal impairment. In addition, based on available evidence from drug labels and published articles, dosing recommendations for the seven ICIs are provided for patients with varying degrees of hepatic or renal impairment.

## Mechanism of action of ICIs

T lymphocytes play important roles in the human immune system by recognizing and destroying abnormal human cells, including cancer cells. As T lymphocytes are regulated by various immune checkpoints (e.g., CTLA-4, PD-1, and PD-L1), cancer cells can suppress the innate T lymphocyte function by activating these immune checkpoints to evade the immune system [12, 13]. Therefore, inhibition of immune checkpoints is one way to treat cancers. To date, several ICIs have been developed and widely used in clinical practice [14]. The ICIs can bind immune checkpoints to re-activate the T lymphocyte tumor suppressing function, resulting in cancer cell death [14]. Current ICIs therapy includes the inhibition of the CTLA-4, PD-1 and PD-L1. Ipilimumab is an inhibitor of the CTLA-4 checkpoint, it binds to CTLA-4 and blocks the interaction of CTLA-4 with its ligands (CD80/CD86), thus leading to T cell activation and proliferation [15]. In addition, inhibition of CTLA-4 can also inhibit T-regulatory cell function, which may contribute to increased T cell response [15]. Pembrolizumab, nivolumab, and cemiplimab are PD-1 inhibitors, they bind to the PD-1 receptor and block the interaction between PD-1 and its ligands PD-L1 and PD-L2, restoring T cell response toward cancer cells [16-18]. Atezolizumab, durvalumab, and avelumab are PD-L1 inhibitors, they bind PD-L1 and block its interaction with PD-1 and CD80 to remove PD-L1/PD-1-mediated inhibition of the immune response, thus restoring anti-tumor T cell responses [19-21]. The mechanisms of action of ICIs are illustrated in **Figure 1**.

## PK of ICIs

All of the seven ICIs are humanized or human immunoglobulin G (IgG) monoclonal antibodies, of which, pembrolizumab, nivolumab, and cemiplimab are IgG4 monoclonal antibodies, whereas the remaining four ICIs are IgG1 monoclonal antibodies [6, 7]. Despite their different mechanisms of action, the seven ICIs display approximately the same PK, including the high molecular weight proteins (from 140 to 150 kDa), a small volume of distribution (from 4 to 8 L) consistent with limited extravascular distribution, and a long half-life (from 6 to 27 days) [6, 7]. In addition, the seven ICIs are immediately and completely bioavailable and are not expected to bind to plasma proteins in a specific manner. Similar to other monoclonal antibodies, ICIs are degraded to small peptides and individual amino acids through the endoplasmic reticulum system and are subsequently taken up by the body and incorporated into other proteins or catabolized [6, 7]. Therefore, ICIs are not metabolized by hepatic enzymes or excreted by the kidneys or liver. The PK parameters of the seven ICIs are shown in **Table 1**.

## Effects of hepatic impairment on the PK of ICIs

Due to the minor involvement of hepatic processes in the clearance of ICIs, hepatic impairment is not expected to influence the clearance of ICIs. Therefore, prospective studies of hepatic impairment effects on the PK of ICIs have not been established. However, limited data showed a trend for exposure decrease with several monoclonal antibodies in patients with hepatic impairment [22]. Hepatic impairment can reduce the transport of gut antigens and endotoxins, leading to B cell activation and proliferation, which can increase the endogenous IgG levels [23]. The increased endogenous IgG level can result in competitive neonatal fragment crystallizable region (Fc) receptor (FcRn) binding with exogenous IgG, which can increase the drug clearance and decrease the drug exposure [24]. Hepatic impairment may increase cytokine levels, leading to increased Fc gamma receptor (FcγR)-mediated elimination pathways, which can result in decreased drug exposure. In addition to alterations in FcRn and FcγR binding, hepatic impairment is associated with higher target-mediated drug disposition (TMDD), which can increase the drug clearance [23, 24]. Therefore, dose adjustment of ICIs in patients with hepatic impairment should be considered, especially for patients with severe hepatic impairment. Based

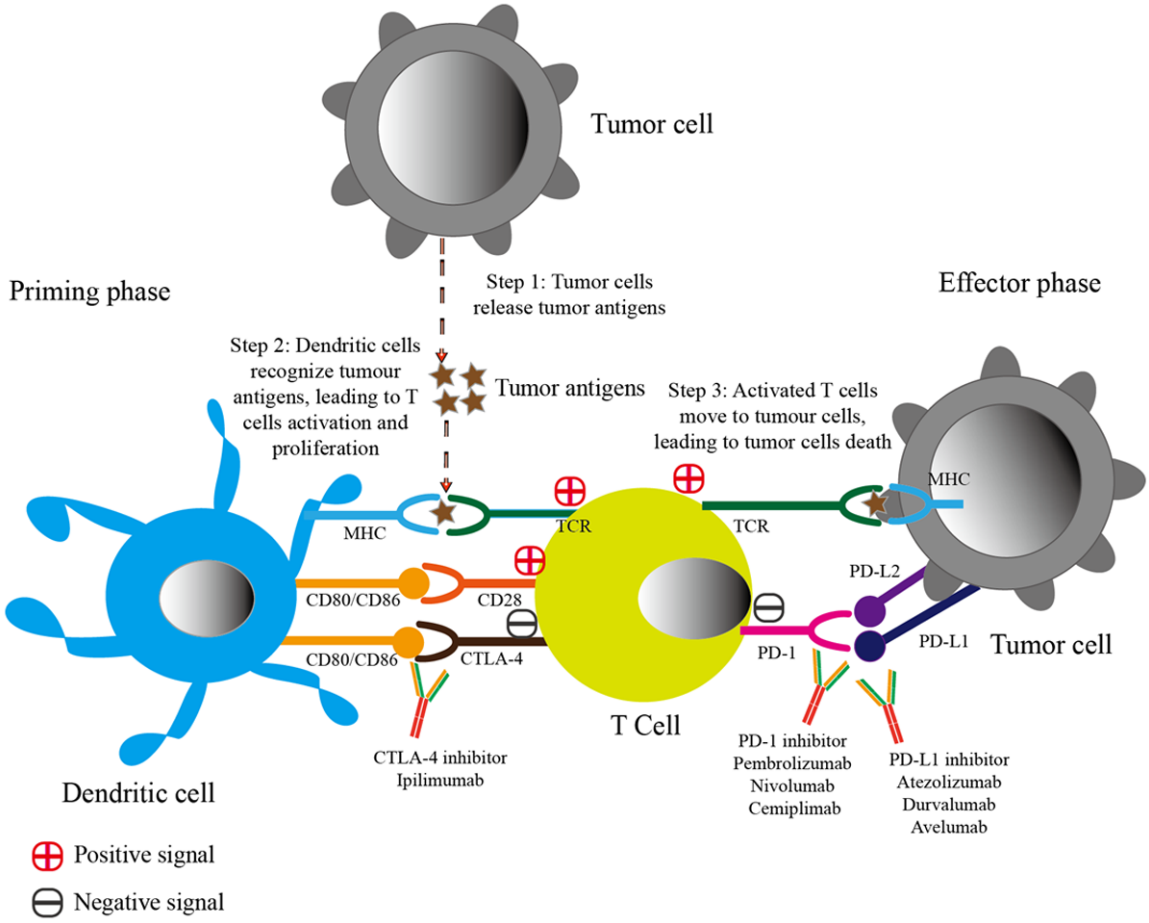


**Figure 1.** The mechanisms of action of ICIs. Priming phase: In the priming phase, T cells are activated by dendritic cells through two interactions: the interaction of major histocompatibility complex (MHC) with T cell receptor (TCR) and the interaction of CD80/CD86 with CD28. T cells also express CTLA-4, which binds to CD80/CD86, and sends an inhibitory signal to inactivate T cells. CTLA-4 inhibitors can bind to CTLA-4 and block the interaction between CTLA-4 and CD80/CD86, thus leading to T cell activation and proliferation. Effector phase: In the effector phase, PD-1 is expressed on activated T cells, whereas PD-L1 and PD-L2 are expressed on tumor cells. The interaction of PD-1 with PD-L1 can inhibit the function of T cells. PD-1 and PD-L1 inhibitors can block this interaction and reinstates T cell response against the tumor cells.

**Table 1.** PK parameters for ICIs

| PK | Molecular weight (kDa) | IgG isotype | Volume of distribution (L) | Metabolism | $T_{1/2}$ (day) | Clearance (mL/h) | Elimination |
|---|---|---|---|---|---|---|---|
| Pembrolizumab | 149 | IgG4 | 6.0 | nonspecific lysosomal degradation | 22 | 8.1 | Intracellular catabolism |
| Nivolumab | 146 | IgG4 | 6.8 | nonspecific lysosomal degradation | 25 | 8.2 | Intracellular catabolism |
| Cemiplimab | 146 | IgG4 | 5.3 | nonspecific lysosomal degradation | 20.3 | 8.3 | Intracellular catabolism |
| Atezolizumab | 145 | IgG1 | 6.9 | nonspecific lysosomal degradation | 27 | 8.3 | Intracellular catabolism |
| Durvalumab | 149 | IgG1 | 5.6 | nonspecific lysosomal degradation | 18 | 8.2 | Intracellular catabolism |
| Avelumab | 147 | IgG1 | 4.7 | nonspecific lysosomal degradation | 6.1 | 24.6 | Intracellular catabolism |
| Ipilimumab | 148 | IgG1 | 7.5 | nonspecific lysosomal degradation | 15.4 | 16.8 | Intracellular catabolism |

on population PK data and case reports, the effects of hepatic impairment on the PK of ICIs and dose adjustment recommendations for ICIs are provided and listed in **Table 2**.

*Pembrolizumab*

A population PK analysis on patients with mild to moderate hepatic impairment showed that

**Table 2.** Effects of hepatic or renal impairment on the PK of ICIs

| Hepatic/renal impairment | The effects are not significant and dose adjustment is not required (Refs.) | Not known |
|---|---|---|
| Mild hepatic impairment (TBil ≤ ULN and AST > ULN, or TBil > 1 to 1.5 × ULN with any AST) | Pembrolizumab [25-28], Nivolumab [29-33], Cemiplimab [34-36], Atezolizumab [37-39], Durvalumab [40-42], Avelumab [43-45], Ipilimumab [46-48] | |
| Moderate hepatic impairment (TBil > 1.5 to 3 × ULN and any AST) | Pembrolizumab [25-28], Nivolumab [29-33], Cemiplimab [34-36], Atezolizumab [37-39], Durvalumab [40-42], Avelumab [43-45] | Ipilimumab |
| Severe hepatic impairment (TBil > 3 to 10 × ULN and any AST) | Pembrolizumab [25-28], Nivolumab [29-33] | Cemiplimab, Atezolizumab, Durvalumab, Avelumab, Ipilimumab |
| Mild renal impairment (60-89 mL/min) | Pembrolizumab [25-27, 51-54], Nivolumab [29-32, 55-61], Cemiplimab [34-36], Atezolizumab [37-39, 62-65], Durvalumab [40-42, 66], Avelumab [43-45, 60, 67, 68], Ipilimumab [46-48, 69-72] | |
| Moderate renal impairment (30-59 mL/min) | Pembrolizumab [25-27, 51-54], Nivolumab [29-32, 55-61], Cemiplimab [34-36], Atezolizumab [37-39, 62-65], Durvalumab [40-42, 66], Avelumab [43-45, 50, 67, 68], Ipilimumab [46-48, 69-72] | |
| Severe renal impairment (15-29 mL/min) | Pembrolizumab [25-27, 51-54], Nivolumab [29-32, 55-61], Cemiplimab [34-36], Atezolizumab [37-39, 62-65], Avelumab [43-45, 50, 67, 68], Ipilimumab [46-48, 69-72] | Durvalumab |
| ESRD on dialysis (< 15 mL/min) | Pembrolizumab [25-27, 51-54], Nivolumab [29-32, 55-61], Atezolizumab [37-39, 62-65], Avelumab [43-45, 55, 67, 68], Ipilimumab [46-48, 69-72] | Cemiplimab, Durvalumab |

TBil, Total Bilirubin; AST, Aspartate Aminotransferase; ULN, Upper Limit of Normal.

model-derived clearance values in patients with mild to moderate hepatic impairment were similar to those with normal hepatic function [25-27]. Therefore, dose adjustment is not required for patients with mild to moderate hepatic impairment [25-27]. Pembrolizumab has not been studied in patients with severe hepatic impairment, but a case report demonstrated that treatment with pembrolizumab was effective and safe in patients suffering from severe hepatic impairment [28].

*Nivolumab*

In a population PK analysis, no clinically significant differences in the clearance of nivolumab were reported between patients with mild to moderate hepatic impairment and patients with normal hepatic function [29]. From a retrospective case series, the frequency of immune-related adverse events (irAEs) was similar between patients with Child-Pugh class B and patients with Child-Pugh class A [30]. Therefore, dose adjustment is not recommended in patients with mild to moderate hepatic impairment [31, 32]. The effects of severe hepatic impairment on the PK of nivolumab have not been conducted, but a case report demonstrated that a patient with severe hepatic impairment was safely and effectively treated with nivolumab at a dose of 3 mg/kg every 2 weeks [33].

*Cemiplimab*

A population PK analysis implied no clinically important differences in the exposure of cemiplimab in patients with mild to moderate hepatic impairment compared with patients with normal hepatic function [34]. Therefore, dose adjustment is not required for these patients [35, 36]. There are insufficient data in patients with severe hepatic impairment for dosing recommendations because cemiplimab has not been studied in these patients.

*Atezolizumab*

The PK data showed no clinically important differences in the clearance of atezolizumab in patients with mild to moderate hepatic impairment compared with patients with normal hepatic function. Treatment was tolerable across groups [37]. Therefore, dose adjustment is not recommended in patients with mild or moderate hepatic impairment [37-39]. Since no available data on patients with severe hepatic impairment, there are no dose adjustment recommendations for such patients.

*Durvalumab*

From a population PK analysis, the PK of durvalumab did not appear to be affected by mild or moderate hepatic impairment [40-42]. The result indicates that dose adjustment is not required for these patients [40-42]. Data are, however, not sufficient to draw a definite conclusion about patients with severe hepatic impairment.

*Avelumab*

The effects of hepatic impairment on the clearance of avelumab was evaluated by a popula-

tion PK analysis [43]. The data showed that patients with mild to moderate hepatic impairment had comparable avelumab clearance to those with normal hepatic function [43]. Therefore, dose adjustment is not needed in patients with mild to moderate hepatic impairment [43-45]. There are limited data from patients with severe hepatic impairment (n=1). Hence the effects of severe hepatic impairment on the PK of avelumab are unknown.

*Ipilimumab*

According to the population PK results, mild hepatic impairment had no clinically important effects on the clearance of ipilimumab, suggesting that dose adjustment is not required in this population [46-48]. As no data are available in patients with moderate or severe hepatic impairment, the potential need for dose adjustment cannot be determined in these patients.

### Effects of renal impairment on the PK of ICIs

The FDA guidance recommends that a study should be conducted to evaluate the effects of renal function on the PK of drugs with molecular weight less than 69 kDa. The molecular weight of seven ICIs is in the range of 140 to 150 kDa, which is expected to prevent ICIs from being filtered through the glomeruli of the kidney and eliminated via the urine. Therefore, renal impairment may have little effect on the PK of ICIs [25, 31, 35, 38, 41, 44, 47]. However, the elimination mechanisms for ICIs are far more complicated than nonspecific and unsaturable catabolism. Similar to hepatic impairment, renal impairment may alter the PK of ICIs via the regulation of neonatal FcRn and FcγR binding, TMDD, transport, tissue distribution, or other unknown mechanisms [6, 7]. Thus, renal impairment, especially severe renal impairment, may affect the PK of ICIs. Prospective studies on the safety and efficacy of ICIs in patients with renal impairment are limited. The use of ICIs in renal impaired patients in clinical practice is almost based on population PK analyses and case reports [49, 50]. Based on the population PK results and case reports, the effects of renal impairment on the PK of ICIs and dose adjustment recommendations for ICIs are listed in **Table 2**.

*Pembrolizumab*

A population PK analysis showed that mild to severe renal impairment had no clinically significant effects on the PK of pembrolizumab [25-27]. A multi-center, single-arm, phase 2 study revealed that pembrolizumab was active and had acceptable toxic effects as a first-line treatment in patients with mild to moderate renal impairment who were ineligible for cisplatin [51]. No PK analysis of pembrolizumab has been performed for patients with end-stage renal disease (ESRD) on dialysis. Only a few case reports have considered pembrolizumab administration for patients undergoing dialysis [52-54]. These case reports showed that pembrolizumab administered as a standard dose was safe and effective in ESRD patients on dialysis [52-54]. The above data suggest that dose adjustment is not needed for patients with renal impairment.

*Nivolumab*

No clinically important differences in the clearance of nivolumab were reported in a population PK analysis between patients with mild to severe renal impairment and patients with normal renal function [29-32]. According to the results of the PIVOT-10 trial, bempegaldesleukin plus nivolumab has the potential to address a high unmet need for effective and well-tolerated treatment in cisplatin-ineligible patients with moderate to severe renal impairment [55]. For ESRD patients on dialysis, several case reports showed that nivolumab seems to be similarly safe for these patients as for patients with normal renal function [56-61]. Thus, dose adjustment might not be necessary for patients with varying degrees of renal impairment.

*Cemiplimab*

No clinically important differences in the PK of cemiplimab were found in a population PK analysis between patients with mild, moderate, or severe renal impairment and patients with normal renal function [34-36]. The result indicates that dose adjustment is unnecessary for these patients [34-36]. Cemiplimab has not been studied in ESRD patients; hence, there are no dose adjustment recommendations for this patient group.

*Atezolizumab*

The population PK data showed that mild and moderate renal impairment did not affect the clearance of atezolizumab [37-39]. In a subgroup analysis from the EAP study, the clinical benefit of atezolizumab occurred in patients with mild, moderate, or severe renal function, and safety was comparable across subgroups [62]. Similarly, in a single-arm, multi-center, phase 2 trial, atezolizumab demonstrated promising response durability and survival coupled with a low incidence of clinically relevant toxicities in cisplatin-ineligible patients with mild to moderate renal impairment [63]. For ESRD patients on dialysis, several case reports revealed that atezolizumab administered as a full dose was effective and well-tolerated [61, 64, 65]. Therefore, dose adjustment is not required for ESRD patients on dialysis.

*Durvalumab*

A population PK analysis performed on patients with normal, mild, moderate, and severe renal impairment showed that the PK of durvalumab in patients with mild or moderate renal impairment was similar to those with normal renal function [40-42]. A pilot combination neoadjuvant trial showed that durvalumab plus tremelimumab had a tolerable safety profile and encouraging efficacy results in cisplatin-ineligible patients with eGFR < 60 mg/ml [66]. Therefore, dose adjustment is not required in patients with mild to moderate renal impairment. Since only two patients with severe renal impairment were included in the population PK analysis, the effects of severe renal impairment on the PK of durvalumab were unknown. Therefore, the dosing recommendation cannot be given in this situation.

*Avelumab*

A population PK analysis showed that patients with mild, moderate, or severe renal impairment had similar clearance relative to patients with normal renal function, suggesting that dose adjustment is not required [43-45]. According to the pooled results from two expansion cohorts of an open-label, phase 1 trial, treatment with avelumab was tolerable and confirmed responses were seen in six cisplatin-ineligible patients with renal impairment [67]. Similarly, from an updated analysis of avelumab in patients with previously treated urothelial carcinoma, avelumab showed prolonged efficacy and acceptable safety in 113 patients with renal impairment (eGFR < 60 ml/min) [68]. Thus, dose adjustment is not required for patients with mild to severe renal impairment. A case report demonstrated that avelumab administered at 10 mg/kg every two weeks was tolerated and effective for an ESRD patient on dialysis [50].

*Ipilimumab*

As shown in a population PK analysis, mild to severe renal impairment did not influence the clearance of ipilimumab [46-48]. In a single-arm feasibility trial, ipilimumab plus nivolumab was well-tolerated and highly active as preoperative treatment in 13 cisplatin-ineligible patients with eGFR < 60 mg/ml [69]. Several case reports demonstrated that a full dose of ipilimumab could elicit clinical benefit in ESRD patients on dialysis, and the toxicity of ipilimumab was manageable [70-72]. Therefore, ipilimumab can be dosed without the consideration of renal function.

## Potential, hepatotoxicity and nephrotoxicity of ICIs

ICIs can cause irAEs, and hepatic and renal toxicities are the common irAEs reported in clinical studies [8-10]. However, it is difficult to obtain accurate data on the incidence or prevalence of ICIs-related hepatic or renal toxicities due to strict diagnosis standards, selection criteria, small sample sizes, and limited duration of follow-ups. When patients do not exhibit pre-existing hepatic or renal impairment but develop ICIs-related hepatic or renal toxicities, the dose modification schedule is based on the grade of the adverse events. For example, if patients experience grade 2 or 3 increased blood creatinine during atezolizumab treatment, the recommendation is to withhold atezolizumab until blood creatinine recovers to grade 0 or 1. Atezolizumab should be permanently discontinued if patients experience grade 4 increased blood creatinine during treatment [38].

## Discussion

In contrast to many cytotoxic anti-cancer agents and small-molecule targeted drugs, which undergo hepatic or renal elimination, ICIs

and other monoclonal antibodies are metabolized to peptides and amino acids by circulating phagocytic cells [6, 7]. Therefore, renal or hepatic impairment would be expected to have minimal impact on the PK of ICIs. However, the elimination mechanisms for ICIs are complicated and not fully understood. Thus, hepatic or renal impairment, especially more advanced hepatic or renal impairment, may affect FcRn and FcγR binding, TMDD, or other factors to influence the elimination of ICIs [11, 22, 73]. Based on a PK study, the AUC of atezolizumab decreased by 8% and 12%, in patients with mild, moderate hepatic impairment, respectively, compared with subjects with normal hepatic function [37]. However, as far as we know, there is a few prospective clinical studies to investigate the PK of ICIs in patients with hepatic or renal impairment. Furthermore, patients with moderate or severe organ impairment were often excluded from clinical trials of those drugs [74-79]. Therefore, information about the efficacy and safety of ICIs in patients with hepatic or renal impairment is basically from the population PK analyses and case reports.

Patients with ESRD on dialysis present a significant challenge to clinicians. There are several considerations in treating this subset of patients with anti-cancer therapy. One important consideration is the potential alteration in drug exposure caused by ultrafiltration. However, ICIs are not expected to be cleared by dialysis due to their high molecular weight [6, 73]. In addition, the elimination of ICIs seems to involve the clearance of IgG through the reticuloendothelial system. Thus, dialysis may not significantly affect the PK of ICIs [6, 7]. Another consideration is drug efficiency in patients with ESRD on dialysis. The ICIs rely on the activation of the immune system for efficacy, and ESRD patients on dialysis have impaired immunity [80]. Theoretically, the efficiency of ICIs might be decreased in cancer ESRD patients on dialysis. However, case reports and case series have showed that pembrolizumab, nivolumab, atezolizumab, avelumab, and ipilimumab can produce sufficient anti-cancer effects in dialysis patients [52-54, 56-61, 64, 65, 70-72]. As for cemiplimab and durvalumab, there are no relevant reports.

As described above, the elimination mechanisms for ICIs are complicated and not fully understood, and data about the safety and efficiency of ICIs in patients with severe hepatic or renal impairment are lacking. In addition, ICIs can induce hepatic and renal toxicities, which can induce worsening organ dysfunction in patients with pre-existing hepatic or renal impairment. Thus, an appropriate dosage of ICIs is essential for maximizing efficacy and minimizing the incidence of adverse events. To date, there are several methods are available to assess the effects of hepatic or renal impairment on the drug PK, such as clinical PK study, physiology-based PK (PBPK) models and population PK studies. In addition, therapeutic drug monitoring (TDM) is an option for dose adjustment. Recent clinical studies have shown an increased benefit for TDM use in monoclonal antibody therapy, suggesting that TDM may be applicable to ICIs [81, 82]. According to current data, TDM strategies are particularly relevant for ipilimumab, which is already characterized by clear exposure-efficacy and exposure-safety relationships [46, 83]. Therefore, TDM can be considered when ICIs are used in patients with severe hepatic or renal impairment.

## Conclusion

According to the population PK analyses, mild to moderate hepatic impairment and mild to severe renal impairment had no clinically significant effects on the PK of most ICIs, and dose adjustment is not required for these patients. Whereas, there are very limited data regarding the use of ICIs in patients with severe hepatic impairment, or ESRD patients on dialysis, making it challenging to select an appropriate ICIs dosage for such patients. In practice, it is difficult to conduct a clinical study to evaluate the drug PK in patients with severe hepatic impairment or ESRD patients on dialysis, therefore, the PBPK model and population PK analysis may be suitable for predicting the drug PK in these patients. Moreover, in order to make a precision and individualized dosage, TDM can be used in patients with severe hepatic impairment or ESRD patients on dialysis. In addition to the use of TDM, ICIs-related adverse reactions should also be monitored for these patients.

## Disclosure of conflict of interest

None.

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