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# Immune Checkpoint Inhibitors in Special Populations

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**Abstract**

Cancer is the second leading cause of death in the worldwide. With the growing burden of cancer, the studies on early diagnosis, treatment and prevention of cancer are rapidly increasing. Recently, many new therapeutic strategies have been discovered, among which immunotherapy has dramatically changed the outlook for cancer treatment. Several clinical trials are underway around the world to produce potential treatments. However, these trials set certain strict joining conditions, so that the clinical data cannot be fully applied in the real world. To help clinical oncologists with treatment decision-making, this review collected recent studies on special populations receiving immunotherapy, including organ transplant patients, pregnant women, pediatric patients, patients with pulmonary tuberculosis, patients with human immunodeficiency virus, and patients with autoimmune diseases and mental illness.

**Keywords**

immunotherapy, cancer, organ transplant, pregnancy, pediatrics tuberculosis

**Abbreviations**

AD, Alzheimer's disease; ALL, acute lymphoblastic leukemia; ART, antiretroviral therapy; BiTEs, bispecific T-cell engagers; CAR-Ts, chimeric antigen receptor T cells; CNS, central nervous system; CR, complete response; CTLA-4, cytotoxic T lymphocyte antigen 4; GVHD, graft-versus-host disease; HIV, human immunodeficiency virus; HL, Hodgkin lymphoma; ICIs, immune checkpoint inhibitors; IFN-γ, interferon-γ; irAEs, immune-related adverse events; KS, Kaposi sarcoma; mAbs, monoclonal antibodies; Mtb, Mycobacterium tuberculosis; NHL, non-Hodgkin lymphoma; NSCLC, non-small cell lung cancer; OS, overall survival; PADs, preexisting autoimmune diseases; PD, progressive disease; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1; PFS, progression-free survival; PTB, pulmonary tuberculosis; PR, partial response; SD, stable disease; SOT, solid organ transplantation; TB, tuberculosis.

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## Introduction

In China, the incidence rate of cancer in men and women was 301.67 per 100 000 and 253.29 per 100 000, respectively, and the mortality rate of cancer in men and women was 207.24 per 100 000 and 126.54 per 100 000, respectively.[1] According to the World Health Organization (WHO), cancer has caused 9.6 million deaths in 2018 globally.[2]

Immunotherapy is revolutionizing the treatment of cancer. It has increased the overall survival (OS) and progression-free survival (PFS) of many types of cancers, such as melanoma,[3-5]advanced non-small cell lung cancer (NSCLC),[6-8] renal cell carcinoma,[9] and Hodgkin lymphoma.[10,11] The targets of immune checkpoint inhibitors (ICIs) include programmed cell death 1 (PD-1) and cytotoxic T lymphocyte antigen 4 (CTLA-4) in T-cells or programmed cell death ligand

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1 (PD-L1) in tumor cells. These ICIs can exert anti-tumor effects in the body by activating T-cells. But they can also causes immune-related adverse events (irAEs) by changing the immune environment, such as checkpoint inhibitor pneumonitis, immune-related thyroiditis, hepatitis, myocarditis, enteritis and diarrhea, fatigue, itching, rash, endocrine disorders and so on.[12-14] IrAEs most commonly occur in the skin, lung, gut, and endocrine system.[12] The incidence of irAEs is 26.82% in patients treated with anti-PD-1/PD-L1inhibitors.[15] Despite of stopping treatment in some patients when conducting clinical trials due to irAEs, most patients develop minimal symptoms during treatment and can still lead a high quality life. Because of concern about potential side effects and compromised efficacy, patients with organ transplant, tuberculosis, HIV, preexisting autoimmune diseases and mental illness have been excluded from prospective randomized trials. At the same time, the majority of current immunotherapy studies are decidedly focused on non-pregnant adult, pediatric and obstetrics space need more attention. Many oncologists can't provide a precise treatment plans when facing trial-ineligible patients. Fortunately, several studies have evaluated the safety and efficacy of immunotherapy in special population of patients who receiving immunotherapy, including organ transplant patients, pregnant women, pediatric patients, patients with pulmonary tuberculosis (PTB), patients with human immunodeficiency virus (HIV), and patients with autoimmune diseases and mental illness. Although the mechanisms of these diseases are all associated with immune system, there are great difference in clinical practice such as treatment, risk of irAEs, outcomes. So, we decided to analyze these special groups of people separately. We hope this review could help oncologists conducting clinical work.

## Transplant

Solid organ transplantation (SOT) or hematopoietic stem cell transplantation is not rare in cancer patients, and cancer is the second leading cause of death in all SOT recipients, indicating a substantial cancer burden in this population.[16] The increasing use of ICIs assists in studying the safety and efficacy of these inhibitors in transplant patients. After transplantation, allograft rejections and graft-versus-host disease (GVHD) can usually be prevented with intense maintenance of immunosuppression.[17] More interestingly, clinical studies have shown that PD-1 or PD-L1 expression is associated with allograft tolerance,[18,19] and PD-1 gene polymorphism contributes to the reduction of allograft failure.[20] So, whether ICI will break the immune tolerance and cause severe post-transplant complications is still a question of discussion.

After reviewing the existing literatures through searching PubMed, it was found that patients treated with ICIs showed different clinical responses. According to Abdel-Wahab *et al*,[21] among 39 cancer patients who underwent solid organ transplantation (59% with prior renal transplantation [n = 23], 28% with hepatic transplantation [n = 11], and 13% with cardiac transplantation [n = 5]), 16 patients (41%) developed allograft rejection after ICI therapy (renal transplantation rejection n = 11, 48%; hepatic transplantation rejection n = 4, 36%; and cardiac transplantation rejection n = 1, 20%). In total, 8 patients (21%) developed irAEs, and adverse reactions are observed in those without allograft rejection. The median OS was 12 months (95% CI 8-16 months) in patients without allograft rejection, and 5 months (95% CI 1-9 months) in those with rejection ($P = 0.03$). Similar conclusions have been reported by De Bruyn *et al*,[22] and they found that among the 48 advanced cancer patients who received ICI treatment, there were 19 liver transplantation recipients and 29 renal transplantation recipients. The rejections were observed in patients receiving liver (37%) and kidney transplant (45%). These results revealed that the patients were at a higher risk of allograft rejection after transplantation. Chae *et al*[23] hypothesized that CTLA-4 inhibitors were safer than PD-1 inhibitors in certain solid organ transplant recipients based on their extensive literature study. Several other clinical data of cancer patients treated with ICIs after solid organ transplantation showed similar results.[24,25]

Some people could tolerate ICI therapy, while others encountered severe posttransplant complications. The PD-1/PD-L1 axis might play a critical role in allograft rejection. It has been shown[26] that PD-L1 of the donor tissue can interact with PD-1 receptor expressed on the recipient's alloreactive T cells, thus down-regulating the recipient's alloreactive T cell responses and limiting the rejections. PD-1/PD-L1 inhibitors could destroy the balance of the immune microenvironment, leading to allograft rejection in SOT patients treated with ICIs. In murine models, MEK inhibition and BTK inhibitor (Ibrutinib) could delay GVHD progression and improve survival.[23] Combination therapy of ICI with MEK or BTK inhibitors could reduce the transplantation failure rate of SOT cancer patients.[23]

## Pregnancy

The incidence rate of cancer during pregnancy is 16.9/100,000 live birth and 24.5/100,000 birth.[27] If cancer occurs during pregnancy, both mother and the embryo are at greater risk of death. It is important to weigh maternal and fetal advantages to prolong survival and reduce the teratogenicity.

Recent studies have reported that the majority of pregnant woman are already at advanced stages when they are diagnosed. In patients with positive driver gene, targeted therapy might be considered a good choice.[28,29] Immunotherapy can be assumed as the next treatment option for pregnant woman with negative driver gene. Flint *et al*[30] analyzed the feasibility of ICI for pregnant woman undergoing ICI by comparing the immunological similarities and differences between pregnancy and cancer. Maternal-fetal immune tolerance involving complex mechanisms might share the same pathway with cancer immune checkpoint block.[30,31] It has been demonstrated[32-34] that the blockade of PD-L1 can reduce the allogeneic fetal survival rate, and CTLA-4 on Treg cells may play a role in the maintenance of pregnancy by inducing an enzyme called indoleamine 2,3-dioxygenase in the dendritic cells and monocytes. Therefore, some people worry about whether immunotherapy

will destroy maternal tolerance to the fetus by blocking the immune check points, and whether it means that pregnant woman cannot receive immunotherapy. On the contrary, 2 cases set forth the possibility of applying immunotherapy in pregnant woman. The first is a case of a metastatic melanoma at 7 weeks of pregnancy, who received nivolumab plus ipilimumab and successfully delivered a healthy baby.[31] Menzer *et al* also reported a similar case of metastatic melanoma at 18 weeks of gestation. The patient was treated with nivolumab plus ipilimumab, but the patient's condition slowly deteriorated and died from underlying disease the day before delivery. Fortunately, a premature female baby was born with no deformities or intrauterine growth retardation.[35]

These reports suggested that certain patients could benefit from the use of ICIs. Multi-center trials are difficult to be conducted due to ethical challenges, different cultures and laws. For doctors, it is important for to balance the benefits and risks, and make decisions in a multidisciplinary setting.

## Pediatrics

In developing country, cancer is the leading disease-related cause of death in children and adolescents.[36] Treatment of cancer in pediatrics is significantly different from that of adults. As reported by Ward *et al*[37] the most common types of cancers in childhood included acute lymphoblastic leukemia (ALL) (26%), brain and central nervous system (CNS) tumors (21%), neuroblastoma (7%), and non-Hodgkin lymphoma (NHL) (6%), whereas the most common cancers in adolescence were Hodgkin lymphoma (HL) (15%), thyroid carcinoma (11%), brain and central nervous system tumors (10%), and testicular germ cell tumors (8%). The principle behind pediatric cancer treatment is similar to that of adults, but there is no specific drug application. Traditional therapies for pediatric cancer include surgery, chemotherapy and radiation therapy. Compared with adult cancer, immunotherapies have been demonstrated to have no significant activity in the front-line treatment of pediatric cancer. However, for many refractory and recurrent tumor patients, immunotherapy has become a viable therapeutic option.[38] Recent studies have reviewed immunotherapy development for pediatric cancer. Immunotherapies included monoclonal antibodies (mAbs), checkpoint inhibitors, bispecific T-cell engagers (BiTEs), and chimeric antigen receptor T cells (CAR-Ts), which may have the chance to treat children with resistant or recurrent cancer.[38] Checkpoint inhibitors such as anti-PD-1 or anti-CTLA-4 inhibitor has a similar safety profile to that of adults, but the response rate of agents to solid cancer in children is far lower than that of adults. Recent reports[39-44] applying immunotherapy in pediatric cancer were collected (Table 1). Geoerger *et al*[39] have enrolled 155 pediatric patients with PD-L1-positive solid tumor or lymphoma (include PD-L1-negative advanced melanoma) and all children were treated with pembrolizumab. At the end of the study, 9 of 15 HL patients achieved an objective response (60.0% [95% CI 32.3-83.7]), 8 of 136 patients with other lymphomas or solid tumors achieved an objective response (5.9% [95% CI 2.6-11.3]), and adverse reactions were shown to be tolerable. The results of phase I study (NCT01445379) in pediatric patients with melanoma and other solid tumors who received CTLA-4 blockade therapy demonstrated good tolerance to anti-CTLA-4 therapy, but there was no objective responses.[42] However, 2 cases treated with mAbs showed obvious efficacy and safety of immunotherapy in recurrent and refractory pediatric cancer.

Pinto *et al*[45] have demonstrated that the levels of PD-1, PD-L1, and PD-L2 are low in pediatric solid tumors. The poor reaction of pediatric cancer patients to PD-1/PD-L1 inhibitor could be associated with the low expression of PD-1/PD-L1. In the same line, Majzner *et al*[46] also believed that low immunogenicity was less likely to respond to single-agent checkpoint inhibition.

There was limited data on the good tolerance of ICIs and mAbs for treating cancer clinically. Compared with chemotherapy and radiotherapy, which could cause neurological dysfunction, skeletal deformities and short stature, immunotherapy was associated with fewer long-term toxicities and more conducive to children who could grow healthy.[38,47-49] Immunotherapy in pediatric cancer is still in the exploratory stage. By identifying optimal targets and accurate biomarkers, we believe that immunotherapy will revolutionizes the treatments for pediatric cancer and increases survival and quality of life of pediatric cancer patients.

## Tuberculosis

According to WHO, more than 10 million people were sick due to tuberculosis (TB) in 2018 globally.[50]As Japanese data, in last 20 years, incidence of active pulmonary tuberculosis in lung cancer patients was 1.9%.[51] Cheon *et al*[52] reported that compared with other cancer, patients with esophageal cancer, multiple myeloma, lung cancer, pancreatic cancer, leukemia, head and neck cancer, and lymphoma were more susceptible to development of TB. Cheng *et al*[53] reported that hematologic cancer patients had the highest rate of active tuberculosis. Dobler *et al*[54] also reported that the relative risk of TB in hematologic cancer in adults was higher than that in adults with solid cancers (IRR: 3.53 vs 2.25; 95% CI 1.63-7.64; 1.96-2.58). In the past few years, some cases have reported the development of acute tuberculosis in cancer patients who were treated with nivolumab or other PD-1/PD-L1 inhibitors (Table 2).[55-65] At the same time, one case with advanced pulmonary adenocarcinoma developed tuberculous pericarditis after nivolumab treatment.[60] At present, there are no big clinical trials that providing accurate data on the incidence of TB reactivation after immunotherapy. Review of the literatures revealed 2 assumptions about the mechanism of TB activation. Firstly, blockade of PD-1/PD-L1 pathway might result in the proliferation of T cells, which in turn could produce interferon-γ (IFN-γ) against Mycobacterium tuberculosis (Mtb).[66] This reaction might be similar to those of HIV/TB coexisting patients receiving antiretroviral treatment, who developed TB rapidly because of restoration of anti-TB

**Table 1.** Efficacy and Safety of Immunotherapy in Pediatric Cancer Patients.

| Reference | Age | Number | Tumor types | Immunotherapy | Key outcomes |
|---|---|---|---|---|---|
| Geoerger *et al*[39] | 13 Y | N = 155 | Relapsed or refractory Solid tumor or lymphoma | Pembrolizumab | **Efficacy:** HL (n = 15) CR 2 (13%) PR 7 (47%) PD 3 (20%) other tumor type (n = 136) CR 0 PR 8 (6%) PD 74 (54%) **Safety:** immune-related: grade 1-2, n = 30 (19%) grade 3, n = 2 (1%) grade 5, n = 1 (<1%) |
| Marjanska *et al*[40] | 7 Y | N = 1 | Recurrent metastatic melanoma | Pembrolizumab | **Efficacy**: CR lasting 12 months **Safety:** irAEs Arthritis, uveitis |
| AlHarbi *et al*[41] | 5 Y | N = 1 | Refractory glioblasto-ma | Nivolumab | **Efficacy:** Durable response lasting 10 months **Safety:** No adverse reactions |
| Merchant *et al*[42] | 13.4 Y | N = 33 | Melanoma/Sarcoma/Renal carcinoma/bladder carcinoma/ Neuroblastoma | Ipilimumab | **Efficacy**: No objective tumor regressions **Safety:** Patients with irAEs n = 18 (55%) |
| Davis *et al* [43] | 14Y | N = 85 | Relapsed or refractory solid tumor or lymphoma | Nivolumab | **Efficacy:** HL (n = 10) CR 1 (10%) PR 2 (20%) SD 5 (50%) **Safety:** Patients with grade 3-4 irAEs n = 27/75 (36%) |
| Geoerger *et al* [44] | 14Y | N = 87 | solid tumor or HL or NHL | Atezolizumb | **Efficacy:** PR 4 (5%) SD 10 (11%) PD 63 (72%) **Safety:** Patients with irAE n = 57 (66%) |

Abbreviations: CR, Complete response; EFS, Event-free survival; HL, Hodgkin's lymphoma; irAEs, immune-related adverse events; NHL, non-Hodgkin's lymphoma; OS, overall survival; PR, partial response; PD, progressive disease; SD, stable disease.

specific immune response by rapid increase of $CD4^+$ T cells.[66,67] Secondly, activation of pulmonary tuberculosis cause diffuse lymphocyte infiltration.[60,66] These hypotheses still warranted clarification. In summary, it was important to pay attention to potential Mtb infection in patients and screen for latent TB clinically.

For PTB patients undergoing ICI treatment, no exact timing to safely apply immunotherapy is present. Anastasopoulou *et al*[58] have suggested that ICI therapy should be paused before PTB was controlled because of potential exaggeration of inflammatory responses caused by immunotherapy. Also 2 weeks interval might be appropriate between anti-tuberculosis treatment and immunotherapy.[58] If anti-tuberculosis treatment and immunotherapy start simultaneously, then the overlapping toxicities caused by them should be focused on, especially the liver dysfunction.[58]

## Autoimmune Disease

About 11.3% patients with advance cancer had a personal history of preexisting autoimmune diseases.[68] Previous studies have shown that PD-1/PD-L1 and CTLA-4 were associated with the development of autoimmune diseases. Nishimura *et al*[69] have demonstrated that PD-1 receptor deficient mice may develop immune-mediated cardiomyopathy. And Klocke *et al*[70] have also showed that CTLA4-deficient mice suffered from various autoimmune diseases. CTLA-4 gene polymorphism is linked with the cause of several autoimmune diseases,

**Table 2.** Development of Acute TB in Cancer Patients Treated With ICIs.

| Reference | Age/sex | Tumor type | ICI |
|---|---|---|---|
| van Eeden *et al*[55] | 56 Y/female | NSCLC | Nivolumab |
| Inthasot *et al*[56] | 69 Y/male | NSCLC | Nivolumab |
| | 57 Y/female | NSCLC | Nivolumab |
| Barber *et al*[57] | 59 Y/male | NPC | Nivolumab |
| | 83 Y/male | MCC | Pembrolizumab |
| Anastasopoulou *et al*[58] | 76 Y/female | Melanoma | Nivolumab |
| | 85 Y/male | Melanoma | Atezolizumab |
| Jensen *et al*[59] | 56 Y/male | NSCLC | Nivolumab |
| Chu *et al*[60] | 59 Y/male | NSCLC | Nivolumab |
| Fujita *et al*[61] | 72 Y/male | NSCLC | Nivolumab |
| Picchi *et al*[62] | 65 Y/female | Melanoma | Pembrolizumab |
| Lee *et al*[63] | 87 Y/male | HL | Pembrolizumab |
| He *et al*[64] | 65 Y/female | Melanoma | Pembrolizumab |
| Elkington *et al*[65] | 62 Y/female | Ocular melanoma | Ipilimumab |

Abbreviations: HL, Hodgkin's lymphoma; ICIs, Immune checkpoint inhibitors; MCC, Merkel cell carcinoma; NSCLC, Non-small cell lung cancer; NPC, nasopharyngeal carcinoma; TB, Tuberculosis.

such as systemic lupus erythematosus, type I diabetes, Graves disease and rheumatoid arthritis.[71-73]Although the exact mechanisms of these diseases should be clarified, the use of ICIs in cancer patients with pre-existing autoimmune diseases (PADs) cause worries, since further immune stimulation may lead to new autoimmune manifestations or underlying symptom flares in patients with PADs.

Johnson and Menzies *et al*[74,75] have assessed 30 and 52 cancer patients with PADs treated with ICIs, respectively. The results showed that 10/30 (33%) experienced grade 3 to 5 irAEs, and 3/30 (10%) experienced both autoimmune disease flare and irAEs. Tumor responses of 30 patients were reported, including a complete response (CR) in 1 patient, and partial response (PR) in 5 patients. The median PFS was 3.0 (95% CI, 2.0-8.3) months, and the median OS was 12.5 months (95% CI, 6.3 months to upper limit not applicable). Among the 52 cancer patients, 20/52(38%) experienced an autoimmune flare (2 patients discontinued treatment due to flare), 15/52 (29%) had conventional irAEs (10% grade 3 [n = 5]). Responses were observed in 17/52 (33%) patients. The median PFS was 6.2 months (95% CI 4.2-8.2).[74,75] These retrospective studies showed that cancer patients with PADs could tolerate ICIs. The objective response rate in the population treated with Ipilimumab was inferior to that of normal cancer patients treated with ICIs.[76] In the stady by Tison *et al*,[77] 112 cancer patients with PADs were enrolled and treated them with ICIs. In total, 71% (n = 79) patients experienced immunotoxicity (21% [n = 24] permanently discontinued treatment due to immune toxicity), and 47% (n = 53) patients had PAD flares (30% grade 3-4 [n = 15]); 42% (n = 47) patients developed irAEs that were unrelated to PAD (40% grade 3-4 [n = 18]). Regarding tumor response of patients, the results revealed that 17 (16%) patients had CR, and 34 (32%) patients had PR. Patients who did not receive immunosuppressive agents during the initiation of ICI treatment initiation had longer PFS than those receiving treatment (median 12 months versus 3.8 months; $P = 0.006$). The rate of immunotoxicities related to ICIs or the rate of grade 3-4 irAEs was higher than other studies. According to another study, Fillon[78] believed that ICI therapy was safe for cancer patients with PADs under efficacy clinical management. Cancer patients with PADs might develop severe irAEs during ICIs treatment, but most of the cases were mild and are manageable with steroids. Arbour *et al*[79] have suggested that more than 10 mg/day use of steroid during the start of ICIs was associated with inferior clinical efficacy. Dr. Cornec[78] also suggested that for cancer patients with stable PADs, declining the use of immunosuppressive treatment during the initiation of ICIs did not reduce the efficacy of cancer treatment. Safety with regard to the use of ICIs in severe autoimmune disease patients is still unknown, and high dose of steroids might reduce the efficacy of ICIs. So, collaboration between a specialist in PAD and oncologist is very important when facing these patients.

## HIV

The risk of cancer is 69% higher in people infected with HIV when compared to healthy population.[80] However, HIV-infected cancer patients were always excluded from the clinical trials. In the past few years, several clinical trials have evaluated the safety and efficacy of immunotherapy in cancer patients with HIV-infection. Uldrick *et al*[81] have enrolled 30 patients with Kaposi sarcoma (KS) (n = 6) and NHL (n = 5) and non-AIDS-defining cancer (n = 19), and all patients were treated with pembrolizumab. The primary objective was to assess safety of pembrolizumab in cancer patients with HIV who were on antiretroviral therapy (ART) with cancer. Grade 1-2 irAEs were observed in 22 patients (73%), and grade 3 irAEs were observed in 6 patients (20%). HIV was shown to be controlled in all participants. With regard to tumor responses in patients, CR was revealed in 1 patient, PR in 2 patients, stable disease (SD) in 17 patients, and progressive disease (PD) in 8 patients, and 2 patients were not evaluable (NCT02595866). Ostios-Garcia *et al*[82] have enrolled 7 lung cancer patients with HIV infection and they were treated with nivolumab (n = 2) and pembrolizumab (n = 5). All these patients accepted ART during immunotherapy. Tumor responses in patients included PR (n = 3), SD (n = 2), and PD (n = 2). Only 4 patients had grade1-2 irAEs. Guaitoli *et al*[83] have summarized clinical efficacy of immunotherapy in 28 HIV-infected cancer patients, which revealed that immunotherapy in HIV-infected patients was, as effective as in general population, with good and its safety and toxicity were similar to those general cancer patients. In summary, these results suggested that, unless there were specific situations, HIV-infected cancer patients receiving ART could be treated similarly to general cancer patients using immunotherapy.

## Mental Illness

According to the Diagnostic And Statistical Manual Of Mental Disorders,[84] Fifth Edition, Alzheimer's disease (AD), depression,

**Table 3.** Summary of Ongoing Clinical Trials.

| Study | Population | Phase | Drug | Treatment schedule | Primary endpoints |
|---|---|---|---|---|---|
| NCT045643133 | Liver transplantation | I | Camrelizumab | Camrelizumab 200 mg every 3 w | ORR |
| NCT03966209 | Liver transplantation | I | Toripalimab | Toripalimab 240 mg every 3 w | Serious adverse event rate<br>acute graft rejection rate |
| NCT03816332 | Kidney transplantation | I | Nivolumab +/ −Ipilimumab | Nivolumab every 4 w or nivolumab plus Ipilimumab every 3w,6 w later nivolumab every 4 w | Percentage of CR, PR or SD<br>Percentage of do not experience allograft loss |
| NCT02304458 | Pediatrics | I/II | Nivolumab+/ −Ipilimumab | Nivolumab 3mg/kg or nivolumab 3mg/kg plus ipilimumab | Frequency of patients experiencing a dose limiting toxicity<br>Frequency of patients with at least PR to nivolumab |
| NCT03816345 | Autoimmune disease | I | Nivolumab | Nivolumab every 4 w | Incidence of adverse events<br>Change in disease assessments<br>Overall response rate |
| NCT03656627 | Autoimmune disease | I | Nivolumab | nivolumab 240 mg days 1,15 every 4 w | Dose-limiting toxicity |
| NCT02595866 | HIV | I | Pembrolizumab | pembrolizumab every 3 w | Frequency of observed adverse events<br>Incidence of immune-related events of clinical interest |
| NCT04514484 | HIV | I | Nivolumab + Cabozantinib | Cabozantinib s-malate qd po on days 1-28 plus nivolumab on day 1 | Incidence of dose limiting toxicities |
| NCT03316274 | HIV | I | Nivolumab | Nivolumab 10 mg injection into a KS lesion every 2 w | Number of dose limiting toxicity<br>Maximum tolerated dose |
| NCT03304093 | HIV | II | Nivolumab | Nivolumab 3mg/kg every 2 w | Disease control rate |
| NCT03094286 | HIV | II | Durvalumab | Durvalumab 1500 mg every 4 w | Number of patients that receive durvalumab at least 4 m |
| NCT04223804 | HIV | I | Budigalimab | Unknown | Number of adverse events grade 3 or higher |
| NCT02408861 | HIV | I | Nivolumab+ Ipilimumab | Nivolumab every 2 w or<br>Nivolumab every 2 w plus Ipilimumab every 6 w or<br>Nivolumab every 2 w plus IPILIMUMAB every 12 w | Maximum tolerated dose of nivolumab |

Abbreviations: CR, complete response; KS, Kaposi Sarcoma; m, months; ORR, objective response rate; PR, partial response; PD, progressive disease; SD, stable disease; w, weeks.

bipolar disorder and anxiety disorder all belong to mental illness. Several recent studies have demonstrated the association between immune system and mental illness. It has been reported[85] that the CNS-specific T cells can promote hippocampal neurogenesis, spatial learning and memory ability through microglial activation. This could partially explain the age-related and HIV-related cognitive impairment, because these patients had various degrees of immune system function declination. Rosenzweig *et al*[86] have successfully mitigated cognitive deficits and reduced pathology in the brain of 5XFAD AD mouse model through blockage of PD1/PD-L1 axis. This result suggested that ICIs might have an excellent clinical application in AD patients.

When faced with health threats, emotional distress such as depression and anxiety could be easily observed in cancer patients. It has been reported[87] that the incidence rate of depression in cancer patients varied from 1% to above 50% depending on the cancer type, stage, treatment, and different depression rating scales. Depression and anxiety are both immune-mediated inflammatory diseases, and that have been extensively investigated from the perspective of chemokines, cytokines, and immune cell numbers.[88-91] Fundamental research has not yet fully explained the relationship between mental illness and immune system. No clinical trials or cases have evaluated the efficacy and safety of immunotherapy in patients with mental illness. We hypothesized that persons who suffered from cancer and mental illness such as AD could benefit more from ICI therapy, and this would require further research in the future.

## Conclusions

With the rapid expansion of ICI treatment in special populations, it is important to clearly understand the safety and

efficacy of it in trial-ineligible population. SOT patients with immunotherapy have the risk of allograft rejection. There are not enough data about the efficacy and safety of immunotherapy in pregnant cancer women. In limited reports, there was no evidence that immunotherapy is associated with the risk of fetal malformation.[92] We advise use of CTLA-4 and/or PD-1 inhibitors during pregnancy only if the benefit to the mother is so great that it outweighs the substantial theoretic risks to the fetus. Patients with Mtb exhibited potential risks for the development of acute PTB when treated with ICIs. Before immunotherapy, a TB screen is important. Pre-existing autoimmune disorder is not an absolute contraindication to ICI therapy. But life-threatening autoimmune disease patients or myasthenia gravis patients may not be considered good candidates for ICI therapy.[93] HIV-infected cancer patients with ART, although viral load and CD4+ T cell numbers during treatment are heterogeneous, immunotherapy efficacy and safety are similar to general cancer patients. We thought HIV is not a contraindication to treatment. Cancer patients with mental illness such as AD may be potential beneficiaries of immunotherapy. We collected ongoing clinical trials about ICIs application in special patients (Table 3). Systematic studies and multicenter clinical trials were warranted to facilitate the acquisition of more useful data, which could guide drug application in special populations. Finally, clinicians can refer to these results to provide patients with a suitable plan by balancing potential benefits and toxicity risks. At the same time, multidisciplinary consultation is also needed for taking decision on treatment.

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